

# Formulation and Evaluation of Metformin HCL and Syzygium Cumini Combination Tablets for Type 2 Diabetes Treatment

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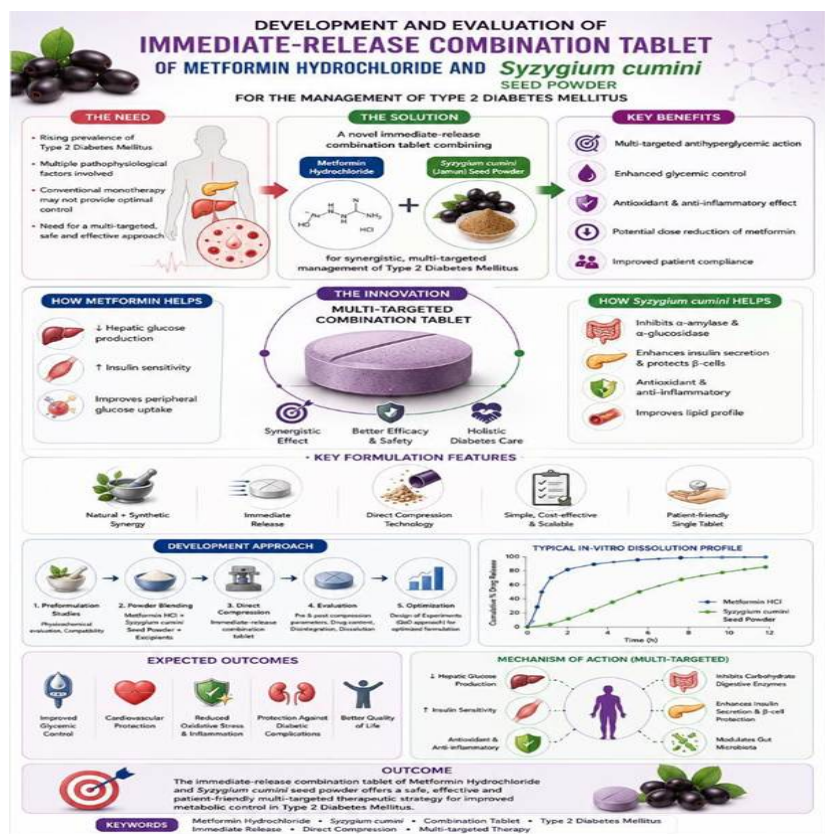
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## ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, impaired insulin secretion, and persistent hyperglycemia, leading to serious microvascular and macrovascular complications. Although Metformin Hydrochloride is the first-line oral antihyperglycemic agent, prolonged therapy may be associated with gastrointestinal adverse effects and does not adequately address oxidative stress or inflammation. Syzygium cumini (Jamun) seed powder possesses well-documented antidiabetic, antioxidant, and hypolipidemic properties, making it a promising herbal adjunct for diabetes management. Therefore, the present study aimed to formulate and evaluate an immediate-release combination tablet of Metformin Hydrochloride and Syzygium cumini seed powder using a Quality by Design (QbD) approach. The tablets were prepared by the direct compression method employing pharmaceutical excipients such as Microcrystalline Cellulose PH102, Polyvinylpyrrolidone K30, Croscarmellose Sodium, Colloidal Silicon Dioxide, and Magnesium Stearate. A 2<sup>3</sup> factorial design was applied to optimize the formulation variables affecting tablet hardness, disintegration time, and percentage drug release. Preformulation studies included organoleptic evaluation, melting point determination, UV spectrophotometric analysis, FTIR, and DSC studies to establish drug identity and drug-excipient compatibility. Powder blends were evaluated for pre-compression parameters, while the compressed tablets were assessed for weight variation, hardness, thickness, friability, disintegration time, drug content, dissolution profile, and stability under long-term storage conditions.

The optimized formulation (F9) exhibited satisfactory pre- and post-compression characteristics with acceptable hardness, friability below pharmacopoeial limits, rapid disintegration, uniform drug content, and excellent in vitro drug release. FTIR analyses confirmed the absence of significant drug-excipient interactions, indicating good compatibility among formulation components. Stability studies demonstrated that the optimized tablets remained physically and chemically stable throughout the study period. The findings of this investigation suggest that the developed immediate-release combination tablet of Metformin Hydrochloride and Syzygium cumini seed powder is a stable, effective, and patient-friendly dosage form. The synergistic combination of synthetic and herbal antidiabetic agents offers a promising therapeutic strategy for improving glycemic control.



**Graphical Abstract:** Development of an Immediate-Release Combination Tablet of Metformin Hydrochloride and Syzygium cumini Seed Powder for Type 2 Diabetes Mellitus.

**Keywords:** Formulation and Evaluation, optimized formulation (F9), Combination Tablets, Type 2 Diabetes.

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## INTRODUCTION

### 1.1 Introduction to Diabetes:

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It has emerged as one of the most significant global health challenges due to its increasing prevalence and association with severe complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy. Type 2 diabetes mellitus (T2DM), which accounts for approximately 90–95% of all diabetes cases, is primarily associated with insulin resistance and impaired pancreatic  $\beta$ -cell function. The rising incidence of diabetes has prompted extensive research into more effective and safer therapeutic approaches that combine conventional pharmacotherapy with natural products possessing antidiabetic potential.<sup>[1]</sup>

Metformin hydrochloride is considered the first-line oral antihyperglycemic agent for the management of Type 2 diabetes mellitus. It belongs to the biguanide class of drugs and acts primarily by reducing hepatic

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glucose production, enhancing peripheral glucose uptake, and improving insulin sensitivity without causing significant hypoglycemia. Despite its proven efficacy and safety profile, prolonged use of metformin may be associated with gastrointestinal disturbances and vitamin B12 deficiency, encouraging researchers to investigate complementary therapies that may enhance its therapeutic effects while reducing adverse reactions.<sup>[2]</sup>

Medicinal plants have been used for centuries in traditional systems of medicine for the management of diabetes and its complications. Among these, *Syzygium cumini* (Jamun) has gained considerable attention because of its rich phytochemical composition and potent antidiabetic properties. Different parts of the plant, including seeds, fruits, bark, and leaves, contain bioactive compounds such as jamboline, ellagic acid, gallic acid, flavonoids, tannins, anthocyanins, and alkaloids, which have demonstrated hypoglycemic, antioxidant, anti-inflammatory, and lipid-lowering activities in various experimental studies. Jamun seed powder, in particular, has shown the ability to delay carbohydrate digestion, improve insulin secretion, and reduce blood glucose levels.<sup>[3]</sup>

The combination of metformin hydrochloride with *Syzygium cumini* powder represents a promising therapeutic strategy that integrates modern pharmaceutical treatment with herbal medicine. Such a combination may provide synergistic effects by targeting multiple pathways involved in glucose homeostasis, potentially improving glycemic control while minimizing drug-related side effects. Furthermore, herbal constituents possessing antioxidant properties may help protect pancreatic  $\beta$ -cells from oxidative stress and reduce the progression of diabetic complications.<sup>[4]</sup>

To ensure patient compliance and convenience, the development of a combination tablet dosage form offers several advantages, including ease of administration, accurate dosing, improved stability, and enhanced therapeutic effectiveness. However, successful formulation requires careful optimization of excipients and manufacturing parameters to achieve acceptable hardness, friability, disintegration time, dissolution profile, and content uniformity. Preformulation studies, compatibility assessment, and systematic optimization techniques such as factorial design play an essential role in obtaining a robust formulation.<sup>[5]</sup>

The present study focuses on the formulation and evaluation of a combination tablet containing Metformin Hydrochloride and *Syzygium cumini* powder using direct compression techniques. The work includes optimization of formulation variables, evaluation of pre-compression and post-compression parameters, and assessment of physicochemical characteristics to develop a stable and effective dosage form. This approach aims to explore the potential benefits of combining a standard antidiabetic drug with a natural herbal ingredient to improve therapeutic outcomes in the management of Type 2 diabetes mellitus.<sup>[6]</sup>

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia resulting from abnormalities in insulin secretion, insulin action, or both. It is one of the fastest-growing non-communicable diseases worldwide and has become a major public health concern due to its increasing prevalence and associated morbidity and mortality. Persistent hyperglycemia leads to disturbances in carbohydrate, protein,

and lipid metabolism, ultimately causing long-term damage to various organs including the eyes, kidneys, nerves, heart, and blood vessels (American Diabetes Association, 2024).<sup>[7]</sup>

The disease is classified into Type 1 diabetes mellitus, Type 2 diabetes mellitus, gestational diabetes mellitus, and other specific forms resulting from genetic defects or secondary causes. Among these, Type 2 diabetes mellitus accounts for approximately 90–95% of all diagnosed cases and is characterized by insulin resistance combined with progressive pancreatic  $\beta$ -cell dysfunction. Lifestyle changes such as sedentary habits, obesity, unhealthy dietary patterns, and genetic predisposition have contributed significantly to the increasing burden of Type 2 diabetes worldwide (International Diabetes Federation, 2021).<sup>[8]</sup>

According to the International Diabetes Federation, more than 537 million adults were living with diabetes globally in 2021, and this number is projected to exceed 783 million by 2045 if effective preventive strategies are not implemented. India is among the countries with the highest number of diabetic patients and is often referred to as the "diabetes capital of the world" because of its rapidly increasing prevalence. Urbanization, population aging, dietary transitions, and reduced physical activity have accelerated the incidence of Type 2 diabetes in the Indian population.<sup>[9]</sup>

The pathogenesis of Type 2 diabetes is multifactorial and involves complex interactions between genetic susceptibility and environmental factors. Insulin resistance develops in peripheral tissues such as skeletal muscle, adipose tissue, and liver, reducing glucose uptake and increasing hepatic glucose production. Simultaneously, pancreatic  $\beta$ -cells gradually lose their capacity to compensate for insulin resistance, resulting in inadequate insulin secretion and persistent hyperglycemia. Chronic exposure to elevated glucose levels further induces glucotoxicity and oxidative stress, exacerbating  $\beta$ -cell dysfunction and promoting disease progression (Rena et al., 2017).<sup>[10]</sup>

Uncontrolled diabetes is associated with numerous acute and chronic complications. Acute complications include diabetic ketoacidosis and hyperosmolar hyperglycemic state, whereas chronic complications involve microvascular and macrovascular damage leading to diabetic retinopathy, nephropathy, neuropathy, coronary artery disease, stroke, and peripheral vascular disease. These complications significantly reduce quality of life and increase healthcare expenditure worldwide.<sup>[11]</sup>

Early diagnosis and appropriate management are therefore essential to prevent disease progression and minimize complications. Current therapeutic approaches include lifestyle modification, oral hypoglycemic agents, injectable therapies, and insulin replacement when necessary. However, despite advances in pharmacotherapy, many patients fail to achieve optimal glycemic control due to adverse effects, poor adherence, or progressive  $\beta$ -cell dysfunction. Consequently, researchers are exploring complementary strategies involving natural products and herbal medicines to improve therapeutic outcomes.<sup>[12]</sup>



## ***1.2 Tablets:***

### **1.2.1 Definition of Tablets:**

Tablets are solid pharmaceutical dosage forms containing one or more active pharmaceutical ingredients (APIs) with or without suitable excipients. They are prepared by compressing or molding powders or granules into a defined shape and size. Tablets represent the most widely used oral dosage form because of their convenience, accurate dosing, stability, ease of manufacturing, and patient acceptability. They may be designed to provide immediate drug release, delayed release, or controlled release depending on the therapeutic requirement. [13]

The active pharmaceutical ingredient is combined with various pharmaceutical excipients such as diluents, binders, disintegrants, lubricants, glidants, and coating materials to ensure adequate mechanical strength, stability, manufacturability, and desired drug release characteristics. Tablets are manufactured in various sizes and shapes and may be coated or uncoated according to the intended use.

Because of their numerous advantages, tablets account for the largest share of pharmaceutical products marketed worldwide and remain the preferred dosage form for oral drug delivery. (14)

### **1.2.2 Advantages of Tablets**

Tablets possess several advantages over other oral dosage forms:

- Accurate and uniform dosing.
- Excellent chemical, physical, and microbiological stability.
- Convenient to handle, transport, and administer.
- Cost-effective for large-scale manufacturing.
- Good patient compliance due to ease of swallowing.
- Possibility of masking unpleasant taste and odor by coating.
- Flexible formulation for immediate, delayed, or modified drug release.
- Easy identification through shape, colour, scoring, and embossing.
- Longer shelf life compared with many liquid dosage forms.
- Suitable for high-speed automated production.

### ***1.2.3 Ideal Characteristics of Tablets***

An ideal tablet should possess the following characteristics:

- Uniform weight and thickness.
- Adequate hardness to withstand handling.
- Low friability (generally less than 1%).
- Uniform drug content.
- Rapid and reproducible disintegration (for immediate-release tablets).
- Appropriate dissolution profile ensuring optimum drug availability.
- Good physical and chemical stability throughout shelf life.
- Elegant appearance with smooth surface.
- Free from capping, lamination, sticking, chipping, and cracking.
- Acceptable taste and odor where applicable.
- Ease of administration and patient acceptability.

#### ***1.2.4 Classification of Tablets:***

Tablets may be classified according to their route of administration and intended therapeutic purpose. [15]

##### ***A. Tablets Intended for Oral Ingestion:***

- |                               |                              |
|-------------------------------|------------------------------|
| • Compressed tablets          | • Modified-release tablets   |
| • Multiple compressed tablets | • Sustained-release tablets  |
| • Sugar-coated tablets        | • Controlled-release tablets |
| • Film-coated tablets         | • Extended-release tablets   |
| • Enteric-coated tablets      | • Delayed-release tablets    |
| • Chewable tablets            | • Dispersible tablets        |
| • Immediate-release tablets   | • Effervescent tablets       |

##### ***B. Tablets Used in the Oral Cavity:***

- |                      |                            |
|----------------------|----------------------------|
| • Buccal tablets     | • Mouth-dissolving tablets |
| • Sublingual tablets | • Orodispersible tablets   |
| • Lozenges           | • Chewable tablets         |

##### ***C. Tablets for Other Routes:***

- Vaginal tablets

- Implantation tablets

- Dental cones
- Hypodermic tablets (obsolete)

### ***1.2.5 Methods of Tablet Manufacturing:***

Tablet manufacturing is a critical pharmaceutical operation designed to produce tablets with consistent quality, strength, and performance. The method selected depends upon the physicochemical properties of the drug substance and excipients. [16]

#### ***A. Direct Compression:***

Direct compression is the simplest and most economical method of tablet manufacturing. The active ingredient is blended with suitable excipients and compressed directly into tablets without any granulation step. This technique requires powders possessing good flowability and compressibility. Direct compression reduces manufacturing time, minimizes processing steps, improves stability of moisture- and heat-sensitive drugs, and is widely employed in Quality by Design (QbD)-based formulations. [17]

#### ***B. Wet Granulation:***

Wet granulation involves mixing powders with a binder solution to form wet mass, followed by screening, drying, milling, lubrication, and compression. This method improves flow properties, compressibility, and content uniformity. Wet granulation is particularly suitable for poorly flowing powders and formulations containing low-dose drugs.

#### ***C. Dry Granulation:***

Dry granulation is employed for materials that are sensitive to heat or moisture. In this process, powders are compacted by slugging or roller compaction, milled into granules, blended with lubricants, and compressed into tablets. It eliminates the need for solvents and drying. [18]

#### ***D. Molding Method:***

In the molding process, tablets are prepared by moistening powders with suitable solvents and molding them into predetermined shapes. Molded tablets are generally soft, porous, and rapidly soluble, although this method is less commonly used in modern pharmaceutical manufacturing. [19]

### ***1.2.6 Immediate-Release Tablets:***

Immediate-release (IR) tablets are designed to disintegrate rapidly after oral administration and release the drug

without any intentional delay or prolonged-release mechanism. They provide rapid dissolution of the active pharmaceutical ingredient in gastrointestinal fluids, resulting in faster absorption and quicker onset of therapeutic action. Immediate-release tablets are particularly useful in conditions requiring prompt pharmacological response, such as the management of Type 2 Diabetes Mellitus with Metformin Hydrochloride. [20]

The present investigation focuses on the formulation and evaluation of an immediate-release combination tablet containing Metformin Hydrochloride and *Syzygium cumini* using a Quality by Design (QbD) approach to achieve optimum tablet quality, rapid disintegration, and efficient drug release. [21]

Immediate Release (IR) tablets are conventional solid dosage forms designed to disintegrate and release the active pharmaceutical ingredient rapidly after administration without any deliberate mechanism to retard or prolong drug release. These tablets provide prompt drug availability in the gastrointestinal tract, resulting in rapid onset of therapeutic action. Immediate release formulations are widely used because of their simplicity, ease of manufacturing, cost-effectiveness, and improved patient compliance. [22]

For the management of Type 2 Diabetes Mellitus, immediate release tablets are advantageous as they provide rapid dissolution and absorption of the active ingredients, thereby facilitating quick therapeutic response. In the present study, a combination tablet containing Metformin Hydrochloride and *Syzygium cumini* powder was developed as an immediate release dosage form using the direct compression method. The formulation was optimized to achieve adequate mechanical strength, rapid disintegration, and maximum drug release within a short period. [23]

The developed immediate release tablet was designed to release both Metformin Hydrochloride and the phytoconstituents of *Syzygium cumini* rapidly after oral administration. Superdisintegrants such as Croscarmellose Sodium were incorporated to facilitate rapid tablet disintegration, while suitable binders and diluents were employed to maintain tablet integrity and ensure uniform drug release. The formulation was further optimized using a 2<sup>3</sup> factorial design to evaluate the influence of formulation variables on critical quality attributes such as hardness, disintegration time, and percentage drug release.

The ideal immediate release tablet should exhibit acceptable hardness, low friability, rapid disintegration, uniform drug content, and not less than 85% drug release within the specified dissolution period as per pharmacopeial requirements. [24]

### ***1.2.7 Advantages of Immediate Release Tablets:***

Immediate-release (IR) tablets are widely used because they provide rapid drug release and quick therapeutic action. The major advantages include:

#### ***1. Rapid Onset of Action***

The tablet disintegrates and releases the drug quickly, resulting in faster absorption and prompt

therapeutic effect.

## **2. *Improved Bioavailability***

Rapid dissolution enhances drug availability for absorption, particularly for highly water-soluble drugs.

## **3. *Simple Manufacturing Process***

Immediate-release tablets are comparatively easy to formulate and manufacture using techniques such as direct compression or wet granulation.

## **4. *Cost-Effective Production***

The absence of complex release-modifying polymers or specialized coating processes reduces manufacturing costs.

## **5. *Better Patient Compliance***

Tablets are convenient to administer, easy to carry, and provide accurate dosing, improving adherence to therapy.

## **6. *Accurate Dose Uniformity***

Each tablet contains a precise amount of active pharmaceutical ingredient, ensuring consistent therapeutic efficacy.

## **7. *Easy Scale-Up and Commercial Manufacturing***

The manufacturing process can be readily scaled from laboratory to industrial production with minimal modifications.

## **8. *Suitable for Drugs Requiring Immediate Therapeutic Effect***

Ideal for medications where rapid symptom relief or quick pharmacological action is required.

## **9. *Good Stability***

Immediate-release tablets generally exhibit excellent physical and chemical stability when stored under recommended conditions.

## **10. *Ease of Quality Control***

Standard pharmacopeial tests such as hardness, friability, disintegration, dissolution, and content uniformity can be easily performed.

#### **1.2.8** *Ideal Characteristics of Immediate Release Tablets:*

- Immediate and complete drug release without any intentional delay.
- Uniform drug content within pharmacopeial limits.
- Adequate hardness to withstand handling and transportation.
- Friability less than 1%.
- Uniform weight and thickness.
- Good mechanical strength and integrity.
- High dissolution rate (generally not less than 85% drug release within the specified time, as per product specification/pharmacopeial requirement).
- Good chemical, physical, and microbiological stability during storage.
- Acceptable appearance, shape, color, and surface finish.
- Easy to swallow and patient-friendly.
- Manufactured using excipients that are compatible with the active pharmaceutical ingredient.
- Reproducible batch-to-batch quality and performance.
- Cost-effective and suitable for large-scale manufacturing.
- Complies with pharmacopeial quality standards (IP/USP/BP). [25]

#### **1.2.9** *Direct Compression Technique*

Direct compression is one of the simplest and most economical methods of tablet manufacturing because it eliminates granulation and drying steps. In this process, active pharmaceutical ingredients and excipients are blended uniformly and compressed directly into tablets without prior wet or dry granulation. The technique reduces manufacturing time, energy consumption, and production costs while preserving the stability of moisture-sensitive and heat-sensitive compounds. [26]

For formulations containing *Syzygium cumini* powder, direct compression offers additional advantages because many phytoconstituents, including polyphenols and anthocyanins, are susceptible to degradation under excessive heat and moisture. Avoiding wet granulation helps maintain the biological activity of these compounds and improves the overall quality of the final product. [27]

However, successful direct compression requires powders with excellent flowability and compressibility.

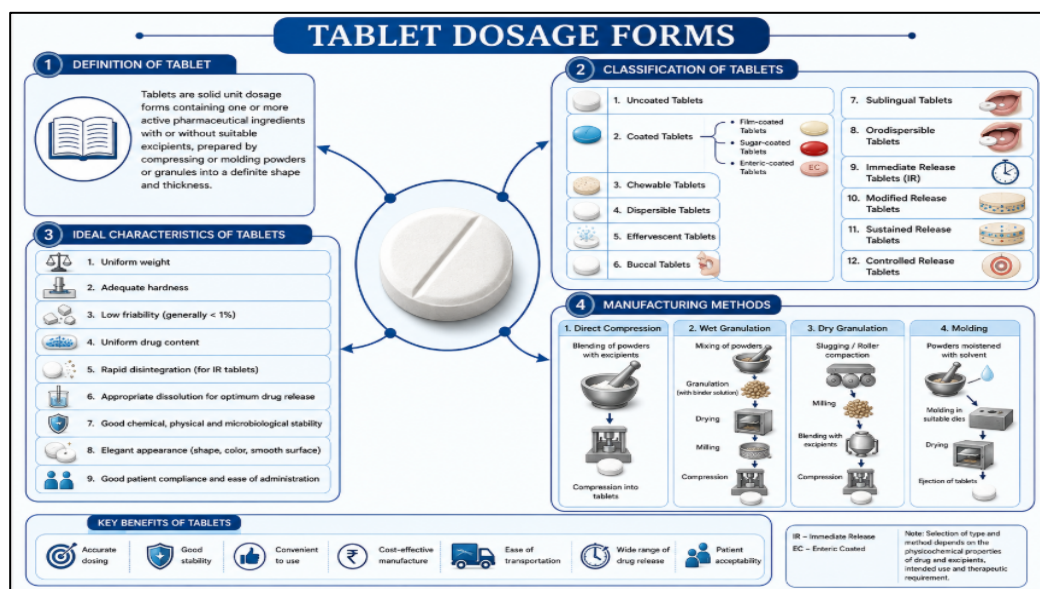
Parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio are routinely evaluated to assess powder characteristics before compression. Optimization of these properties ensures uniform die filling and minimizes weight variation among tablets. [28] The simplicity of direct compression also reduces opportunities for contamination and minimizes processing errors, making it highly suitable for large-scale industrial manufacturing. Consequently, this technique has become the preferred method for producing many immediate-release pharmaceutical tablets. [29]

Direct compression offers several advantages, including shorter manufacturing time, reduced production cost, improved process efficiency, and minimal risk of contamination. When suitable powder flowability and compressibility are achieved, this technique produces tablets with excellent mechanical strength, rapid disintegration, and reproducible drug release, making it an ideal method for immediate-release dosage forms. [30]

Another important advantage of the direct compression technique is its compatibility with the Quality by Design (QbD) approach, as it allows systematic optimization of formulation variables and process parameters with minimal manufacturing complexity. The reduced number of processing steps facilitates better process control, improves batch-to-batch reproducibility, and minimizes variability in the finished product. Owing to these advantages, direct compression is widely adopted in the pharmaceutical industry for the development of immediate-release tablet formulations requiring consistent quality, rapid drug release, and efficient large-scale production.

The direct compression technique was selected for the preparation of Metformin Hydrochloride and *Syzygium cumini* immediate-release combination tablets because of its simplicity, cost-effectiveness, and suitability for both synthetic drugs and herbal powders. The technique enables efficient tablet production while maintaining the stability of the active ingredients and ensuring desirable tablet characteristics such as uniform weight, adequate hardness, rapid disintegration, and consistent drug release. These advantages make direct compression an appropriate manufacturing method for developing a high-quality immediate-release combination tablet.





**Fig 1: Tablet Dosage Form**

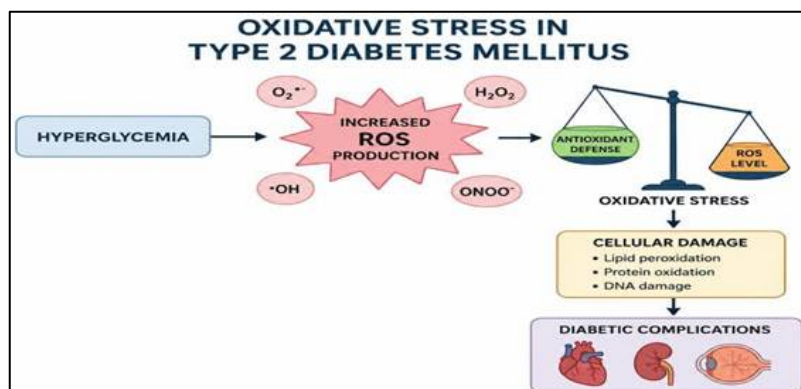
### 1.3 Role of Oxidative Stress in Type 2 Diabetes Mellitus:

Oxidative stress plays a pivotal role in the development and progression of Type 2 diabetes mellitus and its associated complications. Hyperglycemia promotes excessive production of reactive oxygen species (ROS) through multiple biochemical pathways, including glucose autooxidation, protein glycation, and mitochondrial dysfunction. The imbalance between ROS generation and endogenous antioxidant defense mechanisms leads to cellular injury, inflammation, and apoptosis. [31] Pancreatic  $\beta$ -cells are particularly susceptible to oxidative damage because they possess relatively low levels of antioxidant enzymes such as catalase and glutathione peroxidase. Continuous oxidative stress impairs insulin secretion and accelerates  $\beta$ -cell loss, thereby worsening hyperglycemia. In addition, oxidative stress contributes to endothelial dysfunction, dyslipidaemia, inflammation, and vascular injury, which are major contributors to diabetic complications.

Natural antioxidants derived from medicinal plants have attracted considerable interest because they can neutralize free radicals and reduce oxidative damage. Phytochemicals such as flavonoids, phenolic acids, anthocyanins, and tannins exhibit potent antioxidant activity and may improve insulin sensitivity while protecting pancreatic tissue. Therefore, incorporating antioxidant-rich herbal components such as *Syzygium cumini* into antidiabetic therapy represents a promising approach for comprehensive diabetes management. [32]

In addition to its role in insulin resistance, oxidative stress is closely associated with development of long-term diabetic complications. Elevated ROS levels damage cellular proteins, lipids, and nucleic acids through lipid peroxidation, protein oxidation, and DNA damage, ultimately resulting in tissue dysfunction. Oxidative injury to vascular endothelial cells contributes to impaired nitric oxide production, endothelial dysfunction, and accelerated atherosclerosis, thereby increasing the risk of cardiovascular disease. Similarly, oxidative stress plays a major role in the pathogenesis of diabetic nephropathy, retinopathy, and neuropathy by promoting inflammation, fibrosis, and apoptosis within affected tissues. Consequently, therapeutic strategies aimed at reducing oxidative stress through

antioxidant- rich phytochemicals and effective glycemic control have gained significant importance in the comprehensive management of Type 2 Diabetes Mellitus. [33].



**Fig 2: Role of Oxidative Stress in Type 2 Diabetes Mellitus**

**1.4 Need for Combination Therapy in Diabetes Management:** The progressive nature of Type 2 diabetes often necessitates combination therapy to achieve and maintain adequate glycemic control. Monotherapy may become insufficient as pancreatic  $\beta$ -cell function declines over time, requiring medications with complementary mechanisms of action. Combination therapy can improve efficacy, reduce required drug doses, minimize adverse effects, and enhance patient adherence. [34] Metformin primarily decreases hepatic glucose production and improves peripheral insulin sensitivity, whereas phytochemicals present in *Syzygium cumini* may delay carbohydrate absorption, stimulate insulin secretion, protect  $\beta$ -cells from oxidative damage, and improve lipid metabolism. The combination of these mechanisms may provide synergistic benefits by targeting multiple pathogenic pathways simultaneously.

Furthermore, herbal supplementation may reduce oxidative stress and inflammation while improving overall metabolic health, making combination therapy an attractive strategy for long-term management of Type 2 diabetes. Development of a single combination tablet containing Metformin Hydrochloride and *Syzygium cumini* powder may also improve patient convenience and compliance by reducing pill burden and simplifying treatment regimens. [35]

#### 1.5 Rationale for Combining Metformin Hydrochloride with *Syzygium cumini*:

Although metformin effectively reduces hepatic glucose production and improves insulin sensitivity, it does not directly address oxidative stress or provide substantial antioxidant protection. Conversely, *Syzygium cumini* contains phytochemicals capable of reducing oxidative damage, enhancing insulin secretion, and modulating carbohydrate metabolism through complementary pathways. (36) Combining metformin hydrochloride with *Syzygium cumini* powder may therefore produce synergistic therapeutic effects by simultaneously targeting insulin resistance, hepatic gluconeogenesis, oxidative stress, inflammation, and pancreatic  $\beta$ -cell preservation. Such a multidimensional approach has the potential to improve glycemic control while reducing disease progression and long-term complications. [37] Development of a fixed-dose combination tablet may further enhance patient compliance by reducing pill burden and simplifying dosing schedules. The incorporation of herbal and synthetic agents into a single dosage form also represents an innovative strategy aligned with the growing interest in integrative medicine and evidence-based phytotherapy. [38]

#### 1.6 Formulation Strategies for Combination Therapy:

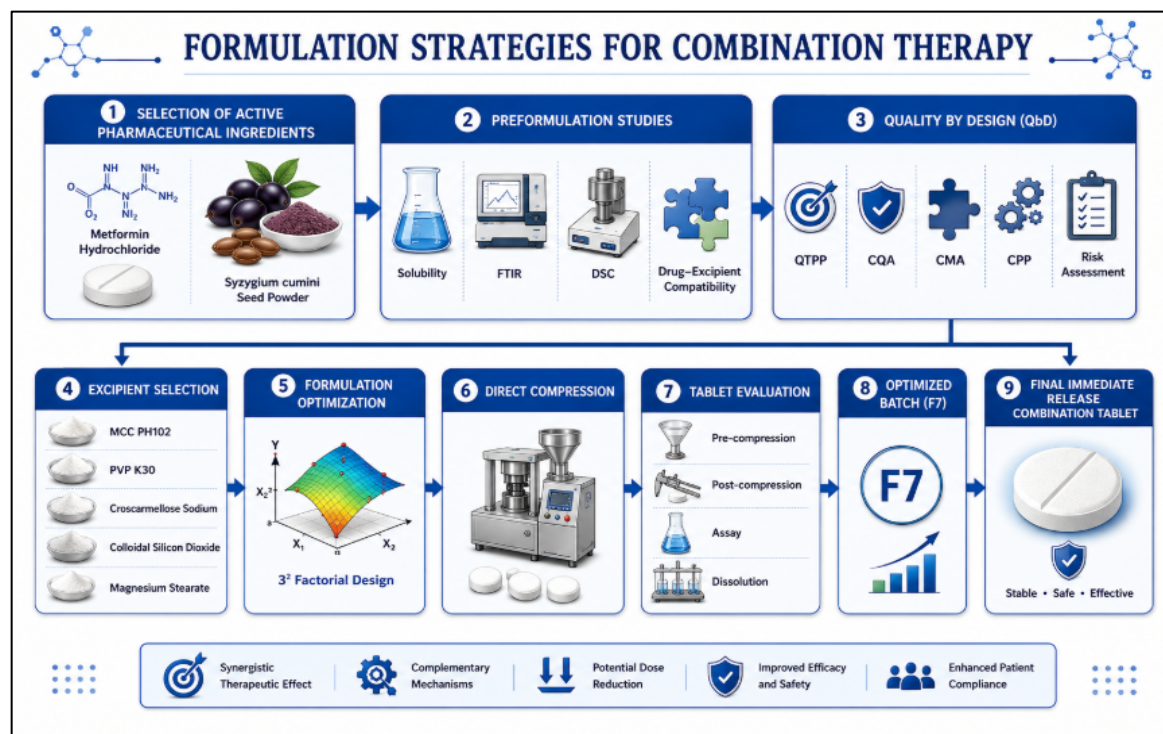
The development of combination tablets containing synthetic drugs and herbal ingredients has emerged as an innovative approach in modern pharmaceutical research. Such formulations aim to combine the proven efficacy of

conventional medicines with the complementary therapeutic properties of medicinal plants to provide enhanced clinical benefits. In the management of Type 2 diabetes mellitus, combination therapy is particularly valuable because the disease involves multiple pathophysiological defects that cannot always be adequately controlled by a single therapeutic agent. [39]

Formulating a combination tablet of Metformin Hydrochloride and *Syzygium cumini* powder presents several pharmaceutical challenges, including differences in particle size, bulk density, flowability, moisture content, compressibility, and compatibility between the active ingredients and excipients. These factors directly influence tablet quality, manufacturing efficiency, and therapeutic performance. Therefore, systematic preformulation studies are essential before final dosage form development.

The selection of suitable excipients plays a crucial role in achieving tablets with acceptable mechanical strength, rapid disintegration, uniform drug distribution, and consistent dissolution characteristics. Fillers such as microcrystalline cellulose and lactose improve compressibility, while superdisintegrants like sodium starch glycolate and croscopolidone facilitate rapid tablet breakup after administration. Lubricants and glidants including magnesium stearate and talc reduce friction during compression and improve powder flow properties. [40]

In addition, herbal powders often exhibit poor flow characteristics and variable particle sizes, making formulation optimization particularly important. Appropriate processing techniques and excipient selection can overcome these limitations and ensure batch-to-batch reproducibility. Modern formulation approaches frequently employ design of experiments (DoE) and factorial design methodologies to optimize multiple variables simultaneously while minimizing experimental trials. [41] A well-designed formulation strategy ensures the development of tablets with consistent quality, stability, and therapeutic performance. The use of scientific formulation approaches and optimization techniques helps minimize variability, improve manufacturing efficiency, and produce a robust dosage form that consistently meets the desired quality attributes and regulatory requirements. [42]



**Fig 3: Formulation Strategies for Combination Therapy**

## 1.7 Metformin Hydrochloride:

### 1.7.1 Introduction:

Metformin Hydrochloride is the most widely prescribed oral antihyperglycemic agent and is regarded as the cornerstone in the management of Type 2 Diabetes Mellitus (T2DM). It belongs to the biguanide class of oral antidiabetic drugs and has been used successfully for more than six decades because of its proven efficacy, favorable safety profile, affordability, and ability to reduce diabetes-related complications. Owing to these advantages, international organizations such as the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and International Diabetes Federation (IDF) recommend metformin as the first-line pharmacological therapy for patients with Type 2 Diabetes Mellitus. [43]

Unlike insulin secretagogues such as sulfonylureas, Metformin Hydrochloride does not stimulate pancreatic  $\beta$ -cells to release insulin. Instead, it lowers blood glucose levels by suppressing hepatic gluconeogenesis, reducing hepatic glucose output, enhancing insulin sensitivity in peripheral tissues, increasing glucose uptake by skeletal muscles, and reducing intestinal glucose absorption. Consequently, metformin effectively lowers blood glucose without causing significant hypoglycemia in most patients.

Apart from its glucose-lowering effect, metformin exhibits several pleiotropic benefits, including improvement in lipid metabolism, reduction of oxidative stress, enhancement of endothelial function, anti-inflammatory activity, and cardioprotective effects. These additional therapeutic benefits have expanded its application beyond diabetes management to conditions such as polycystic ovary syndrome (PCOS), obesity associated with insulin resistance, metabolic syndrome, and certain endocrine disorders. [44]

Despite being highly effective, long-term administration of metformin may be associated with gastrointestinal disturbances, decreased vitamin B12 absorption, and poor intestinal permeability due to its Biopharmaceutical Classification System (BCS) Class III characteristics. Therefore, researchers are exploring novel formulation strategies and combination therapies involving herbal medicines to improve therapeutic efficacy, reduce adverse effects, and achieve better glycemic control. [45]

#### **1.7.2 Pharmacological Classification:**

Metformin Hydrochloride belongs to the biguanide class of oral antihyperglycemic agents. Unlike sulfonylureas or meglitinides, which stimulate insulin secretion, metformin acts primarily by improving insulin sensitivity and reducing hepatic glucose production. It is therefore considered an insulin sensitizer rather than an insulin secretagogue. (46) Because metformin does not directly stimulate insulin release, it carries a very low risk of hypoglycemia when administered alone. This unique property distinguishes it from many other oral antidiabetic drugs. [47]

**1.7.3 Physicochemical Properties:** The physicochemical characteristics of metformin significantly influence its pharmaceutical formulation and therapeutic performance. Metformin is highly hydrophilic and freely soluble in water, facilitating rapid dissolution after oral administration. However, its high polarity limits passive diffusion across biological membranes, resulting in relatively low intestinal permeability. [48].

The drug exists predominantly in ionized form under physiological conditions because of its strong basic nature. Consequently, absorption depends largely on transporter-mediated uptake rather than passive diffusion. The hygroscopic nature of metformin also necessitates careful selection of excipients and appropriate storage conditions during tablet formulation. [49]

#### **1.7.4 Pharmacokinetics:**

##### **A. Absorption:**

Metformin is absorbed primarily from the small intestine. The oral bioavailability ranges between 50–60%, with peak plasma concentrations generally achieved within 2–3 hours after administration of immediate-release tablets.

Absorption occurs mainly through organic cation transporters (OCTs), particularly OCT1 and plasma membrane monoamine transporter (PMAT). [50]

## **B. Distribution:**

Following absorption, metformin exhibits negligible plasma protein binding and distributes extensively into metabolically active tissues including:

- ✓ **Liver**
- ✓ **Skeletal muscle**
- ✓ **Kidneys**
- ✓ **Gastrointestinal tract**

The apparent volume of distribution ranges between 63 and 276 L, indicating extensive tissue penetration. [51]

**E. Metabolism:** Unlike most oral drugs, metformin undergoes virtually no hepatic metabolism. The drug remains chemically unchanged throughout systemic circulation.

**D. Excretion:** Metformin is eliminated unchanged through renal excretion by glomerular filtration and active tubular secretion. Approximately 90% of the absorbed dose is excreted within 24 hours. The elimination half-life ranges between 4 and 8 hours. Because renal elimination is the principal route of excretion, dose adjustment is necessary in patients with impaired renal function. [52].

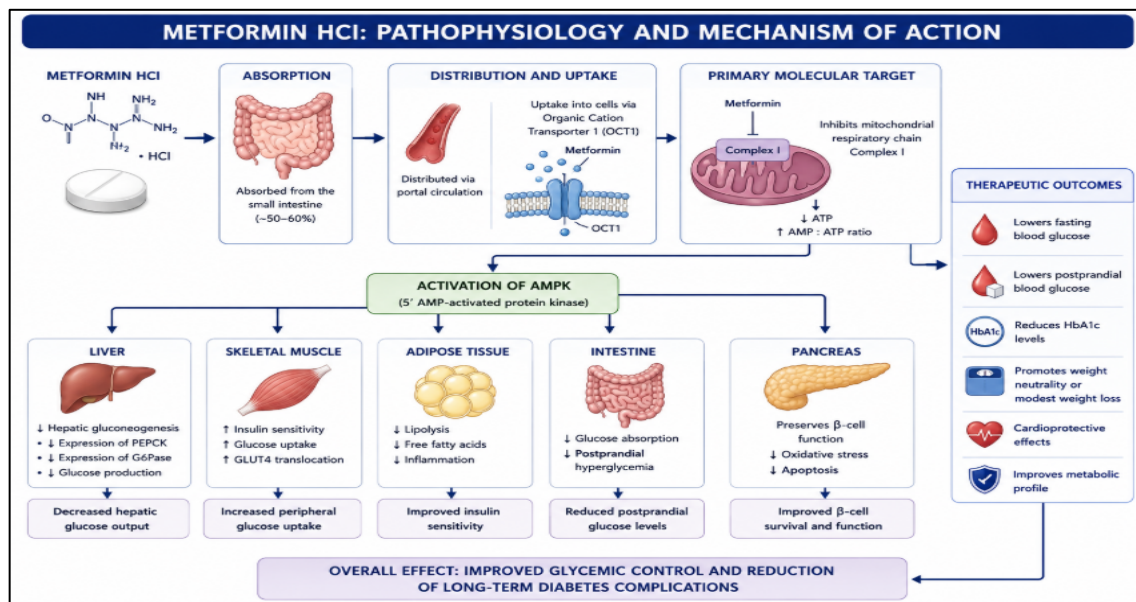
### **1.7.5 Pathophysiology of Type 2 Diabetes Mellitus:**

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder resulting from a combination of insulin resistance and progressive pancreatic  $\beta$ -cell dysfunction. Under physiological conditions, insulin facilitates glucose uptake into skeletal muscle and adipose tissue while suppressing hepatic glucose production. In individuals with Type 2 diabetes, peripheral tissues become less responsive to insulin, leading to decreased glucose utilization and increased endogenous glucose production. [53]

Insulin resistance is influenced by obesity, chronic inflammation, genetic predisposition, sedentary lifestyle, and ectopic lipid accumulation. Adipose tissue in obese individuals releases excessive free fatty acids and pro-inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), which interfere with insulin signaling pathways. Consequently, glucose transporter-4 (GLUT4) translocation is reduced, diminishing glucose uptake by muscle and adipose tissue. Simultaneously, hepatic gluconeogenesis remains elevated, further contributing to hyperglycemia. [54]

Chronic hyperglycemia initiates glucotoxicity and lipotoxicity, which impair mitochondrial function and promote oxidative stress within  $\beta$ -cells. Because pancreatic  $\beta$ -cells possess relatively weak antioxidant defenses. This vicious cycle progressively worsens glycemic control and accelerates diabetic complications. [55].





**Fig 4: Pathophysiology and Mechanism of Action.**

### 1.7.6 Pharmacology of Metformin Hydrochloride:

Metformin hydrochloride is a synthetic biguanide derivative and remains the preferred first-line oral antihyperglycemic agent for the treatment of Type 2 diabetes mellitus. Unlike sulfonylureas, metformin does not stimulate insulin secretion and therefore carries a minimal risk of hypoglycemia when used as monotherapy. The primary mechanism of metformin involves activation of adenosine monophosphate-activated protein kinase (AMPK), a key regulator of cellular energy metabolism. Activation of AMPK suppresses hepatic gluconeogenesis, decreases glucose output from the liver, enhances peripheral glucose uptake in skeletal muscles, and improves insulin sensitivity. Additionally, metformin delays intestinal glucose absorption and positively influences the gut microbiota, contributing to its glucose-lowering effects. [56]

Metformin is rapidly absorbed from the small intestine, exhibits negligible plasma protein binding, and is eliminated unchanged through renal excretion. The elimination half-life ranges between four and eight hours. Common adverse effects include nausea, abdominal discomfort, diarrhea, and metallic taste, while prolonged therapy may be associated with vitamin B12 deficiency. Nevertheless, its favorable cardiovascular profile, weight neutrality, and extensive clinical evidence make it the cornerstone of Type 2 diabetes management. [57]

### 1.7.7 Pharmacokinetic and Pharmacodynamic Considerations of Metformin:

Metformin hydrochloride is characterized by favorable pharmacokinetic properties that contribute to its widespread clinical use. Following oral administration, approximately 50–60% of the administered dose is absorbed from the gastrointestinal tract, primarily in the small intestine. Peak plasma concentrations are generally achieved within 2 to 3 hours for immediate-release formulations and 4 to 8 hours for extended-release preparations. [58]

Unlike many orally administered drugs, metformin undergoes negligible hepatic metabolism and is excreted unchanged through the kidneys by active tubular secretion involving organic cation transporters (OCT1, OCT2, and MATE transporters). Consequently, renal impairment significantly influences drug clearance and may increase the risk of metformin accumulation and lactic acidosis. [59] The pharmacodynamic actions of metformin extend beyond hepatic glucose suppression. Activation of AMP-activated protein kinase (AMPK) improves fatty acid oxidation, inhibits lipogenesis, and enhances insulin-mediated glucose uptake. Recent studies have also demonstrated effects on intestinal glucose absorption, bile acid metabolism, and gut microbiota composition, highlighting its complex mechanism of action.

Metformin has additional pleiotropic benefits including modest weight reduction, improvement of endothelial function, reduction of inflammatory biomarkers, and favorable cardiovascular outcomes. These properties have established metformin as the preferred first-line pharmacological intervention for Type 2 diabetes mellitus in numerous international treatment guidelines. [60] Pharmacodynamically, metformin lowers blood glucose primarily by suppressing hepatic gluconeogenesis, enhancing peripheral insulin sensitivity, increasing glucose uptake in skeletal muscles, and reducing intestinal glucose absorption without stimulating insulin secretion. These characteristics provide effective glycemic control with a low risk of hypoglycemia and additional benefits such as weight neutrality and cardiovascular protection, making metformin a cornerstone in diabetes management.

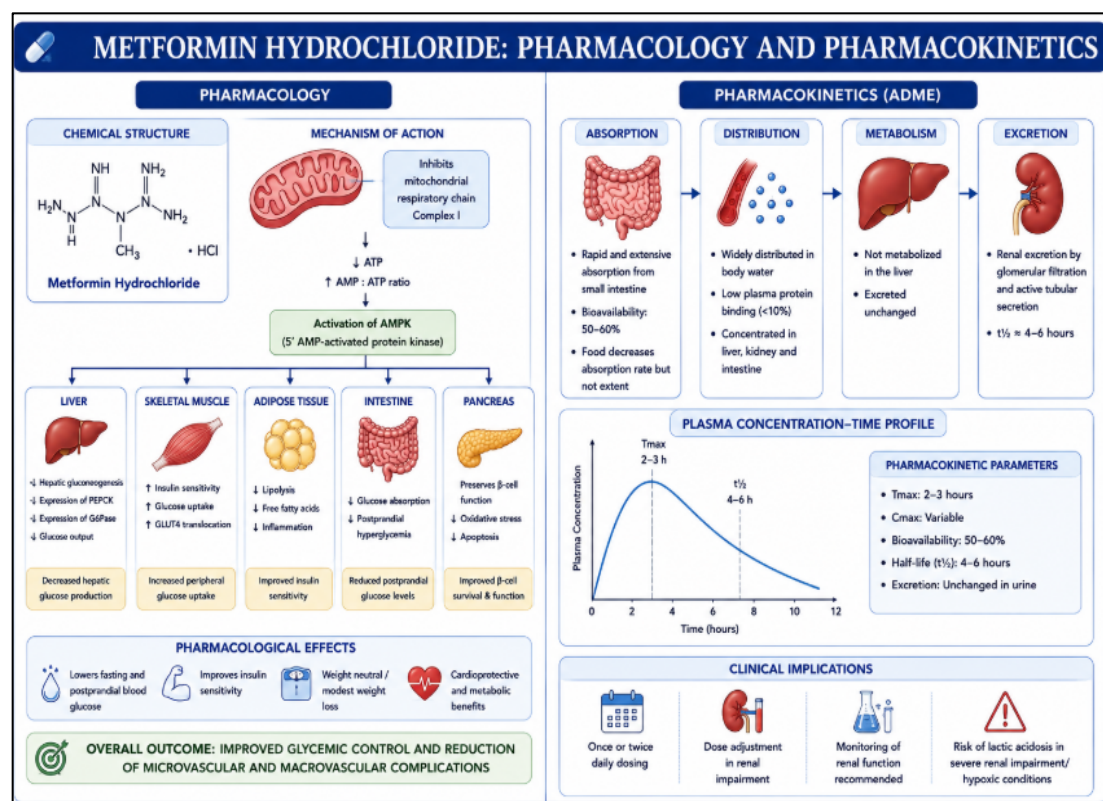


Figure 5: Metformin Hydrochloride: Pharmacology and Pharmacokinetic.

## 1.8 Syzygium cumini:

### 1.8.1 Botanical and Pharmacological Importance:

*Syzygium cumini* (L.) Skeels, commonly known as Jamun or Java plum, belongs to the family Myrtaceae. The evergreen tropical tree is widely distributed throughout India, Sri Lanka, Bangladesh, Southeast Asia, and several tropical regions of the world. Every part of the plant—including fruits, seeds, bark, leaves, and roots—has been utilized in traditional medicine for centuries. [61] Jamun seeds contain numerous biologically active constituents including jamboline, jambosine, ellagic acid, gallic acid, quercetin, anthocyanins, flavonoids, tannins, terpenoids, and phenolic compounds. These phytochemicals exhibit antioxidant, antidiabetic, anti-inflammatory, antimicrobial, hepatoprotective. [62]

Experimental studies suggest that *Syzygium cumini* exerts antidiabetic effects through multiple mechanisms. It delays carbohydrate digestion by inhibiting  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes, enhances insulin secretion from pancreatic  $\beta$ -cells, improves peripheral insulin sensitivity, suppresses oxidative stress, and protects  $\beta$ -cells against free radical-mediated damage. Anthocyanins and polyphenols present in Jamun also improve lipid metabolism and reduce inflammatory responses associated with metabolic syndrome. [63] The antioxidant capacity of *Syzygium cumini* is particularly important because oxidative stress is a major contributor to diabetic complications. Phenolic

compounds scavenge reactive oxygen species and increase endogenous antioxidant enzyme activity, thereby reducing cellular injury and vascular dysfunction. [64].



**Fig 6: Botanical Overview.**

### 1.8.2 Role of Herbal Medicines in the Management of Type 2 Diabetes Mellitus:

Herbal medicines have been used for thousands of years in traditional healthcare systems for the prevention and treatment of various chronic diseases, including diabetes mellitus. In recent decades, there has been renewed scientific interest in medicinal plants because of their diverse pharmacological properties, relatively low incidence of adverse effects, affordability, and widespread availability. According to the World Health Organization (WHO), nearly 80% of the global population relies on traditional herbal medicine for primary healthcare needs, particularly in developing countries where access to modern medicines may be limited. [65]

The management of Type 2 diabetes mellitus (T2DM) requires long-term therapy aimed at maintaining blood glucose levels within the normal range and preventing complications. Although synthetic antidiabetic drugs such as metformin, sulfonylureas, DPP-4 inhibitors, and SGLT2 inhibitors are highly effective, prolonged use may be associated with adverse effects, drug resistance, and declining therapeutic efficacy. Consequently, medicinal plants with antihyperglycemic activity have attracted considerable attention as complementary or adjunctive therapies. Herbal medicines exert antidiabetic effects through multiple mechanisms, including stimulation of insulin secretion, enhancement of peripheral glucose uptake, inhibition of intestinal carbohydrate digestion, suppression of hepatic gluconeogenesis, improvement of insulin sensitivity, and protection of pancreatic  $\beta$ -cells from oxidative stress. Unlike single-target synthetic drugs, phytochemicals often influence several metabolic pathways simultaneously, providing a broader therapeutic effect. [66]

Several medicinal plants have demonstrated promising antidiabetic potential in experimental and clinical studies. These include *Gymnema sylvestre*, *Momordica charantia* (bitter melon), *Trigonella foenum-graecum* (fenugreek), *Azadirachta indica* (neem), *Pterocarpus marsupium*, *Cinnamomum verum* (cinnamon), and *Syzygium cumini* (Jamun). Their therapeutic effects are primarily attributed to bioactive constituents such as flavonoids, alkaloids, terpenoids, glycosides, tannins, saponins, and phenolic compounds. [67] Among these medicinal plants, *Syzygium cumini* has received particular attention because of its potent antioxidant and hypoglycemic properties. Jamun seeds contain jamboline and jambosine, which help regulate carbohydrate metabolism and improve glucose utilization.

Additionally, polyphenols and anthocyanins reduce oxidative stress and inflammation, both of which are major contributors to insulin resistance and diabetic complications. The integration of herbal medicines with conventional



pharmacotherapy offers several advantages. Herbal products may enhance the efficacy of standard drugs, reduce required dosages, minimize adverse effects, and provide protection against secondary complications through antioxidant and anti-inflammatory mechanisms. Such synergistic interactions have encouraged the development of combination formulations incorporating both synthetic and herbal agents.

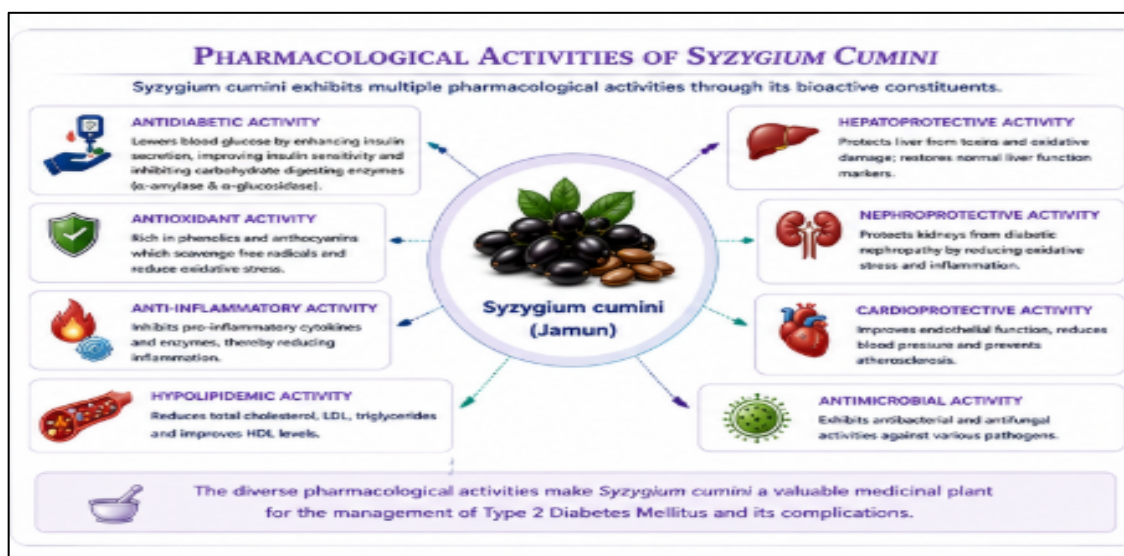
However, despite their therapeutic potential, herbal medicines also present challenges related to standardization, quality control, batch-to-batch variability, and scientific validation. Differences in cultivation practices, harvesting time, geographical location, extraction methods, and storage conditions may significantly affect phytochemical composition and biological activity. Therefore, rigorous quality assurance procedures and standardized manufacturing protocols are essential before herbal products can be incorporated into pharmaceutical dosage forms. [68] Recent advances in pharmaceutical technology have facilitated the formulation of herbal medicines into tablets, capsules, nanoparticles, and controlled-release systems, improving their stability, bioavailability, and patient compliance. Fixed-dose combination tablets containing herbal extracts and conventional drugs represent an emerging area of research that aims to maximize therapeutic benefits while simplifying treatment regimens. [69]

### **1.8.3. Pharmacological Activities of *Syzygium cumini*:**

*Syzygium cumini* (Jamun) possesses a broad spectrum of pharmacological activities owing to its rich phytochemical composition, including flavonoids, phenolic acids, anthocyanins, tannins, alkaloids, terpenoids, glycosides, and other polyphenolic compounds. Among these, its antidiabetic activity is the most extensively investigated. Numerous experimental and clinical studies have demonstrated that the seed powder and seed extracts effectively reduce fasting blood glucose, postprandial blood glucose, and glycated hemoglobin (HbA1c) levels. The hypoglycemic action of *Syzygium cumini* is mediated through multiple mechanisms, including inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes, enhancement of insulin secretion from pancreatic  $\beta$ -cells, improvement of insulin sensitivity, reduction of hepatic gluconeogenesis, and increased peripheral glucose utilization. Bioactive alkaloids such as jamboline and jambosine further contribute to glycemic control by delaying the conversion of starch into glucose and improving carbohydrate metabolism. [70]

In addition to its antihyperglycemic activity, *Syzygium cumini* exhibits potent antioxidant and anti-inflammatory properties that play an important role in preventing diabetes-associated complications. The presence of gallic acid, ellagic acid, quercetin, anthocyanins, and other phenolic compounds enables the plant to scavenge reactive oxygen species (ROS), inhibit lipid peroxidation, and enhance endogenous antioxidant defense enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). These antioxidant effects protect pancreatic  $\beta$ -cells from oxidative damage and reduce chronic inflammation by suppressing pro-inflammatory mediators such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6). [71]

*Syzygium cumini* possesses several additional pharmacological activities that enhance its therapeutic value in the management of Type 2 Diabetes Mellitus. It demonstrates hypolipidemic activity by lowering serum total cholesterol, triglycerides, and low-density lipoprotein (LDL) while increasing high-density lipoprotein (HDL), thereby reducing cardiovascular risk. Its hepatoprotective and nephroprotective properties help preserve liver and kidney function by minimizing oxidative stress and inflammation, whereas its cardioprotective activity contributes to the prevention of atherosclerosis and vascular complications. [72].



**Fig 7: Pharmacological Activities of Syzygium Cumini**

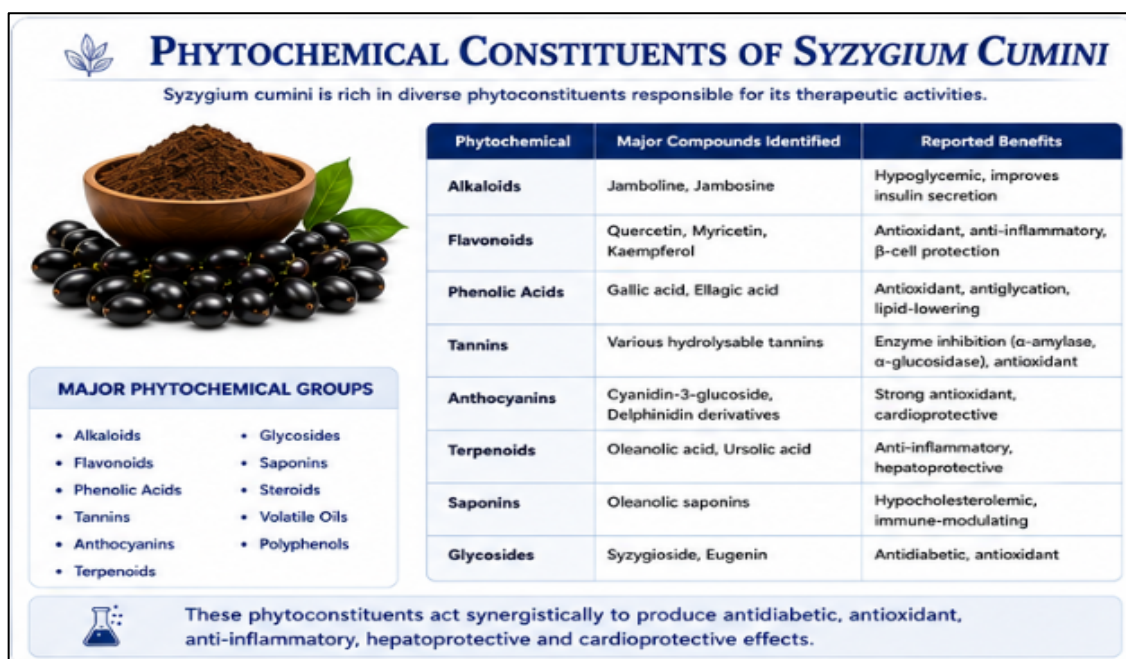
#### 1.8.4 Phytoconstituents of Syzygium cumini and Their Pharmacological Activities:

Syzygium cumini (L.) Skeels is recognized as one of the most valuable medicinal plants because of its rich phytochemical composition and broad spectrum of pharmacological activities. Different parts of the plant, including fruits, seeds, bark, leaves, and roots, contain numerous bioactive compounds that contribute to its therapeutic efficacy. Among these, the seeds are particularly rich in alkaloids, glycosides, flavonoids, tannins, anthocyanins, phenolic acids, terpenoids, and essential oils, making them highly beneficial for the management of diabetes mellitus. [73] One of the principal active constituents of Jamun seeds is jamboline, a glycoside believed to delay the conversion of starch into glucose and thereby reduce postprandial hyperglycemia. Another important alkaloid, jambosine, has been reported to improve glucose metabolism and enhance insulin activity. Polyphenolic compounds such as ellagic acid and gallic acid exhibit strong antioxidant properties by scavenging free radicals and reducing oxidative damage associated with chronic hyperglycemia. [74]

Flavonoids including quercetin, kaempferol, and myricetin have demonstrated anti-inflammatory and antihyperglycemic effects through modulation of cellular signaling pathways involved in insulin sensitivity and glucose transport. Anthocyanins, responsible for the characteristic purple coloration of Jamun fruits, possess potent antioxidant activity and contribute to vascular protection by reducing endothelial dysfunction and lipid peroxidation. The pharmacological profile of Syzygium cumini extends beyond diabetes management. Experimental studies have reported antimicrobial, hepatoprotective, nephroprotective, cardioprotective, gastroprotective, anti-obesity, anti-cancer, and immunomodulatory activities. These effects are attributed to the synergistic interaction of multiple phytochemicals rather than a single active constituent. [75]

Syzygium cumini contains a variety of bioactive phytoconstituents, including flavonoids, phenolic acids, tannins, anthocyanins, alkaloids, glycosides, and terpenoids. Major compounds such as jamboline, jambosine, gallic acid, ellagic acid, quercetin, and anthocyanins exhibit significant antidiabetic, antioxidant, anti-inflammatory, hypolipidemic, and antimicrobial activities. These phytochemicals help improve insulin secretion and sensitivity, inhibit carbohydrate-digesting enzymes, reduce oxidative stress, and protect pancreatic  $\beta$ -cells, thereby contributing to the effective management of Type 2 Diabetes Mellitus.

Several in vivo studies have demonstrated that administration of Jamun seed extract significantly decreases fasting blood glucose, serum cholesterol, triglycerides, low-density lipoprotein cholesterol, and glycated hemoglobin while increasing antioxidant enzyme activity. Histological examination has also revealed preservation of pancreatic islets and regeneration of damaged  $\beta$ -cells, suggesting protective effects against diabetes-induced tissue injury. The therapeutic versatility of Syzygium cumini makes it an attractive candidate for incorporation into pharmaceutical formulations intended for long-term management of Type 2 diabetes mellitus. [76].



**Fig 8: Phytochemical Constituents of *Syzygium cumini***

**1.8.5 Clinical and Experimental Evidence Supporting *Syzygium cumini* in Diabetes Management:** Numerous preclinical investigations have validated the traditional use of *Syzygium cumini* in diabetes management. Animal models of streptozotocin-induced and alloxan-induced diabetes consistently demonstrate reductions in fasting blood glucose following administration of Jamun seed powder or extracts. Improvements in insulin secretion, glycogen storage, antioxidant enzyme activity, and lipid metabolism have also been observed. Experimental evidence suggests that *Syzygium cumini* inhibits intestinal  $\alpha$ -glucosidase and  $\alpha$ -amylase enzymes, thereby slowing carbohydrate digestion and reducing postprandial glucose excursions. In addition, enhanced expression of glucose transporter proteins facilitates increased peripheral glucose uptake, contributing to improved insulin sensitivity. [77]

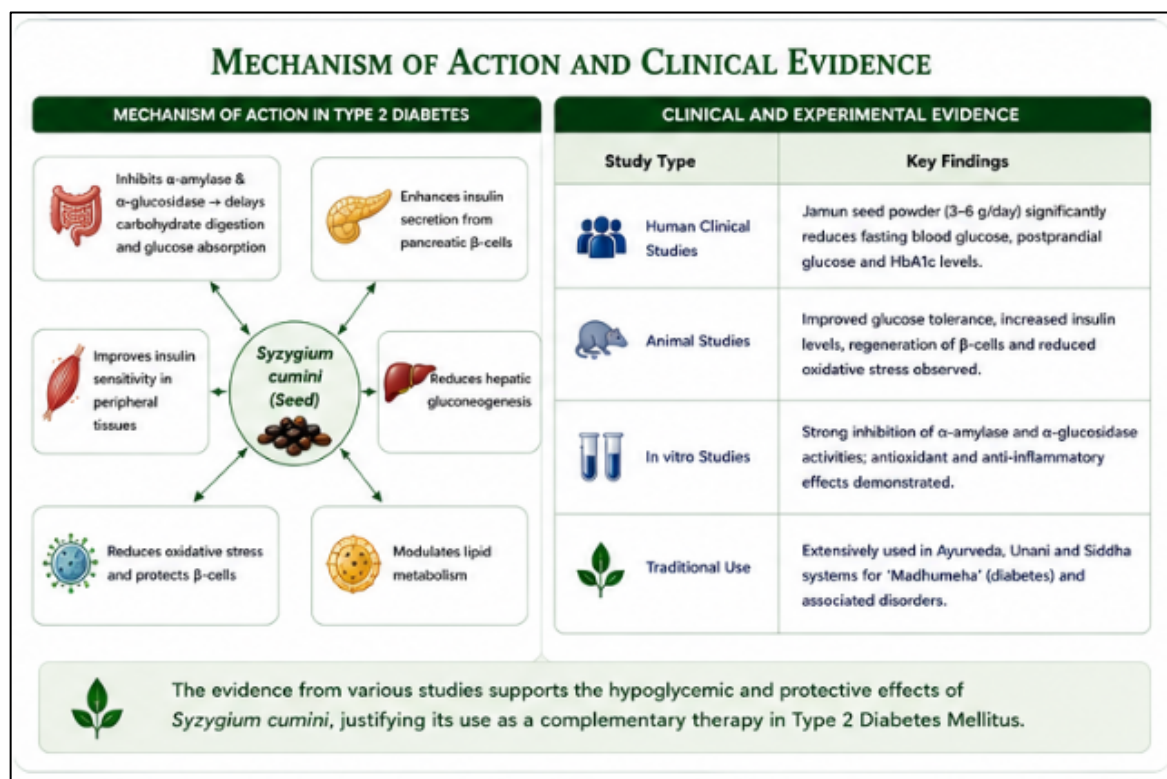
Clinical investigations, although relatively limited, have reported beneficial effects of Jamun seed preparations in patients with Type 2 diabetes mellitus. Several studies have documented reductions in fasting blood glucose, postprandial glucose, and glycosylated hemoglobin after regular supplementation. Improvements in lipid profile and oxidative stress markers have also been noted, suggesting broader metabolic benefits beyond glucose lowering. [78] Importantly, *Syzygium cumini* exhibits a favorable safety profile with minimal toxicity when administered within recommended doses. Toxicological studies have demonstrated low acute toxicity and good tolerability, supporting its use as an adjunct to conventional antidiabetic therapy. Nevertheless, standardized clinical trials with larger sample sizes are still required to establish optimal dosage regimens and long-term efficacy. [79] The accumulating evidence indicates that Jamun seed preparations may complement synthetic drugs such as metformin by targeting additional pathogenic pathways involved in Type 2 diabetes mellitus.

#### **1.8.6 Mechanism of Action of *Syzygium cumini* in the Management of Type 2 Diabetes Mellitus:**

The antidiabetic activity of *Syzygium cumini* is attributed to its ability to influence multiple biochemical and physiological pathways involved in glucose homeostasis. Unlike conventional oral hypoglycemic agents that often target a single mechanism, the phytochemicals present in *Syzygium cumini* exhibit pleiotropic effects, making the plant an attractive candidate for complementary diabetes therapy. [80] One of the primary mechanisms involves inhibition of carbohydrate-hydrolyzing enzymes such as  $\alpha$ -amylase and  $\alpha$ -glucosidase. These enzymes are responsible for breaking down complex carbohydrates into absorbable monosaccharides in the gastrointestinal tract. Inhibition of these enzymes delays carbohydrate digestion and reduces postprandial glucose excursions, thereby improving

glycemic control. Polyphenolic compounds and flavonoids present in Jamun seeds have demonstrated significant inhibitory activity against these enzymes in both in vitro and in vivo studies. The antioxidant constituents reduce reactive oxygen species and preserve mitochondrial integrity, thereby maintaining insulin biosynthesis and secretion. [81]

*Syzygium cumini* also improves peripheral insulin sensitivity by facilitating glucose uptake in skeletal muscle and adipose tissue. Certain flavonoids activate intracellular signaling pathways that enhance glucose transporter-4 (GLUT4) translocation to the cell membrane, promoting efficient glucose utilization. Simultaneously, suppression of hepatic gluconeogenesis contributes to lower fasting plasma glucose concentrations. Improvement in lipid metabolism indirectly enhances insulin sensitivity and reduces cardiovascular risk associated with Type 2 diabetes mellitus. Collectively, these mechanisms suggest that *Syzygium cumini* targets several components of the diabetic process simultaneously, supporting its use as a complementary therapeutic agent alongside metformin. [82].



**Fig 9: Mechanism of Action and Clinical Evidence**

### 1.9 Challenges in Herbal Drug Standardization:

Although medicinal plants possess significant therapeutic potential, standardization remains one of the greatest challenges in herbal pharmaceutical development. Variability in phytochemical composition may arise from differences in geographical origin, climatic conditions, cultivation practices, harvesting season, storage methods, and extraction procedures. [83] For *Syzygium cumini*, concentrations of active constituents such as jamboline, ellagic acid, and anthocyanins can vary considerably depending on environmental factors. Such variability may influence pharmacological activity and compromise reproducibility of clinical outcomes. [84]

Quality control procedures therefore include botanical authentication, physicochemical evaluation, chromatographic fingerprinting, quantification of marker compounds, microbial testing, heavy metal analysis, pesticide residue assessment, and stability studies. Standardization is particularly important when herbal materials are incorporated into fixed-dose pharmaceutical formulations because consistent therapeutic performance depends upon reproducible concentrations of bioactive constituents. Regulatory

agencies increasingly emphasize evidence-based quality assurance to ensure safety, efficacy, and batch-to-batch consistency of herbal medicinal products. [85]

### **1.10 Rationale for Combining Metformin Hydrochloride with *Syzygium cumini*:**

Type 2 Diabetes Mellitus is a multifactorial metabolic disorder involving insulin resistance, impaired insulin secretion, increased hepatic glucose production, oxidative stress, chronic inflammation, and dyslipidemia. Since these pathological mechanisms occur simultaneously, treatment with a single therapeutic agent may not provide optimal glycemic control in all patients. Therefore, combination therapy targeting multiple pathways has become an important strategy for effective diabetes management. [86]

Metformin Hydrochloride remains the first-line oral antihyperglycemic agent because it effectively suppresses hepatic gluconeogenesis, improves peripheral insulin sensitivity, and enhances glucose utilization without causing significant hypoglycemia. However, prolonged therapy may be associated with gastrointestinal adverse effects, vitamin B<sub>12</sub> deficiency, and does not adequately address oxidative stress or inflammation associated with diabetes.

In contrast, *Syzygium cumini* possesses multiple pharmacological activities that complement the therapeutic actions of metformin. Its phytochemical constituents inhibit  $\alpha$ -amylase and  $\alpha$ -glucosidase, delay intestinal carbohydrate digestion, stimulate insulin secretion, improve pancreatic  $\beta$ -cell function, enhance peripheral glucose uptake, reduce oxidative stress, suppress inflammatory cytokines, and improve lipid metabolism. These mechanisms are different from, yet complementary to, those of metformin. [87]

Combining Metformin Hydrochloride with *Syzygium cumini* is therefore expected to produce synergistic therapeutic effects by simultaneously targeting multiple pathways involved in glucose homeostasis. Such a combination may improve glycemic control, reduce postprandial hyperglycemia, protect pancreatic  $\beta$ -cells, minimize oxidative stress, and decrease the progression of diabetic complications including nephropathy, neuropathy, retinopathy, and cardiovascular disease.

Another important advantage of this combination is the possibility of achieving the desired therapeutic response with a lower dose of metformin, potentially reducing dose-dependent adverse effects while maintaining efficacy. Furthermore, the antioxidant and anti-inflammatory properties of *Syzygium cumini* may provide additional protection against long-term diabetic complications, which are not directly addressed by conventional antihyperglycemic drugs.

From a pharmaceutical perspective, incorporation of Metformin Hydrochloride and *Syzygium cumini* seed powder into a single immediate-release tablet offers several advantages, including improved patient compliance, convenience of administration, accurate dosing, reduced pill burden, and enhanced therapeutic effectiveness. The use of direct compression technology further simplifies the manufacturing process while ensuring good tablet quality, stability, and reproducibility. [88]

Therefore, the present investigation focuses on the formulation and evaluation of an immediate-release combination tablet containing Metformin Hydrochloride and *Syzygium cumini* seed powder with the objective of developing a stable, effective, and patient-friendly dosage form capable of providing enhanced therapeutic benefits in the management of Type 2 Diabetes Mellitus.

### **1.11 Preformulation Studies**

Preformulation studies represent the foundation of successful dosage form development by providing critical information regarding the physical and chemical properties of drug substances and excipients. These investigations facilitate rational formulation design and help predict potential manufacturing challenges before large-scale production.

Important preformulation parameters include particle size distribution, moisture content, solubility, pH, polymorphism, hygroscopicity, flow characteristics, compressibility, and drug-excipient compatibility.

Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and X-ray diffraction techniques are commonly employed to identify possible interactions between formulation components. [89]

For herbal products such as *Syzygium cumini* powder, standardization is equally important because phytochemical composition may vary depending on geographical origin, harvesting season, storage conditions, and processing methods. Quantification of marker compounds and evaluation of physicochemical parameters ensure consistency and reproducibility of the herbal ingredient.

Drug-excipient compatibility studies are particularly essential when combining synthetic drugs with plant-derived materials, as unexpected interactions may affect stability, dissolution behavior, and therapeutic efficacy. Proper preformulation assessment therefore minimizes formulation failure and enhances product quality. [90].

### **1.12 Evaluation Parameters for Combination Tablets:**

Following formulation, tablets must undergo comprehensive quality control testing to ensure compliance with pharmacopeial standards and therapeutic effectiveness. Pre-compression parameters include angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner ratio, which collectively assess powder flowability and compressibility.

Post-compression evaluation includes weight variation, thickness, hardness, friability, disintegration time, drug content uniformity, and in vitro dissolution studies. Tablet hardness influences mechanical integrity during transportation and handling, whereas friability measures resistance to abrasion. Disintegration testing determines the time required for tablets to break apart after administration, directly affecting drug release and absorption.

Dissolution testing serves as one of the most critical quality control measures because it predicts in vivo drug availability and therapeutic performance. Uniform drug release profiles are essential for maintaining consistent plasma concentrations and achieving optimal glycemic control. Stability studies conducted under accelerated and long-term storage conditions further establish product shelf life and ensure maintenance of quality throughout storage. Collectively, these evaluation parameters provide comprehensive evidence regarding the suitability, safety, efficacy, and reproducibility of the developed combination tablet formulation. [91]

### **1.13 Quality by Design (QbD) and Optimization in Tablet Formulation:**

Modern pharmaceutical development emphasizes systematic product design through the Quality by Design (QbD) approach. QbD is a science-based methodology that aims to ensure product quality by understanding formulation variables and manufacturing processes rather than relying solely on end-product testing. The concept was introduced by regulatory authorities to improve consistency, efficiency, and robustness in pharmaceutical manufacturing

Quality by Design (QbD) is a systematic, scientific, and risk-based approach to pharmaceutical product development that aims to ensure quality is built into the product from the initial stages of formulation rather than being evaluated solely through final product testing. Unlike the traditional quality-by-testing approach, where product quality is confirmed only after manufacturing, QbD emphasizes a thorough understanding of the relationship between formulation variables, manufacturing processes, and product performance. This approach improves product quality, manufacturing consistency, regulatory compliance, and patient safety.

The concept of Quality by Design was introduced by the United States Food and Drug Administration (USFDA) and later incorporated into the International Council for Harmonisation (ICH) guidelines, particularly ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), ICH Q10



(Pharmaceutical Quality System), and more recently ICH Q11 (Development and Manufacture of Drug Substances). These guidelines encourage pharmaceutical manufacturers to adopt a science-based development strategy supported by process understanding, risk assessment, and continuous improvement. [92]

For herbal formulations containing *Syzygium cumini* powder, QbD principles are particularly valuable because natural materials exhibit inherent variability in particle size, moisture content, and phytochemical composition. Optimization of excipient ratios and compression parameters helps ensure reproducible tablet quality and consistent therapeutic performance. Implementation of QbD therefore enhances formulation robustness, regulatory compliance, manufacturing efficiency, and patient safety, making it an essential component of modern pharmaceutical product development.[38]

QbD begins with defining the intended quality characteristics of the dosage form and identifying the formulation and process variables that may influence those characteristics. Rather than relying on repeated trial-and-error experimentation, QbD utilizes scientific knowledge, statistical methods, and experimental design to establish a robust formulation that consistently meets predefined quality requirements. This approach significantly reduces development time, minimizes manufacturing variability, improves process reproducibility, and facilitates regulatory approval.

In recent years, QbD has become an integral component of pharmaceutical formulation development, particularly for complex dosage forms and fixed-dose combination products. The systematic application of QbD enables researchers to identify critical formulation variables at an early stage, optimize manufacturing conditions, and establish an appropriate design space within which consistent product quality can be achieved. Consequently, pharmaceutical industries increasingly adopt QbD as the preferred strategy for product development and lifecycle management. [93]

#### **1.13.1 Quality Target Product Profile (QTPP)**

The Quality Target Product Profile (QTPP) is the foundation of the Quality by Design approach. It is defined as a prospective summary of the quality characteristics that a pharmaceutical product should possess to ensure its safety, efficacy, stability, and therapeutic performance throughout its intended shelf life. The QTPP provides a clear description of the desired product attributes and serves as a guide for formulation scientists during product development.

The QTPP generally includes information regarding the dosage form, route of administration, dosage strength, intended therapeutic use, release characteristics, stability requirements, packaging system, and patient acceptability. It establishes the overall objectives of formulation development and provides the basis for identifying the Critical Quality Attributes (CQAs) required to achieve the desired product performance.

During pharmaceutical development, the formulation is designed to meet all QTPP requirements while maintaining product quality within predefined limits. A well-defined QTPP ensures that every stage of formulation development remains focused on achieving consistent therapeutic effectiveness and regulatory compliance. [94]

#### **1.13.2 Critical Quality Attributes (CQAs)**

Critical Quality Attributes (CQAs) are the physical, chemical, biological, or microbiological properties of a pharmaceutical product that must remain within specified limits to ensure the desired product quality, safety, and efficacy. These attributes are directly related to the therapeutic performance of the dosage form and therefore require careful monitoring throughout formulation development and manufacturing.

CQAs vary depending on the type of dosage form. For tablet formulations, important quality attributes generally include hardness, friability, weight variation, drug content, content uniformity, disintegration

time, dissolution rate, moisture content, stability, and appearance. These parameters significantly influence the quality and performance of the final product.

Identification of CQAs is one of the most important steps in the QbD approach because it enables researchers to determine which formulation variables and manufacturing processes require strict control. Once CQAs are identified, further studies are conducted to understand the factors affecting these attributes and to establish suitable control strategies.

### **1.13.3 Critical Material Attributes (CMAs)**

Critical Material Attributes (CMAs) are the physical, chemical, and biological characteristics of raw materials, active pharmaceutical ingredients (APIs), excipients, and packaging materials that have a significant impact on the Critical Quality Attributes of the finished pharmaceutical product.

Examples of CMAs include particle size distribution, particle shape, bulk density, tapped density, moisture content, compressibility, flowability, polymorphic form, crystal habit, viscosity, and purity of raw materials. Variations in these material properties may influence powder blending, compression behaviour, tablet hardness, disintegration, dissolution, and overall product stability. Understanding CMAs helps formulation scientists select suitable pharmaceutical ingredients and establish appropriate specifications for raw materials, thereby minimizing variability during manufacturing. [95]

### **1.13.4 Critical Process Parameters (CPPs)**

Critical Process Parameters (CPPs) are manufacturing variables that have a direct influence on the Critical Quality Attributes of the pharmaceutical product. These parameters must be carefully monitored and controlled throughout the manufacturing process to ensure consistent product quality.

Examples of CPPs in tablet manufacturing include blending time, mixing speed, granulation conditions, drying temperature, compression force, turret speed, lubrication time, and environmental conditions such as humidity and temperature.

Improper control of CPPs may result in poor content uniformity, excessive friability, insufficient hardness, delayed disintegration, altered dissolution behaviour, and reduced product stability. Therefore, understanding the relationship between CPPs and CQAs is essential for developing a robust and reproducible manufacturing process.

### **1.13.5 Quality Risk Management**

Quality Risk Management (QRM) is an essential element of the Quality by Design approach. It involves the systematic identification, evaluation, control, communication, and review of risks that may affect product quality during pharmaceutical development and manufacturing.

The primary objective of Quality Risk Management is to identify factors that have the greatest impact on product quality and prioritize them for further investigation and control. Risk assessment allows pharmaceutical scientists to allocate resources efficiently while minimizing process variability.

Several scientific tools are commonly used for risk assessment in pharmaceutical development, including:

- Failure Mode and Effects Analysis (FMEA)
- Ishikawa (Fishbone) Diagram
- Risk Ranking and Filtering
- Hazard Analysis and Critical Control Point (HACCP)
- Fault Tree Analysis (FTA)



These tools facilitate systematic analysis of formulation variables, manufacturing processes, equipments, environmental conditions, analytical methods, and human factors that may influence product quality. [96].

### **1.13.6 Design of Experiments (DoE) in Pharmaceutical Formulation**

Design of Experiments (DoE) is a structured statistical methodology used to evaluate the effects of multiple formulation and process variables simultaneously. Unlike the conventional one-factor-at-a-time approach, DoE investigates interactions between variables, enabling researchers to obtain maximum information with a minimum number of experimental trials.

DoE is widely employed during pharmaceutical formulation development because it improves scientific understanding of the formulation process while reducing development time and experimental cost. Statistical analysis generated through DoE allows formulation scientists to establish mathematical relationships between independent variables and product responses, thereby facilitating optimization of the dosage form.

Common experimental designs used in pharmaceutical research include:

- Full Factorial Design
- Fractional Factorial Design
- Box–Behnken Design
- Central Composite Design
- Response Surface Methodology
- Mixture Design

These statistical tools assist in identifying optimum formulation conditions, establishing design space, and improving manufacturing robustness. The application of DoE within the QbD framework has become a standard practice in modern pharmaceutical development because it enhances product quality, improves process understanding, supports regulatory submissions, and promotes continuous improvement throughout the product lifecycle. [97]

### **1.14 Role of Gut Microbiota in Type 2 Diabetes and Therapeutic Implications**

The human gastrointestinal tract contains trillions of microorganisms collectively known as the gut microbiota, which play essential roles in nutrient metabolism, immune regulation, and maintenance of intestinal barrier integrity. Recent evidence suggests that alterations in gut microbial composition contribute significantly to the development of obesity, insulin resistance, and Type 2 diabetes mellitus.

Dysbiosis, characterized by reduced microbial diversity and altered bacterial populations, increases intestinal permeability and facilitates translocation of lipopolysaccharides into systemic circulation. This process triggers chronic low-grade inflammation and impairs insulin signalling pathways, promoting metabolic dysfunction.

Metformin has been shown to modify gut microbial composition by increasing populations of beneficial bacteria such as *Akkermansia muciniphila* and short-chain fatty acid-producing organisms. These changes improve intestinal barrier function, reduce inflammation, and enhance glucose metabolism. Similarly, polyphenols and dietary fibers present in *Syzygium cumini* may function as prebiotic substrates that promote beneficial microbial growth and increase production of butyrate and other short-chain fatty acids. These metabolites improve insulin sensitivity, regulate appetite, and reduce inflammatory responses.

The combined influence of metformin and *Syzygium cumini* on gut microbiota may therefore represent an additional mechanism contributing to improved glycemic control and metabolic health, further supporting the rationale for their combination in a single pharmaceutical formulation. [99]

### **1.15 Oxidative Stress and Inflammation in Type 2 Diabetes Mellitus**

Oxidative stress is recognized as one of the principal mechanisms responsible for the onset and progression of Type 2 diabetes mellitus and its associated complications. It occurs when the generation of reactive oxygen species (ROS) exceeds the capacity of endogenous antioxidant defense systems, resulting in cellular damage and metabolic dysfunction.

Persistent hyperglycemia stimulates excessive ROS production through several biochemical pathways, including glucose autooxidation, activation of the polyol pathway, protein kinase C activation, advanced glycation end-product (AGE) formation, and mitochondrial electron transport dysfunction. These pathways collectively damage proteins, lipids, DNA, and cellular membranes, impairing normal physiological functions.

Pancreatic  $\beta$ -cells are particularly susceptible to oxidative injury because they possess relatively low concentrations of antioxidant enzymes such as catalase and glutathione peroxidase. Continuous oxidative stress promotes  $\beta$ -cell apoptosis, reduces insulin secretion, and accelerates disease progression. Simultaneously, oxidative damage to vascular endothelial cells contributes to diabetic nephropathy, retinopathy, neuropathy, and cardiovascular disease [100].

Oxidative stress is closely associated with chronic low-grade inflammation, creating a vicious cycle that further aggravates insulin resistance and metabolic dysfunction. Excessive production of reactive oxygen species activates inflammatory signaling pathways, including nuclear factor-kappa B (NF- $\kappa$ B), leading to increased expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), and interleukin-6 (IL-6). These inflammatory mediators interfere with insulin receptor signaling, impair glucose uptake, and contribute to progressive pancreatic  $\beta$ -cell dysfunction. Therefore, therapeutic interventions possessing both antioxidant and anti-inflammatory properties, such as *Syzygium cumini*, may provide additional benefits by reducing oxidative damage, suppressing inflammatory responses, and improving overall metabolic homeostasis in patients with Type 2 Diabetes Mellitus.

Natural antioxidants obtained from medicinal plants can neutralize reactive oxygen species and enhance endogenous antioxidant defences. Polyphenols, flavonoids, anthocyanins, and tannins present in *Syzygium cumini* have demonstrated remarkable free radical scavenging activity and may reduce oxidative damage associated with chronic hyperglycaemia. These properties support the incorporation of antioxidant-rich herbal materials into antidiabetic formulations.

Furthermore, reduction of oxidative stress may preserve pancreatic  $\beta$ -cell function, improve insulin sensitivity, and delay the onset of diabetic complications. Consequently, therapeutic strategies targeting both glycemic control and oxidative stress are increasingly recognized as comprehensive approaches for diabetes management. [101]

### **1.16 Need for the Present Investigation:**

Type 2 diabetes mellitus (T2DM) has emerged as one of the most significant global public health challenges due to its rapidly increasing prevalence, chronic nature, and association with severe microvascular and macrovascular complications. The disease is characterized by complex pathophysiological mechanisms involving insulin resistance, progressive pancreatic  $\beta$ -cell dysfunction, chronic inflammation, oxidative stress, impaired glucose metabolism, and altered lipid homeostasis. Despite considerable advances in

pharmacotherapy, achieving long- term glycemic control remains challenging because of disease progression, medication-related adverse effects, patient non-compliance, and the multifactorial nature of the disorder. Consequently, there is an increasing need for innovative therapeutic approaches that can simultaneously target multiple metabolic pathways while ensuring safety, efficacy, and patient acceptability.

Metformin hydrochloride continues to be the first-line pharmacological agent for the management of Type 2 diabetes mellitus because of its proven efficacy in reducing hepatic glucose production, improving insulin sensitivity, promoting peripheral glucose utilization, and lowering the risk of diabetes-related complications. In addition to its antihyperglycemic activity, metformin has demonstrated beneficial effects on cardiovascular health, body weight management, and metabolic regulation. *Syzygium cumini* (Jamun) occupies a prominent position due to its long history of use in traditional medicine and its diverse pharmacological properties. The seeds of *Syzygium cumini* are rich in flavonoids, polyphenols, tannins, anthocyanins, alkaloids, and phenolic acids, which collectively exhibit antioxidant, anti- inflammatory, antihyperglycemic, hypolipidemic, and  $\beta$ -cell protective effects.

The concept of combining metformin hydrochloride with *Syzygium cumini* powder represents a rational and evidence-based therapeutic strategy aimed at exploiting the complementary mechanisms of both agents. While metformin primarily reduces hepatic glucose output and improves insulin sensitivity, *Syzygium cumini* contributes antioxidant protection, supports pancreatic  $\beta$ -cell function, delays carbohydrate absorption, and improves lipid metabolism. The integration of these mechanisms may provide synergistic benefits, leading to improved glycemic control, reduction in oxidative damage, enhanced metabolic regulation, and potentially lower incidence of long-term diabetic complications. Furthermore, combining herbal and conventional medicines in a single formulation may reduce pill burden, improve medication adherence, and enhance patient convenience.

The incorporation of Quality by Design (QbD) principles and systematic optimization approaches further strengthens the formulation process by identifying critical material attributes and process parameters that influence product quality. Such scientific methodologies improve manufacturing reliability, regulatory compliance, and overall product performance while minimizing variability associated with herbal ingredients. Standardization of *Syzygium cumini* powder through appropriate quality control measures also ensures reproducibility, safety, and efficacy of the final formulation. [104]

In addition to pharmacological and formulation considerations, growing evidence highlights the importance of oxidative stress, chronic inflammation, gut microbiota alterations, and metabolic dysregulation in the progression of Type 2 diabetes mellitus. The antioxidant-rich phytochemicals present in *Syzygium cumini* may provide additional protection against these pathological mechanisms, complementing the glucose-lowering effects of metformin and contributing to a more comprehensive therapeutic approach. Such integrated treatment strategies align with current trends in evidence-based phytotherapy and personalized medicine. [105]

Therefore, the present study on the "Formulation and Evaluation of a Combination Tablet of Metformin Hydrochloride and *Syzygium cumini* for the Treatment of Type 2 Diabetes Mellitus" is scientifically justified and pharmaceutically significant. The proposed formulation aims to combine the established efficacy of metformin with the natural therapeutic potential of *Syzygium cumini* to develop a novel oral dosage form capable of improving glycemic control, enhancing antioxidant protection, and increasing patient compliance. Through systematic formulation development, optimization, and evaluation, this research seeks to provide valuable insights into the feasibility and therapeutic potential of integrating herbal medicine with conventional pharmacotherapy.

## LITERATURE REVIEW

**The literature review provides a comprehensive overview of previous research related to Type**

2 Diabetes Mellitus, conventional antidiabetic therapy, herbal interventions, and pharmaceutical formulation approaches. It serves as a scientific foundation for the present investigation by critically examining published studies on the pharmacological properties of Metformin Hydrochloride and *Syzygium cumini*, their mechanisms of action, therapeutic efficacy, formulation strategies, and optimization techniques. The review also highlights recent advances in the development of combination dosage forms integrating synthetic drugs with herbal medicines to improve glycemic control, reduce disease-related complications, and enhance patient compliance. Furthermore, it identifies existing research gaps and establishes the rationale for developing an immediate-release combination tablet using Quality by Design (QbD) principles for the management of Type 2 Diabetes Mellitus.

### **2.1.1 Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 14th ed. Brunton LL, Hilal-Dandan R, Knollmann BC, editors. McGraw-Hill; 2023.(47)**

Goodman & Gilman's The Pharmacological Basis of Therapeutics is one of the most respected textbooks in pharmacology and therapeutics. It provides detailed scientific information regarding drug mechanisms, pharmacodynamics, pharmacokinetics, therapeutic indications, adverse drug reactions, contraindications, and clinical applications. The textbook thoroughly discusses the pharmacological management of endocrine disorders, including diabetes mellitus, and explains the molecular mechanisms responsible for the therapeutic actions of antidiabetic drugs. The authors describe metformin as a biguanide that effectively lowers blood glucose by suppressing hepatic gluconeogenesis, improving insulin sensitivity.

### **2.1.2 DiPiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Ellingrod V. Pharmacotherapy: A Pathophysiologic Approach. 12th ed. New York: McGraw-Hill Education; 2023.(60)**

Pharmacotherapy: A Pathophysiologic Approach is an authoritative clinical pharmacy textbook that provides evidence-based management of various disease conditions based on their underlying pathophysiology. The book presents comprehensive information on the diagnosis, treatment, prevention, and monitoring of diseases, with particular emphasis on individualized patient care. The diabetes mellitus chapter explains the pathogenesis of Type 2 Diabetes Mellitus, current treatment guidelines, lifestyle modifications, pharmacological interventions, and long-term management strategies. The authors discuss the advantages and limitations of different classes of antidiabetic agents and recommend individualized therapy according to patient-specific clinical conditions.

### **2.1.3 Aulton ME, Taylor KMG (Editors). Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 6th ed. Edinburgh: Elsevier; 2022.(94)**

Aulton's Pharmaceutics: The Design and Manufacture of Medicines is one of the most comprehensive references on pharmaceutical formulation, manufacturing technology, and dosage form design. The book provides detailed information on preformulation studies, excipient functionality, powder technology, tablet compression, granulation methods, coating processes, quality control testing, packaging, stability evaluation, and regulatory considerations. The editors emphasize that successful pharmaceutical formulation requires a systematic understanding of drug properties, excipient interactions, manufacturing processes, and quality assurance to ensure safe, effective, and reproducible pharmaceutical products. The textbook also explains modern pharmaceutical development strategies that integrate scientific principles with industrial manufacturing practices.

### **2.1.4 Shargel L, Yu ABC. Applied Biopharmaceutics & Pharmacokinetics. 8th ed. New York: McGraw-Hill Education; 2022.(79)**

Applied Biopharmaceutics & Pharmacokinetics is a widely recognized textbook that integrates the principles of biopharmaceutics with clinical pharmacokinetics. The authors explain the influence of drug physicochemical properties, formulation variables, route of administration, and physiological factors on drug absorption and bioavailability. The book discusses dissolution, permeability, first-pass metabolism, pharmacokinetic modeling, bioequivalence studies, therapeutic drug monitoring, and dosage regimen optimization. It also provides practical applications of pharmacokinetic principles in drug development and patient care. It emphasizes that formulation characteristics play a crucial role in determining the therapeutic performance of oral dosage forms. Proper formulation design can improve drug absorption, reduce variability, and enhance patient compliance. These principles are directly applicable to the present research involving the development of a combination tablet of Metformin Hydrochloride and Syzygium cumini.

**2.1.5 Allen LV Jr., Ansel HC (Editors). Lachman's The Theory and Practice of Industrial Pharmacy. 5th ed. CBS Publishers & Distributors; 2021.(13)**

Lachman's The Theory and Practice of Industrial Pharmacy is regarded as one of the most authoritative textbooks in pharmaceutical technology and industrial pharmacy. The book provides comprehensive information on pharmaceutical formulation, dosage form design, manufacturing processes, quality assurance, process validation, and regulatory requirements involved in the production of pharmaceutical products. It thoroughly explains tablet manufacturing techniques such as direct compression, wet granulation, and dry granulation, while also discussing the role of pharmaceutical excipients, formulation variables, equipment selection, in-process quality control, and Good Manufacturing Practices (GMP). The text serves as an essential reference for pharmaceutical scientists involved in dosage form development and industrial production. The information provided serves as the scientific basis for selecting formulation techniques, excipients, manufacturing methods, and evaluation parameters required to produce a stable, effective, and pharmaceutically acceptable tablet dosage form.

**2.1.6 Katzung BG. Basic and Clinical Pharmacology. 15th ed. New York: McGraw-Hill; 2021.(56)**

Basic and Clinical Pharmacology by Bertram G. Katzung is one of the most authoritative textbooks in pharmacology, providing comprehensive information on the pharmacodynamics, pharmacokinetics, therapeutic uses, adverse effects, contraindications, and mechanisms of action of drugs. The book thoroughly explains the pharmacological management of diabetes mellitus, including insulin preparations and oral antidiabetic agents such as metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors. It also discusses the pathophysiology of diabetes and the rationale behind selecting appropriate therapeutic agents based on disease progression and patient characteristics.

**2.1.7 Sweetman SC (Editor). Martindale: The Complete Drug Reference. 40th ed. London: Pharmaceutical Press; 2020.(50)**

Martindale: The Complete Drug Reference is an internationally recognized reference that provides detailed and evidence-based information on medicinal substances, pharmaceutical preparations, therapeutic agents, and clinical drug use. The book includes comprehensive monographs describing the drugs classification, mechanisms of action, indications, dosage recommendations, pharmacokinetics, adverse effects, contraindications, precautions, interactions, and storage requirements. It serves as an essential source of reliable information for pharmacists, physicians, researchers, and regulatory professionals involved in pharmaceutical practice and drug development.

**2.1.8 Adejare A. (Editor). Remington: The Science and Practice of Pharmacy. 23rd ed. Pharmaceutical Press; 2020.(22)**

Remington: The Science and Practice of Pharmacy is one of the most respected and comprehensive references in pharmaceutical sciences. The textbook covers fundamental and advanced concepts related to

pharmaceutics, pharmaceutical chemistry, pharmacology, pharmacognosy, biopharmaceutics, pharmaceutical technology, quality assurance, and clinical pharmacy. It provides detailed explanations of dosage form design, excipient selection, drug stability, formulation development, manufacturing processes, packaging, storage conditions, and regulatory aspects of pharmaceutical products. The book also discusses physicochemical properties of drugs and excipients that influence performance and therapeutic efficacy.

**2.1.9 Sheskey PJ, Cook WG, Cable CG (Editors). Handbook of Pharmaceutical Excipients. 9th ed. London: Pharmaceutical Press; 2020.(24)**

Handbook of Pharmaceutical Excipients is one of the most widely accepted references for information on pharmaceutical excipients used in dosage form development. The book provides detailed monographs on hundreds of excipients, including their chemical structure, physicochemical properties, pharmaceutical applications, compatibility, toxicity, regulatory status, stability, storage conditions, and recommended concentrations. It explains the functional roles of diluents, binders, disintegrants, lubricants, glidants, sweeteners, coating agents, preservatives, and other excipients commonly employed in pharmaceutical formulations. Each monograph also discusses incompatibilities and precautions that should be considered during formulation development.

2.1.10 Montgomery DC. Design and Analysis of Experiments. 10th ed. Wiley; 2019.(97) Montgomery's Design and Analysis of Experiments is regarded as one of the most authoritative references on experimental design and optimization. The book comprehensively explains the principles of Design of Experiments (DoE), including factorial design, fractional factorial design, randomized block design, response surface methodology, regression modelling, and optimization techniques. The author emphasizes that systematic experimental planning allows researchers to evaluate the effects of multiple independent variables simultaneously while minimizing experimental error, time, and resource utilization. The book also provides detailed guidance on the application of analysis of variance (ANOVA), model adequacy checking, interaction analysis, and optimization procedures using statistical software.

**2.1.11 Rowland M, Tozer TN. Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications. 5th ed. Philadelphia: Wolters Kluwer; 2019.(58)**

Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications is a leading reference that explains the relationship between drug concentration in the body and the resulting therapeutic response. The book provides comprehensive coverage of drug absorption, distribution, metabolism, excretion (ADME), bioavailability, bioequivalence, clearance, volume of distribution, half-life, and dosage regimen design. It also discusses pharmacodynamic principles, including receptor interactions, dose-response relationships, therapeutic index, and factors influencing drug efficacy and safety. The authors emphasize the importance of understanding pharmacokinetic behavior to optimize drug therapy, improve clinical outcomes, and minimize adverse effects.

**2.1.12 Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. 7th ed. Philadelphia: Wolters Kluwer; 2017.(15)**

Martin's Physical Pharmacy and Pharmaceutical Sciences is one of the most authoritative textbooks in pharmaceutical sciences, providing a detailed understanding of the physicochemical principles governing drug formulation and dosage form development. The book explains fundamental concepts such as solubility, dissolution, diffusion, particle size analysis, surface phenomena, rheology, crystallization, polymorphism, complexation, stability, and drug-excipient interactions. These physicochemical properties significantly influence the bioavailability, stability, manufacturability, and therapeutic performance of pharmaceutical products. The text also discusses the importance of preformulation studies in identifying suitable formulation strategies and optimizing dosage forms before large-scale manufacturing. These principles are directly applicable to the present study involving the formulation and evaluation of a combination tablet of Metformin Hydrochloride and Syzygium cumini.

**2.1.13 Qiu Y, Chen Y, Zhang GGZ, Liu L, Porter WR (Editors). Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice. 2nd ed. Academic Press (Elsevier); 2017.(25)**

Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice provides a detailed overview of the scientific and technological principles involved in the development of oral solid dosage forms. The book covers preformulation studies, formulation design, excipient selection, powder characterization, manufacturing technologies, process development, quality control, stability testing, and regulatory requirements. It explains how physicochemical properties of drug substances influence formulation performance and highlights the importance of systematic formulation development using modern pharmaceutical approaches. The text also discusses tablet compression, capsule filling, coating technologies, dissolution testing, and scale-up strategies used in industrial pharmaceutical manufacturing.

**2.1.14 Rena G, Hardie DG, Pearson ER. The Mechanisms of Action of Metformin. Diabetologia. 2017;60(9):1577–1585.(3)**

Rena and colleagues comprehensively reviewed the molecular mechanisms underlying metformin action. They demonstrated that activation of AMP-activated protein kinase (AMPK) plays a central role in suppressing hepatic gluconeogenesis and improving glucose uptake in peripheral tissues. The review also discussed gut microbiota modulation and mitochondrial effects as additional mechanisms contributing to glucose control. They concluded that metformin exerts its therapeutic effects through several complementary mechanisms rather than a single pathway. This review provides strong scientific evidence supporting the use of metformin in combination with herbal agents such as *Syzygium cumini*, whose antioxidant and antihyperglycemic activities may further improve therapeutic outcomes in diabetic patients.

**2.1.15 Florence AT, Attwood D. Physicochemical Principles of Pharmacy. 6th ed. London: Pharmaceutical Press; 2016.(90)**

Florence and Attwood described the fundamental physicochemical principles that govern pharmaceutical formulation and drug delivery. The book explains important concepts such as solubility, dissolution, diffusion, partition coefficient, micromeritics, surface and interfacial phenomena, rheology, colloidal systems, polymorphism, complexation, and drug stability. The authors demonstrated how these physicochemical properties influence drug absorption, formulation behaviour, manufacturing processes, and therapeutic performance

**2.1.16 Gibson M (Editor). Pharmaceutical Preformulation and Formulation. 2nd ed. Boca Raton: CRC Press; 2016.(42)**

Pharmaceutical Preformulation and Formulation is an important reference that focuses on the scientific principles involved in preformulation studies and dosage form development. The book explains the significance of evaluating physicochemical properties such as solubility, pKa, partition coefficient, polymorphism, hygroscopicity, particle size distribution, compatibility, and stability before formulation development. It also discusses the selection of suitable excipients, manufacturing processes, quality control tests, formulation optimization, and regulatory considerations for developing robust pharmaceutical products. The authors emphasize that systematic preformulation studies reduce development time and improve the quality, stability, and performance of dosage forms.

**2.1.17 Parikh DM (Editor). Handbook of Pharmaceutical Granulation Technology. 3rd ed. Boca Raton: CRC Press; 2015.(17)**

The Handbook of Pharmaceutical Granulation Technology provides an extensive overview of granulation processes used in pharmaceutical manufacturing. The book discusses the principles, mechanisms, advantages, and limitations of wet granulation, dry granulation, fluidized-bed granulation, spray drying, roller compaction, and high-shear granulation. It explains how granulation improves powder flowability,

compressibility, content uniformity, and tablet strength while reducing problems such as segregation, dust formation, and poor die filling. The text also covers formulation variables, equipment design, scale-up considerations, and process optimization to achieve consistent product quality.

**2.1.18 DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 Diabetes Mellitus. Nature Reviews Disease Primers. 2015;1:15019.(10)**

DeFronzo and co-workers described Type 2 diabetes as a multifactorial disease involving insulin resistance,  $\beta$ -cell dysfunction, increased hepatic glucose production, renal glucose reabsorption, and impaired incretin activity. Their work introduced modern concepts explaining disease progression and emphasized that therapies targeting multiple mechanisms may achieve superior glycemic control. This concept is highly relevant to the present study, which focuses on developing a combination tablet of Metformin Hydrochloride and *Syzygium cumini*. The formulation aims to combine the well-established glucose-lowering effects of metformin with

the antioxidant and antihyperglycemic properties of the herbal component to achieve enhanced therapeutic efficacy in the treatment of Type 2 Diabetes Mellitus. The authors highlighted the importance of individualized treatment and combination therapy for achieving long-term glycemic control and preventing diabetic complications. They suggested that therapies acting through different mechanisms can improve treatment efficacy while minimizing adverse effects. This concept strongly supports the rationale of the present study, where Metformin Hydrochloride is combined with *Syzygium cumini* in a single tablet formulation.

**2.1.19 Swarbrick J (Editor). Encyclopedia of Pharmaceutical Technology. 4th ed. New York: Informa Healthcare; 2013.(19)**

The Encyclopedia of Pharmaceutical Technology is a comprehensive reference covering virtually every aspect of pharmaceutical research, formulation development, manufacturing technology, quality control, regulatory affairs, biotechnology, analytical techniques, and novel drug delivery systems. The encyclopedia contains detailed chapters written by internationally recognized experts and provides scientifically validated information on excipients, dosage forms, pharmaceutical processes, process validation, analytical methods, stability testing, and quality assurance. It serves as a valuable resource for pharmaceutical scientists, academicians, researchers, and industrial professionals involved in product development.

**2.1.20 Bolton S, Bon C. Pharmaceutical Statistics: Practical and Clinical Applications. 6th ed. New York: Informa Healthcare; 2010.(40)**

Bolton and Bon presented a comprehensive guide to the application of statistical methods in pharmaceutical sciences, clinical research, and quality assurance. The book explains the importance of statistical tools in designing experiments, validating analytical methods, optimizing pharmaceutical formulations, and interpreting research findings. It provides detailed descriptions of descriptive statistics, probability distributions, hypothesis testing, confidence intervals, regression analysis, correlation, analysis of variance (ANOVA), and multivariate statistical techniques. The authors emphasized that statistical analysis enhances the reliability, reproducibility, and scientific validity of pharmaceutical research while reducing experimental errors and bias. The book also highlights the role of statistical software in data interpretation and pharmaceutical product development.

**2.1.21 Rathbone MJ, Hadgraft J, Roberts MS (Editors). Modified-Release Drug Delivery Technology. 2nd ed. New York: Informa Healthcare; 2008.(20)**

Modified-Release Drug Delivery Technology provides comprehensive knowledge on the design, formulation, and evaluation of modified-release pharmaceutical dosage forms. The book discusses various controlled-release approaches, including sustained-release, delayed-release, extended-release, pulsatile-release, and targeted drug delivery systems. It explains the scientific principles governing drug release



kinetics, diffusion mechanisms, polymer selection, matrix systems, reservoir systems, osmotic drug delivery, and multiparticulate dosage forms. The authors also describe the influence of physicochemical properties of drugs and excipients on release behavior, bioavailability, and therapeutic effectiveness. Additionally, the text highlights the importance of selecting suitable drug delivery systems to improve patient compliance and minimize dosing frequency.

**2.1.22 Carstensen JT, Rhodes CT. Drug Stability: Principles and Practices. 3rd ed. New York: Marcel Dekker; 2000.(89)**

Carstensen and Rhodes provided a comprehensive discussion on the principles governing the stability of pharmaceutical products throughout their shelf life. The book explains various mechanisms of drug degradation, including hydrolysis, oxidation, photolysis, racemization, and thermal degradation, together with environmental and formulation factors affecting stability. The authors described the influence of temperature, humidity, pH, oxygen, light exposure, excipient compatibility, and packaging materials on the chemical and physical stability of pharmaceutical preparations. The text also discusses stability kinetics, accelerated stability studies, shelf-life prediction, and regulatory recommendations for pharmaceutical products.

**2.1.23 Alderborn G, Nyström C (Editors). Pharmaceutical Powder Compaction Technology. 2nd ed. New York: Marcel Dekker Inc.; 1996.(18)**

Pharmaceutical Powder Compaction Technology is a specialized reference that focuses on the science of powder compression and tablet formation. The editors describe the fundamental mechanisms involved in particle rearrangement, elastic deformation, plastic deformation, brittle fracture, and interparticulate bonding during tablet compression. The book explains how powder characteristics such as particle size, particle shape, moisture content, density, and flowability influence compressibility and tablet quality. It also discusses the mechanical behavior of pharmaceutical powders under compression and the factors responsible for achieving optimum tablet hardness and structural integrity.

**2.1.24 Bailey CJ, Turner RC. Metformin. New England Journal of Medicine. 1996; 334(9):574–579. (2)**

Bailey and Turner published one of the landmark on metformin, describing it as the first-line biguanide for the treatment of Type 2 diabetes mellitus. The authors explained that metformin primarily reduces hepatic glucose production and improves peripheral insulin sensitivity without stimulating insulin secretion, thereby minimizing the risk of hypoglycemia. They also highlighted its favorable safety profile and long history of clinical use. This study established metformin as the cornerstone of modern antidiabetic therapy. This landmark publication laid the scientific foundation for the widespread clinical use of metformin and supports its selection as one of the active ingredients in the present combination tablet containing Syzygium cumini for the management of Type 2 Diabetes Mellitus.

**2.1.25 Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Lea & Febiger; 1986.(16)**

The third edition of The Theory and Practice of Industrial Pharmacy by Lachman, Lieberman, and Kanig is regarded as a classic reference in industrial pharmacy. The book comprehensively describes pharmaceutical manufacturing processes, formulation principles, dosage form design, process optimization, equipment selection, and quality assurance. It explains the scientific basis of tablet production using direct compression, wet granulation, and dry granulation techniques while discussing the influence of excipients, compression force, particle characteristics, and processing variables on tablet quality. The authors also provide detailed guidance on Good Manufacturing Practices (GMP), process validation, and industrial-scale production of pharmaceutical dosage forms.

**2.2 Summary of Literature Review:**

**Table 1: Literature Review Summary Table**

| Author (Year)          | Focus Area                           | Key Findings / Contribution                                                                                                                                                     |
|------------------------|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ICH Q2(R2) (2023)      | Analytical method validation         | Defined validation parameters including specificity, linearity, accuracy, precision, robustness, detection limit, and quantitation limit for pharmaceutical analytical methods. |
| Aulton & Taylor (2022) | Pharmaceutics and dosage form design | Explained preformulation, powder technology, compression, quality assurance, CQAs, CPPs, and pharmaceutical product development.                                                |
| Allen & Ansel (2021)   | Industrial pharmacy                  | Discussed modern tablet manufacturing techniques, formulation development, GMP, and quality assurance practices.                                                                |
| Adejare (2020)         | Pharmaceutical formulation           | Provided comprehensive guidance on dosage form design, excipient selection, formulation development, stability, and quality evaluation.                                         |
| Sheskey et al. (2020)  | Pharmaceutical excipients            | Described pharmaceutical excipients, their properties, compatibility, functionality, and recommended concentrations in tablet formulations.                                     |
| Montgomery (2019)      | Design of Experiments                | Described factorial design, response surface methodology, ANOVA, and optimization techniques used in pharmaceutical formulation development.                                    |
| Mukherjee (2019)       | Quality control of herbal drugs      | Emphasized authentication, phytochemical standardization, chromatographic fingerprinting, and quality assurance of herbal formulations.                                         |
| Rena et al. (2017)     | Molecular mechanism of Metformin     | Demonstrated that metformin activates AMPK, suppresses hepatic gluconeogenesis, improves glucose uptake, and exhibits anti-inflammatory and antioxidant properties.             |
| Sinko (2017)           | Physical pharmacy                    | Explained physicochemical principles such as solubility, dissolution, particle size, compatibility, and stability essential for formulation development.                        |
| Qiu et al.             | Solid oral dosage forms              | Discussed systematic formulation development, Quality by Design (QbD), process optimization,                                                                                    |

|                                         |                                                      |                                                                                                                                                                    |
|-----------------------------------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>(2017)</b>                           |                                                      | and quality evaluation of oral tablets.                                                                                                                            |
| <b>DeFronzo et al. (2015)</b>           | Pathophysiology of Type 2 Diabetes Mellitus          | Described the "Ominous Octet" explaining multiple mechanisms involved in T2DM and emphasized the need for combination therapy targeting different pathways.        |
| <b>Chagas et al. (2015)</b>             | Pharmacological evidence of <i>Syzygium cumini</i>   | Reviewed experimental studies confirming antihyperglycemic, antioxidant, and hypolipidemic activities of <i>Syzygium cumini</i> .                                  |
| <b>Ayyanar &amp; Subash-Babu (2012)</b> | Phytochemistry of <i>Syzygium cumini</i>             | Reviewed phytoconstituents including jamboline, ellagic acid, flavonoids, anthocyanins, and tannins responsible for antidiabetic and antioxidant activities.       |
| <b>Baliga et al. (2011)</b>             | Pharmacological activities of <i>Syzygium cumini</i> | Reported antidiabetic, antioxidant, anti-inflammatory, hepatoprotective, nephroprotective, and cardioprotective properties of <i>Syzygium cumini</i> .             |
| <b>Bolton &amp; Bon (2010)</b>          | Pharmaceutical statistics                            | Highlighted statistical methods including ANOVA, regression, and Design of Experiments for pharmaceutical research and formulation optimization.                   |
| <b>Kumar et al. (2008)</b>              | Antidiabetic activity of <i>Syzygium cumini</i>      | Summarized experimental evidence demonstrating reduction in blood glucose, improvement in insulin secretion, and antioxidant activity.                             |
| <b>Modak et al. (2007)</b>              | Indian medicinal plants for diabetes                 | Reported multiple mechanisms of herbal antidiabetic agents including inhibition of carbohydrate digestion, antioxidant activity, and improved glucose utilization. |
| <b>Sagrawat et al. (2006)</b>           | Pharmacological review of <i>Syzygium cumini</i>     | Summarized medicinal properties including antidiabetic, antimicrobial, antioxidant, anti-inflammatory, and hepatoprotective effects.                               |
| <b>Brownlee (2005)</b>                  | Diabetic complications                               | Proposed oxidative stress as the central mechanism responsible for chronic diabetic complications, highlighting the importance of antioxidant therapy.             |

|                                              |                                                 |                                                                                                                                                                                            |
|----------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Ravi et al. (2004)</b>                    | Antioxidant activity of Jamun seed              | Demonstrated improvement in tissue antioxidant enzymes and reduction in lipid peroxidation in diabetic animal models.                                                                      |
| <b>Evans et al. (2002)</b>                   | Oxidative stress in diabetes                    | Reported that oxidative stress contributes significantly to insulin resistance and $\beta$ -cell dysfunction, supporting antioxidant-based therapeutic approaches.                         |
| <b>Prince &amp; Menon (1998)</b>             | Antioxidant potential of <i>Syzygium cumini</i> | Reported increased catalase, superoxide dismutase, and glutathione activity with significant reduction in oxidative stress markers.                                                        |
| <b>Bailey &amp; Turner (1996)</b>            | Clinical pharmacology of Metformin              | Established metformin as the first-line biguanide for Type 2 Diabetes Mellitus by reducing hepatic glucose production and improving insulin sensitivity with minimal risk of hypoglycemia. |
| <b>Lachman, Lieberman &amp; Kanig (1986)</b> | Industrial pharmacy and tablet formulation      | Explained principles of tablet formulation, direct compression, excipient selection, quality control, and manufacturing processes.                                                         |
| <b>ICH Q1A(R2)</b>                           | Stability testing                               | Established international guidelines for accelerated and long-term stability studies of pharmaceutical products under controlled environmental conditions.                                 |

## AIM & OBJECTIVES

### 3.1 Aim & Objectives:

#### 3.2 AIM:

To formulate and evaluate a combination tablet of Metformin Hydrochloride and *Syzygium cumini* using the direct compression technique for the effective management of Type 2 Diabetes Mellitus, with the objective of enhancing therapeutic efficacy, improving patient compliance, by integrating synthetic and herbal therapy into a single oral dosage form and providing a stable and quality pharmaceutical dosage form.

#### 3.3 Objectives:

To develop a stable, effective, and pharmaceutically acceptable combination tablet for the management of Type 2 Diabetes Mellitus

- To develop a herbal–synthetic combination tablet containing Metformin Hydrochloride and *Syzygium cumini* seed powder for the management of Type 2 Diabetes Mellitus.
- To investigate the potential of *Syzygium cumini* as a complementary herbal antidiabetic agent to reduce dependence on a higher dose of Metformin Hydrochloride.

- To perform preformulation studies of Metformin Hydrochloride and *Syzygium cumini* seed powder.
- To evaluate drug–excipient compatibility using FTIR .
- To formulate the combination tablets using the direct compression technique.
- To optimize the formulation using Quality by Design (QbD) and factorial Design of Experiments (DoE).
- To evaluate the prepared tablets for pre-compression and post-compression parameters, including flow properties, hardness, friability, weight variation, disintegration time, drug content, and dissolution.
- To determine the in-vitro drug release of Metformin Hydrochloride and *Syzygium cumini* from the optimized combination tablet.
- To compare the dissolution performance of the optimized formulation with a marketed Metformin Hydrochloride tablet.
- To conduct stability studies of the optimized formulation and establish its suitability for further development.

## **Rationale & Significance:**

### **4.1 Rationale and Significance**

### **4.2 Rationale of the Study:**

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance, impaired insulin secretion, and progressive pancreatic  $\beta$ -cell dysfunction. Despite the availability of several oral antidiabetic drugs, achieving sustained glycemic control remains challenging because of the multifactorial nature of the disease and the progressive decline in  $\beta$ -cell function. Long-term pharmacotherapy is often associated with adverse effects, poor patient compliance, and inadequate control of oxidative stress and inflammation, which contribute significantly to diabetic complications.

Metformin Hydrochloride remains the first-line oral antihyperglycemic agent due to its proven efficacy in reducing hepatic glucose production, improving insulin sensitivity, and lowering blood glucose levels. However, metformin primarily targets glucose metabolism and has limited direct antioxidant or  $\beta$ -cell protective effects. In addition, prolonged therapy may produce gastrointestinal disturbances and vitamin B<sub>12</sub> deficiency in some patients.

*Syzygium cumini* (Jamun) has been widely used in traditional medicine for the management of diabetes because of its rich phytochemical composition, including flavonoids, polyphenols, tannins, anthocyanins, alkaloids, and phenolic acids. These bioactive constituents exhibit antihyperglycemic, antioxidant, anti-inflammatory, hypolipidemic, and  $\beta$ -cell protective activities through multiple mechanisms such as inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes, enhancement of insulin secretion, improvement of insulin sensitivity, and reduction of oxidative stress.

The combination of Metformin Hydrochloride with *Syzygium cumini* seed powder is therefore expected to provide synergistic therapeutic benefits by targeting multiple pathogenic pathways involved in Type 2 Diabetes Mellitus. While metformin primarily improves insulin sensitivity and suppresses hepatic glucose production, *Syzygium cumini* complements these effects by reducing oxidative stress, protecting pancreatic  $\beta$ -cells, delaying carbohydrate digestion, and improving lipid metabolism. Such a combination may enhance glycemic control while potentially allowing the use of a lower dose of metformin, thereby reducing dose-related adverse effects.

Furthermore, development of the combination as an immediate-release tablet offers additional pharmaceutical advantages, including rapid onset of action, accurate dosing, improved patient

compliance, reduced pill burden, ease of administration, and cost-effective manufacturing through the direct compression technique.

### 4.3 Significance of the Study:

The present investigation is scientifically, pharmaceutically, and therapeutically significant because it integrates a well-established synthetic antidiabetic drug with a medicinal plant possessing proven antidiabetic potential. The study contributes to the growing interest in evidence-based herbal–synthetic combination therapy for the management of chronic metabolic diseases.

The significance of the study includes:

- Development of a novel immediate-release combination tablet containing Metformin Hydrochloride and *Syzygium cumini* seed powder for management of Type 2 Diabetes Mellitus.
- Integration of conventional pharmacotherapy with herbal medicine to achieve a multi- targeted therapeutic approach.
- Potential improvement in glycemic control through complementary mechanisms of action.
- Reduction of oxidative stress and inflammation, thereby minimizing diabetes-associated complications.
- Possibility of reducing the required dose of metformin while maintaining therapeutic efficacy, thereby decreasing dose-related adverse effects.
- Enhancement of patient compliance by reducing pill burden through a fixed-dose combination tablet.
- Application of Quality by Design (QbD) principles to ensure systematic formulation development, optimization, and product quality.
- Generation of scientific data that may support future preclinical and clinical investigations on combination therapy involving medicinal plants.

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance, impaired insulin secretion, and progressive pancreatic  $\beta$ -cell dysfunction. Despite the availability of several oral antidiabetic drugs, achieving sustained glycemic control remains challenging because of the multifactorial nature of the disease and the progressive decline in  $\beta$ -cell function. Long-term pharmacotherapy is often associated with adverse effects, poor patient compliance, and inadequate control of oxidative stress and inflammation, which contribute significantly to diabetic complications.

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- Application of Quality by Design (QbD) principles to ensure systematic formulation development, optimization, and product quality.
- Generation of scientific data that may support future preclinical and clinical investigations on combination therapy involving medicinal plants.

#### **Plan Of Work**

##### **5.1 Plan Of Work**

##### **5.2 Literature Survey**

**5.3** Comprehensive review of published research related to Type 2 Diabetes Mellitus, Metformin Hydrochloride, *Syzygium cumini*, herbal–synthetic combination therapy, and direct compression techniques.

##### **5.4 Procurement of Materials**

- Procurement of Metformin Hydrochloride, *Syzygium cumini* powder, and pharmaceutical excipients.
- Authentication and quality assessment of the herbal material.

##### **5.5 Preformulation Studies**

- Evaluation of physical and chemical properties of drug and herbal powder.

- Determination of angle of repose, bulk density, tapped density, Carr's index, Hausner ratio, and moisture content.
- Drug–excipient compatibility studies.

### **5.6 FTIR Compatibility Study**

- Fourier Transform Infrared (FTIR) spectroscopy of Metformin Hydrochloride, *Syzygium cumini* seed powder, and the optimized drug–excipient mixture.

Comparison of characteristic peaks to assess compatibility and detect any possible chemical interactions between the active ingredients and excipients.

### **5.7 Analytical Method Development and Validation**

- Development of a suitable UV spectrophotometric method for estimation of Metformin Hydrochloride and *Syzygium cumini*.
- Validation of the analytical method according to ICH guidelines for accuracy, precision, linearity, robustness, specificity, LOD, and LOQ.

### **5.8 Formulation of Combination Tablets**

- Preparation of combination tablets using the direct compression technique.
- Selection of suitable excipients and optimization of formulation variables.

### **5.9 Optimization Using 3<sup>2</sup> Factorial Design**

- Preparation of four factorial batches by varying selected formulation variables.
- Statistical evaluation to identify the optimized formulation based on desired responses.

### **5.10 Evaluation of Powder Blend (Pre-compression Parameters)**

- |                   |                                |
|-------------------|--------------------------------|
| • Angle of repose | • Carr's compressibility index |
| • Bulk density    | • Hausner ratio                |
| • Tapped density  |                                |

### **5.11 Evaluation of Tablets (Post-compression Parameters)**

- |                    |                              |
|--------------------|------------------------------|
| • Weight variation | • Disintegration time        |
| • Thickness        | • Drug content uniformity    |
| • Hardness         | • In vitro dissolution study |
| • Friability       |                              |

### **5.12 Optimization and Selection of Best Formulation**

- Comparative evaluation of all batches.
- Selection of the optimized formulation based on physicochemical properties and drug release profile.

### **5.13 Stability Studies**

- Accelerated stability testing of the optimized formulation as per ICH guidelines.



- Evaluation of physical appearance, drug content, and dissolution profile during storage.

#### 5.14 Statistical Analysis

- Analysis of experimental data using appropriate statistical tools and factorial design software.
- Interpretation of the effect of independent variables on formulation responses.

#### 5.15 Results and Discussion

- Compilation and interpretation of experimental findings.
- Comparison with previously reported studies and scientific justification of results.

#### 5.16 Conclusion

- Summary of the research findings.
- Assessment of the suitability of the developed combination tablet for the management of Type 2 Diabetes Mellitus. Recommendations for future research and clinical evaluation.

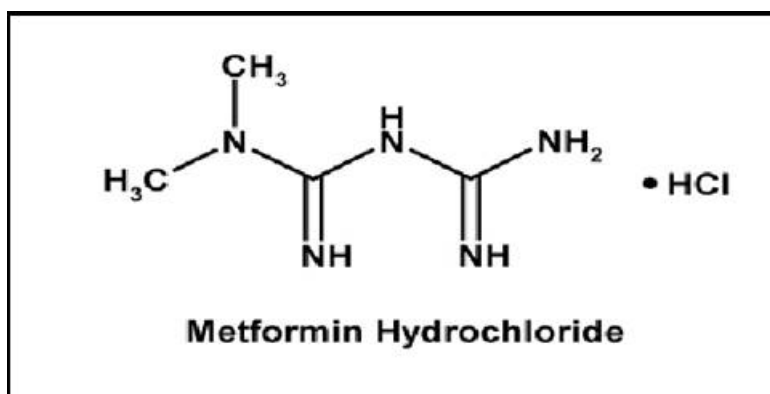
#### 5.17 Compilation and Documentation:

- Preparation of dissertation report
- Statistical data compilation
- Preparation of tables, graphs and figures
- Final thesis submission and presentation

### Drug & Excipients Profile

#### 6.1 Drug Profile:

##### 6.1.1 Metformin Hydrochloride



**Fig 10: Metformin Hydrochloride Chemical Structure**

**Table No 2: Metformin Hydrochloride Drug**

| Parameter                      | Details                                                                                                                                                                |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Drug Name</b>               | Metformin Hydrochloride                                                                                                                                                |
| <b>Chemical Structure</b>      | $  \begin{array}{c}  \text{NH}_2 \\    \\  \text{H}_2\text{N}-\text{C}=\text{NH}-\text{NH}-\text{C}=\text{NH}-\text{N}(\text{CH}_3)_2 \cdot \text{HCl}  \end{array}  $ |
| <b>Chemical Name</b>           | N,N-Dimethylimidodicarbonimidic diamide hydrochloride                                                                                                                  |
| <b>IUPAC Name</b>              | N,N-Dimethylimidodicarbonimidic diamide hydrochloride                                                                                                                  |
| <b>Synonyms</b>                | Metformin HCl, Dimethylbiguanide hydrochloride                                                                                                                         |
| <b>Category</b>                | Oral antihyperglycemic agent (Biguanide)                                                                                                                               |
| <b>Molecular Formula</b>       | $\text{C}_4\text{H}_{11}\text{N}_5 \cdot \text{HCl}$                                                                                                                   |
| <b>Molecular Weight</b>        | 165.63 g/mol                                                                                                                                                           |
| <b>Drug Class</b>              | Biguanide                                                                                                                                                              |
| <b>Physical Appearance</b>     | White to off-white crystalline powder                                                                                                                                  |
| <b>Odour</b>                   | Odourless or almost odourless                                                                                                                                          |
| <b>Taste</b>                   | Bitter                                                                                                                                                                 |
| <b>Solubility</b>              | Freely soluble in water; slightly soluble in ethanol; practically insoluble in acetone, ether, and chloroform                                                          |
| <b>Melting Point</b>           | 223–226°C (with decomposition)                                                                                                                                         |
| <b>pKa</b>                     | 12.4                                                                                                                                                                   |
| <b>Log P</b>                   | –1.43                                                                                                                                                                  |
| <b>BCS Classification</b>      | Class III (High solubility, Low permeability)                                                                                                                          |
| <b>Mechanism of Action</b>     | Activates AMPK, reduces hepatic gluconeogenesis, improves insulin sensitivity, and enhances peripheral glucose uptake.                                                 |
| <b>Pharmacological Action</b>  | Antihyperglycemic                                                                                                                                                      |
| <b>Indications</b>             | Type 2 Diabetes Mellitus, PCOS, Prediabetes                                                                                                                            |
| <b>Route of Administration</b> | Oral                                                                                                                                                                   |
| <b>Bioavailability</b>         | 50–60%                                                                                                                                                                 |
| <b>Protein Binding</b>         | Negligible                                                                                                                                                             |
| <b>Volume of Distribution</b>  | 63–276 L                                                                                                                                                               |
| <b>Metabolism</b>              | Not significantly metabolized                                                                                                                                          |
| <b>Half-life</b>               | 4–8.7 hours                                                                                                                                                            |
| <b>Excretion</b>               | Renal (unchanged)                                                                                                                                                      |
| <b>Therapeutic Dose</b>        | 500–2550 mg/day                                                                                                                                                        |
| <b>Common Adverse Effects</b>  | Nausea, vomiting, diarrhoea, abdominal discomfort, metallic taste                                                                                                      |
| <b>Serious Adverse Effects</b> | Lactic acidosis (rare), Vitamin B12 deficiency                                                                                                                         |
| <b>Storage Conditions</b>      | Store below 30°C in a dry place protected from moisture. [107]                                                                                                         |
| <b>Role in Present Study</b>   | Synthetic antidiabetic drug used in combination with                                                                                                                   |

|                                                      |                                                                                                                                                                                      |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                      | <i>Syzygium cumini</i> seed powder to develop a novel oral tablet for Type 2 Diabetes Mellitus.                                                                                      |
| <b>Therapeutic Class</b>                             | Oral antihyperglycemic agent                                                                                                                                                         |
| <b>Pharmacological Class</b>                         | Biguanide                                                                                                                                                                            |
| <b>ATC Code</b>                                      | A10BA02                                                                                                                                                                              |
| <b>Biopharmaceutical Classification System (BCS)</b> | Class III (High solubility, Low permeability)                                                                                                                                        |
| <b>Partition Coefficient (Log P)</b>                 | Approximately –1.43, indicating a highly hydrophilic nature                                                                                                                          |
| <b>Hygroscopicity</b>                                | Slightly hygroscopic; absorbs moisture under humid conditions                                                                                                                        |
| <b>Stability</b>                                     | Stable under normal storage conditions; should be protected from excessive moisture and heat                                                                                         |
| <b>Incompatibilities</b>                             | May interact with strong oxidizing agents and certain alkaline substances; compatibility studies with excipients are recommended before formulation                                  |
| <b>Storage Conditions</b>                            | Store in a tightly closed container at room temperature (below 30°C), protected from moisture and light                                                                              |
| <b>Official Monograph</b>                            | Included in Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), United States Pharmacopeia (USP), and European Pharmacopoeia (Ph. Eur.)                                           |
| <b>Method of Analysis</b>                            | Quantified using UV spectrophotometry or High-Performance Liquid Chromatography (HPLC) according to validated analytical methods                                                     |
| <b>Identification Test</b>                           | Characteristic FTIR spectrum and UV absorption maxima; conforms to pharmacopoeial identification tests                                                                               |
| <b>Major Metabolic Pathway</b>                       | Not metabolized in the body; eliminated unchanged through renal excretion <sup>[44]</sup>                                                                                            |
| <b>Drug–Drug Interactions</b>                        | Caution with cationic drugs eliminated by renal tubular secretion (e.g., cimetidine), iodinated contrast media, and alcohol due to increased risk of lactic acidosis <sup>(51)</sup> |
| <b>Limitations</b>                                   | Gastrointestinal intolerance, potential vitamin B12 deficiency with prolonged use, contraindicated in severe renal impairment and metabolic acidosis                                 |
| <b>Half-life (t<sub>1/2</sub>)</b>                   | 4–8.7 hours (plasma); approximately 6.2 hours on average                                                                                                                             |

### Profile *Syzygium Cumini*:



**Fig 11: *Syzygium Cumini***

**Table No 3: *Syzygium cumini* Drug Profile**

| Parameter                        | Details                                                                                                                                                     |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Drug Name</b>                 | <i>Syzygium cumini</i> Seed Powder                                                                                                                          |
| <b>Botanical Name</b>            | <i>Syzygium cumini</i> (L.) Skeels                                                                                                                          |
| <b>Common Name</b>               | Jamun, Java Plum, Indian Blackberry, Black Plum                                                                                                             |
| <b>Family</b>                    | Myrtaceae                                                                                                                                                   |
| <b>Kingdom</b>                   | Plantae                                                                                                                                                     |
| <b>Division</b>                  | Magnoliophyta                                                                                                                                               |
| <b>Class</b>                     | Magnoliopsida                                                                                                                                               |
| <b>Order</b>                     | Myrtales                                                                                                                                                    |
| <b>Genus</b>                     | <i>Syzygium</i>                                                                                                                                             |
| <b>Species</b>                   | <i>Syzygium cumini</i> (L.) Skeels                                                                                                                          |
| <b>Biological Source</b>         | Dried and powdered seeds of <i>Syzygium cumini</i> (L.) Skeels                                                                                              |
| <b>Part Used</b>                 | Seeds                                                                                                                                                       |
| <b>Plant Type</b>                | Evergreen tropical tree                                                                                                                                     |
| <b>Geographical Distribution</b> | India, Sri Lanka, Bangladesh, Nepal, Pakistan, Myanmar, Southeast Asia, Australia, and tropical Africa                                                      |
| <b>Vernacular Names</b>          | Hindi – Jamun; Marathi – Jambhul; Sanskrit – Jambu; Tamil – Naval; Telugu – Neredu                                                                          |
| <b>Description of Seed</b>       | Oval or oblong seeds with smooth surface, light brown to greyish-white in colour, hard in texture, possessing a slightly astringent taste. <sup>(108)</sup> |
| <b>Organoleptic Properties</b>   | Colour: Cream to light brown; Odour: Characteristic; Taste: Astringent and slightly bitter; Texture: Fine powder                                            |
| <b>Powder Characteristics</b>    | Free-flowing hygroscopic powder with characteristic herbal odour                                                                                            |
| <b>Major Phytoconstituents</b>   | Jamboline, Jambosine, Gallic acid, Ellagic acid, Quercetin, Kaempferol, Myricetin, Anthocyanins, Flavonoids, Tannins, Phenolic compounds, Terpenoids        |
| <b>Chemical Markers</b>          | Gallic acid, Ellagic acid, Quercetin, Jamboline                                                                                                             |

|                                              |                                                                                                                                                                                                                                               |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Category</b>                              | Herbal antidiabetic agent                                                                                                                                                                                                                     |
| <b>Therapeutic Class</b>                     | Antidiabetic phytopharmaceutical                                                                                                                                                                                                              |
| <b>Mechanism of Action</b>                   | Inhibits $\alpha$ -amylase and $\alpha$ -glucosidase enzymes, enhances insulin secretion, improves insulin sensitivity, reduces oxidative stress, protects pancreatic $\beta$ -cells, and modulates carbohydrate metabolism. <sup>(109)</sup> |
| <b>Pharmacological Activities</b>            | Antidiabetic, Antioxidant, Anti-inflammatory, Hypolipidemic, Antimicrobial, Hepatoprotective, Nephroprotective, Cardioprotective                                                                                                              |
| <b>Primary Active Principle</b>              | Jamboline and polyphenolic compounds responsible for hypoglycemic activity                                                                                                                                                                    |
| <b>Antioxidant Components</b>                | Anthocyanins, Gallic acid, Ellagic acid, Flavonoids, Tannins                                                                                                                                                                                  |
| <b>Mode of Antidiabetic Action</b>           | Delays carbohydrate digestion, reduces postprandial hyperglycemia, scavenges free radicals, and improves glucose utilization.                                                                                                                 |
| <b>Solubility</b>                            | Contains water-soluble and alcohol-soluble polyphenolic constituents; insoluble fibrous material also present                                                                                                                                 |
| <b>Storage Conditions</b>                    | Store in airtight containers in a cool, dry place away from direct sunlight and humidity                                                                                                                                                      |
| <b>Shelf Life</b>                            | Generally 24 months under recommended storage conditions (subject to manufacturer specifications)                                                                                                                                             |
| <b>Identification Methods</b>                | Macroscopic examination, microscopic evaluation, FTIR, HPTLC/HPLC fingerprinting, phytochemical screening                                                                                                                                     |
| <b>Quality Control Parameters</b>            | Foreign matter, loss on drying, total ash, acid-insoluble ash, extractive values, phytochemical profile, microbial load                                                                                                                       |
| <b>Safety Profile</b>                        | Generally regarded as safe at therapeutic doses; excessive intake may potentiate hypoglycemia when used with antidiabetic drugs                                                                                                               |
| <b>Adverse Effects</b>                       | Rare; may include mild gastrointestinal discomfort or excessive lowering of blood glucose in susceptible individuals                                                                                                                          |
| <b>Drug Interactions</b>                     | May exhibit additive hypoglycemic effects when co-administered with oral antidiabetic agents or insulin                                                                                                                                       |
| <b>Analytical Marker for Standardization</b> | Gallic acid or Ellagic acid can be selected as marker compounds for quality evaluation and standardization.                                                                                                                                   |
| <b>Compatibility Study</b>                   | FTIR spectroscopy can be employed to evaluate compatibility between Jamun seed powder, Metformin Hydrochloride, and excipients.                                                                                                               |
| <b>Expected Therapeutic Benefit</b>          | Improved glycemic control through complementary mechanisms, reduction of oxidative stress, enhanced $\beta$ -cell protection, and better patient compliance in Type 2 Diabetes Mellitus. <sup>[110]</sup>                                     |

## 6.2 Excipient Profile:

### 6.2.1 Microcrystalline Cellulose (MCC)

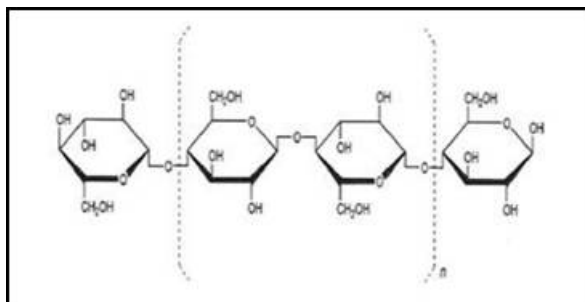
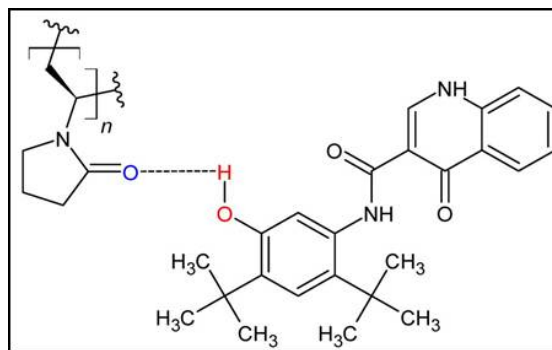


Fig No. 12: Microcrystalline Cellulose Chemical Structure

**Table No. 4: Microcrystalline Cellulose Excipient Profile**

| Parameter             | Details                                                                                                                                                                                                                     |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Excipient Name        | Microcrystalline Cellulose (MCC)                                                                                                                                                                                            |
| Chemical Formula      | $(C_6H_{10}O_5)_n$                                                                                                                                                                                                          |
| Molecular Weight      | Variable (polymeric substance)                                                                                                                                                                                              |
| CAS Number            | 9004-34-6                                                                                                                                                                                                                   |
| Synonyms              | Avicel, Purified Cellulose                                                                                                                                                                                                  |
| Category              | Diluent, Dry Binder                                                                                                                                                                                                         |
| Source                | Purified, partially depolymerized $\alpha$ -cellulose obtained from wood pulp or cotton                                                                                                                                     |
| Appearance            | Fine white or almost white crystalline powder                                                                                                                                                                               |
| Odour                 | Odourless                                                                                                                                                                                                                   |
| Taste                 | Tasteless                                                                                                                                                                                                                   |
| Solubility            | Practically insoluble in water, ethanol, ether, and dilute acids; swells in water                                                                                                                                           |
| pH                    | 5.0–7.5 (aqueous dispersion)                                                                                                                                                                                                |
| Density               | 0.30–0.50 g/cm <sup>3</sup>                                                                                                                                                                                                 |
| Melting Point         | Does not melt; decomposes above 260°C                                                                                                                                                                                       |
| Moisture Content      | Generally less than 7% <sup>[111]</sup>                                                                                                                                                                                     |
| Function in Tablets   | Diluent and dry binder for direct compression                                                                                                                                                                               |
| Advantages            | Excellent compressibility, good flow properties, enhances tablet hardness                                                                                                                                                   |
| Storage Conditions    | Store in a well-closed container in a cool and dry place                                                                                                                                                                    |
| Role in Present Study | Used as a filler and dry binder to improve compressibility, mechanical strength, and uniformity of the Metformin Hydrochloride– <i>Syzygium cumini</i> combination tablets prepared by direct compression. <sup>[112]</sup> |

## POLYVINYLPIRROLIDONE K 30:

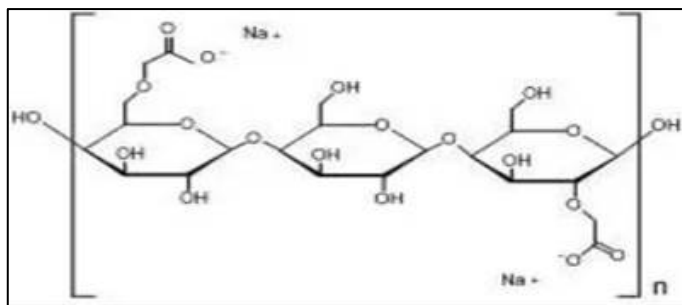


**Fig No. 13: Polyvinylpyrrolidone K30 Chemical Structure**

**Table No. 5: Polyvinylpyrrolidone K30 Excipient Profile**

| Parameter             | Details                                                                                              |
|-----------------------|------------------------------------------------------------------------------------------------------|
| Excipient Name        | Polyvinylpyrrolidone K30                                                                             |
| Synonyms              | Povidone K30, PVP K30                                                                                |
| Chemical Formula      | $(C_6H_9NO)_n$                                                                                       |
| Molecular Weight      | Approximately 40,000 Da                                                                              |
| CAS Number            | 9003-39-8                                                                                            |
| Category              | Binder                                                                                               |
| Appearance            | White to creamy-white hygroscopic powder                                                             |
| Odour                 | Faint or odourless                                                                                   |
| Taste                 | Slightly bitter                                                                                      |
| Solubility            | Freely soluble in water and ethanol                                                                  |
| pH                    | 3.0–7.0 (5% solution)                                                                                |
| Melting Point         | Softens around 150°C                                                                                 |
| Function in Tablet    | Binder to improve tablet cohesion                                                                    |
| Advantages            | Excellent binding property, compatible with most APIs                                                |
| Storage               | Store in airtight containers away from moisture                                                      |
| Incompatibilities     | Strong oxidizing agents and tannins                                                                  |
| Role in Present Study | Enhances binding efficiency and mechanical integrity of direct compression tablets. <sup>[113]</sup> |

## Croscarmellose Sodium

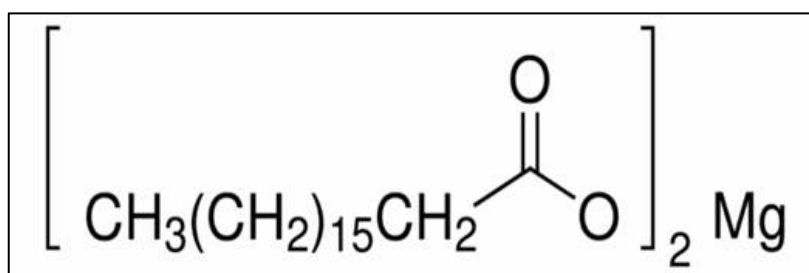


**Fig No. 14: Croscarmellose Sodium Chemical Structure**

**Table No. 6: Croscarmellose Sodium Excipient Profile**

| Parameter                    | Details                                                                             |
|------------------------------|-------------------------------------------------------------------------------------|
| <b>Excipient Name</b>        | Croscarmellose Sodium                                                               |
| <b>Synonyms</b>              | Cross-linked Sodium Carboxymethyl Cellulose                                         |
| <b>Chemical Formula</b>      | Cross-linked polymer of sodium carboxymethyl cellulose                              |
| <b>CAS Number</b>            | 74811-65-7                                                                          |
| <b>Category</b>              | Superdisintegrant                                                                   |
| <b>Appearance</b>            | White or greyish-white fibrous powder                                               |
| <b>Odour</b>                 | Odourless                                                                           |
| <b>Taste</b>                 | Tasteless                                                                           |
| <b>Solubility</b>            | Insoluble in water but swells rapidly                                               |
| <b>pH</b>                    | 5.0–7.0                                                                             |
| <b>Function in Tablet</b>    | Promotes rapid tablet disintegration by swelling                                    |
| <b>Advantages</b>            | Effective at low concentrations, rapid water uptake                                 |
| <b>Storage</b>               | Store in a cool and dry place                                                       |
| <b>Incompatibilities</b>     | Strong acids may reduce performance                                                 |
| <b>Role in Present Study</b> | Facilitates rapid tablet disintegration and improves drug release. <sup>[114]</sup> |

## Magnesium Stearate



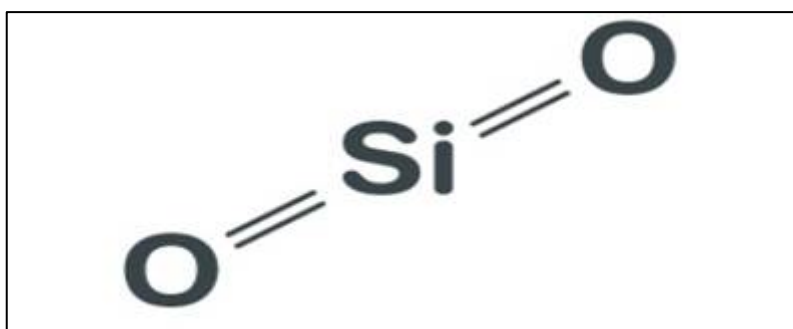
**Fig No. 15: Magnesium Stearate Chemical Structure**

**Table No. 7: Magnesium Stearate Excipient Profile**



| Parameter                    | Details                                                                                                               |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>Excipient Name</b>        | Magnesium Stearate                                                                                                    |
| <b>Synonyms</b>              | Octadecanoic Acid Magnesium Salt                                                                                      |
| <b>Chemical Formula</b>      | $\text{Mg}(\text{C}_{18}\text{H}_{35}\text{O}_2)_2$                                                                   |
| <b>Molecular Weight</b>      | 591.27 g/mol                                                                                                          |
| <b>CAS Number</b>            | 557-04-0                                                                                                              |
| <b>Category</b>              | Lubricant                                                                                                             |
| <b>Appearance</b>            | Fine white powder                                                                                                     |
| <b>Odour</b>                 | Slight characteristic odour                                                                                           |
| <b>Taste</b>                 | Practically tasteless                                                                                                 |
| <b>Solubility</b>            | Insoluble in water and ethanol                                                                                        |
| <b>Melting Point</b>         | Approximately 130–145°C                                                                                               |
| <b>pH</b>                    | Neutral                                                                                                               |
| <b>Function in Tablet</b>    | Reduces friction between tablet and die wall during compression                                                       |
| <b>Advantages</b>            | Improves tablet ejection and prevents sticking                                                                        |
| <b>Storage</b>               | Store in a dry, well-closed container                                                                                 |
| <b>Incompatibilities</b>     | Strong acids and oxidizing agents                                                                                     |
| <b>Role in Present Study</b> | Acts as a lubricant to ensure smooth compression and prevent sticking during tablet manufacturing. <sup>(115)</sup>   |
| <b>Regulatory Status</b>     | Listed in IP, USP, BP, and Ph. Eur.; Generally Recognized as Safe (GRAS) for pharmaceutical use                       |
| <b>Compression Property</b>  | Improves tablet compressibility and facilitates smooth ejection                                                       |
| <b>Flow Property</b>         | Excellent glidant and lubricant characteristics                                                                       |
| <b>Mechanism of Action</b>   | Forms a thin hydrophobic film around powder particles, reducing die-wall friction and preventing sticking and picking |

### 6.2.5 Colloidal Silicon Dioxide:



**Fig No. 16: Colloidal Silicon Dioxide Chemical Structure**

**Table No 8: Colloidal Silicon Dioxide Excipient Profile**

| Parameter                             | Details                                                                                                                                                                                                                                                    |
|---------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Excipient Name</b>                 | Colloidal Silicon Dioxide                                                                                                                                                                                                                                  |
| <b>Synonyms</b>                       | Colloidal Anhydrous Silica, Fumed Silica, Aerosil                                                                                                                                                                                                          |
| <b>Chemical Structure</b>             | Three-dimensional network of silicon and oxygen atoms represented as $(\text{SiO}_2)_n$                                                                                                                                                                    |
| <b>Structural Formula</b>             | $(\text{SiO}_2)_n$                                                                                                                                                                                                                                         |
| <b>Chemical Formula</b>               | $\text{SiO}_2$                                                                                                                                                                                                                                             |
| <b>Molecular Weight</b>               | 60.08 g/mol (monomer unit)                                                                                                                                                                                                                                 |
| <b>CAS Number</b>                     | 7631-86-9                                                                                                                                                                                                                                                  |
| <b>Category</b>                       | Glidant, Adsorbent, Anticaking Agent                                                                                                                                                                                                                       |
| <b>Source</b>                         | Produced by flame hydrolysis of silicon tetrachloride or precipitation methods                                                                                                                                                                             |
| <b>Appearance</b>                     | Very fine, light, white, amorphous powder                                                                                                                                                                                                                  |
| <b>Odour</b>                          | Odourless                                                                                                                                                                                                                                                  |
| <b>Taste</b>                          | Tasteless                                                                                                                                                                                                                                                  |
| <b>Nature</b>                         | Amorphous, non-crystalline silica                                                                                                                                                                                                                          |
| <b>Particle Size</b>                  | Approximately 7–40 nm (primary particles)                                                                                                                                                                                                                  |
| <b>Surface Area</b>                   | 50–400 m <sup>2</sup> /g depending on grade                                                                                                                                                                                                                |
| <b>Solubility</b>                     | Practically insoluble in water, ethanol, and organic solvents                                                                                                                                                                                              |
| <b>pH (4% dispersion)</b>             | 3.5–5.5                                                                                                                                                                                                                                                    |
| <b>Density</b>                        | Approximately 2.2 g/cm <sup>3</sup> (true density)                                                                                                                                                                                                         |
| <b>Melting Point</b>                  | Approximately 1,710°C                                                                                                                                                                                                                                      |
| <b>Boiling Point</b>                  | Approximately 2,230°C                                                                                                                                                                                                                                      |
| <b>Function in Tablet Formulation</b> | Improves powder flow, reduces interparticle friction, acts as a glidant and moisture adsorbent                                                                                                                                                             |
| <b>Advantages</b>                     | Excellent flow enhancer, improves blend uniformity, effective at low concentrations (0.1–1%)                                                                                                                                                               |
| <b>Incompatibilities</b>              | Strong alkalis and hydrofluoric acid                                                                                                                                                                                                                       |
| <b>Storage Conditions</b>             | Store in tightly closed containers protected from moisture                                                                                                                                                                                                 |
| <b>Stability</b>                      | Chemically stable under normal conditions                                                                                                                                                                                                                  |
| <b>Pharmacopoeial Status</b>          | Official in IP, USP, BP, and Ph. Eur.                                                                                                                                                                                                                      |
| <b>Typical Concentration</b>          | 0.1–1.0% w/w in tablet formulations                                                                                                                                                                                                                        |
| <b>Role in Present Study</b>          | Used as a glidant to improve the flowability and uniform mixing of Metformin Hydrochloride, <i>Syzygium cumini</i> seed powder, and excipients during direct compression, resulting in uniform die filling and consistent tablet quality. <sup>[116]</sup> |

## Materials And Instruments

### 7.1 MATERIALS AND INSTRUMENTS:

### 7.2 Materials:

All materials used in the present investigation were procured from authenticated manufacturers and reliable suppliers to ensure the quality and consistency of the formulation. Pharmaceutical-grade active ingredients, excipients, and analytical-grade reagents were utilized throughout the study. Unless otherwise specified, all materials were used as received without any further purification or modification.

**Table No. 9: List of Material and Suppliers**

| Sr. No. | Material                                          | Category                               | Grade/Purity                    | Manufacturer / Supplier                               |
|---------|---------------------------------------------------|----------------------------------------|---------------------------------|-------------------------------------------------------|
| 1       | <b>Metformin Hydrochloride</b>                    | Active Pharmaceutical Ingredient (API) | Pharmaceutical Grade            | Modern Industries, Sinnar, Nashik, Maharashtra, India |
| 2       | <b><i>Syzygium cumini</i> (Jamun) Seed Powder</b> | Herbal Active Ingredient               | Analytical/Pharmaceutical Grade | Local vendor Nashik, Maharashtra                      |
| 3       | <b>Microcrystalline Cellulose (MCC PH 102)</b>    | Diluent                                | Pharmaceutical Grade            | Modern Industries, Sinnar, Nashik, Maharashtra, India |
| 4       | <b>Polyvinylpyrrolidone K30 (PVP K30)</b>         | Binder                                 | Pharmaceutical Grade            | Modern Industries, Sinnar, Nashik, Maharashtra, India |
| 5       | <b>Croscarmellose Sodium</b>                      | Superdisintegrant                      | Pharmaceutical Grade            | Modern Industries, Sinnar, Nashik, Maharashtra, India |
| 6       | <b>Colloidal Silicon Dioxide</b>                  | Glidant                                | Pharmaceutical Grade            | Modern Industries, Sinnar, Nashik, Maharashtra, India |
| 7       | <b>Magnesium Stearate</b>                         | Lubricant                              | Pharmaceutical Grade            | Modern Industries, Sinnar, Nashik, Maharashtra, India |
| 8       | <b>Distilled Water</b>                            | Solvent                                | Analytical Grade                | -                                                     |
| 9       | <b>Methanol</b>                                   | Solvent                                | HPLC/AR Grade                   | Modern Industries, Sinnar, Nashik, Maharashtra, India |

### 7.3 Instruments Used:

Various laboratory instruments and analytical equipment were employed during the present investigation to facilitate formulation development, characterization, and evaluation of the combination tablet. The instruments were used for preformulation studies, tablet manufacturing, physicochemical evaluation, analytical estimation, and stability testing to ensure accurate, reliable, and reproducible experimental results.

**Table No. 10: List of Equipment and Instruments**

| Sr. No. | Instrument | Model | Manufacturer | Purpose |
|---------|------------|-------|--------------|---------|
|---------|------------|-------|--------------|---------|

|    |                                          |                     |                                        |                                                                  |
|----|------------------------------------------|---------------------|----------------------------------------|------------------------------------------------------------------|
| 1  | Digital Analytical Balance               | CG203               | Citizen                                | Accurate weighing of drugs and excipients                        |
| 2  | UV–Visible Spectrophotometer             | LMSP-UV100B         | Labman                                 | Estimation of Metformin Hydrochloride and <i>Syzygium cumini</i> |
| 3  | FTIR Spectrophotometer                   | IRAffinity-1S       | Shimadzu                               | Drug identification and drug–excipient compatibility studies     |
| 4  | Single Punch Tablet Compression Machine  | CMD-3-16 Station    | Cadmach Machinery Co. Pvt. Ltd., India | Compression of tablets by direct compression                     |
| 5  | Tablet Hardness Tester                   | EH-01P              | Electrolab (India) Pvt. Ltd., India    | Determination of tablet hardness                                 |
| 6  | Digital Vernier Caliper                  | CD-6" CSX           | Mitutoyo Corporation, Japan            | Measurement of tablet thickness and diameter                     |
| 7  | Roche Friabilator                        | EF-2                | Electrolab (India) Pvt. Ltd., India    | Determination of tablet friability                               |
| 8  | USP Disintegration Test Apparatus        | DS 8000             | Labindia                               | Measurement of tablet disintegration time                        |
| 9  | USP Dissolution Test Apparatus (Type II) | DS 8000             | Labindia                               | In vitro dissolution studies                                     |
| 10 | Bulk Density Apparatus                   | ETD-1020            | Electrolab (India) Pvt. Ltd., India    | Determination of bulk density                                    |
| 11 | Tapped Density Tester                    | ETD-1020            | Electrolab (India) Pvt. Ltd., India    | Determination of tapped density                                  |
| 12 | Fixed Funnel Apparatus                   | Laboratory Assembly | Borosil Local Laboratory Setup         | Determination of angle of repose                                 |
| 13 | Mechanical Sieve Shaker                  | RX-29               | W.S. Tyler, USA                        | Particle size analysis                                           |
| 14 | Hot Air Oven                             | BTTI-10             | Labtech / Thermolab                    | Drying of samples and glassware                                  |
| 15 | Magnetic Stirrer with Hot Plate          | REMI 2MLH           | Remi Elektrotec                        | Preparation of standard and                                      |
| 16 | Mortar and Pestle                        | Porcelain           | Borosil, India                         | Mixing and trituration of                                        |
| 17 | Thermometer                              | HTC-1               | HTC Instrument                         | Monitoring laboratory                                            |

#### 7.4 Software Used:

Various software applications were employed during the present investigation to facilitate formulation development, analytical evaluation, data processing, and statistical optimization. These software tools enabled accurate data analysis, interpretation of instrumental results, and optimization of formulation variables, thereby ensuring reliability, reproducibility, and scientific validity of the research findings.

Table No. 11: List of Software

| Software                    | Application                                  |
|-----------------------------|----------------------------------------------|
| Microsoft Excel             | Data tabulation and statistical calculations |
| Design-Expert <sup>13</sup> | Factorial design and optimization            |
| UV Software                 | UV spectral analysis                         |
| FTIR Software               | Interpretation of FTIR spectra               |

## 7.5 Chemicals And Reagents:

Various analytical-grade chemicals and reagents were used throughout the study for the preparation of standard and sample solutions, buffer solutions, dissolution media, and instrumental analysis. All chemicals and reagents were procured from reliable sources and used as received without further purification to ensure the accuracy and reproducibility of the experimental results.

All chemicals and reagents used in the study were of analytical or pharmaceutical grade and were obtained from reliable and approved suppliers. They were used for sample preparation, buffer preparation, dissolution studies, and analytical evaluation of the formulation. All reagents were used as received without further purification to ensure accuracy, reproducibility, and reliability of the results.

Table No. 12: List of Chemical/Reagent

| Chemical/Reagent               | Purpose                                                |
|--------------------------------|--------------------------------------------------------|
| Methanol                       | Preparation of standard and sample solutions           |
| Distilled Water                | Solvent                                                |
| Potassium Bromide (KBr)        | FTIR pellet preparation (if KBr pellet method is used) |
| Phosphate Buffer pH 6.8        | Dissolution medium                                     |
| Hydrochloric Acid              | pH adjustment or dissolution medium preparation        |
| Sodium Hydroxide               | pH adjustment                                          |
| Potassium Dihydrogen Phosphate | Buffer preparation                                     |

## Experimental Work

### 8.1 EXPERIMENTAL WORK:

#### 8.2 Experimental Work

Formulation is the process of combining one or more active pharmaceutical ingredients (APIs) with suitable pharmaceutical excipients to produce a safe, effective, stable, and patient-friendly dosage form. The selection of appropriate formulation variables and manufacturing techniques plays a crucial role in determining the quality, therapeutic efficacy, and stability of the final pharmaceutical product. Combination drug therapy has gained significant importance in the

management of chronic diseases such as Type 2 Diabetes Mellitus, as it provides improved therapeutic outcomes by targeting multiple pathological pathways simultaneously. In recent years, the integration of herbal medicines with conventional synthetic drugs has emerged as a promising approach to enhance efficacy while minimizing adverse effects.

Metformin Hydrochloride is the first-line oral antihyperglycemic agent widely used in the treatment of Type 2 Diabetes Mellitus. It primarily acts by reducing hepatic glucose production, improving peripheral insulin sensitivity, and enhancing glucose utilization. However, prolonged therapy may be associated with certain limitations, encouraging the exploration of complementary herbal therapies.

*Syzygium cumini* (Jamun) seed powder has been extensively investigated for its antidiabetic potential due to the presence of bioactive phytoconstituents such as jamboline, gallic acid, ellagic acid, flavonoids, tannins, and anthocyanins. These phytochemicals possess hypoglycemic, antioxidant, anti-inflammatory, and  $\beta$ -cell protective activities that may complement the pharmacological action of Metformin Hydrochloride.

The present investigation was undertaken to formulate and evaluate a combination tablet containing Metformin Hydrochloride and *Syzygium cumini* seed powder using the direct compression technique. The study involved preformulation characterization, drug–excipient compatibility assessment, analytical method development and validation, formulation optimization using a  $2^3$  factorial design, evaluation of pre-compression and post-compression parameters, and stability assessment of the optimized formulation.

### **8.3 Need for Combination Tablet Formulation:**

- To combine the antidiabetic effects of Metformin Hydrochloride and *Syzygium cumini* seed powder in a single dosage form.
- To improve glycemic control through multiple mechanisms of action.  
To provide antioxidant protection against diabetes-associated oxidative stress.
- To enhance patient compliance by reducing pill burden.
- To ensure accurate dosing and uniform drug administration.
- To improve stability and ease of handling compared to conventional herbal preparations.
- To provide a convenient and cost-effective dosage form.
- To explore the therapeutic potential of herbal–synthetic combination therapy for Type 2 Diabetes Mellitus.

### **8.4 The formulation and evaluation of combination tablets were carried out in the following manner:**

- Procurement of Metformin Hydrochloride, *Syzygium cumini* seed powder, and excipients.
- Authentication and quality assessment of herbal material.
- Selection of suitable pharmaceutical excipients.
- Preformulation studies.
- Drug–excipient compatibility study by FTIR spectroscopy.
- Analytical method development and validation.
- Formulation of tablets by direct compression.
- Optimization using  $2^3$  factorial design.
- Evaluation of powder blend (pre-compression studies).

- Evaluation of compressed tablets (post-compression studies).
- Statistical analysis using ANOVA.
- Selection of optimized formulation.
- Stability studies as per ICH guidelines.
- Results, discussion, and conclusion.

## 8.5 Analytical Method Development by UV-Visible Spectrophotometry

8.4.1 Determination of  $\lambda_{\text{max}}$  of Metformin Hydrochloride in Phosphate Buffer pH 6.8 The UV spectrum of Metformin Hydrochloride was obtained using a UV-Visible double-beam spectrophotometer (Shimadzu UV-1800) equipped with matched quartz cells of 1 cm path length. Accurately weighed 10 mg of Metformin Hydrochloride was transferred into a 100 mL volumetric flask and dissolved in a sufficient quantity of phosphate buffer pH 6.8. The volume was made up to 100 mL with the same buffer to obtain a stock solution of 100  $\mu\text{g/mL}$ .(117)

From the above stock solution, 1 mL was withdrawn and diluted to 10 mL with phosphate buffer pH 6.8 to obtain a concentration of 10  $\mu\text{g/mL}$ . The resulting solution was scanned in the wavelength range of 200–400 nm against phosphate buffer pH 6.8 as blank. The spectrum was recorded and the wavelength corresponding to maximum absorbance ( $\lambda_{\text{max}}$ ) was determined.

**Observation:** Metformin Hydrochloride showed maximum absorbance at 233 nm.

### 8.4.1.1 Preparation of Calibration Curve of Metformin Hydrochloride

Aliquots of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 mL were withdrawn from the stock solution (100  $\mu\text{g/mL}$ ) and transferred into a series of 10 mL volumetric flasks. The volume was adjusted with phosphate buffer pH 6.8 to obtain concentrations of 2, 4, 6, 8, 10 and 12  $\mu\text{g/mL}$  respectively.

The absorbance of each solution was measured at 233 nm against phosphate buffer pH 6.8 as blank using a UV-Visible spectrophotometer. Calibration Curve Data of Metformin Hydrochloride in Phosphate Buffer pH 6.8 ( $\lambda_{\text{max}} = 233 \text{ nm}$ )

8.4.2 Determination of  $\lambda_{\text{max}}$  of Syzygium cumini Seed Powder in Phosphate Buffer pH 6.8 The UV spectrum of Syzygium cumini seed powder was obtained using a UV-Visible double beam spectrophotometer (Shimadzu UV-1800) equipped with matched quartz cells of 1 cm path length.(118)

Accurately weighed 10 mg of Syzygium cumini seed powder was transferred into a 100 mL volumetric flask and dissolved in a sufficient quantity of phosphate buffer pH 6.8. The volume was then made up to 100 mL with the same buffer to obtain a stock solution of 100  $\mu\text{g/mL}$ . From the prepared stock solution, 1 mL was withdrawn and diluted to 10 mL using phosphate buffer pH 6.8 to obtain a concentration of 10  $\mu\text{g/mL}$ . The resulting solution was scanned in the wavelength range of 200–400 nm against phosphate buffer pH 6.8 as blank. The absorption spectrum was recorded and the wavelength corresponding to maximum absorbance ( $\lambda_{\text{max}}$ ) was determined.

### 8.4.2.1 Preparation of Calibration Curve of Syzygium cumini Seed Powder Extract

Appropriate dilutions in the concentration range of 2–12  $\mu\text{g/mL}$  were prepared from the stock solution. The absorbance was recorded at 340 nm against phosphate buffer pH 6.8 as blank.

Calibration Curve Data of Syzygium cumini Seed Powder in Phosphate Buffer pH 6.8

( $\lambda_{\text{max}} = 340 \text{ nm}$ )

### 8.5 Drug–Excipient Compatibility Study by FTIR Spectroscopy:

Drug–excipient compatibility studies were performed using an IRAffinity-1S FTIR Spectrophotometer (Shimadzu). The study was conducted to investigate possible interactions between Metformin Hydrochloride, Syzygium cumini seed powder, and the selected excipients used in the formulation.

FTIR spectra of pure Metformin Hydrochloride, pure Syzygium cumini seed powder, and the optimized formulation (F9) were recorded over the spectral range of  $4000\text{--}400 \text{ cm}^{-1}$  at a resolution of  $4 \text{ cm}^{-1}$ . The obtained spectra were carefully analyzed for any significant shifts, disappearance, or appearance of characteristic peaks.

The characteristic absorption bands of the pure drug and herbal powder were compared with those of the optimized formulation to evaluate compatibility. The retention of major functional group peaks without significant alteration indicated the absence of chemical interaction between the formulation components.

#### 8.5.1 Instrumental Conditions for FTIR Analysis:

Fourier Transform Infrared (FTIR) spectroscopy was performed to evaluate the compatibility between Metformin Hydrochloride, Syzygium cumini seed powder, and the selected excipients used in the formulation. The analysis was carried out using a Shimadzu IRAffinity-1S FTIR spectrophotometer under standardized instrumental conditions to obtain accurate and reproducible spectra. The instrumental parameters employed during the FTIR analysis are presented in the following table.

**Table No. 13: Instrumental Parameters for FTIR Compatibility Analysis**

| Parameter       | Condition                            |
|-----------------|--------------------------------------|
| Instrument      | IRAffinity-1S FTIR Spectrophotometer |
| Manufacturer    | Shimadzu Corporation, Japan          |
| Scan Range      | $4000\text{--}400 \text{ cm}^{-1}$   |
| Resolution      | $4 \text{ cm}^{-1}$                  |
| Number of Scans | 32                                   |
| Sampling Method | ATR/KBr Pellet Method                |
| Software        | LabSolutions IR Software             |

### 8.6 Preformulation Studies:

#### 8.6.1 Introduction:

Preformulation studies are the first step in the development of a pharmaceutical dosage form. They involve the investigation of the physicochemical and mechanical properties of the drug substance and excipients before formulation. These studies provide valuable information regarding the identity, purity, compatibility, stability, and flow characteristics of the materials, which ultimately influence the quality and performance of the final dosage form.



In the present investigation, preformulation studies were carried out on Metformin Hydrochloride, *Syzygium cumini* (Jamun) seed powder, and the selected excipients to evaluate their suitability for the preparation of combination tablets by direct compression. The studies included organoleptic evaluation, solubility analysis, FTIR spectroscopy for compatibility assessment, and micromeritic evaluation of the powder blend.

#### 8.6.1.1 Organoleptic Evaluation

##### I. Objective

To evaluate the physical characteristics of Metformin Hydrochloride and *Syzygium cumini* seed powder based on colour, odour, appearance, taste, and texture.

##### II. Procedure

The drug and herbal powder were visually examined under normal daylight conditions. Their colour, odour, appearance, taste, and texture were observed and compared with reported standard characteristics.

**Table No. 14: Organoleptic Evaluation**

| Parameter  | Metformin Hydrochloride  | <i>Syzygium cumini</i> Seed Powder |
|------------|--------------------------|------------------------------------|
| Colour     | White crystalline powder | Brown powder                       |
| Appearance | Fine crystalline powder  | Fine free-flowing powder           |
| Odour      | Odourless                | Characteristic odour               |
| Taste      | Bitter                   | Astringent and slightly bitter     |
| Texture    | Smooth                   | Fine powder                        |

#### 8.6.1.1 Melting Point Determination:

- Procedure:**

A capillary tube containing a little amount of metformin HCl was put inside a digital melting point device. The melting point of the medication was determined by recording the temperature at which it totally melted.

#### 8.6.1.2 Solubility Study

- Procedure:**

An excess amount of drug was added separately to distilled water, methanol, ethanol, and phosphate buffer pH 6.8. The mixtures were kept for 24 hours at room temperature and observed for solubility.

#### 8.6.1.3 Moisture Content Determination

- Procedure:**

About 1 g of sample was accurately weighed and dried in a hot air oven at 105°C until constant weight was obtained. The percentage moisture content was calculated from the loss in weight.

- *Calculation:*

$$\text{Moisture Content (\%)} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

## **8.6.2 Determination of Micromeritic Properties and Flow Characteristics of Powder Blend:**

### **8.6.2.1 Bulk Density:**

- **Definition:**

Bulk density is defined as the ratio of mass of powder to its bulk volume before tapping. It indicates packing ability and flow properties of powder.

- **Formula:**

$$\text{Bulk Density} = \frac{\text{Mass of Powder}}{\text{Bulk Volume}}$$

- **Procedure:**

Accurately weighed quantity of powder blend was transferred into a clean and dry graduated measuring cylinder without disturbing the powder bed. The initial volume occupied by the powder was noted as bulk volume. Bulk density was calculated by dividing the mass of powder by bulk volume.

#### **Interpretation**

- Low bulk density indicates loosely packed particles.
- High bulk density indicates densely packed particles.

### **8.6.2.2 Tapped Density:**

- **Definition:**

Tapped density is the ratio of mass of powder to tapped volume obtained after mechanically tapping the measuring cylinder containing powder.

- **Formula:**

$$\text{Tapped Density} = \frac{\text{Mass of Powder}}{\text{Tapped Volume}}$$

• **Procedure:**

A known quantity of powder blend was introduced into a graduated cylinder. The cylinder was tapped mechanically using tapped density apparatus until constant volume was obtained. The final tapped volume was noted and tapped density was calculated.

**Interpretation**

- **Higher tapped density indicates better packing ability.**
- **Used to determine compressibility characteristics of powder.**

**8.6.2.3 Carr's Index:**

• **Definition:**

Carr's Index or Compressibility Index indicates compressibility and flowability of powder blend.

• **Formula: Missing**

• **Procedure:**

Bulk density and tapped density of powder blend were determined experimentally. The obtained values were substituted into Carr's Index formula to calculate compressibility index.

**Interpretation of Carr's Index:**

**Table No. 15: Standard Interpretation of Carr's Index**

| Carr's Index (%) | Flow Property |
|------------------|---------------|
| 5–15             | Excellent     |
| 16–20            | Good          |
| 21–25            | Fair          |
| >25              | Poor          |

**8.6.2.1 Hausner Ratio**

• **Definition:**

Hausner ratio is the ratio of tapped density to bulk density and indicates flow characteristics of powder blend.

**Formula:**

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

• **Procedure:**

Bulk density and tapped density values were determined experimentally. Hausner ratio was calculated using the formula by dividing tapped density by bulk density.

**Table No. 16: Standard Interpretation of Hausner Ratio**

| Hausner Ratio | Flow Property |
|---------------|---------------|
| 1.00–1.11     | Excellent     |
| 1.12–1.18     | Good          |
| 1.19–1.25     | Fair          |
| >1.25         | Poor          |

#### 8.6.2.5 Angle of Repose

• **Definition:**

Angle of repose is the maximum angle formed between the surface of powder pile and horizontal plane. It indicates flowability of powder.

• **Formula:**

$$h \tan \theta =$$

$$r$$

**Where:**

$h$  = Height of powder pile

$r$  = Radius of powder pile

• **Procedure:**

The powder blend was allowed to flow through a funnel fixed at a certain height onto a flat horizontal surface. The powder formed a conical heap. The height and radius of the powder cone were measured. The angle of repose was calculated using the formula.

• **Interpretation of Angle of Repose:**

**Table No. 17: Standard Interpretation of Angle of Repose**

| Angle of Repose ( $\theta$ ) | Flow Property |
|------------------------------|---------------|
| <25°                         | Excellent     |
| 25–30°                       | Good          |
| 30–40°                       | Passable      |
| >40°                         | Poor          |

### 8.6.3 Analysis of Angle of Repose Results:

Preformulation parameters such as bulk density, tapped density, Carr's Index, Hausner ratio, and angle of repose are important for evaluating flow properties and compressibility of powder blends before tablet compression. These studies help in selecting suitable excipients and manufacturing methods for successful tablet formulation.

## 8.7 Post compression Parameters:

### 8.7.1 Weight Variation Test

#### • Principle:

The weight variation test is performed to ensure uniformity of weight among tablets of a batch. It indicates uniform die filling during compression.

#### • Procedure:

Twenty tablets were selected randomly and individually weighed using a digital weighing balance. The average weight of tablets was calculated. Individual tablet weights were compared with the average weight and percentage deviation was determined.

#### • Formula:

% Weight Variation =

$$\frac{\text{Individual Weight} - \text{Average Weight}}{\text{Average Weight}} \times 100$$

### 8.7.2 Hardness Test

#### • Principle:

Hardness test determines the mechanical strength of tablets and their ability to withstand handling, packaging, and transportation.

#### • Procedure:

The hardness of tablets was measured using Monsanto hardness tester or Pfizer hardness tester. Tablets were placed between the anvils of the tester and force was applied until the tablet broke. Hardness was expressed in kg/cm<sup>2</sup>.

### 8.7.3 Friability Test

#### • Principle:

Friability test determines the resistance of tablets to abrasion and mechanical shock during handling.

#### • Procedure:

A preweighed sample of tablets was placed in Roche friabilator and rotated at 25 rpm for 4 minutes (100 revolutions). Tablets were removed, dedusted, and reweighed.

#### • Formula

$$\% \text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where:

$w_1$  = Initial weight of tablets

$w_2$  = Final weight of tablets

*Acceptance Criteria:*

Friability should generally be less than 1%.

#### 8.7.1 Thickness Test:

- **Principle:**

Thickness test ensures uniform tablet size and appearance.

- *Procedure:*

The thickness of tablets was measured using Vernier caliper or screw gauge. Randomly selected tablets were tested and average thickness was calculated.

#### 8.7.2 Disintegration Time:

- **Principle:**

Disintegration test determines the time required for tablets to break into smaller particles under specified conditions.

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- *Procedure:*

The test was performed using disintegration test apparatus containing distilled water maintained at  $37 \pm 2^\circ\text{C}$ . One tablet was placed in each tube of the basket rack assembly and apparatus was operated. The time required for complete disintegration of tablets was recorded.

- *Acceptance Criteria:*

Uncoated tablets should generally disintegrate within 15 minutes unless otherwise specified.

#### 8.7.3 Dissolution Study:

- **Principle:**

Dissolution study determines the rate and extent of drug release from tablets.

*Procedure:*

The dissolution study was carried out using USP dissolution apparatus containing suitable dissolution medium maintained at  $37 \pm 0.5^\circ\text{C}$ . Tablets were placed in the dissolution medium and apparatus was operated at specified rotation speed. Samples were withdrawn at predetermined time intervals and analyzed using UV-visible spectrophotometer. The cumulative percentage drug release was calculated and dissolution profile was prepared.

### **8.8 In-vitro Dissolution Study**

The in-vitro dissolution study of the formulated Metformin Hydrochloride and *Syzygium cumini* combination tablets was carried out using USP Dissolution Apparatus Type II (Paddle Method).

The dissolution medium consisted of 900 mL of phosphate buffer pH 6.8 maintained at  $37 \pm 0.5^\circ\text{C}$ . The paddle speed was adjusted to 50 rpm. One tablet from each formulation batch (F1–F9) was placed individually into the dissolution vessel.

At predetermined time intervals of 5, 10, 15, 30, and 45 minutes, 5 mL samples were withdrawn and replaced with an equal volume of fresh dissolution medium maintained at the same temperature to maintain sink conditions. The withdrawn samples were filtered through Whatman filter paper.

The filtered samples were suitably diluted and analyzed using a UV-Visible spectrophotometer at the previously determined  $\lambda_{\text{max}}$  values of 233 nm for Metformin Hydrochloride and 340 nm for *Syzygium cumini* extract. The cumulative percentage drug release was calculated using the corresponding calibration curves.

### **8.9 Procedure For Tablet Compression :**

- **Step 1: Weighing**

All ingredients required for the formulation were accurately weighed using a calibrated analytical balance to ensure precise composition and dose uniformity. The required quantities of each ingredient for one tablet were measured individually according to the formulation composition. Care was taken to avoid weighing errors and contamination during the process. The following ingredients were weighed accurately:

1. Metformin Hydrochloride – 250 mg
2. *Syzygium cumini* (Jamun) Seed Powder – 250 mg
3. Microcrystalline Cellulose (MCC PH102) – 50 mg
4. PVP K30 – 30 mg
5. Croscarmellose Sodium – 15 mg
6. Colloidal Silicon Dioxide – 5 mg
7. Magnesium Stearate – 10 mg

The accurately weighed ingredients were transferred into clean, dry, and labelled.



**Fig 17: Ingredients Taken for Formulation of Tablets**

- **Step 2: Sieving (Screening):**

Metformin Hydrochloride, *Syzygium cumini* seed powder, Microcrystalline Cellulose (MCC), PVP K30, and Croscarmellose Sodium were individually passed through a #60 mesh sieve to remove lumps and oversized particles and to obtain a uniform particle size distribution. Sieving improved the flow properties of the powder blend, ensured better mixing of the ingredients, and promoted uniform die filling during tablet compression.

- **Step 3: Initial Blending:**

The accurately weighed Metformin Hydrochloride (250 mg) and *Syzygium cumini* seed powder (250 mg) were transferred into a clean mortar or suitable mixing vessel and blended thoroughly for approximately 10 minutes. This initial blending ensured uniform distribution of both active ingredients throughout the powder mixture and minimized the possibility of segregation before the addition of excipients.



- *Step 4: Addition of Diluent and Super disintegrant:*

After achieving a homogeneous mixture of the active ingredients, Microcrystalline Cellulose (50 mg) and Croscarmellose Sodium (15 mg) were added to the blend. The powder mixture was blended continuously for 10 minutes to obtain uniform distribution of the diluent and super disintegrant.

Microcrystalline Cellulose served as a diluent and compression aid, improving tablet compactibility, while Croscarmellose Sodium acted as a super disintegrant to facilitate rapid tablet disintegration upon contact with the dissolution medium.

- *Step 5: Addition of Binder:*

Following the addition of the diluent and super disintegrant, PVP K30 (30 mg) was incorporated into the powder blend. The entire mixture was blended gently for approximately 5 minutes until a homogeneous powder blend was obtained.

PVP K30 acted as a binder, improving interparticle adhesion and enhancing the mechanical strength of the tablets without adversely affecting drug release.

- *Step 6: Glidant Addition:*

Colloidal Silicon Dioxide (5 mg) was then added to the powder blend and mixed uniformly for approximately 3 minutes. The glidant improved the flowability of the powder blend by reducing interparticle friction, thereby ensuring smooth movement of the powder during compression and promoting uniform die filling.

- *Step 7: Lubrication:*

Finally, Magnesium Stearate (10 mg) was added to the powder blend and mixed gently for 2–3 minutes.

Magnesium Stearate acted as a lubricant by reducing friction between the powder blend and the punches and die wall during compression. The lubricant was added at the final stage and mixed for a short duration to avoid over-lubrication, which could negatively affect tablet hardness and drug dissolution.

- *Step 8: Compression:*

Compress the lubricated blend using a rotary tablet compression machine fitted with suitable punches to produce tablets of 610 mg average weight.

The lubricated powder blend was evaluated for satisfactory flow properties and then compressed using a rotary tablet compression machine fitted with suitable punches. Compression parameters were adjusted to obtain tablets with an average weight of 610 mg while maintaining acceptable hardness, thickness, friability, and weight uniformity. The compressed tablets were collected carefully and stored in clean, airtight containers until further evaluation for post-compression parameters, drug content, dissolution studies, and stability studies.



**Fig 18: Tablet Punching Machine**

## **8.10 Quality by Design :**

### **8.10.1 Defining the Quality Target Product Profile (QTPP):**

The Quality Target Product Profile (QTPP) is a prospective summary of quality characteristics of a pharmaceutical product that ensures safety, efficacy, and quality throughout its shelf life. The QTPP serves as the foundation for formulation development and optimization using the Quality by Design (QbD) approach.<sup>[39]</sup>

#### **8.10.1.1 QTPP for Metformin Hydrochloride and *Syzygium cumini* Combination Tablets:**

**Dosage Form:** Immediate Release Tablet

- *Route of Administration:* **Oral**
- **Dosage Strength:** Metformin Hydrochloride 250 mg + *Syzygium cumini* Powder 250 mg
- **Therapeutic Indication:** Management of Type 2 Diabetes Mellitus
- **Tablet Weight:** 610 mg

- **Drug Release:**  $\geq 85\%$  within 60 minutes
- **Disintegration Time:** Less than 5 minutes
- **Hardness:** 3–5 kg/cm<sup>2</sup>
- **Friability:** Less than 1%
- **Drug Content:** 95–105%
- **Weight Variation:** Within IP limits
- **Stability:** Stable under ICH accelerated stability conditions
- **Appearance:** Uniform, smooth, and defect-free tablets
- **Patient Compliance:** Improved through fixed-dose combination therapy
- **Packaging:** Moisture-resistant container/blister pack

### 8.10.2 Identification of Critical Quality Attributes (CQAs):

Critical Quality Attributes (CQAs) are the physical, chemical, biological, and microbiological properties that should be maintained within predefined limits to ensure the desired product quality.<sup>[40]</sup>

#### 8.10.2.1 CQAs of Metformin Hydrochloride and *Syzygium cumini* Combination Tablets:

**Table No. 18: Quality Target Specifications for the Critical Quality Attributes (CQAs)**

| CQA                        | Target Specification        | Justification                |
|----------------------------|-----------------------------|------------------------------|
| <b>Drug Content</b>        | 95–105%                     | Ensures dose uniformity      |
| <b>Drug Release</b>        | $\geq 85\%$ within 60 min   | Ensures therapeutic efficacy |
| <b>Hardness</b>            | 3–5 kg/cm <sup>2</sup>      | Adequate mechanical strength |
| <b>Friability</b>          | <1%                         | Prevents tablet breakage     |
| <b>Weight Variation</b>    | Within IP limits            | Ensures uniformity           |
| <b>Thickness</b>           | Uniform                     | Consistent tablet dimensions |
| <b>Disintegration Time</b> | <5 min                      | Rapid drug release           |
| <b>Stability</b>           | No significant change       | Maintains product quality    |
| <b>Flow Property</b>       | Good flowability            | Ensures uniform die filling  |
| <b>Content Uniformity</b>  | Within pharmacopeial limits | Uniform drug distribution    |

### 8.10.3 Risk Assessment Tools:

Risk assessment is a systematic process used to identify and evaluate factors that may influence the Critical Quality Attributes (CQAs) of the formulation. It assists in the identification of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs).<sup>(41)</sup>

Common risk assessment tools include:

- Ishikawa (Fishbone) Diagram
- Failure Mode and Effects Analysis (FMEA)
- Risk Ranking and Filtering

### 8.10.3.1 Ishikawa (Fishbone) Diagram

The Ishikawa Diagram was employed to identify potential factors affecting the quality of Metformin Hydrochloride and *Syzygium cumini* Combination Tablets. Before presenting the Ishikawa (fishbone) diagram, the major factors that may influence the quality, consistency, and analytical evaluation of the Metformin HCl and *Syzygium cumini* combination immediate-release tablets should be systematically identified. The fishbone diagram provides a structured approach to classify these potential sources of variation into Materials, Methods, Instruments, Reagents, Environment, Analyst, and Sample Preparation, thereby helping to identify critical factors that may affect the formulation and its evaluation, particularly the Total Phenolic Content (TPC) of *Syzygium cumini*.

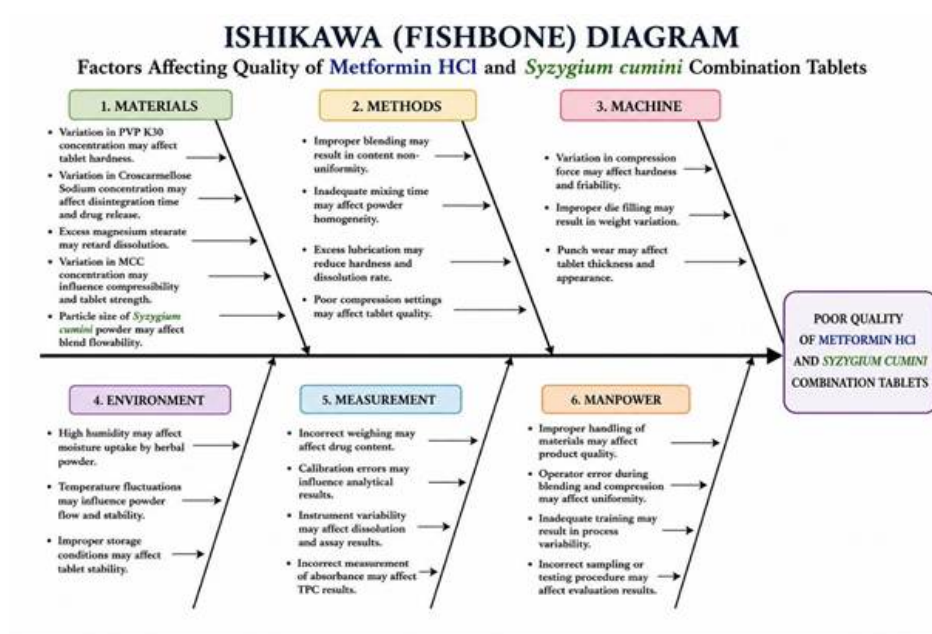


Fig 19: Ishikawa (Fishbone) Diagram

### 8.10.3.1 Categories Included in Ishikawa Diagram:

## 1. Materials

- Variation in PVP K30 concentration may affect tablet hardness.
- Variation in Croscarmellose Sodium concentration may affect disintegration time and drug release.
- Excess magnesium stearate may retard dissolution.
- Variation in MCC concentration may influence compressibility and tablet strength.
- Particle size of *Syzygium cumini* powder may affect blend flowability.

## 2. Methods

- Improper blending may result in content non-uniformity.
- Inadequate mixing time may affect powder homogeneity.
- Excess lubrication may reduce hardness and dissolution rate.
- Poor compression settings may affect tablet quality.

## 3. Machine

- Variation in compression force may affect hardness and friability.
- Improper die filling may result in weight variation.
- Punch wear may affect tablet thickness and appearance.

## 4. Environment

- High humidity may affect moisture uptake by herbal powder.
- Temperature fluctuations may influence powder flow and stability.
- Improper storage conditions may affect tablet stability.

## 5. Measurement

- Incorrect weighing may affect drug content.
- Calibration errors may influence analytical results.
- Instrument variability may affect dissolution and assay results.

## 6. Manpower

- Improper handling of materials may affect product quality.
- Operator error during blending and compression may affect uniformity.
- Inadequate training may result in process variability.

### 8.10.4 Mapping of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) to CQAs:

Mapping of CMAs and CPPs to CQAs helps establish the relationship between formulation variables and product performance. The mapping of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) to Critical Quality Attributes (CQAs) provides a systematic understanding of how material characteristics and manufacturing process variables influence the quality and performance of the formulated Metformin HCl and *Syzygium cumini* combination immediate-release tablets. This relationship helps identify the formulation and process variables that require careful control during tablet manufacturing. The identified CMAs and CPPs were

therefore mapped against the relevant CQAs, including drug release, disintegration time, hardness, friability, drug content, weight variation, thickness, content uniformity, stability, and flow properties, as presented in Table 8.7. This mapping supports the identification of critical factors that may significantly affect the quality, consistency, and performance of the final formulation.<sup>[42]</sup>

**Table No. 19: Mapping of CMAs and CPPs to CQAs**

| CQA                        | Influencing CMAs                                                                     | Influencing CPPs                 |
|----------------------------|--------------------------------------------------------------------------------------|----------------------------------|
| <b>Drug Release</b>        | CCS concentration, MCC concentration, particle size of <i>Syzygium cumini</i> powder | Compression force, blending time |
| <b>Disintegration Time</b> | CCS concentration                                                                    | Compression pressure             |
| <b>Hardness</b>            | PVP K30 concentration, MCC concentration                                             | Compression force                |
| <b>Friability</b>          | Magnesium stearate concentration, PVP K30 concentration                              | Compression pressure             |
| <b>Drug Content</b>        | Blend uniformity, particle size distribution                                         | Blending time                    |
| <b>Weight Variation</b>    | Flow property of powder blend                                                        | Die filling speed                |
| <b>Thickness</b>           | MCC concentration                                                                    | Compression pressure             |
| <b>Content Uniformity</b>  | Blend homogeneity                                                                    | Mixing time                      |
| <b>Stability</b>           | Moisture content of herbal powder                                                    | Storage conditions               |
| <b>Flow Property</b>       | Particle size, MCC concentration                                                     | Mixing process                   |

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Collectively, these mechanisms suggest that *Syzygium cumini* targets several components of the diabetic process simultaneously, supporting its use as a complementary therapeutic agent alongside metformin.<sup>[46]</sup>

#### **8.10.5 Application of Quality by Design (QbD) Approach and 3<sup>2</sup> Factorial Design**

A Quality by Design (QbD) approach was employed for the systematic development and optimization of the combination tablet containing Metformin Hydrochloride and *Syzygium cumini* powder. QbD is a scientific and risk-based approach that emphasizes understanding the relationship between formulation variables and product quality attributes to ensure consistent product performance.

For optimization of the formulation, a 3<sup>2</sup> factorial design was employed using Design-Expert® software. The design consisted of two independent variables evaluated at three levels each,

resulting in nine experimental formulations (F1–F9).

The independent variables selected for the study were:

- Factor A: Magnesium Stearate concentration
- Factor B: PVP K30 concentration

Each factor was studied at low (-1), medium (0), and high (+1) levels. The

dependent variables (responses) evaluated were:

- Hardness ( $Y_1$ )
- Friability ( $Y_2$ )
- Percentage Drug Release of Metformin Hydrochloride ( $Y_3$ )
- Percentage Drug Release of *Syzygium cumini* ( $Y_4$ )

The experimental design enabled the evaluation of the individual and combined effects of the selected formulation variables on the critical quality attributes of the tablets. The generated formulations were prepared according to the design matrix and subsequently evaluated for the selected responses.

The obtained experimental data were subjected to statistical analysis using Design-Expert® software. Polynomial equations were generated to describe the relationship between independent variables and responses. Response surface plots and contour plots were constructed to visualize the influence of formulation variables and identify the optimum formulation region. The optimized formulation was selected based on predefined criteria of acceptable hardness, low friability, and maximum drug release characteristics.

**Table No 20: Independent Variables Selected for  $3^2$  Factorial Design**

| Independent Variable | Code  | Low (-1) | Medium (0) | High (+1) |
|----------------------|-------|----------|------------|-----------|
| Magnesium Sterate    | $X_1$ | 25       | 30         | 35        |
| PVP K 30             | $X_2$ | 5        | 10         | 15        |

**Table No. 21: Dependent Responses (Response Variables) Selected for Optimization Using  $3^2$  Factorial Design**

| Dependent Response                                | Code           |
|---------------------------------------------------|----------------|
| Hardness                                          | Y <sub>1</sub> |
| Friability                                        | Y <sub>2</sub> |
| Drug Release of Metformin Hydrochloride           | Y <sub>3</sub> |
| Percentage Drug Release of <i>Syzygium cumini</i> | Y <sub>4</sub> |

### 8.11 Composition Of Formulation:

**Table No. 22: Composition of Experimental Formulation Batches (F1–F9)**

| Ingredients (mg)          | F1  | F2  | F3  | F4  | F5  | F6  | F7  | F8  | F9  |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Metformin HCl             | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| Jamun Powder              | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| MCC                       | 50  | 50  | 50  | 50  | 50  | 50  | 50  | 50  | 50  |
| PVP K-30                  | 10  | 15  | 20  | 20  | 25  | 30  | 30  | 35  | 40  |
| Croscarmellose Sodium     | 15  | 15  | 15  | 15  | 15  | 15  | 15  | 15  | 15  |
| Colloidal Silicon Dioxide | 5   | 5   | 5   | 5   | 5   | 5   | 5   | 5   | 5   |
| Magnesium Stearate        | 30  | 25  | 20  | 20  | 15  | 10  | 10  | 5   | 0   |
| Total Weight (mg)         | 610 | 610 | 610 | 610 | 610 | 610 | 610 | 610 | 610 |



## Stability Study Procedure:

**Table No. 23: Storage Conditions for Stability Studies**

| Study Type                  | Storage Condition        |
|-----------------------------|--------------------------|
| Long-Term Stability Study   | 30°C ± 2°C / 65% ± 5% RH |
| Accelerated Stability Study | 40°C ± 2°C / 75% ± 5% RH |

### 8.11.1 Stability Study of Optimized Metformin HCl and Jamun Seed Tablet Formulation:

The stability study was carried out according to ICH guidelines to evaluate the effect of storage conditions on the physical and chemical stability of the optimized formulation.

#### **Procedure**

1. The optimized tablet formulation was packed in airtight HDPE containers/aluminium foil strips.
2. The samples were divided into two groups and stored under the following conditions:
3. The samples were stored for a period of 3 months.
4. Tablets were withdrawn at predetermined intervals:
  - Initial (0 month)
  - 1 month
  - 3 months
5. At each interval, the tablets were evaluated for the following parameters:
  - Average Weight
  - Thickness
  - Hardness
  - Friability
  - Disintegration Time
  - Percentage Drug Release of Metformin HCl
  - Percentage Drug Release of Jamun Seed Extract
  - Drug Content of Metformin HCl
  - Drug Content of Jamun Seed Extract
6. The obtained results were compared with the initial values to determine any significant changes during storage.

7. The formulation was considered stable if no significant changes were observed in physical appearance, hardness, friability, drug content, and dissolution profile throughout the study period.

### **9.9 Dissolution Study :**

The dissolution study was carried out to determine the amount of Metformin HCl and released from the formulated tablets under specified conditions.

#### **9.9.1 Apparatus**

USP Dissolution Apparatus Type II (Paddle)|

#### **9.9.2 Dissolution Medium**

900 mL Phosphate Buffer pH 6.8

#### **9.9.3 Temperature**

$37 \pm 0.5^{\circ}\text{C}$

#### **9.9.4 Paddle Speed**

50 rpm

#### **• Procedure:**

1. Nine hundred milliliters of phosphate buffer pH 6.8 was transferred into the dissolution vessel and maintained at  $37 \pm 0.5^{\circ}\text{C}$ .
2. One tablet of the optimized formulation containing Active pharmaceutical ingredient was placed in the dissolution vessel.
3. The paddle was rotated at 50 rpm throughout the study.
4. After 60 minutes, a 5 mL sample was withdrawn from the dissolution vessel and filtered through Whatman filter paper.
5. A standard solution of Metformin HCl was prepared and its absorbance was recorded.
6. The percentage drug release was calculated using the absorbance ratio of sample to standard.

#### **Calculation**

$$\% \text{Drug Release} = \frac{\text{Absorbance of Sample}}{\text{Absorbance of Standard}} \times 100$$

### 9.10 Statistical Treatment of Data:

All experimental evaluations were performed in triplicate ( $n = 3$ ) unless otherwise specified by pharmacopoeial requirements. The obtained results were expressed as Mean  $\pm$  Standard Deviation (SD). For pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio, measurements were performed in triplicate and reported as Mean  $\pm$  SD. Post-compression evaluation parameters including hardness, thickness, friability, weight variation, drug content, disintegration time, and dissolution studies were carried out according to official pharmacopoeial procedures. The results were expressed as Mean  $\pm$  SD.

Statistical analysis of the factorial design batches was performed using Design-Expert® software. A  $3^2$  factorial design was employed to evaluate the effect of independent variables, namely PVP K30 concentration (Factor A) and Magnesium Stearate concentration (Factor B), on the selected responses including hardness, friability, percentage drug release of Metformin Hydrochloride, and percentage drug release of *Syzygium cumini*.

The optimization of the formulation was performed using Design-Expert® software (Version 13, Stat-Ease Inc., USA) based on the  $3^2$  full factorial design. Two independent formulation variables, namely PVP K30 concentration (Factor A) and Croscarmellose Sodium concentration (Factor B), were selected to evaluate their influence on the dependent responses, including tablet hardness, disintegration time, percentage drug release of Metformin Hydrochloride, and percentage drug release of *Syzygium cumini*.

Analysis of Variance (ANOVA) was employed to determine the statistical significance of the developed mathematical models and the effect of formulation variables on the selected responses. A 95% confidence level was adopted, and p-values less than 0.05 ( $p < 0.05$ ) were considered statistically significant. The adequacy of the fitted models was further evaluated using regression coefficient ( $R^2$ ), adjusted  $R^2$ , predicted  $R^2$ , F-value, adequate precision.

Response Surface Methodology (RSM) was utilized to understand the interaction between formulation variables and their influence on the quality attributes of the tablets. Three-dimensional response surface plots and two-dimensional contour plots generated by Design-

Expert® software were used to visualize the relationship between independent variables and responses.

## RESULTS & DISCUSSION

### 9.1 Preformulation Study Of Drug:

#### 9.1.1 Organoleptic Evaluation:

Organoleptic evaluation was performed as a preliminary identification test to assess the physical characteristics of Metformin Hydrochloride and *Syzygium cumini* seed powder. The materials were examined for parameters such as colour, appearance, odour, taste, and texture to confirm their identity and ensure their suitability for further preformulation studies.

**Table No. 24: Organoleptic evaluation of drug**

| Parameter  | Metformin Hydrochloride  | <i>Syzygium cumini</i> Seed Powder |
|------------|--------------------------|------------------------------------|
| Colour     | White crystalline powder | Brown powder                       |
| Appearance | Fine crystalline powder  | Fine free-flowing powder           |
| Odour      | Odourless                | Characteristic odour               |
| Taste      | Bitter                   | Astringent and slightly bitter     |
| Texture    | Smooth                   | Fine powder                        |

#### 9.1.2 Melting Point Determination:

The melting point of Metformin Hydrochloride was determined to confirm its identity and assess its purity.



**Fig 20: Melting point of Metformin HCl by capillary tube method**

Table No 25: Melting Point Determination

| Name          | Melting point |
|---------------|---------------|
| Metformin HCL | 223-225°C     |

## 9.2 Solubility Study:

Table No. 26: Solubility Study of drug

| Solvent/Medium          | Solubility of Metformin HCl | Solubility of Jamun Seed Powder | BCS-relevant Remark         |
|-------------------------|-----------------------------|---------------------------------|-----------------------------|
| Distilled Water         | Freely soluble              | Slightly soluble                | High aqueous solubility     |
| Methanol                | Very soluble                | Soluble                         | Freely soluble              |
| Ethanol                 | Slightly soluble            | Moderately soluble              | Moderately soluble          |
| Phosphate Buffer pH 6.8 | Soluble                     | Slightly soluble                | Suitable dissolution medium |
| Chloroform              | Insoluble                   | Insoluble                       | Practically insoluble       |

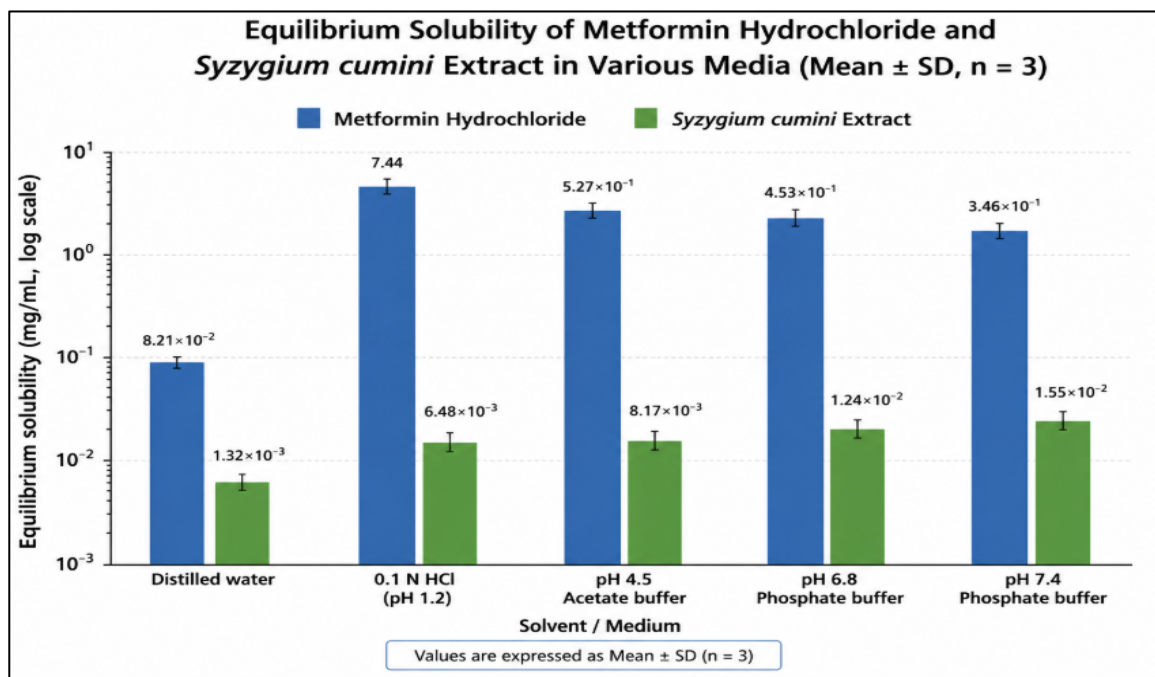
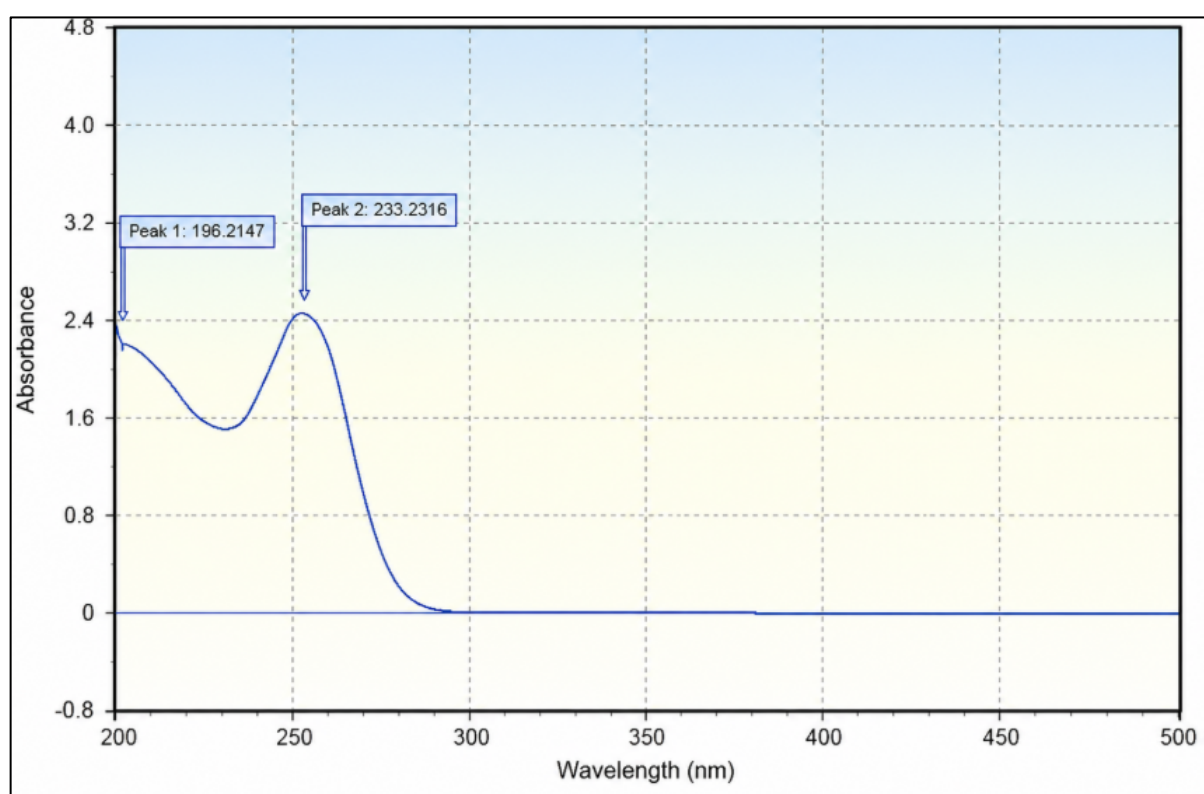


Fig 21: Equilibrium Solubility of Metformin HCl and Syzygium Cumini in various media

Solubility studies indicated that Metformin Hydrochloride was highly soluble in aqueous and hydroalcoholic media, while *Syzygium cumini* powder showed limited solubility in water and improved solubility in organic solvents. Among the tested media, phosphate buffer pH 6.8 exhibited suitable solubility characteristics for both components and was therefore selected for dissolution studies. The solubility profile confirmed the suitability of the selected dissolution medium for evaluating the drug release behaviour of the developed formulation.

### 9.3 Determination of Lambda Max:

### 9.4 Determination of Lambda Max of Metformin HCl:



**Fig 22: Determination of  $\lambda_{\text{max}}$  of Metformin Hydrochloride by UV-Visible Spectroscopy**

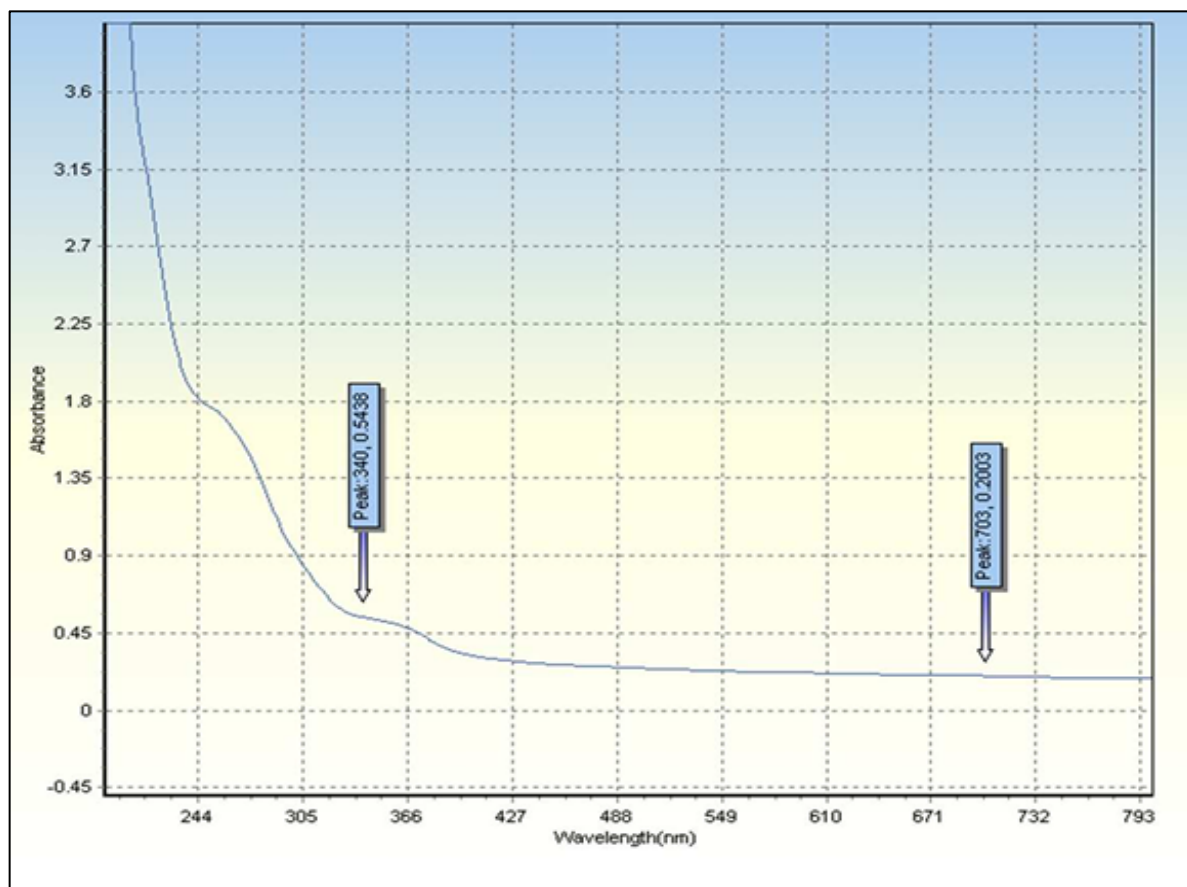
The UV absorption spectrum of Metformin Hydrochloride was recorded in the wavelength range of 200–800 nm using a UV-Visible spectrophotometer. The spectrum exhibited a prominent absorption maximum ( $\lambda_{\text{max}}$ ) at 232.21 nm, which corresponds to the characteristic electronic transition of the drug molecule. A secondary absorption peak was observed at 198.21 nm. The sharp and well-defined peak at 232.21 nm indicated good absorbance characteristics and was selected as the analytical wavelength for quantitative estimation of Metformin Hydrochloride.

The UV spectrophotometric method was developed for the quantitative estimation of Metformin Hydrochloride. The  $\lambda_{\text{max}}$  of Metformin Hydrochloride was found at 233 nm, which was selected as the

analytical wavelength due to its maximum absorbance and good sensitivity. Standard solutions in the concentration range of 2–10 µg/mL were prepared and analyzed.

**Observed  $\lambda_{\text{max}}$ : 232.21 nm**

### 9.3.2 Determination of Lambda Max of *Syzygium cumini*:



**Fig 23: Determination of  $\lambda_{\text{max}}$  of *Syzygium cumini* by UV–Visible Spectroscopy**

The UV absorption spectrum of *Syzygium cumini* extract was recorded over the wavelength range of 200–800 nm. The spectrum showed a characteristic absorption peak at 340.05 nm, which may be attributed to the presence of polyphenolic compounds, flavonoids, anthocyanins, and other phytoconstituents present in the extract. Another minor absorption peak was observed at 703.20 nm.

A UV spectrophotometric method was also developed for the estimation of *Syzygium cumini* extract. The maximum absorbance was observed at 340 nm, which was selected for further analysis.

Observed  
 $\lambda_{\text{max}}$ : 340.05 nm.

#### 9.4.1 UV Spectral Analysis Results:

Table No. 27: UV Spectral Analysis Results

| Parameter                                         | Metformin Hydrochloride | <i>Syzygium cumini</i> Extract |
|---------------------------------------------------|-------------------------|--------------------------------|
| Scanning Range (nm)                               | 200–800                 | 200–800                        |
| Solvent/Medium                                    | Phosphate Buffer pH 6.8 | Phosphate Buffer pH 6.8        |
| Observed $\lambda_{\text{max}}$ (nm)              | 233                     | 340                            |
| Instrumental $\lambda_{\text{max}}$ (nm)          | 232.21                  | 340.05                         |
| Absorbance at $\lambda_{\text{max}}$              | 2.31                    | 0.55                           |
| Reported $\lambda_{\text{max}}$ (Literature) (nm) | 232–234                 | 330–340                        |
| Analytical Wavelength Selected (nm)               | 232.21                  | 340.05                         |
| Application                                       | Drug Content Estimation | Extract Content Estimation     |

#### 9.5 FTIR:

#### 9.6 FTIR Peaks of Metformin Hydrochloride:

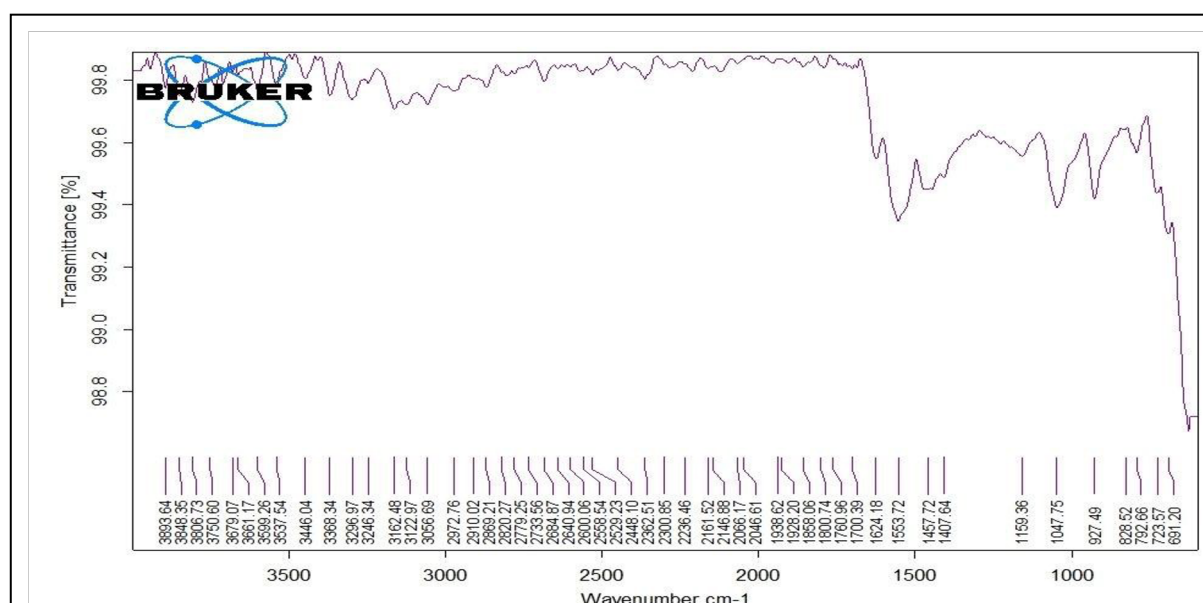


Fig 25: FTIR Spectrum of Metformin Hydrochloride

Table No. 28: FTIR data of Metformin Hydrochloride

| Peak (cm <sup>-1</sup> ) | Functional Group | Assignment |
|--------------------------|------------------|------------|
|--------------------------|------------------|------------|



|         |                |                 |
|---------|----------------|-----------------|
| 3446.04 | N–H Stretching | Primary amine   |
| 3296.97 | N–H Stretching | Secondary amine |
| 3162.48 | N–H Stretching | Amino group     |
| 1624.21 | C=N Stretching | Imine group     |
| 1553.72 | N–H Bending    | Amine group     |
| 1047.75 | C–N Stretching | Aliphatic amine |
| 927.49  | N–H Wagging    | Amine vibration |

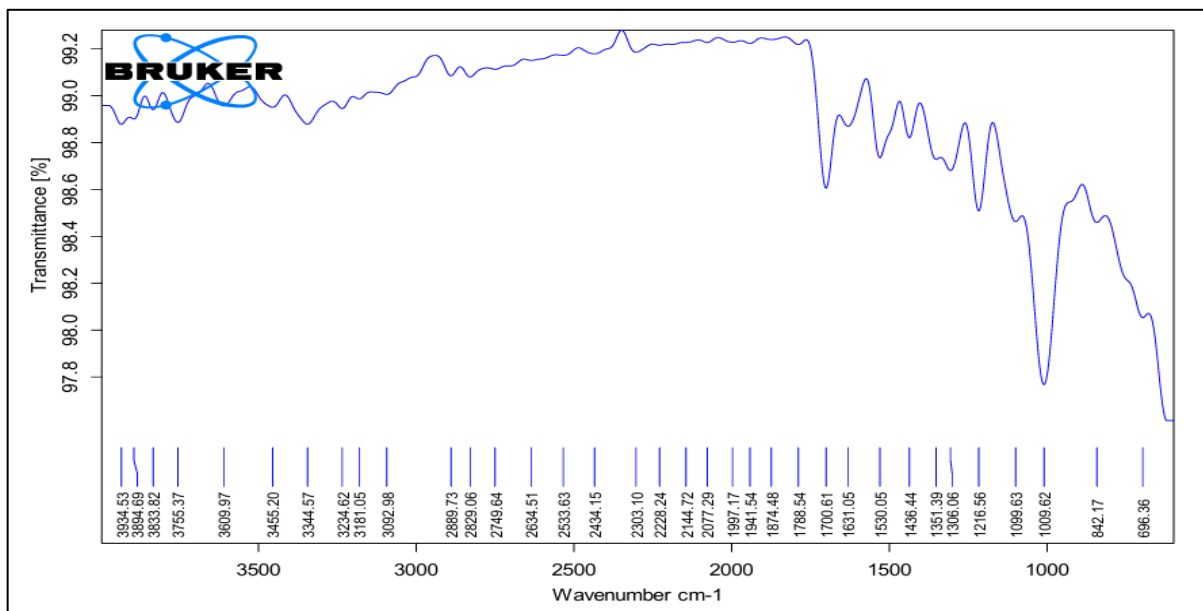
The FTIR spectrum of Metformin Hydrochloride exhibited characteristic absorption bands confirming its chemical identity. A prominent absorption peak observed at 3446.04 cm<sup>-1</sup> corresponded to N–H stretching vibrations of the amino functional group. Additional peaks at 3296.97 cm<sup>-1</sup> and 3162.48 cm<sup>-1</sup> further confirmed the presence of amine groups within the Metformin structure.

The characteristic peak at 1624.21 cm<sup>-1</sup> was attributed to C=N stretching vibrations of the guanidine moiety, which is a distinguishing structural feature of Metformin Hydrochloride. The absorption band at 1553.72 cm<sup>-1</sup> represented N–H bending vibrations, while the peak at 1047.75 cm<sup>-1</sup> corresponded to C–N stretching vibrations. The peak observed at 927.49 cm<sup>-1</sup> was assigned to N–H wagging vibrations.

The presence of these characteristic peaks confirmed the identity and purity of Metformin Hydrochloride and was found to be in agreement with reported literature values.

#### 9.4.2 FTIR Peaks of *Syzygium cumini* Powder:

The FTIR spectrum of *Syzygium cumini* powder exhibited characteristic absorption peaks corresponding to the various functional groups present in its phytoconstituents. The observed peaks confirmed the presence of hydroxyl, carbonyl, aromatic, and C–O functional groups associated with phenolic compounds, flavonoids, tannins, and other bioactive constituents. These findings support the phytochemical composition of *Syzygium cumini* and provide a reference for evaluating its compatibility with Metformin Hydrochloride and the selected excipients during formulation development.



**Fig 26: FTIR Spectrum of *Syzygium cumini***

**Table No. 29: FTIR data of *Syzygium cumini***

| Peak ( $\text{cm}^{-1}$ ) | Functional Group        | Assignment           |
|---------------------------|-------------------------|----------------------|
| 3455.20                   | O–H Stretching          | Phenolic compounds   |
| 2889.73                   | C–H Stretching          | Alkanes              |
| 1631.05                   | C=C Stretching          | Aromatic compounds   |
| 1530.05                   | Aromatic Ring Vibration | Polyphenols          |
| 1436.44                   | O–H Bending             | Phenolic compounds   |
| 1216.56                   | C–O Stretching          | Alcohols             |
| 1099.63                   | C–O Stretching          | Ethers and phenolics |

The FTIR spectrum of *Syzygium cumini* powder exhibited characteristic absorption bands corresponding to various phytoconstituents. A broad absorption peak observed at 3455.20  $\text{cm}^{-1}$  indicated O–H stretching vibrations associated with phenolic compounds and flavonoids. The peak at 2889.73  $\text{cm}^{-1}$  corresponded to aliphatic C–H stretching vibrations.

The absorption band at 1631.05  $\text{cm}^{-1}$  was attributed to aromatic C=C stretching vibrations, while the peak at 1530.05  $\text{cm}^{-1}$  represented aromatic ring vibrations commonly associated with polyphenolic compounds. Peaks observed at 1436.44  $\text{cm}^{-1}$ , 1216.56  $\text{cm}^{-1}$ , and 1099.63  $\text{cm}^{-1}$  indicated O–H bending and C–O stretching vibrations of phenolic and alcoholic groups.

These characteristic peaks confirmed the presence of bioactive phytoconstituents reported in

*Syzygium cumini*, including flavonoids, tannins, and phenolic compounds.

### 9.4.3 Drug–Excipient Compatibility Study:

Drug–excipient compatibility studies are an essential part of preformulation investigations, as they help identify potential physical or chemical interactions between the active pharmaceutical ingredients and the selected excipients. Such interactions may influence the stability, efficacy, safety, and overall quality of the final dosage form. In the present study, compatibility between Metformin Hydrochloride, *Syzygium cumini* powder, and the selected excipients was evaluated using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). The absence of significant changes in the characteristic peaks or thermal behavior confirms the suitability of the selected excipients for the development of the immediate-release combination tablet.

#### Microcrystalline Cellulose

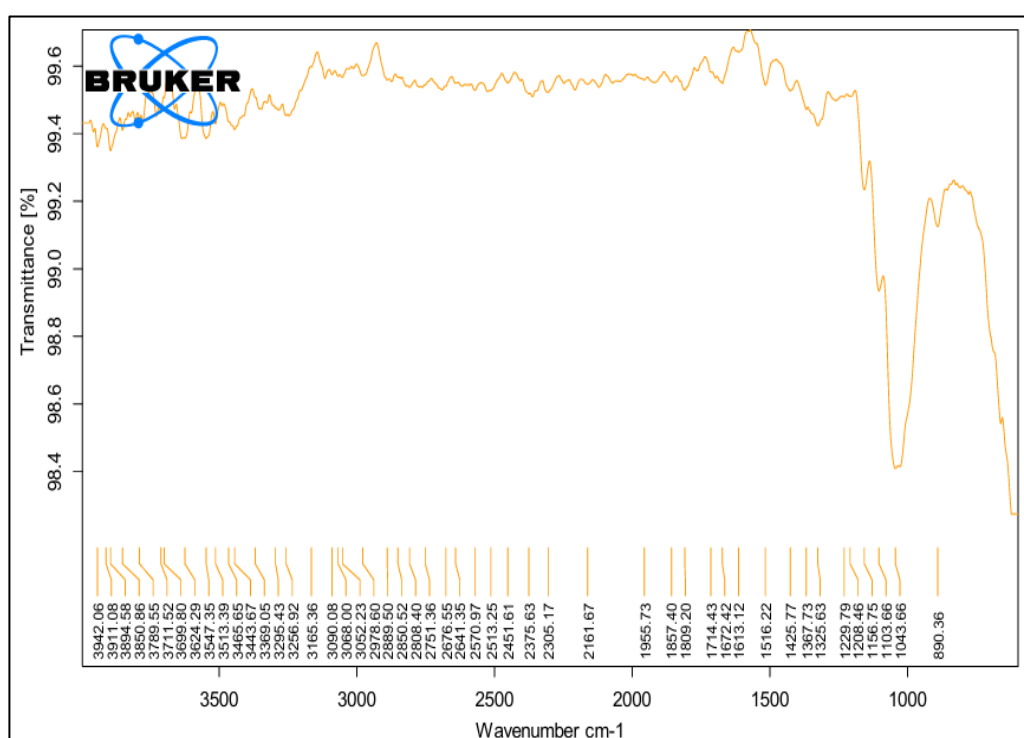


Fig 27: FTIR Spectrum of MCC

Table No. 30: FTIR data of *Syzygium cumini*

| Sr. No. | Functional Group | Characteristic FTIR Peak (cm <sup>-1</sup> ) | Assignment      |
|---------|------------------|----------------------------------------------|-----------------|
| 1       | O–H stretching   | 3200–3500                                    | Hydroxyl groups |
| 2       | C–H stretching   | 2800–3000                                    | Aliphatic C–H   |
| 3       | C–H bending      | 1350–1450                                    | C–H deformation |

|          |                  |           |                    |
|----------|------------------|-----------|--------------------|
| <b>4</b> | C–O–C stretching | 1000–1150 | Ether linkage      |
| <b>5</b> | C–O stretching   | 1020–1100 | Cellulose backbone |

The FTIR spectrum of Microcrystalline Cellulose (MCC PH 102) showed characteristic absorption bands corresponding to O–H stretching ( $3200\text{--}3500\text{ cm}^{-1}$ ), C–H stretching ( $2800\text{--}3000\text{ cm}^{-1}$ ), C–H bending ( $1350\text{--}1450\text{ cm}^{-1}$ ), C–O–C stretching ( $1000\text{--}1150\text{ cm}^{-1}$ ), and C–O stretching ( $1020\text{--}1100\text{ cm}^{-1}$ ). These peaks are characteristic of the cellulose polymeric structure and confirm the presence of hydroxyl, aliphatic, ether, and C–O functional groups in MCC.

## 1. COLLOIDAL SILICON DIOXIDE:

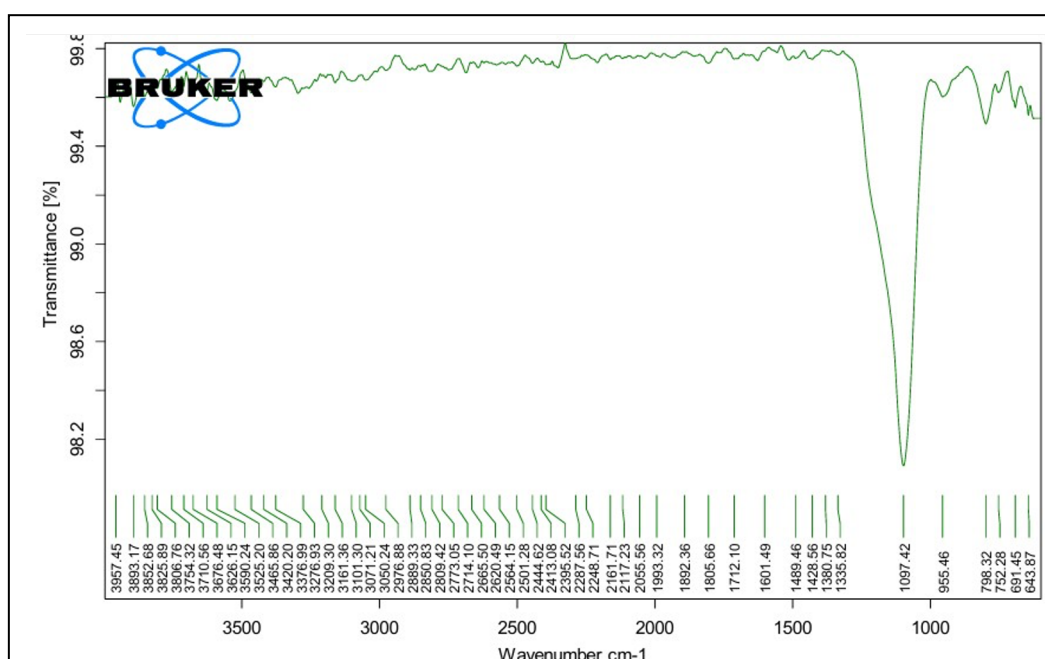


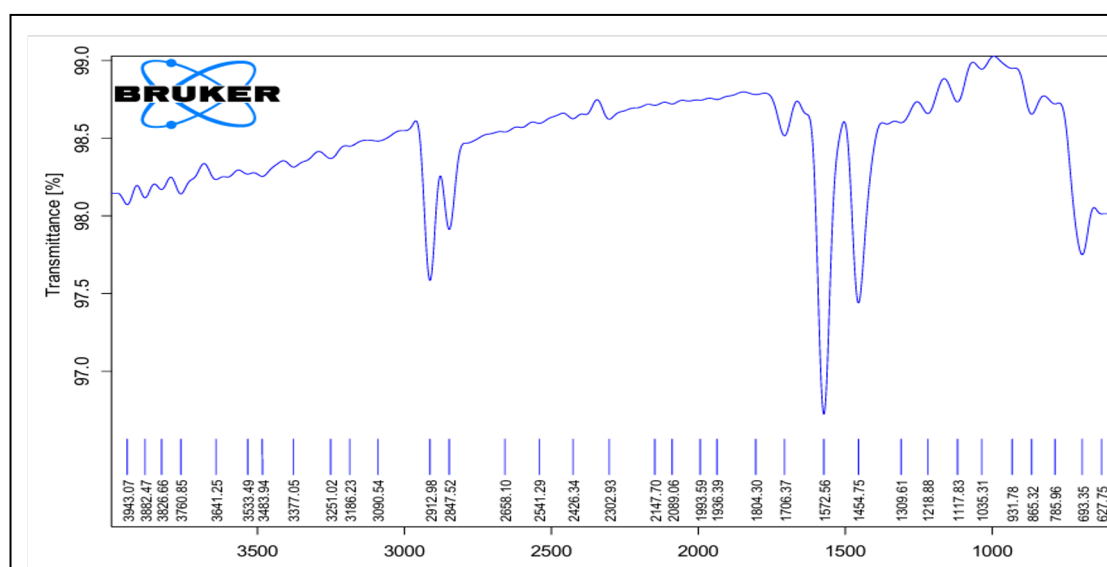
Fig 28: FTIR Spectrum of Colloidal Silicon Dioxide

Table No. 31: FTIR data of Colloidal Silicon Dioxide

| Sr. No. | Functional Group   | Characteristic FTIR Peak (cm <sup>-1</sup> ) | Assignment             |
|---------|--------------------|----------------------------------------------|------------------------|
| 1       | O–H stretching     | 3200–3600                                    | Surface silanol groups |
| 2       | H–O–H bending      | ~1630                                        | Adsorbed water         |
| 3       | Si–O–Si stretching | 1000–1150                                    | Siloxane network       |
| 4       | Si–O stretching    | 800–1000                                     | Silicate structure     |
| 5       | Si–O–Si bending    | ~450–500                                     | Silica framework       |

The FTIR spectrum of Colloidal Silicon Dioxide showed characteristic absorption bands corresponding to O–H stretching ( $3200\text{--}3600\text{ cm}^{-1}$ ) due to surface silanol groups, H–O–H bending around  $1630\text{ cm}^{-1}$  attributed to adsorbed water, and Si–O–Si stretching ( $1000\text{--}1150\text{ cm}^{-1}$ ) associated with the siloxane network. Additional bands at  $800\text{--}1000\text{ cm}^{-1}$  correspond to Si–O stretching vibrations, while the band around  $450\text{--}500\text{ cm}^{-1}$  is attributed to Si–O–Si bending vibrations of the silica framework.

## 2. **MAGNESIUM STERATE:**



**Fig 29: FTIR Spectrum of Magnesium Sterate**

**Table No. 32: FTIR data of Magnesium Sterate**

| Sr. No. | Functional Group                       | Characteristic FTIR Peak (cm <sup>-1</sup> ) | Assignment             |
|---------|----------------------------------------|----------------------------------------------|------------------------|
| 1       | C–H stretching                         | 2850–2950                                    | Long aliphatic chain   |
| 2       | COO <sup>-</sup> asymmetric stretching | 1540–1600                                    | Carboxylate group      |
| 3       | COO <sup>-</sup> symmetric stretching  | 1400–1450                                    | Carboxylate group      |
| 4       | CH <sub>2</sub> bending                | 1400–1470                                    | Aliphatic chain        |
| 5       | CH <sub>2</sub> rocking                | 700–730                                      | Long hydrocarbon chain |

The FTIR spectrum of Magnesium Stearate showed characteristic absorption bands corresponding to C–H stretching vibrations (2850–2950  $\text{cm}^{-1}$ ) associated with the long aliphatic hydrocarbon chain, while the asymmetric and symmetric  $\text{COO}^-$  stretching bands (1540–1600 and 1400–1450  $\text{cm}^{-1}$ , respectively) confirmed the presence of the carboxylate group. The  $\text{CH}_2$  bending vibrations (1400–1470  $\text{cm}^{-1}$ ) and  $\text{CH}_2$  rocking band (700–730  $\text{cm}^{-1}$ ) further indicated the long-chain aliphatic structure of magnesium stearate

### 3. PVP K 30

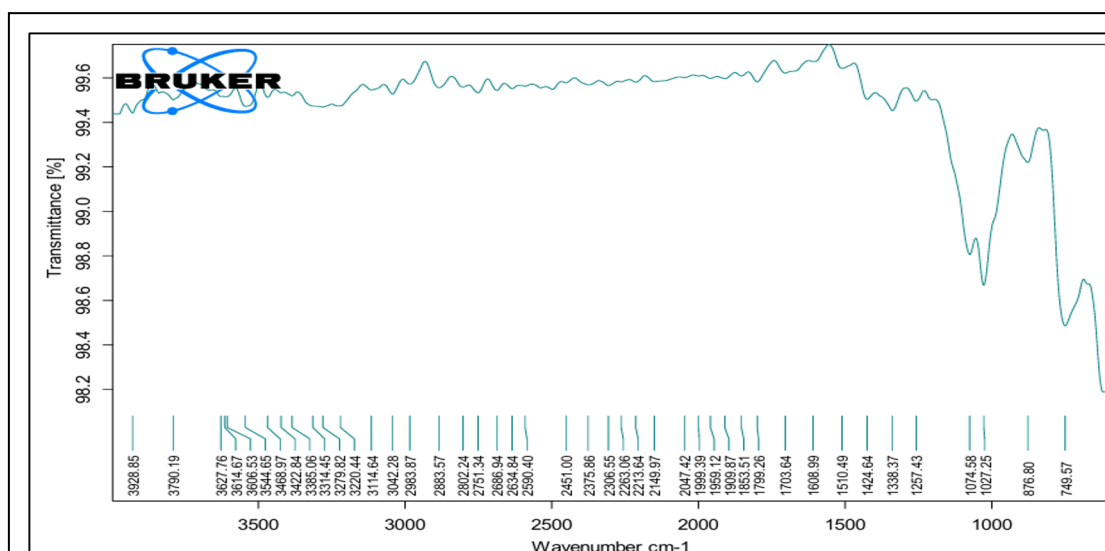


Fig 30: FTIR Spectrum of PVP K 30

Table No. 33: FTIR data of PVP K 30

| Sr. No. | Functional Group   | Characteristic FTIR Peak ( $\text{cm}^{-1}$ ) | Assignment                |
|---------|--------------------|-----------------------------------------------|---------------------------|
| 1       | C–H stretching     | 2800–3000                                     | Aliphatic C–H             |
| 2       | C=O stretching     | 1640–1680                                     | Lactam carbonyl           |
| 3       | C–N stretching     | 1250–1300                                     | C–N bond                  |
| 4       | C–H bending        | 1350–1500                                     | Aliphatic C–H deformation |
| 5       | C–N/C–C vibrations | 1000–1300                                     | PVP backbone              |

The FTIR spectrum of Polyvinylpyrrolidone K30 (PVP K30) exhibited characteristic absorption bands corresponding to C–H stretching vibrations (2800–3000  $\text{cm}^{-1}$ ) of aliphatic C–H groups and a prominent C=O stretching band (1640–1680  $\text{cm}^{-1}$ ) attributed to the lactam carbonyl group. The C–N stretching band (1250–1300  $\text{cm}^{-1}$ ) represents the C–N bond, while the C–H bending vibrations (1350–1500  $\text{cm}^{-1}$ ) are associated with aliphatic C–H deformation. The bands in the 1000–1300  $\text{cm}^{-1}$  region are attributed to C–N and C–C vibrations of the PVP polymer backbone, confirming the characteristic chemical structure of PVP K30.

## 9.5 Pre -Compression Parameters :

### 9.5.1 Pre-compression Evaluation of Powder Blend:

Pre-compression evaluation was carried out to assess the flow and compressibility characteristics of the powder blends prior to tablet compression. Parameters such as angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner ratio were determined, as these properties influence die filling, weight uniformity, and the overall quality of tablets prepared by the direct compression method.

**Table No. 34: Pre-compression Evaluation of Powder Blend**

| Batch | Angle of Repose (°) | Bulk Density (g/mL) | Tapped Density (g/mL) | Carr's Index (%)    | Hausner Ratio      |
|-------|---------------------|---------------------|-----------------------|---------------------|--------------------|
| F1    | 31.82 ± 0.15        | 0.46 ± 0.01         | 0.54 ± 0.01           | 14.81 ± 0.21        | 1.17 ± 0.01        |
| F2    | 31.05 ± 0.12        | 0.47 ± 0.01         | 0.55 ± 0.01           | 14.54 ± 0.18        | 1.17 ± 0.01        |
| F3    | 30.54 ± 0.18        | 0.48 ± 0.01         | 0.56 ± 0.01           | 14.29 ± 0.25        | 1.17 ± 0.01        |
| F4    | 29.96 ± 0.11        | 0.49 ± 0.01         | 0.57 ± 0.01           | 14.04 ± 0.16        | 1.16 ± 0.01        |
| F5    | 29.41 ± 0.14        | 0.50 ± 0.01         | 0.58 ± 0.01           | 13.79 ± 0.20        | 1.16 ± 0.01        |
| F6    | 28.92 ± 0.16        | 0.51 ± 0.01         | 0.59 ± 0.01           | 13.56 ± 0.22        | 1.16 ± 0.01        |
| F7    | <b>27.84 ± 0.13</b> | <b>0.53 ± 0.01</b>  | <b>0.61 ± 0.01</b>    | <b>13.11 ± 0.17</b> | <b>1.15 ± 0.01</b> |
| F8    | 28.36 ± 0.12        | 0.52 ± 0.01         | 0.60 ± 0.01           | 13.33 ± 0.18        | 1.15 ± 0.01        |
| F9    | 28.74 ± 0.15        | 0.51 ± 0.01         | 0.59 ± 0.01           | 13.56 ± 0.21        | 1.16 ± 0.01        |

### 9.5.2 Pre-compression Evaluation of Optimized Batch (F7):

**Table No. 35: Pre-compression Evaluation of Optimized Batch (F7)**



| Parameter                      | F7 Batch (Mean $\pm$ SD) | Acceptable Range / Flow Category |
|--------------------------------|--------------------------|----------------------------------|
| Angle of Repose ( $^{\circ}$ ) | 27.84 $\pm$ 0.13         | 25–30 $^{\circ}$ (Good Flow)     |
| Bulk Density (g/mL)            | 0.53 $\pm$ 0.01          | —                                |
| Tapped Density (g/mL)          | 0.61 $\pm$ 0.01          | —                                |
| Carr's Index (%)               | 13.11 $\pm$ 0.17         | <15% (Excellent Compressibility) |
| Hausner Ratio                  | 1.15 $\pm$ 0.01          | <1.25 (Good Flow Property)       |

The flow characteristics of the powder blends were evaluated before compression to ensure suitability for direct compression processing. The angle of repose values ranged from 27.84 $^{\circ}$  to 31.82 $^{\circ}$ , indicating good flowability of all powder blends. Lower angle of repose values observed in optimized formulations suggested improved flow characteristics resulting from proper selection of excipients.

Bulk density and tapped density values showed only minor variations among formulations, indicating uniform particle packing characteristics. Carr's Index values ranged between 13.11% and 14.81%, while Hausner's Ratio ranged from 1.15 to 1.17, confirming good compressibility and flow properties. The results demonstrated that all powder blends possessed adequate flowability and compressibility, which are essential for uniform die filling and consistent tablet weight during compression.

#### 9.6 Post -Compression Parameters :

The post-compression evaluation of all factorial batches (F1–F9) demonstrated satisfactory tablet quality within acceptable pharmacopoeial limits. The tablets exhibited uniform weight and thickness, adequate hardness, low friability (<1%), and acceptable disintegration time.

**Table No. 36: Post-compression Evaluation of Factorial Batches**

| Batch | Average Weight (mg) | Thickness (mm)  | Hardness (kg/cm <sup>2</sup> ) | Friability (%)  | Disintegration Time (min:sec) |
|-------|---------------------|-----------------|--------------------------------|-----------------|-------------------------------|
| F1    | 608.4 $\pm$ 2.1     | 4.52 $\pm$ 0.03 | 3.4 $\pm$ 0.12                 | 0.78 $\pm$ 0.02 | 4 min 15 sec $\pm$ 0.08       |
| F2    | 609.2 $\pm$ 1.8     | 4.54 $\pm$ 0.02 | 3.5 $\pm$ 0.11                 | 0.71 $\pm$ 0.03 | 3 min 58 sec $\pm$ 0.07       |
| F3    | 610.5 $\pm$ 2.0     | 4.56 $\pm$ 0.04 | 3.6 $\pm$ 0.10                 | 0.65 $\pm$ 0.02 | 3 min 42 sec $\pm$ 0.06       |
| F4    | 609.8 $\pm$ 1.9     | 4.58 $\pm$ 0.03 | 3.7 $\pm$ 0.09                 | 0.59 $\pm$ 0.02 | 3 min 20 sec $\pm$ 0.05       |
| F5    | 610.1 $\pm$ 2.2     | 4.60 $\pm$ 0.02 | 3.8 $\pm$ 0.08                 | 0.52 $\pm$ 0.01 | 3 min 05 sec $\pm$ 0.04       |
| F6    | 610.3 $\pm$ 1.7     | 4.61 $\pm$ 0.03 | 3.9 $\pm$ 0.11                 | 0.44 $\pm$ 0.02 | 2 min 42 sec $\pm$ 0.04       |
| F7    | 610.0 $\pm$ 1.5     | 4.63 $\pm$ 0.02 | 4.1 $\pm$ 0.08                 | 0.31 $\pm$ 0.01 | 2 min 20 sec $\pm$ 0.03       |

|           |             |             |            |             |                     |
|-----------|-------------|-------------|------------|-------------|---------------------|
| <b>F8</b> | 609.7 ± 1.8 | 4.62 ± 0.03 | 4.0 ± 0.09 | 0.38 ± 0.02 | 2 min 31 sec ± 0.04 |
| <b>F9</b> | 610.2 ± 1.6 | 4.61 ± 0.02 | 4.0 ± 0.10 | 0.42 ± 0.02 | 2 min 48 sec ± 0.05 |

**Table No. 37: Drug Content and In-vitro Drug Release of Factorial Batches (F1–F9)**

| <b>Batch</b> | <b>% Assay<br/><i>Syzygium cumini</i></b> | <b>% Assay<br/>Metformin HCl</b> | <b>% Drug Release<br/><i>Syzygium cumini</i></b> | <b>% Drug Release<br/>Metformin HCl</b> |
|--------------|-------------------------------------------|----------------------------------|--------------------------------------------------|-----------------------------------------|
| <b>F1</b>    | 99.15                                     | 98.11                            | 92.68                                            | 95.09                                   |
| <b>F2</b>    | 97.64                                     | 97.48                            | 96.29                                            | 96.10                                   |
| <b>F3</b>    | 98.93                                     | 103.48                           | 95.87                                            | 96.40                                   |
| <b>F4</b>    | 97.84                                     | 95.26                            | 96.91                                            | 94.33                                   |
| <b>F5</b>    | 98.13                                     | 97.37                            | 96.22                                            | 103.69                                  |
| <b>F6</b>    | 96.98                                     | 99.05                            | 96.27                                            | 98.37                                   |
| <b>F7</b>    | <b>100.18</b>                             | <b>99.66</b>                     | <b>96.16</b>                                     | <b>100.05</b>                           |
| <b>F8</b>    | 97.07                                     | 96.51                            | 95.68                                            | 97.45                                   |
| <b>F9</b>    | 96.69                                     | 98.35                            | 100.91                                           | 97.26                                   |

The prepared tablets were evaluated for various post-compression parameters to ensure compliance with pharmacopeial requirements. The hardness values varied depending on the concentration of excipients, particularly Magnesium Stearate and PVP K-30. Hardness value ranging from 2.2–4.1 kg/cm<sup>2</sup> indicated satisfactory mechanical strength without compromising disintegration performance.

## 9.7 CALIBRATION CURVE

### 9.7.1 Calibration Curve of Metformin HCl :

**Table No. 38: Calibration Curve of Metformin HCl**

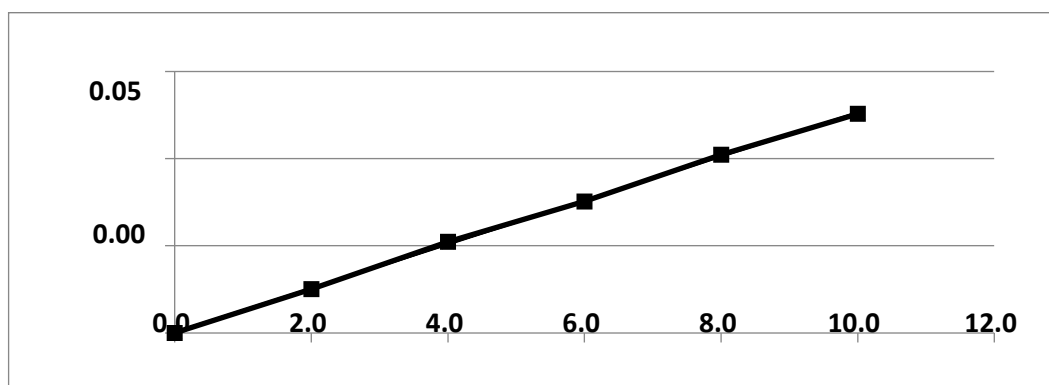
| <b>Concentration (PPM)</b> | <b>Absorbance</b> |
|----------------------------|-------------------|
| <b>0.0</b>                 | 0.0000            |
| <b>2.0</b>                 | 0.0251            |
| <b>4.0</b>                 | 0.0522            |
| <b>6.0</b>                 | 0.0754            |
| <b>8.0</b>                 | 0.1023            |
| <b>10.0</b>                | 0.1257            |

0.15      **Linearity of Metformin Hcl**

$$y = 0.0126x + 0.0004$$

$$R^2 = 0.9996$$

0.10



**Fig 31: Calibration Curve of Metformin HCl**

**Table No. 39: Linear regression parameters of the calibration curves**

| Parameter                         | Value                                                                          |
|-----------------------------------|--------------------------------------------------------------------------------|
| Analyte                           | Metformin Hydrochloride                                                        |
| Wavelength ( $\lambda_{max}$ )    | 233 nm ( <i>or your experimentally determined <math>\lambda_{max}</math></i> ) |
| Y-intercept                       | 0.0004                                                                         |
| Slope                             | 0.0126                                                                         |
| Correlation Coefficient ( $R^2$ ) | 0.9996                                                                         |
| Regression Equation               | $Y = 0.0126x + 0.0004$                                                         |

The absorbance of standard solutions in the concentration range of 2–10 ppm at the chosen wavelength of 233 nm was measured in order to create the Metformin HCl calibration curve. There is a direct correlation between concentration and absorbance since the absorbance rose linearly with increasing concentration. The calibration plot adhered to Beer-Lambert's law and demonstrated excellent linearity over the concentration range under study. The resultant regression equation was  $y = 0.0126x + 0.0004$ , with the intercept (0.0004) indicating minimum instrumental and analytical error and the slope (0.0126) representing the analytical method's sensitivity. The new method's outstanding linearity, precision, and reliability were demonstrated by the correlation coefficient ( $R^2 = 0.9996$ ). These results confirm that the UV spectrophotometric method is suitable for the quantitative estimation of Metformin HCl in pharmaceutical formulations and dissolution studies.

#### 9.7.2 Calibration Curve of *Syzygium cumini*:

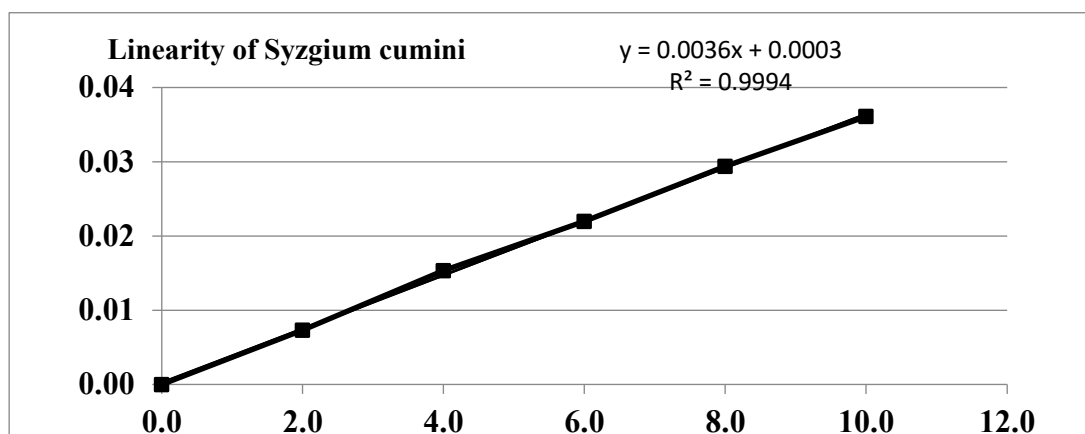


Fig 32: Calibration Curve of *Syzygium cumini*

Table No. 40: Calibration Curve of *Syzygium cumini*

| Concentration (PPM) | Absorbance |
|---------------------|------------|
| 0.0                 | 0.0000     |
| 2.0                 | 0.0073     |
| 4.0                 | 0.1053     |

|             |        |
|-------------|--------|
| <b>6.0</b>  | 0.0220 |
| <b>8.0</b>  | 0.0293 |
| <b>10.0</b> | 0.0361 |

**Table No. 41: Linear regression parameters of the calibration curves.**

| Parameter                             | Value                  |
|---------------------------------------|------------------------|
| Analyte                               | <i>Syzygium cumini</i> |
| Wavelength ( $\lambda_{\text{max}}$ ) | 340 nm (if applicable) |
| Y-intercept                           | 0.0003                 |
| Slope                                 | 0.0036                 |
| Correlation Coefficient ( $R^2$ )     | 0.9994                 |
| Regression Equation                   | $Y = 0.0036x + 0.0003$ |

The absorbance of standard solutions in the concentration range of 2–10 ppm at a wavelength of 340 nm was measured in order to create the *Syzygium cumini* calibration curve. There is a direct correlation between concentration and absorbance since the absorbance was observed to rise proportionately with increasing concentration. The calibration figure met Beer-Lambert's law and showed good linearity across the chosen concentration range. The derived regression equation was  $y = 0.0036x + 0.0003$ , where the intercept (0.0003) denotes minimal analytical and instrumental error and the slope (0.0036) represents the analytical method's sensitivity. The method's outstanding linearity, accuracy, and reliability were demonstrated by the correlation coefficient ( $R^2 = 0.9994$ ), which was found to be extremely close to unity. These findings verify that *Syzygium cumini* may be quantitatively estimated in pharmaceutical formulations and dissolution investigations using the established UV spectrophotometric approach.

The dissolution study demonstrated satisfactory immediate-release characteristics for all factorial batches. The percentage drug release of *Syzygium cumini* ranged from 92.68% to 100.91%, whereas the percentage drug release of Metformin Hydrochloride ranged from 94.33% to 103.69%. All formulations released more than 85% of the drug within the specified dissolution period, complying with pharmacopeial requirements for immediate-release tablets. Among all formulations, batch F7 exhibited an optimum drug release profile, showing 96.16% release of *Syzygium cumini* and 100.05% release of Metformin Hydrochloride. The results indicated that both Magnesium Stearate and PVP K30 influenced the dissolution behavior of the formulation. The optimized batch (F7) provided a desirable balance between mechanical strength, disintegration time, friability, and drug release, and was therefore selected as the final optimized formulation.

### 9.8 Dissolution Profile of Optimized Batch (F7):

The in vitro dissolution study was carried out to evaluate the drug release characteristics of the experimental formulation batches (F1–F9) and to identify the optimized formulation. The percentage drug release of both Metformin Hydrochloride and *Syzygium cumini* was determined under specified dissolution conditions. The results were used to assess the influence of formulation variables on the dissolution profile and to select the formulation exhibiting the most desirable drug release performance. The comparative drug release data of all factorial batches are presented in the following table.

**Table No. 42: Comparative Drug Release of Factorial Batches (F1–F9)**

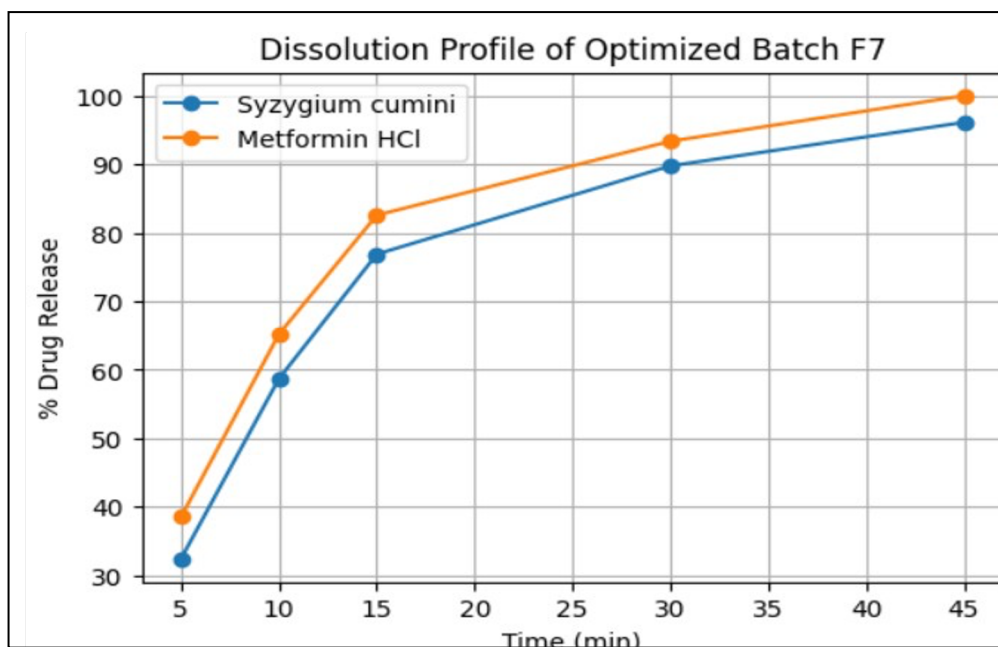
| Batch | Magnesium Stearate (%) | PVP K30 (%) | % Drug Release of <i>Syzygium cumini</i> (Mean $\pm$ SD) | % Drug Release of Metformin HCl (Mean $\pm$ SD) |
|-------|------------------------|-------------|----------------------------------------------------------|-------------------------------------------------|
| F1    | 0.5                    | 2           | 92.68 $\pm$ 0.82                                         | 95.09 $\pm$ 0.76                                |
| F2    | 1.0                    | 2           | 96.29 $\pm$ 0.65                                         | 96.10 $\pm$ 0.84                                |
| F3    | 1.5                    | 2           | 95.87 $\pm$ 0.71                                         | 96.40 $\pm$ 0.67                                |
| F4    | 0.5                    | 3           | 96.91 $\pm$ 0.74                                         | 94.33 $\pm$ 0.88                                |
| F5    | 1.0                    | 3           | 96.22 $\pm$ 0.69                                         | 103.69 $\pm$ 0.59                               |
| F6    | 1.5                    | 3           | 96.27 $\pm$ 0.56                                         | 98.37 $\pm$ 0.72                                |
| F7    | 1.0                    | 4           | 96.16 $\pm$ 0.48                                         | 100.05 $\pm$ 0.54                               |
| F8    | 1.5                    | 4           | 95.68 $\pm$ 0.61                                         | 97.45 $\pm$ 0.63                                |
| F9    | 0.5                    | 4           | 100.91 $\pm$ 0.52                                        | 97.26 $\pm$ 0.69                                |

The dissolution study demonstrated satisfactory immediate-release characteristics for all factorial batches. The percentage drug release of *Syzygium cumini* ranged from 92.68% to 100.91%, whereas the percentage drug release of Metformin Hydrochloride ranged from 94.33% to 103.69%. All formulations released more than 85% of the drug within the specified dissolution period, complying with pharmacopeial requirements for immediate-release tablets.

Among all formulations, batch F7 exhibited an optimum drug release profile, showing 96.16% release of *Syzygium cumini* and 100.05% release of Metformin Hydrochloride. The results indicated that both Magnesium Stearate and PVP K30 influenced the dissolution behavior of the formulation. The optimized batch (F7) provided a desirable balance between mechanical strength, disintegration time, friability, and drug release.

**Table No. 43: Dissolution Profile of Optimized Batch (F7)**

| Time (min) | % Release <i>Syzygium cumini</i> | % Release Metformin HCl |
|------------|----------------------------------|-------------------------|
| 5          | 32.40                            | 38.50                   |
| 10         | 58.70                            | 65.20                   |
| 15         | 76.90                            | 82.60                   |
| 30         | 89.80                            | 93.40                   |
| 45         | 96.16                            | 100.05                  |



**Fig 33: Dissolution Profile of Optimized Batch**

The optimized batch F7 exhibited rapid drug release characteristics typical of an immediate-release tablet formulation. Metformin Hydrochloride showed a cumulative drug release of 100.05% within 45 minutes, while *Syzygium cumini* exhibited 96.16% drug release during the same period. More than 75% of both active ingredients were released within the first 15 minutes, indicating rapid tablet disintegration and efficient dissolution. The dissolution profile confirmed that the optimized formulation complied with the requirements for immediate-release dosage forms and ensured prompt availability of the active ingredients for therapeutic action.

## 9.9 ANOVA for Linear model:

### 9.9.1 Response 1: Hardness

Analysis of Variance (ANOVA) was performed using Design-Expert® software to evaluate



the significance of the linear model and to determine the effect of the selected independent variables, namely Magnesium Stearate (A) and PVP K30 (B), on the hardness of the formulated tablets. ANOVA provides statistical evidence regarding the significance of the model and individual formulation variables based on the F-value and p-value. It also helps to identify whether the observed variations in tablet hardness are due to changes in formulation variables or random experimental error. The statistical analysis was carried out at a 95% confidence level, where a p-value less than 0.05 was considered statistically significant. The results of the ANOVA for the hardness response ( $Y_1$ ) are presented in the following table.

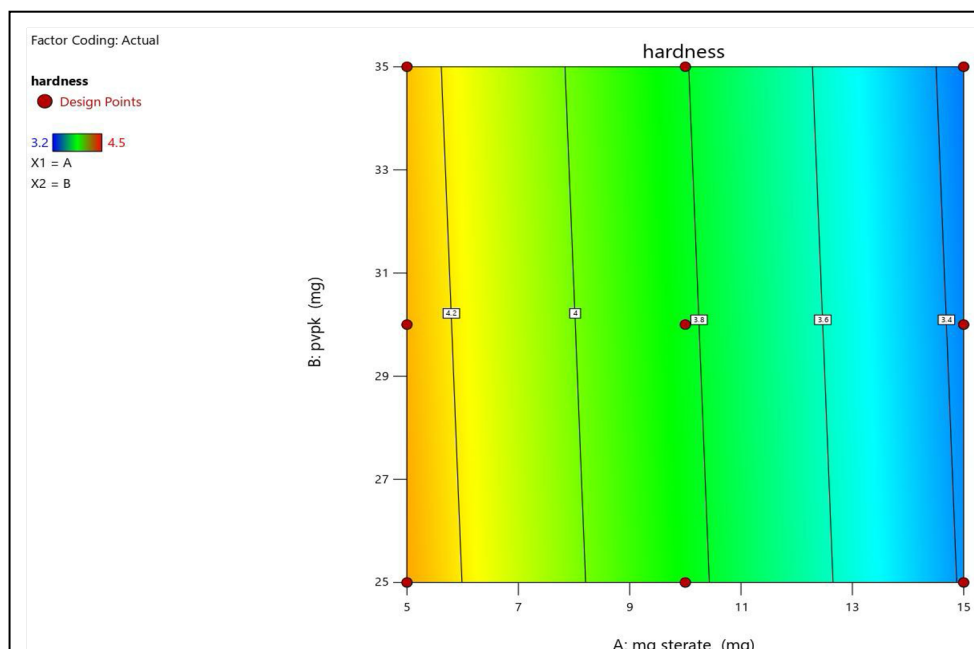
**Table No. 44: ANOVA for Hardness (Response  $Y_1$ )**

| Source                        | Sum of Squares | df | Mean Square | F-value | p-value | Remark      |
|-------------------------------|----------------|----|-------------|---------|---------|-------------|
| <b>Model</b>                  | 1.22           | 2  | 0.6083      | 26.28   | 0.0011  | Significant |
| <b>A – Magnesium Stearate</b> | 1.22           | 1  | 1.2200      | 52.49   | 0.0004  | Significant |
| <b>B – PVP K30</b>            | 0.0017         | 1  | 0.0017      | 0.0720  | 0.7974  | Significant |
| <b>Residual</b>               | 0.1389         | 6  | 0.0231      | —       | —       | —           |
| <b>Corrected Total</b>        | 1.36           | 8  | —           | —       | —       | —           |

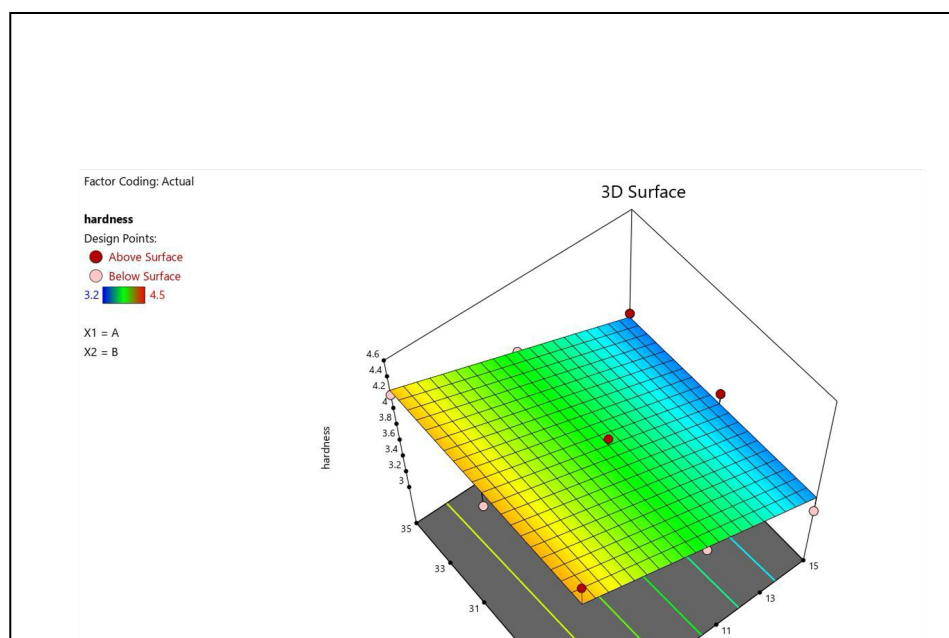
Factor coding is Coded.

Sum of squares is Type III - Partial

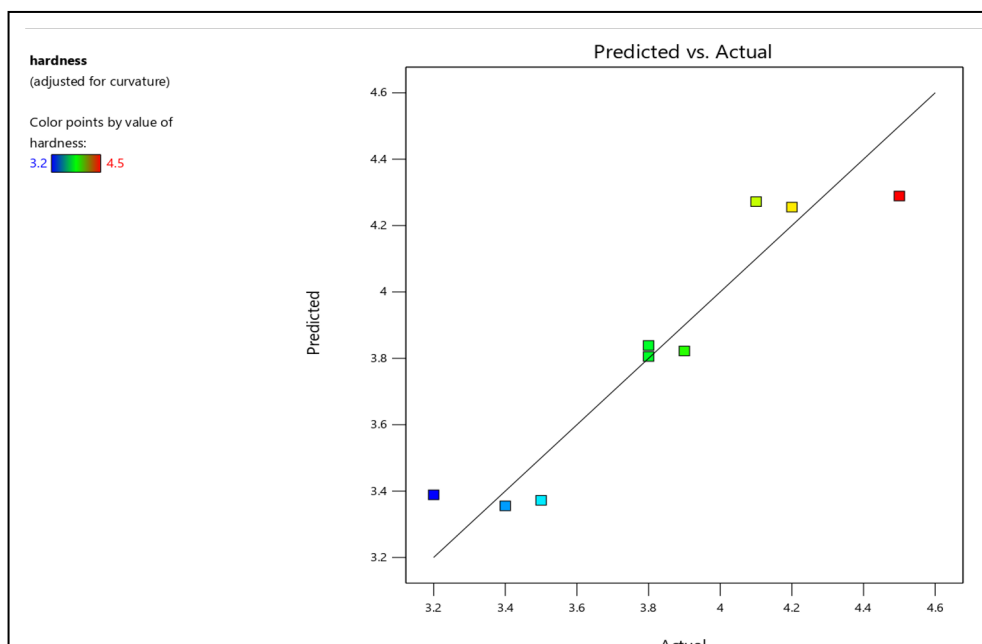
The Model F-value of 26.28 implies the model is significant. There is only a 0.11% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.



**Fig 34: Contour Plot Showing the Effect of Magnesium Stearate (A) and PVP K30 (B) on Tablet Hardness (Y<sub>1</sub>)**



**Fig 35: Three-Dimensional (3D) Response Surface Plot Showing the Effect of Magnesium Stearate (A) and PVP K30 (B) on Tablet Hardness (Y<sub>1</sub>)**



**Fig 36: Predicted versus Actual Plot for Tablet Hardness ( $Y_1$ )**

#### 9.9.1.1 Interpretation of Response Surface Plot, Contour Plot, and Predicted vs. Actual Plot for Hardness ( $Y_1$ ):

The graphical representations generated using Design-Expert® software provide a clear understanding of the influence of the formulation variables, Magnesium Stearate (A) and PVP K30 (B), on the hardness of the formulated tablets. The three-dimensional response surface plot and contour plot illustrate the relationship between the independent variables and the hardness response within the experimental design space. The gradual change in the response surface and contour lines indicates that the formulation variables affected tablet hardness, with Magnesium Stearate exhibiting a more pronounced influence than PVP K30. The contour plot also suggests minimal interaction between the two variables, indicating that the response changed in a predictable manner throughout the design space.

The predicted versus actual plot demonstrates good agreement between the experimentally observed and model-predicted hardness values, as the data points are distributed close to the diagonal reference line. This indicates that the developed linear model adequately predicts the hardness response with good accuracy and reliability. The graphical analysis is consistent with the ANOVA results, confirming the significance of the model and supporting the selection of the optimized formulation. Overall, these plots validate the suitability of the experimental

design and demonstrate that the selected formulation variables can be effectively optimized to achieve the desired tablet hardness.

#### 9.9.1.2 Coefficients in Terms of Coded Factors:

**Table No. 45: Regression Coefficients of the Linear Model for Hardness ( $Y_1$ ) in Terms of Coded Factors**

| Factor                       | Coefficient Estimate | df | Standard Error | 95% CI Low | 95% CI High | VIF    |
|------------------------------|----------------------|----|----------------|------------|-------------|--------|
| <b>Intercept</b>             | 3.82                 | 1  | 0.0507         | 3.70       | 3.95        |        |
| <b>A- Magnesium Stearate</b> | -0.4500              | 1  | 0.0621         | -0.6020    | -0.2980     | 1.0000 |
| <b>B-PVP K 30</b>            | -0.0167              | 1  | 0.0621         | -0.1687    | 0.1353      | 1.0000 |

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-collinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

#### 9.9.1.3 Final Equation in Terms of Actual Factors:

**Table No. 46: Final Regression Equation in Terms of Actual Factors for Hardness Response ( $Y_1$ )**

| Term                          | Coefficient Estimate |
|-------------------------------|----------------------|
| <b>Intercept</b>              | +4.82222             |
| <b>A – Magnesium Stearate</b> | -0.090000            |
| <b>B – PVP K 30</b>           | -0.003333            |

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because

the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

#### **9.9.1.4 Coefficients in Terms of Coded Factors:**

**Table No. 47: Final Regression Equation in Terms of Coded Factors for Hardness Response ( $Y_1$ )**

| Term      | Coefficient Estimate |
|-----------|----------------------|
| Intercept | +3.82                |
| A         | -0.4500              |
| B         | -0.0167              |

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

#### **9.9.1.5 ANOVA Interpretation for Hardness:**

The statistical analysis revealed that the linear model for hardness was significant ( $p = 0.0011$ ), indicating a strong relationship between formulation variables and tablet hardness. Magnesium Stearate was identified as a significant factor ( $p = 0.0004$ ), whereas PVP K-30 exhibited no significant effect ( $p = 0.7974$ ). The negative coefficient of Magnesium Stearate suggested that increasing lubricant concentration decreased tablet hardness.

This reduction in hardness may be attributed to the hydrophobic nature of Magnesium Stearate, which reduces interparticle bonding during compression. Excessive lubricant levels can create a coating around powder particles, thereby reducing tablet compatibility and mechanical strength.

#### **9.9.2 Response 2: Friability:**

**Table No. 48: ANOVA for Friability (Response Y<sub>2</sub>)**

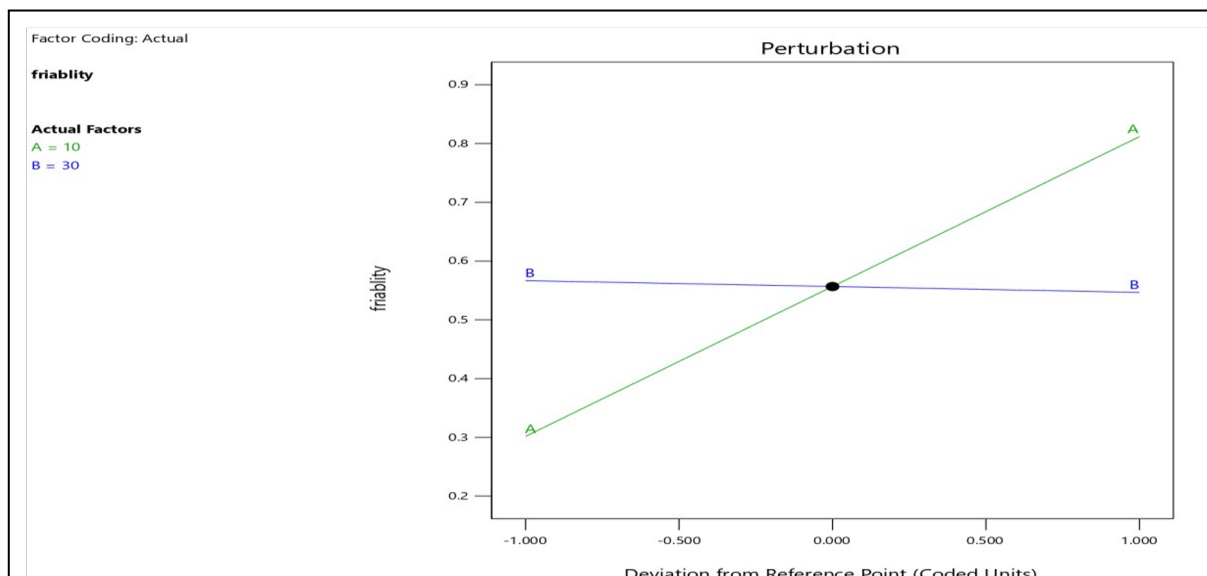
| Source                        | Sum of Squares | df | Mean Square | F-value | p-value  | Remark      |
|-------------------------------|----------------|----|-------------|---------|----------|-------------|
| <b>Model</b>                  | 0.3907         | 2  | 0.1954      | 43.02   | 0.0003   | Significant |
| <b>A – Magnesium Stearate</b> | 0.3902         | 1  | 0.3902      | 85.90   | < 0.0001 | Significant |
| <b>B – PVP K30</b>            | 0.0006         | 1  | 0.0006      | 0.1321  | 0.7287   | Significant |
| <b>Residual</b>               | 0.0273         | 6  | 0.0045      | —       | —        | —           |
| <b>Corrected Total</b>        | 0.4180         | 8  | —           | —       | —        | —           |

Factor coding is Coded.

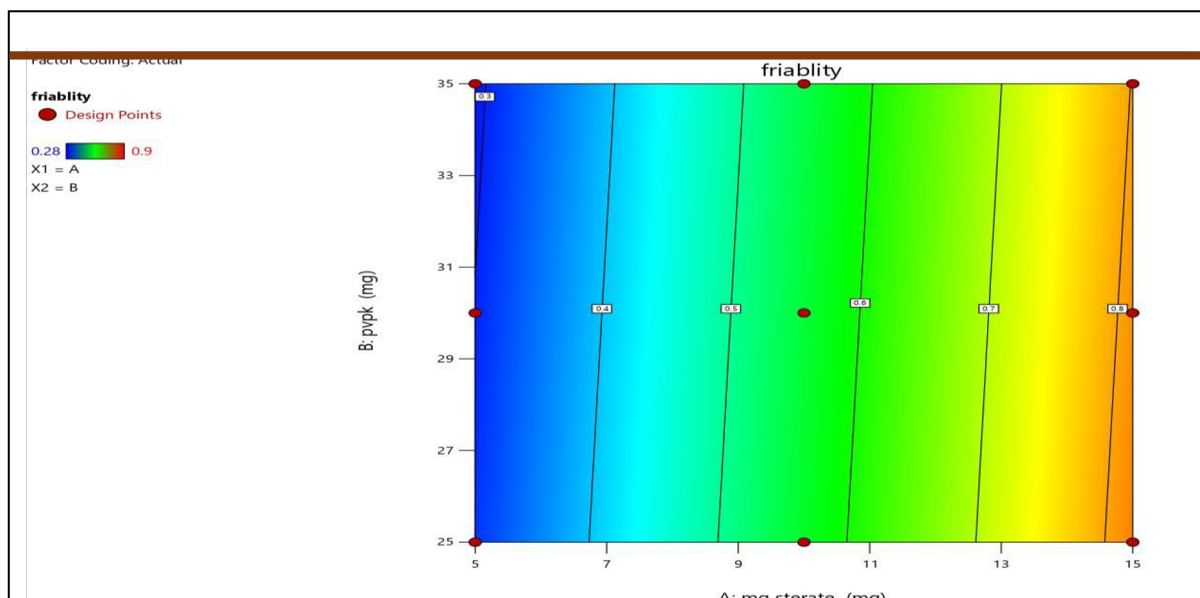
Sum of squares is Type III - Partial

The Model F-value of 43.02 implies the model is significant. There is only a 0.03% chance that an F-value this large could occur due to noise.

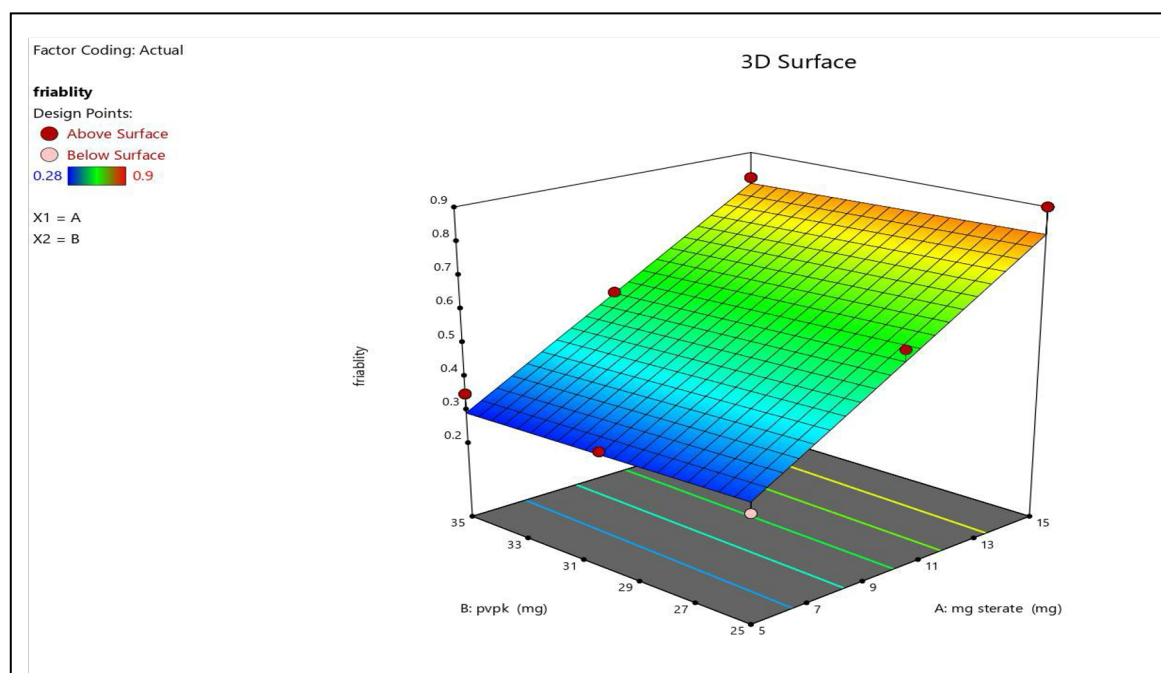
P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.



*Fig 37: Predicted versus Actual Plot for Tablet Friability(Y<sub>2</sub>)*



**Fig 38: Contour Plot Showing the Effect of Magnesium Stearate (A) and PVP K30 (B) on Tablet Friability(Y<sub>2</sub>)**



**Fig 39: Three-Dimensional (3D) Response Surface Plot Showing the Effect of Magnesium Stearate (A) and PVP K30 (B) on Tablet Friability (Y<sub>2</sub>)**

#### 9.9.2.1 Interpretation of Response Surface Plot, Contour Plot, and Predicted vs. Actual Plot for Friability (Y<sub>2</sub>):

The response surface plot and contour plot illustrate the influence of Magnesium Stearate (A) and PVP K30 (B) on the friability of the formulated tablets. The graphical analysis indicates that Magnesium Stearate had a more pronounced effect on friability than PVP K30. An increase in the concentration of Magnesium Stearate resulted in a decrease in friability, suggesting improved resistance of the tablets to abrasion and mechanical stress. In contrast, variations in

the concentration of PVP K30 produced only a slight effect on the friability response. The contour plot further demonstrated a gradual change in the response across the experimental region, indicating a predictable relationship between the formulation variables and tablet friability.

The response surface and contour plots for friability demonstrated that increasing the concentration of Magnesium Stearate increased tablet friability, whereas Crosspovidone showed only a marginal effect. Higher concentrations of lubricant may weaken tablet cohesion and result in increased friability. The contour plot identified the region where friability remained within acceptable pharmacopeial limits (<1%). These observations were consistent with the statistical analysis.

The predicted versus actual plot showed good agreement between the experimentally observed and model-predicted friability values, with most data points located close to the diagonal reference line. The graphical interpretation is in agreement with the ANOVA results, confirming that Magnesium Stearate was the major factor influencing tablet friability, while PVP K30 had no statistically significant effect. Overall, the graphical analysis validated the suitability of the developed model for optimization of tablet friability.

#### 9.9.2.2 *Coefficients in Terms of Coded Factors:*

**Table No. 49: Regression Coefficients of the Linear Model for Friability (Y<sub>2</sub>) in Terms of Coded Factors**

| <b>Factor</b>               | <b>Coefficient Estimate</b> | <b>df</b> | <b>Standard Error</b> | <b>95% CI Low</b> | <b>95% CI High</b> | <b>VIF</b> |
|-----------------------------|-----------------------------|-----------|-----------------------|-------------------|--------------------|------------|
| <b>Intercept</b>            | 0.5567                      | 1         | 0.0225                | 0.5017            | 0.6116             |            |
| <b>A-Magnesium Stearate</b> | 0.2550                      | 1         | 0.0275                | 0.1877            | 0.3223             | 1.0000     |
| <b>B-PVP K 30</b>           | -0.0100                     | 1         | 0.0275                | -0.0773           | 0.0573             | 1.0000     |

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-collinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.



### 9.9.2.3 Final Equation in Terms of Coded Factors:

**Table No. 50: Final Regression Equation in Terms of Coded Factors for Friability Response (Y<sub>2</sub>)**

| Term      | Coefficient Estimate |
|-----------|----------------------|
| Intercept | +0.5567              |
| A         | +0.2550              |
| B         | -0.0100              |

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

### 9.9.2.4 Final Equation in Terms of Actual Factors:

**Table No. 51: Final Regression Equation in Terms of Actual Factors for Friability Response (Y<sub>2</sub>)**

| Term               | Coefficient Estimate |
|--------------------|----------------------|
| Intercept          | +0.106667            |
| Magnesium Stearate | +0.051000            |
| PVP K 30           | -0.002000            |

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

### 9.9.2.5 ANOVA Interpretation for Friability:

The ANOVA results for friability indicated that the developed model was highly significant ( $p = 0.0003$ ).

Magnesium Stearate significantly affected friability, whereas PVP K-30 showed no significant

influence. Increasing Magnesium Stearate concentration increased friability due to weakening of interparticle bonds.

Although friability increased with higher lubricant concentration, all formulations remained well below the pharmacopeial limit of 1%, indicating acceptable tablet durability.

### 9.10 ANOVA for Quadratic model:

#### 9.10.1 Response 3: Percent Drug Release of Metformin HCl( $Y_3$ ):

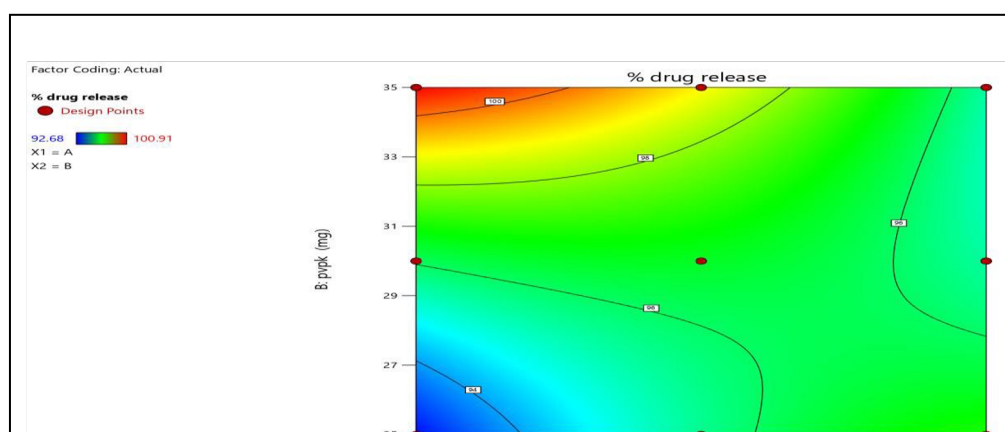
**Table No. 52: Analysis of Variance (ANOVA) for the Quadratic Model of Percentage Drug Release of Metformin Hydrochloride ( $Y_3$ )**

| Source                        | Sum of Squares | df | Mean Square | F-value | p-value | Remark      |
|-------------------------------|----------------|----|-------------|---------|---------|-------------|
| <b>Model</b>                  | 42.01          | 5  | 8.40        | 140.52  | 0.0009  | Significant |
| <b>A – Magnesium Stearate</b> | 0.4593         | 1  | 0.4593      | 7.68    | 0.0695  | Significant |
| <b>B – PVP K30</b>            | 16.17          | 1  | 16.17       | 270.44  | 0.0005  | Significant |
| <b>AB</b>                     | 23.23          | 1  | 23.23       | 388.55  | 0.0003  | Significant |
| <b>A<sup>2</sup></b>          | 0.9988         | 1  | 0.9988      | 16.70   | 0.0265  | Significant |
| <b>B<sup>2</sup></b>          | 1.15           | 1  | 1.15        | 19.24   | 0.0220  | Significant |
| <b>Residual</b>               | 0.1794         | 3  | 0.0598      | —       | —       | —           |
| <b>Corrected Total</b>        | 42.19          | 8  | —           | —       | —       | —           |

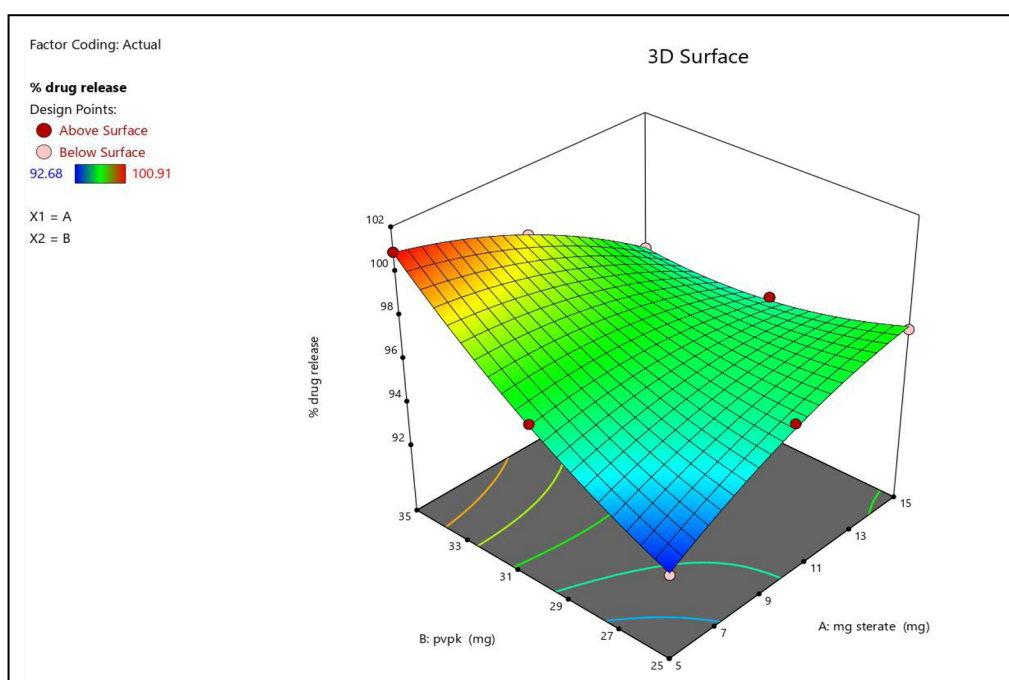
Factor coding is Coded.

Sum of squares is Type III - Partial

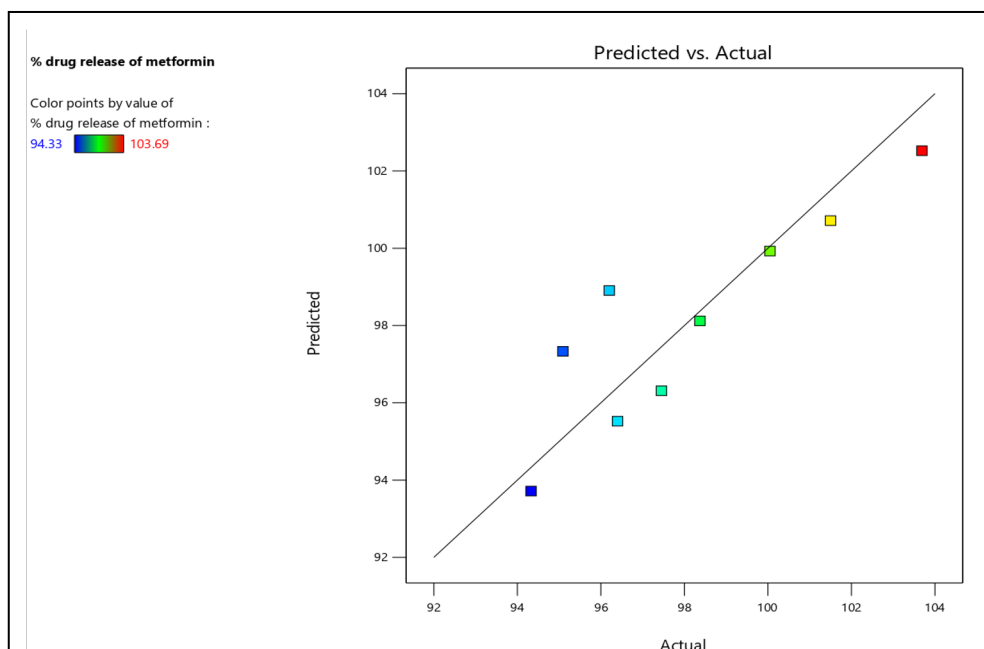
The Model F-value of 140.52 implies the model is significant. There is only a 0.09% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case B, AB, A<sup>2</sup>, B<sup>2</sup> are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy).



**Fig 40: Contour Plot Showing the Effect of Magnesium Stearate (A) and PVP K30 (B) on Percentage Drug Release of Metformin Hydrochloride ( $Y_3$ )**



**Fig 41: Three-Dimensional (3D) Response Surface Plot Showing the Effect of Magnesium Stearate (A) and PVP K30 (B) on Percentage Drug Release of Metformin Hydrochloride ( $Y_3$ )**



**Fig 42: Predicted versus Actual Plot for Percentage Drug Release of Metformin Hydrochloride ( $Y_3$ )**

### 9.10.1.1 Interpretation of Response Surface Plot, Contour Plot, and Predicted vs. Actual Plot for Percentage Drug Release of Metformin Hydrochloride ( $Y_3$ ):

The response surface plot and contour plot illustrate the combined influence of Magnesium Stearate (A) and PVP K30 (B) on the percentage drug release of Metformin Hydrochloride. The graphical analysis indicates that both formulation variables affected the drug release profile, with PVP K30 exhibiting a more pronounced influence than Magnesium Stearate. An increase in the concentration of PVP K30 enhanced the percentage drug release up to an optimum level, while the interaction between Magnesium Stearate and PVP K30 also contributed significantly to the response. The curved nature of the response surface confirms the presence of a quadratic relationship between the formulation variables and the percentage drug release.

The predicted versus actual plot demonstrated a close agreement between the experimentally observed and model-predicted values, with most data points located near the diagonal reference line. This indicates that the quadratic model accurately predicts the percentage drug release of Metformin Hydrochloride within the selected experimental region. The graphical interpretation is consistent with the ANOVA results, confirming the significance of the model and the interaction between the formulation variables.

### 9.10.1.2 Coefficients in Terms of Coded Factors:

**Table No. 53: Regression Coefficients of the Quadratic Model for Percentage Drug Release of Metformin Hydrochloride ( $Y_3$ ) in Terms of Coded Factors**

| Factor                | Coefficient Estimate | df | Standard Error | 95% CI Low | 95% CI High | VIF    |
|-----------------------|----------------------|----|----------------|------------|-------------|--------|
| Intercept             | 98.12                | 1  | 0.5586         | 96.75      | 99.49       |        |
| A- Magnesium Stearate | 2.59                 | 1  | 0.6842         | 0.9209     | 4.27        | 1.0000 |
| B- PVP K 30           | -1.81                | 1  | 0.6842         | -3.48      | -0.1342     | 1.0000 |

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than

indicate multi-collinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

#### 9.10.1.3 Final Equation in Terms of Coded Factors:

**Table No. 54: Final Regression Equation in Terms of Coded Factors for Percentage**

**Drug Release of Metformin Hydrochloride ( $Y_3$ )**

| Term             | Coefficient Estimate |
|------------------|----------------------|
| <b>Intercept</b> | +98.12               |
| <b>A</b>         | -1.81                |
| <b>B</b>         | +2.59                |
| <b>AB</b>        | -1.68                |

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

#### 9.10.1.4 Final Equation in Terms of Actual Factors:

The final regression equation in terms of actual factors was generated using Design-Expert software to describe the relationship between the independent variables and the percentage drug release of Metformin Hydrochloride ( $Y_3$ ). The equation enables prediction of the response by substituting the actual values of Magnesium Stearate and PVP K30 used during formulation. The coefficients of the regression equation are presented in the following table.

**Table No. 55: Final Regression Equation in Terms of Actual Factors for Percentage**

**Drug Release of Metformin Hydrochloride ( $Y_3$ )**

| Term                                 | Coefficient Estimate |
|--------------------------------------|----------------------|
| <b>Intercept</b>                     | +86.16667            |
| <b>Magnesium Stearate</b>            | -0.361667            |
| <b>PVP K 30</b>                      | +0.519000            |
| <b>Magnesium Stearate * PVP K 30</b> | -0.067300            |

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the centre of the design space.

#### 9.10.1.5 Interpretation of Percentage Drug Release of Metformin Hydrochloride ( $Y_3$ ):

Drug release studies demonstrated that both formulation variables significantly influenced the dissolution behaviour of Metformin Hydrochloride. The quadratic model obtained was statistically significant ( $p = 0.0009$ ).

PVP K-30 exhibited a significant positive effect on drug release, whereas Magnesium Stearate showed a negative effect. Higher concentrations of PVP K-30 enhanced tablet wettability and facilitated rapid penetration of dissolution medium into the tablet matrix.

In contrast, Magnesium Stearate retarded drug release due to its hydrophobic nature. Interaction effects between formulation variables were also significant, indicating that simultaneous optimization of both variables was necessary to achieve maximum drug release.

#### 9.10.2 Response 4: Percent Drug Release of *Syzygium cumini* ( $Y_4$ )

Analysis of Variance (ANOVA) was performed using Design-Expert® software to evaluate the significance of the quadratic model and to determine the influence of the selected formulation variables, namely Magnesium Stearate (A) and PVP K30 (B), on the percentage drug release of *Syzygium cumini* ( $Y_4$ ). The statistical analysis was carried out to assess the individual and interaction effects of the formulation variables on the drug release response. The significance of the model and its terms was determined based on the F-value and p-value at a 95% confidence level. The ANOVA results for the percentage drug release of *Syzygium cumini* are presented in the following table.

**Table No. 56: Analysis of Variance (ANOVA) for the Quadratic Model of Percentage Drug Release of *Syzygium cumini* ( $Y_4$ )**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | Remark      |
|--------|----------------|----|-------------|---------|---------|-------------|
| Model  | 71.35          | 3  | 23.78       | 21.51   | 0.0028  | Significant |

|                               |       |   |       |       |        |             |
|-------------------------------|-------|---|-------|-------|--------|-------------|
| <b>A – Magnesium Stearate</b> | 19.62 | 1 | 19.62 | 17.75 | 0.0084 | Significant |
| <b>B – PVP K30</b>            | 40.40 | 1 | 40.40 | 36.55 | 0.0018 | Significant |
| <b>AB</b>                     | 11.32 | 1 | 11.32 | 10.24 | 0.0240 | Significant |
| <b>Residual</b>               | 5.53  | 5 | 1.11  | —     | —      | —           |
| <b>Corrected Total</b>        | 76.88 | 8 | —     | —     | —      | —           |

Factor coding is Coded.

Sum of squares is Type III - Partial

The Model F-value of 21.51 implies the model is significant. There is only a 0.28% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B, AB are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The ANOVA results demonstrated that the quadratic model was statistically significant ( $p = 0.0028$ ), indicating that the selected formulation variables had a significant influence on the percentage drug release of *Syzygium cumini*. Both Magnesium Stearate (A) and PVP K30 (B), along with their interaction (AB), showed significant effects on the response, confirming the suitability of the developed model for optimization and prediction of drug release.

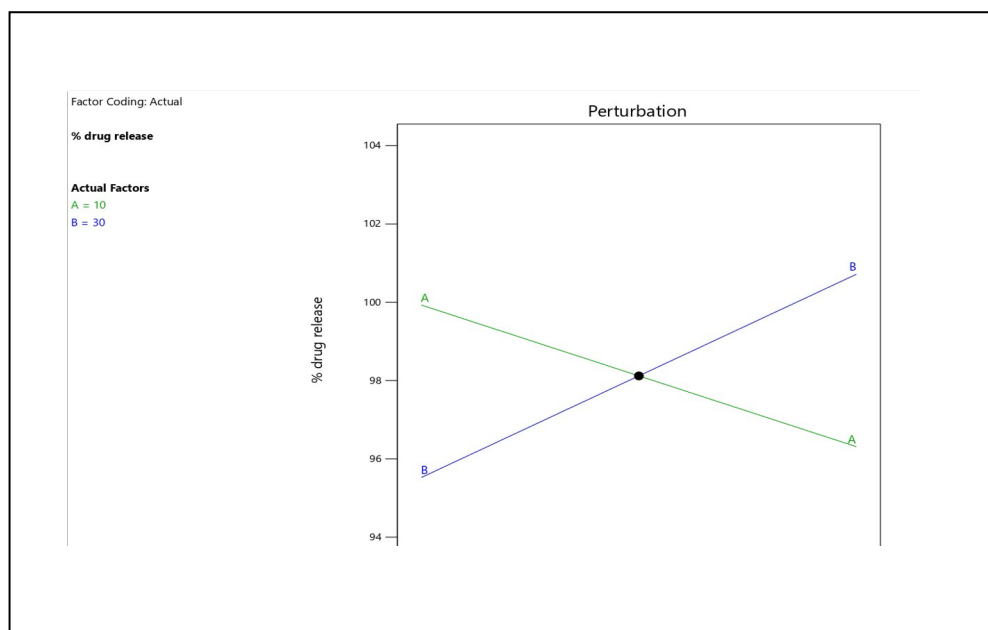


Fig 43: Perturbation Plot Showing the Effect of Magnesium Stearate (A) and PVP K30 (B) on Percentage Drug Release of *Syzygium cumini* (Y<sub>4</sub>)

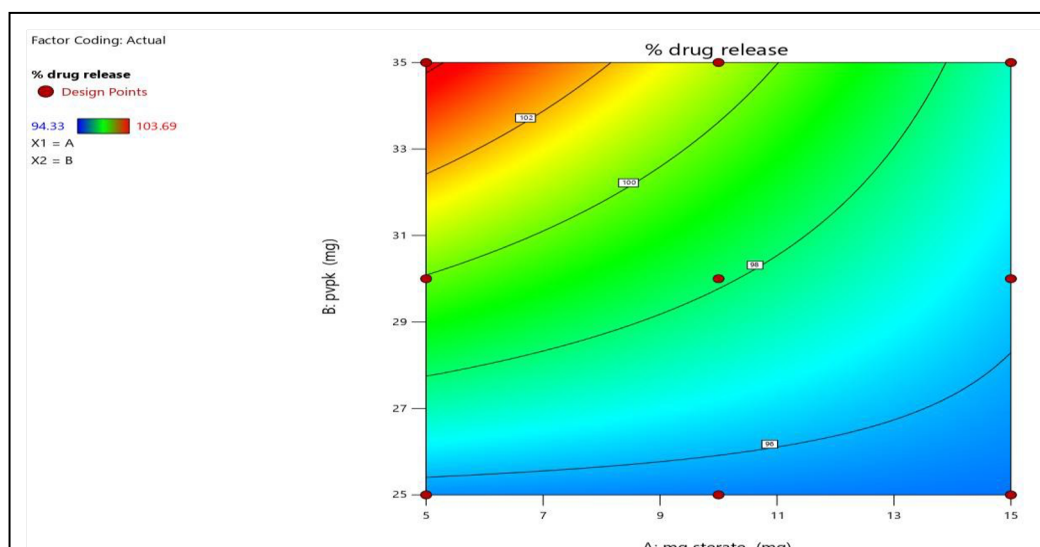


Fig 44: Contour Plot Showing the Effect of Magnesium Stearate (A) and PVP K30 (B) on Percentage Drug Release of *Syzygium cumini* (Y<sub>4</sub>)

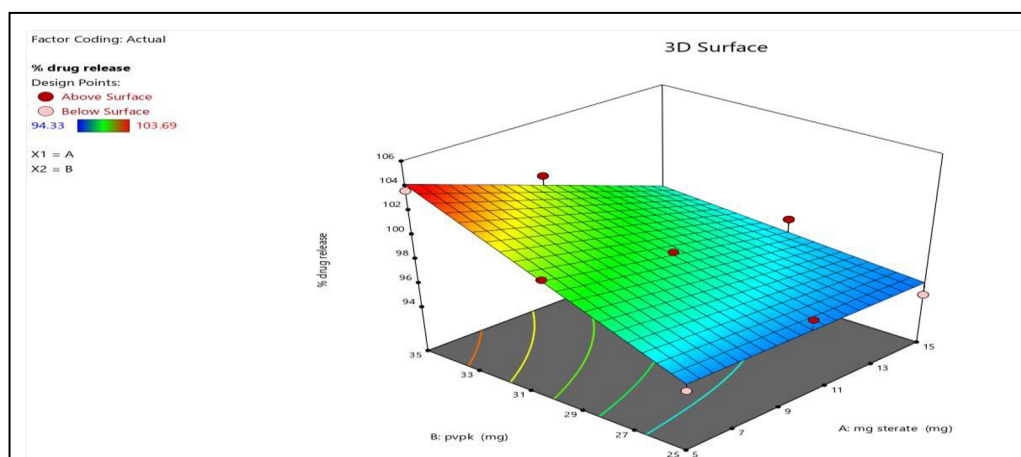


Fig 45: Three-Dimensional (3D) Response Surface Plot Showing the Effect of Magnesium Stearate (A) and PVP K30 (B) on Percentage Drug Release of *Syzygium cumini* (Y<sub>4</sub>)

#### 9.10.2.1 Coefficients in Terms of Coded Factors:

Table No. 57: Coefficient Estimates of the Quadratic Model for Percentage Drug Release of *Syzygium cumini* (Y<sub>4</sub>)



| Factor                       | Coefficient Estimate | df | Standard Error | 95% CI Low | 95% CI High | VIF    |
|------------------------------|----------------------|----|----------------|------------|-------------|--------|
| <b>Intercept</b>             | 98.12                | 1  | 0.3505         | 97.22      | 99.02       |        |
| <b>A- Magnesium Stearate</b> | -1.81                | 1  | 0.4292         | -2.91      | -0.7049     | 1.0000 |
| <b>B-PVP K 30</b>            | 2.59                 | 1  | 0.4292         | 1.49       | 3.70        | 1.0000 |
| <b>AB</b>                    | -1.68                | 1  | 0.5257         | -3.03      | -0.3311     | 1.0000 |

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-collinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

#### 9.10.2.2 Final Equation in Terms of Coded Factors:

**Table No: 58 Final Regression Equation in Terms of Coded Factors for Percentage Drug Release of *Syzygium cumini* (Y<sub>4</sub>)**

| Term             | Coefficient Estimate |
|------------------|----------------------|
| <b>Intercept</b> | +98.12               |
| <b>A</b>         | -1.81                |
| <b>B</b>         | +2.59                |
| <b>AB</b>        | -1.68                |

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

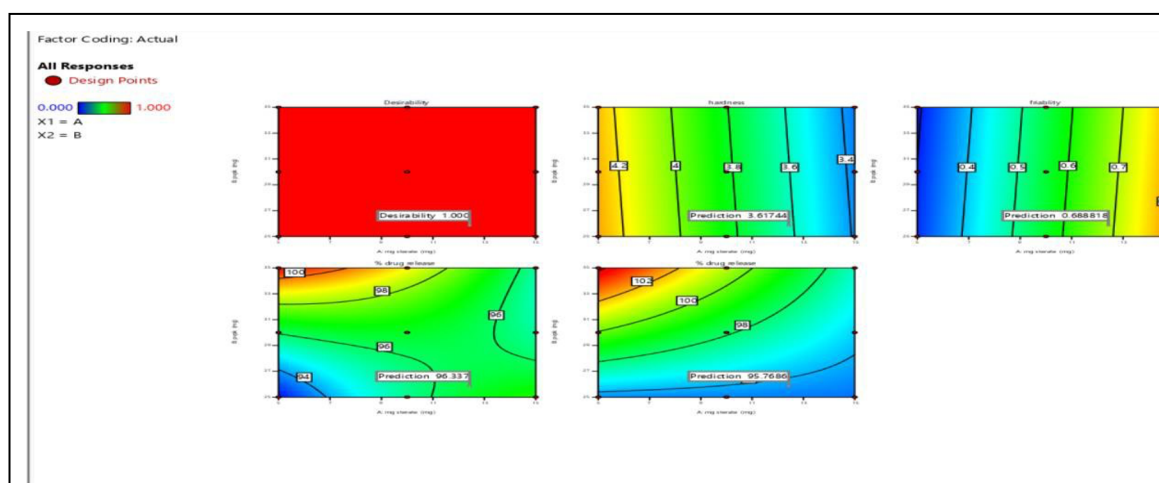
#### 9.10.2.3 Final Equation in Terms of Actual Factors:

**Table No. 59: Final Regression Equation in Terms of Actual Factors for Percentage Drug Release of *Syzygium cumini* (Y<sub>4</sub>)**

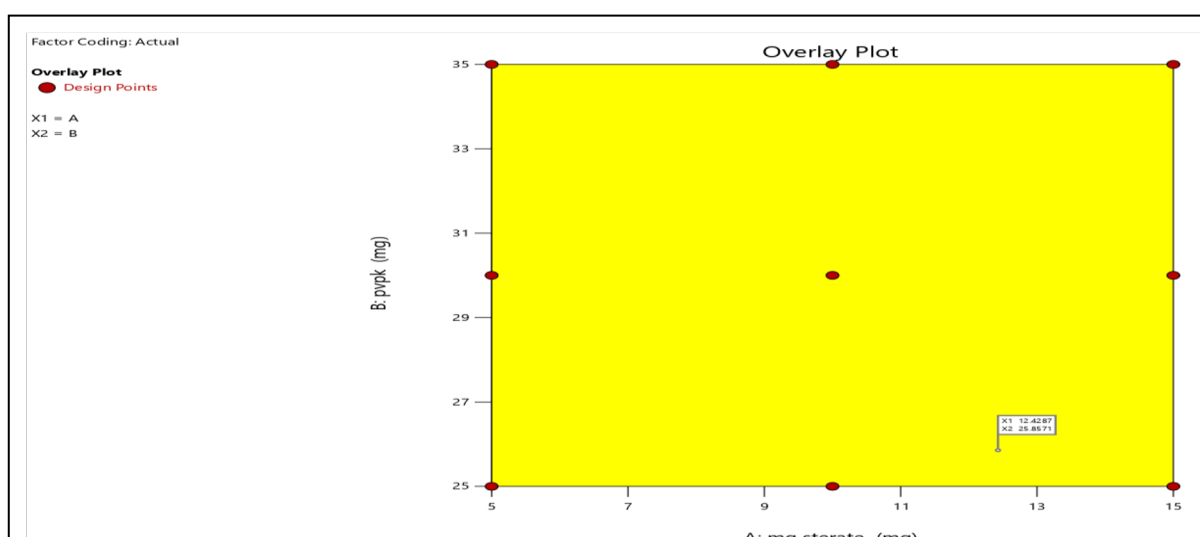
| Term                          | Coefficient Estimate |
|-------------------------------|----------------------|
| Intercept                     | +65.97667            |
| Magnesium Stearate            | +1.65733             |
| PVP K 30                      | +1.19200             |
| Magnesium Stearate * PVP K 30 | -0.067300            |

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the centre of the design space.

The regression equation provides a mathematical relationship between the formulation variables and the percentage drug release of *Syzygium cumini*. It can be used to predict the response within the selected design space and to estimate the effect of changes in the concentrations of Magnesium Stearate and PVP K30 on the drug release profile of the optimized formulation.



**Fig 46: Desirability Plot for Numerical Optimization of the Optimized Formulation (F7)**



**Fig 47: Overlay Plot Illustrating the Design Space for Optimization of the Formulation Variables**

#### **9.10.2.4 Interpretation of Percentage Drug Release of *Syzygium cumini* (Y<sub>4</sub>):**

The percentage drug release of *Syzygium cumini* was significantly influenced by the formulation variables, namely Magnesium Stearate and PVP K30. The ANOVA results confirmed that the quadratic model was statistically significant ( $p = 0.0028$ ), indicating that the developed model adequately described the relationship between the formulation variables and the drug release response. Both Magnesium Stearate and PVP K30, as well as their interaction (AB), exhibited a significant effect on the percentage drug release of *Syzygium cumini*, demonstrating the importance of optimizing these variables to achieve the desired dissolution profile.

An increase in the concentration of PVP K30 improved the percentage drug release by promoting better tablet integrity and facilitating efficient penetration of the dissolution medium into the tablet matrix. In contrast, excessive levels of Magnesium Stearate tended to influence the release characteristics because of its hydrophobic nature, which can reduce the rate of medium penetration and delay drug dissolution. The interaction between the two formulation variables further indicated that an appropriate balance of binder and lubricant was essential for obtaining optimal drug release.

The response surface plots and contour plots supported the statistical findings by illustrating the combined influence of the formulation variables on the drug release response. The optimized formulation achieved a high percentage drug release while maintaining acceptable physical quality attributes, confirming the suitability of the selected formulation composition. These results demonstrate that the optimized batch (F7) successfully fulfilled the desired quality requirements for the immediate-release combination tablet of Metformin Hydrochloride and *Syzygium cumini*.

#### **9.10.3 Interpretation of Optimization Results:**

The factorial design approach successfully evaluated the influence of Magnesium Stearate and PVP K30 on the critical quality attributes of the combination tablet formulation. Statistical analysis demonstrated that variations in the concentrations of these formulation variables significantly affected tablet hardness, friability, and the percentage drug release of both

Metformin Hydrochloride and *Syzygium cumini*. The generated mathematical models, ANOVA results, regression equations, and response surface plots effectively described the relationship between the independent variables and the measured responses.

Based on the desirability function and numerical optimization performed using Design-Expert® software, batch F7 was selected as the optimized formulation. The optimized batch exhibited satisfactory pre-compression and post-compression characteristics, acceptable mechanical strength, low friability, and excellent drug release for both active ingredients. These findings confirmed that the selected formulation variables and their optimized levels were suitable for the successful development of an immediate-release combination tablet of Metformin Hydrochloride and *Syzygium cumini*.

#### 9.11 OPTIMIZED FORMULATION BATCH:

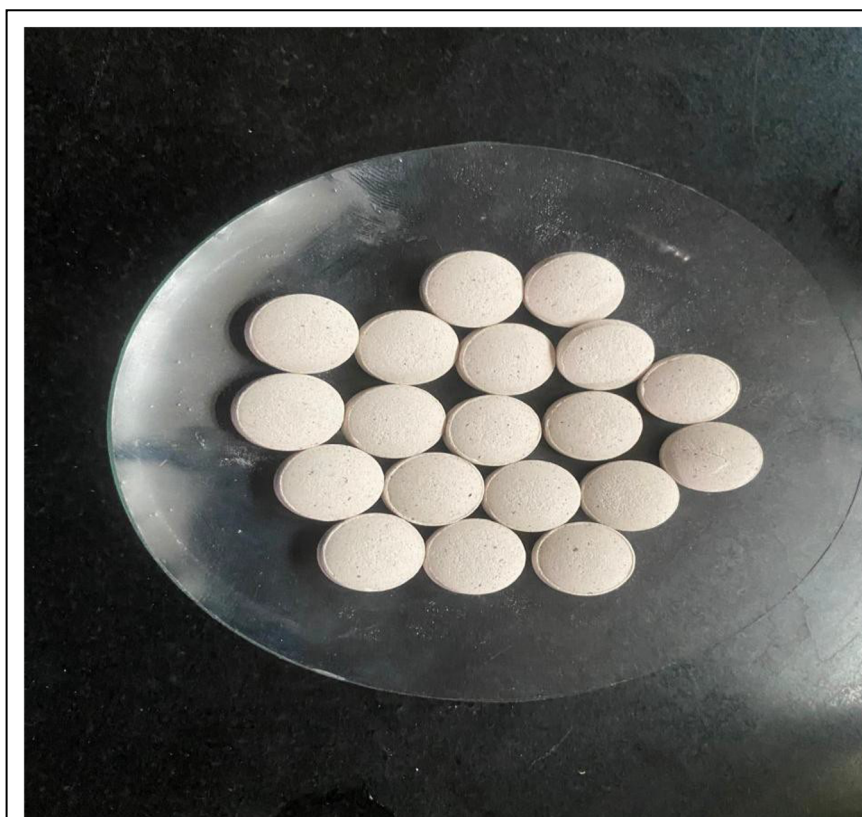
Optimization of the formulation was carried out using the Design-Expert® software based on the principles of Quality by Design (QbD). The objective of the optimization process was to obtain a tablet formulation possessing the desired quality attributes, including adequate hardness, acceptable friability, and maximum drug release of both Metformin Hydrochloride and *Syzygium cumini*. The software generated several formulation solutions based on the experimental data, and the formulation with the highest desirability value was selected as the optimized batch.

The optimized formulation was found to exhibit satisfactory pre-compression and post-compression characteristics along with enhanced in vitro drug release.

**Table No. 60: Composition of the Optimized Tablet Formulation (F7)**

| Ingredient                 | Quantity(mg/tablet) | Role               |
|----------------------------|---------------------|--------------------|
| Metformin HCl              | 250                 | API                |
| Jamun Seed Extract Powder  | 250                 | API                |
| Microcrystalline Cellulose | 50                  | Diluent            |
| PVP K-30                   | 30                  | Binder             |
| Croscarmellose Sodium      | 15                  | Super disintegrant |
| Colloidal Silicon Dioxide  | 5                   | Glidant            |

|                           |              |           |
|---------------------------|--------------|-----------|
| <b>Magnesium Stearate</b> | 10           | Lubricant |
| <b>Total Weight</b>       | <b>610mg</b> | --        |



**Fig 48: Optimized Batch Tablets**

Numerical optimization was performed using Design-Expert® software to identify the most suitable formulation capable of providing the desired tablet characteristics. The optimization criteria were established to obtain adequate hardness, minimum friability, and maximum drug release for both Metformin Hydrochloride and *Syzygium cumini*.

Based on the generated solutions and desirability criteria, formulation F7 was selected as the optimized batch. The optimized formulation exhibited satisfactory physicochemical properties, including acceptable hardness, low friability, good flow characteristics, and enhanced drug release performance. The results demonstrated that the selected concentrations of Croscarmellose Sodium and Magnesium Stearate produced tablets with the desired quality attributes. The optimized formulation showed hardness of approximately 4.1 kg/cm<sup>2</sup>, friability below 1%, and excellent dissolution characteristics for both active ingredients. Therefore, batch F7 was considered the most suitable formulation and was selected for further evaluation and stability studies.

### 9.11.1 *Pre-Compression Evaluation of Optimized Batch (F7):*

The pre-compression evaluation of the optimized formulation batch (F7) demonstrated satisfactory flow and packing characteristics of the powder blend, indicating its suitability for direct compression. The angle of repose was found to be  $27.84 \pm 0.13^\circ$ , which indicates good flowability of the powder mixture.

**Table No. 61: Pre-Compression Evaluation Results of the Optimized Formulation (F7)**

| Parameter       | Result           |
|-----------------|------------------|
| Angle of repose | $27.84 \pm 0.13$ |
| Bulk Density    | $0.53 \pm 0.01$  |
| Tapped Density  | $0.61 \pm 0.01$  |
| Carr's Index    | $13.11 \pm 0.17$ |
| Hausner's Ratio | $1.15 \pm 0.01$  |

The pre-compression evaluation of the optimized formulation batch (F7) demonstrated satisfactory flow and packing characteristics of the powder blend, indicating its suitability for direct compression. The angle of repose was found to be  $27.84 \pm 0.13^\circ$ , which indicates good flowability of the powder mixture. The bulk density and tapped density were  $0.53 \pm 0.01 \text{ g/cm}^3$  and  $0.61 \pm 0.01 \text{ g/cm}^3$ , respectively, reflecting good packing ability and compressibility of the blend. The small difference between the two density values suggests minimal interparticle voids and uniform particle distribution.

The Carr's Index and Hausner's Ratio are important indicators of powder flow properties. The optimized batch exhibited a Carr's Index of  $13.11 \pm 0.17\%$  and a Hausner's Ratio of  $1.15 \pm 0.01$ , both of which fall within the acceptable range for powders with good flow characteristics. These findings indicate that the optimized powder blend possessed excellent flowability and compressibility, ensuring uniform die filling during tablet compression. Overall, the pre-compression results confirmed that the formulation was suitable for the direct compression process and contributed to the production of tablets with consistent quality attributes.

### 9.11.2 *Post-Compression Evaluation Parameters of Optimized Batch F7:*

**Table No. 62: Post-Compression Evaluation Results of the Optimized Formulation Batch (F7)**

| Parameter      | Result      |
|----------------|-------------|
| Average weight | 610.0 ± 1.5 |
| Thickness      | 4.63 ± 0.02 |
| Hardness       | 4.1 ± 0.08  |
| Friability     | 0.31 ± 0.01 |

The optimized formulation batch (F7) was evaluated for post-compression parameters to assess its physical quality and compliance with pharmacopoeial standards. The tablets exhibited an average weight of  $610.0 \pm 1.5$  mg, indicating excellent weight uniformity and consistent die filling during compression. The thickness was found to be  $4.63 \pm 0.02$  mm, demonstrating uniform tablet dimensions and reproducibility of the compression process. These results suggest that the formulation and compression parameters were well optimized, resulting in tablets with consistent physical characteristics.

The hardness of the optimized tablets was  $4.1 \pm 0.08$  kg/cm<sup>2</sup>, providing adequate mechanical strength to withstand handling while maintaining suitable disintegration properties. The friability was  $0.31 \pm 0.01\%$ , which is well below the pharmacopoeial limit of 1.0%, indicating excellent resistance to abrasion and mechanical stress. Overall, the post-compression evaluation confirmed that the optimized batch (F7) possessed satisfactory physical quality attributes and was suitable for further dissolution studies and stability evaluation.

Among all formulations, batch F7 was selected as the optimized formulation because it demonstrated the most desirable balance between hardness, friability, flow properties, and drug release.

The optimized formulation exhibited:

- Hardness: 4.1 kg/cm<sup>2</sup>
- Friability: 0.31%
- Excellent flow properties

- High drug release for both active ingredients

These results indicated successful optimization of formulation variables using factorial design methodology.

#### 9.12 STABILITY STUDIES :

The optimized formulation batch (F7) was subjected to stability studies to evaluate its ability to retain the desired quality attributes during storage. The tablets were stored under long-term stability conditions of 30°C/65% RH, and samples were evaluated initially, after 1 month, and after 3 months. Various physical and pharmaceutical parameters, including average weight, thickness, hardness, friability, disintegration time, drug content, and percentage drug release of both Metformin Hydrochloride and *Syzygium cumini*, were assessed at each interval. The stability study was carried out to determine whether the formulation maintained its physical integrity, mechanical strength, and therapeutic performance throughout the storage period.

Stability studies are an important part of pharmaceutical product development, as they provide evidence regarding the ability of a formulation to maintain its quality, safety, and efficacy throughout its intended shelf life.

##### 9.12.1 Long-Term Stability Study (30°C ± 2°C/65% ± 5% RH):

**Table No. 63: Stability Study Results of Optimized Batch (F7) under Long-Term Storage Conditions (30°C ± 2°C/65% ± 5% RH)**

| Condition 30°C 65% RH (Long Term) |              |               |               |
|-----------------------------------|--------------|---------------|---------------|
|                                   | Initial      | 1Months       | 3Months       |
| <b>Average Weight</b>             | 610.2 ± 1.6  | 610.0 ± 1.5   | 609.8 ± 1.4   |
| <b>Thickness (mm)</b>             | 4.61 ± 0.02  | 4.60 ± 0.02   | 4.59 ± 0.03   |
| <b>Hardness (Kg/cm2)</b>          | 3.6          | 3.5           | 3.6           |
| <b>Friability</b>                 | 0.028%       | 0.031%        | 0.026%        |
| <b>DT</b>                         | 3 Min 43Sec. | 3 Min 51 Sec. | 3 Min 41 Sec. |
| <b>% Drug Release</b>             |              |               |               |
| <b>Metformin</b>                  | 100.05       | 99.98%        | 99.94%        |
| <b>Jamun Seeds</b>                | 100.91       | 100.89%       | 100.83%       |
| <b>Drug Content</b>               |              |               |               |
| <b>Metformin</b>                  | 99.66        | 99.64%        | 99.61%        |



|                    |        |         |         |
|--------------------|--------|---------|---------|
| <b>Jamun Seeds</b> | 100.18 | 100.13% | 100.12% |
|--------------------|--------|---------|---------|

#### 9.12.1.1 Average Weight

- Over the course of the three-month storage period, the average tablet weight stayed nearly unchanged.
- There was no discernible change in the weight of the tablets, suggesting that there was little moisture absorption or loss during extended storage.
- The outcomes show that the formulation has good physical stability and complies with pharmacopeial regulations.

#### 9.12.1.2 *Thickness*

- During storage, tablet thickness hardly little changed.
- The tablets' uniform thickness shows that they retained their dimensional integrity during the course of the study.
- Under long-term storage circumstances, there was no indication of swelling, shrinking.

#### 9.12.1.3 *Hardness*

- Over the course of the three-month storage period, the hardness values (3.5–3.6 kg/cm<sup>2</sup>) stayed nearly constant.
- This shows that during storage, the tablets maintained their structural integrity and mechanical strength.
- There was no discernible impact of humidity or temperature on tablet compactness.

#### 9.12.1.4 *Friability*

- The pharmacopeial limit of 1% was still far below the friability values.
- The findings show that the tablets have good resistance to mechanical stress and abrasion.

#### 9.12.1.5 *Disintegration Time (DT)*

- Throughout the study period, there were only slight changes in the disintegration time.

- Every tablet broke down within reasonable bounds.
- Tablet breakdown was not negatively impacted by storage conditions, and the disintegrant continued to be effective.

#### **9.12.1.6      *Percentage Drug Release – Metformin***

- After three months, drug release dropped little from 100.05% to 99.94%.
- The slight variation shows that Metformin HCl is very stable in the formulation.
- Throughout storage, the dissolution profile virtually stayed the same.

#### **9.12.1.7      *Percentage Drug Release – Jamun Seed***

- The percentage of drugs released stayed between 100.83% and 100.91%.
- Throughout storage, the herbal component retained its releasing properties.
- There was no discernible degradation of the active ingredients in the herbs.

#### **9.12.1.8      *Drug Content – Metformin***

- The drug content stayed between 99.61 and 99.66 percent, which is acceptable.
- The findings show that metformin HCl is uniformly distributed and chemically stable during storage.
- The medication did not significantly deteriorate.

#### **9.12.1.9      *Drug Content – Jamun Seed***

- Over the course of the research, the drug content stayed essentially constant.
- Long-term storage conditions did not affect the stability of the herbal active ingredients.
- There was no discernible decrease of power.

#### **9.12.2      *Accelerated Stability Study (40°C ± 2°C/75% ± 5% RH:***

**Table No. 64: Stability Study Results of Optimized Batch (F7) under Accelerated Storage**

**Conditions (40°C ± 2°C/75% ± 5% RH)**

| <b>Condition (40°C ± 2°C/75% ± 5% RH)</b> |                |                |                |
|-------------------------------------------|----------------|----------------|----------------|
|                                           | <b>Initial</b> | <b>1Months</b> | <b>3Months</b> |
| <b>Average Weight</b>                     | 610.2 ± 1.6    | 609.6 ± 1.7    | 609.1 ± 1.8    |
| <b>Thickness (mm)</b>                     | 4.61 ± 0.02    | 4.59 ± 0.03    | 4.57 ± 0.03    |
| <b>Hardness (Kg/cm<sup>2</sup>)</b>       | 3.6            | 3.4            | 3.3            |
| <b>Friability</b>                         | 0.028%         | 0.029%         | 0.026%         |
| <b>DT</b>                                 | 3 Min 43Sec.   | 3 Min 51 Sec.  | 3 Min 41 Sec.  |
| <b>% Drug Release</b>                     |                |                |                |
| <b>Metformin</b>                          | 100.05         | 99.46%         | 99.24%         |
| <b>Jamun Seeds</b>                        | 100.91         | 100.43%        | 100.19%        |
| <b>Drug Content</b>                       |                |                |                |
| <b>Metformin</b>                          | 99.66          | 99.60%         | 99.56%         |
| <b>Jamun Seeds</b>                        | 100.18         | 100.07%        | 100.07%        |

#### 9.12.2.1 Average Weight

- A slight decrease in average tablet weight was observed during accelerated storage.
- The minor variation may be attributed to the loss of residual moisture due to exposure to elevated temperature.
- However, the change was insignificant and remained within acceptable limits, indicating satisfactory stability of the formulation.

#### 9.12.2.2 Thickness

- Tablet thickness exhibited only a marginal decrease during the study period.
- The slight reduction may be associated with moisture loss and minor densification of the tablet matrix under accelerated conditions.
- Despite this change, the tablets retained their dimensional stability and remained within acceptable specifications.

#### 9.12.2.3 Hardness

- A slight decrease in hardness was observed from 3.6 kg/cm<sup>2</sup> to 3.3 kg/cm<sup>2</sup> after 3

months.

- The reduction may be attributed to the effect of elevated temperature on the tablet matrix.
- However, the hardness values remained within acceptable limits, indicating adequate mechanical strength.

#### **9.12.2.4      *Friability***

- Friability values remained below 1% throughout the study period.
- Only minor fluctuations were observed during storage.
- The tablets maintained good resistance to abrasion and mechanical stress under accelerated conditions.

#### **9.12.2.5      *Disintegration Time (DT)***

- No significant change in disintegration time was observed during storage.
- The tablets continued to disintegrate within the acceptable range.
- This indicates that the disintegrant retained its effectiveness despite exposure to elevated temperature.

#### **9.12.2.6      *Percentage Drug Release – Metformin***

- Drug release decreased slightly from 100.05% to 99.24% after 3 months.
- The minor reduction may be due to slight changes in the tablet matrix during storage.
- However, the dissolution profile remained within acceptable limits, indicating good formulation stability.

#### **9.12.2.7      *Percentage Drug Release – Jamun Seed***

- Drug release decreased marginally from 100.91% to 100.19% during storage.
- The results suggest that the herbal active constituents remained stable under accelerated conditions.
- No significant effect on release characteristics was observed.

#### **9.12.2.8      *Drug Content – Metformin***

- Drug content decreased slightly from 99.66% to 99.56% after 3 months.
- The change was minimal and remained within pharmacopeial acceptance criteria.
- This indicates good chemical stability of Metformin HCl

#### **. 9.12.2.9 Drug Content – Jamun Seed**

- Drug content remained practically constant at approximately 100% throughout study.
- The herbal component showed excellent stability under accelerated storage conditions.
- No appreciable degradation of active constituents was observed.

#### **9.12.3 Discussion of Stability Studies:**

The stability study demonstrated that the optimized formulation remained physically and chemically stable under both long-term and accelerated storage conditions.

No significant changes were observed in:

- Tablet weight
- Thickness
- Hardness
- Friability
- Drug content
- Drug release

The minor variations observed during storage remained within acceptable pharmacopeial limits. These findings confirmed the stability of both Metformin Hydrochloride and Syzygium cumini in the developed formulation.

#### **9.13 DISSOLUTION COMPARISON:**

##### **9.13.1 Dissolution Comparison with the Marketed Sample ( METFORMIN HCl):**

Mfg by: Glenmark Pharmaceutical LTD

Batch no: GMH2502401

The dissolution profile of the optimized formulation (F7) was compared with that of the marketed Metformin Hydrochloride tablet to evaluate its in vitro drug release performance. Dissolution testing was carried out under identical experimental conditions, and the percentage drug release was measured at predetermined time intervals. The comparison was performed to assess the release characteristics of the developed formulation relative to the commercially available product.

The comparative dissolution study was undertaken to determine whether the optimized formulation (F7) could achieve a drug release profile comparable to or better than that of the marketed Metformin Hydrochloride tablet. Drug release at different time intervals provides valuable information regarding the dissolution behavior and release kinetics of the formulation. A formulation exhibiting rapid and complete drug release is expected to enhance drug availability and improve therapeutic performance. The results obtained from the dissolution study facilitate a direct comparison of the release characteristics of the optimized formulation with those of the marketed product under identical test conditions.

Furthermore, the comparative dissolution evaluation provides an indication of the efficiency of the optimized formulation in releasing the drug under simulated physiological conditions. A dissolution profile comparable to or superior to that of the marketed formulation demonstrates the effectiveness of the selected formulation strategy and confirms the suitability of the optimized batch (F7) for immediate-release tablet formulation.

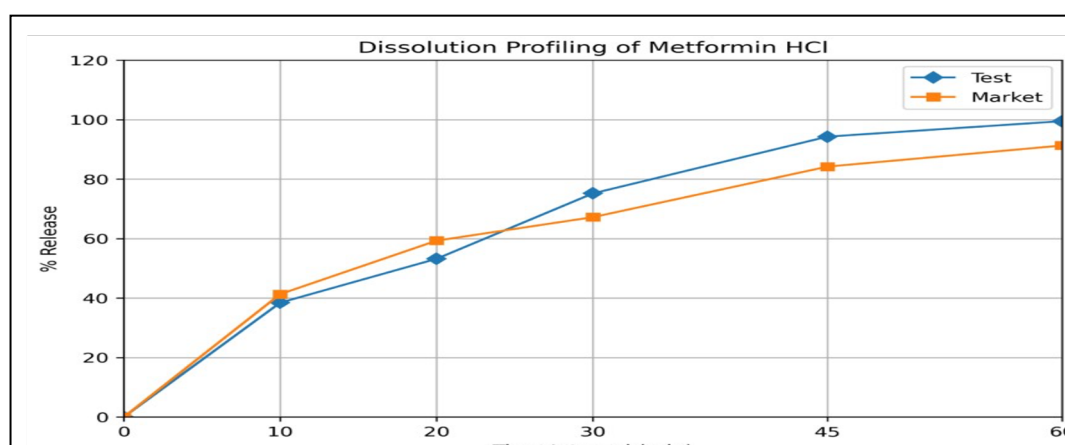
The dissolution study provides valuable information regarding the release behaviour and therapeutic performance of the optimized formulation. A comparable or improved drug release profile indicates that the developed formulation possesses satisfactory dissolution characteristics and has the potential to achieve the desired therapeutic effect. The comparative dissolution data of the optimized formulation and the marketed product are presented in the following table.

***Table No. 65: Comparison of In Vitro Drug Release Profile of the Optimized and Marketed Metformin Hydrochloride Tablets***

| <b>Time (min)</b> | <b>Optimized Formulation (F7) (% Drug Release)</b> | <b>Marketed Formulation (% Drug Release)</b> |
|-------------------|----------------------------------------------------|----------------------------------------------|
| <b>0</b>          | 0.00                                               | 0.00                                         |
| <b>10</b>         | 38.43                                              | 41.30                                        |
| <b>20</b>         | 53.19                                              | 59.30                                        |
| <b>30</b>         | 75.19                                              | 67.20                                        |
| <b>45</b>         | 94.29                                              | 84.20                                        |
| <b>60</b>         | 99.49                                              | 91.30                                        |

The in vitro drug release profile of the optimized formulation (F7) was compared with that of the marketed Metformin Hydrochloride tablet under identical dissolution conditions. Both formulations exhibited a gradual increase in drug release with increasing time. During the initial stages (10 and 20 minutes), the marketed formulation showed slightly higher drug release than the optimized formulation. However, from 30 minutes onward, the optimized formulation demonstrated a faster and more complete release profile.

At 60 minutes, the optimized formulation achieved 99.49% drug release, whereas the marketed formulation exhibited 91.30% drug release. The improved dissolution performance of the optimized formulation may be attributed to the optimized concentrations of excipients, which facilitated rapid tablet disintegration and efficient penetration of the dissolution medium.



**Fig 49: Comparative Dissolution Profile of the Optimized Formulation (F7) and the Marketed Metformin Hydrochloride Tablet**

- In order to compare the optimized formulation's drug release behaviour with that of the commercial product, a dissolving study was conducted.
- In comparison to the test formulation (38.43% and 53.19%), the marketed formulation exhibited slightly higher drug release (41.3% and 59.3%) at 10 and 20 minutes, suggesting a comparatively quicker initial release.
- The modified formulation showed better tablet disintegration and dissolving properties at 30 minutes, with a greater drug release (75.19%) compared to the marketed version (67.2%).
- The marketed product only released 84.2% of the medication at 45 minutes, while the improved formulation released 94.29%, indicating better dissolving performance.
- The improved formulation demonstrated nearly full drug release within the allotted

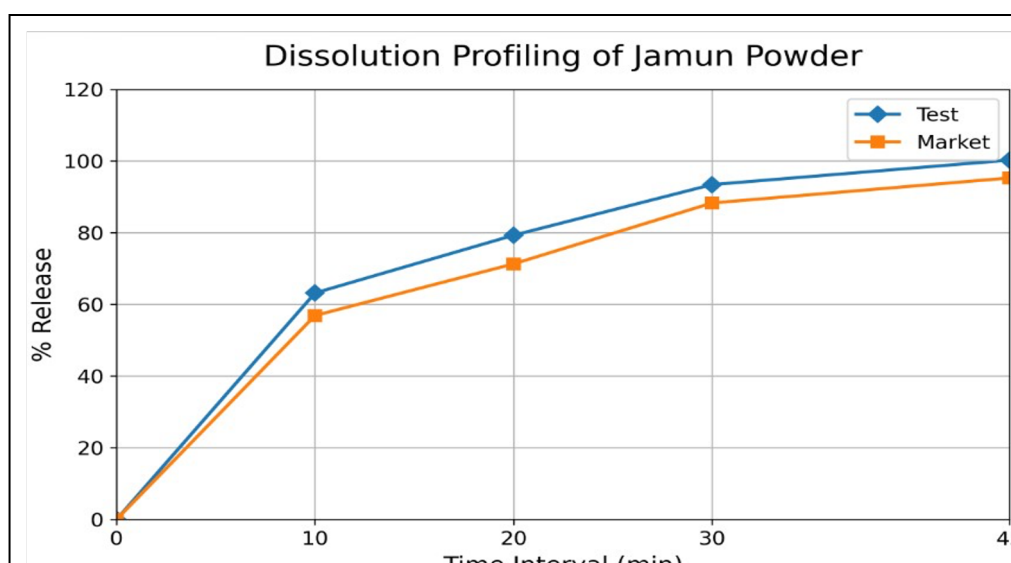
time, with 99.49% drug release at 60 minutes as opposed to 91.3% for the commercial version.

- The optimized excipient concentration, increased tablet porosity, and effective dissolution medium penetration into the tablet matrix may all contribute to the better dissolution profile of the optimized formulation.

Both formulations' dissolution curves showed a comparable release pattern; but, in the later phases of dissolution, the improved formulation demonstrated a relatively quicker and more thorough release.

#### 9.13.1.2 Dissolution Profile Analysis:

A comparative dissolution study was performed between the optimized formulation (F7) and the marketed formulation to evaluate the drug release behaviour of Metformin Hydrochloride. The dissolution profiles demonstrated that both formulations exhibited progressive drug release with increasing time; however, notable differences were observed in the rate and extent of drug release. At 10 and 20 minutes, the marketed formulation exhibited slightly higher drug release (41.3% and 59.3%, respectively) compared to the optimized formulation (38.43% and 53.19%). This may be attributed to differences in excipient composition and tablet disintegration characteristics. However, from 30 minutes onwards, the optimized formulation showed superior dissolution performance. At 30 minutes, the optimized formulation released 75.19% of the drug compared to 67.2% from



**Fig 50: Comparative Dissolution Profile of the Optimized Formulation (F7) and the Marketed *Syzygium cumini* (Jamun Seed Powder) Tablet**



- To compare the release profile of Jamun powder from the optimized formulation with that of the commercial product, a dissolution study was carried out.
- The commercial product demonstrated 56.9% drug release at 10 minutes, while the optimized formulation showed 63.19%, suggesting a quicker initial release from the test formulation.
- The modified formulation showed better dissolving behavior at 20 minutes, releasing 79.29% of the medication as opposed to 71.3% from the commercial version.
- The marketed product released 88.3% of the medication at 30 minutes, but the modified formulation released 93.43%, demonstrating improved release efficiency.
- The improved formulation demonstrated 100.27% drug release at 45 minutes, as opposed to 95.3% for the commercial product, indicating full and quick release of the active ingredients.
- The optimum concentration of excipients, enhanced wettability, improved tablet porosity, and effective dissolving medium penetration into the tablet matrix may all contribute to the optimized formulation's greater dissolution rate.
- Both formulations' dissolving profiles showed a similar pattern, however at every sampling interval, the improved formulation continuously showed higher drug release.

#### **9.13.2.1      *Dissolution Profile Analysis:***

- The dissolution profile of *Syzygium cumini* from the optimized formulation was compared with that of the marketed product to evaluate the release characteristics of the herbal component. The optimized formulation consistently demonstrated higher drug release at all sampling intervals.
- At 10 minutes, the optimized formulation released 63.19% of the active constituents compared to 56.9% from the marketed formulation. At 20 minutes, drug release increased to 79.29% for the optimized formulation, whereas the marketed product showed 71.3% release.
- Further improvement was observed at 30 minutes, where the optimized formulation achieved 93.43% drug release compared to 88.3% from the marketed product. At 45 minutes, the optimized formulation exhibited complete drug release (100.27%), while the marketed formulation released 95.3%.
- The superior dissolution behavior of the optimized formulation may be attributed to enhanced wettability, improved tablet porosity, rapid disintegration, and effective penetration of dissolution medium into the tablet matrix. The optimized concentration of excipients facilitated rapid release of the herbal constituents, resulting in a higher dissolution rate throughout the study.
- Overall, the optimized formulation demonstrated a faster and more complete release profile than the marketed product. These findings confirm the successful optimization of formulation variables and highlight the potential of the developed combination tablet to provide improved bioavailability and therapeutic performance.

#### **9.13.3 Conclusion of Dissolution Comparison:**

The dissolution comparison study revealed that the optimized formulation exhibited superior dissolution characteristics compared to the marketed products for both Metformin Hydrochloride and *Syzygium cumini*. The optimized tablets achieved faster and more complete drug release, which may enhance drug availability and therapeutic effectiveness.

the marketed formulation. Similarly, at 45 minutes, the optimized formulation achieved 94.29% drug release, whereas the marketed product released only 84.2%. At the end of 60 minutes, the optimized formulation exhibited almost complete drug release (99.49%), while the marketed formulation released 91.3%.

The enhanced dissolution performance of the optimized formulation can be attributed to the optimized concentration of super disintegrant, improved tablet porosity, efficient penetration of dissolution medium into the tablet matrix, and appropriate selection of excipients. The results indicate that the developed formulation provides faster and more complete drug release compared to the marketed product, which may contribute to improved therapeutic efficacy and better patient outcomes.

### 9.13.3 ***Dissolution Comparison with the Marketed Sample (JAMUN POWDER TABLET)***

Mfg by: Chaitanya Pharmaceutical Pvt.

Ltd Batch No. : CP2304

Date of Mfg:

02/2024 Date of

Exp:02/2027

The in vitro dissolution profile of the optimized formulation (F7) containing *Syzygium cumini* was compared with that of the marketed Jamun seed powder tablet to evaluate its drug release characteristics.. Comparative evaluation of the dissolution profiles provides an assessment of the release performance of the developed formulation relative to the marketed product and helps determine its potential to deliver the active constituents effectively.

**Table No. 66: Comparison of In Vitro Drug Release Profile of the Optimized and Marketed *Syzygium cumini* (Jamun Seed Powder) Tablet**

| Time | Test | Market |
|------|------|--------|
| 0    | 0    | 0      |

|           |        |      |
|-----------|--------|------|
| <b>10</b> | 63.19  | 56.9 |
| <b>20</b> | 79.29  | 71.3 |
| <b>30</b> | 93.43  | 88.3 |
| <b>45</b> | 100.27 | 95.3 |

## CONCLUSION:

The present research work successfully achieved the formulation and evaluation of an immediate-release combination tablet containing Metformin Hydrochloride and *Syzygium cumini* seed powder for the management of Type 2 Diabetes Mellitus. The study was undertaken with the objective of developing a stable, effective, and patient-friendly formulation capable of providing the complementary therapeutic benefits of a synthetic antidiabetic drug and a herbal bioactive ingredient in a single dosage form.

Comprehensive preformulation studies confirmed that Metformin Hydrochloride and *Syzygium cumini* possessed suitable physicochemical characteristics for tablet formulation. Organoleptic evaluation, melting point determination, UV spectrophotometric analysis, FTIR spectroscopy, and Differential Scanning Calorimetry (DSC) demonstrated the identity, purity, and compatibility of the drug and herbal ingredient. No significant drug–excipient interactions were observed, indicating the suitability of the selected excipients for formulation development.

The powder blends exhibited satisfactory pre-compression characteristics, including acceptable angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner ratio, confirming good flowability and compressibility for direct compression. The tablets prepared by the direct compression technique showed satisfactory post-compression characteristics with respect to weight variation, hardness, thickness, friability, drug content, disintegration time, and in vitro drug release.

Application of the Quality by Design (QbD) approach, together with factorial design, enabled systematic optimization of formulation variables and facilitated identification of the critical factors affecting tablet quality. The optimized formulation demonstrated desirable mechanical strength, rapid disintegration, uniform drug content, and efficient drug release, indicating successful development of an immediate-release combination tablet.

The incorporation of *Syzygium cumini* with Metformin Hydrochloride offers a promising therapeutic strategy by combining the well-established antihyperglycemic action of metformin with the antioxidant, anti-inflammatory, and complementary antidiabetic properties of the herbal component. Such a combination has the potential to improve glycemic control, reduce oxidative stress, enhance metabolic regulation, and improve patient compliance through a single oral dosage form.

## 9 FUTURE SCOPE

The present study successfully demonstrated the feasibility of developing an immediate-release combination tablet containing Metformin Hydrochloride and *Syzygium cumini* seed powder using the direct compression technique and Quality by Design (QbD) principles. Although the formulation exhibited satisfactory pharmaceutical characteristics, further research can expand its therapeutic and commercial potential. The future scope of the present investigation includes the following:

### 9.9 *In-vivo Pharmacological Evaluation*

9.9.1 Conduct animal studies to evaluate the antihyperglycemic efficacy and safety of the developed combination tablet compared with conventional metformin therapy.

### 9.10 *Clinical Evaluation*

9.10.1 Carry out Phase I, Phase II, and Phase III clinical trials to establish the efficacy, safety, tolerability, and long-term therapeutic benefits of the combination tablet in patients with Type 2 Diabetes Mellitus.

### 9.11 *Pharmacokinetic and Bioavailability Studies*

9.11.1 Perform pharmacokinetic studies to evaluate the absorption, distribution, metabolism, excretion, and bioavailability of the combined formulation and compare it with the marketed metformin formulation.

### 9.12 *Long-term Stability Studies*

9.12.1 Conduct real-time and long-term stability studies according to ICH guidelines to determine the shelf life and storage conditions of the developed formulation.

### 9.13 *Standardization of Herbal Material*

- 9.13.1 Further standardization and quantification of bioactive phytoconstituents of *Syzygium cumini* using advanced analytical techniques such as HPLC, LC-MS/MS, or HPTLC to ensure batch-to-batch consistency.

### 9.14 *Dose Optimization*

- 9.14.1 Investigate different dose combinations of Metformin Hydrochloride and *Syzygium cumini* to identify the optimum therapeutic ratio that provides maximum efficacy with minimum adverse effects.

### 9.15 *Evaluation of Antioxidant and Anti-inflammatory Potential*

- 9.15.1 Explore the effect of the combination tablet on oxidative stress markers, inflammatory cytokines, and pancreatic  $\beta$ -cell protection to further establish its role in preventing diabetic complications.

### 9.16 *Development of Novel Drug Delivery Systems*

- 9.16.1 Extend the research to formulate sustained-release, bilayer, multilayer, or orally disintegrating tablets containing Metformin Hydrochloride and *Syzygium cumini* for improved therapeutic performance and patient compliance.

### 9.17 *Commercial Scale-up and Process Validation*

- 9.17.1 Scale up the optimized formulation for pilot and industrial production, followed by process validation to ensure reproducibility and regulatory compliance.

### 9.18 *Regulatory and Commercial Development*

- 9.18.1 Generate comprehensive preclinical and clinical data to facilitate regulatory approval and commercialization of the herbal–synthetic combination tablet as a novel antidiabetic formulation.

### 9.19 *Investigation of Additional Therapeutic Benefits*

- 9.19.1 Evaluate the potential of the formulation in reducing diabetes-associated complications such as diabetic nephropathy, neuropathy, retinopathy, and cardiovascular disorders through long-term experimental and clinical studies.

### 9.20 *Application of Advanced QbD Approaches*

Future studies may utilize advanced Design of Experiments (DoE) models, such as Box–Behnken or Central Composite Design, to further optimize formulation variables and manufacturing parameters.

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