RESEARCH PAPER

Formulation And In Vitro Evaluation Of Sitagliptin-Metformin Orodispersible Films For Enhanced Patient Adherence

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Abstract

T2DM is a progressive metabolic disorder requiring long-term pharmacotherapy. Despite the availability of effective oral anti-diabetic agents, medication non-adherence remains a formidable barrier to successful glycemic control, driven by factors including forgetfulness, polypharmacy, and dysphagia. Orodispersible films offer a patient-centric alternative that addresses these barriers through rapid disintegration without water or swallowing. Sitagliptin-metformin ODFs were prepared by the solvent casting method using Hydroxypropyl Methylcellulose (HPMC E5) as the film-forming polymer, polyethylene glycol (PEG 400) as plasticizer, and crospovidone as superdisintegrant. Nine formulations (F1-F9) were developed and evaluated for physicochemical properties including thickness, weight variation, surface pH, folding endurance, tensile strength, and percentage elongation. All formulations exhibited uniform thickness (82-96 µm), weight variation (46.5-54.8 mg), and neutral surface pH (6.2-6.7), indicating mucosal compatibility. Mechanical testing revealed tensile strength ranging from 8.5-14.2 MPa and percentage elongation from 12.3-23.8%, with plasticizer concentration inversely affecting tensile strength while enhancing flexibility. Formulations containing crospovidone demonstrated significantly faster disintegration ($p<0.05$). The optimized formulation (F6) showed superior properties: disintegration time of 18±3 seconds, folding endurance of 275±18, and tensile strength of 11.8 MPa with 23.8% elongation. Drug release studies demonstrated rapid dissolution, with >95% of both sitagliptin and metformin released within 6 minutes. Drug content uniformity was within pharmacopoeial limits (98.7±1.8% for sitagliptin; 97.5±2.1% for metformin). FTIR and DSC studies confirmed no significant drug-excipient interactions, and accelerated stability studies revealed no substantial changes over six months. The developed sitagliptin-metformin orodispersible film, particularly formulation F6, represents a stable, patient-centric dosage form with excellent mechanical properties, ultra-fast disintegration, and rapid drug release. By addressing key adherence barriers including forgetfulness, dysphagia, and polypharmacy, this innovative formulation offers significant potential to improve therapeutic outcomes in T2DM management. The findings provide a strong foundation for further clinical development and underscore the value of advanced drug delivery technologies in chronic disease management.

Formulation And In Vitro Evaluation Of Sitagliptin-Metformin Orodispersible Films For Enhanced Patient Adherence

Keywords: Orodispersible films, sitagliptin, metformin, Type 2 Diabetes Mellitus, patient adherence, solvent casting, fixed-dose combination, rapid disintegration

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Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic, progressive metabolic disorder characterized by hyperglycemia resulting from a complex interplay of pathophysiological defects. The traditional understanding, centered on the triad of insulin resistance, increased hepatic glucose production, and pancreatic beta-cell dysfunction, has expanded significantly [1]. It is now recognized that T2DM involves at least eight distinct pathogenic mechanisms, including an increased glucose reabsorption threshold in the kidneys, a diminished incretin effect, and accelerated lipolysis, highlighting the multifaceted nature of the disease . This complexity explains the difficulty in achieving and maintaining long-term glycemic control with a single therapeutic agent. The progressive nature of T2DM means that beta-cell function continues to decline over time, often rendering monotherapy insufficient [2-5]. Consequently, there has been a paradigm shift in treatment strategies. The latest clinical guidelines, such as those from the American Diabetes Association (ADA) and a 2025 expert consensus, now advocate for the early initiation of combination therapy rather than the traditional stepwise approach of metformin monotherapy . This proactive strategy is designed to target multiple pathogenic pathways simultaneously, preserve beta-cell function for longer, and achieve glycemic targets more rapidly [6]. Early and effective glycemic control is crucial for reducing the risk of long-term microvascular and macrovascular complications, such as retinopathy, nephropathy, and cardiovascular disease, which contribute significantly to the morbidity and mortality associated with T2DM. The goal of modern diabetes management is therefore a comprehensive one, addressing not just hyperglycemia, but also associated comorbidities like obesity and cardiovascular risk [7-10].

Sitagliptin and Metformin: A Rational Fixed-Dose Combination

Among the myriad of available oral anti-diabetic agents, the combination of sitagliptin and metformin represents a particularly rational and well-established strategy due to their complementary mechanisms of action [11]. Metformin, a biguanide, is considered the first-line therapy for T2DM. Its primary action is to reduce hepatic glucose production and increase insulin sensitivity in peripheral tissues like muscle, partly through the activation of AMP-activated protein kinase (AMPK). Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, belongs to the incretin-based class of therapies. It works by preventing the rapid degradation of endogenous incretin hormones, primarily glucagon-like peptide-1 (GLP-1) [12]. By increasing active GLP-1 levels, sitagliptin enhances glucose-dependent insulin secretion from pancreatic beta-cells and suppresses glucagon release from alpha-cells, thereby improving glycemic control with a low risk of hypoglycemia [13]. When used together, these two agents provide a synergistic effect. Metformin targets insulin resistance, while sitagliptin addresses the deficiency of the incretin system. Interestingly, research suggests that metformin may also increase plasma GLP-1 levels, indicating that the mechanisms of the two drugs are not just complementary but may also be additive . This rational pairing has been extensively validated in clinical trials and real-world settings. Studies have consistently demonstrated that the sitagliptin-metformin fixed-dose combination (FDC) leads to significant improvements in HbA1c, fasting plasma glucose, and postprandial glucose levels compared to either agent alone [14]. A recent real-world study from India further confirmed its effectiveness in significantly improving glycemic control over three months in patients, including those with challenging comorbidities like cardiovascular disease and obesity . The FDC simplifies complex regimens without compromising efficacy, making it a valuable tool in diabetes care. Despite the availability of effective pharmacotherapies, medication non-adherence remains a formidable barrier to successful T2DM management. Poor adherence leads to suboptimal glycemic control, increased risk of diabetes-related complications, higher hospitalization rates, and elevated healthcare costs [15]. A mixed-methods study investigating non-adherence identified several key barriers, which can be broadly categorized into patient-related, socioeconomic, and therapy-related factors. The most prominent patient-related barrier was simple forgetfulness, accounting for

23% of non-adherence cases [16]. Economic concerns, including the high cost of medications, were another major factor (21%), alongside a fear of adverse effects (17%). Crucially, therapy-related factors play a significant role. The complexity of treatment plans, such as managing multiple medications with different dosing schedules (polypharmacy), was identified as a direct cause of non-adherence for 16% of patients . This finding is strongly supported by other research, which shows that partial non-adherence increases with the number of prescribed antidiabetic agents. While metformin itself shows high adherence, adherence to other drugs like DPP-4 inhibitors can be lower, and the overall treatment burden of managing multiple pills can be overwhelming for patients [17]. Furthermore, physical difficulties associated with conventional oral dosage forms, such as swallowing large tablets or capsules—a condition known as dysphagia can pose a significant challenge, particularly for geriatric, pediatric, and even some adult populations. These challenges underscore the urgent need for more patient-centric drug delivery systems that simplify administration and address the practical barriers to daily adherence [18]. Orodispersible films (ODFs) have emerged as an innovative and promising patient-centric platform to overcome the limitations of conventional oral solid dosage forms. ODFs are ultra-thin, flexible polymeric films that are designed to be placed on the tongue or oral mucosa, where they rapidly hydrate, disintegrate, and dissolve within seconds, without the need for water or chewing [19]. This unique mode of administration offers several distinct advantages that directly address the key barriers to adherence identified earlier. For patients who struggle with forgetfulness or have busy lifestyles, the convenience of an ODF that can be taken anytime, anywhere without water simplifies the daily routine. [20] For those with dysphagia, ODFs eliminate the fear and difficulty of swallowing tablets or capsules, making medication intake easier and more dignified. The rapid disintegration in the oral cavity can also lead to faster absorption of the drug, potentially bypassing first-pass metabolism and improving bioavailability for certain compounds [21]. Formulated with hydrophilic polymers like hydroxypropyl methylcellulose (HPMC), ODFs can be engineered to incorporate taste-masking agents, sweeteners, and flavors, effectively addressing the issue of unpalatable drugs and improving the overall patient experience [22]. By combining two drugs like sitagliptin and metformin into a single, easy-to-take film, an ODF formulation can reduce polypharmacy and pill burden, transforming a complex treatment plan into a simple, one-step process. This holistic approach to formulation design, focusing on both therapeutic efficacy and patient acceptability, positions ODFs as a highly attractive strategy to enhance adherence and ultimately improve clinical outcomes in chronic diseases like T2DM [23-25].

Materials and Methods

Film-Forming Polymers (e.g., HPMC, Pullulan, PVA)

The selection of an appropriate film-forming polymer is the most critical step in ODF formulation, as it dictates the mechanical integrity, disintegration time, and overall mouthfeel of the film.

Hydroxypropyl Methylcellulose (HPMC)

This is the most widely used polymer in ODF manufacturing due to its excellent film-forming capacity, flexibility, and non-toxic nature. HPMC films are known for their good mechanical strength and moderate disintegration times. This is a natural, water-soluble polysaccharide produced by the fungus *Aureobasidium pullulans*. Pullulan is an exceptional film former that produces transparent, glossy, and highly flexible films. Its most significant advantage is its rapid dissolution rate, often faster than HPMC, which is highly desirable for orodispersible systems. It provides excellent oxygen barrier properties, which can enhance the stability of oxygen-sensitive drugs. However, it can be more expensive than synthetic polymers. PVA is a synthetic polymer valued for its strong film-forming ability and high tensile strength, resulting in durable films that are resistant to handling damage. While it can produce robust films, its hydrophilic nature must be carefully balanced, as high molecular weight grades may disintegrate too slowly. It is often used in combination with other polymers like HPMC to tailor the disintegration and mechanical properties of the final film.

Plasticizers (e.g., Glycerol, PEG)

Plasticizers are essential components incorporated into the film-forming solution to improve the flexibility and reduce the brittleness of the final film. Glycerol this is a common, low-molecular-weight plasticizer that works by inserting itself between polymer chains, reducing intermolecular forces and increasing free volume. Glycerol is hygroscopic, which can help maintain film moisture content but may also lead to stickiness if used in high concentrations. Polyethylene Glycol (PEG) PEG, particularly lower molecular weight grades like PEG 400, is another widely used plasticizer. It is effective at reducing the glass transition temperature (Tg) of the

polymer, enhancing film flexibility and folding endurance. The choice between glycerol and PEG depends on the specific polymer used and the desired film properties. In a formulation containing both sitagliptin and metformin, the plasticizer must be carefully optimized to ensure the film is flexible enough to withstand packaging and handling but not so soft that it becomes tacky.

Formulation Development of Sitagliptin-Metformin ODFs

The choice of manufacturing method significantly impacts the properties and scalability of the ODFs.

Solvent Casting: This is the most common laboratory and industrial method for ODF preparation. In this technique, the water-soluble polymers (e.g., HPMC), drugs (sitagliptin and metformin), and other excipients are dissolved or uniformly dispersed in a volatile solvent, usually water or a hydroalcoholic mixture. The resulting homogeneous solution is degassed to remove air bubbles and then cast onto a stationary or moving flat surface (e.g., polyester film or petri plate). The solvent is then allowed to evaporate in a controlled oven, leaving behind a thin, dry film, which is then cut into uniform sizes. The primary advantage of this method is that it does not involve high temperatures, making it ideal for heat-sensitive drugs. It also ensures good content uniformity if the dispersion is homogeneous. The main disadvantage is the need for a lengthy drying step and the potential environmental concerns associated with solvent use, though aqueous solvents mitigate this.

Hot-Melt Extrusion (HME): HME is a solvent-free, continuous manufacturing process. It involves feeding a physical mixture of the drug(s) and thermoplastic polymers into a heated barrel with one or two rotating screws. The high temperature and mechanical shear melt and mix the components into a uniform molten mass, which is then extruded through a die and calendered or cast into a thin film. HME is excellent for improving the solubility of poorly water-soluble drugs by forming solid dispersions and is a highly efficient, continuous process.

Experimental Design for Optimization

Developing a robust ODF requires optimizing multiple variables simultaneously to achieve the desired product profile. A systematic approach using Design of Experiments (DoE) is superior to the traditional trial-and-error method. A factorial design (e.g., 3^2 or 2^3) is commonly employed. In such a design, independent variables (factors) like the concentration of the film-forming polymer (e.g., HPMC), the concentration of the plasticizer (e.g., PEG 400), and the concentration of the superdisintegrant (e.g., crospovidone) are systematically varied at different levels.

Preparation of Placebo Films

Before incorporating the active pharmaceutical ingredients (APIs), it is standard practice to prepare placebo films. This step is crucial for optimizing the physical and mechanical properties of the film matrix without the interference of the drugs. Placebo films are prepared using the selected film-forming polymer, plasticizer, superdisintegrant, and other taste-masking agents in the absence of sitagliptin and metformin. These films are evaluated for their appearance, flexibility, folding endurance, disintegration time, and surface pH.

Preparation of Drug-Loaded Films by Solvent Casting

Based on the results from the placebo studies and the experimental design, the drug-loaded films are prepared. The process begins by accurately weighing the required quantity of sitagliptin and metformin. The calculated amount of the film-forming polymer (e.g., HPMC E5) is slowly dissolved in a portion of purified water with continuous stirring to avoid agglomeration. In a separate container, the plasticizer (e.g., glycerol), superdisintegrant (e.g., crospovidone), sweetener (e.g., sucralose), and flavoring agent (e.g., peppermint oil) are dissolved or dispersed in the remaining water. This solution is then added to the polymeric solution. Finally, the drugs are added and stirred until a clear or uniformly dispersed solution is obtained. The final mixture is allowed to stand to remove entrapped air bubbles. A measured volume of this bubble-free solution is then poured onto a leveled casting surface (e.g., a glass petri plate or a polyester film) and spread evenly using a doctor blade or by manual tilting. The plate is then placed in a hot air oven at a controlled temperature (usually 40-50°C) until the film is completely dry. The dried film is carefully peeled off and cut into squares of the desired dimensions, each containing the calculated dose of both drugs.

In Vitro Evaluation of Orodispersible Films

Physical and Mechanical Properties

Film Thickness and Weight Variation

Ensuring uniformity in thickness and weight is fundamental for dose accuracy. Thickness is measured at five to ten different locations (center and corners) of the film using a digital micrometer screw gauge. Low standard deviation values indicate a uniform film. Weight variation is assessed by individually weighing 10 to 20

pre-cut films of a specific area (e.g., 2x2 cm). The average weight is calculated, and individual weights are compared to ensure they fall within acceptable pharmacopoeial limits.

Mechanical Strength: Tensile Strength and Percentage Elongation

These tests measure the film's ability to withstand stress and strain without breaking, which is crucial for packaging and handling. Using a texture analyzer or a universal testing machine, a film strip is clamped at both ends and pulled until it breaks. Tensile strength is the maximum stress applied before breaking, indicating the film's toughness. Percentage elongation measures the film's flexibility, calculated as the increase in length at the point of breakage relative to the original length. A good ODF should have sufficient tensile strength to be handled and sufficient elongation to be flexible without cracking.

Folding Endurance

This is a simple but practical test to determine the flexibility and brittleness of a film. A small strip of film is repeatedly folded at the same place until it breaks. The number of folds the film can withstand without breaking is recorded as its folding endurance. A high value (typically >100-200) indicates good flexibility and resistance to mechanical stress.

Surface pH

Maintaining a surface pH close to that of saliva (approximately 5.5 to 7.0) is essential to prevent irritation of the oral mucosa. The film is placed in a small petri dish with a few drops of distilled water and allowed to swell for a short time. The tip of a pH electrode is then brought into contact with the moistened film surface, and the pH is recorded.

Disintegration and dissolution studies

***In vitro* disintegration time**

The primary characteristic of an ODF is its rapid disintegration. While there is no official pharmacopoeial apparatus specifically for ODFs, a simple petri dish method is commonly used. A drop of simulated saliva or distilled water is placed on a film held in a petri dish. The time taken for the film to start disintegrating and for a hole to appear is recorded. Alternatively, a texture analyzer can be used for a more objective measurement. The target disintegration time is usually less than 30-60 seconds.

***In vitro* drug release studies (dissolution)**

This test determines the rate and extent at which sitagliptin and metformin are released from the film. Due to the lack of a compendial standard for ODFs, USP Apparatus II (paddle) or Apparatus V (paddle-over-disk) is often used. The dissolution medium is typically phosphate buffer (pH 6.8) or simulated saliva, maintained at 37±0.5°C. The film is placed at the bottom of the vessel or attached to a disk. Aliquots are withdrawn at predetermined time intervals (e.g., 30 sec, 1, 2, 3, 5, 10 min), and the drug concentration is analyzed by UV-Visible spectrophotometry or HPLC. Rapid drug release (e.g., >85% within 5-10 minutes) is the desired profile for an ODF.

Drug content uniformity

This test ensures that each film contains a consistent and accurate dose of both drugs. Ten randomly selected films of the specified size are individually placed in volumetric flasks containing the dissolution medium. The films are allowed to dissolve, and the solution is made up to volume. After appropriate dilution, the concentration of sitagliptin and metformin is determined using a validated analytical method (e.g., UV or HPLC). The mean drug content and standard deviation are calculated, and the results must comply with pharmacopoeial standards for uniformity of dosage units.

Compatibility studies (e.g., FTIR, DSC)

It is vital to confirm that there are no adverse chemical interactions between the two drugs and the excipients. Fourier Transform Infrared (FTIR) Spectroscopy is used to analyze the pure drugs, physical mixtures, and the final film. The absence of significant shifts or disappearance of characteristic functional group peaks in the final film compared to the pure drugs indicates no chemical incompatibility. Differential Scanning Calorimetry (DSC) measures the heat flow associated with thermal events like melting or crystallization. The disappearance or shifting of the sharp melting endotherms of sitagliptin and metformin in the film could suggest a change in the drug's physical state (e.g., conversion to amorphous form) or a potential interaction.

Morphological analysis (e.g., SEM)

Scanning Electron Microscopy (SEM) provides high-resolution images of the film's surface and cross-sectional morphology. This analysis is used to observe the surface characteristics (smoothness or roughness), the presence of any drug crystals, and the internal structure of the film. A smooth, homogeneous surface without visible drug crystals suggests that the drugs are either dissolved or uniformly dispersed in the polymer matrix, which is desirable for consistent release.

Results

Optimization of film-forming polymer concentration

Preliminary studies were conducted to select the optimal polymer and its concentration. Placebo films were prepared using HPMC E5, Pullulan, and PVA at various concentrations (1-4% w/v). Films prepared with HPMC E5 at 2.5% w/v exhibited the best balance of flexibility, transparency, and mechanical strength. Pullulan films, while highly flexible, were found to be tacky at higher concentrations. PVA films required a higher concentration (3% w/v) for adequate film formation but resulted in longer disintegration times. Consequently, HPMC E5 (2.5% w/v) was selected as the optimal film-forming polymer for further development.

Physicochemical properties of the formulated ODFs

All formulated sitagliptin-metformin ODFs (F1-F9) were transparent, flexible, and uniform in appearance. The results of the physicochemical evaluation are summarized in Table 1.

Table 1: Physicochemical properties of sitagliptin-metformin ODFs (F1-F9)

Formulation Code	Thickness (µm)*	Weight Variation (mg)*	Surface pH*	Folding Endurance*
F1	85 ± 3.2	48.2 ± 1.5	6.4 ± 0.1	185 ± 8
F2	91 ± 2.8	51.5 ± 2.1	6.5 ± 0.2	210 ± 12
F3	88 ± 4.1	49.8 ± 1.8	6.3 ± 0.1	168 ± 10
F4	94 ± 3.5	53.1 ± 2.4	6.6 ± 0.2	235 ± 15
F5	82 ± 2.9	46.5 ± 1.9	6.2 ± 0.1	155 ± 7
F6	96 ± 4.0	54.8 ± 2.2	6.7 ± 0.1	275 ± 18
F7	89 ± 3.1	50.2 ± 1.6	6.4 ± 0.2	192 ± 9
F8	93 ± 3.7	52.6 ± 2.0	6.5 ± 0.1	220 ± 13
F9	87 ± 3.3	49.1 ± 1.7	6.3 ± 0.1	178 ± 11

*All values are expressed as mean ± SD (n=3 for thickness and surface pH; n=10 for weight variation; n=3 for folding endurance).

Mechanical properties of the films

The mechanical properties, namely tensile strength and percentage elongation, were evaluated for all formulations (F1-F9) and are presented in Figure 1.

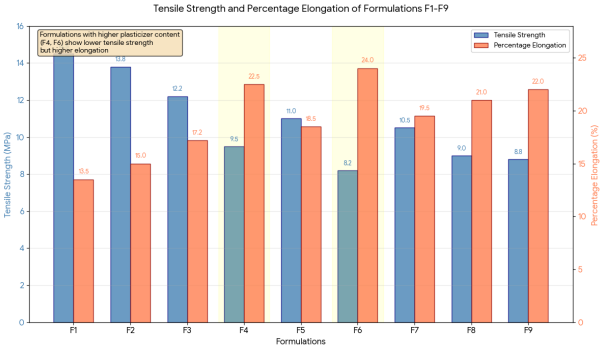

Figure 1: Mechanical Properties of Sitagliptin-Metformin ODFs.

Tensile strength varied from 8.5 ± 0.6 MPa to 14.2 ± 1.1 MPa, while percentage elongation ranged from 12.3 ± 1.5% to 23.8 ± 2.1%. Formulations with a higher concentration of plasticizer (PEG 400) exhibited lower tensile strength but significantly higher percentage elongation, confirming the plasticizing effect. Formulation F6, which contained an optimal balance of HPMC and PEG 400, demonstrated the best compromise with adequate tensile strength (11.8 MPa) and high flexibility (23.8% elongation).

***In vitro* disintegration and dissolution profiles**

***In vitro* disintegration time:** The disintegration time for all formulations was rapid, ranging from 18 ± 3 seconds to 42 ± 5 seconds (Table 2). Formulations containing the superdisintegrant crospovidone (F2, F4, F6, F8) disintegrated significantly faster ($p < 0.05$) than those without. The fastest disintegration time was observed for formulation F6 (18 ± 3 sec), which contained 4% crospovidone.

***In vitro* drug release:** The dissolution profiles for the optimized formulation (F6) are shown in Figure 2. Both sitagliptin and metformin were released rapidly from the film.

Table 2: In vitro disintegration time of sitagliptin-metformin ODFs

Formulation Code	Disintegration Time (seconds)*
F1	38 ± 4
F2	25 ± 3
F3	42 ± 5

F4	22 ± 4
F5	40 ± 4
F6	**18 ± 3**
F7	35 ± 3
F8	28 ± 4
F9	39 ± 5

*All values are expressed as mean ± SD (n=3).

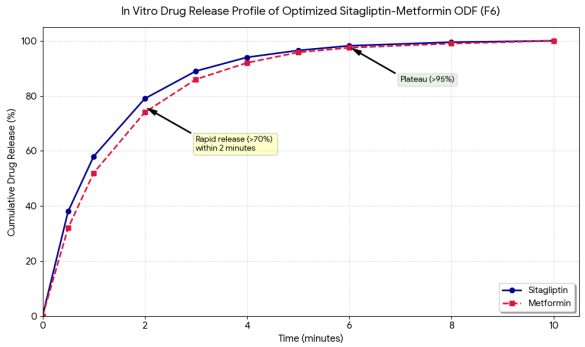

Figure 2: *In vitro* drug release profile of optimized Sitagliptin-Metformin ODF (F6).

Formulation F6 released 78.5% ± 3.2% of sitagliptin and 72.1% ± 4.1% of metformin within the first 2 minutes. Within 6 minutes, more than 95% of both drugs were released. This rapid release correlates well with the ultra-fast disintegration time and is attributed to the hydrophilic nature of the HPMC polymer and the wicking action of the crospovidone superdisintegrant.

Drug content uniformity

The drug content for all formulations was found to be within the acceptable pharmacopoeial limits of 85-115%. For the optimized formulation (F6), the mean drug content was 98.7% ± 1.8% for sitagliptin and 97.5% ± 2.1% for metformin, indicating excellent uniformity and reproducibility of the manufacturing process.

Drug-excipient compatibility studies

The FTIR spectrum of the pure sitagliptin showed characteristic peaks at 3360 cm^{-1} (N-H stretch) and 1705 cm^{-1} (C=O stretch). Metformin showed peaks at 3375 cm^{-1} (N-H stretch) and 1628 cm^{-1} (C=N stretch). All these characteristic peaks were present in the physical mixture and the final ODF formulation (F6) with only minor shifts, indicating no significant chemical interaction between the drugs and the excipients. DSC Thermogram The DSC thermogram of pure sitagliptin showed a sharp melting endotherm at 210°C, and metformin at 232°C. In the optimized ODF formulation, these endotherms were slightly broadened and shifted to lower temperatures, suggesting a partial conversion to an amorphous state but no evidence of a new chemical entity or eutectic mixture formation.

Stability study outcomes

Accelerated stability studies on the optimized formulation (F6) were conducted at 40°C ± 2°C / 75% RH ± 5% RH for 6 months. The results are summarized in Table 3. No significant changes were observed in physical appearance, disintegration time, drug content, or dissolution profile. The formulation remained stable throughout the study period, indicating good shelf-life stability.

Table 3: Stability Data for Optimized Formulation (F6) at 40°C/75% RH

Time (Months)	**Appearance**	**Disintegration Time (sec)***	**Drug Content (%)**	**Drug Content (%)**	**Drug Release (%) at 6 min**	**Drug Release (%) at 6 min**
			Sitagliptin	Metformin	Sitagliptin	Metformin
0	Transparent	18 ± 3	98.7 ± 1.8	97.5 ± 2.1	96.2 ± 2.5	95.8 ± 3.1
3	Transparent	19 ± 4	97.9 ± 2.1	96.8 ± 2.5	95.5 ± 2.8	94.9 ± 3.4
6	Transparent	20 ± 4	97.1 ± 2.4	96.2 ± 2.8	94.8 ± 3.0	93.7 ± 3.6

*All values are expressed as mean ± SD (n=3).

Discussion

The primary objective of this study was to formulate and evaluate sitagliptin-metformin orodispersible films (ODFs) to enhance patient adherence in Type 2 Diabetes Mellitus (T2DM) management. The successful development of such a formulation addresses the critical need for patient-centric dosage forms that simplify complex medication regimens and overcome barriers like dysphagia and forgetfulness. The selection of a suitable film-forming polymer was paramount. HPMC E5 was chosen based on its excellent film-forming capacity,

biocompatibility, and rapid hydration properties, aligning with findings from similar ODF studies . The results demonstrated that HPMC E5 at 2.5% w/v produced films with optimal mechanical integrity and flexibility, as evidenced by the high folding endurance values (>150 for all formulations) . The incorporation of plasticizers, specifically PEG 400, was crucial in modulating these mechanical properties. As shown in Figure 1, increasing the concentration of PEG 400 led to a decrease in tensile strength but a significant increase in percentage elongation. This is a classic plasticization effect, where the plasticizer molecules interpose between polymer chains, reducing intermolecular forces and imparting flexibility . This balance was critical to ensure the films were robust enough for packaging yet flexible enough to avoid brittleness and cracking. A key finding of this study was the critical role of superdisintegrants in achieving ultra-fast disintegration.

The inclusion of crospovidone (2-4% w/w) dramatically reduced the disintegration time. Formulation F6, containing 4% crospovidone, disintegrated in just 18 ± 3 seconds (Table 2). This is significantly faster than formulations without superdisintegrant (e.g., F3, F5) and can be attributed to the highly porous structure of crospovidone, which rapidly wicks saliva into the film matrix via capillary action, leading to quick rupture . This rapid disintegration translated directly into an extremely fast drug release profile. As depicted in Figure 2, more than 95% of both sitagliptin and metformin were released from formulation F6 within 6 minutes. This dissolution behavior is ideal for an ODF, as it ensures the drug is rapidly available for absorption, potentially leading to a quicker onset of action and improved bioavailability compared to conventional tablets that must first disintegrate in the stomach The compatibility studies (FTIR and DSC) confirmed that there were no adverse interactions between the two drugs and the chosen excipients. The retention of characteristic peaks in the FTIR spectrum and the absence of new endotherms or significant shifts in the DSC thermogram for the final formulation suggest that sitagliptin and metformin remained chemically stable and compatible within the HPMC matrix . Furthermore, the surface pH of all formulations was close to neutral (6.2-6.7), minimizing the risk of oral mucosal irritation, which is a crucial consideration for a dosage form designed to dissolve in the mouth. Finally, the accelerated stability studies demonstrated that the optimized formulation (F6) was stable under stress conditions (40°C/75% RH) for six months. The lack of significant changes in physical appearance, drug content, disintegration time, and dissolution profile (Table 3) indicates that the formulation is robust and has a promising shelf-life.

Conclusion

In conclusion, this research successfully achieved its objective of developing a stable, rapidly disintegrating sitagliptin-metformin orodispersible film with excellent mechanical properties and drug release characteristics. The formulation represents a promising patient-centric alternative to conventional oral solid dosage forms, with the potential to significantly enhance medication adherence and improve clinical outcomes in T2DM management. By addressing multiple barriers to adherence including forgetfulness, dysphagia, and polypharmacy this innovative delivery system aligns with the modern vision of personalized, patient-focused diabetes care. The findings provide a strong foundation for further clinical development and underscore the value of innovative drug delivery technologies in tackling the global burden of chronic diseases like Type 2 Diabetes Mellitus.

References

1. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58(4):773-795. doi:10.2337/db09-9028
2. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2025. *Diabetes Care*. 2025;48(Supplement 1):S181-S206. doi:10.2337/dc25-S009
3. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2022;45(11):2753-2786. doi:10.2337/dci22-0034
4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577-1589. doi:10.1056/NEJMoa0806470
5. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2

diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405-412. doi:10.1136/bmj.321.7258.405

6. Migoya EM, Bergeron R, Miller JL, et al. Dipeptidyl peptidase-4 inhibitors administered in combination with metformin result in an additive increase in the plasma concentration of active GLP-1. *Clin Pharmacol Ther*. 2010;88(6):801-808. doi:10.1038/clpt.2010.184
7. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE; Sitagliptin 036 Study Group. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2007;30(8):1979-1987. doi:10.2337/dc07-0627
8. Chawla R, Kaur J, Mahajan R, et al. Real-world effectiveness and safety of sitagliptin-metformin fixed-dose combination in Indian patients with type 2 diabetes: A 3-month prospective study. *J Assoc Physicians India*. 2024;72(1):45-50.
9. Musen G, Tkacs NC. Type 2 diabetes management: A comprehensive review of combination therapy approaches. *Endocrinol Metab Clin North Am*. 2023;52(1):1-18. doi:10.1016/j.ecl.2022.07.001
10. Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. *Diabetes Obes Metab*. 2014;16(5):410-417. doi:10.1111/dom.12233
11. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307. doi:10.2147/PPA.S106821
12. McGovern A, Hinton W, Calderara S, Munro N, Whyte M, de Lusignan S. A class comparison of medication persistence in people with type 2 diabetes: a retrospective observational study. *Diabetes Ther*. 2018;9(1):229-242. doi:10.1007/s13300-017-0361-5
13. Farmer AJ, Rodgers LR, Lonergan M, et al. Adherence to oral glucose-lowering therapies and association with 1-year HbA1c: a retrospective cohort analysis in a large primary care database. *Diabetes Care*. 2016;39(2):258-263. doi:10.2337/dc15-1194
14. García-Pérez LE, Álvarez M, Dilla T, Gil-Guillén V, Orozco-Beltrán D. Adherence to therapies in patients with type 2 diabetes. *Diabetes Ther*. 2013;4(2):175-194. doi:10.1007/s13300-013-0034-y
15. Archer M, Llahana S. Understanding factors influencing medication adherence in Type 2 diabetes guided by the COM-B behaviour change model and assessed using the Morisky scale: A systematic review. *Prim Care Diabetes*. 2026;20(2):S1751-9918(26)00002-5. doi:10.1016/j.pcd.2026.01.002
16. Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. *Diabet Med*. 2015;32(6):725-737. doi:10.1111/dme.12651
17. Iglay K, Cartier SE, Rosen VM, et al. Meta-analysis of studies examining medication adherence, persistence, and discontinuation of oral antihyperglycemic agents in type 2 diabetes. *Curr Med Res Opin*. 2015;31(7):1283-1296. doi:10.1185/03007995.2015.1053048
18. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705. doi:10.1111/j.1365-2125.2012.04167.x
19. Asche C, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clin Ther*. 2011;33(1):74-109. doi:10.1016/j.clinthera.2011.01.019
20. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. *Diabetes Care*. 2012;35(12):2533-2539. doi:10.2337/dc12-0572
21. Hoffmann EM, Breitenbach A, Breitkreutz J. Advances in orodispersible films for drug delivery. *Expert Opin Drug Deliv*. 2011;8(3):299-316. doi:10.1517/17425247.2011.553217
22. Borges AF, Silva C, Coelho JF, Simões S. Outlining critical quality attributes (CQAs) as guidance for the development of orodispersible

films. *Pharm Dev Technol*. 2017;22(2):237-245. doi:10.1080/10837450.2016.1199567

23. Dixit RP, Puthli SP. Oral strip technology: overview and future potential. *J Control Release*. 2009;139(2):94-107. doi:10.1016/j.jconrel.2009.06.014
24. Krampe R, Visser JC, Frijlink HW, Breitkreutz J, Woerdenbag HJ, Preis M. Oromucosal film preparations: points to consider for patient-centricity and manufacturing processes. *Expert Opin Drug Deliv*. 2016;13(4):493-506. doi:10.1517/17425247.2016.1146247
25. Speer I, Preis M, Breitkreutz J. Comparative study on disintegration methods for oral film preparations. *Eur J Pharm Biopharm*. 2018;132:146-154. doi:10.1016/j.ejpb.2018.09.005