REVIEW ARTICLE

Latest Advancements on Gastro Floating Bi-Layer Tablets of Metformin and Pioglitazone for the Treatment of Diabetes Mellitus

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Received: 28th Aug, 2024; Revised: 30th Oct, 2024; Accepted: 9th Nov, 2024; Available Online: 25th December, 2024

ABSTRACT

The synergistic mode of action of pioglitazone hydrochloride (PG) and metformin hydrochloride (MH) has great potential for the treatment of type 2 diabetes mellitus. Because of their complementary modes of action, metformin hydrochloride (MH) and pioglitazone hydrochloride (PG) have great potential for the therapy of type 2 diabetes mellitus. Short half-life and the low absorption of metformin hydrochloride in lower gastrointestinal tract might restrict the action towards its expected therapeutic usefulness. This work aimed to create gastro-floating bilayer matrix tablets that would each contain two different drugs. The primary objective was to improve the absorption of pioglitazone hydrochloride through rapid release, while ensuring a sustained release of metformin hydrochloride. After optimisation, with a floating lag time of five minutes, the tablets floated in the testing medium for over twenty-four hours. They allowed the active substance to be released within 12 hours using a diffusion-dependent release mechanism with total release of the active substance being achieved within 5 minutes. Furthermore, it was viewed that, metformin hydrochloride yielded a stable plasma concentration, bio-availability increased by 1.5 times, C_{max} decrease and T_{max} was reduced. Furthermore, pioglitazone hydrochloride's in vivo behaviour matched that of the approved product. In addition to having improved mechanical and physical qualities, all formulations had a pleasing appearance. Stability testing and infrared spectroscopy analysis were done on the formulation, and the results showed that it produced the best results in terms of drug release and duration of buoyancy in vitro. The findings suggest that the medication and polymer did not interact chemically and that the formulation remained stable. The study finds that by achieving simultaneous sustained release of metformin hydrochloride with enhanced absorption and immediate release of pioglitazone hydrochloride, a gastro-floating bilayer tablet facilitated a more effective combination therapy for diabetes mellitus. The benefits of combining pioglitazone and metformin into a single tablet are reviewed in this review, with particular attention paid to how this combination may improve glycemic control, compliance, metabolic characteristics of people with type 2 diabetes mellitus.

Keywords: Metformin hydrochloride, Pioglitazone hydrochloride, Gastro-floating, Bilayer matrix tablets, Diabetes mellitus.

How to cite this article: Vijay K, Naruka P S. Latest Advancements on Gastro Floating Bi-Layer Tablets of Metformin and Pioglitazone for the Treatment of Diabetes Mellitus. International Journal of Drug Delivery Technology. 2024;14(4):2541-46. doi: 10.25258/ijddt.14.4.76

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Oral drug distribution is one of the most known and effective strategies for giving drugs. The success of this delivery method is affected by various factors. While oral administration is the preferred route for the majority of drug formulations, certain medications require local administration to enhance absorption. The absorption process within the gastrointestinal tract is influenced by multiple elements, such as the speed at which the dosage moves through the gastrointestinal system, the drug's release properties from its formulation and the speed at which food leaves the stomach.[1] A gastric-retentive medication delivery method is designed to prolong the presence of a drug in the stomach, enabling localized release within the upper gastrointestinal tract, which ultimately produces a systemic effect. It is often referred to as a floating drug delivery system (FDDS).[2-4] Within this low-density system, there exists a range of FDDS types. The two main types of these systems are effervescent and non-effervescent. Effervescent drug delivery systems are commonly created by integrating swellable polymers with effervescent agents. The resulting bubbly formulation typically includes a combination of acids like citric and tartaric acid, as well as carbonate or bicarbonate salts, such as sodium bicarbonate. One biguanide drug that is used to treat elevated blood sugar is metformin hydrochloride. This activator of protein kinase is dependent on AMP. In order to manage type 2 diabetes, this medication is typically used as the first-line option. For the treatment of polycystic ovarian syndrome, this medication is also a highly recommended choice. It achieves this by preventing the liver's glucogenesis process from occurring. Additionally, it enhances the body's sensitivity to insulin and boosts the synthesis of growth differentiation factors.[5,6] For patients with type 2 diabetes mellitus, pioglitazone hydrochloride and metformin hydrochloride together have a significant therapeutic benefits, because their mechanisms of action work well together.[7] An extended half-life in the stomach can be highly beneficial for medications, particularly those that focus on the stomach, are likely to degrade in the

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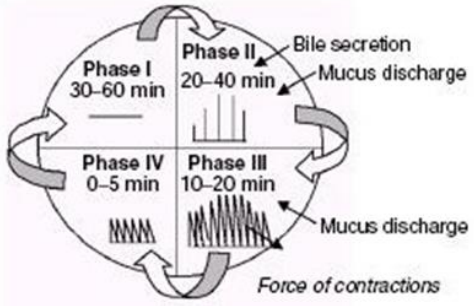

Figure 1: Patterns of gastrointestinal motility in the absence of food intake.

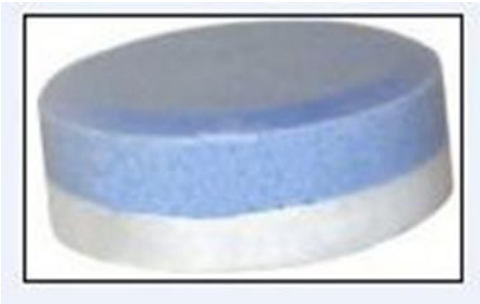

Figure 2: Bi-layer tablet

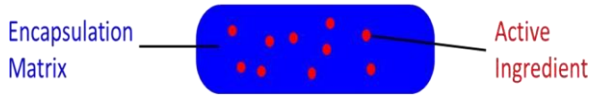

Figure 3: Sustained release formulation

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intestinal or colonic environments after being absorbed in the upper gastrointestinal tract.[8] This type of system can prolong the drug's effects, minimize its influence on lower intestinal flora, optimize drug delivery through the small intestine, reduce inactivation in the lower tract, and lower the frequency of administration. Because floating drug delivery methods don't impede gastrointestinal motility, they are thought to be the most effective of the gastro-retentive dose forms. There are currently several different floating dose forms on the market. The matrix bilayer tablet, which consists of two distinct release layers, functions as a biphasic delivery system capable of releasing two drugs either simultaneously or at different rates. This system provides several benefits, such as the ability to combine incompatible medications, achieve simultaneous release with different profiles, enhance drug efficacy through synergistic effects, reduce the burden on dosing units, and improve patient compliance and adherence.[9]

Fundamental gastrointestinal tract physiology

The morphology of the stomach reveals its division into 3 main parts: the fundus, the antrum (also called as pylorus), and the body. While the antrum uses its propulsion mechanisms to mix and propel gastric emptying in the proximal regions, fundus and body serve mainly as storage for undigested materials.[10] Gastric emptying takes place during and following the consumption of food. Nevertheless, the dynamics of these two phases differ significantly. During a fast, an electrical sequence that occurs in an inter-digestive manner in the stomach and intestines cycles every two to three hours. The inner digestive myoelectric cycle (IDC), also referred as the migrating myoelectric cycle (MMC) or the IDC, is a four-stage phenomenon, shown in Figure 1.

Phase I, also referred to as the basal phase, is characterised by sporadic contractions and usually lasts 40–60 minutes.

Phase II, referred to as the pre-burst phase, is marked by irregular contractions and action potentials, lasting between 40 to 60 minutes. Throughout this phase, there is a gradual increase in both intensity and frequency of these contractions.

Phase III, sometimes referred to as the burst phase, It takes lasts for four to six minutes. For a short while, there are strong, frequent contractions. This wave facilitates the passage of everything not yet digested from the stomach into the small intestine. The term "housekeeper wave" is an alternative designation for it.

Phase IV is characterized as the time span between the phases III and I in two back-to-back cycles, with a length that can vary from zero to five minutes.

The pattern of contractions shifts from the fed state to the fasting state after a mixed meal. The digestive motility pattern is the term used to describe this change, as it resembles the ongoing contractions that are characteristic of phase II of fasting. These contractions break down food particles to sizes under 1 mm, allowing them to remain suspended as they move toward the pylorus. The initiation of the migrating motor complex (MMC) is prolonged in the fed state, leading to a slower rate of gastric emptying. Research involving scintigraphy analysis of gastric emptying rates has highlighted two key complications associated with oral controlled-release dosage forms: a brief transit through the stomach and a variable rate of gastric emptying.

Methods for stomach retention

To extend the time that oral dosage forms are retained in the stomach, a variety of tactics have been used. The previously mentioned devices—high-density systems, floating systems, swelling and expansion mechanisms, and modified shapes—are specifically designed to impede gastric emptying. It also makes use of highly porous biodegradable hydrogel systems and magnetic systems. Hydrodynamic balance systems (HBS) are systems that use buoyant materials to keep the system afloat. Delivery devices are positioned within the body's lumens and cavities using bioadhesive or mucoadhesive systems to improve targeted drug absorption. One tactic is to introduce bioadhesive polymers, which adhere to the digestive tract's epithelial surface. The processes of electrostatic interactions and hydrogen bonding that are suggested for bioadhesion at the mucus-polymer interface.[11] Shape systems that have been modified are geometric arrangements that are resistant to disintegration, created from mixtures of polyethylene or silastic elastomer. The design of the drug delivery device is determined by multiple factors, including its dimensions, shape, and flexural modulus. With a density of 1.004 gm/cm3, coated pellets in high-density formulations are denser than what the stomach can hold. This is accomplished by the medication's use of a thick, inert material like barium sulphate, zinc oxide, or

titanium dioxide. The concept behind these high-density pellets is that their larger size allows them to reside in the lower antrum, thus prolonging their stay in the stomach.[12] Employing digestible polymers or fatty acid salts in sham feeding represents a noteworthy treatment avenue for delayed gastric emptying. This technique mimics the motility patterns typical of a fed state, this impacts the velocity of stomach emptying and permits a significant prolongation of medication release.

Gastric retention: Factors influencing density

The dose form's density affects how quickly the stomach empties. The density of a floating dose form is 1.004 gm/ml, compared to gastric fluids, it is lower. Therefore, because the dose unit is not connected to the pyloric sphincter, it stays in the stomach for a longer amount of time.[13]

Fasting or fed state

Migrating myoelectric complexes (MMC) are a notable motor activity in the gastrointestinal system that are triggered by fasting and happen around every 1.5 to 2 hours. Since the MMC is responsible for clearing undigested food from the stomach, the gastric retention time for a formulation taken alongside the MMC is expected to be relatively short. Research suggests that in fed patients, the size of a dose form may affect how quickly the stomach empties. Larger tablets are typically expelled by the stomach's cleansing waves, while smaller tablets are more readily digested and absorbed.

Biological factor

Many biological factor, like age, gender, body mass index (BMI), posture, some medical diseases including Cohn's disease and diabetes, affect how quickly the stomach empties. Generally, older adults tend to have a slower rate of gastric emptying. Women, on average, experience slower gastric emptying compared to men. The patient's posture, whether they are lying down or standing, can also affect the timing of gastric release. Additionally, stress is associated with an increase in gastric emptying speed, while depression is linked to a decrease in this rate.

Frequency of feed

Since MMC is rare, feeding a patient more than one meal can increase their gastro-retentive time by more than 400 minutes.

Swelling index

Using a 0.1 N hydrochloric acid solution (pH 1.2), swelling index of the tablets at room temperature was determined. At prearranged intervals, we kept an eye on the enlarged tablets' weight. To determine the swelling index, the following formula was utilised.

$$\text{Swelling Index} = \frac{W_t - W_0}{W_t}$$

Here,

W_0 refers, starting weight of the tablet.

W_t signifies, weight of the tablet at time t.

Gastric retention by bioadhesion

The use of bio/mucoadhesive systems significantly enhances the duration and proximity of interaction between dosage forms and biological membranes, thereby extending the retention time in the gastrointestinal tract.[14] This principle is derived from Git, which acts as a self-defense mechanism. Mucus is constantly released throughout the gastrointestinal tract by specialised goblet cells, provides a protective barrier for these cells. This viscous, gel-like substance is mainly composed of glycoproteins and its thickness diminishes from the membrane surface to the gastrointestinal lumen. Mucus is essential for protecting mucosal cells from the damaging effects of acids and peptidases.[15] It not only aids in the lubrication of solid movement but also serves as a defense against bacteria, viruses, and antigens. Bio-adhesive microspheres float on the contents of the stomach after being released from a capsule containing water. Certain microspheres stick to the stomach wall during gastric emptying in order to prolong their retention in the stomach.

Evaluation of bioadhesion

To assess the bioadhesive strength of a polymer, one can measure the force necessary to separate a polymer sample that is positioned between layers of a biological membrane, such as rabbit stomach tissue, or an artificial membrane like cellophane. This measurement can be conducted using an automated texture analyzer or a modified precision balance.

Overview of the Bi-Layer Tablet

The production of bi-layer tablets entails the sequential layering of various granulations within a die, followed by their compression. Each layer is equipped with a unique weight management system, tailored to a specific feed frame.[16] Rotary tablet presses are utilized to manufacture tablets with two or three layers. While it is possible to produce tablets with more layers, such designs significantly change. To ensure accurate weight verification for monitoring, it is advisable to compress each layer lightly and eject them individually.[17] An illustration of a bi-layer tablet is provided in Figure 2.

Advantages of Bi-layer Tablets

It is feasible to divide incompatible materials into two distinct layers, akin to a tablet, or to create a barrier between the two layers with an inert third layer. Tablets with two layers may be made for sustained release, with the first layer releasing the medication immediately and the second layer releasing it gradually over time to keep the blood level elevated.

Introduction to sustained release formulation

Maintaining zero-order disintegration while delivering medication to the body gradually and steadily is the primary objective of a sustained-release drug delivery system. This technique is often utilized for prolonged duration, effectively minimizing side effects while maintaining a constant level of medication in the system. The focus remains on achieving a reliable release of the active component, irrespective of its concentration in the dosage form.[18] The rationale underlying sustained-release or timed-release pharmaceuticals is linked to the drug's half-life within the body.

Sustained release mechanisms

In modern extended-release drug formulations, the active pharmaceutical ingredient (API) is often enclosed in a matrix composed of insoluble substances such as chitin or acrylics. The effectiveness of these formulations is largely

dependent on the drug's dissolution through the matrix's pores. In certain cases, the API is incorporated into sustained-release formulations within a matrix designed to facilitate its dissolution. When swallowed, the matrix expands to form a gel, which permits the API to gradually permeate the surface of the gel. (Shown in Fig. 3)

The active elements suitable for systems that facilitate SR should consist of:

Consistently absorbed throughout the digestive tract. When taken in comparatively tiny amounts. Applied to long-term issues as opposed to sudden ones.

Introduction to Immediate release formulation

No specific rate-controlling methods, like coatings or other additives, are used, the immediate-release tablet us composition allows it to dissolve and release its prescribed amount. In order to effectively deliver the medication, immediate-release tablets are made to dissolve and break down quickly. A medication's ability to dissolve and disintegrate when taken orally depends on a number of physiological variables. The use of an immediate-release dosage form offers patients a more user-friendly approach to medication intake, and it also allows manufacturers to enhance their market presence.[19]

Merits of Immediate Release Drug Administration Systems

Enhanced adherence and convenience, along with improved solubility, stability, and bioavailability. Supports elevated drug loading capabilities in a cost-effective manner. Competence in presenting the benefits associated with liquid medications as a solid dosage form. Flexible enough to be integrated with current packaging and processing equipment. Shorter dissolution and disintegration times for oral dosage forms that are meant to be taken right away.

Proficiency with Metformin and Pioglitazone

Pioglitazone and Metformin are commonly prescribed as oral medications for the treatment of type 2 diabetes. They can be used alone or in combination. Their methods of operation are complementary. Pioglitazone is a thiazolidinedione class member, treats insulin resistance, while metformin, a kind of biguanide, affects liver function by reducing the liver's synthesis of glucose. By lowering fasting plasma glucose levels and HbA1c in an additive way, Combining pioglitazone with metformin treatment results in long-term, sustained glycaemic control. With the exception of metformin, which has been around since the late 1950s, both of these drugs have the benefit of long-term use, meaning their safety profiles have been thoroughly studied. Importantly, the risk of hypoglycemia is negligible or nonexistent when used either alone or in combination.[20] Blood sugar levels can be lowered with the oral medication metformin. Its plasma half-life is relatively short, lasting 1.5 to 4.5 hours, and its absolute bioavailability ranges from 50 to 60%. It is not completely absorbed by the gastrointestinal tract.[21,22] Rather than promoting insulin release or leading to hypoglycemia, Pioglitazone works by attaching itself to the PPR-γ and turning it on (peroxisome proliferator-activated receptor). This medication can effectively decrease HbA1c levels both independently and in combination with other therapies. Its use in conjunction with metformin has demonstrated improvements in glycaemic control, insulin sensitivity, and beta cell function.[23] With a peak plasma level reached in two to three quarters of an hour, pioglitazone has an oral bioavailability of 83%. The half-life of pioglitazone elimination varies between 3 and 7 hours. Metformin hydrochloride (MH) is a commonly used drug in treatment of type 2 diabetes. It works by raising peripheral insulin sensitivity to lower blood glucose levels. It accomplishes this by reducing hepatic glucose output, speeding up the absorption of glucose in striated muscle, and blocking the absorption of glucose in the colon. However, the long-term insulin resistance that results from this medication often reduces the treatment's beneficial effects on people with type 2 diabetes mellitus.[24] The absorption of water-soluble medications is influenced by their location within the gastrointestinal tract (GIT); specifically, the colon exhibits limited absorption capabilities, whereas the upper GIT facilitates maximum absorption. This variation in absorption leads to a reduced bioavailability of 50–60% in patients using standard formulations, including sustained-release dosage forms. Additionally, the short half-life of less than three hours necessitates frequent high-dose administration to sustain plasma concentrations.[25] Furthermore, more than thirty percent of the dose is excreted in the faeces unaltered, rendering traditional sustained-release formulations impractical due to the site-specific nature of drug absorption in the Gastro-intestinal tract. An oral medicine known as pioglitazone hydrochloride (PG) significantly decreases blood glucose levels by reducing insulin resistance in the liver, striated muscle, and adipose tissue. Pioglitazone hydrochloride is a white, odorless crystalline powder classified as a BCS II drug, with a water solubility of approximately 14 μg/ml, unaffected by the medium's pH. Compared to other hypoglycemic agents like glimepiride, pioglitazone hydrochloride demonstrates a significantly slower progression of atherosclerosis. It has been recognized for its superior cardioprotective properties and is particularly beneficial for managing diabetic dyslipidemia, thereby reducing the risks associated with stroke, mortality, and myocardial infarction. pioglitazone hydrochloride was approved by the FDA in 1999 in treatment of type 2 diabetes mellitus because it can successfully control blood glucose levels with just one daily dose of traditional tablets.[26]

Pharmacology and Efficacy of Metformin with Pioglitazone

The main goal of the biguanide medication metformin is to make the body more sensitive to insulin. The liver serves as its main site of action, where it diminishes hepatic gluconeogenesis by enhancing insulin sensitivity. There is a possibility that metformin can improve the ability of the liver and splanchnic organs to utilize glucose. Metformin dramatically affects peripheral insulin sensitivity via AMP-activated protein kinase phosphorylation and activation, particularly in muscle tissue and to a lesser extent in fat cells. As a result, metformin not only lowers blood sugar levels but also reduces insulin levels, likely leading to decreased stress on the beta cells. Pioglitazone, a thiazolidinedione derivative, is a potent PPAR-gamma

agonist that stimulates cell proliferation. This receptor, which functions as a ligand coactivator, is a vital transcription factor involved in the metabolism of fats and carbohydrates. Furthermore, pioglitazone also slightly activates PPAR-alpha, another transcription factor involved in fat oxidation and lipid metabolism. PPAR-gamma receptors are found in numerous blood vessels, adipose tissues, and macrophages, indicating their potential role in modulating inflammation and contributing to the progression of atherosclerosis beyond their metabolic functions.[27] More than 200 genes are expressed when thiazolidinediones activate PPAR; roughly one-third of these genes are unique to each agent. Pioglitazone's distinct gene-activation profile appears to be the cause of its lipid effects as well as its safety for the heart and liver. Through a number of distinct mechanisms from those involving metformin, PPAR activation enhances insulin sensitivity. On the other hand, there is some evidence that AMP-kinase activation may also contribute to some of the insulin sensitivity that pioglitazone achieves.

Safety of Metformin/Pioglitazone

Given the association of pioglitazone hydrochloride with serious adverse events over the past decade, albeit to a lesser extent, considerable research has focused on the safety profiles of metformin and pioglitazone.[28,29] The primary concern regarding metformin is the infrequent risk of lactic acidosis, especially in patients with liver or kidney issues; those with congestive heart failure should be particularly cautious. According to research by Masoudi and colleagues, metformin-treated patients with chronic heart failure have superior clinical outcomes, which shows that the advantages of insulin sensitisation may exceed the patient population's comparatively low risk of lactic acidosis[30-34].

CONCLUSION

Fixed-dose combinations should only be used when they provide better tolerability and comparable efficacy to the medications taken one at a time, or when they provide better tolerability and comparable efficacy. Metformin and pioglitazone work together to effectively manage high blood sugar levels over the long term while lowering the risk of hypoglycemia episodes. When compared to other oral glucose-lowering combinations, pioglitazone and metformin have shown additional benefits, such as improvements in diabetic dyslipidaemia and decreases in atherosclerotic risk markers (inflammatory indicators) and heart-related outcomes. When used alone or in combination, metformin and pioglitazone are usually well tolerated, with a low incidence of hypoglycemia reported. Evidence supports that the fixed-dose combination of these medications is bioequivalent to the administration of each drug at its individual dosage. When taken together at a predetermined dosage, pioglitazone and metformin may be able to lessen the frequency and intensity of the negative side effects that are often connected to each medication when taken alone. In addition, by minimizing the number of pills taken daily, a fixed-dose combination may lead to better adherence to prescribed treatment among patients. It offers a more practical and efficient method of managing type 2 diabetes.

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