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Formulation And Evaluation Of Pioglitazone Gastro Retentive Floating Tablets

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Abstract: The present study focuses on the development of gastro-retentive floating matrix tablets of Pioglitazone to enhance its oral bioavailability and therapeutic efficacy in the management of Type II diabetes mellitus. Pioglitazone possesses low aqueous solubility and a short biological half-life (3–7 hours), resulting in frequent dosing and fluctuations in plasma drug levels. To overcome these limitations, floating tablets were formulated using Hydroxypropyl Methylcellulose (HPMC K15M) and Sodium Alginate as release-retarding polymers, Sodium Bicarbonate as the gas-generating agent, and PVP as a binder. The tablets were prepared by direct compression and evaluated for pre-compression and post-compression parameters such as hardness, friability, weight variation, drug content, floating lag time, buoyancy duration, swelling index, and in-vitro drug release. The optimized formulation (F4) exhibited excellent floating behavior with a floating lag time below one minute and buoyancy extending beyond 15 hours. In-vitro dissolution studies confirmed controlled drug release for up to 12 hours, following zero-order kinetics with a non-Fickian diffusion mechanism. Stability studies conducted under ICH conditions indicated no significant changes in physical or chemical properties. Overall, floating matrix tablets of Pioglitazone successfully prolonged gastric residence time and improved sustained drug delivery, offering better therapeutic outcomes and patient compliance.

Index Terms **- Pioglitazone, HPMC K15M, Floating tablets.**

I. INTRODUCTION

Oral drug delivery remains the most preferred and widely accepted route of administration due to its convenience, patient compliance, and cost-effectiveness. However, achieving controlled and predictable drug release through the oral route is challenging because of the physiological variability associated with the gastrointestinal (GI) tract. Variations in gastric emptying rate, pH, peristaltic movement, and the presence or absence of food significantly influence the residence time of dosage forms, especially those designed for controlled or sustained release. Most drugs are optimally absorbed in the upper part of the small intestine, and the short gastric retention time often leads to incomplete drug release or reduced bioavailability. Hence, developing oral formulations capable of prolonging gastric residence is of significant importance for improving therapeutic efficacy of drugs with narrow absorption windows [1-3]. Gastro-retentive drug delivery systems (GRDDS) have emerged as a promising strategy to ensure prolonged gastric residence, thereby enhancing drug absorption from the stomach and upper intestine. Prolonged retention in the stomach offers several advantages including improved solubility for drugs that are poorly soluble in alkaline pH, enhanced local action in the stomach, reduced drug waste, and sustained therapeutic levels. GRDDS also minimizes fluctuations in plasma concentration and reduces dosing frequency, ultimately improving patient compliance. Among the various approaches to achieve gastric retention, floating drug delivery systems (FDDS) have gained substantial attention due to their simplicity and effectiveness [4-7].

Floating systems operate on the principle of buoyancy. These dosage forms possess a bulk density lower than that of gastric fluids, allowing them to remain afloat without affecting normal gastric emptying. As the system floats, drug release occurs gradually at a controlled rate. Once the drug is fully released, the remaining system is emptied from the stomach. This prolonged gastric residence enhances the bioavailability of drugs that are primarily absorbed in the stomach or proximal small intestine. FDDS may be further classified into effervescent and non-effervescent systems. Effervescent systems employ gas-generating agents like sodium bicarbonate and citric acid to generate carbon dioxide, enabling buoyancy. Non-effervescent systems, on the other hand, utilize polymers such as HPMC, chitosan, and alginates, which swell upon contact with gastric fluid and reduce system density.

Pioglitazone, an oral antidiabetic drug belonging to the thiazolidinedione class, is widely used in the management of Type II diabetes mellitus. Despite its therapeutic significance, its low water solubility and short biological half-life (3–7 hours) limit its efficacy when administered in conventional dosage forms. These limitations result in frequent dosing and fluctuations in plasma drug concentration, which may compromise glycemic control and patient adherence [8-11]. Since Pioglitazone is predominantly absorbed in the upper GI tract and exhibits low solubility at higher pH, it serves as an ideal candidate for gastro-retentive floating systems.

Developing a floating matrix tablet of Pioglitazone ensures prolonged gastric residence, sustained drug release, and improved absorption. Polymers such as Hydroxypropyl Methylcellulose (HPMC K15M) and Sodium Alginate play a vital role in controlling drug release by forming a gel barrier that governs water penetration and drug diffusion. Sodium bicarbonate assists in achieving buoyancy through in situ gas generation, while excipients such as PVP function as binders to ensure tablet integrity.

In summary, the concept of gastro-retentive floating tablets offers a valuable platform for enhancing the therapeutic performance of Pioglitazone. By maintaining the dosage form in the stomach for prolonged periods, the system provides controlled release, improved bioavailability, and reduced dosing frequency. The present work focuses on the formulation and evaluation of Pioglitazone floating matrix tablets using suitable polymers and excipients to achieve optimal buoyancy, sustained drug release, and stability. This study aims to address the limitations associated with conventional Pioglitazone therapy and to develop a more efficient and patient-friendly dosage form for effective diabetes management [12].

II. MATERIALS AND METHODS

Pioglitazone was procured from Rakshith Pharma, Parawada, and used as the active pharmaceutical ingredient in the development of gastro-retentive floating matrix tablets. Hydroxypropyl Methylcellulose (HPMC K15M) and Sodium Alginate, obtained from Yarrow Chemicals and Choice Organ Chem LLP, respectively, were selected as release-retarding polymers due to their gel-forming and swelling properties. Sodium bicarbonate (S.D. Fine Chemicals) served as the effervescent gas-generating agent to provide buoyancy, while Polyvinylpyrrolidone (PVP) acted as a binder. Microcrystalline cellulose (MCC) was incorporated as a diluent, and magnesium stearate and talc were used as lubricant and glidant. All excipients were of analytical grade. Drug–excipient compatibility was initially assessed through physical mixing of Pioglitazone with individual excipients in a 1:1 ratio, followed by storage at 40°C/75% RH for three months as per ICH guidelines. Samples were periodically examined for color changes, odor, physical appearance, and further confirmed by FT-IR spectroscopy, which demonstrated no significant interaction between the drug and polymers.

Floating matrix tablets were formulated by the direct compression method. All ingredients were passed through a #100 sieve and accurately weighed. Pioglitazone, polymers, sodium bicarbonate, PVP, and MCC were blended uniformly using geometric dilution to ensure even distribution of the active ingredient. Lubricants were added at the final stage and gently blended for five minutes to prevent interference with tablet hardness and buoyancy. The prepared blend was compressed into tablets using an eight-station rotary tablet punching machine (Shakti, Ahmedabad), maintaining a target weight of 350 mg and a hardness range of 4–6 kg/cm². Pre-compression evaluation included determining angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index to assess flow properties using standard procedures.

Post-compression evaluations were carried out to assess the physical quality of tablets. Tablet hardness was measured using a Pfizer hardness tester, friability was evaluated using a Roche friabilator, and weight variation and thickness were recorded using standard methods. Drug content was determined by dissolving powdered tablets in methanol, diluting appropriately with 0.1N HCl, and measuring absorbance at 269 nm using a UV-

Visible spectrophotometer. In-vitro buoyancy studies were performed by placing tablets in 100 mL of 0.1N HCl (pH 1.2) and recording floating lag time and total floating duration.

Swelling behavior was evaluated using USP Dissolution Apparatus II at 37 ± 0.5°C and 100 rpm in 0.1N HCl. Tablets were removed at specific time intervals, blotted to remove excess fluid, and swelling index was calculated using the formula $(W_2–W_1)/W_1 \times 100$. In-vitro drug release studies were carried out using USP Apparatus II with 900 mL of 0.1N HCl at 37 ± 0.5°C and paddle rotation of 50 rpm. Samples were withdrawn hourly up to 12 hours, filtered, and analyzed at 269 nm. Drug release kinetics were analyzed by fitting dissolution data to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine mechanism of release. Stability studies were conducted on the optimized formulation by storing tablets at 30°C/75% RH for three months and evaluating changes in drug content, floating characteristics, hardness, and dissolution behavior.

III. RESULTS AND DISCUSSION

The formulation of gastro-retentive floating matrix tablets of Pioglitazone was successfully achieved using HPMC K15M and Sodium Alginate as release-retarding polymers. The study began with the evaluation of pre-compression parameters, where the powder blends exhibited good flow properties with angle of repose values between 25° and 27°, bulk density ranging from 0.50 to 0.56 g/mL, tapped density between 0.58 and 0.71 g/mL, Hausner's ratio from 1.10 to 1.23, and Carr's index between 11.8% and 20.25%, confirming suitability for direct compression. Post-compression evaluations demonstrated that all tablets complied with pharmacopeial requirements, where hardness ranged from 3.26 to 5.6 kg/cm², friability remained below 1%, and weight variation was uniform across batches. Drug content was consistent, varying between 98.3% and 99.85%, indicating proper drug distribution throughout the formulations. These results confirmed that the direct compression method produced tablets with acceptable physical integrity and uniformity. Floating behavior is a critical parameter for gastro-retentive drug delivery. The developed formulations exhibited excellent buoyancy, with floating lag times decreasing significantly as polymer concentrations increased. The optimized formulation F4 showed a floating lag time of less than one minute and remained buoyant for more than 15 hours, a feature attributed to rapid gel formation by HPMC K15M and effective CO_2 entrapment generated by sodium bicarbonate in acidic medium. This prolonged floating ability is essential to ensure extended gastric residence time, which directly influences drug absorption for drugs like Pioglitazone that have a narrow absorption window in the upper gastrointestinal tract. Swelling behavior further contributed to sustained drug release. All formulations demonstrated continuous swelling in acidic conditions, forming a stable and consistent gel layer around the tablet core. This hydrated gel barrier modulates water penetration and drug diffusion. Among all formulations, F4 exhibited optimal swelling characteristics, maintaining structural integrity while expanding adequately to control the release over time. The combination of HPMC K15M and Sodium Alginate proved effective in forming a strong gel matrix that enhanced both buoyancy and release modulation.

Table 1: Buoyancy studies of formulations

Formulation code	Floating lag time (sec)	Floating duration (hrs)
F1	60	>12
F2	60	>16
F3	60	>12
F4	60	>15
F5	60	>15
F6	60	>15
F7	60	>15
F8	60	>15

In vitro dissolution studies revealed that polymer composition played a major role in determining the release profile. While all formulations sustained drug release over a 12-hour period, F4 displayed the most desirable release behavior, delivering approximately 99.9% drug at the end of the 12th hour. Formulations with higher polymer concentrations released the drug more slowly due to the formation of a thicker gel barrier that increased diffusional resistance. In contrast, formulations with lower polymer content showed more rapid release. The dissolution data clearly demonstrated that the combination and ratio of HPMC K15M and Sodium Alginate used in F4 were optimal for achieving controlled and sustained release over the required duration.

Drug release kinetics were studied to understand the mechanism governing Pioglitazone release from the matrix tablets. The optimized formulation F4 followed zero-order kinetics, indicating that drug release remained constant over time and was independent of drug concentration. The Higuchi model further confirmed diffusion as a major mechanism, while the Korsmeyer–Peppas release exponent (n = 1.16) suggested a non-Fickian, anomalous transport mechanism involving a combination of diffusion and polymer relaxation processes. This aligns with the expected behavior of hydrophilic polymer-based matrix systems, where erosion and diffusion occur simultaneously during release. Stability studies conducted at accelerated conditions (40°C/75% RH for three months) showed no significant deviations in drug content, hardness, floating capacity, or dissolution performance. F4 retained its dissolution efficiency and mechanical properties, confirming robustness and stability of the final formulation during storage. Overall, the results demonstrate that Pioglitazone floating matrix tablets developed using HPMC K15M and Sodium Alginate successfully achieved prolonged gastric retention, predictable buoyancy, controlled drug release, and strong stability profiles suitable for therapeutic applications

IV. CONCLUSION

The present study successfully developed and evaluated gastro-retentive floating matrix tablets of Pioglitazone to enhance its gastric residence time and sustain drug release for improved therapeutic efficacy. Through systematic formulation using HPMC K15M and Sodium Alginate as release-retarding polymers, and sodium bicarbonate as a gas-generating agent, tablets exhibited excellent physical integrity, good flow characteristics, and uniform drug content. The direct compression method proved efficient and reproducible, producing tablets with consistent hardness, friability below 1%, and acceptable weight variation. Floating studies confirmed that all formulations remained buoyant for extended periods, while the optimized formulation F4 demonstrated a floating lag time of less than one minute and a total buoyancy exceeding 15 hours, ensuring prolonged gastric retention essential for Pioglitazone absorption. In-vitro dissolution studies revealed that polymer concentration significantly influenced drug release. Among all formulations, F4 showed the most controlled and sustained release pattern, achieving nearly 100% release at 12 hours. Kinetic modeling confirmed that the optimized formulation followed zero-order release with a non-Fickian diffusion mechanism involving both diffusion and polymer relaxation. Swelling behavior supported this release mechanism by forming a stable gel matrix that modulated drug diffusion. Stability studies conducted under accelerated conditions demonstrated that F4 retained its physical characteristics, drug content, and dissolution profile over three months, confirming the formulation's robustness and long-term stability. It concludes that gastro-retentive floating matrix tablets of Pioglitazone offer a promising approach to overcoming its limitations of low solubility and short biological half-life. The optimized formulation ensures prolonged gastric residence, sustained release, and improved bioavailability, suggesting strong potential for enhanced therapeutic outcomes and better patient compliance in the management of Type II diabetes mellitus. This work provides a reliable foundation for future scale-up, in-vivo evaluation, and potential clinical application.

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