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Development of Sustained Release Matrix Tablets A comparative study of natural and synthetic polymers

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ABSTRACT

The present study focuses on the development and evaluation of Pioglitazone sustained-release matrix tablets using both natural (pectin) and synthetic (HPMC) polymers. The formulation was prepared by direct compression, and drug-excipient compatibility was assessed using FTIR spectroscopy, confirming no significant interactions. Micromeritic properties, including angle of repose, bulk density, and Carr's index, indicated good flowability and compressibility, ensuring uniform tablet formation.Post-compression evaluation parameters such as hardness, friability, disintegration time, and wetting time were within acceptable limits, with formulations F2 and F4 exhibiting optimal characteristics. In vitro dissolution studies conducted in 0.1N HCl using USP Type I apparatus showed that formulations F5 and F6 demonstrated the highest drug release (95.88% and 88.22% at 60 min, respectively), making them potential candidates for immediate-release formulations.The study concludes that the selected polymers effectively controlled drug release, improving therapeutic efficacy and patient compliance. The optimized formulations can be further explored for in vivo pharmacokinetic studies to establish bioavailability and long-term stability. This research provides a comparative approach between natural and synthetic polymers in sustained-release drug delivery systems, ensuring an efficient and controlled drug release profile for improved diabetes management.

Keywords: *Pioglitazone, Sustained-release, Matrix tablets, Drug release*

1. INTRODUCTION

The term "sustained release" has been extensively documented in medical and pharmaceutical literature for several decades, describing dosage forms specifically designed to modulate the release of therapeutic agents, ensuring a prolonged and controlled presence in systemic circulation (1). This mechanism allows for a delayed onset of action while extending the therapeutic effect, thereby improving patient compliance and reducing dosing frequency (2).

Formulation Techniques for Sustained Release Dosage Forms

One of the simplest methods for formulating sustained-release dosage forms involves the direct compression of a mixture containing the active drug, retardant polymers, and excipients (3). In such a matrix system, the drug is embedded within a polymeric network that controls its release through diffusion, swelling, or erosion mechanisms (4). The rate of release is influenced by the physicochemical properties of the polymer, the solubility of the drug, and the presence of additional additives (5).

Polymers Used in Sustained Release Systems

Sustained-release formulations rely on both hydrophilic and hydrophobic polymers:

Hydrophilic Polymers: These include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), xanthan gum, sodium alginate, and poly(ethylene oxide) (6). These polymers swell in contact with gastrointestinal fluids, forming a gel barrier that regulates drug diffusion and release (7).

Hydrophobic Polymers: Ethylcellulose and acrylic polymers such as Eudragit® RS and RL are commonly used to create less permeable matrices, reducing drug release rates (8). Eudragit® polymers come in various grades, allowing precise control over permeability and release kinetics (9).

Mechanisms of Drug Release from Matrix Systems

The controlled release of drugs from matrix systems follows different mechanisms:

Diffusion: The drug migrates from the polymer matrix into surrounding fluids through small pores or channels (10).

Swelling-Controlled Release: Hydrophilic polymers absorb water, swell, and gradually allow drug diffusion through the gel barrier (11).

Erosion: The matrix degrades over time, leading to sustained drug release (12).

These mechanisms can work independently or in combination, depending on the formulation and polymer properties (13).

Advantages of Sustained Release Dosage Forms

Reduced Dosing Frequency: Maintaining therapeutic levels for extended periods reduces the need for frequent dosing, enhancing patient adherence (14).

Stable Plasma Drug Concentration: Prevents fluctuations in drug levels, minimizing peaks and troughs that could cause toxicity or subtherapeutic effects (15).

Improved Therapeutic Outcomes: Helps in the long-term management of chronic conditions by ensuring consistent drug action (16).

Challenges in Developing Sustained Release Formulations

Despite their advantages, sustained-release formulations present challenges:

Drug Properties: Poorly soluble or unstable drugs may not be suitable for sustained release (17).

Polymer Selection: Finding the right polymer to achieve the desired release rate without compromising drug stability is crucial (18).

Manufacturing Complexity: Ensuring uniform drug distribution within the matrix and maintaining batch-to-batch consistency can be technically demanding (19).

Pioglitazone is an oral antidiabetic medication belonging to the thiazolidinedione class, primarily used in the management of type 2 diabetes mellitus. It functions by increasing insulin sensitivity, which helps improve glycemic control. This mechanism is mediated through the activation of peroxisome proliferator-activated receptor-gamma (PPAR-γ), leading to enhanced glucose uptake by peripheral tissues and reduced hepatic glucose production (20).

In clinical practice, pioglitazone is often prescribed in conjunction with lifestyle modifications such as diet and exercise. It can be used as monotherapy or in combination with other antidiabetic agents like metformin, sulfonylureas, or insulin, depending on the patient's condition (21).

While pioglitazone is effective in lowering blood glucose levels, its use requires careful consideration due to potential adverse effects. Common side effects include weight gain, fluid retention, and an increased risk of heart failure. There have also been concerns regarding its possible link to bladder cancer, though studies provide mixed results. Therefore, its use should be carefully assessed based on the patient's overall health status (22). Despite these risks, pioglitazone remains a valuable therapeutic option for patients with type 2 diabetes, particularly those who need improved insulin sensitivity. Its role in diabetes management should be individualized, balancing its benefits with potential side effects (23).

2. MATERIALS AND METHODS

Materials: Pioglitazone was obtained from Sun Pharmaceuticals Ltd., Ahmedabad. Other excipients, including hydroxypropyl methylcellulose (HPMC), microcrystalline cellulose (MCC), lactose, starch, talc, and magnesium stearate, were of laboratory grade. Fresh Lemon fruits were purchased from the local market.

Extraction of Pectin

The extraction of pectin begins with the selection of citrus fruit, specifically Lemon. A total of 500 grams of Lemon peel is taken and dried for four days before being ground into a fine powder. For the extraction process, a total of 50 mL of hydrochloric acid (HCL) and 5 liters of distilled water are prepared and distributed evenly among five different beakers. The mixture is allowed to stand for 24 hours to facilitate extraction. Following this, 1 liter of filtrate from each beaker is mixed with 1 liter of 95% ethanol. The resulting solution is then processed using a centrifugation apparatus. After centrifugation, the mixture is left undisturbed for one hour before being filtered through a Buchner funnel. A measured quantity of acidified ethanol is added to the residue, which is then washed with 250 mL of acetone. The product is subsequently dried at room

temperature for one day. Once dried, it is ground into a fine powder and passed through a 40–42 mesh sieve to separate pectin from fiber. Finally, the purified pectin powder is collected and weighed. (24, 25,26)

Formulation of PioglitazoneTablets

The formulation of pioglitazone sustained-release matrix tablets via direct compression has been extensively studied in pharmaceutical research. In one study, pioglitazone hydrochloride was formulated into sustained-release tablets using processed Aloe vera mucilage as a release modifier. The matrices were prepared by dry blending selected ratios of polymer and ingredients, followed by direct compression (27).

Another study focused on the development of multilayered tablets combining pioglitazone hydrochloride and metformin hydrochloride. Pioglitazone HCl was formulated as an immediate-release layer using the direct compression method with superdisintegrants like crospovidone and Avicel PH 102, while metformin HCl was incorporated as a controlled-release layer using hydrophilic polymers such as HPMC K4M (28).

Additionally, research has been conducted on the formulation and evaluation of sustained-release dual matrix tablets using Compritol 888 ATO. In this approach, immediate-release granules of pioglitazone and sustained-release granules of caffeine were combined to enhance patient compliance and therapeutic efficacy (29).

These studies collectively highlight the versatility and effectiveness of the direct compression method in formulating pioglitazone sustained-release matrix tablets, employing various polymers and excipients to achieve desired release profiles (30).

Table 1 Different Formulations Codes

Ingredients	F1	F2	F3	F4	F5	F6
Pioglitazone (mg)	15	15	15	15	15	15
Lactose	200	150	200	150	200	150
Microcrystalline Cellulose	-	50	-	100	-	-
Starch	48	48	48	48	48	48
Pectin	-	-	50	-	100	-
Hydroxypropyl Methylcellulose	50	-	-	-	-	-
Magnesium Stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1

Preformulation Studies of Drug

It is the primary step in the rational development of dosage forms of a medicinal substance. It can be defined as a study of physicochemical properties of drug substances. The general purpose of Preformulation study is to generate information which is useful for the researcher to develop a stable dosage form.

FTIR Compatibility Analysis

Fourier Transform Infrared Spectroscopy (FTIR) was conducted to evaluate the compatibility between Pioglitazone and selected excipients. The analysis was performed using an FTIR spectrometer, where pure drug and physical mixtures of the drug with excipients were scanned over a wavelength range of 4000–400 cm^{-1}. The spectra obtained were analyzed for any significant shifts, disappearance, or appearance of new peaks, which could indicate potential chemical interactions. The retention of characteristic functional group peaks of Pioglitazone in the presence of excipients confirmed the absence of incompatibility, ensuring the stability of the formulation.

Standard Calibration Curve:

A stock solution of 100 µg/mL was prepared by diluting 10 mL of the drug solution to 100 mL with 0.1N HCl. From this stock solution, aliquots of 0.1, 0.2, 0.4, 0.6, 1.2, and 2.0 mL were transferred into 10 mL volumetric flasks and diluted to volume with 0.1N HCl, resulting in final concentrations of 1, 2, 4, 6, 12, and 20 µg/mL. The absorbance of each solution was measured at 230 nm using 0.1N HCl as a blank. A calibration curve was constructed by plotting drug concentration versus absorbance, and linear regression analysis was performed on the absorbance data points. A straight-line equation was derived to facilitate the accurate calculation of drug concentration.

Organoleptic Characterization

Physical appearances such as nature, color, odor etc. were performed by visual observations.

Color: A little amount of drug was kept in butter paper & view in illuminated set (34).

dour: Extremely small amount of drug was smelled to obtain the odour. [31]

Micromeritic Properties of Drug

Angle of Repose (α): It was determined by the funnel method (104). The mixture was poured through a funnel that can be raised vertically until a maximum cone height (*h*) was obtained.

A = tan-1 (*h/r*)

The radius of the heap (*r*) was measured & angle of repose can be calculated. .

Bulk Density (ρb): Density of fine particles is often determined by using a measuring cylinder; it is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed amount of powder into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this, the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml.

Bulk Density=Mass of powder/Bulk volume of powder

Whereas: M = Powder mass

Vb = Powder bulk volume (ρb) = Bulk density [32]

Tapped Density (ρt): The measuring cylinder containing a known mass of blend was tapped for a set time. The minimum volume (vt) occupied in the cylinder and the weight (m) of the blend was measured. The tapped density was calculated using the following formula

ρt=M/Vt

Whereas: (ρb) = Bulk density

M = Mass of powder

Vt = Tapped volume of the powder

Carr's Compressibility Index: The simplest method of measurement of powder flow is compressibility and sign of the ease with which a material can be induced to flow is given by compressibility (37). The compressibility index of the granules was calculated by Carr's compressibility index which is determined by using the following formula:

$C= (V_0-V_t / V_0) \times 100$ [33]

Hausner's Ratio: It is an indirect index of ease of powder flow (109). It is determined by the following formula:

Hausner's ratio = ρt /ρb

Whereas:

ρt = Tapped density ρb = Bulk density.

Lower Hausner's Ratio (<1.25) Indicates better flow properties than higher ones (>1.25). [34]

3. POST COMPRESSION PARAMETERS STUDIES

Weight Variation Test

A total of twenty tablets were randomly selected, and their individual weights were recorded. The mean weight of the tablets was then calculated. According to standard guidelines, no more than two tablets should deviate from the average weight by more than the allowed percentage variation, and none should exceed twice that limit (35).

Hardness Test

Tablets must possess adequate mechanical strength to endure the handling process during manufacturing, packaging, shipping, and dispensing. This parameter is particularly critical for sustained-release formulations or those sensitive to variations in drug release profiles. Hardness was measured using a Monsanto hardness tester, where the tablet was placed vertically between the lower and upper plungers. The initial reading was recorded before applying force through a threaded bolt, causing the upper plunger to press against a spring. The tablet was subjected to force until it fractured, with the difference between the initial and final readings representing the tablet's hardness. The results were expressed in Kg/cm^2 (36).

Thickness Measurement

The thickness of individual tablets was determined using a Vernier caliper, with the average thickness recorded in

millimeters. This parameter ensures uniformity among the tablets, which is important for proper packaging and overall quality control (37).

Friability Test

Friability assesses a tablet's ability to withstand mechanical stresses such as shocks and abrasion encountered during manufacturing, packaging, shipping, and handling. Tablets prone to breaking, chipping, or excessive powdering may lack consumer appeal and fail quality standards. In this test, ten tablets were initially weighed and placed in a Roche friabilator. The device, operating at 25 rpm, subjected the tablets to repeated falls within a rotating plastic drum, covering a distance of six inches per revolution. After 100 revolutions, the tablets were removed, dedusted, and reweighed. Acceptable friability limits typically range between 0.5% and 1%. The percentage friability was calculated using the standard formula (38).

$$\text{Friability (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

where:

Initial weight = Total weight of tablets before the test

Final weight = Total weight of tablets after 100 revolutions in the friabilator

Wetting Time and Water Absorption Ratio

To determine the wetting time, a piece of tissue paper was folded twice and placed in a small 6.5 cm diameter Petri dish containing 6 mL of water. A pre-weighed tablet was gently placed on the surface of the tissue paper and allowed to absorb water completely. The time taken for the water to reach the upper surface of the tablet and fully wet it was recorded as the wetting time.

After complete wetting, the tablet was reweighed, and the water absorption ratio (R) was calculated using the following formula:

$$R = \frac{W_b - W_a}{W_a} \times 100$$

where:

Wb = Weight of the tablet after absorption

Wa = Initial weight of the tablet before absorption

This test is essential for assessing the hydrophilic properties of the formulation, which play a crucial role in ensuring efficient disintegration and dissolution of the tablet [39]

. Disintegration Test

The disintegration test was performed in 900 mL of distilled water, simulated gastric fluid, or simulated intestinal fluid, maintained at 37°C ± 2°C. The disintegration time for tablets from each formulation was determined using a disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus, each containing distilled water. A disk was added to each tube to ensure uniform testing conditions. The time taken (in seconds) for the complete disintegration of the tablets, where no palpable mass remained in the apparatus, was recorded as the disintegration time [40].

In Vitro Dissolution Studies

The dissolution study was conducted using a USP Dissolution Apparatus Type I (Basket Method). A dissolution medium consisting of 900 mL of 0.1 M hydrochloric acid was used to simulate gastric conditions. The apparatus was operated at a rotation speed of 50 RPM, while the temperature was maintained at 37°C ± 0.5°C to ensure consistency. Samples of 10 mL were withdrawn at predetermined time intervals of 5, 10, 15, 20, 25, 30, 45, and 60 minutes. The withdrawn samples were analyzed using UV spectroscopy at a wavelength of 230 nm, ensuring accurate measurement of drug release over time [41].

4. RESULT & DISCUSSION

FTIR

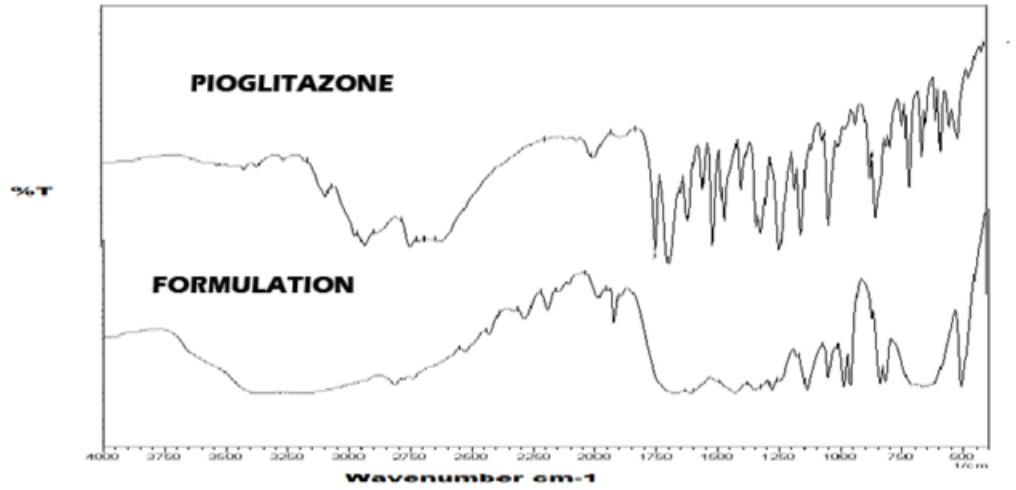

Figure 1 FTIR Spectra of Pioglitazone Pure Drug and Formulation

The FTIR spectra of pure Pioglitazone and its formulation were analyzed to assess drug-excipient compatibility. The characteristic peaks of Pioglitazone were observed in both spectra without significant shifts, disappearance, or the appearance of new peaks. This indicates that no major chemical interactions occurred between Pioglitazone and the excipients. The retention of functional group peaks confirms that the drug remains stable within the formulation, suggesting good compatibility with the selected excipients.

Calibration Curve

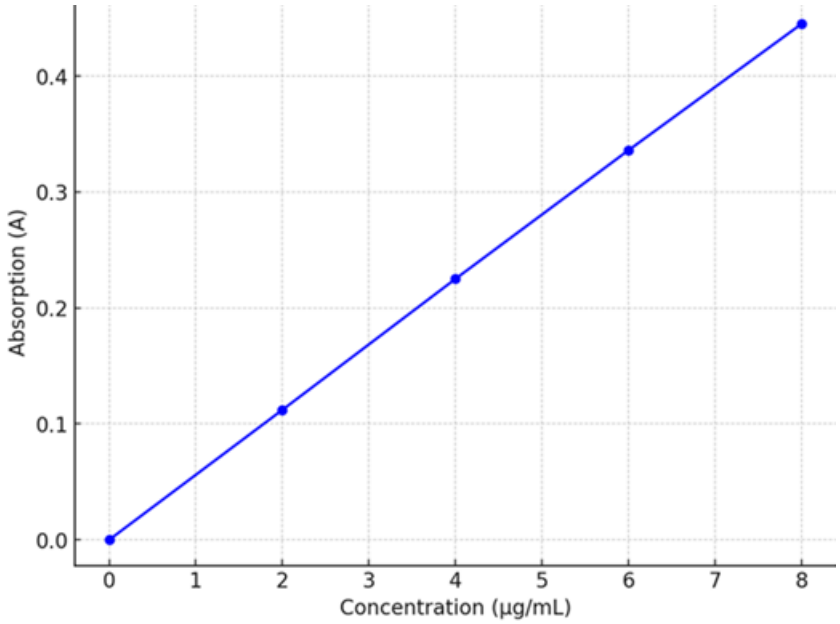

Figure 2 Calibration Curve of Pioglitazone

The calibration curve of Pioglitazone exhibits a linear relationship between concentration (µg/mL) and absorbance, confirming adherence to Beer-Lambert's Law. The straight-line equation obtained indicates a consistent and reliable method for quantifying Pioglitazone in further analytical studies.

Organoleptic Characteristics

Table 2 Organoleptic Characteristics of Pioglitazone

S.No.	Drug	Test	Specification	Observation
1.	Pioglitazone	Color	White crystalline powder	White crystalline powder
2.	Pioglitazone	Odor	Odorless	Odorless

The organoleptic evaluation of Pioglitazone confirmed that the drug appears as a white crystalline powder and is odorless, aligning with standard specifications. The consistency in color and odor indicates the purity and stability of the drug, ensuring its suitability for further formulation development.

Table 3Micromeritic Properties of Drug

Formulation	Angle of Repose (°) ± SD	Bulk Density (g/mL) ± SD	Tapped Density (g/mL) ± SD	Carr's Index (%) ± SD
F1	35.85 ± 0.42	0.49 ± 0.02	0.62 ± 0.03	26.8 ± 1.4
F2	37.90 ± 0.51	0.47 ± 0.01	0.54 ± 0.02	12.9 ± 1.1
F3	36.40 ± 0.38	0.45 ± 0.02	0.60 ± 0.02	33.5 ± 1.6
F4	38.10 ± 0.45	0.50 ± 0.02	0.59 ± 0.03	23.5 ± 1.3
F5	35.20 ± 0.47	0.54 ± 0.02	0.67 ± 0.03	26.7 ± 1.2
F6	37.20 ± 0.50	0.46 ± 0.01	0.58 ± 0.02	23.9 ± 1.5

The micromeritic properties of Pioglitazone formulations were evaluated, including angle of repose, bulk density, tapped density, and Carr's Index. The angle of repose values ranged from 35.20° to 38.10°, indicating satisfactory flow properties. The bulk density and tapped density values showed minimal variation, suggesting uniform packing characteristics across formulations. The Carr's Index ranged between 12.9% and 33.5%, where lower values indicate better flowability, while higher values suggest moderate compressibility. The observed standard deviation (SD) values confirm consistency in measurements, ensuring reproducibility of the formulation process.

Table 4 Post Compression Studies

Formulation Code	Average Weight (mg) ± SD	Thickness (mm) ± SD	Hardness (kg/cm²) ± SD	Percentage Friability (%) ± SD	Disintegration Time (sec) ± SD	Wetting Time (sec) ± SD
F1	0.298 ± 0.002	0.61 ± 0.01	4.6 ± 0.2	16.85 ± 1.3	142 ± 3	90 ± 2
F2	0.300 ± 0.003	0.59 ± 0.01	4.4 ± 0.3	11.10 ± 1.1	27 ± 2	98 ± 2
F3	0.299 ± 0.002	0.62 ± 0.01	2.6 ± 0.2	37.80 ± 1.5	126 ± 3	54 ± 2
F4	0.302 ± 0.003	0.60 ± 0.01	5.4 ± 0.3	11.05 ± 1.2	19 ± 2	58 ± 3
F5	0.305 ± 0.002	0.61 ± 0.01	4.3 ± 0.2	25.12 ± 1.4	14 ± 2	95 ± 2
F6	0.301 ± 0.003	0.60 ± 0.01	4.7 ± 0.2	22.85 ± 1.3	20 ± 2	99 ± 2

The evaluated tablet formulations (F1-F6) exhibited consistent average weights ranging from 0.298 to 0.305 mg, indicating minimal batch-to-batch variability. Tablet thickness was uniform across formulations (0.59–0.62 mm), reflecting controlled manufacturing processes. Hardness values varied significantly, with F4 demonstrating the highest hardness (5.4 kg/cm²) and F3 the lowest (2.6 kg/cm²), suggesting differences in formulation integrity. Friability percentages ranged from 11.05% (F4) to 37.80% (F3), with formulations F3 and F5 exhibiting higher friability, thus indicating lower mechanical strength. Disintegration times were rapid across all formulations, with F2 and F4 showing notably quicker disintegration (27 sec and 19 sec respectively), making them favorable candidates for fast-disintegrating tablets. The wetting times aligned well with disintegration results, as formulations with shorter wetting times (F3: 54 sec, F4: 58 sec) generally disintegrated faster. Overall, formulations F2 and F4 demonstrated optimal balance in hardness, low friability, rapid disintegration, and wetting times, indicating superior potential for further development as effective fast-disintegrating tablet formulations.

Invitro Dissolution Studies

Table5 Dissolution Profile of Tablet Formulations (Mean ± SD, n=3)

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
5	28.12 ± 0.15	29.72 ± 0.21	29.58 ± 0.18	28.92 ± 0.20	30.16 ± 0.22	29.88 ± 0.19
10	39.36 ± 0.28	44.02 ± 0.35	44.32 ± 0.32	43.38 ± 0.30	47.20 ± 0.38	44.32 ± 0.33
15	48.18 ± 0.36	52.02 ± 0.30	51.24 ± 0.34	50.58 ± 0.32	55.38 ± 0.40	52.18 ± 0.31
20	50.06 ± 0.41	56.18 ± 0.38	56.02 ± 0.36	54.90 ± 0.35	57.92 ± 0.42	58.56 ± 0.37
25	55.34 ± 0.34	60.02 ± 0.40	58.08 ± 0.38	59.20 ± 0.39	63.84 ± 0.44	63.36 ± 0.41
30	63.38 ± 0.43	67.36 ± 0.37	63.38 ± 0.35	65.82 ± 0.40	68.18 ± 0.45	67.36 ± 0.38
45	64.22 ± 0.42	74.56 ± 0.44	64.18 ± 0.41	73.68 ± 0.46	82.14 ± 0.50	76.18 ± 0.44
60	73.62 ± 0.45	76.66 ± 0.47	66.58 ± 0.43	80.26 ± 0.48	95.88 ± 0.52	88.22 ± 0.46

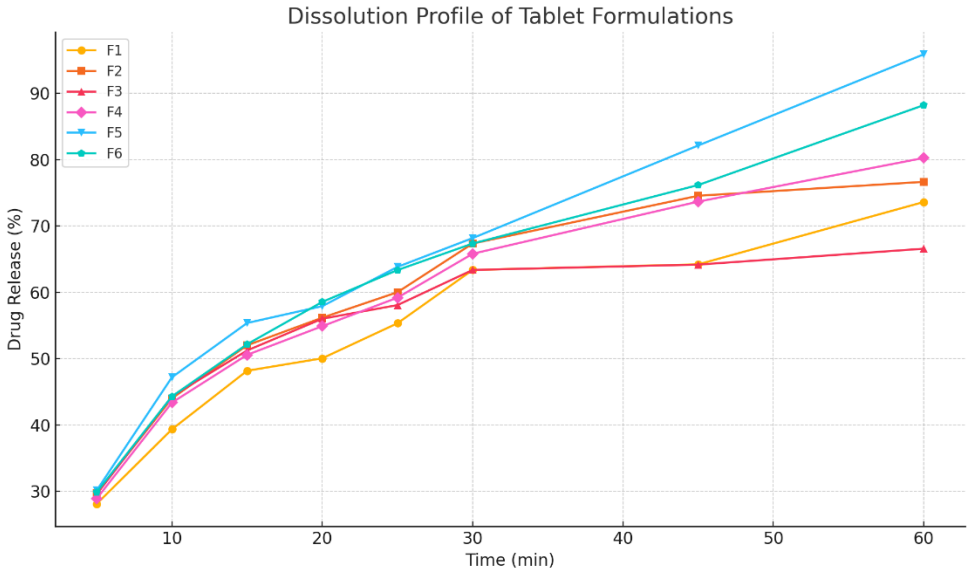

Figure 3 Dissolution Profile of Table Formulation

The dissolution profiles of tablet formulations (F1–F6) demonstrated a progressive increase in drug release over the observed 60-minute period. Formulation F5 exhibited the highest cumulative drug release (95.88% at 60 min), indicating superior dissolution characteristics likely attributed to optimized excipient interactions enhancing drug solubility and tablet disintegration. Formulation F6 also showed significant release (88.22%), followed closely by F4 (80.26%), suggesting good dissolution efficiency. In contrast, formulations F1 and F3 showed comparatively lower drug release (73.62% and 66.58%, respectively), indicating slower dissolution behavior possibly linked to higher friability or weaker tablet integrity. Overall,

formulations F5 and F6 demonstrated promising dissolution properties, making them favorable candidates for further development and potential clinical evaluation as immediate-release dosage forms.

5. CONCLUSION

The study successfully developed and evaluated sustained-release matrix tablets of Pioglitazone using both natural (pectin) and synthetic (HPMC) polymers. The FTIR analysis confirmed no significant drug-excipient interactions, ensuring formulation stability. The micromeritic properties indicated good flowability and compressibility, facilitating tablet production. The post-formulation studies demonstrated acceptable weight variation, thickness, hardness, friability, disintegration, and wetting time, with formulations F2 and F4 showing an optimal balance of mechanical strength and rapid disintegration. The in vitro dissolution studies revealed that formulations F5 and F6 exhibited the highest drug release, suggesting their suitability for immediate-release formulations. Overall, the optimized formulations demonstrated promising sustained-release characteristics, ensuring enhanced therapeutic efficacy and patient compliance. Future studies can focus on in vivo evaluation to establish bioavailability and pharmacokinetic parameters.

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