RESEARCH PAPER

Formulation, Development and Evaluation of a Gastro-Retentive Drug Delivery System of Metformin Hydrochloride using RAFT Technology For Extended Release

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ABSTRACT
Metformin Hydrochloride, an antidiabetic drug with a short biological half-life and narrow absorption window, is rapidly absorbed from the upper gastrointestinal tract (GIT) and eliminated from the systemic circulation. Consequently, frequent dosing is required to maintain effective plasma drug concentrations. The development of an orally administered controlled-release formulation offers a potential solution by ensuring gradual and sustained release of the drug within the GIT, thereby maintaining prolonged therapeutic levels in the bloodstream. However, challenges such as short gastric residence time (GRT) and variable gastric emptying can limit the complete release and absorption of the drug, ultimately reducing its therapeutic efficacy. The present study focuses on the formulation and development of a gastro-retentive drug delivery system in the form of a granules of Metformin Hydrochloride, aimed at extending the gastric residence time and achieving extended drug release. Prolonged GRT enhances the duration of drug release, minimizes dosing frequency, improves bioavailability, and facilitates dissolution of drugs with poor solubility at higher intestinal pH. Moreover, sustained gastric retention can promote localized drug action in the upper GIT, contributing to improved therapeutic outcomes.

Keywords: Gastro-retentive drug delivery, Metformin Hydrochloride, Powder for oral suspension, Gastric retention, Controlled release, Bioavailability.
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INTRODUCTION

Gastro-retentive drug delivery systems (GRDDS) have emerged as an important advancement in oral pharmaceutical technology, offering the ability to prolong the residence time of a dosage form in the stomach and upper gastrointestinal tract (GIT). Extending gastric residence time (GRT) enhances the absorption of drugs that are preferentially absorbed in the stomach or proximal small intestine and improves bioavailability, particularly for drugs with narrow absorption windows or poor stability in the intestinal or colonic environment[1]. By maintaining the dosage form in the stomach for an extended duration, GRDDS can achieve localized drug release, reduce fluctuations in plasma drug levels, and provide more consistent therapeutic outcomes[1,2].

The efficiency of gastro-retentive formulations is influenced by several physiological and formulation-related factors. Key parameters such as dosage form size, shape, density, and the presence of food significantly affect gastric retention. Dosage forms with a density lower than 1.0 g/cm³ exhibit buoyant behaviour, allowing them to float on gastric fluids and resist gastric emptying. Larger formulations, especially those exceeding 7.5 mm in diameter, and structures with specific geometries like tetrahedral or ring shapes, demonstrate improved gastric retention due to their inability to pass rapidly through the pyloric opening[3,4].

Among various GRDDS strategies, floating drug delivery systems have gained considerable attention due to their low density, which allows them to remain buoyant on gastric contents for extended periods. Their prolonged GRT ensures sustained drug release, improved bioavailability, and reduced variability in plasma concentrations. An effective floating system must maintain a density lower than gastric fluids, form a cohesive gel barrier, and release the drug in a controlled manner[5].

Metformin hydrochloride (MF), a widely used oral antihyperglycemic agent for type 2 diabetes, is an ideal candidate for gastro-retentive formulation. MF is primarily absorbed in the upper GIT, exhibits high water solubility, and has limited absorption in the colon. Conventional sustained-release formulations often release a significant fraction of the drug beyond the upper GIT, resulting in suboptimal absorption and inconsistent therapeutic effects. A gastro-retentive formulation can maintain the drug within the stomach and proximal intestine for extended periods, thereby improving absorption, reducing gastrointestinal side effects, and enhancing glycemic control[6].

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Metformin is a white to off-white crystalline compound (molecular weight 165.63 g/mol) with high water solubility and a pKa of 12.4. Its physicochemical properties make it suitable for sustained-release delivery systems, including floating and expandable forms. Designing a formulation that achieves 90% drug release over approximately 8 hours aligns with the ideal pharmacokinetic profile for once-daily administration. Various gastro-retentive technologies—including floating systems, high-density systems, mucoadhesive polymers, and expandable structures—have been explored, with floating systems offering a simple and effective strategy for prolonging gastric retention[7].

Present study aims to develop a dual-functional, gastro-retentive, extended-release formulation of metformin hydrochloride that is economical, robust, and suitable for scale-up. Using a Quality by Design (QbD) approach, the formulation and process parameters will be optimized, and the resulting dosage form will be evaluated for expansion characteristics, floating behavior, toxicity, and pharmacokinetic performance in animal models.

MATERIAL AND METHODS:

Material

Metformin hydrochloride was obtained as a gift sample from Harman Finochem Ltd. The polymers and excipients used in the formulation included acacia, sodium bicarbonate, citric acid, croscarmellose sodium, xanthan gum, Methocel K100M, and distilled water. All chemicals, polymers, and reagents employed in the study were of pharmaceutical excipient grade.

Methods

Physicochemical Characterization of API

Physicochemical characterization of Metformin Hydrochloride (Metformin HCl) was performed to evaluate its suitability for formulation development. The assessment included physical description, determination of solid-state form, measurement of melting point, and evaluation of aqueous solubility across different pH levels. Hygroscopicity was examined to determine moisture uptake behavior, while density and flowability were measured through bulk and tapped density tests to understand powder handling properties. Additionally, stress studies were conducted to assess the stability of the API under thermal, humidity, and oxidative conditions[8,9].

Procedure for Product Development Trials

The product development trials were carried out using Metformin HCl as the active ingredient, with varying concentrations of xanthan gum, Methocel K100M, and sodium bicarbonate to optimize the gastro-retentive formulation. Trial Batch 1 was prepared as granules using xanthan gum and sodium bicarbonate in a 1:5 ratio, while Trial Batch 2 involved tablet formulation with the same excipients in a 1:2.5 ratio. Trial Batches 3, 4, 5, and 6 consisted of granule formulations containing xanthan gum and sodium bicarbonate in ratios of 1:1.6, 1:1.25, 1:1, and 3:1, respectively. In Trial Batch 7, granules were prepared using xanthan gum, Methocel K100M, and sodium bicarbonate in a 5:1:0.5 ratio to assess the influence of a dual-polymer system. Trial Batch 8 served as a reproducible batch using the optimized ratio of xanthan gum, Methocel K100M, and sodium bicarbonate (5:1:0.5) to confirm formulation consistency [9].

Physical and Solid-State Characterization of Metformin Hydrochloride

Particle Size Distribution

Particle size distribution of Metformin Hydrochloride (Form A) was assessed for three API batches using a Malvern particle size analyzer operating on laser diffraction principles. The system measured particle size at three defined percentiles—d10, d50, and d90—representing fine, median, and coarse fractions of the material, respectively. Prior to analysis, samples were dispersed uniformly to prevent agglomeration and ensure accurate measurement. The resulting particle size profiles were used to evaluate batch-to-batch variability and determine the suitability of each batch for subsequent formulation processes, given that particle size can influence flowability, compressibility, and dissolution behaviour[10].

X-ray Diffraction (XRD)

X-ray diffraction analysis was carried out to characterize the crystalline structure of the API and confirm the presence of the desired polymorphic form. Diffraction patterns were recorded for freshly received API batches and for samples stored under accelerated stability conditions (40°C/75% RH) for six months. The diffractograms were examined for characteristic peaks, and comparisons were made based on peak intensity, 2θ values, and corresponding d-spacing data. The absence of new peaks or significant shifts in diffraction patterns indicated that the material retained its crystalline integrity and did not undergo polymorphic transformation during storage[11].

Melting Point Determination

The melting point of Metformin Hydrochloride was determined using a calibrated melting point apparatus to confirm identity and assess thermal behaviour. A small quantity of the API was placed in a capillary tube and subjected to control heating. The temperature range over which the substance transitioned from solid to liquid was recorded. Consistency in the melting point values was used to verify purity and support the solid-state characterization data[12].

Aqueous Solubility Testing

Aqueous solubility studies were conducted to determine the solubility profile of Metformin Hydrochloride across physiologically relevant pH conditions. Approximately 1 g of the API was dispersed in 50 ml of each medium—0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. The mixtures were allowed to equilibrate with gentle agitation, and solubility was assessed visually based on pharmacopeial solubility descriptors. These studies were performed to confirm pH-independent solubility, which is critical for predicting dissolution behavior *in vivo*[13].

Hygroscopicity

Hygroscopicity testing was performed to evaluate the tendency of Metformin Hydrochloride to absorb moisture under controlled humidity conditions. Accurately weighed samples were exposed to a specified relative humidity environment for a defined duration. The percentage weight gain due to moisture uptake was calculated. Materials absorbing less than 2% moisture were categorized as slightly hygroscopic, indicating minimal risk of moisture-induced instability during storage and handling[14.]

Density and Flowability

Bulk density, tapped density, compressibility index, and Hausner ratio were measured according to established USP guidelines to assess the flow characteristics of the API. Bulk and tapped densities were determined by measuring the volume occupied by the powder before and after standardized tapping. These values were used to calculate the compressibility index and Hausner ratio, which serve as indicators of powder flowability. The results were interpreted against pharmacopeial criteria to determine the need for granulation or flow-enhancing excipients in formulation development[15].

Thermal and Spectroscopic Characterization

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed to assess the thermal behavior of Metformin HCl and to investigate potential interactions between the drug and polymeric excipients used in the formulation. Approximately 1–2 mg of the pure drug and the corresponding drug–polymer physical mixtures were accurately weighed and sealed in punctured aluminum pans to allow controlled vapor release during heating. The samples were scanned over a temperature range of 40–350°C at a constant heating rate of 10°C/min using an empty aluminum pan as the reference. The resulting DSC thermograms were analyzed for characteristic endothermic or exothermic transitions, including melting point, decomposition events, and any shifts or disappearance of peaks that could indicate drug–polymer interactions or changes in crystalline structure[15,16.]

Fourier Transform Infrared Spectroscopy (FTIR)

Fourier Transform Infrared Spectroscopy (FTIR) was carried out to further evaluate potential chemical interactions between Metformin HCl and the selected excipients. Spectra for the pure drug, individual polymers, and drug–polymer physical mixtures were recorded over the spectral range of 4000–400 cm^{-1} using an FTIR spectrophotometer. The characteristic absorption peaks of Metformin HCl, particularly in functional group regions such as N–H, C=N, and C–N stretching, were compared with the spectra of the physical mixtures. Any significant shifts, peak broadening, or disappearance of characteristic bands were noted as indicators of possible intermolecular interactions or modifications in chemical environment induced by the excipients[17,18].

Forced Degradation Studies

Forced degradation studies were conducted to evaluate the intrinsic stability profile of Metformin HCl and to determine its susceptibility to degradation under various stress conditions. API samples were exposed to oxidative, acidic, alkaline, and photolytic environments to simulate potential degradation pathways encountered during manufacturing, storage, and physiological conditions. After exposure, samples were visually inspected for changes in color or clarity and analyzed spectrally to detect degradation products or alterations in the characteristic absorbance pattern. Oxidative, acidic, and alkaline conditions resulted in noticeable degradation, confirming the drug's sensitivity to chemically harsh environments. In contrast, samples exposed to photolytic stress showed minimal or no change, demonstrating that Metformin HCl is photostable under ambient light exposure. These findings provided important guidance for formulation design and storage recommendations[19].

Analytical Development

Preparation of Standard Stock Solution

A standard stock solution of Metformin HCl was prepared to establish a reliable quantitative analytical method. Drug equivalent to 100 mg of Metformin HCl was accurately weighed and transferred to a 100 ml volumetric flask containing 30 ml of distilled water. The mixture was subjected to 15 minutes of sonication to ensure complete dissolution. The resulting solution was filtered through a 0.22 µm nylon membrane filter to remove particulate matter and transferred to another volumetric flask. Distilled water was added to make up the final volume to 100 ml, yielding a stock solution with a concentration of 1 mg/ml[20].

Working Standard and Calibration Curve

From the stock solution, a working standard solution of 40 µg/ml was prepared by diluting 2 ml of the 1 mg/ml stock to 50 ml with distilled water. Calibration standards were prepared by transferring appropriate aliquots of the 40 µg/ml working solution into 10 ml volumetric flasks and diluting with water to obtain final concentrations of 2, 4, 6, 8, 10, and 12 µg/ml. These solutions were analyzed using a Shimadzu UV-1800 UV–Visible spectrophotometer. Absorbance readings were recorded at the identified λmax values of 232 nm and 233 nm using 1 cm quartz cuvettes and a slit width of 2 nm. Calibration curves were constructed by plotting absorbance versus concentration to confirm linearity and determine the analytical equation[21].

Preparation of Placebo Extracts

To evaluate potential interference during quantification, placebo extracts were prepared following the same procedure as the pure drug. Placebo equivalent to 100 mg Metformin HCl were dispersed in 100 ml of distilled water and subjected to a combined solubilization process involving 15 minutes of sonication followed by a 30-minute hot water bath treatment. The mixture was sonicated again for 15 minutes to ensure complete extraction of the drug or excipient components. The resulting dispersion was filtered through a 0.22 µm nylon filter and diluted to obtain stock

solutions of 1 mg/ml and working solutions of 40 µg/ml. Calibration standards within the concentration range of 2–12 µg/ml were prepared similarly for comparative analysis[21,22].

UV Interference Study

To confirm the specificity of the analytical method, UV absorbance spectra of blank (distilled water), placebo extract, and granule extract, and standard drug solutions were recorded over the wavelength range of 200–400 nm. The absorbance profiles were examined for overlapping peaks or any extraneous absorbance at 232 nm and 233 nm, the selected analytical wavelengths for Metformin HCl quantification. The absence of interfering peaks from the excipients or sample matrix confirmed that the formulation components did not affect the assay accuracy, validating the suitability of λmax 232/233 nm for dissolution and assay measurements[23].

Formulation Development

Preparation of Optimization Batches (F1–F8)

A total of eight formulation batches (F1–F8) were prepared to optimize the concentrations of polymeric components responsible for raft formation, buoyancy, and sustained drug release. Each batch contained a fixed amount of Metformin HCl (500 mg per unit) to maintain consistent drug loading across formulations. Xanthan gum was incorporated at varying levels ranging from 100 mg to 1500 mg, enabling the evaluation of its impact on swelling behavior, gel strength, and raft stability. Additionally, selected batches (F7 and F8) included Methocel K100M at 500 mg to investigate the synergistic effect of a high-viscosity hydrophilic polymer on sustained drug release. The progressive variation of polymer content across these batches enabled systematic optimization of the formulation to achieve the desired physicochemical and performance characteristics[24.]

Wet Granulation Method

All ingredients were weighed and sifted through 30#. The dry mix was blended in a Rapid Mixer Granulator for 15 minutes. Purified water was added for wet massing, and granules were dried at 60°C for 15 minutes. Dried granules were passed through 20#, blended with extra granular sodium bicarbonate (where applicable), and filled into sachets[25].

Physicochemical Evaluation of Formulations

Raft Thickness

Raft thickness was evaluated to determine the extent of swelling and the structural robustness of the floating raft formed by the granules in an acidic environment. A predetermined quantity of granules was carefully placed on the surface of 0.1N HCl in a 250 ml beaker to simulate gastric conditions. The granules hydrated and formed a swollen raft structure, whose thickness was measured using a calibrated scale at specific intervals (0, 1, 4, and 8 hours). These time-dependent measurements provided insight into the swelling kinetics and long-term stability of the raft, both of which are critical for ensuring gastric retention during the intended release period [26.]

Raft Formation Time

Raft formation time was recorded as the duration required for the granules to hydrate, swell, and rise to the surface of the simulated gastric fluid to form a coherent floating raft. Granules were gently dispensed onto 0.1N HCl, and a stopwatch was started immediately upon contact. The time taken for the swollen mass to overcome initial sinking and achieve buoyancy was noted. This parameter is essential in raft-forming systems since shorter raft formation times improve retention in the gastric environment and enhance therapeutic efficacy[27].

Swelling Index

The swelling index was determined to assess the hydration capacity and structural expansion of the granules upon contact with gastric fluid. One gram of granules was accurately weighed and transferred into a 25 ml measuring cylinder, and the initial volume (W1) was recorded. The cylinder was then filled with 0.1N HCl to fully cover the granules. After a suitable swelling period, the final swollen volume (W2) was measured. This parameter indicates the ability of the polymer matrix to absorb gastric fluid, which directly influences raft formation, gel strength, and drug release behaviour[28]. The swelling index was calculated using the formula:

$$\text{Swelling Index (\%)} = ((W2 - W1) / W1) \times 100$$

Buoyancy Study (Floating Lag Time and Floating Duration)

Buoyancy characteristics were evaluated by measuring both the floating lag time and the total floating duration in simulated gastric fluid. A known amount of granules was placed on the surface of 0.1N HCl, and the time taken for the granules to rise and float (floating lag time) was recorded. After achieving buoyancy, the granules were observed over an extended period to determine the total floating duration. This study is critical for confirming that the formulation remains afloat in the stomach for prolonged periods, ensuring consistent drug release during the desired therapeutic window[29].

Flow Properties of Granules

Flowability of granules was assessed to ensure uniform processing and reproducible sachet filling during manufacturing. Flow parameters evaluated included bulk density, tapped density, compressibility index, Hausner ratio and particle size distribution. These tests were performed on granules prepared manually (F7) and via rapid mixer granulator (F8) to evaluate the effect of processing scale-up on granule behavior. Flow measurements were conducted according to USP procedures, and particle size distribution was determined using sieve analysis. These evaluations helped determine whether the granules possessed adequate flow characteristics for large-scale production[30].

Matrix Integrity

Matrix integrity was examined to evaluate the structural stability of the hydrated granule matrix during the swelling and raft formation process. Granules were exposed to 0.1N HCl and allowed to swell, following which thin sections of the hydrated mass were observed under a microscope. The matrix was assessed for cohesiveness, gel uniformity, and resistance to erosion or fragmentation. Strong matrix integrity is essential to maintain raft stability, control drug release, and ensure sustained gastric retention[31].

***In-Vitro* Drug Release (Dissolution Study)**

Dissolution studies were conducted to compare the drug release profiles of batches F6, F7, and the scale-up batch F8. The test was carried out in 500 ml of 0.1N HCl using USP Apparatus I (basket) operated at 50 rpm and 37°C ± 0.5°C to simulate gastric conditions. Samples were withdrawn at predetermined time intervals ranging from 0 to 10 hours, filtered, and analyzed using the validated UV-Visible spectrophotometric method at 233 nm. At each time point, the withdrawn volume was replaced with fresh medium to maintain sink conditions. The dissolution profiles obtained were used to evaluate the rate and extent of drug release, assess sustained-release performance, and determine batch suitability for scale-up and further development[32.]

***In-Vivo* Swelling and Gastric Retention Study by X-ray Radiography:**

The in vivo swelling behavior and gastric retention of the floating metformin granules were evaluated in male Wistar rats (180–250 g, n = 3). The granules were formulated with 10% w/w barium sulphate as a radiopaque marker to enable X-ray visualization without altering buoyancy or swelling properties. All animals were fasted overnight with free access to water prior to dosing. The test granules were administered via oral gavage using a small volume of purified water. Serial abdominal radiographs were captured at predetermined time points: 0, 30, 45, and 60 minutes post-administration. Radiographs were acquired using a digital X-ray system operated at 40–50 kVp, 1–3 mAs, and a source-to-image distance (SID) of 100 cm. Animals were positioned in the supine (AP) or oblique (left-oblique) orientation according to each sequence. To ensure animal comfort and immobility, imaging was performed under brief isoflurane anesthesia (induction at 3–4%, maintenance at 1.5–2%). A radiopaque calibration marker was placed in the field of view for geometric correction. Granule visibility, gastric localization, buoyancy, and swelling progression were assessed by measuring the radiopaque projected area of the granules at each time point relative to the baseline (0 min)[33, 34].

RESULTS AND DISCUSSION

Physical and Solid-State Characterization of Metformin Hydrochloride

Particle size distribution

Metformin HCl is a white, crystalline powder. Malvern (3-tier) particle size analysis for three API batches showed moderate batch variability (Table 1). Batch MH/1617557 is comparatively coarser across all percentiles, which can influence flow and dissolution behavior. Larger median and top-end particle sizes in MH/1617557 may reduce specific surface area and slow dissolution; batches with smaller median diameters are expected to wet and dissolve faster but require granulation to improve flow (Table 1).

Table 1. Particle Size Distribution of Metformin Hydrochloride (Form A)

Batch no.	MH/1718354	MH/1718010	MH/1617557
d (0.1) (µm)	6.4	6.5	10
d (0.5) (µm)	36	33	51
d (0.9) (µm)	89	107	132

Solid State Form

Crystalline form of Metformin Hydrochloride API is the most commonly produced, widely used, and thermodynamically stable form. From a medicinal perspective, pharmacopeia's does not specify any preference for a particular polymorph. XRD analysis of both the initial sample and the six-month stability sample stored at 40°C/75% RH showed identical peaks at corresponding two-theta and d-spacing values, confirming that the crystalline form remained unchanged and that no polymorphic transformation occurred during storage as depicted (Figure 1).

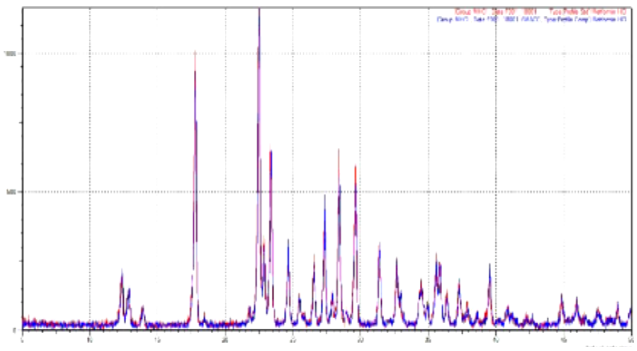

Figure 1. XRD patterns of Metformin Hydrochloride API

Metformin Hydrochloride demonstrated high aqueous solubility across all tested pH conditions. Solubility studies conducted using 1 g samples in 50 ml of different media—including 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer—confirmed that the drug is freely soluble in each medium, indicating pH-independent solubility and consistent dissolution behavior in physiological environments. Metformin Hydrochloride demonstrated high aqueous solubility across all tested pH conditions. Solubility studies conducted using 1 g samples in 50 ml of different media—including 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer—confirmed that the drug is freely soluble in each medium, indicating pH-

independent solubility and consistent dissolution behaviour in physiological environments (Table 2).

Table 2. Aqueous solubility of Metformin Hydrochloride in different pH media

Sr. No.	Weight of sample (gm)	Media	Quantity of solvent (ml)	Solubility
1	1.0020	0.1N HCl	50	Freely soluble
2	1.0029	pH 4.5 acetate buffer	50	Freely soluble
3	1.0014	pH 6.8 phosphate buffer	50	Freely soluble

Hygroscopicity

Metformin Hydrochloride was found to absorb less than 2% moisture during hygroscopicity testing, indicating that it exhibits slight hygroscopicity and has minimal tendency to take up water under typical storage conditions.

Density (Bulk, Tapped, and True) and Flowability

Density measurements, including bulk and tapped density, along with calculated Hausner ratio and compressibility index values, indicate that Metformin Hydrochloride exhibits poor flowability, necessitating granulation to improve its handling and processing characteristics (Table 3).

Table 3. Density and flow ability parameters of Metformin Hydrochloride

Physical properties	MH/1718354	MH/1718010	MH/1617557
Bulk density (gm/ml)	0.57	0.51	0.54
Tapped density (gm/ml)	0.78	0.69	0.71
Compressibility index (%)	26.92	26.08	23.94
Hausner ratio	1.36	1.35	1.31

DSC analysis

Differential Scanning Calorimetry (DSC) was performed by placing approximately 1–2 mg of the drug and the physical mixture of the drug with polymers into punctured aluminium pans. Samples were analysed individually over a temperature range of 40–350°C at a heating rate of 10°C/min, using an unfilled aluminium pan as the reference. This assessment was conducted to evaluate thermal behaviour and to detect any potential drug–polymer interactions

FTIR

Fourier Transform Infrared Spectroscopy (FTIR) was carried out for the pure drug, polymers, and their physical mixture over the spectral range of 4000–400 cm^{-1}. The characteristic absorption peaks of the mixture, particularly those observed between 1800–600 cm^{-1}, were compared with the spectra of the pure drug to identify any shifts or modifications indicative of possible chemical interactions.

Degradation Products

Metformin Hydrochloride is susceptible to degradation under oxidizing, acidic, and alkaline conditions, indicating its sensitivity to harsh chemical environments. However, the drug demonstrated stability under photolytic conditions, with no significant degradation observed upon exposure to light, confirming its resistance to photolysis.

Analytical Method Development (Dissolution and Assay)

For analytical quantification, a UV–Visible spectrophotometric method was developed and validated. A stock solution was prepared by dissolving drug equivalent to 100 mg of Metformin HCl in a 100 ml volumetric flask containing 30 ml of distilled water, followed by 15 minutes of sonication. The solution was filtered through a 0.22 µm nylon filter, transferred to another volumetric flask, and diluted to obtain a final concentration of 1 mg/ml. From this, 2 ml of stock solution was further diluted to 50 ml to yield a working concentration of 40 µg/ml. Standard solutions were prepared by transferring aliquots of the 40 µg/ml stock solution into separate 10 ml volumetric flasks and diluting with water to achieve final concentrations of 2, 4, 6, 8, 10, and 12 µg/ml. Analysis was performed using a Shimadzu UV-1800 UV–VIS spectrophotometer over a wavelength range of 200–400 nm, employing a 2 nm slit width and 1 cm quartz cuvette, with distilled water used as the blank (Figure 2 and 3).

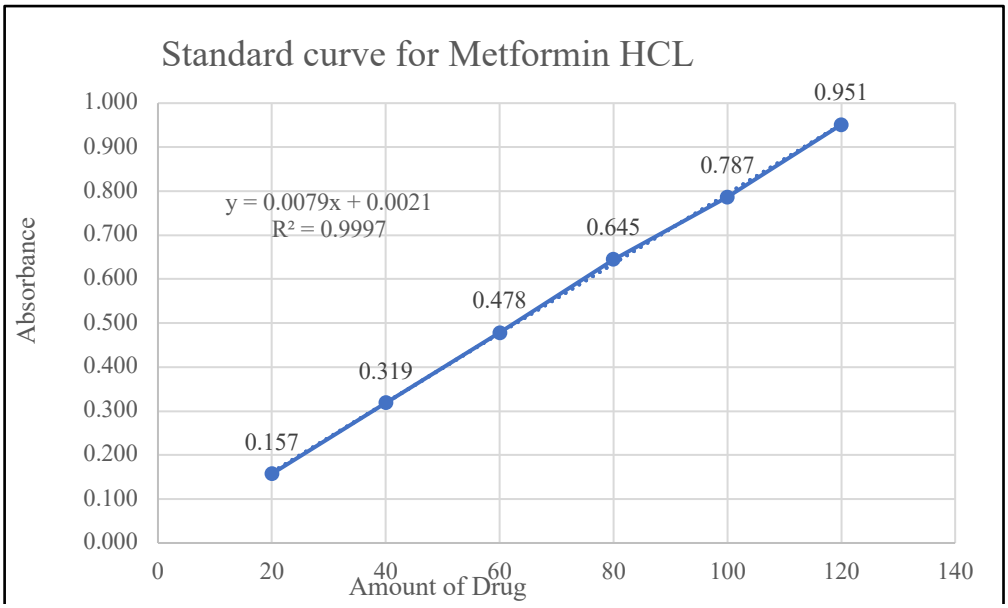

Figure 2. Standard Curve for Metformin HCL

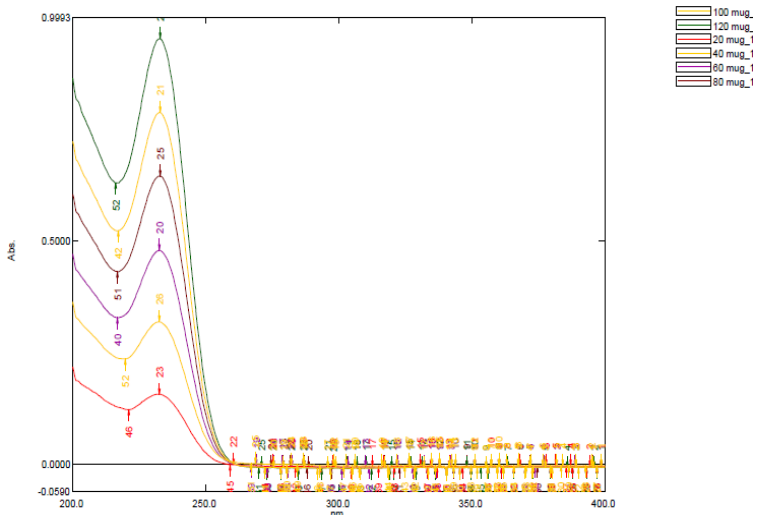

Figure 3. Linear curve for Metformin HCL

Preparation of Standard Curve

A stock solution was prepared by dissolving drug equivalent to 100 mg Metformin HCl in a 100 ml volumetric flask containing 30 ml distilled water, followed by sonication for 15 minutes. The solution was filtered through a 0.22 µm nylon filter and made up to 100 ml to yield a 1.0 mg/ml stock. From this, 2.0 ml of stock was diluted to 50 ml with water to obtain a 40 µg/ml intermediate. Aliquots of the 40 µg/ml intermediate were further diluted in 10 ml volumetric flasks to prepare calibration standards of 2, 4, 6, 8, 10, and 12 µg/ml. Spectra were recorded on a Shimadzu UV-1800 UV–VIS spectrophotometer using 1 cm quartz cuvettes, 2 nm slit width, and distilled water as blank. Analyses were performed at λmax = 232 nm and 233 nm (Figure 4 and 5).

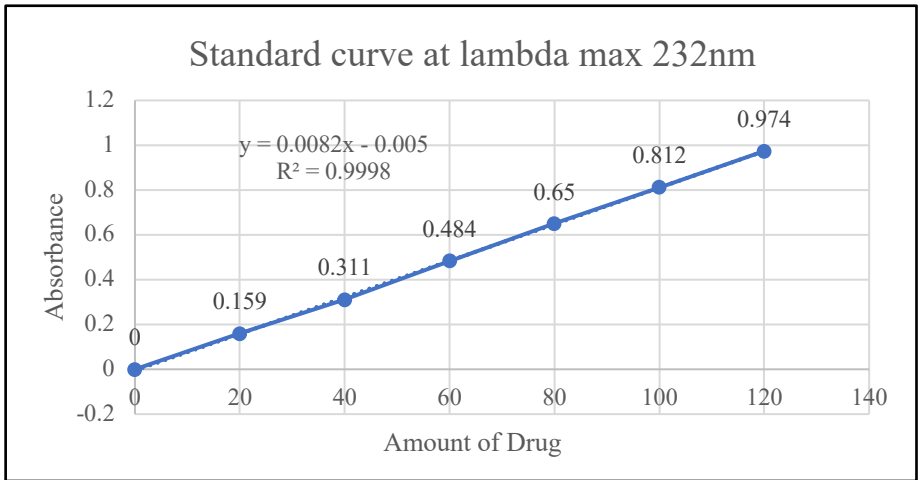

Figure 4. Standard Curve for Metformin HCl at 232 nm

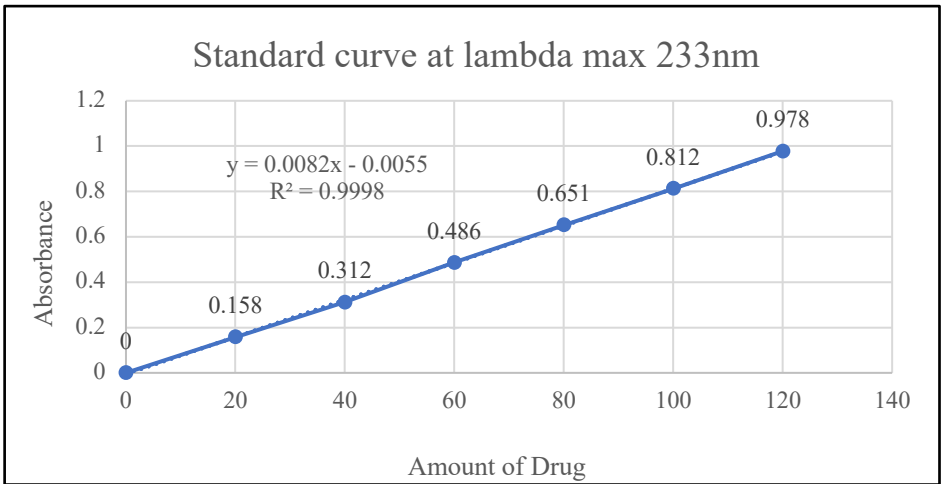

Figure 5. Standard Curve for Metformin HCl at 233 nm

Preparation of Stock and Standard Solutions (Granules)

Granules equivalent to 100 mg Metformin HCl were accurately weighed and added to a 100 ml volumetric flask containing 30 ml distilled water, then sonicated for 15 minutes. As the granules did not disperse completely, the dispersion was placed in a hot water bath for 30 minutes followed by an additional 15 minutes of sonication to achieve solubilization; the volume was adjusted to 100 ml to obtain a 1.0 mg/ml stock solution. Ten milliliters of this solution were filtered through a 0.22 µm nylon filter, and 2.0 ml of the filtrate was diluted to 50 ml with water to give a 40 µg/ml intermediate stock. Aliquots of this intermediate (in 10 ml volumetric flasks) were diluted with water to prepare calibration standards at 2, 4, 6, 8, 10, and 12 µg/ml. Analyses were performed on a Shimadzu UV-1800 spectrophotometer using 1 cm quartz cuvettes and a 2 nm slit width at λ = 232 nm and 233 nm; distilled water served as the blank.

Preparation of Stock and Standard Solutions (Placebo)

Placebo equivalent to the formulation mass was processed similarly: placebo material was added to a 100 ml volumetric flask containing 30 ml distilled water, sonicated for 15 minutes, filtered through a 0.22 µm nylon filter, and diluted to 100 ml to produce a 1.0 mg/ml placebo stock. 2.0 ml of this stock was diluted to 50 ml to obtain a 40 µg/ml intermediate, from which the same standard concentrations (2–12 µg/ml) were prepared in 10 ml volumetric flasks for spectral comparison. For the placebo–standard interaction study, UV scans were recorded over 200–400 nm (instrument and cell as above), with distilled water as blank.

Comparative UV Analysis

Comparative UV spectra were acquired for blank (water), placebo extract, granule sample, and standard solutions. No overlapping peaks or significant absorbance contributions from the placebo or sample matrix were observed at 232 nm or 233 nm; therefore, no spectral interference was detected at the chosen assay wavelengths. This supports the suitability of 232/233 nm for assay and dissolution analysis of Batch F34 without matrix correction.

Product Development Trials (Polymer concentration optimization batch)

Based on the results obtained from preliminary trials, a series of optimization batches were formulated using varying concentrations of xanthan gum to evaluate its effect on raft formation, buoyancy, and drug release characteristics. The compositions of batches F1–F8 are shown in Table 4.

Table 4. Composition of Optimization Batches Containing Varying Concentrations of Xanthan

Batch Details	F1	F2	F3	F4	F5	F6	F7	F8
Intragranular/ Dry Mixing	**mg/tab**							
Metformin	500	500	500	500	500	500	500	500
Sodium Bicarbonate	500	500	500	500	500	500	--	--
Methocoel K 100 M	--	--	--	--	--	--	500	500
Xanthan gum	100	200	300	400	500	1500	1500	1500
Granulation								
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Lubrication								
Sodium Bicarbonate	--	--	--	--	--	--	250	250
Total granules weight	1100	1200	1300	1400	1500	2500	2750	2750

All formulation batches (F1–F8) were prepared using a standard wet granulation method. Initially, all ingredients were accurately weighed according to the batch formula and passed through a 30# sieve to ensure uniform particle size. The sifted API and excipients were then mixed manually (F1-F7) for 15 minutes to achieve a homogeneous blend. Granulation was carried out manually (F1-F7) using purified water for approximately 5 minutes until suitable granules were formed, which were subsequently dried in a tray drier at 60°C for 15 minutes. The dried granules were passed through a 20# sieve to break up agglomerates and ensure uniformity, after which they were blended with sodium bicarbonate, as required by the formulation, for an additional 30 minutes. Finally, the granule blend was filled into sachets based on the predetermined average granule weight to complete the batch manufacturing process.

Physicochemical Parameters

Raft thickness

Raft thickness was evaluated by first ensuring that all required glassware was clean and properly dried. A 250 ml beaker was filled with 0.1N HCl to simulate gastric conditions, and a known quantity of granules was gently placed onto the surface of the medium. The thickness of the resulting swollen raft was measured at predetermined time intervals, specifically at 0, 1, 4, and 8 hours, to assess the extent and stability of raft formation over time.

Raft formation time

Raft formation time was assessed as the duration required for the granules to form a cohesive raft and rise to the surface of simulated gastric fluid during in vitro testing. The performance of batches F1–F7 was compared based on their raft thickness and raft formation time, with raft thickness values ranging from 13 mm in F1 to 34 mm in F7, and raft formation times varying between 22 and 35 seconds. Among these formulations, batches F6 and F7 demonstrated superior raft-forming ability, exhibiting thicker rafts and acceptable floating initiation times. Therefore, based on their improved raft characteristics, batches F6 and F7 were selected for further dissolution studies to evaluate drug release behaviour (Table 5).

Table 5. Raft thickness and raft formation time of formulation batches F1–F7.

Batch Details	F1	F2	F3	F4	F5	F6	F7
Granulation							
Raft thickness (mm)	13	23	26	26	31	30	34
Raft formation time (sec)	35	35	27	22	23	30	33

Dissolution

Dissolution studies were conducted for batches F6 and F7 to compare their drug release profiles over a 10-hour period. Batch F6 showed rapid initial release, with 69% drug dissolved at 2 hours and only marginal increases thereafter, reaching 80% at 10 hours. In contrast, batch F7 exhibited a more controlled release pattern, with 23%, 42%, 57%, and 72% of the drug released at 2, 4, 6, and 8 hours respectively, and achieving 86% at 10 hours. The extended release up to 8 hours observed in batch F7 indicated superior sustained-release characteristics compared to F6. Consequently, batch F7 was selected for scale-up, leading to the preparation of batch F8 with an increased batch size to assess formulation robustness and process feasibility. Both F7 (100 sachets) and the scale-up batch F8 (1000 sachets) shared the same qualitative and quantitative composition, including 500 mg Metformin HCl, 500 mg Methocel K100M, 1500 mg xanthan gum, and 250 mg sodium bicarbonate added during lubrication, resulting in a final granule weight of 2750 mg per sachet (Table 6).

Table 6. Dissolution profile of batches F6 and F7 in 0.1N HCl over a 10-hour period.

% Drug dissolved in hrs	F6	F7
0	0	0
2	69	23
4	72	42
6	75	57
8	78	72
10	80	86

This table summarizes the percentage of Metformin HCl released at predetermined time intervals for batches F6 and F7. Batch F7 exhibited a more sustained and extended drug release up to 8 hours compared to batch F6, supporting its selection for further optimization (Table 7).

Table 7. Comparison of formulation composition and batch size for batches F7 and F8.

Batch Details	**F7**	**F8**
Batch size	**100 sachets**	**1000 sachets**
Intragranular/Dry Mixing		
Metformin HCl	500	500
Sodium Bicarbonate	--	--
Methocoel K 100 M	500	500
Xanthan gum	1500	1500
Granulation		
Purified Water	q.s.	q.s.
Lubrication		
Sodium Bicarbonate	250	250
Total granules weight	2750	2750

This table provides the qualitative and quantitative composition of the optimized batch F7 and its scale-up batch F8. Both batches share identical formulation components, and batch F8 was manufactured at an increased batch size (1000 sachets) to assess process feasibility and reproducibility.

Flow properties of powder

Flow properties of the powder blend were assessed for batches F7 and F8 to evaluate the impact of scale-up on material handling characteristics. Batch F7 was prepared manually, while batch F8 was processed using a 2 L Rapid Mixer Granulator (RMG) to determine process feasibility at a larger scale. The evaluated parameters included bulk density, tapped density, Hausner ratio, compressibility index, Flodex value, and particle size distribution. Bulk densities for Trial 1 and Trial 2 were 0.45 g/ml and 0.51 g/ml, respectively, while tapped densities were 0.64 g/ml and 0.67 g/ml. The corresponding Hausner ratios (1.42 and 1.32) and compressibility indices (29.68% and 23.88%) indicated poor to borderline flow characteristics. Flodex values were recorded as 16 mm and 9 mm, further supporting restricted flow behavior. Particle size distribution analysis showed cumulative retention across sieves #20 to #100, confirming consistency in granule size between the two trials. Overall, the flow properties suggested that although F8 demonstrated slightly improved flow compared to F7, both required careful handling during large-scale processing (Table 8).

Table 8. Flow properties and particle size distribution of batches F7 and F8.

Parameters	**Trial 1**	**Trial 2**
Bulk density (gm/ml)	0.45	0.51
Tapped density (gm/ml)	0.64	0.67
Hausner ratio	1.42	1.32
Compressibility index	29.68	23.88
Flodex (mm)	16	9
Particle size distribution	% cumulative retained	
#20	37	31
#40	58	45
#60	64	51
#80	68	58
#100	76	69
Pan	100	100

Swelling index

The swelling index of the granules was determined to assess their hydration capacity and matrix-forming potential in acidic conditions. All required glassware was first cleaned and dried, after which 1 g of granules was accurately weighed using a calibrated electronic balance and transferred to a 25 ml measuring cylinder. The initial volume of the granules (W1) was recorded, and 0.1N HCl was added to the cylinder to completely immerse the granules. The granules were allowed to swell in the acidic medium, and the final swollen volume (W2) was measured. The swelling index was then calculated using the formula:

Swelling Index (%) = ((W2 – W1) / W1) × 100

The results showed a swelling index of 667% for batch F7 and 466% for batch F8, indicating greater hydration and matrix expansion in F7 compared to F8.

Buoyancy Study (Floating Lag Time and Floating Duration)

The buoyancy characteristics of the granules were evaluated by determining both the floating lag time and the total floating duration in simulated gastric fluid. For this test, all required glassware was cleaned and dried, and a 250 ml beaker was filled with 0.1N HCl to mimic gastric conditions. A known quantity of granules was then gently placed onto the surface of the medium, and a stopwatch was started immediately upon contact. Although the granules occasionally sank momentarily, the time required for them to rise and remain afloat on the surface was recorded as the floating lag time. Additionally, the total duration for which the granules remained buoyant was monitored to determine floating time. The results showed floating lag times of 30 seconds for batch F7 and 33 seconds for batch F8, while both batches demonstrated excellent buoyancy, remaining afloat for more than 24 hours (Table 9).

Table 9. Buoyancy parameters of granule batches F7 and F8.

Parameters	F7	F8
Floating Lag time (sec)	30	33
Floating time (hrs)	>24	>24

Raft thickness

Raft thickness was evaluated for batches F7 and F8 to assess the stability and expansion of the raft over time in acidic conditions. At the initial time point (0 hours), the raft thickness measured 30 mm for F7 and 26 mm for F8. After 1 hour, the thickness increased to 32 mm for F7 and 27 mm for F8, indicating early swelling and raft formation. By the 4-hour mark, F7 showed further expansion to 33 mm, while F8 maintained a thickness of 27 mm. At 8 hours, F7 reached its maximum thickness of 34 mm, whereas F8 showed a slight increase to 29 mm. By 10 hours, the raft thickness stabilized at 34 mm for F7 and 30 mm for F8. These results demonstrate that both batches formed stable rafts over the evaluation period, with F7 exhibiting greater overall swelling, while F8 showed relatively faster initial raft development.

Matrix integrity

Matrix integrity for batch F8 was assessed microscopically to evaluate the structural stability of the swollen granules during the raft-forming process. Microscopic observations revealed that the hydrated matrix remained cohesive, intact, and resistant to disintegration throughout the evaluation period, indicating strong gel formation and structural robustness. Based on all evaluated parameters—including swelling behavior, buoyancy, and raft thickness—it was concluded that the prototype formulation was able to maintain its raft structure effectively for up to 8 hours, demonstrating adequate matrix strength suitable for sustained gastric retention (Figure 6).

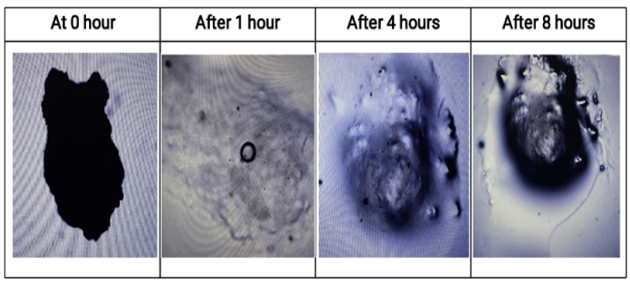

Figure 6. Microscopic evaluation of matrix integrity for batch F8.

Drug release study

The dissolution profiles of batches F7 and F8 were evaluated in 0.1N HCl over a 10-hour period to compare their drug release behaviour. Both formulations showed no drug release at the initial time point (0 hours). At 2 hours, batch F8 exhibited a substantially higher release of 44%, compared to 23% from batch F7. As the study progressed, batch F7 demonstrated a gradual and sustained release pattern, reaching 42%, 57%, 72%, and 86% at 4, 6, 8, and 10 hours, respectively. In contrast, batch F8 released the drug more rapidly, achieving 68%, 82%, 89%, and 90% at the corresponding intervals. Although F8 displayed faster initial dissolution, batch F7 provided a more controlled and extended release up to 8 hours, indicating superior sustained-release characteristics suitable for prolonged therapeutic activity. This figure/table illustrates the percentage drug release from batches F7 and F8 at specified time intervals. Batch F7 exhibited a slower but more extended and controlled release pattern, while batch F8 released the drug more rapidly. The sustained-release behavior of F7 supports its suitability for formulations requiring prolonged gastric retention and extended drug delivery (Figure 7).

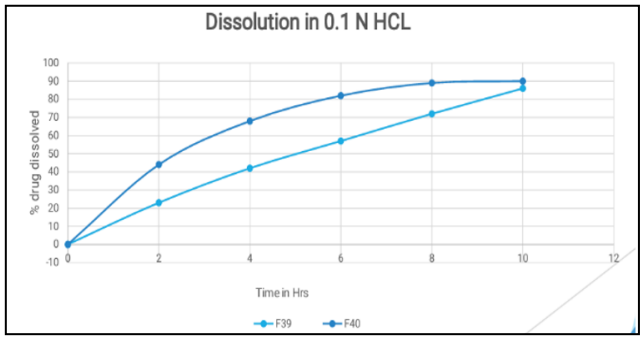

Figure 7. Comparative dissolution profiles of batches F7 and F8 in 0.1N HCl over 10 hours.

***In-Vivo* Swelling and Gastric Retention Study by X-ray Radiography**

Radiographic evaluation confirmed clear visualization and consistent gastric retention of the barium-incorporated metformin granules at all time points, with the granules initially appearing as a distinct compact radiopaque mass in the upper gastric region at 0 minutes, indicating successful delivery. Progressive swelling was observed over the 60-minute period, as evidenced by a gradual increase in the radiopaque area: the granules appeared compact at 0 minutes, showed noticeable enlargement at 30 minutes, expanded further with a more dispersed outline at 45 minutes, and reached maximal swelling at 60 minutes with a larger and irregular radiopaque appearance. Throughout the study, the granules consistently remained in the upper gastric region in both AP and oblique projections, demonstrating sustained buoyancy, absence of gastric emptying, and structural integrity of the floating system. Overall, the radiographic findings confirm that the barium-tagged floating metformin granules remain buoyant in vivo, exhibit time-dependent swelling consistent with hydration-controlled expansion, and maintain gastric residence for at least 60 minutes, supporting their design for prolonged gastric retention and controlled drug release (Figure 8).

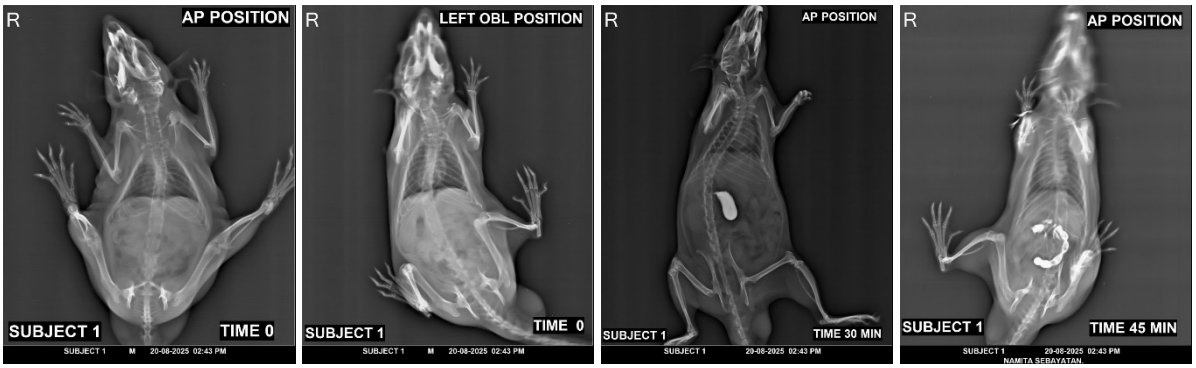

Figure 8. Serial X-ray radiographs showing gastric retention and swelling of barium-loaded floating metformin granules at 0, 30, and 45 minutes. The granules remain visible in the stomach and progressively increase in size, confirming sustained buoyancy and time-dependent swelling in vivo.

CONCLUSION

Polar medicines with a small absorption window and primary absorption in the upper gastrointestinal tract benefit from gastro-retentive drug delivery systems, according to research. Such systems lengthen stomach residence time, improve acidic medium dissolving, and improve medication absorption, reducing dose frequency and lower intestinal drug loss. Metformin Hydrochloride, a water-soluble, polar medication absorbed only in the stomach and upper small intestine, is ideal for gastro-retentive formulations. Although extensively used as a first-line treatment for type 2 diabetes, conventional immediate-release formulations require frequent dosage and may cause plasma drug level changes. A gastro-retentive strategy may improve patient compliance and glycemic management by enhancing absorption and therapeutic efficacy. Metformin HCl is off-patent, readily available, and cheap, making formulation development feasible and commercially viable. Optimizing Metformin into a gastro-retentive system can improve clinical effectiveness without intellectual property or supply issues due to its availability and therapeutic value. The study suggests that a gastro-retentive Metformin HCl formulation may increase therapeutic performance and patient outcomes.

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