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FORMULATION AND EVALUATION OF EUDRAGIT-BASED MULTIPARTICULATE DRUG DELIVERY SYSTEM OF METFORMIN HYDROCHLORIDE FOR CONTROLLED ORAL DRUG RELEASE

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Keywords:

Metformin Hydrochloride, Multiparticulate Drug Delivery System, Solution Layering, Eudragit RS100, Controlled Drug Release

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ABSTRACT

Background: Metformin hydrochloride is the first-line oral antihyperglycemic agent for the management of Type 2 Diabetes Mellitus. However, its short biological half-life, high dosing frequency, and gastrointestinal side effects associated with conventional dosage forms necessitate the development of an improved drug delivery system. Objective: The present study aimed to formulate and evaluate a multiparticulate drug delivery system of Metformin HCl capable of providing controlled drug release, improved therapeutic efficacy, and enhanced patient compliance. Methods: Drug-loaded pellets were prepared by the solution layering technique using sugar spheres as inert cores and polyvinylpyrrolidone K30 as the binder. The pellets were subsequently coated with different ratios of Eudragit RS100 and Eudragit RL100 employing a pan coating technique to obtain sustained-release multiparticulates. The prepared formulations were evaluated for micromeritic properties, friability, drug content, particle size distribution, in vitro drug release, release kinetics, and stability according to ICH guidelines. Results: The prepared pellets exhibited excellent flow properties, low friability, uniform particle size distribution, and satisfactory drug content. Polymer-coated multiparticulates provided controlled drug release over an extended period compared with the immediate-release formulation. The release profile was significantly influenced by the ratio of Eudragit RS100 to RL100, where higher RS100 content produced slower drug release because of its lower permeability. The optimized formulation demonstrated reproducible release characteristics, satisfactory mechanical strength, and stability under accelerated storage conditions without significant changes in physicochemical properties. Conclusion: The developed Eudragit-coated multiparticulate system successfully achieved controlled release of Metformin HCl and may represent a promising alternative to conventional oral formulations by improving therapeutic efficacy, reducing dosing frequency, minimizing gastrointestinal adverse effects, and enhancing patient compliance in Type 2 Diabetes Mellitus.

Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most prevalent chronic metabolic disorders worldwide and is characterized by persistent hyperglycemia resulting from impaired insulin secretion and insulin resistance [1]. Metformin hydrochloride remains the first-line pharmacological treatment due to its ability to suppress hepatic gluconeogenesis, improve peripheral insulin sensitivity, and reduce intestinal glucose absorption [2]. Despite its clinical effectiveness, conventional immediate-release Metformin formulations require multiple daily doses because of their relatively short biological half-life and moderate oral bioavailability. Frequent dosing often results in poor patient compliance, fluctuating plasma drug concentrations, and gastrointestinal adverse effects, thereby limiting therapeutic effectiveness.

Multiparticulate drug delivery systems (MDDS) have emerged as an advanced oral drug delivery approach to overcome the limitations associated with conventional single-unit dosage forms. These systems consist of numerous discrete subunits such as pellets, microspheres, or beads that distribute uniformly throughout the gastrointestinal tract, minimizing dose dumping, reducing inter- and intra-subject variability, and improving drug absorption. In addition, multiparticulate formulations provide greater flexibility for designing controlled, sustained, delayed, or site-specific drug release profiles while reducing localized gastrointestinal irritation [3-4].

Among the available pelletization techniques, solution layering offers several advantages, including excellent drug loading, uniform coating, reproducible particle size distribution, and suitability for functional polymer coating [5]. Eudragit RS100 and Eudragit RL100 are widely used polymethacrylate polymers for sustained-release formulations because of their pH-independent permeability and excellent film-forming characteristics. Their permeability can be precisely controlled by varying their ratio, enabling modulation of drug release [6].

Therefore, the present investigation was undertaken to develop and evaluate Eudragit-coated multiparticulate pellets of Metformin hydrochloride using the solution layering technique. The prepared formulations were characterized for physicochemical properties, flow behavior, drug content, particle size, in vitro drug release, release kinetics, and accelerated stability to identify an optimized formulation capable of providing controlled drug delivery and improved therapeutic performance [7].

Material and Methods

Determination of Melting Point

Melting point of Metformin HCl was determined by capillary method. Fine powder of Metformin HCl was filled in the glass capillary tube which was sealed at end. The capillary tube is tied to thermometer and the thermometer was placed in melting point apparatus. The powder at what temperature it will melt was noticed as melting temperature of drug [8-9].

Solubility

Solubility of Metformin HCl was determined in different aqueous and non-aqueous solvents. Solubility studies performed by taking excess amount of Metformin HCl in different beakers containing the solvents [10-11].

UV Spectroscopy

Ultraviolet (UV) spectroscopy is a simple, rapid, and cost-effective analytical technique widely employed for the qualitative and quantitative estimation of drugs in pharmaceutical formulations. UV spectrophotometry is based on the absorption of ultraviolet radiation by molecules containing chromophoric groups, resulting in electronic transitions from lower to higher energy levels. Metformin hydrochloride is freely soluble in water and exhibits good solubility in phosphate buffer solutions. For the present study, distilled water and phosphate buffer pH 6.8 was used as the solvent, as it simulates intestinal conditions and provides reproducible absorbance values without interference. A standard stock solution of metformin hydrochloride (100 µg/mL) was prepared in the selected solvent. The solution was scanned in the wavelength range of 200–400 nm using a UV–Visible spectrophotometer against the solvent blank. Metformin hydrochloride showed a well-defined absorption maximum (λmax) at 233 nm, which was selected for further quantitative analysis [12]. Weighed accurately 100 mg of Metformin HCl was taken and dissolved in a suitable quantity phosphate buffer 6.8 in 100 ml volumetric flask. Then the volume was made

up to 100 ml with phosphate buffer 6.8, which gives 1000 µg/ml concentration. The standard stock solution was then serially diluted with phosphate buffer 6.8 to get 1 to 10 µg/ml of Metformin Hcl. The absorbance of the solutions was measured against buffer solution as blank at 233 nm using spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve [13].

Drug Excipients Compatibility Studies

Drug-excipient compatibility studies are an essential part of preformulation and formulation development processes in the pharmaceutical industry. These studies assess the compatibility of a drug substance with various excipients that are used to formulate the final dosage form. he primary purpose of drug-excipient compatibility studies is to evaluate potential interactions between the drug substance and excipients [14]. These studies aim to identify any chemical, physical, or mechanical interactions that could affect the stability, efficacy, or safety of the final dosage form. By assessing compatibility early in the development process, formulation scientists can make informed decisions regarding excipient selection, formulation design, and process optimization. Compatibility study of drug with the excipients was determined by I.R. Spectroscopy (Shimadzu, Japan). The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of the drug and other ingredients in the formulations were compared with that of the pure drug [15].

Preparation of Core Drug Loaded Pellets of Metformin HCl

Drug loaded pellets was prepared by solution layering technique. (500 mg Metformin HCl/dose in 0 Size capsule) (Table 1). To begin the formulation, accurately weighed 22.5 g of sugar spheres (0.6–0.8 mm) were taken as inert cores for all batches. Separately, 25 g of Metformin HCl and 1 g of PVP K30 were dissolved in a sufficient quantity of isopropyl alcohol (IPA) to prepare a clear drug-binding solution. The non-pareil seeds were transferred into a coating pan (25 rpm), and the drug solution was sprayed onto them in a controlled manner (1 ml/min). Spraying was carried out intermittently, allowing partial drying between each spray cycle to prevent pellet aggregation. The inlet air temperature was maintained at 45°C. This layering process continued until the entire drug solution was applied evenly. After the final spray, the drug-loaded pellets were subjected to drying in a tray dryer until a dry and free-flowing product was obtained. The pellets were then passed through a sieve #20 to remove any clumps and ensure uniform particle size distribution [16].

Table 1: Composition of Metformin HCl Loaded Pellets

Ingredients	Mg/Capsule	Qty/50 Capsules	Function
Sugar Spheres (0.6-0.8 mm)	450 mg	22.5g	Starter core
Metformin HCl	500 mg	25g	Active Drug
PVP K30 (4% of Drug)	20 mg	1g	Binder
Talc (1% of Solids)	10 mg	0.5g	Anti-tacking agent
Total	980 mg		

Formulations of Coated Multiparticulate Pellets

The coating of Metformin HCl drug-loaded pellets was carried out using the pan coating technique. Each formulation (F1 to F4) was prepared with a total of 5 g of coating material using different ratio of Eudragit RS100 to Eudragit RL100 over 50 g of drug-loaded pellets.

Table 2: Formulation of Coated Pellets

Batch	Eudragit RS100 (g)	Eudragit RL100 (g)	Total Polymer (g)	Triethyl Citrate (20% of polymer) (g)	Talc (g)	RS:RL Ratio
F1	2.5	2.5	5	1	1.25	50:50
F2	3.0	2.0	5	1	1.25	60:40
F3	3.5	1.5	5	1	1.25	70:30
F4	4.0	1.0	5	1	1.25	80:20

Initially, the required quantities of Eudragit RS100 and Eudragit RL100 were accurately weighed based on the specific formulation ratios (Table 2). These polymers were gradually dispersed in a mixture of isopropyl alcohol and water (60:40 v/v) under continuous stirring to form a uniform polymer solution. To this solution, triethyl citrate (20% of total polymer weight) was added as a plasticizer to enhance the flexibility and adhesion of the coating film. Talc (25% of polymer weight) was then incorporated as an anti-adherent to prevent sticking of pellets during coating. The drug-loaded pellets (50 g) were placed into a rotating stainless-steel coating pan (25 rpm), pre-warmed to around 35–40°C. The prepared coating solution was sprayed onto the pellets using a spray gun at the rate of 1 ml/min. The inlet air temperature was carefully controlled at 40–45°C to achieve uniform coating without over wetting or clumping. The coating was applied in thin, successive layers, allowing sufficient drying time between each pass to ensure solvent evaporation and film build-up. The process was continued until the complete deposition of 5 g of coating solids. After completion of coating, the pellets were allowed to dry in a tray dryer at 40°C for 1 hour to ensure complete solvent removal and curing of the polymer layer. The coated pellets were then stored in airtight containers and subjected to further evaluation [17-18].

Evaluation of pellets

Friability

The friability test is an important quality control measure in pharmaceutical manufacturing, primarily for solid oral dosage forms such as tablets. It assesses the mechanical strength and resistance to abrasion of tablets during handling, packaging, and transportation. The friability test ensures that tablets maintain their physical integrity and withstand mechanical stress under normal handling conditions. Tablets with low friability are less likely to break or crumble during manufacturing, packaging, shipping, and handling, thereby preserving their quality and appearance. Friability testing helps ensure uniformity of drug content within tablets. Tablets that are prone to excessive friability may lose drug particles or powder during handling, leading to variations in drug content among individual tablets. By identifying friable tablets, manufacturers can take corrective actions to maintain dosage uniformity and ensure consistent therapeutic outcomes for patients [19].

Regulatory authorities, such as the United States Pharmacopeia (USP), European Pharmacopoeia (Ph. Eur.), and others, mandate friability testing as part of quality control requirements for solid oral dosage forms. Compliance with these standards is essential for obtaining regulatory approval and ensuring product quality, safety, and efficacy. Tablets with excessive friability may produce fine particles or dust, which can accumulate in packaging materials, compromise seal integrity, and affect product stability. By assessing tablet friability, manufacturers can evaluate the suitability of packaging materials and minimize the risk of contamination, moisture ingress, or degradation during storage and distribution. Friability testing helps ensure the safety and efficacy of pharmaceutical products. Tablets that are excessively friable may pose a risk of dose variability, incomplete drug delivery, or inadequate therapeutic response for patients. By maintaining appropriate tablet integrity, manufacturers uphold their commitment to patient safety and well-being. Friability of pellets was determined by subjecting 10 g of pellets in (Roche friabilator) at 4 min at 25 rpm. The abraded samples were sieved and the pellets retained on the sieve were weighed and percent friability was calculated from the difference in the weight of the pellets before and after friability [20].

$$F = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ X } 100$$

Flow Properties

The flow properties of polymer coated pellets were studied by determining its Carr's compressibility index and Hausner ratio. The data of the tapped density and bulk densities were utilized for the determination of flow properties of the coated pellets [21].

Drug Content

Required weight of drug loaded pellets containing equivalent weight of 15 mg of Metformin HCl were taken and crush to powdered. The powder was then transferred in to 100 ml volumetric flask and dissolved in 100 ml of methanol. The solution was shaken and then filtered. After appropriate dilution

the drug content was measured using a UV spectrophotometer by taking absorbance of sample at 233 nm [22].

Mean Particle Size

The mean particle size of the drug coated multiparticulate pellets was determined by the standard sieve analysis method using a mechanical sieve shaker. Accurately weighed 10 g of coated pellets from each formulation batch was taken and placed on the top of a nest of standard stainless-steel sieves arranged in descending order of aperture size, followed by a collecting pan at the bottom. The sieve assembly was mounted on a mechanical sieve shaker and operated for 10 minutes at constant vibration intensity to allow proper separation of pellets based on size. After sieving, the pellets retained on each sieve were carefully collected and weighed individually using an analytical balance. The percentage weight retained on each sieve was calculated with respect to the total pellet weight. The mean particle size was then calculated by multiplying the mean aperture size of each sieve fraction by the corresponding weight fraction retained and summing the values using the formula:

Mean particle size = $\Sigma(d \times w) / \Sigma w$

where

d represents the mean sieve diameter

w represents the weight fraction retained.

The obtained mean particle size values were expressed in millimetres. [23]

In Vitro Drug Release Study

The *in vitro* dissolution study of the Metformin HCl pellet formulations (F1 to F5) was performed using a USP Type I (Basket) apparatus to assess the drug release profile over 8 hours. Each formulation, equivalent to 15 mg of Metformin Hcl, was placed in size '0' hard gelatin capsules. The study was conducted in two sequential phases to mimic physiological pH changes in the GI tract [24].

Initially, the capsules were subjected to 900 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm for 2 hours to simulate gastric conditions. After 2 hours, the dissolution medium was replaced with 900 mL of phosphate buffer (pH 6.8) to simulate intestinal fluid conditions for the remaining 6 hours. Samples of 5 mL were withdrawn at predetermined time intervals and replaced with an equal volume of fresh medium to maintain sink conditions. The withdrawn samples were filtered through Whatman filter paper No. 1, and the drug concentration was determined spectrophotometrically at λmax 233 nm using UV-Visible spectrophotometer. The cumulative percentage of drug release was calculated and plotted against time to evaluate the release pattern. Each formulation was tested in triplicate (n=3), and results were reported as mean ± standard deviation [25].

Drug Release Kinetics

The *in vitro* drug release data were tested with the various mathematical models. The best fitted model was found out to describe the kinetics of drug release [26].

Stability Study

A stability study is a systematic investigation conducted to assess the chemical, physical, and microbiological stability of pharmaceutical products under various environmental conditions over time. These studies are essential for evaluating the shelf-life, storage requirements, and quality attributes of pharmaceutical formulations. The primary purpose of stability studies is to determine how the quality attributes of a pharmaceutical product change over time under different storage conditions, such as temperature, humidity, light exposure, and packaging materials. Stability studies help establish the shelf-life of a product, which is the period during which the product remains within acceptable quality standards under specified storage conditions [27-28].

The accelerated stability studies were carried out according to ICH guidelines on optimized formulation. The formulation was packed in strip of aluminum foil and was stored in stability chamber maintained at 40°C and 75% RH for the period of 3 months. The beads formulation was evaluated before and after 3 months for change in floating behaviours, drug content and *in-vitro* drug release [29].

RESULTS AND DISCUSSION

Determination of Melting Point

The melting point of Metformin HCl was determined by capillary method, melting point of Metformin HCl was found to be 223 to 225°C. Melting point compared with pharmacopoeial standards, that confirmed the purity of drug sample.

Solubility

The solubility study of drug was carried out in different solvents. The results are shown in table 3.

Table 3: Solubility Profile of Metformin HCl in Different Solvents

Solvents	Solubility
Water	Soluble
Methanol	Slightly soluble
Ethanol	Slightly soluble
DMSO	Soluble
Acetone	Insoluble
Chloroform	Insoluble
Phosphate buffer Solution pH 6.8	Soluble

UV-Spectroscopy

The solution containing 10 ug/ml of Metformin HCl in phosphate buffer pH 6.8. was prepared and scanned over 200 -800nm against phosphate buffer pH 6.8. solution as a blank using Shimadzu UV spectrophotometer. The maximum wave length was observed at 233 nm, which match with reported wave length. The stock solution is used to prepare 2 to 10 µg/ml of Metformin HCl in 6.8 pH phosphate buffer and analysed at 133 nm. The graph v/s concentration was plotted and data was subjected to linear regression analysis. The data of absorbance shown in figure 1. The standard calibration curve of Metformin HCl in in the concentration 2 µg/ml to 10 µg/ml was straight line. The absorbance increased with increased in concentration. Thus, the standard curve follows the Beer-Lamberts Law.

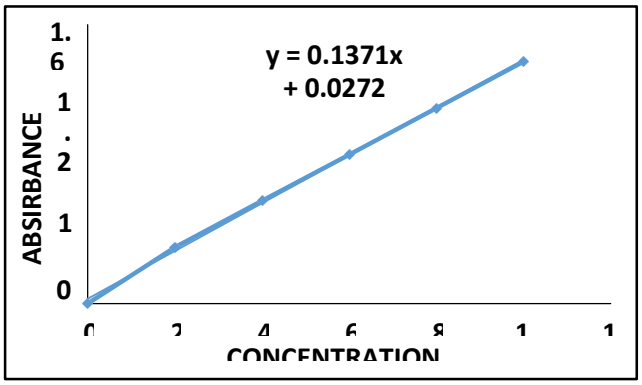
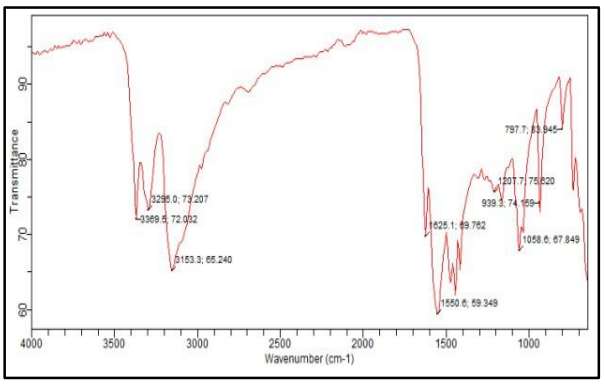


Figure 1: Standard Calibration Curve of Metformin HCl in Phosphate Buffer pH 6.8

Figure 2: FTIR Spectra of Pure Drug Metformin HCl



Compatibility Studies (FT-IR)

The FTIR spectrum of Metformin HCl (figure 2) exhibited prominent characteristic absorption peaks at 3369.5, 3295.0, and 3153.3 cm^{-1}, corresponding to N–H stretching vibrations of amino groups. The strong absorption band observed at 1625.1 cm^{-1} was assigned to C=N stretching of the guanidine nucleus, while the peak at 1550.6 cm^{-1} represented N–H bending vibrations. Further peaks at 1207.7 and 1058.6 cm^{-1} confirmed C–N stretching vibrations. The fingerprint region also showed characteristic bands at 939.3 and 797.7 cm^{-1}, attributed to N–H wagging and deformation vibrations, respectively. These observations confirmed the structural integrity and purity of Metformin HCl and were found to be consistent with reported literature values. The major peak in the drug infrared spectra was found to remain unchanged and detectable in the spectra of drug with eudragit, indicating that there was no physical interaction due to bond formation between the two substances.

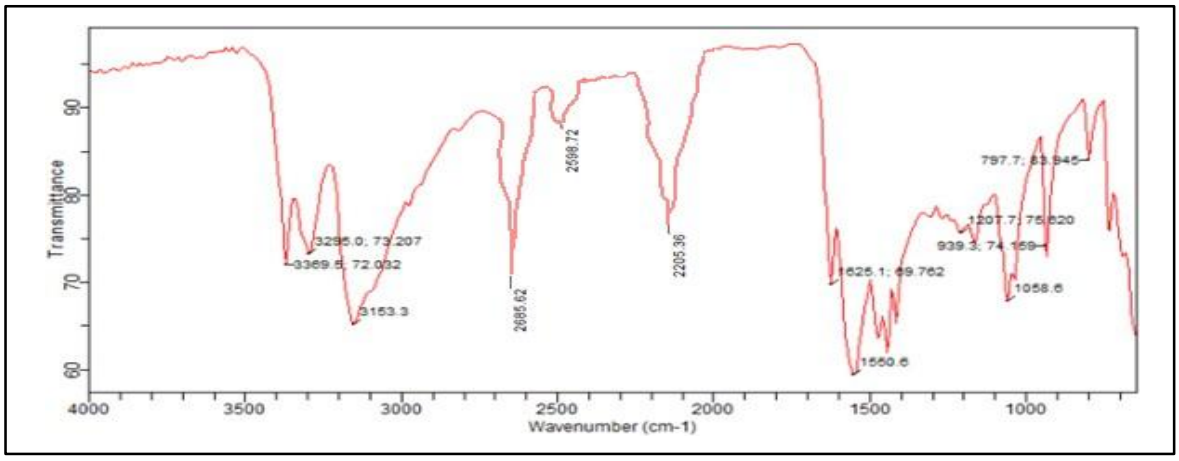


Figure 3: FTIR Spectra of Metformin HCl + Eudragit RS 100 and RL100

Evaluation of pulsatile pellets

The coated multiparticulate pellets of Metformin HCl prepared using Eudragit RS100 and Eudragit RL100 by pan coating technique were evaluated for friability, flow properties, drug content, and mean particle size to assess the suitability of the formulations for sustained drug delivery applications. The results are presented in the table 4.

Friability

The friability values of all formulations were found in the range of 0.43 ± 0.01% to 0.82 ± 0.03%, which were well below the acceptable pharmacopeial limit of 1%. This indicates that all coated pellets possessed sufficient mechanical strength and resistance to abrasion during handling, packaging, and further processing. A gradual decrease in friability was observed from F1 to F4, which can be attributed to the increase in coating weight, resulting in the formation of a stronger and more continuous polymeric film around the pellets. The higher polymer deposition in F4 imparted better surface integrity and reduced surface erosion during tumbling. The results are shown in table 4.

Flow Properties

The Carr's index values ranged from 12.95 ± 0.14% to 14.26 ± 0.21%, while the Hausner ratio values ranged from 1.14 ± 0.01 to 1.17 ± 0.01. These values indicate good flow properties of all pellet batches, making them suitable for downstream processing such as capsule filling or sachet packaging. The slight improvement in flowability with increasing coating level may be due to smoother pellet surface and reduced interparticulate friction after polymer coating.

The angle of repose was found between 24.88 ± 0.28° and 27.84 ± 0.42°, which further confirmed the excellent flow behavior of the coated pellets. Generally, angle of repose values below 30° indicate good flowability. The decrease in angle of repose from F1 to F4 suggests that coating levels improved pellet sphericity and surface smoothness, thereby facilitating better movement of pellets over one another. The results are shown in table 4.

Drug Content

The drug content of all formulations was found within the range of 98.42 ± 0.54% to 100.36 ± 0.42%, demonstrating uniform drug loading and minimal loss of drug during the coating process. The results confirm the reproducibility and efficiency of the pan coating method in maintaining consistent drug distribution among the pellet batches. The low standard deviations further reflect the reproducibility of the layering process. The results are shown in table 4.

Mean Particle Size

The mean particle size of the coated pellets increased progressively from 0.71 ± 0.02 mm in F1 to 0.78 ± 0.01 mm in F4. This increase in particle size is directly related to the coating of pellets, which led to gradual deposition of the polymeric coat over the 0.6–0.8 mm sugar sphere cores. The observed increase in size confirmed successful coating and uniform film build-up on the pellet surface. The study concluded that, all coated multiparticulate pellet formulations exhibited acceptable physicochemical and flow properties. The results are shown in table 4.

Table 4: Evaluation of Coated Pellets (F1 to F4)

Batch	riability (%)	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)	Drug Content (%)	Mean Particle Size (mm)
F1	0.82 ± 0.03	14.26 ± 0.21	1.17 ± 0.01	27.84 ± 0.42	98.42 ± 0.54	0.71 ± 0.02
F2	0.69 ± 0.02	13.84 ± 0.18	1.16 ± 0.01	26.92 ± 0.36	99.18 ± 0.47	0.74 ± 0.02
F3	0.55 ± 0.02	13.32 ± 0.16	1.15 ± 0.01	25.76 ± 0.31	99.74 ± 0.39	0.77 ± 0.01
F4	0.43 ± 0.01	12.95 ± 0.14	1.14 ± 0.01	24.88 ± 0.28	100.36 ± 0.42	0.78 ± 0.01

All values represent mean ± standard deviation (n=3)

In-Vitro Dissolution Study

The *in vitro* dissolution study of Metformin HCl loaded coated multiparticulate pellets (F1–F4) was carried out for 12 hours to evaluate the effect of polymer ratio (Eudragit RS100:RL100) on drug release behavior. In the present study, the total polymer concentration was kept constant (5 g) for all formulations, while the ratio of Eudragit RS100 (less permeable) and Eudragit RL100 (more permeable) was varied systematically from 50:50 (F1) to 80:20 (F4).

Table 5: *In vitro* Dissolution Study of Coated Pellets of Metformin HCl (F1 to F4)

Time (h)	F1	F2	F3	F4
1	18.42 ± 0.54	12.36 ± 0.42	8.84 ± 0.31	6.28 ± 0.24
2	31.76 ± 0.62	22.84 ± 0.51	16.42 ± 0.38	11.74 ± 0.29
3	44.58 ± 0.71	33.62 ± 0.58	24.96 ± 0.42	17.88 ± 0.33
4	56.94 ± 0.76	44.18 ± 0.63	33.48 ± 0.47	24.52 ± 0.36
5	67.82 ± 0.82	54.96 ± 0.69	42.76 ± 0.53	31.68 ± 0.41
6	77.64 ± 0.88	65.74 ± 0.74	52.84 ± 0.58	39.46 ± 0.46
7	85.18 ± 0.91	75.68 ± 0.79	62.96 ± 0.62	47.82 ± 0.51
8	91.42 ± 0.95	84.52 ± 0.83	72.84 ± 0.67	56.76 ± 0.56
9	98.46 ± 0.99	91.36 ± 0.87	81.42 ± 0.71	65.38 ± 0.61
10	-	99.18 ± 0.94	88.74 ± 0.76	73.96 ± 0.66
11	-	-	94.82 ± 0.81	82.48 ± 0.71
12	-	-	99.26 ± 0.84	89.84 ± 0.76

All values represent mean ± standard deviation (n=3)

The dissolution profiles clearly demonstrated that drug release was significantly influenced by the relative proportion of RS100 and RL100, confirming that polymer permeability plays a dominant role in controlling drug release from coated pellets, even when coating thickness remains constant (Table 5). Formulation F1 (50:50) exhibited the fastest drug release, with 18.42 ± 0.54% drug release within 1 hour, increasing rapidly to 91.42 ± 0.95% at 8 hours, and achieving almost complete release (98.46 ± 0.99%) by the 9th hour. The faster release observed in F1 can be attributed to the higher proportion of Eudragit RL100, which contains a greater number of quaternary ammonium groups, resulting in increased permeability of the coating membrane. This enhanced permeability facilitated rapid penetration of dissolution medium and faster diffusion of drug molecules, leading to a slight initial burst effect followed by rapid release. Formulation F2 (60:40) showed a moderately controlled release profile, with 12.36 ± 0.42% drug release at 1 hour, gradually increasing to 84.52 ± 0.83% at 8 hours, and 99.18 ± 0.94% at 10 hours. The reduction in RL100 content compared to F1 resulted in decreased membrane permeability, thereby slowing the drug release rate. The formulation exhibited a more controlled and extended release pattern, suitable for intermediate sustained release applications. Formulation F3 (70:30) demonstrated the most desirable sustained release behavior, with a gradual and uniform release profile

throughout the study. The formulation released 52.84 ± 0.58% drug at 6 hours, 72.84 ± 0.67% at 8 hours, and 99.26 ± 0.84% at 12 hours, indicating efficient control over drug release for a full 12-hour period. This optimized performance can be attributed to the balanced ratio of RS100 and RL100, which provided an ideal combination of permeability and diffusional resistance, allowing controlled penetration of dissolution medium and sustained drug diffusion. The absence of burst release and uniform release kinetics make F3 the most suitable formulation. Formulation F4 (80:20) showed the slowest drug release profile, with only 6.28 ± 0.24% release at 1 hour and 89.84 ± 0.76% release after 12 hours, indicating incomplete release within the study duration. The high proportion of Eudragit RS100, which is less permeable, resulted in the formation of a dense and less porous polymeric membrane, significantly restricting the ingress of dissolution medium and drug diffusion. This formulation may extend drug release beyond 12 hours, possibly up to 14–16 hours, making it suitable for prolonged or once-daily extended-release systems. The study clearly indicates that drug release from coated multiparticulate pellets is predominantly governed by polymer permeability rather than coating thickness in this formulation approach. Eudragit RS100: Low permeability, acts as release retardant while Eudragit RL100: High permeability, enhances drug diffusion. As the RS100 content increased from F1 to F4, membrane permeability decreased, diffusion resistance increased, drug release rate decreased and release duration increased.

The study confirms that Eudragit RS100:RL100 ratio is a critical formulation variable in controlling drug release from coated multiparticulate pellets. By adjusting the polymer ratio, it is possible to achieve a wide range of release profiles without altering coating thickness. Among all formulations, F3 (70:30 ratio) exhibited the most ideal release pattern, providing uniform and complete drug release over 12 hours, and was therefore selected as the optimized formulation. The percentage drug release of Metformin HCl from the coated pellets are graphically shown in figure 4, 5, 6, 7 & 8 respectively.

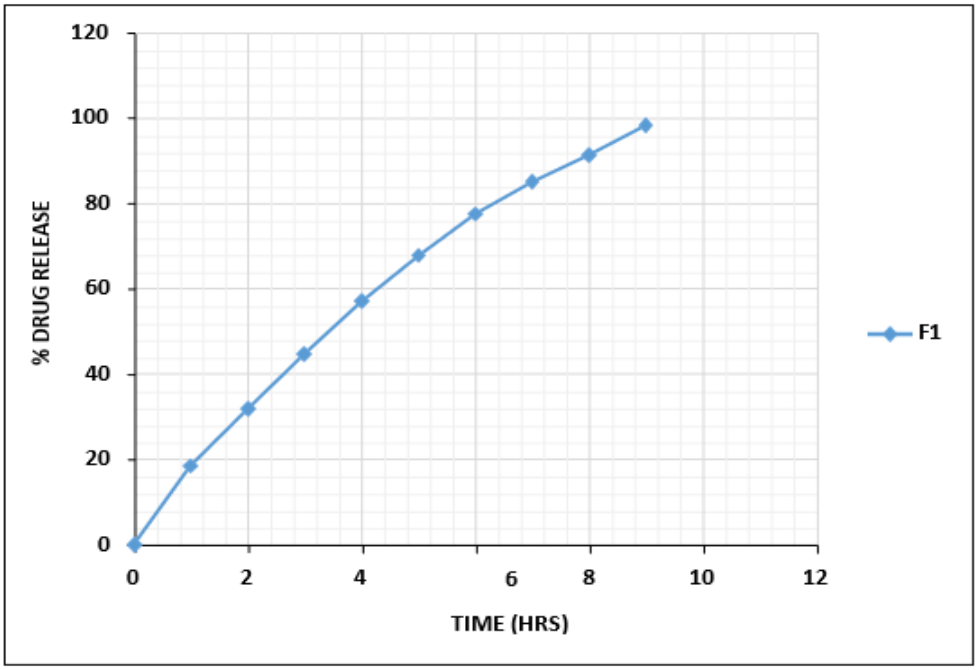


Figure 4: *In vitro* Dissolution profile of Sustained Release Multiparticulate Pellets of Metformin HCl (F1)

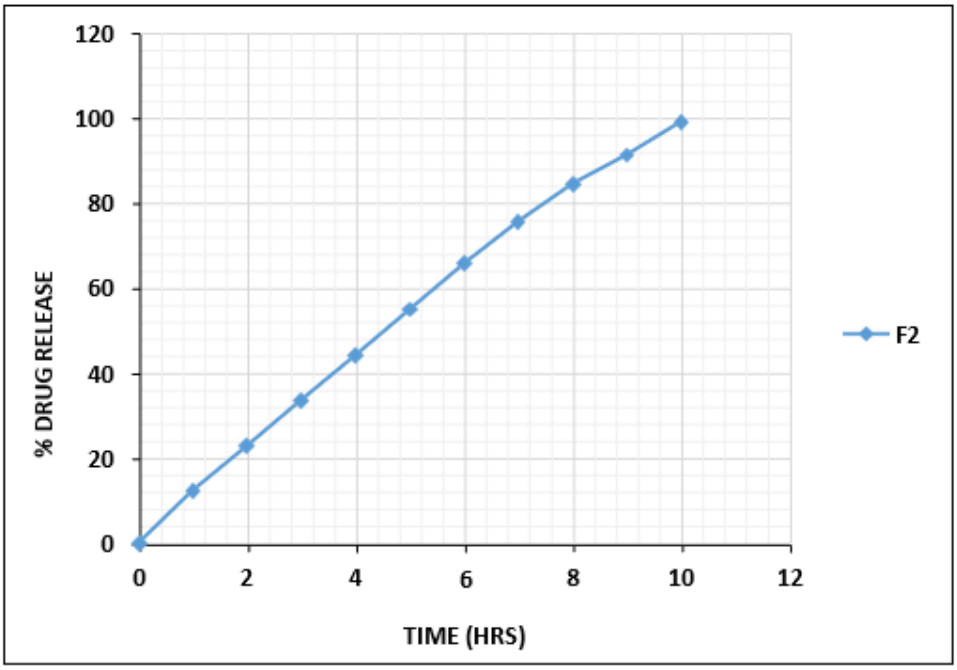


Figure 5: ***In vitro*** **Dissolution profile of Sustained Release Multiparticulate Pellets of Metformin HCl (F2)**

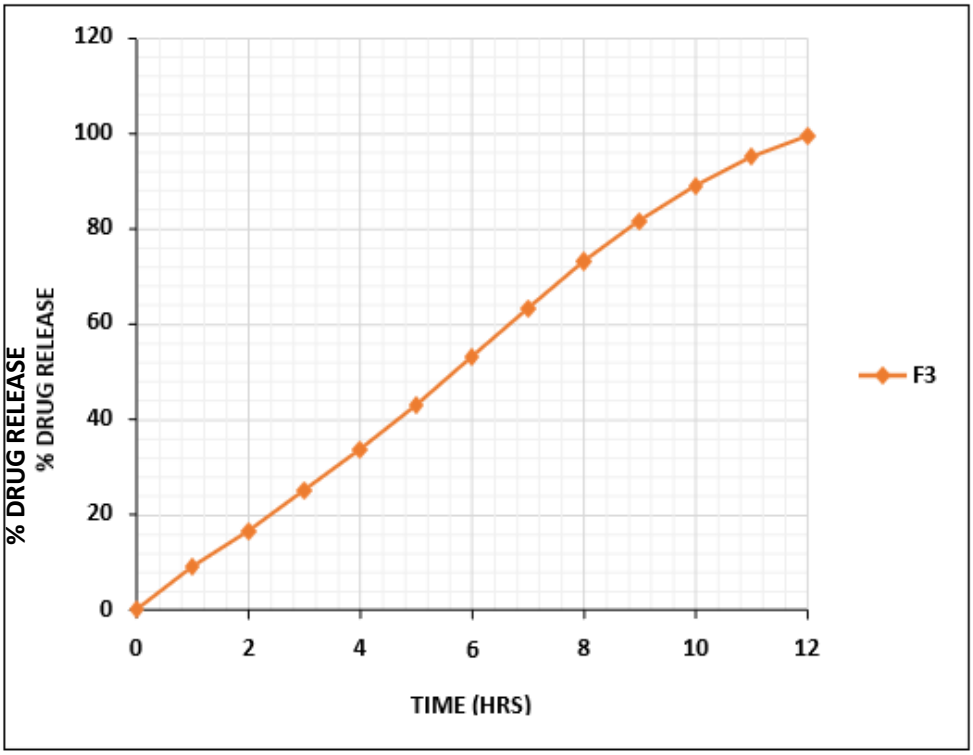


Figure 6: ***In vitro*** **Dissolution profile of Sustained Release Multiparticulate Pellets of Metformin HCl (F3)**

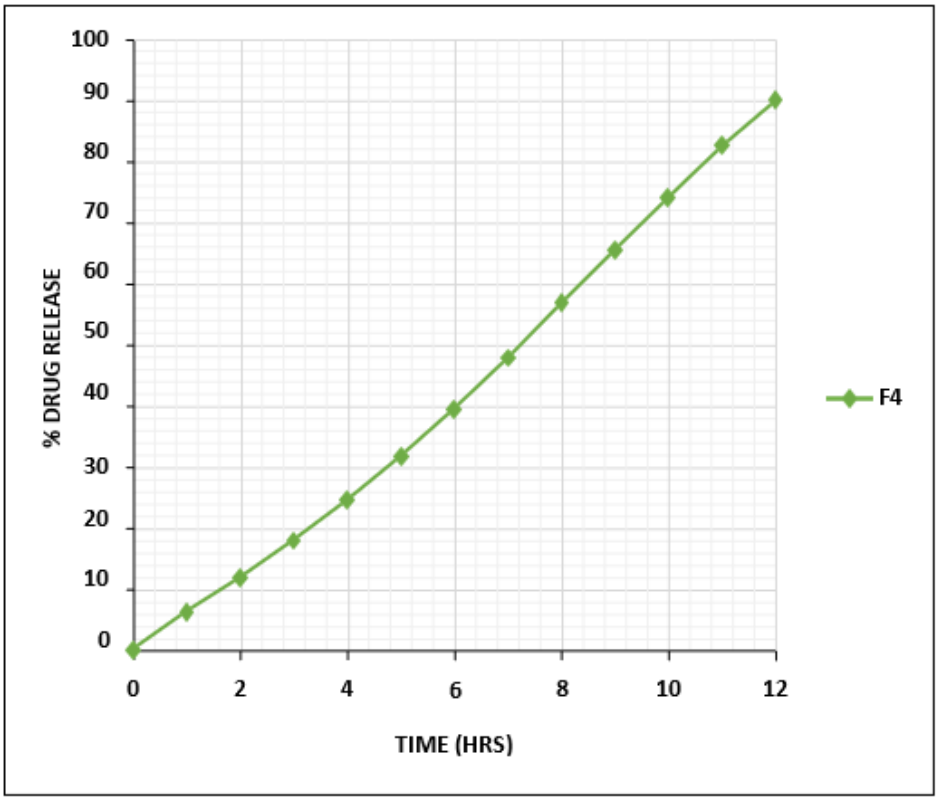


Figure 7: *In vitro* Dissolution profile of Sustained Release Multiparticulate Pellets of Metformin HCl (F4)

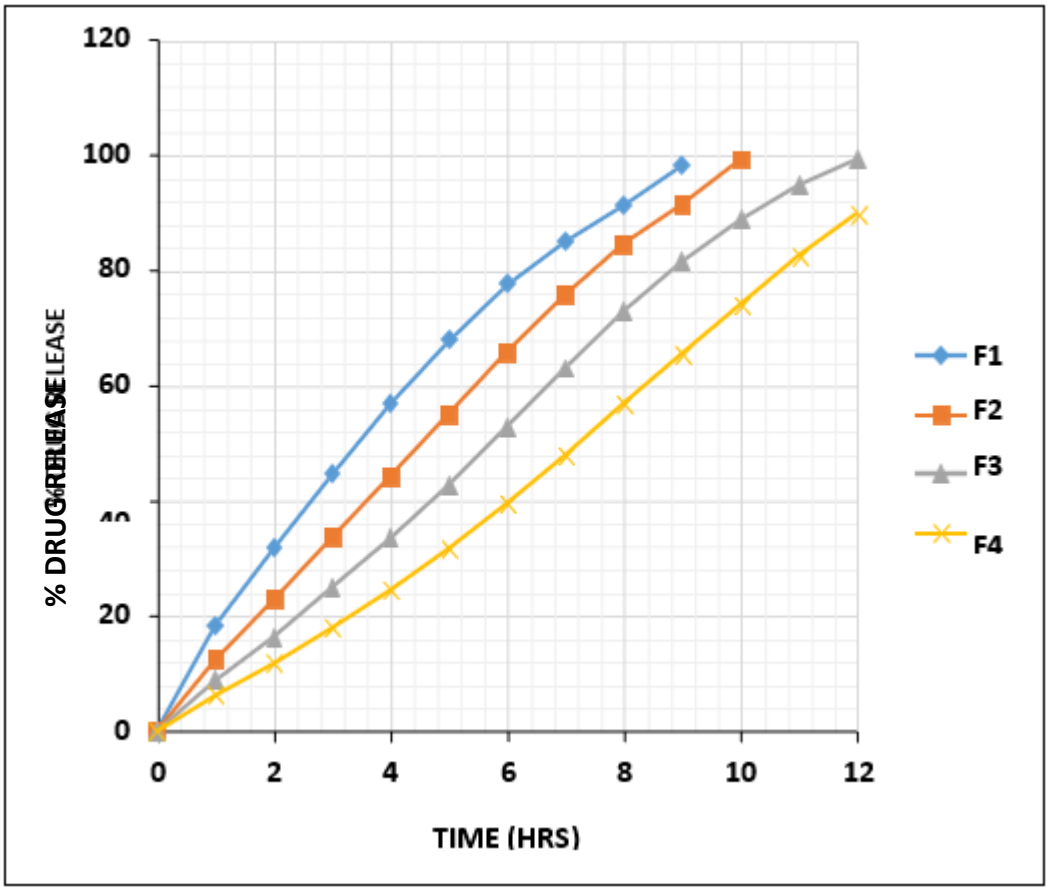


Figure 8: Competitive *In vitro* Dissolution profile of Pulsatile Release Pellets of Metformin HCl (F1 to F4)

Drug Release Kinetics

To understand the mechanism of drug release from the coated multiparticulate pellet formulations (F1–F4), the in vitro dissolution data were fitted into various kinetic models, namely Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The model showing the highest correlation coefficient (R^2) was considered as the best-fit model for each formulation. The kinetic model fitting results demonstrated that all formulations exhibited high correlation values with Korsmeyer–Peppas models, indicating that the drug release was primarily governed by polymer membrane-controlled diffusion and relaxation mechanisms.

Formulation F1 showed an R^2 value of 0.976 for Zero-order, 0.856 for First-order, 0.971 for Higuchi, and 0.997 for Korsmeyer–Peppas model, with a Peppas release exponent (n) value of 0.774. The Korsmeyer–Peppas model showed the highest correlation coefficient. The n value between 0.5 and 1.0 suggests an anomalous (non-Fickian) transport mechanism, where drug release is controlled by a combination of diffusion through the polymeric membrane and relaxation of the coating film. The thinner 10% coating level in F1 may have allowed easier medium penetration, leading to a more uniform release rate. Formulation F2 exhibited R^2 values of 0.995 (Zero-order), 0.762 (First-order), 0.940 (Higuchi), and 0.999 (Korsmeyer–Peppas), with an n value of 0.920. The highest correlation with the Korsmeyer–Peppas model indicates that the drug release was predominantly governed by polymer swelling, relaxation, and diffusion through the Eudragit membrane. The exponent value close to unity indicates a Case II transport approaching super Case II release, where polymer relaxation contributes significantly to the release process. Formulation F3, considered the optimized 12-hour sustained release batch, showed R^2 values of 0.995, 0.781, 0.923, and 0.997 for Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models respectively, with an n value of 1.03. The release exponent value slightly greater than 1 strongly suggests a super Case II transport mechanism, indicating that the release is governed mainly by polymer chain relaxation and erosion of the coating membrane rather than simple diffusion alone. This behavior is ideal for sustained release formulations intended for prolonged therapeutic effect. The 20% coating weight gain likely formed an optimal diffusional barrier that regulated both fluid ingress and controlled polymer relaxation over 12 hours. Formulation F4 showed R^2 values of 0.994 (Zero-order), 0.884 (First-order), 0.884 (Higuchi), and 0.996 (Korsmeyer–Peppas) with an n value of 1.10. Similar to F3, the release followed the Korsmeyer–Peppas model, with a higher release exponent indicating pronounced super Case II transport mechanism (Table 6). The thicker 25% polymer coat may have resulted in a denser and stronger film, where drug release was largely controlled by polymer relaxation and structural reorganization of the Eudragit membrane over time.

The kinetic analysis clearly indicates that polymer concentration and membrane thickness strongly influenced the release mechanism.

F1: Anomalous diffusion (n = 0.774) F2: Near Case II transport (n = 0.920) F3: Super Case II transport (n = 1.03) F4: Super Case II transport (n = 1.10)

The gradual increase in Peppas exponent (n) from F1 to F4 confirms that increasing coating concentration shifted the mechanism from diffusion-dominant release toward polymer relaxation-controlled release. Film relaxation and reorganization become more dominant at higher polymer loads. The release kinetics study confirmed that the drug release from coated multiparticulate pellets was best explained by the Korsmeyer–Peppas model, for all formulation, indicating that the release mechanism was predominantly controlled by polymer film relaxation. Among all the optimized batch, F3 showed the most desirable kinetic behavior with super Case II transport and optimum 12-hour sustained release, confirming it as the optimized formulation. The graphical representation of zero order, first order, higuchi release mechanism and korysmeyer-peppas model of all batch formulation was shown in figure 9, 10, 11 and 12 respectively.

Table 6: Model Fitting Release Profile of Metformin HCl Loaded Multiparticulate Pellets Formulations F1 To F4

Batch	Zero Order (R^2)	First Order (R^2)	Higuchi Model (R^2)	Korsmeyer-Peppas (R^2)	'n' (Peppas Exponent)	Best Fit Model
F1	0.976	0.856	0.971	**0.997**	0.774	Zero Order
F2	0.995	0.762	0.940	**0.999**	0.920	Korsmeyer-Peppas
F3	0.995	0.781	0.923	**0.997**	1.03	Korsmeyer-Peppas
F4	0.994	0.884	0.884	**0.996**	1.10	Korsmeyer-Peppas

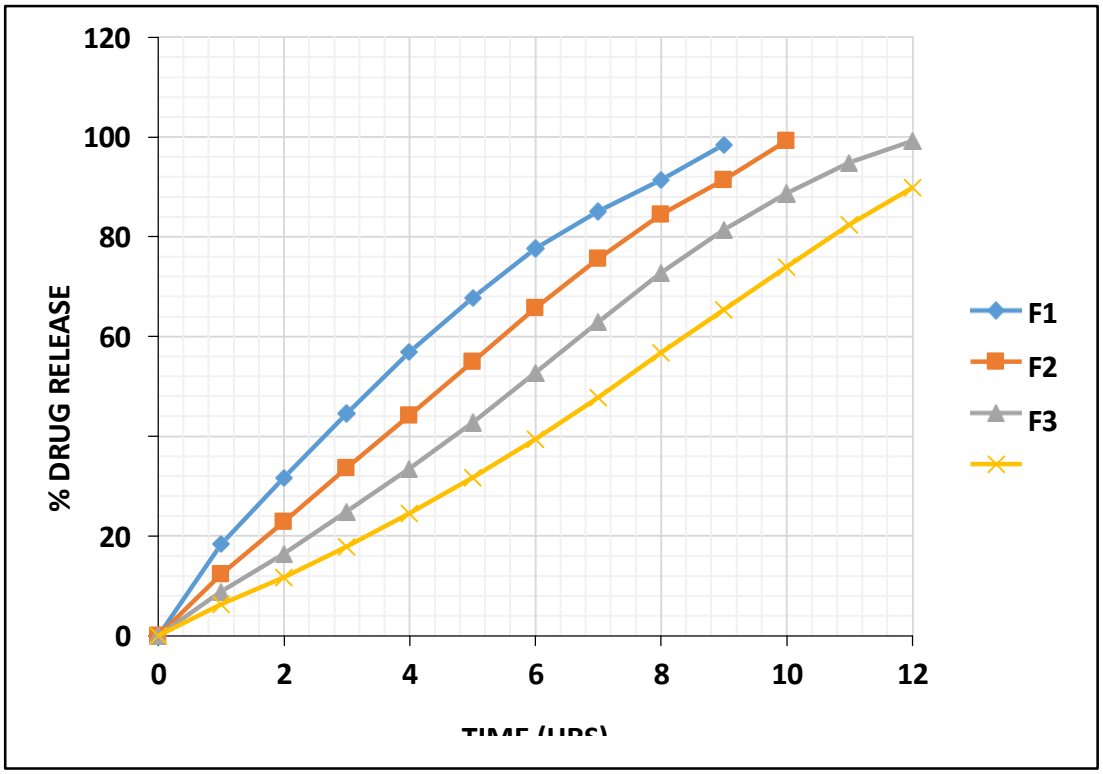


Figure 9: Cumulative % Drug Release v/s Time (Zero order kinetics) of batch F1 to F4

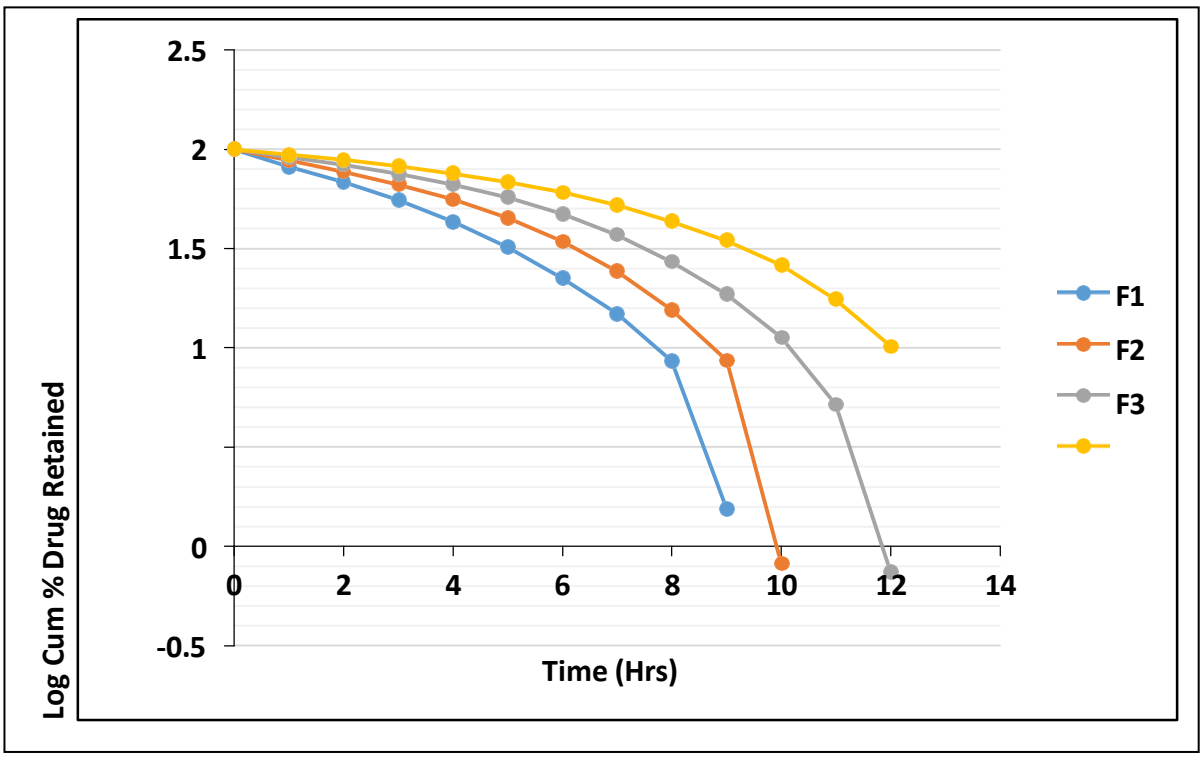
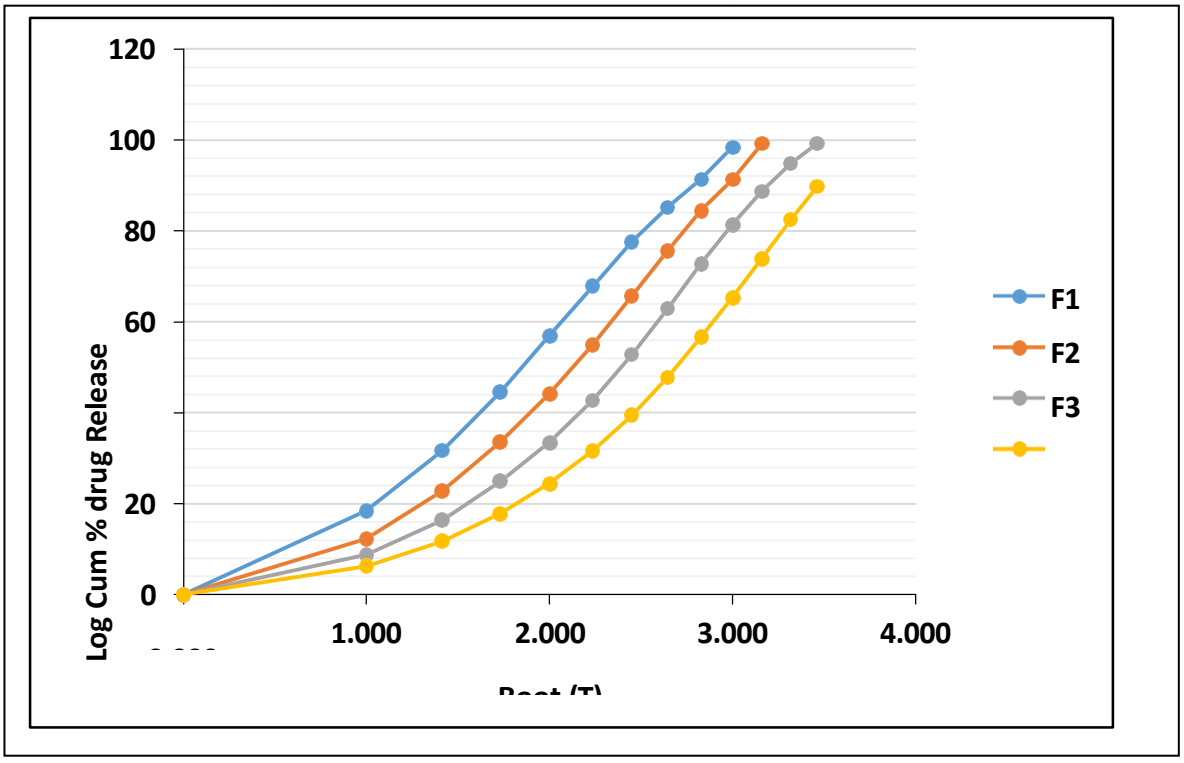


Figure 10: Log Cumulative % Drug Retained v/s Time (First order kinetics) of batch F1 to F4

Figure 11: Cumulative % Drug Release v/s Square Root of Time (Higuchi Release Mechanism) of batch F1 to F4



Stability Study

The optimized formulation F3, which showed the most desirable 12-hour sustained drug release profile, was subjected to a short-term accelerated stability study for 3 months to evaluate its physical and chemical stability. The study was carried out as per ICH recommended stability conditions (40 ± 2°C / 75 ± 5% RH), and the formulation was analyzed for drug release and drug content before storage and after completion of the storage period.

The stability data revealed that the formulation remained highly stable throughout the 3-month study period, with only negligible changes observed in the evaluated parameters. The percentage cumulative drug release of formulation F3 was found to be 99.26 ± 0.84% before storage, which slightly decreased to 98.85 ± 1.06% after 3 months of storage. The observed difference was minimal and within acceptable experimental variation limits, indicating that the polymeric coating membrane remained intact and functionally stable during storage. The sustained release performance of the optimized pellets was therefore preserved even under accelerated conditions. This suggests that the Eudragit RS100 and RL100 coating system provided an effective and stable diffusion barrier, resistant to possible environmental effects such as temperature and humidity.

Similarly, the drug content of F3 was found to be 99.74 ± 0.39% initially, which marginally reduced to 99.28 ± 0.64% after 3 months. The slight decrease in drug content was statistically insignificant and indicates the chemical stability of Metformin HCl within the multiparticulate pellet system. No significant degradation of the drug was observed, confirming that the selected formulation components and coating materials successfully protected the drug from environmental stress conditions.

The minor changes observed in both drug release and drug content may be attributed to normal analytical variation or slight moisture interaction during storage, but these variations remained well within acceptable pharmacopeial and ICH limits. Importantly, no significant alteration in release profile was observed, demonstrating that the optimized polymer concentration (20% coating weight gain) maintained its membrane integrity and permeability characteristics over time.

The excellent stability performance of F3 may be due to the hydrophobic and moisture-resistant nature of Eudragit RS100, along with the controlled permeability contributed by Eudragit RL100, which together formed a robust and stable coating film around the sugar sphere cores.

The accelerated stability study confirmed that the optimized formulation F3 remained stable for 3 months without any significant change in drug content or sustained release behavior. Therefore, the developed Metformin HCl loaded multiparticulate pellet formulation can be considered physically and chemically stable, suitable for further scale-up and long-term storage studies. The results of stability data were shown in table 7.

Optimized Metformin HCl Loaded Multiparticulate Pellets Formulations F3

Formulation	Parameter	Before storage (0 month)	After storage (3 month)
F3	% Drug Release	99.26 ± 0.84	98.85±1.06
	Drug Content (%)	99.74 ± 0.39	99.28 ±0.64

CONCLUSION

The present investigation successfully developed and evaluated a multiparticulate drug delivery system of Metformin hydrochloride using the solution layering technique followed by polymer coating with Eudragit RS100 and Eudragit RL100. The prepared pellets exhibited satisfactory physicochemical characteristics, including uniform particle size distribution, excellent flow properties, low friability, and high drug content uniformity, indicating the suitability of the selected formulation method for producing high-quality multiparticulates.

The polymer-coated formulations effectively modified the release behavior of Metformin hydrochloride, demonstrating sustained drug release over an extended period. The release profile was influenced by the proportion of Eudragit RS100 and RL100, where increasing the concentration of Eudragit RS100 reduced

polymer permeability and prolonged drug release. The optimized formulation showed controlled release characteristics, desirable mechanical strength, and reproducible performance, making it suitable for sustained oral drug delivery. Drug release kinetic studies suggested that the release mechanism was predominantly diffusion-controlled with polymer matrix contribution.

Accelerated stability studies performed according to ICH guidelines demonstrated that the optimized multiparticulate formulation remained physically and chemically stable throughout the storage period without significant alterations in appearance, drug content, or dissolution profile. These findings confirm the robustness and stability of the developed formulation.

Overall, the developed Eudragit-coated multiparticulate drug delivery system represents an effective alternative to conventional immediate-release Metformin formulations. The formulation has the potential to reduce dosing frequency, minimize gastrointestinal adverse effects, improve plasma drug concentration profiles, enhance patient compliance, and achieve better long-term glycemic control. Future investigations involving in vivo pharmacokinetic studies, IVIVC establishment, and clinical evaluation are warranted to confirm its therapeutic advantages and support its translation into a commercially viable sustained-release dosage form.

REFERENCES

1. Law MFL, Deasy PB. Effect of common excipients on extrusion-spheronization. J Microencapsul. 1997;14(5):647-657.
2. Nguyen HL, et al. Mechanism of pellet growth and characterization techniques in multiparticulate drug delivery: a review. Curr Drug Targets. 2021;22(10):125-130.
3. Ramu S, Ramakrishna G, Balaji M, Kondala Rao K, Haranadh Reddy S, Pavan Kumar D. Multiple unit drug delivery system: Pelletization techniques. Am J Adv Drug Deliv. 2013;1(1):11-21.
4. Tawde VVT, Mahale AM, Redasani SS, Thakre MT. Multiparticulate drug delivery systems: A brief review on pharmaceutical pellets and pelletization techniques. J Emerg Technol Innov Res. 2024;11(1):385-395.
5. Marconati M, Lopez F, Tuleu C, Orlu M, Ramaioli M. *In vitro* and sensory tests to design easy-to-swallow multiparticulate formulations. arXiv. 2018;1808.09052.
6. Bodhankar SS, Sihare M. Formulation and evaluation of multiparticulate pellet systems for antidiabetic and antihypertensive drugs: Application of extrusion-spheronization and solution layering techniques. Int J Drug Deliv Technol. 2025;15(2):444-451.
7. Anabousi S, Naseef H, Qurt M, AbuKhalil A, Rabba A. Fast disintegrating pellets: Formulation and evaluation. F1000Res. 2025;14:711.
8. Rajesh N, Swetha A, Vidya JS. Formulation and evaluation of multiparticulate drug delivery system. World J Pharm Res. 2017;6(8):1429-1441.
9. 28. Shekhar S, Rachh PR. Formulation and development of multiparticulate systems based sustained release tablets of glibenclamide. Ilkogretim Online. 2023;22(6):1477-1489.
10. Sipos E, Szabó E, Vigh T, Nagy ZK, Marosi G. Comparison of mini-tablets and pellets as multiparticulate drug delivery systems for controlled drug release. Coatings. 2023;13(5):912.
11. Sahoo J, Murthy PN, Biswal S, Manikandan L. Development and characterization of Eudragit RL100-based aceclofenac sustained-release matrix pellets prepared via extrusion-spheronization. Drug Dev Ind Pharm. 2023;49(1):45-56.
12. Khan SA, Patel VB. Design of sustained-release pellets of ofloxacin using hot melt coating technique. Int Arch BioMed Clin Res. 2022;8(2):14-20.
13. Dhanorkar Y, Shah M. Development and characterization of multiparticulate system as an alternative to unit dosage forms containing drugs with diverse release profiles. Future J Pharm Sci. 2021;7:209.
14. Ibrahim MA, Alshora DH. Development and characterization of Eudragit RL100-based aceclofenac sustained-release matrix pellets prepared via extrusion-spheronization. Polymers (Basel). 2021;13(22):4034.
15. Chore SA, Dighade SJ. Formulation and evaluation of immediate-release pellets of metoprolol by extrusion-spheronization. World J Pharm Med Res. 2020;6(12):216-232.
16. Salve V, Shrivastava M, Patil S, et al. Development and optimization of a floating multiparticulate drug delivery system for norfloxacin. Int J Pharm Sci Res. 2019.
17. Shelar VS, Shirolkar SV. Formulation optimization of promethazine theoclate immediate-release pellets using extrusion-spheronization technique. Int J Appl Pharm. 2018;10(1):30-35.
18. Krishna Murthy DTEG. Formulation and evaluation of multiparticulate drug delivery

systems comprising telmisartan. Asian J Pharm. 2015;9(3):190-194.
19. Nayak UY, Shavi GV, Mutalik S, Udupa N. Formulation and evaluation of multiparticulate drug delivery system of valsartan. Res J Pharm Technol. 2013;6(1):96-104.
20. Chaudhari PM, Chaudhari PD. Formulation and evaluation of multiparticulate system for chronotherapeutic delivery of salbutamol sulphate. J Pharm Bioallied Sci. 2012;4(Suppl 1):S71-S73.
21. Cheboyina S, O'Haver J, Wyandt CM. A mathematical model to predict the size of the pellets formed in freeze pelletization techniques: Parameters affecting pellet size. J Pharm Sci. 2006;95(1):167-180.
22. Chaudhari MP, Chaudhari DP. Formulation and evaluation of multiparticulate system for chronotherapeutic delivery of salbutamol sulphate. J Pharm Bioallied Sci. 2012;4(Suppl 1):S71-S73.
23. Sultana S, Ahmed I, Islam MR, Rahman H. Development of salbutamol sulphate sustained-release pellets using acrylic polymer and polyvinyl acetate polymer and evaluation of *in vitro* release kinetics. Dhaka Univ J Pharm Sci. 2010;9(2):109-118.
24. Mahajan AN, Pancholi SS. Formulation and evaluation of timed delayed capsule device for chronotherapeutic delivery of terbutaline sulphate. Ars Pharm. 2010;50(4):215-223.
25. Gupta VK, Beckert TE, Price JC. A novel pH- and time-based multiunit potential colonic drug delivery system. I. Development. Int J Pharm. 1993;3:83-91.
26. Radke RS, Gangane PS, Kawtikwar PS, Rai S. Formulation and evaluation of sustained-release system for an effective management of motion sickness. Res J Pharm Technol. 2008;1(4):426-429.

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