Creation and Design of a Metformin Hydrochloride Sustained Release Matrix Tablet and Analysis of Different Factors Influencing Dissolution Rate

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KEYWORDS

Metformin hydrochloride, HPMC K100M, Wet granulation technique, SR Matrix tablet, HPMC K100M, Wet granulation technique, *In vitro* drug dissolution

ABSTRACT

An oral hypoglycemic medication called metformin hydrochloride (MET) lowers baseline plasma glucose levels and increases glucose tolerance in people with type 2 diabetes. The development and optimisation of MET matrix tablets for SR use was the goal of this work. Sodium carboxymethyl cellulose and hydroxyl propyl methylcellulose of various viscosity classes (HPMC K4M, HPMC K15M, and HPMC K100M) were used in the wet granulation process to create the SR matrix tablet of MET. The impact of altering the ratios of polymers was assessed. The drug's physicochemical characteristics were not altered by the excipients employed in this investigation. MET has a low absolute bioavailability and a comparatively short plasma half-life. Patient satisfaction may suffer if bigger doses must be administered two or three times each day. For daily MET dosage, an SR formulation that would sustain plasma levels for 8–12 hours might be adequate. For MET to increase patient compliance and extend its duration of action, SR products are required. The pre-compression and post-compression methods were used to assess the created tablet formulation (F1 to F6). Every parameter's results were found to be within the acceptable range. Stability investigations of the optimised formulations (F6) revealed no appreciable changes in the drug content, physicochemical characteristics, or release pattern. The RP-HPLC and UV methods were used to assay the formulation and pure medication. Using the Basket method and USP apparatus Type I, the in vitro drug dissolving investigation was conducted, and the release processes were investigated. The drug release rate from a dosage form is characterised by the mean dissolution time, which shows that the drug release is degrading the polymer's efficiency. The extended release profile of formulation (F6) after 12 hours in comparison to the marketed formulation is confirmed by the in vitro release studies, which show release up to 94.8% over an extended period of time. The in vitro drug release data were fitted to different release models beyond the potential mechanism of the drug release. To sum up, the creation of MET SR tablets is a smart way to manage the release rate in order to avoid frequent administration and to release the medication for an extended amount of time, keeping the plasma level above the MEC for the appropriate amount of

time. Additionally, pharmacokinetic studies in humans are required to evaluate the effectiveness of the produced formulations.

Introduction

Sustained-release (SR) oral delivery systems are intended to achieve therapeutically effective drug concentrations in systemic circulation over a long period of time [1] in the direction of novel drug delivery of pharmaceutical technology; SR matrix tablets have contributed to a new development [2]. Reservoir type dosage forms are designed to release drug continuously and continuously over a satisfactory prolonged period of time to maintain plasma drug concentration within a therapeutic level [3]. Drug products that reduce the incidence of dosing by altering the rate of drug absorption have been on the market for many years.The matrix system is a release mechanism that regulates and extends the release of a medication that has been dissolved or distributed. Actually, a matrix is a well combination of one or more medications and a gelling agent, such as a hydrophilic polymer [4-6]. An estimated 300 million people are predicted to receive a diabetes diagnosis by 2025 [7, 8]. Patients with Type 2 diabetes who are unable to control their condition with diet and exercise alone are treated with metformin hydrochloride (MET), an oral anti-hyperglycemic medication [9]. Since MET does not cause weight gain like insulin and sulfonylureas do, it is the first choice for treating type 2 diabetes. It is also used to lower insulin resistance in obese individuals with type 1 diabetes [10]. MET is a hydrophilic, biguanide, BCS class-III medication that is chemically known as N, N-dimethyl imidodicarbonimidic diamide hydrochloride [11,12]. By decreasing intestinal absorption of glucose, decreasing hepatic gluconeogenesis, and increasing glycogenesis, lipogenesis, and glucose uptake by adipocytes and muscle cells, it improves glucose tolerance by lowering both basal and postprandial glucose [9, 13].A highly water-soluble medication (0.5 g/ml), MET is taken up to 2.5 g/day in three different dosages with meals to reduce the risk of gastrointestinal adverse effects like diarrhoea, nausea, anorexia, and abdominal pain [14]. Food, however, also reduces the drug's absorption [15]. Successful treatment may be hampered by the occurrence of side effects and the requirement for three times-daily dosing [16]. Unlike other biguanide medications as buformin and phenformin, MET does not cause lactic acidosis [17].Additionally, MET does not bind to plasma proteins, and the kidneys' active tubular secretion is the primary method by which the drug is eliminated unaltered. Higher plasma concentrations for the latter were observed in the steady-state following a 500 mg single dosage of an immediate and modified release MET [18]. A flip-flop model and approximately 61% bioavailability are shown by a single immediate release dosage of MET. Following a single oral 500 mg immediate release dose, the tmax and t1/2 of MET were approximately 2 and 2.6 hours, respectively [19]. However, compared to the immediate release formulation, a 250 mg sustained-release MET pellet demonstrated a 165% increase in bioavailability, a tmax of 7.3 hours, and a t1/2 of 8.3 hours. As a result, tmax relied on the dose.with example, with an immediate release dosage of 0.5 and 1.5 g, the tmax was 2.2 h and 1.5 h, respectively [17]. Additionally, around 20% of the single rapid release dose is recovered in faeces, suggesting limited absorption in the colon's terminal segment and saturable absorption [20–22]. Because of this issue, a customised release device is required in order to adjust the release and, consequently, the absorption of MET. As a result, a redesigned release method makes it possible to achieve the best possible treatment, enhance patient safety and compliance, and lower the frequency of adverse effects, dose dumping, and plasma variations. To prepare hydrophilic matrixes for a once-daily controlled release, formulations of MET, Sod CMC, HPMC, gelatin, aerosil 200, and magnesium stearate were prepared by wet granulation and then tableting in the current investigation. For a long duration (24 hours), this offers a lower yet regulated medication concentration. The matrices' subsequent release kinetics and dissolution characteristics were also assessed.

Materials and methods

Materials

A gift sample of metformin HCl was obtained from Arbro Pharmaceuticals Ltd. in New Delhi, India. Merck Ltd., India, provided acetonitrile, methanol, and orthophosphoric acid of HPLC grade. We bought sodium hydroxide, cobalt (II) chloride, ammonium thiocynate, and ammonium di-hydrogen phosphate from S.D. Fine Chem. Ltd. in Mumbai. We bought magnesium stearate, sodium CMC, and hydroxy propyl methyl cellulose from Himedia Chem. Lab in Mumbai. We bought sodium alginate, magnesium stearate, and starch from Loba Chemicals Pvt. Ltd. in Mumbai. We bought the Riomet 1000 MG SR Tablet (Ranbaxy Lab. Ltd.) at the neighbourhood market. The remaining ingredients were all analytical grade. In-house triple-distilled water was produced.

Methods

Drug excipient compatibility studies

Using the Jasco FTIR-410, KBr pellet technique IR spectrum measurements were performed on the drug and excipient. This approach involved mixing the medication and KBr at a 1:100 ratio. These combinations were then compressed into a pellet. The KBr pellet method was used to record the FTIR spectra in the 400–4000 cm-1 range.Pure drug, pure excipients, and drug plus excipients all had their spectra recorded.

Preformulation studies

Melting point

The open capillary method was used to find the melting point of MET. A capillary containing the drug sample was put inside a melting point device. The temperature at which the medication melted was recorded after the tube was heated.

Loss on drying

The weighing bottle was allowed to cool after being dried in the oven for thirty minutes. With a cover, the bottle was precisely weighed. After removing the cap, 100 mg of the sample was added to the bottle and weighed. The material was then heated for three hours at 105°C. After that, the bottle was taken out and put inside the desiccators. After allowing the material to come to room temperature, it was weighed and calculated. There should be no more than 0.5 mg between consecutive weights.

The following formula is used to determine the drying loss:

$$\% \text{ LOD} = \frac{(W2 - W3)}{(W2 - W1)} \times 100$$

Where, W1 = Weight of empty weighing bottle
W2 = Weight of weighing bottle + sample
W3 = Weight of weighing bottle + dried sample

Determination of λ max of drug by UV spectrometer

After precisely weighing 100 mg of MET, it was transferred to a 100 ml volumetric flask. To get a stock solution of 1000 µg/ml, it was dissolved in a sufficient volume of phosphate buffer pH 6.8 and the volume was increased to 100 ml with phosphate buffer pH 6.8. The aforementioned stock solution was diluted with phosphate buffer pH 6.8 to a concentration of 6 µg/ml. The resultant solution was then scanned between wavelength ranges of 200 nm and 400 nm using a double-beam UV-visible spectrophotometer (Unicam Helios UV 052514).

Calibration curve of metformin hydrochloride in phosphate buffer pH 6.8

A standard curve covering concentrations between 1 and 10 µg/ml was created. A stock solution was made for the calibration curve preparation by dissolving 100 mg of precisely weighed MET in 100 millilitres of phosphate buffer with a pH of 6.8. Additionally, 10 millilitres of this solution were pipetted into 100 millilitres of volumetric solution and diluted with 100 millilitres of phosphate buffer (pH 6.8). To obtain 1–10 µg/ml of etophylline and theophylline, respectively, pipette 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1 ml into a series of 10 ml volumetric and volume was increased up to 10 ml with phosphate buffer pH 6.8. In a

UV spectrophotometer, the optical density values of the resultant solutions were measured at 233 nm.

Calibration curve of metformin hydrochloride in water

A 100 ml volumetric flask was filled with precisely weighed 100 mg of MET. To create a stock solution of 1000 µg/ml, it was dissolved in a sufficient volume of water and the volume was increased to 100 ml. Serial dilution in water is used to prepare 1–10 µg/ml from stock solution conc. A standard plot was created using the data from the measurement of the diluted solution's absorbance at 233 nm. Linear regression analysis was used to get the correlation coefficient.

Micromeritic properties[23]

Angle of repose

A funnel that is fixed with its tip at a specific height, h, and maintained 2 cm above graph paper that is set on a level horizontal surface is used in the fixed funnel and freestanding cone procedures. The following formula can be used to calculate the angle of repose:

θ = tan-1 (h/r)

Where, $\theta$is the angle of repose, h is height of pile; r is radius of base of the pile.

Bulk Density (BD)

Each formula's precisely weighed powder blend was added to a measuring cylinder after being gently shaken to break up any agglomerates that had formed. Bulk volume was determined by measuring the volume occupied by the powder. The following formula was used to calculate the BD of powder mixtures.

Bulk density = Total weight of powder/Total volume of powder

Tapped bulk density (TBD)

Each formula's precisely weighed powder blend was put into a measuring cylinder after being gently shaken to break up any agglomerates that had developed. The tapped volume was obtained by tapping the measuring cylinder until no more volume change was seen. The following formula was used to calculate the TBD of powder mixtures.

TBD = Total weight of powder/Total volume of tapped Powder.

Carr's compressibility index

The blend's bulk density (BD) and tapped density were used to compute the Carr's compressibility index. A 10 ml measuring cylinder was filled with 2 g of blend from each formulation. After measuring the initial bulk volume, the cylinder was allowed to tap from a height of 2.5 cm. The blend's tapped volume was measured using a tapped frequency of 25 ± 2/min. The bulk volume and tapped volume were used to compute the BD and tapped density. To determine Carr's compressibility index, the following formula was used.

Carr's compressibility index (%) = [(Tapped density-Bulk density) ×100]/Tapped density.

Hausner's ratio

Hausner's ratio can be determined by the following equation.

Hausner's ratio = TBD / BD

Where, TBD -Tapped bulk densities & BD- bulk densities

Physical Compatibility Studies

The medicine is in close contact with one or more excipients in the tablet dosage form; these excipients may have an impact on the drug's stability. Therefore, the formulator can choose the right excipients with the use of knowledge on drug-excipient interactions. For known medications, this information might already be available. The pre-formulation scientist must produce the necessary data for novel medications or excipients. According to the formulas chosen for the tabletting, MET thoroughly mixed with the excipients. A tiny amount of this combined powder was then stored in a stability chamber at room temperature and 40 ± 2 oC/75 ± 5 RH in a cleaned and dried vial or vials. For seven days, visible physical observation has been conducted.

Assay of metformin hydrochloridepowder (HPLC method)

The HPLC method is used to assay or determine the MET's percentage purity. A Perkin-Elmer 200 (Autosampler) with a UV/VIS dual detector made up the HPLC apparatus used for

analysis, and Total Chrom software was used to analyse the data produced. Lichrosphere (C-18) Column (250 X 4.6 mm, 5µm) was used for chromatographic separation. A RP-C18 analytical column was used for the chromatographic analysis, which was carried out at room temperature. The mobile phase consisted of a 17 g/l solution of ammonium dihydrogen phosphate that had been adjusted to pH 3.5 with phosphoric acid and was isocratically eluted at a flow rate of 1 ml/min. For every sample run, a tiny sample volume of 20 µl was fed into the HPLC apparatus. The entire analysis period for MET was five minutes, and the chromatogram was observed using UV detection at a wavelength of 218 nm. It was determined that the RT of MET was 3.32+0.5 min. The assay was calculated using the formula and the graph that was obtained.

$$\% \text{ purity} = \frac{\text{Ave. sample area}}{\text{Ave. standard area}} X \frac{\text{Standard dilution}}{\text{Sample dilution}} X \frac{\text{Standard purity}}{100} X 100$$

Selection of target release profile

The Riomet 1000 MG SR (Ranbaxy Lab. Ltd.) Tablet commercial product's release profile is considered a standard profile and an innovator sample.

Preparation of tablets

Six formulations in all were made using the wet granulation process. After properly mixing the necessary amounts of the medication, polymers, and diluents, enough granulating agent (starch + gelatin) was gradually added to achieve dough mass. After being sieved through 10 mesh, the bulk was dried for two hours at 50º. After passing through 16 different processes, the partially dried granules were dried for an additional two hours. The final dry granules were combined with 1% magnesium stearate and 2% talc. On a 16-station automatic Cadmach tablet punching machine, tablets were squeezed using 22 mm ×10 mm caplet concave shaped punches to achieve a goal weight of 1400 mg, maintaining the hardness of each tablet at a compression force of 1.5 tonnes.between 13-15 kg /cm^2**.**The amount of the active component in each formulation is equal to 1000 mg of MET. Table 1 displays each tablet's composition.

Table 1: Composition of metformin hydrochloride sustained release matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Metformin HCl	1000	1000	1000	1000	1000	1000
Sod. CMC	100	100	100	100	100	100
HPMCK-100	-	-	200	150	200	150
HPMC K-15	100	150	-	-	50	100
HPMC K-4	50	50	-	50	-	-
Talc	10	10	10	10	10	10
Starch	20	20	20	20	20	20
Gelatin	5	5	5	5	5	5
Aerosil 200	10	10	10	10	10	10
Mg Stearate	10	10	10	10	10	10
Theoretical wt	1305	1355	1355	1355	1405	1405

In order to achieve the same drug release profile from the sustained release dosage form of MET tablets as the innovator sample of Ranbaxy (RIOMET SR tablets), the theoretical weight is modified by varying the proportions of various polymers while maintaining a constant mixture of all ingredients.

Evaluation of tablets [24]

Weight Variation

Twenty pills were chosen at random, weighed, and their average weight was compared to the weight of each individual tablet. The weight variation as a percentage was computed. In accordance with Indian Pharmacopoeial specifications, tablets weighing between 80 and 250 mg on average should have a percentage deviation of no more than ±7.5%, while tablets weighing more than 250 mg should not have a departure of more than ±5%.

Friability Test

Twenty tablets were chosen at random, and after having their surfaces scrubbed with a hair brush to get rid of any dust that might have adhered, they were weighed and put in the friabilator (Electro Lab USP EF-2). After that, they were free to fall 100 times from a height of 6 inches while moving at 25 rpm for four minutes. After that, the tablets were weighed and powdered. Weight loss as a percentage was calculated for any weight loss brought on by fracture or abrasion. Each formulation's replicate determinations were averaged. The following formula was used to determine friability.

$$F = 100\left[\frac{W_0 - W}{W}\right]$$

F = Friability, W = Final weight, Wo = Initial weight

Hardness Test

The Monsanto Hardness tester was used to measure the tablets' hardness. The unit of measurement is kg/cm². From each formulation, ten tablets were chosen at random, and the mean and standard deviation were computed..

Uniformity of thickness

For tablet size consistency, tablet thickness and diameter were crucial. A computerised vernier calliper was used to measure the diameter and thickness.

In vitro dissolution studies

USP type I (basket) apparatus was used to perform in vitro drug release investigations from the produced MET SR matrix tablets at 37°C± 0.50C and 100 rpm. 900 millilitres of phosphate buffer with a pH of 6.8 were utilised as the dissolution media. Remove the necessary amount of sample at the designated time, measure the absorbance using a UV-Visible Spectrophotometer (Unicam Helios UV 052514), and compute the percentage release.

***Kinetics of drug release*[25]**

Drug release data can be graphically treated to evaluate the order of release. If the drug release follows zero order (i.e., concentration independent release), the plot of the percentage of drug left vs time would be linear.If the drug release is first order (i.e., concentration dependent release), then the log of the percentage of drug left over time would be linear.

The linear equation for zero order drug release plot is:

$C_t = C_0 - Kt$

Where, C_t = concentration remaining at time t, C_o = original concentration, t = time, K = release rate

The linear equation for first order release plot is

$$\log C = \frac{\log C_0 Kt}{2.303}$$

As the name suggests, a matrix device is made up of a medication evenly distributed across a polymer matrix. According to this hypothesis, the drug dissolves first in the outer layer that is exposed to the bathing solution before diffusing out of the matrix. As the process progresses, the interface between the solid medication and the bathing solution moves inward. The pace at which drug particles dissolve within the matrix must obviously be significantly quicker than the rate at which dissolved drug diffuses out of the matrix in order for this system to be diffusion regulated. The following presumptions are included in the mathematical model's deviation to explain this system.

1) A pseudo study state is maintained during drug release.
2) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
3) The bathing solution provides sink conditions at all times and

4) The diffusion coefficient of drug in the matrix remains constant (ie. no change occurs in the characteristics of the polymer matrix).

A polymer that swells in water is present in hydrophilic matrix tablets. The tablet surface gels upon coming into touch with stomach juices, preventing more liquid from penetrating the tablet core and acting as a layer that regulates pace. The drug diffuses out through the gelled layer after dissolving at the gel core contact. In addition to erosion, drug diffusion through the swelling, hydrated matrix and water penetration via a gel layer created by hydrating the polymer limit drug release. The polymer ratio determines how much release is controlled by diffusion or erosion. The Hopfenberg mechanism of release from the erodable matrix has been described. A straightforward statement that characterises release from erodable is

$$\left(1-\frac{Mt}{M}\right)^{1/3} = 1 - Kt$$

Where, Mt = mass of drug release at time t, M = mass release at the infinite time, K = rate of erosion, t = time

Thus a plot of $[1 - Mt / M]^{1/3}$ versus the time will be linear. If the release of drug from the matrix is erosion controlled.

In order to ascertain whether the drug release occurs by diffusion or erosion, the drug release data was subjected to following modes of data treatments.

1) Amount of drug release versus square root of time (Higuchi Plot).
2) $[1 - Mt / M]^{1/3}$ versus time.

Determination of drug content in tablets

The sustained formulation's twenty pills were weighed and ground into a fine powder. A 1000 mg MET powder was weighed, diluted in 100 ml of water, sonicated for 10 minutes, and then filtered using Whatmann filter paper No. 42. Lastly, a serial dilution process was used to create various tablet sample concentrations. Using an HPLC technique and a UV/visible spectrophotometer set at 233 nm, the total amount of medication in each tablet was analysed spectrophotometrically. There is no possibility of detecting any degradation products because we have opted for HPLC.

Accelerated stability studies

To observe the impact of temperature and relative humidity on the chosen formulation (F6), an accelerated stability study was conducted. The formulation was kept at 40°± 2°C in airtight high density polyethylene bottles for three months at a relative humidity of 75±5%. Every month a physical examination was conducted.

Gel layer dynamics

The tablet is permeated with water after hydrophilic matrix former matrices were hydrated in cobalt (II) thiocynate solution (6.8 gm cobalt chloride and 4.3 gm ammonium thiocynate in 100 ml water). When diluted, cobalt (II) thiocynate produces a pink hue and combines with amino group-containing chemicals to form a blue complex. As a result, the hydrated portion of the tablet that contained etophylline and theophylline turned blue, while the drug-free hydrated portion looked pink because of cobalt (II) thiocynate. The off-white hue of the matrix's unhydrated glassy core persisted. Figure 1 shows the intersection of these zones, which represent the many fronts seen in a hydration matrix.

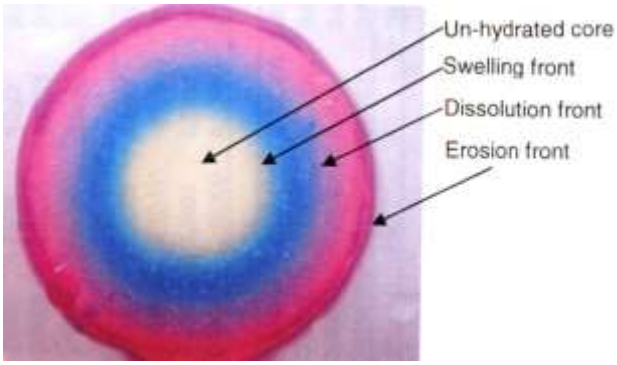


Figure 1: Hydrophilic matrix containing drug after hydration for 8 hours in cobalt (II) thiocynate solution. The white region is the unhydrated core, blue region is the hydrated region-containing drug and pink region is the drug free hydrated polymer.

Mass degree of swelling

After being pre-weighed and given five hours to equilibrate with 100 millilitres of water, the final formulation tablet is taken out, blotted with tissue paper, and weighed [26]. The following formula was then used to determine the mass degree of swelling:

Q = mass of the swollen gel / mass of the dry powder (tablet)

Factors studied to match the release profile

To match and achieve the intended drug release rate, a number of parameters that impact the rate of dissolution from tablet dosage forms are examined, including the following:

Polymer viscosity

In two formulations, the same percentage (30%) of two distinct viscosity classes of a hydrophilic matrix former HPMC K 100M and K 15M were utilised. Dissolution studies are conducted on X and Y, which have lower and greater viscosity classes, respectively. It is widely acknowledged that greater viscosity grades of HPMC polymer result in slower medication breakdown from tablets. High viscosity polymers produced more viscous gel layers, which caused the drug to diffuse more slowly, and it also took longer to reach the disentanglement concentration at the tablet surface, which translates into increased resistance to surface erosion [27, 28].

pH challenge studies

Using various dissolve media, including 0.1N HCl, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer, and pure water, the pH challenge study on the dissolution of the final chosen formulation is carried out up to 16 hours at intervals of 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 16 hours.

Results and Discussion

The powdered pill, excipients, and pure medication all had FTIR spectra collected in the 400–4000 wavenumber (cm-1) range. There are no peaks that obstruct the primary drug peaks. Table 2 provides a summary of the many peaks that were found.

Table 2: FT-IR peaks of various components

Name of component	**Peaks Obtained (Wavenumber, cm $^{-1}$)**
Drug (MET)	1622.80, 1566.88, 1474.31, 1447.31, 1417.42, 1166.72, 1060.66, 935.31, 799.35, 736.67, 636.39, 575.65, 539.01, 419.44
Tablet (MET with excipients)	1625.70, 1567.84, 1474.31, 1448.28, 1417.42, 1166.72, 1062.59, 937.23, 800.31, 736.67, 635.43, 583.36, 540.93, 420.41
HPMC K- 100 M	1653.66, 1457.92, 1376.93, 1060.66, 945.91, 567.93

HPMC K- 15 M	1771.30, 1733.69, 1716.34, 1698.02, 1652.70, 1558.20, 1540.85, 1520.60, 1507.10, 1456.96, 1375.00, 1339.32, 1062.59, 945.91, 568.32, 418.48
CMC Sodium	1617.02, 1419.35, 1327.75, 1056.80, 472.47

Wet granulation was used to manufacture the matrix tablets. The most important step in creating a matrix tablet sustained release dosage form is granulation. An essential component of matrix tablet formulation is the granules' characteristics, which must be assessed to guarantee the correct formulation of the tablet dosage form. All formulations' granules underwent a number of pre-compression analyses, including Hausner's ratio Table 3, bulk and tapped density, compressibility index, and angle of repose.

Table 3:Results of physical evaluation of Pre-compression blend

Formulations	Angle of repose (degree± SD)	Bulk Density (g/ml± SD)	Tapped Density (g/ml± SD)	Carr's Index (%± SD)	Hausner's ratio (%± SD)
F1	27.31±0.43	0.423±0.33	0.531±0.17	20.33±0.11	1.25±0.03
F2	27.62±0.04	0.382±0.02	0.481±0.09	20.58±0.18	1.26±0.06
F3	27.01±0.02	0.396±0.16	0.505±0.03	21.58±0.03	1.27±0.03
F4	27.17±0.11	0.431±0.25	0.532±0.12	18.98±0.11	1.23±0.07
F5	26.59±0.14	0.436±0.90	0.546±0.04	20.14±0.22	1.25±0.02
F6	26.77±0.11	0.420±0.07	0.517±0.20	18.76±0.17	1.22±0.10

Physical characteristics such as hardness, thickness, friability, and drug contents were assessed for each of the formed tablets (F1–F6) that contained the active ingredients (Table 4). For tablets weighing more than 250 mg, the pharmacopoeial limit of percentage deviation in a weight variation test is ±5%.Less than 1% was the average percentage variation of all the pills, which was judged to be within the limit. It was determined that the tablets' hardness was consistent and appropriate throughout batches. Additionally, the medication content was confirmed to be consistent and within the recommended range. Friability is another indicator of tablet strength. Generally speaking, conventional compressed pills that lose less than 1% of their weight are acceptable. The friability test results were likewise found to be within the acceptable range.

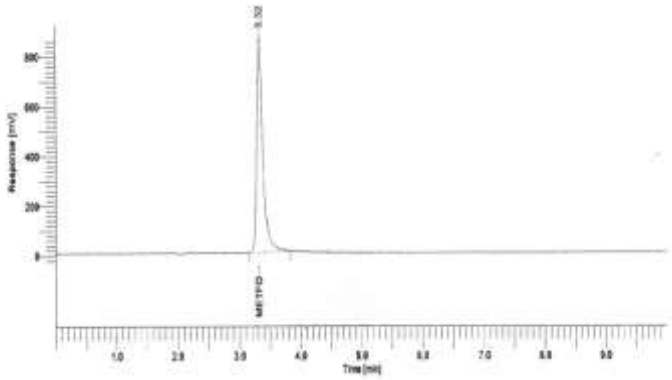
Table 4:Physical properties and drug content of SR matrix tablet

F code	Weight Variation (%)n=20	Thickness (mm) n=10	Hardness (kg/cm^2) n=6	Friability (%) n=10	% Drug Content n=3
F1	0.95	7.72±0.12	9.5 ± 0.14	0.37±0.24	99.03 ± 0.12
F2	0.89	7.76±0.24	9.4 ± 0.11	0.42±0.05	98.09 ± 0.12
F3	0.54	7.80±0.26	9.6 ± 0.07	0.38±0.12	98.02 ± 0.03
F4	1.01	7.69±0.33	9.4 ± 0.15	0.51±0.03	97.03 ± 0.12
F5	0.96	7.76±0.54	9.4 ± 0.08	0.47±0.22	96.09 ± 0.12
F6	0.45	7.72±0.09	9.6 ± 0.21	0.42±0.54	99.03 ± 0.12

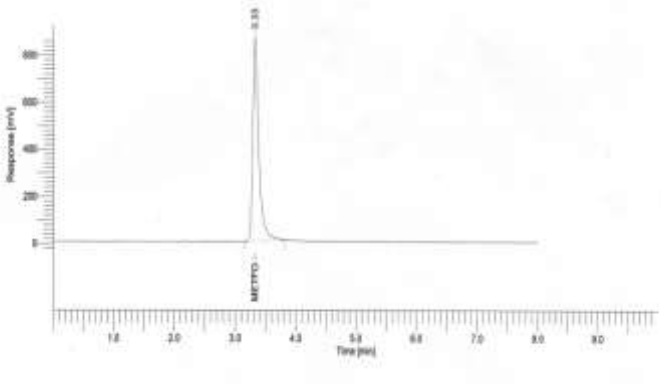
Assay was carried out for finally selected formulation (F6) and the result was found to be 102.7% MET by HPLC Table 5& Figure 2.

Table 5: HPLC Chromatographic parameter of pure drug and formulation (F6)

Material	Average area	Height	RT	% Purity
Std. MET	6015500	870891	3.32	102.7
Test Sample	5958353	862031	3.33	



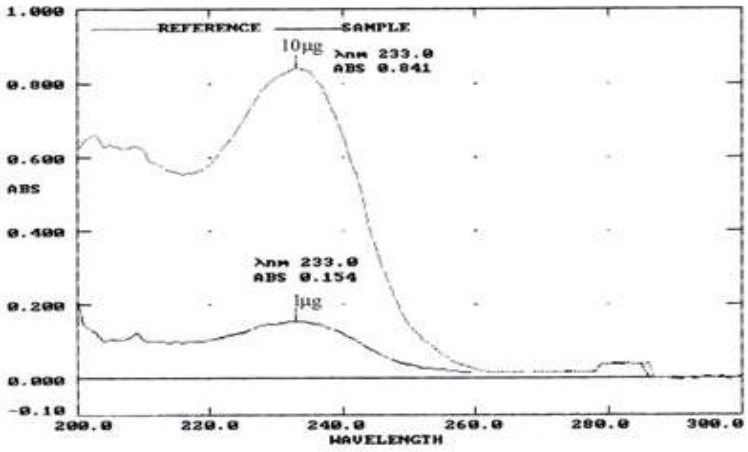
(A)



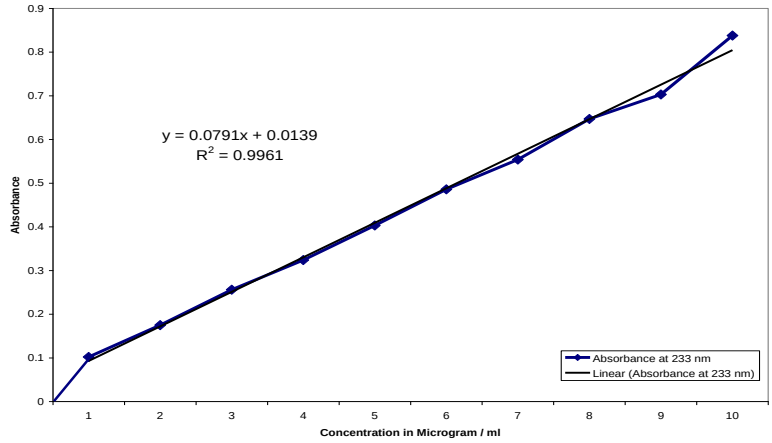
(B)

Figure2: Representative chromatogram of (A) Standard Drug (B) Formulation (F6)

It was discovered that the drug's maximal absorption in pH 6.8 phosphate buffer and water was 233 nm. Regression coefficient r2 values for the medication were found to be 0.996 in water and 0.999 in pH 6.8 phosphate buffer, with concentrations ranging from 1µg/ml to 10µg/ml. Figure 3.



(A)



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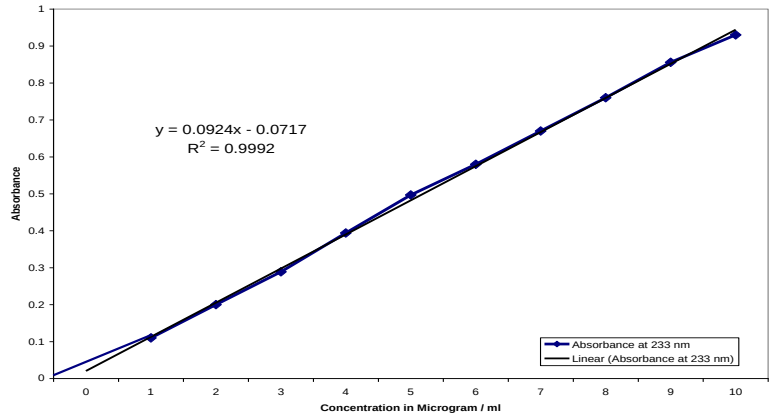


(C)

Figure 3:UV Graph of pure drug at high & low conc. (A), calibration curve of drug in water (B), calibration curve of drug in phosphate buffer pH 6.8

We focused on the innovator product's release profile because the main goal of the project was to create a generic version of the innovator product. USP Apparatus I was used to develop the drug release profiles for the marketed formulation (Riomet 1000 MG SR Tablet) at 100 rpm in phosphate buffer 6.8 pH. Dissolution tests on prototype formulations have been conducted under the same conditions (Table 6 and Figure 4).

Table 6: % Drug release of marketed formulation

Time (hours)	**Limit (% drug release)**	**Observed value**
1	20-40	35.7
4	50-70	61.2
8	75-95	85.7
12	NLT 85	94.7

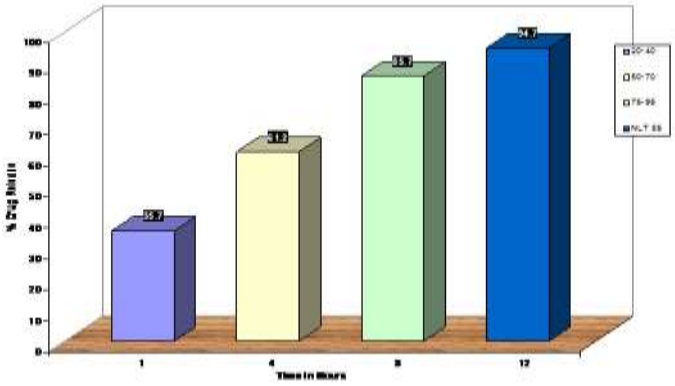


Figure 4: Release profile of market tablet (Riomet 1000 MG SR Tablet)

The results of mass degree of swelling properties of matrix tablet formulation are given in Table 7.

Table 7: swelling properties of matrix tablet formulation

Formulation	Mass degree of swelling (Q)
1.	1.8735
2.	1.8625
3.	1.7649

Hydrophilic matrix former combinations were used to create a variety of batches. The release profiles from the majority of the combinations were fairly similar. However, the formulation F6 is being released near Table 8, the innovator.

Table 8: Data of In-Vitro drug release studies of sustained-release matrix tablets of MET and marketed formulation

Time (Hr)	F5	F6	Innovator
1	32.0	35.1	35.7
4	68.7	62.3	61.2
8	92.7	87.9	85.7
12	100.2	94.8	94.7

It shows that the medicine releases from the tablet more quickly when 0.1N HCl is used as the medium than when other media are used, and more slowly when water is used as the medium than when buffer solutions are used. Table 9 shows that the medication release rates for the 6.8 and 7.4 pH phosphate buffer solutions are nearly identical. Based on the graph, it was determined that the formulation produced a much faster release at pH 1.2 (0.1N HCl) but did not significantly alter the dissolving profile at pH 6.8, 7.4, or water. Figure 5's pH-dependent swelling behavior provides an explanation for this.

Table 9:Data of drug release Profile in different dissolution medium (F6)

Time (Hour)	0.1 N HCl	Phosphate Buffer 6.8 pH	Phosphate Buffer 7.4 pH	Water
0.5	30.1	25.7	26.1	25.9
1	36.1	35.2	35.8	35.0
2	55.9	47.6	48.3	48.5
3	66.8	61.0	62.1	61.6
4	72.7	65.5	64.8	65.3
6	77.3	82.1	83.2	78.9
8	92.4	90.6	88.9	86.9
12	100.0	98.5	97.6	95.9
16	95.0	101.5	100.8	96.9

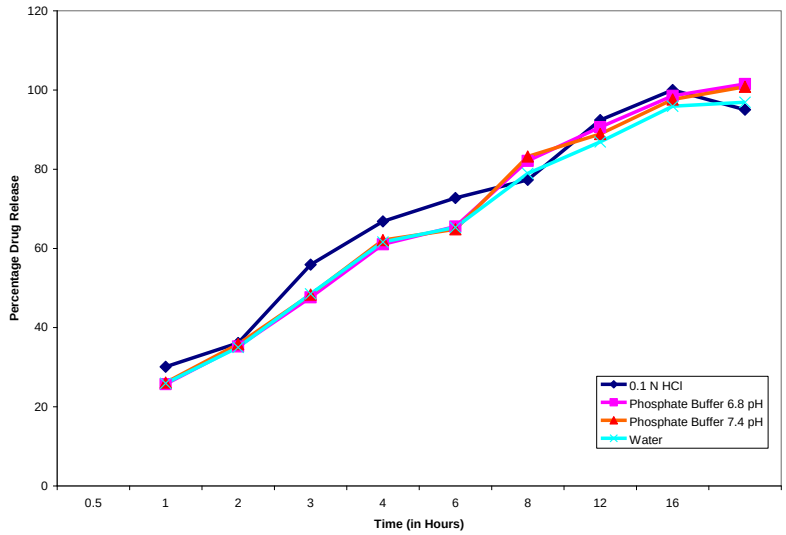


Figure 5: Comparative chart of % drug dissolved in different dissolution medium

Formulation matrices were shown to swell considerably less in the acidic media. It was thought that the polymer-drug ionic interaction had a significant role in regulating the drug's release from the matrices. Figure 6.

0.1 N HCL

Phosphate Buffer 6.8 pH

Water

Phosphate Buffer 7.4 pH

Figure 6: Showing swelling characteristics of matrix tablet in different dissolution medium

It was discovered that the formulations' dissolving profiles varied from batch to batch. However, it was discovered that the F6 formulation had the most desired release profile. When compared to the innovator sample of Riomet 1000 mg SR Tablet, the release of formula F6 was the most reliable, accurate, and comprehensive. Table 12 shows that the F6 formulation for the matrix tablet containing HPMC K 100, HPMC K 15 has excellent drug release kinetics based on the evaluation of the dissolving research. Because the medication is soluble, its release from the matrix tablet occurs by diffusion. Additionally, the F6 formulation has favorable micromeritic and physical characteristics. Figure 7-9, Table 10.

The F6 formulation was selected for further experiment.

Table 10:Summary of drug release kinetics of formulations (F6)

Time (hr)	**$\sqrt{\text{Time}}$**	**Cumulative % release**	**Amount of drug release**	**% of drug remained**	**Log % of drug remained**	**$\left(1-\frac{M_t}{M}\right)^{1/3}$**
0.5	0.707	25.7	257	743	2.87	0.906
1	1	35.6	356	644	2.81	0.864
2	1.414	45.7	457	543	2.73	0.816
3	1.732	58.2	582	418	2.62	0.748
4	2.0	65.3	653	347	2.54	0.703
6	2.449	78.2	782	218	2.34	0.602
8	2.828	86.6	866	134	2.13	0.512
12	3.464	95.2	952	48	1.68	0.363
16	4.0	99.8	998	2	0.30	0.126

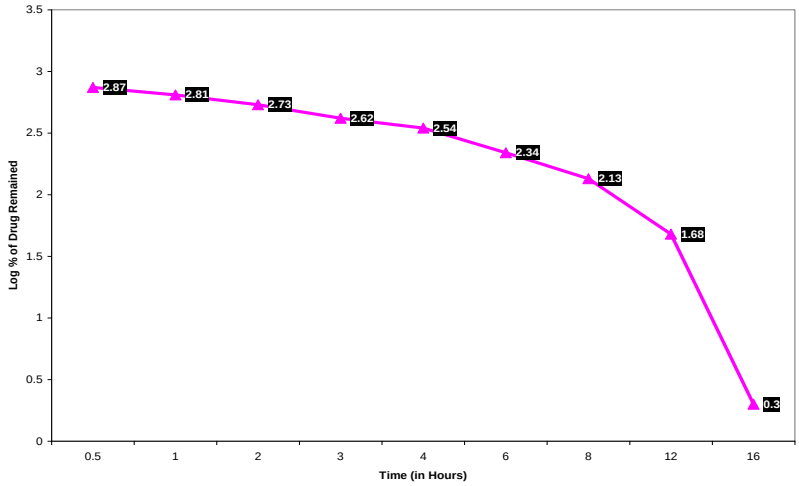


Figure 7: Showing relationship between log % drug remaining Vs Time (y = -0.2525x + 3.4869, R^2 = 0.7227)

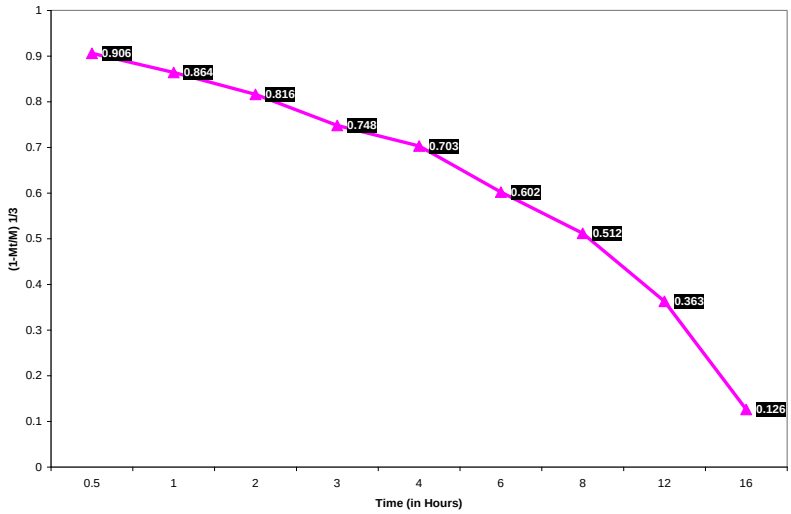


Figure 8 Showing relationship between $(1-Mt/M)^{1/3}$ Vs Time (y = -0.0896x + 1.0748, R^2 = 0.9184)

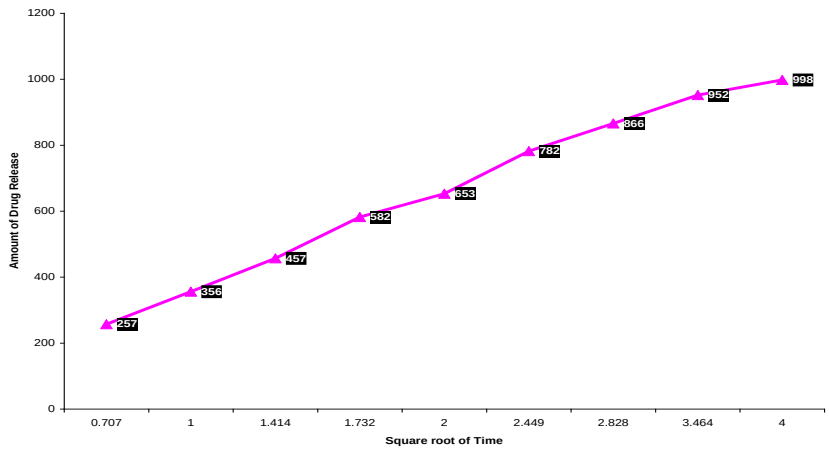
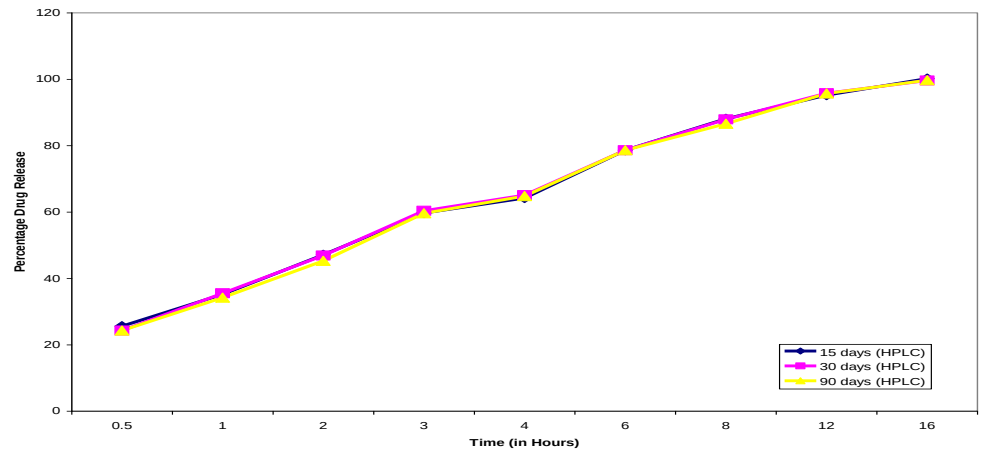


Figure 9 Showing relationship between Amounts of Drug Release Vs Square root of time

In order to conduct stability studies, the tablets were stored in a stability chamber for 90 days at room temperature (250 C ± 20C / 60% ± 5% RH) and at an accelerated temperature (400 C ± 20C / 75% ± 5% RH). The F-6 formulation was found to be stable at the tested temperature, as shown by the results of stability studies that showed no change in physical appearance, hardness, drug content, or in-vitro dissolution profiles. Additionally, the obtained IR spectrum showed no incompatibility.

Table 11:Comparison of dissolution data of stability samples at accelerated condition

Time (Hr)	**Initial (0 days)**	**15 days (UV)**	**15 days (HPLC)**	**30 days (UV)**	**30 days (HPLC)**	**90 days (UV)**	**90 days (HPLC)**
0.5	25.7	26.2	25.6	24.6	24.3	24.6	24.3
1	34.2	35.1	35.2	35.3	35.5	34.6	34.2
2	47.6	46.7	47.1	47.3	46.9	45.6	45.3
3	59.3	60.2	59.7	60.2	60.4	60.1	59.6
4	65.2	65.3	64.2	65.4	65.1	64.8	64.8
6	78.2	78.7	78.6	78.2	78.6	78.2	78.6
8	88.6	87.9	88.1	88.5	87.9	87.1	86.6
12	94.9	94.8	95.2	95.3	95.8	95.3	95.7
16	101.5	100.8	100.2	100.6	99.6	100.2	99.7



. **Figure 10:**Comparison of dissolution data of stability samples at accelerated condition by HPLC

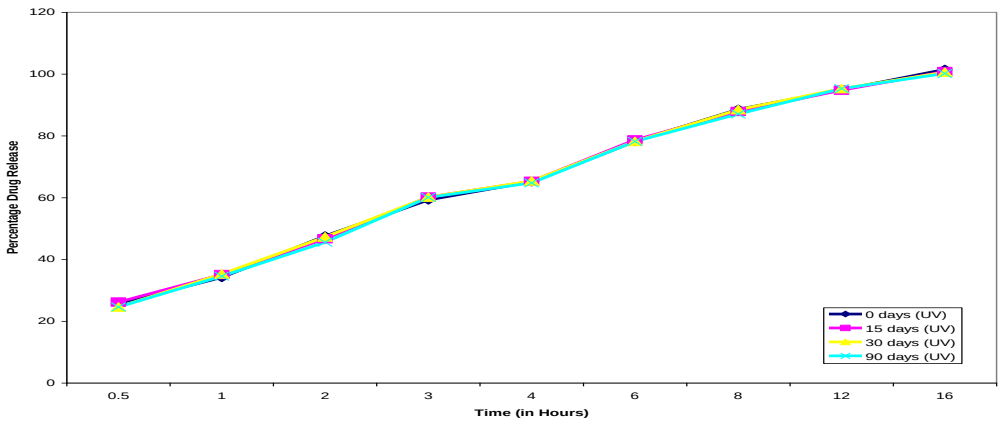


Figure 11: Comparison of dissolution data of stability samples at accelerated condition by UV

Table12:Comparison of dissolution data of stability samples at room temperature

Time (Hr)	Initial (0 days)	15 days (UV)	15 days (HPLC)	30 days (UV)	30 days (HPLC)	90 days (UV)	90 days (HPLC)
0.5	25.3	26.0	25.3	24.9	24.5	25.2	25.3
1	34.4	35.3	35.6	36.2	36.5	35.6	35.2
2	47.6	46.2	46.8	47.3	47.9	46.6	46.3
3	59.6	60.5	60.9	59.2	59.4	60.1	59.6
4	65.5	65.8	65.2	64.9	65.1	64.2	65.8
6	78.7	78.9	78.2	79.2	78.6	79.2	79.6
8	88.9	87.2	88.1	88.5	87.9	88.1	87.6
12	95.3	94.0	95.6	96.2	95.8	96.3	95.7
16	100.5	101.8	100.2	100.6	99.2	99.7	99.2

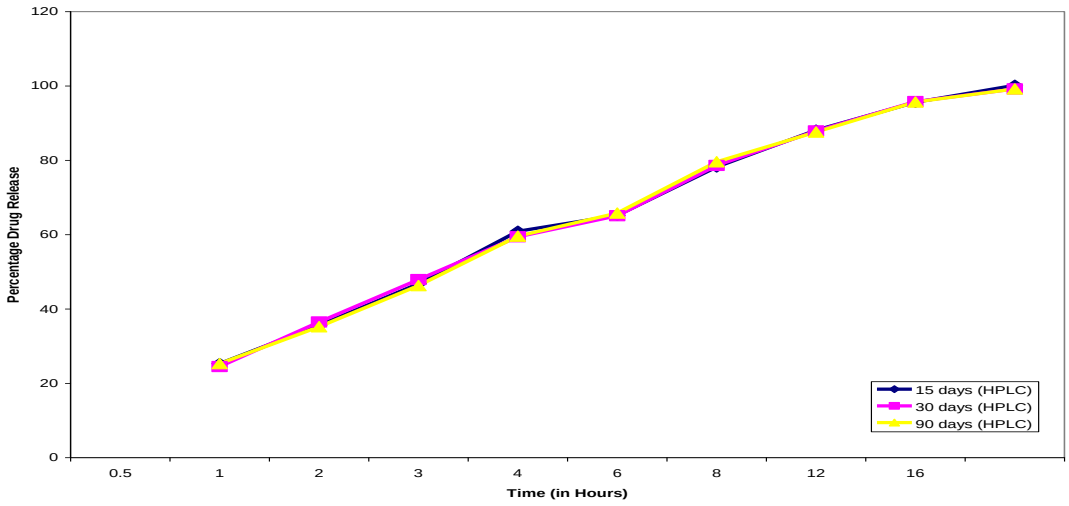


Figure 13: Comparison of dissolution data of stability samples at room temperature by HPLC

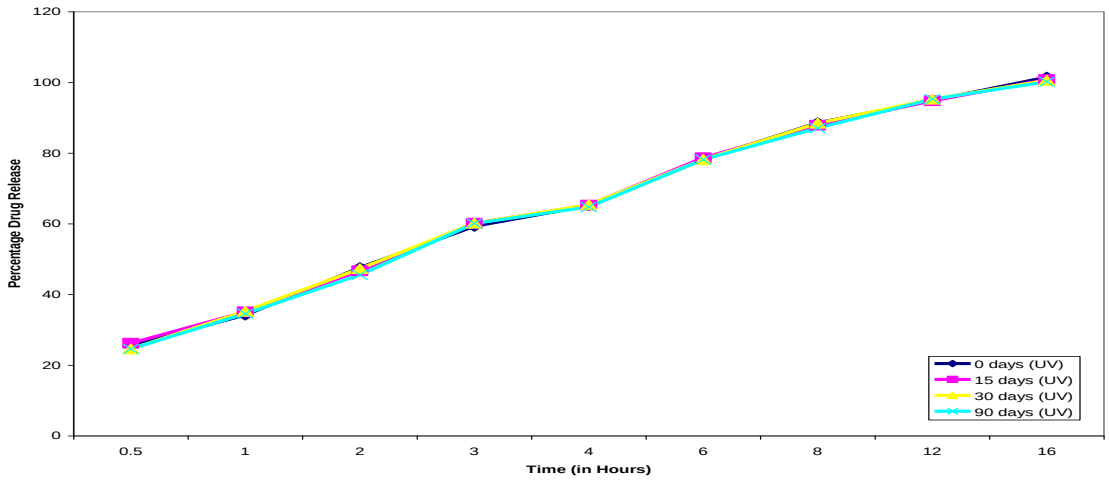


Figure 14: Comparison of dissolution data of stability samples at room temperature by UV

Conclusion

The way the medication, polymers, and medium interacted determined the size of the release rate and release sequence. The goal of the current study was to create a 1000 mg sustained release once-daily formulation that would effectively release the medication for 16 hours. Wet granulation was used to create SR matrix tablets of MET. According to an in vitro investigation, formulation F6 was a good fit for an extended release formulation. The final formulations that were chosen demonstrated anomalous diffusion of non-fickian transport and were shown to have almost zero to zero order drug release, controlled by diffusion via a swelling matrix and matrix erosion. Based on the results, it can be said that formulation F-6 has met the goals of long-term drug release, patient convenience, and cost effectiveness when taken as a single daily dose. It also seems to be evaluated further by performing long-term stability testing and bioavailability studies in human volunteers.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this paper

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