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# Formulation Development of Sustained Release Matrix Tablet Containing Metformin Hydrochloride and Study of Various Factors Affecting Dissolution Rate

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**Abstract** **Original Research Article**

Metformin hydrochloride (MET) is an oral hypoglycaemic agent which improves glucose tolerance in patients with type 2 diabetes and diminishes basal plasma levels of glucose. The aim of this study was to develop and optimize MET matrix tablets for SR application. The SR matrix tablet of MET was prepared by wet granulation technique using Sodium carboxymethyl cellulose and hydroxyl propyl methylcellulose of different viscosity grades (HPMC K4M, HPMC K15M, and HPMC K100M). The influence of varying the polymer ratios was evaluated. The excipients used in this study did not modify physicochemical properties of the drug. MET has relatively short plasma half-life, low absolute bioavailability. The need for the administration 2 to 3 times a day when larger doses are required can decrease patient fulfilment. SR formulation that would maintain plasma level for 8-12 h might be sufficient for daily dosing of MET. SR products are needed for MET to prolong its duration of action and to improve patient compliances. The developed formulation of tablet (F1 to F6) was evaluated for pre-compression and post–compression method. The results of all parameter were found to be within the limits. The optimized formulations (F6) were subjected to stability studies and shown there were no significant changes in drug content, physicochemical parameters and release pattern. Assay of the pure drug and formulation was carried out by using UV and RP-HPLC method. The *in vitro* drug dissolution study was carried out using USP apparatus Type I, Basket method and the release mechanisms were explored. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release is retarding efficiency of the polymer. The in vitro release studies exhibits the release up to 94.8%, over a prolonged period of time which confirms the extended release profile of formulation (F6) after 12 hrs as compared to marketed formulation, in- vitro drug release data obtained were fitted to various release model excess the possible mechanism of the drug release. In conclusion, development of MET SR tablets is a good approach to sustain the release rate to overcome frequent administration and also to release the drug for prolongs period thus maintaining plasma level above the MEC for desired time period. Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies in humans.

**Keyword:** Metformin hydrochloride, SR matrix tablet, HPMC K100M, Wet granulation technique, *In vitro* drug dissolution.



## INTRODUCTION

Sustained-release (SR) oral delivery systems are designed to attain therapeutically effective concentrations of drug in systemic circulation over an extended period of time [1] towards novel drug delivery of pharmaceutical technology; SR matrix tablets have given a new development [2]. Reservoir type of dosage forms designed to release drug constantly and continuously over satisfactory prolonged period of time to maintain plasma drugs concentration within therapeutic level [3]. Drug products designed to reduce the occurrence of dosing by modifying the rate of drug absorption are available since many years. Among various dosage forms, matrix tablets are widely accepted for oral sustained release (SR) as they are effortless and easy formulate. Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed. In fact, matrix is defined as a well complex of one or more drugs with a gelling agent i.e. hydrophilic polymer [4-6]. It is estimated that by 2025 around 300 million people will be diagnosed with diabetes [7, 8]. Metformin hydrochloride (MET) is an oral anti-hyperglycaemic

drug used in the treatment of Type 2 diabetes in patients who cannot manage the disease with only diet and exercise [9]. Different from Insulin and the Sulfonylurea, MET does not promote weight gain; therefore it becomes the first choice for treatment of type 2 diabetes and is even used in obese patients with type 1 diabetes to reduce insulin resistance [10]. Chemically, MET is (N, N-dimethyl imidodi carbonimidic diamide hydrochloride) belongs to the class of biguanides, hydrophilic, BCS class- III drug [11, 12]. It improves glucose tolerance by lowering both basal and postprandial glucose by decreasing intestinal absorption of glucose, decreasing hepatic gluconeogenesis, increasing glycogenesis, lipogenesis and glucose uptake by adipocytes and muscle cells [9, 13]. MET is a highly water soluble drug (0.5 g/ml) administered up to 2.5 g/day in three separate doses given with meals to minimize possible gastrointestinal side effects such as anorexia, abdominal discomfort, nausea and diarrhea [14]. However, food also decreases the absorption of the drug [15]. The presence of side effects and the need for three-times-a-day administration could reduce patient compliance and hinder successful treatment [16]. MET does not produce lactic acidosis as seen in other biguanide drugs such as phenformin and buformin [17]. Further, MET does not bind to plasma proteins and the elimination of the unchanged drug mainly occurs by active tubular secretion through the kidneys. A single dose of 500 mg of an immediate and modified release MET showed higher plasma concentrations for the latter in the steady-state [18]. A single immediate release doses of MET exhibits a flip-flop model and a bioavailability of about 61%. The tmax and t1/2 of MET after a single immediate release oral dose of 500 mg was ~2 h and 2.6 h, respectively [19]. However, a 250 mg sustained-release MET pellet showed a tmax of 7.3 h and t1/2 of 8.3 h and a 165% increase in bioavailability in comparison to the immediate release formulation and thus, tmax depended on the dose. For instance, tmax was 2.2 h and 1.5 h for an immediate release dose of 0.5 and 1.5 g, respectively [17]. Further, ~20% of the single immediate release dose is recovered in faeces, indicating saturable absorption and low absorption in the terminal segment of the colon [20-22]. This problem creates the need for a modified release device to modulate the release and hence, the absorption of MET. Thus, a modified release system allows for achieving an optimal therapy, improving patient compliance and safety, reducing dose dumping, plasma fluctuations and the incidence of side effects. In the present study, formulations of hydrophilic matrixes composed of MET, Sod CMC, HPMC, gelatin, aerosil 200 and magnesium stearate were prepared by wet granulation followed by tableting to achieve a once-a-day controlled release preparation. This provides a lower but controlled drug concentration over an extended period of time (24 h). The resulting dissolution profiles and release kinetics of the matrices were also evaluated.

## MATERIALS AND METHODS

### Materials

Metformin HCl was received as a gift sample from Arbro Pharmaceuticals Ltd, New Delhi (India). Acetonitrile, methanol and ortho-phosphoric acid were of HPLC grade supplied by Merck Ltd., India. Ammonium thiocynate, ammonium di-hydrogen phosphate, cobalt (II) chloride, sodium hydroxide were purchased from S.D. Fine Chem. Ltd. Mumbai. Hydroxy propyl methyl cellulose, sodium CMC, magnesium stearate was purchased from Himedia Chem. Lab, Mumbai. Magnesium stearate and sodium alginate, starch was purchased from Loba Chemicals Pvt. Ltd. Mumbai. Riomet 1000 MG SR Tablet (Ranbaxy Lab. Ltd.) was purchased from local market. All other ingredients used were of analytical grade. Triple distilled water was generated in house.

### Methods

#### Drug Excipient Compatibility Studies

Drug and excipient were analyzed by IR spectral studies by KBr pellet technique using Jasco FTIR-410. In this method, the drug and KBr were mixed at the ratio of 1:100. Then these mixtures were pressed in to a pellet. The FTIR spectra were recorded using KBr pellet method in the region of 400-4000 cm-1. Spectra were recorded for pure drug, pure excipients and drug with excipients.

#### Preformulation Studies

#### Melting Point

The melting point of MET was determined using the open capillary method. The drug sample was filled into a capillary and placed in a melting point apparatus The tube was heated and the temperature at which the drug melted was noted.

#### Loss on Drying

The weighing bottle was dried for 30 minutes in oven then it was allow to cool. The bottle was accurately weighed with cover. Then cover was removed and 100mg of sample was placed in to the bottle and weight. Then sample was heated at 105°C for 3 hour. Then the bottle was removed and it was placed in the desiccators. Then the material was allowed to reach room temperature and weigh and calculate. The difference between successive weights should not be more than 0.5 mg.

The loss on drying is calculated by the formula:

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

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**

100mg of MET was accurately weighed and transferred to a 100 ml volumetric flask. It was dissolved in an adequate amount of phosphate buffer pH 6.8 and the volume was made up to 100 ml with phosphate buffer pH 6.8 so as to obtain a stock solution of 1000 µg/ml. A dilution of 6 µg/ml concentration was made from the above stock solution with the phosphate buffer pH 6.8 and the resulting solution was scanned on a double-beam UV-visible spectrophotometer (Unicam Helios UV 052514) between wavelength ranges of 200 nm to 400 nm.

**Calibration curve of metformin hydrochloride in phosphate buffer pH 6.8**

A standard curve was prepared in the concentration range of 1-10 µg/ml. For the preparation of calibration curve, stock solution was prepared by dissolving 100 mg of accurately weighed MET in 100 ml of phosphate buffer pH 6.8. Further 10ml of this solution was pipette into 100 ml of volumetric and diluted to 100 ml with phosphate buffer pH 6.8. From this 0.1, 0.2,0.3, 0.4,0.5, 0.6,0.7, 0.8, 0.9 and 1 ml pipette into a series of 10 ml volumetric and volume was made up to 10 ml with phosphate buffer pH 6.8 to get 1-10 µg/ml of etophylline and theophylline respectively. The optical density values of resulting solutions were measured at 233 nm in UV spectrophotometer

**Calibration curve of metformin hydrochloride in water**

100 mg of MET was accurately weighed and transferred to a 100 ml volumetric flask. It was dissolved in an adequate amount of water and the volume was made up to 100 ml with water so as to obtain a stock solution of 1000 µg/ml. From stock solution conc. range 1-10 µg/ml are prepared by serial dilution technique in water. The absorbance of the diluted solution was measured at 233 nm and a standard plot was drawn using the data obtained. The correlation coefficient was calculated by linear regression analysis.

**Micromeritic Properties** [23]

**Angle of Repose**

The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which was kept 2cm above graph paper that is placed on a flat horizontal surface. Angle of repose can be determined by following equation:

$\theta = \tan^{-1}(h/r)$

Where,

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

**Bulk Density (BD)**

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The BD of powder blends was determined using the following formula.

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

**Tapped Bulk Density (TBD)**

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of powder blends was determined using the following formula.

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

**Carr's Compressibility Index**

The Carr's compressibility index was calculated from bulk density (BD) and tapped density of the blend. A quantity of 2 g of blend from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25 ± 2/min to measure the tapped volume of the blend. The BD and tapped density were calculated by using the bulk volume and tapped volume. Carr's compressibility index was calculated using the following formula.

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**

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already be in existence for known drugs. For new drugs or new excipients, the pre formulation scientist must generate the needed information. MET mixed well with the excipients

according to the formulas selected for the tabletting and kept small portion of this mixed powder in cleaned and dried vial(s) in stability chamber at 40°C ± 2°C/75 ± 5RH and room temperature. Physical observation has been carried out visually for 7 days.

**Assay of metformin hydrochloride powder (HPLC method)**

Assay or percentage purity of the MET is done by HPLC method. The HPLC apparatus used for analysis was composed of a Perkin-Elmer 200 (Autosampler) equipped with a UV/VIS dual detector and generated data were analyzed using Total Chrom software. For chromatographic separation Lichrosphere (C-18) Column (250 X 4.6 mm, 5µm) was applied. The chromatographic analysis was performed at ambient temperature on a RP-C18 analytical column with a mobile phase composed of 17 g/l solution of ammonium di-hydrogen phosphate adjusted to pH 3.5 with phosphoric acidmand was isocratically eluted at a flow rate of 1 ml/ min. A small sample volume of 20 µl was used for each sample run, being injected into the HPLC system. The chromatogram was monitored with UV detection at a wavelength of 218 nm and total analysis time was 5 min for MET. The RT of MET was found to be 3.32± 0.5 min. The calculation of assay was done with the help of graph obtained and using the formula;

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

**Selection of target release profile**

The release profile of marketed product of Riomet 1000 MG SR (Ranbaxy Lab. Ltd.) Tablet is taken as an innovator sample and its release profile is taken as standard profile.

**Preparation of Tablets**

A total number of 6 formulations were prepared by wet granulation method. Required quantity of drug, polymers and diluents were mixed thoroughly and a sufficient quantity of granulating agent (starch + gelatin) was added slowly to get dough mass. The mass was sieved through 10 mesh and dried at 50º for 2 h. the half dried granules was again pass through 16 no. mess and dried more for 2 h. the dried granules obtained finally were mixed with 2% talc and 1% magnesium stearate. Tablets were compressed using 22 mm * 10 mm caplet concave shaped punches to get tablets with target weight 1400 mg on a 16 station automatic Cadmach tablet punching machine, at a compression force of 1.5 ton with hardness of all tablets maintained between 13-15 kg /cm$^2$. In all formulations, the amount of the active ingredient is equivalent to 1000 mg of MET. The composition of each tablet is shown in Table-1.

**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 |

The theoretical weight is adjusted by changing the proportions of different polymers and by keeping all the ingredients constant so as to achieve the target drug release profile from the sustained release dosage form of MET tablet as that of the innovator sample of Ranbaxy (RIOMET SR tablet).

**Evaluation of tablets [24]**

**Weight Variation**

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated. As per Indian Pharmacopoeial specification, tablets with an average weight between 80 –250 mg, the percentage deviation should not more than ± 7. 5 % and tablets with an average weight more than 250 mg should not be more than ±5 %.

**Friability Test**

Twenty tablets were selected at random; their surfaces cleaned with a hair brush to remove any adhering dust, weighed and placed in the friabilator (Electro Lab USP EF-2). They were then allowed to fall freely 100 times from a height of 6 inch at a speed of 25 rpm for 4 min. The tablets were then dusted and

weighed. Any loss in weight due to fracture or abrasion was recorded as a percentage weight loss. The replicate determinations of each formulation were averaged. Friability was calculated by the following formula.

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

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

**Hardness Test**

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm². Ten tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

**Uniformity of Thickness**

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using digital vernier calliper.

**In Vitro Dissolution Studies**

*In vitro* drug release studies from the prepared MET SR matrix tablets were conducted using USP type I(basket) apparatus at 37°C± $0.5^0$C at 100 rpm. Dissolution mediums used were 900 ml of phosphate buffer of pH 6.8. At specified time, withdrawn required amount of sample and take absorbance by UV-Visible Spectrophotometer (Unicam Helios UV 052514) and calculate percentage release.

**Kinetics of Drug Release [25]**

The order of drug release can be assessed by graphical treatment of drug release data. A plot of % drug remaining versus time would be linear if the drug release follows zero order (ie. concentration independent release). A plot of log of % remaining drug versus time would be linear, if the drug release follows first order (ie. concentration dependent release) 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

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

A matrix device as the name implies, consists of drug dispersed homogeneously throughout a polymer matrix. In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior. Obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Deviation of the mathematical model to describe this system involves the following assumptions.

- A pseudo study state is maintained during drug release.
- The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
- The bathing solution provides sink conditions at all times and
- The diffusion coefficient of drug in the matrix remains constant (ie. no change occurs in the characteristics of the polymer matrix).

Hydrophilic matrix tablets contain a water swellable polymer. On contact with gastric juices the tablet surface gels, impeding further liquid penetration into the tablet core and providing a rate controlling layer. Dissolution occurs at the gel core interface and drug diffuse out through the gelled layer. Drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of drug through the swollen, hydrated matrix, in addition to erosion. The extent to which diffusion or erosion controls release depends on the polymer ration.

Mechanism of release from erodable matrix has been described by Hopfenberg. A simple expression describing 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.

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

**Determination of Drug Content in Tablets**

Twenty tablets of the sustained formulation were weighed and crushed to fine powder. Powder equivalent to 1000 mg MET was weighed and dissolved in 100 ml Water, sonicated for 10 min and filtered through whatmann filter paper No. 42, finally different concentrations of tablet sample were prepared by serial dilution technique. The total amount of drug for each tablet was analyzed spectrophotometrically by using UV/ Visible spectrophotometer at 233 nm and HPLC method. As we have chosen the HPLC so there is no chance of detection of any degradation products.

**Accelerated Stability Studies**

Accelerated stability study was carried out to observe the effect of temperature and relative humidity on selected formulation (F6), by keeping at 40°± 2°C, in air tight high density polyethylene bottles for three months, at RH 75±5%. Physical evaluation was carried out in each month.

**Gel Layer Dynamics**

When 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) is permeated into the tablet along with water. Cobalt (II) thiocynate gives a pink colour when diluted and forms a blue complex with compounds containing amino groups. Thus a blue colour was developed in the hydrated region of the tablet containing etophylline & theophylline while drug free hydrated region appeared pink due to cobalt (II) thiocynate. The un-hydrated glassy core of the matrix retained its off- white colour. The junction of these regions mark the different fronts observed in a hydrating matrix and are marked in Figure-1.

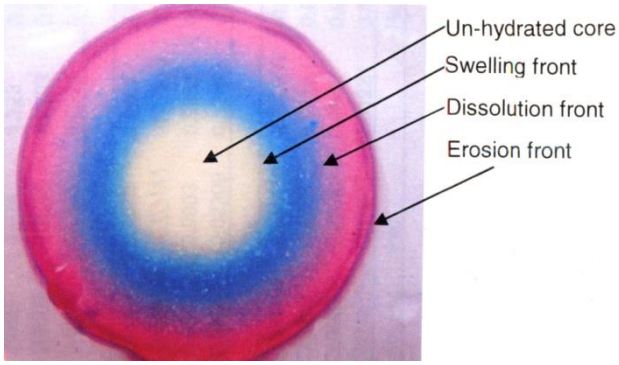



**Fig-1: Hydrophilic matrix containing drug after hydration for 8 hours in cobalt (II) thiocynate solution. The white region is the unhydrated core, blue region is the hydrated region-containing drug and pink region is the drug free hydrated polymer**

**Mass Degree of Swelling**

Tablet of final formulation is pre-weighed and allowed to equilibrate with 100 ml of water for 5 h, was then removed, blotted using tissue paper and weighed [26]. The mass degree of swelling then was calculated using the formula:

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

**Factors Studied To Match the Release Profile**

Various factors which affect the dissolution rate from tablet dosage form is studied to match and obtained desired drug release rate, such as follows:

**Polymer Viscosity**

Two different viscosity grades of a hydrophilic matrix former HPMC K 100M and K 15M were used at the same proportion (30%) in two formulations. X and Y containing lower and higher viscosity grades respectively and dissolution study are done. It is generally accepted that drug dissolution from tablet is slower for higher viscosity grades of HPMC polymer. This is mainly due to longer period of time required to reach the disentanglement concentration at the tablet surface, which in turn equates to greater resistance to surface erosion and also high viscosity polymers created more viscous gel layers, thus causing the drug to diffuse more slowly [27, 28].

**pH Challenge Studies**

The pH challenging study on dissolution of final selected formulation is performed up to 16 hours at the time interval of 30 min, 1Hr, 2Hr, 3Hr, 4Hr, 6Hr, 8Hr, 12Hr and 16Hr by using different dissolution medium such as 0.1N HCl, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer and purified water.

## RESULTS AND DISCUSSION

The FTIR spectra of the pure drug, excipients and powdered tablet were recorded in between 400 to 4000 wavenumber ($cm^{-1}$). No peaks are observed which interfere with the main drug peaks. The different peaks obtained are summarized in Table-2.

**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 |

Matrix tablets were formulated according to wet granulation method. Granulation is the key process in the production of matrix tablet sustained release dosage form. The properties of granules which should be evaluated to ensure the proper formulation of the tablet dosage form are an important aspect in matrix tablet formulation. Granules of all the formulations were subjected for various pre-compression evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio Table-3.

**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 |

All the formulated tablets (F1-F6) containing the active drugs were evaluated to find the physical properties like hardness, thickness, friability and drug contents (Table 4). In a weight variation test, the pharmacopoeial limit of percentage deviation for tablets whose weight is more than 250 mg is ±5%. The average percentage deviation of all the tablets was found within the limit which was less than 1%. Hardness of the tablets was found acceptable and uniform from batch to batch variation. The drug content was also found uniform and within the prescribed limit. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. Results of friability test were also has been found within limit.

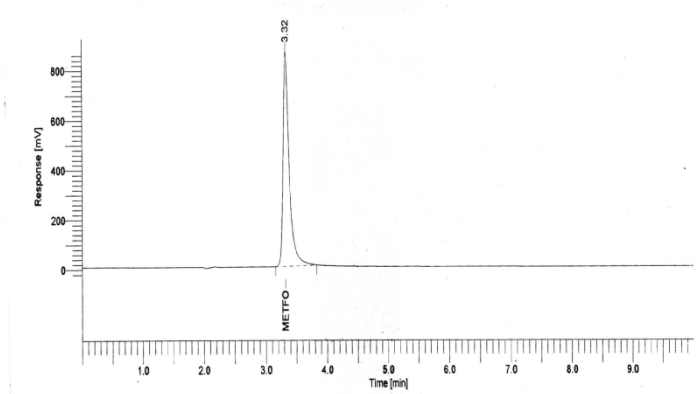
**Table-4: Physical properties and drug content of SR matrix tablet**

| 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 |

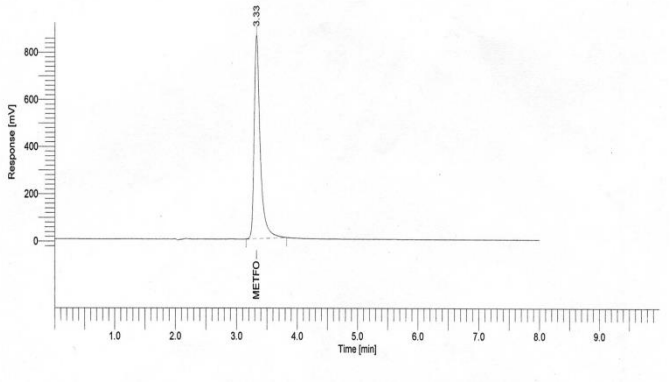
Assay was carried out for finally selected formulation (F6) and the result was found to be 102.7% MET by HPLC Table-5 & Figure-2.

**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 | |



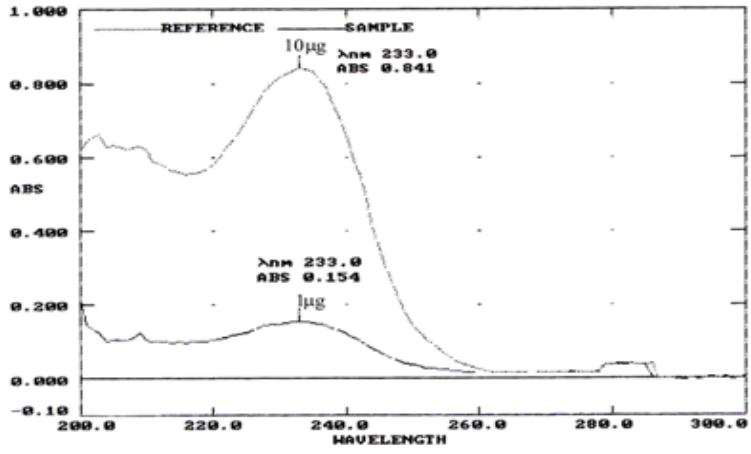

**(A)**



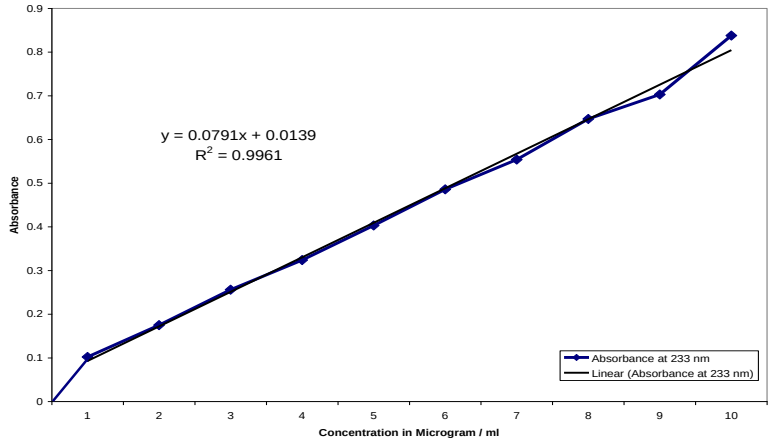

**(B)**

**Fig-2: Representative chromatogram of (A) Standard Drug (B) Formulation (F6)**

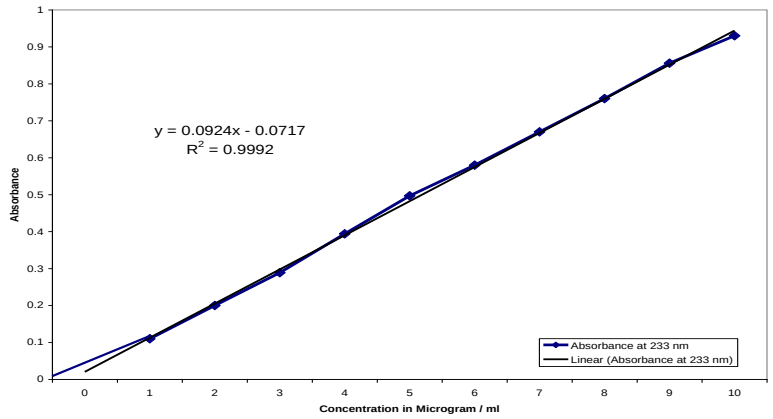
The absorption maximum for drug was found to be233 nm in pH 6.8 Phosphate buffer and water. The concentrations in range of 1µg/ml to 10µg/ml, Regression coefficient $r^2$ Values of drug was found to be in water is $r^2 = 0.996$ and in pH 6.8 Phosphate buffer is $r^2 = 0.999$ Figure-3.




**(A)**




**(B)**




**(C)**

**Fig-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**

The primary aim of the project was to develop a generic equivalent of the innovator product, hence we targeted to the release profile of innovator product. The drug Release profiles for marketed formulation (Riomet 1000 MG SR Tablet) was generated in phosphate buffer 6.8 pH using USP Apparatus I at 100 rpm. The same conditions have been used for dissolution studies on prototype formulations Table-6 & 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 |

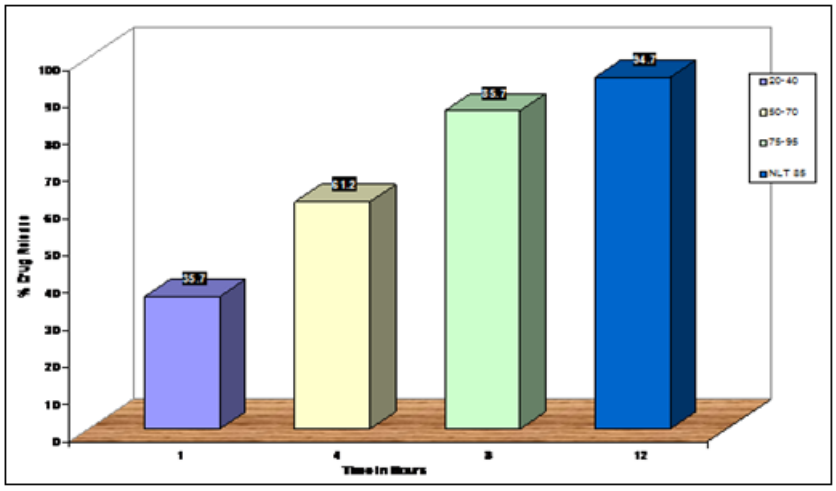



**Fig-4: Release profile of market tablet (Riomet 1000 MG SR Tablet)**

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 |

A number of batches were prepared using combinations of hydrophilic matrix former. Most of the combinations yielded largely similar release profiles. But the formulation F6 giving release close to the innovator Table-8.

**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 reveals that the rate of drug release from the tablet in 0.1N HCl as a medium is faster in comparison to other medium and also the drug release is slower in case of water as a medium in comparison to the buffer solutions. In case of both the 6.8 and 7.4 pH phosphate buffer solution the drug release rate is almost similar with each other Table 9. From the graph, it was concluded that, the formulation does not show a significant change in the dissolution profile at pH 6.8, 7.4 and water but gave substantially faster release at pH 1.2(0.1N HCl). This can be explained based on the pH dependent swelling behaviour of formulation Figure-5.

**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 |

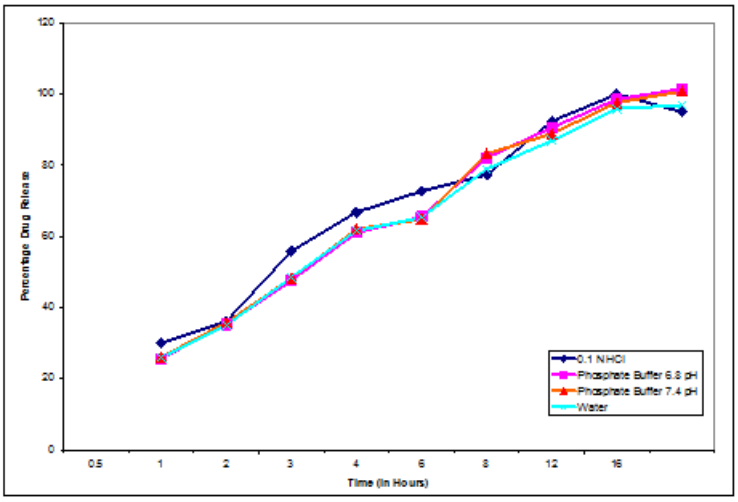



**Fig-5: Comparative chart of % drug dissolved in different dissolution medium**

It was observed that formulation matrices swelled to a much lesser extent in the acidic medium. It was believed that the ionic interaction between the polymer and drug are of importance in controlling the release from the matrices Figure-6.

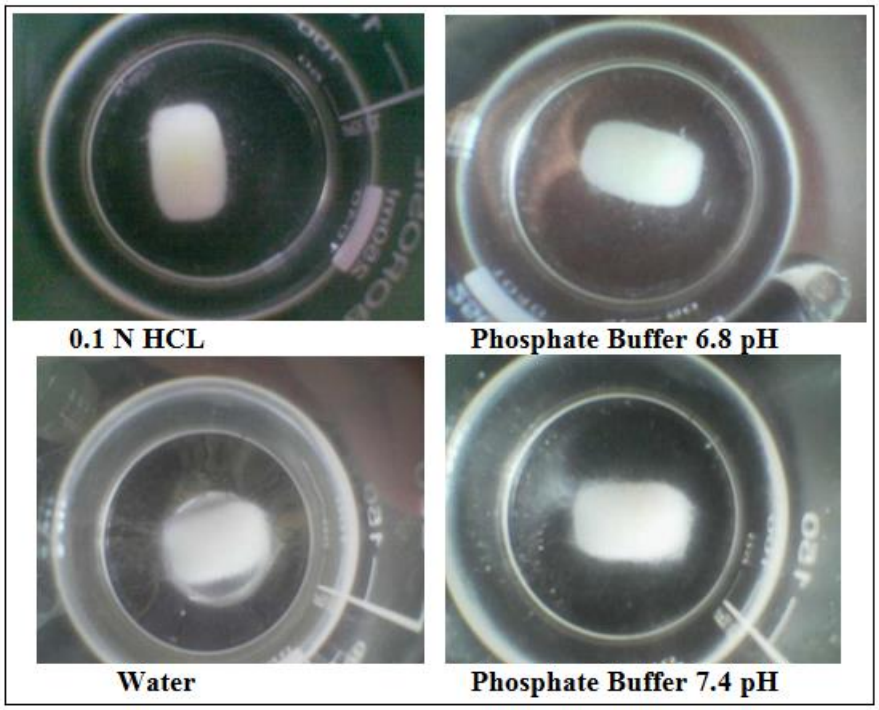



**Fig-6: Showing swelling characteristics of matrix tablet in different dissolution medium**

The dissolution profile for the formulations was found to be different from batch to batch. But the formulation of F6 was found to be the most desired release profile for the formulation. The release of formula F6 was most consistent, accurate and complete in comparison to that of the innovator sample of Riomet 1000 mg SR Tablet. After the evaluation of dissolution study it can be concluded that the F6 formulation for the matrix tablet containing HPMC K 100, HPMC K 15 possesses excellent drug release kinetics Table-12. The mechanism of drug release from matrix tablet is through diffusion due to soluble nature of drug. The formulation of F6 also possesses good micromeritic and physical properties Table-10, Figure 7-9. 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 |

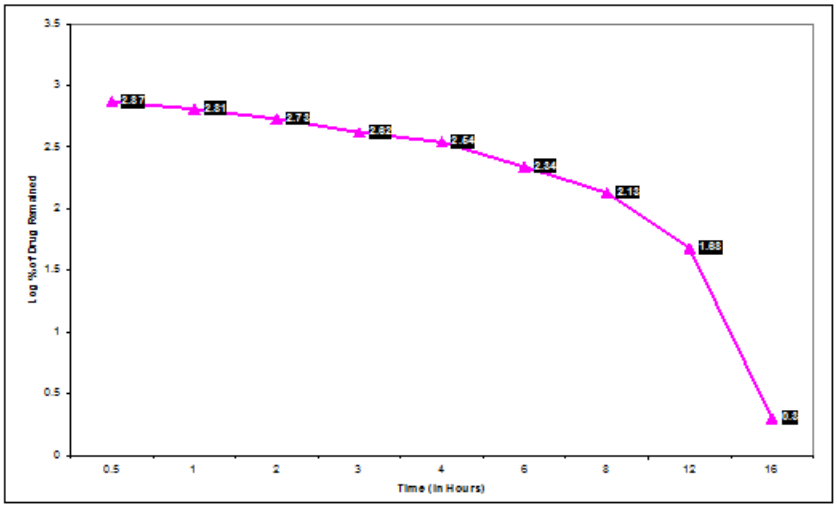



**Fig-7: Showing relationship between log % drug remaining Vs Time (y = -0.2525x + 3.4869, $R^2$ = 0.7227)**

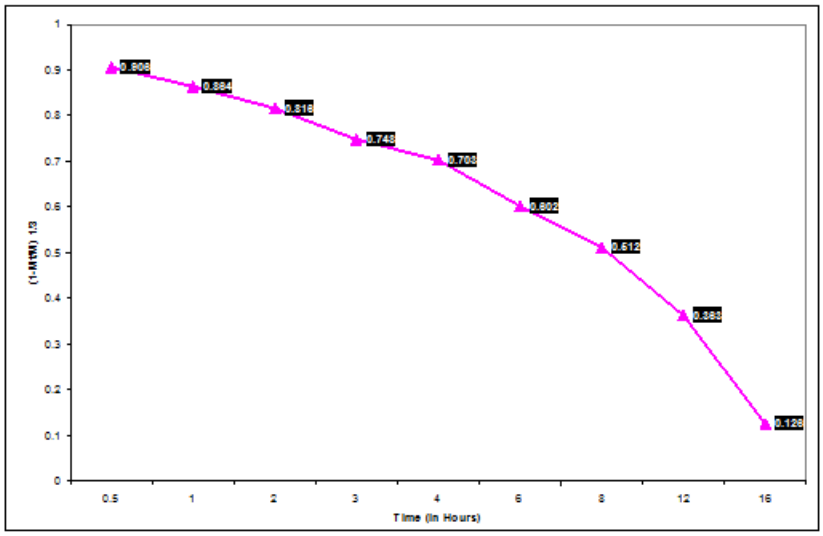



**Fig-8: Showing relationship between $(1-Mt/M)^{1/3}$ Vs Time (y = -0.0896x + 1.0748, $R^2$ = 0.9184)**

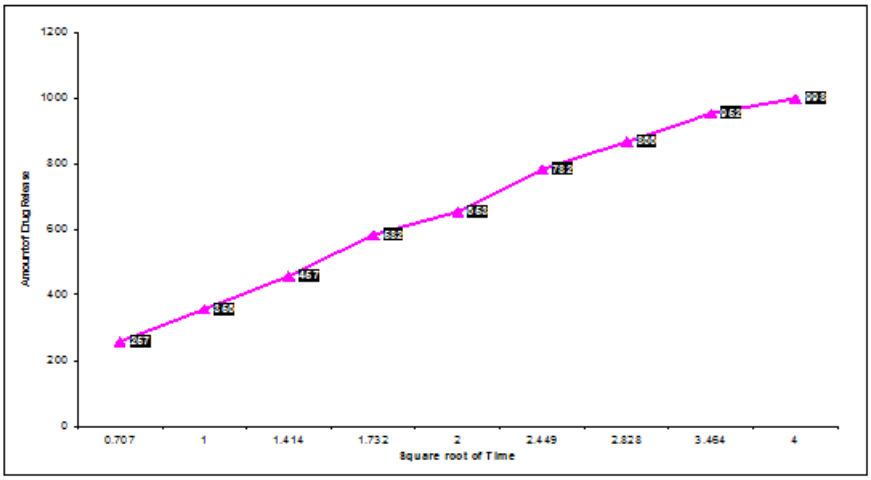



**Fig-9: Showing relationship between Amounts of Drug Release Vs Square root of time**

Stability studies were carried out by keeping the tablets at room temperature ($25^0$ C ± $2^0$C / 60% ± 5% RH) and at accelerated temperature ($40^0$ C ± $2^0$C / 75% ± 5% RH) in Stability chamber for 90 days. The result of stability studies conducted on F-6 revealed no change in physical appearance, hardness, drug content and in-vitro dissolution profiles whereas IR spectrum obtained exhibits no incompatibility, hence F-6 formulation was found to be stable at tested temperature Table 11, 12 & Figure 10-14 .

**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 |

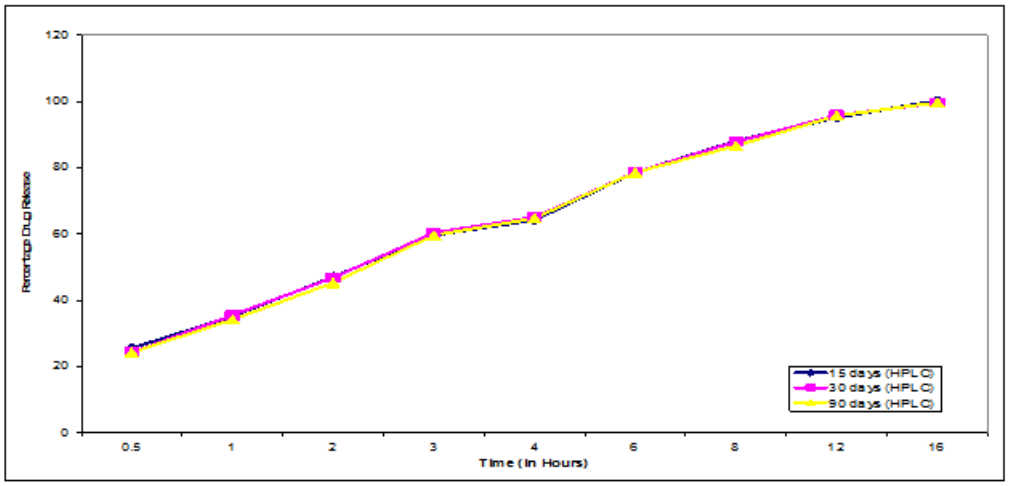



**Fig-10: Comparison of dissolution data of stability samples at accelerated condition by HPLC**

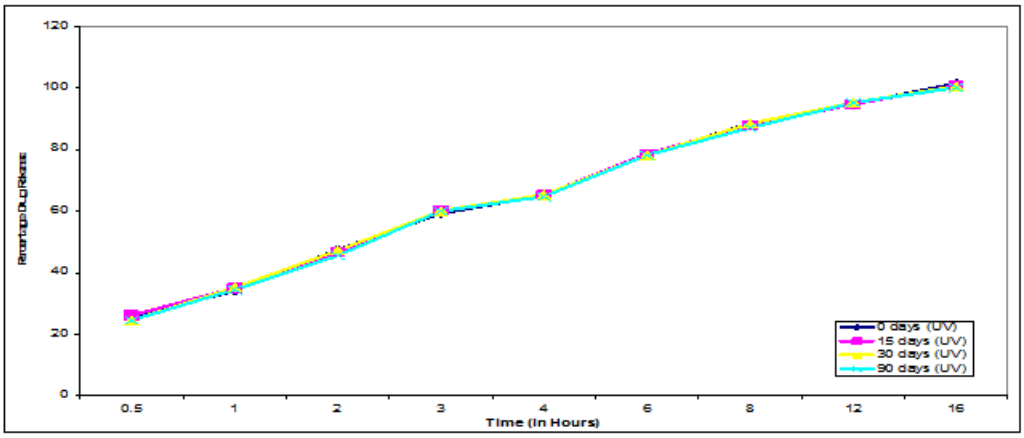



**Fig-11: Comparison of dissolution data of stability samples at accelerated condition by UV**

**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 |

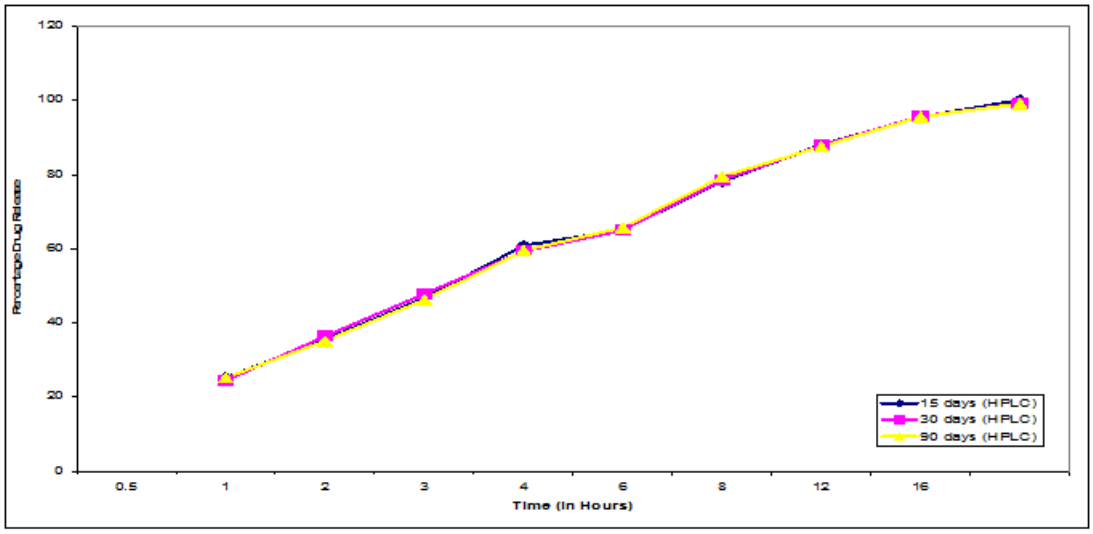



**Fig-13: Comparison of dissolution data of stability samples at room temperature by HPLC**

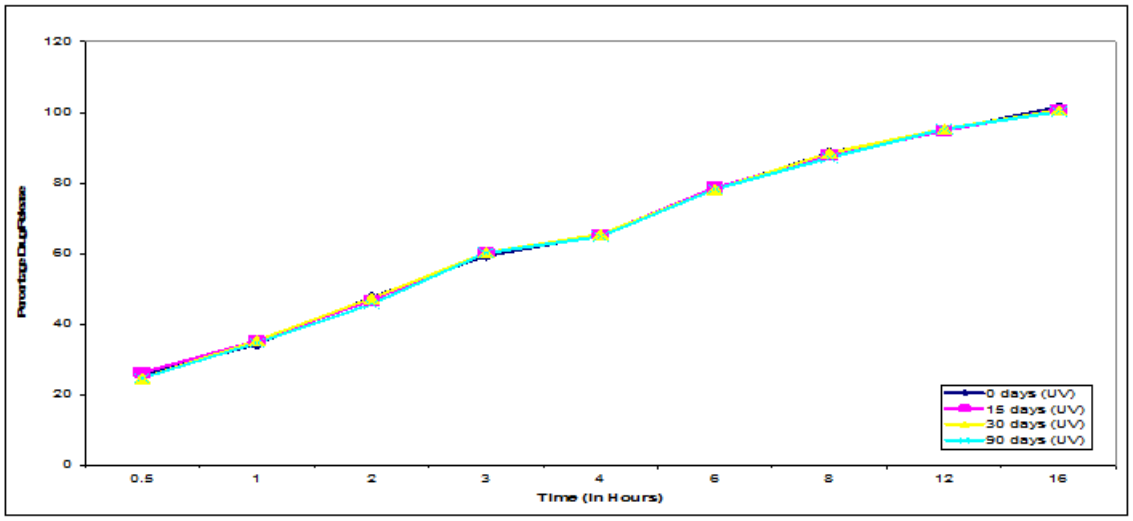



**Fig-14: Comparison of dissolution data of stability samples at room temperature by UV**

## CONCLUSION

The magnitude of release rate and release order depended on the interactions between the drug, polymers and the medium employed. In the present study attempts were made to formulate 1000mg sustained release once daily formulation which can provide effective drug release for 16 hours. SR matrix tablets of MET were prepared by wet granulation. In vitro study showed formulation F6 were well suited to be extended release formulation. Final selected formulations were found to be nearly zero to zero order drug release, governed by diffusion through swollen matrix and erosion of the matrix, showing anomalous diffusion of non fickian transport. From the results obtained, it can be concluded that formulation F-6 has achieved the objective of sustained drug release, patient convenience and cost effectiveness as a single daily dose of the drug and appears to be assessed further by conducting bioavailability studies in human volunteers and long term stability testing.

**Conflicts of Interest**

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

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