# FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE MATRIX TABLETS BY USING NATURAL GUM AS RELEASE MODIFIER

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## ABSTRACT

The main aim of present study is to prepare and evaluate Metformin HCl tablets using natural polymer Xanthan gum as release retarding agent by wet granulation method for effective treatment of type II Diabetes mellitus. An attempt was made to reduce the dose, dosage frequency; dose related gastrointestinal side effects of Metformin HCl and to improve its bioavailability which in turn improve the patient compliance. Preformulation studies including drug excipients compatibility was conducted. Six formulations (F1- F6) of Metformin HCl tablets with increasing concentrations of xanthane for sustained release were prepared by wet granulation method using natural polymers like Xanthane gum and were evaluated for tests such as weight variation, thickness, hardness, and drug content uniformity and *in vitro* drug release. The *in vitro* dissolution study was carried out for 12 hours using USP paddle apparatus in hydrochloride (0.1N) and phosphate buffer (pH 6.8) as dissolution media. The rate of drug release from a dosage form is characterized by mean dissolution time and indicates the drug release retarding efficiency of polymer. Based on the *in vitro* dissolution data F2 was selected as the best formulation for Metformin where the drug release was retarded up to 12 hours with 94.87 % drug release which follows Zero order and Non-Fickian mechanism.

**Key words:** Sustain release, Metformin HCl, Xanthane Gum, Wet granulation, and Release kinetics.

## 1. INTRODUCTION:

Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained release (SR) or controlled release (CR) drug

delivery systems [1]. SR dosage form is one of the drug products categorized under the term modified release dosage forms (FDA, 1997). It refers to products, which are formulated to make the drug available over an extended period after ingestion; thus, it allows a reduction in dosing frequency compared to a conventional type i.e. immediate release (IR) dosage form. Several advantages of SR products over IR ones have long been recognized [2,3]. SR delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half - life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance [4,5]. SR solid oral dosage forms can be classified into two broad groups: (i) single unit dosage forms (e.g. tablets) and (ii) multiple unit dosage forms or multi particulate pellet systems. The systems can be further subdivided into two concepts regarding to the design of dosage forms: (i) Matrix systems and (ii) Reservoir systems [6].

Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in developing a sustained-release drug delivery system [7]. Recent trend in development of sustained-release drug delivery systems was the use of gums of plant origin to fulfill the aim of retarding the drug release [8,9]. Natural gums are biodegradable, non-toxic and have capability to swell on contact with aqueous media. The natural polymers used do hold advantages over the synthetic polymers generally because they are nontoxic, less expensive and freely available [10,11]. Most common examples of natural gums are Guar gum, Xanthane gum, Pectin and Gum Tragacanth. Guar gum is a polysaccharide derivative having glycosidic linkage which is intended to be used as a matrix former for controlled release of drugs (eg., Diltiazem) [12]. Pectin, a natural hydrophilic polymer is rich in galacturonic acid is used as a gelling agent and thickening agent. Pectin gum has been shown to be useful for the construction of drug delivery systems for targeted drug delivery [13]. Xanthane gum is an extra cellular polysaccharide, produced by viscous fermentation of *Xanthomonas campestris*. It is used as thickening agent, suspending agent and emulsifying agent [13,14]. Gum Tragacanth is obtained from *Astragalus gummifer* and is odour less, tasteless and a viscous water-soluble mixture of polysaccharides.

Diabetes mellitus is a condition in which a person has a high blood sugar level, either because the body doesn’t produce enough insulin, or because body cells don’t properly respond to the insulin that is produced. Insulin is a hormone produced in the pancreas which enables body cells to absorb glucose, to turn into energy. If the body cells do not absorb the glucose, the

glucose accumulates in the blood, leading to vascular, nerve, and other complications [15]. The recent estimation that there were 171 million people in the world was with diabetes in the year 2000 and this will be increase to 366 million by 2030. Diabetes is a condition primarily defined by the level of hyperglycemia giving rise to risk of micro vascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related micro vascular complications, increased risk of macro vascular complication (ischemic heart disease, stroke and peripheral vascular disease), and diminished quality of life [16,17].

Diabetes mellitus is mainly classified as four types. They are, Type -I, Type –II, Gestational diabetes and other types of diabetes. Metformin HCL, the only available biguanide, remains the first line drug therapy for patients with Type 2 diabetes mellitus (T2DM), acts by decreasing hepatic glucose output and peripheral insulin resistance [17]. The advantages of Metformin are a very low risk of hypoglycaemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality [18]. It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60 % with relatively short plasma half-life of 1.5 - 4.5 hrs.

An obstacle to more successful use of Metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea, that especially occur during the initial weeks of treatment [19]. Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. A sustained-release formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of Metformin [20]. SR products are needed for Metformin to prolong its duration of action and to improve patient compliance.

## 2. MATERIAL AND METHODS:

### *2.1.Materials:*

Metformin HCL was obtained as a gift sample from Amratlal and Co. Chennai. Xanthane Gum, Magnesium stearate, Talc, PVP-K30, Isopropyl Alcohol were obtained from Loba Chemie Pvt. Ltd; Mumbai. Microcrystalline cellulose was obtained from Paxmy Speciality Chemicals, Chennai and all other ingredients used were of analytical grade.

*2.2.Experimental Methods*

**A)** Calibration of Standard Curve

100mg of Metformin HCL was accurately weighed and transferred into 100ml volumetric flasks. It was dissolved and diluted to volume with 0.1N HCl and Phosphate buffer pH 7.4 to give stock solution containing 1000µg/ml [21]

The standard stock solutions were then serially diluted with 0.1N HCl and Phosphate buffer pH 7.4 to get 1 to 10µg/ml of Metformin HCl. The absorbances of the solution were measured at 233nm against 0.1N HCl and Phosphate buffer 7.4 as blank using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve [21].

**B)** Preformulation Studies

**I. Identification of pure drug**

**(a). Solubility Analysis:**

Pre-formulation solubility analysis was done, which included the selection of suitable solvent system to dissolve the drug [22].

**(b). Melting Point Determination**

Melting point determination of the obtained drug sample was done by using melting point apparatus.

**II. Drug Excipients Compatibility Studies:**

The excipients are selected for formulation design by doing physical observation.

Metformin HCL was mixed with different proportions with all excipients to be used in our formulations in different ratios and kept at $40^0$C / 75% Relative Humidity (RH) conditions for two months. The physical properties (Colour change) were monitored regularly [22,23].

**C)** Preparation of Metformin HCl Sustained Release Tablets

**I. Preparation of Wet Granules:**

Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed geometrically, to this mixture required quantity of Metformin HCl was added and mixed slightly with pestle. Granulation was performed by using PVP K30 as a binder and Isopropyl alcohol as a solvent to form damp mass. The mass was passed through sieve No.18 and the granules so prepared were dried at 25-$27^0$C for 2 hrs. Afterwards granules

were sized through sieve-18. Finally, magnesium stearate and Talc were added separately and mixed for further 2-3 minutes [24]. These dried granules are then subjected to the pre-compression studies such as Angle of Repose, Bulk Density and Tapped Density, Compressibility Index and Hausner Ratio

**II. Compression of Metformin HCl sustain release Tablets**

The tablets were prepared by wet granulation method as Table:1 [25]. The required quantities of the ingredients were blend to a dry granules and blend were compressed on flat beveled edged punch set, on single punch Tablet Compressing Machine (CADMECH MUMBAI) to constant weight and at approximately of equal hardness with equal compression force and were subjected to evaluation.

**Table No:1** Formula for preparation of Metformin HCl SR Tablets

| Batch No | Metformin HCl (mg) | MCC (mg) | Xanthane Gum (mg) | PVP-K30 (mg) | Talc (mg) | Magnesium Stearate (mg) | IPA (mg) | Total (mg) |
|---|---|---|---|---|---|---|---|---|
| **F1** | 500 | 117.6 | 12.8 | 30 | 6.4 | 3.2 | Q.S | 670 |
| **F2** | 500 | 104.8 | 25.6 | 30 | 6.4 | 3.2 | Q.S | 670 |
| **F3** | 500 | 92 | 38.4 | 30 | 6.4 | 3.2 | Q.S | 670 |
| **F4** | 500 | 79.2 | 51.2 | 30 | 6.4 | 3.2 | Q.S | 670 |
| **F5** | 500 | 66.4 | 64 | 30 | 6.4 | 3.2 | Q.S | 670 |
| **F6** | 500 | 53.6 | 76.8 | 30 | 6.4 | 3.2 | Q.S | 670 |

## EVALUATION

**I. Pre-compression Parameters:**

**1. Angle of Repose:**

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface

[26,27]. The diameter of the powder cone was measured and angle of repose (θ) was calculated using the following equation

$$\theta = \tan^{-1}\frac{h}{r}$$

Where, h = height, r = radius.

2. **Bulk Density:**

30gms of material was passed through a sieve no. 25 to break up agglomerates and introduced into a dry 100 ml cylinder, without compacting, the powder was carefully levelled without compacting and the unsettled apparent volume, Vo, was read [26]. The bulk density was calculated, in grams per ml, using the formula.

$$\text{Bulk or fluff density} = \frac{\text{Mass}}{\text{Bulk volume}}$$

3. **Tapped Density:**

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a mechanical tapped density tester (Electro lab) that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement was less than 2% and then tapped volume, was measured to the nearest graduated unit [27]. The tapped density was calculated, in g per ml, using the formula:

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Tapped volume}}$$

4. **Measures of Powder Compressibility:**

The Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter-particulate interactions. As such, they are measures of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value [27]. For poorer flowing materials, there are frequently greater inter-particle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio, which are calculated using the following formulae:

$$\% \text{ CI } = \frac{\text{Tapped density} - \text{ bulk density}}{\text{Tapped density}} \text{ X } 100$$

5. **Hausner Ratio** :

   It indicates that the flow properties of the powder and measured by the ratio of taped density to bulk density.

$$\text{Hausner's ratio } = \frac{\text{Tapped density}}{\text{Bulk density}}$$

**II. Post-compression Parameters:**

1. **Shape of Tablets:** Compressed tablets were examined under the magnifying lens for the shape of the tablet [28].
2. **Weight variation:** After each film unit was weighed individually, the average weight of ten films was taken as the weight of film.

$$\text{Percentage deviation } = \frac{(\text{individual weight } - \text{ average weight})}{(\text{average weight})} X\ 100$$

3. **Thickness:** Six films of each formulation were used to measure the thickness using screw gauge and the average was taken as film thickness.
4. **Hardness:** Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm$^2$.
5. **Friability Test:**

$$\text{Friability } = \frac{(W_1 - W_2)}{W_1} X\ 100$$

   % Friability of tablets less than 1% are considered acceptable.

6. **Content Uniformity:** Twenty uncoated tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar individually and accurately weighed amount of tablet triturate from each blend was taken. Then, samples were transferred to twenty different volumetric flasks and were diluted up to the mark with purified water. The content was shaken well for some time and kept for 30 minutes for dissolving of drug completely. The mixtures were filtered and appropriate dilutions were made [29]. The drug content in each tablet was estimated at λmax233 nm against blank reference and reported.

7. ***Invitro* Dissolution Studies:**

The dissolution conditions used for studying the drug release from the sustain release matrix tablets of Metformin HCL are [30]:

**Apparatus** : USP Type 2 (paddle)

**Agitation speed(rpm)**: 100

**Medium** : 1.2 pH HCL& pH 7.4 Phosphate Buffer 900ml

**Temperature** : 37.0 ± 0.5 C

**Time** : 15 min, 30 min, 1 hr, 2hr in HCL, 3, 4, 5,6,7, 8,9, 10,11 and 12hr in Phosphate Buffer

**Wavelength** : 233 nm.

8. **Kinetic modeling of drug release:**

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing as follows:

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation) [30].

## 3. RESULTS AND DISCUSSION

*In vitro* drug release of Metformin HCl tablets shows controlled release pattern, which may be attributed to the using various concentration of xanthan gum. Based on mathematical data revealed from models, it was concluded that the release data was best fitted with zero order and Higuchi equation. Higuchi equation explains the diffusion-controlled release mechanism, the diffusion exponent 'n' values were found to be more than 0.5 for the Metformin HCl tablets indicating Non-Fickian diffusion.

**Table – 2: Measurement of absorbance of standard working solutions (Calibration curve)**

| Sr.No | Concentration (µg/ml) | Absorbance in 0.1 N HCl | Absorbance in phosphate Buffer (pH7.4) |
|---|---|---|---|
| **1** | 0 | 0 | 0 |
| **2** | 2 | 0.0422 | 0.1563 |
| **3** | 4 | 0.0813 | 0.2901 |
| **4** | 6 | 0.1238 | 0.4199 |
| **5** | 8 | 0.1561 | 0.5801 |
| **6** | 10 | 0.1971 | 0.7184 |

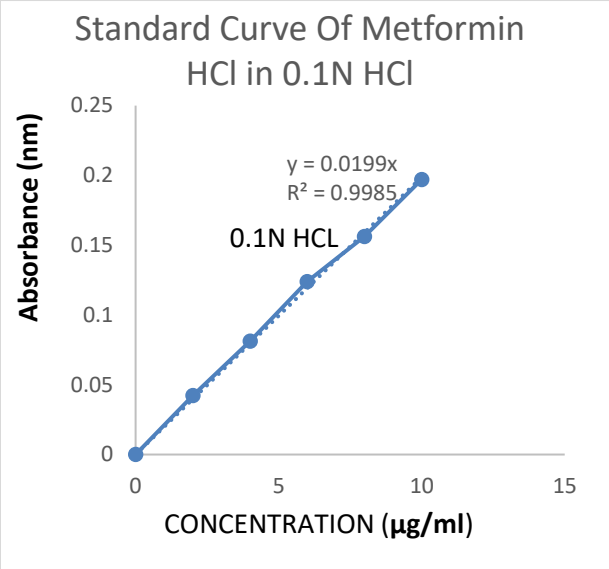


**Fig-1: Standard curve of Metformin HCl in 0.1N HCl**

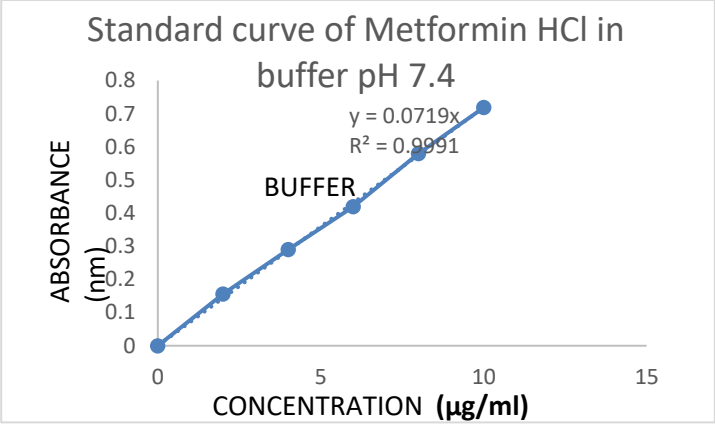


**Fig-2: Standard curve of Metformin HCl in phosphate buffer pH 7.4**

**Preformulation studies**

I. Identification of pure drug

**(A) Solubility Analysis:**

Metformin HCl is freely soluble in water and the solubility of drug in water (99.58%), in 0.1N HCl (99.65%) and 7.4 pH phosphate buffer (100.10%).

| Medium used | % Found | mg/100 ml |
|---|---|---|
| Water | 99.58 | 99.58 |
| 0.1N HCl | 99.65 | 99.65 |
| Phosphate buffer pH -7.4 | 100.10 | 100.10 |

**(B) Melting Point Determination:**

The melting point of the pure drug was determined at 222-224°C

| Reported melting point | Observed melting point |
|---|---|
| 222-226°C | 222-224°C |

**II. Drug excipients compatibility studies:**

Metformin HCl was mixed with different proportions with all excipients to be used in our formulation in different ratios and kept at 40ºC/75% RH for four weeks**.** The physical properties (colour change) were monitored regularly. The change in colour in any mixture was basis for discarding from study.

**Table-3: Drug-Excipient compatibility study.**

| Exposed conditions 40ºc/75%RH for 30 days | | | | | | |
|---|---|---|---|---|---|---|
| Ingredients | **D:E** | **Initial observation** | **Week1** | **Week2** | **Week3** | **Week4** |
| Drugs alone | **----** | **White powder** | **NC** | **NC** | **NC** | **NC** |
| Drugs + Xanthane Gum | **1:1** | **White powder** | **NC** | **NC** | **NC** | **NC** |
| Drugs +Magnesium stearate | **1:0.5** | **White powder** | **NC** | **NC** | **NC** | **NC** |
| All physical mixture with drug | **---** | **White powder** | **NC** | **NC** | **NC** | **NC** |
| Physical mixture without drug | **---** | **White powder** | **NC** | **NC** | **NC** | **NC** |

**NC – No** color change, **D: E-** Drugs:Excipient

**Pre-Compression Parameters**

**Table -4: Evaluation of Pre-compression Parameters**

| Batch no. | Angle of repose (°) | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's Index (%) | Hausner ratio |
|---|---|---|---|---|---|
| **F1** | 25 | 0.614 | 0.789 | 22.2 | 1.28 |
| **F2** | 21 | 0.668 | 0.726 | 15.4 | 1.08 |
| **F3** | 20 | 0.699 | 0.776 | 9.92 | 1.11 |
| **F4** | 23 | 0.621 | 0.712 | 12.78 | 1.14 |
| **F5** | 22 | 0.656 | 0.722 | 9.14 | 1.10 |
| **F6** | 23 | 0.698 | 0.725 | 14.3 | 1.18 |

**Post-Compression Parameters**

**Table-5: Evaluation of Post-compression Parameters**

| Batch no. | Thickness mm (n=5) | Hardness kg/cm$^2$ (n=5) | Content Uniformity (%) | Friability (%) (n=10) | Weight Variation (%) (n=20) |
|---|---|---|---|---|---|
| **F1** | 6.10 | 4.01 | 99.18 | 0.58 | 0.12 |
| **F2** | 6.09 | 4.50 | 99.78 | 0.50 | 0.19 |
| **F3** | 6.10 | 5.02 | 99.12 | 0.32 | 0.25 |
| **F4** | 6.11 | 5.57 | 99.19 | 0.30 | 0.62 |

| | | | | | |
|---|---|---|---|---|---|
| **F5** | 6.10 | 6.05 | 98.68 | 0.12 | 0.42 |
| **F6** | 6.11 | 5.35 | 99.12 | 0.26 | 0.24 |

# where n is number of Tablets.

**Evaluation of invitro release studies:**

The dissolution conditions used for studying the drug release from the sustain release matrix tablets of Metformin

**Table -6: *In Vitro* dissolution Studies**

| S.no | Time (min) | Cumulative % drug release | | | | | |
|---|---|---|---|---|---|---|---|
| | | **F1±SD** | **F2±SD** | **F3±SD** | **F4±SD** | **F5±SD** | **F6±SD** |
| 1 | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| 2 | 15 | 4.00±0.11 | 3.07±1.62 | 3.0±0.61 | 2.95±1.06 | 2.75±0.59 | 2.05±0.23 |
| 3 | **30** | 6.86±0.11 | 5.5±1.06 | 5.06±0.61 | 4.93±0.61 | 4.77±0.59 | 4.11±0.23 |
| 4 | **60** | 9.05±0.20 | 9.8±1.06 | 8.05±0.61 | 7.89±1.06 | 6.84±0.59 | 6.02±0.23 |
| 5 | **120** | 14.67±0.41 | 20.8±1.23 | 13.67±0.61 | 13.27±0.0 | 12.50±0.5 | 10.9±0.23 |
| 6 | **180** | 23.57±0.31 | 28.45±2.2 | 21.57±1.06 | 20.46±0.6 | 19.60±0.5 | 15.26±0.6 |
| 7 | **240** | 27.13±0.35 | 41.65±1.6 | 27.13±0.61 | 26.22±0.6 | 25.90±1.0 | 20.46±0.0 |
| 8 | **300** | 38.1±0.23 | 49.6±2.21 | 40.1±1.06 | 39.45±1.0 | 35.84±0.59 | 34.96±0.2 |
| 9 | **360** | 49.66±0.11 | 64.7±1.62 | 46.66±0.61 | 45.62±1.2 | 44.83±0.5 | 39.29±0.6 |
| 10 | **480** | 69.34±0.12 | 86.0±1.23 | 65.34±1.06 | 64.58±1.0 | 57.13±1.5 | 54.61±0.4 |
| 11 | **600** | 84.07±0.63 | 97.07±1.2 | 81.07±1.06 | 77.28±0.6 | 70.04±2.0 | 60.06±0.4 |
| 12 | **720** | 98.82±0.32 | _ | 94.87±1.04 | 85.64±1.2 | 81.67±1.58 | 76.08±0.2 |

SD=standard deviation (n=3)

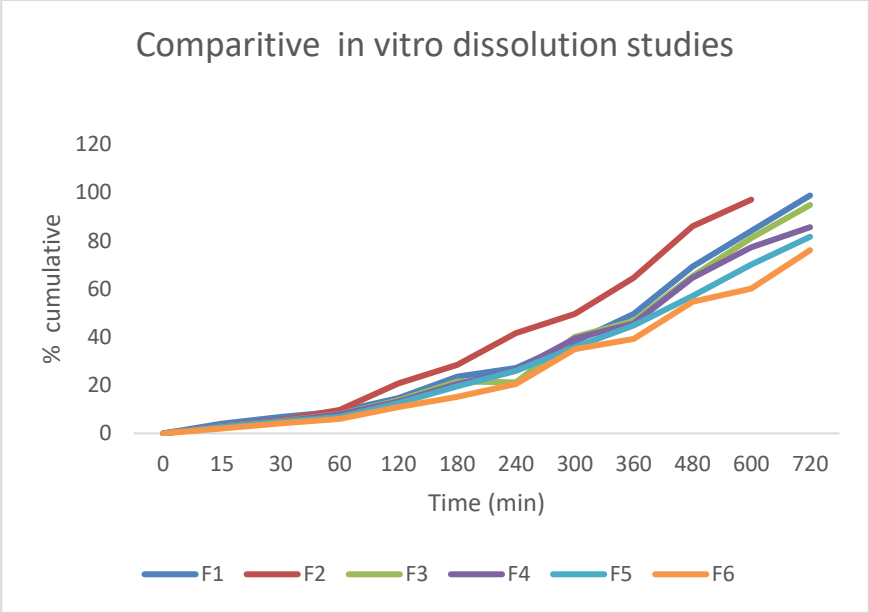


**Fig-3: Comparative *invitro* release profile**

*3.5 Kinetic Modeling of Drug Release*

**Table -7: Zero Order Release Kinetics Data**

| S.no | Time (min) | Cumulative % drug release | | | | | |
|---|---|---|---|---|---|---|---|
| | | **F1±SD** | **F2±SD** | **F3±SD** | **F4±SD** | **F5±SD** | **F6±SD** |
| 1 | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| 2 | 15 | 4.00±0.11 | 3.07±1.62 | 3.0±0.61 | 2.95±1.06 | 2.75±0.59 | 2.05±0.23 |
| 3 | **30** | 6.86±0.11 | 5.5±1.06 | 5.06±0.61 | 4.93±0.61 | 4.77±0.59 | 4.11±0.23 |
| 4 | **60** | 9.05±0.20 | 9.8±1.06 | 8.05±0.61 | 7.89±1.06 | 6.84±0.59 | 6.02±0.23 |
| 5 | **120** | 14.67±0.41 | 20.8±1.23 | 13.67±0.61 | 13.27±0.0 | 12.50±0.5 | 10.9±0.23 |
| 6 | **180** | 23.57±0.31 | 28.45±2.2 | 21.57±1.06 | 20.46±0.6 | 19.60±0.5 | 15.26±0.6 |
| 7 | **240** | 27.13±0.35 | 41.65±1.6 | 27.13±0.61 | 26.22±0.6 | 25.90±1.0 | 20.46±0.0 |
| 8 | **300** | 38.1±0.23 | 49.6±2.21 | 40.1±1.06 | 39.45±1.0 | 35.84±0.59 | 34.96±0.2 |
| 9 | **360** | 49.66±0.11 | 64.7±1.62 | 46.66±0.61 | 45.62±1.2 | 44.83±0.5 | 39.29±0.6 |
| 10 | **480** | 69.34±0.12 | 86.0±1.23 | 65.34±1.06 | 64.58±1.0 | 57.13±1.5 | 54.61±0.4 |
| 11 | **600** | 84.07±0.63 | 97.07±1.2 | 81.07±1.06 | 77.28±0.6 | 70.04±2.0 | 60.06±0.4 |
| 12 | **720** | 98.82±0.32 | _ | 94.87±1.04 | 85.64±1.2 | 81.67±1.58 | 76.08±0.2 |

SD=standard deviation (n=3)

**Table -8: First Order Release Kinetics Data**

| Time (min) | Log Cumulative % drug release remain to be released | | | | | |
|---|---|---|---|---|---|---|
| | **F1±SD** | **F2±SD** | **F3±SD** | **F4±SD** | **F5±SD** | **F6±SD** |
| 0 | **0** | **0** | **0** | **0** | **0** | **0** |
| **15** | 1.98±0.004 | 1.98±0.008 | 1.98±0.002 | 1.98±0.008 | 1.98±0.003 | 1.99±0.003 |
| 30 | 1.96±0.005 | 1.97±0.008 | 1.97±0.003 | 1.97±0.079 | 1.97±0.001 | 1.98±0.002 |
| 60 | 1.95±0.005 | 1.95±0.006 | 1.96±0.009 | 1.96±0.009 | 1.96±0.056 | 1.97±0.001 |
| 120 | 1.93±0.008 | 1.89±0.005 | 1.93±0.007 | 1.93±0.009 | 1.94±0.004 | 1.94±0.003 |
| 180 | 1.88±0.005 | 1.85±0.003 | 1.89±0.008 | 1.90±0.007 | 1.90±0.002 | 1.92±0.001 |
| 240 | 1.86±0.005 | 1.76±0.003 | 1.86±0.045 | 1.86±0.008 | 1.86±0.008 | 1.90±0.02 |
| 300 | 1.79±0.003 | 1.70±0.021 | 1.77±0.046 | 1.95±0.005 | 1.80±0.002 | 1.81±0.005 |
| 360 | 1.70±0.023 | 1.54±0.001 | 1.72±0.008 | 1.73±0.005 | 1.74±0.003 | 1.78±0.078 |
| 480 | 1.48±0.045 | 1.14±0.056 | 1.53±0.005 | 1.54±0.006 | 1.63±0.006 | 1.65±0.00 |
| 600 | 1.20±0.004 | 0.46±0.007 | 1.27±0.046 | 1.35±0.023 | 1.47±0.068 | 1.60±0.00 |
| 720 | 0.07±0.006 | - | 0.71±0.004 | 1.15±0.005 | 1.26±0.056 | 1.38±0.089 |

SD=standard deviation (n=3)

**Table -9: Higuchi release mechanism kinetics data**

| √T (min) | Cumulative % drug release | | | | | |
|---|---|---|---|---|---|---|
| | **F1±SD** | **F2±SD** | **F3±SD** | **F4±SD** | **F5±SD** | **F6±SD** |
| 0 | **0** | **0** | **0** | **0** | **0** | **0** |
| **3.872** | 4.00±0.11 | 3.07±1.62 | 3.0±0.61 | 2.95±1.06 | 2.75±0.59 | 2.05±0.23 |
| **5.477** | 6.86±0.11 | 5.5±1.06 | 5.06±0.61 | 4.93±0.61 | 4.77±0.59 | 4.11±0.23 |
| **7.745** | 9.05±0.20 | 9.8±1.06 | 8.05±0.61 | 7.89±1.06 | 6.84±0.59 | 6.02±0.23 |
| **10.954** | 14.67±0.41 | 20.8±1.23 | 13.67±0.61 | 13.27±0.0 | 12.50±0.5 | 10.9±0.23 |
| **13.416** | 23.57±0.31 | 28.45±2.2 | 21.57±1.06 | 20.46±0.6 | 19.60±0.5 | 15.26±0.6 |
| **15.491** | 27.13±0.35 | 41.65±1.6 | 27.13±0.61 | 26.22±0.6 | 25.90±1.0 | 20.46±0.0 |
| **17.32** | 38.1±0.23 | 49.6±2.21 | 40.1±1.06 | 39.45±1.0 | 35.84±0.59 | 34.96±0.2 |
| **18.973** | 49.66±0.11 | 64.7±1.62 | 46.66±0.61 | 45.62±1.2 | 44.83±0.5 | 39.29±0.6 |
| **21.908** | 69.34±0.12 | 86.0±1.23 | 65.34±1.06 | 64.58±1.0 | 57.13±1.5 | 54.61±0.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **24.494** | 84.07±0.63 | 97.07±1.2 | 81.07±1.06 | 77.28±0.6 | 70.04±2.0 | 60.06±0.4 |
| **26.832** | 98.82±0.32 | _ | 94.87±1.04 | 85.64±1.2 | 81.67±1.58 | 76.08±0.2 |

SD=standard deviation (n=3)

**Table -10: Peppas Release Kinetics Data**

| Log Time (min) | Log Cumulative % drug release | | | | | |
|---|---|---|---|---|---|---|
| | **F1±SD** | **F2±SD** | **F3±SD** | **F4±SD** | **F5±SD** | **F6±SD** |
| 0 | **0** | **0** | **0** | **0** | **0** | **0** |
| **1.176** | 0.60±0.008 | 0.48±0.006 | 0.47±0.005 | 0.46±0.005 | 0.43±0.005 | 0.31±0.00 |
| **1.477** | 0.83±0.007 | 0.74±0.007 | 0.74±0.008 | 0.6±0.009 | 0.67±0.006 | 0.61±0.023 |
| **1.778** | 0.95±0.002 | 0.95±0.003 | 0.90±0.007 | 0.89±0.007 | 0.83±0.005 | 0.77±0.009 |
| **1.079** | 1.16±0.004 | 1.31±0.008 | 1.13±0.006 | 1.12±0.007 | 1.09±0.007 | 1.03±0.007 |
| **2.255** | 1.37±0.004 | 1.4±0.005 | 1.33±0.005 | 1.31±0.006 | 1.2±0.006 | 1.18±0.009 |
| **2.38** | 1.43±0.009 | 1.61±0.004 | 1.43±0.007 | 1.41±0.006 | 1.41±0.005 | 1.31±0.00 |
| **2.477** | 1.580.027 | 1.69±0.008 | 1.60±0.006 | 1.59±0.076 | 1.55±0.007 | 1.54±0.02 |
| **2.556** | 1.69±0.004 | 1.81±0.065 | 1.66±0.076 | 1.65±0.008 | 1.65±0.005 | 1.59±0.007 |
| **2.681** | 1.84±0.008 | 1.93±0.065 | 1.81±0.008 | 1.81±0.008 | 1.75±0.006 | 1.73±0.00 |
| **2.778** | 1.92±0.008 | 1.98±0.027 | 1.90±0.008 | 1.88±0.076 | 1.84±0.007 | 1.84±0.007 |
| **2.857** | 1.99±0.076 | - | 1.97±0.009 | 1.93±0.008 | 1.91±0.005 | 1.88±0.023 |

SD=standard deviation (n=3)

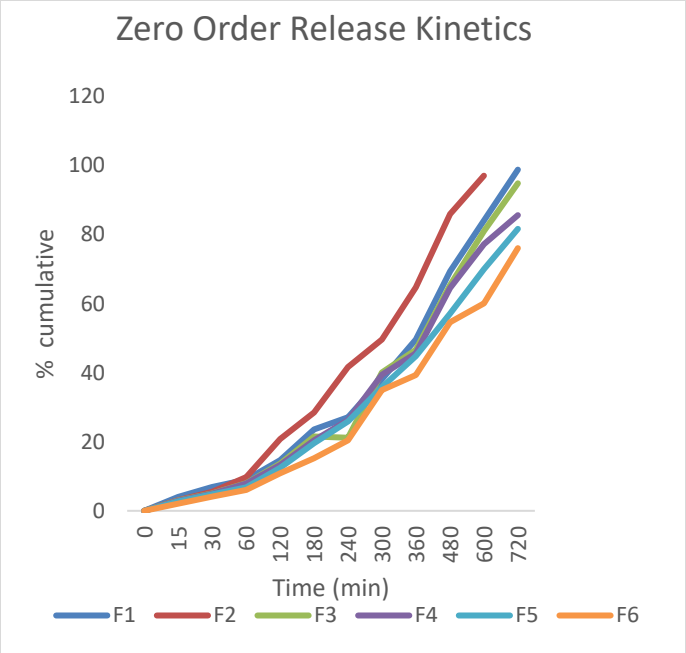


**Fig-4: Zero order kinetic**

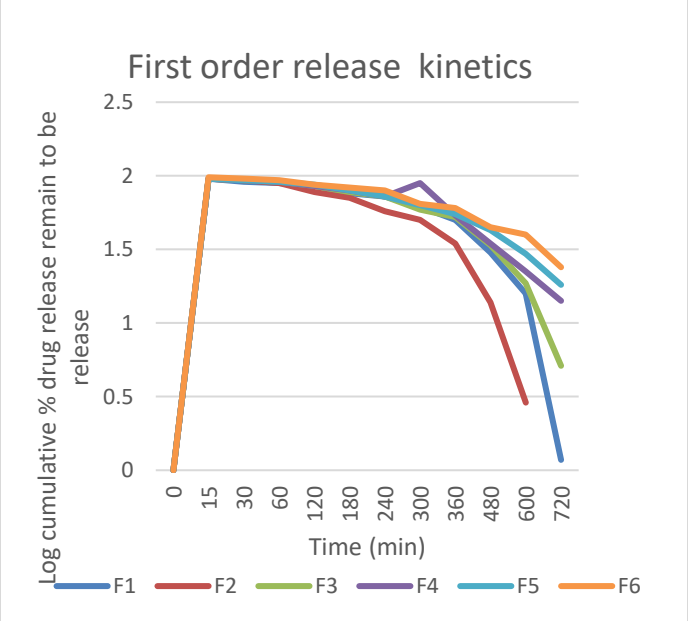


**Fig-5: First order kinetic**

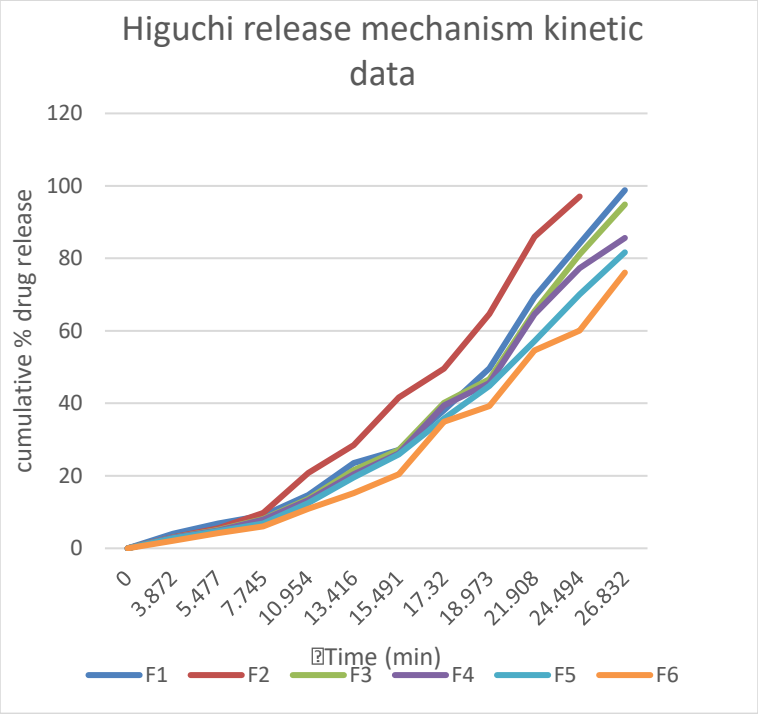


**Fig-6: Higuchi release kinetics**

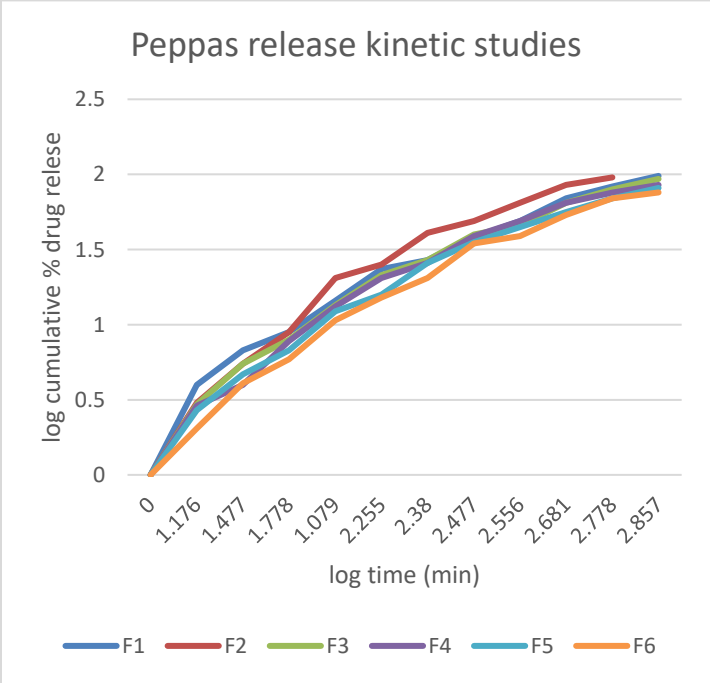


**Fig-7: Peppas release kinetics**

**Table-1: Regression co-efficient ($r^2$) of different kinetic models and diffusion exponent (n) of Peppas model**

| Batch no | Zero order $r^2$ | First order $r^2$ | Higuchi matrix $r^2$ | Peppas plot | |
|---|---|---|---|---|---|
| | | | | $r^2$ | n |
| **F1** | 0.993 | 0.962 | 0.903 | 0.908 | 0.653 |
| **F2** | 0.994 | 0.998 | 0.926 | 0.903 | 0.649 |
| **F3** | 0.998 | 0.970 | 0.903 | 0.896 | 0.666 |
| **F4** | 0.992 | 0.900 | 0.909 | 0.891 | 0.662 |
| **F5** | 0.996 | 0.958 | 0.924 | 0.889 | 0.656 |
| **F6** | 0.989 | 0.958 | 0.908 | 0.869 | 0.652 |

## 4. CONCLUSION:

As per the release studies F2 formulation is considered to be the best formulation, the drug was retarding up to 12 hrs with 94.87 % drug release which follows Zero order and Non-Fickian mechanism. The formulation F2 showed maximum cumulative amount of release than other formulationF1, $F_3$, F4, F5 and F6.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

## Acknowledgements

The authors are thankful to Amratlal and Co. Chennai, India for providing Metformin HCl as gift sample and we also thank Vijaya Institute of Pharmaceutical Sciences for women, Andhra Pradesh, India for providing necessary facilities to carry out this work.

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