INTRODUCTION

Oral drug delivery is preferred route of administration for most of the active drug molecules due to its several advantages like greater flexibility in design and high patient compliance. Because of greater stability, accuracy in dose, easy of production, formulation of tablets is preferred oral dosage form. Tablet availability in market range from relatively simple immediate-release (IR) formulation to complex sustained release (SR) or modified release dosage forms [1].

Sustained release drug delivery system was aimed to release the medication in a prolonged rate to maintain plasma drug levels. The drugs having shorter half life are suitable for the sustained drug delivery system. The main objective in designing sustained delivery system is to reduce dosing frequency and thereby increasing the action [2]. The drug molecules shows better sustained drug release profile in matrix systems by different mechanisms [3].

Type-2 diabetes mellitus is a chronic progressive disorder characterized by defective insulin secretion and increased insulin resistance. It is widely accepted that it required intense and tight glycemic control to prevent several cardiovascular complications. Metformin hydrochloride is an orally administered biguanide, widely used in the management of type-2 diabetes, a common disease that combines defects of both insulin secretion and insulin action (6). It is a hydrophilic drug which slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability is reported to be of 50 - 60% has relatively short biological half life of 1.5 - 4.5 hours. However, frequent dosing schedule and risk of gastrointestinal symptoms make its dose optimization complicated. Thus, it is reasonable to assume the requirement of sustained release metformin formulation to prolong its duration of action and to improve patient compliance [4].

In the present study Metformin HCl sustained release tablets were prepared by wet granulation method using natural and synthetic polymers in varying concentrations.

MATERIALS & METHODS

Materials:

Metformin was obtained as gift sample from Madras Pharmaceuticals Ltd, Chennai, Hydroxy propyl methyl cellulose, Eudragit, Xanthan gum and Guar gum

ABSTRACT

The oral route of administration for sustained release drug delivery systems has received greater attention because of more flexibility in design and high patient compliance. Metformin hydrochloride is an antidiabetic agent which improves glucose tolerance in patients with type 2 diabetes and reduces basal plasma levels of glucose. The present study was aimed to formulate Metformin sustained release tablets using wet granulation method using polymers Xanthan gum, Guar gum, HPMC and Eudragit. Different formulations were prepared by changing ratios of polymers. The prepared tablets were characterized for different physical parameters to comply with pharmacopeial limits. In vitro dissolution profiles of the all formulations were studied in 0.1 N HCl for first 2 hours then 6.8 pH phosphate buffer for next 10 hours. It was found that sustained release tablets formulated with Guar gum produced drug release for 12 hours and they showed significant slower drug release rates than other formulations. The kinetics studies revealed that most of the formulations followed the zero-order release pattern. FTIR spectral studies showed that there is no interaction between the drug and excipients. In conclusion, development of Metformin HCl sustained release tablets is a good approach to sustain the release rate to overcome frequent administration and also to release the drug for a prolong 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.

Keywords: Metformin Hydrochloride, Guar gum, Sustained release tablets, FTIR.
were received as gift samples from Drugs India, Hyderabad. All others reagents and chemicals used were purchased from Merck chemicals, India, and were of analytical reagent grade.

METHODS

Pre formulation studies
Drug-Excipient Compatibility Studies
FTIR was used for the detection of any possible chemical reaction between the drug and the excipients. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks [5].

Preparation of Metformin HCl Sustained Release Tablets
Different formulations containing Metformin HCl were prepared by wet granulation technique using 20, 25 and 30 % concentrations of polymer and lactose as filler. All the powders were passed though #60 sieve. To this a liquid binder is added, passing the wetted mass through a screen of the desired mesh size, drying the granulation and then passing through a second screen of smaller mesh to reduce further the size of the granules [6,7]. Dried granules were passed through #20 and lubricated it with magnesium stearate and Aerosil. Then the lubricated granules were compressed into tablets using tablet punching machine. The compressed tablets were de dusted and evaluated for various tablet properties shown in Table 2.

Table 1: Formulation of Metformin HCL Tablets (F1-F12)

<table>
<thead>
<tr>
<th>Ingredients(mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
<th>F11</th>
<th>F12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>HPMC</td>
<td>160</td>
<td>200</td>
<td>240</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>Guar gum</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>160</td>
<td>200</td>
<td>240</td>
<td>--</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td>Xanthan gum</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>160</td>
<td>200</td>
<td>240</td>
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<td>--</td>
</tr>
<tr>
<td>Eudragit</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>160</td>
<td>200</td>
<td>240</td>
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</tr>
<tr>
<td>Lactose monohydrate</td>
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<td>88</td>
<td>48</td>
<td>128</td>
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<td>88</td>
<td>48</td>
<td>128</td>
<td>88</td>
<td>48</td>
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<tr>
<td>Magnesium stearate</td>
<td>8</td>
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<td>8</td>
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<td>8</td>
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<td>Aerosil</td>
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<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total weight</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>800</td>
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<td>800</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>800</td>
</tr>
</tbody>
</table>

EVALUATION

Pre Compression Studies

Angle of Repose:
The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface [8]. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

\[ \tan \theta = \frac{h}{r} \]

Table 2: Pharmacopoeial specifications for angle of repose

<table>
<thead>
<tr>
<th>Angle of repose(°)</th>
<th>Type of flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>Excellent</td>
</tr>
<tr>
<td>25 – 30</td>
<td>Good</td>
</tr>
<tr>
<td>30 – 40</td>
<td>Passable</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>Very Poor</td>
</tr>
</tbody>
</table>

Where h and r are the height and radius of the powder cone respectively.

Bulk Density:
Both loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated by using the following formulas.

\[ \text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the powder}} \]

\[ \text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the powder}} \]

Compressibility Index:
The compressibility index of the granules was determined by Carr’s compressibility index [9].

\[ \text{Carr’s index (}% = \frac{\text{TBD-LBD}}{\text{TBD}} \times 100 \]

Table 3: Pharmacopoeial specifications for Carr’s index

<table>
<thead>
<tr>
<th>% Comp. Index</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-15</td>
<td>Excellent</td>
</tr>
<tr>
<td>12-18</td>
<td>Good</td>
</tr>
<tr>
<td>18-21</td>
<td>Fair</td>
</tr>
<tr>
<td>23-35</td>
<td>Poor</td>
</tr>
<tr>
<td>33-38</td>
<td>Very poor</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Very very poor</td>
</tr>
</tbody>
</table>

Hausner's ratio:
Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following Formula

\[ \text{Hausner’s ratio} = \frac{D_T}{D_B} \]

Where, \(D_T\) is the tapped density, \(D_B\) is the bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression parameters

Weight variation:
All prepared matrix tablets were evaluated for weight variation. In this twenty tablets of each batch were used to evaluate weight variation among tablets and standard deviation was calculated [10].
Friability: 
Friability testing was done by Friability test apparatus (Lab India Friability Apparatus FT 1020). The percentage friability was then calculated by,

\[ \% \text{ Friability} = \left\{ \left( \frac{W_1 - W_2}{W_1} \right) \times 100 \right\} \]

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

Hardness: 
Hardness of all batches was determined using Tablet hardness tester (Monsanto hardness tester).

Thickness: 
Thickness was measured by vernier calipers and readings were carried out in triplicate and average value was noted.

Drug content: 
Twenty tablets were weighed and its average weight was taken which was crushed in motor and pestle. The powder weight equivalent to single tablets i.e. 500 mg was dissolved in 10 mL water in a 100 mL volumetric flask and allowed to stand for 10 min. To that 75 mL of methanol was added initially followed by addition of sufficient methanol to produce 100 mL which was then filtered through whatmann filter paper. 5 mL of this resulting solution was further diluted to 50 mL with 7.2 pH phosphate buffer: methanol (1: 1). Again 5 mL was diluted to 50 mL by the same solvent. The absorbance of each of the standard and sample solution were taken in UV-visible spectrophotometer at 233 nm using equal volumes of 7.2 pH phosphate buffer and methanol as blank [11].

In vitro drug release studies: 
The in vitro release of drug from Metformin matrix Tablets was carried out for 12 hours using paddle type tablet dissolution apparatus containing 900 ml of dissolution medium maintained at 37±0.5°C and speed of agitation at 100 rpm. For the first 2 hours, 0.1N HCl buffer solution was used as dissolution medium and then the dissolution medium was changed by replacing with pH 6.8 phosphate buffer for further 10 hours. At prefixed time interval, 5 ml of solution was withdrawn and analyzed spectrophotometrically at 233 nm after suitable dilution [12].

Release Kinetics 
The order of drug release from matrices was described by using zero order and first order kinetics [13, 14].

Zero order equation: 
This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fitted into the zero order equation:

\[ Q = Q_0 - K_0 t \]

Where,
\( Q \) = Amount of drug released at time \( t \),
\( Q_0 \) = Amount of drug released initially,
\( K_0 \) = Zero order rate constant.

A graph of concentration vs. time would yield a straight line with a slope equal to \( K_0 \) and the intercept at the origin of the axis. The zero order plot is derived from plotting the cumulative percent drug dissolved vs. time.

First order equation: 
The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species. Release behaviour generally follows the following first order release equation:

\[ \ln M = \ln M_0 - K_1 t \]

Where, 
\( M \) is the amount of drug undissolved at time \( t \),
\( M_0 \) is the amount of drug undissolved at \( t = 0 \) and
\( K_1 \) is the corresponding release rate constant.

A graph of log concentration of drug remaining Vs time yields a straight line with a negative slope.

Higuchi square root law: 
A form of the Higuchi Square Root Law is given by equation

\[ Q = K_2 t^{1/2} \]

Where, 
\( Q \) = Amount of drug dissolved at time \( t \)
\( K_2 \) = Higuchi rate constant

The Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

Korsmeyer- peppas equation: 
The Korsmeyer equation which derived from the linear line of log cumulative percentage drug release Vs log time curve is

\[ \frac{M_t}{M_{\infty}} = Kt^n \]

Where \( M_t \) and \( M_{\infty} \) are the absolute and the cumulative amount of drug released in time \( t \) and infinite time; \( k \) is a constant incorporating the structural and geometric characteristics of the device and \( n \) is the release exponent which is indicative of the mechanism of release. This is also known as the power law, if \( n \) is equal to 0.89, the release is case II transport. If \( n \) is equal to 0.45 the release is best explained by Fickian diffusion, and if 0.45 < \( n < 0.89 \) then the release is through anomalous diffusion or non Fickian diffusion (Swellable & Cylindrical Matrix) [17]. In this model, a plot of \( \log (M_t/M_{\infty}) \) versus \( \log (t) \) is linear.

RESULTS

FTIR Studies: 
The compatibility of Metformin with different polymer was studied by FTIR spectroscopy. The IR spectra of pure drug of Metformin are depicted in Figure 1. The IR spectra of Metformin along with polymer are shown in Figure 2. The overall observation of IR study suggested that formulation development of drugs in combination with excipients, the functionalities of drugs were unreacted and hence combination of drugs along with excipients can be formulated safely.

Evaluation of Granules: 
The precompression parameters of powder blend for metformin sustained release tablets are shown in Table 4. The bulk density was within range of 0.612 to
0.680 gm/cm³ with tapped density in range of 0.754 to 0.847 gm/cm³ indicated good to fair packaging capacity of blend. The Carr’s compressibility index was within 18.27 to 20.67 value suggested fair compressibility of powder blend. The angle of repose was 25.48 to 29.51º suggested good flowability with Hausner’s ratio of 1.22 to 1.26 suggested fair flowability of powder blend. Hence all the precompression parameters obtained for the powder blends to be compressed as Metformin sustained release tablets were within the acceptable limits of pharmacopoeial specification.

**Evaluation of Tablets:**

The sustained release tablets of Metformin was formulated by Wet granulation method using different drug to polymer ratios and finally optimized in the ratio of 1:2.5 for the drug to polymer. In all the formulations, the ratio of Metformin was fixed. All the batches were produced under similar condition to avoid processing variables. The prepared sustained release tablets of Metformin were evaluated for post compression parameters and drug content and results were tabulated in Table 5. The hardness of prepared Metformin tablets was in the range of 7.25-7.94 kg/cm² which was in acceptable range of sustained release formulation. The hardness was high for the layers containing Xanthan gum and low hardness was observed in layer containing HPMC. The thickness of all the formulated sustained release tablets was in range of 6.10 to 6.41 due to the constant tablet press setting across all the batches irrespective of weight variation. The average weight of formulated layer was found to be uniform in the range of 800-803mg and the percent deviation in weight variation for all the formulated tablets was within the acceptable range of pharmacopoeial specification. The percent friability value for all formulated tablets was in range 0.31 to 0.58% indicated good handling properties of tablets. The drug content was in the range of 95.08 to 98.94% for all the tablets suggested uniform dispersion of Metformin in formulated sustained release tablets.

**In Vitro drug release:**

The in vitro drug release study of Metformin from sustained release tablets was conducted for first two hour in 0.1N HCl and then the dissolution study was continued in pH 6.8 phosphate buffer for next 10 hours. The in vitro release data of Metformin from sustained release tablets is tabulated in Table 6 and illustrated in figure 3. The in vitro release of Metformin was slow in 0.1N HCl due to the slow swelling of polymer matrix used in the preparation of sustained release tablets. After two hours 57 % from HPMC, 46% from Guar gum, 69 % from Xanthum gum and only 63 % from Eudragit polymer matrix of sustained release tablets was released. The in vitro release was rapid in pH 6.8 phosphate buffer due to the more swelling of polymer matrix in alkaline medium. A maximum of 98 % from Guar gum polymer matrix of sustained release layer was released within 12h. The in vitro release is depending upon nature of drug, nature of polymer, drug to polymer ratio and the medium used. The overall results of in vitro release study suggested that the addition of a Guar gum more pronouncedly retard the drug release.

**Drug release Kinetics:**

The mechanism of release for the optimized formulation was determined by fitting dissolution data in to different kinetic models viz. Zero-order, First-order, Higuchi, and Korsmeyer-Peppas corresponding to the release data of formulations. For most of the formulations the R² value of Korsmeyer-Peppas and zero-order model is very near to 1 than the R² values of other kinetic models. Thus it can be said that the drug release follows Korsmeyer-Peppas and zero-order model mechanism. The drug release kinetics for optimized formulation (F5) showed in Figures 4, 5, 6 and 7.

---

*Fig. 1: FTIR of Metformin*
Table 4: Precompression parameters of Metformin Sustained Release Tablets

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Bulk density (gm/ml)</th>
<th>Tapped density (gm/ml)</th>
<th>Carr’s Index (%)</th>
<th>Hausner’s ratio</th>
<th>Angle of repose (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.61±0.01</td>
<td>0.75±0.04</td>
<td>18.56±0.05</td>
<td>1.22±0.03</td>
<td>28.38±0.06</td>
</tr>
<tr>
<td>F2</td>
<td>0.66±0.01</td>
<td>0.81±0.03</td>
<td>18.59±0.06</td>
<td>1.22±0.02</td>
<td>27.36±0.04</td>
</tr>
<tr>
<td>F3</td>
<td>0.64±0.02</td>
<td>0.79±0.02</td>
<td>18.27±0.03</td>
<td>1.23±0.03</td>
<td>25.55±0.03</td>
</tr>
<tr>
<td>F4</td>
<td>0.61±0.01</td>
<td>0.76±0.03</td>
<td>20.12±0.03</td>
<td>1.25±0.02</td>
<td>29.11±0.06</td>
</tr>
<tr>
<td>F5</td>
<td>0.66±0.01</td>
<td>0.82±0.02</td>
<td>19.34±0.03</td>
<td>1.23±0.02</td>
<td>27.72±0.07</td>
</tr>
<tr>
<td>F6</td>
<td>0.66±0.03</td>
<td>0.82±0.03</td>
<td>19.19±0.05</td>
<td>1.23±0.02</td>
<td>28.14±0.07</td>
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<tr>
<td>F7</td>
<td>0.67±0.02</td>
<td>0.84±0.03</td>
<td>20.19±0.02</td>
<td>1.25±0.04</td>
<td>28.39±0.06</td>
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<tr>
<td>F8</td>
<td>0.65±0.02</td>
<td>0.83±0.02</td>
<td>20.67±0.01</td>
<td>1.26±0.04</td>
<td>26.31±0.02</td>
</tr>
<tr>
<td>F9</td>
<td>0.63±0.02</td>
<td>0.78±0.02</td>
<td>19.53±0.01</td>
<td>1.24±0.03</td>
<td>25.48±0.06</td>
</tr>
<tr>
<td>F10</td>
<td>0.66±0.01</td>
<td>0.83±0.02</td>
<td>19.64±0.02</td>
<td>1.24±0.05</td>
<td>28.47±0.04</td>
</tr>
<tr>
<td>F11</td>
<td>0.68±0.02</td>
<td>0.83±0.04</td>
<td>18.57±0.03</td>
<td>1.22±0.04</td>
<td>27.23±0.05</td>
</tr>
<tr>
<td>F12</td>
<td>0.66±0.03</td>
<td>0.81±0.01</td>
<td>18.73±0.03</td>
<td>1.23±0.05</td>
<td>29.51±0.04</td>
</tr>
</tbody>
</table>

Each value represents as mean ± SD of three determinants

Table 5: Evaluation parameters of Metformin sustained release Tablets

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Hardness Kg/cm²</th>
<th>Thickness (cm)</th>
<th>Friability (%)</th>
<th>Weight Variation (mg)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7.25±0.02</td>
<td>6.10±0.03</td>
<td>0.58±0.05</td>
<td>800±0.01</td>
<td>98.70</td>
</tr>
<tr>
<td>F2</td>
<td>7.53±0.02</td>
<td>6.12±0.03</td>
<td>0.50±0.05</td>
<td>800±0.03</td>
<td>99.25</td>
</tr>
<tr>
<td>F3</td>
<td>7.46±0.01</td>
<td>6.10±0.02</td>
<td>0.52±0.05</td>
<td>802±0.03</td>
<td>98.42</td>
</tr>
<tr>
<td>F4</td>
<td>7.31±0.03</td>
<td>6.40±0.01</td>
<td>0.33±0.05</td>
<td>801±0.02</td>
<td>97.52</td>
</tr>
<tr>
<td>F5</td>
<td>7.59±0.03</td>
<td>6.41±0.01</td>
<td>0.31±0.03</td>
<td>800±0.03</td>
<td>99.24</td>
</tr>
<tr>
<td>F6</td>
<td>7.87±0.02</td>
<td>6.41±0.01</td>
<td>0.32±0.05</td>
<td>801±0.03</td>
<td>98.63</td>
</tr>
<tr>
<td>F7</td>
<td>7.94±0.05</td>
<td>6.11±0.02</td>
<td>0.45±0.04</td>
<td>800±0.05</td>
<td>98.15</td>
</tr>
<tr>
<td>F8</td>
<td>7.81±0.06</td>
<td>6.11±0.03</td>
<td>0.49±0.01</td>
<td>803±0.04</td>
<td>99.42</td>
</tr>
<tr>
<td>F9</td>
<td>7.48±0.05</td>
<td>6.12±0.02</td>
<td>0.51±0.01</td>
<td>800±0.05</td>
<td>99.14</td>
</tr>
<tr>
<td>F10</td>
<td>7.66±0.06</td>
<td>6.18±0.03</td>
<td>0.37±0.01</td>
<td>800±0.05</td>
<td>99.25</td>
</tr>
<tr>
<td>F11</td>
<td>7.87±0.04</td>
<td>6.19±0.03</td>
<td>0.34±0.02</td>
<td>800±0.04</td>
<td>99.30</td>
</tr>
<tr>
<td>F12</td>
<td>7.75±0.06</td>
<td>6.18±0.02</td>
<td>0.41±0.01</td>
<td>800±0.05</td>
<td>99.17</td>
</tr>
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</table>

Each value represents as mean±SD of three determinants
Table 6: *In vitro* Drug release data of Metformin Sustained Release Tablets

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
<th>F11</th>
<th>F12</th>
</tr>
</thead>
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<tr>
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<td>38</td>
<td>35</td>
<td>37</td>
<td>28</td>
<td>23</td>
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<td>39</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
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Figure 3: Comparison of Dissolution Profile of all formulations containing Metformin as sustained release layer (F1-F12)

Figure 4: zero Order Kinetics of Optimized formulation (F5)
Figure 5: First Order Kinetics of Optimized formulation (F5)

Figure 6: Higuchi Plot of Optimized formulation (F5)

Figure 7: Korsmeyer- Peppas Plot of Optimized formulation (F5)

CONCLUSION

In the present study, to reach an intended target release profile, SR formulation of Metformin HCl tablets were developed with natural and synthetic polymers such as Xanthan gum, Guar gum, HPMC and Eudragit by wet granulation method. All the prepared tablets were evaluated for various evaluation parameters. From results of the present study clearly indicated a promising potential of sustained release Metformin HCl tablets containing Guar gum as rate controlling polymer (F5) demonstrated slow release when compared with other formulations. In conclusion, development of Metformin HCl sustained release tablets could be used for effectively treating diabetes mellitus, increasing patient compliance, reducing the dosing frequency and also produces desirable blood concentrations and decrease the incidence of adverse effects.

REFERENCES


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