FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE SUSTAINED-RELEASE ORAL MATRIX TABLETS

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ABSTRACT

Objective: The aim of this investigation was to develop and optimize metformin hydrochloride matrix tablets for sustained release application. The sustained release matrix tablet of metformin hydrochloride was prepared by wet granulation technique using chitosan, xanthan gum, and hydroxypropyl methylcellulose at varying concentrations.

Material and Methods: Extended release of metformin hydrochloride matrix tablets was prepared by wet granulation method. The influence of varying the polymer ratios was evaluated. The excipients used in this study did not alter physicochemical properties of the drug.

Results: All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity. The in vitro drug dissolution study was carried out using USP apparatus Type II, paddle 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. This study revealed that as the concentration of matrix material increased, drug release from matrices decreased. This may be due to slower penetration of the dissolution medium into the matrices.

Conclusion: Formulation with chitosan MS1 drug release was 86%, xanthan gum MS489%, and finally MS7 with hydroxypropyl methylcellulose which exhibited the highest drug release retardation also had the lowest matrix concentration. Hence, lower concentration of polymers is suitable to prepare metformin hydrochloride tablets compared to higher concentrations.

Keywords: Sustained release tablet, Metformin hydrochloride, Hydroxypropyl methyl cellulose, Xanthan gum, Chitosan.

INTRODUCTION

Oral route of administration is considered as widely accepted route due to ease of convenience by self-administration, compactness, and simple manufacturing process. It was observed that drugs administered by oral route produce 90% of systemic effects [1]. Tablets being most popular oral formulations available in the market are widely preferred by patients and physicians alike in long-term therapy for the treatment of chronic conditions [2]. Conventional dosage form produces the wide range of fluctuation in drug concentration in bloodstream which leads to a loss in drug effectiveness or increases the incidence of side effects with subsequent undesirable toxicity and poor efficiency. However, sustained or controlled drug delivery systems can decrease the frequency of the dosing and also increases effectiveness of the drug by localization at the site of action, reducing the dose required and providing uniform drug delivery [3]. Sustained release matrix tablets is relatively easy to fabricate by incorporating the drug in slowly dissolving or inert porous polymer materials [4]. Drug release through matrix system is determined by water penetration, polymer swelling, drug dissolution, drug diffusion, and matrix erosion that lead to a rapid formation of external layer, allowing drug release modification [5]. The major therapeutic goals in subjects with Type II diabetes are to optimize blood glucose control, reduce overweight, and elevate blood pressure. However, pharmacological treatment with oral hypoglycemic agents or insulin is required [6]. An oral biguanide metformin hydrochloride used in the management of Type II diabetes, a common disease that combines defects of both insulin secretion and insulin action. Unlike other antidiabetic drugs metformin Hcl does not induce hypoglycemic at any reasonable dose, and hence it is called as an antihyperglycemic rather than a hypoglycemic drug. The compound has a relatively short plasma half-life of 1.5–4.5 h with low bioavailability of 50–60% so need for the administration of 2–3 times a day when larger doses are required can decrease patient compliance [7]. The objective of the present study was to prepare oral sustained release matrix tablet of metformin hydrochloride by wet granulation using polymers such as chitosan, xanthan gum, and hydroxypropyl methylcellulose and to evaluate the effect of concentration of polymers for the release of the drug. Such a sustained release formulation if achieved would be substantially more affordable to the patient.

MATERIAL AND METHODS

Materials

Metformin hydrochloride was the gift sample from Aurobindo Pharma Ltd., Hyderabad. All other ingredients used throughout the study were of analytical grade such as chitosan, hydroxypropyl methylcellulose, and xanthan gum were received from Loba Chemicals, Mumbai. Isopropyl alcohol, talc, and magnesium stearate were procured from S.D. Fine Chemicals, Mumbai.

Nine different tablet formulations were prepared using wet granulation method. The composition of tablets was given in Table 1. Sustained release matrix tablets of metformin hydrochloride were prepared using different polymer ratios. All ingredients were passed through a #80 sieve weighed on a digital balance (Shimadzu, Japan) and blended. Tablets weighing 750 mg were prepared containing 500 mg of metformin hydrochloride, hydroxypropyl methylcellulose, xanthan gum, and chitosan. Required quantities of drug, diluents, and polymers were mixed thoroughly by
adding a sufficient quantity of binding agent like isopropyl alcohol slowly. After enough cohesiveness was obtained, the wet mass was sieved through #16 mesh. The sifted granules were dried at 50°C for 1 h in hot air oven (BTL, Bio Technics, Mumbai). The dried granules were mixed with talc as a dihent and magnesium stearate as a lubricant for 5 min [6]. Finally, tablets were compressed by 10 mm punches on 16 Station Rotary tablet machine (Saimach Ltd., India). All tablets were stored in air tight containers for further study. Before compression, the granules were evaluated for their flow and compressibility characteristics.

EVALUATION OF POWDER BLENDS OF METFORMIN HYDROCHLORIDE

The powder blends of metformin hydrochloride formulations were evaluated before compression to assess the flow properties of the powder.

Bulk density
Required amount of powder m was transferred into the measuring cylinder, and apparent volume Vₐ was measured, bulk density in g per ml is calculated by the formula.

\[
\text{Bulk density} = \frac{m}{V_a}
\]

Where m-mass of powder, Vₐ-apparent volume.

Tapped density
After determination of bulk density the measuring cylinder Va volume in ml was measured initially, later the same cylinder was set for 100 tappings on tapped density apparatus and measure the tapped volume finally Vₜ. Calculate tapped density in g per ml by the formula [9].

\[
\text{Tapped density} = \frac{V_a}{V_b}
\]

Where Va - initial volume, Vₜ-final tapped volume.

Carr’s index
It is an indirect method of measuring powder flow from bulk densities to measure bridge strength and stability. Carr’s index of each formulation was calculated according to the equation.

\[
\text{Carr’s index} = (\text{Tapped density - bulk density})/\text{tapped density} \times 100.
\]

HAUSNER RATIO
It is essential to determine the compressibility strength of powder. It was calculated according to equation [10].

\[
\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{bulk density}}
\]

Lower Hausner’s ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of repose
Accurately weighed quantity of powder was funnel into a funnel which was adjusted to a height of 2 cm in such a way that the tip of funnel touches apex of a pile of powder heap [11]. Finally, the height and radius of powder cone were measured using the following equation.

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

Where \( \theta \) = angle of repose, h = height of pile, r = radius of pile base.

EVALUATION OF METFORMIN HYDROCHLORIDE SUSTAINED-RELEASE MATRIX TABLETS

Weight variation
Ten tablets from each batch were selected randomly and weighed on a digital balance (Shimadzu, Japan) individual weights were compared with average weight. The percentage difference in the weight variation should be within the permissible limits [12].

Thickness
The thickness of all formulations was determined on screw gauge (Pharma Labs, Ahmedabad, India). Standard deviation values indicate all formulations were within the range [13].

Tablet hardness
Hardness of the tablets for shipping or breakage under conditions of storage, transportation, handling depends on hardness which was determined using Monsanto hardness tester [14] (E30, Dwarka Mai, Hyderabad).

Friability
The Friability of five tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at the height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and was subjected to 100 revolutions dedusted and reweighed [15]. The friability (F) is given by the formula:

\[
F = (1-W/W_0)\times 100
\]

Where, Wₒ is the weight of the tablets before the test. W is the weight of the tablet after the test.

Drug content
Five tablets were weighed accurately and powdered, powder equivalent to 10 mg of drug was dissolved in phosphate buffer pH 7.4, filtered using 0.2 um membrane filter [16]. The drug content was measured by ultraviolet (UV)-spectrophotometer (Shimadzu, Japan) at 233 nm.

In vitro drug release
In vitro, drug release studies for the prepared tablets were conducted using USP Type II paddle dissolution apparatus (Electrolab, Mumbai, India) at 100 rpm. One matrix tablet was placed in each flask of dissolution apparatus the study was conducted in 900 ml 0.1 N HCl 37±0.5°C in first 2 h and later 900 ml of phosphate buffer pH 7.4 for remaining 12 h. 5 ml samples were withdrawn at regular intervals and same volume was replaced to maintain sink conditions [17]. The samples were analyzed after suitable dilutions with UV-spectrophotometer (Shimadzu, Japan) at 233 nm. All the experimental units were carried in triplicates.

Kinetic analysis of dissolution data
The in vitro drug release data were fitted into zero-order, first-order, and Higuchi by employing the method of least squares the mechanism of drug release was compared for all the formulations.

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

\[
\frac{M_t}{M_\infty} = \frac{b}{K}t^{1/2}
\]

\[
\frac{M_t}{M_\infty} = a+Kt^3
\]

In Peppas equation, \( \frac{M_t}{M_\infty} \) is the fraction of drug released up to time t, K kinetic constant and n is the release exponent indicative of the release mechanism. In Higuchi and zero-order release equations, k₁, k₂, and k₃ are constants [18]. On the other hand, Higuchi equation expresses a diffuse release mechanism.

RESULTS AND DISCUSSION

In the present work, sustained-release tablets of metformin hydrochloride were prepared by wet granulation method as it was feasible and simple. Formulations were prepared by varying amount of polymers to see the effect of various polymer concentration on drug release rate. The prepared mixed powder was physically evaluated with some parameters and was suggested to be suitable for compression into tablets.
Evaluation of powder blends of metformin hydrochloride sustained-release tablets

The method employed for the preparation of metformin hydrochloride sustained-release tablets was wet granulation method, mixture of drug and excipients should possess good flow properties. Flow properties of powder blend metformin hydrochloride were checked by studying the angle of repose, compressibility index, and Hausner's ratio. The powder blends were found to be free flowing with good flow properties as shown in Table 2.

Bulk density was found to be in the range of 0.500–0.640 (g/ml) and tapped density between 0.623 and 0.647 (g/ml) for all the formulations. The % compressibility index was calculated using the density data. The obtained values 11.15–15.91% which were found to be good flow and Hausner's ratio values were in the range of 1.131–1.189 for all powder blends. This was further supported by the angle of repose values between 17.17 and 20.55°. As it was below 30° it indicated good flow properties of powder blend.

Preparation and evaluation of metformin hydrochloride sustained-release tablets

The studies were carried to find the effect of different concentrations ranges of polymers. Evaluation data of metformin hydrochloride sustained-release tablets were shown in Table 3.

All the tablets were having beveled edges flat surface in round shape with white color. Average weight of tablets was in the range of 740–769 mg and weight variation was according to the limits. Thickness of the tablets was in the range of 4.18–5.32 mm. The hardness of tablets was determined and found in the range of 6.10–7.41 Kg/cm². As the aim of the study is to release the drug slowly, hardness was kept in the high range. The % of content uniformity in tablets was determined by UV spectrophotometer (Shimadzu, Japan). All formulations are subjected to content uniformity and were in the range of 98.4–101.1%. It was observed that all the formulations were as per I.P specification limits (90.0–110.0%). The % drug release data and plot which were obtained for the metformin hydrochloride sustained-release tablets in 0.1N HCl in first 2 h and phosphate buffer pH 7.4 up to 12 h at 233 nm was shown in Table 4 and Fig. 1, respectively.

From the drug release it was observed that at low concentrations of the polymers, the matrices of the tablets readily disintegrated during dissolution test. This was not, however, the case when the content of the matrix former was increased, thus indicating that a minimum level of the polymers is required to form a proper matrix that would not readily disintegrate. This study revealed that as the concentration of matrix material increased, drug release from matrices decreased. This may be due to slower penetration of the dissolution medium into the matrices. Formulations with xanthan gum were 86% for MS1, xanthan gum was 89% for MS4, and finally MS7 with hydroxypropyl methyl cellulose for 92% which exhibited highest drug release retardation with the lowest matrix concentration. Hence, a lower concentration of polymers is suitable to prepare metformin hydrochloride tablets compared to higher concentrations. The initial drug release may be attributed to "burst" release of the drug on the tablet surface. It has stated that the drug particles present on the surface of a matrix system

### Table 1: Formulation of metformin hydrochloride sustained-release tablets

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>MS1</th>
<th>MS2</th>
<th>MS3</th>
<th>MS4</th>
<th>MS5</th>
<th>MS6</th>
<th>MS7</th>
<th>MS8</th>
<th>MS9</th>
</tr>
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<tr>
<td>Metformin hydrochloride</td>
<td>500</td>
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<td>100</td>
<td>150</td>
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<tr>
<td>Xanthan gum</td>
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<td>-</td>
<td>100</td>
<td>150</td>
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<td>HPMC</td>
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<tr>
<td>Magnesium stearate</td>
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<td>Talc</td>
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<td>Isopropyl alcohol</td>
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<td>QS</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
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<td>QS</td>
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<tr>
<td>Total weight (mg)</td>
<td>750</td>
<td>750</td>
<td>750</td>
<td>750</td>
<td>750</td>
<td>750</td>
<td>750</td>
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</tbody>
</table>

HPMC: Hydroxypropyl methylcellulose

### Table 2: Evaluation of powder blend of sustained-release tablets

<table>
<thead>
<tr>
<th>Batch No</th>
<th>Angle of repose (°)</th>
<th>Bulk density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS1</td>
<td>19.03±0.11</td>
<td>0.56±0.02</td>
<td>0.63±0.02</td>
<td>11.62 (Good)</td>
<td>1.131 (Good)</td>
</tr>
<tr>
<td>MS2</td>
<td>19.03±0.11</td>
<td>0.56±0.06</td>
<td>0.64±0.03</td>
<td>15.91 (Good)</td>
<td>1.189 (Good)</td>
</tr>
<tr>
<td>MS3</td>
<td>17.17±0.11</td>
<td>0.54±0.06</td>
<td>0.64±0.06</td>
<td>15.85 (Good)</td>
<td>1.189 (Good)</td>
</tr>
<tr>
<td>MS4</td>
<td>20.55±0.51</td>
<td>0.54±0.05</td>
<td>0.62±0.05</td>
<td>11.85 (Good)</td>
<td>1.134 (Good)</td>
</tr>
<tr>
<td>MS5</td>
<td>19.03±0.11</td>
<td>0.50±0.06</td>
<td>0.64±0.03</td>
<td>15.91 (Good)</td>
<td>1.189 (Good)</td>
</tr>
<tr>
<td>MS6</td>
<td>17.17±0.11</td>
<td>0.54±0.06</td>
<td>0.64±0.06</td>
<td>15.85 (Good)</td>
<td>1.189 (Good)</td>
</tr>
<tr>
<td>MS7</td>
<td>20.55±0.51</td>
<td>0.54±0.05</td>
<td>0.62±0.05</td>
<td>11.85 (Good)</td>
<td>1.134 (Good)</td>
</tr>
<tr>
<td>MS8</td>
<td>19.01±0.11</td>
<td>0.54±0.05</td>
<td>0.64±0.03</td>
<td>11.15 (Good)</td>
<td>1.189 (Good)</td>
</tr>
<tr>
<td>MS9</td>
<td>17.17±0.11</td>
<td>0.64±0.06</td>
<td>0.64±0.06</td>
<td>15.85 (Good)</td>
<td>1.189 (Good)</td>
</tr>
</tbody>
</table>

### Table 3: Evaluation data of metformin hydrochloride sustained-release tablets

<table>
<thead>
<tr>
<th>Batch No</th>
<th>Weight variation (mg)</th>
<th>Thickness (mm)</th>
<th>Hardness (Kg/cm²)</th>
<th>Friability (%)</th>
<th>Content uniformity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS1</td>
<td>757±0.86</td>
<td>4.40±0.01</td>
<td>6.10±0.23</td>
<td>0.192±0.57</td>
<td>98.4±0.73</td>
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<tr>
<td>MS2</td>
<td>741±1.16</td>
<td>4.59±0.05</td>
<td>6.85±0.25</td>
<td>0.198±0.12</td>
<td>101±1.61</td>
</tr>
<tr>
<td>MS3</td>
<td>762±3.57</td>
<td>4.38±0.88</td>
<td>7.41±0.05</td>
<td>0.218±0.17</td>
<td>99.2±0.12</td>
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<tr>
<td>MS4</td>
<td>759±0.88</td>
<td>4.38±0.07</td>
<td>7.22±0.15</td>
<td>0.236±0.27</td>
<td>99.1±0.40</td>
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<tr>
<td>MS5</td>
<td>758±0.88</td>
<td>4.18±0.07</td>
<td>6.15±0.98</td>
<td>0.216±0.07</td>
<td>99.8±0.19</td>
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<tr>
<td>MS6</td>
<td>769±0.12</td>
<td>5.32±0.07</td>
<td>6.15±0.83</td>
<td>0.226±0.21</td>
<td>99.1±0.14</td>
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<tr>
<td>MS7</td>
<td>740±0.88</td>
<td>4.18±0.03</td>
<td>6.15±0.75</td>
<td>0.246±0.07</td>
<td>99.8±0.78</td>
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<tr>
<td>MS8</td>
<td>743±1.11</td>
<td>4.38±1.12</td>
<td>6.35±0.14</td>
<td>0.219±0.45</td>
<td>99.6±0.69</td>
</tr>
<tr>
<td>MS9</td>
<td>745±0.12</td>
<td>4.36±0.15</td>
<td>6.15±0.56</td>
<td>0.286±0.32</td>
<td>99.8±0.42</td>
</tr>
</tbody>
</table>

Each value is an average of ten determinations, each value is an average of three determinations, each value is an average of five determinations.
Formulations with chitosan MS1 drug release are 86%, xanthan gum MS4 was 89%, and finally MS7 with hydroxypropyl methylcellulose was 92% which exhibited the highest drug release retardation, also had the lowest matrix concentration. Hence, a lower concentration of polymer such as hydroxypropyl methylcellulose is optimized batch suitable to prepare metformin hydrochloride tablets compared to higher concentrations. On analyzing regression coefficient values of all batches, it was found that tablets exhibited almost zero-order kinetics, followed Higuchi model.

ACKNOWLEDGMENT

The authors express their sincere thanks to management Dr. G. Srinivas Reddy, Karim Nagar, India, for providing required facilities to carry out this research work.

REFERENCES


Table 4: % drug release data of metformin hydrochloride sustained-release tablets

<table>
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<tr>
<th>Time (H)</th>
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<th>MS3</th>
<th>MS4</th>
<th>MS5</th>
<th>MS6</th>
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</table>

Fig.1: Cumulative % drug release plot of sustained-release tablets were initially released into the surrounding media generating many pores and cracks which facilitate further release of drug and also the formation of channels within the matrix.

To describe the kinetics of drug release from matrix tablets, release data were analyzed according to different kinetic equations. The data were analyzed by the regression coefficient method and regression coefficient values (r^2) of all batches. On analyzing regression coefficient values of all batches, it was found that tablets exhibited almost zero-order kinetics, followed Higuchi model. The in vitro release profile of the drug from all these formulations could be best expressed by Higuchi’s equation as the plots showed the highest linearity (r^2=0.98–0.99). To confirm diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation.

CONCLUSIONS

The present investigation was carried out to develop the sustained delivery of metformin hydrochloride for an effective and safe therapy using three polymers such as chitosan, hydroxypropyl methylcellulose, and xanthan gum.

The term modified-release dosage form is used to describe products that alter the timing and rate of release of drug substance. A modified-release dosage form is defined as one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms.

It is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of Type II diabetes in particular, in overweight and obese people and those with normal kidney function.