DESIGNING OF OLANZAPINE SUSTAINED RELEASE MATRIX TABLETS FOR THE TREATMENT OF SCHIZOPHRENIA

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ABSTRACT

The aim of the current study was to design sustained release-based drug delivery system for olanzapine. The objective of the present work was to develop an oral sustained release olanzapine tablet prepared by wet granulation method using xanthum gum and HPMC K4M polymer as rate controlling factor. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity and in vitro drug release. Hydrophilic matrix of xanthum gum alone could not control the olanzapine release effectively for 12 hr whereas when combined with hydroxyl propyl methyl cellulose (HPMCK4M) could slow down the release of drug and can be successfully employed for formulating sustained-release matrix tablets. The dosage regimen of olanzapine is 10mg tablet once in a day. Olanzapine was chosen as a model drug with an aim to develop a sustained release system for a period of 12 hrs. The sustained release tablet was prepared by wet granulation technique using controlled release polymer (HPMCK4M) and using xanthum gum combinely for controlling release rate. The tablet formulation containing 26mg of HPMCK4M and 140mg of xanthum gum considered as overall best formulation (with an in vitro release of 98.37%). This sustained release system was found to deliver OZP at a zero-order rate for 12 hrs. Short term stability study (at 40±2ºC/ 75±5% RH for three months) on the best formulation indicated that there no significant changes in drug content. IR spectroscopic study indicated that there are no drug excipient interactions.

Key words: Sustained release, Olanzapine, Xanthum gum, Zero order, IR.

INTRODUCTION

Controlled drug delivery system (Presscott, 1989) has taken major role in the pharmaceutical development various dosage forms. It offers temporal or spatial control over release of drug.

This is due to improved patient convenience and compliance, reduction in fluctuation in steady state plasma level so decrease intensity of local or systematic side effects and increase safety margin of high potency drugs. In control release systems there is maximum utilization of drug enabling reduction in total amount of dose administered and possibility of delivering drugs having short biological half life. In the form of novel drug delivery system, an existing drug molecule can get a new
life there by increasing its market value competitiveness and patent life among the various novel drug delivery systems available in the market. Among various novel drug delivery system per oral sustained release system hold the major market share now a days.

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time (Chien, 1992). The dissolution can be diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer of polymer. The gel (Gul Majid Khan, 2001) forming properties of HPMC and xanthum gum has been used to develop sustained release dosage forms. Hydrophilic matrix system release drug sequentially by swelling to form gel, diffusion of drug molecules and finally surface erosion (Nishihata et al., 1995; Talukdar and Plaizier-Vercammen, 1993) of matrix.

Olanzapine is classified as a thienobenzodiazepine, an atypical antipsychotic drug used in the treatment of schizophrenia (Lerner, 2003). It is also used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia. Future uses may include the treatment (Kurtz et al., 2008; Bull, 2005) of obsessive-compulsive disorder and severe behavioral disorders in autism. Olanzapine's antipsychotic activity is likely due to a combination of antagonism at D2 receptors in the mesolimbic pathway and 5HT2A receptors in the frontal cortex.

Antagonism at D2 receptors relieves positive symptoms while antagonism at 5HT2A receptors relieves negative symptoms of schizophrenia. It is well absorbed after oral administration; absorption is not changed by food. Peak plasma levels occur 5-8 hours after an oral dose. Plasma levels appear to have a correlation with therapeutic effect, requiring about 23 ng/mL for an antischizophrenic effect. Onset of antipsychotic effects is seen after 1-2 weeks of treatment. Half-life ranges from 21-54 hours (mean 30 hours). Highly protein bound (about 93%) with a volume of distribution of 10-18 L/kg. Metabolized in the liver to inactive metabolites mainly by cytochrome P450 isozyme CYP1A2, flavin-containing monooxygenas 3, and N-glucuronidation. Minor pathways involve CYP2D6 and possibly CYP2C19 isozymes. About 40% is metabolized in the first pass through the liver. Because of the number of possible routes of metabolism, inhibition of cytochrome oxidase pathways does not markedly affect elimination of olanzapine. About 57% of a dose is excreted in urine principally as metabolites (only 7% as unchanged drug) and about 30% in the feces (Callaghan, 1993). In general, olanzapine elimination is slower in women, the elderly and non-smokers. Olanzapine is not removed by dialysis. It is practically insoluble in water, having only 60% oral bioavailability. Olanzapine undergoes extensive first pass metabolism. The objective of this study was to develop matrix sustained-release tablets of olanzapine using xanthum gum as suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices HPMCK4M with respect to in vitro drug release rate (Badshah et al., 2010).

MATERIALS AND METHODS

Materials

Olanzapine was obtained from Macleods Pharmaceutical Ltd, India. Microcrystalline cellulose (MCC, Avicel pH 102) was purchased from S. D. Fine Chem. Labs, (Mumbai, India). HPMC K4M was obtained as a gift sample from Hetero Drugs Pvt Ltd, Hyderabad. Xanthan gum was obtained as gift samples from Zydus Healthcare Pvt. Ltd, Ahmedabad. All other ingredients were of laboratory reagents and used as such without further testing. All other solvents and reagents used were of analytical grade.

Drug excipient studies

The IR allows identification of functional groups in various chemicals as well as incompatibilities between the drug and excipients. From the IR study it can be concluded that the major peaks of drug remains intact and no interaction was found between the drug and polymer.

Preparation of sustained release matrix tablets

The tablets were prepared by wet granulation technique. Accurately weighed quantities of ingredients mentioned in Table-1 were passed through sieve No. 30 and lubricant and glidant were passed through sieve No. 80. All the ingredients except lubricant (magnesium stearate), glidant (talc) were manually blended homogeneously in a mortar by way of geometric dilution. The mixture was moistened with aqueous solution and granulated through sieve No. 30 and dried in a hot air oven at 60°C for sufficient (3-4 hrs). So that the moisture content granules reached to 2-4%. The dried granules were passed through sieve No. 30 and blended with talc and magnesium stearate. The homogenous blend was then compressed into round tablets (200 mg each) with standard concave punches (diameter 5mm) using 27 station rotary compression machine (CMB4D-27 Cadmach, Engg, Ahmedabad, India).

Evaluation of granules

Pre compression parameters of sustained release matrix tablets (Sahoo et al., 2012; Srivastava et al., 2005)

Angle of repose

The angle of repose of granules blend was determined by the fixed funnel method. The accurately
weighed quantity of granules was taken in a funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules are allowed to flow through the funnel freely onto the surface. The diameter of powder cone was measured and angle of repose was calculated using the following equation
\[
tan \theta = \frac{h}{r}
\]
\[
\theta = tan^{-1} \left( \frac{h}{r} \right)
\]
Where \( \theta \) is the angle of repose, \( h \) is the height of cone in cm and \( r \) is the radius of the cone base in cm.

**Bulk density \( (\varepsilon_b) \)**

Bulk density was determined by pouring the granules into a graduated cylinder. The bulk volume \( V_b \) and mass \( (m) \) of the granules was determined. The bulk density was calculated by using the following formula.

Bulk density \( (\varepsilon_b) = \frac{\text{Mass of granules}(m)}{\text{Bulk volume of granules}(V_b)} \)

**Tapped density \( (\varepsilon_t) \)**

The measuring cylinder containing known mass of granules blend was tapped 1000 times for a fixed time. The minimum volume occupied in the cylinder \( V_t \) and mass of the granules \( (m) \) was measured. The tapped density was measured by using the following formula.

Tapped density \( (\varepsilon_t) = \frac{\text{Mass of granules}(m)}{\text{Tapped volume of granules}(V_t)} \)

**Compressibility index \( (\text{Carr’s index}) \)**

The compressibility index determines the flow property characteristics of granules developed by Carr. The percentage compressibility of granules is a direct measure of the potential powder arch and stability. The Carr’s index can be calculated by the following formula.

\[
\%\text{Carr’s index} = \left( \frac{\varepsilon_t - \varepsilon_b}{\varepsilon_b} \right) \times 100
\]

Where \( \varepsilon_t \) is the tapped density of granules and \( \varepsilon_b \) is bulk density of granules.

**Hausner’s ratio**

Hausner’s ratio is used for the determination of flow properties of granules. The ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density.

**Post compression parameters of sustained release matrix tablets** (Sahoo et al., 2011; Kulkarni et al., 2011):

**Thickness**

The thickness of individual tablets are measured by using vernier caliper which gives the accurate measurement of thickness. It provides information of variation of thickness between tablets.

Generally the unit for thickness measurement is mm. The limit of the thickness deviation of each tablet is \( \pm 5\% \).

**Hardness**

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm\(^2\). Test was done in triplicate.

**Friability**

Friability of tablets was performed in a Roche friabilator. Ten tablets were initially weighed \( (W_0) \) together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the Plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed \( (W) \). The percentage of friability was calculated using the following equation.

\[
\%\text{Friability} = \left( 1 - \frac{W_0}{W} \right) \times 100
\]

Where, \( W_0 \) and \( W \) are the weight of the tablets before and after the test respectively. The limit for percentage of friability is between 0.5-1%.

**Weight Variation**

The weight variation test was done by weighing 20 tablets individually (Shimadzu digital balance), calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with USP specifications.

**Drug Content**

Drug content for OZP tablet was done by the assay method. First the prepared tablet \( (10mg \text{ API}) \) was crushed and added to 100ml of phosphate buffer pH 6.8. After 30 minutes the solution was filtered and from 10ml solution 1ml solution was withdrawn diluted up to 10 ml with phosphate buffer pH 6.8(10 µg/ml). This solution concentration for the drug content of formulation were calculated using calibrated standard curve equation \( y=0.0539x+0.018 \). The drug content was determined at \( \lambda_{max}255 \text{ nm} \) by UV-spectrophotometer (ELICO164) against blank.

**In vitro drug release study**

The release rate of olanzapine sustained release matrix tablets was determined using United States pharmacopeia (USP) dissolution testing apparatus (Reddy et al., 2013) type 2 (paddle method). The dissolution test was performed using 900 ml of Phosphate buffer pH 6.8, at \( 37^\circ \pm 0.5^\circ \text{ C} \) and 50 rpm. In specified time intervals an aliquot of 5ml samples of the solution were withdrawn from the dissolution apparatus and with replacement of fresh fluid to dissolution medium. The samples were filtered through filter paper of 0.45 µm. Absorbance of these solutions were measured at \( \lambda_{max}255 \text{ nm} \) using a UV/Visible Spectrophotometer (ELICO164).
The drug release was plotted against time to determine the release profile of various batches.

**Statistical analysis**
Except dissolution all evaluation parameters were expressed as mean ± standard deviation.

**Stability studies**
Short term stability studies on the above promising formulation (at 40±2°C/75±5% RH for 3 months) have shown no significance changes in physical appearance and drug content.

**RESULT AND DISCUSSIONS**

**Drug excipient studies**
From the FTIR study it was observed that there was no significant changes in the spectrum of olanzapine and xanthum gum polymer. Hence there may not be any incompatibility between drug and excipients.

**Pre compression parameters**
All the compressible excipient by wet granulation method was prepared using xanthum gum along with HPMCK4M. The granules of different batches were evaluated for pre compression parameters such as bulk density, tapped density, Angle of repose, Hausner’s ratio and Carr’s index. (Table-2) The bulk density of pre compression blends was found to be in the range of 0.57 to 0.59 gm/cc, tapped density in the range of 0.64 to 0.69 gm/cc, the Carr’s index values were in the range of 12.28 to 14.49%, Hausner’s ratio in the range of 1.12 to 1.16 and angle of repose in the range of 25.42 to 28.42.

**Post compression parameters**
All the formulated batches of olanzapine were evaluated for post compression parameters such as hardness, weight variation, friability, thickness and drug content uniformity (Table-3). The hardness of the tablet formulations was found to be in the range of 6.8 to 7.1 kg/cm². The friability values were found to be in the range of 0.52 to 0.64%.
The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed USP limits. The percent drug content of all the tablets was found to be in the range of 98.85 to 99.88% of the expected OZP content, which was within the acceptable limits. The results are shown in Table-3. The thickness values were found to be in range of 3.49-3.50mm.

**Content uniformity**
From the content uniformity test by assay method it was found that the percentage of drug content (%D.C) was maximum in OZP4 formulation (99.88±0.12).
Hence it was the best formulation among the various formulations like OZP1, OZP2 and OZP3.

**In vitro drug release study**
From the in vitro drug release study it was found that the percentage of drug release (%D.R) was maximum in OZP4 formulation giving 98.37% of drug release.
Hence it was the best formulation among the various formulations like OZP1, OZP2 and OZP3. (Figure-2)

| Table 1. Composition of Olanzapine (OZP) sustained release matrix tablets |
|--------------------------|-----------------|-----------------|-----------------|-----------------|
| Ingredients(mg)          | OZP1            | OZP2            | OZP3            | OZP4            |
| Olanzapine(OZP)          | 10              | 10              | 10              | 10              |
| Xanthum Gum              | 35              | 70              | 105             | 14              |
| MCC(Microcrystalline cellulose) | 120          | 85              | 50              | 15              |
| HPMCK4M                  | 26              | 26              | 26              | 26              |
| Magnesium Stearate       | 4               | 4               | 4               | 4               |
| Talc                     | 5               | 5               | 5               | 5               |
| Total Weight(mg)         | 200             | 200             | 200             | 200             |

| Table 2. Pre compression parameters of Olanzapine(OZP) formulations |
|--------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Formulation code         | Bulk density (gm/cc)±S.D,n=3 | Tapped density (gm/cc)±S.D,n=3 | Angle of repose (degree) ±S.D,n=3 | Carr’s Index (%) ±S.D, n=3 | Hausner’s ratio±S.D, n=3 |
| OZP1                     | 0.57±0.06       | 0.64±0.05       | 26.27±0.98      | 12.28±0.01      | 1.12±0.01       |
| OZP2                     | 0.58±0.05       | 0.66±0.01       | 28.36±0.89      | 12.12±0.03      | 1.13±0.03       |
| OZP3                     | 0.58±0.03       | 0.67±0.03       | 28.42±1.06      | 13.43±0.02      | 1.15±0.03       |
| OZP4                     | 0.59±0.04       | 0.69±0.03       | 25.42±1.03      | 14.49±0.01      | 1.16±0.04       |

S.D=Standard Deviation, n=number of readings
Table 3. Postcompression parameters of Olanzapine (OZP) formulations.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (kg/cm²) ±S.D., n=3</th>
<th>%Friability±S.D., n=3</th>
<th>%Drug content±S.D., n=3</th>
<th>Average wt. of 1 tablet±S.D., n=3</th>
<th>Thickness (mm)±S.D., n=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OZP1</td>
<td>6.9±0.114</td>
<td>0.58±0.01</td>
<td>98.85±0.01</td>
<td>200.2±0.01</td>
<td>3.50±0.28</td>
</tr>
<tr>
<td>OZP2</td>
<td>6.8±0.118</td>
<td>0.88±0.03</td>
<td>97.73±0.42</td>
<td>200.5±0.13</td>
<td>3.50±0.11</td>
</tr>
<tr>
<td>OZP3</td>
<td>6.8±0.152</td>
<td>0.64±0.08</td>
<td>97.60±0.13</td>
<td>200.3±0.21</td>
<td>3.49±0.07</td>
</tr>
<tr>
<td>OZP4</td>
<td>7.1±0.155</td>
<td>0.52±0.01</td>
<td>99.88±0.12</td>
<td>200.3±0.14</td>
<td>3.50±0.12</td>
</tr>
</tbody>
</table>

CONCLUSION

A sustained release based drug delivery system can be designed for olanzapine using HPMC as controlled release polymer and xanthum gum as gum that helped in controlling the drug release from matrix. From the findings of the present study states that the hydrophilic matrix of HPMC alone could not control the olanzapine release effectively for 12 hr whereas when combined with xanthan gum could slow down the release of drug from their matrices and can be successfully employed for formulating sustained-release matrix tablets. Diffusion coupled with erosion might be the mechanism for the drug release which can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional olanzapine tablets. It was evident from the results that rate of drug release can be controlled through HPMC and xanthan gum. From the developed formulations the release of olanzapine was best in OZP4 formulation i.e. (in-vitro study). From the FTIR study, it was confirmed that the drug & excipients in the formulations were compatible with each other.

REFERENCES


