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Formulation and evaluation of olanzapine sustained release matrix tablets for the treatment of schizophrenia

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ABSTRACT

The present study was undertaken to design sustained release matrix tablets of olanzapine(OZ) for the treatment of schizophrenia. The tablets were prepared by wet granulation method along with benecel and HPMC K4M polymer as release retardant polymer. The amount remains fixed(10mg) for all the batches of formulation. All the batches were evaluated for the precompression parameters and post compression parameters. The release kinetics of tablets using hydrophilic matrix of benecel alone could not control the olanzapine release effectively for 12 hr whereas when combined with HPMC K4M could slow down the release of drug. The dosage regimen of olanzapine is 10mg tablet once in a day. It was chosen as a model drug with an aim to develop a sustained release system for a period of 12 hrs. The batch(OZ4) formulation containing 140mg of benecel and 26mg of HPMCK4M considered as overall best formulation (with an in vitro release of 98.63%).This sustained release system was found to deliver olanzapine 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.

Keywords: Sustained release; Olanzapine; Benecel; Zero order; IR; Wet granulation.

INTRODUCTION

Controlled drug delivery system 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. Controlled drug delivery system[1] gives to an existing drug molecule to get a new design of dosage forms by increasing its market value, competitiveness and patent life among the various novel drug delivery system

available in the market. Out of various novel drug delivery systems oral sustained release system mostly used in now a days.

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations[2]of drug in the systemic circulation over an extended period of time. The goal in designing sustained release drug delivery system[3]is to reduce the frequency of the dosing, reducing the dose & providing uniform drug delivery. So, Sustained release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Sustained release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. It includes any drug delivery system achieves release of drug over an extended period of time, which not depend on time. Hydrophilic polymer matrix[4] is widely used for formulating a sustained dosage form. Hydrophilic matrix system release drug sequentially by swelling to form gel, diffusion of drug molecules and finally surface erosion[5] of matrix. The present study utilizes the polymer combination concentration of HPMCK4M and benecel which forms gel to control the drug release .

Olanzapine is an atypical antipsychotic drug used in the treatment of schizophrenia[6]. 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[7] of obsessive-compulsive disorder and severe behavioral disorders in autism. The antipsychotic activity of drug is 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[8,9] of schizophrenia. The drug is well absorbed after oral administration and absorption is not changed by food. Peak plasma levels occur 5-8 hours after an oral dose. The half-life of drug ranges from 21-54 hours (mean 30 hrs). The drug is highly protein bound (about 93%) with a volume of distribution of 10-18 L/kg. About 40% of drug is metabolized in the first pass through the liver[10]. About 57% of a dose is excreted in urine principally as metabolites (only 7% as unchanged drug) and about 30% in the feces 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. The objective of present investigations were to prepare sustained release matrix tablets of olanzapine by using benecel in four different batches and to compare the in vitro drug release study of the different matrix tablets.

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. Benecel was obtained as gift samples from Zydus Healthcare Pvt. Ltd. Ahmedabad.. All other ingredients used 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 to identify of functional groups[11] in various chemicals as well as incompatibilities between the drug and excipients. The IR study explains about the major peaks of drug ,polymers and various excipients and their interactions.

Preparation of sustained release matrix tablets

The tablets were prepared by wet granulation technique. Accurately weighed[12]quantities of ingredients mentioned in Table-1 were passed through sieve No. 30 except lubricant and glidant. They were passed through sieve No. 80. All the ingredients except lubricant (magnesium stearate), glidant (talc) were manually blended homogenously 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 60ºC 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).

Table-1: Composition of Olanzapine (OZ) sustained release matrix tablets

Ingredients(mg)/Tablet	OZ1	OZ2	OZ3	OZ4
Olanzapine(OZ)	10	10	10	10
Benecel	35	70	105	140
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

Evaluation of granules

Pre compression parameters of sustained release matrix tablets[13,14]

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

$\tan\Theta = h/r$

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

Where Θ 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 (e_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 (e_b)=Mass of granules(m)/Bulk volume of granules(V_b)

Tapped density(e_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(e_t)= Mass of granules(m)/Tapped volume of granules(V_b)

Compressibility index(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.

$\%\text{Carr's index} = e_t - e_b / e_t \times 100$

Where e_t is the tapped density of granules and e_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

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 ±5%.

Hardness
The hardness[15] 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[16]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.

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

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.

Content uniformity
Drug content[17]for OZ tablet was done by the assay method. First the prepared tablet (10mg 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 upto 10 ml with phosphate buffer pH 6.8(10 µg/ml). This solution concentration for the drug content of formulations were calculated using calibrated standard curve equation y=0.0539x+0.018.The drug content was determined at λmax255 nm by UV-spectrophotometer (ELICO164)against blank.

***In vitro* drug release study**
The release rate of olanzapine sustained release matrix tablets[18.19] was determined using United States pharmacopeia (USP) dissolution testing apparatus type 2 (paddle method) .The dissolution test was performed using 900 ml of Phosphate buffer pH 6.8, at $37^0 \pm 0.5^0$ 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 λmax 255nm 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±2ºC/75±5% RH) have done for 3 months.

RESULTS AND DISCUSSION

Drug excipient studies
IR Spectrum of olanzapine and benecel polymer exhibited a sharp signal at about 3434 cm-1 corresponding to NH absorption and CN function absorption at 2084 cm-1.. The band at 778 cm-1 corresponds to theNH2 wagging and the band at 1632 cm-1 corresponds to the N-H bending motions. The C-N stretching is located at 1044 cm-1. Since there are no significant changes in the spectrum of olanzapine and benecel polymer to that of olanzapine spectrum, there may not be any incompatibility.

Pre compression parameters
All the compressible excipient by wet granulation method was prepared using benecel along with HPMC4M. The granules of different batches were evaluated for precompression 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 0.56 to 0.60 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 12.5 to 13.63% ,Hausner's ratio in the range of 1.14to1.15 and angle of repose in the range of 25.42 to 28.42.

Table-2: Pre compression parameters of Olanzapine(OZ) 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'sratio ±S.D, n=3
OZ1	0.56±0.06	0.64±0.05	26.27±0.98	12.5±0.01	1.14±0.01
OZ2	0.57±0.05	0.66±0.01	28.36±0.89	13.63±0.03	1.15±0.02
OZ3	0.58±0.03	0.67±0.03	28.42±1.06	13.43±0.02	1.15±0.01
OZ4	0.60±0.04	0.69±0.03	25.42±1.03	13.04±0.01	1.15±0.01

S.D=Standard Deviation, n=Number of readings

Post compression parameters

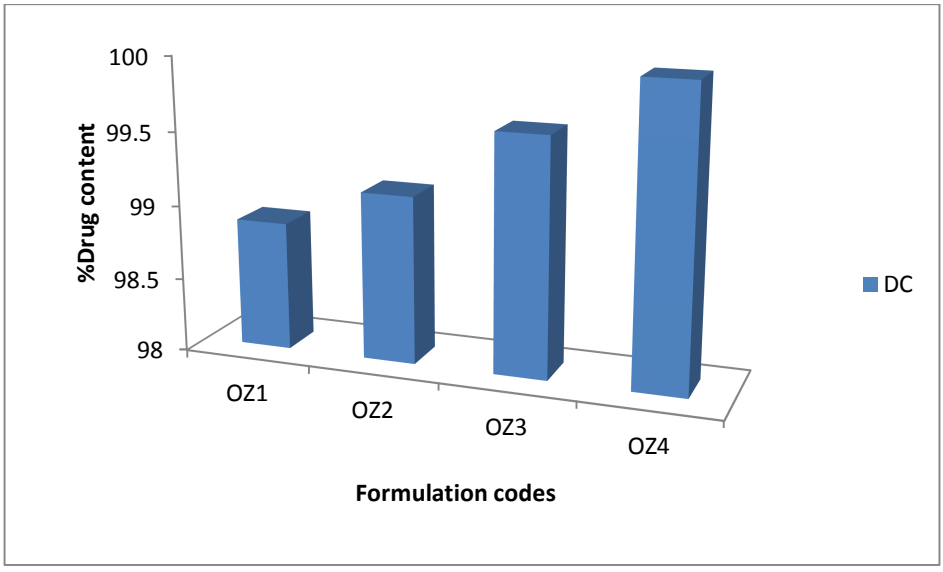
All the formulated batches of olazapine were evaluated for post compression parameters such as hardness, weight variation, friability, thickness and drug content uniformity (Table-3). The hardness of the tablet formulations was found to be in the range of 6.9 to 7.1 kg/cm^2. The friability values were found to be in the range of 0.52 to 0.68%. 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 98.87 to 99.99% of the expected OZ 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.

Table-3: Post compression parameters of Olanzapine(OZ) formulations

Formulation code	Hardness (kg/cm^2) ±S.D,n=3	%Friability±S.D, n=3	%Drug content ±S.D, n=3	Average wt. of 1tablet ±S.D,n=3	Thickness(mm) ±S.D), n=3
OZ1	6.9±0.114	0.58±0.01	98.87±0.01	200.2±0.01	3.50±0.28
OZ2	6.9±0.118	0.68±0.03	99.13±0.42	200.5±0.13	3.50±0.11
OZ3	7.0±0.152	0.54±0.08	99.60±0.13	200.3±0.21	3.49±0.07
OZ4	7.1±0.155	0.52±0.01	99.99±0.12	200.3±0.14	3.50±0.12

S.D=Standard deviation, n=Number of readings

Fig.1: Comparison of content uniformity various batches of OZ formulations



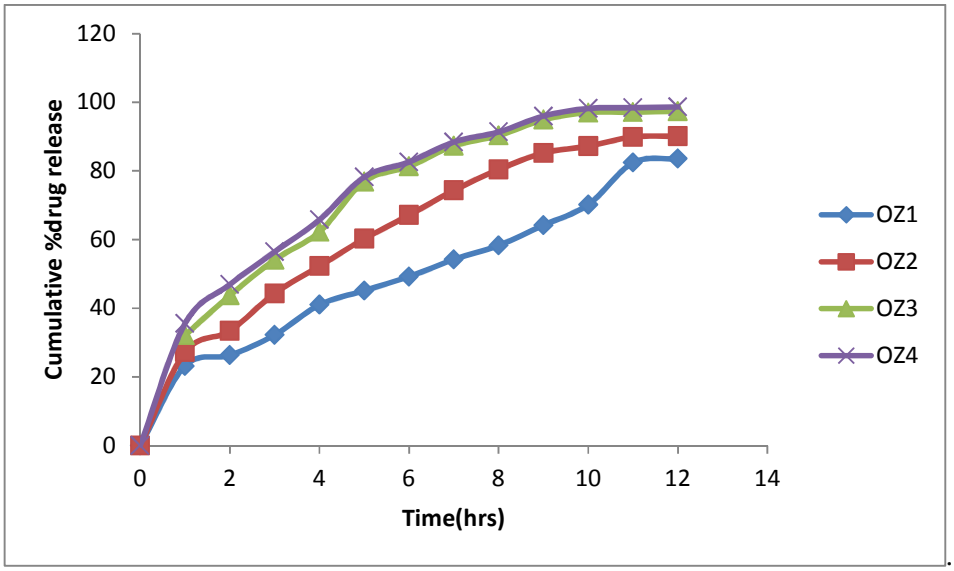
Content uniformity

From the content uniformity test by assay method it was found that the percentage of drug content (%D.C) was maximum in OZ4 formulation (99.99±0.12). Hence it was the best formulation among the various formulations like OZ1, OZ2 and OZ3.

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 OZ4 formulation giving 98.63% of drug release. Hence it was the best formulation among the various formulations like OZ1(83.59%),OZ2(90.12%) andOZ3(97.63%). (Fig.2)

Fig.2: Comparision of *in vitro drug release* study of various batches of OZ formulations



Stability studies:

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

CONCLUSION

A sustained release based drug delivery system can be designed for olanzapine using benecel and HPMCK4M as controlled release polymer that helped in controlling the drug release from matrix. From the findings of the present study states that the hydrophilic matrix of benecel alone could not control the olanzapine release effectively for 12 hr whereas when combined with HPMCK4M 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 benecel and HPMCK4M. From the developed formulations the release of olanzapine was best in OZ4 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.

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