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Der Pharmacia Lettre, 2015, 7 (4):266-273
(http://scholarsresearchlibrary.com/archive.html)

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ISSN 0975-5071
USA CODEN: DPLEB4

Formulation and optimization 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 matrix tablets of olanzapine(OLZ) for the treatment of schizophrenia. The tablets were prepared by wet granulation method using glyceryl behenate and HPMC K4M polymer as release retardant polymer. All the batches were evaluated for pre compression parameters and post compression parameters. Hydrophilic matrix of glyceryl behenate alone could not control the olanzapine release effectively for 12 hr whereas when combined with HPMC K4M 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 tablet formulation containing 140mg of glyceryl behenate and 26mg of HPMCK4M considered as overall best formulation (with an in vitro release of 98.13%).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, glyceryl behenate, zero order, IR

INTRODUCTION

Controlled release systems have been developed to improve the temporal and spatial presentation of drug in the body, to protect drug from physiological degradation or elimination, to improve patient compliance, and to enhance quality control in manufacturing of drug products. When designing controlled release systems[1,2], it is important to identify and understand particular mechanisms involved in the release process. Often, more than one mechanism is involved at a given time or different mechanisms may dominate at different stages of the drug delivery process. Controlled release systems are designed to enhance drug therapy. Controlled release systems have been devised to enable superior control of drug exposure over time, to assist drug in crossing physiological barriers, to shield drug from premature elimination, and to shepherd drug to the desired site of action while minimizing drug exposure elsewhere in the body. In controlled drug delivery system therapeutic regimen[3] of the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while

minimizing toxic effects. Hence out of various novel drug delivery systems oral sustained release system mostly used in now a days.

The goal in designing sustained release drug delivery system is to reduce the frequency of the dosing, reducing the dose and 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. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval and at right site of action to maintain therapeutic range of drug in blood plasma. Hydrophilic polymer matrix[4] is widely used for formulating a sustained dosage form. Hydrophilic matrix system release drug sequentially by swelling to form gel[5,6], diffusion of drug molecules and finally surface erosion of matrix. The present study utilizes the polymer combination concentration of HPMCK4M and glyceryl behenate which forms gel to control the drug release .

Olanzapine (OLZ) is a thienobenzodiazepine derivate structurally similar to clozapine that is effective in treating schizophrenia[7] and acute manic episodes, and in preventing the recurrence of bipolar disorders. It is also used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia.It has a low propensity to cause extrapyramidal effects or sustained increases in prolactin levels.OLZ shares higher affinity to 5-HT2A receptors than D2 receptors (high 5-HT2A/D2 ratio). In comparison to the other atypicals, olanzapine presents high affinity for serotoninergic 5-HT2A, 5-HT2C, 5-HT3, and 5-HT6 receptors, medium affinity for dopaminergic D1, D2, D3, D4, D5, and muscarinic M1–M5 receptors, low affinity for adrenergic α1 and α2 receptors, and the highest affinity for histamine H1 receptors (olanzapine is the most potent histamine H1 antagonist known) . The antipsychotic[8] 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 of schizophrenia.The drug is well absorbed after oral administration and absorption is not changed by food. 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. About 57% of a dose is excreted in urine principally as metabolites (only 7% as unchanged drug) and about 30% in the feces[9]. It is practically insoluble in water, having only 60% oral bioavailability and protein binding is 93%.Symptoms of an overdose of the drug includes tachycardia, agitation, dysarthria, decreased consciousness and coma. Death has been reported after an acute overdose of 0.45g of olanzapine. The objective of present investigations were to prepare sustained release matrix tablets of olanzapine by using glyceryl behenate 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 Pharamceutical 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. Glyceryl behenate 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 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 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 (OLZ) sustained release matrix tablets

Ingredients(mg)	OLZ1	OLZ2	OLZ3	OLZ4
Olanzapine(OLZ)	10	10	10	10
Glyceryl behenate	35	70	105	140
MCC(Microcrystalline cellulose)	120	85	50	15
HPMCK4M	26	26	26	26
Mgnesium 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[10,11]:

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 characterstics 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[12-15]:

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 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.

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

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 for OLZ tablet was done by the assay[16] 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 was determined using United States pharmacopeia (USP) dissolution testing apparatus type 2 (paddle method) .The dissolution test[17,18] 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/VisibleSpectrophotometer(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 (Fig1) of olanzapine exhibited a sharp signal at about 3434 cm-1 corresponding to NH absorption and CN function absorption at 2076 cm-1.NH2 symmetric stretching vibrations occur at 3374 cm-1. The band at 781 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. IR Spectrum of olanzapine and glyceryl behenate polymer (Fig2) exhibited a sharp signal at about 3462 cm-1 corresponding to NH absorption and CN function absorption at 2068 cm-1.. The band at 755 cm-1 corresponds to theNH2 wagging and the band at 1635 cm-1 corresponds to the N-H bending motions.The C-N stretching is located at 1004 cm-1.Since there are no significant changes in the spectrum of olanzapine and glyceryl behenate polymer to that of olanzapine spectrum, there may not be any incompatability.

Figure 1. FTIR peak area spectra of pure drug olanzapine

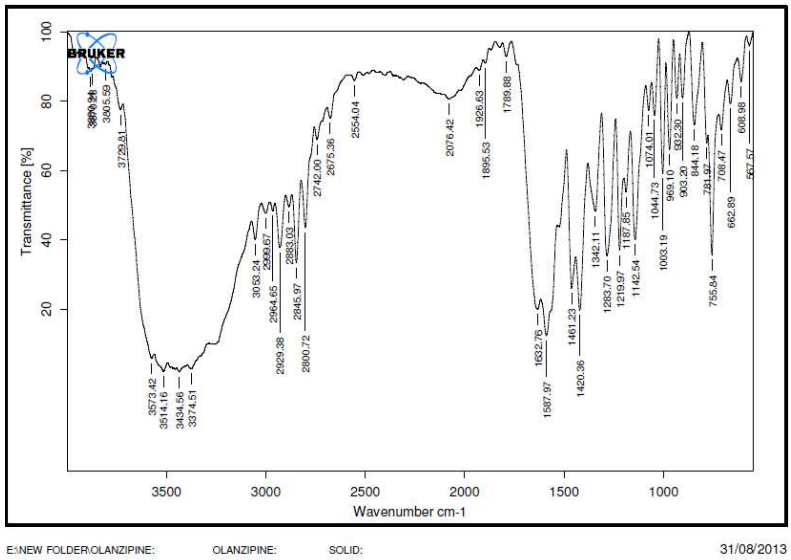
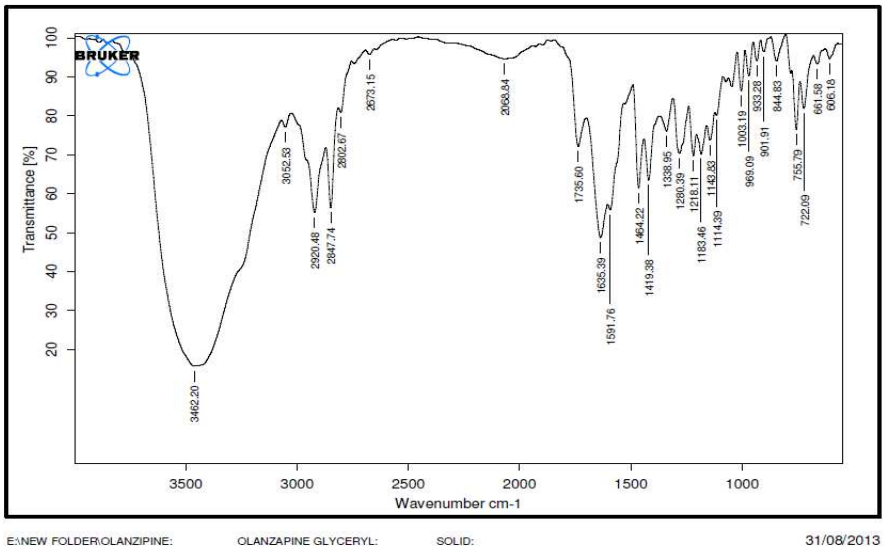


Figure 2. FTIR peak area spectra of olanzapine and glyceryl behenate polymer



Pre compression parameters

All the compressible excipient by wet granulation method was prepared using glyceryl behenate 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 0.56 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 12.5 to 14.49% ,Hausner's ratio in the range of 1.14to1.16 and angle of repose in the range of 25.42 to 27.41.

Table-2 Pre compression parameters of Olanzapine(OLZ) 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
OLZ1	0.56±0.06	0.64±0.05	26.27±0.98	12.5±0.01	1.14±0.01
OLZ2	0.57±0.05	0.66±0.01	28.36±0.89	13.63±0.03	1.15±0.02
OLZ3	0.58±0.03	0.67±0.03	27.41±1.06	13.43±0.02	1.15±0.01
OLZ4	0.59±0.04	0.69±0.03	25.42±1.03	14.49±0.01	1.16±0.01

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

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 6.9 to 7.2 kg/cm^2. The friability values were found to be in the range of 0.52 to 0.67%. 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 99.98% 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(OLZ) formulations.

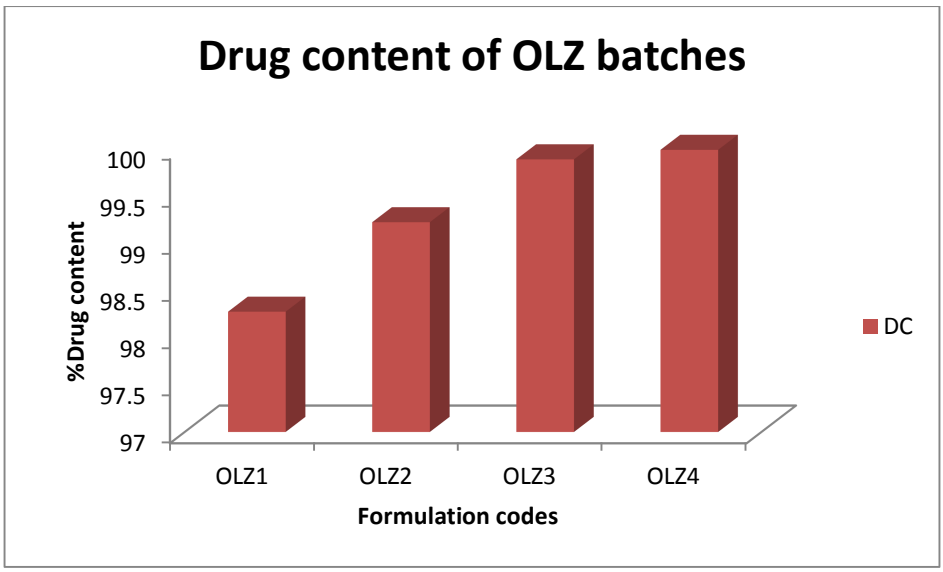
Formulation code	Hardness (kg/cm^2) ±S.D,n=3	%Friability±S.D, n=3	%Drug content ±S.D, n=3	Average wt. of 1tablet ±S.D,n=3	Thickness(mm) ±S.D), n=3
OLZ1	6.9±0.114	0.58±0.01	98.27±0.01	200.2±0.01	3.50±0.28
OLZ2	6.9±0.118	0.67±0.03	99.22±0.42	200.5±0.13	3.50±0.11
OLZ3	7.0±0.152	0.54±0.08	99.88±0.13	200.3±0.21	3.49±0.07
OLZ4	7.2±0.155	0.52±0.01	99.98±0.12	200.3±0.14	3.50±0.12

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

Content uniformity

From the content uniformity test by assay method it was found that the percentage of drug content (%D.C) was maximum in OLZ4 formulation (99.98±0.12). Hence it was the best formulation among the various formulations like OLZ1, OLZ2 and OLZ3(Fig-3).

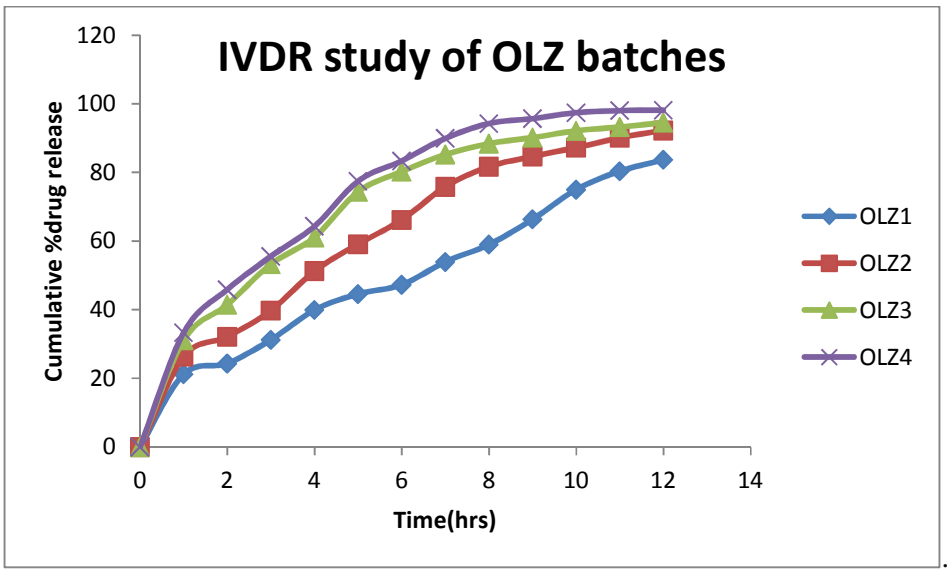
Figure-3:Comparision of content uniformity various batches of OLZ formulations



In vitro drug release study(IVDR)

From the in vitro drug release study it was found that the percentage of drug release (%D.R) was maximum in OLZ4 formulation giving 98.13% of drug release. Hence it was the best formulation among the various formulations like OLZ1(83.66%),OLZ2(92.24%) andOLZ3(94.46%) (Fig-4).

Figure-4:Comparision of *in vitro drug release* study of various batches of OLZ formulations



CONCLUSION

A sustained release based drug delivery system can be designed for olanzapine using glyceryl behenate and HPMCK4M as controlled release polymer that helped in controlling the drug rlease from matrix.From the findings of the present study states that the hydrophilic matrix of glyceryl behenate 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 glyceryl behenate and HPMCK4M. From the developed formulations the release of olanzapine was best in OLZ4 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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