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Research Article

Development and Evaluation of Solid Dispersion Formulations of Olanzepine

Kamal Jeet, Kapil Kumar, Aparna Joshi, Ikram, Vaishali Rajput*

Department of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Kashipur- 244713, Uttarakhand, India

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*Address for Correspondence:

Vaishali Rajput, Department of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Kashipur- 244713, Uttarakhand, India

Abstract

The purpose of present study was to enhance the aqueous solubility of olanzapine by using the Solid dispersion technique. Solid dispersions of olanzapine were prepared by the dispersion method using PGS and SSG as carriers. Drug-carrier ratios such as 1 : 1, 1 : 2, 1 : 4, 1 : 6, 1: 8 and 1 : 10 were tried for optimization. Characterization was done by phase solubility, in-vitro release, saturation solubility, permeation, wettability, XRD and FTIR analysis. Solid dispersions showed higher solubility and an improved drug release profile than the pure drug. Solid dispersion and physical mixture with a drug-polymer ratio of 1 : 10 showed the best release profile in comparison with the other samples. Phase solubility results verified the solubilization effect of the carrier. XRD and NIR analysis confirmed the reduction of crystallinity in the samples. The release study findings were well supported by the results of wettability, saturation solubility and permeability studies. IR analysis substantiated the inertness of the carrier. It was concluded that pregelatinised starch (PGS) and sodium starch glycollate (SSG) could be utilized as effective carriers to improve the aqueous solubility of poorly soluble drugs.

Keywords: Olanzapine, solid dispersion, solubility, evaluation.

INTRODUCTION

The enhancement of oral bioavailability of poor water-soluble drugs remains oneof the most challenging aspects of drug development. The development of soliddispersions as a practically viable method to enhance bioavailability of poorlywater-soluble drugs overcame the limitations of previous approaches such as saltformation, solubilization by cosolvents, and particle size reduction.[1] The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability.[2]Lipophilic molecules, especially those belonging to the bio pharmaceuticsclassification system (BCS) class II and IV, dissolve slowly, poorly and irregularly,and hence pose serious delivery challenges, like in complete release from the dosageform, poor bioavailability, increasedfood effect, and high inter-patient variability.[3] In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water soluble drugs can be overcome. This method, which was later, termed solid dispersion which involved the formation of eutectic mixture of drugs with water-soluble carriers by the melting of their physical mixtures[4]. The term solid dispersion refers to a group of solid products consisting of at least two different compounds, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particle (clusters) or in crystalline particles[5]. Solid dispersion can be prepared by various methods such as solvent evaporation and melting method. Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug. According to this method, a drug is thoroughly dispersed in a water-soluble carrier by suitable method of preparation. The mechanism by which the solubility and the dissolution rate of the drug are increased includes: reduction of the particle size of drug to submicron size or to molecular size in the case where solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from amorphous to crystalline form, the high energetic state which is highly soluble; finally, the wet ability of the drug particle is improved by the hydrophilic carrier[6]. Solid dispersion of drug helps to reduce the particle size of drug due to molecular dispersion[7]. Particle size reduction by micronization or nanonization can enhance the dissolution rate; however, the apparent solubility remains unaltered. At the molecular level, polymorphs offer a limited solubility advantage because of a small difference in free energy. In contrast, amorphous systems with excess thermodynamic properties and lower energetic barrier can offer significant solubility benefits.

MATERIAL AND METHOD

Olanzepine is purchased from Dr. Reddy's Laboratories, Hyderabad, India. Sodium Alginate,Potassium Di-Hydrogen Orthophosphate, $CaCO_3$, Ethanol, Calciumchloride, Sodium Hydroxide pellets, HCl, Sodium lauryl sulfate, Di-Sodium Hydrogen Phosphate A.R., PVP K30, PEG 6000 (mg), PEG 6000 (mg) and Octanol were purchased from Indo Chemicals Pvt. Ltd, Haryana, India.

Preparation of Olanzepine SD formulations

Fusion Technique[8]

Steps followed are-

1. Desired amount of Olanzepine, polymers and other ingredients were weighted out accurately.
2. They were taken in a beaker
3. And placed it into water bath for melting at 70 ^{0}c.
4. After melting, accurately weighted amount of drug was added in that glass beaker containing PEG
5. Then they were mixed by glass rod to obtain a viscous mass.
6. The mixture was stirred vigorously for uniform mixing and was kept in normal room temperature for 72 hour until a solid mass was formed.
7. Solidified mixture was then triturated in a mortar by the means of pestle.
8. Obtained powder was sieved (40 mesh size).
9. The resulted samples (Solid dispersion) were weighted and transferred in a fresh vial with proper labeling.
10. Finally, the SD formulations stored in a desiccator.

Solvent evaporation method[9]

Following steps were used-

1. Accurately weighted amount of Olanzepine, polymers and other ingredients were taken in screw capped test tube and dissolved in very less amount of methanol to get transparent solution.
2. Prepared solution of ingredients was kept in room temperature for few days until the solvent was evaporated from the solution.
3. Residues was allowed to solidify and after it solidified mixture was then grinded to convert powder particles in a mortar with the means of pestle
4. The obtained powder was sieved (mesh size 40).
5. Then the resulted solid dispersion formulation were weighted and transferred in fresh vials with proper labeling.
6. Finally all obtained SD formulations were kept in desiccators.

Characterization of SD

Micromeritic characterization

Angle (θ) of repose

SD formulations were weighed and kept and dropped from the funnel. A cone like structure gets appear. Heap was measured for radius (r in cm), height (h in cm). Following equation was used to get value of θ[10].

$$\theta = tan^{-1}\frac{h}{r}$$

Bulk density (BD)

It was determined by filling the already weighed granules (M) in a measuring cylinder. Bulk volume (BV) is recorded from it. BD was determined by following equation[11].

$$BD = \frac{M}{BV}$$

Tapped density (TD)

The granules were filled in a measuring cylinder having known mass (M). After filling the granules were tapped 100 times. The tapped volume (TV), thus measured. TD was measured using below formula[12].

$$TD = \frac{M}{TV}$$

Carr's index (CI)

CI for the prepared granules was calculated by below formula[13].

$$CI = \frac{TD - BD}{BD} x100$$

Hausner's ratio (HR)

This also indicate the potential of granules to flow. It was calculated by below formula[14].

$$HR = \frac{TD}{BD}$$

If it is less than 1.25, means good flow, but if its value is more than 1.25 it means poor flow of any system.

Solubility estimation

Solubility of Olanzepine and SD formulations of Olanzepine was determined in triplicate using saturation solubility method. Excess amount of SD was mixed in a vial with 10ml buffer (pH 6.8). Content of vials was mixed vigorously for 30 minutes and further solutions were shaken mechanically to equilibrate. After 72 hrs each vial was rotated at 2500 rpm for 10 min in a centrifuge in order to separate the content. Later on it was filtered by the means of 0.45µ pore size membrane filter. Obtained filtrate was diluted with suitable solvent. The concentration of Olanzepine was measured by the means of UV spectrophotometr at 281 nm[15].

Drug content

SD formulations were tested for estimation of amount of drug content by the means of UV spectrophotometer. SD formulations (equv. To 100mg) were weighed accurately and mixed in a flask with 5ml alcohol. It was mixed properly and diluted to 1oo ml with buffer (6.8 pH). After filterations, dilutions samples checked by UV spectrophotometer at 281nm[16].

Percentage Yield

In order to determine the efficiency of used method to prepare SD formulations of Olanzepine, the yield was calculated. It was calculated on the basis of used amount of Olanzepine and PVP K30, PEG 6000 and other used ingredients and the final weight of the obtained product[17].

$$\text{Percentage yield} = \frac{\text{Actual weight of products}}{\text{Weight of drug and excipients}} x100$$

***In vitro* dissolution study**

USP (type II appar.) was used for this study. Paddle speed kept 75rpm and buffer temperature (900 ml, pH 6.8) was kept 37°C. SD formulations (500 mg equivalent wt of drug) were used

5ml sample were taken at regular interval and replaced 5ml buffer solution. Samples were checked through UV spectrophotometer at 281nm[18].

Drug release kinetic data analysis:

The obtained data of in-vitro dissolution study was evaluated through PCP disso software for the kinetic models. Zero, first, Higuchi's and Peppa's model were studied[19]

Accelerated stability study

Based on different evaluation parameters SD formulation of Olanzepine of two batches SD4 and SD8 were found to be optimum formulations. These two formulations were subjected to accelerated study for the three months at different temperatures. The formulations of two batches SD4 and SD8 were air tight packed and kept for three months on 40°C and 75% RH. The samples were observed by UV spectrophotometer at 281nm for the absorbance. By the means of the calibration curve the amount of the Olanzepine was estimated[19].

RESULT

PF (pre-formulation) studies:

Appearance: Pale yellow crystalline powder.

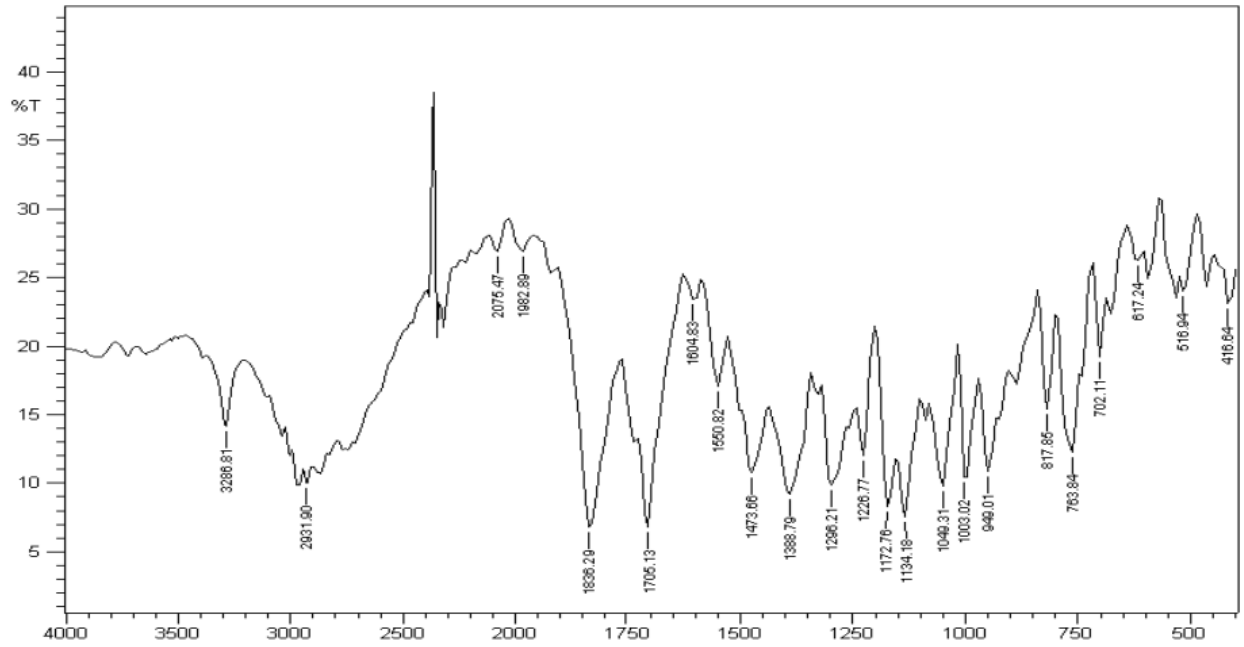

Figure 1: Olanzepine FTIR.

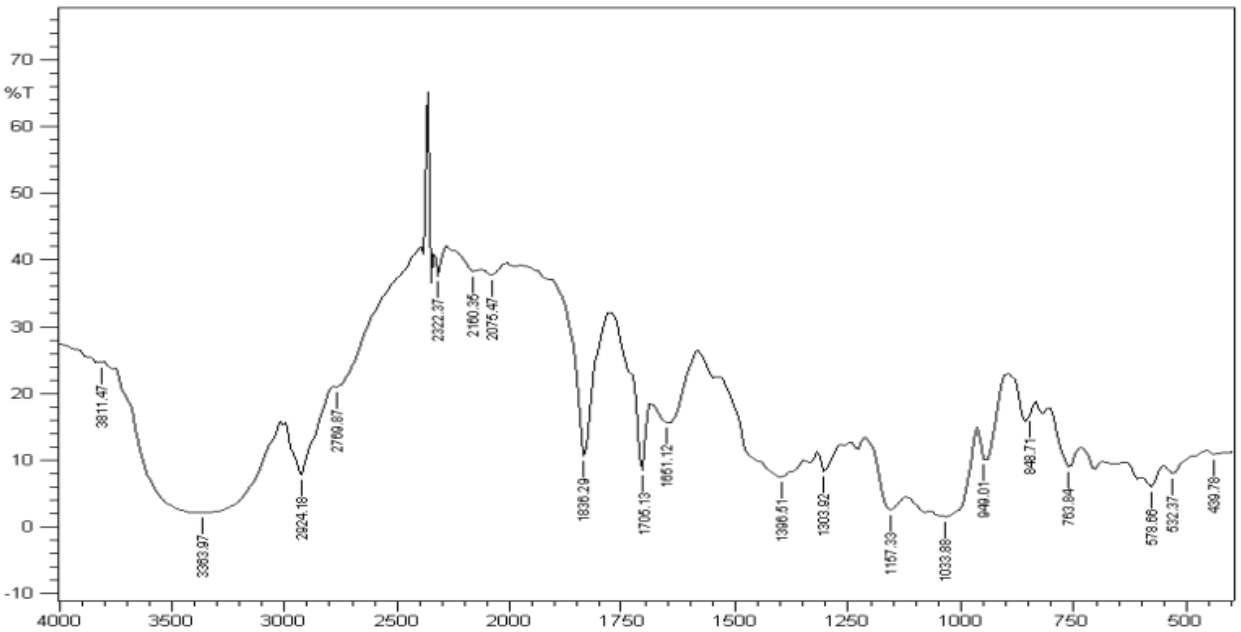

Figure 2: Olanzepine +PVP K30 FTIR+ PEG 6000 FTIR.

Table 1: SD formulations composition.

S. No.	Formulation code	PVP K30	β cyclodextrin (mg)	PEG 6000 (mg)	Method
1	SD1	300	-	300	Solvent evaporation method
2	SD2	400	-	400	Solvent evaporation method
3	SD3	-	400	100	Solvent evaporation method
4	SD4	-	300	200	Solvent evaporation method
5	SD5	-	200	300	Fusion method
6	SD6	-	100	400	Fusion method
7	SD7	400	100	-	Solvent evaporation method
8	SD8	300	200	-	Solvent evaporation method
9	SD9	200	300	-	Fusion method
10	SD10	100	400	-	Fusion method
11	SD11	100	-	100	Fusion method
12	SD12	200	-	200	Fusion method

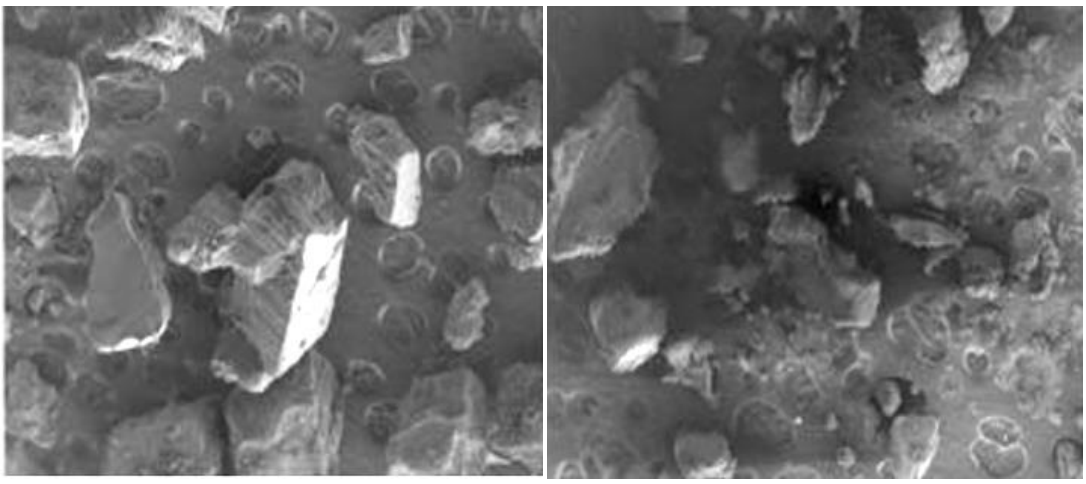

Figure 3: SEM images of formulation SD4 and SD8.

Table 2: Micromeritic properties of Olanzepine SD formulations.

Batch	BD* (g/cm^2)	TD* (g/cm^2)	θ*	CR* (%)	HR*
SD1	0.486±0.06	0.522±0.09	21.38±0.08	7.76±0.08	1.072
SD2	0.478±0.03	0.528±0.08	26.63±0.06	6.79±0.12	1.222
SD3	0.424±0.08	0.444±0.13	28.49±0.15	7.81±0.08	1.096
SD4	0.463±0.08	0.533±0.08	29.56±0.09	8.56±0.09	1.103
SD5	0.482±0.09	0.552±0.04	20.65±0.38	6.51±0.12	1.081
SD6	0.446±0.13	0.486±0.03	28.47±0.58	7.40±0.23	1.091
SD7	0.471±0.09	0.531±0.09	23.75±.19	6.98±0.36	1.086
SD8	0.423±0.11	0.543±0.11	24.83±0.09	8.79±0.28	1.084
SD9	0.442±0.08	0.467±0.07	23.68±0.04	9.43±0.19	1.104
SD10	0.495±0.21	0.555±0.05	25.42±0.11	6.61±0.09	1.082
SD11	0.467±0.08	0.487±0.13	27.58±0.14	7.04±0.13	1.087
SD12	0.476±0.13	0.516±0.08	24.31±0.42	8.90±0.09	1.085

θ- Angle of repose, BD- Bulk density, CR- Carr's compressibility index, TD- Tapped density, HR- Hausner's ratio, n = 3

Table 3: Properties of different SD formulations of Olanzepine

Batch code	Solubility (mg/ml)*	% Content*	% Yield*
SD1	0.215±0.31	98.52±0.24	91.73±0.21
SD2	0.188±0.42	98.35±0.41	96.48±0.31
SD3	0.187±0.51	99.48±0.52	94.32±0.41
SD4	0.198±0.08	96.63±0.11	97.62±0.18
SD5	0.186±0.11	99.79±0.09	95.49±0.09
SD6	0.198±0.22	97.57±0.06	96.53±0.21
SD7	0.215±.93	98.21±0.09	89.73±0.43
SD8	0.203±1.09	96.41±0.11	85.46±0.55
SD9	0.222±0.77	99.67±0.02	91.96±0.67
SD10	0.218±0.62	99.78±0.08	95.32±0.08
SD11	0.217±0.09	98.63±0.13	94.52±0.12
SD12	0.215±.93	97.21±0.09	89.73±0.43

Solubility of pure drug= 0.128mg/ml. * n = 3

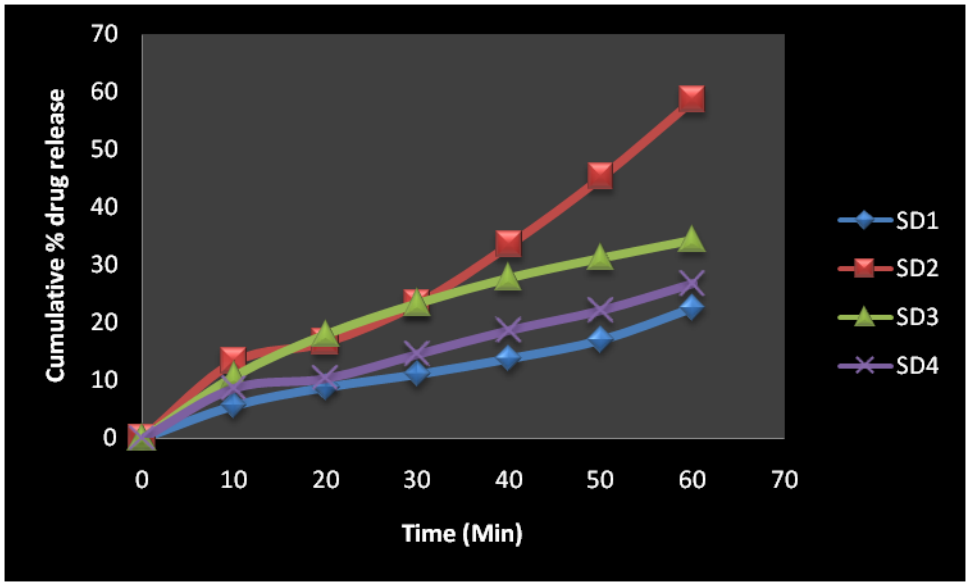

Figure 4*: In vitro* dissolution profile of Olanzepine SD formulations (SD1-SD4).

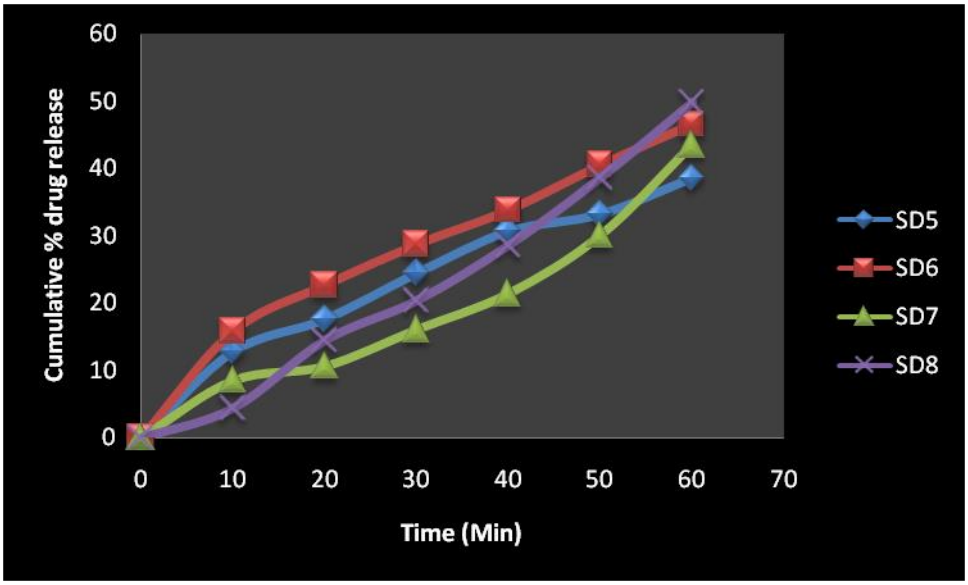

Figure 5: *In vitro* dissolution profile of Olanzepine SD formulations (batch SD5-SD8).

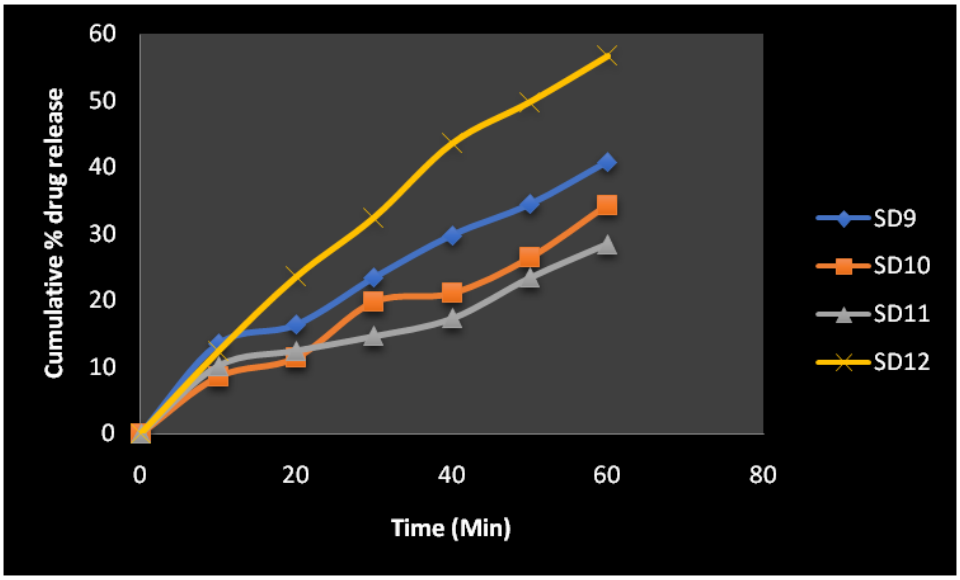

Figure 6: Table 10: *In vitro* dissolution profile of Olanzepine SD formulations (SD9-SD12).

Table 4: Different release models for Olanzepine SD.

Code	Zero		First		Higuchi		Korsmeyer-Peppas		
	R	K	R	K	R	K	Slope(n)	R	K
SD1	0.9331	2.6735	0.9464	-0.0389	0.9627	8.5322	0.7418	0.9932	3.3079
SD2	0.9748	4.3742	0.9550	-0.0615	0.9530	10.8363	0.6403	0.9977	9.2404
SD3	0.8143	3.3783	0.9543	-0.0407	0.9326	9.2572	0.7152	0.9944	8.3949
SD4	0.8598	2.9234	0.9437	-0.0325	0.9463	9.3642	0.8688	0.9965	6.5982
SD5	0.9325	3.5862	0.9368	-0.0281	0.9242	10.8364	0.8635	0.9922	3.4810
SD6	0.9788	4.8714	0.9410	-0.0530	0.9611	8.4782	0.9417	0.9893	12.9121
SD7	0.9681	2.6382	.9464	-0.0675	.9737	9.3573	.5235	.9983	6.5471
SD8	0.8645	3.6361	0.9345	-0.0448	0.9635	10.8944	0.6076	0.9978	5.3378
SD9	0.8644	1.0225	0.9674	-0.0443	0.9366	9.3905	0.7264	0.9946	3.4016
SD10	0.9548	3.2187	0.9510	-0.0668	0.9644	9.9466	0.6722	0.9955	6.6969
SD11	0.8232	3.6474	0.9430	-0.0448	0.9454	8.4173	0.7187	0.9968	8.3554
SD12	0.8593	4.0264	0.9643	-0.0532	0.9844	9.6149	0.8014	0.9979	5.8353

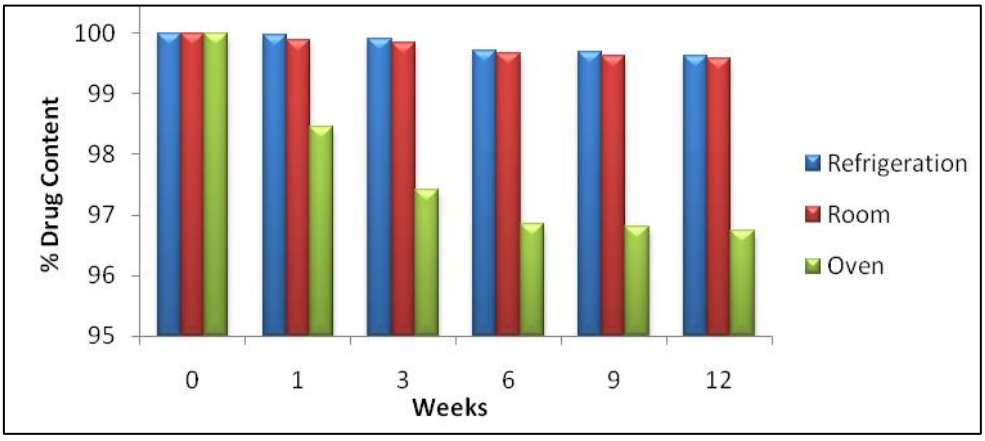

Figure 7: Stability studies of Olanzepine SD formulations of batch SD8 at different temperature.

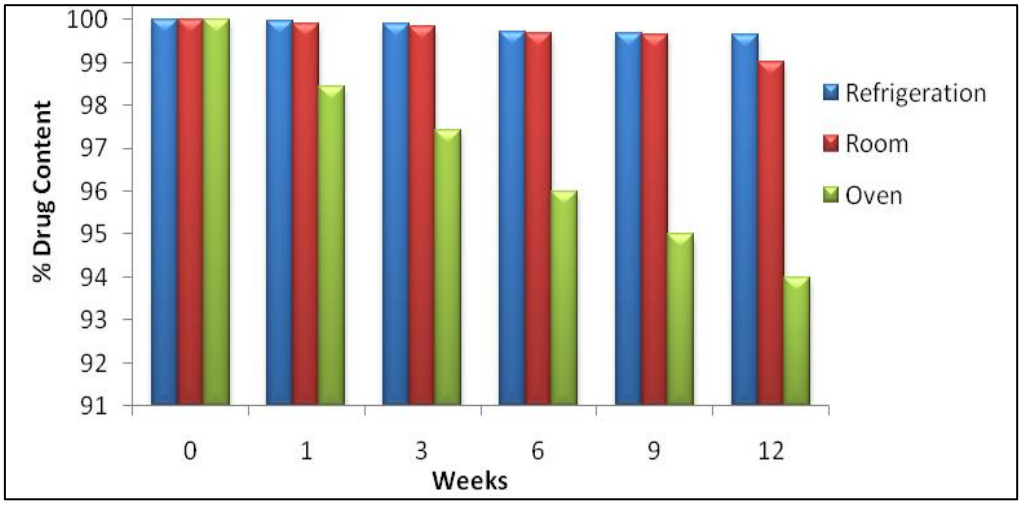

Figure 8: Stability studies of Olanzepine SD formulations of batch SD4 at different temperature.

DISCUSSION

Olanzepine was received from Dr. Reddy's Laboratories, Hyderabad, India as a gift sample. The received sample was authenticated by different test i.e. melting point, test according to Indian Pharmacopoeia and analytical methodology was performed on sample to justify the authenticity of sample. The m.p of the received sample was in the range of 310-313ºC, that was matching with the data as mentioned in Indian pharmacopoeia. This justifies the authenticity of given sample of Olanzepine.

The absorption spectrum of drug was evaluated in between 200-500 nm. The sample was prepared with buffer (pH 6.8) having conc. 10 µg/ml. The absorption spectra of Olanzepine showed peak at 281 nm, which represents the maximum absorption (λ_{max}).

FTIR studies were performed for Olanzepine and mixture of Olanzepine and PVP K30 and PEG 6000. There is no change in peak indicating compatibility of drug and polymers. Although there were some mild changes in band width this may be due to formation of band between drug and surfactants but all other peaks and band shows in presence of drug in formulation. In the FTIR spectra Olanzepine+PVP K30 and Olanzepine+PEG 6000, there was not any significant change in the peaks, it indicates that the compatibility of Olanzepine with PVP K30 and PEG 6000.

Twelve Olanzepine SD formulations were developed by incorporating different ingredients i.e. PVP K30, β cyclodextrin, PEG 6000 in different ratio by Fusion method and Solvent evaporation method. The bulk densities of the prepared granules was found to be in between 0.423±0.11 to 0.495±0.21. Low densities leads to increase in porosity and thus improved capacity of packing. The tapped densities of the prepared granules was found to be in between 0.444±0.13 to 0.555±0.05g/cm^3.

All SD formulations has shown good flow properties. Repose angle values were in between 20.65±0.38 to 29.56±0.09. These values are in between 20 to 40, indicates good flow properties and they are non-aggregated. Carr's index for all SD formulations were in between 6.61±0.09 to 9.43±0.19 %. These values indicate, excellent compressibility. So, they having good packabiltywhile filling in capsule. Hausner's Ratio values for all twelve formulations were in the range of 1.074–1.222. As the amount were<1.25, means good flow was there.

% drug content in developed 12 SD formulations of Olanzepine was found to be in between 96.41±0.11 to 99.79±0.09 indicating good amount of drug in all formulations. This indicate very less waste of the drug during manufacture of the formulations.

The percentage yield of the floating beads was between 85.46±0.55 to 97.62±0.18.

Result of saturation solubility study revealed that there was increase in solubility. In current study drug has shown solubility of 0.132 mg/ml, while formulations has shown solubility range in between 0.186±0.11 to 0.222±0.77. Maximum solubility was shown by the SD formulations of batch SD9 having PVP K30. It revealed remarkable decrease in crystallinity of Olanzepine in molecular dispersion form with PVP-K30. Those formulations that were developed by fusion method has shown more solubility in comparison to those prepared by another method of solvent evaporation.Study reveals that Olanzepine released amount was depending on the used polymers amount. This study indicate that the amount of drug release is affected by the amount of polymers used. In 60 min study, the batch SD12 has shown maximum drug release 56.71±0.25%. Different kinetic model for *in-vitro* release study of SD formulations of Olanzepine are shown in Table 11. With the help of PCP disso software, obtained results were checked for different kinetic models.

The highest regression coefficient (r^2) value was obtained for Korsmeyer– Peppas (0.9983) followed by Higuchi (0.9844), by, zero (0.9748), and first (0.9464) model using PCP disso version 2 software. Study reveals that release was governed by the diffusion.

Accelerated stability studies for 12 weeks shows that the selected SD formulations of Olanzepine SD4 and SD8 are capable to be stable at 45^{0}C as well as at refrigeration temperature. Therefore, the SD12 formulations of Olanzepine may be kept at room temperature without affecting the properties.

CONCLUSION

The present was an effort to develop and evaluate Olanzepine SD formulations with a view of improving its solubility and thus bioavailability. Study concludes successfully delivery of the Olanzepine by the the means of SD formulations. On basis different evaluation parameters, current study concludes, formulation of batch SD4 was the optimum formulation.

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