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Formulation and Evaluation of Solid Dispersions of Olanzapine

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ABSTRACT

The present research work was aimed to enhance the solubility and dissolution rate of Olanzapine using Poloxamer as carrier by preparing solid dispersion. The solid dispersions and physical mixtures prepared was also evaluated for the drug content and percentage drug yield and characterization of prepared systems is done with the help of *in-vitro* drug release, FTIR, XRD and DSC analysis. The results obtained showed that the percentage yield and percentage drug content was 98.32% and 99% respectively. It was clear that there was no loss of drug and polymer. The rate of dissolution of the drug in the case of solid dispersions was much enhanced as compared to the pure drug and their physical mixtures. FTIR spectra showed that there was not any interaction or hydrogen bonding between the drug and polymers in solid dispersions as well as physical mixtures. The polymorphic changes were studied with the XRD gave the idea that the solid dispersions were quite amorphous in nature as compared to the pure drug. In the diffraction pattern for solid dispersions, the number of crystalline peaks due to drug had disappeared. DSC showed that there was shifting in melting endotherm of drug in case of solid dispersion. From the XRD and DSC it was confirmed that the increase in the solubility and dissolution rate was due to polymorphic transition of drug from crystalline to amorphous form.

Keywords: Solid Dispersion, Olanzapine, Poloxamer-407, Dissolution

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INTRODUCTION

The dissolution of a drug from its solid oral dosage forms depends upon its release from the dosage form and its subsequent mixing into physiological fluids. It has been estimated that nearly 35-40% of the drugs suffer from poor aqueous solubility, thereby affecting their absorption from the gastrointestinal tract, which leads to poor oral bioavailability, high intra- and inter-subject variability, increase in dose, reduction in therapeutic efficiency and finally failure in formulation development[1]. The development of solid dosage forms for water-insoluble drugs has been a major challenge for pharmaceutical scientists for decades. Various formulation strategies such as micronisation, micellar solubilization, complexation, dendrimers for drug solubilization, formation of solid solutions or dispersions with hydrophilic carriers, self-microemulsifying drug delivery systems, spray drying, nano approaches, pro-drug approaches and salt synthesis[2] have been developed to increase the dissolution rate of water-insoluble drugs. An attractive possibility is employing a simple solid dispersion technique making use of various hydrophilic carriers[3,4,5]. Solid dispersions (SDs) are defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix in a solid state, and are prepared by the fusion, solvent or solvent-fusion method[3]. This technique enables reducing particle size to a nearly molecular level, offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems of poor water-soluble drugs that are cost-effective and significantly reduced in dosage[4,6]. It has been widely demonstrated that a hydrophilic carrier dissolves rapidly, exposing the drug particles to the dissolution medium as fine particles facilitating quick dissolution and absorption. The mechanisms for increased dissolution rate may include reduction of crystallite size, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersability of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier or conversion of the drug to an amorphous state[7,8]. Schizophrenia is a severe non-curable illness of the brain with serious consequences if not properly treated and kept under control. It is the most common form of severe mental illness. Olanzapine (OLZ;2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno-[2,3-*b*],[1,5]benzodiazepine) is a relatively new benzodiazepine atypical antipsychotic medication, which belongs to the class of the thienobenzodiazepines and has proven efficacy against the positive and negative symptoms of schizophrenia, bipolar disorder and other forms of psychosis. It exhibits poor water solublility and belongs to Biopharmaceutic Classification System (BCS) class II of drugs (low solubility and high permeability), highly bound to plasma protein (about 93%)[9, 10]. Following oral administration, C_{max} is reached within 5–6 h of dosing. OLZ

undergoes extensive pre-systemic metabolism in the liver, resulting in relatively very low oral bioavailability[11,12]. The objective of this work is to enhance the aqueous solubility of poorly water-soluble drug OLZ by adopting a solid dispersion approach using mannitol as the hydrophilic carrier and to physico-chemically characterize the *in vitro* dissolution behavior of the solid dispersions.

MATERIAL AND METHODS

Materials

Olanzapine was purchased from Indo-Swift Private Limited (Chandigarh, India). Poloxamer- 407 was obtained as a gift sample from Signet labs Mumbai, India. All the other chemicals and reagents used in the study were of analytical grade.

Preformulation studies

Physicochemical characterization and identification of Olanzapine

Solubility

The solubility of Olanzapine was estimated in Water, 0.1N HCl, 6.8 Phosphate buffer, 7.4 Phosphate buffer and in organic solvents Dichloromethane, Tetrahydrofuran and Ethanol. For this a saturated solution of Olanzapine was prepared in a 10 mL of solvent. To facilitate maximum solubilization of the drug in the solvent at room temperature it was kept in water bath incubator shaker for 24 h at 25 °C to achieve equilibrium. The solution was then observed for a clear transparent solution. If the solution was not transparent, it was filtered through 0.45 µm membrane filter. The amount of Olanzapine present in the solvent was then estimated using UV visible spectrophotometer after appropriate dilutions.

Partition coefficient

Partition co-efficient of Olanzapine in n-octanol-saline and 0.1N HCl (because maximum solubility of drug is in 0.1 N HCl and also dissolution study was carried out in the same medium) was determined. Equal volumes of hydrochloric acid and n-octanol (10 ml) were taken in separating funnel and 10 mg Olanzapine was added in the separating funnel and shaken for 2 hours. Then the aqueous and octanol layers were separated. From the aqueous layer 0.1ml solution was pipette out and diluted to 10ml and absorbance was determined by UV spectrophotometer. The residue was dissolved in 0.1 M sodium hydroxide solution and after appropriate dilution the concentration of drug was determined by UV spectrophotometer at 250 nm.

Melting point

Melting point was determined by capillary method. In this method Olanzapine was filled

into capillary tube sealed at one end at a height of 3 mm from the closed end. The capillary was introduced into the melting point apparatus. The temperature at which test substance becomes liquid was noted. The melting point was also determined by DSC studies, conforming the melting endotherm and purity of the model drug Olanzapine.

Infrared spectral analysis

Infrared spectral analysis of Olanzapine was carried out using IR spectrophotometer using small discs of model drug with KBr Rkin-Elmer FTIR Spectrophotometer. The IR spectra in absorbance mode were obtained in the spectral region 500-4000 cm^{-1} using a resolution of $2cm^{-1}$ and 4 scans.

Phase solubility study

Phase solubility study was performed according to the Higuchi and Connors[13] method. Excess amount of Olanzapine was added to aqueous solutions containing Poloxamer-407 in the concentrations (0.5, 1, 2, 4, 6, 8 and 9%) then shaken in a remi orbital incubator shaker at 37°C and 24°C for 24 h.The container containing the pure drug and water alone was used as a control. After 24 h the solutions were filtered, diluted and the absorbance levels were measured at 250 nm[14].The Gibbs free energy of transfer (ΔGtr°) of Olanzapine from water to aqueous solutions of carrier was calculated[15,16] using the following equation:

$$\text{Eq1 } \Delta G_{tr}{}^{o} = -2.303\ RT \log (Sc/S_o)$$

Where $\Delta G_{tr}{}^{\circ}$ is Gibbs free energy of transfer, R (8.314 J/ ºCmol) is gas rate constant, T is temperature at which phase solubility studies were conducted and S_c/S_o is the ratio of molar solubility of Olanzapine in aqueous solution of carrier to that of water. The acquired values of $\Delta G_{tr}{}^{\circ}$ indicate that whether the drug solubilization in the aqueous solution is favorable or not i.e. negative $\Delta G_{tr}{}^{\circ}$ values indicate favorable conditions and as the values increases more negative means more favorable conditions.

Table 1: Physical compatibility study of Olanzapine with excipients

Composition	Preparation	Final Weight
Olanzapine	_	20 mg
Polaxamer 407	_	20 mg
Olanzapine : Polaxamer 407	1:1	40 mg
Olanzapine : Polaxamer 407	1:2	60 mg
Olanzapine : Polaxamer 407	1:4	100 mg
Olanzapine : Polaxamer 407	1:6	140 mg
Olanzapine : Polaxamer 407	1:8	180 mg

Physical compatibility study of Olanzapine with excipient

The samples (Table 1) were exposed to condition of 40 °C/75 % RH (closed) in glass vials for

a period of one month. The glass vials used for the study were through fully washed with detergent, rinsed with distilled water and finally with small amount of methanol and dried completely. The initial color and appearance of samples were recorded. These samples were then periodically examined against a control sample.

Preparation of solid dispersion

Solid dispersions of Olanzapine with Poloxamer-407 were prepared by the hot melt method. Poloxamer-407 was first of all pulverized in mortar and passed through mesh # 100. Olanzapine was also passed through the same sieve. The physical mixture of Olanzapine and poloxamer-407 in different proportions as shown in Table 2. The mixtures were stirred for 15 minutes at this temperature for the solubilization of the drug in the carrier and the resulting homogeneous preparations were rapidly cooled on ice cool water, leading to rapid solidification[17]. Subsequently, the dispersions were pulverized, passed through sieve #100 and then stored in vacuum desiccator at room temperature until use. The composition of Olanzapine -Poloxamer solid dispersions prepared by this are shown in Table 2.

Table 2: The composition of Olanzapine-Poloxamer solid dispersion prepared by Hot-melt method and Olanzapine-Poloxamer physical mixture prepared by geometrical mixing

Formulation	Drug:Carrier
S-1	1:1
S-2	1:2
S-3	1:4
S-4	1:6
S-5	1:8
P-1	1:1
P-2	1:2
P-3	1:4
P-4	1:6
P-5	1:8

Preparation of Physical mixture

Physical mixture of the Olanzapine and Poloxamer-407 was also prepared by geometrical mixing of two components in a mortar for 5 minutes and then sieving through #100 (as shown in Table 2).

Evaluation of Solid Dispersion

The prepared solid dispersions and physical mixtures were evaluated for percentage yield, percentage drug content and *in-vitro* dissolution studies.

Percentage drug content

Physical mixtures and solid dispersions equivalent to 20 mg of drug were

dissolved in a mixture of ethanol and 0.1N HCl. The drug concentration was determined by UV-visible spectrophotometer after appropriate dilution, using 0.1N HCl as blank.

Percentage drug yield

Solid dispersions and Physical mixture were calculated for the percentage drug yield[18]. The equation is as following:

$$Y = \left(\frac{a}{b+c} \right) \times 100$$

Where a is the weight of solid dispersion sifted through mesh no.100, b is the weight of Olanzapine taken and c is the weight of polymer (Poloxamer) taken for solid dispersion/physical mixture preparation.

In *vitro* drug dissolution studies

Pure drug, physical mixtures and solid dispersions equivalent to 20mg of the dose were filled in empty capsule shells and subjected to dissolution studies. The dissolution media (900 mL) consisted of 0.1N HCl. Dissolution was assessed using a paddle rotating at 80 rpm and a temperature of 37± 1ºC was maintained in each study (USP XXIV method 2). The release was followed for 2 h and samples were taken after 0, 10, 15, 30, 45, 60, 90, 120 minutes. An aliquot of 5 mL was drawn at each point and replaced the same with buffer. The sample was filtered through 0.45 µm filter and concentration of Olanzapine was quantified with UV spectrophotometer at 250 nm.

Wettability study

Pure drug and selected formulations of about 50 mg were weighed and placed in a Buchner glass funnel. Methylene blue powder (50 mg) was layered uniformly on the surface of the powder in the funnel and plunged into a beaker containing water at the same level as the powder. The time required for wetting the methylene blue powder was taken as the wetting time. A tissue paper was placed in a petri dish with a diameter of 10 cm. Methylene blue, a water soluble dye, was added to the petri dish. A tablet compressed from the selected batch was carefully placed on the surface of the tissue paper and the dye solution was used to distinguish when complete wetting of the tablet surface had occurred. The time required for water to reach the upper surface of the tablets and completely wet their surface was taken as the wetting time. The weight of the tablet was noted before (Wb) and after the study period (Wa). From the data, water absorption ratio R, was calculated as using the following equation. (14, 15).

$$R = 100^* (Wa - Wb) / Wb$$

FTIR Spectroscopy

Drug–carrier interactions in the solid dispersions and physical mixture were determined based on the FTIR spectra measured using Rkin-Elmer FT-IR spectrometer. The IR spectra in absorbance mode were obtained in the spectral region 500-4000 cm^{-1} using a resolution of 2 cm^{-1} and 4 scans. The FTIR spectra of pure drug, physical mixture and solid dispersions were compared to check any interactions between the drug and polymer or change in the positions of the functional group of the drug.

X-ray diffraction studies

XRD were carried out to determine the physical state of the drug in the solid dispersion systems. The XRD of pure drug, carrier, physical mixtures and solid dispersion were recorded using X' Pert PRO instrument. The radiation used was generated by a Cu Kα source fitted with a nickel filter at 0.154 nm wavelengths at 40 mA and 45 kV. Samples were scanned for 2θ values over a range from 5-45°, at a scan rate of 10°C/min. All XRD spectra were compared.

Differential Scanning Calorimetry

The thermal behaviour of Olanzapine, Poloxamer-407, Physical mixtures and Solid dispersions were investigated using a Diamond DSC (Perkin, USA). Accurately weighed samples (3.13 mg) were placed in standard aluminum pans and covered with a pierced lid. Dry nitrogen was used as the purge gas, at a flow rate of 5 mL/min. The thermograms were obtained by heating the samples at a rate of 10°C /min from 3°C temperatures to 300°C

RESULTS AND DISCUSSION

Preformulation studies

Identification & characterization of Olanzapine

The sample of Olanzapine was identified and characterized as per requirements of COA (certificate of analysis) issued by the manufacturer. The identification and characterization of Olanzapine are given in Table 3.

Table 3: Appearance, Melting point and Partition coefficient of Olanzapine

Parameter	References	Observation
Appearance	Yellow powder	Yellow powder
Melting point	195^0C	190^0C ± 0.6
Partition coefficient	5.93	5.80 ± 0.2

Data are represented as mean ± S.D (n=3)

Solubility of Olanzapine

The solubility of Olanzapine was determined by shake flask method in various solvents and dissolution media. The results are shown in Table 4 and Table 5. The solubility of Olanzapine in

various solvents meets the specifications as per COA (Certificate of Analysis) issued by the manufacturer.

Table 4. Solubility of Olanzapine in different media at 25 ºC

Dissolution media	Solubility	
	Qualitative	Quantitative
0.1N HCl	++	90.3 ± 2.3 (mg/ml)
Water	+	43.4 ± 1.74 (µg/ml)
6.8 Phosphate buffer	+	173 ± 1.70 (µg/ml)
7.4 Phosphate buffer	+	145.4 ± 4.2 (µg/ml)

Data are represented as mean ± S.D (n=3)

Table 5. Solubility of Olanzapine in organic solvents at 25 ºC

Solvents	Solubility (Qualitative)
Dichloromethane	++++
Tetrahydrofuran	++
Ethanol	+++

Where: + Insoluble; ++ sparingly soluble; +++ very slightly soluble; ++++ freely soluble

Phase solubility study

Phase solubility studies indicated that drug solubility was increased with increasing concentration of Poloxamer (Figure 1). At Poloxamer concentration of 6 % w/v there was a sharp increase in solubility. Although, the solubility was increased further by adding more poloxamer to the aqueous solution but a constant phase was observed thereafter. All the ΔGºtr values were negative at all the levels of the carriers, demonstrating spontaneity of the drug solubilization process (Table 6). The process of drug transfer from the dissolution media to the carrier solution is more favorable at higher carrier levels.

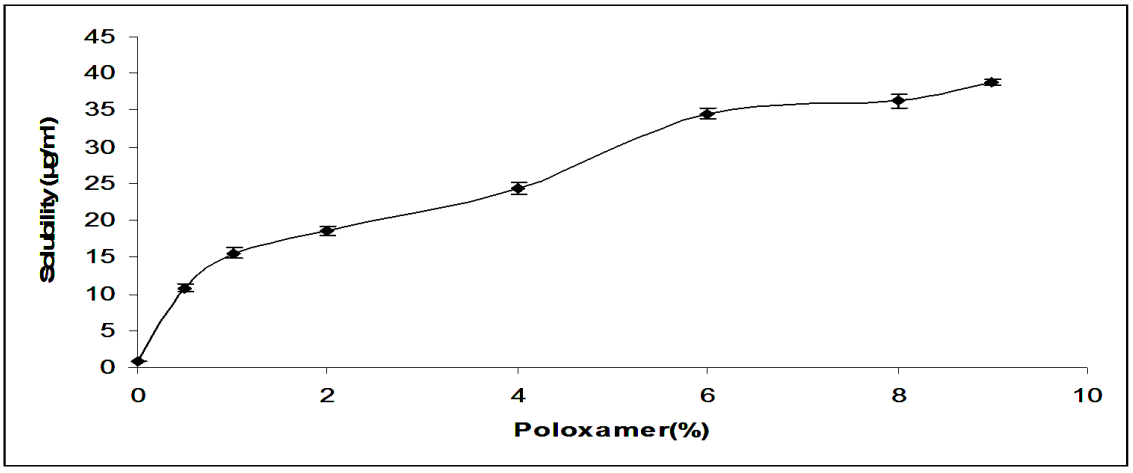

Figure 1. Phase solubility behavior of Olanzapine at 25 ºC in Poloxamer-407 solutions in distilled water

Table 6. Thermodynamic parameter for the solubilization process of Olanzapine in aqueous solution of Poloxamer-407

Carrier	Temp. (°C)	Slope	Intercept	Ka	ΔG kJ/mol	ΔH kJ/mol	ΔS kJ/mol
Poloxamer- 407	25	534.63	-19.430	0.0511	-2.608	-2.6086	-2.599
	37	662.53	-24.057	0.0416	-2.686	-2.6869	-2.678

Physical compatibility study

The physical compatibility study was designed to determine the interaction of drug with excipient used in the study. The drug along with physical mixtures with excipient was kept at 45 °C and 65 % relative humidity in environmental chamber for compatibility studies as shown in Table 15. A comparison of the control sample and samples of the physical mixture of drug with excipient kept at 45 °C temperature and 65 % RH for physical changes was made periodically at different time. The drug was found to be physically compatible with Poloxamer 407. No colour changes or lump formation occurred in samples with Poloxamer as shown in Table 7.

Table 7. Physical compatibility study of olanzapine with excipients

Composition	Ratio (w/w)	Total Weight (mg)	Initial (color)	Closed Condition (Weeks)		
				1	2	3
Olanzapine	-	20	Yellow	-	-	-
Olanzapine:Poloxamer	1:1	40	Yellow	-	-	-
Olanzapine:Poloxamer	1:2	60	Yellow	-	-	-
Olanzapine:Poloxamer	1:4	100	Yellow	-	-	-
Olanzapine:Poloxamer	1:6	140	Yellow	-	-	-
Olanzapine:Poloxamer	1:8	180	Yellow	-	-	-

- Indicates No change in color

Characterization of solid dispersions and physical mixtures

The prepared solid dispersions and physical mixtures were evaluated for percentage yield and percentage drug content, in-vitro drug release, FTIR Spectroscopy, X –Ray diffraction and DSC analysis.

Determination of percentage drug content and percentage yield

The results of drug content and percentage yield indicates that solid dispersions and physical mixtures prepared in different proportions possesses the same amount of drug as taken previously as shown in Table 8.

***In vitro* drug release from pure drug, physical mixtures and solid dispersions**

As compared to pure drug olanzapine (Olz), which was released only 39% at the end of 2 hrs. Physical mixture having high proportion of carrier (P-4) released 47% of the drug

at the end of 2 hrs (Figure 2). Solid dispersion of the optimized formulation released (S-4) 90% of drug. Also for the optimized solid dispersion more than 95% of the drug was released in 60 min, thus comply the official requirements as shown in figure 2.

Table 8. Percentage yield and Percentage drug content of Olanzapine-Poloxamer 407 physical mixtures and solid dispersions prepared by Hot-Melt method.

Formulation Numb	Percentage Yie	Percentage Drug Conte
P-1	99.23	98.90 ± 0.123
P-2	99.50	99.36 ± 0.245
P-3	98.00	98.00 ± 0.315
P-4	98.19	98.32 ± 0.187
S-1	99.00	99.98 ± 0.183
S-2	98.87	99.15 ± 0.201
S-3	99.00	97.50 ± 0.301
S-4	98.32	98.00 ± 0.164
S-5	99.80	99.00 ± 0.185

Data are represented as mean ± S.D (n=3)

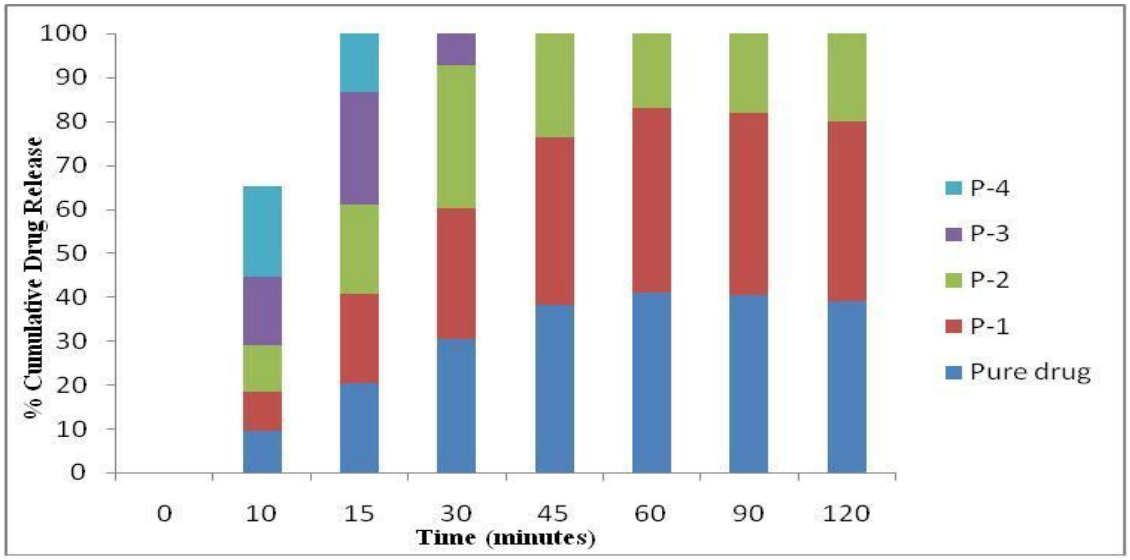

Figure 2. *In vitro* % cumulative drug release of pure drug and physical mixtures

Wettability Studies

The results of wettabilty studies done is shown in Table 9

Table 9. Results of Wettability studies

Formulation	Buchner Funnel Method (min)	Water Absorption Ratio
Pure Drug	80	4.01
P-4	42	7.63
S-4	54	6.10

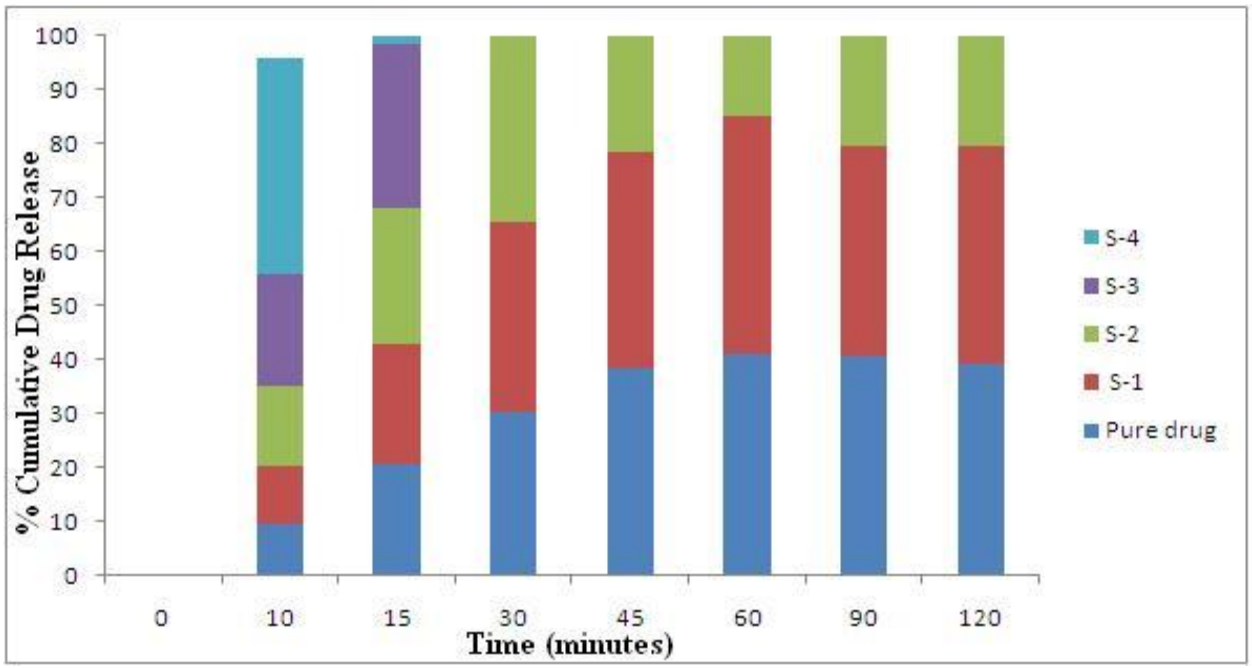

Figure 3. *In vitro* % cumulative drug release of pure drug and solid dispersions

FTIR Studies

The FTIR spectra of Olanzapine showed comparable principal absorption bands (Stretching) at 3229 cm^{-1} (O-H), 2931 cm^{-1} (C-H), 1587 cm^{-1} (N-H) and 1415 cm^{-1} (C=C). The FTIR spectra of Poloxamer-407 showed the principal absorption bands (Stretching) at 3460 cm^{-1} (O-H), 2885 cm^{-1} (C-H), 1112.5 cm^{-1} (C-O). There was no significant change in the absorption spectra of solid dispersion and physical mixture as incorporation of drug into Poloxamer did not modify the position of functional groups. The FTIR spectra of pure drug Olanzapine, Poloxamer-407, Physical mixture (P-4) and Solid dispersion (S-4) are shown in Figure 4.

X-Ray Diffraction

X-Ray diffraction of pure drug Olanzapine shows the intense diffraction peaks at 2Θ values 8.5º, 10.5º, 18.5º, 20.0º, 21.5º, 24.3º. Poloxamer the crystalline carrier used in the study shows the intense diffraction peaks at 2Θ values of 19.2º and 23.2º. One peak of drug at 18.5º and one peak of poloxamer at 19.5º are present as a single peak at 19.2º. Similarly instead of drug peak at 22.5º and carrier peak at 23.0º there is single peak at 23.0º with reduced intensity indicating that some crystallinity has been reduced (Figure 5). In the diffraction pattern for S-4 (1:6) solid dispersion, crystalline peaks due to drug has disappeared.

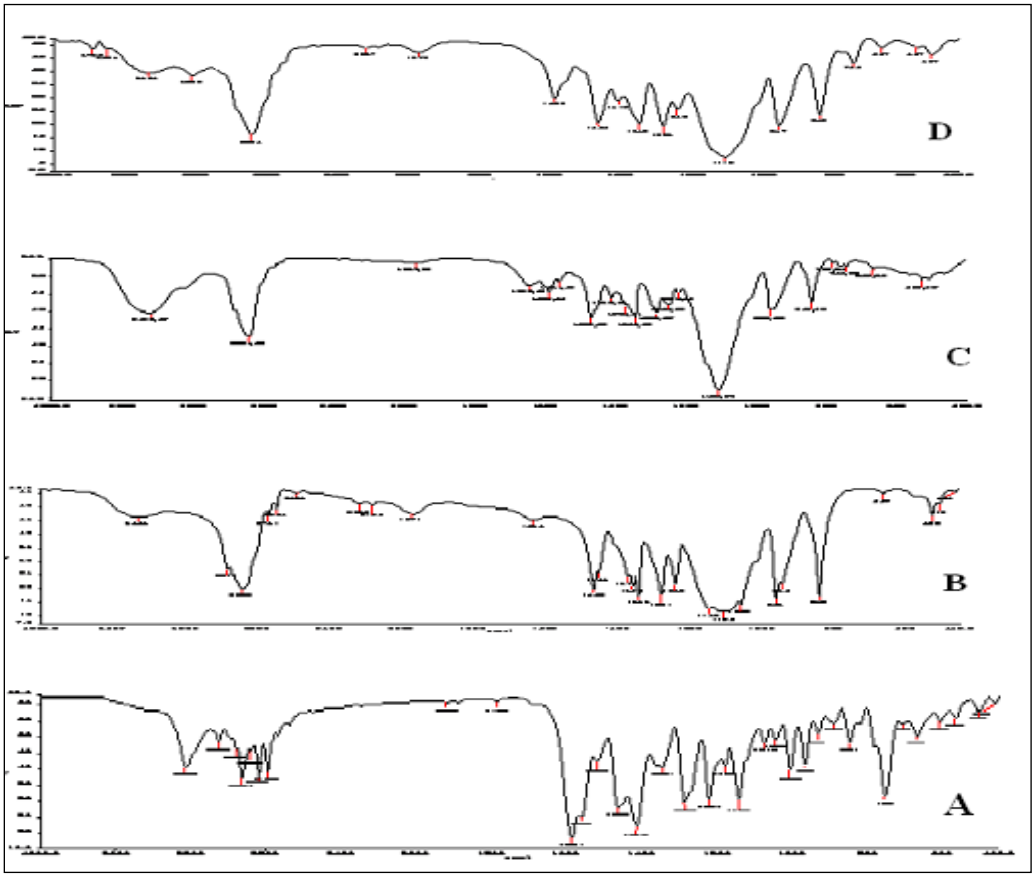

Figure 4. FTIR Spectra of Olanzapine and Poloxamer in different weight proportions. A) olanzapine (B) Poloxamer-407 (C) Physical mixture (P-4) (D) Solid dispersion (S-4).

Differential scanning calorimetry

DSC of pure drug Olanzapine shows sharp melting endothermic peak (T_m) at 195 ºC. Poloxamer-407 shows the endothermic peak (T_m) at 54.29 ºC. The Physical mixture of Olanzapine and poloxamer-407 (P-4) shows two endothermic peaks (T_m) at 190.23 ºC and 52.60 ºC with reduction in the peak areas and melting endotherms (ΔH value). Solid dispersion on the other hand (S-4) shows only one endothermic peak due to the poloxamer alone. No another peak was detected due to the drug, showing the loss of crystalline nature of the drug. The drug was converted to the amorphous form as shown in Figure 6.

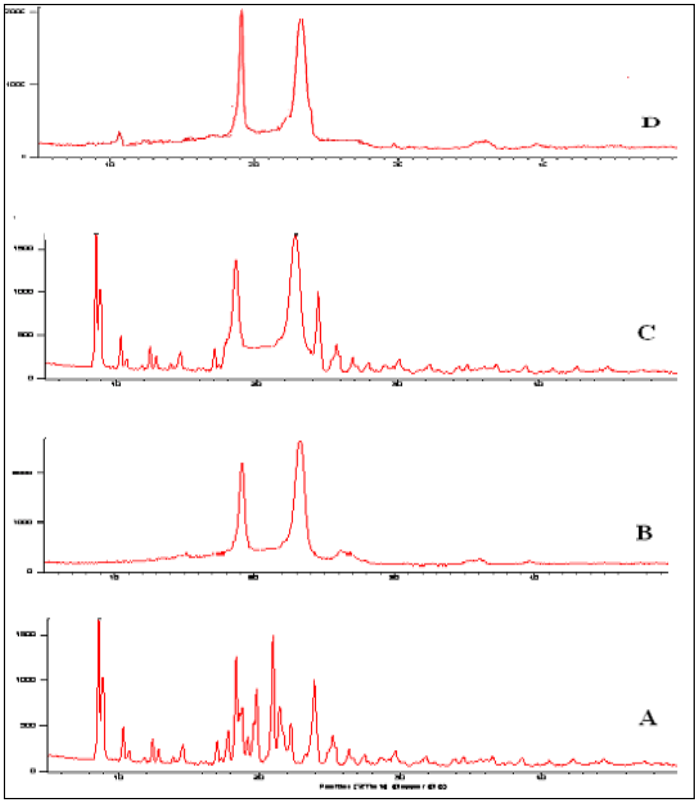

Figure 5. X-Ray diffraction studies of (A) Olanzapine (B) Poloxamer-407 (C) Physical mixture (P-4) (D) Solid dispersion (S-4).

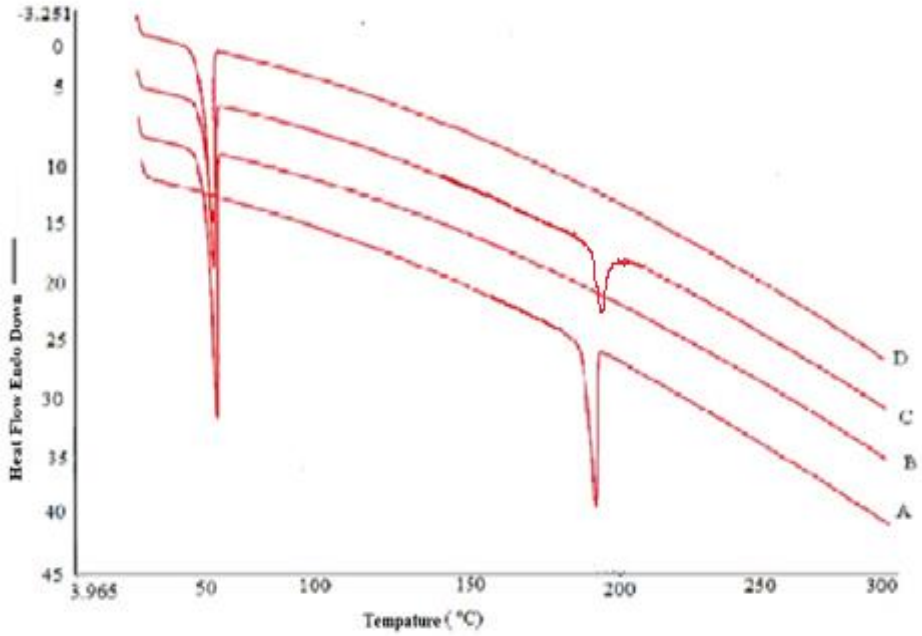

Figure 6. Differential scanning calorimetric Study, A) Pure Drug Olanzapine, B) Poloxame-407, C) Physical mixture of Olanzapine and Poloxamer-407 (P-4), D) Solid dispersion of Olanzapine and Poloxamer 407 (S-4).

CONCLUSION

In the present study, Olanzapine was chosen as model drug, as it possesses low solubility and hence low oral bioavailability. Solid dispersions and physical mixture of Olanzapine were prepared by using carrier Poloxamer-407. A comparison was done for its ability to increase the dissolution profile of water insoluble drug Olanzapine. Olanzapine- Poloxamer (S-1, S-2, S-3, S-4, S-5) systems were prepared by Hot melt Method. Solid dispersions and physical mixtures were evaluated for Percentage drug yield, Drug content, in vitro drug release studies, FTIR Spectroscopy, X-Ray Diffraction and Differential scanning calorimetry analysis. The results obtained showed that the percentage yield and percentage drug content was 98.32% and 99% respectively. It was clear that there was no loss of drug and polymer. The rate of dissolution of the drug in the case of solid dispersions was much enhanced as compared to the pure drug and its physical mixtures. From the XRD and DSC it was confirmed that the increase in the solubility and dissolution rate was due to polymorphic transition of drug from crystalline to amorphous form.

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