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ENHANCEMENT OF DISSOLUTION RATE OF ZALEPLON BY SOLID DISPERSION TECHNOLOGY USING HYDROPHILIC POLYMERS AND SOLID STATE CHARACTERIZATION

Ghorpade Pranita*, Sakhare Sfurti, Gharge Varsha, Salunkhe Prajakta, Yadav Adhikrao

Gourishankar Institute of Pharmaceutical Education & Research, Limb, Satara, Maharashtra, India

Keywords:

Zaleplon, PEG 6000, poloxamer 407, enhanced drug solubility, dissolution rate.

Abstract

Objective:

Enhancement of dissolution rate of zaleplon by solid dispersion technology using hydrophilic polymers and solid state characterization & dissolution behavior

Methods:

Formulation parameters by the solvent evaporation method at different drug: polymer ratios

Results:

The results showed that PEG 6000-based solid dispersion exhibited significantly higher zaleplon dissolution. zaleplon has high melting point, which is indicative of strong crystal lattice energy. All solid dispersions of zaleplon prepared with PEG 6000 and poloxamer 407 polymers showed enhanced drug solubility over the pure zaleplon (0.11) mg/ml in distilled water and (0.23)mg/ml in phosphate buffer 6.8. The *in vitro* release studies were carried out for the zaleplon solid dispersions prepared by melting method. The dissolution rate of pure zaleplon was very poor and during 120 min a maximum about 28.55% of the drug was released. Pure zaleplon exhibit a peak at 187.52 °C which represent the melting point of zaleplon. DSC curve of PEG 6000 showed a peak at 64.34°C and poloxamer 407 showed peak at 58.67°C The patterns of the poloxamer 407 and PEG 6000 also showed few peaks indicating its crystallinity nature.

Conclusion:

The formulation of solid dispersion of a drug with hydrophilic crriers is a potential approach used to improve the solubility and dissolution rate of practically water insoluble or less soluble drugs.

Introduction

Development of bioavailable dosage form of these drugs is the most important challenge faced by the formulators. The oral route of administration is the most convenient and preferred method of drug delivery. At least 90% of all drugs used to produce systemic effects are administered by oral route When a drug is taken orally it passes through the mouth, esophagus, stomach, duodenum, jejunum (small intestine), colon (large intestine) and finally leaves the body if not absorbed[1]. oral bioavailability of drugs can be improved by the enhancing solubility and dissolution rate of poorly water soluble drugs , and another is enhancing the permeability of poor permeable drugs[2]. The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry[3]. Solid dispersion technique was firstly demonstrated by Sekiguchi and Obi in 1961, to increase the dissolution and oral absorption of poorly water-soluble drugs.Solid Dispersion is defined as a dispersion of one or more active ingredients in an inert carrier, usually highly water-soluble compound, which could be prepared by different methods including melting, solvent and melting-solvent techniques[4, 5, 6, 7]. Zaleplon is a water insoluble drug with a log P of 1.23. Zaleplon is a nonbenzodiazepine hypnotic from the pyrazolo pyrimidine class and is indicated for the short-term treatment of insomnia. Zaleplon is having

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poor water solubility (BCS class II). The oral bioavailability is approximately 30% because it undergoes significant presystemic metabolism.The present investigation relates to developing solid dispersion to improve solubility and dissolution rate of Zaleplon by using oral drug delivery system.[8, 9,10]

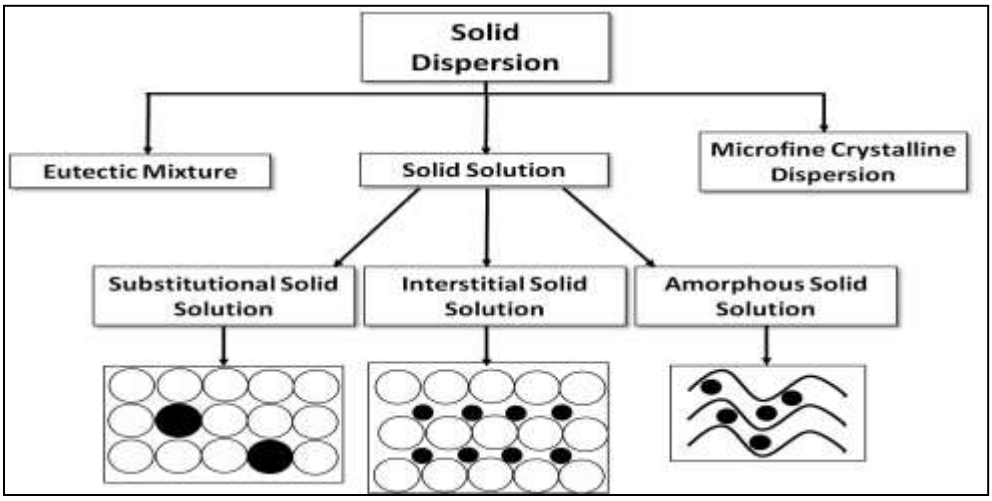

Figure 1: Classification of Solid dispersion

Materials and Method

Materials

Zaleplon was obtained from Precise Chemipharma Pvt. Ltd. PEG 6000 Rajesh Chemicals, Mumbai. Polaxamer 407 Ozone ®international. Mumbai. All other chemicals and ingredients were used for study are of Analytical grade.

Method

Phase solubility studies

The Phase solubility study of Zaleplon was done by Higuchi-Connor's method with two carriers of Pluronic F127 and PEG 6000. Excess amount of drug was added to screw-capped vials containing 10 ml of aqueous solution and phosphate buffer 6.8 of PEG 6000 and Pluronic F127 with varying concentrations. Vials were shaken with magnetic stirrer for 48 hr at a controlled temperature at 37ºC±2ºC. After 48 hours the solution was filtered through Whatman filter paper (0.22µm). The filtrate was then diluted and assayed spectrophotometrically at 232nm. The Gibbs free energy of transfer (ΔGtrº) of zaleplon from water to aqueous solutions of carrier was calculated using the following equation:

$$\Delta Gtr^{o} = -2.303\ RT \log (Sc/So)$$

Where ΔGtr º 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 Sc/So is the ratio of molar solubility of Zaleplon in aqueous solution of carrier to that of water. The acquired values of ΔGtr º indicate that whether the drug solubilization in the aqueous solution is favorable or not i.e. negative ΔGtr º values indicate favorable conditions and as the values increases more negative means more favorable conditions.

Preparation of solid dispersion by melting method [11-16]

The melting or fusion method was used to prepare PEG 6000 and Poloxamer 407based solid dispersion of Zaleplon in the ratio of 1:1,1:2 and 1:3 heated directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under constant stirring. The solid mass of PEG 6000 and Poloxamer 407 based Zaleplon solid dispersion was

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finally crushed and pulverized. The obtained powder of solid dispersion was passed through sieves (No.44) and stored in desiccators until use for further studies.

Preparation of Physical Mixture [17-19]

Physical mixtures were prepared by simple mixing of two components. The appropriate amounts of drug and carrier were blended in a mortar and pestle to form physical mixture. The mixture was passed through sieve number 44 to obtain uniform size distribution

Table No.1: Composition of Zaleplon loaded solid dispersion

Formulation code	Carrier	Drug : carrier	Method
F1	PEG 6000	1:1	Melting / Fusion method
F2		1:2	
F3		1:3	
F4	Poloxamer 407	1:1	
F5		1:2	
F6		1:3	

Characterization of Solid Dispersion

a) Drug Content: [20]

Drug content was determined by dissolving solid dispersions equivalent to 10mg of drug in 10ml of methanol and sonicated for 10 minutes. The volume was adjusted to 100ml with phosphate buffer 6.8. The solution was filtered through Whatman filter paper (0.22µm), suitably diluted and assayed spectrophotometrically at 232nm. [21-23]

b) Saturation solubility studies: [24]

The saturation solubility study of Zaleplon was done by with solid dispersion. Equivalent to 10mg drug and solid dispersion was added to screw-capped vials containing 10 ml of phosphate buffer 6.8 of PEG 6000 and Pluronic F127 with varying concentrations. Vials were shaken with magnetic stirrer for 48 hr at a controlled temperature at 37ºC±2ºC. After 48 hours the solution was filtered through Whatman filter paper (0.22µm). The filtrate was then diluted and assayed spectrophotometrically at 232nm

c) In-vitro drug release study: [25]

The drug release was studied using USP type I apparatus at 37 ± 0.5°C and at 50 rpm using 900 ml of phosphate buffer pH 6.8 as a dissolution medium. 5ml of the sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably and analyzed spectrophotometrically at 232 nm. Equal amount of the fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved at different time intervals was calculated using the Lambert-Beer's equation. The result was obtained in triplicate and the average value reported.

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Figure 2: Dissolution test apparatus of in-vitro drug release

d) Analysis of in vitro drug release kinetics and mechanism: [26]

In order to investigate the mechanism of drug release, the data were fitted to various drug release kinetic model equations such as zero order (cumulative % release vs. time), first order (log of cumulative % drug remaining vs. time), Higuchi's square root of time model (cumulative % release vs. square root of time), Hixson Crowell cube root plot (cube root of % drug remaining vs. time) and Korsmeyer Peppas kinetic plot (fraction release of drug vs. time). The zero order rate Eq. (1) describes the system where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles. The Korsmeyer Peppas exponential model Eq. (5) describes the drug transport mechanism.

$C = K_0 t$….. (1)

Where K0 is zero order rate constant expressed in units of concentration/time and t is the time.

$\text{Log } C = \text{Log } C_0 - Kt / 2.303$….. (2)

Where C0 is the initial concentration of drug and K is the first order rate constant.

$Q = Kt^{1/2}$….. (3)

Where Q is the amount of drug released at time t, and K is the diffusion rate constant.

$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$….. (4)

Where Qt is the amount of drug released in time t, Q0 is the initial amount of the drug in the Solid dispersion and K_{HC} is the rate constant for Hixson–Crowell rate equation.

$Mt / M8 = Kt^n$….. (5)

Where Mt/M8 is the fractional release of the drug,

t is the release time, K is a constant incorporating structural and geometric characteristic of the release device and the diffusional exponent 'n' is dependent on the geometry of the device as well as the physical mechanism for release. In this context, n=0.43 indicates Fickian (case I) release and n=<0.85 indicates a purely relaxation controlled delivery which is referred to as Case II transport. Intermediate values 0.43< n< 0.85 indicate an anomalous behavior (non Fickian kinetics corresponding to coupled diffusion/polymer relaxation). Occasionally, values of n>1 have been observed, which are regarded as Super Case II kinetics.

e) **Fourier transforms infrared spectroscopy:**[27-29]

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Fourier transform infrared spectra were obtained using Shimadzu FTIR-8400S spectrometer, Japan. Samples of Zaleplon, physical mixtures and optimized formulation of solid dispersion were taken for the study. The scanning range was 400 to 4000 $cm^{-1}$and the resolution was 4 cm^{-1}

f) Differential scanning calorimetric (DSC):[30-32]
DSC analysis of the samples was carried out on a Perkin-Elmer DSC7, USA. Samples (3.3350 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10 °C/min over the temperature range of 30 and 300 °C. DSC analysis was carried out under nitrogen gas flow of 20 ml/min.

g) X-Ray Diffraction (XRD) Studies: [33, 34, 35]
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 5-50 º, at a scan rate of 5ºC/min. All XRD spectra were compared.

Result & Discussions

Phase solubility study:

Table no.2: Phase solubility and the thermodynamic parameters of the samples at temperature.

Carriers	Concentration of carriers (%w/v))	Concentration of Zaleplon (mg/ml) at 37^0c	ΔG_{tr}° (J/mol)
PEG 6000	0	0.23	-
	1	0.33	-207.55 J/mol
	2	0.43	-212.57 J/mol
	3	0.5	-227.76 J/mol
Poloxamer 407	1	0.28	-57.57J/mol
	2	0.33	-106.88 J/mol
	3	0.39	-154.72 J/mol

The phase solubility study showed that PEG 6000 and Polaxamer 407 have a significant solubilizing effect on Zaleplon Figures hows the phase-solubility curve of Zaleplon in the presence of PEG 6000 and Polaxamer 407. From this curve, it can be seen that the apparent solubility of Zaleplon increased with greater carrier concentrations. Both carriers show an A_L type of linear graph with increasing concentration of carriers. The obtained values of Gibbs free energy transfer (ΔGo tr) (Table13) for apparent stability constants (Ks) were 43.46 and 130.38, for slope 1.88×10-2 and 5.3×10-3 with R2 values 0.999 and 0.999, for PEG 6000 and Poloxamer 407, respectively.

The results of phase solubility are in accordance with the well-established formation of soluble complexes between water-soluble polymeric carriers and poorly water-soluble drugs. ΔG_{tr}° values were all negative for carriers at various concentrations indicating the spontaneous nature of the drug Solubilization. From results of phase solubility study it was clear that drug is more soluble in phosphate buffer (pH 6.8) hence phosphate buffer was chosen as the dissolution medium.

a) Drug content:
The melting method is a convenient method for the preparation of solid dispersion with good drug content. Drug content of all eight batches based on PEG 6000 and Poloxamer407concentration was found to be in the range of (90.12%- 94.16) which might be due to loss of drug during pulverization and sieving processes. It was observed that

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with the increase in polymer concentration drug content also increased. It indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for preparation of solid dispersion.

Table no3: Drug content

Formulation	Drug content (%)
F1	91.73% ±0.001528
F2	93.07% ±0.001
F3	94.16% ±0.001528
F4	90.12% ±0.001528
F5	91.18%±0.001528
F6	92.40%±0.001

b) Saturation solubility study:

All solid dispersions of Zaleplon prepared with PEG 6000 and poloxamer 407 polymers showed enhanced drug solubility over the pure Zaleplon (0.11) mg/ml in distilled water and (0.23)mg/ml in phosphate buffer 6.8. The maximum solubility achieved by using PEG 6000 especially at the ratio f3 1:3 drug-to-carriers, where the solubility was (0.79±0.001414) mg/ml. regarding the effect of the type of poloxamer407, which was between (0.60± 0.001528) mg/ml

Table no.4: Saturation solubility study of solid dispersion

Formulation code	Saturation solubility in mg/ml
Pure drug in PBS 6.8	0.23
F1	0.411
F2	0.608
F3	0.796
F4	0.375
F5	0.469
F6	0.603

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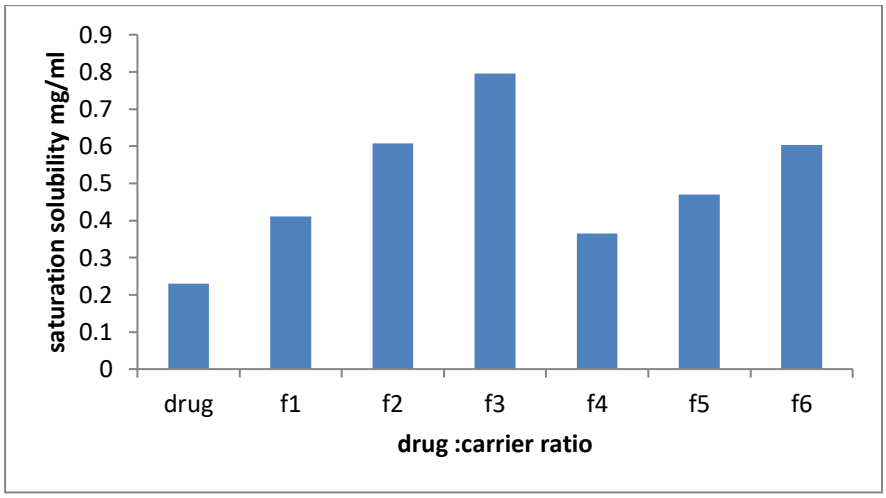

Figure 3: Saturation solubility study of solid dispersion

c) In-vitro drug release/dissolution studies:

The *in vitro* release studies were carried out for the Zaleplon solid dispersions prepared by melting method. The dissolution rate of pure Zaleplon was very poor and during 120 min a maximum about 28.55% of the drug was released .The results of in-vitro release studies are given in table and the graph for percentage cumulative release are given in Figures. The experimentally determined solubility and dissolution of the pure Zaleplon and its solid dispersions in phosphate buffer pH 6.8. All drug-carrier combinations showed an increase in solubility and dissolution of Zaleplon as compared to pure Zaleplon. This might be due to hydrophilic nature of the carriers. Dissolution profiles of all solid dispersion are shown in table which indicated that the SD ratio 1:3 of drug: PEG 6000 fast dissolution of drug as compared to poloxamer 407. Moreover, improvement of the solubility and the dissolution rate of Zaleplon in its solid dispersion, which can be formulated as tablets or capsules with better dissolution characteristics. The rapid dissolution of Zaleplon from its solid dispersion may be attributed to the decrease in the drug crystallinity and its molecular and colloidal dispersion in the hydrophilic carrier matrix. As the soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution.The result of drug release in following order F3> F2> F1> F6> F5>F4.showed the dissolution profiles of selected solid dispersions as compared to plain drug.

Table no5: In vitro drug release profile of Zaleplon Solid Dispersion with PEG 6000 and poloxamer 407

Time (min.)		**% drug release**					
	Drug	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0	0
10	6.92	19.03	20.87	23.07	10.67	12.68	14.99
20	8.65	20.76	23.07	25.28	16.43	15.28	17.88
30	10.38	25.96	26.82	30.57	17.59	19.32	23.66
40	13.84	28.26	30.86	33.94	23.07	22.28	26.53
50	15.57	31.15	35.76	38.07	25.66	25.37	36.45
60	17.30	33.27	40.45	42.68	31.95	34.03	40.96
70	19.03	40.09	46.06	48.45	35.75	36.79	45.28

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80	21.63	45.86	52.49	57.11	44.12	48.45	55.09
90	23.26	57.69	58.12	62.88	47.88	53.64	60.57
100	25.96	62.88	66.34	74.70	57.97	59.13	68.65
110	27.69	69.22	74.70	81.91	58.87	64.03	75.57
120	28.55	76.43	83.36	93.45	65.19	70.65	82.49

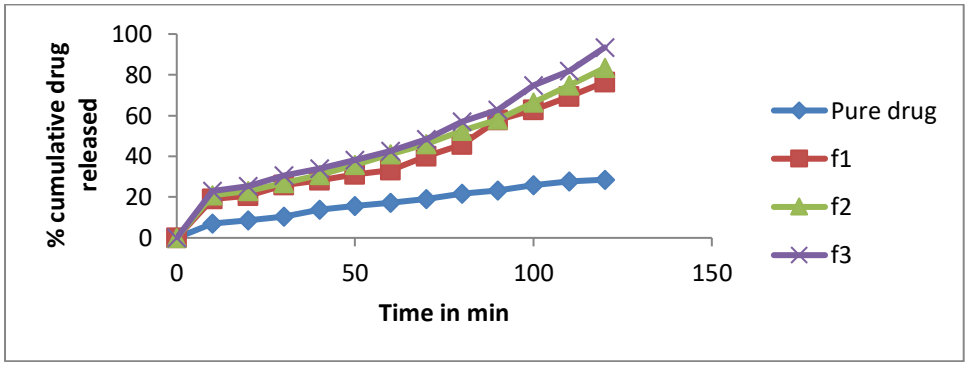

Figure 4: Comparison of pure drug % drug release of solid dispersion with PEG 6000 F1 to F3 batch

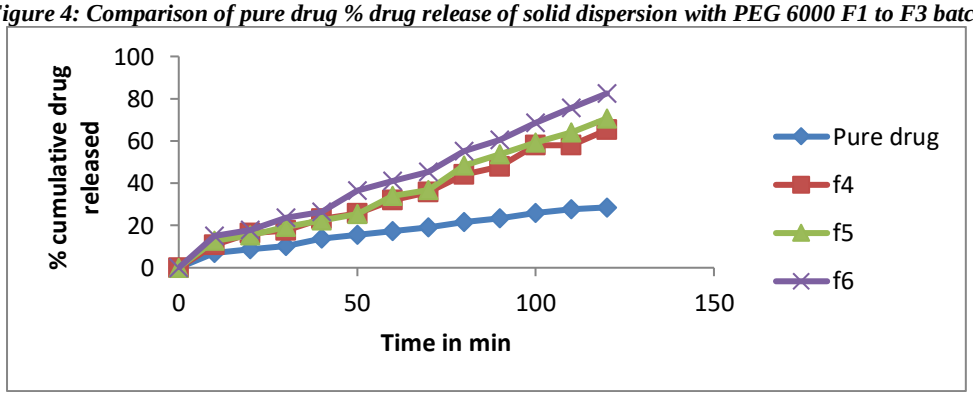

Figure 5: Comparison of pure drug and % drug release of solid dispersion with Poloxamer 407F4 to F6 batch

d) Drug Release kinetics Modelling

There is a plethora of literature available to study drug release kinetics from solid dispersions which is primarily based on properties of the drug without any focus on the role of carrier within the system. In the present work drug release kinetics and release mechanism were assessed by evaluating both carrier and drug release concurrently for the same polymeric composition and measuring polymer dissolution in addition to drug release mechanism. Drug release data for PEG 6000 and Poloxamer 407 were analyzed according to kinetic equations zero order, first order, Higuchi, and Peppas equation. models. Drug release Table shows the regression parameters obtained after fitting various release kinetic models to the *in-vitro* dissolution data. The obtained regression coefficients ($R^{2)}$ for zero-order kinetics, first-order kinetics and Higuchi model were 0.957-0.989, 0.774-0.962 0.882-0.957and 0.982-0.998 respectively. The (R^2) values of zero order models were found to be higher than that of first order kinetics and Higuchi order kinetics. Accordingly, the release of the drug from the prepared solid dispersions followed predominantly zero order models. According to Korsemayer-peppas model n-value was used to characterize different release mechanisms as given in Table. The n value was 0.55-0.827 which refers that the *in-vitro* release exhibits case II Non-Fickian diffusion refers a combination of both diffusion and erosion release.

Indian Journal of Medical Research and Pharmaceutical Sciences
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Table no 6: Release kinetics

Release kinetics					
Formulation	**Zero order r^2**	**first order r^2**	**Higuchi r^2**	**Korsemeyer peppas r^2**	**n (Slope)**
F1	0.957	0.882	0.882	0.881	0.585
F2	0.978	0.878	0.910	0.998	0.555
F3	0.961	0.774	0.887	0.892	0.577
F4	0.985	0.954	0.957	0.937	0.749
F5	0.980	0.944	0.924	0.944	0.748
F6	0.989	0.962	0.943	0.958	0.827

e) IR Spectroscopy (FT – IR) Analysis

IR spectra of Zaleplon and its combination with excipients are shown in table no 18. an IR spectra of pure Zaleplon showed characteristic peaks at 3086cm^{-1} (C-H aromatic), 2981 cm^{-1} (C-H aliphatic), 2231.14cm^{-1} (C≡N), 1645.21 cm^{-1} (C=O stretch), 1228.87 cm^{-1} (C-N), 1543.05 cm^{-1} (C= C aromatics), 692.cm^{-1} (m substituted benzene). Zaleplon shows strong absorption peaks at 2233.14cm^{-1} and 1647.21 cm^{-1} indicating presence of cyanide and amide carbonyl group respectively while, peaks at 696.30 cm^{-1} may be assigned to aromatic stretching of the phenyl group in the molecule which is m-substituted. These peaks can be considered as characteristic peaks of Zaleplon and were not affected and prominently observed in IR spectra of Zaleplon along with excipient as shown in the table indicated no interaction between Zaleplon and excipients.

The FTIR spectrum of the PEG 6000 sample only (Fig), shows principal peaks at3442.27 cm^{-1}(O-H stretching),2879.24 (C-H stretching) .These observed principle peaks were comparable to the reference peaks of the PEG 6000. This observation confirmed the purity and authenticity of the PEG 6000.

The FTIR spectrum of the Polaxamer 407 sample only (Fig), shows principal peaks at 2885.51 (C-H stretching (aliphatic), 1344.38(in plane O-H bend), 1091.71(C-O).These observed principle peaks were comparable to the reference peaks of the Polaxamer 407. This observation confirmed the purity and authenticity of the Polaxamer 407.

Analysis of the spectra for the solid dispersion revealed that peaks of both drug as well as formulation were observed and interpreted shown in the table So this clearly suggests that drug, polymers and excipient used for the current study were compatible. There is no significant or any shift in the positions of the characteristic absorption bands of drug in the formulations.

Table no. 7: IR Interpretation Of solid dispersion

Functional Group	**Reported Frequencies (cm^{-1})**	**Observed Frequencies (cm^{-1})**	
		solid dispersion(F3	**solid**

Indian Journal of Medical Research and Pharmaceutical Sciences
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		batch)	**dispersion(F6 batch)**
C-H aromatic	3000-3100	3088.03	3084.18
C-H aliphatic	2850-3000	2935.66	2881.85
C≡N	2260-2220	2233.57	2233.57
C=O stretch	1640-1690	1649.14	1649.14
C-N	1080-1360	1238.30	1240.23
C= C aromatics	~1600 ~1475	1544.98	1546.91
Phenyl group.	690-710	696.30	692.44

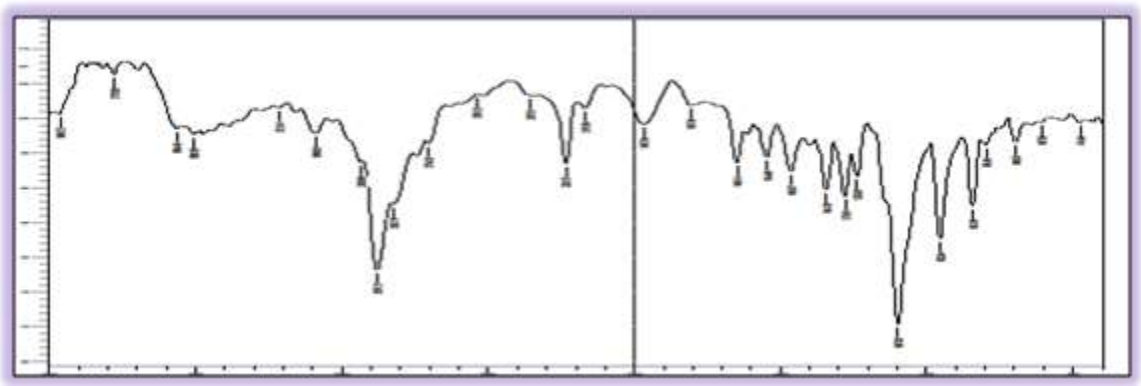

Figure 6: IR spectra of solid dispersion –F3

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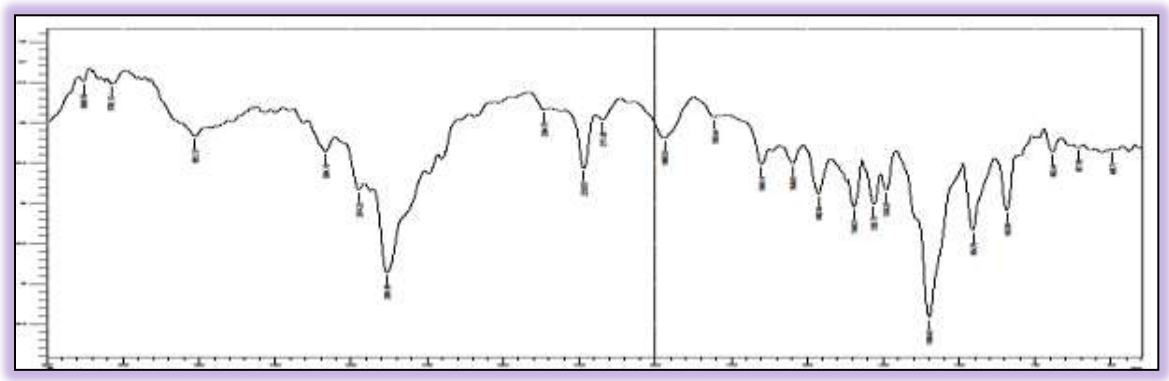


Figure 7: IR spectra of solid dispersion –F6

f) Differential Scanning Calorimetry studies:

The DSC curve obtained for pure Zaleplon, PEG 6000 and poloxamer 407 in solid dispersion were displayed in the fig. Pure Zaleplon exhibit a peak at 187.52 °C which represent the melting point of Zaleplon. DSC curve of PEG 6000 showed a peak at 64.34°C and poloxamer 407 showed peak at 58.67°C corresponding to the melting point of polymers. The DSC profiles for Zaleplon: PEG 6000, Poloxamer 407 solid dispersions for the different drug: polymer ratios (1:1, 1:2, 1:3) showed a complete disappearance of Zaleplon. Deeper analyzing of the DSC results showed a great shift of the endothermic peak as shown in batch F3(58.35°C), F6(54.19°C), this may be attributed to the presence of PEG 6000 in case of F3 and Polaxamer 407 in the case of F6 in the molten state. This result indicated that the presence of PEG 6000 was sufficiently important to decrease the drug crystalinity to the amorphous state and at this ratio (1:3) drug existed in amorphous form and the amount of polymers used was sufficient to solubilise of the drug. Zaleplon homogenizes with the carriers in an amorphous form.

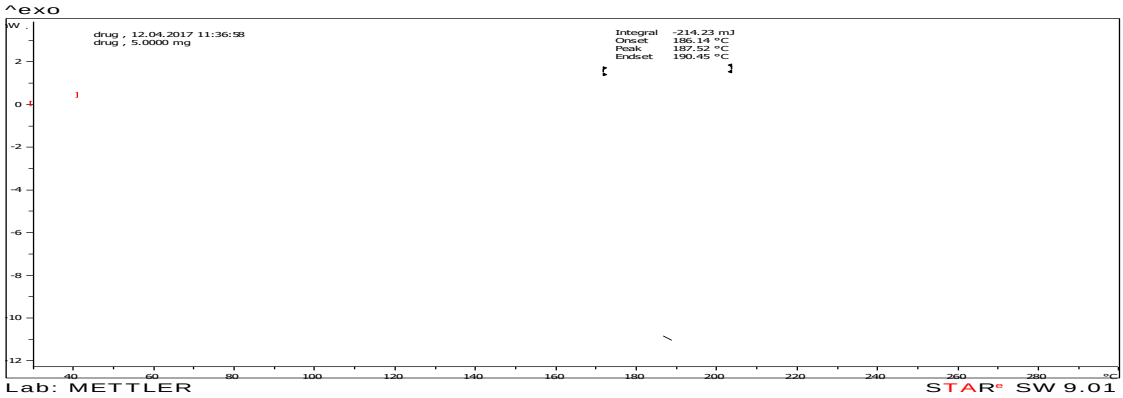
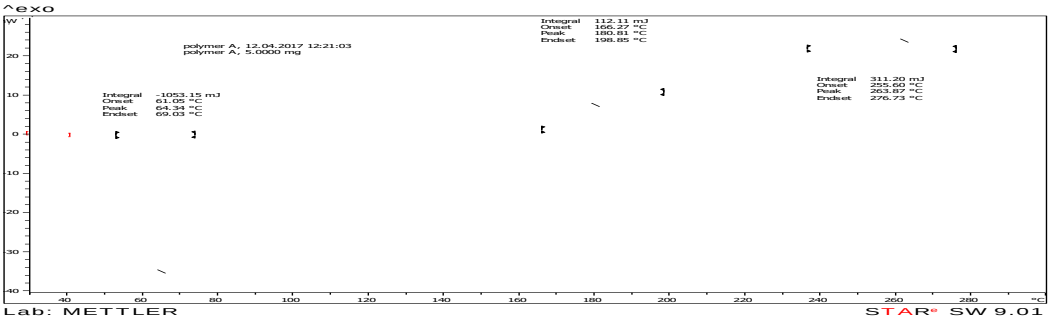


Figure 8: DSC spectra of pure Zaleplon



Indian Journal of Medical Research and Pharmaceutical Sciences
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Figure 9: DSC spectra of PEG 6000

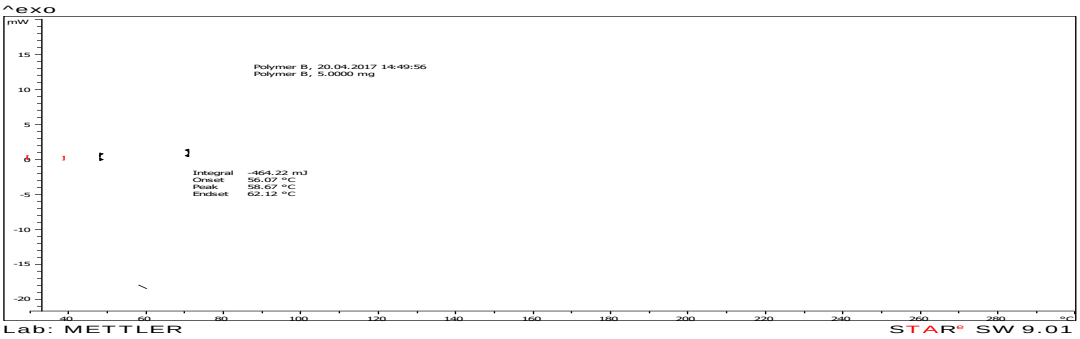

Figure 10: DSC spectra of Poloxamer 407

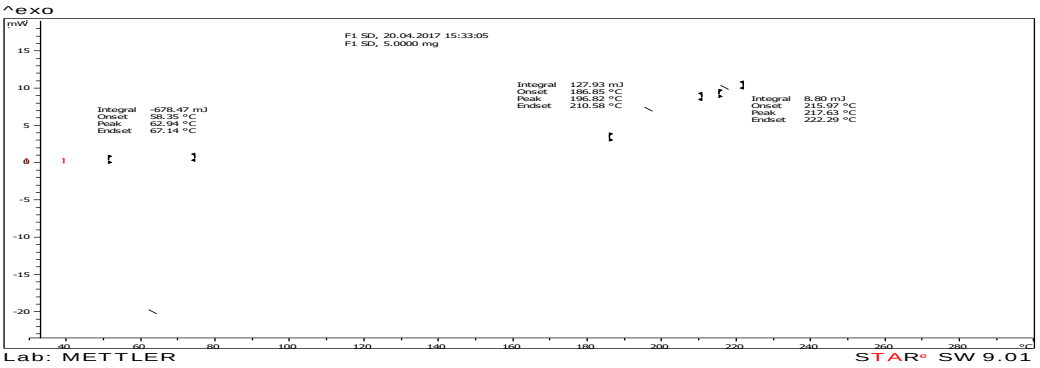

Figure 11: DSC spectra of Solid Dispersion (Drug +PEG 6000)

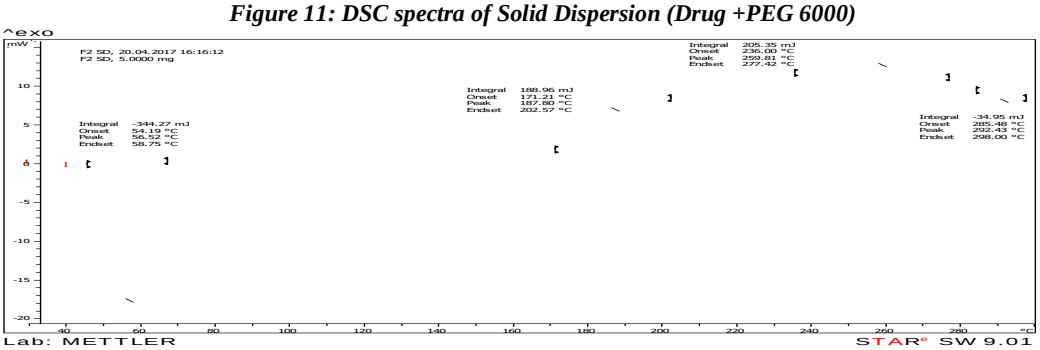

Figure 12: DSC spectra of Solid Dispersion (Drug +Poloxamer 407)

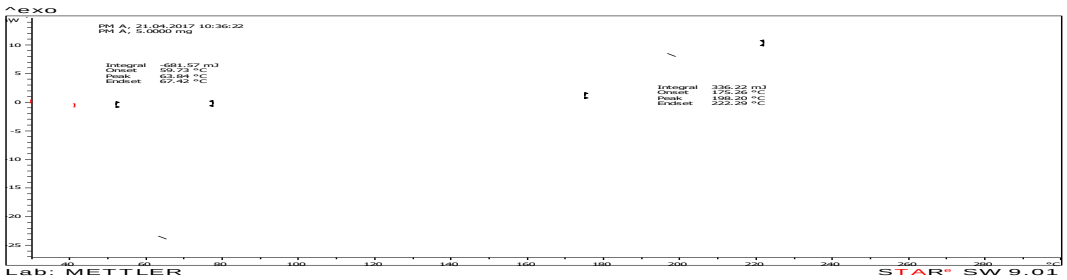

Figure 13: DSC spectra of Physical Mixture (Drug + PEG 6000)

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
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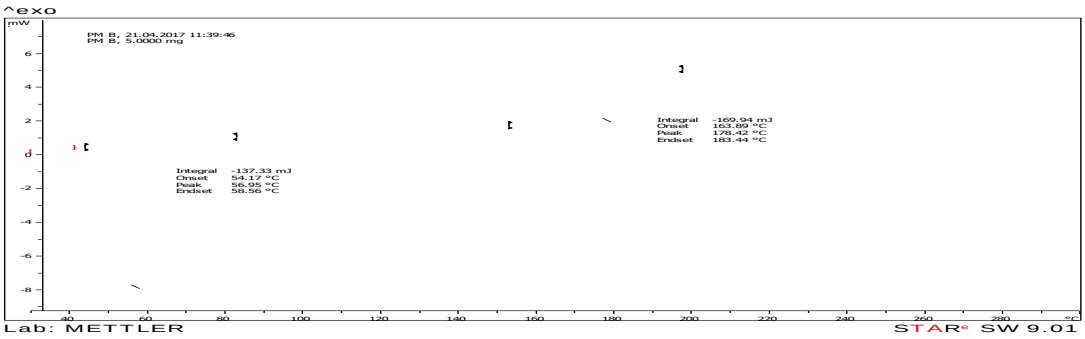

Figure 14: DSC spectra of Physical Mixture (Drug +Poloxamer 407)

g) X-Ray Diffraction Studies:

XRD study was performed to determine the physical state of the Zaleplon. The X-ray diffraction patterns for the Zaleplon, carriers, physical mixture and the solid dispersion are depicted in Figures35, 36, 37, 38,39,40,41. The Zaleplon has crystalline characteristics which are represented by peaks in X- ray diffractograms, and the most evident & intense peaks appear at 2θ = 10.4, 14.06, 16.7, 17.42, 19.52, 25.37, 26.6, showed in figure no.25. Zaleplon has high melting point, which is indicative of strong crystal lattice energy. The patterns of the poloxamer407 and PEG6000 also showed few peaks indicating its crystallinity nature. In the physical mixture, the distinctive diffraction peaks of Zaleplon persisted with a marked decrease in their intensity compared to pure Zaleplon crystals. The XRD peaks of crystalline Zaleplon in all the physical mixtures were similar to those in the pure drug, indicating that the Zaleplon did not change in the physical mixtures. The solid dispersion F6 exhibited lesser and broader peaks, indicating that the drug was present in the amorphous form in the dispersion. The number of peaks and the peak height was reduced in solid dispersions F3 as the polymer concentration increased. This indicates that the zaleplon has been completely converted to an amorphous state in the presence of PEG 6000.The XRD results confirmed the results of DSC studies and accounted for the formation of the amorphous state of zaleplon in the presence of PEG6000 and Poloxamer 407in solid dispersion samples.

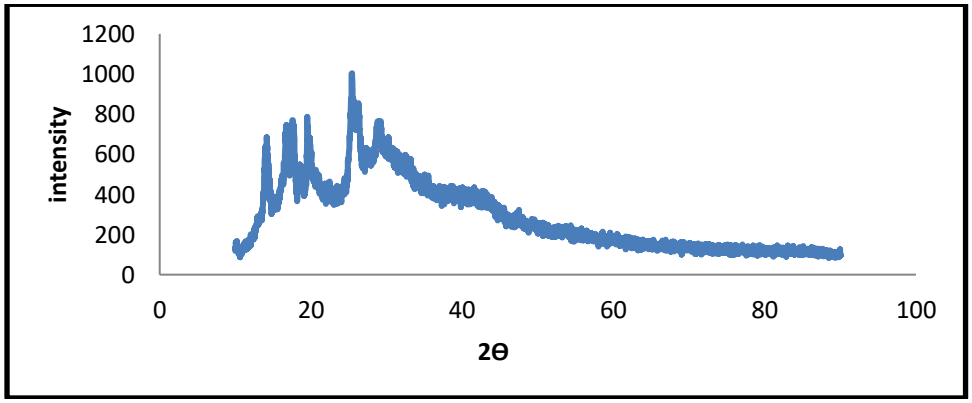

Figure 15: XRD OF Pure Zaleplon

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
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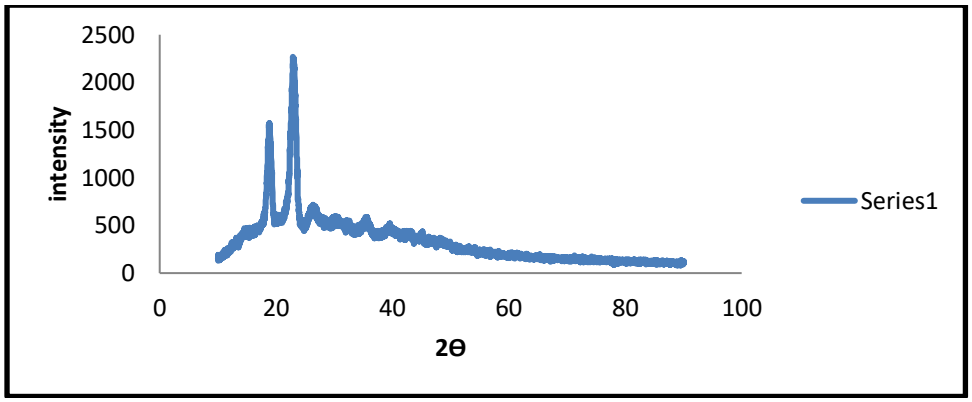


Figure 16: XRD OF pure PEG 6000

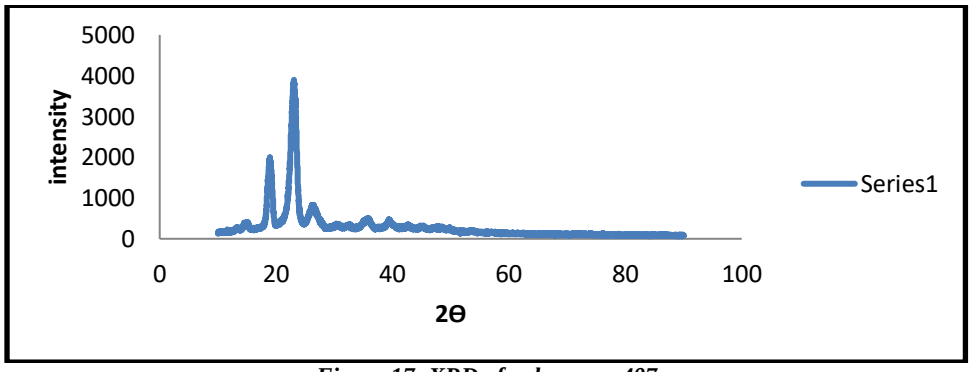


Figure 17: XRD of poloxamer 407

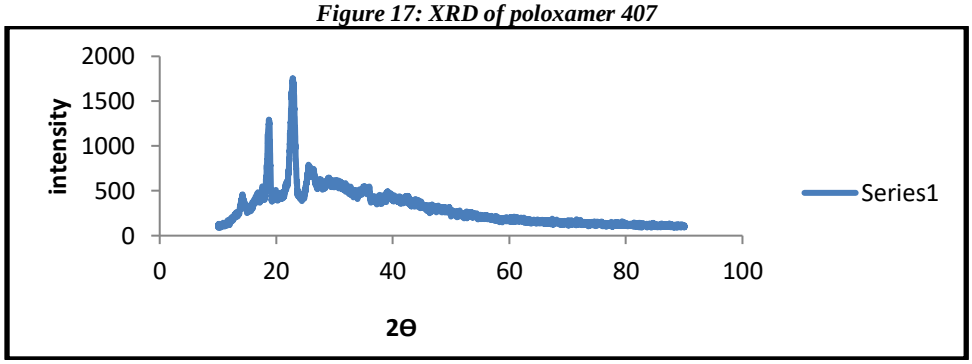
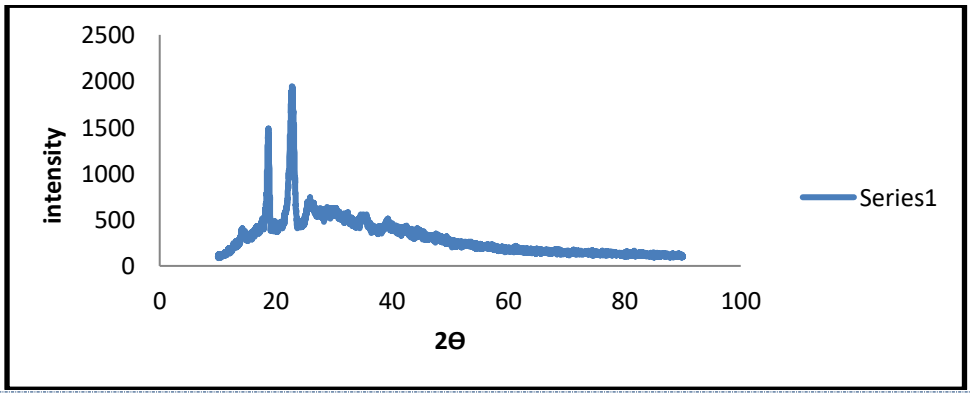


Figure 18: XRD of Physical mixture of drug+ PEG 6000



Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437440 Impact Factor: 4.054

Figure 19: XRD of Physical mixture of drug+ poloxamer 407

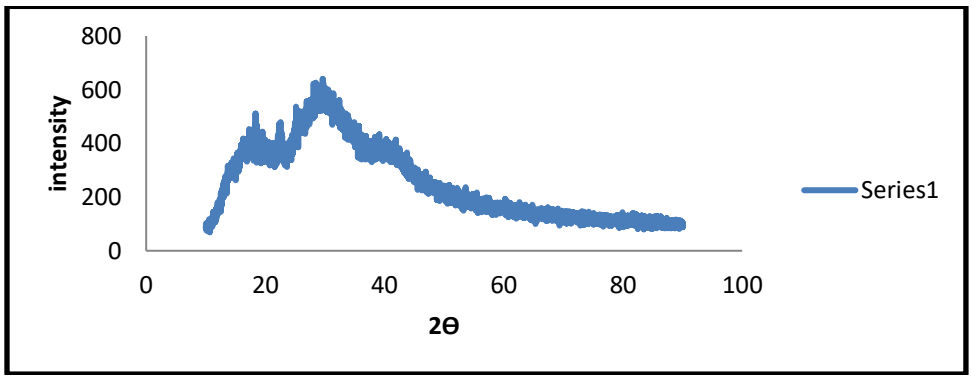


Figure 20: XRD of solid dispersion F3

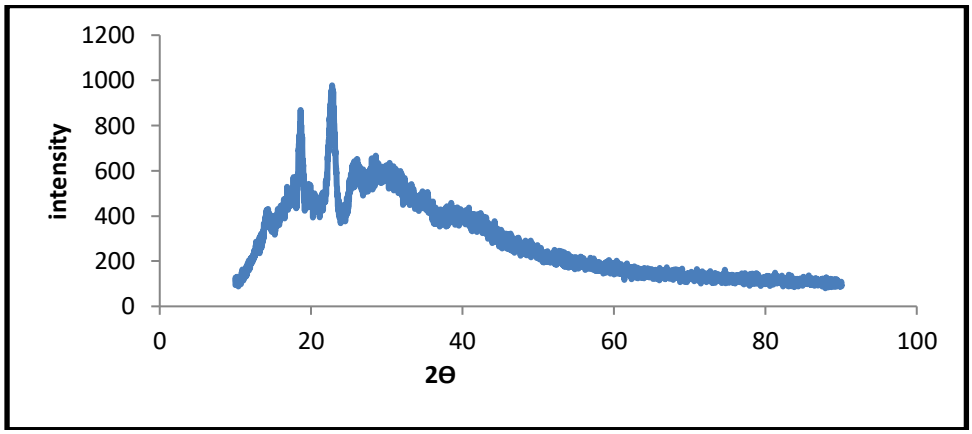


Figure no 21: XRD of solid dispersion F6

Conclusion

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Dissolution of drug is the rate determining step for oral absorption of these drugs, which can subsequently affect the drug's inherent efficacy as a result of irreproducible clinical response. The basic goal of any drug delivery system is to achieve steady state of blood concentration or tissue level that is therapeutically effective and safe for an extended period of time. Currently, only 8% of new drug candidates have both high solubility and permeability. Solid dispersions prepared with hydrophilic polymer or surfactants with special physicochemical properties are one of the most attractive approaches to enhance the solubility of a poorly water soluble drug as well as its delivery.

From the present study was performed to enhance the dissolution rate and aqueous solubility of Zaleplon, a poorly soluble drug using PEG- 6000 and Polaxamer 407as carrier. Nature and amount of carrier used to play an important role in the enhancement of dissolution rate.

Phase solubility study indicates that solubility of Zaleplon increased with polymers concentration. The Negative values of Gibbs free energy indicated spontaneity of transfer. The improvement in solubility can be attributed to effect of polymer.

The solubility of Zaleplon in distilled water was found to be (0.11mg/ml); while it was (0.23mg/ml) in pH 6.8. Dissolution of Zaleplon alone was very slow and incomplete up to 120 min. According to the obtained results,

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only28.55±0.24 % of drug was dissolved after 2 hr. Hence, as the intrinsic solubility as well as rate of drug dissolution is poor, there is strong need to enhance its solubility and dissolution.

FTIR, XRD and DSC analyses apparently did not indicate any interaction of the drug with the polymers.DSC, XRD studies revealed that Zaleplon was molecularly dispersed in the polymer matrix.

In vitro drug release study showed that drug release can be modified by varying drug to polymer ratio. The release rate was found to be increased in accordance with the increase in the ratio of polymer used. The release profile of drug follows the zero order models with non-fickian release. Zero order model indicated that the drug release from these solid dispersion followed sustained release pattern. non – fickian refers to a combination of both diffusion and erosion controlled drug release. & which also indicates initial burst release followed by near zero order release.

Solid dispersions prepared with PEG 6000 showed higher solubility and dissolution rate than those pepared with pluronic F-127. Hence, the solid dispersion method, using a hydrophilic carrier such as PEG 6000, could be considered as an appropriate technique for dissolution enhancement of Zaleplon, which is a poorly-soluble drug.
Finally it can be concluded that, solid dispersion system containing Zaleplon and carriers with aid of Melting technique was efficient to form amorphous dispersion of Zaleplon. On comparison the two formulations second generation amorphous carrier (PEG 6000) has better dissolution rate and solubilizing action on Zaleplon than third generation (Poloxamer407) crystalline carrier with surface active property. Thus, the formulation of solid dispersion of a drug with hydrophilic crriers is a potential approach used to improve the solubility and dissolution rate of practically water insoluble or less soluble drugs.

References

1. Podczeck F., Course N., Newton J.M., Short M.B. Gastrointestinal transit of a model mini-tablet controlled release oral dosage forms in fasted human volunteers. Journal of Pharmacy and Pharmacology. 59(7), 941-5, 2007.
2. Rani SK ,Pournima G, Krishnaveni A, Brahmaiah B, Nama S. A Review on solid dispersions. Asian J. Pharm. Res, 2013;3 (2): 93-98
3. Vijay J, Sahadevan J T. Gilhotra R M. A basic insight into the stability and manufacturing aspects of solid dispersions. Chronicles of Young Scientists, 2012; 3(2):95-105
4. Kaushik Anu , Chauhan V. Recent Review On Solid Dispersion Of Hydrotropes. IJARIIE,2017;3(1): 1283-1292
5. Karande S, Pawar N, Falguni R, Rawat S, Sharma Y . A Review on Solid Dispersion. IJUPLS,2013; 3(5): 50-72
6. Chavan D V., Waghmare P.V., Chinchole A.S., Bhusnure O.G., Usnale S.V. Solubility Enhancing Methods for Poorly Soluble Drugs: A Review. Int. Res J Pharm. App Sci., 2013; 3(2):190-203
7. Ingale US, Gaikwa PD, Bankar VH, Pawar SP. A Review on solid dispersion : A dissolution enhancement technique. Nijrap, 2011; 2(3): 751-757
8. Teja SB Patil SP, Shete G, Patel S, Bhansal AK. Drug – excipient behavior in polymeric amorphous solid dispersions. J. Excipients and food chem.. sept 2013; 4(3) : 70-94
9. Hideaki N, Kazuhiro Kitazumi, Megumi Mori, Yoji S, and Toshiharu S, Effect of Zaleplon, a Non-benzodiazepine Hypnotic, on MelatoninSecretion in Rabbits. J Pharmacol Sci. 2003; 93: 204 –209.
10. Morera AL, Abreu-Gonzalez P, Henry M. Zaleplon increases nocturnal melatonin secretion in humans. Progress in NeuroPsychopharmacology & Biological Psychiatry, 2209; 33: 1013–1016
11. Ahmen E ,Sayad R ,Ahmed MO, Younis MA. Improvement of domperidone solubility and dissolution rate by dispersion in various hydrophilic carriers. JAPS,2016,6(07): 133-139.
12. Samal H B, kumar N N, Sneha S. In- Vitro dissolution enhancement of aceclofenac using hydrophilic carriers. JPR , 2012,5(8):4496-4503
13. Bandarkar F S, Khattab I S " Lyophilized Gliclazide Poloxamr solid dispersion for enhancement of In-vitro Dissolution and in vivo bioavailability " IJJPS , 2011;3 (2): 122-127 issn -0975-1491

September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437440 Impact Factor: 4.054

14. Biswal S, Sahoo J, Murthy PN. Properties of solid dispersions of Gliclazide in polyvinylpyrrolidone K-90. AAPS, June 2009; 10(2): 329-334
15. Shah MR, Sancheti PP, Vyas VM,Karekar PS,Pore YV. Proton magnetic resonance (1 HNMR) spectroscopy and physicochemical studies of zaleplon-hydroxypropyl-β-cyclodextrin inclusion compounds. DDTJ,2010;4(2):70-76
16. Homoyouni A, Sadeghi,Nokhodchi A, Varshosaz J, Garekani HA. Preparation and characterization of celecoxib solid dispersions : comparision of poloxamer- 188 and pvp k-30 as carrier. Iran J Basic Med Sci, 2014; 17(5) : 322-331
17. Kurmi r, mishra d, Jain D. Solid dispersion : A novel means of solubility enhancement. J Crit Rev, 2015 3(1):1-8
18. Adel A, Randa M, Shahira F. Menshawi EI, Ahmed B . Effect of binary and ternary solid dispersions prepared by fusion method on the dissolution of poorly water soluble diacerein. IJDD,2013; 5(1):99-109
19. Jafari E. Preparation ,charaacterizatyion and dissolution of solid disp[ersion of Diclofenac sodium using Eudragit E-100. JAPS,2013; 3(08): 167-170
20. Mohanty SS , Biswal S, Sahoo J. Enhancement of Dissolution Rate of Glimepiride using Solid Dispersions with Polyvinylpyrrolidone K 90. Indian J. Pharm. Educ. Res. 2010;44(1):71-75
21. Al-Nima AM, Al-Kotaji MM, Khayrallah AA. Preparation and Evaluation Of meloxicum solid dispersions by solvent evaporation method. Int, Res.J. Pharm,2014;5(11): 833-845.
22. Hadziabdic J, Elezovic A, Rahic O, Vranic E. Kinetics and mechanism of diazepam release from solid dispersions, Bulletin of the chemist and technologist,2014; 21-28
23. Sathali AH, Jayalakshmi J. Enhancement of solubility and dissolution of olmesartan medoxomil by solid dispersion technique, J.Curr.Chem.Pharm.Sci., 2013;3(2) :123-134.
24. Dhilon N, Midha K, Nagpal , Pahwa R. Formulation Optimization and Characterization of solid dispersion of glibenclamide. Pharma Methods, 2015; 6(2): 72-82.
25. Biswal S, Sahoo J, Murthy PN. Physiochemical Properties of solid dispersions of Gliclazide in polyvinylpyrrolidone K-90. AAPS, June 2009; 10(2): 329-334.
26. Jagdale S C, Musale V, Khuchekar BS. Physicochemical characterization and solubility enhancement studies of allopurinol solid dispersions. BJPS, 2011; 47(3): 513-523.
27. Mali AM, Ghodake G, Gharge V. Enhancement of bioavailability of ibuprofen by using solid dispersion technique, ejpmr, 2018;5(6): 376-380.
28. Shavi G V, Kumar AR, Usha YN, Armugam K, Ranjan O R, Ginjupalli K, Pandey S . Enhanced dissolution and bioavailability of gliclazide using solid dispersion techniques, IJDD, 2010; 49-57.
29. Afifi S. Solid Dispersion Approach Improving Dissolution Rate of stiripentol: a novel antiepileptic drug. Iran. J. Pharm, Res,2014; 14(4) 1001-1014
30. Sharma A. Jain C P, Tanwar Y. Preparation and characterization of solid dispersions of carvedilol with poloxame188. J.Chil.Chem.SOC,2012; 58 (1) : 1553-1557.
31. Al-Nima AM, Al-Kotaji MM, Khayrallah AA. Preparation and Evaluation Of meloxicum solid dispersions by solvent evaporation method. Int, Res.J. Pharm, 2014; 5(11): 833-845.
32. Kumar P, Moham C, Mara kanam su, Gulati M, " Physiochemical characterization and release rate studies of solid dispersion of ketoconazole with pluronic F-127 and pvp l-30" Iran . J. of Pharm Res. 2010; 10(4): 685-69**4**
33. Bhise S, Mathure D, Patil V,Patankar R " Solubuility enhancement of antihypertensive agent by solid dispersion technique" IJPLS, 2011;2(8): 970-975
34. Asija R, Bhatt S, Asija S, Shah I, Yadav A " Solubility enhancement of nebivolol by solid dispersion technique" Asian J.Pharm. Tech. 2014; 4(3): 134-140
35. Sultana S, Saifuddin A H M "Review article: Solid dispersion currently practiced in pharmaceutical field" IJOART, March 2016; 5(3):170-175.