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Research Article

Preparation and Characterization of Solid Dispersion by Microwave and Freeze Drying Method for Solubility and Dissolution Rate Enhancement of Poorly Soluble Drug Ziprasidone

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ABSTRACT

Abstract
The aim of the present study was to enhance the solubility, dissolution rate and thus oral bioavailability of a poorly soluble, BCS class II drug Ziprasidone hydrochloride (ZPH), using its solid dispersions (SDs) with poloxamer 188 (PX) and HPMC E15.Solid dispersions were prepared by co-grinding, kneading, freeze drying and microwave methods. The dispersions were evaluated for various *in vitro* parameters such as solubility study, dissolution study, fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), scanning electron microscopy (SEM). Microwave generated solid dispersions in 1: 5 ZPH - PX ratio exhibited significant improvement in solubility and dissolution rate compared to that of pure drug. The superior dissolution profile observed for microwave induced solid dispersions is attributed to amorphization of the drug by microwaves, improved surfactant and wetting characteristics of the carrier with the drug. Thus, microwave technology offers a simple, efficient, solvent free promising alternative method to prepare solid dispersion of ZPH with significant enhancement of the *in vitro* dissolution rate.

INTRODUCTION

The oral route of drug administration is the most common and preferred route of drug delivery due to convenience and ease of ingestion. The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programs are poorly water soluble [1]. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing the permeability of poorly permeable drugs [2]. In recent years it has been estimated that up to 40% of the new drugs discovered by the pharmaceutical industry are poorly water soluble or lipophilic compounds [3].

Following are the class permeability of drugs according to solubility according to Biopharmaceutical Classification System such as High solubility High permeability, Low solubility High permeability, High solubility Low permeability and Low solubility Low permeability [4].

The Solid Dispersion is one of the best and convenient method which is used for the increased solubility of poorly water soluble drug. The Solid Dispersion is used to be reduced particle size, improve wettability, improve porosity of drug, decrease the crystalline structure of drug in to amorphous form, improve dissolvability in water of a poorly water-soluble drug, mask the taste of the drug substance,

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prepare rapid disintegration oral tablets, obtain a homogenous distribution of small amount of drugs at solid state, stabilize unstable drugs, dispense liquid or gaseous compounds [5, 6].

Sugars, Polyols and their Polymers, Polymers, Urea, Surfactants are the commonly used as carriers for the Solid Dispersion method which is used for increase solubility of poorly soluble drug [7, 8].

Following methods are commonly used for the preparation of solid dispersion such as Melting method, Solvent method, Melting solvent method (melt evaporation), Melt extrusion method, Lyophilization Technique, Lyophilization Technique, By using of surfactant, Electro spinning Method, Super Critical Fluid (SCF) Technology, Direct capsule filling Method, Dropping solution Method, Co-precipitation Method, Co-grinding Method, Kneading Method, Microwave Irradiation Method, Spray drying technique but in present study we are solid dispersion is prepared by Co-grinding method, Kneading method, Microwave method, Freeze drying [9, 10] .

Evaluation of solid dispersion is done by solubility study, solubility is the phenomenon of dissolution of a solute in a solvent to give a homogenous system, is one of the important parameters to achieve the desired concentration of drug in systemic circulation for a desired (anticipated) pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development [11].

Ziprasidone Hydrochloride monohydrate (ZPH) belongs to anti-psychotics category. ZPH is a faint white to nearly white powder and it is practically insoluble in water and freely soluble in methanol. Its Partition Coefficient is Strongest acidic 13.18, Strongest basic 7.09. ZPH is extensively metabolized after oral administration with only a small amount excreted in the urine. ZPH antipsychotic activity is likely due to a combination of its antagonistic function at D2 receptors in the mesolimbic pathways and at 5HT2A receptors in the frontal cortex. Alleviation of positive symptoms is due to antagonism at D2 receptors while reliefs of negative symptoms are due to 5HT2A antagonism [12 - 14].

MATERIAL AND METHOD

Materials

Ziprasidone hydrochloride, HPMC E15 and Poloxamer 188 were gift sample from Cadilla Healthcare Pvt. Ltd PTC Thane, Mumbai, India. All other solvents and chemicals used for enhancing solubility by using solid dispersion method were of analytical grade.

Methodology

Preparation of Physical Mixture

Physical mixtures of ZPH with HPMC E15 and PX were prepared by blending of drug and polymer in 1:1, ratio (drug: polymer) in mortar and pestle and passed through 100 mesh sieve.

Solid Dispersion by Microwave Method

Microwave activated solid dispersions of ZPH and HPMC E15 / PX were obtained by gently mixing ZPH and polymers in a beaker in 1:1, 1:3, and 1:5 drug-to-carrier ratio, to obtain the physical mixtures. Then, a fixed amount of each physical mixture (i.e. 1 g) was taken into a glass beaker and subjected to microwave irradiation for different periods at the chosen power of 600 W in a microwave oven [15]. Only one beaker at a time was placed inside the microwave oven in an accurate place. The samples were then grounded in a glass mortar and then sieved through a 100 mesh screen. The formulation codes for solid dispersions prepared by microwave method are denoted in Table 1.

Solid Dispersion by Freeze Drying Method

The dispersion of ZPH with HPMC E15 / PX was made in a vial by dissolving ZPH and polymers in methanol in three different ratios of drug and polymer (1:1, 1:3, and 1:5). This dispersion was subjected to freeze drying for 48 hr. to get final solid dispersions. The samples were then grounded in a glass mortar and then sieved through a 100 mesh screen. The formulation codes for solid dispersions prepared by freeze drying method are depicted in Table 1.

Drug Content

Solid dispersions equivalent to 10 mg of ZPH were accurately weighted and dissolved in 100 ml of methanol. The solution was sonicated for 15 min, filtered through a 0.45-µm millipore filter, diluted, and analyzed at 316 nm using UV spectrophotometer. Each sample was analyzed in triplicate and calculated mean values were considered for drug content [16].

Solubility Study

The apparent solubility of ZPH and solid dispersions prepared by microwave method and freeze drying method was determined in the pH 6.8 phosphate buffer at 37 ± 0.2° C. The method for determining the solubility of the ZPH involves weighing an equivalent of 10 mg of ZPH into each of vials. Then, 10 ml pH 6.8 phosphate buffer was added to each of the ZPH containing vials and allowed to equilibrate at 37 ± 0.2° C with shaking on a glass shaker incubator for 48 h. A 1 ml aliquot was taken from each vial and filtered through a 0.45µm millipore filter. ZPH concentration in each sample was analyzed using UV spectrophotometer at 316 nm [17].

Table 1: Formulation batches of Solid Dispersion

Formulation Code	Polymer	Drug to Polymer Ratio	Method	% Drug Content	Solubility mcg / ml
Z 1	HPMC E15	1:1	Microwave method	98.31 ± 1.5	64.12 ± 5.32
Z 2	HPMC E15	1:3		98.46 ± 3.4	88.6l ± 5.32
Z 3	HPMC E15	1:5		98.70 ± 2.3	130.11 ± 5.32
Z 4	HPMC E15	1:1	Freeze drying method	95.44 ± 2.2	54.21 ± 5.32
Z 5	HPMC E15	1:3		95.88 ± 3.1	60.47 ± 5.32
Z 6	HPMC E15	1:5		96.20 ± 3.5	69.78 ± 5.32
Z 7	Poloxamer 188	1:1	Microwave method	98.93 ± 3.8	83.74 ± 5.32
Z 8	Poloxamer 188	1:3		98.95 ± 1.7	94.68 ± 5.32
Z 9	Poloxamer 188	1:5		98.99 ± 4.2	157.16 ± 5.32
Z 10	Poloxamer 188	1:1	Freeze drying method	95.88 ± 1.8	56.21 ± 5.32
Z 11	Poloxamer 188	1:3		95.93 ± 2.7	63.14 ± 5.32
Z 12	Poloxamer 188	1:5		96.12 ± 3.6	74.88 ± 5.32

Dissolution Studies

Dissolution studies of ZPH and solid dispersions prepared by microwave method and freeze drying method were performed in 900 ml of pH 6.8 phosphate buffer dissolution medium at 37±0.5°C using USP dissolution test apparatus (TDT 08L Plus — ELECTROLAB, Mumbai, India) type 2 with a stirrer rotation speed of 50 rpm. At a time interval of 5, 15, 30, 45, 60 and 90 min, aliquots of 5-ml samples were withdrawn, filtered through 0.45-µm Millipore filter, diluted, and analyzed at 316 nm using UV spectrophotometer. Each sample was studied in triplicate for dissolution rate, and calculated mean values of cumulative drug release were used while plotting the release curves.

Characterization of Solid Dispersion

Fourier Transform Infra-Red Spectroscopy (FT-IR)

Fourier transform infra-red (FTIR) spectra were obtained by using Shimadzu FTIR-281 spectrophotometer. The samples were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:100 (Sample: KBr) ratio. The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential Scanning Calorimetry (DSC)

The differential scanning calorimetry (DSC) measurements were performed using a Shimadzu DSC-60 (Kyoto, Japan). Samples of weight approximately 5 mg were sealed in aluminum pans and analyzed in an inert atmosphere of nitrogen. A temperature range of 0°C to 300°C was used, and the heating rate was 10°C/min.

X-ray Diffraction Study (XRD)

X-ray diffraction study was done to study the powder characteristic of ZPH and its optimized solid dispersion formulation. X-ray diffractograms were obtained by Philips diffractometer (PW 1140) and Cu-Kα radiation diffractograms were run at a scanning speed of 2º/min and a chart speed of 2º/2cm/2θ.

Scanning Electron Micrographs (SEM)

Scanning Electron micrographs of ZPH, polymers and optimized solid dispersions were obtained using scanning electron microscope (JSM 6390LV, JEOL, Peabody MA, USA) operating at 10-kV accelerating voltage.

RESULT AND DISCUSSION

Drug Content

Drug content study was performed in order to determine the % amount of drug in solid

dispersion. Results (Table 1), shows that almost 90 to 105% of the drug was incorporated in the solid dispersions.

Solubility

Solubility studies were performed in order to analyse solubility enhancing properties of polymers. Results of solubility studies are depicted in Table 1. Solubility study reveals that HPMC E15 and PX have significant solubility enhancement property. The probable reasons for solubility enhancement by HPMC E15 can be attributed to swelling and water retention nature, which markedly enhances the solubility of ZPH due to the increased surface of the carrier. This improved surface with water retention capacity helps in wetting of the hydrophobic ZPH crystals and thus improving its solubility. The enhancement of solubility by PX can be attributed to a number of factors namely, decrease in crystallinity of drug, wetting, solubilizing and surface active properties of the polymer. Solid dispersion of ZPH: PX (1:5 ratio) by microwave method presented the highest increase in solubility among all solid dispersions with solubility reading of 157.16 ± 5.32 mcg/ml. The superior solubility profile observed for microwave induced solid dispersions is attributed to, amorphization of the drug by microwaves, improved surfactant and wetting characteristics of the carrier with the drug [18 – 20].

Dissolution Study

In vitro dissolution studies of ZPH and solid dispersions were performed in 900 ml of pH 6.8 phosphate buffer. The dissolution profile of ZPH and solid dispersions prepared with HPMC E15 is shown in Fig. 1. The dissolution profile of ZPH and solid dispersions prepared with poloxamer 188 is shown in Fig. 2. Solid dispersion prepared by microwave method with HPMC E15 (Z 3) and poloxamer 188 (Z 9) showed a maximum cumulative release of 81.82 ± 1.54 % and 88.00 ± 2.40 % respectively. Solid dispersion prepared by freeze drying method with HPMC E15 (Z 6) and poloxamer 188 (Z 12) showed a cumulative release of 65.28 ± 3.14 % and 71.25 ± 0.51 % respectively while the corresponding percentage of ZPH alone was only 40.22 ± 2.26 %. These results suggest remarkable enhancement of dissolution rate of ZPH from solid dispersions. The superior dissolution profile observed for microwave induced solid dispersions is attributed to amorphization of the drug by microwaves improved surfactant and wetting characteristics of the carrier with the drug. The improved wetting of drug is due to better intimate contact between the RG and poloxamer 188. Microwave equipment uses electromagnetic waves that pass through the material and cause the molecules to oscillate, generating heat at each point of the material by the interaction of the electromagnetic field with its molecular and electronic structure. Thus microwaves, with their ability to penetrate any substance, allow the production of heat throughout the sample at the same rate resulting in rapid and uniform volumetric heating providing molecular dispersions with better intimate contact between drug and carrier [15 – 19].

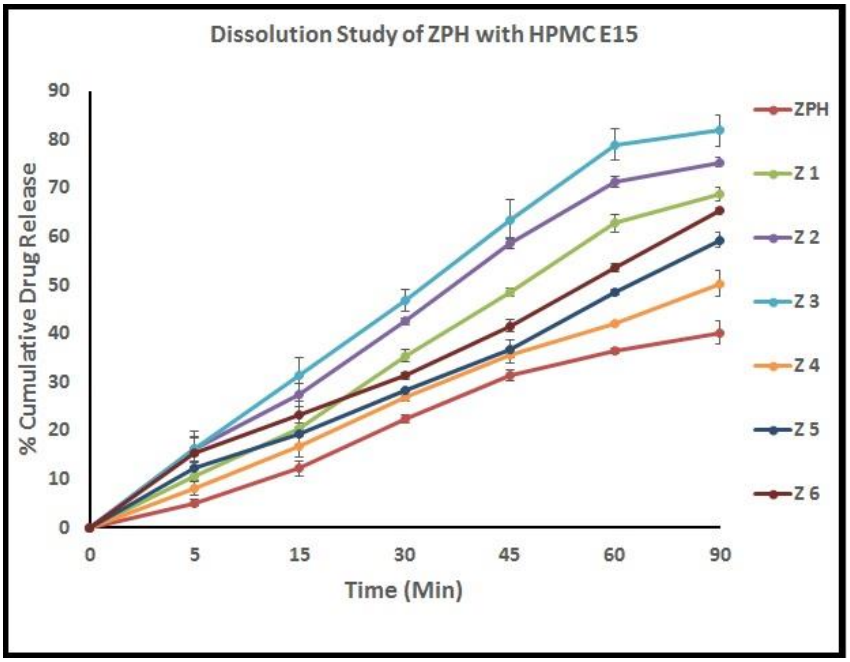

Figure 1: Dissolution profile of ZPH and solid dispersions prepared with HPMC E15.

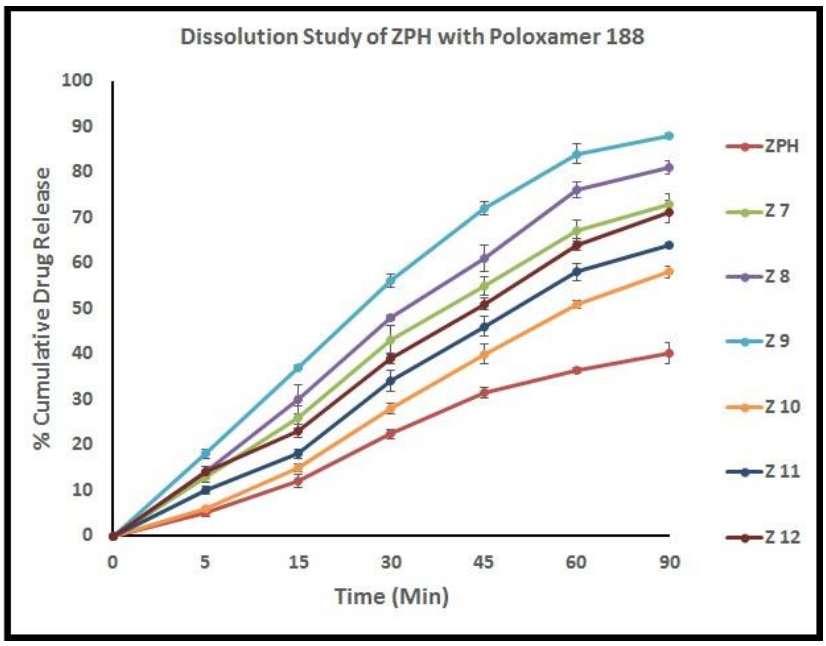

Figure 2: Dissolution profile of ZPH and solid dispersions prepared with Poloxamer 188.

Fourier Transform Infra-Red Spectroscopy

FT-IR spectra were used to investigate the possibility of interactions between ZPH, HPMC E15, and PX in the solid state. Infrared spectra's of ZPH, HPMC E15, physical mixture and solid dispersion prepared by microwave method (Z 3) are presented in Fig 3. Pure ZPH spectra showed sharp characteristic peaks at 3354 cm^{-1} due to N-H stretching, 2931.7 cm^{-1} due to C-H bending, 1631.5 cm^{-1} due to C=N, 1492.9 cm-1 due to H-C-H bending, 1381.03 cm^{-1} due to –C-N, 1178.51 cm^{-1} due to C-O stretching, 972.12 cm^{-1} due to the =C-H bond of the alkenes group. All the above characteristic peaks appear in the spectra of all binary systems at the same wave number.

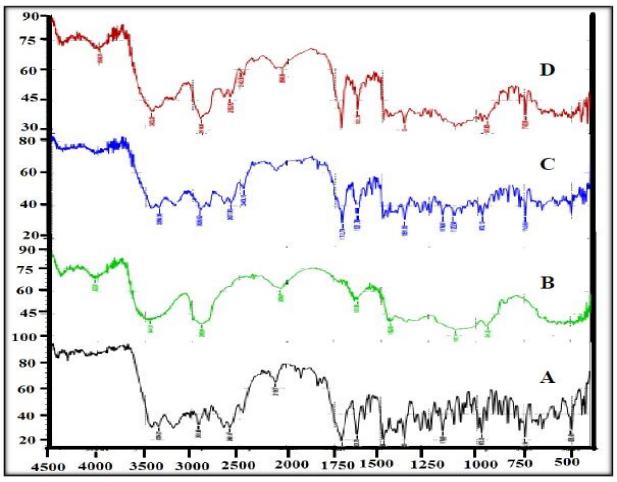

Figure 3: FT IR spectra of A) ZPH B) HPMC E15 C) Physical mixture of drug and HPMC E15 D) Microwave induced solid dispersion of ZPH and HPMC E15 (1:5 ratio)

The spectra of the physical mixture and solid dispersion were identical and the main absorption bands of ZPH appeared in all the spectra in the region of N-H, C=N, C-O regions.

Infrared spectra's of ZPH, PX, physical mixture and solid dispersion prepared by microwave method (Z 9) are presented in Fig 4. The spectra of the physical mixture and solid dispersion were identical and the main absorption bands of ZP appeared in all the spectra in the region of N-H, C=N, C-O regions. This indicated that there was no distinction between the internal structures and conformation of these samples at the molecular level.

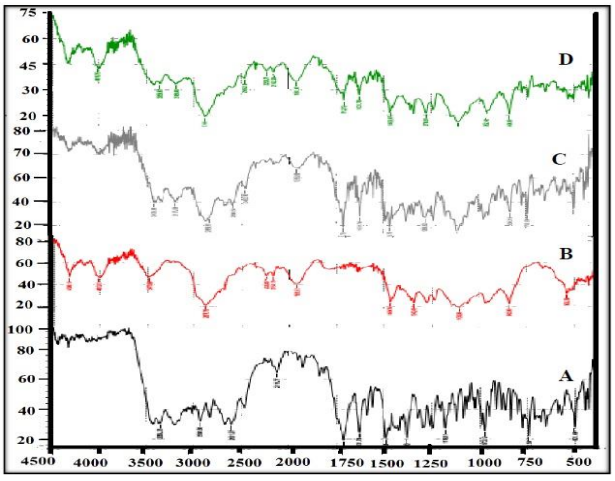

Figure 4: FTIR spectra of A) ZPH, B) Poloxamer 188, C) physical mixture of ZPH and Poloxamer 188, D) Microwave induced solid dispersion of ZPH and Poloxamer 188 (1:5 ratio).

Differential Scanning Calorimetry

The DSC thermograms of ZPH, HPMC E15, physical mixture and microwave induced solid dispersion (Z 3) are shown in Fig 5. The thermal curve of ZPH was typical of a crystalline anhydrous substance with a broad endothermic peak at 119.46°C and sharp endothermic peak at 227.58°C corresponding to its melting point, HPMC E15 exhibited characteristic peaks at 92.67°C and 193.14°C. The DSC curve of the physical mixture, as well as solid dispersion prepared by microwave method, showed endothermic peak corresponding to the melting point of HPMC E15. It was noticed that the intensity of the endothermic peak of ZPH in microwave induced solid dispersion was decreased in comparison to pure ZPH. The reduction in the peak intensity in microwave induced solid dispersion may probably be due to the partial conversion of a crystalline form of ZPH to microcrystalline form which could be further confirmed by XRD and SEM studies.

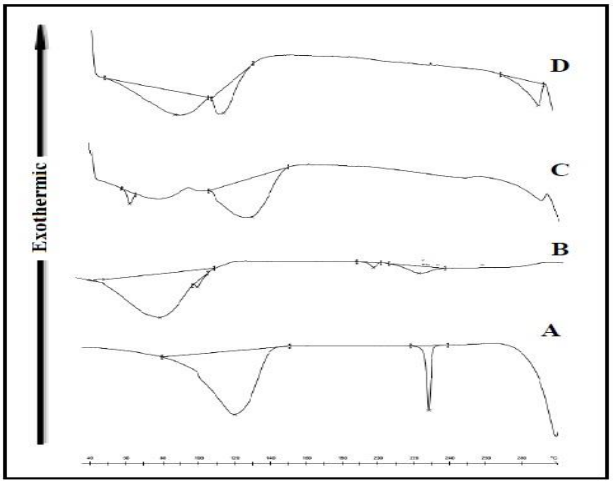

Figure 5: DSC thermogram of A) ZPH B) HPMC E15 C) Physical mixture of drug and HPMC E15 D) Microwave induced solid dispersion of ZPH and HPMC E15 (1:5 ratio).

The DSC thermograms of ZPH, Poloxamer 188, physical mixture and microwave induced solid dispersion (Z 9) are shown in Fig 6. The thermal curve of ZP was typical of a crystalline anhydrous substance corresponding to its melting point, Poloxamer 188 exhibited a characteristic peak at 59.48°C. In thermogram of the physical mixture, the sharp endothermic peak corresponding to the melting of poloxamer 188 and small endothermic peak with decreased intensity and sharpness corresponding to melting of ZPH was observed. Solid dispersion prepared by microwave method showed an endothermic peak corresponding to the melting point of poloxamer 188. The absence of ZPH peak in case of solid dispersion could be attributed to molecular dispersion of drug in poloxamer 188 and conversion of a crystalline form of ZP to amorphous form which could be further confirmed by XRD and SEM studies [15].

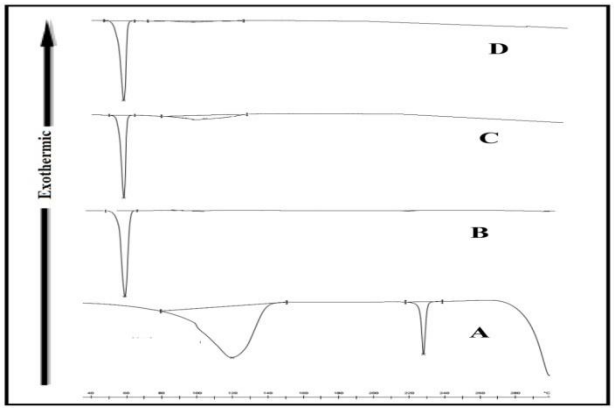

Figure 6: DSC thermogram of A) ZPH, B) Poloxamer 188, C) physical mixture of ZPH and Poloxamer 188, D) Microwave induced solid dispersion of ZPH and Poloxamer 188 (1:5 ratio).

X-ray Diffraction Study (XRD)

Diffraction spectra of pure ZPH, HPMC E15, physical mixture and solid dispersions prepared by microwave induced solid dispersion method (Z 3) are presented in Fig 7.

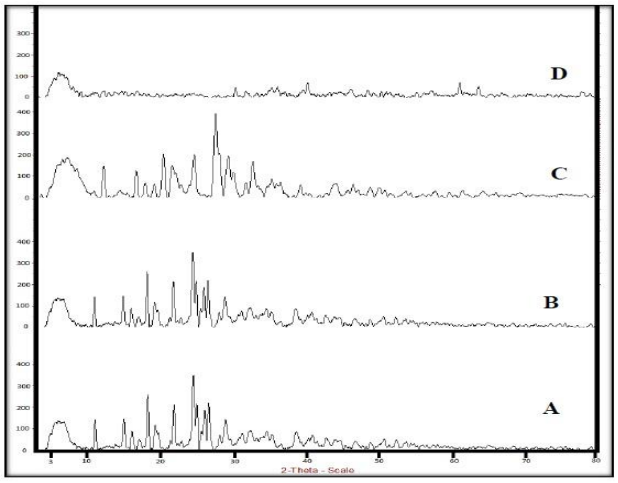

Figure 7: XRD Spectra ofA) ZPH B) HPMC E15 C) Physical mixture of drug and D) HPMC E15 Microwave induced solid dispersion of ZPH and HPMC E15 (1:5 ratio).

The X-ray diffractogram of ZPH has sharp peaks at diffraction angles (2θ) 10.76°, 14.73°, 18.03°, 24.29°, 28.75°, 34.43° showing a typical crystalline pattern. XRD pattern of HPMC E15 showed sharp peaks at diffraction angles (2θ) 28.46°, 31.05°. Physical mixture showed a peak

at (2θ) 18.03°, 24.29°, 28.46°, and 31.05°. Solid dispersion showed diffraction peaks at diffraction angles (2θ) 28.46°, 31.05° corresponding to HPMC E15. The result of XRD supports the findings of the DSC study. The results indicate the reduction in crystallinity of the drug and conversion to microcrystalline form in microwave induced solid dispersion.

Diffraction spectra of pure ZPH, Poloxamer 188, physical mixture and solid dispersions prepared by microwave induced solid dispersion method (Z 9) are presented in Fig 8. The X-ray diffractogram of ZPH has sharp peaks at diffraction angles (2θ) 10.76°, 14.73°, 18.03°, 24.29°, 28.75°, 34.43° showing a typical crystalline pattern. XRD pattern of poloxamer 188 showed sharp peaks at diffraction angles (2θ) 18.74°, 22.874°. Physical mixture showed a peak at (2θ) 19.068° and 23.031°. Solid dispersion showed diffraction peaks at diffraction angles (2θ) 19.037° and 23.192° corresponding to poloxamer 188. The absence of ZPH peak in case of solid dispersion could be attributed to the conversion of a crystalline form of ZPH to amorphous form [17].

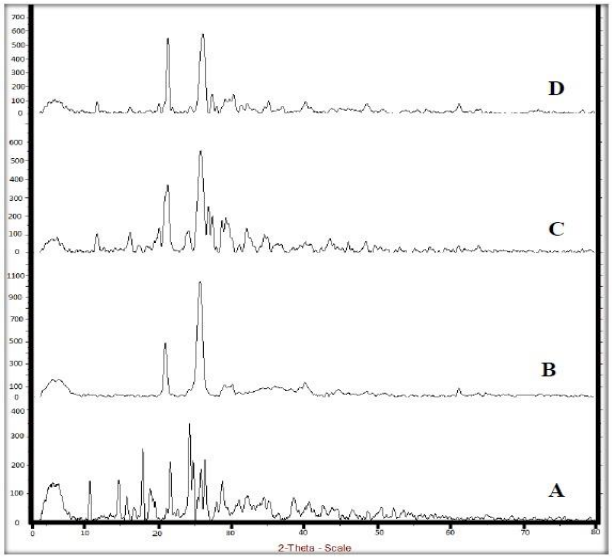

Figure 8: XRD Spectra of A) ZPH, B) Poloxamer 188, C) physical mixture of ZPH and Poloxamer 188, D) Microwave induced solid dispersion of ZPH and Poloxamer 188 (1:5 ratio).

Scanning Electron Microscopy

The SEM photographs of ZPH, HPMC E15, Poloxamer 188 and microwave induced solid dispersion are shown in Fig. 9

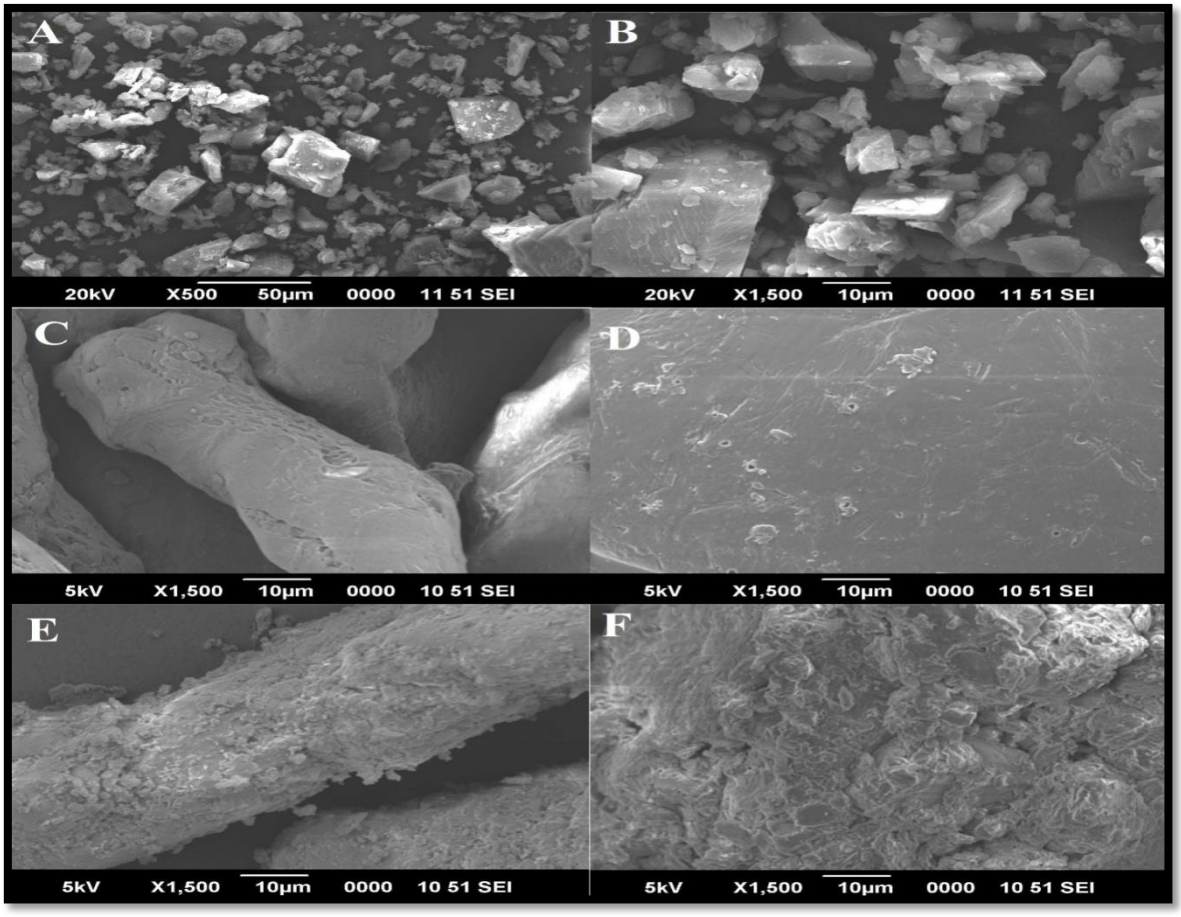

Figure 9: SEM Photom of A) ZPH, B) ZPH, C) HPMC E15, D) Poloxamer 188, E) HPMC E15 Microwave induced solid dispersion of ZPH and HPMC E15 (1:5 ratio) and F) Microwave induced solid dispersion of ZPH and Poloxamer 188 (1:5 ratio).

In SEM photographs ZPH appeared as smooth surfaced needle shaped crystalline form, whereas microwave induced solid dispersions appeared as rough surfaced homogeneously mixed mass as a single component with the transformation of longer needle shaped crystalline forms of ZPH to amorphous form [19].

CONCLUSION

The study employed microwave method and freeze drying method with HPMC E 15 and poloxamer 188 as a carrier to generate solid dispersions for dissolution enhancement of ZPH. The dissolution rate of ZPH from microwave generated solid dispersions was enhanced significantly. The enhancement of dissolution of ZPH from microwave induced solid dispersion can be attributed to the conversion of a crystalline form of ZPH to amorphous form, increased wettability, and dispersibility. Thus, the study ensured the proclaimed claims of microwave technique as a green, effective, solvent free alternative mean for making the solid dispersions for poorly soluble dugs like ZPH.

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