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Preparation and characterization of solid dispersions of Valsartan with Poloxamer 188

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Abstract

Solid dispersions in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate and hence possibly bioavailability, of a range of hydrophobic drugs. The poor solubility of valsartan leads to poor dissolution and hence variation in bioavailability. The purpose of the investigation was to increase the solubility and dissolution rate of valsartan for enhancement of oral bioavailability. In this investigation solid dispersions with poloxamer 188 were prepared by melting method and evaluated for physico-chemical parameters and dissolution. The physical mixture(s) and solid dispersion(s) were characterized for flow properties, particle size, drug-carrier interaction, drug content, solubility and dissolution rate. The solubility of drug increased with increasing polymer concentration. The dissolution rate was substantially improved for valsartan from its solid dispersion compared with pure drug and physical mixtures. As indicated from X-ray diffraction pattern, DSC thermograms and SEM photographs, valsartan was in the amorphous form, which confirmed the better dissolution rate of solid dispersions. The solid dispersion was stable under accelerated storage conditions. The solid dispersion technique with poloxamer 188 as a carrier provides a promising way to enhance the solubility and dissolution rate of valsartan.

Key words: Valsartan, Poloxamer 188, Solid Dispersions.

INTRODUCTION

The formulation of poorly soluble drug compounds for oral delivery now presents one of the greatest challenges to formulation scientists in the pharmaceutical industry. Solid dispersions are dosage forms whereby the drug is dispersed in a biologically inert matrix. They can be used to

increase the dissolution rate of a drug with low aqueous solubility, thereby improving its oral bioavailability [1-4].

Valsartan, (VAL) is a potent and specific competitive antagonist of the Angiotensin II AT1-receptor. The drug, used orally for the treatment of hypertension, exhibits a low bioavailability (AUC 23%), probably related to its poor water solubility. According to the Biopharmaceutical Classification Scheme, VAL can be considered a class II compound, i.e. a water-insoluble, lipophilic and highly permeable compound. Therefore, it is possible to improve the VAL bioavailability by increasing its apparent solubility in water through solid dispersion technology [5-8].

Poloxamer block copolymers have been exploited in pharmaceutical formulations for solubilization of poorly water-soluble drugs. Poloxamer consists of a ethylene oxide hydrophilic corona and polypropylene oxide hydrophobic core blocks arranged in a tri block structure resulting in an amphiphilic structure. Owing to their low melting point, they are suitable for the melt technique in solid dispersions. Their ability to self-aggregate, thereby forming micelles and liquid crystalline phases and greater hydrophilicity is another advantage for the solubilization of poorly water-soluble drugs. For drug delivery purposes, hydrophobic drugs may be solubilized within the core of the micelle or conjugated to the micelle-forming polymer. These amphiphilic co-polymers are available in different grades as poloxamer 188 and poloxamer 407 [9-11].

This work was aimed to enhance the dissolution rate of valsartan with solid dispersion technique using poloxamer 188 as a hydrophilic carrier. Solid dispersion systems of valsartan were prepared with poloxamer 188 in different ratios using the melting technique. Differential scanning calorimetry, powder X-ray diffractometry (PXRD), dissolution and stability studies were used to characterize the pure valsartan and its solid dispersion systems.

MATERIALS AND METHODS

Materials

Valsartan was provided by Ranbaxy Pvt. Ltd., India and Poloxamer 188 from BASF Corporation, Mumbai, India as a gift sample. All other chemicals and reagents used were of analytical grade.

Preparation of Physical Mixtures and Solid Dispersions of` Valsartan

The drug and carriers in ratio of 1:1, 1:3, 1:5 (PM1, PM2, PM3) were mixed thoroughly in a mortar with pestle and passed through a 60-mesh (250 μm) screen to obtain physical mixtures (PMs). Solid dispersions (SDs) of valsartan in poloxamer 188 containing different weight ratio 1:1, 1:3, 1:5 (SD1, SD2, SD3) were prepared by melt method. Poloxamer 188 was heated at 60^0C in an oil bath, until it melted completely. The drug was added to the molten polymer and mixed thoroughly in mortar with pestle. The dispersion was cooled to ambient conditions, milled and passed through a 40-mesh (425 μm) screen.

Characterization of Physical Mixtures and Solid Dispersions of Valsartan

Phase Solubility Studies

Solubility measurements were performed according to method reported by Higuchi and Connors [12]. An excess amount of the drug was added to 10 ml volumetric flask containing 10%, 20%, 30%, 40% aqueous solution of carriers. The samples were allowed to shake for 48 hours at 25 ±1°C. The solutions were filtered through membrane filter (0.45μ). After 48 hours, the valsartan concentration was determined spectrophotometrically at 248nm. Solubility studies of physical mixtures and solid dispersion was also performed in same manner.

Flow Properties

The flow properties of PMs and SDs were characterized in terms of angle of repose, Carr index and Hausner ratio [13]. For determination of angle of repose (θ), the sample was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The sample was poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan^{-1}$ of the (height of the pile / radius of its base) gave the angle of repose [14].

Sample was poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess sample was removed using a spatula and the weight of the cylinder with powder required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Hausner ratio (HR) and Carr index (IC) were calculated according to the two equations given below:

$HR = \rho t/\rho b$
$IC = (\rho t - \rho b)/\rho t$

Particle Size Analysis

The size distribution in terms of average diameter (d_{avg}) of the powder of physical mixtures and solid dispersions was determined by an optical microscopic method. A compound microscope (Olympus NWF 10 X; Educational Scientific Stores, India) fitted with a calibrated ocular micrometer and a stage micrometer slide was used to count at least 100 particles.

Drug Content

SDs and PMs of valsartan were tested for drug content uniformity. Accurately weighed amount of sample was dissolved in 10 ml of methanol and stirred on magnetic stirrer for 10 minutes. The solution was filtered through membrane filter (0.45μ), diluted suitably and assayed for valsartan content spectrophotometrically at 248 nm [15].

Powder X- Ray Diffraction (PXRD)

PXRD patterns were recorded using Philips PW 1729 X- ray generator, USA fitted with a copper target, a voltage of 40 kV and a current of 30 mA. The scanning rate was 1°/min over a 2θ range of 1–50°. Powder X- ray diffraction patterns were traced for valsartan, physical mixture and solid dispersions. The samples were slightly ground and packed into the aluminum sample container.

Differential Scanning Calorimetric (DSC)

Differential Scanning Calorimetry (DSC) analysis of the samples was carried out on a Perkin-Elmer DSC7. Samples (6.5-10 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10^0C/min over the temperature range of 5 and 300^0C. DSC analysis was carried out under nitrogen gas flow of 20 lb/in^2.

Scanning Electron Microscopy (SEM)

The SEM analysis was carried out using scanning electron microscope (S3400, Hitachi, JAPAN). Prior to examination, samples were mounted on an aluminum stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 24nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 KV.

Dissolution Studies

The release rate of valsartan from SDs and PMs was determined using United States Pharmacopeia (*USP*) Dissolution Testing Apparatus 2 (paddle method; Veego Scientific, Mumbai, India) [16]. The dissolution test was performed using phosphate buffer pH 6.8 as dissolution medium at 37 ± 0.5°C and 50 rpm for 2 hours [17]. The solid dispersions or physical mixtures equivalent to 40 mg of valsartan were added into the dissolution medium. A 5 ml aliquot was withdrawn at different time intervals and filtered using a 0.45 µ nylon disc filter; each sample was replaced with 5 ml of fresh dissolution medium. The filtered samples were suitably diluted, if necessary and assayed by measuring the absorbance at 248 nm. The dissolution experiments were conducted in triplicate.

Stability Studies

The accelerated stability study of prepared solid dispersion was carried out as per ICH guidelines at 40°C/75%RH for up to 3 months [18]. An accurately weighed amount of sample was placed into glass vials with aluminum-lined caps, stored in sealed desiccators in microprocessor controlled humidity chamber and characterized as a function of exposed time. The samples were removed and evaluated for flow properties, particle size, solubility, drug content, dissolution, PXRD and DSC studies.

RESULTS AND DISCUSSION

The results of physicochemical characterization of physical mixtures and solid dispersions of valsartan are summarized in Table 1. The solubility of valsartan in purified water at 25°C was found to be 0.17 mg/ml. The effect of poloxamer 188 concentration upon the solubility of valsartan is presented in Fig. (1). The increase in solubility was linear with respect to the weight fraction of the carrier. The solubility of drug was increased upto 48 fold in 5% w/v poloxamer188 aqueous solution at 25°C compared with pure drug. The increase in solubility with increasing poloxamer concentration indicates the solvent properties of poloxamer 188 for the drug. Poloxamer 188 causes a decrease of interfacial tension between the drug and dissolution medium. This behaviour suggests the feature of A_L type solubility phase diagram Fig. (1). This finding is in accordance with the increased solubility of Rofecoxib [19]. The solubility of valsartan in solid dispersion SD1, SD2, SD3 was found to enhance by 75, 80, 93 folds respectively in comparison with pure drug. These results could be explained that the reduction in

crystallinity of drug led to a decrease of the energy required in the dissolving process and also to a highly dispersed state of the drug.

Particle size was determined by optical microscopy. It was found to be 74.81 to 85.49 µm for PMs and 49.67 to 56.72 µm for SDs. The particles of solid dispersion were smaller than PMs. This indicates that reduction in particle size may also be factor influencing solubility of drug in physical mixture and solid dispersion.

The formulations were evaluated for their flow properties. Angle of repose was in the range of 51.37 to 58.81. Carr index was found to be 0.36 to 0.45 and Hausner ratio ranged from 1.57 to 1.81. These values indicate that the particles of solid dispersions exhibited poor flow properties which suggest addition of glidants during formulation of solid dosage form employing solid dispersion of valsartan.

The drug content was found in the range of 98.2 to 99.7% indicating the acceptability of fusion method for preparation of solid dispersions. Low values of standard deviation in drug content of PMs and SDs indicated uniform drug distribution in all the prepared batches.

Table 1: Physicochemical Characterization of PMs and SDs of valsartan

Code	Ratio	Average Particle Size (µm)	Solubility (mg/ml)	Drug content (%)	Angle of repose (θ)	Hausner ratio (H_R)	Carr index (IC)
PM1	1:1	74.81±0.92	8.84	98.2±0.51	52.34±0.26	1.71	0.42
PM2	1:3	79.26±1.36	9.86	98.6±0.67	58.81±0.36	1.81	0.45
PM3	1:5	85.49±1.21	10.88	98.7±0.61	56.31±0.21	1.75	0.43
SD1	1:1	49.67±0.91	12.75	98.1±0.71	54.81±0.67	1.61	0.38
SD2	1:3	53.81±0.98	13.6	99.4±0.81	51.37±0.71	1.65	0.39
SD3	1:5	56.72±1.06	15.8	99.7±0.66	58.42±0.52	1.57	0.36

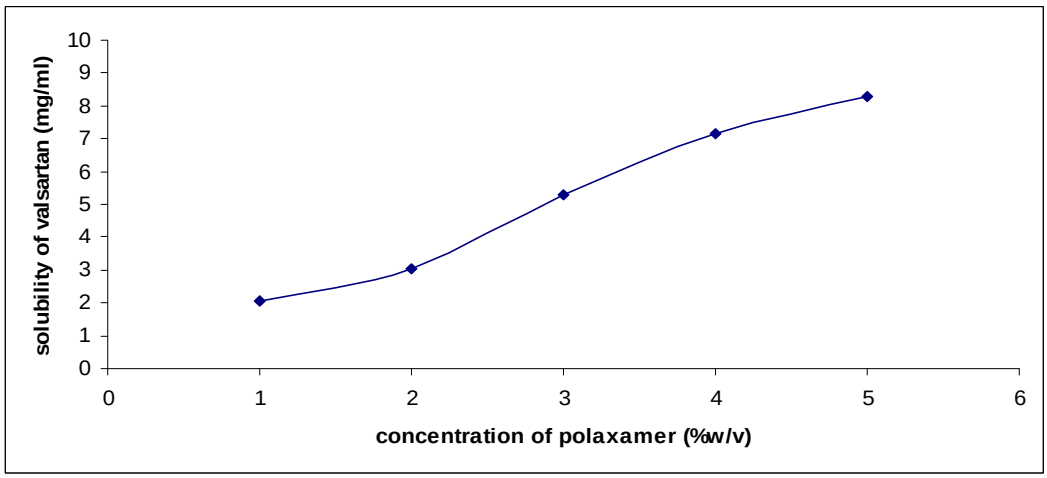

Fig. 1: Solubility curve of valsartan with Poloxamer 188

Powder X- Ray Diffraction Studies

Powder X-ray diffraction analysis can be used to judge any changes in crystallinity of the drug which precipitated in an amorphous form, when formulated into a solid dispersion. PXRD could be used to study any changes in crystallinity of the drug which could be one of the mechanisms responsible for improved dissolution.

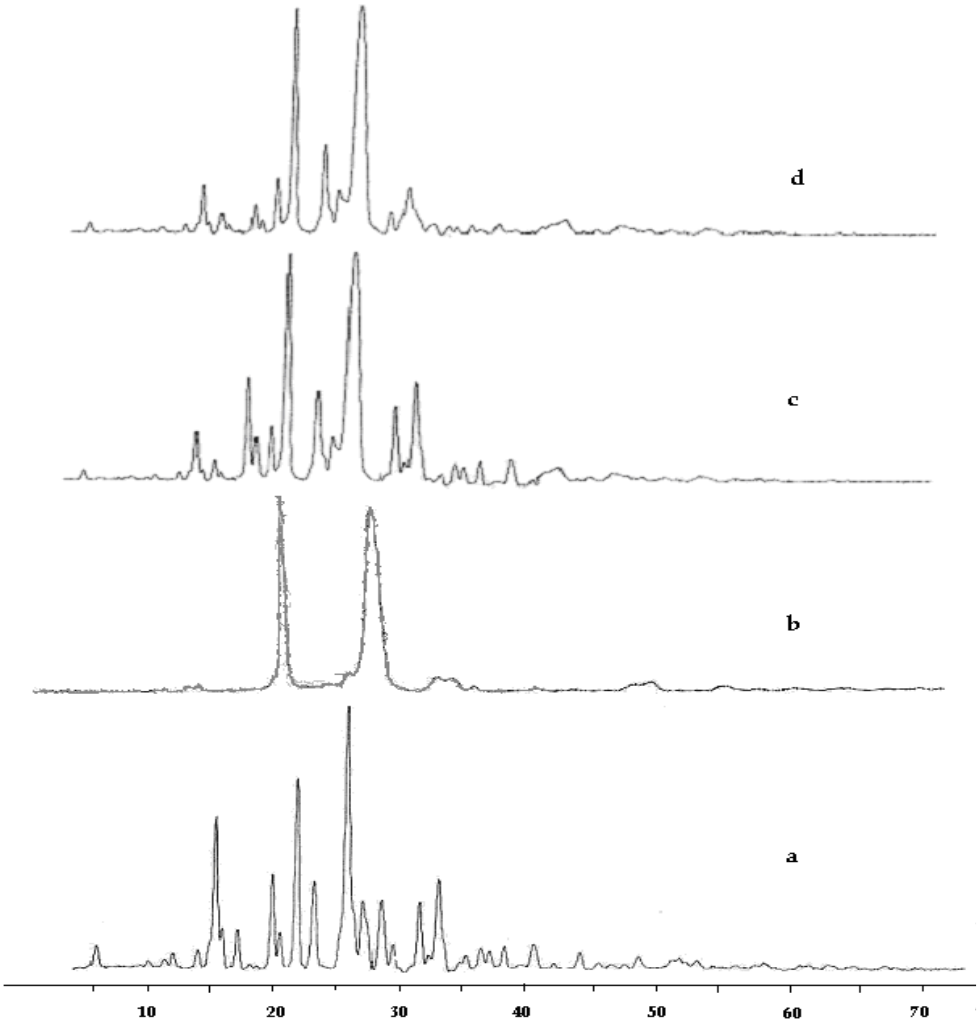

Fig. 2: Powder X-ray diffraction pattern of (A) Valsartan, (B) Poloxamer 188, (C) Physical mixture and (D) Solid dispersion

The X-ray diffractograms of pure valsartan, poloxamer 188, physical mixture and solid dispersion are shown in Fig. (2). The diffraction spectrum of pure valsartan showed that the drug was of crystalline in nature as demonstrated by numerous, distinct peaks at 2θ of 5.6°, 10.5°, 12.9°, 18.8°, 20.6°. Poloxamer 188 is crystalline in nature and gives two characteristic peaks, one at 19° and the other broader one between 22° and 23°. The spectrum of solid dispersion prepared with poloxamer 188 showed that some peaks of pure valsartan were absent and intensity of peaks was reduced. The result indicates that the drug in solid dispersion is amorphous as compared to the pure drug. Hence, increased dissolution of the drug was observed. In the case of physical

mixture, the XRD pattern showed the peaks of both valsartan and poloxamer 188. It was confirmed that the crystallinity of the valsartan does not change in the physical mixture with carrier.

Differential Scanning Calorimetric Studies

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic and exothermic phase transformations). The thermograms for pure valsartan, poloxamer 188, physical mixture and solid dispersion are presented in Fig. (3). The valsartan showed a melting endotherm at 115°C whereas pure poloxamer 188 showed a melting endotherm at 30^0C. Thermograms of dispersion showed the absence of a valsartan peak, suggesting that valsartan is completely soluble in the liquid phase with poloxamer 188. However, the melting peak of poloxamer in solid dispersion was observed at slightly lower temperatures (between 27°C - 30°C) than that of pure poloxamer 188 (30°C), indicating the miscibility of the drug in carrier. The physical mixture formulation showed valsartan derived peak with reduced intensity suggests decrease in crystallinity of valsartan.

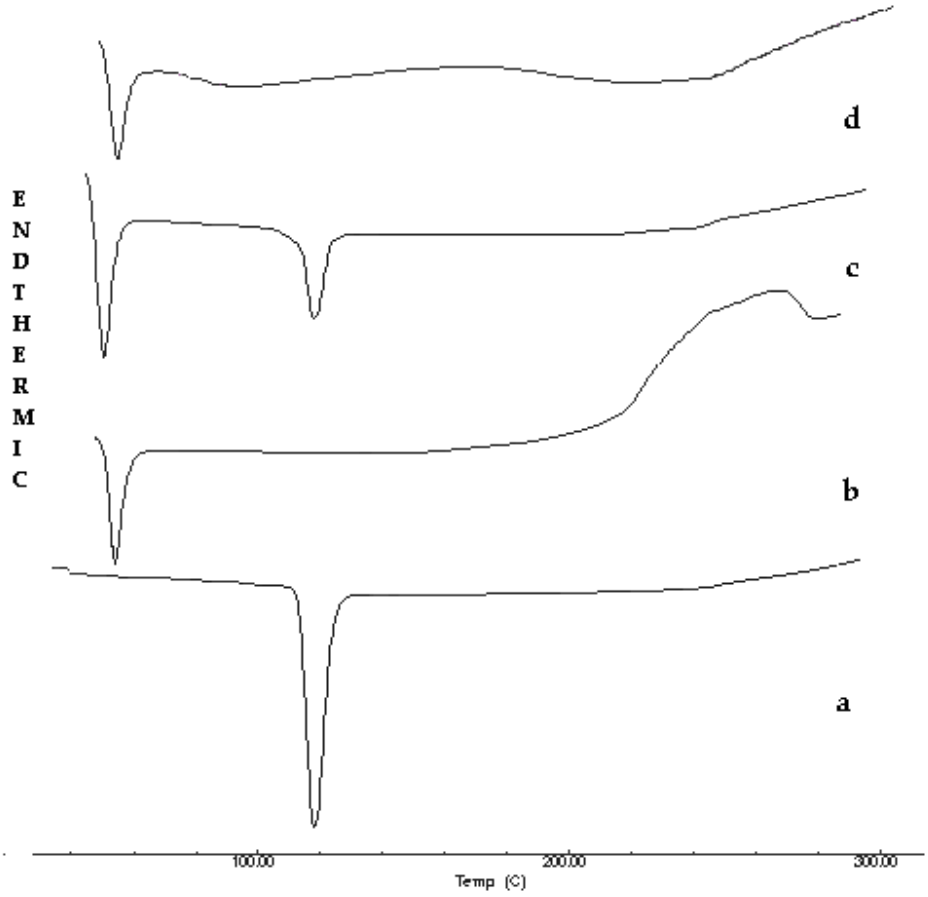

Fig. 3: DSC thermogram of (A) Valsartan, (B) Poloxamer 188, (C) Physical mixture and (D) Solid dispersion

Scanning Electron Microscopy (SEM)

SEM of valsartan and poloxamer 188 showed crystal form and globular form respectively in Fig. (4). In solid dispersion the structure of valsartan crystal or mixture is completely different. This indicates that a kind of new structure formed in solid dispersion of Poloxamer 188. These findings demonstrated that the drug was changed in amorphous form which was confirmed by PXRD and DSC studies.

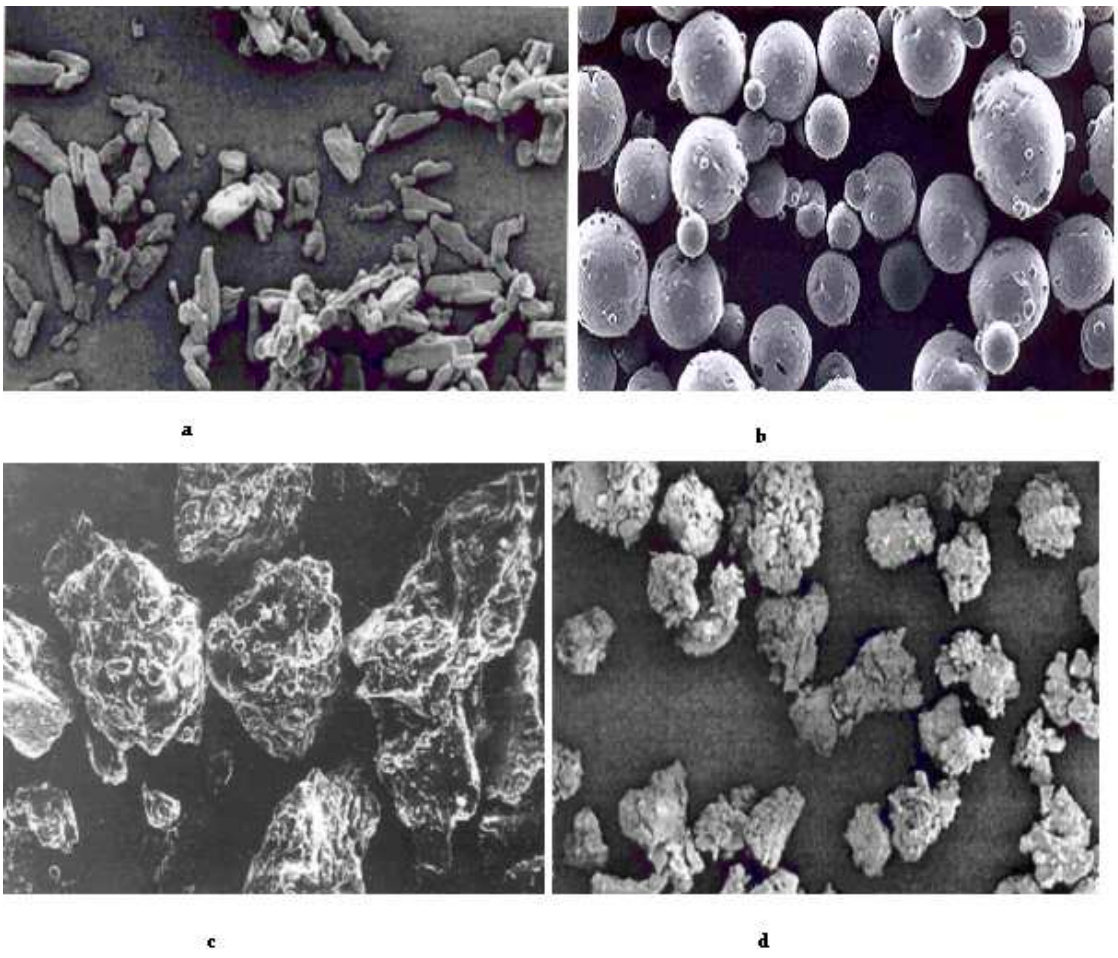

Fig. 4: Scanning Electron Photomicrograph of (A) Valsartan, (B) Poloxamer 188, (C) Physical mixture (D) Solid dispersion

Dissolution Studies

The dissolution profile of pure drug, physical mixtures and solid dispersions are shown in Fig. (5). Both physical mixtures and solid dispersions showed enhanced dissolution rate as compared with pure drug. Physical mixtures increased the solubility and maximizing the surface area of the drug that came in contact with the dissolution medium as the carrier dissolved. This might due to the surface tension lowering effect of polymer to the medium, resulting in wetting of hydrophobic drug of crystalline surface. Several mechanisms may be possible for the enhanced release of valsartan in solid dispersion formulation with water soluble polymeric surfactant

poloxamer 188. This can be attributed to the reduction of crystallinity of drug resulting in improved release (supported by X-ray diffraction); reduction of particle size to expand the surface area for dissolution. The initial high drug release is observed at the 10-min time point and gets reduced at subsequent time points. This may be because of initial rapid flux of the drug from the solid dispersion particles to the dissolution medium resulted in a high concentration, which got reduced with time. Slow dissolution was observed subsequently till the equilibrium concentration was reached.

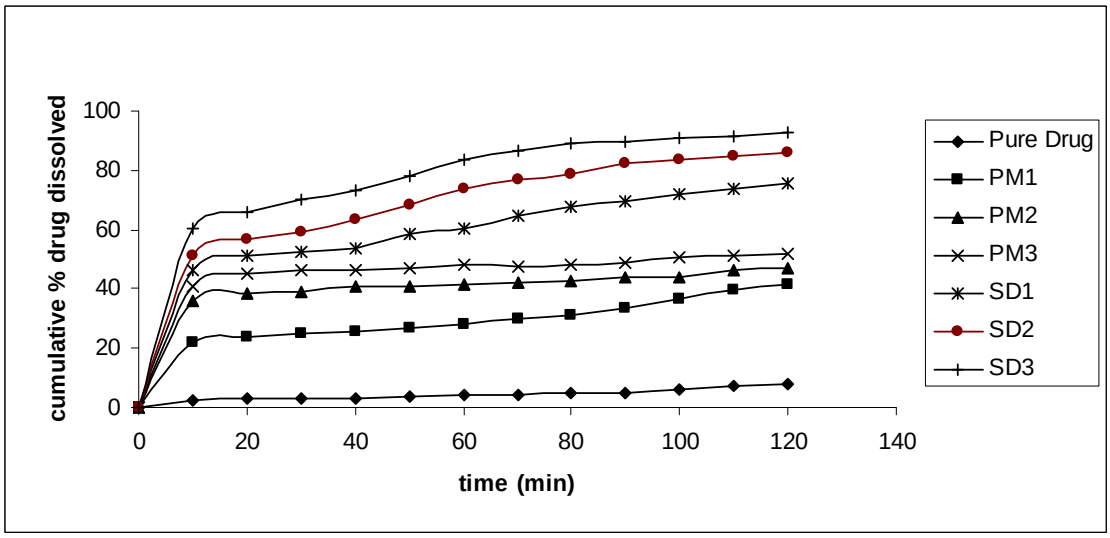

Fig. 5: Dissolution profile of Pure drug, PMs and SDs

Stability Studies

Stability studies were carried out for the solid dispersions obtained by melt method by exposing them to 40°C/75%RH. The flow properties, particle size, drug content, solubility, dissolution, PXRD and DSC were carried out at the end of 3 months and compared to day zero. No significant changes observed in flow properties, particle size, drug content, solubility, dissolution rate after six months. Also the PXRD and DSC patterns of the solid dispersion recorded after 3 months gave identical patterns to the initial ones.

CONCLUSION

The solid carrier played a significant role in the initial enhancement of drug dissolution in our studies. The above studies indicate that poloxamer 188 inhibited the crystallization of drugs, resulting in the amorphous state form of the drug in solid dispersion. The rate of the dissolution of valsartan from solid dispersion depended on the concentration of the carrier. Dissolution of drug increased with an increase in carrier content. A high proportion of poloxamer 188 in the solid dispersion significantly affected the improvement in the dissolution rate. PXRD, DSC and SEM results confirmed the amorphous state of drug in solid dispersion. In the stability study, no significant changes were recorded with respect to flow properties, particle size, drug content, solubility, dissolution rate, PXRD, DSC over a period of 3 months.

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