

Effect of Recrystallization on the Pharmaceutical Properties of Valsartan for Improved Therapeutic Efficacy

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ABSTRACT

Valsartan (VAL) is a potent, highly selective and orally active antihypertensive drug and is poorly soluble in aqueous fluids, especially in gastric fluids, and its absorption is thus dissolution rate limited. In the present research work an attempt has been made to improve the aqueous solubility of VAL by the recrystallization of VAL from a variety of different organic solvents, and evaluating the recrystallized VAL products for its physicochemical characteristics and *in-vitro* dissolution properties. The water solubility of methanol (MET), ethanol (ETH), isopropanol (ISP) and acetonitrile (AN) recrystallized products of VAL is significantly higher when compared to untreated VAL. Physicochemical characterization techniques like scanning electron microscopy, differential scanning calorimetry, powder X-RD reveal the change in crystallinity of VAL with recrystallized products and hence the increase in the solubility and superior dissolution properties when compared to the untreated VAL.

INTRODUCTION

The enhancement of oral bioavailability of sparingly water soluble drugs remains one of the most challenging aspects of drug development. Together with the permeability, the solubility characteristics of a drug are a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Crystallization is the natural/artificial process for the formation of solid crystals from a uniform solution. It is the formation of solid crystals from a homogeneous solution. Since the structural properties of a solid material (e.g. polymorphism) can dramatically affect the

physicochemical properties and solubility characteristics (i.e. dissolution rate, for example), monitoring and controlling the isolation of solids for the various applications through crystallization is of paramount interest. Crystals can be modified by recrystallizing the drug under different conditions, which will affect physical and physicochemical properties such as melting point, solubility, true density, dissolution profile, flowability, and tableability (Hlaeblian et al., 1969; Rasenack et al., 2000) Valsartan (VAL) is a potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. VAL has much greater affinity (about 20,000-fold) for the angiotensin II type 1 (AT1) receptor than for the angiotensin II type 2 (AT2) receptor, thereby relaxing blood vessels and causing them to widen, which lowers blood pressure and improves blood flow (Philipp et al., 2007; Carey et al., 2003).

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In order to afford therapeutic efficacy, VAL needs to have a quick onset of action. However, VAL is sparingly soluble in aqueous fluids, especially in gastric fluids, and its absorption is thus dissolution rate limited. The poor aqueous solubility and hence the undesirable dissolution properties of a drug like VAL often results in variable oral bioavailability. The mean absolute oral bioavailability is determined to be 25% (10-35%) (Flesch *et al.*, 1997). Several reports have been published that have focused on improving the dissolution properties of VAL. Most or all of these studies have involved cyclodextrin inclusion complexation and solid dispersion and other solubilization technologies for improving the solubility and dissolution properties of VAL (Carlos *et al.*, 2010; Anshu., 2010; Mbah., 2006; Raja., 2011; Dixit *et al.*, 2010). Thus far, no reports have been published on the application of different recrystallization techniques in order to improve the pharmaceutical properties of VAL, such as aqueous solubility and *in-vitro* dissolution characteristics. Hence, in the present investigation an attempt has been made to improve the aqueous solubility of VAL by investigating the recrystallion of VAL from a variety of different organic solvents, and evaluating the recrystallized drug for its physicochemical characteristics and *in-vitro* dissolution properties.

EXPERIMENTAL

Materials and Methods

VAL was provided by Aurobindo Pharma Ltd (Hyderabad, AP, INDIA). Hydrochloric acid, formic acid, sodium hydroxide, sodium acetate, potassium dihydrogen phosphate, boric acid, potassium chloride, glacial acetic acid, methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, ethyl acetate, dichloromethane, tetra butyl methyl ether, N,N-dimethyl formamide, tetra hydro furan were purchased from Loba Chemie Pvt, Ltd., (Mumbai, MS, INDIA). Chemicals and reagents used in HPLC studies are of HPLC grade.

Preparation of VAL Recrystallization Products

2 g of VAL were added to 5mL of a specific pure organic solvent in a 15 mL beaker and heated slowly to 45°C to afford a supersaturated solution. The resulting mixture was then cooled down to room temperature. The resulting recrystallized drug was then collected, dried at 40°C for 15min, and passed through a #80 sieve to afford a product of uniform particle size. The powdered drug was packed in glass bottles and stored in a dessicator until experimentation.

Analytical Procedures

Both UV-VIS spectrophotometric and RP-HPLC analytical methodologies were utilized in the present investigation. UV-VIS spectrophotometric analysis (UV-Double Beam Spectrophotometer, UV-1800, Shimadzu, Japan) utilized absorbance at 250nm in a methanolic stock solution of VAL. A reverse phase HPLC system was used for the analysis of VAL and its recrystallized samples. Chromatographic analysis of VAL was

performed on a Shimadzu Prominence HPLC system equipped with LC 10 AVP binary pumps, DGU 20A Degasser, M20 A PDA detector and LC 10ATVP auto sampler that incorporated a 200 μ L volume loop. LC solution software was used to collect and process the analytical data. The mobile phase consisted of 0.02% v/v formic acid: acetonitrile (30:70%) at 1.0mL/min flow rate and was filtered through a membrane filter (Millipore Nylon disc filter of 0.45 μ) and sonicated for 3 min in ultrasonic bath before use. A Phenomenex C₁₈ column (150mm x4.6mm, 5.0 μ) was used and separation was carried out at ambient temperature with an injection volume of 10 μ L. For quantitative analytical purposes, eluents were monitored at 250nm.

Solubility Studies

Excess of VAL and its recrystallized products (50mg) were added to 5mL of different aqueous fluids in 10mL stopper conical flasks and the mixtures were shaken for 24 hours at room temperature on a rotary flask shaker. After 24 hours of shaking, 0.5mL aliquots were withdrawn at different time intervals and filtered immediately using a 0.45 μ nylon disc filter. The filtered samples were diluted if necessary and assayed for VAL content utilizing the above RP-HPLC method. Shaking was continued until three consecutive estimations afforded consistent results. All solubility experiments were run in triplicate.

Physicochemical Characterization of VAL Recrystallized Products

Scanning Electron Microscopy

Crystal surface morphology of VAL and its recrystallized products were studied using a scanning electron microscope (Joel model JSM T200, Tokyo, Japan). The specimens were mounted on metal stub with a double sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation.

Particle Size Analysis

The particle size distribution of VAL and its recrystallized samples was determined using a particle size analyzer (Microtrac X-100, version 7.02b) over the range of analysis of 0.021 -704.0 microns laser diffraction analysis from an average of 3 runs and a run time of 30 sec.

Differential Scanning Calorimetry (DSC)

Thermal analysis was carried out on a Shimadzu DSC 60 (Japan) unit. Accurately weighed VAL and its recrystallized samples were placed in sealed aluminum pans and heated at a rate of 10°C/min over the temperature range of 30-300°C.

Powder X-ray Diffraction

Powder X-ray diffraction analysis of VAL and its recrystallized samples were recorded on a Bruker D8 Advance diffractometer (Bruker-AXS, Karlsruhe, Germany) using Cu-K α X-radiation ($\lambda = 1.5406 \text{ \AA}$) at 40 kV and 30mA power. X-ray diffraction patterns were collected over the 2 θ range of 5-50° at a scan rate of 1°/min.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectral measurements of VAL and recrystallized VAL were taken at ambient temperature using a Shimadzu FTIR spectrophotometer, Model 8033, JAPAN). Samples were dispersed in KBr powder and pellets were produced by applying 5 tons of pressure (2 mg sample in 200 mg KBr). FTIR spectra were then obtained by powder diffuse reflectance.

In-vitro Dissolution Studies

In vitro dissolution studies of VAL and its recrystallized products were carried out in 1000mL of phosphate buffer, pH 6.8 using USP XXI type 2 (paddle method) Dissolution Rate Test Apparatus (DISSO 2000, Lab India). The powder samples were dispersed in dissolution medium. Samples equivalent to 40mg of VAL, at a paddle speed of 50 rpm and a temperature of $37 \pm 1^\circ\text{C}$ were used in each test. A 5mL aliquot was withdrawn at different time intervals, filtered using a 0.45μ nylon disc filter, and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted if necessary and assayed for VAL content by the above RP-HPLC method. Each dissolution experiment was conducted in triplicate.

RESULTS AND DISCUSSION

Preparation of VAL Recrystallized Products

VAL was recrystallized from a variety of organic solvents that were selected based upon their boiling points. Solvents with relatively low boiling points were selected, since the lower the boiling point of the solvent, the faster will be the drying process. The process of recrystallization of VAL in different solvents took different duration of time to produce a dry product, though all the samples were dried under similar temperature and moisture conditions. Among all the solvents used methanol, ethanol, isopropanol, acetone gave dry product quickly in few minutes even at room temperature. Whereas, with the tetrahydrofuran and N, N-Dimethyl formamide as recrystallization solvents a rubbery mass was obtained and the products were not dried even after 3 months and were excluded from the further studies.

Solubility Studies

A solubility study of VAL carried out in different buffer solutions and the pH solubility profile of VAL is shown in Fig. 1. Increasing pH caused an increase in the aqueous solubility of VAL up to pH 6.8, at higher pH fluids the aqueous solubility decreased. This may be due to the fact that VAL contains two weakly acidic functions with pKa values of 3.9 and 4.7, which likely coexist in solution at physiological pH values as the undissociated acid, the mono-anionic species and the di-anionic species. In a buffered solution, the increase in solubility is likely due to the formation of the dianionic species. At higher pH values precipitation of VAL was observed and hence the lower VAL solubility. In phosphate buffer of pH 6.8, VAL solubility is $43.53 \pm 3.18\text{mg/mL}$. Solubility studies of the VAL and its recrystallized products were

carried out in pure distilled water and the results are shown in Fig 2. The solubility of untreated VAL in water is 0.249 ± 0.020 mg/mL. A 2.1, 1.88, 1.80 and 2.08 fold increase in the solubility of VAL in water when compared to the untreated VAL was observed with methanol (MET), ethanol (ETH), isopropanol (ISP) and acetonitrile (AN) recrystallized products, respectively. The increase in the solubility may be due the increase in the wettability and decrease in crystallinity of VAL with the recrystallized products. Based on the results obtained with the water solubility studies, methanol (MET), ethanol (ETH), isopropanol (ISP), and acetonitrile (AN) recrystallized VAL products were selected for further physicochemical characterization and *in vitro* dissolution studies.

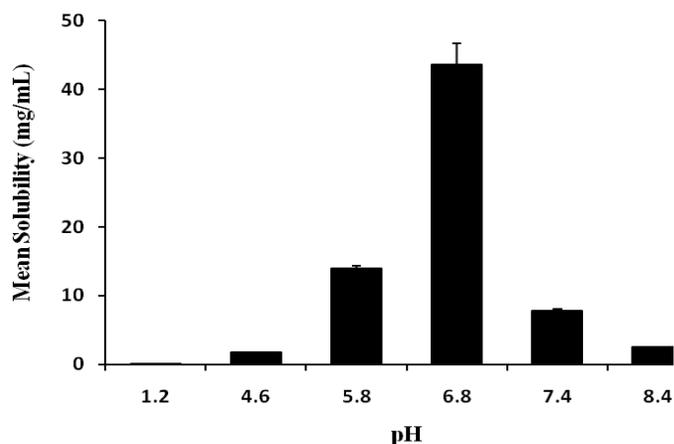


Fig. 1: pH solubility profile of VAL.

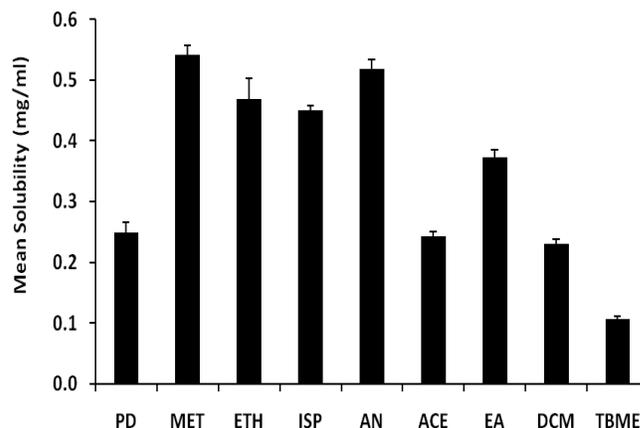


Fig. 2: Water solubility of VAL and its recrystallized products (PD: untreated VAL; MET: methanol; ETH: Ethanol; ISP: Isopropanol; AN: Acetonitrile; ACE: Acetone; EA: Ethyl acetate; DCM: Dichloromethane; TBME: Tetrabutyl methyl ether).

SEM Studies

Crystal morphology or habit is an important property of a drug molecule that can influence many properties like powder flow, compaction and stability, and even dissolution rate (Haleblian *et al.*, 1975). The SEM studies were carried out to assess the effect of recrystallization on crystal shape and size of VAL (surface morphology). The SEM photographs of untreated VAL, methanol, ethanol, isopropanol, acetonitrile, acetone, ethyl

acetate, dichloromethane, tetrabutylmethyl ether products are shown in Fig 3. VAL crystals are acicular (elongated needle-like prisms) and are smaller in size when compared to the recrystallized products. The shape was retained with all recrystallized products; however, modification of surface morphology was observed, and with the TBME product, the VAL particles were found to be spherical.

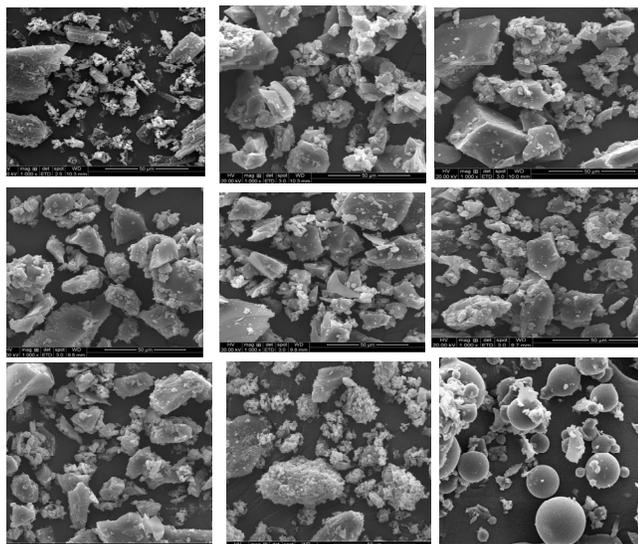


Fig. 3: SEM photographs of VAL and its recrystallized products

Particle Size Studies

One of the reasons for studying particle size distribution is to explain the alteration in solubility properties from dissolution studies carried out on recrystallized drug, when compared to untreated drug. From the particle size distribution curves it was observed that median particle sizes of VAL pure drug and MET and ETH recrystallized products were 8.59μ , 14.33μ and 15.17μ , respectively. From these results it can be concluded that the commercial VAL is a finer powder when compared the two recrystallized products which was also further confirmed by SEM studies. The particle size distribution was more uniform in case of the ETH-recrystallized VAL product.

DSC Studies

DSC was one of the techniques employed for the characterization of the crystals. DSC studies were performed in order to study changes in crystal nature that can be assessed from melting point information. The physicochemical properties (melting point) of the recrystallized VAL products MET, ETH, ISP, and AN, along with pure VAL, were also inferred from the DSC thermograms. The DSC thermograms of the samples are shown in Fig 4. The untreated VAL shows a sharp endothermic peak at 105.7°C , which corresponding to melting point of VAL (Carlos *et al.*, 2010). However, with the four recrystallized products: MET, ETH, ISP and AN, broad endothermic peaks were observed at 75.2°C , 65.9°C , 64.6°C and 80.6°C , respectively, an indication of

the existence of different crystalline forms of VAL obtained after recrystallization from methanol, ethanol, isopropanol and acetonitrile. The shift in the melting peaks with all four recrystallized products also may be due to changes in crystal lattice structure and hence in crystallinity. The formation of solvates may also not be precluded, since the thermograms of the recrystallized VAL products showed broad endothermic peaks below 100°C .

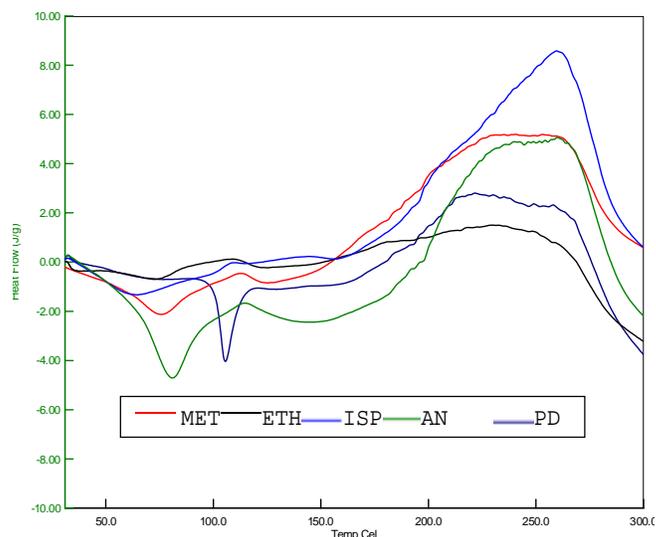


Fig. 4: DSC thermograms of VAL and its recrystallized products.

Powder X-RD studies

Powder X-ray diffraction patterns of VAL and its recrystallized products MET, ETH, ISP and AN were also studied in order to gain insights into the crystallinity differences. The powder X-ray diffractograms are shown in Fig 5. The powder X-ray diffractogram of untreated VAL shows characteristic crystalline peaks at 6.36° , 14.5° , 20.8° , and 22.3° . The highest intense peak was observed at 6.36° . The characteristic peak of VAL at 6.36° was retained, but with less intensity, and newer peaks were observed at 15.5° and 18.6° in the MET product when compared to untreated VAL. The formation of newer peaks is an indication of a different form of VAL obtained after methanol recrystallization. With ETH, the characteristic peaks of VAL at 6.36° and 20.8° were observed however, with lower intensities. The characteristic peaks at 14.5° and 22.3° were almost unobservable. A new peak at 19.3° was also observed and is also an indication of different form of VAL after ethanol recrystallization. With ISP, the characteristic peak of VAL at 6.36° was observed, but with less intensity when compared to the pure VAL. The other peaks at 14.5° , 20.8° , and 22.3° were also unobservable.

With AN, characteristic peaks at 6.36° , 14.5° were observed, but the 14.5° peak intensity was reduced when compared to the pure VAL. A new peak at 19.23° was observed and the peaks at 20.8° and 22.3° were not observed. The formation of the new peak is an indication of different form of

VAL after acetonitrile recrystallization. Overall, the characteristic peak of VAL at 6.36° was retained in all recrystallized products, but with lower intensity when compared to pure VAL. These results indicate that the crystallinity of VAL is affected by the specific recrystallization method utilized to afford VAL recrystallized products with reduced crystallinity. A decrease in the intensities of the existing peaks and the appearance of the new peaks is an indication of change in the crystal habit of VAL which appears to be solvent-dependent. Along with the DSC and X-RD data, one can confirm the existence of new forms of VAL resulting from recrystallization with methanol, ethanol and acetonitrile solvents.

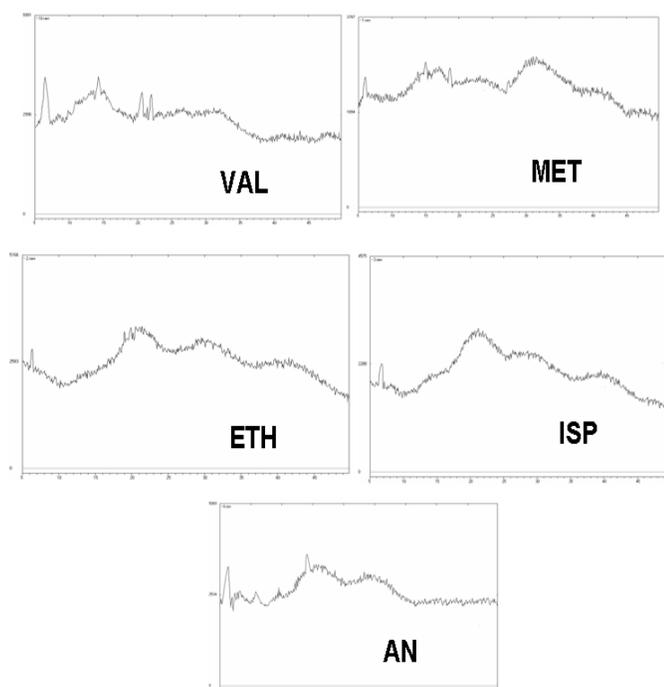


Fig. 5: Powder X-RD of VAL and its recrystallized products.

FTIR Studies

VAL has two characteristic carbonyl absorption bands at 1725 and 1598 cm^{-1} that correspond to carboxyl and amide carbonyl stretching frequencies, respectively. The peak at 3393 cm^{-1} indicates the presence of an N-H functional group. The band at 2961 cm^{-1} indicates the presence of a C-H group stretching vibration. The spectrum reveals the characteristic peaks in the typical range of $1205\text{-}1052\text{ cm}^{-1}$, confirming the presence of the tetrazole ring in the VAL. The complex region of $900\text{-}600\text{ cm}^{-1}$ indicates skeletal vibration and the presence of an aromatic ring in the drug substance. All the characteristic peaks of VAL were retained in the FTIR spectra of the recrystallized products and represent criteria for structural identification of the recrystallized products for VAL.

These results were further confirmed by the HPLC analysis. A retention time of 2.5 min was observed with untreated VAL and its recrystallized products and is indication of the purity of VAL and that no chemical change has occurred during the

recrystallization procedure. Moreover, the peak purity index was found to be 1.0000 with all the samples. These results from the HPLC studies were further confirmed by UV spectral studies. A characteristic λ_{max} of 250 nm was observed with all the VAL samples.

In vitro Dissolution Studies

The dissolution studies were performed to analyze the solubility characteristics of the recrystallized VAL products and to compare the results obtained with that of untreated VAL. The *in-vitro* dissolution studies were performed for all the samples using phosphate buffer of pH 6.8 as the dissolution medium to assess various dissolution properties such as drug percent released at 10 min (DP_{10}) and 120min (DP_{120}), dissolution efficiency at 20 min (DE_{20}), time to release 50% of VAL, and first order and Hixson-Crowell rate constants. The release profiles are shown in the Fig 6 and data are given in Table I. One way ANOVA was used to test the statistical significance of differences between different samples. Significance of differences in the means was tested using Fisher's LSD at 95% confidence.

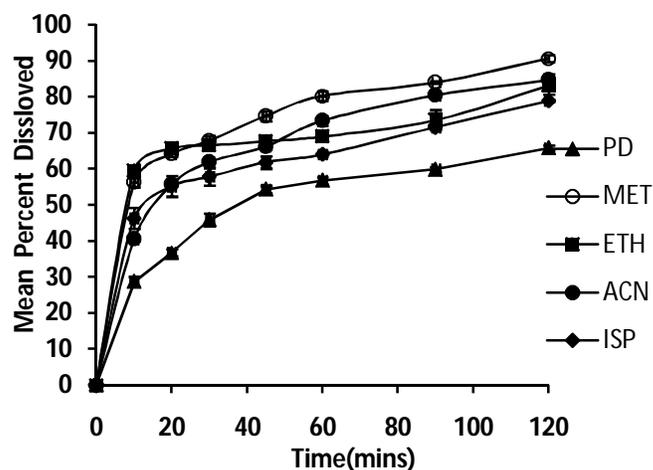


Fig. 6: Comparative *In-Vitro* dissolution profiles of VAL and its recrystallized products.

The $t_{50\%}$ values for VAL and its recrystallized products MET, ETH, ISP and AN were 47.76 ± 4.14 , 26.60 ± 1.32 , 33.44 ± 0.00 , 37.61 ± 0.00 and $31.21 \pm 1.93\text{ min}$, respectively. The $t_{50\%}$ values for MET, ETH, ISP and AN were significantly lower ($P < 0.05$) when compared to the untreated VAL and are in the order of VAL > ISP > ETH > AN > MET (Table I). The DP_{10} values for VAL and its recrystallized products MET, ETH, ISP and AN were 29.40 ± 1.23 , 56.29 ± 1.33 , 59.56 ± 0.66 , 46.32 ± 2.88 and 40.52 ± 0.68 , respectively, whereas, DP_{120} values were 65.85 ± 1.98 , 90.69 ± 1.01 , 83.13 ± 2.40 , 78.91 ± 0.38 and 84.71 ± 1.67 , respectively for VAL and its recrystallized products MET, ETH, ISP and AN. The DP_{10} and DP_{120} values for are significantly higher ($P < 0.05$) when compared to pure VAL. The DP_{10} values are in the order ETH > MET > ISP > AN > VAL, whereas, for DP_{120} the values are in the order MET > AN > ETH > ISP > VAL. The discrepancy in the order of values may be because of the wettability of the

recrystallized products in the dissolution medium. A 1.37, 1.28, 1.26 and 1.19 fold increase in the DP_{120} values for MET, AN, ETH and ISP was observed when compared to the untreated VAL (Table I). The DE_{20} values for MET, ETH, ISP and AN were significantly higher ($P < 0.05$) when compared to the pure VAL and are in the order of $MET \geq ETH > ISP > AN > VAL$. A 1.78, 1.86, 1.49 and 1.37 fold increase in the DE_{20} values for MET, ETH, ISP and AN was observed when compared to the pure VAL (Table I).

Table. 1: *In-vitro* Dissolution properties of VAL and its recrystallized products (n=3).

AMPLE	DP_{10}	DP_{120}	DE_{20} (%)	$t_{50\%}$ (min)
PD	29.404 ± 1.23	65.846 ± 1.98	11.04 ± 0.21	47.764 ± 4.14
	56.294 ± 1.33	90.685 ± 1.01	19.61 ± 0.37	26.596 ± 1.32
MET	59.559 ± 0.66	83.128 ± 2.40	20.49 ± 0.64	33.435 ± 0.00
	40.522 ± 0.68	84.710 ± 1.67	15.17 ± 0.18	31.206 ± 1.93
ETH	46.323 ± 2.88	78.925 ± 0.38	16.39 ± 0.32	37.614 ± 0.00
ISP				

PD= Untreated VAL

The percent drug release data was also fitted to release kinetics models such as first order and Hixson-Crowell equations to obtain release rate constant values for comparison of dissolution data. The data is given in Table II. The first order rate constant (k^{-min} , 0-120min) values for MET, ETH, ISP and AN were significantly higher ($P < 0.05$) when compared to pure VAL and are in the order $MET > AN > ETH > ISP > VAL$. A 1.77, 1.53, 1.42 and 1.26 fold increase in 'k' values respectively was observed for MET, AN, ETH and ISP when compared to pure VAL. The Hixson-Crowell release rate constant (K_{HC}^{-min}) values for MET, ETH, ISP and AN were significantly higher ($P < 0.05$) when compared to pure VAL and are in the order $MET > AN > ETH > ISP > VAL$. A 1.31, 1.25, 1.14 and 1.09 fold increase in ' K_{HC} ' values was observed respectively for MET, AN, ETH and ISP when compared to pure VAL. However, the r^2 values for first order release kinetics are superior when compared to the values obtained utilizing the Hixson-Crowell kinetic model (Table II).

Overall, it can be concluded that the increased dissolution properties of the recrystallized VAL products is a result of various factors: (i) an increase in solubility, (ii) improved wettability, and (iii) a decrease in crystallinity, as evidenced by DSC and X-RD studies. It was also observed that, although there was an increase in particle size, the recrystallized VAL products showed improved dissolution profiles because of the reduction in crystallinity. For BCS class II and IV compounds drug absorption can often be improved by rendering the drug amorphous when low solubility presents a significant barrier for oral absorption (Amidon *et al.*, 1995). Thus, the utilization of metastable solid forms, such as amorphous phases, and amorphous solid dispersions, can be a powerful tool in combating the poor ADME

profiles of many modern drug candidates (Hancock *et al.*, 1997; Law *et al.*, 2001; Law *et al.*, 2004; Six *et al.*, 2005; Yamashita *et al.*, 2003). Selecting the appropriate solid forms for development is thus critical to the facile development of high quality products.

Table. 2: Release kinetics data of VAL and its recrystallized products (n=3).

Sample	First order release kinetics		Hixson-Crowell release kinetics	
	k^{-min}	r^2	K_{HC}^{-min}	r^2
PD	0.0146 ± 0.001	0.894 ± 0.023	0.361 ± 0.015	0.823 ± 0.025
	0.0261 ± 0.001	0.806 ± 0.043	0.470 ± 0.011	0.666 ± 0.030
MET	0.0207 ± 0.000	0.604 ± 0.009	0.410 ± 0.006	0.542 ± 0.008
	0.0223 ± 0.001	0.868 ± 0.013	0.450 ± 0.005	0.766 ± 0.008
ETH	0.0184 ± 0.000	0.740 ± 0.035	0.393 ± 0.016	0.656 ± 0.025
ISP				

CONCLUSION

Hence, utilizing recrystallization technique, VAL can be transposed into either amorphous phases or amorphous dispersions, as evidenced by the present DSC and powder X-RD studies, that exhibit improved aqueous solubility and dissolution properties and potentially therapeutic efficacy.

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