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Spherically agglomerated solid dispersions of valsartan to improve solubility, dissolution rate and micromeritic properties

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Abstract

The objective of the present work was to enhance the solubility and dissolution rate of valsartan (VAL) a poorly water soluble antihypertensive, by spherically agglomerated solid dispersions using methanol, water and dichloromethane as good solvent, poor solvent and bridging liquid, respectively. The hydrophilic polymers like polyvinyl pyrrolidone, Hydroxypropyl β-cyclodextrin, Hydroxypropyl methylcellulose were used in agglomeration process. The pure drug (VAL) and its agglomerates with different polymers were characterize by differential scanning calorimetry (DSC), X-ray diffraction (XRD), IR spectroscopic studies and scanning electron microscopy (SEM). The DSC results indicated that decrease in melting enthalpy related to disorder in the crystalline content. XRD studies also showed changes in crystallanity, IR spectroscopy revealed that there were no chemical changes in the recrystallized agglomerates. The spherically agglomerated solid dispersions with different polymers exhibited marked increase in solubility, dissolution rate and micromeritic properties (bulk density, flow property, compactability) compared with VAL. The SEM studies showed that the agglomerates posseeses a good spherical shape.

Keywords: Valsartan; Spherical agglomeration; Solid dispersion; Solubility; Dissolution rate; Micromeritic properties.

Introduction

Aqueous solubility and dissolution are two of the crucial factors influencing drug absorption from the gastrointestinal tract. The solubility behavior of a drug is the key determinant of its oral bioavailability. Potential bioavailability problems are prevalent with extremely hydrophobic drugs due to erratic or incomplete absorption from GIT. Several methods have been used to increase the solubility and dissolution of poorly soluble substances like reduction in particle size, use of surfactants etc. but none of them have really been successful to improve solubility of poorly soluble drugs. The solid dispersion technique for water-insoluble drugs is one of the most efficient methods to improve the dissolution rate, leading to high bioavailability. At present the solvent method and melting method are widely used in the preparation of solid dispersions [1-3]. In general, subsequent grinding, sieving, mixing and granulation are necessary to produce the different desired formulations. The spherical agglomeration technique has been used as an efficient particle preparation technique [4-6]. Initially, spherical agglomeration technique was used to improve powder flowability and compressibility [7, 8]. Then polymers were introduced in this system to modify their release [9, 10]. Currently, this technique is used more

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frequently for the solid dispersion preparation of water-insoluble drugs in order to improve their solubility, dissolution rate and simplify the manufacturing process [11]. Spherical agglomeration is carried out by following method, 1) Solvent Change System, 2) Quasi-emulsion solvent diffusion system (QEDS), 3) Ammonia diffusion system, 4) Neutralization technique [12]. Out of these techniques, the QEDS is most commonly used. This method employs three solvents 1) Good solvent: solvent that dissolves API, 2) Poor solvent: solvent in which API is insoluble, 3) Bridging liquid: solvent that dissolves API and is immiscible with poor solvent while miscible with good solvent. When bridging liquid plus good solvent containing API are poured into the poor solvent under agitation, quasi-emulsion droplets of bridging liquid or good solvent form in the poor solvent and induces crystallization of the drug followed by agglomeration [13, 14].

Valsartan (VAL) is a potent and specific competitive antagonist of angiotensin-II AT_1- receptor [15, 16]. It is used orally for the treatment of hypertension and has low bioavailability. According to the Biopharmaceutical Classification Scheme [17], VAL is considered as a class II compound, i.e. water-insoluble and highly permeable [18].

In the present study, to overcome the problems related to solubility, dissolution rate, flowability, and compressibility, the spherically agglomerated solid dispersions of VAL were prepared by QEDS, which is more convenient and is cheaper. In addition, incorporating hydrophilic polymers (Polyvinyl pyrrolidone, Hydroxypropyl β-cyclodextrin, Hydroxypropyl methylcellulose) during agglomeration imparted better solubility, dissolution rate, flowability and compressibility.

Materials and methods

Materials

Valsartan was obtained as a gift sample from Lupin Research Park, Pune, India. Hydroxypropyl methylcellulose- 50 cps (HPMC), Polyvinyl pyrrolidone K-30 (PVP K-30), Hydroxypropyl β-cyclodextrin were obtained as a gift sample from Signetchem, Mumbai, India. Aerosil 200 Pharma was obtained as gift sample from Evonik Degussa Group, France. Glyceryl monosterate, polyvinyl alcohol, acetone, and dichloromethane were purchased from Lobachemie, Mumbai, India. All other chemicals used were of analytical grade.

Preparation of spherically agglomerated solid dispersion

All spherical agglomerates were obtained by the quasi emulsion solvent diffusion method. At room temperature using distilled water (as external phase and poor solvent). The internal phase contained a good solvent (methanol) and a bridging liquid (dichloromethane). VAL (1 g) was added in the solution of methanol (3 mL), glyceryl monostearate (0.05 g), and polymer. A bridging liquid (dichloromethane 1 mL) was added to above mixture. Drug was crystallized by adding the above solution to a 250 mL capacity beaker containing a mixture of polyvinyl alcohol (0.25 g) and Aerosil 200 pharma (0.5 g) in distilled water (100 mL). The mixture was stirred continuously for a period of 0.5 h using a controlled speed mechanical stirrer (Remi Motors, India) at 800 rpm to obtained spherical agglomerated solid dispersions. As the good solvent diffused into the poor solvent, droplets gradually solidified and formed spherically agglomerated solid dispersion. The agglomerates were separated by filtration using Whatman filter paper (No.1) and dried in desiccator at room temperature. The amount of polymers was altered to get desired agglomerates. The composition is given in the table 1.

Table 1. **Composition of spherical agglomerates.**

Ingredients	V-1	V-2	V-3	V-4	V-5	V-6
Valsartan (g)	1	1	1	1	1	1
Methanol (mL)	3	3	3	3	3	3
PVP K-30 (mg)	50	100	--	--	--	--
HPβCD (mg)	--	--	50	100	--	--
HPMC (mg)	--	--	--	--	50	100
Glyceryl Monostearate (mg)	50	50	50	50	50	50
DCM (mL)	1	1	1	1	1	1
Distilled Water	100	100	100	100	100	100
PVA (mg)	250	250	250	250	250	250
Aerosil 200 Pharma (mg)	500	500	500	500	500	500
Stirring speed (rpm)	800	800	800	800	800	800

Infrared spectroscopy, differential scanning calorimetry (DSC) and Powder X-ray diffraction studies (PXRD)

The infrared (IR) spectra of powder VAL, and the agglomerates were recorded on an IR-spectrophotometer (IRAFFINITY-1, Shimadzu, Japan). Differential scanning calorimetry (DSC) analysis was performed using a DSC 823 calorimeter (Mettler Toledo model) operated by star e software. Samples of VAL and its agglomerates were sealed in an aluminium crucible and heated at the rate of 10 ^{0}C min^{-1} up to 300 ^{0}C under a nitrogen atmosphere (40 mL min^{-1}). Powder X-ray diffraction patterns (XRD) of the pure drug and spherical agglomerates were monitored with an x-ray diffractometer (Panalytical Xpert pro MPD xrd machine) using copper as x-ray target, a voltage of 40 KV, a current of 30 mA and with 1.5404 Angstorm wavelength. Xcelerator RTMS with secondary monochromator was used as a detector. The samples were analyzed over 2θ range of 7.02-59.98^0 with scanning step size of 0.02^0 (2θ) and scan step time of one second.

Micromeritic properties

The size of agglomerates was determined by microscopic method using stage and eyepiece micrometers. The shape of the agglomerates was observed under an optical microscope (60x magnification) attached to a computer. The loose bulk density (LBD) and tapped bulk density (TBD) of plain VAL and its spherical agglomerates were determined. Carr's index and Hausner's ratio were calculated using LBD and TBD values [19]. The angle of repose was accessed by the fixed funnel method [20].

Scanning electron microscopy

The surface morphology of the agglomerates was accessed by scanning electron microscopy (SEM). The crystals were splutter coated with gold before scanning.

Drug loading

The drug loading efficiency of agglomerates was determined by dissolving 100 mg of crystals in 5 mL methanol and diluting further with distilled water (100 mL), followed by measuring the absorbance of appropriately diuted solution spectrophotometrically (PharmaSpec UV-1700, UV-Vis spectrophotometer, Shimadzu) at 250 nm.

Solubility studies

A quantity of crystals (about 100 mg) was shaken with 10 mL distilled water in stoppered conical flask at incubator shaker for 24 h at room temperature. The solution was then passed through a whatmann filter paper (No. 42) and amount of drug dissolved was analyzed spectrophotometrically.

***In vitro* dissolution studies**

The in vitro dissolution studies were carried out using an 8 station USP 23 dissolution testing apparatus (Electrolab, India). The dissolution medium used was 500 mL of distilled water [21] or 900 mL of Phosphate buffer pH 6.8 [22]. The dissolution medium was kept at in a thermostatically controlled water bath at 37±0.5 ^{0}C. The agglomerates and pure drug containing 80 mg of VAL were weighed and introduced into the dissolution medium. The medium was stirred at 50 rpm using paddle. The dissolution tests were carried out for 60 min. At predetermined time intervals 5 mL of samples were withdrawn and analyzed spectrophotometrically. At each time of withdrawal, 5 mL of fresh corresponding medium was replaced into the dissolution flask. The cumulative amount of drug release was calculated and plotted versus time.

Dissolution efficiency studies

The dissolution efficiency of the batches was calculated by the method mentioned by Khan [23]. It is defined as the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y100, over the same time period or the area under the dissolution curve up to a certain time, t, (measured using trapezoidal rule) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time equation (01) [24].

$$\text{Dissolution efficiency} = \frac{\int_0^t y\,dt}{y100\ (t_2 - t_1)} \times 100\% \quad (1)$$

DE_{30} values were calculated from dissolution data and used to evaluate the dissolution rate.

Statistical analysis

The results were analyzed using the Graph Pad Instat Software (GPIS; version 5.0), and Microsoft Excel 2007. One-way analysis of variance (ANOVA) and

Dunnett Multiple Comparisons Test were used to test statistical significance of the data.

Results and discussion

Formulation and development

Spherically agglomerated solid dispersions of VAL were prepared by the quasi emulsion solvent diffusion method. A typical crystallization system involved a good solvent, poor solvent and bridging liquid. The selection of these solvents depends on the miscibility of the solvents and the solubility of the VAL in individual solvents. Since VAL is highly soluble in methanol, but poorly soluble in water. Also it is soluble in dichloromethane which is immiscible in water; therefore in the present study methanol, dichloromethane, and water were selected as good solvent, bridging liquid and poor solvent respectively. When the good solvent with drug and polymer is dispersed in the poor solvent quasi emulsion droplets produced. This is due to an increase in the interfacial tension between good and poor solvent. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplets induces the crystallization of the drug within the droplet due to the decrease in solubility of the drug in the droplet containing the poor solvent. In the present study, the polymers (PVP-K30, HPβCD, HPMC) produced a high viscosity during the formation of coacervation droplets, and often caused the droplets to agglomerate into masses of irregular shapes and adhere to the propeller or the vessel wall. To overcome this Glyceryl monostearate, as an emulsion stabilizer and Aerosil 200 Pharma, as a dispersion agent were introduced into the formulation to avoid the coalescence of the droplets. It was also found that the addition of PVA to the aqueous dispersion medium prevented coalescence of the droplets. In the present study, distilled water containing PVA (0.25% w/v) was selected as a poor solvent and this result in the successful preparation of spherical agglomerates.

IR, DSC, and PXRD studies

The possible interaction between the drug and the carrier was studied by IR spectroscopy. The infrared spectra of VAL as well as its spherical agglomerates are presented in figure 1.

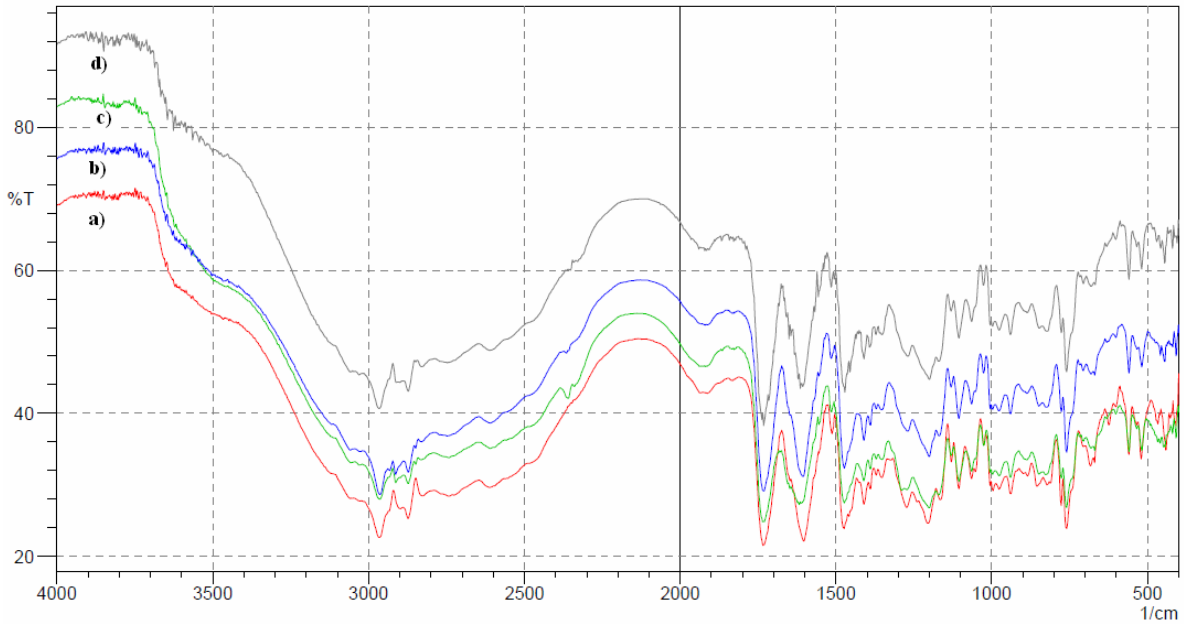

Figure 1. IR spectra of (a) pure drug, (b) Spherical agglomerates V-2, (c) Spherical agglomerates V-4, (d) Spherical agglomerates V-6.

The principal IR peaks of pure VAL, and spherical agglomerates are shown in table 2. IR spectra of VAL showed characteristic peaks at 2966.52 (C-H str., -CH_3), 1734.01 and 1604.77 cm^{-1} (C=O str., Carboxyl

and C=O str., amide, respectively). There were no considerable changes in the IR peaks of the spherical agglomerates when compared to pure VAL. If there is any strong interaction between drug and carrier, it often leads to identifiable changes in the IR profile and melting point of the drug. The results of IR spectra indicated the absence any well-defined interaction between VAL and PVP K-30, HPβCD, HPMC, Glyceryl monostearate, PVA, Aerosil in presence of methanol, dichloromethane, and water.

The DSC patterns of pure VAL and its agglomerates are shown in figure 2. Pure VAL showed a single endotherm at 101.95 ^{0}C, which was ascribed to drug melting. This may indicated that the pure VAL is in its polymorph II form [25].

Table 2. Major IR peaks of pure valsartan, spherical agglomerates.

Sample	Major peaks (wave numbers, cm^{-1})	Chemical moiety
VAL	2966.52	C-H str., $-CH_3$
	1734.01	C=O str., Carboxyl
	1604.77	C=O str., amide
V-2	2964.59	C-H str., $-CH_3$
	1735.93	C=O str., Carboxyl
	1612.49	C=O str., amide
V-4	2962.66	C-H str., $-CH_3$
	1732.08	C=O str., Carboxyl
	1604.77	C=O str., amide
V-6	2966.52	C-H str., $-CH_3$
	1732.08	C=O str., Carboxyl
	1606.7	C=O str., amide

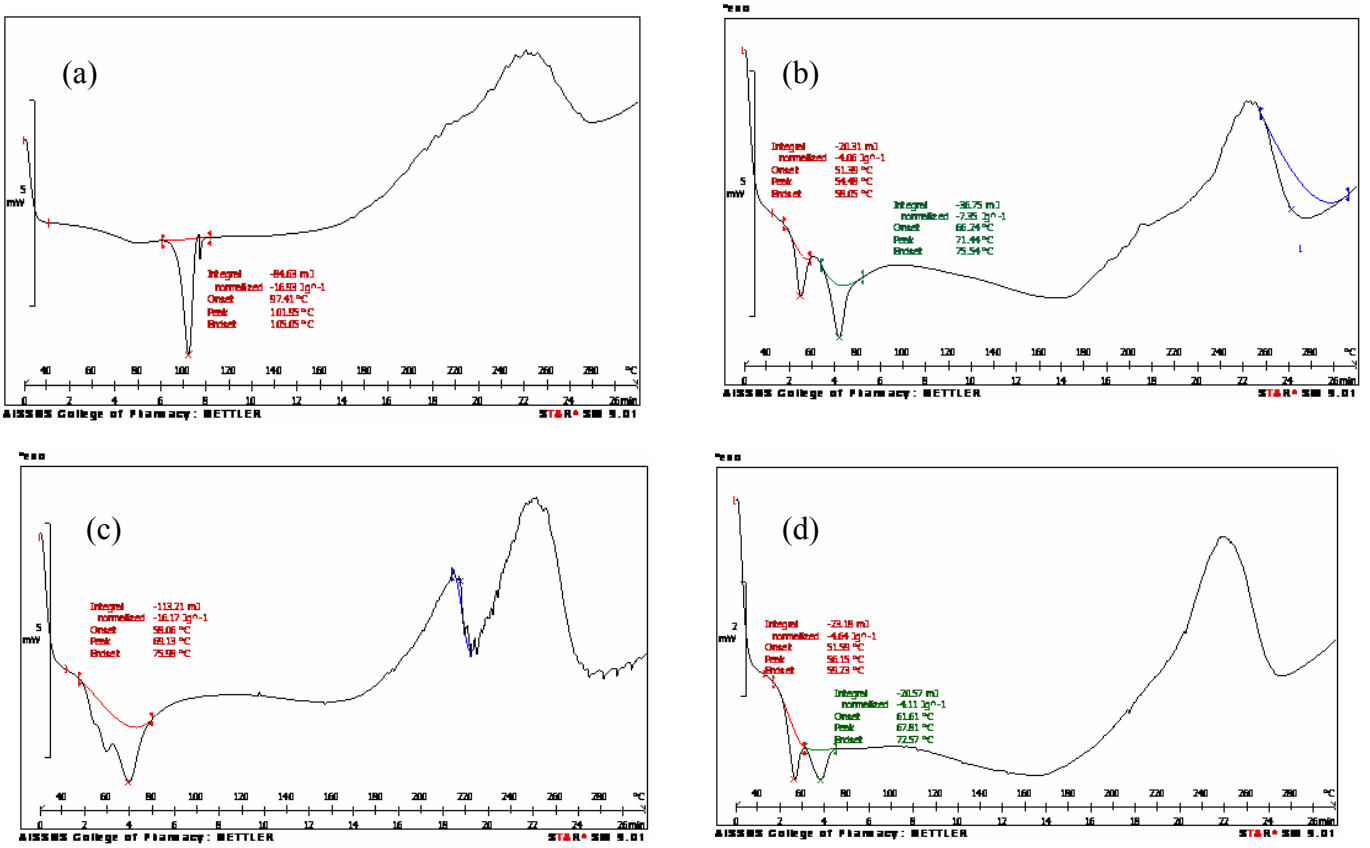

Figure 2. DSC patterns of a) valsartan, b) Spherical agglomerates V-2, c) Spherical agglomerates V-4, d) Spherical agglomerates V-6.

The DSC thermogram of spherical agglomerates with PVP K-30 showed two melting endotherms. The first one at 54.48 ^{0}C could be due to the melting of glyceryl monostearate and the second one at 75.54 ^{0}C was ascribed to the melting of VAL which may get converted into its polymorph I form due to agglomeration process [26]. In case of DSC thermogram of spherical agglomerates with HPβCD a

broad endotherm at 50-80 ^{0}C was shown. It may be ascribed to the melting of glyceryl monostearate and VAL polymorph I. Also DSC thermogram of spherical agglomerates with HPMC showed two melting endotherms. Endotherm at 56.15 ^{0}C was due to melting of glyceryl monostearate and endotherm at 72.57 ^{0}C may be due to VAL polymorph I. Thus DSC studies conclude that the agglomerates show lower melting point melting points than pure drug but this may not be related to a change in the internal structure of the drug molecule. However change in the melting peak indicate a different arrangement of the molecules and hence suggest the conversion of VAL polymorph II to polymorph I.

Table 3. Micromeritics, solubility and drug loading efficiency data for the agglomerates and pure drug[a].

Samples	Loose Bulk Density (LBD) (g mL^{-1})	Tapped Bulk Density (TBD) (g mL^{-1})	Carr's index (%)	Hausner's Ratio	Angle of Repose (^{0})	Particle Size (μm)	Solubility in Water (mg mL^{-1})	Drug Loading (%)
VAL	0.19 ± 0.02	0.30 ± 0.01	36.66 ± 2.63	1.57 ± 0.03	38.65 ± 1.65	40.45 ± 6.28	0.21 ± 0.25	100.0 ± 0.0
V-1	0.23 ± 0.01[b]	0.25 ± 0.01 [b]	8.00 ± 1.51 [b]	1.08 ± 0.01 [b]	18.14 ± 1.78 [b]	144.4 ± 10.18 [b]	0.62 ± 0.35 [b]	97.0 ± 0.6
V-2	0.23 ± 0.01 [b]	0.24 ± 0.02 [b]	3.67 ± 2.15 [b]	1.03 ± 0.01 [b]	19.29 ± 1.67 [b]	135.45 ± 9.21 [b]	0.89 ± 0.27 [b]	97.4 ± 0.5
V-3	0.30 ± 0.02 [b]	0.32 ± 0.01 [b]	6.25 ± 2.36 [b]	1.06 ± 0.02 [b]	14.32 ± 2.31 [b]	155.36 ± 12.10 [b]	0.92 ± 0.15 [b]	98.6 ± 0.6
V-4	0.31 ± 0.03 [b]	0.34 ± 0.01 [b]	8.82 ± 2.30 [b]	1.09 ± 0.02 [b]	13.13 ± 1.45 [b]	148 ± 7.54 [b]	1.23 ± 0.38 [b]	98.2 ± 0.3
V-5	0.25 ± 0.01 [b]	0.27 ± 0.01 [b]	7.40 ± 2.69 [b]	1.08 ± 0.01 [b]	15.82 ± 1.65 [b]	218.89 ± 10.25 [b]	0.45 ± 0.63 [b]	94.1 ± 0.5
V-6	0.32 ± 0.02 [b]	0.34 ± 0.01 [b]	4.77 ± 3.12 [b]	1.05 ± 0.01 [b]	14.93 ± 1.30 [b]	373.40 ± 10.93 [b]	0.59 ± 0.54 [b]	95.5 ± 1.2

[a] Mean ± SD, n = 3.; [b] Significantly different compared to pure celecoxib ($p < 0.05$).

The results of the powder X-ray diffraction pattern of VAL and spherical agglomerated solid dispersions are shown in figure 3. PXRD pattern of VAL indicates its amorphous nature. Investigation of PXRD patterns of agglomerates revealed a number of changes in the location of the peaks (appearance and disappearance) with respect to VAL. There is a difference in d-spacing between the PXRD spectra of VAL and agglomerated samples referring to the habit modification and change in the intensity of peaks, which indicate a different arrangement of molecules hence confirming the development of a different polymorphic form. This observation further supports the DSC results, which indicated the conversion of VAL polymorph II to polymorph I.

Micromeritic properties

The mean particle diameter of agglomerates is shown in table 3. The pure drug exhibited a very small particle size (40.45 ± 6.28 μm, n = 3) whereas the size of prepared agglomerates was found between 135.45 ± 9.21 and 373.40 ± 10.93 μm, n = 3, which is significantly different from that of pure drug ($p < 0.05$).

The shape of the crystals, when observed using an optical microscope was spherical in all the prepared agglomerated formulation shown in figure 4 (a).

Table 4. Drug release and dissolution efficiency[a].

Spherical Agglomerates	Water		Phosphate Buffer pH 6.8	
	DP_{60} (%)	DE_{30} (%)	DP_{60} (%)	DE_{30} (%)
VAL	22.18 ± 0.19	3.07 ± 0.01	39.64 ± 1.32	14.38 ± 0.26
V-1	61.75 ± 0.78	11.70 ± 0.23[b]	56.26 ± 1.13[b]	28.76 ± 0.66[b]
V-2	74.29 ± 1.73[b]	27.66 ± 0.86[b]	85.59 ± 1.01[b]	46.86 ± 0.67[b]
V-3	65.77 ± 0.75	19.27 ± 1.00[b]	69.59 ± 0.85[b]	39.89 ± 0.20[b]
V-4	76.91 ± 1.55[b]	32.75 ± 0.49[b]	92.86 ± 1.22[b]	52.05 ± 0.28[b]
V-5	56.80 ± 0.31	10.31 ± 0.27[b]	63.93 ± 0.51[b]	36.48 ± 0.61[b]
V-6	69.31 ± 1.34[b]	23.69 ± 0.68[b]	81.97 ± 0.49[b]	48.59 ± 0.32[b]

DP_{60} – Percent drug release at 60 min.; DE_{30} – Dissolution Efficiency at 30 min.; [a] Mean ± SD, n = 3.; [b] Significantly different compared to pure valsartan ($p < 0.05$).

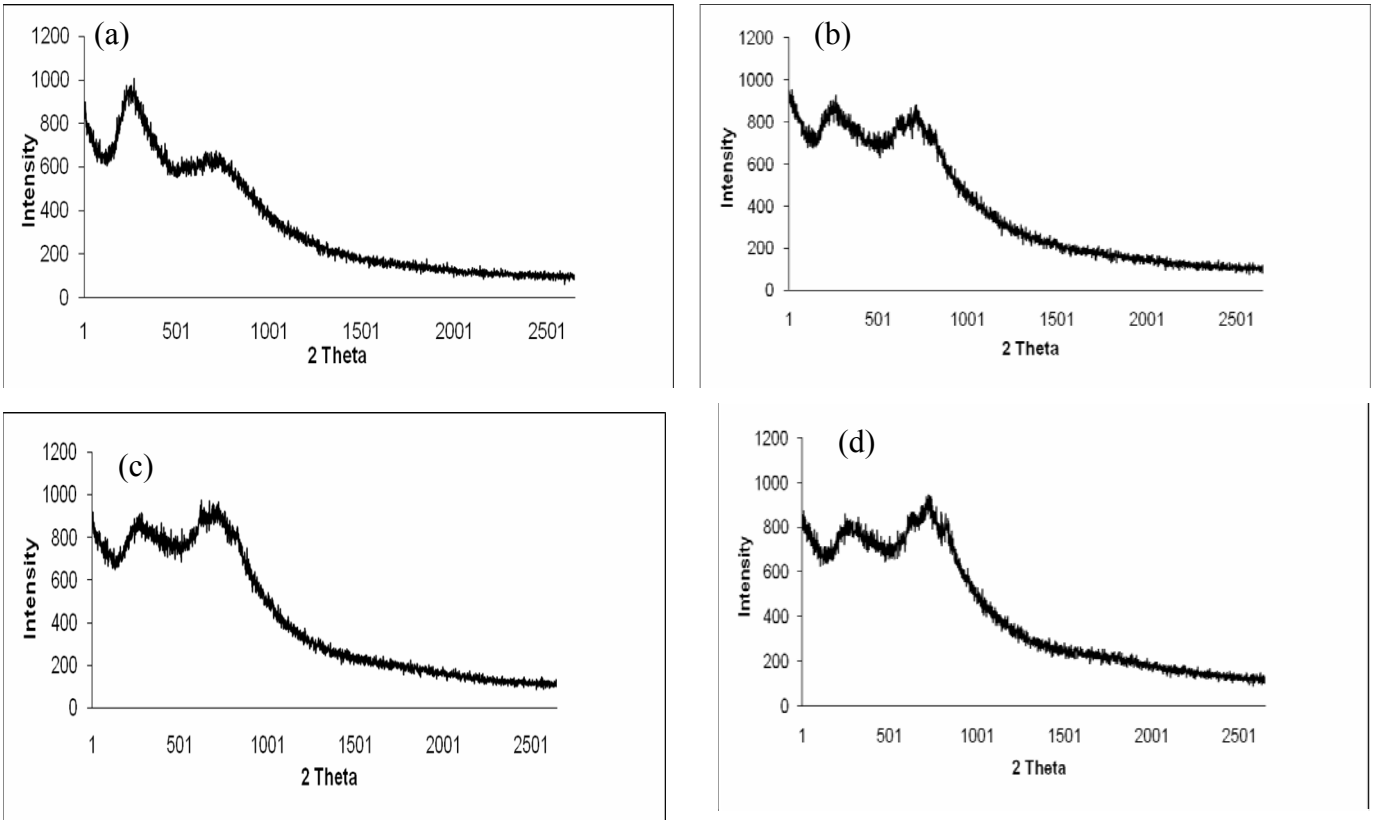

Figure 3. X-ray diffraction spectra: a) pure drug b) Spherical agglomerates V-2, c) Spherical agglomerates V-4, d) Spherical agglomerates V-6.

The results of loose bulk density (LBD), tapped bulk density (TBD), Carr's index, Hausner's ratio, angle of repose are presented in table 3. These parameters were used to assess the packability, flow and compressibility properties of the agglomerates. The LBD, TBD, Carr's index, Hausner's ratio and angle of repose values for pure drug VAL were 0.19 ± 0.02 g mL^{-1}(n = 3), 0.30 ± 0.01 g mL^{-1} (n = 3), 36.66 ± 2.63 % (n = 3), 1.57 ± 0.03 (n = 3), 38.65 ± 1.65^0 (n = 3), respectively, indicating poor flow and packability properties. On the other hand, all prepared spherical agglomerates exhibited higher LBD (0.23 ± 0.01 to 0.32 ± 0.02 g mL^{-1}, n = 3) and TBD (0.24 ± 0.02 to 0.34 ± 0.01 g mL^{-1}, n = 3) values which indicate good packability. Also all the prepared agglomerates exhibited low Carr's index, Hausner's ratio and angle of repose values, indicating excellent flow properties and compressibility (Carr's index: 3.67 ± 2.15 to 8.82 ± 2.30% , n = 3; Hausner's ratio: 1.03 ± 0.01 to 1.05 ± 0.01, n = 3; angle of repose: 13.13 ± 1.45^0 to 19.29 ± 1.67^0, n = 3). The improved flowability and compressibility of spherical agglomerates may be due to the sphericity, regular and larger size of crystals.

Scanning electron microscopy

The results of surface morphology studies are shown in figure 4. The SEM results revealed the spherical structure of agglomerates. The surface morphology studies also revealed that the agglomerates were formed by very small crystals, which were closely compacted into spherical form. These photo-micrographs show that the prepared agglomerates were spherical in shape which enabled them to flow very easily.

Drug Loading and Solubility Studies

The results of drug loading efficiency and aqueous solubility are shown in table 3. The drug loading of agglomerates was uniform among the different spherical agglomerates prepared and range from 94.1 ± 0.5 to 98.6 ± 0.6 % (n = 3), indicating negligible loss of drug during agglomeration process. The result

of solubility studies indicate that pure VAL possesses a very low solubility in water (0.21 ± 0.25 mg mL^{-1}, n = 3); the drug solubility from crystals increased significantly ($p < 0.05$), demonstrating that the incorporation of hydrophilic polymers enhances the drug solubility. Also as the concentration of hydrophilic polymer increased, the drug solubility also increased. Amongst the hydrophilic polymers used HPβCD spherical agglomerates shows maximum solubility (1.23 ± 0.38 mg mL^{-1}, n = 3).

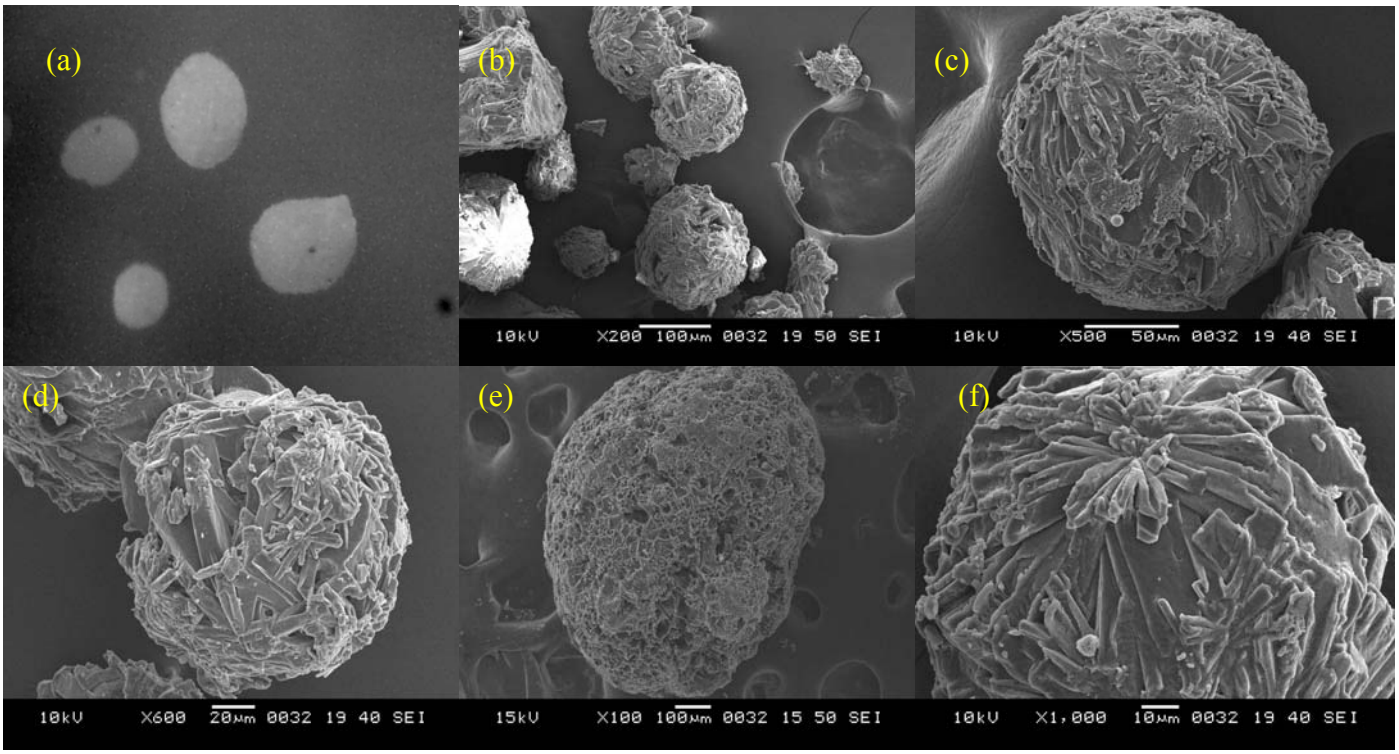

Figure 4. a) Optical micrograph of spherical agglomerates (50x), Scanning electron micrographs of: b) spherical agglomerates containing PVP K-30 (V-2) at 200x, c) spherical agglomerates containing PVP K-30 (V-2) at 500x, d) spherical agglomerates containing HPβCD (V-4) at 600x, e) spherical agglomerates containing HPMC (V-6) at 100x, f) surface morphology of spherical agglomerates (V-4) at 1000x.

***In vitro* dissolution studies**

The results of in vitro dissolution studies are shown in figure 5 and table 4. Pure VAL exhibited less release at the end of 60 min in water (22.18 ± 0.19%, n = 3) and in phosphate buffer pH 6.8 (39.64 ± 1.32%, n = 3); spherically agglomerated solid dispersion improved the dissolution rate of VAL in water and phosphate buffer pH 6.8 as dissolution medium. The agglomerates (V-4) released 76.91 ± 1.55% (n = 3) drug in water and 92.86 ± 1.22% (n = 3) drug in phosphate buffer pH 6.8 at the end 60 min. The dissolution efficiency at 30 min (DE_{30}) for pure drug was 3.07 ±0.01% (n = 3) and 14.38 ± 0.26 (n = 3) in water and phosphate buffer pH 6.8 respectively, whereas for agglomerates (V-4) was 32.75 ± 0.49% (n = 3) in water and 52.05 ± 0.28% (n = 3) in phosphate buffer pH 6.8 respectively. The results revealed that the spherically agglomerated solid dispersion showed significant increase ($p < 0.05$) in drug release compared to the pure drug. Among the different hydrophilic polymer tested, HPβCD showed better effect on solubility and dissolution rate compared to other polymers. The increase in the dissolution rate of agglomerates could be attributed to deposition of polymer onto the recrystallized drug surface and better wettability of the spherically agglomerated solid dispersions. The percent drug release from different agglomerates was increased in the following order: HPβCD>PVP-K30>HPMC.

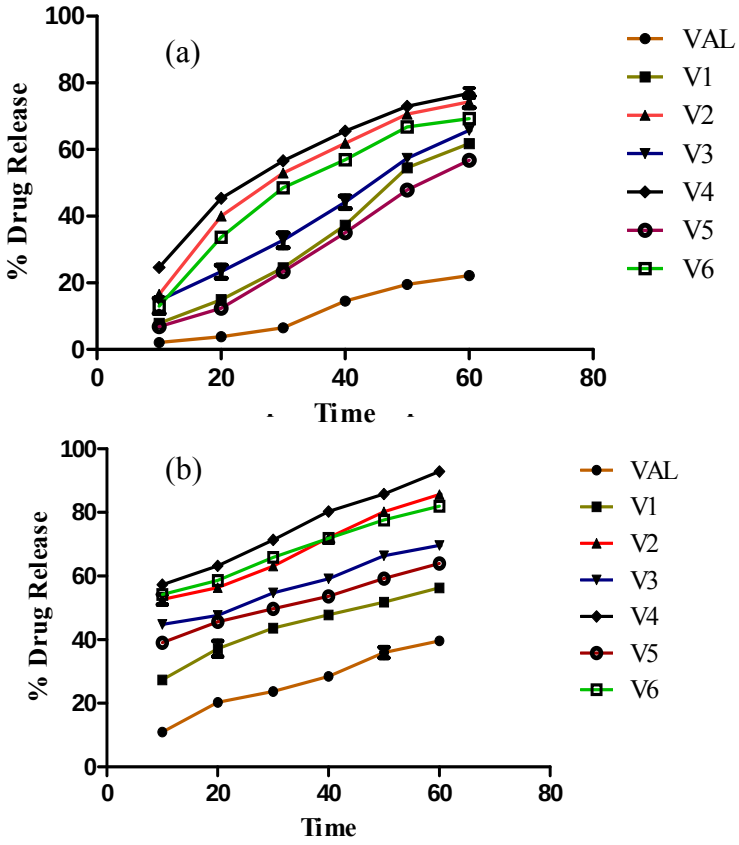

Figure 5. Dissolution profile of pure drug and agglomerates: (a) water, (b) Phosphate Buffer pH 6.8. (n = 3).

Conclusion

The present study shows that spherically agglomerated solid dispersion of VAL prepared with HPβCD, PVP K-30, and HPMC exhibited improved solubility and dissolution rate in addition to improving the micromeritics properties. This technique may be applicable for producing oral solid dosage forms of VAL with improved dissolution rate with improving physicochemical and micromeritic properties.

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