ORIGINAL ARTICLE

Crystallo-co-agglomeration of Valsartan for Improved Solubility and Powder Flowability

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Abstract

Introduction: Direct compression is the process of choice for tablet manufacturing due to its simplicity and lesser steps involved. For direct compression, the material of interest should have compressibility and compactibility. The aim of present work to convert valsartan drug powder into crystals those are directly compressible material. **Materials and Methods:** For the crystallo-co-agglomeration technique process, a system of Dimethylformamide-Water-Dichloromethane as good solvent-poor solvent-bridging liquid is used. Hydroxypropyl cellulose (HPC) was used to stabilize the system. Talc confirms its role as a bulking agent as well as the substrate for the spherical crystals. **Results:** The spherical crystals obtained in the presence of 0.5% HPC had greater particle size distribution, mechanical strength, compressibility, and compactibility in comparison to pure drug crystals. Drug content of the spherical crystals ranged around 84% and *in vitro* release for the optimized batch was 98.73%. *In vivo* bioavailability studies were performed in the Wistar rats, bioavailability (AUC) of the spherical crystals (18.90 ± 3.254 µg/ml*h) was significant ($P < 0.05$) to the pure drug (13.68 ± 0.902 µg/ml*h), and marketed preparation (17.49 ± 2.5 µg/ml*h). Stability studies in accordance to ICH guidelines indicated stability of the obtained products. **Conclusion:** Valsartan pure drug crystals were converted into the directly compressible material by crystallo-co-agglomeration technique. The obtained spherical crystals had greater solubility and flowability as compared to the original crystals.

Key words: Bioavailability enhancement, crystallo-co-agglomeration, improved flow property, spherical crystallization, valsartan

INTRODUCTION

Small particle size of crystals is preferred over large particle size for having greater bioavailability. A common method for particle size reduction is micronization, which produces smaller particle size but gives rise to other problems such as poor compressibility, poor packability, and poor flowability. To overcome the problems, the fine crystals are agglomerated to larger particle sizes by granulation.[1] Wet granulation processes need high energy and may cause stability problems to heat labile and moisture sensitive active pharmaceutical ingredients. Dry granulation, hot melt extrusion, melt granulation, spray congealing, and melt solidification provide an innovative solution for the improvement of the physical and mechanical properties of the drugs, but they are still less cost-effective than direct compression technique.[2] Crystallo-co-agglomeration is an extension of spherical crystallization technique proposed by Kadam *et al*. for overcoming the limitation of the earlier techniques where applications were limited to size growth of high dose pharmaceuticals. Spherical agglomerates can be produced in a single step having excellent flow characteristics, micromeritics, and compressibility. With rationale selection of polymers, the dissolution rate can be increased or decreased.[3]

Valsartan is a BCS Class II drug with poor dissolution and high permeability, which indicates that bioavailability from the oral dosage forms is dissolution rate limited. In

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Received: 01-05-2018
Revised: 11-08-2018
Accepted: 23-08-2018

earlier works, Valsartan spherical crystals were prepared by spherical crystallization technique using a combination of excipients for improving solubility, dissolution, and micromeritics.[4]

In the present study to overcome the problems of solubility, dissolution, compressibility spherically agglomerated crystals of valsartan has been prepared by crystallo-co-agglomeration technique using Talc as a substrate for size enlargement and hydroxypropyl cellulose (HPC) for improving sphericity and hydrophilicity.

MATERIALS AND METHODS

Materials

The materials used in the study were valsartan in crystalline form which was purchased from Yarrow Chemicals, Mumbai. Talc and HPC were purchased from CDH Limited, New Delhi. Solvents such as dichloromethane (DCM), chloroform, benzene, toluene, and hexane used were of the analytical grade of Merck Limited. Wherever, required double distilled water was utilized.

Selection of solvent system

Based on the solubility studies and considering the ICH guideline for residual solvents N,N-Dimethylformamide was selected as solvent and water were chosen as antisolvent. For selecting bridging liquid trials were conducted at a preliminary level using benzene, chloroform, DCM, hexane, and toluene for the agglomeration behavior.

Ternary phase diagram for three solvent systems of crystallo-co-agglomeration method

To define the region of mutual immiscibility and miscibility of the three solvent systems and the proportion of solvent to be utilized was determined by constructing a triangular phase diagram. N,N-Dimethylformamide was filled in test tubes starting from 1 ml to 9 ml. 1 ml of DCM was added to the test tubes and double distilled water (poor solvent) was added to the test tubes with intermittent shaking on a vortex mixture. The amount of water was noted when the contents of the test tubes turned turbid. The ternary phase diagram was potted using XLSTAT add-in. The experiment was repeated in triplicate.[5]

Optimization of the CCA process

Variables such as mode of addition of bridging liquid, agitation speed (rpm), agitation time (min.), and temperature (°C) were optimized.

Spherical crystallization of valsartan crystals

Spherical crystals of valsartan were produced by the advanced technique of spherical crystallization called crystallo-co agglomeration. Here, 3 g of valsartan was dissolved in 27 ml of N,N-Dimethylformamide and was poured into 63 ml of an aqueous polymeric solution of HPC in which 1% Talc has been previously dispersed and maintained at 5°C temperature. DCM was used as bridging liquid, taken in an amount of 10 ml, and added dropwise to crystallization system. The whole system was stirred for 15 min at the speed of 600 rpm. Spherical crystals formed were separated by filtration and dried at 40°C for 12 h. The dried spherical crystals were kept in desiccator for further evaluations. Formulation codes are given in Table 1.

Characterization of spherical crystals

Angle of repose

It was measured by fixed funnel method.[6]

$$\theta = \tan^{-1}(h/r) \quad \text{(Eq.1)}$$

Where, θ = Angle of repose, h = Height of pile & r = Radius of pile.

Carr's index

5 g of powder was poured into a 250 ml graduated cylinder, the poured volume was measured, and the volume was again noted after 100 taps.

Carr's Index (%) = (Tapped density – Bulk density)/Tapped density (Eq.2)

Hausner ratio

Hausner ratio was calculated by taking the ratio of tapped density and bulk density of the powder.

Hausner ratio = Tapped Density/Bulk Density (Eq.3)

Practical yield and drug content

For the calculation of percentage yield, the obtained spherical crystals were subjected to drying and then weighing. For determination of drug content, 100 mg of the spherical crystals were crushed and dissolved in methanol and were analyzed spectrophotometrically.[7]

Solid-state characterization

Fourier transform infrared spectroscopy

The pellet of approximately 1 mm diameter of the sample was prepared with 100–150 mg KBr. The sample pellet

was mounted in Shimadzu make fourier-transform infrared system and scanned at wave no. 40–4000 cm^{-1} resolution was 1/cm.[7]

Differential scanning calorimetry

10 mg of the sample was weighed and transferred to the aluminum crucible. An empty aluminum pan was used as a reference. The instrument (Shimadzu DSC60) was set to heat at a rate of 10°C in the range of 20°C–250°C and the peak and the enthalpy were obtained by the system software.[7]

X-ray diffraction (XRD)

The XRD patterns of spherical agglomerates were recorded using Bruker X-ray diffractometer (Model: D8 Advance) with a copper target at 30 kV voltage and 30 mA current. The scanning speed was 1 per minute.[7]

Scanning electron microscopy

Scanning electron photographs were taken using JEOL5400 at an accelerating voltage of 20 kV and micrographs obtained were examined.[7]

Particle size distribution

For the evaluation of the particle size of the pure drug was obtained by Malvern Zetasizer AT and for spherical crystals, it was obtained by sieving method. Sieve (#) 16, 30, 44, 60, 85, 100, and 120 were kept in descending arrangement according to their mesh size. 5 g of sample was weighed and was poured over the top sieve. The mean geometric diameter was calculated accordingly.[8]

Solubility analysis

The solubility of the spherical crystals was determined by adding an excess amount of the spherical crystals in well-stoppered vials containing 5 ml of water or suitable buffer solution to make a saturated solution.[9]

Mechanical properties

Friability of spherical crystals

Sample of 5 g from each batch of agglomerates with size (which are retained between sieve # 16 to #85) and 20 plastic balls (each of 0.95 cm diameter and 500 mg weight) were placed on #85 and shaken for a fixed interval of time. For each time interval, the mean geometric diameter was calculated.[10]

Percentage friability index (FI) as a function of time can be calculated at each time using the following equation

$$FI = (dg)_t/(dg)_0 \times 100 \quad \text{(Eq. 4)}$$

Here, $(dg)_t$ = mean geometric diameter after time t
$(dg)_0$ = mean geometric diameter at initial time.

Crushing strength

The granules for crushing strength were tested using the apparatus devised by Jasroz and Parrot. A minimum of 10granules was tested, and the average load in grams was taken as the crushing strength, *F*g.[11]

Heckel analysis

Heckel analysis was performed by compressing the 500 mg spherical crystals under different pressures (10, 20, 30, 40, 50, and 60 KN). Using Heckel equation, k value was determined, and the compression behavior of the spherical crystals was observed.[12]

Tensile strength

Tensile strength was determined by the force required to break the compacts diametrically. The force was determined by a Monsanto hardness tester.[13]

$$\sigma_t = 2F/\pi Dt \quad \text{(Eq. 5)}$$

Where, D = diameter and t = thickness of compacts.

Compactibility and packability

Packability parameters such as *a* (value of initial porosity of the powder bed, degree of volume reduction for the bed of particles at infinite applied pressure), 1/*b* (pressure needed to compress the powder to one half of the total volume), and K (apparent packing rate) were determined at different taps 50, 100,150, 200, and 250. The values of *"a"* and *"b,"* respectively, were calculated from the slope and intercept of the linear plot of n/C versus n.

Kawakita Equation

$$N/C = 1/ab + N/a \quad \text{(Eq. 6)}$$

Kuno Equation

$$\ln(q_t - q_n) = -K_n + \ln(q_t - q_0) \quad \text{(Eq. 7)}$$

Here, $Y = n/C$, Slope (m)= n/a, Intercept (C)= $1/ab$

Where, $C = \frac{V_0 - V_n}{V_0}$; n is the number of taps; V_0 and V_n are the initial and volume after n (number of) taps; q_0, q_n, and q_t

Table 1: Formulation details of the of spherical crystals of valsartan

Batch code	Conc. of polymer (HPC) (%)	Agitation speed (RPM)	Agitation time (min)	Temperature of crystallization system (°C)
VS_1	0.1	600	15	5±2
VS_2	0.5	600	15	5±2
VS_3	1.0	600	15	5±2

are the density without tapping, after nth taps and after infinite taps, respectively; a, b, and K are the constants representing the flowability and the packability of the powder when subjected to mechanical force.[13]

Elastic recovery

500 mg of spherical crystals were subjected to different compression pressures (10, 20, 30, 40, 50, and 60 KN). The thickness was noted by digital Vernier calipers (Mitutoyo 150 mm Digimatic Caliper) at 0 h, 24 h, and 7 days for each of the compacts to observe any change and percent elastic recovery was calculated.[13]

In vitro dissolution studies

In vitro dissolution studies of spherical crystals were carried out in USP Type II paddle apparatus by taking compacts of 100 mg equivalent samples of pure drug and spherical agglomerates which were compressed in 10 mm beveled flat punch. The amount of phosphate buffer pH 6.8 used as dissolution media was kept at 900 ml and the temperature was maintained at 37 ± 0.5°C for the particular study. Samples were withdrawn at 0, 5, 10, 15, 30, 45, 60, 90, and 120 min for each of the batches. The dissolution profile was reported as the mean of total 6 trials for each batch studied.[14]

Similarity(f_2) and dissimilarity (f_1) factors

The Dissimilarity (f_1) factor was calculated between the dissolution profile of each batch of spherical crystals and pure drug crystals using the formula:

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \qquad \text{(Eq. 8)}$$

Where n is the number of time points, Rt is the mean dissolution value for the reference product at time t, and Tt is the mean dissolution value for the test product at that same time point.

The similarity (f_2) factor was calculated between the dissolution profile of each batch of spherical crystals and pure drug crystals using formula:

$$f_2 = 50 \times Log_{10}\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{n} (R_t - T_t)^2}{n}}} \right) \qquad \text{(Eq.9)}$$

Where n, R_t, T_t, and t remain same as that used for the calculation of dissimilarity factor.[15]

In vivo bioavailability studies

Approval of protocol

All the experimental procedures and protocols used in the present study were reviewed and approved by the Institutional Animal Ethical Committee (*IAEC*) of "*School of Pharmaceutical Sciences*, *Jaipur National University, Jaipur, India,*" constituted under Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The submitted protocol was approved, namely no. JNU/IEAC/2016/III/5/A dated 04/11/2016. Ethical guidelines were strictly followed during all the experiments.

Selection of animal species

Healthy young adult male Wistar rats (weighing 150–200 g) were selected for the experimental purpose.

Housing and feeding conditions: The animal house was maintained at a temperature range of 22°C ± 3°C and relative humidity 50–60%, and the animals were housed at 12 h light, 12 h dark cycle. For feeding, conventional laboratory diets were used with an unlimited supply of drinking water. The bioavailability study for the formulated valsartan spherical crystals was carried out in overnight fasted animals.

Bioavailability study of valsartan spherical crystal

The 18 adult male Wistar rats were selected for study and were divided into three groups containing 6 in each.

Group I was treated with a suspension prepared with pure drug, i.e., valsartan and served as control. Group II was treated with valsartan spherical crystal. Group III was treated with the suspension prepared from the marketed tablet (Valent-80, Lupin, India) and served as standard.

All the animals were treated at the dose level of 10 mg/kg body weight, orally, using an oral feeder.

Collection of blood samples

The animals were anesthetized using Thiopental sodium (30 mg/kg bw), and blood sample (approximately 1 ml) was collected through the retro-orbital vein using heparinized capillary, at different time interval, i.e., 0.5, 1, 1.5, 2, 3, 4, 6 8, 10, 12, 18, and 24 h.

Processing with collected blood sample

The collected blood samples were immediately transferred to the heparinized microcentrifugation tube, vortexed, and centrifuged on a laboratory centrifuge at 5000 rpm for 20 min at ambient temperature.

The plasma was separated out and subjected to liquid-liquid extraction with diethyl ether. For the uniform mixing, the contents were vortexed and allowed to stand for 10 min. The supernatant layer was collected.

The extract was subjected to drying under the high pressure of nitrogen for 2 min. Reconstitution was done with a suitable solvent (Methanol). The content of drug was determined by UV spectroscopy.[16]

Stability studies

Accelerated stability studies were performed in accordance to ICH guidelines (40 ± 2°C and 75 ± 5% RH for a period of 6 months) to ensure the stability of the spherical crystals during the shelf life of the final marketed dosage form. The samples were withdrawn at 30, 60, 90, and 180 days and evaluated for the drug content and *in vitro* drug release at 90 min.[17]

RESULTS AND DISCUSSION

Selection of solvents

For the spherical crystallization process, by the crystallo-co-agglomeration method, involves three solvents, a solvent in which the drug is freely soluble, a solvent in which it is poorly soluble and a third solvent which acts as a bridging liquid. An inert material is used as substrate. From the review of literature, it was determined that a polymer should be present during the crystallization process to slow the growth of nuclei and imparts smoothness to the surface as well as may increase solubility.

The selection of these solvent depends on the miscibility of the solvents and solubility of the drug in individual solvents. Valsartan had the highest solubility in N,N-Dimethylformamide (31.654 ± 0.013 mg/ml) and the lowest in distilled water (0.084 ± 0.09 mg/ml) among all the solvents. Further trials were taken for selecting bridging liquid among acetone, chloroform, benzene, hexane, toluene, and DCM. Acetone formed a pasty whereas other solvents failed to produce spherical crystals except DCM.

From the ternary phase diagram as represented in Figure 1, in the agglomeration zone best results were found at 27 ml dimethylformamide, 63 ml water and 10 ml DCM, and hence, were selected for further studies.

Process optimization

The process was optimized for four parameters, mode of addition of bridging liquid, agitation speed, agitation time, and temperature were considered. It was concluded from this set of optimization experimentation that when a crystallization system is kept at 5 ± 2°C for 15 min under agitation speed of 600 rpm and the bridging liquid is added dropwise spherical agglomerates can be obtained [Table 2].

Flowability

Pure drug exhibited poor flowability and compressibility as indicated by the high value of Carr's index (29.21%), Hausner's ratio (1.37), and angle of repose (42.09°). This could be due to the irregular shape and small size of powder, which put hurdles in the uniform flow of powder from the funnel. The agglomerates prepared (VS1–VS3) showed improved flowability (Carr's index: 4.21–20.45%; Hausner ratio: 1.04–1.25; and angle of repose: 25.43°– 37.97°) when compared to pure drug. Results have been tabulated in Table 3.

The improved flowability of spherical agglomerates may be due to good sphericity and larger size of spherical crystals.

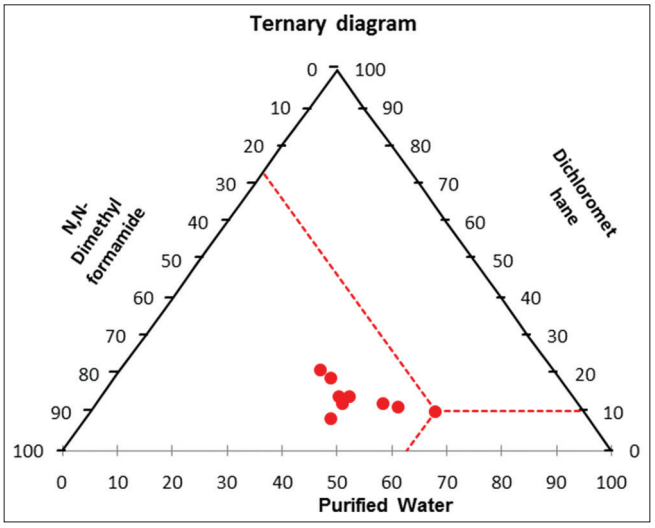

Figure 1: Ternary phase diagram of N,NDimethylformamide -dichloromethane-Water

Table 2: Effect of variables on formulation of spherical agglomerates of valsartan

Parameter	Variable	Observation
Mode of addition of Bridging Liquid	Whole amount at a time	Irregular shape agglomerates
	Dropwise	Spherical shaped agglomerates
Agitation Speed (rpm)	200	Large clumps
	400	Small agglomerates
	600	Spherical agglomerates
	800	Irregular shaped agglomerates
	1000	Large amount of fines produced
Agitation time (min.)	5	Clump formation
	10	Incomplete formation of spherical agglomerates
	15	Spherical agglomerates
	20	Broken agglomerates
	30	Fines of irregular shape
Temperature (°C)	5±2	Spherical agglomerates
	30±2	No agglomeration
	40±2	No agglomeration

Table 3: Micromeritic properties of spherical agglomerates

Batch	Angle of repose (º)	Carr's index	Hausner ratio
Valsartan	42.09±0.59	29.21	1.365
VS1	32.60±0.26	14.17	1.165
VS2	25.43±0.35	4.21	1.044
VS3	37.97±0.59	20.45	1.257

During the tapping process, smaller agglomerates may have creep into the voids between larger particles, which could result in improved packability.[13] Among different agglomerates prepared, formulations VS1 and VS2 showed maximum flowability as evident by low values of Carr's index, Hausner ratio, and Angle of repose. Hence, further studies were carried over the batches VS1 and VS2.

Practical yield and drug content

The practical yield for the batch VS1 was found out to be 83.64 ± 0.303%, and for VS2, it was 84.81 ± 0.856%, which indicated that polymer at concentration 0.5% had better productive results. Similarly, drug content for the batches VS1 and VS2 was determined to be 94.09 ± 2.58% and 95.26 ± 0.986%, respectively.

Solid-state characterization

The fourier-transform infrared (FTIR) spectrum of valsartan spherical crystals Batch VS1 and VS2 exhibited characteristics band consistent with the pure valsartan [Figure 2] which indicated that no chemical interaction occurred between the drug and excipients used in the formulation.[17]

Differential scanning calorimetry (DSC) thermograms [Figure 3] of pure drug and spherical crystals have a sharp endothermic peak for valsartan, which indicates the crystalline nature. The single peak of valsartan in all the thermograms shows that no interaction occurs between in the polymer and the drug. However, when the enthalpies were compared it was found that partial amorphization had occurred when agglomerates were prepared in the presence of HPC, and the reduction of enthalpy was not due to any incompatibility with polymers.[13]

The XRD scan of pure valsartan shows intense peaks of crystallinity [Figure 4] whereas the XRD pattern of the agglomerates exhibited halo pattern with less intense and more denser peaks when compared to pure valsartan, indicating the decrease in crystallinity or partial amorphization of the drug in its agglomerated form.[18] This supported the DSC results which demonstrated partial amorphization of the drug in agglomerates.

The scanning electron microscope (SEM) photomicrographs of the pure drug are shown in Figure 5a and the SEM photographs of agglomerates are shown in Figure 5b and c. The photomicrographs confirmed that the agglomerates formed were spherical in shape and the surface of the agglomerates was somewhat smooth which may be due to the presence of the polymer.[19]

Particle size distribution

The median particle size of the pure drug was found out to be 845.5 nm, the mean geometric diameter (by weight) for batch VS1 was 293.02 µm and for VS2 was 313.33 µm. Results indicate that agglomeration took place and particle size had increased. Increasing polymer ratio had an incremental effect on the particle size of the spherical agglomerates. Particle size distribution of the spherical crystals of batch VS1 and VS2 comparative to the particle size distribution of the pure drug crystals has been illustrated in Figures 6–8.[19]

Phase solubility studies

The results of solubility study revealed that the spherical agglomerates (VS10.512 ± 0.041 mg/ml and VS2 0.579 ± 0.034 mg/ml) showed increased solubility as compared to the pure drug (0.084 ± 0.09 mg/ml). In addition, as the

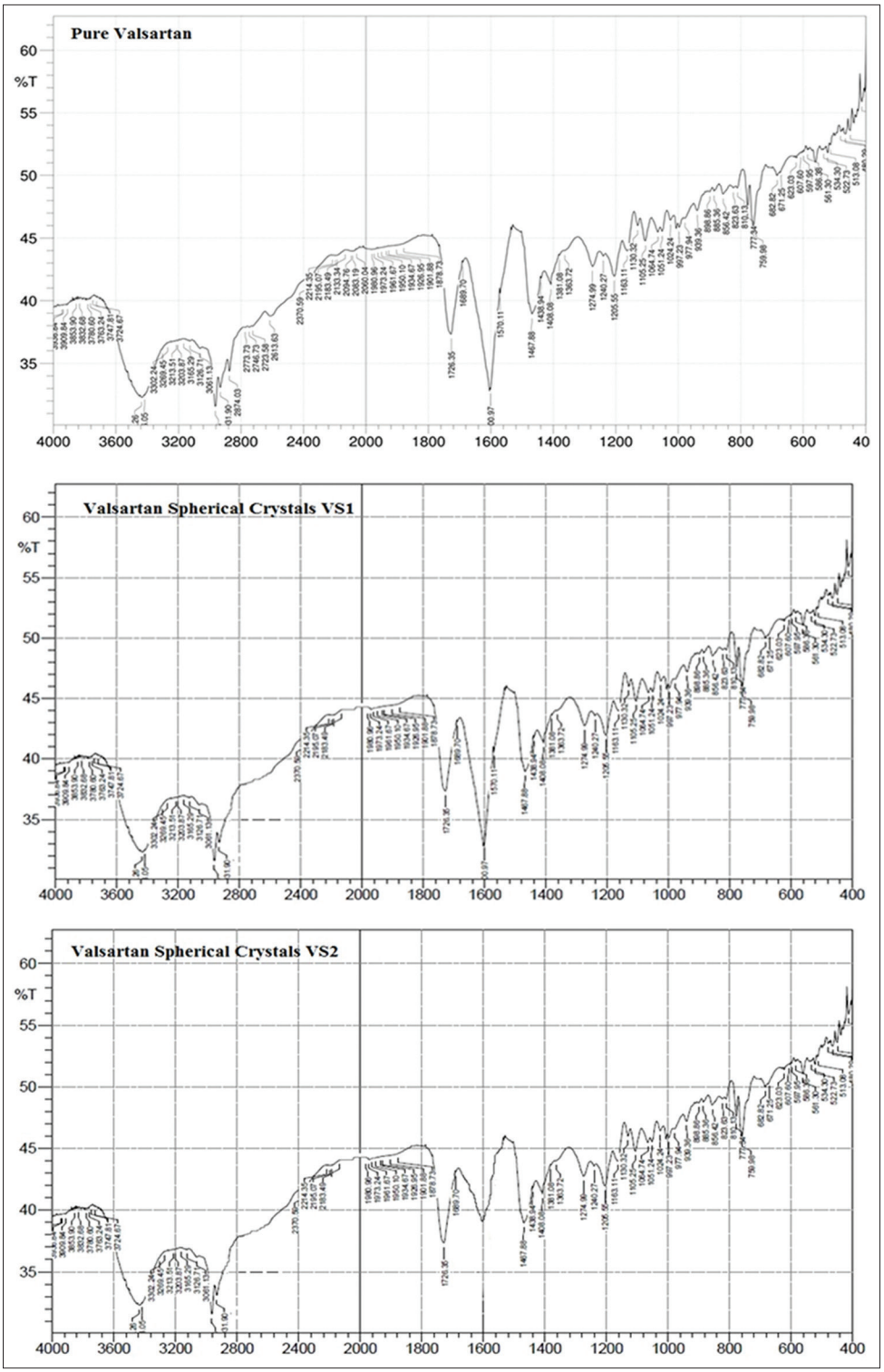

Figure 2: The fourier-transform infrared spectrum of valsartan spherical crystals batch VS1 and VS2

concentration of HPC was increased in the cocrystals, the solubility increased which may be due to the amorphization of the drug as suggested by the DSC and XRD studies.

Mechanical properties

Percent FI of valsartan spherical crystals was found to decrease with time as shown in Figure 9. As from Table 4, it is clear that VS2 batch has a higher value of C and lower value of K in comparison to VS1 batch, which may be attributed to higher surface strength and higher overall strength of the agglomerate and resistant to abrasion.[14,20]

Crushing strength determined for the spherical crystals was found to be 106.07 ± 4.19 g for VS1 and 110.55 ± 1.78 g for VS2. Higher crushing strength indicates the better handling

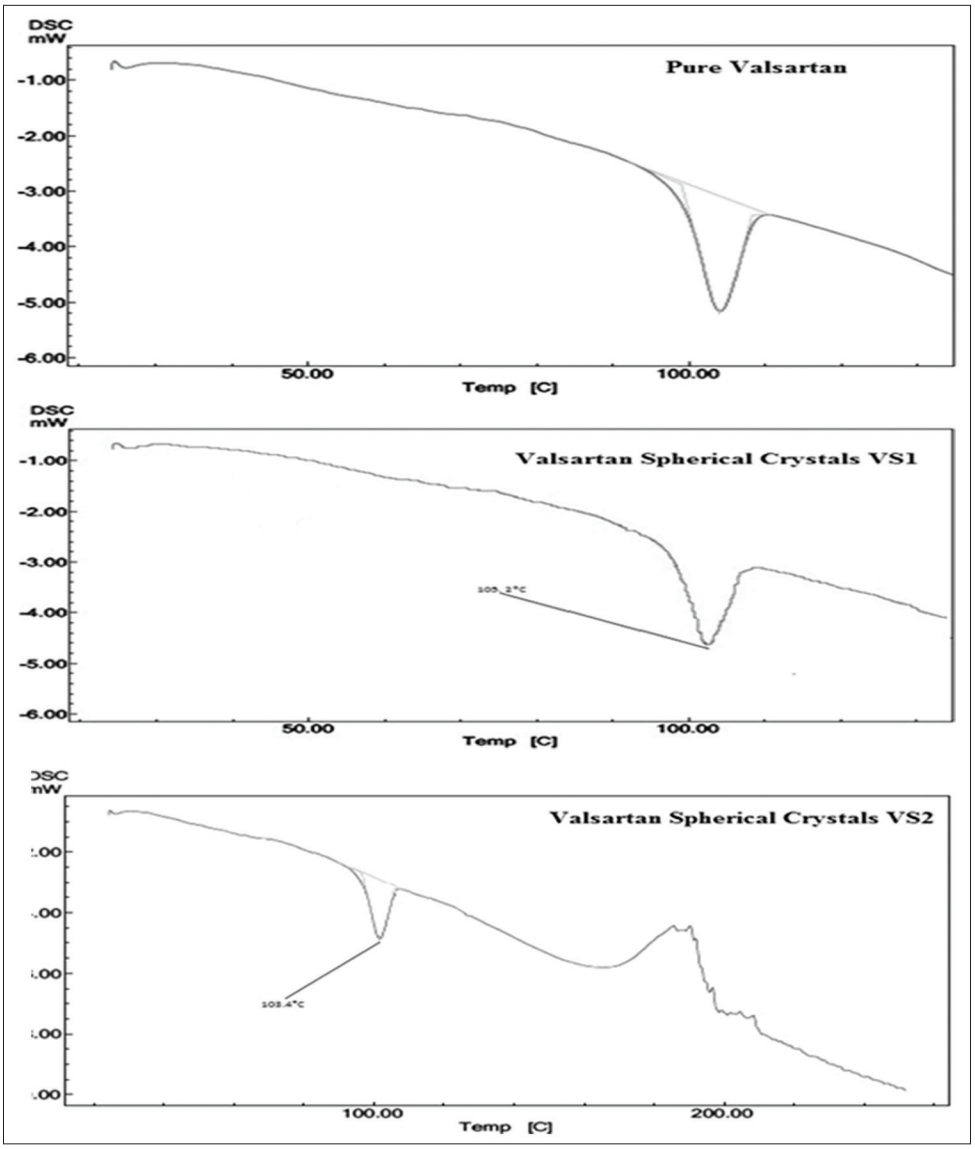

Figure 3: Differential scanning calorimetry thermograms of pure drug and spherical crystals

Table 4: Regression analysis of percent FI data of valsartan spherical crystals

Batch	Parameters		
	K	C	R
VS1	−1.391	51.79	0.953
VS2	−1.583	63.03	0.991

qualities of the crystals. As the polymer concentration was increased the crushing strength also increased, which can be attributed to greater binding ability of the excipients.[19]

In Heckel analysis as represented in Figure 10, more linearity of the curve for batch VS2 indicated greater plasticity than batch VS1 and pure valsartan crystals. From the data tabulated in Table 5, lower values P_y of VS2 batch indicated that it is softer in comparison to the pure drug crystal and batch VS1.

Similarly, the lower value of constant A represented that lower pressure was required for closer packing, fracturing texture and densifying the fractured particles. All the data suggest that agglomerates break at the lower pressure and new surfaces formed after plastic deformation yielded better compressible material.[13]

From Figure 11, higher values of tensile strength were observed with increasing compression pressure for spherical crystals of batch VS2 as compared to spherical crystals of batch VS1. It was also deduced that higher concentration of polymers added tensile strength to the agglomerates. The presence of HPC coating on valsartan at the intergranular contact points contributed to the bonding and strength of the agglomerates.[12]

For valsartan, Kawakita parameter was deduced by linear regression [Figure 12]. The linear region studied was between

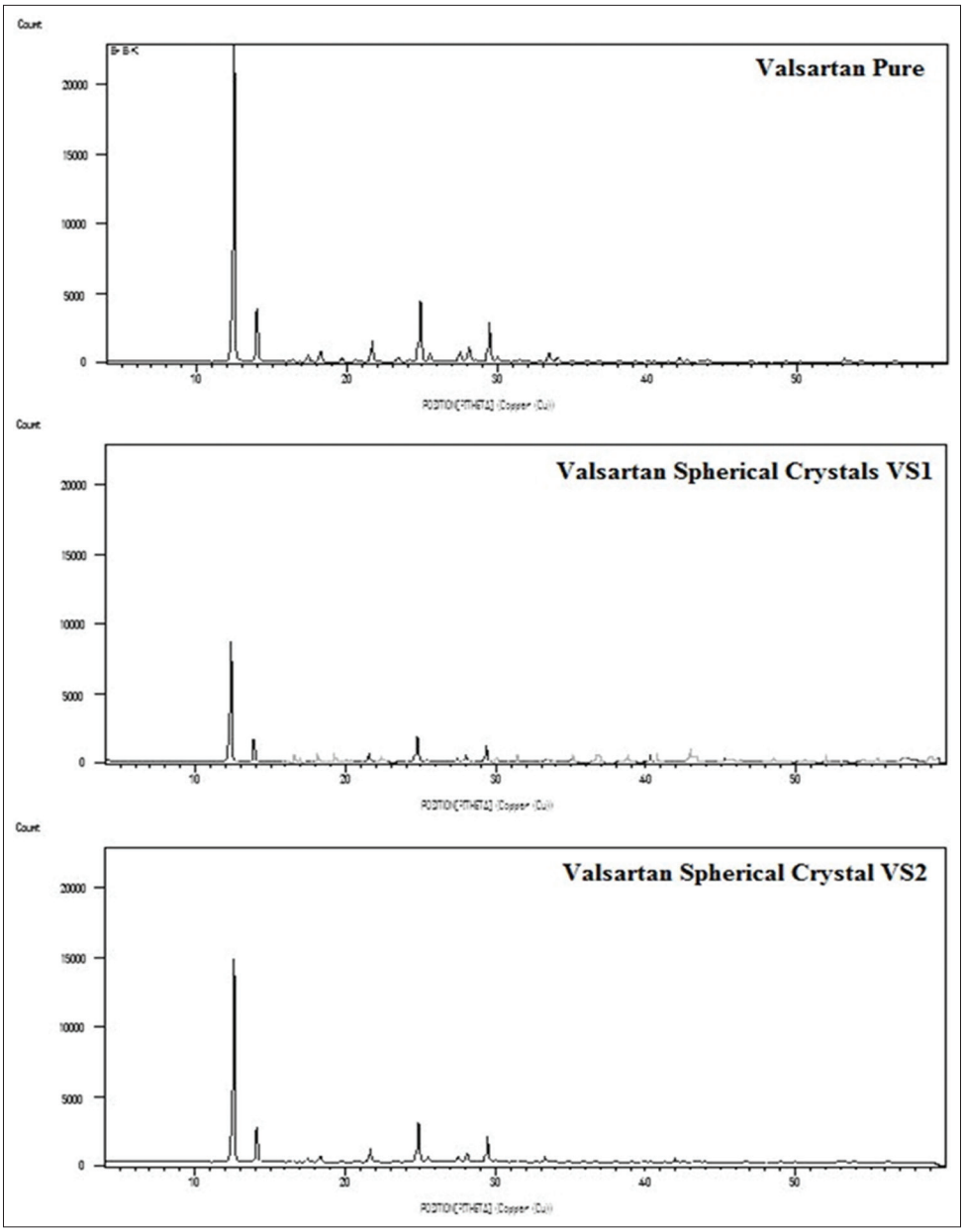

Figure 4: The X-ray diffraction scan of pure valsartan and spherical crystals

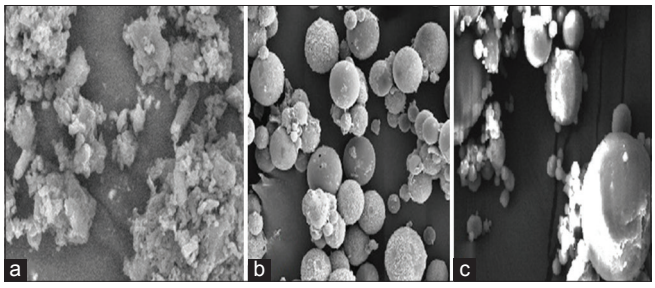

Figure 5: The scanning electron microscope photomicrographs of the (a) pure drug and (b-c) spherical crystals VS1 & VS2

0 and 250 taps. For spherical crystals, the values of "a" for agglomerates were significantly smaller than the value for pure valsartan crystals as shown in Table 6, which indicated toward the better packability and flowability of the agglomerates.

Value of parameter "b" was comparatively higher for the agglomerates than the pure crystal. It was evident that apparent packing velocity was high even without tapping due to their better flowability and packability.[21]

The value of the parameter "k" was greater for spherical crystals than the value that for pure valsartan crystals as shown in Table 7, which it can be implied that the agglomerates will show smooth flow from hopper thereby forming tablets of uniform weight.

From Figure 13, the elastic recovery of all prepared agglomerates was very small (>0.31%). Capping/lamination of the original coarse crystals occurred at compression pressures of 30 KN and above. At the same time, the elastic recovery of the pure drug was very high (>8.0%). Spherically

Table 5: Determination of Heckel parameters

Batch	Yield pressure (Py) KN	Constant (A)	Slope (K)	Yield strength	R^2
Valsartan Pure	83.33	3.046	0.012	27.78	0.885
VS1	52.63	1.354	0.019	17.54	0.745
VS2	27.77	0.961	0.036	9.25	0.970

Table 6: Packability constant a and b in Kawakita's equation for valsartan and its spherical crystals

Batch	a	b
Valsartan	0.511	0.0094
VS1	0.0605	0.0196
VS2	0.0581	0.0120

Table 7: Determination of *k* value for valsartan and its spherical crystals by Kuno equation

Batch	ρ_0	ρ_f	ρ_n	k
Valsartan	0.60	0.92	0.83	1.312
VS1	0.41	0.43	0.43	1.750
VS2	0.30	0.32	0.31	1.840

Table 8: Comparison of similarity of valsartan spherical crystals (Batches VS1 and VS2) with valsartan pure drug

Batch	Similarity Factor (f_2)
VS1	12.98
VS2	14.16

Table 9: Comparison of dissimilarity of valsartan spherical crystals batches (VS1 and VS2) with valsartan pure drug

Batch	Dissimilarity Factor (f_1)
VS1	97.15
VS2	90.75

agglomerated crystals of valsartan had significantly better tabletability than coarse crystals because of agglomerates making the crystals fracture easily under compression, this increased the points of contact among particles facilitated plastic flow, thereby increasing the contact area, and new high-energy surfaces appeared because of fracturing, which strongly bonded the particles.[22]

In vitro dissolution studies

In the case of valsartan pure drug, a cumulative drug release of 55.02 ± 1.36% was seen whereas the spherical crystals of batch VS1 had a cumulative drug release of 96.59 ± 2.07% and for batch VS2 it was 98.73 ± 1.23%. It may be concluded that as the solubility of the spherical crystals was greater than the

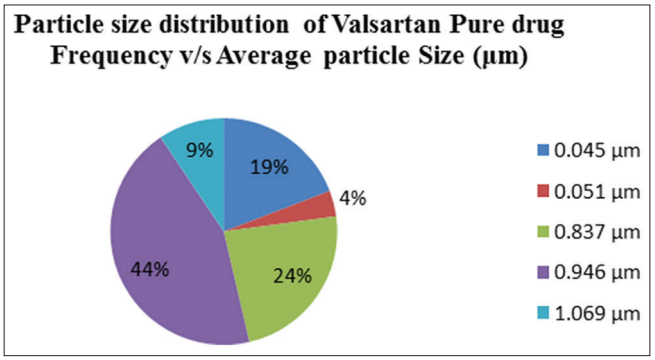

Figure 6: Particle size distribution of pure valsartan drug

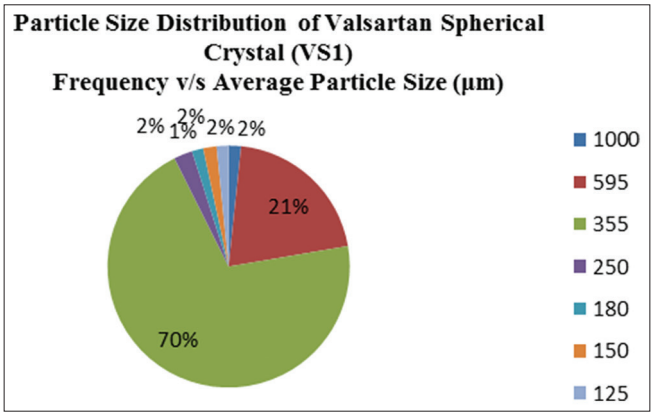

Figure 7: Particle size distribution of spherical crystals of batch VS1

pure drug, the dissolution profile was enhanced. Batch VS1 of spherical crystals had lower cumulative drug release than batch VS2 [Figure 14] which may be due to the role of polymer concentration. Higher the concentration of polymer, higher cumulative drug release. Furthermore, the reduced crystallinity may have attributed to the increased drug release.[13]

From Table 8 for batches, VS1 and VS2 similarity factor were around 12–14 indicating a very low similarity or a larger dissimilarity between the batches of spherical crystals and pure drug.

Difference factor having values >15 indicated a larger difference between the product and the reference group. For valsartan spherical crystals as shown in Table 9, the dissimilarity factor was near to 100, which indicated the difference between the pure drug and spherical crystals.[15]

From the above studies, it was clear that spherical crystals of batch VS2 had better performance than spherical crystals of

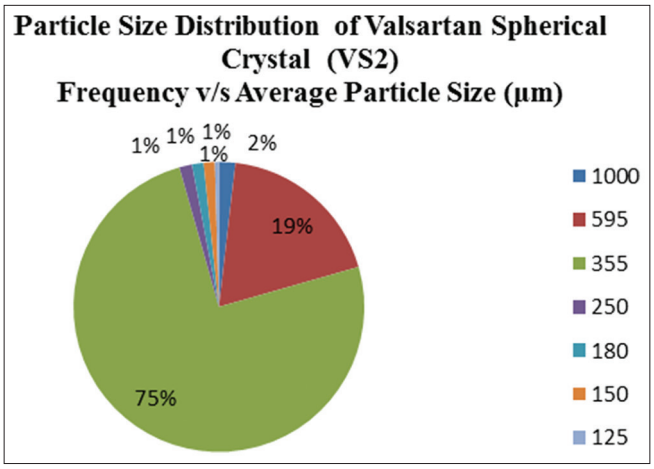

Figure 8: Particle size distribution of spherical crystals of batch VS2

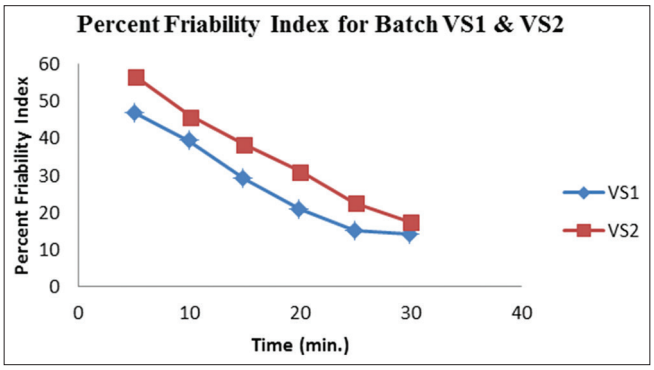

Figure 9: Percent friability index for spherical agglomerates

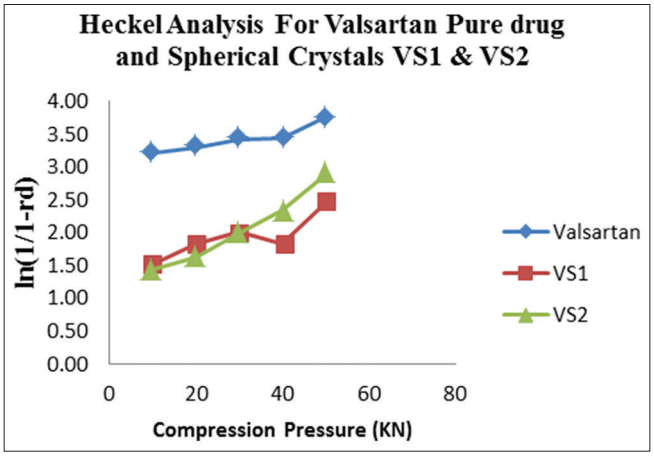

Figure 10: Heckel analysis for valsartan pure crystal and spherical crystals VS1 & VS2

Batch VS1. Hence, further animal studies and shelf life stability studies were performed on batch VS2 Spherical Crystals.

Pharmacokinetic studies

In vivo bioavailability studies were performed according to the protocol designed and approved by the IAEC. The

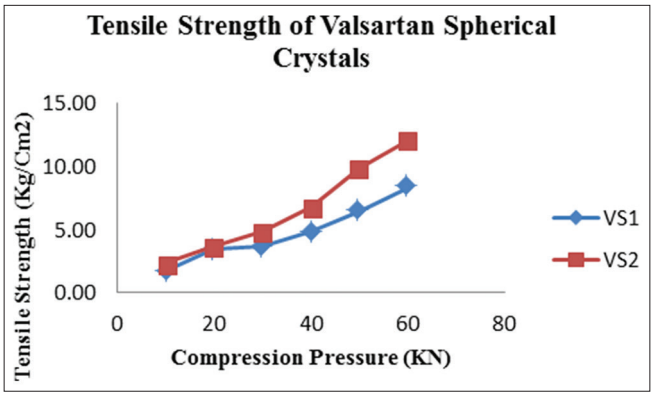

Figure 11: Tensile Strength and Compression Pressure Relation

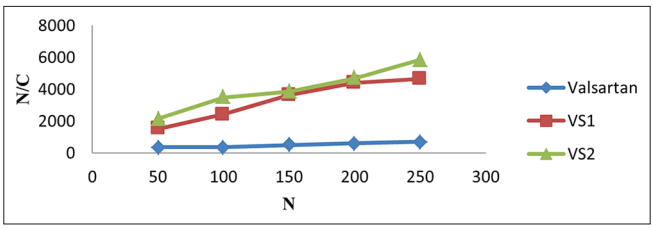

Figure 12: Compressibility studies of glipizde and its spherical crystals by Kawakita equation

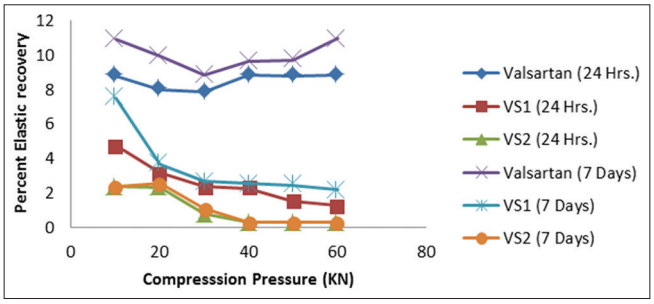

Figure 13: Percent elastic recovery for pure valsartan and its spherical crystals

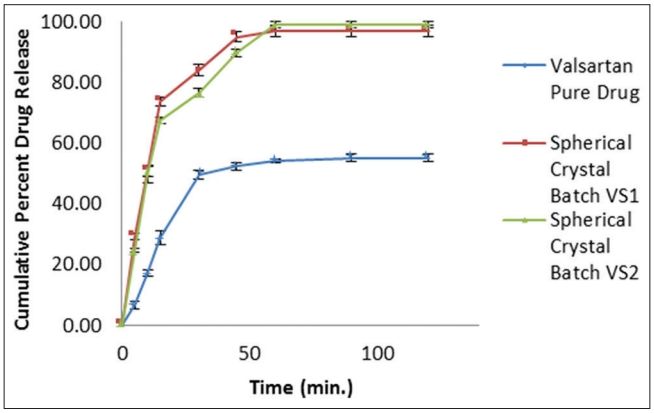

Figure 14: Cumulative percent drug release from valsartan and spherical crystal compacts

data obtained from the studies were further analyzed by an MS-Excel add-in PK Solver for the pharmacokinetic parameters such as C_{max}, $T_{1/2}$, T_{max}, and AUC.

Table 10: Pharmacokinetic parameters for valsartan in rats

Group	AUC (µg/ml*h)	C_{max} (µg/ml)	$t_{1/2}$
Standard (Marketed Tab 80 mg)	17.49±2.5*	1.91±0.100*	9.58±0.323
Test (Valsartan Spherical Crystals)	18.90±3.254**	2.12±0.399**	7.65±2.341
Control (Pure Valsartan Drug)	13.68±0.902	1.46±0.177	9.73±0.703

**Significantly different when compared to pure Valsartan (control group) (P<0.05) and marketed tablet (Standard group) (P<0.05).
*Significantly different from Pure drug (control group) (P<0.05)

C_{max} of spherical crystals (VS2) was greater than the marketed tablet and pure valsartan drug, which is self-explanatory of the higher rate of absorption from the spherical crystals [Figure 15]. From Table 10, AUC value was comparatively higher than the marketed tablet and pure drug for spherical crystals which suggests the higher extent of absorption of the drug. It may assert the improved solubility and dissolution rate of the spherical crystals of the valsartan.[7]

Stability studies

The accelerated stability studies for the batch of the optimized spherical crystals were carried out in accordance with ICH guidelines at 40 ± 2°C and 75 ± 5% RH for a period of 6 months and results were summarized in Table 11, no major changes during the storage of the spherical crystals were observed.[17]

Table 11: Stability studies of the optimized batches of spherical crystals of valsartan

Formulation code	0 Days		30 days		60 Days		90 Days		180 Days	
	Percent drug content	Cumulative percent drug release (at 90 min.)	Percent drug content	Cumulative percent drug release (at 90 min.)	Percent drug content	Cumulative percent drug release (at 90 min.)	Percent drug content	Cumulative percent drug release (at 90 min.)	Percent drug content	Cumulative percent drug release (at 90 min.)
VS2	95.26±0.99	98.73±2.22	94.21±1.2	98.23±1.1	92.33±1.0	98.45±1.0	92.20±1.10	97.50±1.1	91.20±1.0	97.65±1.0

CONCLUSION

Spherical crystallization techniques comprise crystallization and agglomeration of particles in a single step. Review of literature shows that spherical crystallization not only modifies crystal habit but also brings changes in the physicochemical parameters such as solubility, dissolution rate, and flow property of the active pharmaceutical ingredients.

Valsartan is an anti-hypertensive drug having limited bioavailability due to its low solubility in the aqueous medium and is wet granulated for the manufacture of a tablet as the crystals have an irregular shape with poor flow.

For the preparation of spherical crystals, valsartan was dissolved in N, N-dimethylformamide and poured into an aqueous solution of HPC in which talc has been previously dispersed. DCM was used as bridging liquid. The mixtures were subjected to the different modes of addition of bridging liquid, agitation speed, time, and temperature. The concentration of polymer was taken in three ratios. The

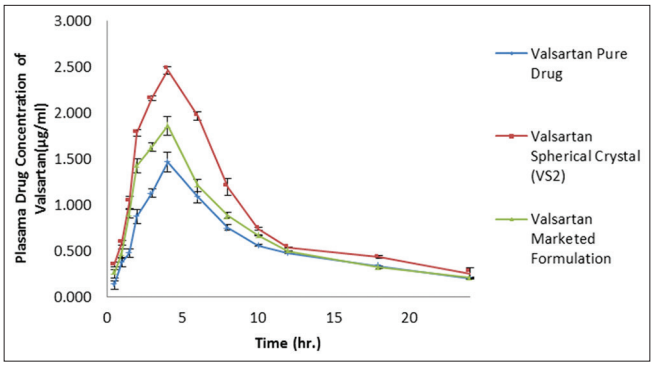

Figure 15: Plasma drug concentration curves for valsartan pure drug (control), marketed preparation (standard), and spherical crystal (VS2) (Test)

spherical crystals obtained were subjected to parameters such as solid-state characterization, flow property, micrometric properties, compression analysis, solubility, *in vitro* dissolution studies, and *in vivo* pharmacokinetic studies. For obtaining an optimized batch of spherical crystals, polymer concentration was kept at 0.5%. The crystallization system was agitated at 600 rpm for 15 min at 5 ± 2°C.

Spherical crystals obtained were characterized by FT-IR, DSC, XRD, and SEM for their conformity with the original molecular arrangement of the pure drugs. Spherical crystals of valsartan had a good percentage yield and drug content.

Spherical crystals obtained had higher compressibility, compactibility, and better flowability. The solubility of the spherical crystals valsartan showed an increase of 120%–175%. The effect of increased solubility was evident on the *in vitro* drug release and pharmacokinetic data. The spherical crystals had higher C_{max} values with lower $t_{1/2}$ and greater AUC, indicating that the drug from spherical crystals has been absorbed in greater extent in comparison to the pure drug.

Therefore, it can be concluded that spherical crystals of valsartan prepared by crystallo-co-agglomeration method can be used for scale-up and can be successfully used as directly compressible material.

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Source of Support: Nil. **Conflict of Interest:** None declared.