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Formulation of Crystallo-Co-Agglomerates of Valsartan: Evaluation of Effect of Polymers on Drug Release

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Abstract : The aim of the present work was to develop spherical agglomerates of Valsartan by crystallo-co-agglomeration technique. Alcohol-chloroform-water system was used as crystallization medium. PVP K30, PEG 4000 and Sodium Alginate were used as carriers. Alcohol acted as a good solvent for valsartan, chloroform as bridging liquid and aqueous phase as non-solvent.The compatibility study was done by DSC, FTIR and surface morphology was studied by SEM. The growth of particle size and the spherical form of the agglomerates resulted in formation of products with good flow and packing properties. Drug release studies were performed in phosphate buffer pH 6.8 for 25 min. The dissolution data demonstrated that the rate of drug release was dependent upon the nature and concentration of polymer used in the formulation. FTIR and DSC studies showed that valsartan particles, crystallized in the presence of PVP K30, PEG 4000 and Sodium Alginate showed compatibility with carriers. Formulation P1 containing polymer PVP K30 in the ratio 1:0.50 was selected as an optimized formulation which showed better results with respect to percent drug release (106.72±0.46), percent yield (85.66±0.04%), MDT (4.76 hrs) and % DE (82.83%) when compared to other formulations.
Key words: Valsartan, Spherical agglomerates, Crystallo-co-agglomeration, PVP K30, Sodium Alginate, PEG 4000.

Introduction:

Recently there have been greater advancements in powder technology and different attempts are made to design primary and secondary particles of pharmaceutical substances for several applications. Enlargement of particle size is an important process in manufacturing of tablets and is used to impart some degree of functionality to particles such as improvement in flowability, micromeritic, compression and compactability properties. Different techniques for enlargement of particle size are important tools in modifying primary and secondary properties of pharmaceutical substances. Now-a-days several new techniques combining granulation and crystallization are being developed to improve particle properties like extrusion-spheronisation, melt solidification, melt granulation, melt extrusion and spherical agglomeration.[1] These techniques are advantageous due to less number of unit operations and economic in terms of processing cost and depend on the desired properties of the enlarged particle and the physicochemical properties of the drug and excipients.[1]

Spherical agglomeration can be defined as "a novel particle engineering technique by which agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form".[2,3]This technique can also be exploited to increase solubility, dissolution and hence bioavailability of poorly soluble drugs.[4,5] spherical agglomeration employs three solvents: one is the drug dissolution medium i.e. good solvent; another is a medium which partially dissolves the drug and have wetting

property i.e. bridging liquid; and the last one is immiscible with the drug substance i.e. bad solvent.[6] The spherical agglomeration has been applied to several drugs, and it has been found that the product properties are quite sensitive to the amount of the bridging liquid. As the amount of bridging liquid varied, there is a wider size distribution of crystals obtained, So the amount of bridging liquid is the critical process parameter in agglomeration process.

The two most commonly used techniques of spherical agglomeration are wet spherical agglomeration method (WSA), quasi-emulsion solvent diffusion method (QESD, Transient emulsion).[7,8] But there are two extensions of these techniques, ammonia diffusion system (ADS) and crystal-co-agglomeration technique (CCA).[9,10]

CCA is a novel technique developed by Kadam *et al.* to overcome the limitations of spherical crystallization, known as CCA.[11]It is a modification of the spherical crystallization technique and used for size enlargement of all, low dose, high dose, poorly compressible drugs and combination of drugs with or without diluents. In this technique drug is directly crystallized and agglomerated in combination with an excipient or with another drug with help of bridging liquid. Excipient or drug may or may not be crystallized in this system[12]. An excipient which is used in this technique should have affinity toward the bridging liquid.

In the present study, the agglomerates of valsartan was carried out in the presence of hydrophilic polymers such as PVP K30, PEG 400 and Sodium alginate. The aim of this study was to investigate the micromeritic and dissolution properties of valsartan agglomerates in presence of above mentioned polymers.

Materials:

Valsartan was obtained as a gift sample from Watson Pharma Pvt Ltd, Mumbai, India. PVP K 30 was procured from HIMEDIA Laboratories Pvt. Ltd., Mumbai, India. PEG 4000, Sodium alginate and Choroform was procured from SD fine chemicals, Mumbai, India. All other chemicals and reagents used were of analytical grade.

Experimental:

Standard plot of valsartan was obtained in phosphate buffer pH 6.8

Preparation of Crystallo-co-agglomerates:

Preparation of valsartan agglomerates by using PVP K30, PEG 4000 and Sodium alginate:

Valsartan agglomerates were prepared using a three solvent system comprising alcohol: chloroform: water (good solvent, bridging liquid and bad solvent, respectively). In a vessel, PVP K30 was dissolved in sufficient amount of distilled water. Valsartan was dissolved in alcohol maintained at 50^{o}C. The latter dispersion was added immediately to the dispersion containing dissolved polymer under constant stirring conditions (600 rpm) kept at room temperature. The stirring was continued for 20 min and bridging liquid chloroform was added drop wise to obtain agglomerates, which were then filtered and dried overnight. Three batches were prepared by changing the concentration of PVP K30 (1:05, 1:0.6, and 1:0.7). The same procedure was followed for other carriers like PEG 4000 and Sodium alginate.

Table 1: Composition (gm) of valsartan-polymer agglomerates

Formulation	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**
Valsartan	1	1	1	1	1	1	1	1	1
PVPK30	0.20	0.16	0.14	-	-	-	-	-	-
PEG4000	-	-	-	0.20	0.16	0.14	-	-	-
Sodiumalginate	-	-	-	-	-	-	0.20	0.16	0.14

Quantities of all ingredients are mentioned in gram units.

Evaluation of prepared agglomerates:

Solubility studies:

To evaluate the solubility of valsartan and its agglomerates solubility, measurements were conducted. Excess amount drug or agglomerates was added to 50 ml volumetric flask containing distilled water. The system was agitated on a rotary shaker for 48hr at 100 rpm maintained at room temperature and filtered. The filtrate was suitably diluted and analyzed at 250 nm by using UV visible spectrophotometer (UV-1601, Shimadzu, Japan).

Micromeritic parameters:

A. Bulk density (D_b):

It is the ratio of weight of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and studies were conducted in triplicate and are given by,

$$D_b = {}^{M}/_{V_o}$$

Where, D_b = Bulk density (gm/ml)
M = mass of powder (g)
V_o = bulk volume of powder (ml)

B. Tapped density (D_t):

Accurately weighed sample of 10 gm was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and studies were conducted in triplicate and are given by,

$$D_t = {}^{M}/_{V_t}$$

Where, D_t = Tapped density (gm/ml)
M = mass of powder (g)
V_t = tapped volume of powder (ml)

C. Compressibility index (CI):

The compressibility of the powder was determined by the Carr's compressibility index and studies were conducted in triplicate and are given by,

$$CI(\%) = \left[\frac{(D_t - D_b)}{D_t}\right] \times 100$$

D. Hausner ratio:

Hausner ratio is used for predicting powder flow characteristics and studies were conducted in triplicate and are given by,

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

E. Angle of repose (θ):

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel until

the apex of the conical pile just touches the tip of funnel and studies were conducted in triplicate and are given by,

$$\theta = tan^{-1}\left(h/r\right)$$

Where,
θ = angle of repose
h = height of pile,
r = radius of the base of the pile.

Drug content:

An accurately weighed quantity of agglomerates equivalent to 100 mg of valsartan was taken in a 100 ml volumetric flask. The drug was then extracted by using phosphate buffer pH 6.8 by subjecting to continuous shaking on a rotary shaker for 4 h. Valsartan in the extracted fluid was analyzed at 250 nm by using UV-visible spectrophotometer (UV-1601, Shimadzu, Japan) against phosphate buffer pH 6.8 solution as blank and studies were conducted in triplicates.

In-vitrodrug release studies:

The in-vitrodrug dissolution study was performed using eight station dissolution test apparatus (Dissolution tester (USP) TDT-08L, Electrolab, India) with a paddle speed of 50 rpm. Dissolution medium consisted of 900 ml of phosphate buffer pH 6.8 maintained at 37 ± 0.5º C. At a predetermined time intervals an aliquot was withdrawn and replenished with fresh medium. Amount of drug in each aliquot was assayed on a UV-Spectrophotometer(UV-1601, Shimadzu, Japan) at 250 nm using phosphate buffer pH 6.8 as blank. All the trials were conducted in triplicate and the average (± S.D) reading was noted.

Model independent kinetics:

A. Dissolution efficiency:

Dissolution efficiency is used to translate the profile difference into a single value. Dissolution efficiency was calculated by using following equation.

$$DE\ \% = \frac{\int_0^t y\ dt}{y_{100}} t \times 100$$

Where, y is the drug percent dissolved at time t.

B. Mean dissolution time:

Mean dissolution time represents the mean time for drug molecules to completely dissolve. It is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of the polymer. MDT was calculated by using the following equation.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Where *'i'* is the dissolution sample number, *'n'* is the number of dissolution sample time, *'tmid'* is the time at the midpoint between *'i'* and *'i-1'*, and *'ΔM'* is the amount of drug dissolved between *'i'* and *'i-1'*.

FT-IR Spectrophotometric analysis:

The samples of drug, polymer and their mixture were prepared in the form of KBr pellets and subjected for scanning from 4000 cm^{-1} to 400 cm^{-1} using FT-IR spectrophotometer (FT-IR-8400, Shimadzu, Japan).

Differential scanning calorimetric analysis:

Approximately 2 mg samples of drug, polymer and their mixture was taken in aluminum pan, sealed with aluminum cap and kept under nitrogen purging (atmosphere). The samples were scanned from 0-400°C with the scanning rate of 10°C rise/min using differential scanning calorimeter (DSC-60, Shimadzu, Japan).

Scanning Electron microscopy:

The shape and surface topography of agglomerates were observed through a scanning electron microscope (Joel- LV-5600, USA).

Results and Discussion

Calibration curve of valsartan:

The calibration curve ofValsartan was developed in the range of 5-30µg/ml at wavelength 250nm. Good linearity with regression coefficient of 0.998 (r^2 value) was observed.

Formulation development:

Valsartan was crystallized from alcohol-chloroform-water and agglomerated with hydrophilic polymers such as PVP K30, PEG 4000 and Sodium Alginate. Valsartan is freely soluble in alcohol (good solvent), but practically insoluble in water (non-solvent). Also it is soluble in chloroform (bridging liquid) which is immiscible with water. Hence, this solvent system was selected for the present study. In this process, crystallization of drug was performed by the addition of drug solution to the anti-solvent phase (water). The alcohol solution (maintained at 50°C) containing drug was added immediately to the aqueous dispersion containing hydrophilic polymers viz. PVP K30, PEG 4000, Sodium Alginate and quasi-emulsified droplets of drug solution were produced. The addition of bridging liquid (chloroform) promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals were formed by coalescence of these dispersed crystals.

Solubility studies:

The results for solubility studies of pure Valsartan and drug-polymer agglomerates were shown in table no 2. The solubility of Valsartan in distilled water was found to be 0.09±0.06 mg/ml.The solubility of Valsartan from agglomerates prepared by using PVP K30 in drug polymer ratio (1:0.5, 1:0.6, 1:0.7) was in the range of 0.309±0.002 to 0.449±0.004 mg/ml. In case of agglomerates prepared by using PEG 4000, the solubility of Valsartan was in the range of 0.203±0.005 to 0.312±0.004 mg/ml and from the agglomerates prepared by using Sodium Alginate, the solubility of Valsartan was in the range of 0.293±0.004 to 0.316±0.008 mg/ml. In all the above cases the solubility progressively improved with increasing the polymer proportion in the agglomerates, P1 showing the highest solubility of 0.449±0.004 mg/ml.

Table 2: solubility studies of pure valsartan and drug-polymer agglomerates.

Formulation	Solubility(mg/ml)
Valsartan0.09±0.06	
P1	0.449±0.004
P2	0.309±0.002
P3	0.315±0.003
P4	0.312±0.004
P5	0.203±0.005
P6	0.258±0.030
P7	0.316±0.008
P8	0.309±0.010
P9	0.293±0.004

Values are mean ±SD, n=3

Micromeritic properties:

The results for micromeretic properties of pure Valsartan and drug agglomerates were shown in Table 3. The agglomerates showed improvement in flow property when compared to pure Valsartan. Among different agglomerates prepared, formulation P1 showed maximum flowability as evident by low values of angle of repose (21.80±0.28^0), Hausner's ratio (1.17±0.17) and Carr's index (15.19±1.00 %).

Table 3: Micromeritics of pure valsartan and drug-polymer agglomerates.

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr'sindex (%)	Hausner ratio	Angle of repose (θ)
Valsartan	0.201±0.02	0.30±0.013	6.66±3.56	1.50±0.03	38.65±1.65
P1	0.664±0.07	0.783±0.11	15.19±1.00	1.17±0.17	21.80±0.28
P2	0.662±0.01	0.815±0.26	18.77±0.42	1.23±0.043	23.19±0.69
P3	0.665±0.05	0.835±0.03	20.35±0.34	1.25±0.32	26.56±0.47
P4	0.650±0.16	0.883±0.03	26.38±0.11	1.35±0.12	26.56±1.11
P5	0.649±0.04	0.863±0.14	24.79±0.34	1.32±0.28	21.80±0.19
P6	0.657±0.02	0.836±0.10	21.41±0.43	1.27±0.01	24.77±0.84
P7	0.664±0.07	0.80±0.11	17.00±0.01	1.20±0.25	30.45±0.25
P8	0.662±0.01	0.836±0.12	20.81±0.30	1.26±0.24	33.66±0.12
P9	0.666±0.05	0.856±0.13	22.19±0.06	1.28±0.25	30.96±0.19

Valuesare mean±SD,n=3

Drug content and percent yield:

The percentage drug content of all the formulations (agglomerates) in phosphate buffer pH 6.8 varied from 97.5±0.01 to 101.3±0.06 as shown in Table 4. This showed that there was uniform distribution of drug throughout the batch**.**

The percent yield of agglomerates prepared by using PVP K30 was more for the formulations P1 followed by P2 and P3 which varied from 84.83±0.7 to 85.66±0.04 %.

Table 4:Drugcontent(%)and percentyield ofvalsartan-polymeragglomerates.

Formulation	P1	P2	P3	P4	P5	P6	P7	P8	P9
Drug content(%)	99.5± 0.01	100± 0.05	101.3± 0.06	99.8± 0.02	99.4± 0.86	97.5± 0.01	100± 0.06	100.3± 0.10	98.8± 0.6
%yield	85.66 ±0.04	81.83 ±0.07	84.83 ±0.7	83.01± 0.02	80.41± 0.01	78.5± 0.03	80.16± 0.05	77.83± 0.03	78.33± 0.02

Values are mean±SD,n=3

In-vitro dissolution studies

Dissolution behavior of pure Valsartan and agglomerates was studied using phosphate buffer pH 6.8 as dissolution medium **(table 5-7 and figure 1-3)**. The amount of pure Valsartan dissolved in phosphate buffer pH 6.8 was 40.43±0.58 % at 25 min.

Among the agglomerates prepared by using PVP K30, formulations P1 showed maximum drug release followed by P2 and P3 which varied from 100.72±0.46 to 106.72±0.48 % at 25 min. In case of agglomerates prepared by using PEG 4000, showed drug release which varied from 63.92±0.50 to 67.14±0.47 % and from the agglomerates prepared by using Sodium Alginate, showed drug release which varied from 93.11±0.33 to 98.85±0.47 % at 25 min.

From this it can be seen that as the concentration of polymers increases, drug release also increases. This is true for all the formulation containing PVPK30, PEG4000 and Sodium Alginate.

Table 5:Comparison of in-vitro dissolution profile data of valsartan in pure form and P1, P2 &P3.

Time(min)	Cumulative	Released		
	Valsartan	P1	P2	P3
0	0	0	0	0
5	10.55±1.27	88.46±0.84	85.56±0.43	83.57±0.23
10	20.22±0.17	91.06±1.67	88.90±0.74	88.90±2.16
15	28.99±0.36	93.68±0.45	92.88±0.89	92.98±0.72
20	36.41±0.51	99.13±0.44	97.78±0.78	97.78±0.52
25	40.43±0.58	106.2±0.46	103.33±0.51	101.54±0.48

Values are mean ±SD, n=3

Table 6:Comparison of in-vitro dissolution profile data of valsartan in pure form and P4, P5 &P6.

Time(min)	Cumulative	Released		
	Valsartan	P4	P5	P6
0	0	0	0	0
5	10.55±1.27	54.06±0.46	52.61±0.47	49.14±0.47
10	20.22±0.17	57.81±0.47	56.01±0.54	55.35±0.18
15	28.99±0.36	62.29±0.70	61.86±0.24	59.93±0.71
20	36.41±0.51	63.34±0.23	62.65±0.32	61.37±0.25
25	40.43±0.58	67.14±0.47	64.59±0.48	63.92±0.50

Values are mean ±SD, n=3

Table 7:Comparison of in-vitro dissolution profile data of valsartan in pure form and P7, P8 &P9.

Time(min)	Cumulative	Released		
	Valsartan	P7	P8	P9
0	0	0	0	0
5	10.55±1.27	74.57±0.23	72.41±047	69.71±0.46
10	20.22±0.17	84.00±0.61	81.52±0.23	78.30±0.46
15	28.99±0.36	91.53±0.46	89.89±0.46	83.25±0.23
20	36.41±0.51	96.74±0.71	94.44±0.13	89.63±0.23
25	40.43±0.58	98.85±0.47	96.44±0.44	93.11±0.33

Values are mean ±SD, n=3

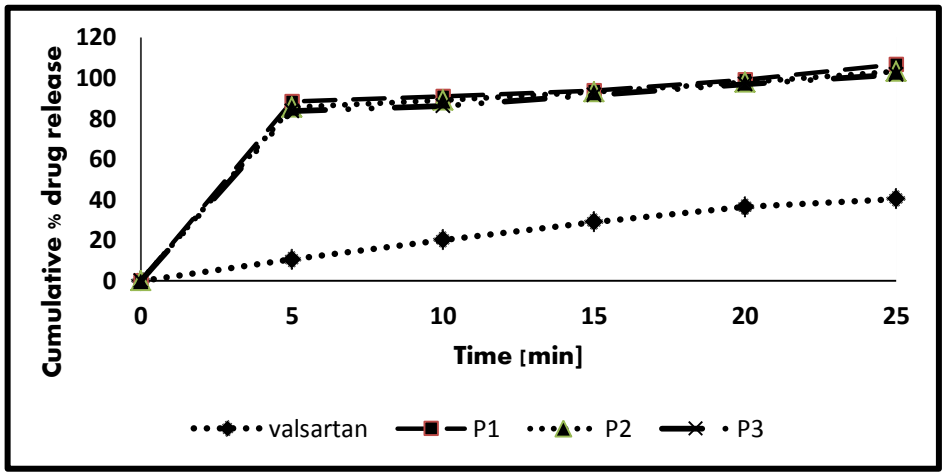

Figure 1: Comparison of in-vitro dissolution profile data of valsartan in pure form and P1, P2 & P3.

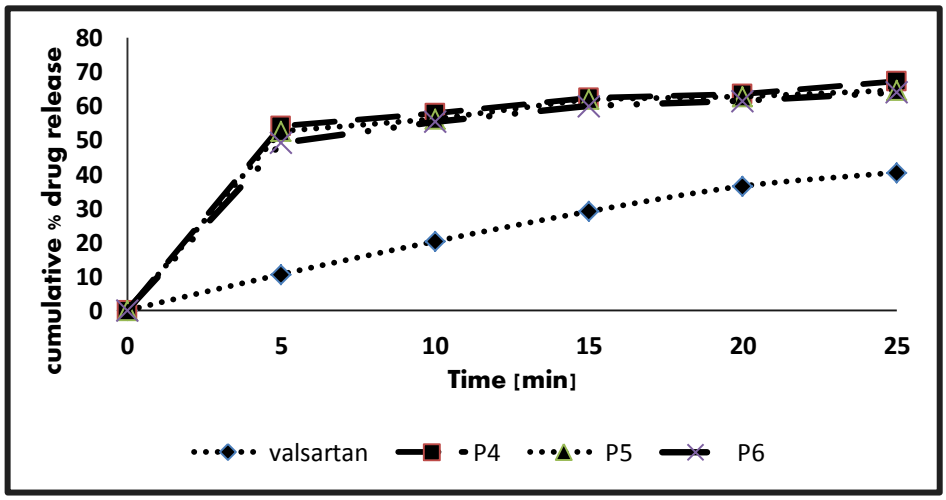

Figure 2: Comparison of in-vitro dissolution profile data of valsartan in pure form and P4, P5 & P6.

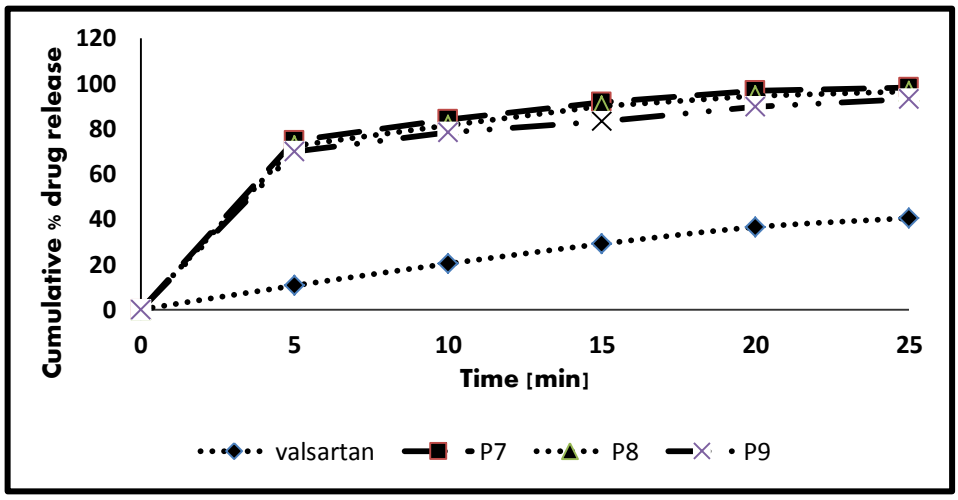

Figure 3: Comparison of in-vitro dissolution profile data of valsartan in pure form and P7, P8 & P9.

Table 8:Model Independent Kinetics

Formulation	MDT (min)		$\%DE_{25min}$
P1	4.76		82.83
P2	4.82		80.69
P3	4.88		80.47
P4	4.81		80.74
P5	4.45		82.19
P6	4.83		80.64
P7	4.81		80.74
P8	4.96		80.12
P9	5.26		78.92

Model independent kinetics:

MDT and % DE was determined for the all the formulations (table 8) and the values varied between 4.45 to 5.26 min and 78.92 to 82.83 %. Formulation, P1 was selected as an optimized formulation which showed better results with respect to percent yield, percent drug release, MDT and %DE when compared to other formulations.

Characterization of Valsartan-polymer agglomerates:

Fourier Transform Infrared Spectroscopy

Infrared spectrum of pure Valsartan is shown in figure 4. The characteristic absorption peaks of Valsartan were obtained at 3779.56 cm^{-1} due to Secondary Amine N-H stretch, 2982.54 cm^{-1} due to aromatic C-H stretch, 1714.72 cm^{-1} due to C=O stretch, 1596.71 cm^{-1} due to C⎓C (S) stretch and at 1055.95 cm^{-1} due to C-N stretch.

By comparing the FTIR spectrum of valsartan with the drug-polymer agglomerates **(Figure 4-7)** it was concluded that all the characteristic absorption bands of Valsartan were retained, hence the results indicated there was no chemical interaction between Valsartan and hydrophilic carriers.

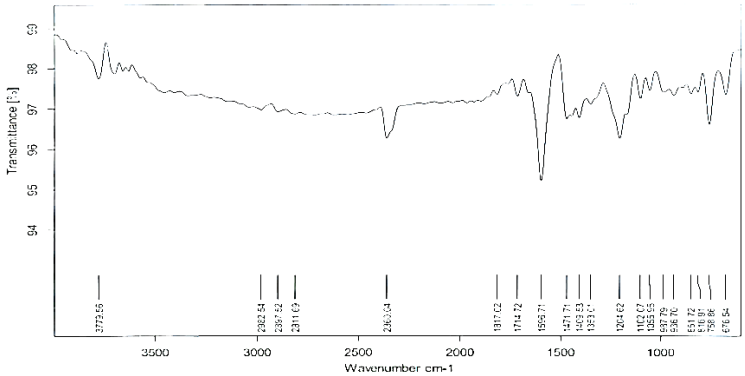

Figure 4: FTIR spectra of pure valsartan

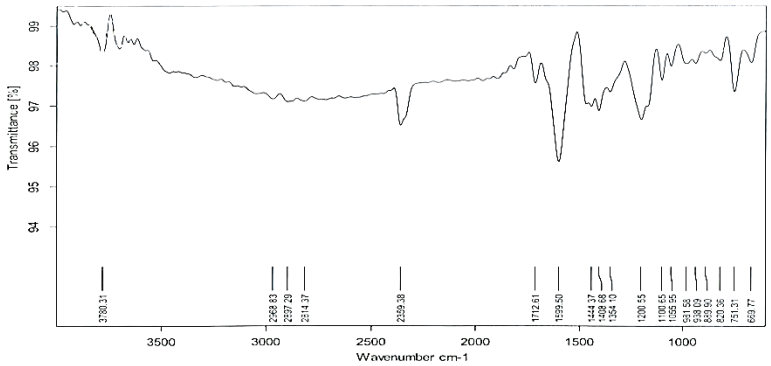

Figure 5: FTIR spectra of P1

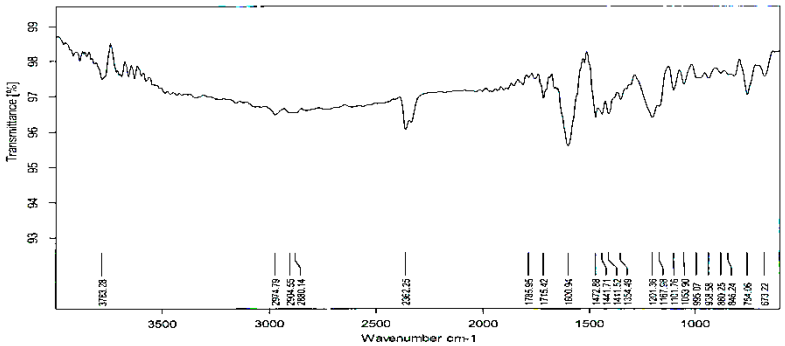

Figure 6: FTIR spectra of P4

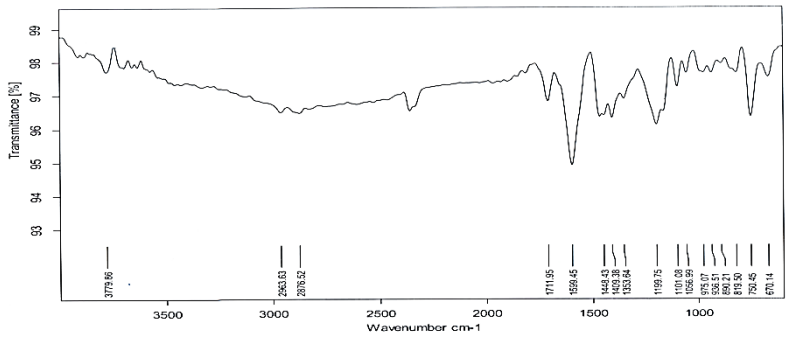

Figure 7: FTIR spectra of P7

Differential Scanning Colorimetry

DSC was used to assess the thermal behaviour of the drug (Valsartan) and its drug-polymer agglomerates. From the DSC results (figure 8-11), a considerable reduction in crystallinity of Valsartan was observed in the prepared drug polymer agglomerates. This indicated that valsartan was converted into amorphous form and uniformly dispersed at molecular level.

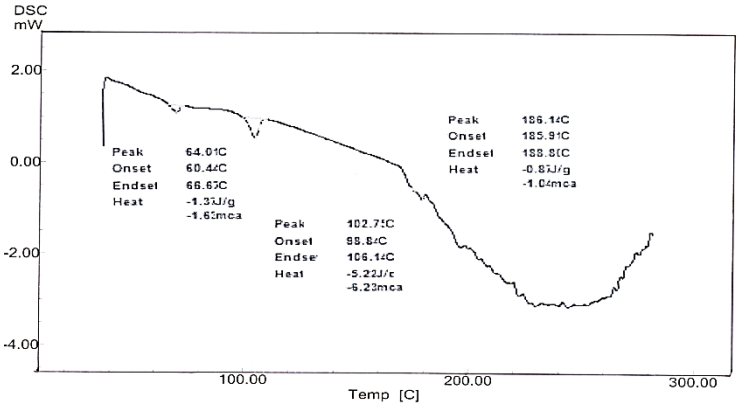

Figure 8: DSC thermogram of pure valsartan

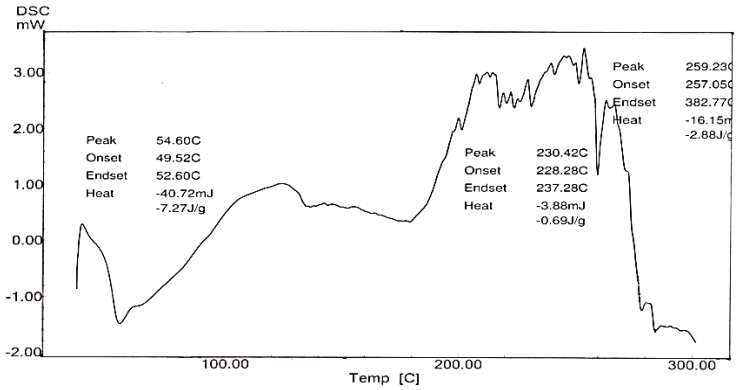

Figure 9: DSC thermogram of formulation P1

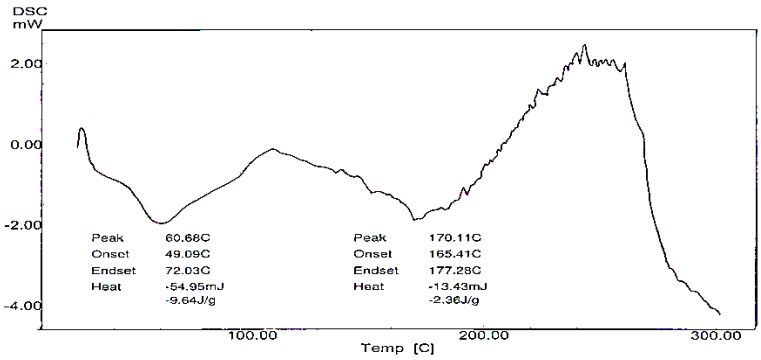

Figure 10: DSC thermogram of formulation P4

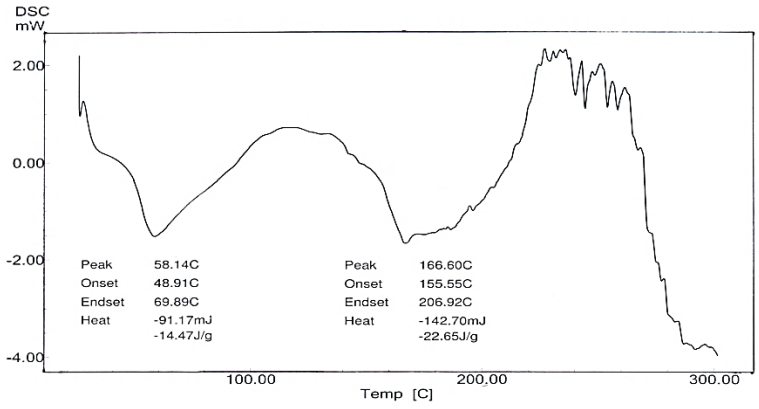

Figure 11: DSC thermogram of formulation P7

Scanning Electron Microscopy (SEM):

SEM studies of drug-polymer agglomerates [figure 12(A1, A2 & A3] indicated that the agglomerates prepared were spherical in shape with rough surface.

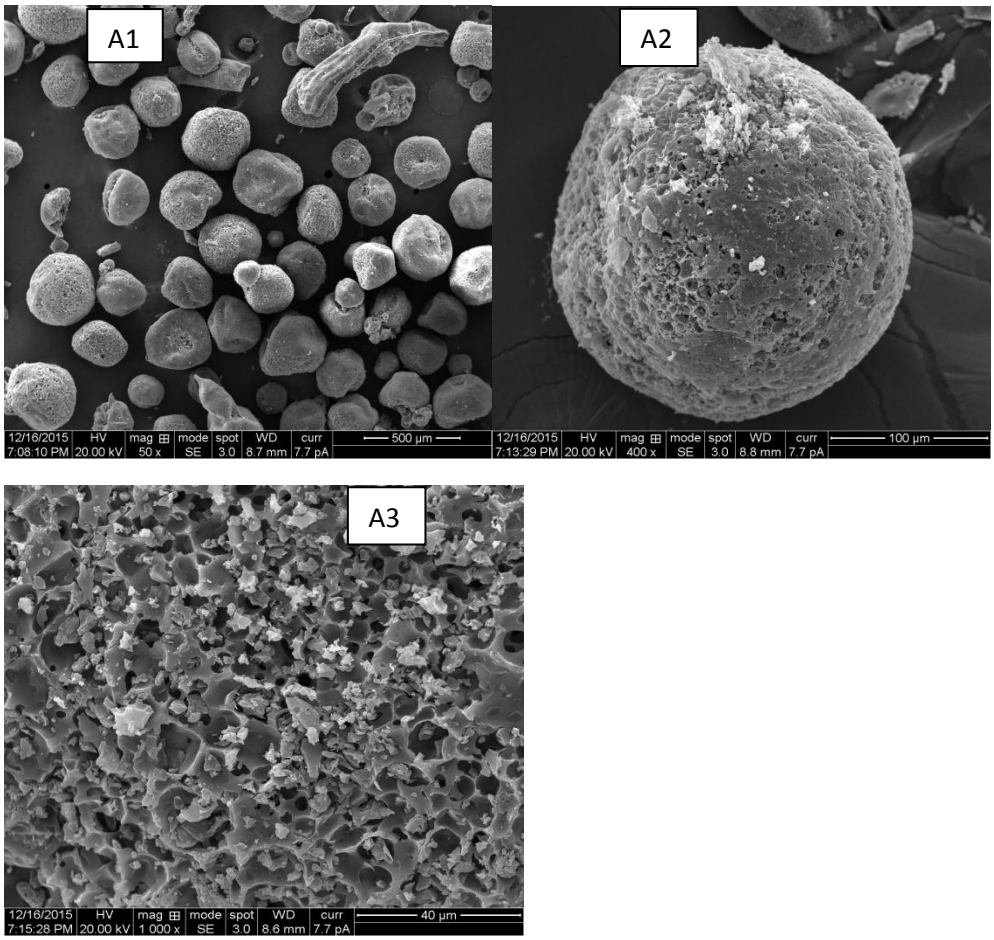

Figure 12: Scanning electron micrographs of agglomerates (A1),Shape (A2) and Surface Morphology of agglomerates of formulation P1.

Conclusion

Valsartan agglomerates were successfully prepared by CCA technique using hydrophilic polymers like PVP K30, PEG 4000 and Sodium Alginate. Spherical agglomerates exhibited improved micromeritic properties compared to pure drug. Formulation, P1 was selected as an optimized formulation which showed better results with respect to percent drug release, percent yield, MDT and % DE when compared to other formulations. Hence this CCA technique can be used for formulation of tablets of Valsartan by direct compression with directly compressible tablet excipients.

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