Research Article
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Solid dispersion of valsartan for solubility improvement using β-cyclodextrin

Abstract

The objective of work was to prepare and characterize solid dispersions of valsartan using β-Cyclodextrin to improve its aqueous solubility and rate of dissolution by solvent evaporation technique. Solid dispersions showed marked improvement in the solubility behaviour and improved drug release. From all the formulations VSD4 was found to be optimized formulation based on the characterization, solubility and dissolution studies. The results obtained showed that the aqueous solubility and rate of dissolution was significantly improved when formulated in solid dispersion as compare to pure drug. The enhancement of dissolution rate depends on the nature and amount of the carrier and increases with the increase in the concentration of the carrier. Increase in the dissolution rate may be attributed to; the reduced particle size of drug deposited on the surface of carrier and enhanced wet ability of the drug particles by the carrier. The optimized formulations were evaluated by differential scanning Calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and Scanning electron microscopy (SEM).

Keywords: valsartan, solid dispersions, β-cyclodextrin, solubility, pure drug, dissolution studies

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Introduction

The number of new drug candidates with poor aqueous solubility and dissolution rate has grown steadily over the past two decades due to the use of high throughput and combinatorial screening tools during the drug discovery and selection phase.[1] Improvement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Many approaches, such as salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs.[2] However; all these techniques have potential limitations. All poorly soluble drugs are not suitable for improving their solubility by salt formation. Use of co-solvents or surfactants to improve dissolution rate pose problems and decreasing particle size increases solubility but there is poor wetting and flow.[3–6] Solid dispersions can overcome these problems. Many carriers used in solid dispersions also cause problems due to their hygroscopic nature. Hence, continuous search for new carriers and new techniques is going on which will be useful for large scale manufacturing. Research for alternative carriers has been increasing to suit for the industrial applications as well as to reduce the production cost and toxic effects. Many polymers have limitations in enhancing solubility of poorly water soluble drugs due to their high viscosity. Use of polymers with low viscosity and high swelling capacity offers better alternative for these types of polymers. Use of natural polymer is more beneficial because of their low cost, biocompatibility, and biodegradability.[7] Cost effective pharmaceutical excipients are always desirable. Pharmaceutical excipients developed from natural sources are economic. Present day consumers look for natural ingredients in food, drugs and cosmetics as they believe that anything natural will be safer and devoid of side effects.[8,9] Natural excipients show lack of toxicity, easy availability and economic considerations in pharmaceutical industry as compared to their synthetic counterparts. Naturally, derived excipients have shown promising results in the modification of drug release from the formulations.[10]

The aim of this work was to formulate Valsartan solid dispersions by a solid dispersion technique by solvent evaporation method using β-cyclodextrin in order to enhance its solubility, dissolution, in vitro release and hence its bioavailability.

Materials and method

Materials

Valsartan pure drug was gift sample from Abbott Health Care Pvt Ltd, Mumbai India. β-cyclodextrin was obtained from SD fine chemicals, Mumbai. All other chemicals used were of analytical grade.

Method

Saturation solubility and phase solubility study

The solubility of drug is a very important physicochemical property because it directly affects the rate of drug release from formulation into the dissolution medium, bioavailability of the drug and consequently the therapeutic efficacy of the pharmaceutical product. The solubility of Valsartan was determined by the equilibrium solubility method, in which a saturated solution of the material was obtained by stirring an excess of drug in the constant quantity of solvent until saturation or equilibrium was achieved in vortex mixer. Then it was filtered through whatmann filter paper (No. 1) and then concentration was analyzed by UV spectrophotometer. Solubility of Valsartan was determined in distilled water and pH across the GIT. i.e. in pH 1.2, 4.5 and pH 6.8. Phase solubility studies of Valsartan was carried out to evaluate the possible solubilising effect of the carrier by adding an excess of drug to 10ml of aqueous solutions containing increasing concentrations of β-cyclodextrin (0–2%w/v) and shaken at 25°C in

a temperature controlled bath for 72hrs. Drug concentrations were assessed spectrophotometrically.[10]

Preparation of solid dispersions and physical mixtures

Valsartan solid dispersions were prepared using β-cyclodextrin by the solvent evaporation method. A 1g quantity of Valsartan and β-cyclodextrin were dissolved separately in 100 ml of absolute methanol. The solution was stirred for 1h and the solvent was allowed to evaporate at room temperature. The solid dispersions obtained (VSD1) were pulverized sieved through 22meshes and then stored in screw cap vials at room temperature pending further use. The same procedure was carried out for all the formulations presented in Table 1. Physical mixtures of the Valsartan and β-cyclodextrin, having the same composition of the solid dispersions were prepared (VSDM1) by simply triturating the drugs and the polymers in a porcelain mortar.[11] The mixtures were sieved and stored in screw cap vials at room temperature pending further use. The same procedure was carried out for all the formulations presented in Table 2.

Table 1 Composition of valsartan solid dispersions

Formulation	Formulation code	Valsartan: β-cyclodextrin
Solid dispersion	VSD1	1:1
	VSD2	1:2
	VSD3	1:3
	VSD4	1:4

Table 2 Composition of valsartan physical mixture

Formulation	Formulation code	Valsartan: β-cyclodextrin
Physical mixture	VSDM1	1:1
	VSDM2	1:2
	VSDM3	1:3
	VSDM4	1:4

Solubility studies of various solid dispersions

Valsartan loaded-solid dispersions, physical mixtures and pure valsartan equivalent to 10mg were weighed and transferred to four flask containing 50ml distilled water, pH 1.2 acetate buffer, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4. The sample was agitated at 80 rpm in thermostated shaking water bath at 37+0.50 for 8 hrs. The supernant solution was then filtered through a Whatmann filter paper. The filtrate was diluted and the absorbance was measured using UV-Vis spectrophotometer.[10]

Percentage yield of solid dispersion

The percent yield of Valsartan solid dispersions was determined according to method described using the following expression12

% yield=Weight of prepared SD x100 Eq. 1

Wt. of drug+carrier

Drug content

Valsartan solid dispersion and physical mixture were weighed separately and dissolved in 100ml of methanol. Then 1 ml of the stock was diluted to 50ml with distilled water. These solutions was shaken vigorously and filtered and the filtrate analyzed spectrophotometrically for drug content at 240nm for Valsartan.[12]

In vitro dissolution studies

The dissolution test of best formulations of Valsartan Physical mixture and solid dispersions based on solubility studies was determined as described in the USP (USP 2011) using dissolution apparatus type II. For this 500ml volume of pH 6.8 Phosphate buffer was used as dissolution medium for the period of 90min at a rate of 50rpm. Samples were placed in a polycarbonate dialysis membrane which was pre-treated by soaking in distilled water for 24h prior to commencement of each release experiment. In each case, samples equivalent to 100 mg Valsartan was placed in the dialysis membrane and securely tied with a thermo-resistant thread and then immersed in the dissolution medium.[13] At predetermined time intervals, 2ml portions of the dissolution medium were withdrawn. An equivalent volume of the fresh medium maintained at the same temperature was added to maintain sink conditions throughout the study period. Withdrawn samples were filtered through a 0.45µm Whatmann filter paper and assayed spectrophotometrically at 240nm.

FTIR

Compatibility studies of each drug (valsartan) with β-cyclodextrin were carried out using Fourier Transform Infrared (FT-IR) spectroscopy. Sample from each of drug alone, carrier alone and physical mixture of drug and polymer by ATR sampling technique, the spectrum was scanned over the frequency range between 4000 and 600cm-1and at 4cm resolution. Appearance, disappearance or broadening of absorption band(s) on the spectra of the solid dispersions and the polymeric carriers in comparison with the spectrum of drug were used to determine possible interactions between pure drugs and polymers.

Differential scanning calorimetry

A Mettler Toledo DSC STARe SYSTEM was used for all the DSC studies performed on the Drug, polymer, physical mixtures and solid dispersions. The DSC uses Stare Software V8.10 for its operation. Samples ranging from 8 to 15mg were used and the results were normalized using Stare software so that the results could be compared. The samples were placed in a 100µL pan. The pans are covered with a lid and the lid is crimped into place. A pinhole is made on the lid to vent out any gas which might result while heating. The pan is then placed inside the furnace using an empty pan as a blank. The DSC was calibrated using indium (5-10mg) with a melting onset temperature at 156±0.2ºC and zinc with a melting onset temperature of 419.6±0.70C as the standards. The two processes show a heat flow of 28.45±0.6J/g and 107.5±3.2J/g for indium and zinc, respectively.

Scanning electron microscopy (SEM)

Surface morphology of the raw materials and the formulated product were studied using a Scanning electron microscope equipped with JOEL JSM 7500. Snappy 4 software was used to obtain the digital picture. Samples were placed on brass stubs using double sided adhesive tape. The samples were coated with a layer of gold using a gold sputter technique to improve the conductivity of the surface of the sample to obtain good images. A Denton Vacuum Desk II was used for the gold sputter technique. Pictures were taken at magnifications whereby they could be compared with each other, which best shows the surface features of the various materials.

Results & discussion

Preformulation studies of valsartan

In the preformulation study of drug, λ-max of Valsartan was found

at 250nm. Similarly Partition coefficient of Valsartan was found to be 5.8 by shake flask method, which indicates that valsartan is lipophilic. So it can pass cell membrane easily once it got solubilized.

Solubility determination of drug in different media

The solubility data of Valsartan in distilled water, Acetate buffer pH 1.2, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4 at 250C are depicted in Table 3. The comparative statement of Valsartan in different solvent is presented graphically in Figure 1. Phase solubility curve of Valsartan in presence of β-cyclodextrin is shown in Figure 2. A systematic increase of solubility of drugs was observed with an increasing concentration of β-cyclodextrin in water. Increased solubility may be due to improved dissolution of drugs in water by β-cyclodextrin. This might be due to solubilisation effect that increased wetting property of drug. The data obtained from phase solubility study were depicted in Table 4.

Table 3 Solubility data of valsartan in different solvent

Solubility solvents	Concentration (µg/ml)
Water	197
Acetate buffer pH 1.2	60
Phosphate buffer pH 6.8	200
Phosphate buffer pH 7.4	320

Table 4 Phase solubility data for valsartan in carriers

Conc. of β-cyclodextrin	Solubility of valsartan(µg/ml)
0.25%	62.45
0.50%	68.23
1%	72.65
2%	84.32
Pure drug	45.12

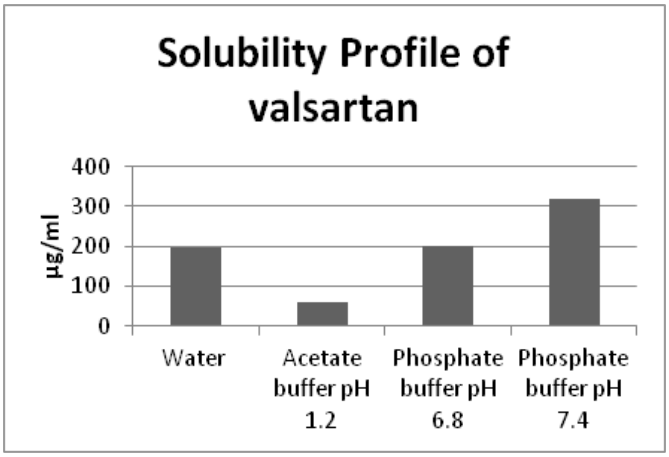

Figure 1 Solubility profile of valsartan.

Preparation of valsartan solid dispersions

Solid dispersions of Valsartan were prepared by using β-cyclodextrin in different drug and carrier ratios Table 1. All the solid dispersions prepared were found to be fine and free flowing powders.

Solubility study of solid dispersions and physical mixture

Solubility data of pure valsartan were depicted in Table 3 and indicated that 45.12µg/ml of pure valsartan was soluble in distilled water; hence they are considered as poorly water soluble drugs. Here the solubility data of physical mixture (Figure 3) containing Valsartan and β-cyclodextrin is shown in Table 5. The solubility of valsartan in solid dispersion prepared by solvent evaporation method in different solvent also studied and the data for the same is depicted in Table 6. As compare to pure and physical mixture, the solid dispersion prepared by solvent evaporation showed highest solubility in distilled water, pH 1.2 acetate buffers, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4. (Figure 4)

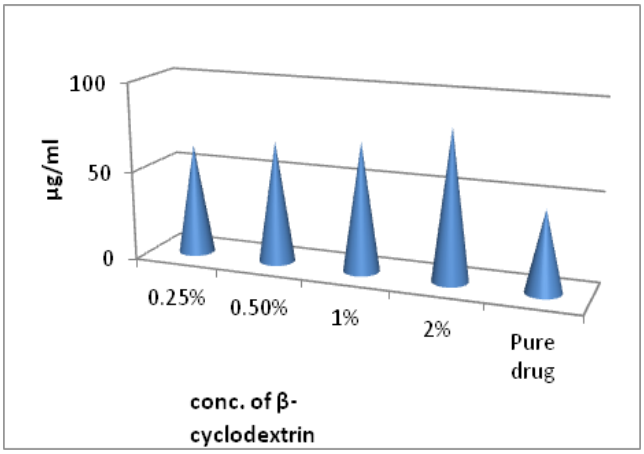

Figure 2 Phase solubility of valsartan with β-cyclodextrin.

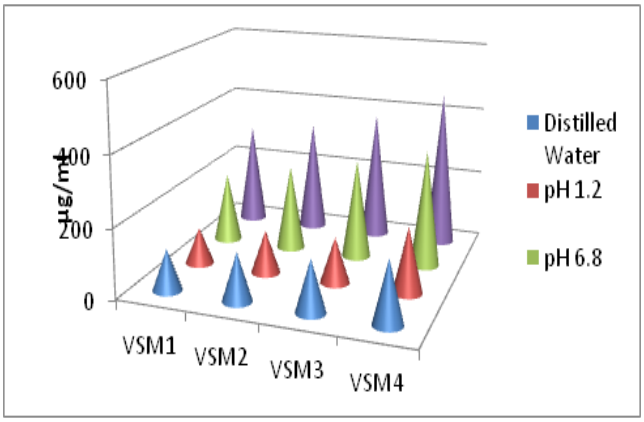

Figure 3 Solubility profile of valsartan physical mixture.

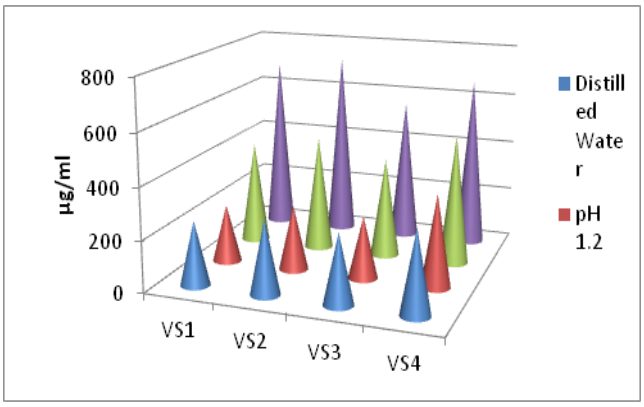

Figure 4 Solubility profile of valsartan solid dispersion.

This investigation suggested that, it might be possible due to preparation of solid dispersion (Figure 5) using varying concentration

of β-cyclodextrin which formed eutectic mixture and hence solubility (Table 7).

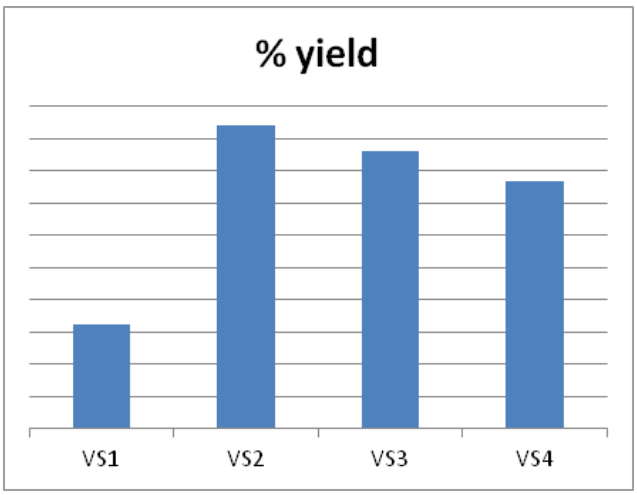

Figure 5 Effect of composition of polymers on yield of valsartan solid dispersion.

Table 5 Solubility of physical mixture of valsartan and β-cyclodextrin

Formulation code	Distilled Water (µg/ml)	pH 1.2 (µg/ml)	pH 6.8 (µg/ml)	pH 7.4 (µg/ml)
VSDM1	120±0.56	106±0.97	204±0.66	298±0.83
VSDM2	139±0.46	124±0.24	250±0.28	325±0.45
VSDM3	150±0.41	132±0.66	290±0.68	375±0.74
VSDM4	180±0.66	189±0.88	340±0.10	456±0.23

Mean±SD(n=3)

Table 6 Solubility of solid dispersion of valsartan and β-cyclodextrin

Formulation code	Distilled water(µg/ml)	pH 1.2 (µg/ml)	pH 6.8 (µg/ml)	pH 7.4 (µg/ml)
VSD1	250±0.56	226±0.97	404±0.66	688±0.83
VSD2	289±0.46	254±0.24	450±0.28	725±0.45
VSD3	270±0.41	242±0.66	390±0.68	555±0.74
VSD4	320±0.66	359±0.88	510±0.10	666±0.23

Table 7 Percent yield of valsartan solid dispersion

Formulation code	Valsartan: β-cyclodextrin	% yield
VSD1	1:1	80.5
VSD2	1:2	92.8
VSD3	1:3	91.2
VSD4	1:4	89.4

Percentage yield of solid dispersions

Valsartan solid dispersion with β-cyclodextrin had a yield of 80.5 and 92.8 % for the Valsartan: β-cyclodextrin combination ratios of 1:1, and 1:2 (VSD1 and VSD2) respectively. The yield recorded for Valsartan: β-cyclodextrin solid dispersions at ratios of 1:3, and 1:4 were 91.2 and 89.4 % (VSD3 and VSD4) respectively.

Drug content of solid dispersion and physical mixture

A fundamental quality attribute for all pharmaceutical preparations is the requirement for constant dose of drug between dispersion. In each of the mentioned formulae, no more than preparations outside this limit nor is one individual outside the limit. All the formulations and physical mixture contained active ingredients within the general limit of 90-110%. Valsartan content (%) with in physical mixture and Solid dispersion with different drug: carrier ratio is shown in Table 8, Table 9 respectively. The entire percent drug shown in tables was found within general specification. It is proved that the formulation were prepared can be continue for further evaluation.

Table 8 Drug content of valsartan physical mixture

Formulation code	Valsartan: β-cyclodextrin	Drug amount (%)
VSDM1	1:1	98.23
VSDM2	1:2	98.46
VSDM3	1:3	97.99
VSDM4	1:4	98.21

Table 9 Drug content of Valsartan solid dispersion

Formulation code	Valsartan: β-cyclodextrin	Drug amount (%)
VSD1	1:01	97.15
VSD2	1:02	97.45
VSD3	1:03	98.26
VSD4	1:04	98.56

In-vitro dissolution study of SD's and PM's of valsartan using natural carrier

Dissolution studies were performed to compare the drug release from the physical mixtures and solid dispersions, to that of the pure drug. The dissolution test was carried out for a period of 90min in pH 6.8 Phosphate buffer. The drug release data obtained for formulations VSDM1-VSDM4 are tabulated in Table 10. It shows the cumulative percent drug released as a function of time for all formulations. The cumulative percent drug released after 90min was shown in table. In vitro studies reveal that there is marked increase in the dissolution rate of Valsartan from all the physical mixtures when compared to pure Valsartan itself. From the in vitro drug release profile, it can be seen that formulation VSDM4 containing Valsartan β-cyclodextrin (1:4) shows higher dissolution rate i.e. 91.2±2 % compared with other formulations. It is predicted that, increasing concentration of carrier, increases the drug dissolution rate. The graphical presentation of dissolution profile of physical mixture of valsartan and β-cyclodextrin over the period of 2hrs is shown in Figure 6.

Percent drug released from solid dispersion of valsartan using β-cyclodextrin is shown in Table 11. As compare to physical mixture of valsartan with β-cyclodextrin, solid dispersion showed highest dissolution rate for valsartan. Maximum drug released up to 10min was 48.8% with drug-carrier ratio (VSD4). While over the period of 90min, maximum 92% drug was released. The percent drug released was increased with increasing concentration of carrier. This was might be due to absence of aggregation and agglomeration with crystalline drug, water soluble carrier increased wet ability and good dispersibility and conversion of drug to amorphous state. Less viscosity and good water holding capacity of carrier helps to dissolve the drug rapidly by increasing free kinetic energy. The graphical presentation of drug released is shown in Figure 7. The literature reveals that the solvent evaporation method of solid dispersion solubilizes the drug and

carrier in molecular level. Hence form eutectic mixture and increased solubility of poorly water soluble drug.

Table 10 Drug released profile of PM's of valsartan using β-cyclodextrin

Time in min	% drug release			
	VSDM1	VSDM2	VSDM3	VSDM4
0	0	0	0	0
5	26.8±2	30.3±2	23.3±3	23.4±2
10	30.3±2	36.9±1	36.2±1	28.8±2
20	46.5±3	46.5±2	46.3±2	31.5±1
30	59.5±3	58.2±2	72.1±2	32.8±1
45	64.5±1	64.5±2	83.2±1	37.5±1
60	70.9±3	77.3±2	91.5±3	41.9±1
90	84.4±1	86.5±2	88.8±3	91.2±1

Table 11 Drug released profile of SD's of valsartan using β-cyclodextrin

Time in min	% drug release			
	VSD1	VSD2	VSD3	VSD4
0	0	0	0	0
5	29.8±2	31.3±2	28.3±3	29.4±2
10	40.3±2	46.9±1	47.2±1	48.8±2
20	56.5±3	54.5±2	56.3±2	59.5±1
30	69.5±3	68.2±2	72.1±2	72.8±1
45	74.5±1	78.5±2	82.2±1	77.5±1
60	80.9±3	87.3±2	91.5±3	81.9±1
90	90.4±1	91.5±2	93.8±3	92.2±1

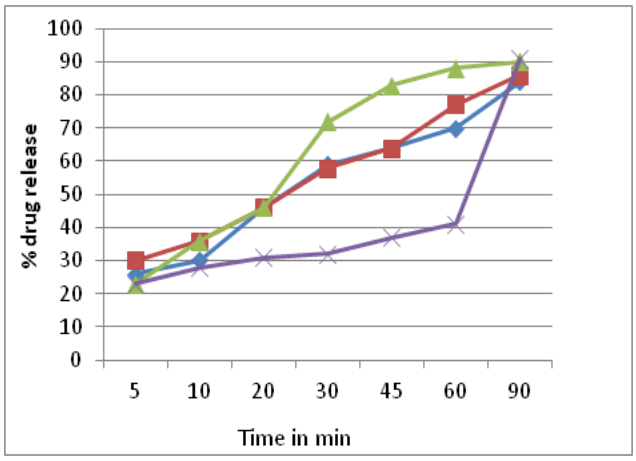

Figure 6 Drug release pattern of PM's of valsartan using β-cyclodextrin.

Fourier transforms infrared (FT-IR) spectral studies

Infra-red spectrum of Valsartan is shown in Figure 8. The characteristic peaks of functional groups presents in the drugs were checked and depicted in Table 12. The functional groups present in the structure of Valsartan were identified correctly and hence the drugs was confirmed and considered for further uses.

The FTIR spectra of pure Valsartan displayed bands at 3419.9cm-1 due to N-H stretch, at 2962.76cm-1 due to C=N stretching, at 1732.13cm-1 due to Carboxylate stretching. The spectra also showed bands at 1631.83cm-1 due to C=O bending at 1107.18 due to C-N bonding (Figure 8). The infrared spectrum of physical mixture of valsartan and β-cyclodextrin mixture is shown in Figure 9. From the spectrum it was observed that chemical groups N-H stretch, C=N stretching, Carboxylate stretching. C=O bending and C-N bonding were found with the same wave number as that of valsartan (Figure 8).

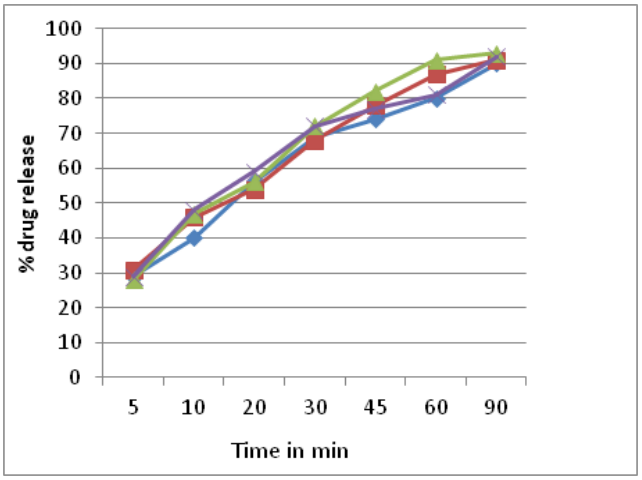

Figure 7 Drug release pattern of SD's of valsartan using β-cyclodextrin.

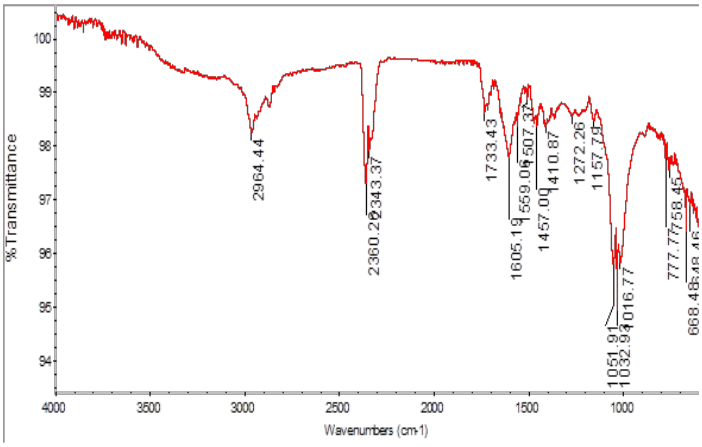

Figure 8 Infra-red spectrum of valsartan.

Table 12 Characteristic peaks of valsartan

Peak (cm-1)	Intensity (%T)	Chemical groups
3419.9	100.3	N-H stretch
2962.76	93.9	C=N stretching
1732.13	96.57	Carboxylate stretching
1631.83	72.04	C=O bending
1107.18	76.51	C-N bonding

DSC study of valsartan and natural carrier solid dispersion and physical mixture

DSC spectra of solid dispersion VSD4 (1:4) of valsartan and β-cyclodextrin as drug carrier is shown in Figure 10. The individual spectra valsartan, β-cyclodextrin, their physical mixture VSD4 and solid dispersion VSD4 (1:4) shown with combined in Figure 11. The DSC thermo gram of Valsartan pure drug was shown endothermic peak

at 103^{0}C indicating that the drug is highly crystalline. The absence of drug peak in the solid dispersion formulation VSD4 indicating the drug was converted into an amorphous form. As the intensity of the endotherm was markedly decreased in the solid dispersion, the faster dissolution rate of the drug from the solid dispersion is attributed to the reduction in the crystallinity of the drug. Crystallization inhibition is attributed to the entrapment of the drug molecules in the polymer matrix during solvent evaporation.

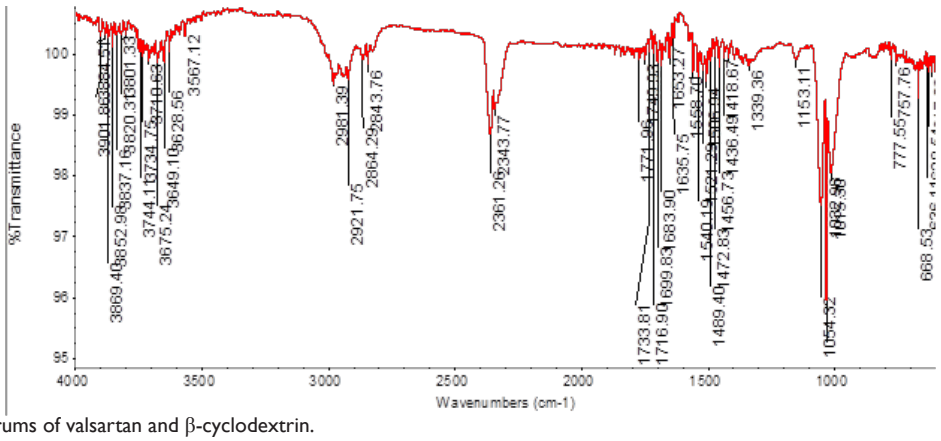

Figure 9 infrared spectrums of valsartan and β-cyclodextrin.

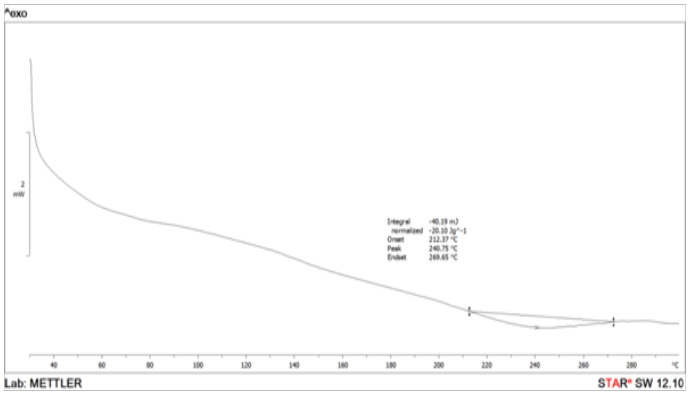

Figure 10 DSC spectra of solid dispersion of valsartan and β-cyclodextrin.

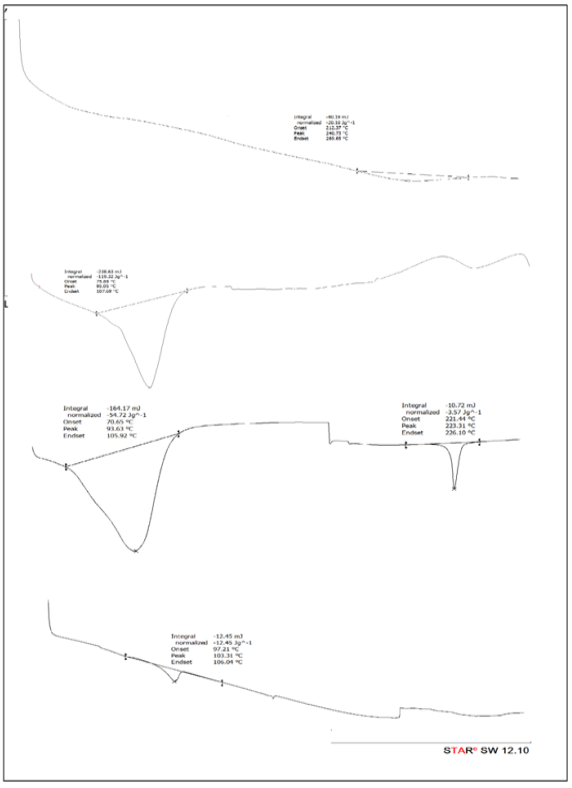

Figure 11 DSC theogram of A-valsartan, B-β-cyclodextrin, C-valsartan and β-cyclodextrin physical mixture and D-solid dispersion.

SEM study of valsartan and solid dispersion using natural carrier

SEM photographs for pure drug and optimized formulation VSD4 is shown in Figure 12, Figure 13 respectively. The drug crystals seemed to be smooth-surfaced, irregular in shape and size. In case of Solid dispersions, it was difficult to distinguish the presence of drug crystals. The drug surface in solid dispersion seems to be more porous in nature. Solid dispersions appeared as uniform and homogeneously mixed mass with wrinkled surface. Drug crystals appeared to be incorporated into the particles of the polymers.

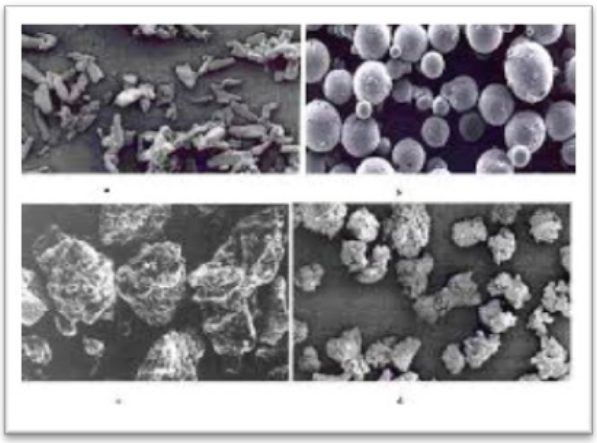

Figure 12 SEM of valsartan.

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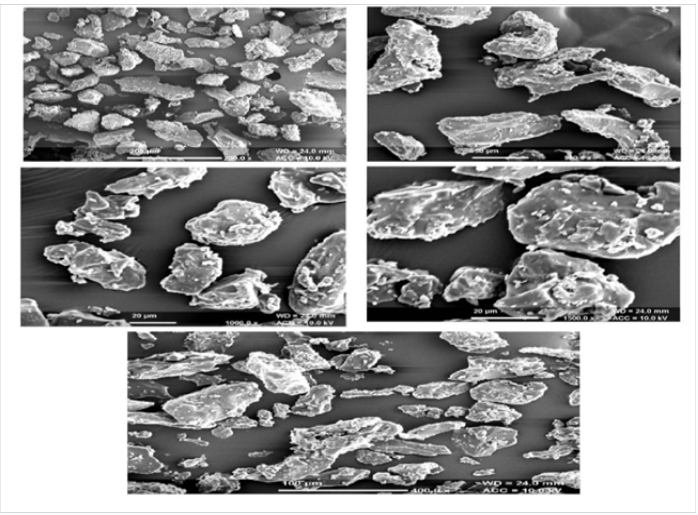

Figure 13 SEM study of valsartan solid dispersion using β-cyclodextrin.

Conclusion

In the present study it was demonstrated that Valsartan solid dispersion formulation can be effectively produced by processing via solvent evaporation method with enhanced solubility and dissolution rate. B-cyclodextrin combinations were optimized and stable SD systems were developed successfully. Utilization of β-cyclodextrin offers excellent possibilities to develop stable amorphous solid dispersion. Furthermore, this Valsartan incorporated solid dispersion gave higher dissolution and solubility values compared to the pure Valsartan drug. I*n vitro* drug release studies of optimized formulation VSD4 exhibited a cumulative release of 92% after 90 min. FTIR spectrum revealed that no chemical interaction occurred between the drug and excipients used in the formulation. Analysis by differential scanning Calorimetry showed that Valsartan existed in the amorphous form within the solid dispersion formulation fabricated using the solvent evaporation process. Additionally, scanning electron microscopy studies suggested the conversion of crystalline Valsartan to an amorphous form. The dissolution rate and solubility of Valsartan solid dispersions was improved significantly using β-cyclodextrin.

Acknowledgments

None.

Conflicts of interest

Author declares that there are no conflicts of interest.

References

1. Lipinski CA. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev.* 2001;46(1-3):3–26.
2. Wadke DA, Serajuddin ATM, Jacobson H. Preformulation testing. In: Lieberman WA, Lachman L, Schwartz JB, editors. *Pharmaceutical Dosage Forms: Tablets*. New York: Marcel Dekker; 1989. p. 1–73.
3. Serajuddin ATM. Solid dispersion of poorly water soluble drugs: early promises, Subsequent problems and recent breakthroughs. *J Pharm Sci.* 1999;88(10):1058–1066.
4. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm.* 2000;50(1):47–60.
5. Temeljotov DF, Mohar M, Kofler B, et al. Solubilization and dissolution enhancement for sparingly soluble fenofibrate. *Acta Pharm.* 1996;46(2):131–136.
6. Sjokvist E, Nystrom C, Alden M. Physicochemical aspects of drug release. IX. Investigation of some factors that impair dissolution of drugs from solid particulate dispersion systems. *Int J Pharm.* 1989;54(2):161–170.
7. Murali Mohan Babu GV, Prasad Ch DS, Raman Murthy KV. Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water soluble drug nimodipine. *Int J Pharm.* 2002;234(1−2):1–17.
8. Patel DB. Natural Excipient in controlled Drug Delivery Systems. *J Pharmacy Res.* 2009;2(5):900–907.
9. Sapkal S, Narkhede M, Babhulkar M, et al. Natural polymers: Best carriers for improving bioavailability of poorly water solubl3e drugs in solid dispersion. *Marmara Pharm J.* 2013;17:65–72.
10. Shirwaikar A, Prabhu SL, Kumar GA. Herbal Excipient in Novel Drug Delivery Systems. *Indian J Pharm Sci.* 2008;70(4):415–422.
11. Monica R, Yogesh M, Kaushik T. Dissolution improvement of simvastatin by surface solid dispersion technology. *Dissolution Technologies.* 2010; 27–34.
12. Higuchi T, Connors KA. Phase solubility techniques. *Adv Anal Chem Instrum.* 1965;4:117–212.
13. Lakshmi K, Pranav kumar Reddy M, Rajesh kaza. Dissolution enhancement of telmisartan by surface solid dispersion technology. *International Journal of Innovative Pharmaceutical Research.* 2012;3(4):247–251.