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SOLUBILITY ENHANCEMENT OF VALSARTAN USING SOLID DISPERSION TECHNIQUE WITH NOVEL CARRIERS

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Abstract:

Solubility is an important physicochemical factor affecting absorption of the drug and its therapeutic effectiveness. Drugs having poor aqueous solubility is one of the major confronts better absorption for good bioavailability of such drugs. The purpose of this study was to prepare and characterize solid dispersions of the poorly water soluble antihypertensive agent valsartan with water soluble carriers such as Kolliphor P 407, Kolliphor P 188, Kolliwax GMS II, HPMC AS and Soluplus in proportions viz. 1:1, 1:2, 1:3 (Drug: Carrier) to improving its aqueous solubility and rate of dissolution by solvent evaporation technique. All the formulations showed marked improvement in the solubility behavior and improved drug release. From all the formulations SD6 was found to be optimized formulation using soluplus as a carrier based on the 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.

Keywords: *Valsartan, solid dispersions, soluplus, aqueous solubility*

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INTRODUCTION:

Solid dispersion technique can be used to enhance the solubility, dissolution rate and absorption of several insoluble drugs [1]. Solid dispersion is one of the techniques used to increase the dissolution rate of the lipophilic drugs [2-4]. Formulation development would lead to being a failure if drug having poor aqueous solubility so the low dissolution rate and low solubility of drug substances in water in aqueous G.I.T fluid frequently lead to inadequate bioavailability [5].

Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in the solid state prepared by melting, dissolution in a solvent or melting-solvent method. Solid Dispersion technology has been successfully been used for improving the solubility of the drugs and hence bioavailability [6]. Solid dispersions of drugs were generally produced by melt or solvent evaporation methods. The materials, which were usually semisolid and waxy in nature, were hardened by cooling to very low temperatures [7].

Valsartan belongs to angiotensin II receptor blocker and is widely used for the treatment of hypertension. It is selected as a model drug in the present work because of its relatively poor aqueous solubility and bioavailability (25%) [8].

MATERIALS AND METHODS:

Materials:

Valsartan pure drug was a generous gift from Aurobindo Pharma limited, Hyderabad, India. Kolliphor P 407, Kolliphor P188 were obtained from BASF, Mumbai. Kolliwax GMS obtained from Signet Chemical Corp. Pvt. Ltd, Mumbai. HPMC AS and Soluplus were gifted from BASF, Germany. Urea and PVP K-30 and were gifted from MSN Laboratories, Hyderabad. All other chemicals used were of analytical grade.

Preliminary solubility studies of Valsartan

Solubility measurement of Valsartan was performed according to a published method [9]. An excess amount of Valsartan was added to 25mL of an aqueous solution of water-soluble carriers with an equal proportion of Urea, PVP K-30, Kolliphor P 188, Kolliphor P 407, Kolliwax GMS, HPMC AS and Soluplus, in various ratios in screw capped bottles. Samples were shaken for the 48 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solutions were analyzed for the valsartan in UV 250 nm.

Preparation of solid dispersions of Valsartan by solvent evaporation method:

Valsartan solid dispersions of fifteen formulations were prepared by using various carriers shown in table 1 like Kolliphor P 407, Kolliphor P 188, Kolliwax GMS II, HPMC AS and Soluplus in proportions viz. 1:1, 1:2, 1:3 (Drug: Carrier). The drug and carrier were dissolved in methanol and triturated in a dry mortar until the solvent is evaporated and a clear film of drug and carrier was obtained. Then the dispersion was subjected to methanol solvent evaporation by placing in 50^0C in hot air oven for 30 min. The resultant solid dispersion was scraped out with a spatula. Solid dispersions were pulverized in a mortar and pestle and passed through a 45µm sieve before packing in an airtight container [10].

Solubility studies of Valsartan solid dispersion by solvent evaporation method:

Solubility measurements of Valsartan were performed according to published method [9]. Samples were shaken for the 48 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solutions were analyzed for the Valsartan in UV 250 nm.

Table 1: Formulation table for the Valsartan solid dispersions

S. No.	Ingredients (Units)	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8	SD9	SD10	SD11	SD12	SD13	SD14	SD15
1	Valsartan (gm)	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
2	Kolliwax GMS (gm)	0.8	1.6	2.4	-	-	-	-	-	-	-	-	-	-	-	-
3	Soluplus (gm)	-	-	-	0.8	1.6	2.4	-	-	-	-	-	-	-	-	-
4	Kolliphor P407 (gm)	-	-	-	-	-	-	0.8	1.6	2.4	-	-	-	-	-	-
6	Kolliphor P 188 (gm)	-	-	-	-	-	-	-	-	-	0.8	1.6	2.4	-	-	-
7	HPMC AS (gm)	-	-	-	-	-	-	-	-	-	-	-	-	0.8	1.6	2.4
8	Methanol (mL)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Evaluation of Valsartan solid dispersions:

Solid dispersions obtained by the above method were tested for their % Practical yield, drug content and *in vitro* release studies.

% Practical Yield:

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in the selection of the appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation [11].

$$\% \text{ Practical Yield} = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + Polymer)}} \times 100$$

Drug content:

Solid dispersions equivalent to 80 mg of Valsartan have weighed accurately and dissolved in 100 mL of methanol. The solution was filtered, diluted suitable and drug content was analyzed at λ_{max} 250 nm against blank by UV spectrometer. The actual drug content was calculated using the following equation as follows [11].

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

***In vitro* release studies:**

In vitro dissolution studies of pure Valsartan and solid dispersions were conducted with the USP type II apparatus (paddle type). The dissolution studies were performed using 900mL phosphate buffer of pH 6.8 as dissolution medium at 37 ± 0.5^0C with 50 rpm speed. Samples of each preparation equivalent to 10 mg of drug were added to the dissolution medium. The samples of 5mL aliquots were withdrawn periodically at 5, 10, 15, 30, 45, 60 and 90 minutes time intervals and filtered through a 0.45µ membrane filter. The withdrawn sample was replaced every time with the same quantity of fresh dissolution medium. The filtered solutions were diluted suitably and the samples were analyzed for their drug content by using UV spectrophotometer at a wavelength of 250 nm [12].

Characterization:

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR spectra for the pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at a pressure of seven to ten tons [13].

Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having the TA60 software, Shimadzu, Japan. Accurately weighed samples were placed on the aluminum plate, sealed with aluminum lids and heated at a constant rate of 5ºC/min, over a temperature range of 0 to 250ºC [14].

Powder X-ray diffraction:

A Bruker D8 diffractometer was used to perform powder X-ray diffraction (PXRD) of all samples. A Cu K-α 1 tube was the source, set at 40 KV and 50mA. A scan from 2 to 60^0 2 θ was carried out at a rate of 0.01220^0 2θ/s. The diffractometer was calibrated using powdered α-alumina. Hot-melt extruded samples were ground before analysis [15].

Scanning electron microscopy:

The shape and surface morphology of the Valsartan and optimized formulation of solid dispersion prepared by solvent evaporation was examined using XL 30 model JEOL 6800 scanning electron microscope (Japan) [16].

Stability studies:

Prepared solid dispersions were placed inside sealed 40cc HDPE container with the child-resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) with a relative humidity of 75%±5%RH and temperature of $40^0C±2^0C$ for stability studies. Samples were removed after 1, 2, 3 and 6 months, evaluated for % drug content and in vitro dissolution study and compared with that SD tested immediately after preparation (initial) [17].

RESULTS & DISCUSSION:

Preliminary solubility studies of Valsartan

In the case of solid dispersions initially, preliminary solubility analysis was carried out to select the appropriate water soluble carriers for the preparation of a solid dispersion in which pure drug solubility was found to be 0.18 mg/mL (**Table 2**). From this study, drug and Soluplus in the ratio of 1:1 shown highest drug solubility i.e. 5.56 mg/mL, almost 30 fold increased compared to that of pure drug. For all the water soluble carriers used in preliminary solubility studies, urea and PVP K-30 shown low solubility when compared with other carriers and did not include in the preparation of Valsartan solid dispersions. The graphical representation of solubility studies of Valsartan physical mixtures was shown in **Figure 1**.

Table 2: Preliminary solubility studies of Valsartan in different polymers

Sample (Physical mixtures)	Drug & Polymer ratios	Solubility(mg/mL)
Pure drug	-	0.18±0.04
Drug: Urea	1:1	1.91±0.01
Drug: PVP K-30	1:1	2.45±0.02
Drug: Kolliwax GMS	1:1	3.21±0.01
Drug: Soluplus	1:1	5.56±0.03
Drug: Kolliphor P407	1:1	3.46±0.02
Drug: Kolliphor P 188	1:1	3.68±0.01
Drug; HPMC AS	1:1	3.11±0.04

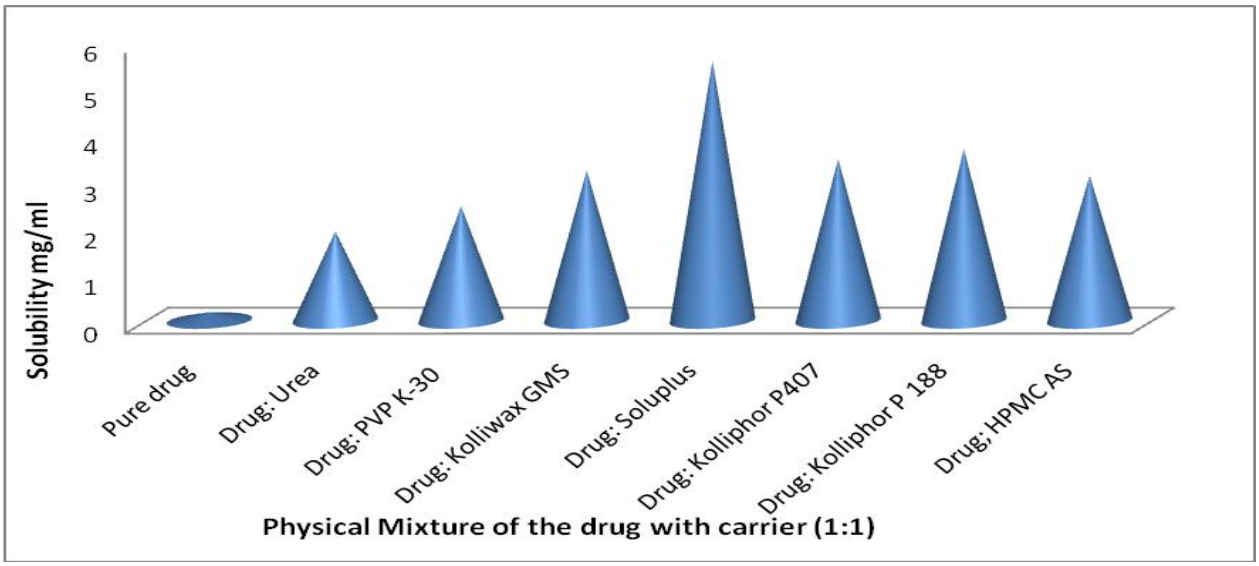

Fig. 1: Solubility studies of Valsartan physical mixture

Fig 2: Valsartan Solid Dispersions

Preparation of Valsartan solid dispersions

Solid dispersions of Valsartan were prepared by using Kolliphor P407, Kolliwax GMS, Kolliphor P 188, HPMC AS and Soluplus as a carrier in different in different proportions with the drug, i.e., in the ratios of 1:1, 1:2 and 1:3. In the present investigation, 15 formulations were prepared and their complete composition was shown in **Table 1.** All the solid dispersions prepared were found to be fine and free flowing powers.

Evaluation parameters:

Solubility studies of Valsartan solid dispersions:

Different formulations of valsartan solid dispersions were prepared by a solvent evaporation method with their respective carriers. After preparation of solid dispersion solubility analysis was carried out. The formulation (SD6) with Soluplus in the ratio of 1:3 (drug: carrier) shown highest solubility i.e. 15.35±0.02mg/mL, almost 90 fold compared to that of the pure drug (Pure drug solubility is 0.18±0.04mg/mL). The results are tabulated in **Table 3** and graphical representation was shown in **Figure 3**.

Table 3: Solubility studies of solid dispersions prepared by solvent evaporation method:

S. No.	Formulation code	Solubility (mg/ml)*
1	Pure drug (Valsartan)	0.18±0.04
2	SD1	5.11±0.02
3	SD2	7.62±0.03
4	SD3	10.15±0.02
5	SD4	9.89±0.05
6	SD5	12.26±0.03
7	SD6	15.35±0.02
8	SD7	6.29±0.04
9	SD8	8.37±0.03
10	SD9	11.27±0.02
11	SD10	7.16±0.04
12	SD11	10.86±0.01
13	SD12	12.56±0.02
14	SD13	6.35±0.04
15	SD14	8.16±0.03
16	SD15	11.06±0.04

***Mean** ± SD, n=6

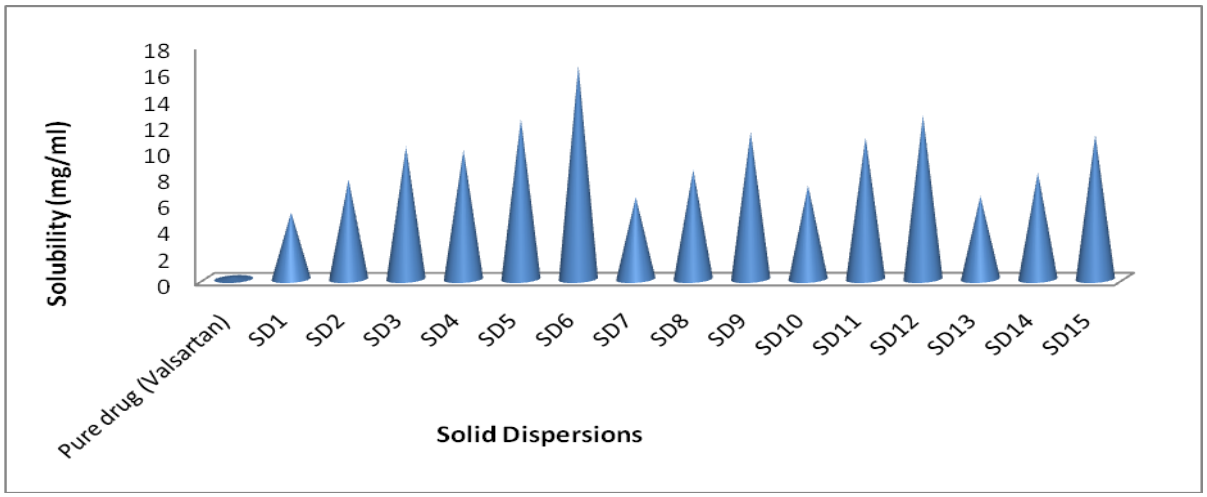

Fig. 3: Solubility studies of Valsartan solid dispersion

Table 4: % Practical yield and drug content for Valsartan solid dispersions

S. No	Formulation	% Yield	% Drug content
1	SD1	95.21%	91.47
2	SD2	92.46%	94.77
3	SD3	93.68%	87.62
4	SD4	94.88%	95.08
5	SD5	96.55%	92.47
6	SD6	98.68%	97.92
7	SD7	91.98%	93.50
8	SD8	96.22%	94.52
9	SD9	91.87%	91.53
10	SD10	94.26%	92.56
11	SD11	91.99%	94.57
12	SD12	96.12%	91.64
13	SD13	91.87%	92.43
14	SD14	93.27%	89.37
15	SD15	94.26%	92.52

% Practical yield and drug content:

The results of % practical yield for all formulations of solid dispersions found to be 91.98% - 98.68%. The results of % practical yield studies are shown in **Table 4**. Maximum yield was found to be 98.88% in formulation SD6. Actual drug content of all 15 formulations is shown in **Table 4**. The drug content of the prepared solid dispersions was found to be in the range of 87.62 - 97.92%. Maximum % drug content i.e. 97.92% was found in the formulation SD6.

***In vitro* dissolution studies**

The drug release data obtained for formulations SD1-SD15 are tabulated in **Table 5, 6 & 7**. *In vitro* studies reveal that there is marked increase in the dissolution rate of Valsartan from all the solid dispersions when compared to pure Valsartan itself. From the *in vitro* drug release profile, it can be seen that formulation SD6 containing Soluplus (1:3 ratio of drug: Soluplus) shows higher dissolution rate i.e. 99.2±2.3 % compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to the hydrophilic carrier. The increase in dissolution rate is in the order of Soluplus > Kolliphor P188> Kolliphor P407 >Kolliwax GMS> HPMC AS>. The graphical representation of solid dispersions of SD1-SD5, SD6-SD10& SD11-SD15 with the pure drug was depicted in **Figures 4, 5 & 6**.

Table 5: In vitro dissolution profile of pure drug and different formulations of Valsartan solid dispersions (SD1-SD5)

Time in Min	Cumulative % drug release					
	Pure drug	SD1	SD2	SD3	SD4	SD5
0	0	0	0	0	0	0
5	12.6±2.8	26.8±2.0	30.3±2.5	23.3±3.4	23.4±2.9	21.5±1.3
10	17.5±2.5	30.3±2.9	36.9±1.5	36.2±1.4	28.8±2.3	31.0±2.4
20	21.9±2.5	46.5±3.3	46.5±2.7	46.3±2.3	31.5±1.6	32.5±3.3
30	25.8±1.7	59.5±3.8	58.2±2.6	72.1±2.9	32.8±1.8	33.1±2.6
45	30.6±1.9	64.5±1.9	64.5±2.2	83.2±1.4	37.5±1.7	36.0±2.4
60	34.6±1.8	70.9±3.3	77.3±2.9	91.5±3.6	41.9±1.8	41.2±4.3
90	37.6±0.5	84.4±3.1	86.5±2.8	88.8±3.3	91.2±1.2	94.8±3.4

Table 6: In vitro dissolution profile of pure drug and different formulations of Valsartan solid dispersions (SD6-SD10)

Time in Min	Cumulative % drug release					
	Pure drug	SD6	SD7	SDV8	SD9	SD10
0	0	0	0	0	0	0
5	12.6±2.8	40.1±2.3	28.2±2.9	29.1±1.9	25.2±3.7	26.6±2.9
10	17.5±2.5	59.2±2.8	36.8±3.0	35.6±2.5	32.6±1.9	36.7±3.9
20	21.9±2.5	68.5±2.2	48.2±2.6	47.8±2.7	44.6±2.5	58.8±2.0
30	25.8±1.7	77.2±2.3	58.4±2.3	58.2±2.4	56.8±1.4	63.4±1.4
45	30.6±1.9	89.4±3.0	66.2±2.8	65.6±3.4	68.5±2.7	77.7±3.8
60	34.6±1.8	96.6±1.6	75.2±2.4	78.2±2.0	79.9±2.9	84.4±2.2
90	37.6±0.5	99.2±2.3	85.2±2.8	87.2±2.2	89.1±3.8	90.6±1.7

Table 7: In vitro dissolution profile of pure drug and different formulations of Valsartan solid dispersions (SD11-SD15)

Time in Min	Cumulative % drug release					
	Pure drug	SD11	SD12	SD13	SD14	SD15
0	0	0	0	0	0	0
5	12.6±2.8	29.1±1.9	25.2±3.7	26.6±2.9	25.2±3.7	26.6±2.9
10	17.5±2.5	35.6±2.5	32.6±1.9	36.7±3.9	32.6±1.9	36.7±3.9
20	21.9±2.5	47.8±2.7	44.6±2.5	58.8±2.0	44.6±2.5	58.8±2.0
30	25.8±1.7	58.2±2.4	56.8±1.4	63.4±1.4	56.8±1.4	63.4±1.4
45	30.6±1.9	65.6±3.4	68.5±2.7	77.7±3.8	68.5±2.7	77.7±3.8
60	34.6±1.8	78.2±2.0	79.9±2.9	84.4±2.2	79.9±2.9	84.4±2.2
90	37.6±0.5	92.2±2.2	93.1±3.8	82.6±1.7	85.1±3.8	88.6±1.7

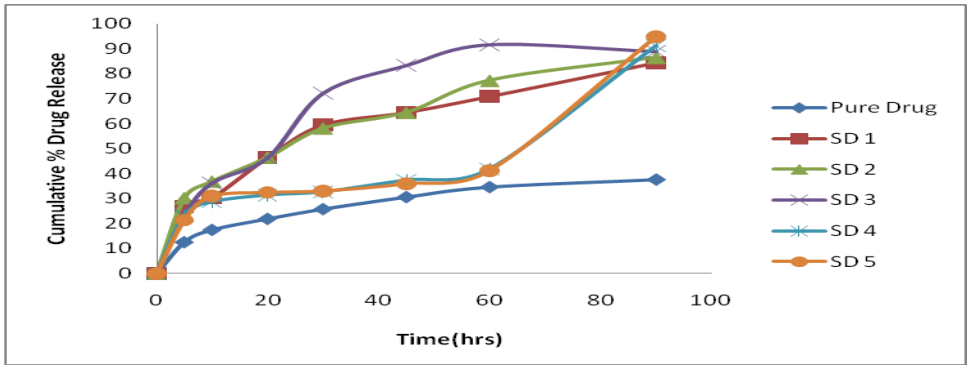

Fig 4: In vitro dissolution profile of pure drug and different formulations of Valsartan solid dispersions (SD1-SD5)

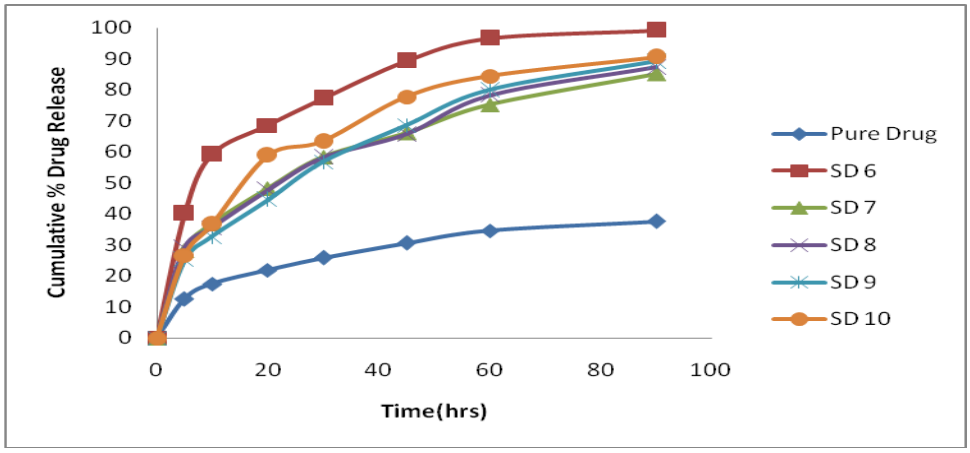

Fig 5: In vitro dissolution profile of pure drug and different formulations of Valsartan solid dispersions (SD 6-SD 10)

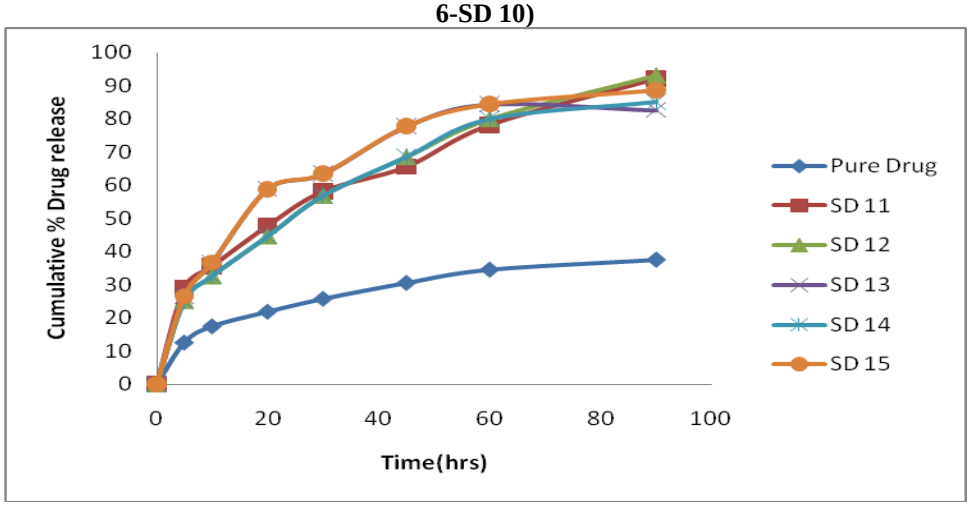

Fig 6: In vitro dissolution profile of pure drug and different formulations of Valsartan solid dispersions (SD 11-SD 15)

FTIR studies:

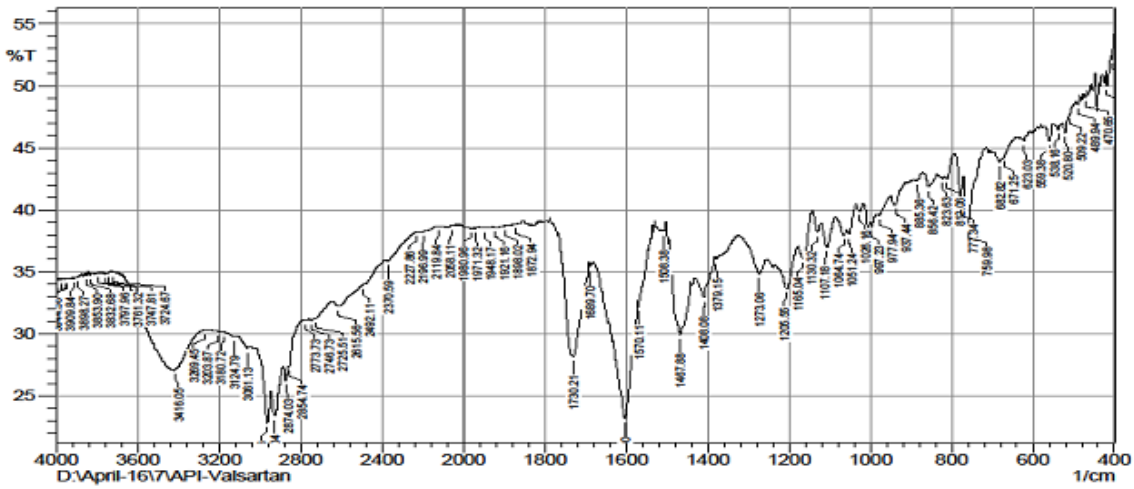

Figure 7: FTIR Spectrum of Valsartan pure drug

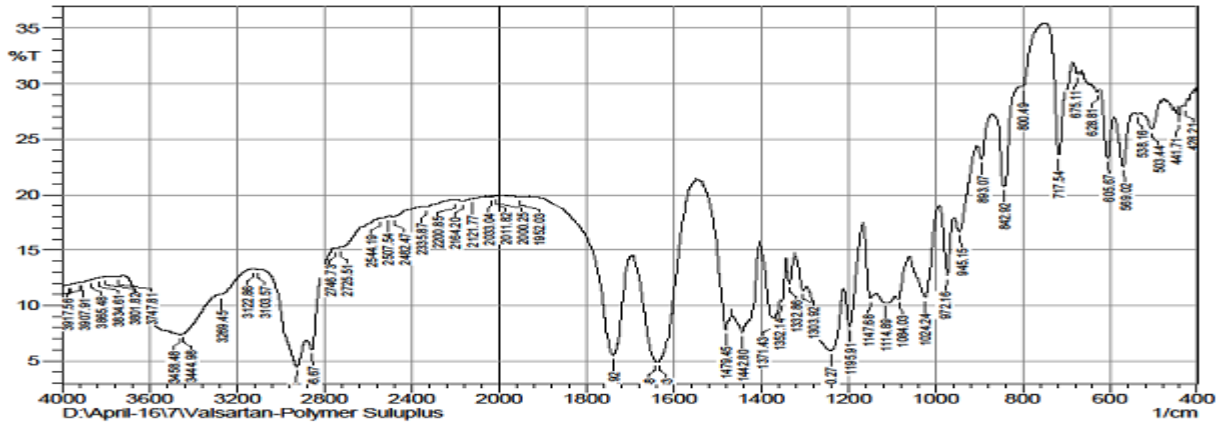

Figure8: FTIR Spectrum of soluplus

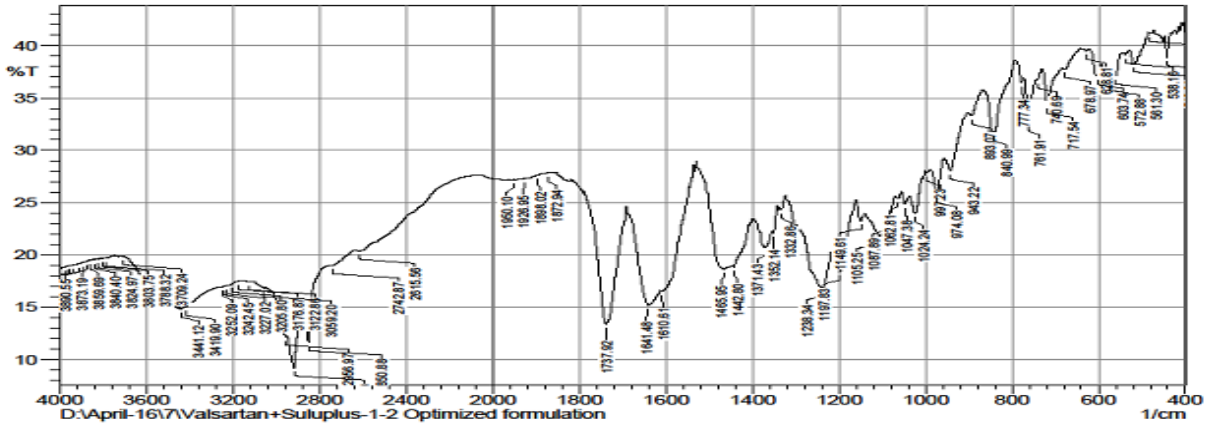

Figure 9: FTIR Spectrum of Valsartan optimized formulation SD6

The FTIR spectra of pure Valsartan displayed bands at 3419.9 cm^{-1} due to N-H stretch, at 2962.76 cm^{-1} due to C=N stretching, at 1732.13 cm^{-1} due to Carboxylate stretching. The spectra also showed bands at 1631.83 cm^{-1} due to C=O bending at 1107.18 due to C-N bonding (**Figure 7**). The FTIR spectrum of Valsartan solid dispersion of optimized formulation SD6 exhibited characteristic bands consistent with the molecular structure of Valsartan which indicated that no chemical interaction occurred between the drug and excipients used in the formulation (**Figure 9**).

Differential Scanning Calorimetry:

The DSC thermograms of pure Valsartan showed in (**Figure 10**)**,** sharp endothermic peak at melting point 116^0C, indicating that the drug is highly crystalline. The absence of drug peak in the solid dispersion formulation SD6 indicating the drug was converted into an amorphous form. As the intensity of the endotherm was markedly decreased in the drug - Soluplus 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.

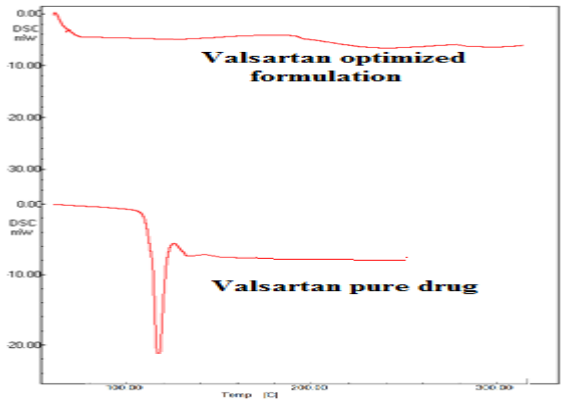

Fig. 10: DSC thermograms of Valsartan pure drug and optimized formulation SD6.

X-Ray Diffraction patterns:

The Valsartan solid dispersions were analyzed in Bruker D8 advanced PXRD instrument to find out whether the solid dispersions of various drug-polymer ratios are crystalline or amorphous. The presence of numerous distinct peaks in the XRD spectrum of pure valsartan indicates that Valsartan was present as a crystalline material (**Figure 11**). On the other hand, the spectrum of optimized formulation SD6 of solid dispersion was characterized by the complete absence of any diffraction peak, which is characteristic of an amorphous compound (**Figure 12**). The enhancement in the dissolution rate of the drug from the drug-Soluplus solid dispersion is ascribed to the marked reduction in the crystallinity of the drug.

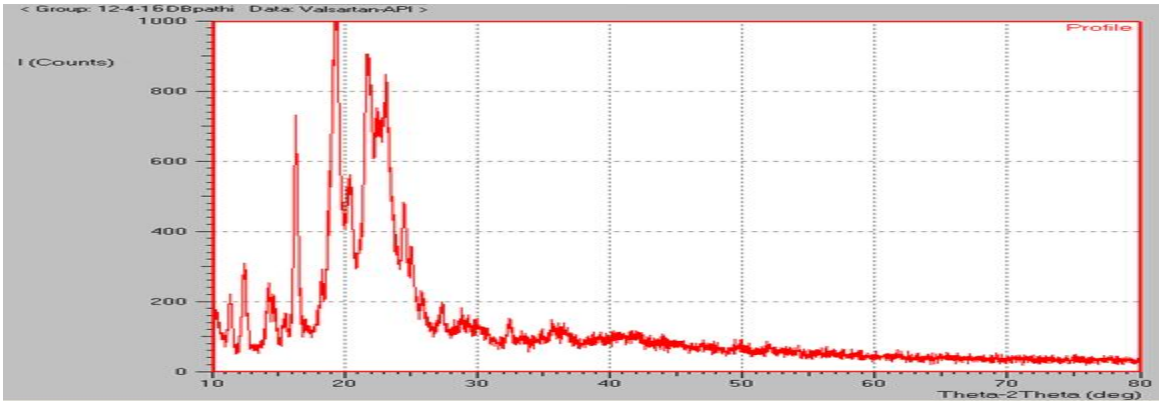

Fig 11: X-Ray powder diffractograms of Valsartan pure drug

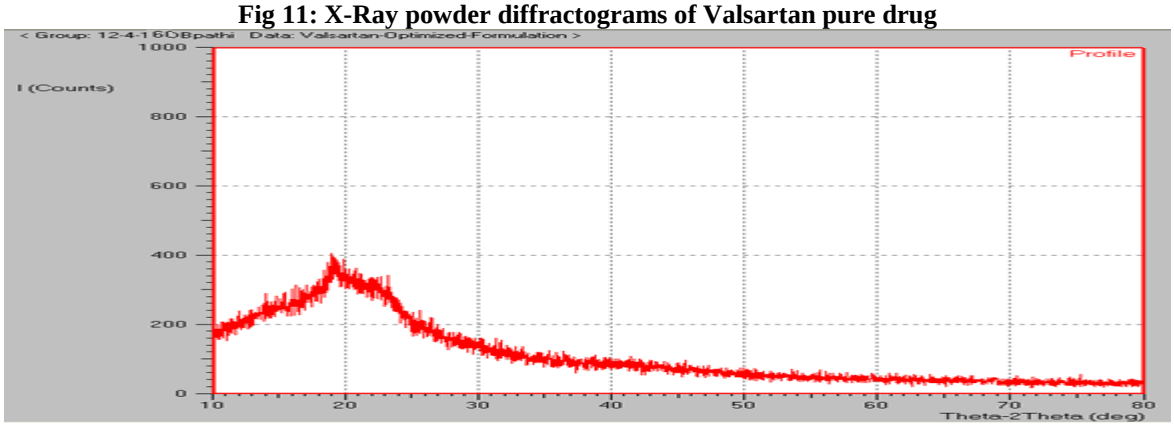

Fig 12: X-Ray powder diffractograms of valsartan optimized formulation SD6

SEM Studies:

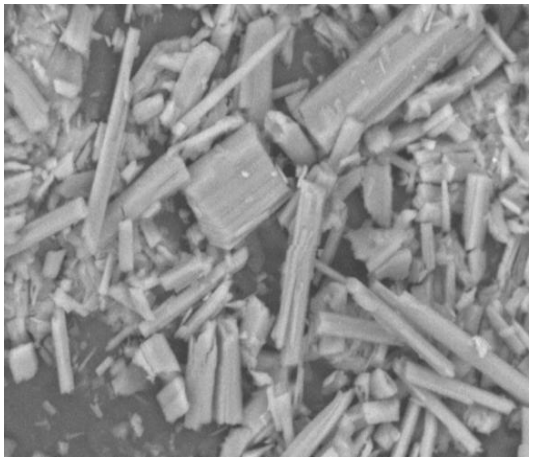

Fig 13: Pure drug of Valsartan

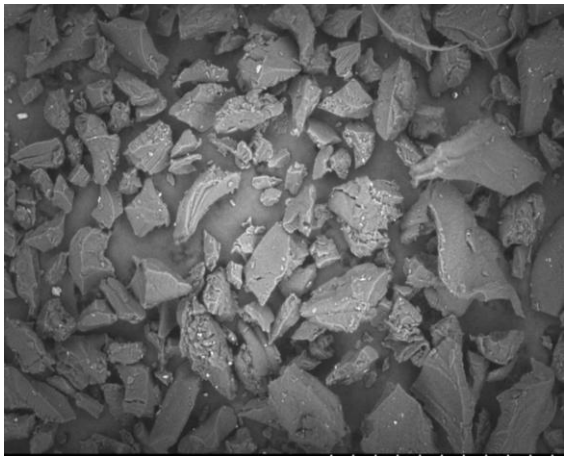

Fig 14: Valsartan formulation SD6

SEM photographs for pure drug and optimized formulation SD 6 are shown in **Figures 13 & 14** The drug crystals seemed to be smooth-surfaced, irregular in shape and size. In the 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 a wrinkled surface. Drug crystals appeared to be incorporated into the particles of the polymers. The solid dispersion looked like a matrix particle. The results could be attributed to the dispersion of the drug in the molten mass of the polymer.

Stability studies:

Optimized formulation (SD 6) was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months at accelerated stability conditions according to ICH guidelines. To evaluate the physical state of the drug, the systems were evaluated for drug content, In vitro drug release profile and characterized by XRD after storage for 6 months. The systems were stable during a 6-month period. From these results, it was concluded that optimized formulation is stable and retained their original properties with minor differences which depicted in **Table 8.**

Table 8: Evaluation parameters of optimized formulation (SD6) stored at 40 ±2^{0}C /75 ±5%RH

Retest time for optimized formulation (SD6)	% Drug content	*In-vitro* drug release (%) (at 90 min)
0 days (Initial)	97.92	99.2±2.3
30 days	96.20	97.8±1.3
60 days	95.75	96.2±2.3
90 days	95.05	95.7±3.1
180 days	94.52	95.2±6.4

CONCLUSION:

In the present study, it was clearly demonstrated that Valsartan solid dispersion formulation can be effectively produced by processing via solvent evaporation method with enhanced solubility and dissolution rate. Novel polymer–surfactant combinations were optimized and stable SD systems were developed successfully. Utilization of Soluplus 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 SD6 exhibited a cumulative release of 99.2% as compared to 37.6% for the pure drug after 90min. FTIR spectrum revealed that no chemical interaction occurred between the drug and excipients used in the formulation. Analysis by differential scanning calorimetry and powder X-ray diffraction 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. Finally, it could be concluded that solid dispersion of Valsartan using novel carriers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.

REFERENCES:

1.M. Mayer sohn and M. Gibaldi. J.pharm. sci 1996;55:1323.

2.Arias MJ, Gines JM, Moyano JR, Rabasco AM. The application of solid dispersion technique with D-mannitol to the improvement in oral absorption of triamterene. Journal of drug targeting. 1994; 2(1):45-51.

3.Lee S, Nam K, Kim MS, Jun SW, Park JS, Woo JS, Hwang SJ. Preparation and characterization of solid dispersions of itraconazole by using aerosol solvent extraction system for improvement in drug solubility and bioavailability. Archives of pharmacal research. 2005; 28(7):866-74.

4.Palmieri GF, Cantalamessa F, Di Martino P, Nasuti C, Martelli S. Lonidamine solid dispersions: in vitro and in vivo evaluation. Drug development and industrial pharmacy. 2002; 28(10):1241-50.

5.Ford JL. The current status of solid dispersions. Pharmaceutica Acta Helvetiae. 1985; 61(3):69-88.

6.Chaulang G, Patel P, Hardikar S, Kelkar M, Bhosale A, Bhise S. Formulation and evaluation of solid dispersions of furosemide in sodium starch glycolate. Tropical Journal of Pharmaceutical Research. 2009; 8(1):43-51.

7.Serajuddin A. Solid dispersion of poorly water- soluble drugs: Early promises, subsequent problems, and recent breakthroughs. Journal of pharmaceutical sciences. 1999; 88(10):1058-66.

8.Gupta A et al., Recent trends of fast dissolving tablet-An overview of formulation technology. International Journal of Pharmaceutical & Biological Archive. 2010; 1(1):1-10

9.Higuchi T, Connors KA. Phase-solubility techniques. Adv Anal Chem Instrum 1965; 4: 117–122.

10.Rao M, Mandage Y, Thanki K, Bhise S. Dissolution improvement of simvastatin by surface solid dispersion technology. Dissolution technologies. 2010; 17(2):27-34.

11.Lakshmi K, M. Pranav kumar reddy, Rajesh kaza. Dissolution enhancement of telmisartan by surface solid dispersion technology. International Journal of Innovative Pharmaceutical Research. 2012; 3(4): 247-251.
12.Ketan S, Chauhan CS, Dumaniya D, Patel B. Formulation Development and Evaluation of Immediate Release Tablet of Poorly Soluble Candesartan Cilexetil. Journal of Pharmaceutical science and Bioscientific Research. 2013; 3 (2):77-90.
13.Chaudhari MD, Sonawane RO, Zawar LA, Nayak SA, Bari SB. Solubility and dissolution enhancement of poorly water-soluble Glimepiride by using solid dispersion technique. Int J Pharm Pharm Sci. 2012; 4(5):534-9.
14.Jambarapu PK, Ramarao T, Jayaveera KN, Dvrn B, Yamsani MR. Design and In vivo evaluation of Metoprolol Tartrate bilayer floating tablets in healthy human volunteers. International Journal of Drug Delivery. 2014; 6(1):14.
15.Fule R, Amin P. Development and evaluation of lafutidine solid dispersion via hot melt extrusion: Investigating drug-polymer miscibility with advanced characterisation. asian journal of pharmaceutical sciences. 2014; 9(2):92-106.
16.Mahmah O, Tabbakh R, Kelly A, Paradkar A. A comparative study of the effect of spray drying and hot- melt extrusion on the properties of amorphous solid dispersions containing felodipine. Journal of Pharmacy and Pharmacology. 2014; 66(2):275-84.
17.Breitenbach J. Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics. 2002; 54(2):107-17.