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Co-Crystals of Valsartan: Preparation and Characterization

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Abstract
Valsartan is an angiotensin II receptor antagonist effectively used in the management of hypertension. Valsartan has poor solubility and dissolution rate which leads to the poor a bioavailability (about 23%). Thus an attempt was made to prepare Co-crystals of Valsartan with different coformer to improve the solubility and dissolution rate. The valsartan Co-crystals using coformer such as succinic acid, fumaric acid and oxalic acid was prepared by Solvent evaporation method. The prepared Valsartan Co-crystals were evaluated for saturation solubility, dissolution rate and micromeritic studies. The Valsartan Co-crystals were characterized by Fourier Transform Infrared Spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC), X-Ray Diffraction (X-RD) and Scanning Electron Microscopy (SEM). The solubility and dissolution rate of Valsartan Co-crystals was significantly improved compare with the pure valsartan. The melting point of Valsartan cocrystals was shifted to lower temperature supports the solubility enhancement. The Valsartan cocrystals showed improvement in the flow properties which was helpful during the compression of cocrystals into the tablet. The FT-IR data showed the slight shifting of the peaks in the co-crystals spectra which supports the formation of new solid phase. The DSC spectra indicate the slight decrease in the melting point of Valsartan cocrystals compare to pure valsartan. The crystallinity of the cocrystas was decrease in the Co-crystals due to lattice arrangement between Valsartan and Coformer. The SEM photomicrograph showed difference in the habit of Valsartan co-crystals and the pure valsartan. Thus Cocrystals techniques was successfully employed in the solubility and dissolution rate enhancement of Valsartan.

Keywords
Valsartan, FT-IR, Solubility, melting point, X-RD, Dissolution rate.

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INTRODUCTION

Majority of drugs marketed worldwide are administered by oral route. About 40% of the new molecular entities coming from discovery were never brought to the market because of biopharmaceutical issues like low solubility, low dissolution rate, low permeability and first-pass metabolism. There are various methods to improve the dissolution/ bioavailability of poorly soluble drugs including Pro-drug approach, Salt synthesis, Particle size reduction, Complexation, Change in physical form, Solid dispersions & Spray drying. Amongst them Salt formation is one of the most frequently used approaches to improve physiochemical properties of moieties which involve formation of ionic bonds[1,2,3]. In the pharmaceutical industry, the shortage of properties of biopharmaceutical drugs such as ineffective medication constitutes 1 % of the major cases in the market.[4] These issues are the direct results of the solubility property of the drug. Approximately 70 % of candidate drugs have problems with the solubility, therefore, it is a big challenge in the field of pharmaceuticals to developing drugs and drug dosage forms to show a good profile of solubility and dissolution rate, especially for oral preparations[5]. Pharmaceutical cocrystals have attracted phenomenal interest in recent years for their potential for improving the physicochemical properties of drug substances[6,7]. Apart from offering potential improvements in solubility, dissolution rate, bioavailability and physical stability, pharmaceutical cocrystals can enhance other essential properties of the APIs such as flow ability, chemical stability, compressibility and hygroscopicity[8,9]. Cocrystals are homogeneous solid phases containing two or more neutral molecular components in a crystal lattice with defined stoichiometry, which are solids at room temperature and are held together by weak interactions, mainly hydrogen bonding[10,11]. In cocrystals at least one component is molecular and a solid at room temperature i.e. co-former and forms a supramolecular synthon with a molecular or ionic API[12]. Valsartan is angiotensin II receptor antagonist, widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction, and in the management of heart failure. This drug is a BCS class II drug with poor aqueous solubility. Valsartan is rapidly absorbed after oral dose with bioavailability of about 23%. Peak plasma concentration occurs within 2-4 hrs and its plasma half-life 5-7 hrs after oral dose[13]. Thus, an attempt was made to prepare valsartan Co-crystals using co-former such as p- amino benzoic acid by Solvent evaporation method to improve the solubility and dissolution rate and micromeritic properties.

MATERIALS AND METHODS

Valsartan obtained as a gift sample from Alembic Ltd. Baroda, Gujrat, India. Succinic acid, fumaric acid, oxalic acid and other solvents purchased from SD Fine Chemical Mumbai and all the solvents used are of analytical grade.

Preparation of Co-crystals of Valsartan

The Valsartan- succinic acid, Valsartan fumaric acid and Valsartan oxalic acid Cocrystals were prepared using Solvent evaporation method. The 1:1 ratio of Valsartan and co-former was dissolved with methanol in a beaker. The beaker was covered with a paper having hole, for allowed to evaporate the solvent at ambient temperature. The Co-crystals were collected by filtration through a Whatmann filter paper, dried in air for 24 hr. and stored in desiccators until further characterization and evaluations[14].

Characterization of Cocrystals

Scanning electron microscopy

Photomicrographs of the Valsartan Co-crystals and pure Valsartan were obtained by (JEOL 5400, Japan) scanning electron microscope. Samples were mounted on a metal stub with an adhesive and coated with gold ions for 5-6 minutes under vacuum[15].

Fourier Transform Infrared Spectroscopy

Valsartan Co-crystals and pure Valsartan were scanned and recorded in the range of 400-4000 cm^{-1} by using Infrared spectrophotometer, (Thermo, India). The sample of Co-crystals were placed uniformly on the sample holder and analyzed using the FT-IR software and the spectra were recorded.[16].

Differential scanning calorimetry

DSC thermograms were obtained by heating the samples (2 mg) of Valsartan Co-crystals and pure valsartan at a constant heating rate of 10^0C/min with chart speed of 50/100 mL/min under an atmosphere of nitrogen. The exact peak temperatures, melting point and heat of fusion were automatically calculated. The temperature range for the scan was 30^0 to 300^0 C for all the samples[17].

X-ray diffraction spectroscopy

X-ray diffraction pattern of Valsartan Cocrystals and pure Valsartan were obtained using the X-ray diffractometer (Bruker, D8 Advance, Germany) at 50 kV, 34 mA and a scanning rate of 0.02° /min at the diffraction angle 2θ over the range of 3°C to 35°C using Cu (as anode) radiation of wavelength 1.5406 Å[18].

Solubility studies

Solubility measurements of Valsartan were performed according to a published method. Valsartan Co-crystals equivalent to 100 mg of valsartan was shaken with 10ml distilled water in stoppered conical flask in an orbital shaker for 24 hrs. at room temperature. Subsequently, the solutions were filtered through a Whatman filter paper no 1. Filtered solution was diluted properly with pH 7.4 phosphate buffer. The diluted solutions were analyzed for the Valsartan in UV 250 nm. (Shimadzu, UV-1800, Japan.)[19].

Dissolution studies

Dissolution study was carried out to determine the rate and extent of dissolution. Weight accurately 40 mg of Valsartan Co-crystals and fill into the capsule shell. The dissolution study of Valsartan was performed separately in 900ml at 37ºC+0.5ºC at 50 rpm. Aliquots of 5ml from the dissolution medium were withdrawn at 5 min time interval and replenished by an equal volume of fresh dissolution medium. The samples were filtered through what man filter paper and analyzed by UV visible Spectrophotometer by measuring absorbance at 250 nm.[20] (Shimadzu, UV-1800, Japan)[20].

Micromeritic Properties of Co-crystal

Angle of repose:

It was determined by fixed funnel method. Accurately weighed quantity (5gm) of drug was taken in a funnel; the height of the funnel is adjusted such that the tip of the funnel just touches the apex of heap of the blend. Then the drug is allowed to flow through the funnel freely on to the surface. The diameter is then measured and angle of repose was calculated by following equation[21].

Where θ is angle of repose, his height of the cone and r is radius of the cone base.

Bulk and Tapped density:

It was determined by pouring a weighed quantity (5gm) of drug in to a graduated cylinder. The cylinder was dropped at 2 sec intervals on hard wood surface three times from the height of 1 inch. It was then calculated by the equation given below.

$$\text{Bulk Density} = \frac{\text{Weight of Powder}}{\text{Bulk Volume}}$$

It was determined by pouring a drug (5gm) in a measuring cylinder. The cylinder was dropped at 2 sec intervals on hard surface 100 times from the height of 1 inch. Then the final volume occupied by the drug was measured.

$$\text{Tapped Density} = \frac{\text{Weight of Powder}}{\text{Final Volume}}$$

Compressibility index and Hausner ratio

The compressibility index (Carr's index) is a measure of a powder to be compressed.

Carrs Index =W1-W2/W1*10

W1= tapped density, W2= bulk density

The Hausner ratio of powder was calculated according to equation given below.

$$\text{Tapped Density} = \frac{Dt}{Df}$$

here, Dt = tapped density, Df = bulk density

RESULT AND DISCUSSION

Scanning electron microscopy

The crystal morphology of pure Valsartan and its Co-crystals prepared using solvent evaporation method were studied using Scanning electron microscopy. The SEM showed that the pure Valsartan was small rod like crystals. While Co-crystals formed using succinic acid, oxalic acid and fumaric acid possess irregular and smaller size crystals compare to pure Valsartan. The change in the habit of Valsartan Co-crystal compared to pure Valsaran indicates the formation of new solid phase. The photomicrograph of pure valsartan and its cocrystals were shown in Fig.1(a)-(d).

FT-IR Infrared spectroscopy

The possible interaction of Valsartan and coformers were studied by FT-IR spectroscopy. The FT-IR spectra of pure Valsartan showed sharp characteristics peaks. The spectra of pure Valsartan show Characteristic peaks appeared at 2922.24 cm^{-1} (C-H stretching), 1552.28 cm^{-1} (C-N stretching), 1733.94 cm^{-1} (C=O stretching), 1472.80 cm^{-1} (C=C stretching).

The FT-IR spectra of Co-crystals of Valsartan with Succinic acid, Valsartan with fumaric acid and Valsartan with oxalic acid when compared with the spectra of pure Valsartan, shown slightly or no change in the characteristics peaks. These results indicated that there is no chemical interaction between Valsartan and co-former using methanol as a solvent. The FT-IR spectra were shown in Fig. 2(a)-2(d).

Differential scanning calorimetry

DSC is one of the techniques used for the characterization and confirmation of formation of Co-crystals. The thermal behavior of pure Valsartan and Co-crystals were shown in fig 3(a)-3(d). The DSC curve showed that Valsartan appeared on sharp endothermic peak at about 103.31^{0}C corresponding to its melting point. However, the Co-crystals obtained in the presence of coformer such as succinic acid, fumaric acie and oxalic acid showed the shift of endothermic peak towards lower temperature at 93.63^{0}C, 94.84^{0}C and 95.05^{0}C respectively. Shift of endothermic peak towards lower temperature

indicates the decrease in the melting point of drug in Co-crystals. This decreased melting point in the co-crystals indicates increased in the solubility of Valsartan.

XRD studies:

The XRD patterns of Valsartan co-crystals shows a variation in intensity of peaks as compared to that of the pure Valsartan and co-formers shown in Fig.4(a)-4(d). From XRD spectra it was observed and concluded that, the intensity and number of peaks were reduced in the XRD spectra of valsartan co-crystals compare to pure Valsartan indicate that the reduction in crystallinity and formation of new bonding's in the co-crystals This variation in the XRD pattern of pure valsartan and its Co-crystals due to change in the crystal lattice structure of valsartan and co-former owing to the interaction between the drug and the co-former.

Solubility and Dissolution studies

Pure Valsartan shows 45.12 ± 0.26 mg/ml aqueous solubility. Co-crystallization technique shows significant improvement in the aqueous solubility of Valsartan. Formation of Co-crystals using co-formers like Succinic acid, fumaric acid and Oxalic acid leads to the improvement of solubility. VLN- SA Cocrystals showed Highest solubility (470.58 ± 0.25) whereas the VLN- FA Cocrystals (383.11 ± 0.23) and VLN- OA Co-crystals (355.35 ± 0.24) solubility compared to pure Valsatan. VLN- SA Co-crystals improved solubility nearly 11 time whereas VLN- SA Cocrystals nine time and VLN- SA Cocrystals 8 time compared to pure Valsartan. The solubility data are shown in Table.1.

The dissolution curves of pure Valsartan and its Co-crystal in phosphate buffer pH7.4 were shown in Fig. 5. It was evident that the VLN Co-crystals have improved the drug dissolution rate (80.50%-96.35%) significantly as compared to pure Valsartan (65.23%) within 60 min. The faster dissolution of Valsartan from Co-crystals form might be due to altered crystallinity pattern, size and shape and crystal habit which lead to improve wettability and solubility of crystals in dissolution media. VLN- SA Cocrystals showed Highest dissolution rate (96.35%) whereas the VLN- FA Cocrystals (85.84 %) and VLN- OA Co-crystals (80.50%) compared to pure Valsartan (35.20%) in 60 min.

Micromeritic properties study:

The prepared cocrystals showed improved flow ability properties when compared to pure drug as observed from the values of angle of repose (24.05^{o}-25.34^{o}), Hausnar's ratio (1.12–1.13) and Carr's index (16.02–18.34%). All Co-crystals prepared using co-former showed maximum flow ability as evident by low values of angle of repose, Hausnar's ratio and Carr's index. Whereas Pure Valsartan exhibited poor flow ability and compressibility as indicated by high value of angle of repose (42.40^{0}), Hausnar's ratio (1.45) and Carr's index (36.63%). The micromeritic data are shown in Table.2.

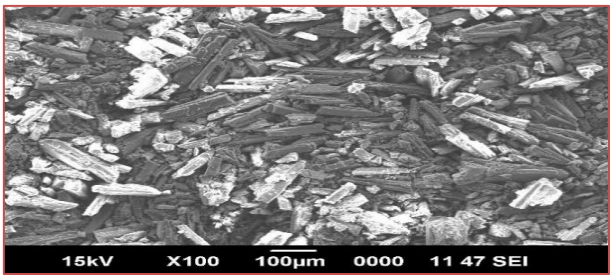

Fig. 1. (a) Pure Valsartan

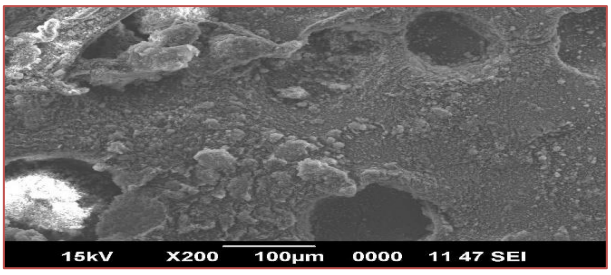

Fig. 1. (b) VLN- SA Co-crystals

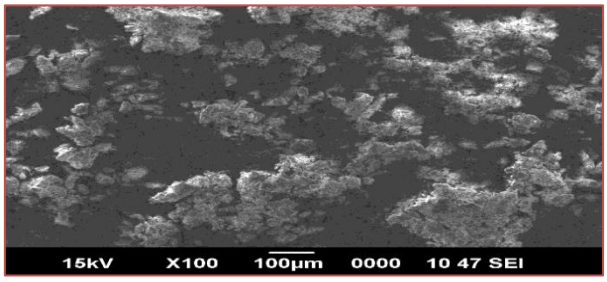

Fig. 1. (c) VLN- FA Co-crystals

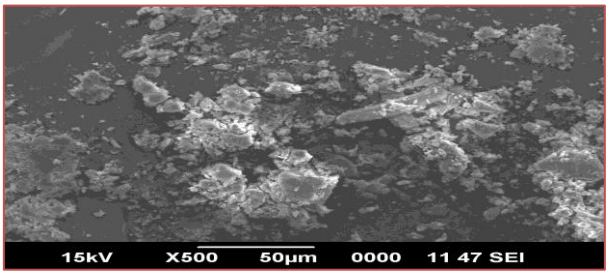

Fig. 1. (d) VLN- OA Co-crystals

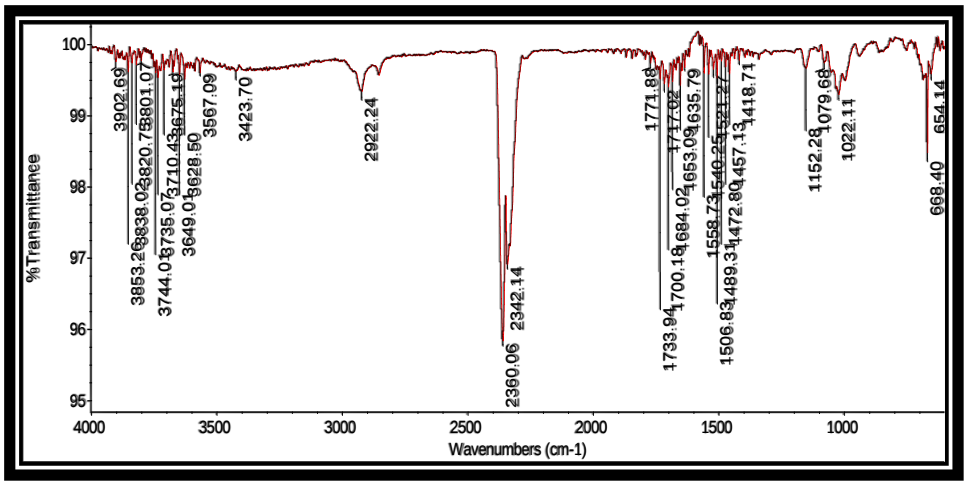

Fig.2 (a). FT-IR Spectra of Pure Valsartan

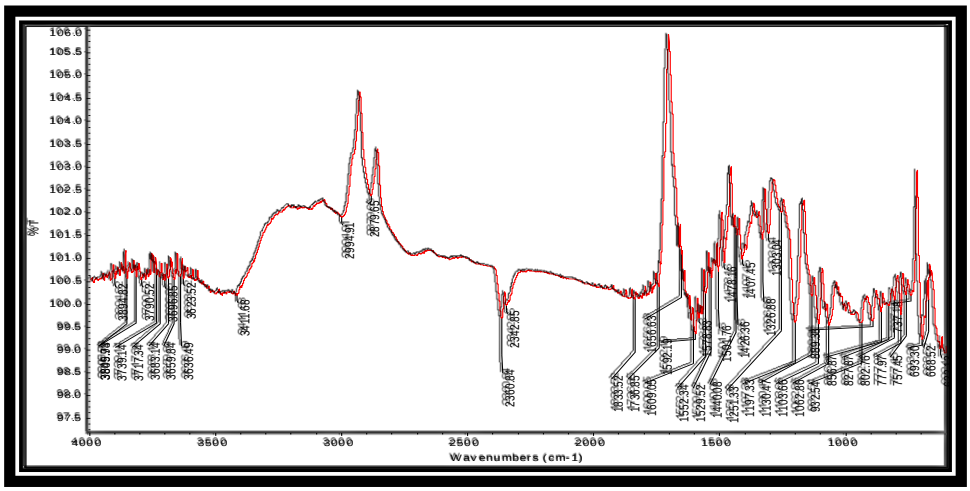

Fig.2 (b). FT-IR Spectra of Valsartan- Succinic Acid Co-crystals

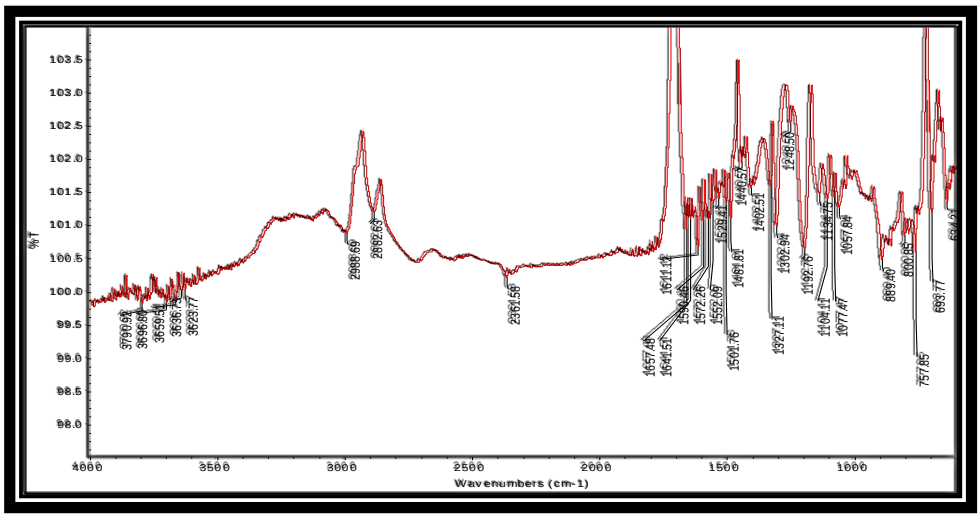

Fig.2 (c). FT-IR Spectra of Valsartan- Fumaric Acid Co-crystals

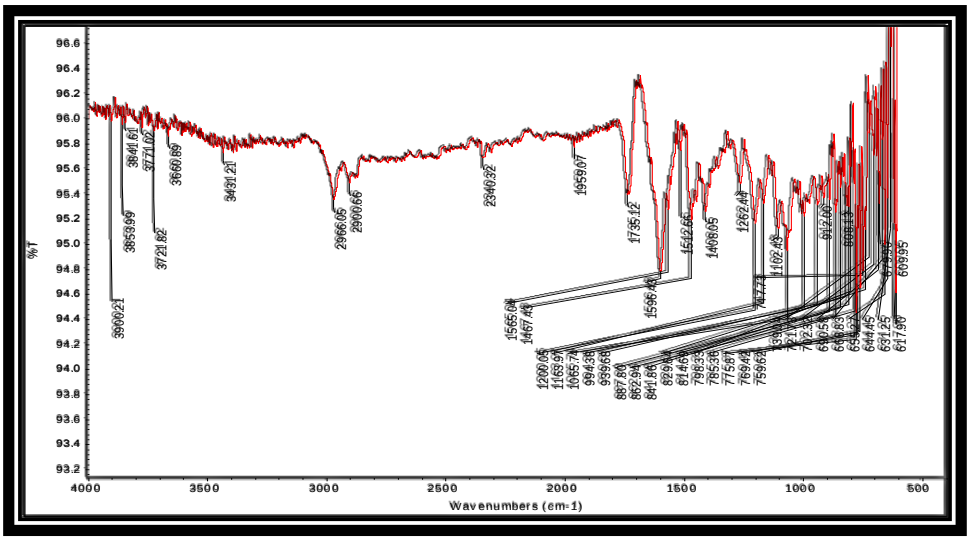

Fig.2 (d). FT-IR Spectra of Valsartan- Oxalic Acid Co-crystals

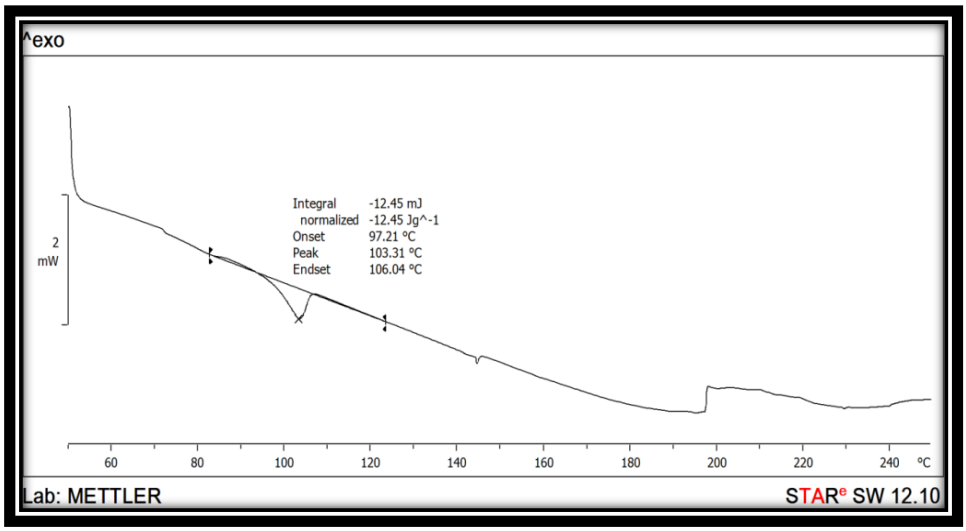

Fig.3. (a). DSC Spectra of Pure Valsartan

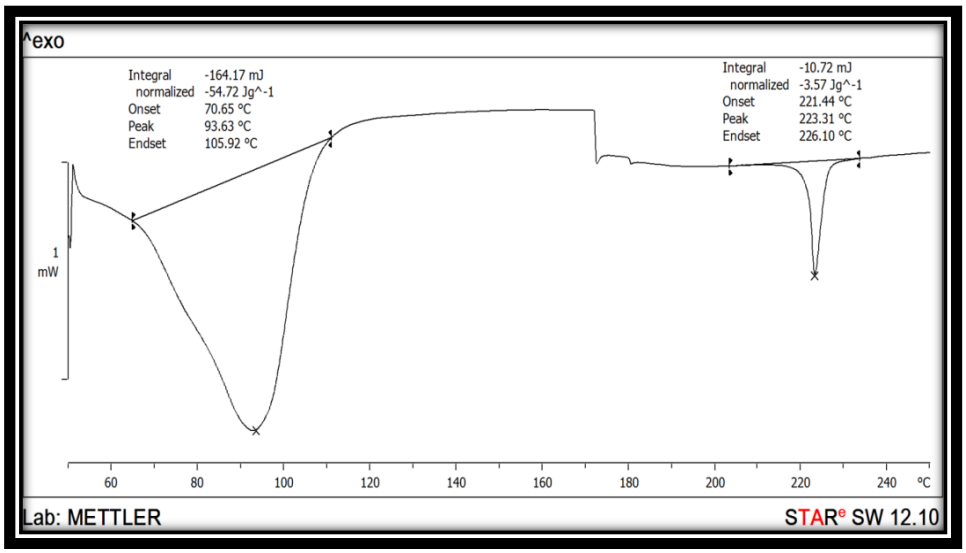

Fig.3. (b). DSC Spectra of Valsartan- Succinic Acid Co-crystals

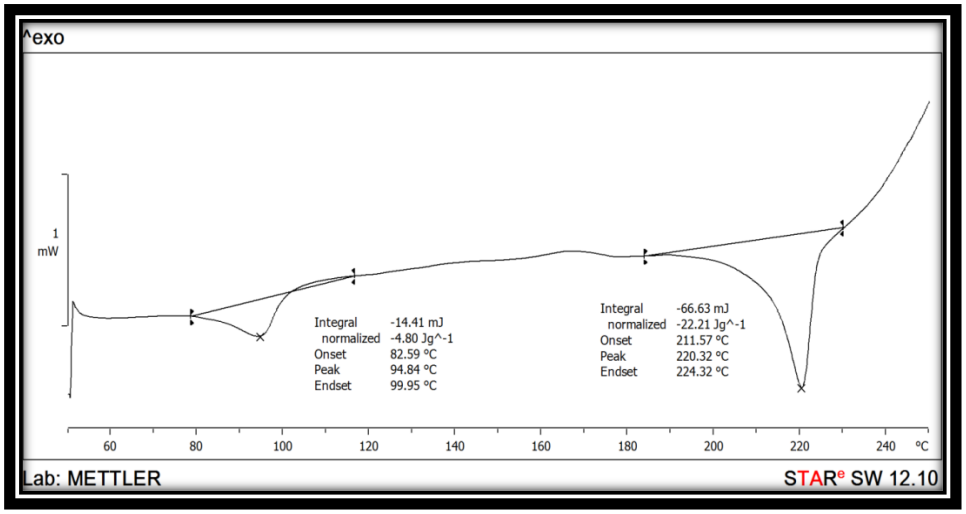

Fig.3. (c). DSC Spectra of Valsartan- Fumaric Acid Co-crystals

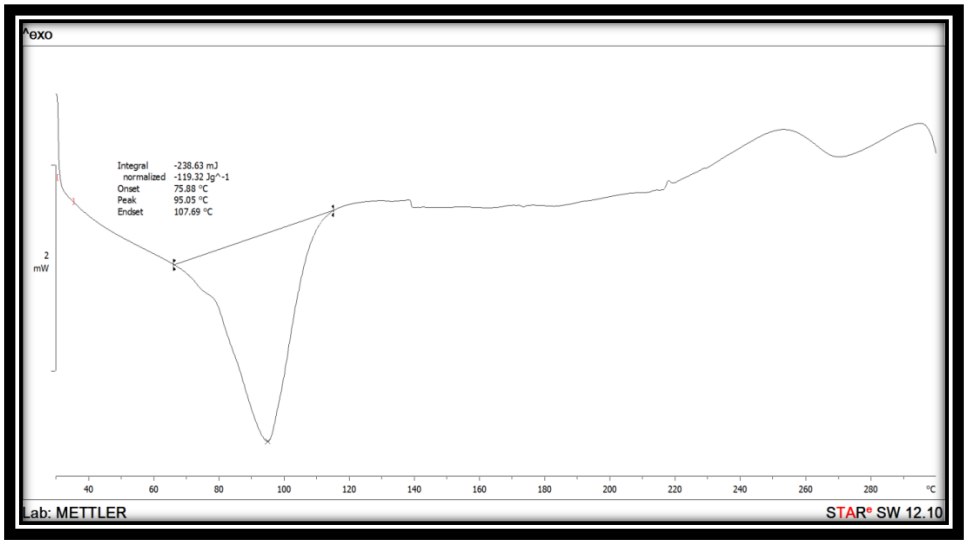

Fig.3. (d). DSC Spectra of Valsartan- Oxalic Acid Co-crystals

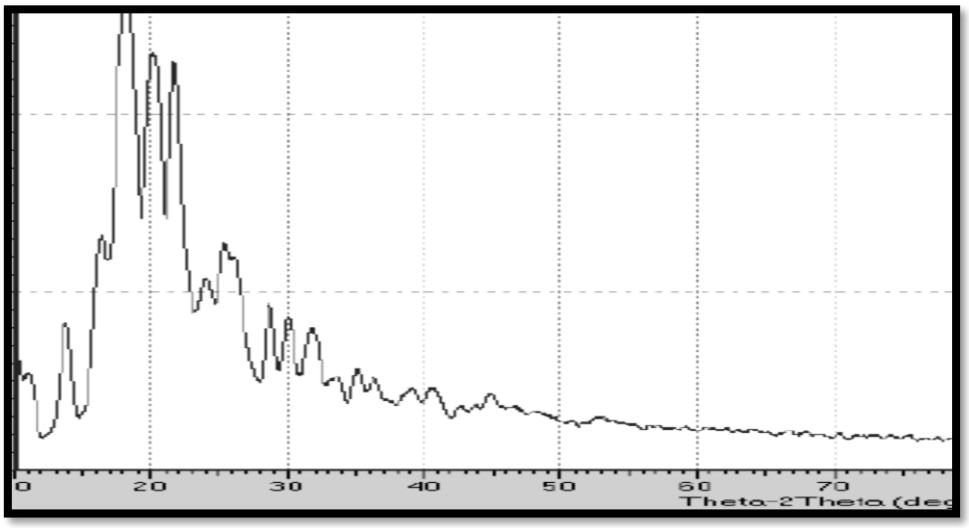

Fig.4. (a). XRD Spectra of Pure Valsartan

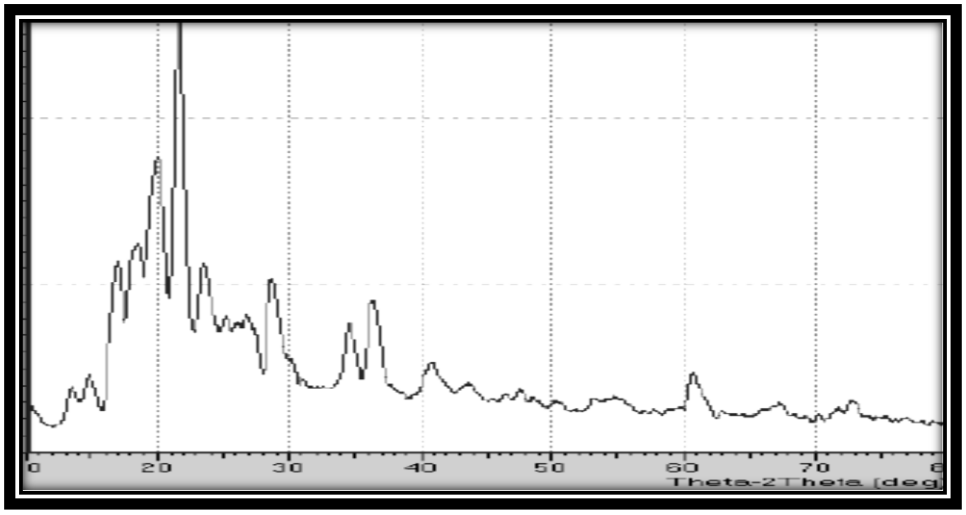

Fig.4. (b). XRD Spectra of Valsartan- Succinic Acid Co-crystals

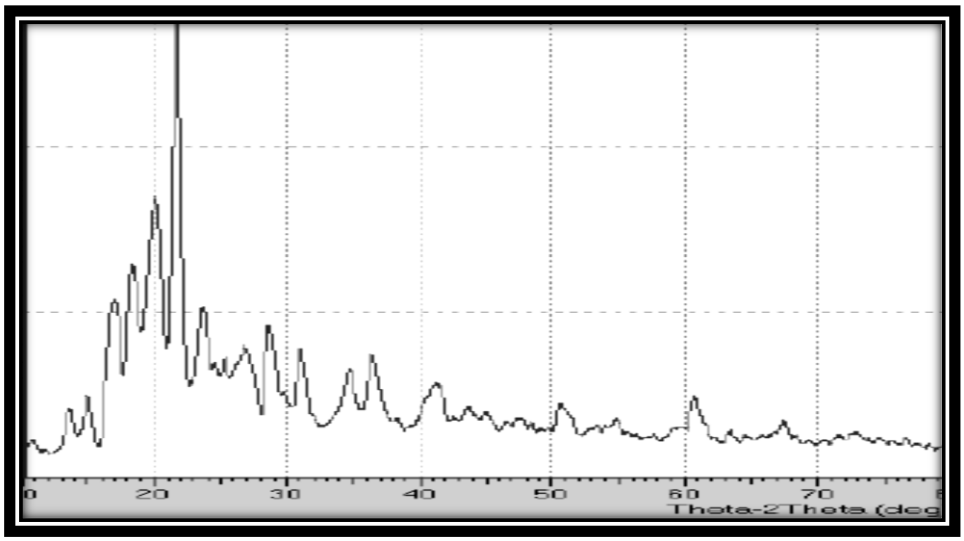

Fig.4. (c). XRD Spectra of Valsartan- Fumaric Acid Co-crystals

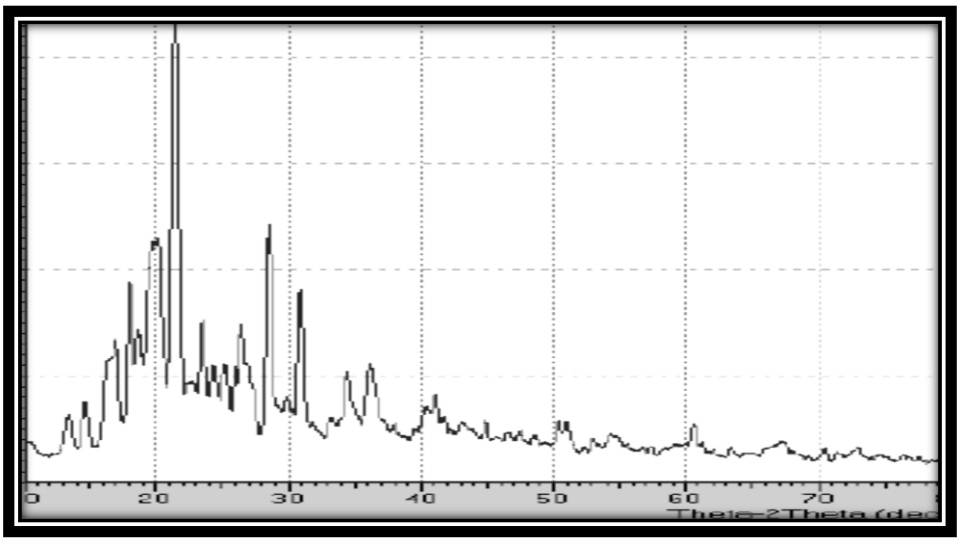

Fig.4. (d). XRD Spectra of Valsartan- Oxalic Acid Co-crystals

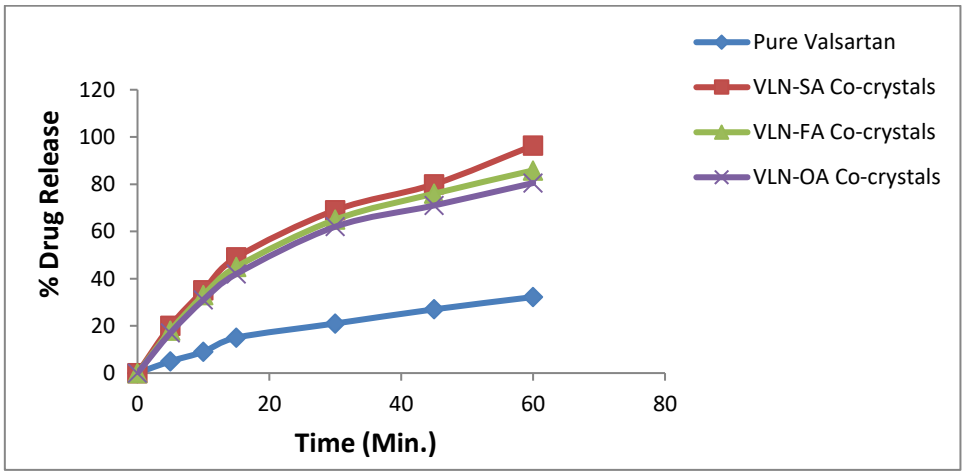

Fig.5. Dissolution Studies of Pure Valsartan and its Co-crystals.

Table No. 1: Saturation solubility studies of Pure Valsartan and its Co-crystals

Sr. no	Formulation code	Saturation solubility (µg/ml)	Folds increase in solubility
1	Pure Valsartan	45.12 ± 0.26	--
2	VLN-SA Co-crystals	470.58 ± 0.25	10.42
3	VLN-FA Co-crystals	383.11 ± 0.23	8.49
4	VLN-OA Co-crystals	355.35 ± 0.24	7.87

Table No.2. Micromeritic studies of Pure Valsartan and its Co-crystals

Sr. No.	Formulation code	Angle of repose (θ°)	Hausnar's ratio	Compressibility index
1.	Pure Valsartan	42.40 ± 0.11	1.45 ± 0.06	36.63 ± 0.11
2.	VLN-SA Co-crystals	24.05 ± 0.07	1.12 ± 0.05	16.69 ± 0.01
3.	VLN-FA Co-crystals	25.34 ± 0.18	1.13 ± 0.05	18.34 ± 0.06
4.	VLN-OA Co-crystals	24.26± 0.13	1.12 ± 0.11	16.02 ± 0.12

CONCLUSION

The present deals with the study of solubility enhancement of Valsartan by Co-crystals technique. The prepared Valsartan Co-crystals with all the co-former showed improvement in the solubility, dissolution and micromeritic properties compared to pure Valsartan. The analytical studies showed that there was no chemical interaction between the drug

and co-former and also confirmed the formation of co-crystals. Thus Co-crystal method is successfully employed for the improvement of solubility and dissolution rate of Valsartan.

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CONFLICT OF INTEREST

I/ we certify that have declare no conflict of interest for this publication.

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