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Original Article

CO-CRYSTALS OF CARVEDILOL: PREPARATION, CHARACTERIZATION AND EVALUATION

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ABSTRACT

Objective: Carvedilol an antihypertensive drug, exhibits poor solubility and dissolution rate. Hence an attempt has been made to prepare the Co-crystals of Carvedilol to increase the solubility and dissolution rate.

Methods: The Co-crystals of Carvedilol were prepared using coformer such as succinic acid, fumaric acid and oxalic acid by Solvent evaporation method. The prepared Co-crystals were evaluated for solubility, dissolution rate and micrometric properties. The Co-crystals were characterized by scanning electronic Microscopy (SEM), FT-Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) and X-ray Diffractometry (XRD).

Results: SEM of pure carvedilol and Cocrystals morphology clearly showed the formation of a new solid phase with the coformer. The FT-IR spectra indicate the shifting of characteristic peak in the Co-crystals but does not show any interaction between the co-former used. DSC data showed the change in the endotherm with the melting point of Co-crystals. XRD spectra indicate the notified difference in the 2θ and the intensity of the peaks. Solubility of CAR-SA Cocrystals (2.225±0.35), CAR-FA Cocrystals (1.880±0.20) and CAR-OA Cocrystals (1.128±0.23) was markedly improved compared to pure Carvedilol (0.376±0.06). Thus the increased in dissolution rate for CAR-SA Cocrystals (93.72 %). was highest whereas CAR-FA Cocrystals (91.56 %), CAR-OA Cocrystals (88.93 %) compared to pure Carvedilol (40.3) within 60 Min. The Carvedilol cocrystals were also showed improvement in the flow properties compare to pure Carvedilol.

Conclusion: Hence the Co-crystal formation could be helpful to improve the solubility, dissolution and micromeritic properties of Carvedilol.

Keywords: Carvedilol, Co-crystals, Solubility, FT-IR, Dissolution rate, Micromeritic properties

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INTRODUCTION

For hydrophobic drugs, the dissolution process act as the rate-controlling step and which determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans. Thus, one of the major challenges of drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water [1]. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity [2-4]. Bioavailability of poorly water-soluble hydrophobic drugs [Class II in Biopharmaceutics Classification System] is limited by their solubility and dissolution rate. As a result, more than 40% of new candidates entering the drug development pipeline fail because of non-optimal biopharmaceutical properties [5]. Many approaches have been adopted for improving the aqueous solubility of drugs including micronization, emulsifications, solubilization using co-solvents, and the of polymer drug vehicles for delivery of poorly water soluble drug. Although these techniques have been shown to be effective at enhancing oral bioavailability, the success of these approaches dependent on the specific physiochemical nature of the molecule being studied [6]. Over the last decade, there has been growing interest in the design of pharmaceutical co-crystals, which has emerged as a potential method for enhancing the bioavailability of drugs with low solubility. Co-crystal can be defined in a number of ways. A restrictive definition utilized by that co-crystals are structurally homogenous crystalline materials containing two or more components present in definite stoichometric amounts. The co-crystals components are discrete neutral molecular reactants which are solid at ambient temperature. Based on this definition of co-crystal, a pharmaceutical co-crystal means co-crystals with one of the co-crystal component as an Active Pharmaceutical Ingredient (API) and other components are called conformers [7, 8]. Co-crystals incorporate pharmaceutically acceptable guest molecules into the crystal lattice along with active pharmaceutical ingredient (API). Co-crystal has gained attention as attractive alternate solid forms for drug development. Physicochemical properties of pharmaceutical can be improved by obtaining co-crystals using co-crystallization. Co-crystallization with pharmaceutically acceptable compounds does not affect pharmacological activity of the API but can improve physical properties, such as solubility, hygroscopisity, compaction behavior [9].

The present study deals with preparation and characterization of Carvedilol cocrystals using suitable coformer to improve the solubility, dissolution rate and micromeritic properties.

MATERIALS AND METHODS

Carvedilol obtained as a gift sample from Glenmark generics, limited, Goa, India. Succinic acid, fumaric acid, oxalic acid and solvents were purchased from SD Fine Chemical Mumbai. All the solvents used are of analytical grade.

Preparation of co-crystals of carvedilol

Carvedilol Co-crystals were prepared by using the solvent evaporation method. Carvedilol and coformer (1:1 molar ratio) were dissolved in methanol and left aside for slow evaporation. The fine crystals were obtained after 24 h. The prepared co-crystals were collected, dried and store in desiccators at room temp for the further studies [10].

Characterization of co-crystals

Scanning electron microscopy (SEM)

Photomicrographs of pure Carvedilol and its Cocrystal were obtained from scanning electron microscope (JEOL 5400, Japan.). The surface morphology of the sample was accessed by SEM. The samples were sputter coated with gold before scanning, operated at an acceleration voltage of 15 kV [11, 12].

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of pure Carvedilol and its Cocrystal were obtained using Fourier Transform Infrared Spectrometer (Thermo-Fischer, Switzerland). The sample was placed in the holder and spectra were

recorded in the range of 4000-400 cm^{-1}. The FT-IR studies are generally carried out to check the interaction between drug and coformer [11, 12].

Differential scaninng calorimetry (DSC)

Thermograms of the pure Carvedilol and its Cocrystal were obtained from (Metlar Toledo, DSC 1) Phase transition of the Carvedilol and its Co-crystals were analyzed by DSC. Samples were sealed in an aluminum crucible and heated at the rate of 10 ˚C/min up to 300 ˚C under a nitrogen atmosphere (40 ml/min). The exact peak temperature and melting point and heat of fusion were automatically calculated [11, 12].

Powder X-ray diffraction studies

Powder X-ray diffraction patterns (XRD) of the pure Carvedilol and its Cocrystals were monitored with an x-ray diffractometer (Bruker, D8 advance, Germany.) using copper as an x-ray target, a voltage of 40 KV, a current of 25 mA and with 2.28970 Å wavelengths. The samples were analyzed over the 2θ range of 10.01-99.99 ° with a scanning step size of 0.020 (2θ) and scan step time of 0.8 second [11, 12].

Solubility study of carvedilol

An excess quantity of pure Carvedilol and Cocrystals were dissolved in 10 ml vial containing distilled water. The samples were stirred for 24 h at 37±0.5 ˚Cwith the help of magnetic stirrer with hot plate at 70 rpm. The sample was then filtered through a whatman filter paper (No. 42) and the amount of drug dissolved was analyzed spectrophotometrically at 285 nm [13].

Micromeretic study

The flow properties of pure Carvedilol and its Co-crystals were determined in terms of angle of repose, bulk density, tapped density, Carr's Index and Hausner's ratio. Angle of repose was determined by the fixed funnel method whereas Carr's Index and Hausner's ratio were calculated from the bulk and tapped densities. Hausner's ratio was taken as a ratio of tapped density to bulk density. Carr's Index was calculated according to the given equation [14].

Angle of repose

Angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between the surface of pile of powder or granules and the horizontal plane [14].

$$\emptyset = \tan^{-1} h/r$$

Where, Ø= angle of repose

h = height of heap, r = radius of base of heap circle.

Compressibility index and hausner's ratio

In recent years, compressibility index and the closely related Hausner's ratio have become the simple, fast and popular methods of predicting powder flow characteristics. Compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and Hausner's ratio are determined by measuring both bulk density and the tapped density of a powder [14].

$$\text{Carrs Index} = W1 - W2/W1 * 10$$

Where, W1 = Tapped density, W2= Bulk density

$$\text{Hausners ratio} = \text{Tapped density/bulk density.}$$

Dissolution studies

Dissolution studies of pure Carvedilol and Co-crystals were carried out using USP Dissolution Testing Apparatus Type II (Electrolab dissolution tester TDT-081, India.) Pure Carvedilol and Co-crystals filled into a muslin cloth and tied it to the paddle with thread. The phosphate buffer pH 6.8. (900 ml) was used as a dissolution medium. The paddles were stirred at 50 rpm, and the temperature was maintained at 37±0.5 ˚C after a specific time interval, 5 ml of aliquot was withdrawn and replaced with the same amount of dissolution medium. The samples were suitably diluted with dissolution medium and absorbance was measured using UV Spectrophotometer (UV-1800, Shimadzu, Japan.) at 285 nm [15].

RESULTS AND DISCUSSION

Characterization of Co-crystals

Scanning electron microscopy (SEM)

The morphology of pure Carvedilol and Co-crystals with different conformers has studied using scanning electron microscopy. The pure carvedilol have showed the plate type crystals whereas the Co-crystals prepared using coformer showed the irregular shape of crystals. This change in the crystal habits indicates the formation of Co-crystals.

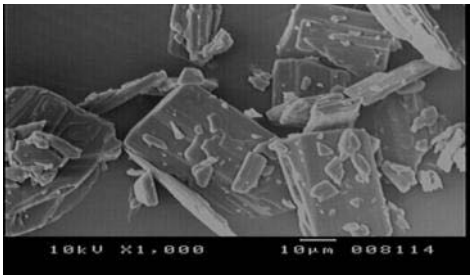

Fig. 1(A): SEM of pure carvedilol

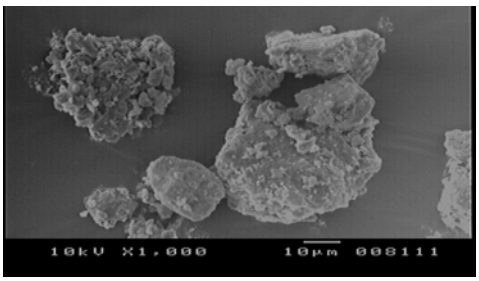

Fig. 1(B): CAR-SA Co-crystals

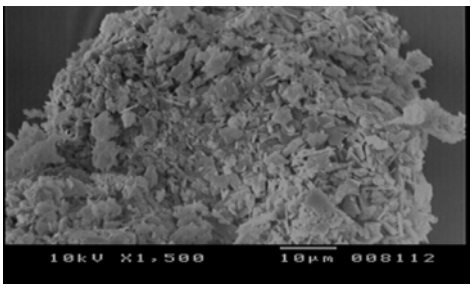

Fig. 1(C): CAR-FA Co-crystals

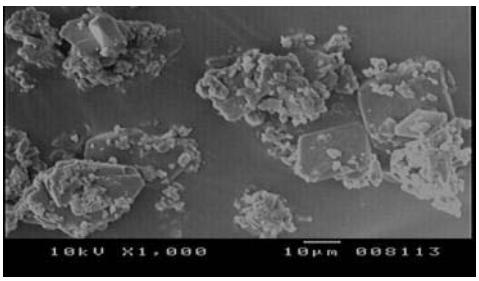

Fig. 1(D): CAR-OA Co-crystals

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra is useful to check the interaction between the drug and coformer. The characteristic peaks of Carvedilol appeared at 2923.4 cm^{-1} (C-H stretching), 1594.1 cm^{-1} (C=C stretching), 3060.2 cm^{-1} (-C-H-stertching), 3344.9 cm^{-1} (O-H stretching), 752.0 cm^{-1}(=C-H stretching), 1100.1 cm^{-1} (C-O-C stretching) and 1217.6 cm^{-1}(C-N stretching). The FTIR spectra cocrystals with succinic acid show the (C=C stretching) at 3022.1 cm^{-1} and (C-H-stretching) at 3402.8 cm^{-1}. For Cocrystal with fumaric acid show (C-H-stretching) at 3047.9 cm^{-1} and rest of peaks as that of pure carvedilol. The spectra of cocrystal with oxalic acid show (C-H-stretching) at 3081.3 cm^{-1} and (O-H-stretching) at 3400.09 cm^{-1}. There is no appearance of new peaks in the spectra of cocrystals indicate that no interaction between the drug and polymer. The FTIR spectra of prepared co-crystals indicate shifting in the functional group compared to pure Carvedilol. This shift in the Co-crystals indicates the formation of new bonding during the formation of Co-crystals [16]. Thus FTIR spectroscopy helpful for the confirmation of the formation of co-crystals.

Table 1: FTIR data of pure carvedilol and its cocrystals

Characteristics peaks	Pure carvedilol	CAR-SA Co-crystal	CAR-FA Co-crystal	CAR-OA Co-crystal
C-H Stretching	2923.4	2927.2	2927.9	2932.5
C=C Stretching	1594.1	1594.6	1597.4	1594.8
-C-H-Stretching	3060.2	3022.8	3047.9	3081.3
O-H Stretching	3344.9	3402.1	3345.6	3400.9
=C-H Stretching	752.0	751.1	750.9	751.9
C-O-C Stretching	1100.1	1099.9	1099.8	1100.3
C-N Stretching	1217.6	1220.4	1219.5	1220.1

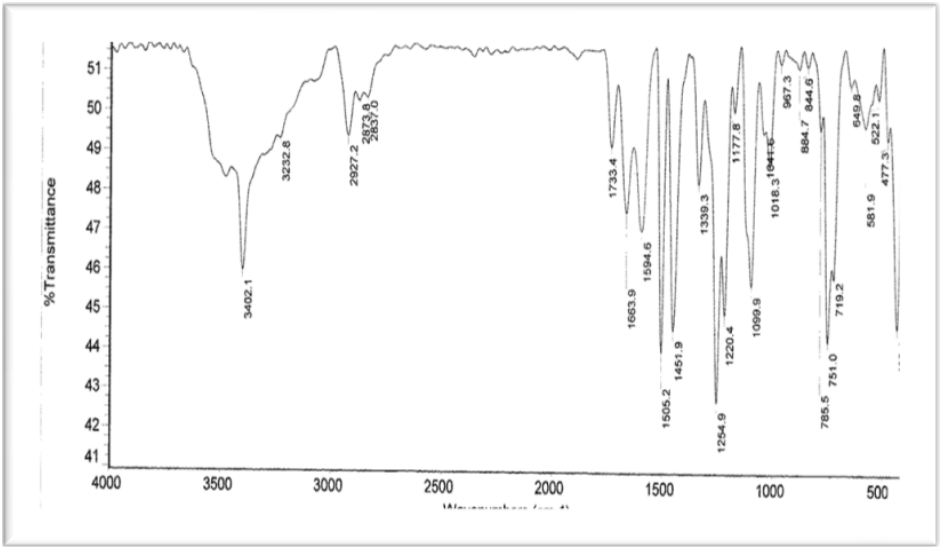

Fig. 2(A): FTIR spectra of pure carvedilol

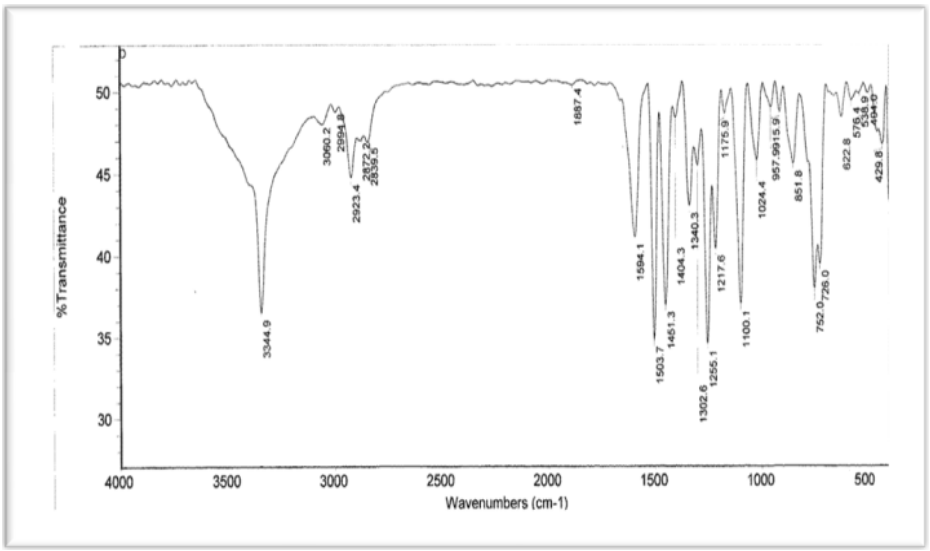

Fig. 2(B): FT-IR spectra of CAR-SA Co-crystals

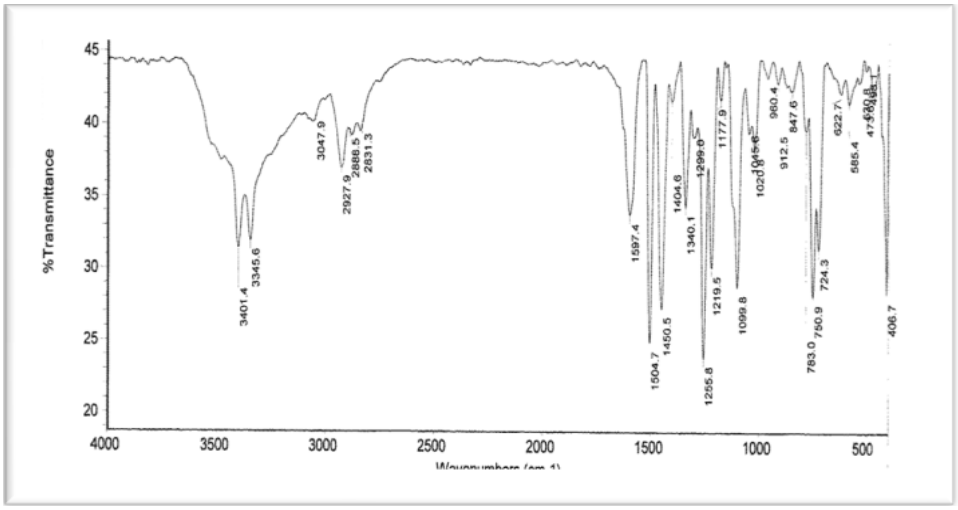

Fig. 2(C): FT-IR spectra of CAR-FA Co-crystals

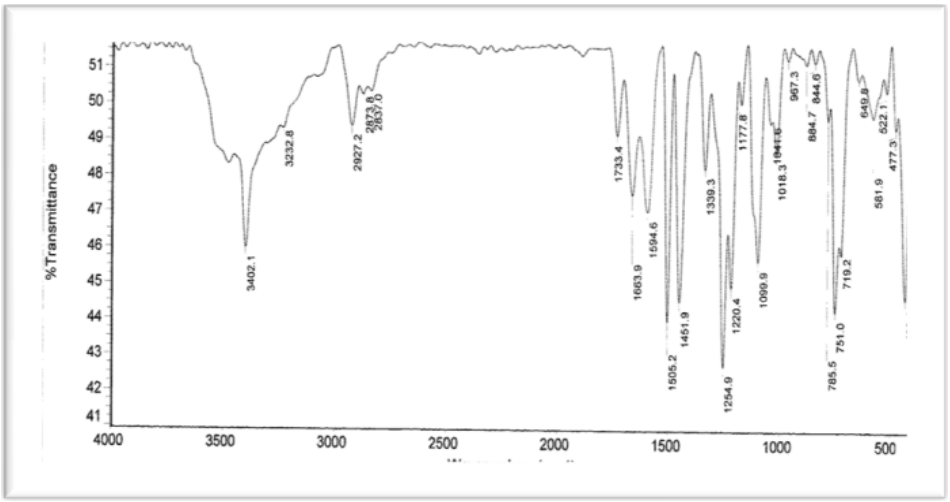

Fig. 2(D): FT-IR spectra CAR-OA of Co-crystal

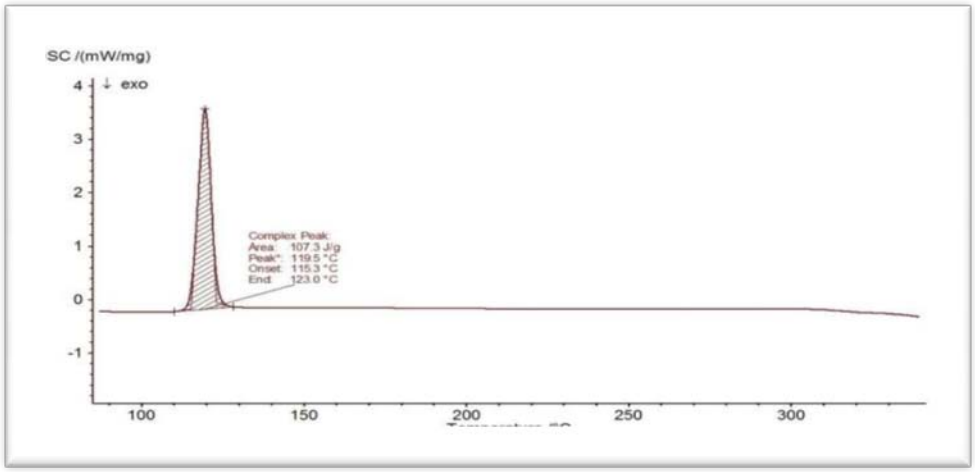

Fig. 3(A): DSC thermogram of pure carvedilol

Differential scaninng calorimetry (DSC)

DSC thermographs of pure Carvedilol and Co-crystals prepared using succinic acid, fumaric acid and oxalic acid showed a sharp endothermic peak (Tm) at 119.5 ˚C, 94 ˚C, 115 ˚C and 100.5 ˚C respectively corresponding to the melting point of Carvedilol**.** Melting endotherm appreciably change in Carvedilol Co-crystals. This observation confirmed the formation of new solid phase and their value obtained in DSC thermogram shown in fig. 2 (A-D). The Shift of the endothermic peak towards lower temperature dictates

decreased melting point of the drug in the Co-crystals. This decreased melting point of Co-crystals accounts for increased solubility of the drugs. The decrease in the solubility of drug in cocrystals was reported by Researcher [17, 18].

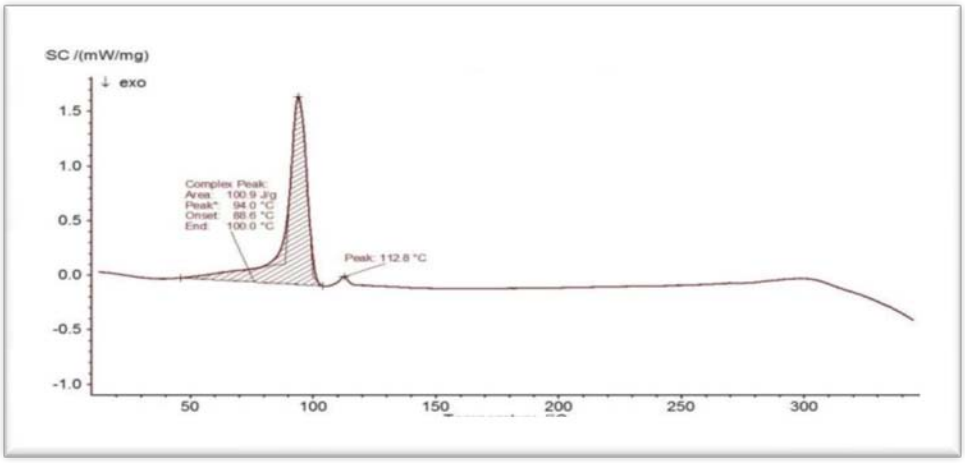

Fig. 3(B): DSC Thermogram CAR-SA Co-crystals

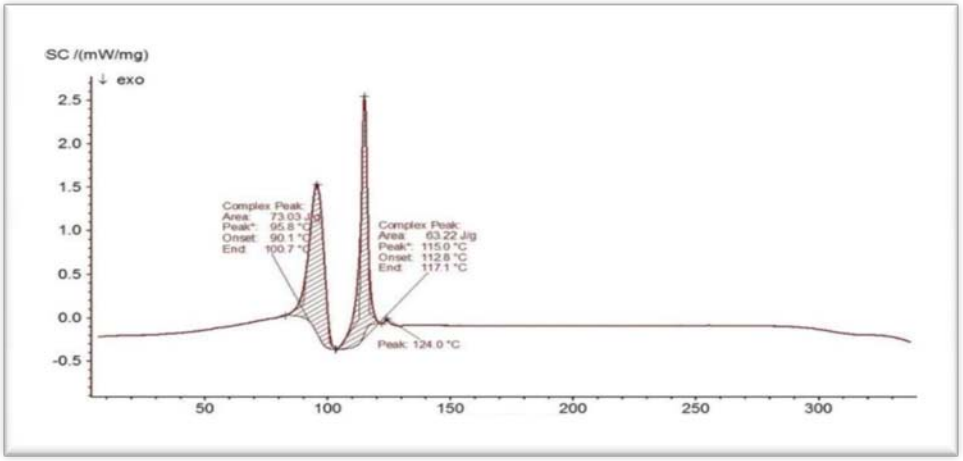

Fig. 3(C): DSC Thermogram CAR-FA Co-crystals

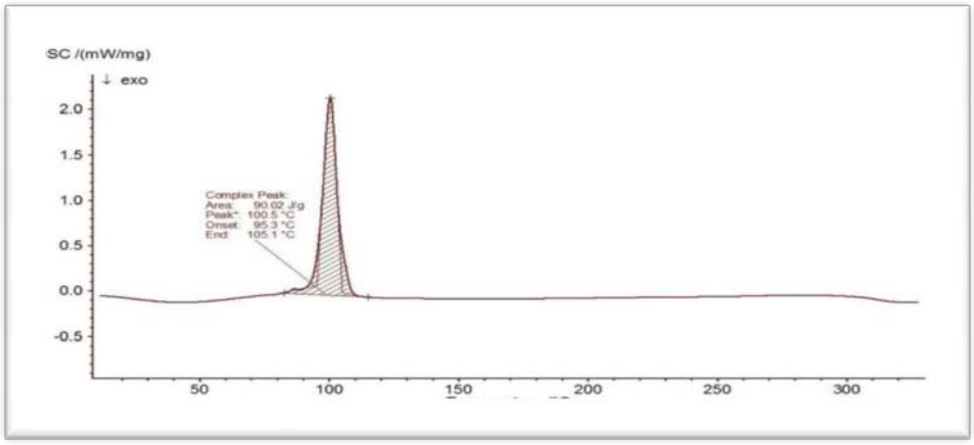

Fig. 3(D): DSC Thermogram CAR-OA Co-crystals

X-ray diffraction

XRD pattern of Pure Carvedilol fig. 4 (A) showed intense and sharp peaks indicating its crystalline nature. The diffractogram of the Cocrystals with succinic acid, fumaric acid and oxalic acid shown in fig. 4 (B)-(D) From XRD spectra it was observed and concluded that, the intensity and number of peaks were reduced in the XRD spectra of Carvedilol co-crystals compare to pure Carvedilol indicate that the reduction in crystallinity and formation of new bonding in the co-crystals This variation in the XRD pattern of pure Carvedilol and its Co-crystals due to changes in the crystal lattice structure of drug and conformer [19].

It means that Co-crystals with these conformers enhance solubility and, ultimately the dissolution by retaining crystallinity of the drug.

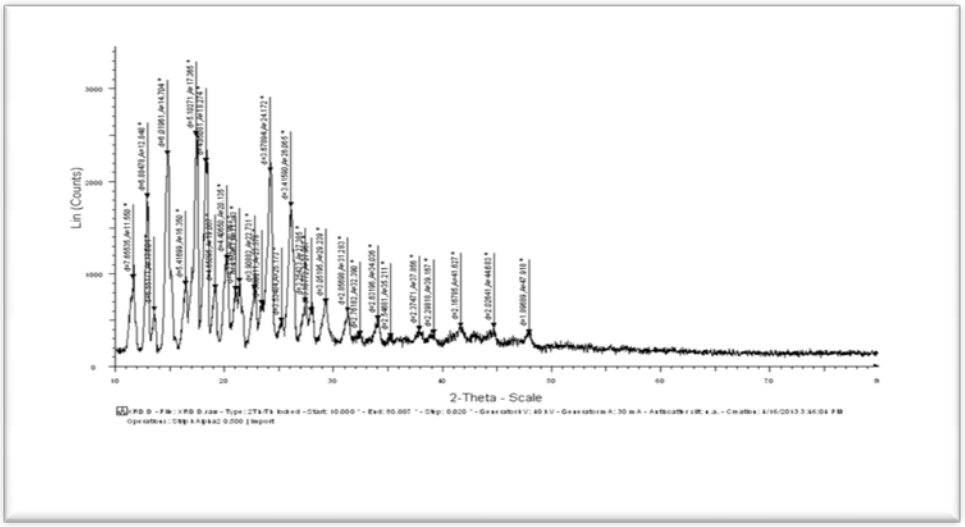

Fig. 4(A): XRD spectra of pure carvedilol

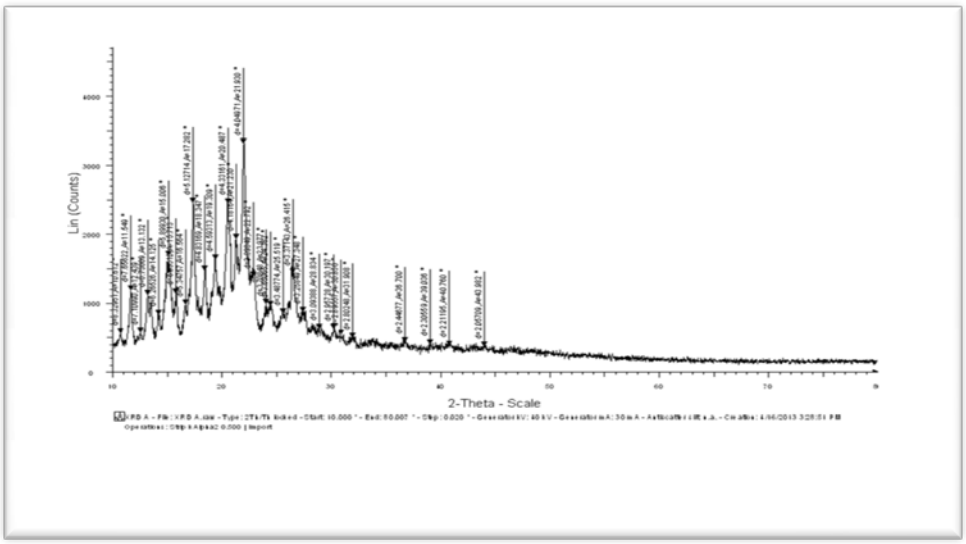

Fig. 4(B): XRD spectra CAR-SA Co-crystals

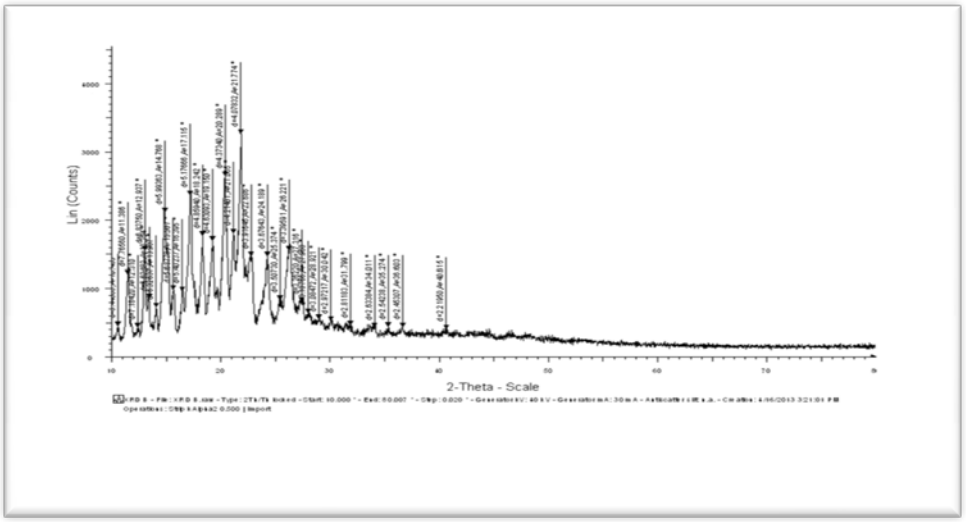

Fig. 4(C): XRD Spectra CAR-FA Cocrystals, This is the file that I received from where I send samples for characterization. This is the good quality of picture that I have please consider

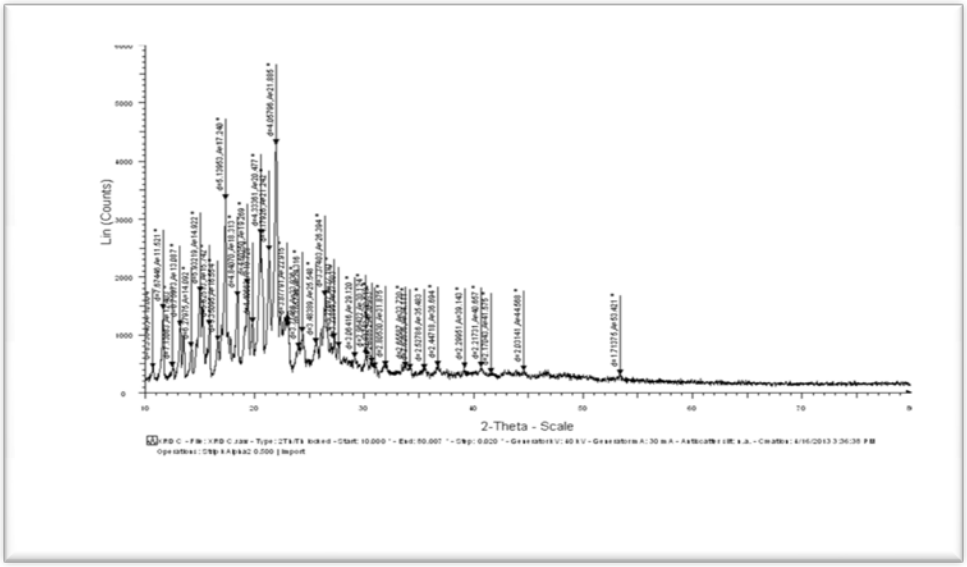

Fig. 4(D): XRD Spectra CAR-OA cocrystals

Solubility study

Pure Carvedilol shows poor aqueous solubility (0.376 (µg/ml). CAR-SA Co-crystals showed higher solubility compare to CAR-OA and CAR-FA Co-crystals. This significant improvement in the aqueous solubility of Co-crystals of Carvedilol is due to the formation of new solid-phase between drug and conformer [20]. The order of increased solubility was CAR-SA Co-crystals>CAR-FA Co-crystals>CAR-OA Co-crystals. The CAR-SA Co-crystals increased six-fold solubility, CAR-FA Co-crystals increased fivefold solubility and CAR-OA Co-crystals increased three-fold solubility compared to the pure Carvedilol. The solubility data of pure Carvedilol and its Co-crystals were shown in table 2.

Table 2: Solubility studies of pure carvedilol and its co-crystals

S. No.	Formulation code	Saturation solubility in distilled water (µg/ml)	Increase in solubility
1	Pure Carvedilol	0.376±0.06	--
2	CAR-SA Co-crystals	2.225±0.35	Six fold
3	CAR-FA Co-crystals	1.880±0.20	Five fold
4	CAR-OA Co-crystals	1.128±0.23	Three fold

Standard deviation (n=3)

Micromeritic studies

The micromeritic properties such as flowability of Co-crystals are shown in Table.3. The flowability represented in terms of the angle of repose, Carr's index and Hausner' ratio. The Co-crystals prepared using succinic acid, fumaric acid and oxalic acid showed improved micromeritic properties compared to pure Carvedilol. The Hausner ratio for cocrystals with succinic acid, fumaric acid and oxalic acid was found to be less than 1.25 whereas pure carvedilol has greater than 1.25 indicating improvement in their flow properties. The angle of repose of Carvedilol Co-crystals in the range of 24.68-25.85 ° compared to pure Carvedilol 38.49. The cars index for Carvedilol co-crystals were in the range of 14.33-17.45. The value of Carr's index indicates the better flowability compare to pure Carvedilol (34.49) these findings proved that the flowability of Co-crystals was preferably improved as compared to pure Carvedilol crystals.

Table 3: Micromeritic properties of pure carvedilol and cocrystals

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (°)	Carr's index (%)	Hausner ratio
Pure Carvedilol	0.56±0.05	0.85±0.03	38.49±1.5	34.49±1.79	1.52±1.2
CAR-SA Co-crystals	0.60±0.01	0.68±0.02	24.68±0.9	14.33±1.35	1.11±0.02
CAR-FA Co-crystals	0.61±0.02	0.72±0.05	25.85.±1.3	17.45±1.40	1.21±0.03
CAR-OA Co-crystals	0.60±0.03	0.70±0.04	25.10±1.2	16.92±1.38	1.19±0.03

Standard deviation (n=3)

Dissolution studies

In vitro release drug profile of Pure Carvedilol (40.30) and Co-crystals with succinic acid, fumaric acid and benzoic acid shown in fig. 5. CAR-SA Co-crystals showed 93.72 % drug release, whereas CAR-FA Co-crystal and CAR-OA Co-crystals have 91.56 % and 88.93 % drug release in 60 min respectively. The drug release data of Carvedilol Co-crystals showed a dramatic enhancement in dissolution rate compared to pure Carvedilol. This increase in the release pattern was due to the decrease in crystallinity and formation of new solid phase.

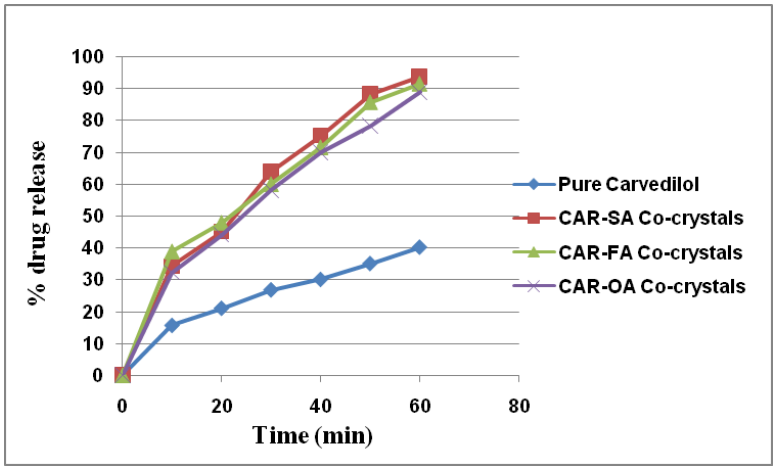

Fig. 5: Dissolution profile of pure carvedilol and Co-crystals (All the values were calculated as mean±SD) n=3

CONCLUSION

Carvedilol Co-crystals using different coformer viz. succinic acid, fumaric acid and oxalic acid were prepared by the solvent evaporation method. Co-crystals showed significant improvement in the solubility and dissolution rate compare to pure Carvedilol. The SEM, FT-IR, DSC and XRD data also support and confirmed the formation of new solid phase. Thus Cocrystals could be one of the successful techniques to improve the solubility and dissolution rate of Carvedilol.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Author declares no conflict of Interest

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