



ENHANCEMENT OF WATER SOLUBILITY AND DISSOLUTION RATE OF FELODIPINE USING MODIFIED β -CYCLODEXTRINS

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ABSTRACT

The aim of this study was to increase the solubility and dissolution rate of felodipine by complexation process. Complexes were prepared using modified β -cyclodextrin (SBE- β -CD). Different techniques were employed for preparation of complexes with modified β cyclodextrin like physical mixture, kneading technology and solvent evaporation. The properties of the prepared solid mass of felodipine was characterized by *in vitro* dissolution studies, UV- spectroscopy, Fourier transform infrared spectroscopy, differential scanning calorimetry (DSC) and X-ray powder diffraction spectroscopy. Additionally, phase solubility studies were performed to support the *in vitro* dissolution study. The results of Fourier transform infrared spectroscopy shows the compatibility of drug with cyclodextrin, while differential scanning calorimetry (DSC) showed the confirmation of complexation of modified cyclodextrin with felodipine. X-ray powder diffraction patterns revealed a partial loss of crystallinity of FDP, a potential source of dissolution enhancement. Enhancement in the dissolution properties of FDP with modified cyclodextrin might be attributed due to the complexation and their better wettability. The dissolution characteristics of FDP in all solid dispersion systems showed significant improvement in the solubility and dissolution rate compared to that of pure drug.

Key words: Felodipine, Cyclodextrins, SBE- β -CD, Dissolution Rate, Solid Dispersions

INTRODUCTION

Felodipine (4 RS)-4-(2, 3-dichlorophenyl)-2,6-dimethyl-1, 4-dihydropyridine-3,5-dicarboxylate is a calcium channel blocker used as antihypertensive and antianginal drug.^{1,2} According to biopharmaceutical Classification System, felodipine is class II drug, i.e., low solubility and high permeability. Felodipine has poor water solubility and hence poor dissolution and bioavailability after oral administration. Felodipine undergoes extensive first- pass metabolism with a bioavailability of about 15%.³ The major drawback in the therapeutic application and efficacy of felodipine as oral dosage form is its low aqueous solubility, which is expressed to be approximately 19.17 mg/L at 25°C. Hence, improvement of its water solubility and dissolution is of therapeutic importance.^{4,5} The enhancement of the solubility of poor water- soluble drug is one of the major current challenges to pharmaceutical

sciences. Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, micro emulsion and self-emulsifying systems are available to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS Class II drugs.⁶ Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs.

Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected.^{7,8} Cyclodextrins can also be used to prevent drug-drug and drug additive interactions, convert liquid drugs into microcrystalline powder, decrease volatility, modify gastrointestinal or ocular irritation and

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mask of objectionable taste or odor of drugs^{9,10}. This ability to form inclusion complexes alter the chemical and physical properties of guest (drug) molecules, and effect improved water solubility, prolong in vivo stability, reduce toxicity and irritancy, and improve bioavailability¹¹. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies^{12, 13}.

Sulfobutylether beta cyclodextrin (SBE- β -CD) is an anionic β -cyclodextrin derivative with a sodium sulfonate salt separated from the hydrophobic cavity by a butyl spacer group¹⁴. SBE- β -CD is a uniquely modified cyclodextrin, whose chemical structure was rationally designed to maximize safety and optimize interaction to improve the solubility^{15,16}, stability^{17,18}, bioavailability or lessen volatility, irritation, smell or taste in oral solid dosage forms. SBE- β -CD is not a single chemical species, but comprised of a multitude of polymeric structures of varying degrees of substitution¹⁹ and positional/regional isomers dictated and controlled to a uniform pattern by a patented manufacturing process consistently practiced and improved to control impurities. SBE- β -CD can form non-covalent complexes with many types of compounds including small organic molecules, peptides²⁰ and proteins.²¹

The application of SBE- β -CD and its desirable safety profile and drug solubilization properties was based upon extensive evaluations of the mono, tetra and hepta-substituted dominated compositions. Several hundred of pre-clinical and clinical studies have been performed and indicate that SBE- β -CD is safe when administered parenterally or orally and does not exhibit the nephrotoxicity associated with beta-cyclodextrin. Relative to beta-cyclodextrin, SBE- β -CD provides higher interaction characteristics and superior water solubility in excess of 100 grams/100 ml a 50-fold improvement. SBE- β -CD showed greater stability enhancement of many chemically unstable drugs than other cyclodextrins^{22,23}. SBE- β -CD was investigated as complexing agent in osmotic tablets of poorly water soluble drugs such as testosterone, prednisolone, chlorpromazine, indometacin and naproxen^{24, 25}.

In the present study, Solid dispersions were prepared by solvent evaporation method and kneading method using modified Cyclodextrin i.e SBE- β -CD as a carrier. By using different drug polymer ratios and through different techniques (physical mixing, solvent evaporation method and kneading method), SD and physical mixture (PM) were prepared. After assessing the drug content of the solid dispersions, the prepared solid dispersions were characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD). Drug polymer interactions in aqueous solution were investigated by phase solubility analysis.

EXPERIMENTAL

Materials and Methods:

Felodipine was a gift sample from M/s. Aurobindo Pharma Ltd., Hyderabad. Sulfobutyl ether β -Cyclodextrin (SBE- β -CD) was gift sample from M/s. Cydex Pharma Inc., USA. Methanol (Qualigens), Sodium di hydrogen Phosphate (Qualigens) and sodium hydroxide (Qualigens) were procured from commercial sources.

Methods

Phase Solubility

Phase solubility studies were carried out as described by Higuchi and Connors²⁶. Excess drug (50mg) was added to 15ml of sulfobutyl ether β -Cyclodextrin (SBE- β -CD) solutions taken in a 25ml stopped conical flask and the mixtures were shaken for 24h at room temperature ($28 \pm 1^\circ\text{C}$) on Rotary Flask Shaker. After 24h of shaking, 2ml aliquots were withdrawn at 2h interval and filtered immediately using a 0.45μ disk filter. The filtered samples were diluted suitably and assayed for felodipine by measuring absorbance at 343nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for six times ($n=6$).

The apparent 1:1 stability constant was calculated from the phase solubility graph using

$$K_s = \frac{\text{Slope}}{S_o (1 - \text{slope})}$$

Where S_o is the solubility of FDP the absence of polymer.

Estimation of Felodipine:

An UV Spectrophotometry method based on the measurement of absorbance at 364nm in a phosphate buffer of pH 6.5 with 0.5% Sodium lauryl sulphate (SLS) was used for the estimation of felodipine. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-40µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variation were found to be 0.85% and 1.0% respectively. No interference by the excipients used in the study was observed.

Preparation of Felodipine-CD complexes with New Modified Cyclodextrin:

Solid inclusion complexes of Felodipine-CD were prepared in four different ratios (1:0.5, 1:1, 1:2 and 1:4) by solvent evaporation and kneading methods²⁷. Physical mixtures of Felodipine with the SBE-β-CD were prepared by blending the constituents. In case of Solvent evaporation method, drug and CDs were dissolved in minimum volume of organic solvent (methanol) and solvent was evaporated on hot plate. In kneading method, Felodipine and SBE-β-CD was triturated in a mortar with a small volume of methanol. The thick slurry formed was kneaded for 45min and then dried at 55°C until it was completely dried. In all the cases dried mixtures were then powdered in mortar, sieved through 120 mesh screen. The prepared solid dispersions stored in desiccators were used in subsequent analysis. For ease of discussion, preparations are designated by abbreviations as shown in Table-1.

Dissolution rate study:

The dissolution rate of felodipine as such and from CD complexes prepared was studied in 500ml of phosphate buffer of pH 6.5 with 0.5% SLS using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 25 rpm²⁸. A temperature (37±1°C) was maintained throughout the study. Felodipine or Felodipine-CD complex equivalent to 5 mg of felodipine was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed for felodipine at 364nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh

fluid. The dissolution experiments were replicated six times (n=6).

Characterization Studies

Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FTIR) spectroscopy was carried out to identify the possible interactions between the drug and two modified Cyclodextrins in prepared solid systems. Samples of FDP, carriers, and their preparations were characterized by FTIR spectroscopy (Shimadzu 8400, Japan) using the potassium bromide (KBr) pellet method. The scanning range was 4000–400 cm⁻¹ at a resolution of 1 cm⁻¹.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) of pure FDP, carriers, and all preparations was done using a Shimadzu DSC 60 TSW 60 (Japan). Accurately weighed samples were crimped in aluminum pans and heated from 30 to 250°C at a heating rate of 10°C/min in air atmosphere. An empty sealed aluminum pan was used as reference.

Powder X-ray Diffraction

Powder X-Ray diffraction (PXRD) patterns of pure FDP, carriers, and solid systems of FDP with carriers were recorded using a powder X-ray diffractometer (Phillips X-Pert MPD, The Netherlands) with a copper tube anode over the interval 1–40° 2θ-1. The operational parameters were as follows: generator tension (voltage) of 45 kV; generator current of 40 mA; scan step time of 9 sec-1, and scan step size of 0.008° (2θ).

RESULTS AND DISCUSSION

Phase Solubility Studies

Drug solubility increased with an increase in carrier concentration. Phase solubility curves are shown in Figure 1. Various parameters calculated from the phase solubility studies are shown in Table 2. The stability constant for 1:1 drug-carrier interactions was 101.76 M⁻¹ with cyclodextrin used, indicating physical interactions among drug and carriers. The curves obtained were of AL type with the resultant slopes less than unity.

Percentage Drug Content

Percentage drug content was in the range of 94.37 ± 0.81% to 99.15 ± 0.48%. All determinations are mean ± SD (n = 3).

In Vitro Release Studies

The dissolution curves of FDP, solid dispersions, and physical mixtures with modified cyclodextrin are shown in Figure 2. The dissolution rate of FDP was improved with the solid dispersions as compared with pure drug. Various dissolution parameters were given in Table 3. According to these results, the dissolution characteristics of FDP in all solid dispersion systems showed significant improvement in the solubility and dissolution rate respectively. Enhancement in the dissolution properties of FDP with modified cyclodextrin might be attributed due to the complexation and their better wettability. The dissolution rate of FDP in the physical mixture also improved but to a lesser extent than for the respective solid dispersions. The probable reason for the improvement in the dissolution rate in the physical mixture was the local solubilizing action of the carriers.

Characterization Studies

To investigate the mechanism of improved dissolution properties of FDP in the prepared solid dispersions with cyclodextrin were characterized by the following studies.

Fourier Transform Infrared Spectroscopy

Analysis by FTIR spectroscopy was carried out to assess any possible interaction between drug and modified cyclodextrin. Figure 3 depicts the FTIR spectra of drug, modified cyclodextrin, and the formulations with modified cyclodextrin. The spectrum of pure FDP (Figure 3a) shows characteristic peaks at 3369.5 cm^{-1} (O–H stretch), 2919.3 cm^{-1} (C–H stretch), 1886.8 cm^{-1} (lactone ring C=O stretch), 1722.2 cm^{-1} (C=O stretch), 1604.6 cm^{-1} (C=C stretch), 1443.9 cm^{-1} (C–N stretch), 1398.6 and 1268.9 cm^{-1} (C–F stretch), 1222.0 cm^{-1} (C–O stretch), and 828.8 cm^{-1} (ring vibration of para-disubstituted benzene). FTIR spectra of solid dispersion in modified cyclodextrin (Figures 3c) show no substantial shifting of the position of the functional groups. The peaks are only broadened, indicating no major interaction between FDP and cyclodextrin. Although hydrogen bonding could also be expected between the hydrogen atom of the OH– group of FDP and the OH– group present in the modified cyclodextrin.

Differential Scanning Calorimetry

DSC curve of pure FDP, modified cyclodextrin, physical mixtures and solid dispersions are

shown in Figure 4. DSC thermogram of FDP (Figure 4a) show an endothermic peak at 146.7°C corresponding to the melting point of FDP and no sharp Endothermic peaks was observed for modified cyclodextrin. The DSC thermograms of solid dispersion in modified cyclodextrin (Figure 4c), the endothermic peak corresponding to melting peak of felodipine shifted to lower temperature (144.3°C) with reduced intensity in solid dispersions, which might be because of complete complexation of FDP with the modified cyclodextrin.

Powder X-ray Diffraction

PXRD patterns of pure FDP, polymers, and of binary systems are shown in Figure 5. The powder X-ray diffraction of FDP (Figure 5a) shows sharp peaks at diffraction angles (2θ) of 10.1°, 12.4°, 16.3°, 19.5°, 20.6°, 23.2°, 24.4°, 25.4°, 26.4° and 27° indicating its crystalline nature. Modified cyclodextrin (Figure 5b) does not show any peaks, it indicated that modified cyclodextrin is amorphous in nature. Diffraction patterns of solid dispersions (Figures 5c) show the characteristic peaks of FDP, but the intensity and number of drug peaks are reduced, indicating a decrease in drug crystallinity. Thus, a decrease in drug crystallinity might be responsible for the improvement in dissolution of FDP.

CONCLUSION

Solid-state characterization studies revealed a partial loss of drug crystallinity of FDP, a potential source of dissolution enhancement. Enhancement in the dissolution properties of FDP with modified cyclodextrin might be attributed due to the complexation and their better wettability. Solid inclusion complexes of modified β -cyclodextrin (SBE- β -CD) with felodipine, showed enhanced dissolution characteristics than physical mixtures. Among the inclusion complexes, kneading method was found to be superior to solvent evaporation technique in the conditions studied.

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Table 1: List of solid dispersions prepared with Sulfobutyl ether β -Cyclodextrin (SBE- β -CD)

Method of Preparation	Drug Polymer Ratio	Formulation Code
Physical Mixing	1:0.5	FPM1
	1:1	FPM2
	1:2	FPM3
	1:4	FPM4
Solvent Evaporation	1:0.5	FSE1
	1:1	FSE2
	1:2	FSE3
	1:4	FSE4
Kneading Method	1:0.5	FKN1
	1:1	FKN2
	1:2	FKN3
	1:4	FKN4

Table 2: Phase solubility study of felodipine in water at 37° C

SBE- β -CD concentration (mM)	Amount of felodipine dissolved (mM)
10	0.0267
20	0.05
30	0.07
40	0.091
50	0.117

Table 3: Dissolution Parameters for FDP and Solid Dispersions Prepared

Formulation	DP10 min (%)	K ₁ (min ⁻¹)	DE ₂₀ (%)
FDP	3.28	0.001	0.619
FPM1	5.24	0.007	5.88
FPM2	10.39	0.008	9.89
FPM3	15.09	0.009	12.5
FPM4	17.74	0.010	14.25
FSE1	35.42	0.022	29.21
FSE2	45.71	0.028	38.22
FSE3	63.5	0.035	48.7
FSE4	78.15	0.075	60.33
FKM1	73.01	0.049	56.41
FKM2	83.29	0.150	64.19
FKM3	93.57	0.182	71.13
FKM4	98.71	0.435	74.41

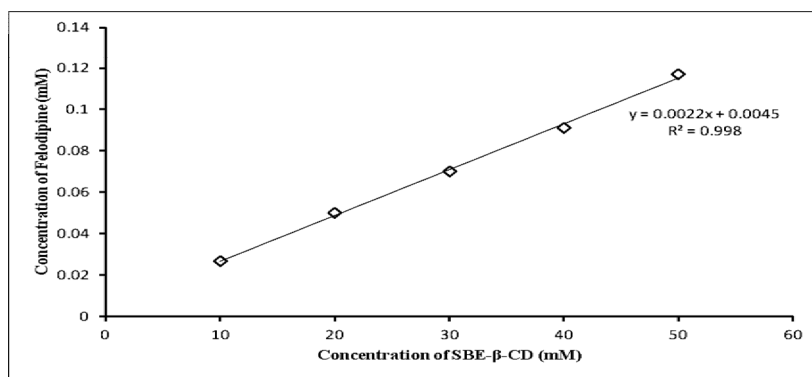


Figure 1: Phase solubility curve of FDP with SBE-β-CD

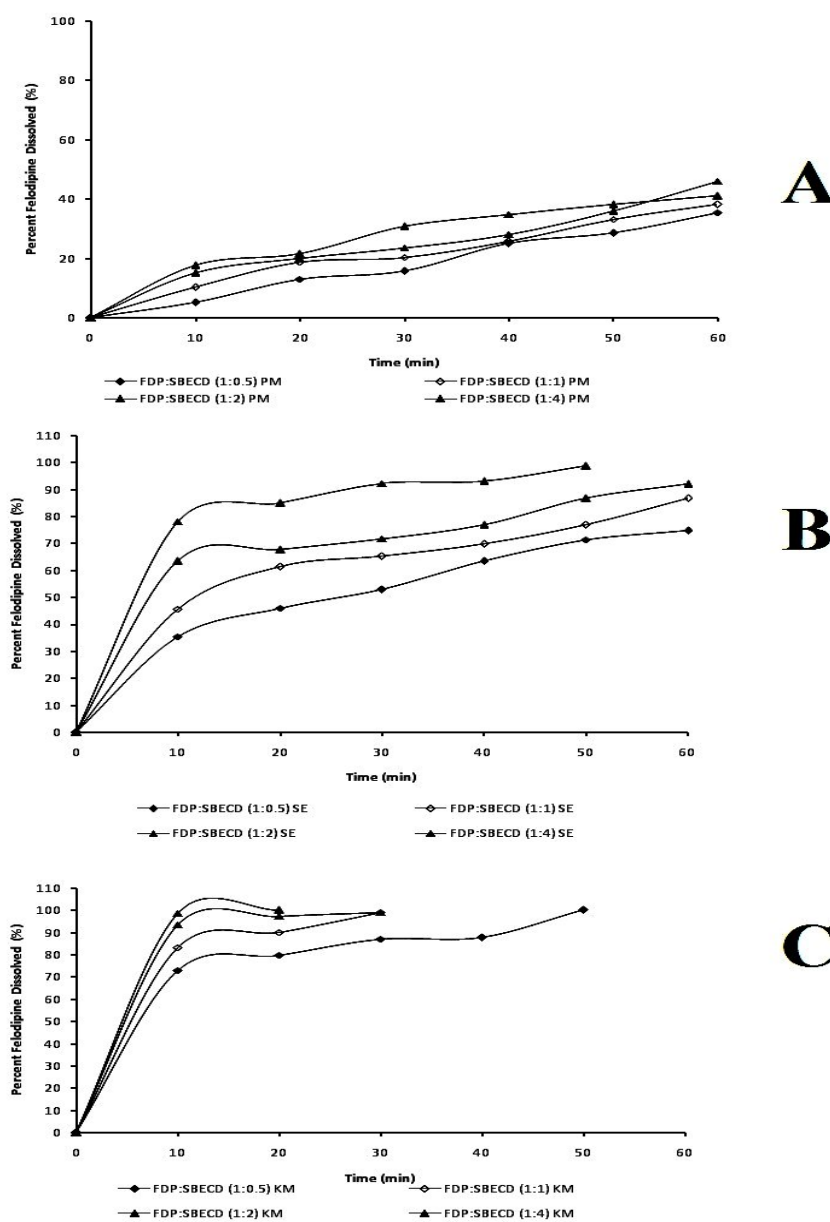


Figure 2: *In vitro* dissolution release profiles of FDP solid dispersions, and of (a) FDP: SBE-β-CD physical mixtures (b) FDP: SBE-β-CD Solid dispersions (SE), and (c) FDP: SBE-β-CD Solid dispersions (KM)

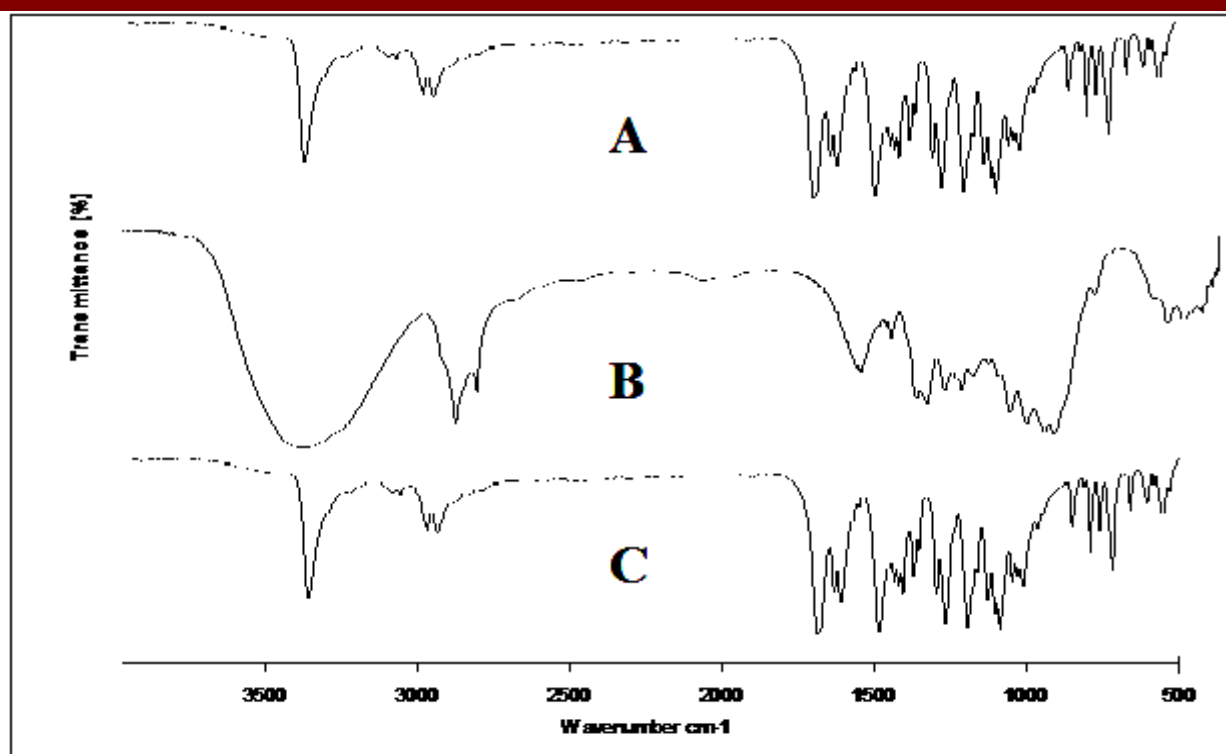


Figure 3: FTIR spectrum's of (a) FDP, (b)SBE- β -CD, (c)FDP:SBE- β -CD Solid dispersion(1:4)(KM)

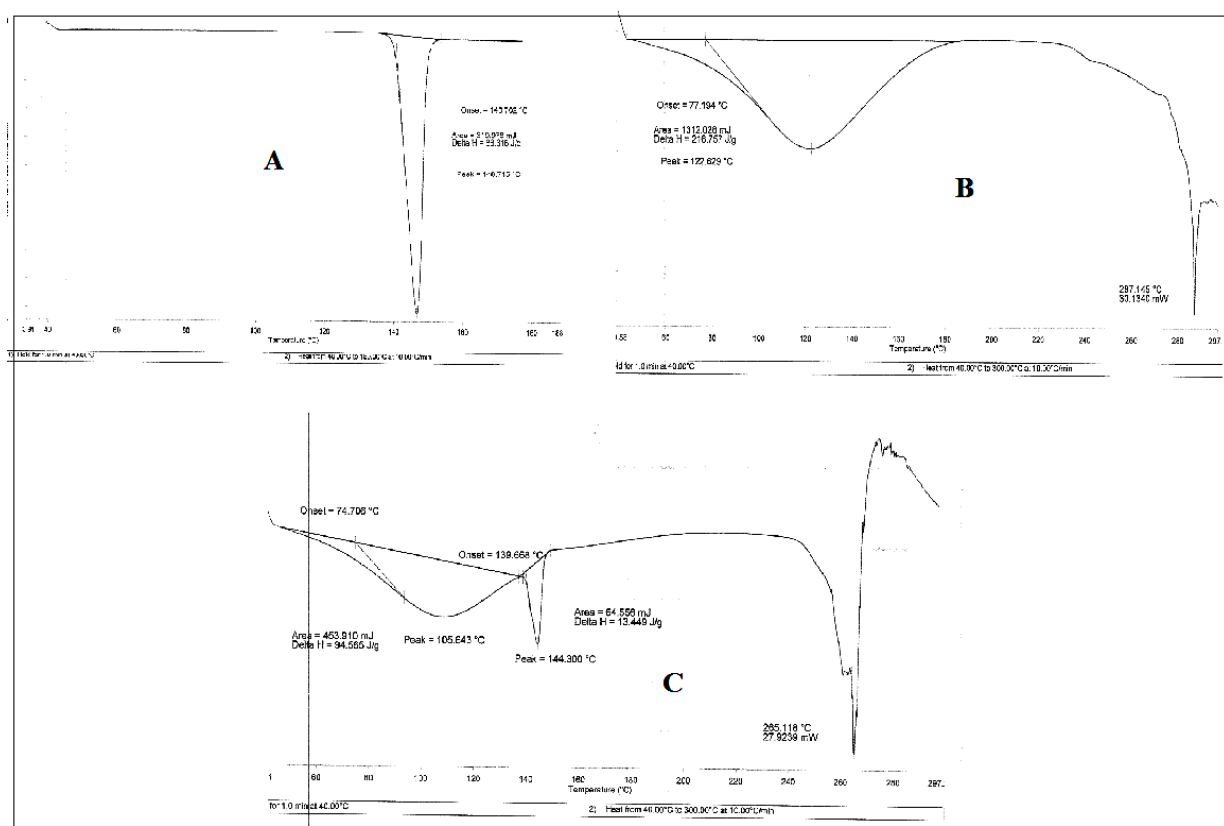


Figure 4: DSC Thermograms of (a) FDP, (b)SBE- β -CD, (c)FDP:SBE- β -CD Solid Dispersion(1:4) (KM)

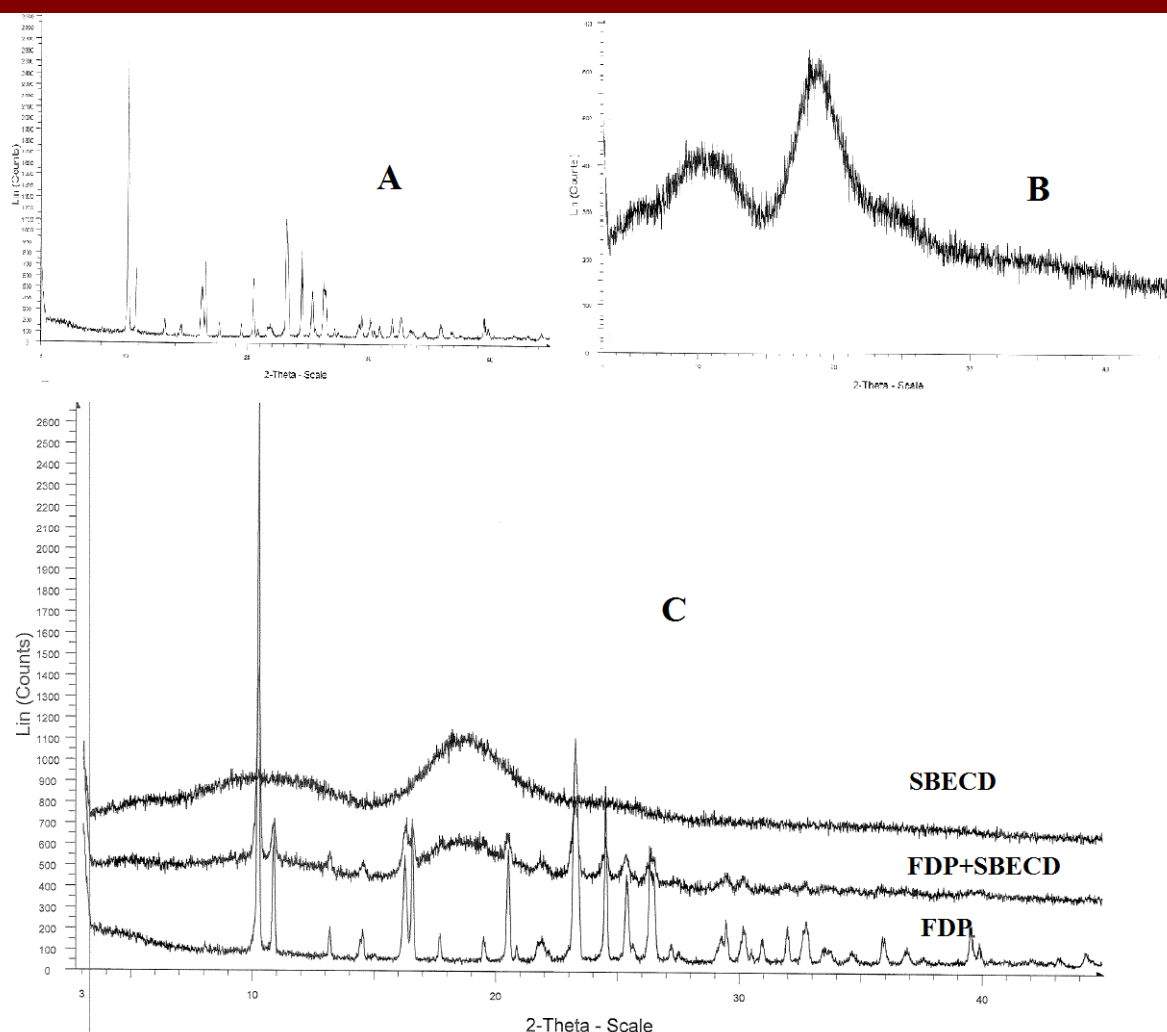


Figure 5: PXR D diffractogram's of (a) FDP, (b) SBE-β-CD, (c) FDP:SBE-β-CD Solid Dispersion(1:4)(KM)

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