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Physical Characterization and Enhance the Solubility of Fexofenadine-β-Cyclodextrin Inclusion Complexes

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Abstract
The purpose of the study is to formulate Fexofenadine hydrochloride complex with inclusion complex with β-Cyclodextrin, because Fexofenadine hydrochloride having a poorly solubility and bioavailability. Inclusion complex with β-Cyclodextrin improve the characteristic and dissolution rate as compare to marketed product. Fexofenadine hydrochloride is an antihistaminic agent used for treatment of relieving hay fever and allergy symptoms, such as sneezing and red, itchy, tearing eyes. Its poor solubility is major problem for the patient compliance. Cyclodextrin have ability to molecularly encapsulate wide variety of drugs into their hydrophobic cavity without formation of any covalent bonds. Cyclodextrin (CDs), especially β-Cyclodextrin (β-CD), are widely used in the pharmaceutical field owing to their ability to stabilize drug molecules as well as for taste masking purpose. Phase solubility study records shown that the stability constant and complex stoichiometry of Fexofenadine β- CD complexes gives linearly improve with the concentration of β- CD, beside Fexofenadine - HP β- CD complexes does not shows more change in solubility curve. Hence β- CD was chosen to prepare inclusion complexes. Inclusion complexes with β- CD were prepared by physical mixture, kneading method and Co-precipitation method. Complexes were analyzed by UV-VIS spectroscopy and were characterized by infrared spectroscopy, thermal analysis, XRPD. Within 30 min, more than 90 % drug was released from the complexes, were good as compare to marketed product which shown in release profile.

Key Words
Fexofenadine, Inclusion complex, β-Cyclodextrin.

Introduction
Fexofenadine hydrochloride (FEXO) is an antihistaminic agent used primarily for treatment of sudden allergic attacks. The drug has poor solubility in water and an extremely bitter unpleasant taste.[1] The drug is used for relieving hay fever and allergy symptoms, such as sneezing and red, itchy, tearing eyes. It belongs to the class of antihistamines. It is available in both tablets and capsules form. The drug acts by blocking histamine, a substance in the human body responsible for causing allergic symptoms.[2] It causes less drowsiness when compared to other antihistamines. Cyclodextrin (CD) is crystalline, cyclic oligosaccharides derived from starch. Among the most commonly used forms are α-, β-, and γ-cyclodextrin, which have respectively 6, 7, and 8 glucose units. Molecular weight of β- cyclodextrin is 1135.[3] β -Cyclodextrin is widely used in taste masking purpose; in which β-Cyclodextrin make an inclusion complex with drug (guest) molecules & act as a hydrophobic host cavity so drugs make a complex in inert carrier matrix. Applications of CDs in oral drug delivery include improvement of drug bioavailability due to increased drug solubility, improvement of rate and extent of dissolution and /or stability of the drug at the absorption site**,** reduction of drug induced irritation, taste masking, etc. β-Cyclodextrin (β-CD) is cyclic malto oligosaccharides in which the glucose units are linked by α- 1, 4 glycoside bonds. The peculiar arrangement of the glucose units imparts the molecule a cone like structure, which makes the exterior of the cone hydrophilic and interior of the cone hydrophobic in nature. This characteristic of the polymer enables encapsulation of the drug in the cavity resulting in the improvement in the solubility, drug release as well as taste masking.[4-7]

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Materials and Methods

Fexofenadine and β-CD was kindly supplied by Vaikunth Bulk Pharmaceutical- Panoli as a gift sample. Conventional tablets (Cipla Pvt Ltd, Mumbai) labeled to contain Fexofenadine (120 mg) were purchased from the local market.

Determination of stability constant (K)

Complexation studies were performed according to the method reported by Higuchi[8]. The apparent stability constant was calculated for this complex using the equation K = Slope / intercept (1 − slope).

Preparation of Inclusion complexes[5-8]

The complexes were prepared in 1:1 molar ratio by following methods,

Physical mixture:

Fexofenadine makes smooth paste with β-CD.

Kneading method:

Fexofenadine was added to aqueous paste of β-CD and the mixture was levigated for 45 min. The paste was dried at 50 °C and the dried mass was pulverized and sieved through # 100 meshes.

Co-Precipitation:

Both Fexofenadine and β-CD mixed in suitable solvent, stir well till evaporation of solvent, finally guest molecules bind with host molecules called as complex. It is also called as solvent evaporation or co-evaporation method.

Characterization of Solid Complexes

The complexes were characterized and evaluated by the following methods,

Differential Scanning Calorimetry (DSC)

Thermal behavior of Fexofenadine, β-CD, and each complex were examined by using a DuPont (Wilmington, DE) model 910 thermal analyzer. DSC analysis was performed at a heating rate of 12°C/min using argon as the carrier gas at flow rate of 38 cc/min. The sample size was 5 mg and XRPD of the samples was performed using a high-power X-ray Diffractometer RU-200B from M/s Riguao, (Tokyo, Japan). The scanning rate was 4°/min. The voltage/current used was 40-kV/50 mA and the target/filter (monochromator) was copper.

Fourier Transform Infra Red spectroscopy (FT-IR)

FT-IR spectral studies were carried on FT-IR 460 PLUS by JASCO series II instrument using DRIFT method (JASCO Analytical Instruments, Madison, WI). Scanning was done from 4000 to 400 cm^{-1}.

***In vitro* Dissolution Rate Studies**

Dissolution studies were carried for inclusion complexes using USP paddle type dissolution apparatus at 37 °C ± 1 °C at 100 rpm. The dissolution medium used was 900 ml of 0.1 N HCl.

Result and Discussion

In the present work inclusion complexes of Fexofenadine were prepared with β-Cyclodextrin by Physical mixture, Kneading method & Co-Precipitation method. The complexes were prepared in different molar ratios of drug and Cyclodextrin namely 1:1 and 1:2. The prepared complexes were characterized by Fourier transform infrared spectroscopy (FT-IR) and powder x-ray Diffraction study (XR-PD) and differential scanning calorimetry (DSC) are given in Result. Prepared complexes were evaluated for *in vitro* drug release and short-term stability studies. The phase solubility diagram (fig. 1) for Fexofenadine and β-CD system in distilled water suggest that the molar ratio of the complex is 1:2. The apparent stability constant Kc was calculated according to Higuchi and Connor's method from the initial straight line of solubility diagram. Phase solubility diagram of Fexofenadine with β-CD illustrate the solubility enhancement capability of Cyclodextrin. In case of β-CD the solubility diagram which is classified as Bs type shows atypical curve whose initial rising position is followed by a plateau region. Further increase in β-CD resulted in decrease in solubility but again increase in concentration of β-CD resulted in an increase in the solubility of Fexofenadine. The stability constant (K_C) of Fexofenadine -β-CD 1:2M inclusion complex was found to be 149.45M^{-1}. FTIR patterns of Fexofenadine - β-CD are represented in Fig.2. FTIR studies of Fexofenadine exhibited peaks at 3564.77cm^{-1}, 3267.71cm^{-1} and 1651.22cm^{-1} due to –OH, -NH, and C=O stretching respectively which conforms the structure of Fexofenadine. In the spectra of FBP_1 showed peak at 3557.06cm^{-1}, 3379cm^{-1}, 1647.36cm^{-1} and 3566.70cm^{-1}, 3248.42cm^{-1}, 1653.14cm^{-1} because of –OH, -NH and C=O stretching. Slight shift in the peaks in the formulation indicate weak interaction between drug and Cyclodextrin. FTIR spectrum of FBK_1 (1:1M) showed characteristic peaks for –OH, -NH and C=O stretching at 3613cm^{-1}, 3396.95cm^{-1}, 1647.36cm^{-1} when compared with the characteristic peak values of pure drug. This shift in the values of peaks

indicates the interaction between drug and polymer. The FRIR spectrum of FBP_2 and FBK_2 have showed characteristic peaks at 3732.60cm^{-1}, 3373.80cm^{-1}, 1647.36cm^{-1} and 3528.12cm^{-1}, 3385.38cm^{-1}, 1647.36cm^{-1} for –OH, -NH and C=O stretching respectively. Shift of peaks in the FTIR spectrum of these formulations indicates the interaction between drug and polymer. The XRPD patterns of Fexofenadine:β-CD systems are represented in Fig.3. The diffractograms of Fexofenadine and β-CD exhibited a series of intense peaks, which is an indicative of their crystalline nature. X-RD pattern of physical mixture (FBP_1) is simply the superimposition of each component indicating no formation of new structure. Physical mixture (PM) and co-precipitation (FBC_2) methods showed a diffraction pattern quite similar to that of physical mixture, while those obtained from kneading method (FBK_1) showed less peaks with low intensity. This indicates that the inclusion complex prepared by kneading method is less crystalline than the complexes prepared by physical mixture, common solvent and co-precipitation method. The thermal behavior of the Cyclodextrin inclusion complexes was studied using DSC in order to confirm the formation of solid inclusion complexes. When the guest molecules are incorporated in Cyclodextrin cavity or in the crystal lattice, their melting, boiling and sublimation points usually shifted to a different temperature or disappear within the temperature range, where the Cyclodextrin lattice is decomposed. The thermograms of pure Fexofenadine and β-CD and corresponding Cyclodextrin complexes are presented in figure 25 to 32. The DSC thermogram of Fexofenadine showed an endothermic peak at 316.69°C corresponding to its melting point. The thermogram of β-CD showed a very broad endothermic effect, which attained a maximum around 80 to 90°C due to the release of water molecules and peak at 337.64°C corresponding to its melting point. The thermograms of Fexofenadine and β-CD (1:1 M) prepared by physical and kneading method i.e., FBP_1 and FBK_1, respectively showed broadened endothermic peaks at 255-320°C. This may be due to shift of characteristic peak of Fexofenadine which was observed at 316.69°C, indicates a strong interaction of drug and β-CD. In case of Fexofenadine- β-CD complexes (1:1 M) prepared by co-precipitation method exhibited a small peaks at 235.40°C and 257.64°C instead of 316.69°C indicating strong interaction between drug and β-CD at 1:1 molar ratio. Further the Micromeritic properties of complexes were evaluated using properties such as bulk density, angle of repose and compressibility (Carr) index (Table no.13). It was found that the flow and compressibility of KN & PM complexes is satisfactory.

In-vitro dissolution studies for pure Fexofenadine and inclusion complexes prepared were carried out in 900 ml of distilled water and phosphate buffer of (pH=4) using USP XXIII dissolution rate test apparatus (Electrolab) with a paddle stirrer. The dissolution data of Fexofenadine, Fexofenadine-β-CD systems are given in table 06 to 11. Figure 05 to 10 shows the dissolution rate profiles of pure Fexofenadine and of prepared inclusion complexes prepared by physical, kneading, and co-precipitation method, it is evident that the complex prepared by all method exhibited a faster dissolution when compared to pure drug dissolution data. The dissolution rate of Fexofenadine from various inclusion complexes was found to be 74.15 to 99.59% in 30 minutes, when compared to pure drug which exhibited only 12 to 34% of drug in 120 minutes. Inclusion complexes of Fexofenadine prepared with β-CD exhibited release of 96.23%, 95.21%, 93.83%, 96.95% and 93.59% of Fexofenadine from FBP_1, FBP_2, FBK_1, FBK_2 & FBC_2 in 30 minutes, using distilled water as dissolution method respectively. Using phosphate buffer (pH=4) as dissolution medium the formulations FBP_1, FBP_2, FBK_1, FBK_2 & FBC_2 showed 96.23%, 91.67%, 93.35%, 90.95% and 75.83% release of Fexofenadine respectively. The dissolution data were evaluated on the basis of dissolution efficiency parameter at 30 minutes in distilled water and phosphate buffer and results are given in table 12. The dissolution efficiency values were compared at 30 minutes for pure drug and for formulations FBP_1, FBP_2, FBK_1, FBK_2, FBC_2, A 9.53, 10.01, 9.93, 10.62, 10.02 fold increased in DE values were observed for the formulations FBP_1, FBP_2, FBK_1, FBK_2, FBC_2 respectively using distilled water as a dissolution medium. Improvement in dissolution rates of Fexofenadine was observed with FBK_2 & FBK_1 prepared by kneading and co-precipitation method respectively. The higher dissolution rates observed with inclusion complexes

prepared by kneading and co-precipitation method may be due to better interaction of drug and Cyclodextrin.

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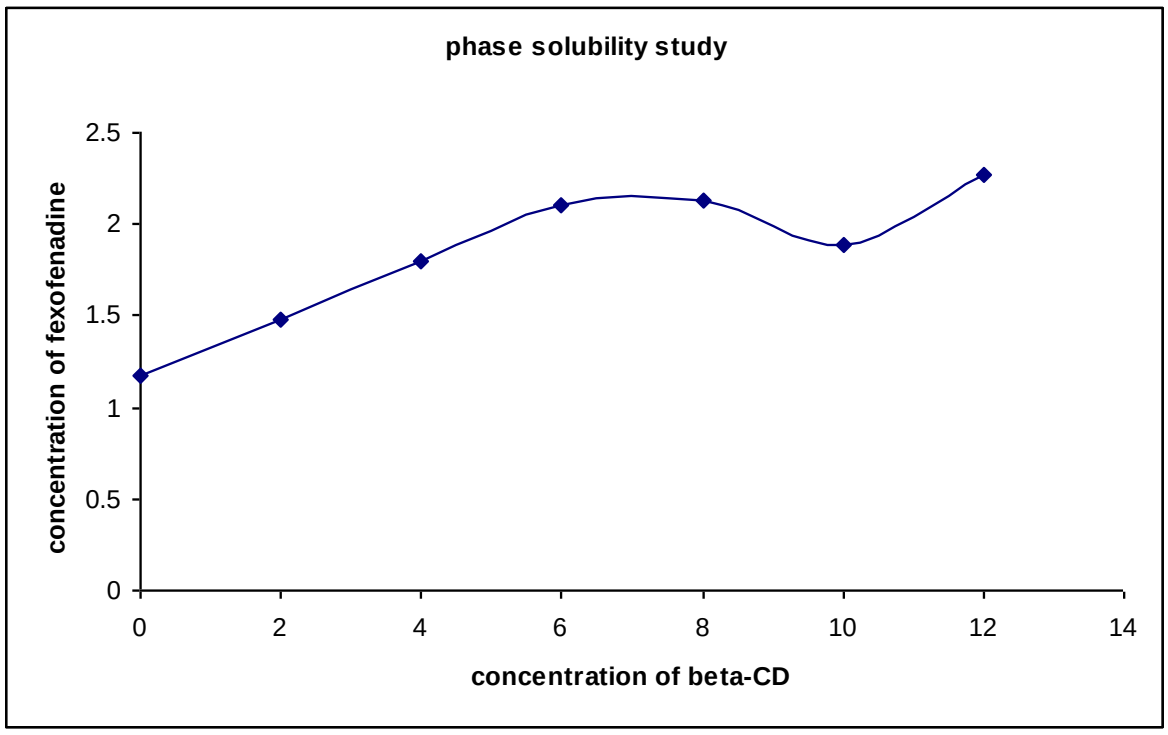

Fig.1: Phase solubility study.

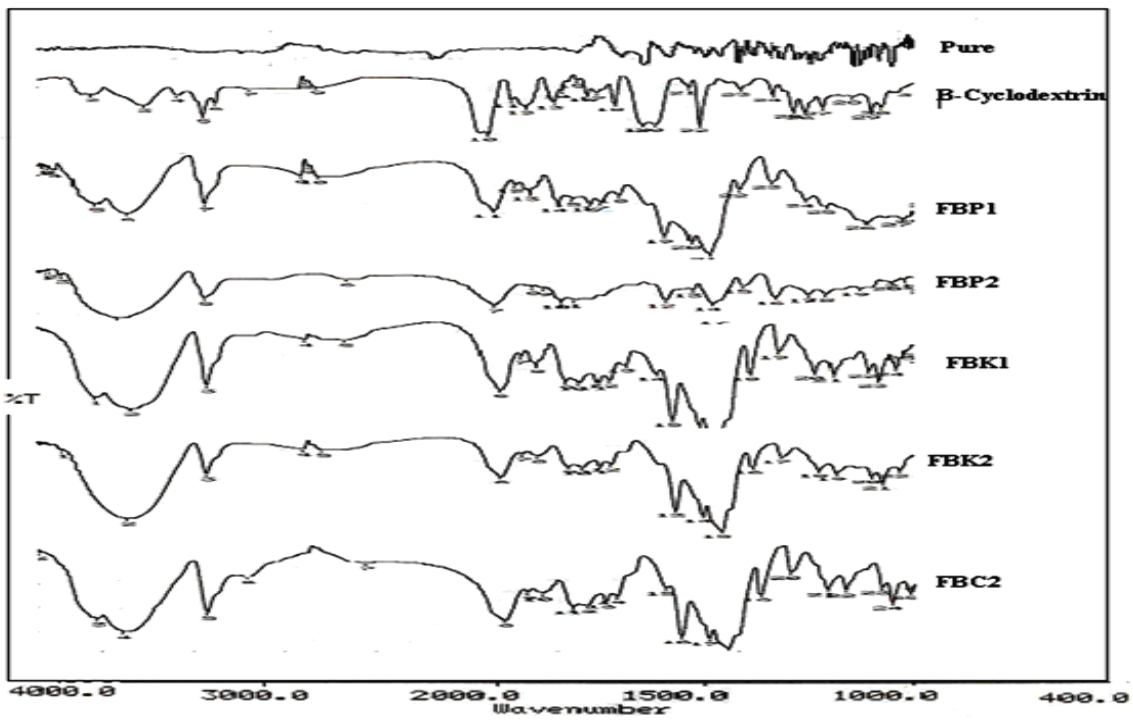

Fig. 2: FT-IR Spectrum of Fexo: β- CD complexes.

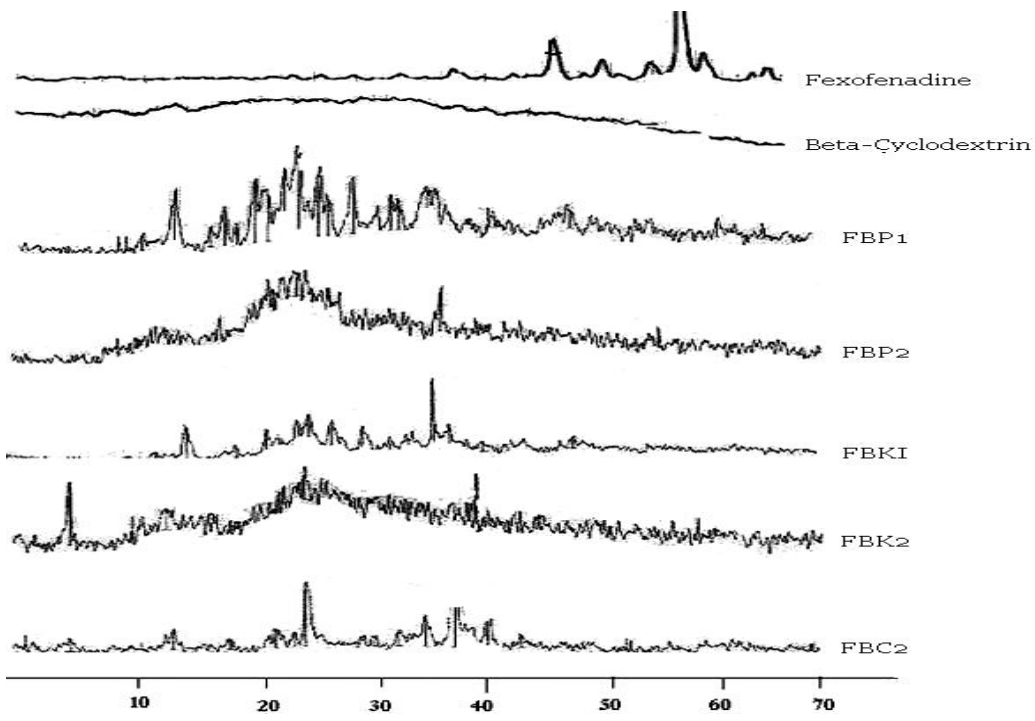

Fig.3: X-Ray Powder Diffraction Study of Fexo: β- CD complexes.

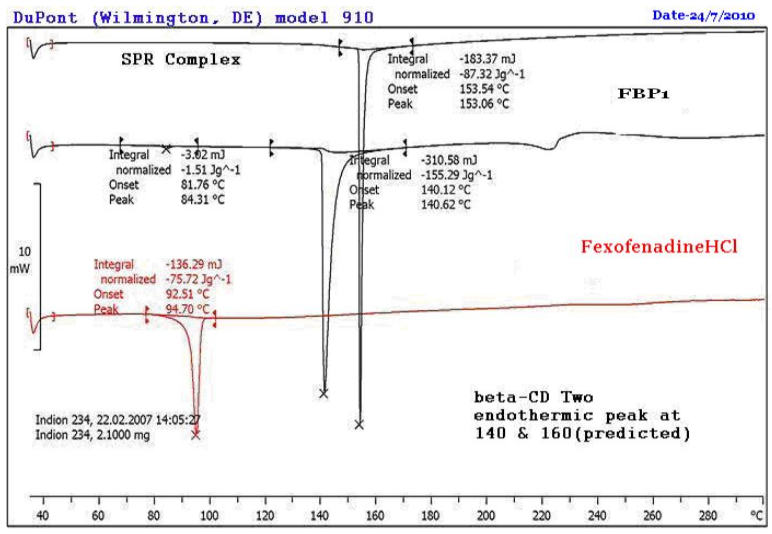

Fig.4: a) Differentiate Scanning Calorimetry of Fexo: β- CD complexes.

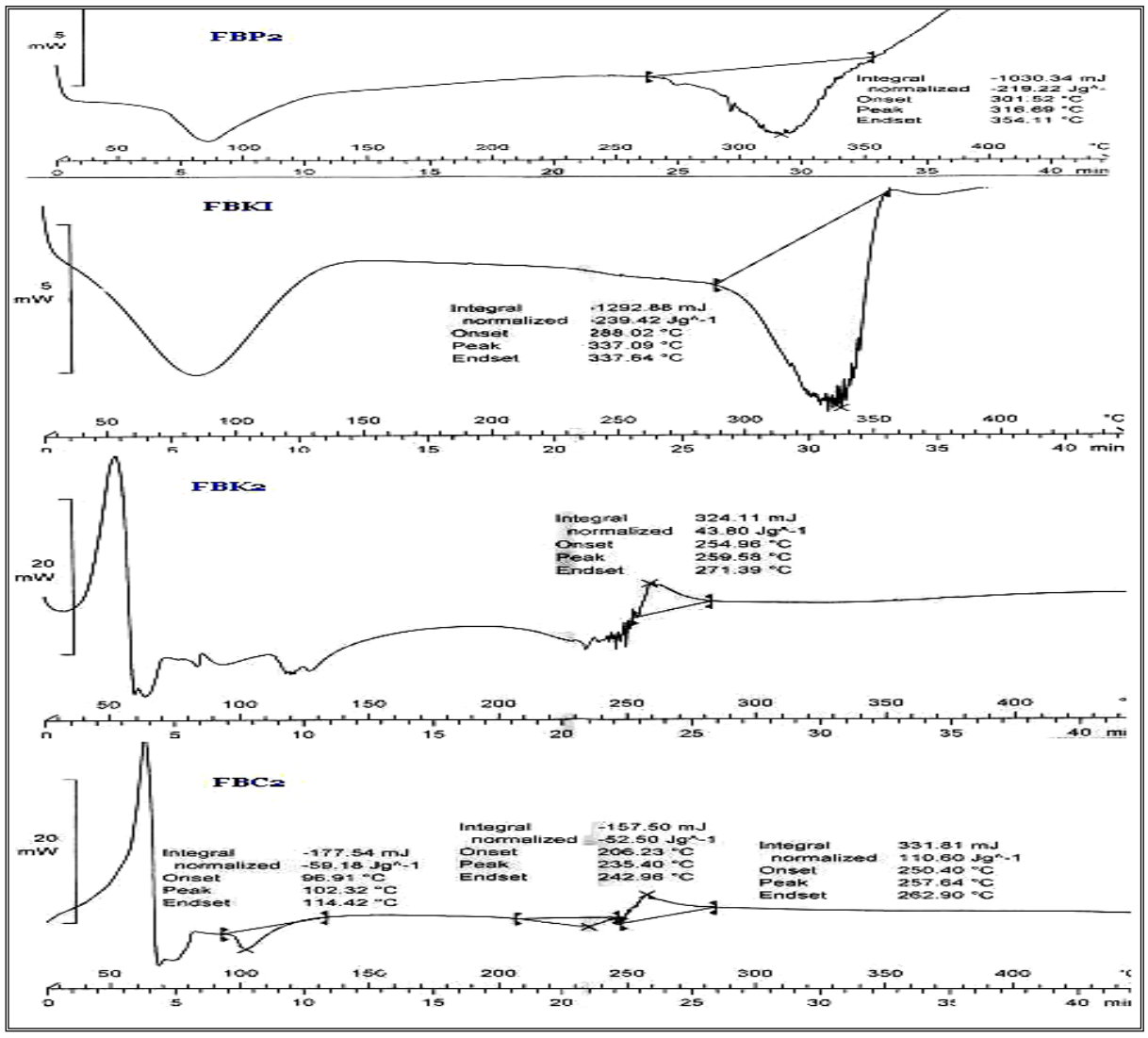

Fig.4: b) Differentiate Scanning Calorimetry of Fexo: β- CD complexes.

Table 1: Different formulations of Fexofenadine with β-Cyclodextrin.

Method	**Drug to Carrier**	**Drug to Carrier ratio**	**Code**
Physical Mixture	FEXO: βCD	1:1	FBP_1
	FEXO: βCD	1:2	FBP_2
Kneading Method	FEXO: βCD	1:1	FBK_1
	FEXO: βCD	1:2	FBK_2
Co-precipitation	FEXO: βCD	1:2	FBC_2

Table 2: Drug content estimation of Fexofenadine in the inclusion complexes.

Code	**Percent drug content ± SD**
FBP_1	24.35 ± 1.0
FBP_2	38.1 ± .71
FBK_1	29.85 ± .58
FBK_2	26.50 ± .21
FBC_2	26.10 ± .29

Table 3: Dissolution Studies of Fexofenadine Complexes (FBP_1, FBP_2, FBK_1, FBK_2, FBC_2 & pure drug) in Distilled water.

Time (Min.)	Percent Drug Released					
	FBP_1	**FBP_2**	**Pure Drug**	**FBK_1**	**FBK_2**	**FBC_2**
0	0	43.44	0	42.96	40.32	43.44
5	38.64	62.39	4.8	67.43	58.08	62.39
10	56.64	76.31	6.8	78.23	74.15	76.31
15	71.27	84.13	8.3	85.91	88.55	84.13
20	91.43	93.59	8.35	93.83	96.95	93.59
30	96.23	96.23	10.60	98.39	98.63	96.23
45	96.95	99.35	11.54	99.59	101.51	99.35

Average of three determinations

Table 4: Dissolution Studies of Fexofenadine Complexes (FBP_1, FBP_2, FBK_1, FBK_2, FBC_2& pure drug) Phosphate Buffer (pH=4)

Time (Min.)	Percent Drug Released					
	FBP_1	**FBP_2**	**Phosphate Buffer pH=4**	**FBK_1**	**FBK_2**	**FBC_2**
5	44.64	45.84	10.0	49.44	42.96	34.32
10	46.15	71.51	12.48	63.11	63.11	47.52
15	75.83	75.83	14.02	78.95	74.87	54.96
20	86.39	88.55	20.40	88.55	81.83	65.99
30	96.23	91.67	21.33	93.35	90.95	75.83
45	98.87	94.31	32.40	101.51	93.35	82.55

Average of three determinations

Table 5: Dissolution Efficiency (DE) of Fexofenadine Complexes in Distilled water & Phosphate Buffer (pH = 4).

Formulation Code	Dissolution Efficiency (%)	
	30 Minutes	
	Distilled water	**Phosphate Buffer**
Fexofenadine	6.58	14.30
FBP_1	62.72	63.80
FBP_2	65.88	67.75
FBK_1	65.35	64.65
FBK_2	69.85	70.16
FBC_2	65.93	50.83

Table 6: Micromeritic properties of drug & β-CD complex.

Property	Drug	KN complex	PM complex
Carr index	20.17 %	18.29 %	17.19 %
Bulk density	0.481 g/ml	0.3943 g/ml	0.3761 g/ml
Angle of repose	29.81	28.61	27.24

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