ORIGINAL RESEARCH

EFFECTS OF β- CYCLODEXTRIN INCLUSION ON PROPERTIES OF CANDESARTAN CILEXETIL

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ABSTRACT:

Candesartan cilexetil is an solubility rate limited low bioavailability antihypertensive agent. Though many novel methods are available for enhancing solubility , this research focused on formation of complexes of candesartan cilexetil with β- cyclodextrins.complexes were prepared by four methods namely physical mixing, kneading, freeze drying and spray coating in 1:1 and 1:2 drug:βCD ratio. Prepared complexes were characterized by FTIR,DSC and XRD . Further evaluation for drug content, enhancement in solubility and enhancement in multimedia dissolution was carried out for each system. A marked enhancement in solubility and dissolution was seen with all complexes as compared to pure drug. Freeze dried complexes showed more benefit than others.

KEYWORDS: Candesartan cilexetil, β-cyclodextrin, complexation, solubilisation, enhancement in dissolution.

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INTRODUCTION

Candesartan cilexetil is a poorly soluble antihypertensive agent with limited bioavailability (15%).[1] To get the proper benefit of administered dose, it is necessary to make administered drug available to body. Solubilisation is the fundamental step in bioavailability of drug as it creates the concentration gradient necessary for permeation. candesartan cilexetil is having solubility limited bioavailability.Hence to improve therapeutic benefit, it is necessary to enhance the solubility of candesartan cilexetil.[2-4] Many novel drug delivery systems are available to enhance the solubility namely micronisation, cogrinding, solid dispersions, complexation, liquisolid techniques, self microemulsifying drug delivery systems, nanoparticles, antisolvent precipitation etc.[5-43] Considering the ease in manufacturing, scale up and cost effectiveness, present research focused on preparing the complexes of candesartan cilexetil and B cyclodextrin and evaluating them for enhancement in solubility and dissolution.

Cyclodextrins (CD) comprise a family of three well-known industrially produced major, and several rare, minor cyclic oligosaccharides. The three major CDs are crystalline, homogeneous, nonhygroscopic substances, which are torus-like macro-rings built up from glucopyranose units. The α-cyclodextrin comprises six glucopyranose units, βCD comprises seven and γCD comprises eight such units.[44-46]

In an aqueous solution, the slightly apolar cyclodextrin cavity is occupied by water molecules that are energetically unfavored (polar–apolar interaction), and therefore can be readily substituted by appropriate "guest molecules", which are less polar than water. The dissolved cyclodextrin is the "host" molecule, and part of the "driving force" of the complex formation is the substitution of the high-enthalpy water molecules by an appropriate "guest" molecule. One, two, or three CD molecules contain one or more entrapped "guest"molecules. Most frequently the host: guest ratio is 1:1.This is the simplest and most frequent case. However, 2:1, 1:2, 2:2, or even more complicated associations, and higher order equilibria exist, almost always simultaneously.

The inclusion complexes formed can be isolated as stable amorphous or microcrystalline sub- stances. Upon dissolving these complexes, an equilibrium is established very rapidly between dissociated and associated species, and this is expressed by the complex stability constant K_a.

Higuchi and Connors have classified complexes based on their effect on substrate solubility as indicated by phase solubility profiles. A-type phase-solubility profiles are obtained when the solubility of the substrate (i.e.drug) increases with increasing ligand (i.e.cyclodextrin) concentration. When the complex is first order with respect to ligand and first or higher order with respect to substrate then A_L-type phase-solubility profiles is obtained. If the complex is first order with respect to the substrate but second or higher order with respect to the ligand then A_P-type phase solubility profiles is obtained. A_N-type phase solubility profiles can be difficult to interpret. B-type phase-solubility profiles indicate formation of complexes with limited solubility in the aqueous complexation medium. In general, the water soluble cyclodextrin derivatives form A-type phase-solubility profiles while the less soluble natural cyclodextrins frequently form B-type profiles. Many researches reported use of cyclodextrins in enhancement of solubility.

MATERIALS AND METHODS

Drug was provided as a gift sample by alembic research laboratory, Baroda. β- cyclodextrin was provided as gift sample by Signet chemical company, Mumbai, India. All chemicals and solvents were of analytical grade by s.d. fine chemicals, Mumbai.

1. Incompatability studies

Drug and cyclodextrin were mixed in 1:2 w/w ratio in a vials. Compatability studies were carried out at room temperature and accelerated temperature for one month. Results were analysed by physical examination, assay and FTIR spectra of the mixture.

1.1Physical observation

Mixture was observed visually for appearance, change in color and odor.

1.2 Assay

An amount of mixture equivalent to 10 mg of drug was taken and diluted suitably with methanol to get a final concentration of 8 ppm analysed with uv – spectrophotometer at 254 nm.

1.3 FTIR

FTIR spectra of the mixture was recorded with traditional KBr pellet method.

2. Phase solubility study

Solubility measurements were performed according to Higuchi and Connors. Excess amounts of drug were added to 10 ml of aqueous solution of CD's in a concentration range of 0.002-0.01 M in glass vials .Solution was vortexed for 2 minutes using cyclomixer and then shaken in rotary shaker for 2 days at 37°C. [47-48] Resultant solutions were then centrifuged for 15 minutes at 2000 rpm. Supernatant was taken diluted suitably, filtered through whatmann filter paper 0.45 µm pore size and absorbance was taken. Each experiment was carried out in triplicate. The apparent affinity constants were calculated from the slope.

The apparent stability constants were calculated from the phase solubility diagrams with the assumption of 1:1 stoichiometry according to the following equation[49]

$$K_s = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad \text{..... Equation 1}$$

Where S0 is the solubility of drug in absence of CD.

3. Preparation of drug cyclodextrin complexes

3.1 Physical mixing

Presieved (sieve no 60) drug and cyclodextrin were mixed together by weighing required quantity to form a homogeneous mixture and again sieved to maintain homogeneity. This mixture was stored suitably and used for further evaluation.

β-cyclodextrin was used in two molar ratio's 1:1 and 1:2 with drug. Two products were prepared by this method. The yield of each product was calculated.

3.2 Kneading

Presieved (# 60) drug and cyclodextrin were weighed in required quantity. Cyclodextrin was wetted in a ceramic mortar with ethanol –water 50% (v/v) solution until a paste was obtained. The required amount of drug was then slowly added and the slurry was kneaded for about 45 minutes. During this process an appropriate quantity of solvent was added in order maintain a suitable consistency. Further this product was dried at room temperature for about two hours and at 50˚C in hot air oven for 24 hours.[50]

Complexes were stored in suitable container till further evaluation.

- cyclodextrins was used in two molar ratio's 1:1 and 1:2 with drug. Two products were prepared by this method.

3.3 Freeze drying

Weighed amount of drug and cyclodextrin were dissolved in 3.5%v/v ammonia solution in respective ratio with sonication and lyophilized for one lyophilization cycle with temperature of prefreezing between -40 to -50º C. Temperature of primary and secondary drying varying in between 20-25º C. Complexes were stored in suitable container till further evaluation.

B cyclodextrins was used in two molar ratio's 1:1 and 1:2 with drug. Two products were prepared by this method.

3.4 Fluidised bed coating

Weighed amount of drug and cyclodextrin were dissolved in 3.5%v/v ammonia solution [105] in respective ratio and spray coated on microcrystalline cellulose (Avicel 200) in mini glat processor by using top spray technique.[51]

The instrument parameters were set as follows:

- Temperature set at 65°C
- Fluidized air= 0.45 bar
- Atomized air= 0.25 bar
- Flow rate = 1 ml/minute

Complexes were stored in suitable container till

further evaluation.
B cyclodextrins was used in two molar ratio's 1:1 and 1:2 with drug. Two products were prepared by this method.

Table 1: Formulations prepared with B cyclodextrins

Sr.No.	Formulation code	Process of complexation	Drug: βCD	Yield
1	F1	PM	1:1	95
2	F2	PM	1:2	96
3	F3	K	1:1	63
4	F4	K	1:2	72
5	F5	FD	1:1	82
6	F6	FD	1:2	86
7	F7	FBC	1:1	96
8	F8	FBC	1:2	97

PM-Physical mixing, K-Kneading, FD-Freeze drying, FBC-Fluidised bed coating

4. Evaluation and characterization of complexes

4.1 Saturation solubility testing

An amount of complex equivalent to 20 mg of drug was added to 10 ml solvent in a glass vial. Vial is stoppered properly and vortexed for 2 minutes on a cyclomixer and then kept in rotary shaker for 48 hours at 37˚C. Resultant solutions were then centrifuged for 15 minutes at 2000 rpm. Supernatant was diluted suitably and absorbance was checked using UV spectrophotometer. Concentration in each solution was calculated**.**

Solvents used for this study were water, 0.1 N HCl and phosphate buffer pH 6.8.

4.2 Drug content

An amount of mixture equivalent to 10 mg of drug was taken and diluted suitably with methanol to get a final concentration of 8 ppm. Absorbance of this solution was checked using a UV spectrophotometer at 254 nm and concentration was calculated.

4.3 In vitro multimedia dissolution studies

In vitro multimedia dissolution studies in different solvents such as water,0.1 N HCl,phosphate buffer pH 6.8 and OGD medium was carried out using a USP type II apparatus. Dissolution was carried out for one hour with sampling points at 5 min, 10 min, 15 min,20 min,30 min,45 min and 60 min. At each time point 5 ml of sample was withdrawn from dissolution vessel and replaced with fresh dissolution medium.

Amount of drug released at each time point and at the end of analysis was calculated by measuring absorbance using appropriate blank solution and drug content was calculated using calibration curve equation.

4.4 Physicochemical characterization

Physicochemical characterization of given sample was done by FTIR,DSC and XRD .

RESULTS AND DISCUSSION

There was no change found in the physical appearance of compatability testing samples. FTIR of compatability samples was found to be matching with reference spectra indicating no change.Drug content of the sample was 99.8%. All results of compatability testing concluded in suitability of usage of β cyclodextrin as a complexing agent for candesartan cilexetil.

Phase solubility analysis

Results of phase solubility indicated a A_L type diagram as shown in figure 1. A linear host-guest correlation was found with a r^2 value of 0.998 with slope less than 1, which suggests formation of 1:1 complex with respect to B cyclodextrins . The apparent stability constants K1:1 obtained from slope of linear phase solubility diagrams was 287.07 for βCD.

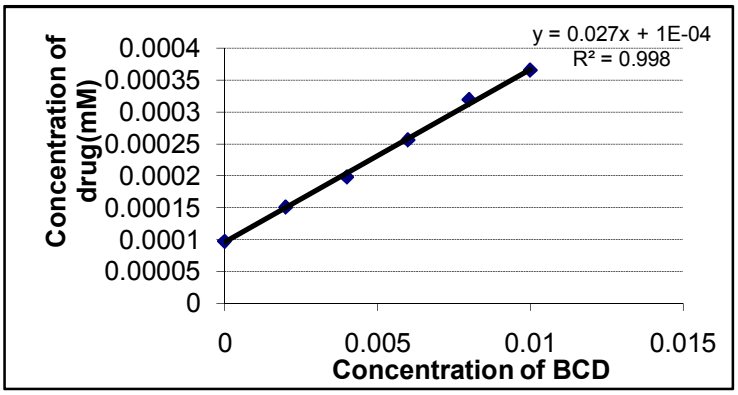

Figure 1: Phase solubility diagram with βCD

Saturation solubility testing

Saturation solubility of drug in 0.1N HCl, water and phosphate buffer pH 6.8 was studied not much difference in solubility was seen in all media was seen. The solubility of pure drug was found around 0.003 mg/ml in all three medias as shown in figure 2.Solubility of complexes was found to be increased

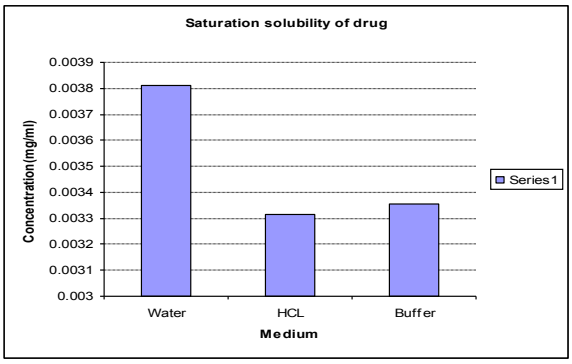

Figure 2: Saturation solubility of drug

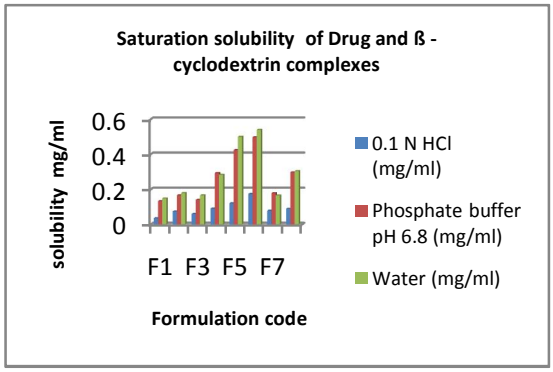

Figure 3: Saturation solubility of complexes

considerably as compared to pure drug as shown in figure 3. Freeze dried complexes were more soluble as compared to other complexes.

Drug content

Drug content of all complexes was found to be in a acceptable range of 98-102% as shown in figure 4.

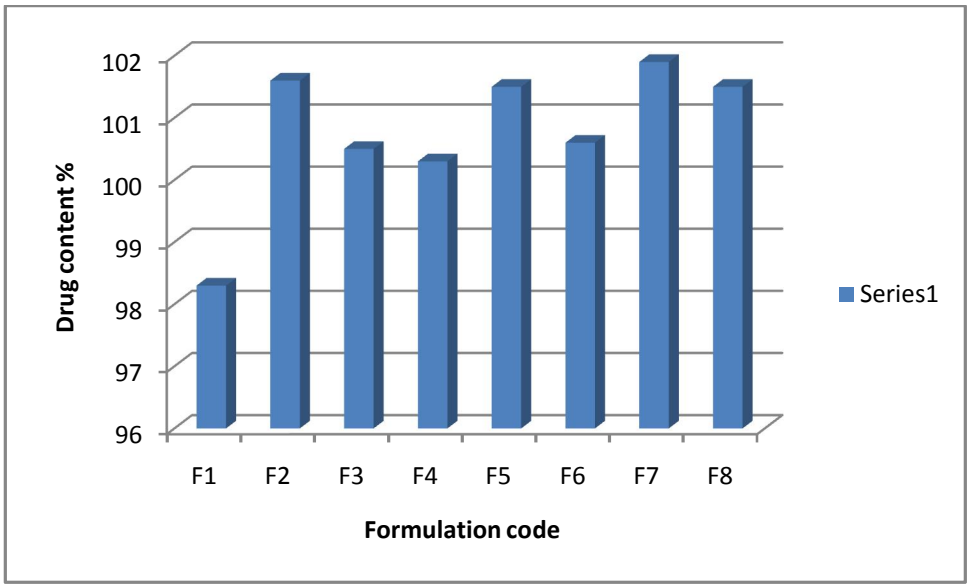

Figure 4: Drug content of complexes

In vitro multimedia dissolution studies

In- vitro multimedia dissolution studies was carried out as discussed in section 4.3.Prepared complexes were found to exhibit significant increase in dissolution in almost every media as compared to pure drug as shown in figures 5-9.

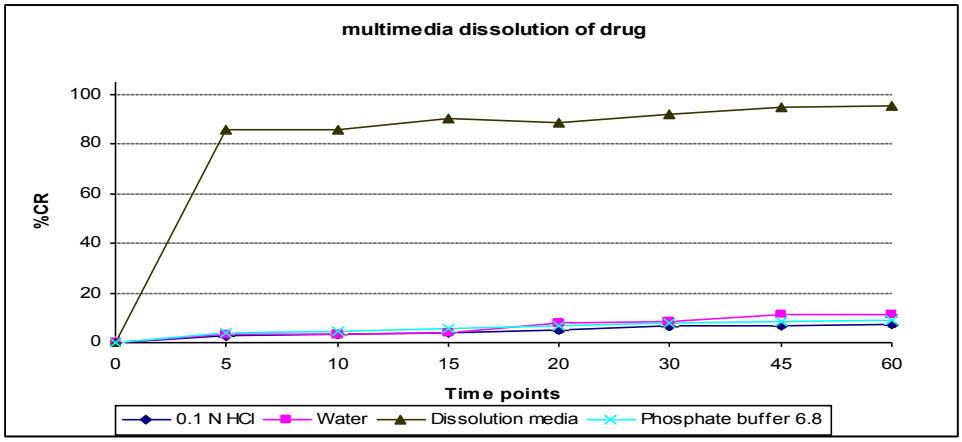

Figure 5: Multimedia dissolution of drug

In multimedia dissolution study highest % CR of drug in 0.1N HCl, phosphate buffer pH 6.8, water and OGD media was found to be 7%, 9%, 11% and 95% respectively while that of the complexes was found to be 29%,66%,68% and 102% respectively.

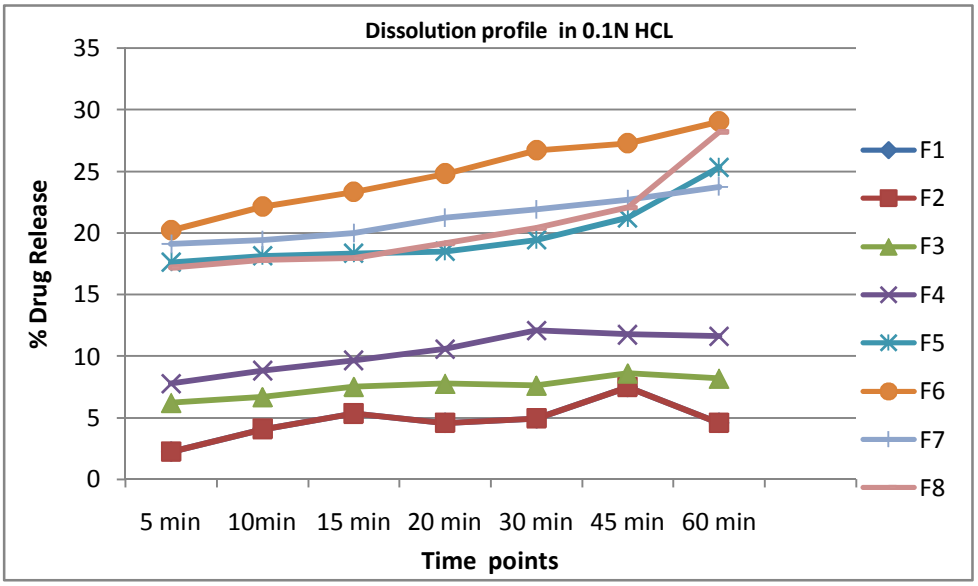

Figure 6: Dissolution of complexes in 0.1N HCl

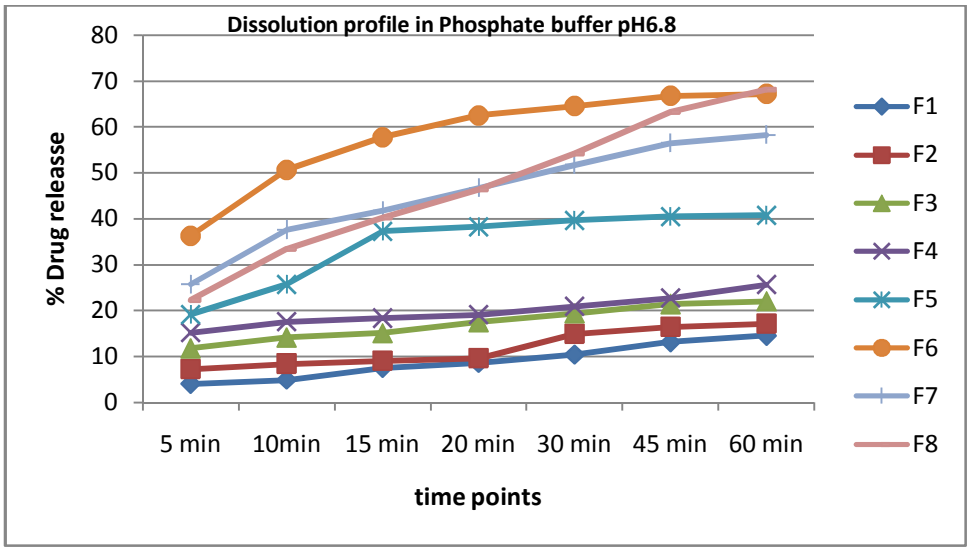

Figure 7: Dissolution of complexes in phosphate buffer 6.8

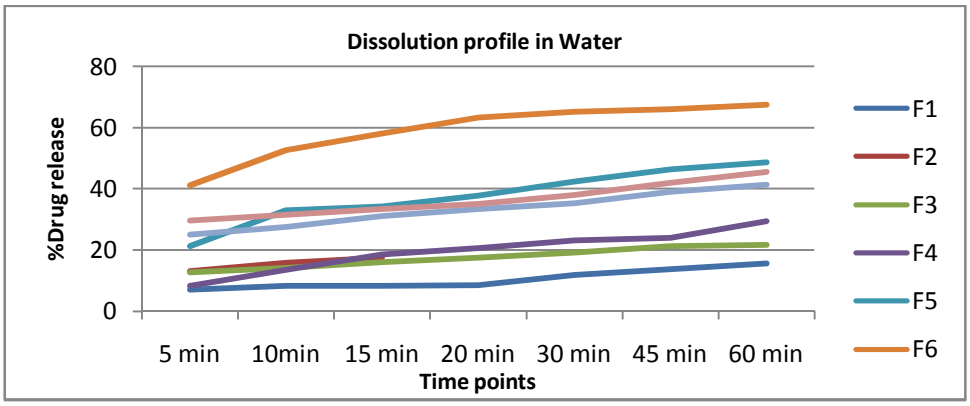

Figure 8: Dissolution of complexes in water

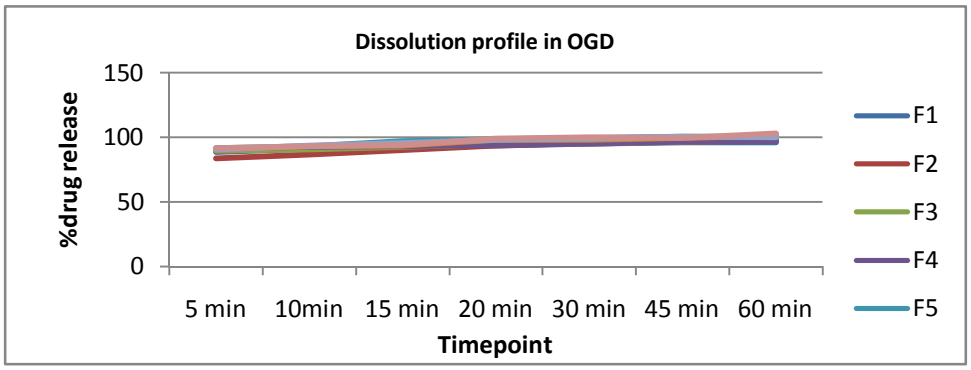

Figure 9: Dissolution of complexes in OGD media

From the results of multimedia dissolution studies it was found that there is a steady increase in dissolution of all formulations in all medias with an acceptable relative standard deviation.. Dissolution of F6 was found comparatively higher than any other complex in all medias.

In OGD dissolution media more than 85% release was seen within 5 min with overall release ranging in between 95-103% at the end of 60 minutes.

Physicochemical characterization

In physicochemical characterization by FTIR drug showed the reported peak at 1717 cm-1 due to carbonyl starching vibrations and in that region βCD, doesn't showed any prominent peak as shown in figures 10 and 11 respectively.

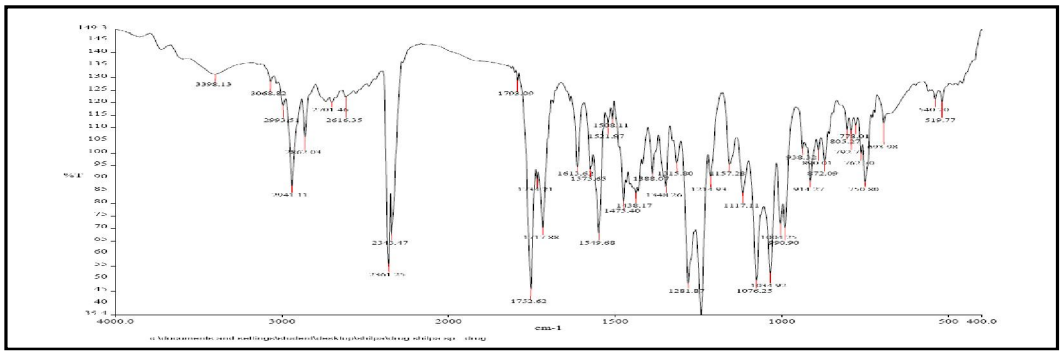

Figure 10: FTIR spectra of drug

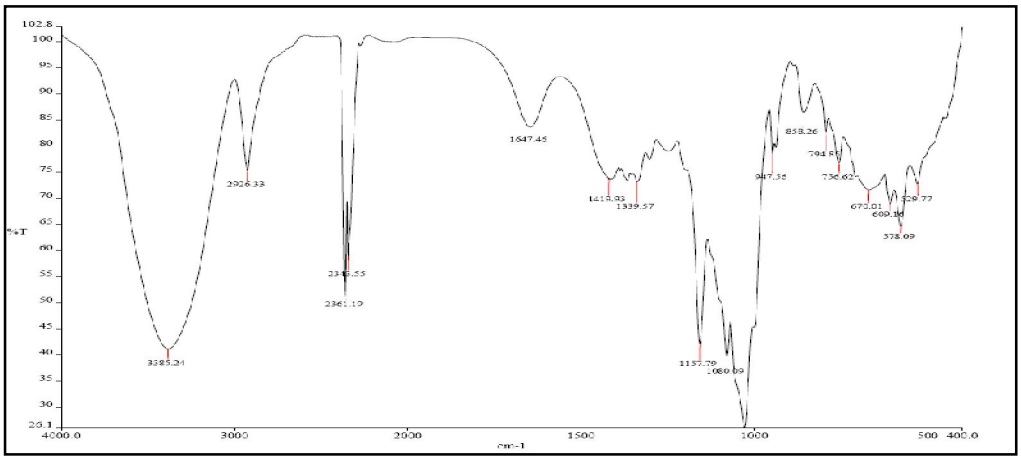

Figure11: FTIR spectra of βCD

In physical mixing and kneading complexes peak at 1717cm^{-1} was found to be present with a lesser intensity and in freeze drying and fluidized bed processing absence of this peak was seen indicating complete complexation of drug and cyclodextrins as shown in figures 12-19.

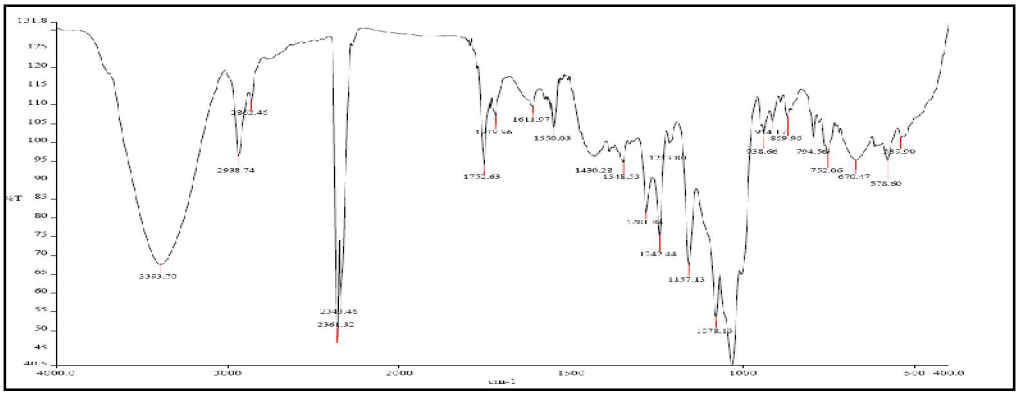

Figure 12: FTIR spectra of F1

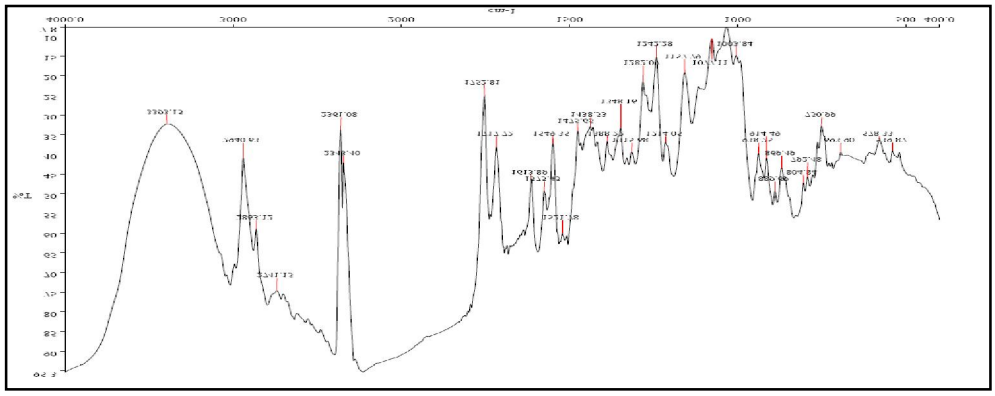

Figure 13: FTIR spectra of F2

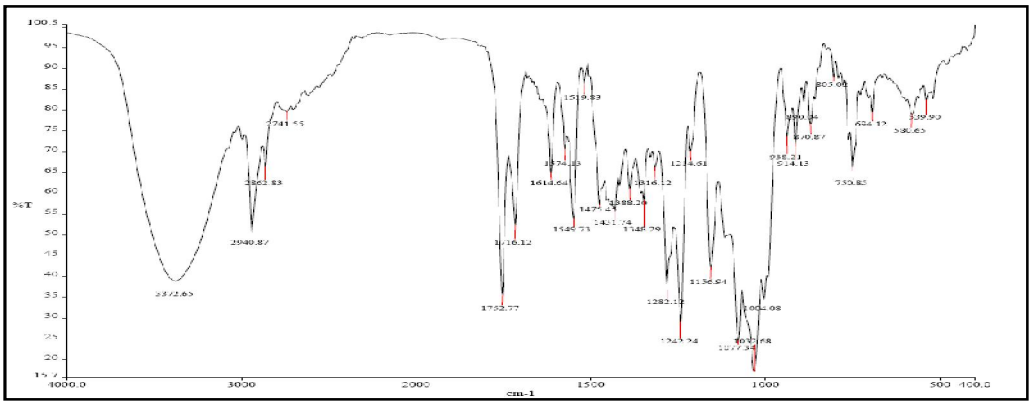

Figure 14: FTIR spectra of F3

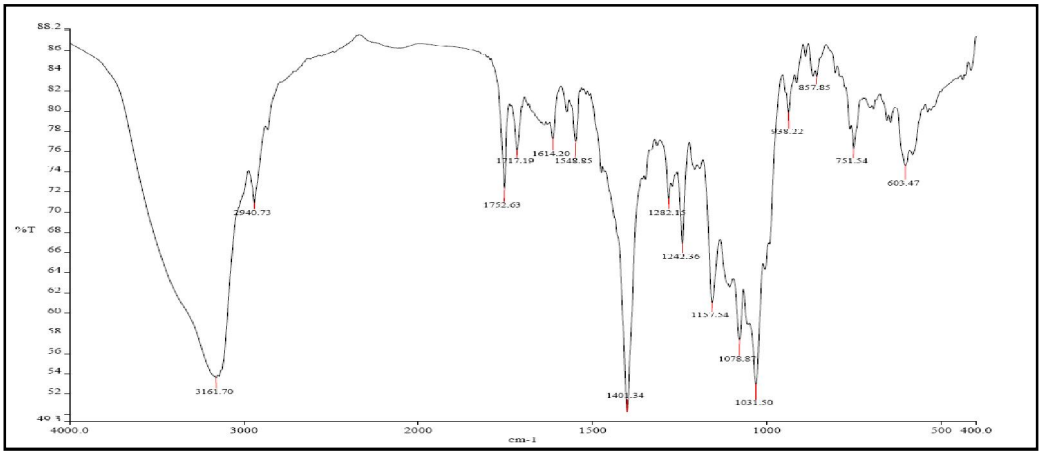

Figure 15: FTIR spectra of F4

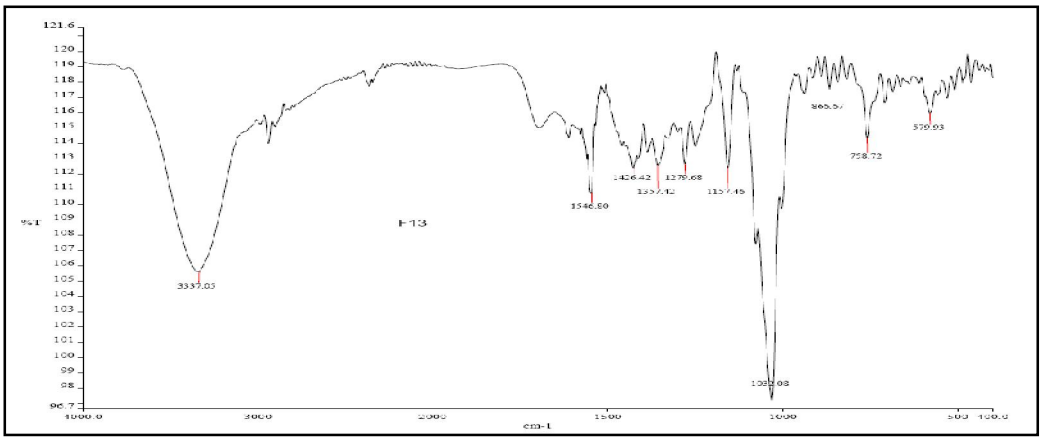

Figure 16: FTIR spectra of F5

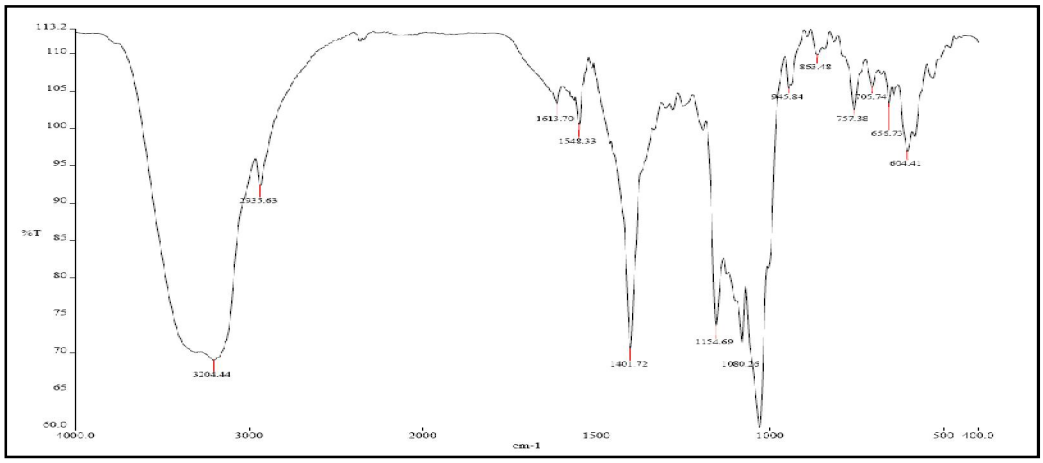

Figure 17: FTIR spectra of F6

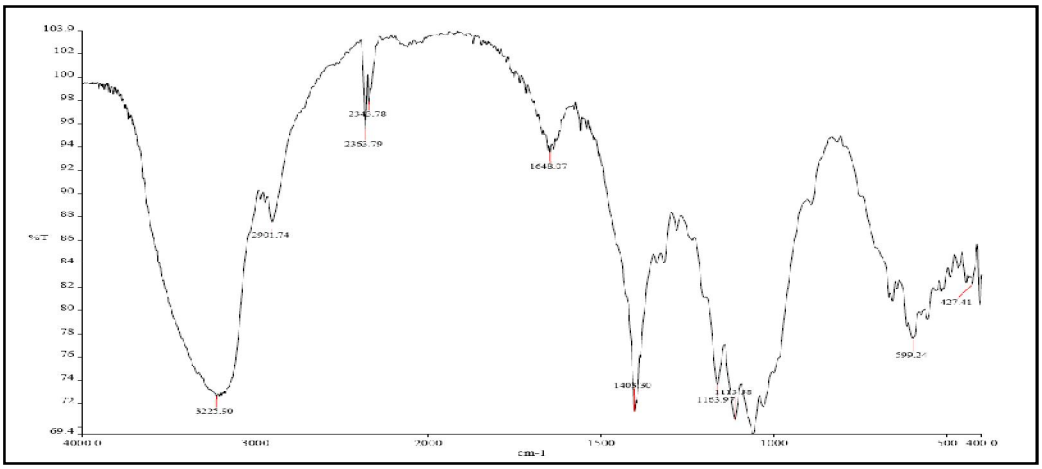

Figure 18 : FTIR spectra of F8

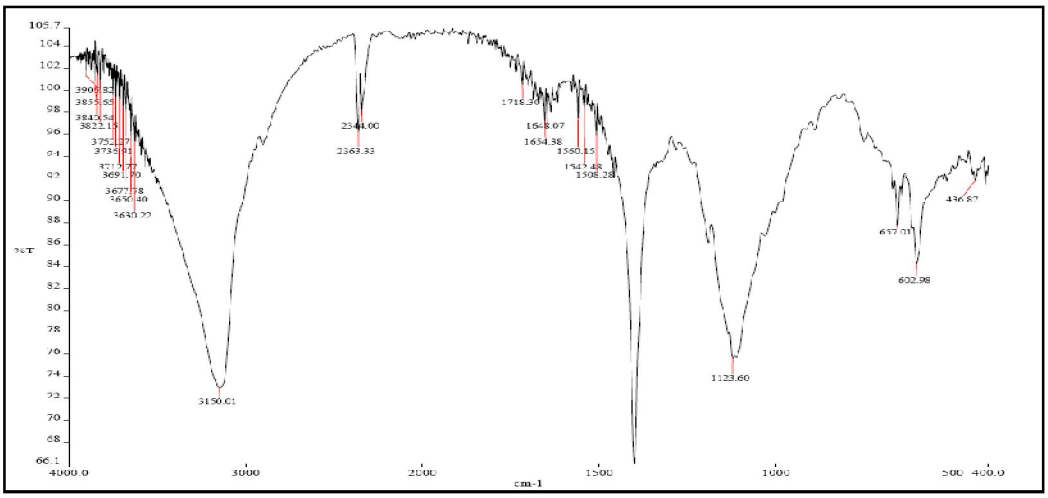

Figure19: FTIR spectra of F8

In X ray diffraction analysis 2θ at 9.8 which is characteristic of drug was seen in most of the complexes but presence of amorphous structure was confirmed in the complexes prepared by fluidized bed coating process as shown in figures 20-24

DSC studies also confirm formation of complex by showing a shift in endothermic peaks of drug and cyclodextrins as shown in figures 25-30

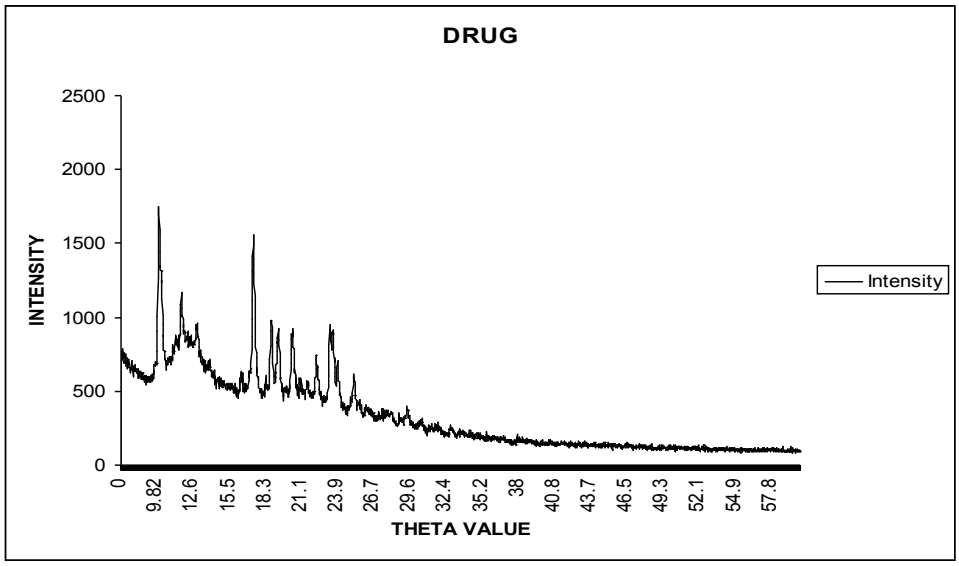

Figure 20 XRD spectra of drug

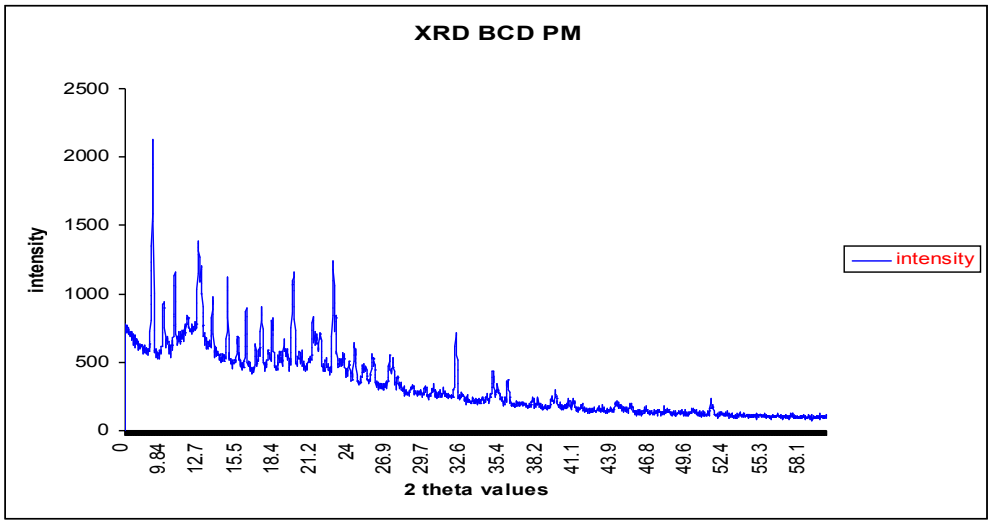

Figure 21: XRD spectra of F2

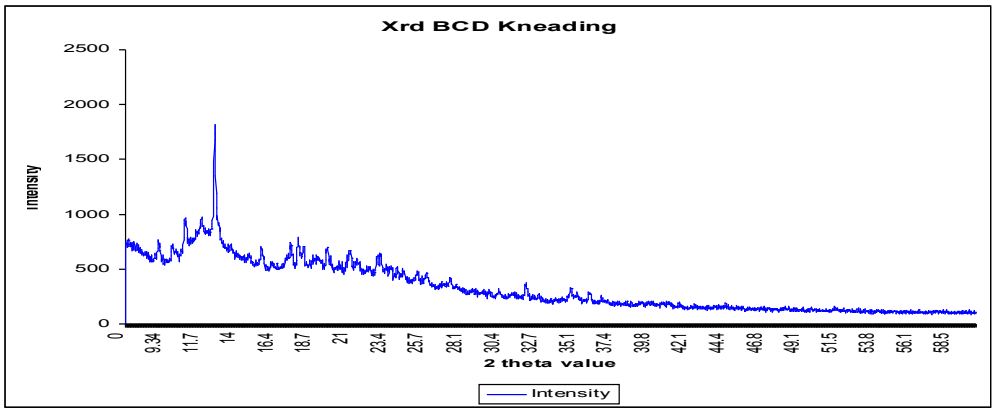

Figure 22: XRD spectra of F4

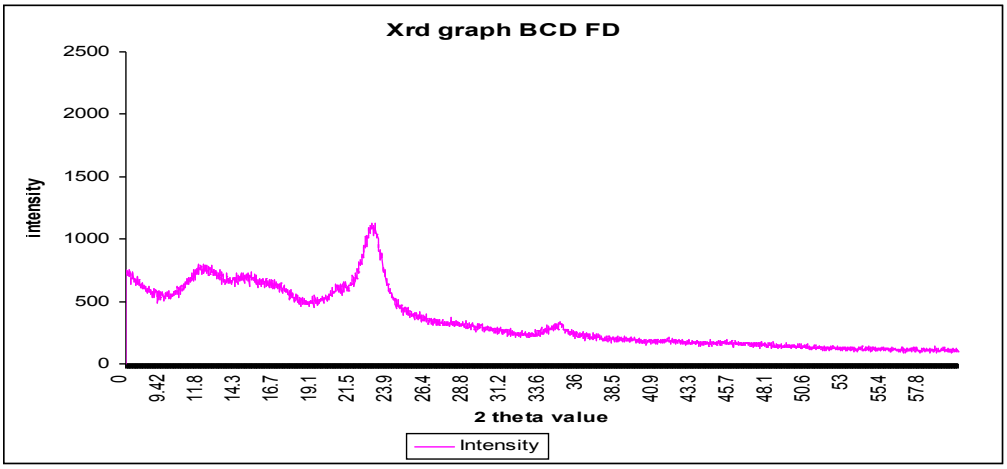

Figure 23: XRD spectra of F6

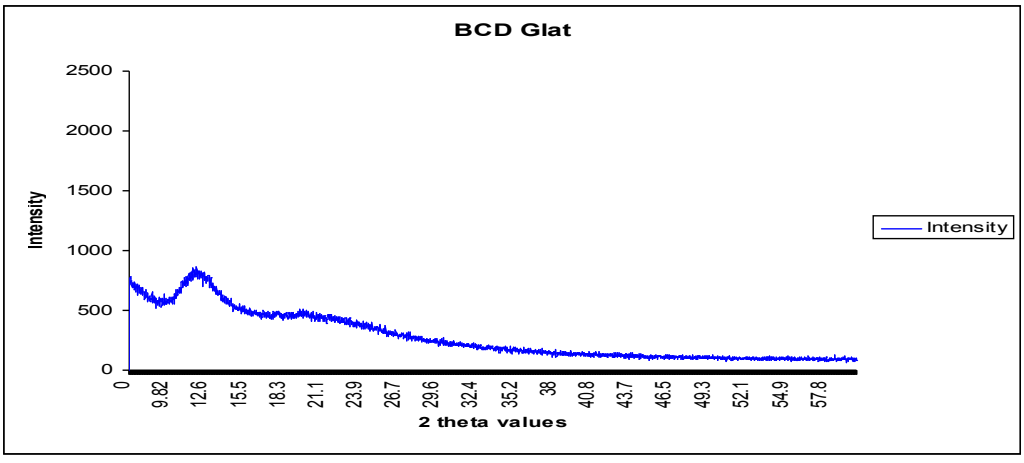

Figure 24: XRD spectra of F8

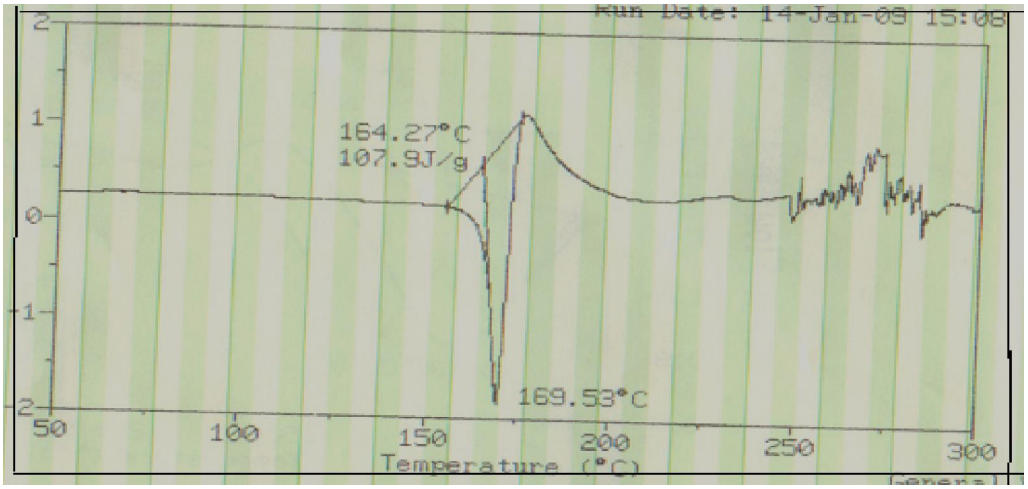

Figure 25: DSC thermogram of drug

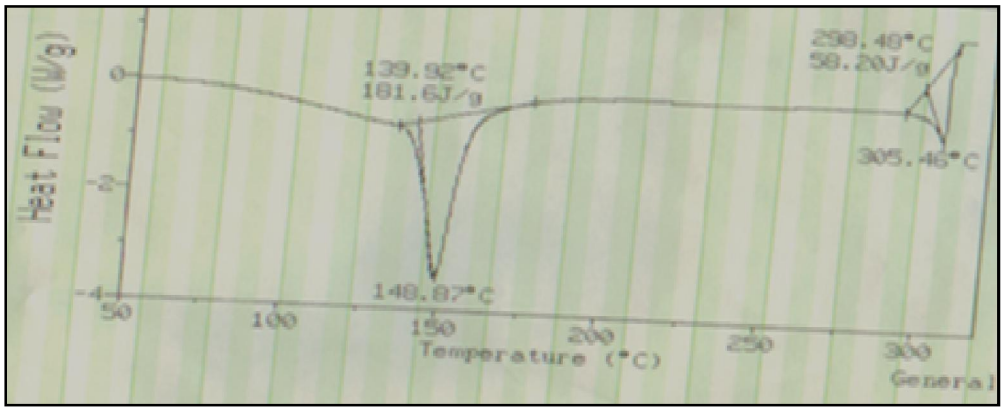

Figure 26 :DSC thermogram of BCD

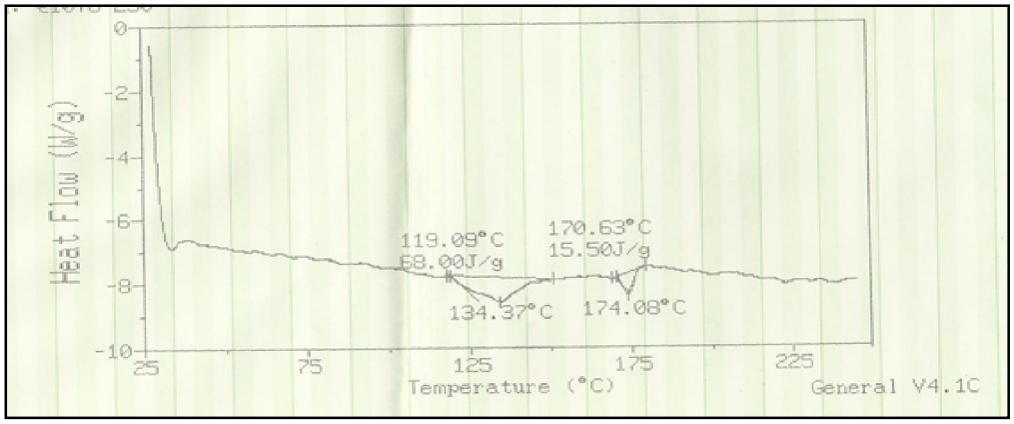

Figure 27 : DSC thermogram of F2

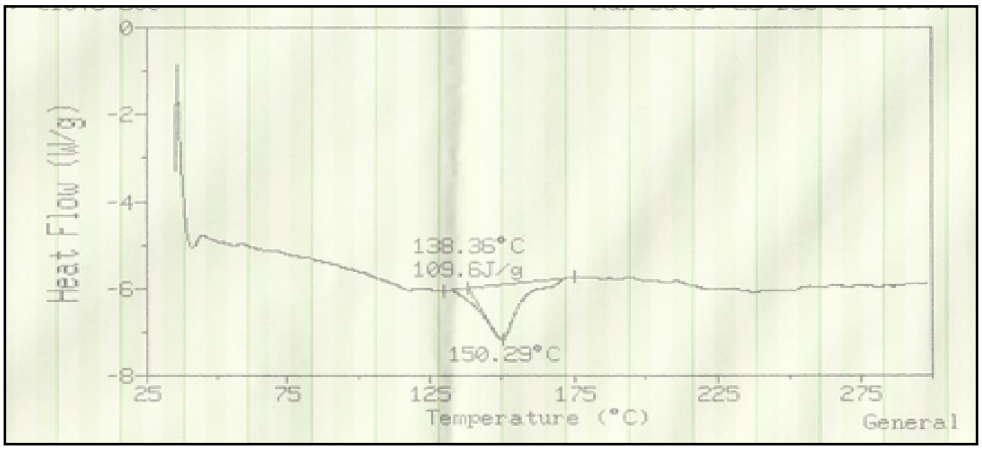

Figure 28:DSC thermogram of F8

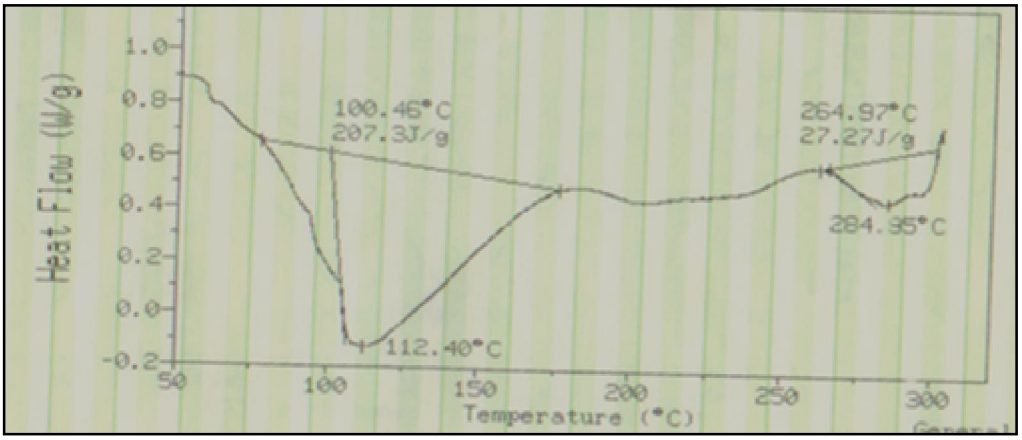

Figure 29: DSC thermogram of F14

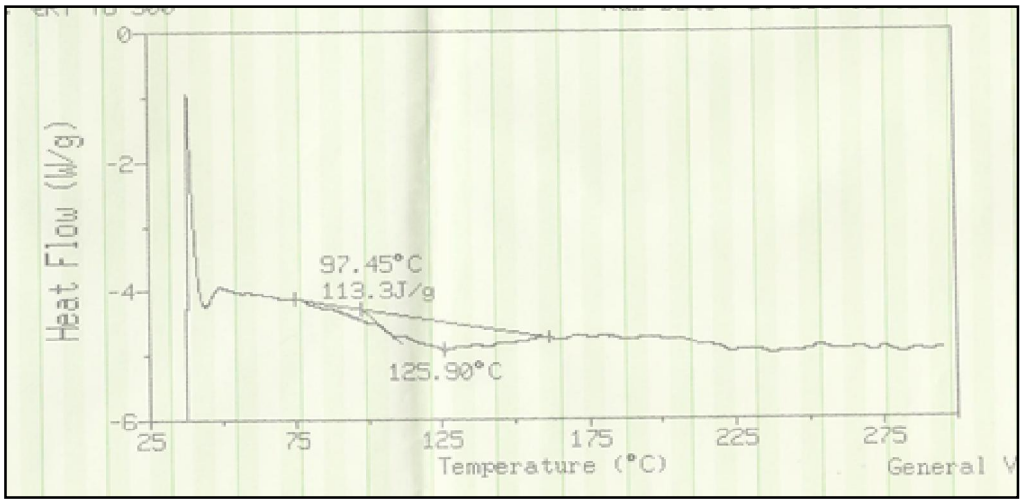

Figure 30: DSC thermogram of F20

Thus it can be said that complexation with β cyclodextrin is useful in enhancing solubility and dissolution rate of candesartan cilexetil.From all complexes prepared and from the results obtained F6 prepared by the method of freeze drying was selected as the best complex. From the above results it can be concluded that complexation with β cyclodextrins can be considered as an effective method to enhance the solubility of drug which offere the advantages of **easy manufacturing and scale up.**

ACKNOWLEDGEMENT:
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CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE REPORTED