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Comparative Efficiency of Cyclodextrins in Enhancing Solubility and Dissolution of Candesartan Cilexetil by a Novel Process of Fluidized Bed Coating

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ABSTRACT

Effect of cyclodextrins such as beta cyclodextrins (βCD), gamma cyclodextrins (γCD) and a modified cyclodextrins such as hydroxypropylated beta cyclodextrins (HPβCD) was assessed on enhancing solubility and dissolution of a poorly water soluble drug candesartan cilexetil. Stoichiometry of the reaction and affinity constant values for all above mentioned cyclodextrins were found out by phase solubility analysis. Drug and cyclodextrin complexes were prepared in two ratio's as 1:1 and 1:2 by a novel process of fluidized bed coating using pam glat coater. All complexes were evaluated for increase in solubility and dissolution rate and characterized by differential scanning calorimetry(DSC), Fourier transform infrared spectroscopy(FTIR) and X-ray diffraction analysis (XRD).

Key words- candesartan cilexetil, cyclodextrin complexes, fluidized bed coating, phase solubility analysis, solubility.

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INTRODUCTION

The emergence of high-throughput screening has led to an increase in the number of poorly water-soluble drugs. The delivery of such drugs into the body in a sufficiently bioavailable form has been challenging for formulation researchers. Solubility and dissolution are the rate limiting steps in absorption of such kind of drugs[1]. Candesartan cilexetil is a poorly soluble antihypertensive drug with oral bioavailability of 15%.[2] It is a prodrug which is hydrolyzed to candesartan during absorption from the gastrointestinal tract[3]. Various methods are reported for modification of solubility such as micronization[4], solubilization[5], solid dispersion[6], nanoparticles[7].Cylodextrin (CD) complexation is also reported to have a great impact on enhancing solubility and dissolution of many drugs[8-12] . There are various methods of preparing complexes with cyclodextrins, most commonly used were physical mixing, kneading and lyophilization. Instead of routine methods of complex formation, a novel method of fluidized bed coating was tried to check the efficiency of cyclodextrins and modified cyclodextrin in enhancing solubility of poorly soluble candesartan cilexetil.

MATERIALS AND METHODS

Candesartan cilexetil was obtained as a gift sample from Alembic research laboratory, Baroda, Cyclodextrins were obtained as a gift sample from signet chemical company, Mumbai, India. All chemicals used in this research were purchased from SD fine chemicals Ltd. Mumbai, India.

Phase solubility analysis-

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^{o}C [13-14]. Resultant solutions were then centrifuged for 15 minutes at 2000 rpm. Supernatant was taken diluted suitably, filtered through whatman 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 according to the following equation[15]

$Ks = slope/S_0(1\text{-}slope)$

Where S_0 is the solubility of drug in absence of CD.

Preparation of drug cyclodextrin complexes by fluidized bed coating

Weighed amount of drug and cyclodextrin were dissolved in 3.5%v/v ammonia solution in respective ratio and spray coated on microcrystalline cellulose (Avicel 200) in mini glat processor by using top spray technique.[16]

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. Three above mentioned cyclodextrins were used in two molar ratio's 1:1 and 1:2 and were coded as F1 and F2 for βCD, F3 and F4 for HPβCD and F5and F6 for γCD as shown in Table 1. The yield of products was found to be in between 80-90%.

Table 1-Formulation codes of complexes

Complexing agent	Ratio of Drug: Complexing agent	Formulation code
βCD	1:1	F1
βCD	1:2	F2
HP βCD	1:1	F3
HP βCD	1:2	F4
γCD	1:1	F5
γCD	1:2	F6

EVALUATION AND CHARACTERIZATION OF COMPLEXES.[17]

Saturation solubility testing

An amount of complex equivalent to 20 mg of drug was added to 10 ml solvent in a glass vial. Vial was stopper 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.

Drug content

An amount of complex equivalent to 8 mg of drug was taken in a 10 ml volumetric flask and half the amount of acetonitrile was added in to it. The solution was sonicated for 5 minutes and volume was made up to 10 ml to give solution of 800 ppm. This solution was then filtered using whatman filter paper (45 micron pore size). 0.1 ml from this solution was then diluted to 10 ml with same solvent in another 10 ml volumetric flask to give a solution of 8 ppm. Absorbance of this solution was checked using a UV spectrophotometer and concentration was calculated.

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 USP type 2 dissolution test apparatus

with 900 ml of dissolution medium , speed of paddle was 50 revolutions per minute. The sample was withdrawn till one hour with sampling points of 5, 10,15.20,30,45 and 60 minutes.

Physicochemical characterizations

Physicochemical characterization of given sample was done by DSC, FTIR and XRD. IR spectra were recorded by the conventional KBr pellet method. DSC was performed with heating rate of 10˚ C /min under nitrogen stream. For XRD, Voltage and current were set at 40 kV and 20 mA respectively and XRD patterns were collected. All patterns were scanned over the range 0-60^o 2θ angle with a scan rate of 1.5^o/min.

RESULT AND DISCUSSION

Phase solubility diagrams were plotted for Drug with βCD, HPβCD and γCD as shown in figure 1, 2 and 3 respectively. Phase solubility profile in all cases can be classified as A_L type. A linear host-guest correlation was found with a r^2 value of 0.98-0.99 in all cases with slope less than 1, which suggests formation of 1:1 complex with respect to all cyclodextrins in study. The apparent stability constants K1:1 obtained from slope of linear phase solubility diagrams were 287.07, 514.16 and 431.73 for βCD, HPβCD and γCD respectively, which suggest formation of more stable complex with HPβCD than βCD and γCD. Drug content of all the complexes was found to be in between 98-101.5% as shown in figure 4.

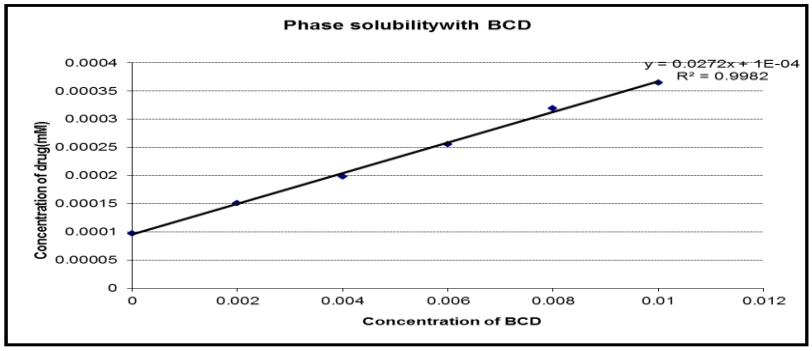

Figure 1 Phase solubility diagram with βCD

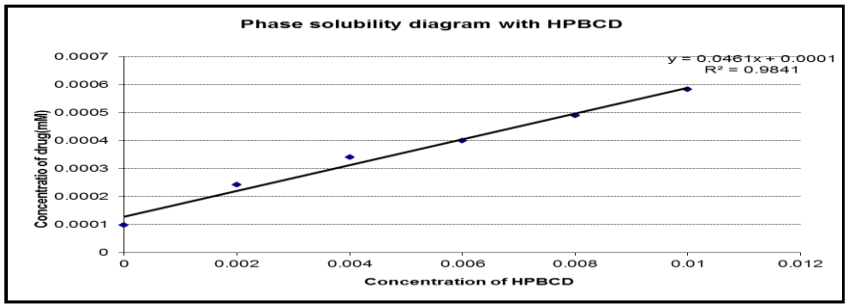

Figure 2 Phase solubility diagram with HPβCD

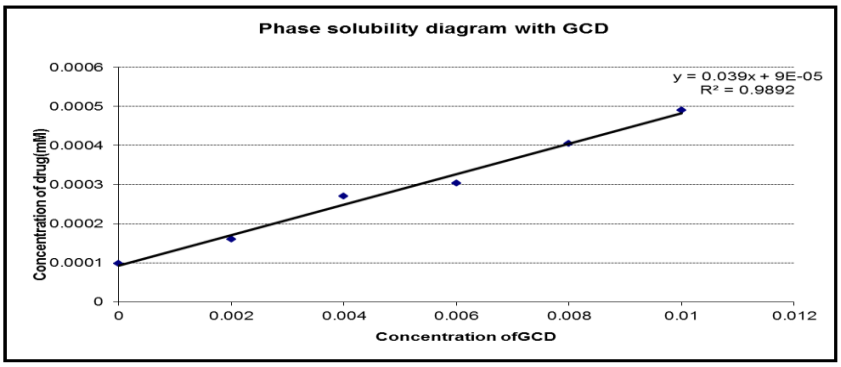

Figure 3 Phase solubility diagram with γCD

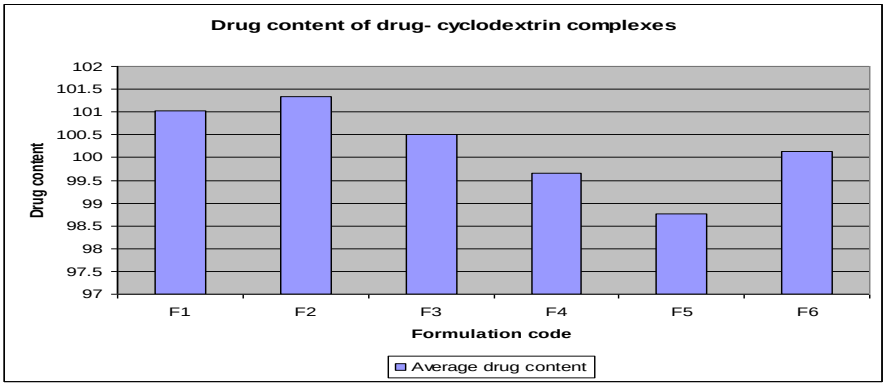

Figure 4 Drug content of cyclodextrins complexes

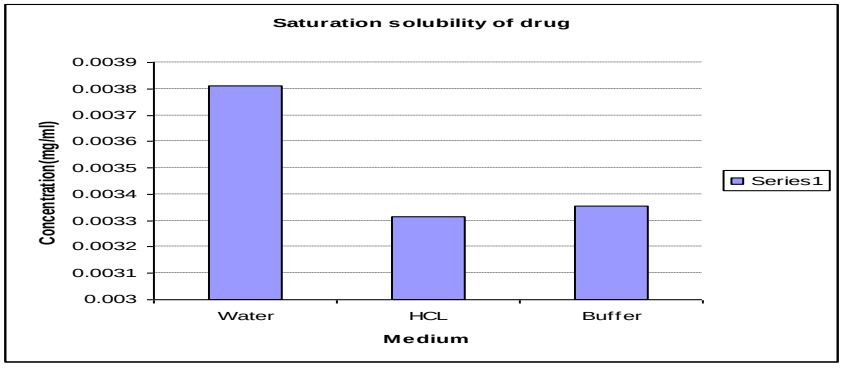

Figure 5 Saturation solubility testing of drug

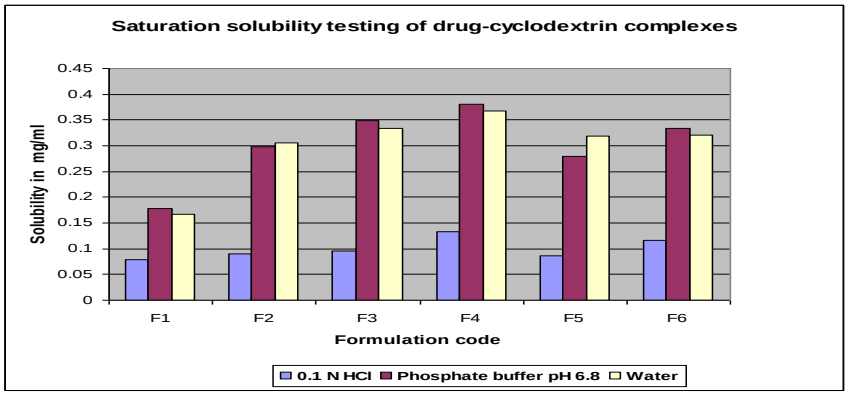

Figure 6 Saturation solubility testing of drug-cyclodextrin complexes

In saturation solubility testing considerable enhancement was seen as compared to that of the pure drug as shown in figures 5 and 6 respectively. F4 complex comprising 1:2 molar ratio of drug and HPβCD was found to possess maximum solubility in all three media. Multimedia dissolution testing of pure drug and prepared complexes was carried out. As shown in figure 7, Drug release was found to be lower in 0.1N HCl as compared to other media of dissolution. In 0.1 N HCl the drug release was low (below 10%) which was found to be increased with all complexes ranging in between 25-35% as depicted in figure 8.In case of Phosphate buffer pH 6.8 and water as shown in figures 9 and 10 respectively, release with complexes was found to be increased in between 40-50% as compared to around 10% in case of pure drug. In OGD (Office of generic drugs) medium release was found to be around 95-103% in case of pure drug as well as complexes as given in figure 10 and 11.

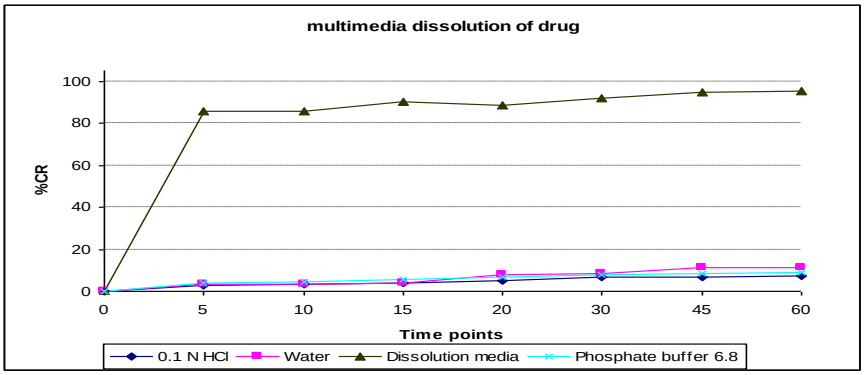

Figure 7 Multimedia dissolution of drug

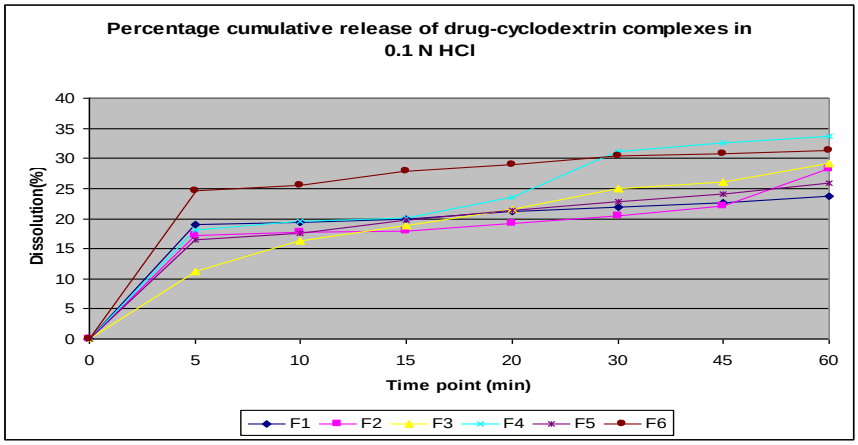

Figure 8 Dissolution of drug-cyclodextrin complexes in 0.1N HCl

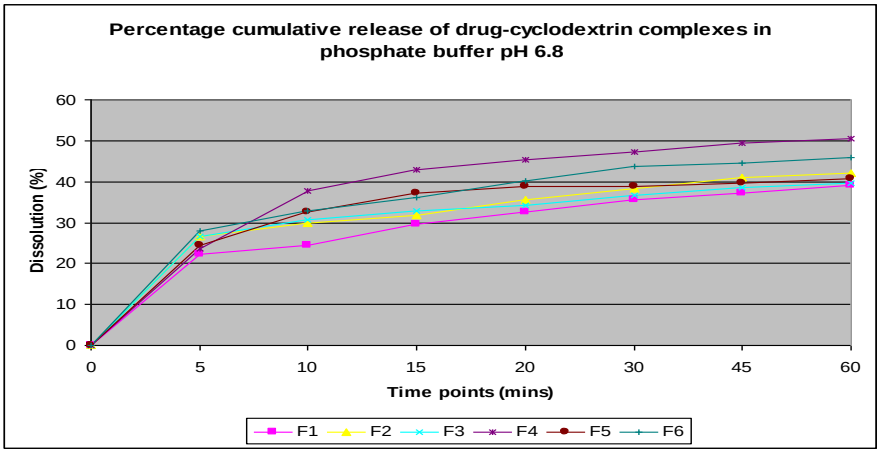

Figure 9 Dissolution of drug-cyclodextrin complexes in Phosphate buffer pH 6.8

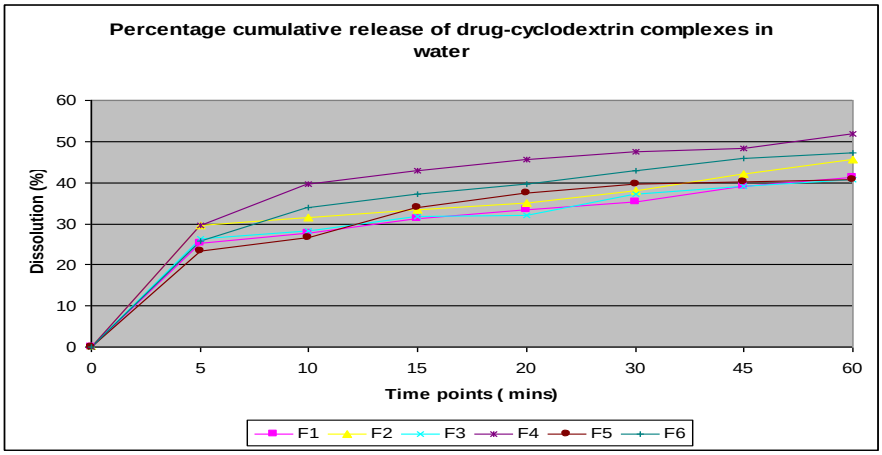

Figure 10 Dissolution of drug-cyclodextrin complexes in water

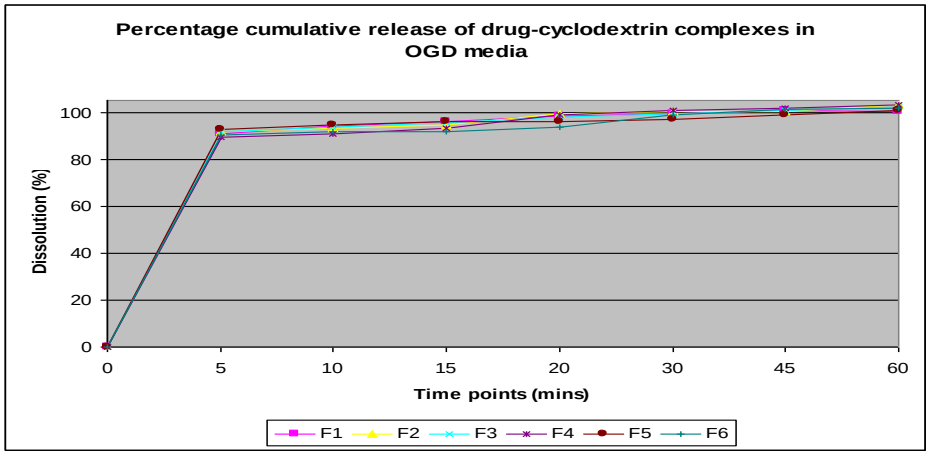

Figure 11 Dissolution of drug-cyclodextrin complexes in OGD medium

In physicochemical characterization by FTIR drug showed the reported peak at 1717 cm-1 due to carbonyl starching vibrations and in that region βCD, HPβCD and γCD doesn't showed have any prominent peak as shown in **figures 12-18,** after complexation complete absence of this peak indicates complex formation. In X ray diffraction analysis, as can be seen in figures from 19-22,

2θ at 9.8 which is characteristic of drug, was found to be absent which confirms formation of complex by fluidized bed coating process. DSC studies also confirm formation of complex by showing a shift in endothermic peaks of drug and cyclodextrins as shown in **figures 23-29.**

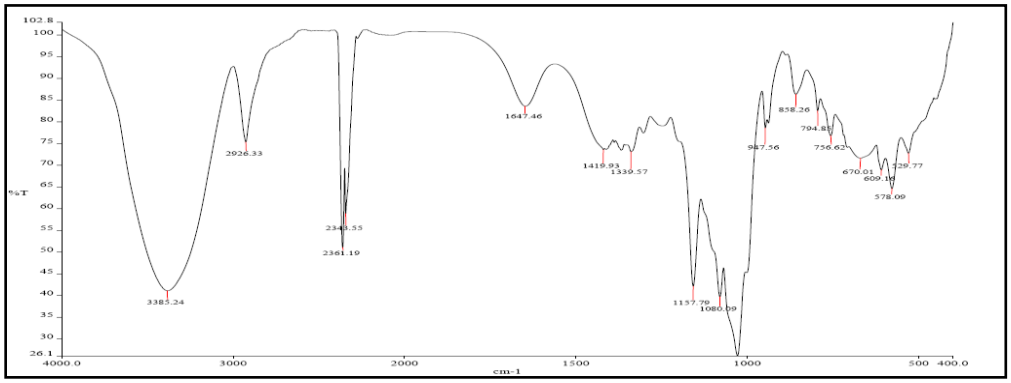

Figure 12 FTIR spectra of βCD

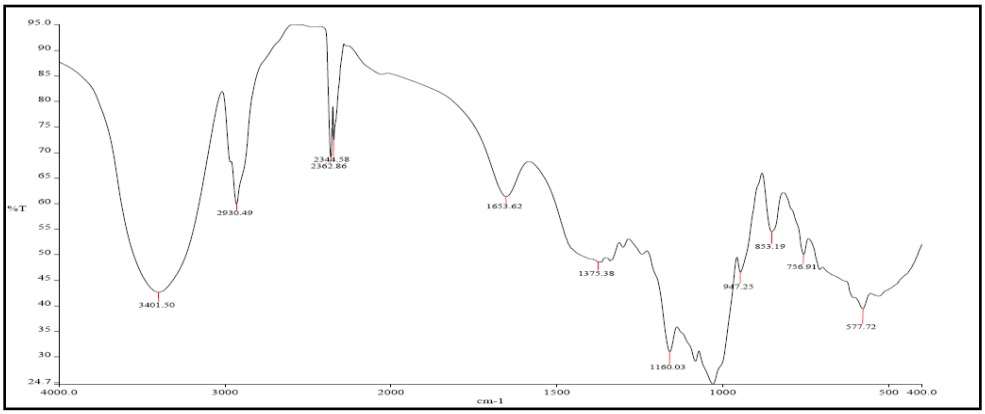

Figure 13 FTIR spectra of HPβCD

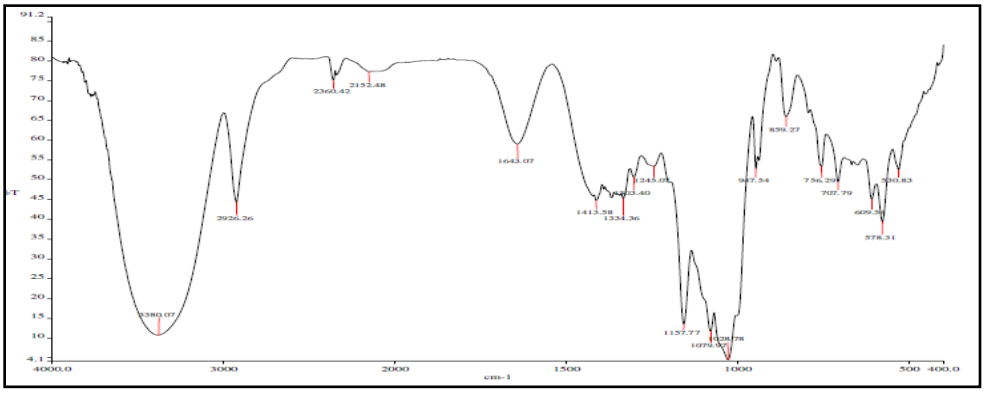

Figure 14 FTIR spectra of γCD

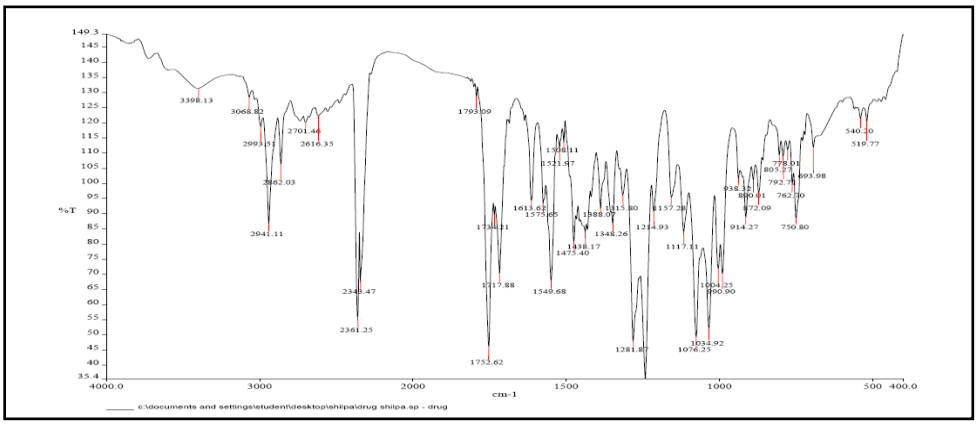

Figure 15 FTIR spectra of pure drug

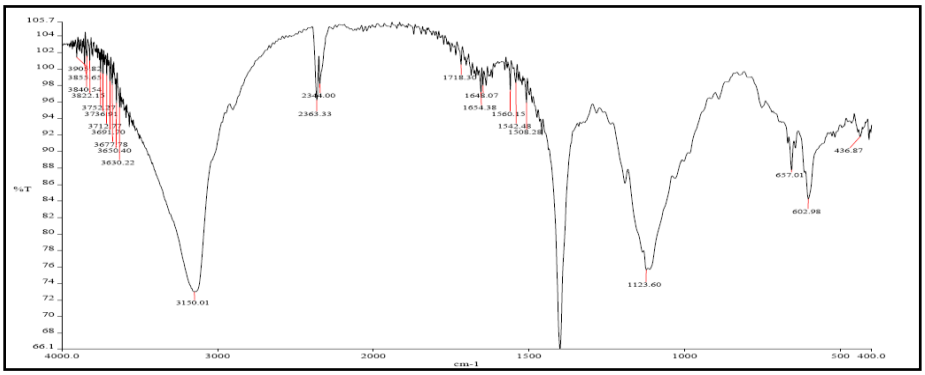

Figure 16 FTIR spectra of F2

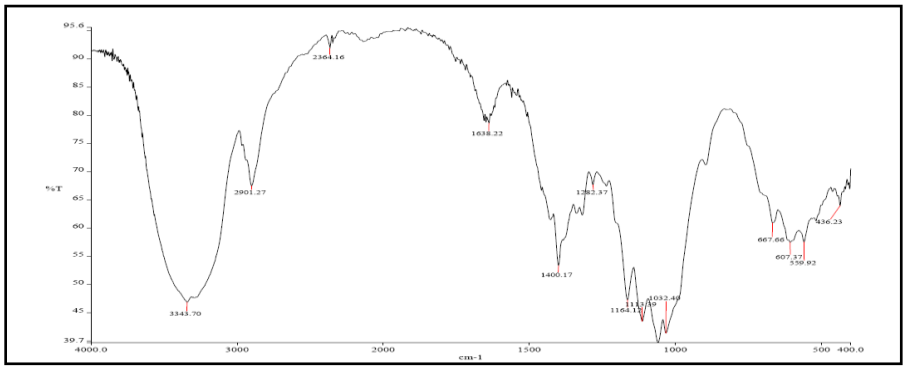

Figure 17 FTIR spectra of F4

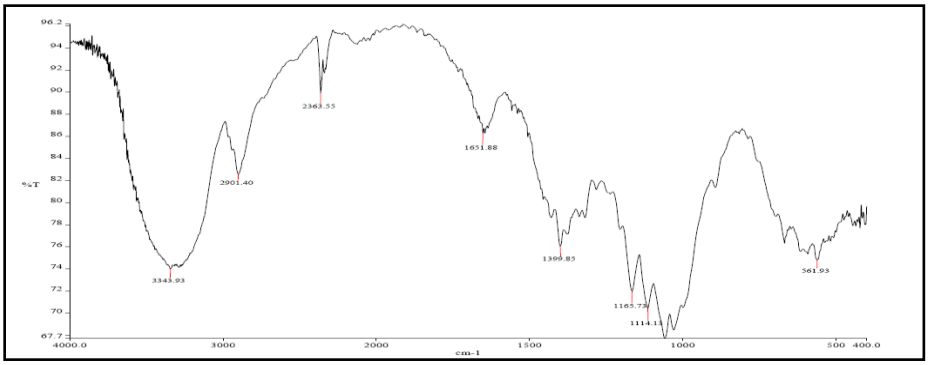

Figure 18 FTIR spectra of F6

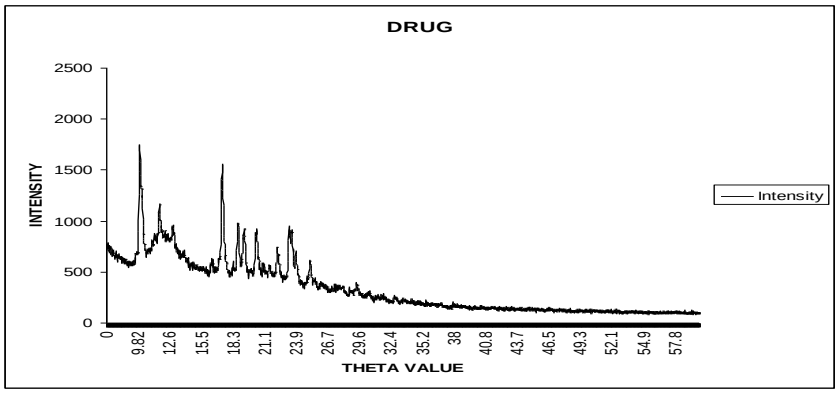

Figure 19 XRD spectra of pure drug

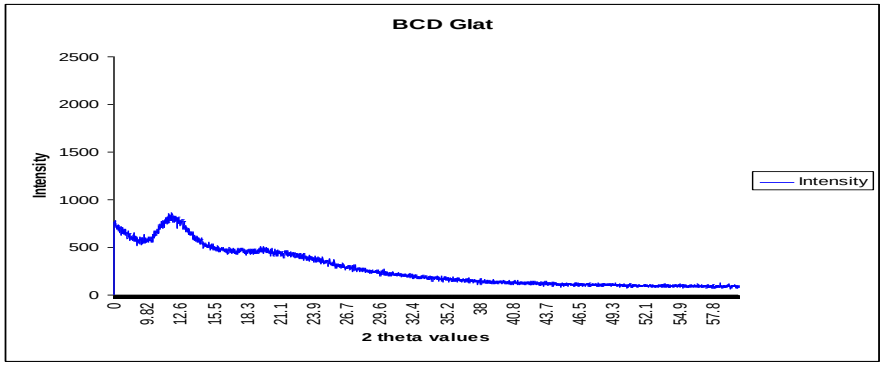

Figure 20 XRD spectra of F2

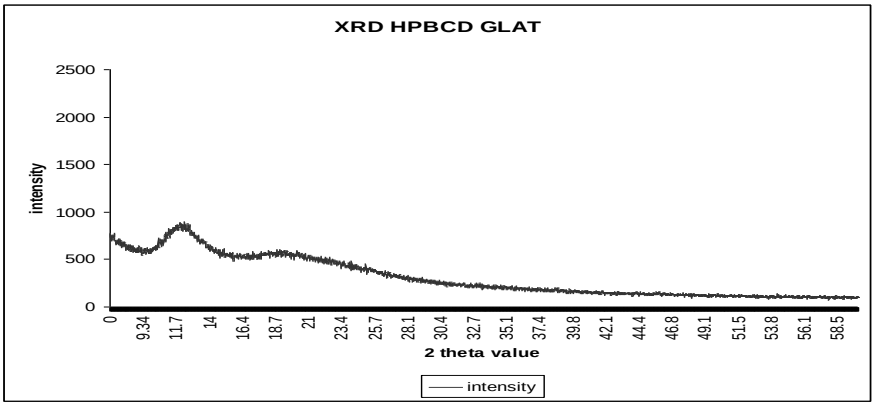

Figure 21 XRD spectra of F4

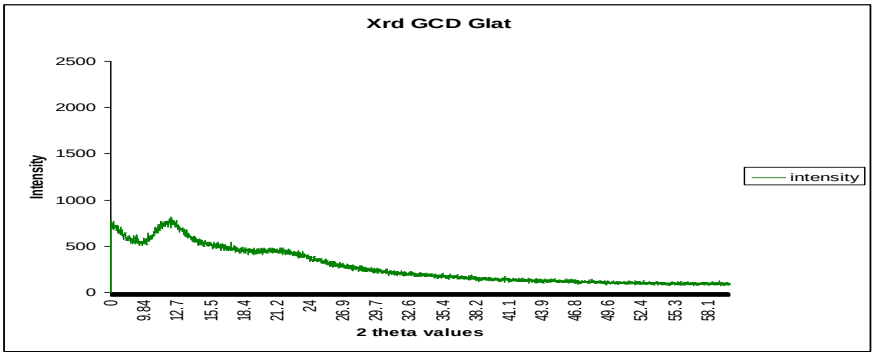

Figure 22 XRD spectra of F6

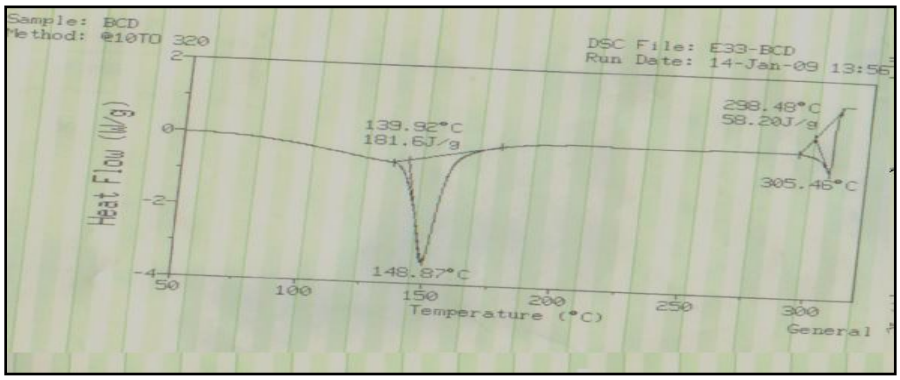

Figure 23 DSC thermogram of βCD

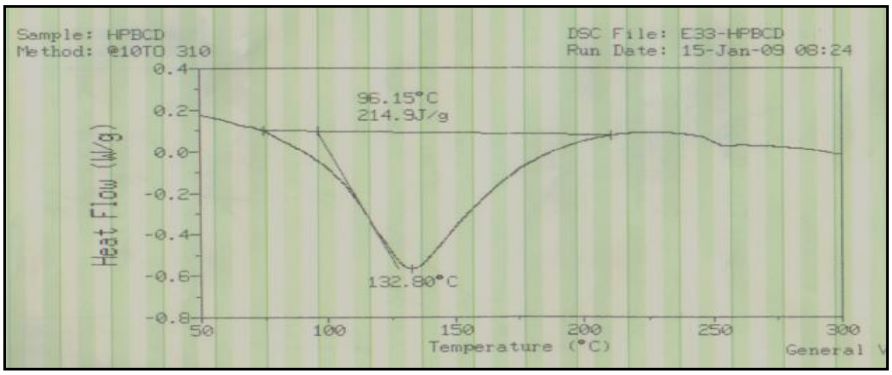

Figure 24 DSC thermogram of HPβCD

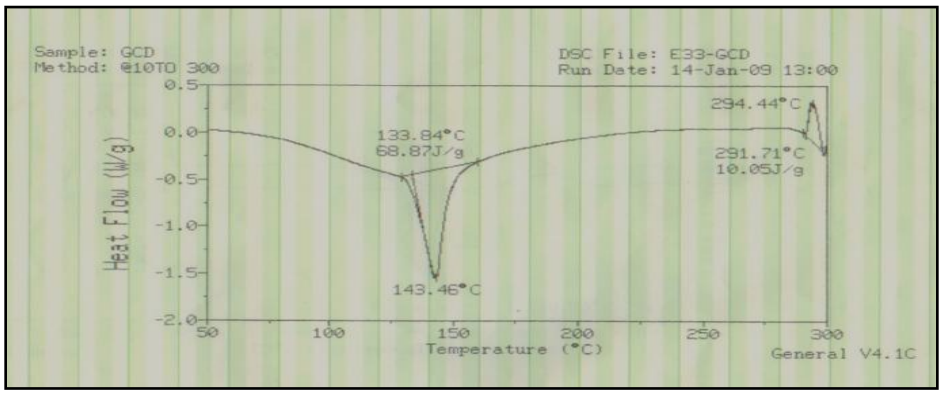

Figure 25 DSC thermogram of γCD

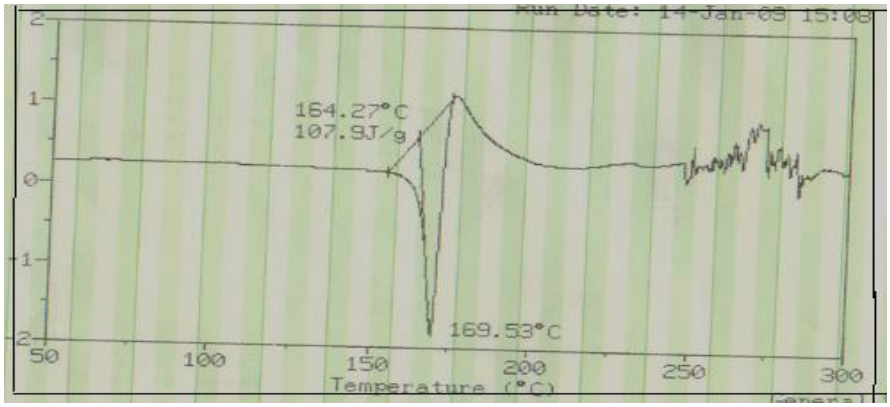

Figure 26 DSC thermogram of pure drug

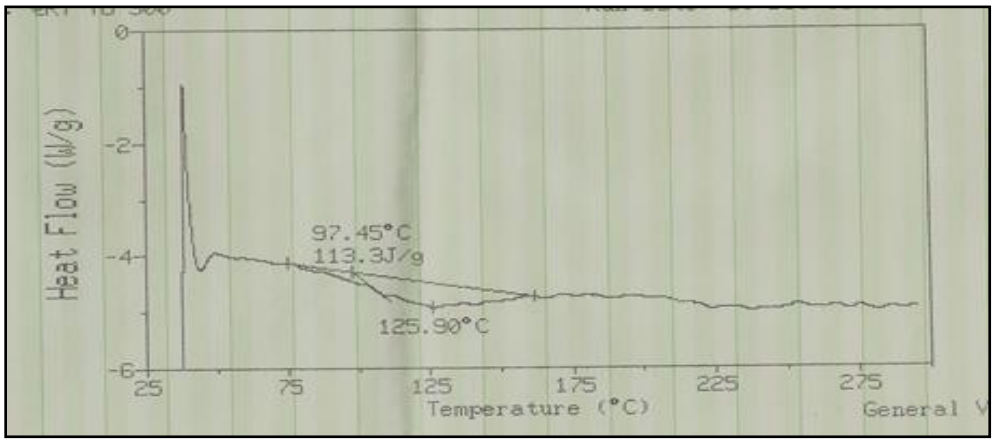

Figure 27 DSC thermogram of F2

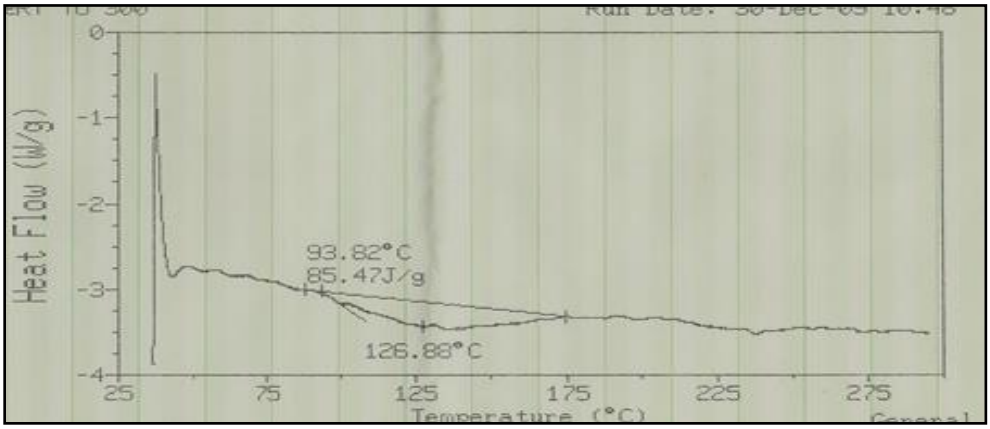

Figure 28 DSC thermogram of F4

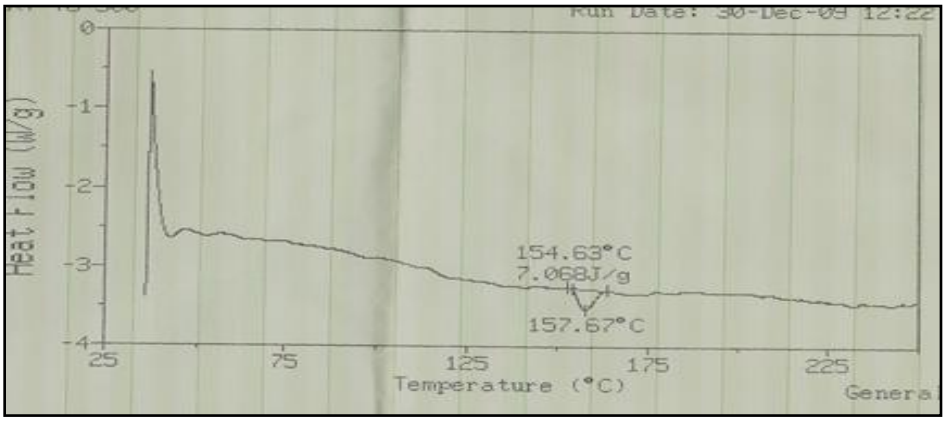

Figure 29 DSC Thermogram of F6

CONCLUSION

Complexation with cyclodextrins can be done efficiently by the process of fluidized bed coating. This process is proved to be useful in enhancing solubility and dissolution of candesartan cilexetil. In all cyclodextrins tried HPβCD was found to be more efficient in enhancing solubility and dissolution rate of candesartan cilexetil by the process of fluidized bed coating.

ACKNOWLEDGEMENTS

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