Preparation And Evaluation Of β-Cyclodextrin Inclusion Complexes Of Cefpodoxime Proxetil.

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ABSTRACT:
Cefpodoxime proxetil, a third-generation cephalosporin antibiotic used in the treatment of various diseases like respiratory tract infection, urinary tract infection. Due to its low aqueous solubility, it has reported 40–50% oral bioavailability. In the present research work, Cefpodoxime proxetil inclusion complexes were prepared with β-cyclodextrin in different molar ratios employing two different methods. The solubility data shows that an increased aqueous solubility of Cefpodoxime proxetil when formulated as an inclusion complex when compared with plain pure drug Cefpodoxime proxetil and also increased concentration of cyclodextrins, increases the solubility of Cefpodoxime proxetil.
Interaction between the drug and polymer was assessed by IR, and DSC thermogram provided strong evidence. The in vitro release study of Cefpodoxime proxetil inclusion complexes were carried out in 6.8 pH phosphate buffer as dissolution media.
The inclusion complexes prepared with β-cyclodextrin showed better release when compared with inclusion complexes prepared by various methods. Among the two methods, release rate was better with complexes prepared by kneading method in comparison to physical mixture method.
The formulations BF_3A i.e. Cefpodoxime proxetil β-cyclodextrin inclusion complex (1:3 molar ratio) prepared by kneading method showed better T70 (16 minutes) and T90 (22.5 minutes) values.
Cefpodoxime proxetil's response was enhanced by increasing its water solubility and dissolution rate by inclusion complex formulation with cyclodextrins.

Keywords: Cefpodoxime proxetil; Cyclodextrin; Inclusion complex; Solubility; In vitro dissolution.

1. INTRODUCTION:[(1-5)]

Cefpodoxime proxetil, a third-generation cephalosporin antibiotic used in the treatment of various diseases like respiratory tract infection, urinary tract infection. Due to its low aqueous solubility, it has reported 40–50% oral bioavailability. In the present research work, Cefpodoxime proxetil inclusion complexes were prepared with β-cyclodextrin and hydroxypropyl β-cyclodextrin in different molar ratios employing two different methods. The solubility data shows that an increased aqueous solubility of Cefpodoxime proxetil when formulated as an inclusion complex when compared with plain pure drug Cefpodoxime proxetil and also increased concentration of cyclodextrins, increases the solubility of Cefpodoxime proxetil.
These medication carriers have many benefits, like as

- They possess a distinct chemical structure that offers many possible locations for chemical modification or conjugation.
- Various CDs with varying cavity diameters are accessible.
- Both toxicity and pharmacological activity are modest in these natural carriers.
- They are very soluble in water.
- They guard against the conjugated or incorporated medicines' biodegradation.

The CD are oligosaccharides connected by α-D-glucopyranose that having a hydrophilic outer surface as well as hydrophobic interior cavity. CDs are toroidal or cone-shaped molecules instead of completely cylindrical ones because there is no rotation around the links joining glucopyranose units. The main hydroxyl groups are found on the narrow side of the torus, whereas the secondary hydroxyl groups are found on the broader edge, according to this design. Alpha (α-), beta (β-), and gamma (γ-) CD are the names given to the parent or natural CDs, which have 6, 7, or 8 glucopyranose units. The cyclic character of the molecule is seen in the chemical structure of β-CD. When compared to non-cyclic carbohydrate within the same molecular weight range, CDs exhibit a variety of unique chemical features due to his typical shape.[(17)]
The smallest cavity diameter, α-CD with 6 glucose units, is often too tiny for a medicinal compound. The reason β-CDs with seven glucose units are more practical is that the size of a polar cavity is ideal for a lot of molecules. γ-CDs with

eight glucose units ought to be the finest, without a doubt. However, since it requires cutting-edge technology to make, it is rarely produced extensively. Therefore, its industrial use is still unfeasible. But the price is too high. Therefore, it is recognized that β-cyclodextrin is the most practical of the three forms of CDs .[19]

- Cyclodextrins, sometimes referred to as cyclo-amylose, are a kind of polymers consisting of glycone compound was bonded in a ring structure known as cyclic oligo di-saccharides. As in amylase, cyclodextrins are made up of 4 to 5 as well as more alpha-D-glucopyranoside units connected
- by 1, 4. Glucose monomers in a typical cyclodextrin ring, which forms a cone shape, range in number from six to eight units. Thus, as seen in Figure 1.1
- α–Cyclodextrin: A sugar ring molecule with six members.
- β–Cyclodextrin: A molecule with seven sugar rings.
- γ–Cyclodextrin: A molecule with eight sugar rings.

An enzymatic conversion process yields cyclodextrins from starch. The culinary, pharmaceutical, and chemical sectors have discovered several uses for them in the last few years.[18]

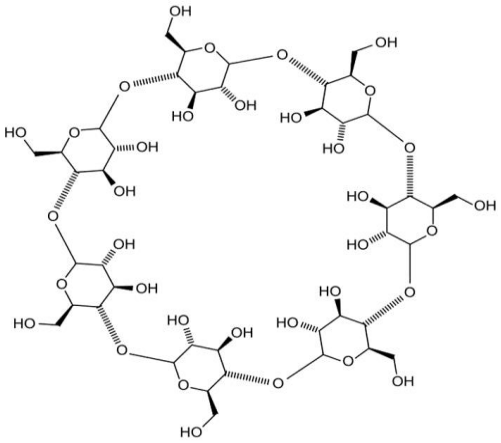

Figure 1.1 β-Cyclodextrins

2. MATERIALS AND METHODS:

2.1 Materials: Cefpodoxime Proxetil was obtained as a gift sample from Orex Pharma Pvt. Ltd., Mumbai. Beta cyclodextrin was procured from Sisco Research Laboratory Pvt. Ltd., Delhi. Dehydrated Ethanol, Sodium hydroxide, Sodium chloride were purchased from SD Fine chemicals, Mumbai.

2.2 Compatibility Study:[6,7] The I.R. Spectroscopy was used to verify the compatibility study. I.R. Spectroscopy was used to get the FTIR spectra of the formulation and Beta cyclodextrin. The resulting FT-IR spectra were used to determine the compatibility between the pure medication and polymer. The sample was scanned over the wave number, and the 4000-400 cm^{-1} wave number was used to record the spectra.

2.3 Preparation OF Cefpodoxime Proxetil Inclusion Complexes by using β– Cyclodextrin:[8, 9]

2.3.1 Kneading Technique:

The cefpodoxime proxetil BCD were taken in different molar ratios. To get a slurry-like consistency, a tiny amount of purified water was added in the mortar after β-cyclodextrin has been added. After that, the drug is gradually added to the slurry, and the trituration process is carried out for an 1hr hour. The prepared mass air-dried further twenty-four hours at 25ºC, ground up, and sieved through 100 mesh size and placed in desiccator containing fused calcium chloride.

2.3.2 Physical Mixture:

The various molar ratios of drug with β-cyclodextrin were combined in a mortar for about an one hour while undergoing continuous trituration. The prepared combination was then pass by sieve No. 100 and kept in a desiccator over fused calcium chloride.[25]

Table 1: Different variables of Inclusion Complex

Inclusion Complex Composition	Drug- Polymer Ratio	Code	Method
Cefpodoxime proxetil: β- cyclodextrin	1:1	BF_1A	Kneading
	1:2	BF_2A	
	1:3	BF_3A	
	1:1	BF_1B	Physical Mixture
	1:2	BF_2B	
	1:3	BF_3B	

2.4 Characterization And Evaluation:[10]

2.4.1 Physical Analysis:

Colour and appearance of inclusion complexes were analysed.

2.4.2 Solubility Study of β -Cyclodextrin Inclusion Complexes:

It is done by method reported by Bayomi et al. in various fluid.

A "series of 100 ml stoppered conical flasks holding 20 ml of each fluid were filled with excess cefpodoxime proxetil (20 mg) and excess cefpodoxime proxetil: hydroxypropyl β-cyclodextrin molar complexes (equal to 20 mg of cefpodoxime proxetil); following shaking the mixture for 24 hours at 37±0.5ºC, the sample was filtered using Whatmann filter paper 1002, and aliquots were taken out of the filtered solution to be tested for drug content following the proper solvent dilution."

2.4.3 Differential Scanning Calorimetry:

The DSC studies were carried out to know the thermal behaviour of drug and polymer that is carried out by using DSC (METTLER TOLEDO). For various formulation pure drug and polymer.

2.4.4 I R Spectroscopy:

It is used for detection of chemical interaction between drug and polymer which allows for chemical identification is infrared spectroscopy. Cefpodoxime proxetil and its complexes' infrared spectra were acquired using the KBr pellet technique and an FTIR device (SHIMADZU MODEL FTIR 8400S).

2.4.5 Drug Content:

A precisely measured quantity of the complex, which is equal to 50 milligrams of cefpodoxime proxetil, was added in small amount of solvent i.e. dehydrated ethanol, the volume was mark up to 50 ml. Above prepared solution, I had taken 1 ml and diluted with dehydrated ethanol. Then, 1.2 ml of the aforesaid dilution was taken and amount was increased up to 10 milliliters. The absorbances were calculated at 232 nm and calibration curve was prepared.

2.4.6 In-vitro Dissolution Study of Formulations:

Procedure:

The dissolution study was done by using USP disintegration apparatus (TDT-06L) and a basket stirrer, the cefpodoxime proxetil inclusion complex was dissolved in vitro. The dissolving media utilized was 900 ml 6.8 pH phosphate buffer. 100 rpm was set as the stirrer's rotational speed. Throughout the experiment, maintain the temperature 35±2ºC. which were previously warmed. For each test, a complex corresponding to 100 mg of cefpodoxime proxetil was utilized. The 5ml sample withdrawn at various time intervals and replaced by same dissolution media by using syringe equipped with a pre-filter at predetermined intervals of time. The absorbance at 232 nm was then measured to determine the drug release. A new volume of dissolving liquid was added to the volume removed at each time interval. Graph of percent of cefpodoxime proxetil released v/s time was computed. In contrast, Solubility of pure cefpodoxime proxetil was also investigated.[43]

3. RESULTS AND DISCUSSION:

3.1 FTIR Spectra:

The pure form of salbutamol's FTIR spectrum was captured. Figure 2 displays the sample drug's FTIR spectrum. FTIR spectroscopy was used to analyse the infrared spectra of pure drugs utilising the KBR.

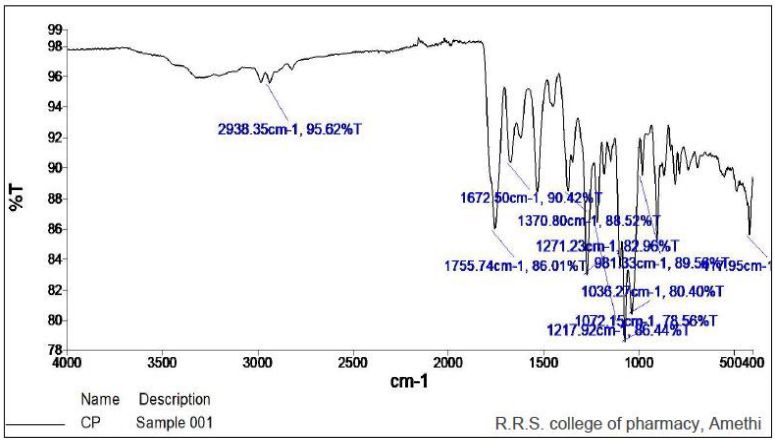

Figure 2 FTIR Spectra of Cefpodoxime Proxetil

3.2 Compatibility Study:

By employing FTIR spectroscopy, the medication and polymer were found to be compatible. For the medication, β–Cyclodextrin, and formulation BF1A, infrared spectroscopy examination was done. Figures 3 and 4 show the FTIR spectra of Formulation BF1A and β–Cyclodextrin.

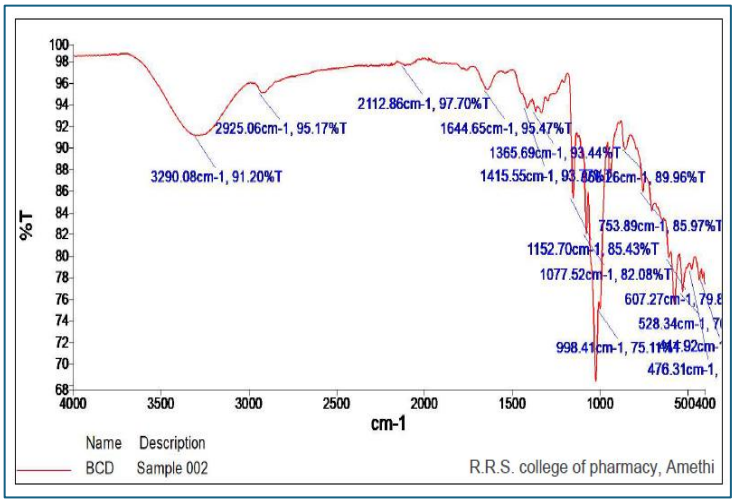

Figure 3: FTIR Spectra of β–Cyclodextrin

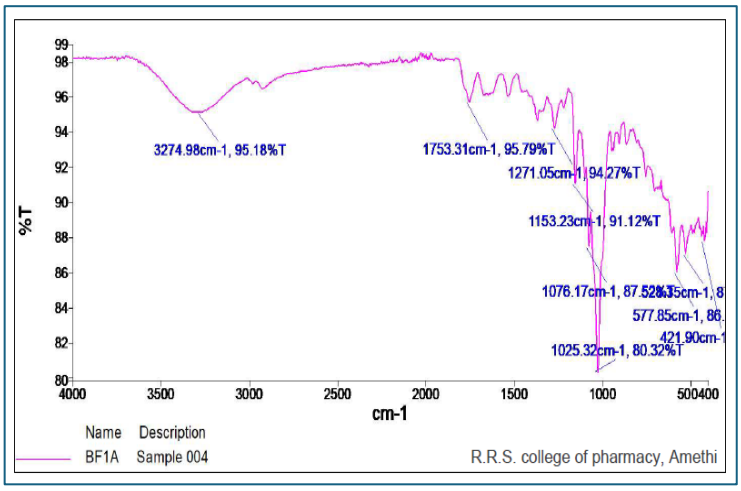

Figure 4: FTIR Spectra of Formulation BF1A

The FTIR spectra of β–Cyclodextrin and formulation BF1A revealed that the distinctive peaks of the medication and polymer did not move or vanish. This implies that the medication and polymer do not interact. Thus, it can be said that the medication keeps its original form without interacting chemically with β–Cyclodextrin.

3.3 Parameter Related to Pre-formulation:

1) Physical characteristics:

In the current study, cefpodoxime Proxetil inclusion complexes were created by using β-cyclodextrin at varying molar concentrations to increase the dissolution rate, solubility behaviour, bioavailability, and ultimately, effectiveness. Cefpodoxime proxetil BCD complexes produced in the current investigation using the kneading technique and physical mixing method in various ratios of 1:1, 1:2 &1:3 (molar ratio). The kneading process yields cream-colored tiny granular powder inclusion complexes, while the physical combination method produces fine powder with a cream colour.

Table 2 Physical appearance of formulations

Formulation Code	Physical appearance	
	Colour	Appearance
BF_1A	White creamy	Powder (granular)
BF_2A	White creamy	Powder (granular)
BF_3A	White creamy	Powder (granular)
BF_1B	Creamy	Fine Powder
BF_2B	Creamy	Fine Powder
BF_3B	Creamy	Fine Powder

2) Melting Point Analysis:
Cefpodoxime proxetil was discovered to have a melting point of 111–113°C, which is in close proximity to the literature value of 110–111.5°C, verifying the medication sample's identification and purity.

3) Solubility Analysis of Medicament:
The medicaments show freely soluble in dehydrated ethanol, soluble in methanol and acetonitrile, very slightly soluble in purified water. Drug was discovered to be very marginally soluble in water, freely soluble in acetonitrile and methanol, and soluble in dehydrated ethanol Because the medication must dissolve in both the employed dissolving medium and the solvents, solubility analysis is crucial.

Table 3 Solubility Study:

S. No.	Solvent	Drug
1.	Dehydrated Ethanol	Freely soluble
2.	Acetonitrile and in Methanol	Soluble
3.	Ether	Slightly Soluble
4.	Water	Very slightly Soluble

4) FTIR study of Drug:
The IR spectrum of Cefpodoxime proxetil (Fig. 2) was found to be in concordance with the reference spectrum (IP 2010) of Cefpodoxime proxetil. The typical peaks of the analysed sample of the drug were also interpreted and results showed that the peaks from 500cm-1 to 4000cm-1 match with reference spectra.

Table 5 Interpretation of IR-spectra of Cefpodoxime Proxetil Pure Drug:

Pure Medicament Frequency in cm-1	Functional Group
2938.35	C-O-CH3, (C-H Str)
1755.74 and 1217.92	Ester (C= O str and C= O Str)
1755.74	Beta lactum (C= O str)
1672.5	Aryl ketone
1370.80	Gem dimethyl (C = H str)
1071.23	= C – O – C | ⩽

5) UV-Spectrophotometric Methods for Determination of Cefpodoxime Proxetil:
a) Scanning of Cefpodoxime Proxetil in 6.8 pH Phosphate buffer and Dehydrated Ethanol by using UV-spectrophotometer:
Cefpodoxime proxetil (microgram/milliliter) was dissolved in dehydrated ethanol & 6.8 pH phosphate buffer to create solutions, which were then screened for absorption maxima (λmax) between 200 and 400 nm. The drug's authenticity as cefpodoxime proxetil was confirmed by the λmax obtained, as indicated in Table 3.2, which was close to the value reported in the literature.

Table 6 Spectrophotometric determination of Cefpodoxime proxetil:

S. No.	Media	Experimental λ_{max}	Literature λ_{max}
1.	Dehydrated Ethanol	232	232
2.	Phosphate Buffer pH 6.8	232	232
3.	Distilled water	231	230

b) Calibration Curve for the Estimation of Cefpodoxime Proxetil in Dehydrated Ethanol:
CP (Cefpodoxime Proxetil) calibration curves were created using the procedure outlined in section. The dilutions' absorbance values, which range from 5 to 25 µg/ml in dehydrated ethanol, are created and listed in Table 3.4. Plotting the data without a standard deviation resulted in calibration curves (Fig. 3.3) that were in accordance with Beer-Lambert law.

Table 7 Data oeef calibration curve of cefpodoxime proxetil in dehydrated ethanol:

Date	02.11.2023
Calibration curve for	Cefpodoxime proxetil
Solvent	Dehydrated Ethanol
λ_{max}	231
Concentration Unit	mcg/ml
Slope of the calibration curve	0.1693
Constant of the calibration curve	0.0065
Coefficient correlation of the calibration curve	0.9993

Table 8 Observation of Absorbance in dehydrated ethanol:

Concn (microgram/milliliter)	Abs in dehydrated ethanol
5	0.16
10	0.328
15	0.51
20	0.677
25	0.832

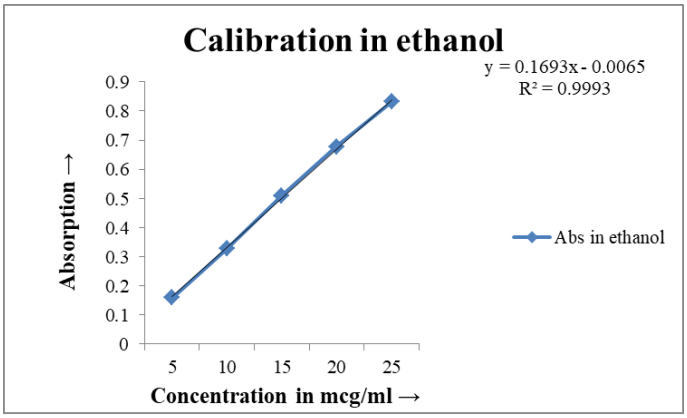

Figure 5 Calibration curve of cefpodoxime proxetil in dehydrated ethanol.

c) Standard Curve of Cefpodoxime proxetil in 6.8 pH Phosphate buffer for determination of Cefpodoxime proxetil:

Cefpodoxime proxetil calibration curves were created using the procedure,The dilutions' absorbance values, The lambert beer's range 5 -25 microgram/mililitre in 6.8 pH phosphate buffer, are listed in Table 3.2. Plotting the data without a standard deviation resulted in calibration curves (Figs. 3.3 and 3.4).

Table 9 Calibration curve data in 6.8 pH Phosphate buffer

Date	02.11.2023
Calibration curve for	Cefpodoxime proxetil
Solvent	pH6.8 Phosphate Buffer
λ_{max}	232
Concentration Unit	mcg/ml
Slope of the calibration curve	0.1339
Constant of the calibration curve	0.0119
Coefficient correlation of the calibration curve	0.9998

Table 10 Observation of absorbance in Phosphate buffer pH 6.8

Conc^{n} (microgram/milliliter)	Abs
5	0.145
10	0.283
15	0.409
20	0.55
25	0.681

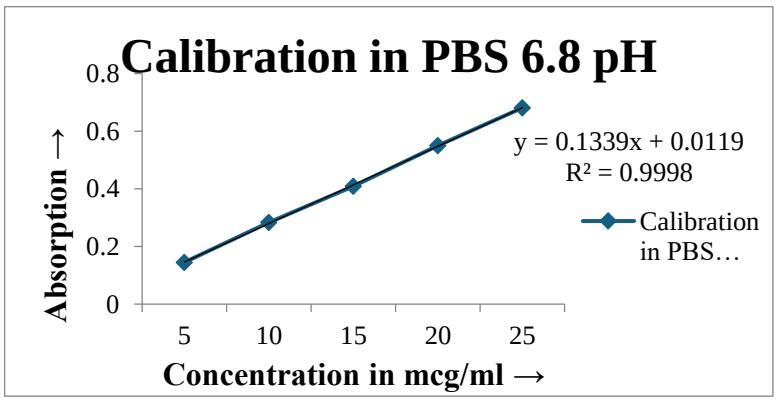

Figure 7 Standard curve in 6.8 pH Phosphate buffer for cefpodoxime proxetil.

d) Standard Curve in Purified Water for Determination of Cefpodoxime proxetil:

Cefpodoxime proxetil calibration curves were created using the procedure outlined in section The dilutions' absorbance values, which were made in the range of concentration of 5–25 µg/ml in purified water, Plotting data without a standard deviation resulted in calibration curves that were in accordance with Beer-Lambert law.

Table 11 Data of standard curve of cefpodoxime proxetil in Purified water:

Date	02.11.2023
Calibration curve for	Cefpodoxime proxetil
Solvent	Distilled Water
λ_{max}	231
Concentration Unit	mcg/ml
Slope of the calibration curve	0.1186
Constant of the calibration curve	0.0098
Coefficient correlation of the calibration curve	0.9995

Table 12 Observation table for calibration curve in purified water

Conc^n (microgram/milliliter)	Abs
5	0.124
10	0.249
15	0.371
20	0.485
25	0.599

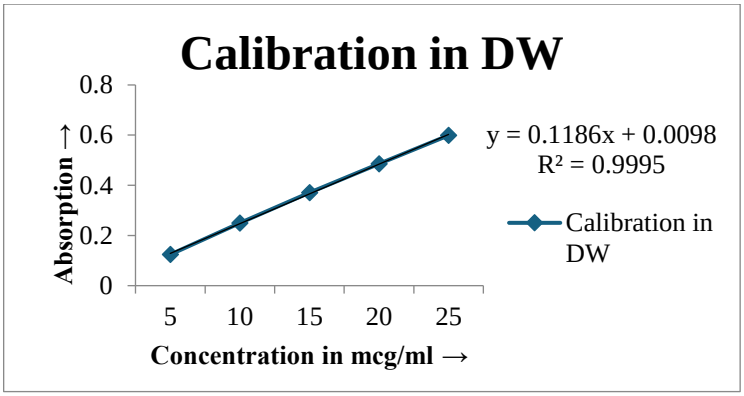

Figure 8 Standard curve of cefpodoxime proxetil in Purified water.

3.4 Characterization and Evaluation:

3.4.1 Solubility Studies of Cefpodoxime Proxetil and its Complex:

All the binary systems of cefpodoxime proxetil- hydroxypropyl β-cyclodextrin showed enhancement in the aqueous solubility. The 1:3 cefpodoxime proxetil- hydroxypropyl β- cyclodextrin inclusion complex formed by kneading method showed higher solubility than all other binary systems of cefpodoxime proxetil- hydroxypropyl β-cyclodextrin. The fundamental reason for the increase in solubility of the complex is the stable inclusion complex that forms between hydroxypropyl β-cyclodextrin and cefpodoxime proxetil

Table 13 Solubility of Cefpodoxime proxetil & its Inclusion Complexes in 6.8 pH Phosphate buffer and Purified Water

Sr. No.	Formulation details	Formulation code	Solubility in Phosphate buffer pH 6.8(mcg/ml)	Solubility in DW (mcg/ml)
1.	Cefpodoxime proxetil pure drug	CP	362.82	256.50
2.	Cefpodoxime proxetil, β-cyclodextin (1:3) by physical mixture method	BF3A	588.86	456.50

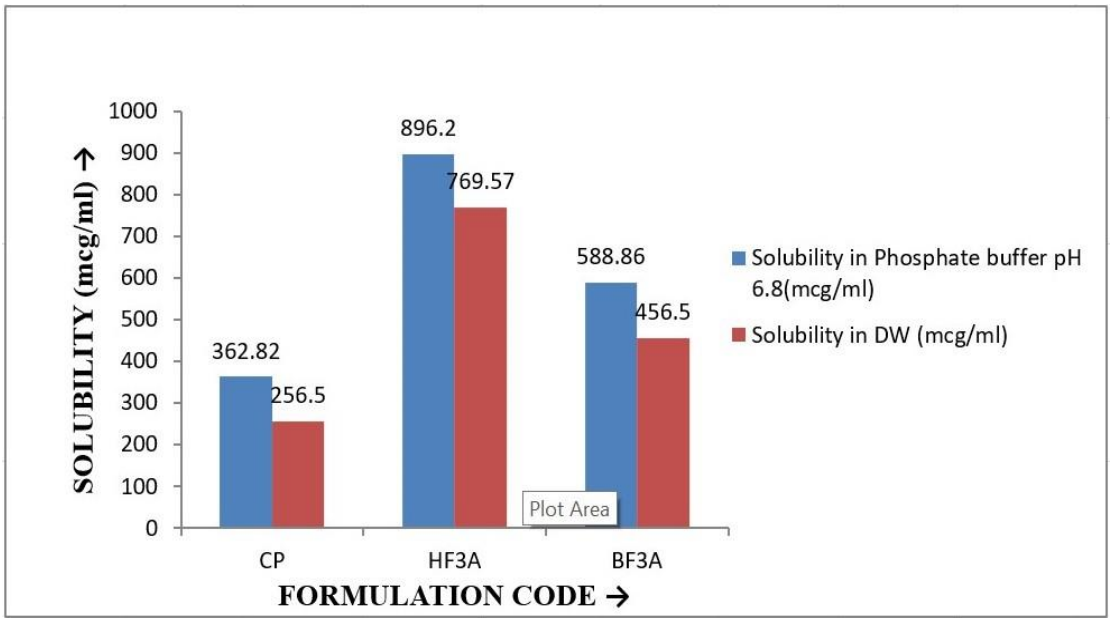

Figure 9 Solubility of Cefpodoxime proxetil & their Inclusion Complexes in 6.8 pH phosphate buffer and Purified water

3.4.2 DSC:

The DSC thermogram of cefixime exhibited an endothermic peaks starts at 163.02ºC, 164.36ºC, 165.00 ºC, 167.25ºC, 168.43ºC, 173.56ºC and ends at 178.97ºC, corresponding to its melting point. β-cyclodextrin shows broad endothermic peak at 65.05ºC - 113.03ºC and 300.71ºC - 304.04ºC respectively. The thermogram of F1B, HF1A and HF2B showed the persistance of endothermic peak (reduced area) of cefpodoxime proxetil. This seems to indicate the partial inclusion complex were formed, whereas the DSC thermogram of BF3A did not show the melting endotherm of cefpodoxime proxetil. The disappearance of endothermic peak with this complex indicated the formation of a solid inclusion complex of cefpodoxime proxetil.

3.4.3 FTIR of Formulation:

IR spectra of various cefpodoxime proxetil-β-cyclodextrin combinations in comparison to cefpodoxime proxetil in its purest form. The observations are clearlyshown in table below. No new peaks were observed in the spectra of any cefpodoxime proxetil or β-cyclodextrin system, suggesting that no chemical bands were produced in the synthesized compounds. Certain I-R peaks absorptions are coprecipitated in the products obviously distinct from those in equivalently mixes physically, which displayed the superposition of pure component spectra. These could point to constraints inside the cyclodextrin cavity caused by intermolecular hydrogen interaction between cefpodoxime proxetil and tested β-cyclodextrin. After inclusion complex preparation between cefpodoxime proxetil, BCD, findings supported the notion that β-cyclodextrin and cefpodoxime proxetil interact strongly.

Table 14 Interpretation of FTIR Spectra of Formulation BF1A, beta-cyclodextrin and Pure drug:

Functional Group		Beta-cyclodextrin	BF1A	Pure drug
ALKANE	C-H	2925.06		2938.35
	C-C	856.26, 937.86, 998.41, 1023.35, 1077.52, 1100.42, 1152.70.	421.90, 528.35, 577.85, 1025.32, 1076.17, 1153.23, 1271.05.	808.54, 903.75, 981.33, 1036.27, 1072.15, 1217.92, 1271.23.
ALKENE	=C-H			
	C=C			1672.50

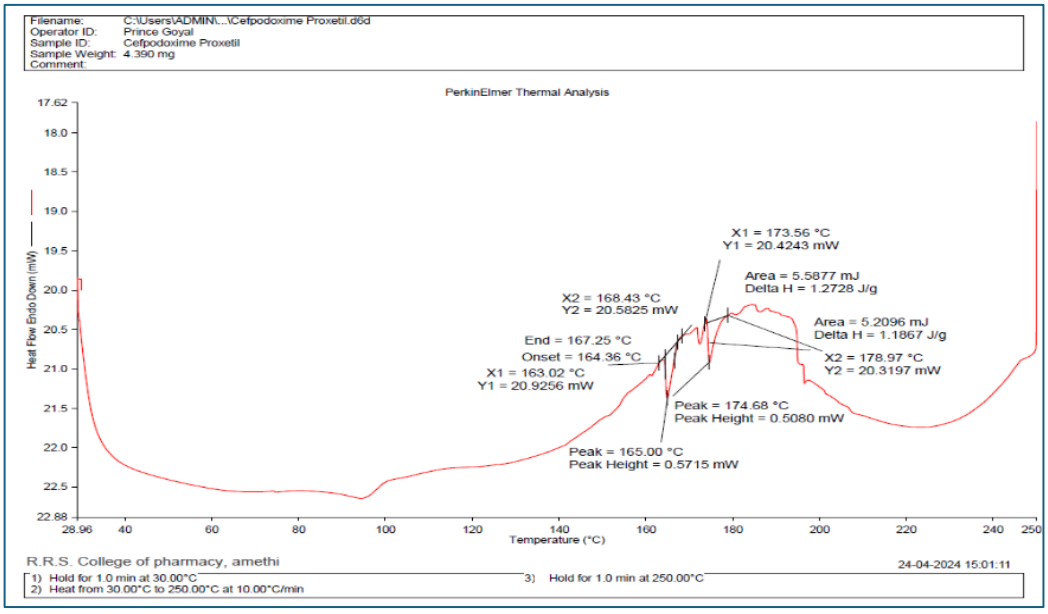

Figure 10: DSC of Drug.

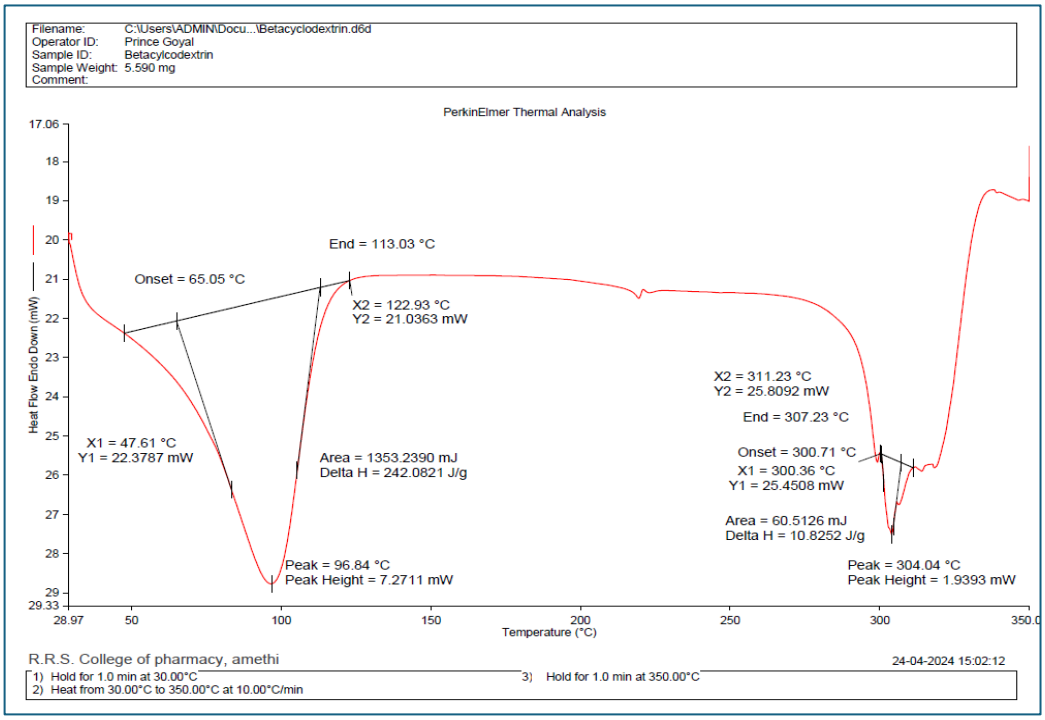

Figure 11 : DSC of Beta-cyclodextrin

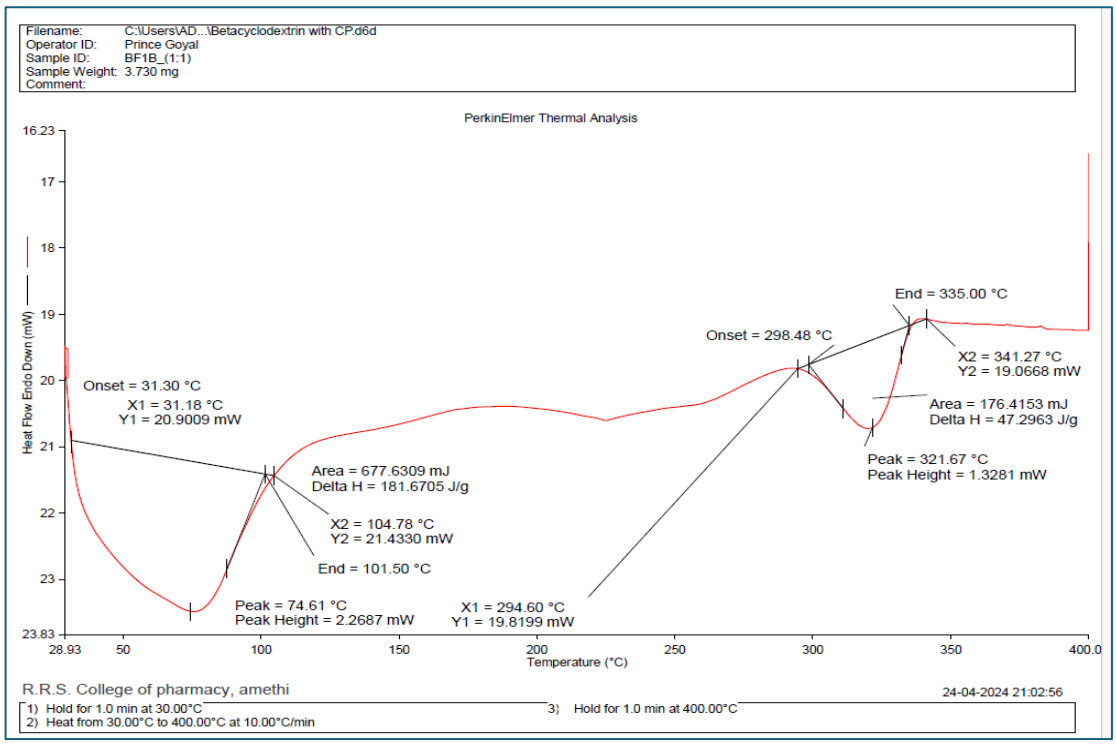

Figure 12: DSC of formulation BF1A

3.4.4 Drug Content Study:

Drug content in the samples were found to be in the range from 97.19 to 99.12% (table 3.12).

Table 15 %Drug content

Inclusion Complex Composition	Drug- Polymer Ratio	Code	Method	Drug Content (%)
Cefpodoxime proxetil: β-cyclodextrin	1:1	BF1A	Kneading	98.08
	1:2	BF2A		98.50
	1:3	BF3A		99.12
	1:1	BF1B	Physical Mixture	97.19
	1:2	BF2B		98.73
	1:3	BF3B		98.60

3.4.5 In-vitro Dissolution Study of Formulations:

When compared to the medication alone, the in-vitro dissolution rate increased for all kneading and physical combination systems. One explanation for this improvement is that the presence of the carrier in the system has made it more hydrophilic, which lowers the tensile tension at the interface between the poorly soluble drug and the dissolving medium. Furthermore, in the early stages of the dissolving process of β-cyclodextrin, the medication dissolved more slowly than the carrier. As a result, it can influence the hydrodynamic layer that envelops the drug's particles, causing a "in-situ" inclusion process that facilitates the drug's better breakdown. Indeed, the drug dissolution was faster in the systems with the increased β-cyclodextrin content. It also demonstrates that the complex made by physical combination disintegrated more slowly than the complex made by kneading method.

Table 16 Dissolution Profile of Cefpodoxime proxetil inclusion complexes formation with BCD in different ratios made using the physical mixing technique and kneading.

FORMULATION CODE	Time (min)	CPDR	PDR	Log CPDR	Log PDR
CP (PURE DRUG)	15	24.95	75.05	1.3970	1.8753
	30	43.44	56.56	1.6378	1.7525
	45	50.02	49.98	1.6991	1.6987
	60	54.11	45.89	1.7332	1.6617
BF1A	15	63.54	36.26	1.8030	1.8011
	30	89.50	10.30	1.9518	1.0128
	45	93.06	6.74	1.9687	0.8286

	60	98.21	1.59	1.9921	0.2013
BF2A	15	65.14	34.66	1.8138	1.5398
	30	91.46	8.34	1.9612	0.9211
	45	97.68	2.12	1.9906	0.3263
	60	98.75	1.05	1.9945	0.02118
BF3A	15	78.12	21.68	1.8927	1.3360
	30	96.26	3.54	1.9834	0.5490
	45	99.46	0.34	1.9976	-0.4685
	60	96.10	3.9	1.9827	0.5910
BF1B	15	55.19	44.61	1.7418	1.6494
	30	78.83	21.00	1.8966	1.222
	45	88.08	11.72	1.9448	1.0689
	60	96.20	3.60	1.9831	0.5563
BF2B	15	62.12	37.68	1.7932	1.5761
	30	79.50	19.9	1.9003	1.2988
	45	97.68	2.12	1.9898	0.3263
	60	98.57	1.23	1.9937	0.0899
BF3B	15	65.86	34.00	1.8186	1.5314
	30	81.32	18.48	1.9101	1.2667
	45	95.72	4.08	1.9810	0.6106
	60	99.28	0.52	1.9968	-0.2839

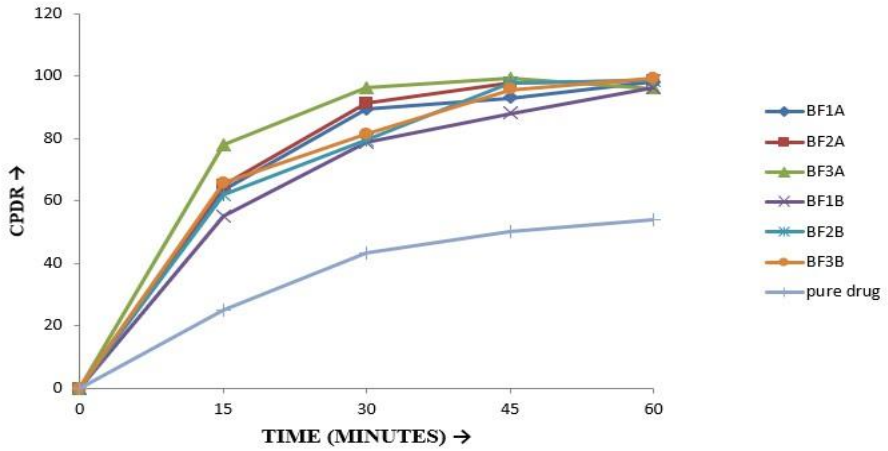

Figure 14 Cefpodoxime proxetil pure drug release in-vitro & inclusion complexes formation with BCD in different ratios made using the physical mixing technique and kneading.

4. CONCLUSION:

From the experimental data it was finally concluded that the inclusion complexes prepared by using Beta-cyclodextrin by different methods in different molar ratios, all formulation showed better solubility, Dissolution rate and In-vitro release studies. Among all formulations the formulation BF3A showed best result.

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