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Kinetics of Hydrolytic Degradation, Assessment of Thermodynamic Parameters of Cefpodoxime Proxetil

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ABSTRACT: Background: Cefpodoxime Proxetil is coming under the Cephalosporin medication category for the treatment of wide varieties of Bacterial infections. **Aim:** The present work describes the kinetic measurements of the hydrolytic degradation of Cefpodoxime proxetil (CP), and evaluates the effect of captisol complexation and water-soluble polymers on that degradation. **Method:** The phase solubility of cefpodoxime proxetil (CP) in Captisol was determined. The pH and temperature were the most important functions of kinetic measurements. All the samples of phase-solubility analysis and kinetic measurements were assayed by High-performance liquid chromatography (HPLC). With the help of HPLC, we also analyzed the chromatographic separation of the degradation products. FT-IR spectroscopy was used to investigate the presence of any interaction between Cefpodoxime proxetil (CP) and Captisol and soluble polymer. **Results:** The phase-solubility study showed AL-type behavior. The pH-rate profile of cefpodoxime proxetil (CP) exhibited a U-shaped profile whilst the degradation of cefpodoxime proxetil (CP) alone was markedly accelerated with elevated temperature. A strong stabilizing influence of the cefpodoxime proxetil (CP) - Captisol complexation and hypromellose was observed against aqueous mediated degradation, as compared with povidone and macrogol. **Conclusion:** Due to the steric hindrance, the effect of povidone and macrogol might be undesirable, which prevented the guest molecule from entering the cyclodextrin cavity, whereas hypromellose did not produce any steric hindrance.

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Keywords: Cefpodoxime Proxetil, Hydrolytic Degradation, Captisol complexation, Phase Solubility, Cephalosporin.

INTRODUCTION:

Few drugs are susceptible to hydrolytic degradation. Hydrolysis is the most common degradation method for such above functional groups drugs because of the prevalence of such groups and the ubiquitous nature of water. Functional groups like esters, amides, lactones, or lactams drugs have been degraded by hydrolytic degradation. As many more Cephalosporin groups of drugs available as an injectable preparation and in my work we trying to formulate one of the third-generation Cephalosporin drug molecules as an Oral drug dosage form for that we had tried to protect the particular drug

protected from the hydrolytic degradation [1-3]. Cefpodoxime proxetil is a third-generation cephalosporin group of drugs that are most active against both Gram-positive and Gram-negative organisms. It acts as a transpeptidase enzyme that inhibits transpeptidation reaction, blocks peptidoglycan synthesis, and incincreasesrease the permeability of cell membrane. It is used in upper and lower respiratory tract infections including bronchitis, pneumonia, skin, and soft tissue infection. Also, use in the treatment of UTI and gonorrhea. We have studied the effect of captisol complexation and water-soluble polymers on that degradation [4].

Cyclodextrin is important for increasing the solubility of very poorly water-soluble drugs. Cyclodextrins contain glucose monomers which have six to eight units in a monomer ring. Cyclodextrins have outer hydrophilic and inner lipophilic cavities that have mostly interacted with a guest molecule to form non-covalent inclusion complexes. As β- cyclodextrin has limited aqueous solubility meaning that complexes resulting from the interaction of lipophiles with this cyclodextrin can be of limited solubility to make the solution precipitated. Cyclodextrins can solubilize hydrophobic drugs in pharmaceutical applications, and crosslink to form polymers used for drug delivery [5,6].

The study was undertaken for possible improvement of poor stability and solubility properties of Cefpodoxime Proxetil by β- cyclodextrin, the combined effect of water-soluble polymers such as HPMC, PVP, and PEG on β- cyclodextrin complexation also studied on hydrolysis of Cefpodoxime proxetil. Phase solubility studies have been used to study cyclodextrin complexation, which provides important information regarding the stability constant and the stoichiometry of the inclusion complex formed [7]. By DSC, SEM, and FT-IR the final products of preparation of the Cefpodoxime proxetil-β- cyclodextrin inclusion complex [8] with and without water-soluble polymers (prepared by kneading method) in the solid-state is to be analyzed and characterized.

The objective of the study is to kinetic measurements of the hydrolytic degradation of Cefpodoxime proxetil.

MATERIALS AND METHODS:

Cefpodoxime Proxetil was obtained as a gift sample from Orchid Chemicals and Pharmaceuticals Ltd, Chennai, India. HPMC E5 LV premium and β-Cyclodextrin was from Loba Chemie PVT Ltd, Mumbai, India. All reagents and solvents which were used in this work were of analytical grade.

Analytical methods used in the study for the estimation of Cefpodoxime proxetil:

Cefpodoxime proxetil was soluble in acetone, sparingly soluble in water. Cefpodoxime Proxetil shows maximum Ultraviolet absorbance at λ_{max} 259 nm [9]. Based on this information, a standard graph was constructed using 0.5 % SLS solution of the drug.

Phase solubility studies:

The Phase solubility technique permits the evaluation of the affinity between β-cyclodextrin and Cefpodoxime proxetil in water. Phase solubility studies had performed as reported by Higuchi and Connors [10].

Determination of free energies of transfer and stability constant:

The equation for the free energies of transfer of cefpodoxime proxetil from aqueous solution to the cavity of the sol butyl ether β- cyclodextrin and β-cyclodextrin and β- cyclodextrin has been derived from the thermodynamic relationship for the chemical potential of a solute according to the analysis of drugs [11,12].

Preparation of Cefpodoxime proxetil-β-cyclodextrin inclusion complex without and with water-soluble polymers (by kneading Method):

The inclusion complex of Cefpodoxime proxetil with β-cyclodextrin was prepared by the Kneading method. β-Cyclodextrin (84 mg) was wetted with acetone in an agate mortar and kneaded to form a paste, Cefpodoxime proxetil (41 mg), and acetone were added. The sample was kneaded for approximately 60 min and vacuum dried to constant mass at ambient temperature [13].

Similarly, dispersion of Cefpodoxime proxetil-β-cyclodextrin complex and polymer were prepared with the water-soluble polymers (drug: polymer) 1:1 w/w by kneading method to examine the interaction using FTIR study.

Kinetic measurements (Temperature-rate profile):

Cefpodoxime proxetil (30 mg) alone and equivalent amount cefpodoxime proxetil-β- cyclodextrin complex/polymer dispersions were weighted into 100 ml volumetric flasks (Borosil^R) and dissolved to the desired volume with glass-distilled water in the aqueous solution of different polymers (0.5, 1 and 2 % w/v of HPMC E5LV).

To assess the kinetics of degradation of cefpodoxime proxetil in aqueous solution as a function of temperature, the flask containing the studied substance was placed in an incubator previously adjusted at 303, 313, 323 and 333 °K and the drug content was analyzed Spectrophotometrically. The t_{50} and t_{90} of the drugs were calculated from the slope of the kinetic curves [14].

FT-IR study:

The FT-IR spectra were obtained using a Perkin Elmer, Switzerland IR instrument. The prepared samples of binary and ternary systems of cefpodoxime proxetil, β-cyclodextrin and polymer were previously ground and mixed thoroughly with KBr and discs were prepared by compressing the powder. The scans were executed at resolution of 4 cm^{-1} from 4000 to 500 cm^{-1} and accumulations used [15].

RESULT AND DISCUSSION:

Phase solubility studies:

Phase solubility studies of cefpodoxime proxetil in β–Cyclodextrin were constructed by plotting the evaluated equilibrium concentration of cefpodoxime proxetil against the concentration of β–Cyclodextrin (Fig 1).

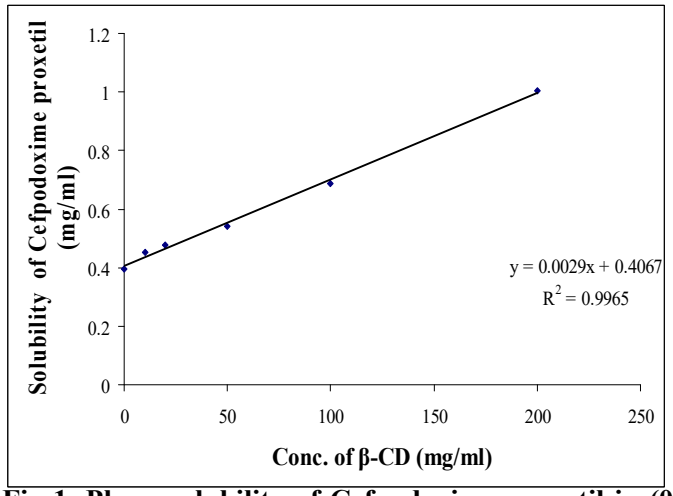


Fig 1. Phase solubility of Cefpodoxime proxetil in (0 to 1.2mg/ml) of β-CD.

As it appears in the figure, the aqueous solubility of cefpodoxime proxetil was linearly increased as a function of β–Cyclodextrin concentration with a slope of 0.0029 (R^2 =0.9965) during the concentration range investigated, suggesting the information of inclusion complex as A_L type. Since the slope of the Phase solubility line is smaller than 1, it gives the observation that the formation of 1:1 cefpodoxime proxetil – β-Cyclodextrin complex, entrapped the drug molecule in the cavity. Thus, one can expect that more cefpodoxime proxetil will dissolve in presence of β-Cyclodextrin than in absence of β- Cyclodextrin and consequently, the aqueous solubility of the drug increases with increasing concentration of β-Cyclodextrin.

The free energy of transfer $\Delta_{trans}G^0$ of cefpodoxime proxetil from aqueous solution to the cavity of β-Cyclodextrin has been calculated from equation 1 and tabulated in (Table 1). As can be observed from (Table 1), $\Delta_{trans}G^0$ values are negative and increase negatively with increasing ß – Cyclodextrin concentration. Negative values of $\Delta_{trans}G^0$indicate that β-Cyclodextrin is a more favorable environment than water for cefpodoxime proxetil. Since $\Delta_{trans}G^0$ increases negatively with increasing β-Cyclodextrin concentration, the interaction between cefpodoxime proxetil- β-Cyclodextrin increases with increasing β-Cyclodextrin content.

Table 1. Solubility and free energy transfer of Cefpodoxime proxetil in presence of β-cyclodextrin.

CP (mM)	β-CD	Increase in solubility of Drug (%)	$-\Delta_{trans}G$ (cal $mole^{-1}$)
0.7118	----	---	---
0.8095	8.8106	13.73	77.19
0.8583	17.6211	20.58	112.67
0.9698	44.0529	36.26	186.01
1.2351	88.1057	73.52	331.81
1.8002	176.2115	152.91	558.63

CP – Cefpodoxime proxetil, CD – cyclodextrin in (mM) × 10^{-4}.

The percentage increase in the solubility of cefpodoxime proxetil and corresponding free energy of transfer of cefpodoxime proxetil from aqueous solution to the lipophilic cavity β-Cyclodextrin (CD) in presence of the excess amount of cefpodoxime proxetil (CP) at 25 °C have been shown in Table 1. The stability constant (Ks') for CP in the aqueous solution of β-CD calculated from equation 2 was 89.65 M^{-1}.

Phase solubility studies of cefpodoxime proxetil in captisol® were constructed by plotting the evaluated equilibrium concentration of cefpodoxime proxetil against the concentration of captisol® (Fig 2).

As it appears in the figure, the aqueous solubility of cefpodoxime proxetil was linearly increased as a function of captisol® concentration with a slope of 0.1307 (R^2 =0.9914) during the concentration range investigated, suggesting the information of inclusion complex as A_L type. Since the slope of the phase solubility line is smaller than 1, the formation of 1:1 cefpodoxime proxetil-captisol complex, the free drug

molecules are in equilibrium with the drug molecule entrapped in the cavity.

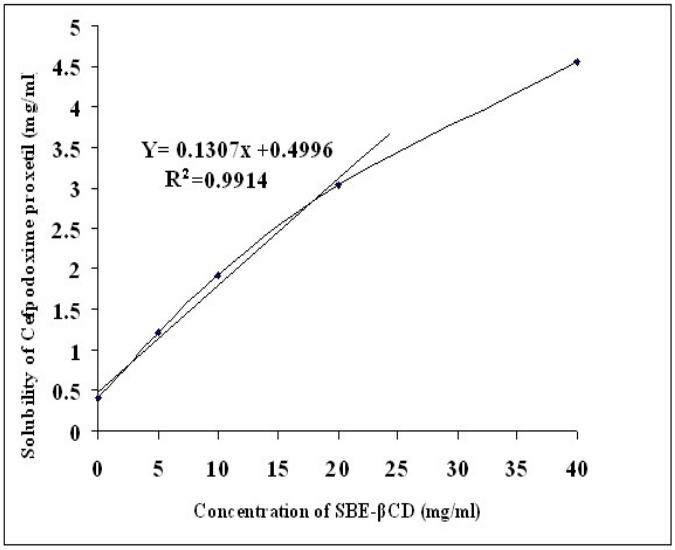


Fig 2. Phase solubility of Cefpodoxime proxetil in presence of Captisol.

Thus, one can expect that more cefpodoxime proxetil will dissolve in presence of captisol® than in absence of captisol® and consequently, the aqueous solubility of cefpodoxime proxetil increases with increasing concentration of captisol®.

The free energy of transfer $\Delta transG^0$ of cefpodoxime proxetil from aqueous solution to the cavity of captisol® has been calculated from equation 1 and tabulated in Table 2.

Table 2. Solubility profile and free energy transfer of

CP (mM)	SBE β-CD (M)	Increase in solubility of Drug (%)	$-\Delta_{trans}G$ (K cal mole^{-1})
0.7118	----	---	---
2.1780	0.0231	205.99	3.445
3.4420	0.0462	383.57	3.721
5.4537	0.0924	666.18	3.998
8.1832	0.1849	1049.65	4.243

Cefpodoxime proxetil in presence of Captisol.

CP – Cefpodoxime proxetil, CD – Cyclodextrin.

As can be observed from Table 2, $\Delta transG^0$ values are negative and increase negatively with increasing captisol® concentration. Negative values of $\Delta transG^0$ indicate that captisol® is a more favorable environment than water for cefpodoxime proxetil. Since $\Delta transG^0$ increases negatively with increasing captisol® concentration, the interaction between cefpodoxime proxetil – captisol® increases with increasing captisol® content.

The percentage increase in the solubility of cefpodoxime proxetil and corresponding free energy of transfer of cefpodoxime proxetil from aqueous solution to the lipophilic cavity captisol® in presence of the excess amount of cefpodoxime proxetil at 25 °C have been shown in Table 2. The stability constant (Ks") for cefpodoxime proxetil in the aqueous solution of captisol® calculated from equation 2 was 57.60 M^{-1}.

We concluded from the observation that Cefpodoxime proxetil-β-Cyclodextrin complex is most favorable for the drug as compared with the Captisol complex which is presented in Tables 1 and 2.

Kinetic measurements (Temperature – rate profile):

The apparent first-order rate constant for degradation of cefpodoxime proxetil in an aqueous solution was studied at different temperatures. The rate of degradation of cefpodoxime proxetil alone was markedly accelerated with elevated temperature shown in Fig 3.

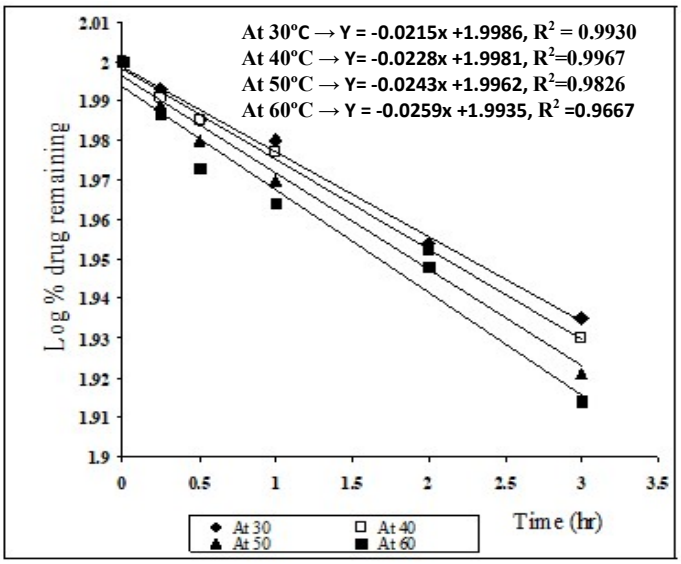


Fig 3. Hydrolytic degradation of Cefpodoxime proxetil alone.

The speed of reaction increased about two times with every 10 °C rise in temperature. Fig 4 depicts the effect of β-Cyclodextrin on the degradation of cefpodoxime proxetil at elevated temperatures. The effect of different concentrations of polymers such as 0.5, 1, and 2% of HPMC on degradation has also been examined at 303, 313, 323, and 333 °K. Fig 5 depicts the effect of 1 % HPMC polymer on the degradation of cefpodoxime proxetil and (Fig 6) depicts the influence of β-Cyclodextrin complexation and HPMC on the degradation of cefpodoxime proxetil on elevated

temperature. The degradation rate constant of Cefpodoxime Proxetil is recorded in Table 3 which has drugs alone and with different polymer complexations.

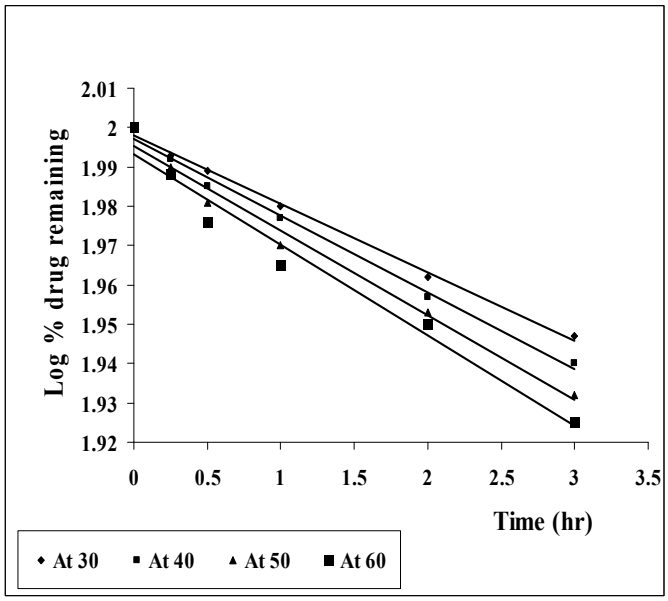


Fig 4. Hydrolytic degradation of Drug in presence of β-CD.

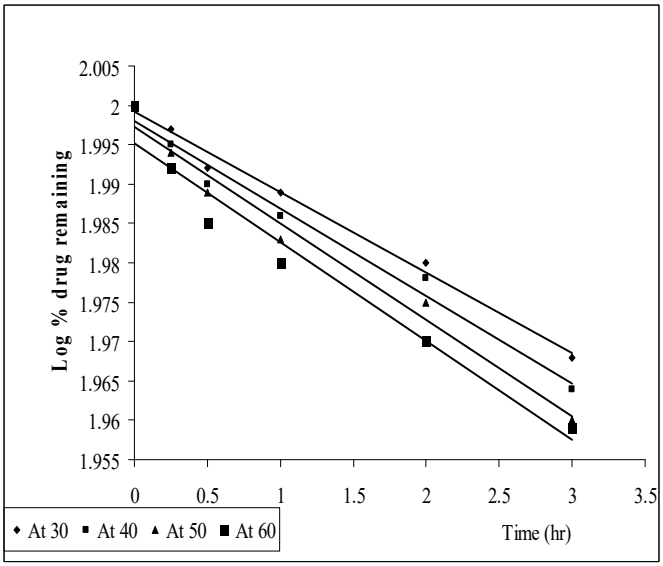


Fig 5. Hydrolytic degradation of Drug in presence of HPMC.

The degradation rate decreases with the combination of Drug-β-Cyclodextrin- HPMC complexation which is shown in Table 3. The influence of β-Cyclodextrin complexation and HPMC on the degradation rate of cefpodoxime proxetil and corresponding t_{50} and t_{90} of degradation as a function of temperature have been tabulated in Table 4. The result indicated a strong stabilizing influence exerted by β- Cyclodextrin (drug complex in a molar ratio 1:1) and HPMC. The degradation rate of cefpodoxime proxetil in presence of β- Cyclodextrin (drug complex in a molar ratio 1:1) and HPMC. The degradation rate of cefpodoxime (1:1 molar complex) and HPMC also increased about two times with every 10 °C rise in temperature.

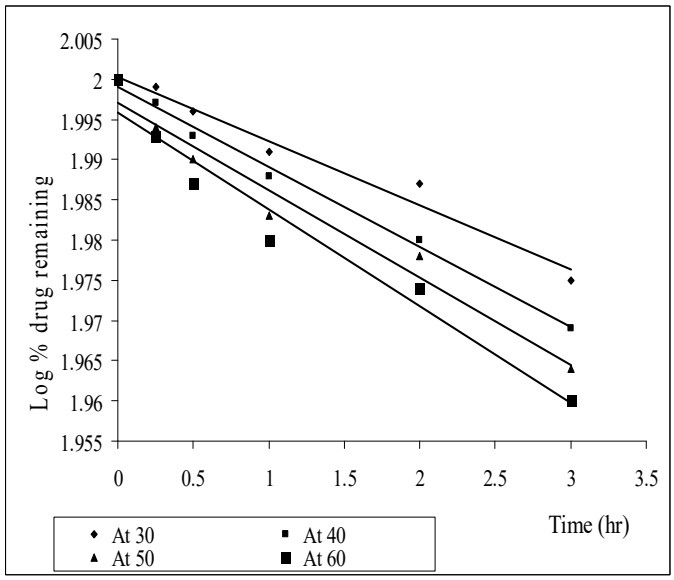


Fig 6. Hydrolytic degradation of Drug in β-CD and HPMC Complexes.

The effect of temperature on the equilibrium constants was obtained by using the Van't Hoff equation [16].

Ln k = Ln A-ΔH/ RT …..(1)

Ln k =ΔS/R -ΔH/RT ……(2)

ΔG = ΔH –T ΔS ……...(3)

Where A is the coefficient of frequency, ΔH is enthalpy change, ΔS is entropy change, ΔG is free energy change, R is the universal gas constant. T is the absolute temperature in K.

From the Van't Hoff equation, we easily determined the ΔH and ΔG value, which is tabulated in Table 4. As we know ΔH value is more and ΔG value is less means the drug is mostly protected from degradation. Various thermodynamic parameters are calculated and presented in Table 5. From Fig 7, 8, and 9, we also found the slope of the graph which is helpful for determining the t_{50} and t_{90} of the Cefpodoxime proxetil with or without the presence of drug-polymer complexes. The t_{50} and Shelf life of the drug were calculated and tabulated in Table 5. The rate constants are independent of drug concentration. The degradation of cefpodoxime proxetil proceeds with elevated temperature which is tabulated in Table 5. The statement is supported by the increased value of degradation constants with increased incubation temperature.

Table 4. t_{50} and t_{90} in hour of Cefpodoxime Proxetil.

Temperature (°K)	Cefpodoxime Proxetil alone		Cefpodoxime proxetil-β-CD inclusion complex		Cefpodoxime proxetil with HPMC		Cefpodoxime proxetil-β-CD complex in HPMC	
	t_{50}	t_{90}	t_{50}	t_{90}	t_{50}	t_{90}	t_{50}	t_{90}
298	14.68	2.22	18.09	2.74	30.39	4.60	40.76	6.17
303	14.00	2.12	17.32	2.62	29.48	4.46	38.50	5.83
313	13.20	2.00	15.40	2.33	27.17	4.11	31.50	4.77
323	12.39	1.87	14.00	2.12	24.75	3.75	28.87	4.37
333	11.62	1.76	13.07	1.98	23.89	3.62	26.65	4.03

Table 5. Thermodynamic parameter for the degradation of Cefpodoxime proxetil in aqueous solution.

Sample	Slope	Ln A	r^2	ΔH (Kcal.mole^{-1})	ΔS e.u.	ΔG (Kcal.mole^{-1})			
						303 °K	313 °K	323 °K	333 °K
CP	0.063	3.064	0.9983	12.47	6.088	10.62	10.57	10.51	10.45
CP-β-CD inclusion complex	0.073	3.262	0.9989	14.50	6.481	12.54	12.48	12.41	12.35
CP with HPMC	0.090	3.165	0.9975	17.88	6.288	15.98	15.91	15.85	15.79
CP-β-CD complex in HPMC	0.093	3.137	0.9993	18.47	6.233	16.59	16.52	16.46	16.40

ΔH and ΔS increased in presence of β- Cyclodextrin, and HPMC indicating the cefpodoxime proxetil has been protected from its degradation in an aqueous solution. ΔH and ΔG value tabulated in Table 5 which is shown in a combination of HPMC, β-Cyclodextrin, and drug the ΔH value were higher and ΔG value was lower that means in Cefpodoxime proxetil-β-Cyclodextrin and HPMC inclusion complexes, Cefpodoxime Proxetil was more protected from the hydrolytic degradation [17].

Fig 7. Van't Hoff plot for Cefpodoxime proxetil in absence and presence of β-cyclodextrin.

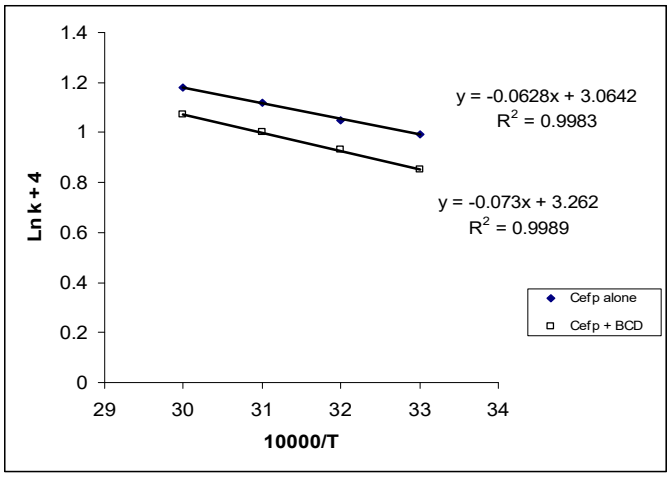
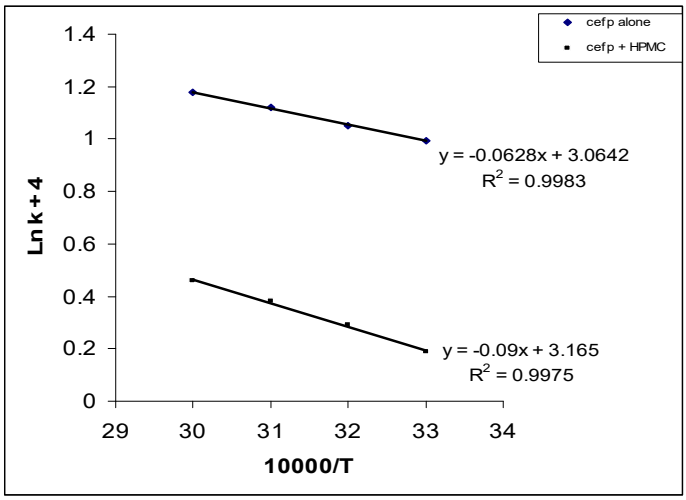


Fig Table 8. Van't Hoff plot for Cefpodoxime proxetil in absence and presence of HPMC (1% w/v).



CONCLUSION:

The aqueous degradation of cefpodoxime proxetil studied appears to be temperature-dependent. Since $\Delta_{trans}G^0$ of cefpodoxime proxetil increased negatively with increasing β-cyclodextrin concentration (complex formed 1:1 molar ration) the β-cyclodextrin created a more favorable environment than water for cefpodoxime proxetil in its increased concentration. The rate of hydrolysis of cefpodoxime alone was markedly

accelerated with elevated temperature. A strong stabilizing influence of cefpodoxime proxetil-β-cyclodextrin complexation and HPMC has been observed against aqueous mediated degradation rather than the drug alone. ΔG decreased in the presence of β-cyclodextrin and HPMC indicated that cefpodoxime molecules have been protected from degradation in an aqueous system to some extent.

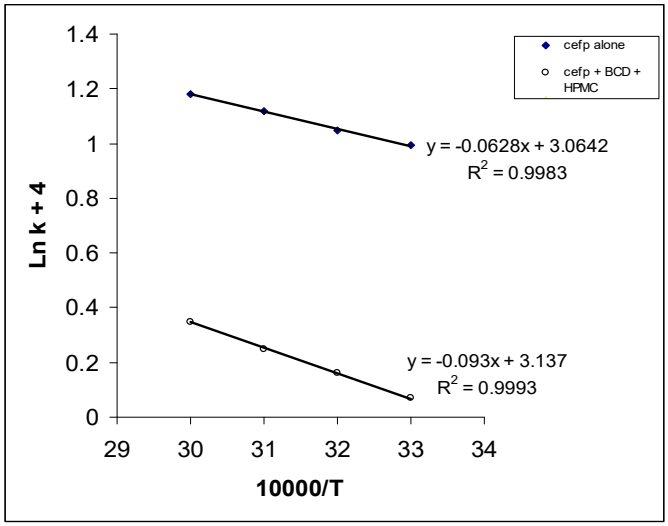


Fig 9. Van't Hoff plot for Cefpodoxime proxetil in absence and presence of HPMC (1% w/v) and β-cyclodextrin (1:1 molar ratio).

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