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FORMULATION AND EVALUTION STUDY OF ODT (CEFPOXIME PROXITIL)

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Keywords:

Cefpodoxime proxetil, Kyron T-114, Orally Disintegrating Tablet (ODT), by 3^2 full factorial

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ABSTRACT

Urinary tract and respiratory tract infections are most commonly observed in children. Cefpodoxime proxetil is a choice of drug for treating these diseases in children. However the bitter taste of the drug limits its use in pediatrics. Hence to overcome all these difficulties Orally Disintegrating Tablet (ODT) formulation with taste masked cefpodoxime was formulated to improve patient compliance. The first step of taste masking was achieved by complexing the drug with ion exchange resin Kyron T-114. The conditions of complexation such as drug: resin ratio, pH, temperature, stirring time and drug concentration were optimized. The complex was evaluated for drug loading, *in-vitro* drug release and swelling studies. The complex was also analyzed by IR, DSC,and XRD studies. The final optimized complex was selected to be formulated into ODT. The ODT formulations were designed by first selecting the suitable superdisintegrant i.e. Kyron T-314 and the diluent blend of Pharmaburst 500 and MCC. These concentrations of these excipients were further optimized by 3^2 full factorial design. The formulation F25 with Kyron T-314 at concentration of 5% and diluent blend of Pharmaburst: MCC in the ratio of 1:2 was selected as optimum which showed a disintegration time of 11 seconds. Optimized formulations were found to be stable after 3 months accelerated stability studies. Hence with the proposed method elegant ODTs of taste masked cefpodoxime proxetil could be successfully formulated that would help improve the patient compliance.

1. INTRODUCTION

Specific objectives include:

1) To formulate taste masked Drug-Ion exchange Resin Complexes of Cefpodoxime Proxetil.

a. Screening of the suitable ion exchange resin.

b. To optimize various formulation parameters such as drug: polymer ratio, drug concentration and process parameters such as temperature, pH and stirring time which affect the process of complexation.

2) To carry out *in-vitro* evaluation of the optimized formulation.

3) To formulate and evaluate Orally Disintegrating Tablets (ODTs).

a. To select the suitable superdisintegrant and diluents.

b. To optimize the concentration of the super disintegrant and the diluent blend using 3^2 factorial design (Central Composite Design).

4) To evaluate orally disintegrating formulations containing the taste masked Drug-Resin Complex and compare it with available marketed product.

5) To carryout stability studies of standardized formulation as per ICH guidelines.

Plan of work

1. Preformulation studies
    - Drug and excipients compatibility studies using FTIR, DSC, and XRD
    - UV-Spectrophotometric estimation of Cefpodoxime Proxetil and preparation of standard graphs.
    - Partition coefficient studies of the drug.
    - Solubility studies of the drug.
2. To prepare taste masked drug-ion exchange resin complex by using different resins.
3. To evaluate and select the suitable resin for complexation.
4. To optimize the parameters affecting complexation such as

a. Formulation parameters

- Drug : polymer ratio
- Drug concentration

b. Process parameters

- pH
- Temperature
- Stirring time

5. To carry out *in-vitro* evaluation of the final optimized complex.

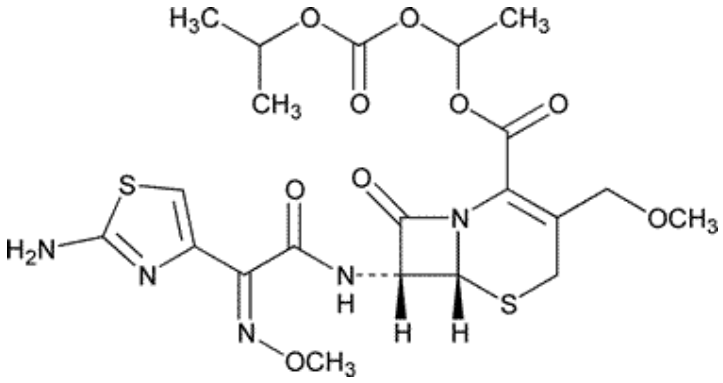
6. To evaluate the optimum complex with FTIR, XRD, DSC and proton NMR.
7. To formulate and evaluate ODTs using different superdisintegrants and diluents.
10. To optimize the concentration of the selected superdisintegrant and diluent using 3^2 factorial design (Central Composite Design).
11. To carry out *in-vitro* evaluation and mathematical modeling of drug release of the final optimized ODT formulation.
12. To carry out SEM studies of the tablet cross section.
13. To compare the *in-vitro* dissolution of the optimized ODT formulation with the available marketed product.
14. Carry out stability studies of the final ODT

2.DRUG PROFILE:-

CEFPODOXIME PROXETIL- DRUG PROFILE

Cefpodoxime Proxetil is a broad-spectrum third-generation cephalosporin most widely in the treatment of respiratory and urinary tract infections.

Chemical structure:



Chemical Name: 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-carboxylic acid,7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-,1-[[(1-methylethoxy)carbonyl]oxy]ethyl ester,[6R-[6a,7b(Z)]]-.

(±)-1-Hydroxyethyl(+)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,72-(Z)-(O-methyloxime),isopropyl carbonate (ester).

Molecular formula: $C_{21}H_{27}N_5O_9S_2$

Molecular weight: 557.61

Appearance: A white to slightly brownish white powder with a bitter taste and no odor or a slight unique smell.

Solubility: Very soluble in acetonitrile or methanol, freely soluble in dehydrated ethanol, slightly soluble in ether and very slightly soluble in water.

Stability: Very stable in methanol.

Melting point: 111-113 °C

Storage: Preserve in tight containers, at a temperature not exceeding 25°C.

Indications: Cefpodoxime Proxetil is a broad-spectrum third-generaation cephalosporin, having very good in vitro activity against Enterobacteriaceae, Hemophilus spp. and Moraxella spp., including β-lactamase producers and many strains resistant to other oral agents. It also has activity against Gram-positive bacteria, especially against streptococci. Cefpodoxime has no activity against enterococci. It is well tolerated and is one of the first third-generation cephalosporins to be available in oral form. While the compound has been used most widely in the treatment of respiratory and urinary tract infections, its utility has also been demonstrated in the treatment of skin structure infections, acute otitis media, pharyngitis, tonsillitis, and sexually transmitted diseases.

Mechanism of Action: Cefpodoxime, like other β-lactam antibiotics, exerts its inhibitory effect by interfering with cell wall biosynthesis. In Gram-negative organisms, this interference is primarily the result of cefpodoxime binding to, and interfering with, the bacterial transpeptidases PBP-1 (a and b) and PBP-3, both of which are essential for synthesis of a rigid cell wall

3.RESULTS

3.1 PREFORMULATION STUDIES:

3.1.1 Estimation of Cefpodoxime Proxetil by U.V spectrophotometric method:

λ_{max} of Cefpodoxime Proxetil

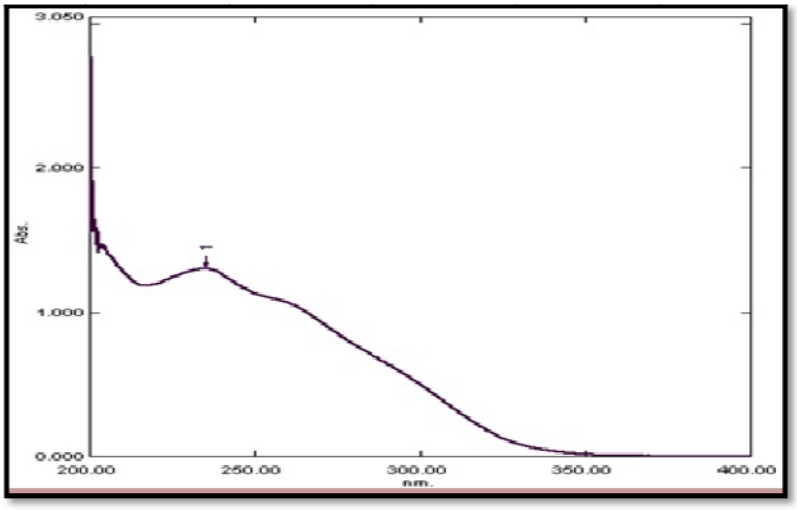


Fig1: Spectrum of Cefpodoxime Proxetil

λmax of in Cefpodoxime Proxetil in methanol was found to be 235 nm.

3.1.2 Standard calibration curve of Cefpodoxime Proxetil by UV-Visible spectrophotometry:

A simple fast and precise spectrophotometric method of estimation of Cefpodoxime Proxetil was carried out. Cefpodoxime Proxetil content was estimated by dissolving the drug in 50 ml of methanol and further diluted to get the concentration of the drug in Beer's range of 2-20µg/mL at a λmax of 235nm.

Table 1: Standard Calibration data of Cefpodoxime Proxetil

Sl.No	Concentration (µg/mL)	Absorbance			Average Absorbance	S.D	Absorptivity	Sandells sensitivity (mcg/sq.cm)
		1	2	3				
1	0	0	0	0	0	0	0	0
2	2	0.061	0.072	0.068	0.067	±0.005568	18679.94	1.910448
3	4	0.112	0.131	0.125	0.122	±0.009713	17100.04	2.086957
4	6	0.155	0.172	0.164	0.163	±0.008505	15210.36	2.346232
5	8	0.221	0.249	0.231	0.233	±0.014189	16286.86	2.191155
6	10	0.278	0.301	0.289	0.289	±0.011504	16133.52	2.211982
7	12	0.337	0.356	0.345	0.346	±0.009539	16077.76	2.219653
8	14	0.4	0.427	0.413	0.413	±0.013503	16462.77	2.167742
9	16	0.446	0.482	0.461	0.463	±0.018083	16135.84	2.211663
10	18	0.503	0.526	0.514	0.514	±0.011504	15933.19	2.239793
11	20	0.576	0.601	0.586	0.587	±0.012583	16384.44	2.178106

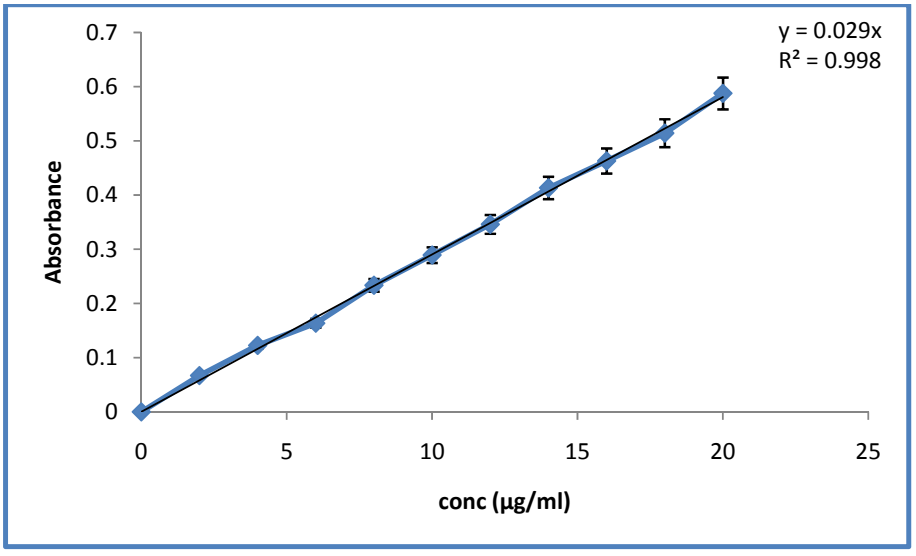


Figure 2: Standard graph of Cefpodoxime Proxetil by UV Spectroscopy

Table 3: Intraday studies 1st Reading

Sl.No	Concentration (µg/mL)	Absorbance			Average Absorbance	S.D	Absorptivity	Sandells sensitivity (mcg/sq.cm)
		1	2	3				
1	0	0	0	0	0	0	0	0
2	2	0.056	0.058	0.054	0.056	0.002	15613.08	2.285714
3	4	0.098	0.102	0.105	0.101667	0.003512	14172.59	2.518033
4	6	0.158	0.151	0.149	0.152667	0.004726	14188.08	2.515284
5	8	0.223	0.22	0.225	0.222667	0.002517	15520.15	2.299401
6	10	0.283	0.281	0.285	0.283	0.002	15780.36	2.261484
7	12	0.327	0.321	0.33	0.326	0.004583	15148.41	2.355828
8	14	0.38	0.381	0.385	0.382	0.002646	15214.79	2.34555
9	16	0.444	0.441	0.448	0.444333	0.003512	15485.29	2.304576
10	18	0.495	0.498	0.491	0.494667	0.003512	15323.95	2.328841
11	20	0.562	0.56	0.569	0.563667	0.004726	15715.31	2.270846

Table 4: Intraday studies 2nd Reading

Sl.No	Concentration (µg/mL)	Absorbance			Average Absorbance	S.D	Absorptivity	Sandells sensitivity (mcg/sq.cm)
		1	2	3				
1	0	0	0	0	0	0	0	0
2	2	0.067	0.071	0.066	0.068	0.002646	18958.74	1.882353
3	4	0.12	0.13	0.128	0.126	0.005292	17564.72	2.031746
4	6	0.161	0.167	0.166	0.164667	0.003215	15303.3	2.331984
5	8	0.223	0.238	0.227	0.229333	0.007767	15984.82	2.232558
6	10	0.28	0.293	0.279	0.284	0.00781	15836.12	2.253521
7	12	0.348	0.342	0.351	0.347	0.004583	16124.22	2.213256
8	14	0.403	0.419	0.42	0.414	0.009539	16489.32	2.164251
9	16	0.451	0.476	0.462	0.463	0.01253	16135.84	2.211663
10	18	0.51	0.531	0.521	0.520667	0.010504	16129.39	2.212548
11	20	0.582	0.598	0.589	0.589667	0.008021	16440.2	2.170718

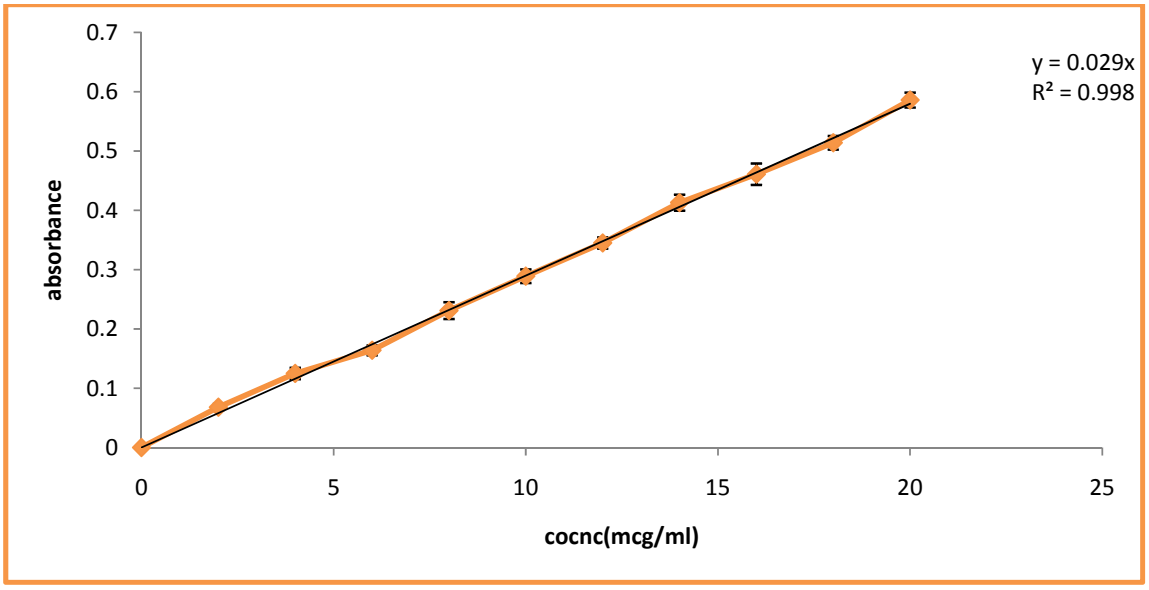


Figure 3: Intraday studies 1st Reading

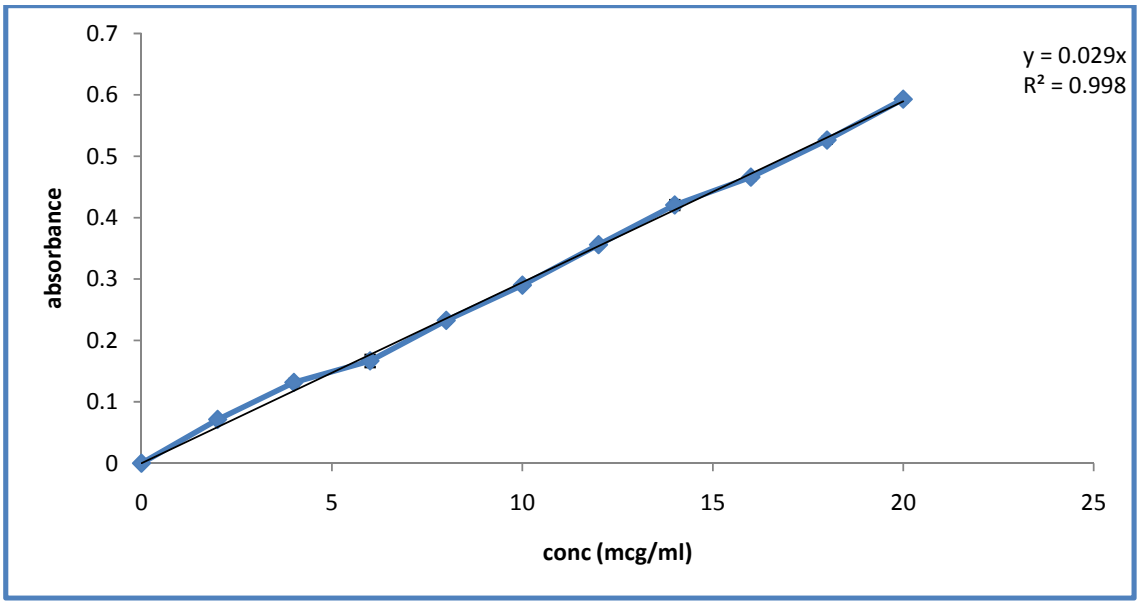


Figure 4: Intraday studies 2nd Reading.

3.2 Partition coefficient of Cefpodoxime in n-Octanol-water system:

Partition coefficient of Cefpodoxime Proxetil was found to be 1.51 hence concluding its lipophilic behavior.

3.3 Solubility studies

Table 5: Solubility study of Cefpodoxime Proxetil

Media	*Solubility (mg/mL) ± SD
Water	1.51 ± 0.104
Acidic buffer pH 1.2	9.86 ± 0.387
Phosphate buffer pH 6.8	0.81 ± 3.339
Phosphate buffer pH 7.4	0.461 ± 0.041
Phosphate buffer pH 8.0	0.363 ± 0.054

Results point to the fact that solubility of Cefpodoxime Proxetil increases with a decrease in the pH of the media resulting in higher solubility of the drug in acidic media as compared to the basic pH.

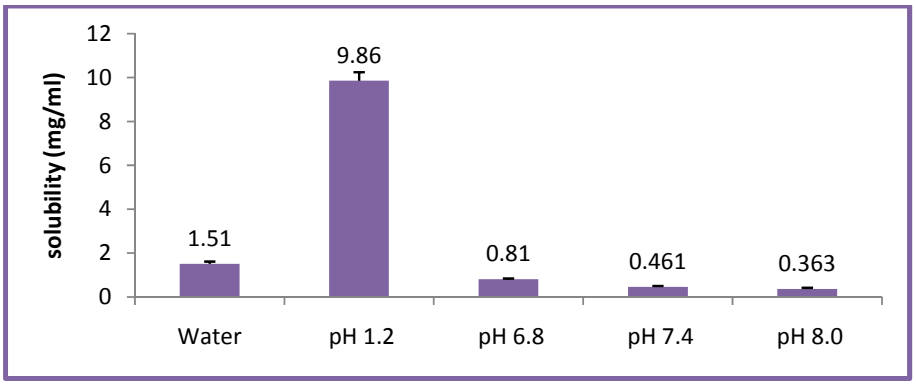


Fig 5: Solubility study of Cefpodoxime Proxetil

3.4 Drug-Excipients compatibility analysis:

3.4.1 IR studies:

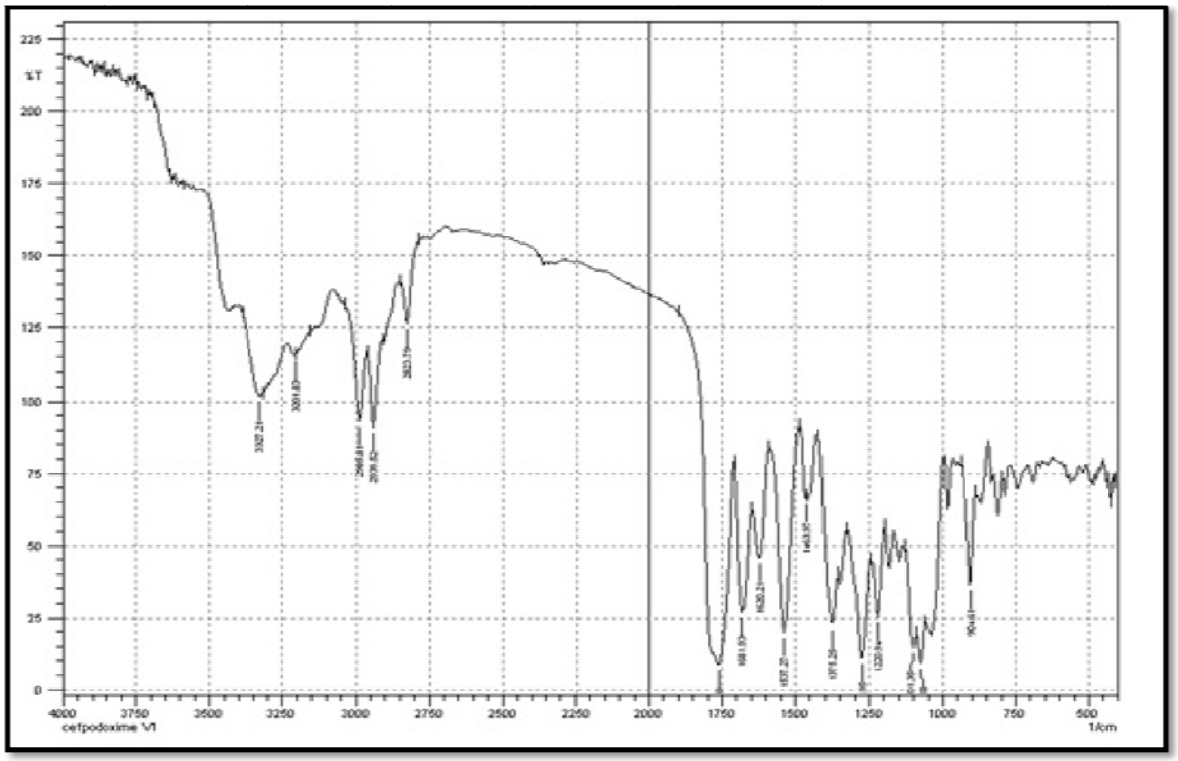


Fig 6: IR spectra of Cefpodoxime Proxetil

Table 6: Interpretation of IR spectra of Cefpodoxime Proxetil pure drug

Sl. No.	FUNCTIONAL GROUP	Frequency of pure drug (cm^{-1})
1	Primary Amine (-NH_2)	**3327**
2	Secondary Amine (-NH-)	**3201.87**
3	Ester (-C=O)	**1750**
4	Ether (-C-O-C-)	**1060**
5	Cyano (-C=N)	**1641**

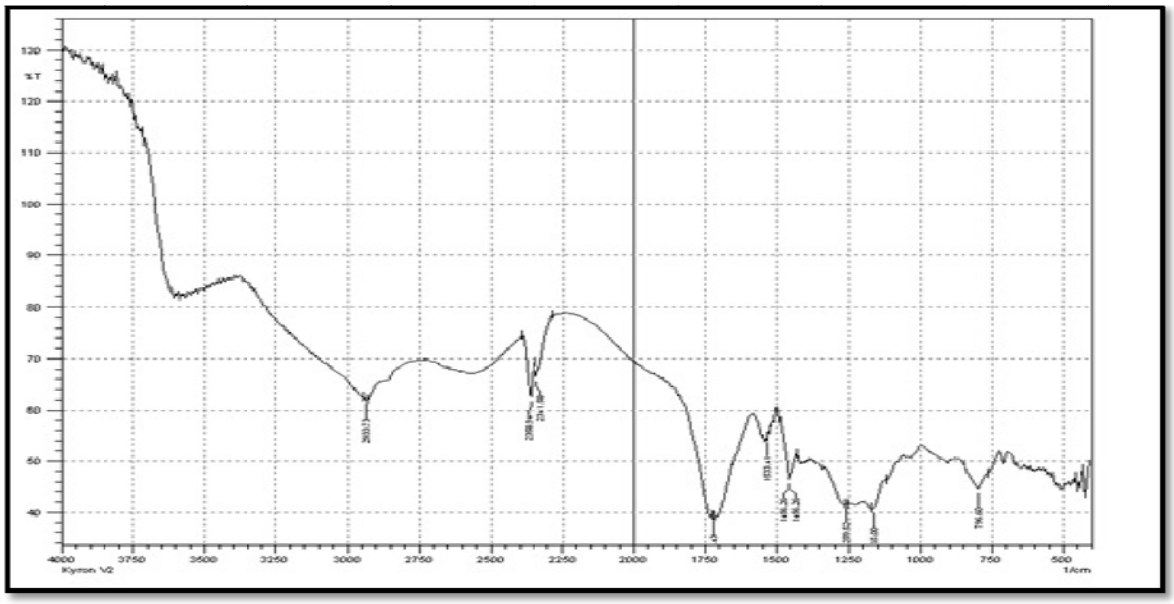


Fig 6: IR spectra of Kyron T-114

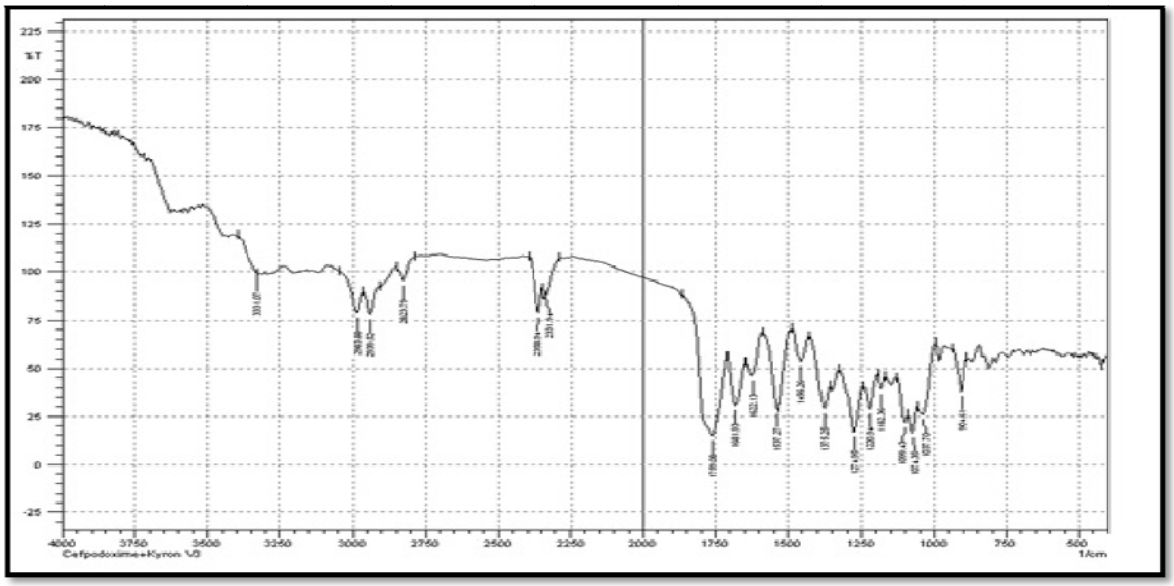


Fig 7: I.R Spectra of Physical Mixture:

Table 7: Interpretation of I.R spectra of Drug Resin Complex (F43)

Sl. No.	FUNCTIONAL GROUP	Frequency of pure drug (cm^{-1})
1	Primary Amine ($-NH_2$)	**3331**
2	Secondary Amine (-NH-)	**3200**
3	Ester (-C=O)	**1749**
4	Ether (-C-O-C-)	**1074**
5	Cyano (-C=N)	**1681**

3.5 Selection of the suitable Ion Exchange Resin (IER):

Table 8: Comparison of drug loading of different ion exchange resins

Sl. No.	Ion Exchange Resin Grade	Percent of drug complexed*
1	Kyron T-104	38.21±1.17
2	Kyron T-114	58.34±1.42
3	Kyron T-134	41.66±1.01
4	Kyron T-154	32.14±1.63

*** mean of three determinations**

3.6 Effect of formulation parameters such as drug: polymer ratio, drug concentration and process parameters like temperature, pH and stirring time affecting the process of complexation.

3.6.1 Table 9: Effect of drug: resin ratio

Sl .No.	Time (min)	% Drug Loading*		
		A (1:1)	B (1:2)	C (1:3)
1	00	0	0	0
2	10	12±0.83	14±0.63	15±1.43
3	20	26±0.66	29±1.83	31±0.34
4	30	38±1.21	43±1.22	44±1.75
5	40	44±1.36	52±1.61	55±0.64
6	50	54±0.45	61±0.11	64±0.75
7	60	56±0.89	69±0.83	70±0.12

*** mean of three determinations.**

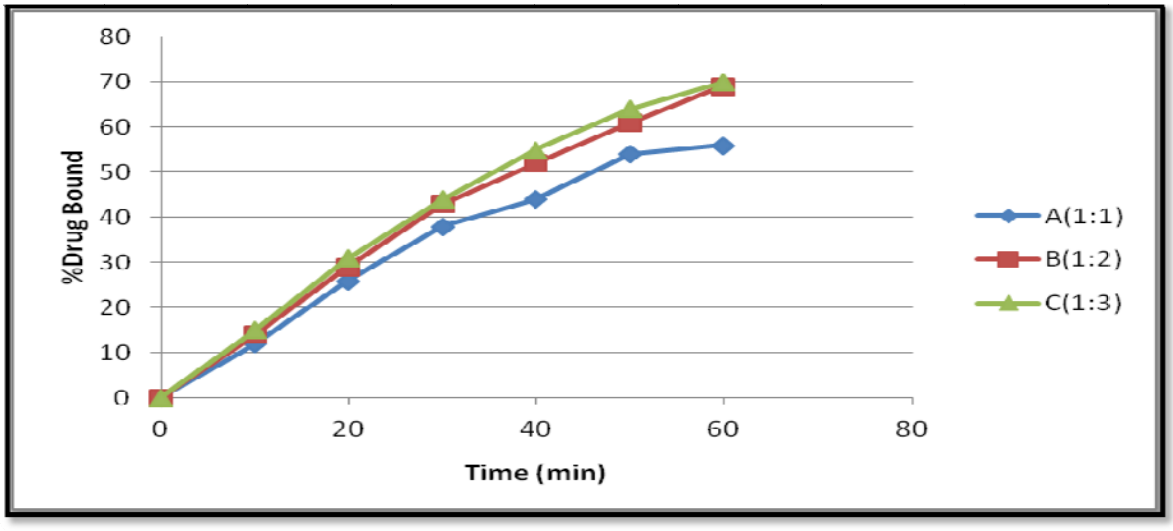


Figure 8: Effect of drug: resin ratio (%Drug bound vs Time)

3.6.2 Table 10: Effect of pH on drug loading:

Sl. No.	Drug: Polymer Ratio	pH	Percentage Drug Complexed after 1 hr*
1	1:2	3	46±0.57
2		4	52±0.81
3		5	70±0.67
4		6	74±0.12
5		7	69±1.11
6		8	54±0.23

*** Results are the mean of three determinations.**

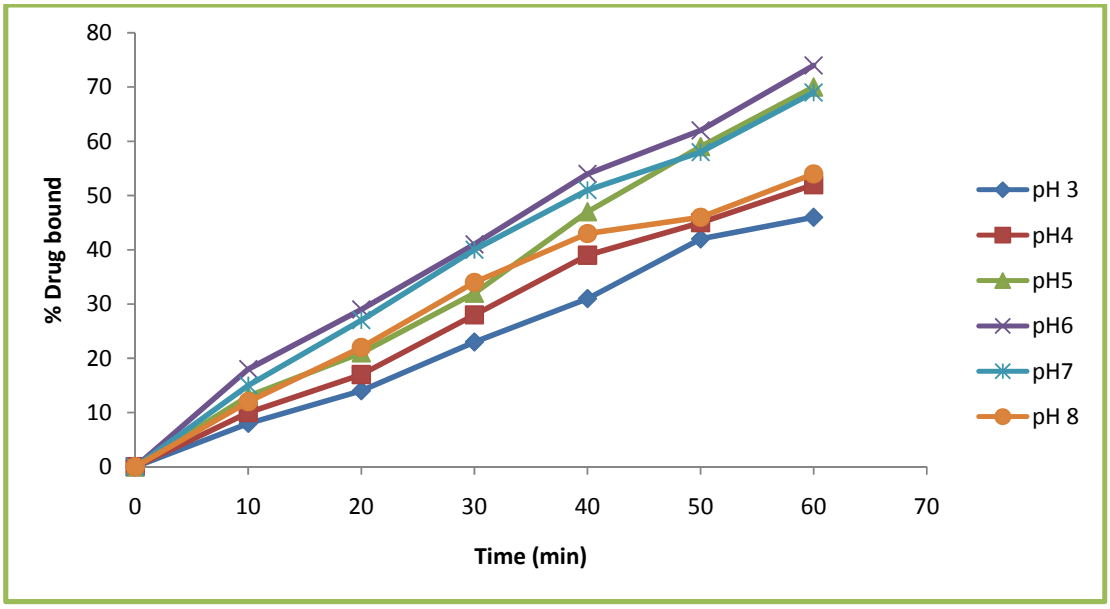


Figure11: Effect of pH on drug loading (%Drug bound vs Time)

3.6.3 Table 12: Effect of temperature on drug loading:

Sl No.	Drug: Polymer Ratio	pH	Temperature (°C)	Percentage Drug Complexed after 1 hr*
1	1:2	6	30	74±0.98
2			40	76±0.57
3			50	84±0.43
4			60	75±1.56

*** mean of three determinations.**

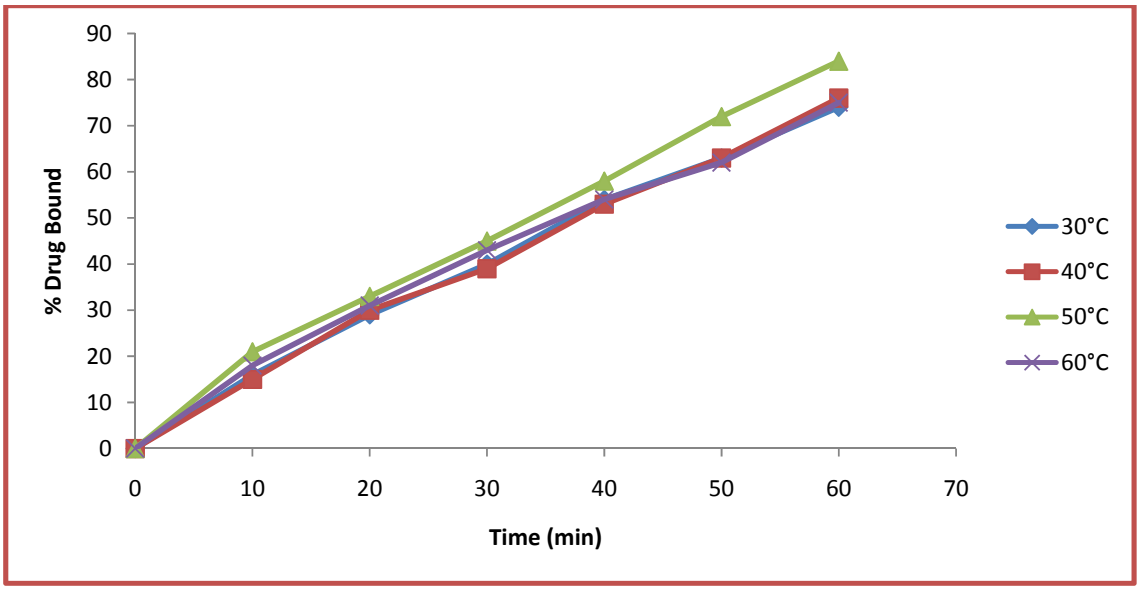


Figure 12: Effect of temperature on drug loading (%Drug Bound vs Time)

3.6.4 Table 13: Effect of stirring time on drug loading:

Sl No.	Drug: Polymer Ratio	pH	Temp. °C	Stirring Time (hr)	Percentage Drug Complexed after 1 hr*
1	1:2	6	50	1	84±0.53
2				4	86±1.56
3				12	89±1.21
4				24	95±0.76
5				36	Drug degradation reported

*** mean of three determinations.**

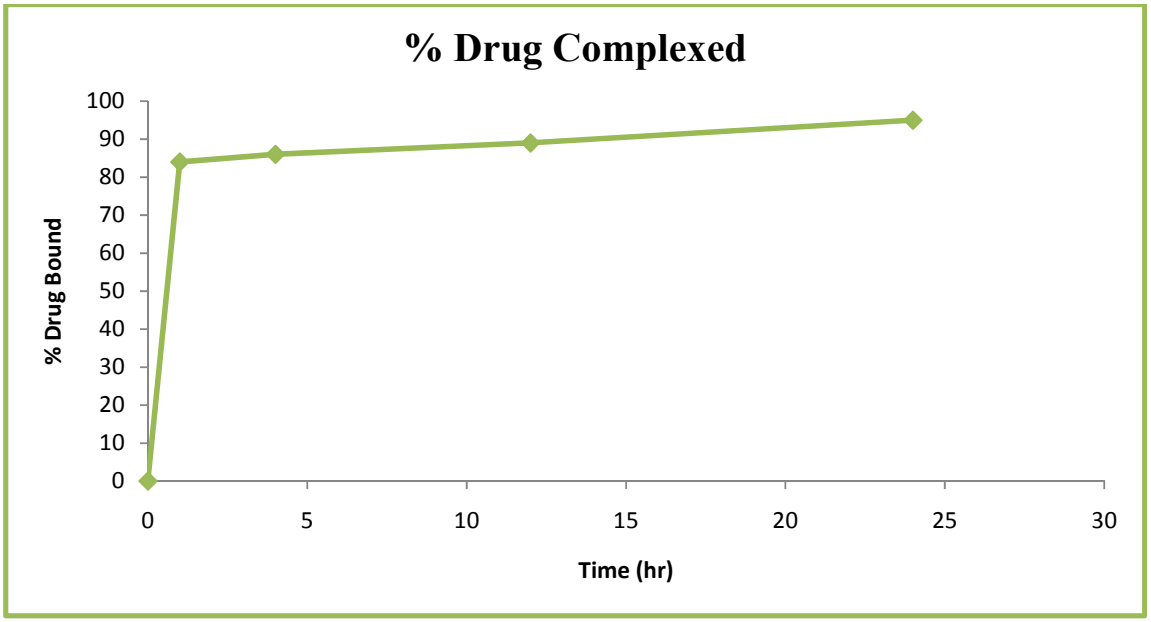


Figure 13: Effect of stirring time on drug loading

3.6.5 Table 14: Effect of drug concentration on drug loading:

Sl No.	Drug: Polymer Ratio	pH	Temperature °C	Stirring Time (hr)	Drug concentration (mcg/ml)	Percentage Drug Complexed after 24 hrs*
1	1:2	6	50	24	2	98±0.53
2					4	91±1.56
3					6	88±1.21

*** mean of three determinations.**

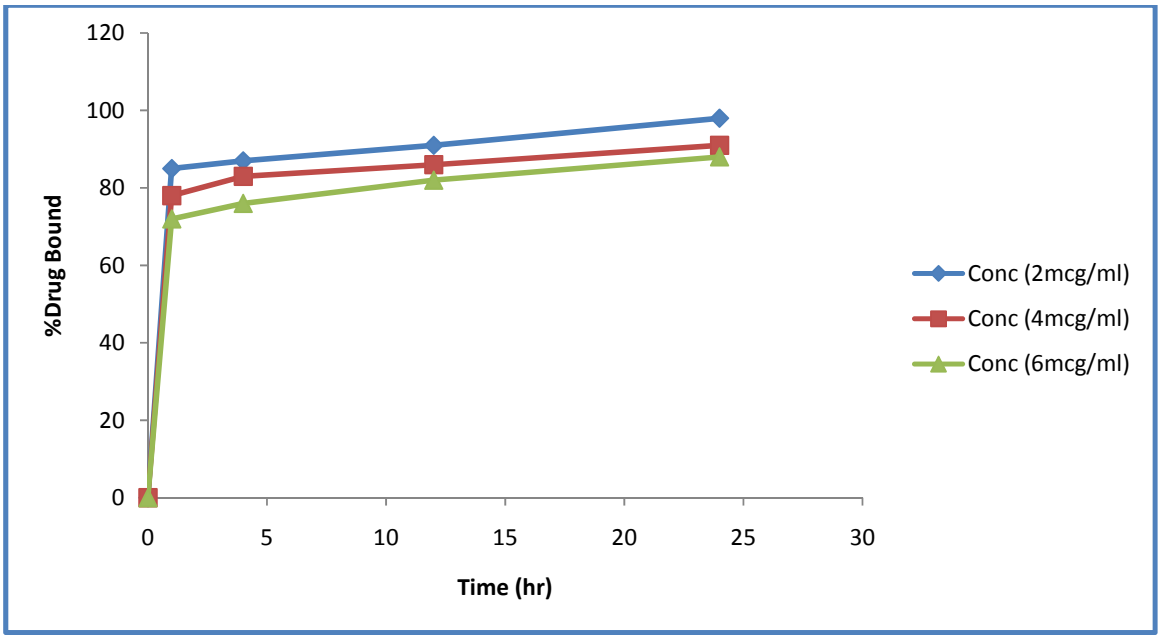


Figure 14: Effect of drug concentration on drug loading (% Drug bound vs Time)

3.6.6 Table 15: Parameters for Final Optimized Formulation (F-43):

Sl No.	Drug: Polymer Ratio	pH	Temperature °C	Stirring Time (hr)	Drug concentration (mcg/ml)	Percentage Drug Complexed after 24 hrs*
1	1:2	6	50	24	2	98±0.53

***mean of three determinations.**

3.7 Evaluation of the optimized Drug Resin Complex:

3.7.1 Percentage yield and Drug Content:

The Percentage yield for the final formulation determined in triplicate was found to be 98.97±0.234 with a drug content of 99.12±0.172.

Table 16: Percentage yield and drug content:

Formulation Code	Percentage yield*	Drug Content*
F-43	98.97±0.234	99.12±0.172

***mean of three determinations.**

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