

Formulation and Evaluation of Oral Reconstitutable Suspension of Cefpodoxime Proxetil

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Abstract

Cefpodoxime proxetil (CFPD PRXL) is broad spectrum, third generation cephalosporin; antibiotic. It is extremely bitter taste resulting in poor patient compliance. The aim of the present work was to prepare drug resin complex (DRC) using ion exchange resin (Kyron T-114) for taste masking and formulate oral reconstitutable suspension of DRC. DRC was evaluated for effect of variables like drug:resin ratio, pH, temperature, soaking time of resin, & stirring time. Reconstitutable suspension was prepared using Xanthun gum and microcrystalline cellulose as suspending agents. Formulated reconstitutable suspension was evaluated for before reconstitution parameters like flow properties, particle size and drug content and after reconstitution parameters like aesthetic appeal, sedimentation rate, redispersibility, particle size, viscosity, pH and drug content. Formulated CFPD PRXL reconstitutable suspension has acceptable sedimentation properties. In evaluating period of 14 days no significant change was observed in pH, viscosity, particle size and drug content. From the results it is concluded that effective taste masking of Cefpodoxime proxetil was achieved using Kyron T-114 and successfully evaluated in reconstitutable suspension.

Keywords: Sedimentation Rate; Ion Exchange Resin; Stability

Introduction

Cefpodoxime proxetil, is a third generation cephalosporin antibiotic useful in the treatment of infections of respiratory tract and urinary tract. Cefpodoxime proxetil is extremely bitter in taste and hampers the oral delivery in paediatrics and geriatrics patients. Several methods can be employed to mask the bitter taste, like microencapsulation, ion exchange resin, coating etc. [1-3]. Gandhi R et al. patented on the masking of bitter taste of the cefpodoxime proxetil dry suspension by coating with Eudragit RD 100. The suspension of cefpodoxime proxetil and combination of binder carrageenan and microcrystalline cellulose was prepared [4]. Fernandez MI et al. patented on the preparation of stable taste masked, pharmaceutical composition comprising a coated, non-disintegrating discrete dosage units, said units comprising of a core comprising one or more cephalosporins such as cefuroxime axetil and cefpodoxime proxetil and one or more coating layers of lipid [5].

Suspension defined as an intimate mixture of dry, finely divided drug with excipients, which, upon the addition of suitable vehicle, yields a suspension [6]. Reconstitutable suspension is reconstituted at the time of use and thus can be used as liquid formulation which avoids swallowing problem. Moreover, stability of products for tropical countries is a great challenge as these products are exposed to elevated temperatures (up to 40 °C) and relative humidity (up to 90%) especially during transport and storage.

Ion exchange resins (IER) are solid insoluble high molecular weight polyelectrolyte that can exchange their mobile ions of equal charge with the surrounding medium reversibly and stoichiometrically. In IER method, weak cation exchange or weak anion exchange resins are used for taste masking, depending on the nature of drug. Bitter cationic drugs can get adsorbed on to the weak cation exchange resins of carboxylic acid and form the complex which is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected. Further drug resin complex (DRC) can be formulated as lozenges, chewing gum, suspension or dispersible tablet [7-9].

The objective of present work was to taste mask Cefpodoxime proxetil using ion exchange resin Kyron T-114 and check the feasibility of incorporating the DRC into reconstitutable suspension to increase patient compliance.

Materials and Methods

Material

Cefpodoxime proxetil was gift sample from Indica Lab. Pvt. Ltd., Ahmadabad. Kyron T-114 was obtained as gift sample from Corel Pharma Chem., Ahmadabad. Xanthun gum, Sucrallose, Methyl paraben and Propyl paraben were obtained as gift sample from Welable Pharmaceuticals. All other chemicals and reagents used were of analytical grade. Deionized distilled water was used throughout study.

Preparation DRC

Weight ratio of Kyron T-114 was placed in a beaker containing required quantity of deionized water and allowed to swell for 2 hrs. Weighed amount of CFPD PRXL was added into it and stirred for 4 hrs. The mixture was filtered and residue was washed with three portions of 75 ml of deionized water and dried. Bound drug in complex was calculated as drug-loading efficiency. DRC was optimized for various parameters like drug to resin ratio, effect of pH, effect of temperature, effect of soaking time of resin and effect of stirring time on taste masking efficiency of drug.

Preparation of oral reconstitutable suspension [10]: The oral reconstitutable suspension of CFPD PRXL was prepared from the optimized DRC (drug resin weight ratio 1:3). The formula is presented in Table 1. All the ingredients for suspension were sieved through mesh no. 40 to make uniform particle size dispersion. The DRC equivalent to 50 mg/ 5 ml of suspension was mixed with the excipients. The prepared suspension was evaluated for before and after reconstitution parameters.

Ingredients	Functional category	Quantity (mg/5 ml)
Drug resin complex (Equivalent to 50mg/5ml of CFPD PRXL)	Taste masked drug	230
Xanthun gum	Suspending agent	30
Microcrystalline cellulose	Suspending agent	50
Sucrallose	Sweetener	10
Mannitol	Filler	50
Methyl paraben	Preservative	10
Propyl paraben	Preservative	1
Sodium citrate	Buffer	25
Strawberry flavor	Flavoring agent	20
Erythrosine supra	Coloring agent	4

Table 1: Formulation of CFPD PRXL oral reconstitutable suspension

Evaluation of DRC

Percentage yield: Percentage yield of DRC was calculated using following equation.

$$\% \text{ yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}}$$

Drug content: DRC equivalent to 100 mg of drug was dissolved in 100 ml 0.1 N Hydrochloric acid in volumetric flask. The mixture was sonicated for 15 min and filtered using Whatman filter paper. The above solution was suitably diluted to get solution of 10 µg/ml. Drug content was estimated using UV spectrophotometer at 262.5 nm using calibration curve equation. The drug content was measured using following equation,

Theoretical concentration of CFPD PRXL = 1000µg/ml

$$\% \text{ drug content} = \frac{\text{Practically Obtained CFPD PRXL Concentration}}{100} \times 100 \text{ [Eq.2]}$$

Taste Evaluation [11-13]: The taste of suspension was checked by panel method. The study protocol was explained and written consent was obtained from volunteers. The optimised DRC and CFPD PRXL were subjected for taste evaluation. Taste evaluation was performed by testing the samples on 6 volunteers in the age group 22–28 years. Each volunteer held DRC equivalent to 25 mg in the mouth for 30 seconds and then spit out. The scale used was (a) 0-Tasteless, (b) 1-Slightly bitter, (c) 2- Bitter, and (d) 3-Very bitter.

Physical properties of DRC

Physical properties of DRC such as particle size, angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio were determined [14]. All parameters were performed in triplicate.

Characterization of DRC

Molecular properties on complexation were studied by Fourier transform infrared spectroscopy (FTIR). Infrared spectra of CFPD PRXL, Kyron T-114 and DRC were obtained using FTIR-8400S, Shimadzu. The pellets were prepared on KBr press, and the spectra were recorded over the wave number 4000 to 400 cm^{-1} . The spectra were obtained comparatively analyzed.

Thin Layer Chromatography (TLC)

The samples were analyzed for compatibility by TLC. Stationary phase used was Aluminium backed silica gel 60F254 TLC plate and Mobile phase was Chloroform:Methanol:Toluene (4:2:4 v/v/v). Reference solution was prepared by dissolving 10mg of CFPD PRXL in 100 ml of methanol. Test solution was prepared by DRC equivalent to 10mg CFPD PRXL dissolved in 100 ml methanol.

In-vitro Drug release study from DRC

In-vitro Drug release studies were performed using USP type II apparatus (Electrolab). Simulated Salivary Fluid pH 6.8, Water and 0.1 N HCl buffer were used as dissolution media. The volume of dissolution medium was 900 mL and it was maintained at Temperature (37 ± 0.5 °C) and stirred at 50 rpm. 10 mL samples were collected at time intervals of 5, 10, 15, 30, minutes. The withdrawal samples were replaced by equal amount of dissolution medium to maintain constant volume. Samples were analyzed by UV Spectrophotometry for determination of CFPD PRXL content using calibration curve equation data.

Evaluation of oral reconstitutable suspension [15-17]

Dry powder blend, ready for reconstitution was evaluated for physical properties like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio.

After reconstitution, parameters like sedimentation volume and redispersibility of suspension, taste evaluation, particle size, viscosity, pH, drug content and *in-vitro* drug release study were evaluated. Taste evaluation, drug content and *in-vitro* drug release study was performed as per method given earlier.

Sedimentation volume and redispersibility of suspension [18,19]

The formulated suspension was evaluated for physical stability by determining the sedimentation volume. Fifty ml of suspension was taken in 100 ml stopped graduated measuring cylinder. The suspension was dispersed thoroughly by moving upside down for three times. Later, the suspension was allowed to settle for three minutes and the volume of sediment was noted. This is the original volume of sediment (H_0). The cylinder was kept undisturbed for 14 days. The volume of sediment read at 0 day, on 7th day and on the 14th day was considered as final volume of sediment (H_u). The redispersibility of the suspension was checked by moving the stoppered cylinder upside down until there was no sediment at the bottom of the cylinder.

$$\text{Sedimentation volume} = \frac{H_u}{H_0} \quad [\text{Eq.3}]$$

Particle size Analysis [18]

The particle size was measured using an optical microscope (Labomed CX RIII, Ambala, India). The slide containing suspension particles was mounted on the stage of the microscope and diameter of at least 100 particles was measured using a calibrated optical micrometer.

Determination of Viscosity

Viscosity study was carried out using a Brookfield viscometer with spindle no. S61. Viscosity was measured at 100 rpm, at 25 °C.

pH of the suspension

pH of the suspension was determined using calibrated digital pH meter.

Stability study

The prepared suspension was subjected to short term stability study for a period of three months as per ICH guidelines. In the present study, stability studies were carried out at 25 °C / 60% RH and 40 °C / 75% RH up to three months. Photostability chamber was used. Physical stability was analyzed by change in appearance and chemical stability was analyzed by the change in the drug content and drug dissolution.

Results and discussion of prepared DRC

As presented in Table 2 the complexation of drug with Kyron T-114 in a weight ratio of 1:3 gave efficient drug loading and taste masking. There was no significant difference in drug loading as well as taste, when drug: resin ratio was changed from 1:3 to 1:5. The stirring time for all subsequent complexation process was fixed to 4 h. Stirring time between 4 and 5 h showed no significant change. The pH and temperature of solution did not show any significant effect on drug loading. Therefore, pH 7 and room temperature were selected for optimized batch preparation. No significant difference was observed, when soaking time of resin in deionized water was changed from 45 min to 120 min. Thus, the soaking time of resin in deionized water was fixed to 45 min.

Drug: resin ratio	% drug loading	Bitterness*
1:1	61.54 ± 0.61	3
1:2	73.03 ± 2.01	2
1:3	85.78 ± 0.71	1
1:4	86.64 ± 1.29	1
1:5	87.29 ± 1.06	1

* Bitterness level graded from (1) no bitter, (2) less bitter, (3) moderate bitter, (4) bitter and (5) very bitter

Table 2: Optimization of Drug: resin ratio

Taste Evaluation

The drug and the DRC of optimized ratio were subjected to taste evaluation. Taste evaluation in volunteers confirmed that the taste of drug was excellent bitter while in optimized DRC the taste of drug was not appeared.

Flow properties

Table 3 presents the results of micromeritic studies for DRC. The Carr's index value between 5-12% indicates excellent compressibility. The values of hausner's ratio less than 1.25% and angle of repose below 30° indicates good flowability of DRC.

Parameter	Result
Bulk density (gm/cc)	0.625 ± 0.018
Tapped density (gm/cc)	0.689 ± 0.017
Compressibility index	9.29
Hausner's ratio	1.102
Angle of repose (θ)	28.72 ± 1.45
Average particle size (µm)	386 ± 24.3
% yield	85.78 ± 0.71
Assay	99.74 ± 0.88

*Mean ± S.D. (n=3 determinations)

Table 3: Flow properties of DRC

In vitro drug release from DRC

Figure 1 demonstrates the drug release studies of CFPD PRXL from the DRC in 0.1 N HCl, simulated salivary pH 6.8 and deionized water.

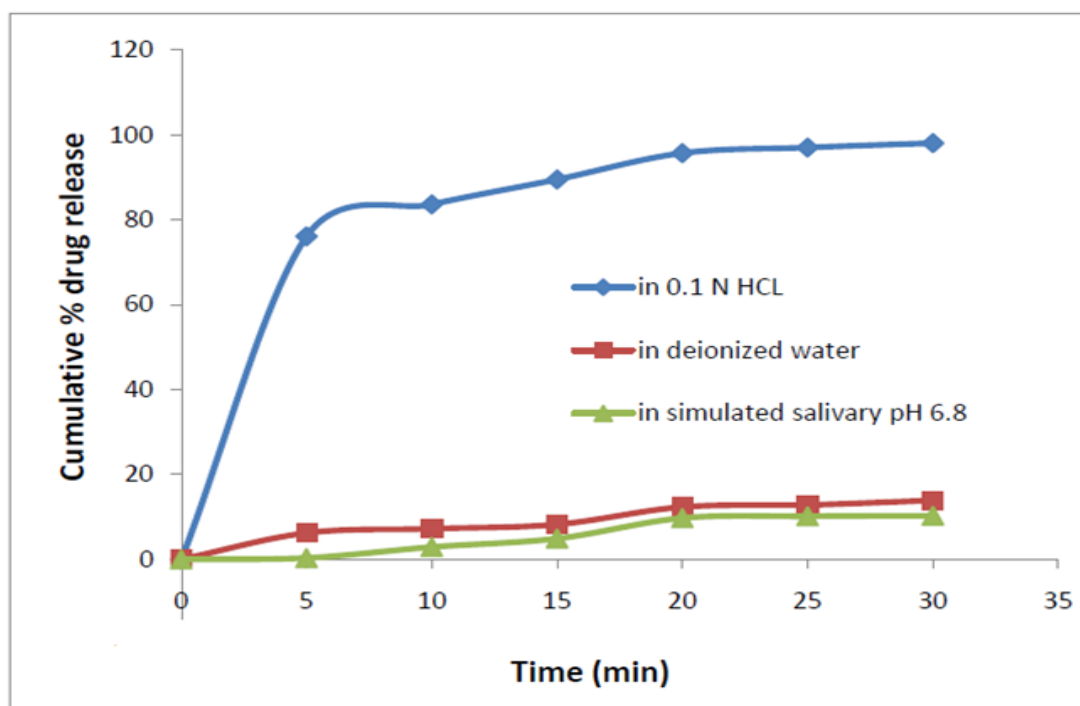


Figure 1: In-vitro drug release profile of drug-resin complex in 0.1 N HCl, deionized water and simulated salivary pH 6.8

In 0.1 N HCl more than 80% of drug release was released in 15 min, whereas in simulated salivary pH 6.8 and deionized water, less than 10% drug was released in 15 min. The exchange process of drug release follows



Where, X^+ represents the ions in the GI tract.

The presence of H^+ ion in the 0.1 N HCl causes displacement of CFPD PRXL, thus facilitating drug release. The amount of drug released was insufficient to impart bitter taste in deionized water and simulated salivary pH 6.8 [20].

Characterization of DRC

FTIR Spectroscopy: The FTIR spectra of pure drug showed characteristic peaks at 1724.24 cm^{-1} ($\text{C}=\text{O}$ stretching) together with peaks at 1070.42 cm^{-1} and 3492.85 cm^{-1} characterizing C-O stretching of ester group and N-H stretching of amide groups respectively. The peak at 1328.86 cm^{-1} indicated the presence of aromatic ether in the drug moiety. Significant reduction in the intensity of distinctive peaks of drug demonstrates the formation of complex between drug and the resin molecule (Figure 2).

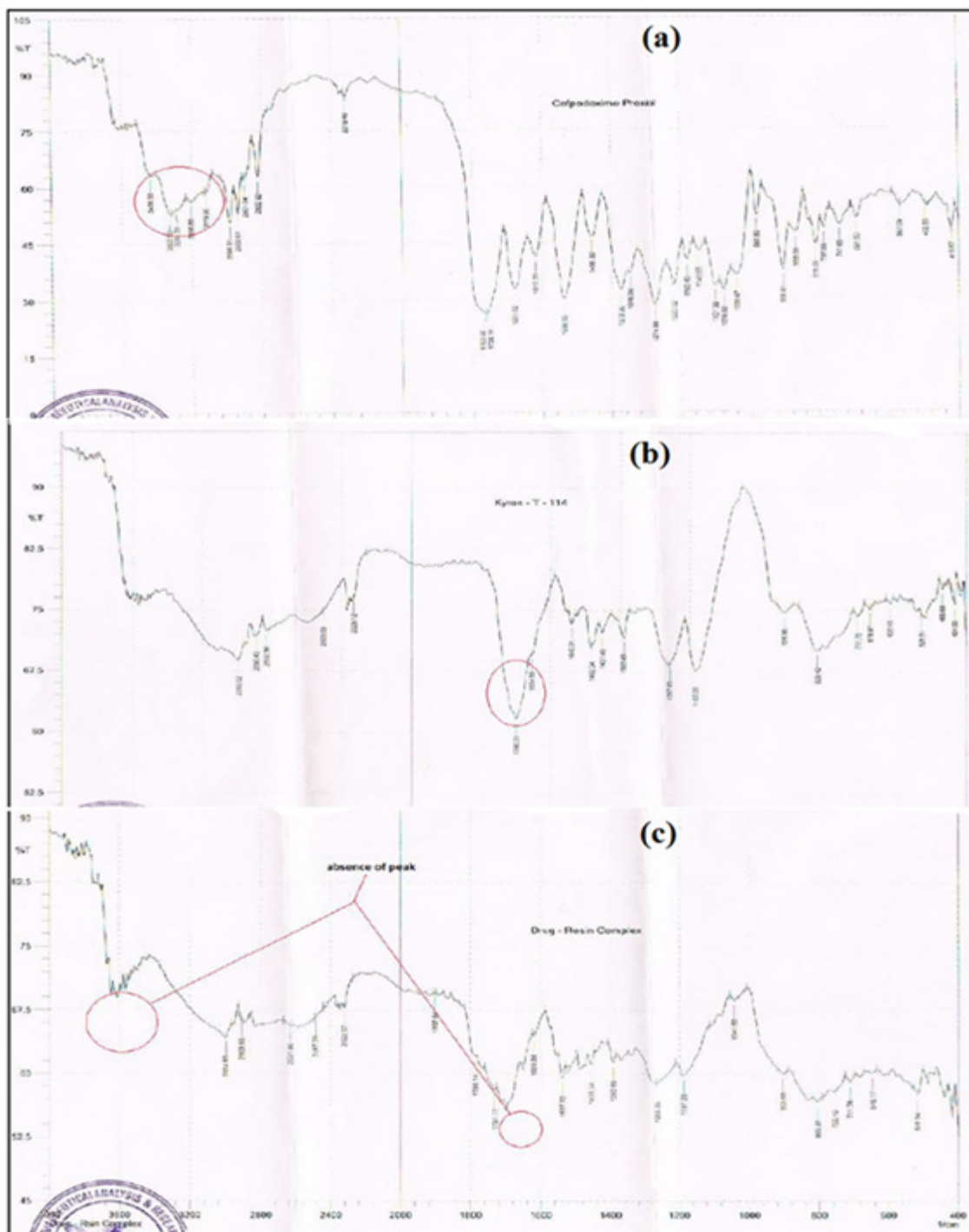


Figure 2: Infrared spectra of (a) CFPD PRXL, (b) Kyron T-114 and (c) DRC

TLC

R_f values of drug and DRC were found to be 0.627 and 0.621 respectively. The R_f value of drug in both reference solution and that of complex were nearly same indicating that both CFPD PRXL and Kyron T-114 were compatible with each other in prepared DRC (Figure 3).

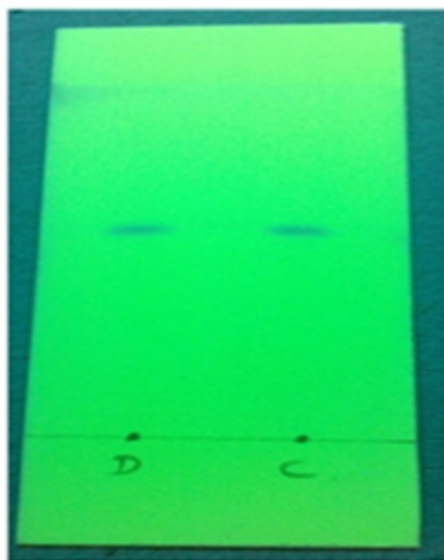


Figure 3: TLC plate showing spots of drug (D) and complex (C)

Reconstitution suspension

Prepared suspension was evaluated for flow properties before reconstitution. Results are shown in Table 4. Results showed that reconstitutable blend has an excellent flow properties and optimum drug content value.

Bulk density (gm/cc)	0.833
Tapped density (gm/cc)	0.943
Compressibility Index (%)	11.66
Hausner's ratio	1.13
Angle of repose (θ)	27.38
Particle size (μm)	426 \pm 14.2
Drug content (%)	97.43 \pm 0.547

Table 4: Pre-reconstitution evaluation of dry powder blend

Sedimentation volume of suspension

The ultimate height of the solid phase after settling depends on the concentration of solid and the particle size. In prepared formulation, there was little sedimentation after 7 and 14 days and it could be easily redispersed and gave uniform dispersion after 2-3 stroke. Results are shown in Table 5.

Time (days)	H _u	H _o	Sedimentation ratio (H _u /H _o)	Redispersibility (No. of stroke)
0	100	100	1.0	0
7	80	100	0.80	1
14	73	100	0.73	1

Table 5: Sedimentation study of suspension

Particle size analysis of suspension

Particle size of the particles in suspension was reasonably constant even after 14 days. This indicated no crystal growth.

Viscosity of suspension

Sedimentation rate depends on the viscosity of the medium. From sedimentation volume data, it can be seen that suspension is stable and easily redisperse after 14 days. Thus, viscosity of the suspension is sufficient for stability of the suspension.

pH

The reconstitutable blend for suspension was subjected for stability for a period of 14 days. The samples were reconstituted in purified water to formulate a suspension. This was analyzed for pH at 0, 7 and 14 days after reconstitution. There was no appreciable change observed in pH.

Sr. No	Test	Observations		
		0 day	7 days	14 days
1	Appearance	Uniform	Uniform	Uniform
2	Taste	Palatable	Palatable	Palatable
3	pH	7.0	6.9 ± 0.1	6.9 ± 0.1
4	Viscosity (cps)	67	60	56
5	Particle size (µm)	302 ± 8.3	307 ± 6.3	311 ± 10.7
6	Drug content (%)	97.22 ± 0.12	96.58 ± 0.54	96.11 ± 0.85

Table 6: Evaluation Parameter of after reconstitution oral Suspension

Taste evaluation

Taste evaluation in volunteers confirmed that the taste of bitter drug in reconstitutable suspension was not appeared. All volunteers found to be tasteless and agreeable of taste of suspension.

Drug content of the suspension

No significant change was observed in the drug content.

In vitro drug release

Results of % drug release are shown in Figure 4. It was observed that resin was not retard the release of drug from suspension.

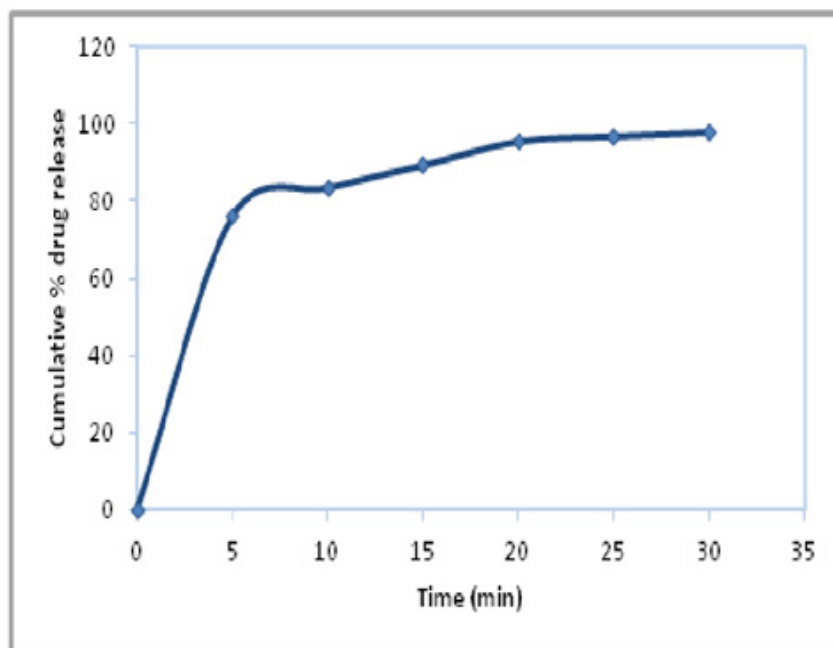


Figure 4: *In-vitro* Dissolution Profile of reconstituted oral Suspension in 0.1 N HCl

Conclusion

In the present study, an attempt was made to mask bitter taste of CFPD PRXL by Kyron T-114 (cation exchange resin). Various parameters affecting taste masking like drug: resin ratio, pH, temp, soaking time of resin and stirring time were optimized with efficient loading of drug. The volunteers rated the complexes as tasteless and agreeable. Drug release from DRC in simulated salivary pH 6.8 and in deionized water was insufficient to impart bitter taste. Complete drug release was observed at gastric pH. This approach can be utilized for taste masking of bitter pharmaceutical ingredients leading to improved patient compliance. Taste masked DRC was showed excellent flow properties. Formulated CFPD PRXL reconstitutable suspension has acceptable sedimentation properties. In evaluating period of 14 days no significant change was observed in pH, Viscosity, particle size and drug content. This method is simple and cost effective to prepare taste masked reconstitutable suspension of CFPD PRXL that may be acceptable to the industry.

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