



Development of Taste-Masked Oral Dispersible Tablets of Cefpodoxime Proxetil

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Cefpodoxime proxetil (CFPD PRXL) is a third-generation cephalosporin antibiotic with broad-spectrum activity. However, its bitter taste often leads to poor patient compliance. This study aimed to develop a taste-masked drug resin complex (DRC) using the ion exchange resin Kyron T-114. Various variables, including resin ratio, pH, temperature, soaking time, and stirring time, were investigated for their impact on drug loading and taste reduction. A dispersible tablet was then formulated using the DRC and other pharmaceutical excipients. The formulated tablet underwent evaluation for weight variation, hardness, dimension uniformity, friability, content uniformity, wetting time, *in-vitro* disintegration time, and *in-vitro* drug release. Results demonstrated that the wetting and disintegration times of the tablets, as well as the *in-vitro* drug release, were comparable to those of the commercially available CFPD PRXL product. In conclusion, the developed method for taste masking CFPD PRXL and preparing orodispersible tablets proved to be simple, cost-effective, and potentially suitable for industrial application.

Cefpodoxime proxetil (CFPD PRXL) is a third-generation cephalosporin antibiotic with broad-spectrum activity commonly prescribed in both solid and liquid forms to treat various bacterial infections, including upper respiratory infections, ear infections, skin infections, and urinary tract infections (1–3). However, its extremely bitter taste poses a challenge for patient compliance, particularly among pediatric and geriatric populations. Solid dosage forms such as tablets are frequently used for these patients (1–3).

Ion exchange resins are solid, high-molecular weight polyelectrolytes that can reversibly and stoichiometrically exchange their mobile ions with the surrounding medium. These resins are available in various sizes and can be utilized to adsorb bitter cationic drugs onto weak cation exchange resins containing carboxylic acid. This interaction forms a complex that effectively masks the bitterness of active ingredients (4). Resinates can then be formulated into lozenges, chewing gum, suspensions, or dispersible tablets, effectively concealing the taste (3).

The binding of drugs to the resin can be achieved through repeated exposure or prolonged contact with the resin. By forming weak ionic bonds between the drugs and the oppositely charged resin substrates or resinates, the drug-resin complex (DRC) remains stable under salivary pH conditions, successfully masking the unpleasant taste and odor of the drugs.

The objective of this study was to incorporate the DRC into a dispersible tablet to enhance patient compliance (5–6). In a previous study, the preparation and evaluation of the DRC was performed using Kyron T-114, a weak acid derivative of methyl acrylic acid cross-linked polymer having a carboxylic acid functional group, which is responsible for its taste masking property for a pharmaceutical suspension; however, its use in tablet formulation was not investigated. Therefore, the specific

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objective of this present study was to develop and evaluate an orally disintegrating tablet (ODT) of CFPD PRXL using the optimized DRC that were utilized for suspension formulation (6).

A pharmaceutical tablet is a solid unit dosage form of medication containing appropriate excipients, prepared either by compression or molding (7). Dispersible tablets, as defined by FDA's Center for Drug Evaluation and Research (CDER), consist of a fine mixture of dry, divided drugs and/or chemicals that, when combined with suitable vehicles, yield a tablet (8). However, ensuring tablet stability in tropical countries presents a significant challenge due to exposure to high temperatures (up to 40 °C) and humidity (up to 90%) during transportation and storage (9). In recent years, there has been considerable interest in fast dispersible tablet (FDT) technologies that enable tablets to disintegrate in the mouth without the need for chewing or additional water intake (10–11). FDTs are also referred to as fast melting, fast disintegrating, rapid dissolve, rapid melt, or quick disintegrating tablets. ODTs are the classification assigned by FDA to all approved FDTs. The *European Pharmacopoeia* has adopted the term ODT to describe tablets that disperse or disintegrate in the mouth within three minutes before swallowing (12). These tablets transform from a hard solid into smaller granules or a gel-like structure, making them easier to swallow.

Materials

CFPD PRXL was received from UCB India Private Limited (Vapi, India). The resin, Kyron T-114 (Batch no. 3009022), was procured from Corel Pharmachem (Ahmadabad, India). Starch 1500 was procured from Welable Pharma (Mehsana, India). Microcrystalline cellulose PH101, crosscarmellose sodium, powdered mannitol, talc, magnesium stearate, and pineapple dry flavor were obtained from S.D. Fine Chemicals (Mumbai, India). Deionized distilled water was used throughout the study.

Methods

Preparation of DRC. A cation exchange resin, Kyron T-114, was utilized to prepare the DRC with the desired drug in different stoichiometric ratios. The method involved weighing Kyron T-114 according to the optimized drug-resin ratio of 1:3 and placing it in a beaker with the appropriate amount of deionized water. The mixture was allowed to swell for 45 minutes. CFPD PRXL was accurately measured and stirred into the solution at 37 °C for four hours. The resulting mixture was filtered using Whatman filter paper, and the residue was washed three times with 75 mL of deionized water per wash and subsequently dried. The drug content within the complex was evaluated as drug loading efficiency. Further comprehensive information can be found in previous publications (5–6,13).

Preparation of tablets. The FDT of CFPD PRXL was formulated using the direct compression technique. The compositions of the orodispersible tablets are provided in **Table I**. Prior to mixing, all raw materials were passed through a No. 60 sieve. The DRC (equivalent to 50 mg of CFPD PRXL), crosscarmellose sodium, microcrystalline cellulose PH 101, starch 1500, and mannitol were mixed for 15 minutes. Talc and magnesium stearate were added last and thoroughly mixed before compression. The final mixture, ready for compression, was compressed into tablets using a multi-tooling rotary compression machine fitted with a 10.3-mm concave punch. Each tablet, weighing 350 mg, contains 50 mg of CFPD PRXL. A compression force of 12–13 kN was used for preparation of tablets to get hardness ≥ 30 N and a disintegration time ≤ 60 s.

Table I. Formulation of cefpodoxime proxetil (CFPD PRXL) orally disintegrating tablet.

Ingredients	Functional category	Quantity (mg) per tablet
Drug-resin complex (equivalent to 50 mg CFPD PRXL)	API	233
Crosscarmellose sodium	Super disintegrant	10.50
Microcrystalline cellulose: starch 1500 (50:50)	Diluents	60
Powdered mannitol	Diluents and sweetener	39.15
Talc	Glidant	3.5
Magnesium stearate	Lubricant	3.5
Dry essence pineapple	Flavoring agent	0.35
Total		350

Evaluation of FDT. The dry powder blend, prepared for compression, underwent evaluation for flow properties and drug content. After tablet preparation, various parameters were assessed including weight variation, dimensions, hardness, friability, uniformity of content, wetting time, *in-vitro* disintegration time, and *in-vitro* drug release study.

To ensure uniformity, 20 tablets from the formulation batch were weighed and subjected to the weight variation test as per the official method outlined in the *Indian Pharmacopoeia (IP)*. The diameter and thickness of six tablets were measured using a Vernier caliper with an accuracy of ± 0.01 mm. The average values were calculated. The hardness of six tablets was determined by a digital hardness tester. The average values were calculated. The friability of 20 tablets was determined using a friability testing apparatus (Roche Friabilator, Basel, Switzerland). Pre-weighed tablets were rotated at 25 rpm for four minutes. After removing

finest, the tablets were reweighed, and the percentage weight loss was calculated (14). The drug content in the prepared tablets was tested. Ten tablets were finely powdered, and an amount equivalent to 50 mg of CFPD PRXL was accurately weighed and transferred to a 100-mL volumetric flask. The flask was initially shaken with 20 mL of 0.1 N hydrogen chloride (HCl) for 10 minutes. The volume was then filled to the 100-mL mark with the same solvent. The solution was sonicated for five minutes, filtered using Whatman filter paper, appropriately diluted, and the absorbance of the resulting solution was measured spectrophotometrically at λ_{max} 262.5 nm (15). The wetting time of the tablets was determined using a simple procedure. Five circular tissue papers with a diameter of 6 cm were placed in a glass petridish (10 cm diameter). Ten mL of water containing eosin dye was added to the dish. A tablet was weighed and carefully placed on the tissue paper's upper surface. The time taken for water to reach the center of the tablet was recorded as the wetting time (16). Disintegration time was determined using a United States Pharmacopeia (USP) tablet disintegration test apparatus in 900 mL of distilled water at a temperature of 37 ± 0.5 °C, without a disk (17).

In-vitro drug release. The dissolution characteristics of the FDT of CFPD PRXL in 0.1 N HCl were determined using a USP XXIV type II dissolution apparatus. A tablet was added to 900 mL of 0.1 N HCl at 50 rpm and 37 ± 0.5 °C for 30 minutes. At predefined intervals (5, 10, 15, 20, 25, and 30 minutes), 10-mL samples were collected and replaced with an equal volume of fresh medium. The drug content in the collected samples was analyzed spectrophotometrically at λ_{max} 262.5 nm. *In-vitro* drug release was also performed in deionized water and simulated salivary fluid at pH 6.8, following the same procedure (17,18).

Accelerated stability study. The stability of the formulation was evaluated in accordance with International Council for Harmonisation's Q1A (R2) guideline (19). Samples were sealed in aluminium foil, such as alu-alu pouch to simulate final packaging. The formulations were stored under accelerated (40 ± 2 °C/ $75 \pm 5\%$ relative humidity [RH]) and long-term (30 ± 2 °C/ $65 \pm 5\%$ RH) test conditions in a stability chamber for six months. During stability studies critical parameters such as appearance, disintegration time, moisture uptake, and drug content were evaluated according to their standard procedure (20).

Results and discussion

Results of DRC. DRC ratio of 1:3 was selected and incorporated into the tablet formulation along with other excipients. The prepared blend was evaluated for its physical properties, including flowability, assay, and yield. The results, presented in **Table II**, demonstrate excellent flow properties, confirming the suitability of the DRC for direct compression formulations, specifically for FDTs.

Results of tablets. Post-compression parameters were evaluated to assess the quality of the tablets. Based on

the results obtained, the appropriate amount of the DRC was determined, and tablets were prepared accordingly. The prepared tablets underwent evaluation for various pharmacotechnical properties including weight variation, hardness, drug content, and friability. The results are presented in **Table III**. It was observed that the tablets exhibited acceptable pharmacotechnical properties such as weight variation, hardness, content uniformity, friability, and wetting time, comparable to the marketed products. *In-vitro* disintegration time, an important characteristic of dispersible tablets, was also assessed. The disintegration of tablets is influenced by factors such as pore size distribution, water penetration into the tablets, and swelling of the disintegration substance. The disintegration time of the tablets complied with the standards set by IP, which require dispersible tablets to disintegrate within three minutes (14).

In-vitro drug release. **Figure 1** presents the drug release profiles of CFPD PRXL from the tablet formulation in different media, namely 0.1 N HCl, simulated salivary pH 6.8, and deionized water. In 0.1 N HCl, more than 80% of the drug was released within 15 minutes, indicating a rapid release. However, in simulated salivary pH 6.8 and deionized water, less than 10% of the drug was released within the same timeframe. The presence of H⁺ ions in

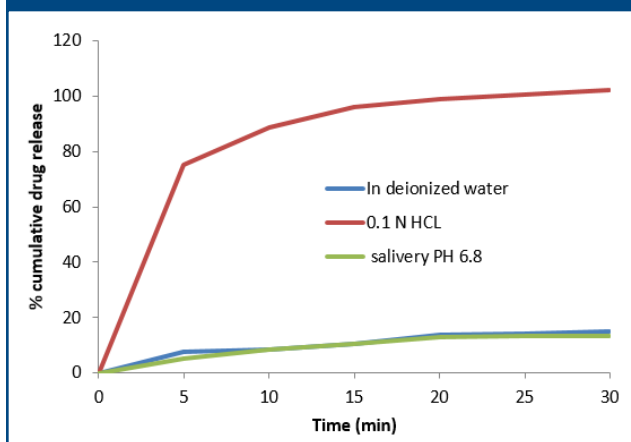
Table II. Pre-evaluation of dry powder blend.

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
Average particle size (µ)	386 ± 24.3
Angle of repose (θ)	28.72 ± 1.45
% yield	85.78 ± 0.71
Assay	99.74 ± 0.88

Table III. Evaluation parameters of prepared oral tablet.

Parameters	Formulated batch	Marketed batch
Physical appearance	White to off white	White
- Color	Odorless	Odorless
- Odor	Concave	Concave
- Shape		
Diameter (mm)	10.37 ± 0.015	9.46 ± 0.005
Thickness (mm)	4.24 ± 0.026	4.15 ± 0.005
Average weight (mg)	352.8 ± 15.82	277.4 ± 8.38
Content uniformity (%)	101.62 ± 0.76	102.08 ± 0.41
Hardness (N)	31.38 newton	34.32 newton
Friability (%)	0.782	0.498
Wetting time (sec)	15 ± 0.57	11.33 ± 0.757
<i>In-vitro</i> disintegration time (sec)	14.40 ± 1.09	12.72 ± 0.25

Figure 1: *In-vitro* drug release profile in different dissolution media. HCl is hydrogen chloride.



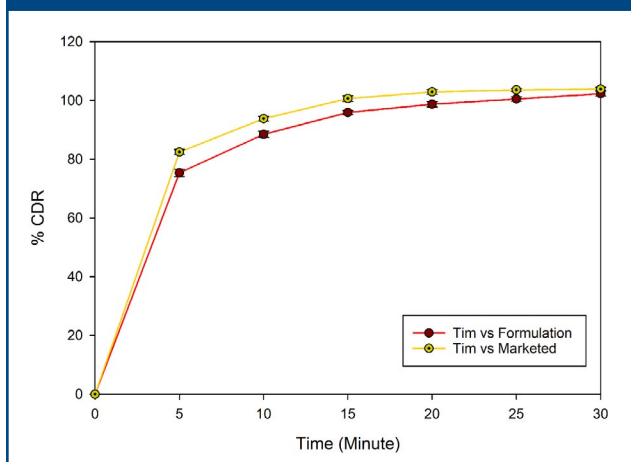
the 0.1 N HCl medium facilitated the release of free CFPD PRXL, leading to a significant drug release. Conversely, the release of the drug in deionized water and simulated salivary pH 6.8 was limited, with only a small amount of the drug being released within the specified time. This limited release in these media is insufficient to impart a bitter taste to the formulation, ensuring a more pleasant experience for the patients. The exchange process of drug release is given in **Equation 1**:



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

Furthermore, an *in-vitro* drug release study was conducted on the prepared tablets as well as a commercially available tablet in 0.1 N HCl dissolution media. The results are presented in **Figure 2**. Comparison of the drug release profiles between the marketed 50 mg dispersible tablet of cefpodoxime proxetil (Cefpoglen, Glenmark Pharmaceuticals) and formulated batches showed no significant difference ($p > 0.05$) at 5% significance. This indicates that the

Figure 2: *In-vitro* drug release profile in 0.1 N hydrogen chloride.



taste-masking approach employed in the formulation did not adversely affect the therapeutic potential of the drug in its dissolution medium.

Accelerated stability study. The stability of the dispersible tablet was assessed through a six-month stability study, and no significant changes in appearance, hardness, total moisture, disintegration time and assay were observed. This indicates that the FDT of CFPD PRXL remained physically and chemically stable under both selected storage conditions.

Conclusion

In conclusion, this study successfully achieved the taste masking of CFPD PRXL using Kyron T-114 as an ion exchange resin. The optimization of various parameters allowed for efficient drug loading and taste masking in the form of a stable DRC. On the one hand, the DRC exhibited excellent stability at salivary pH 6.8, ensuring minimal drug release within 60 seconds and providing a tasteless experience to the patient. On the other hand, the DRC was designed to dissolve in gastric pH 1.2, which facilitated drug release in the stomach. The taste-masked DRC demonstrated favorable flow properties, making it suitable for formulation into an ODT. The formulated CFPD PRXL ODT exhibited desirable characteristics, including appearance and drug content, during a three-month evaluation period. This indicates the physical and chemical stability of the tablet over time. Overall, the developed method offers a simple and cost-effective approach to prepare a taste masked FDT of CFPD PRXL. The findings of this study provide promising insights for the pharmaceutical industry in formulating palatable oral dosage forms and improving patient compliance.

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