Advances in Bioresearch
Adv. Biores., Vol 16 (6) November 2025: 46-55
©2025 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.16.6.4655

Advances in Bioresearch

ORIGINAL ARTICLE

Enhancement of Dissolution Rate of Cefpodoxime Proxetil through Sodium Salt Formation

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ABSTRACT

Cefpodoxime proxetil's slower dissolution rates and poor water solubility cause severely insufficient and irregular absorption. Cefpodoxime proxetil's sodium salt was created, and its solubility and dissolving properties were compared to those of the untreated medication. Cefpodoxime proxetil and sodium hydroxide were combined in equimolar concentrations in an aqueous-ethanolic mixed phase to form the salt. To establish salt production, sodium cefpodoxime proxetil was extensively studied using spectroscopy and differential scanning calorimetry. The solubility and dissolution of the produced tablets were further tested in vitro at pH values of 1.2, 4.5, and 6.8. At pH levels of 4.5 and 6.8, sodium cefpodoxime proxetil became much more soluble. The solubility of unbuffered distilled water increased by 235 times, which was the most noticeable rise. Additionally, in all examined environments, but particularly at pH 4.5 and 6.8, the rate of sodium cefpodoxime proxetil solubility increased. The sodium equivalent of cefpodoxime proxetil dissolved most easily (60%) at pH 6.8 after 30 minutes. The sodium version of cefpodoxime proxetil exhibits better solubility and drug dissolution, which may improve the medication's overall bioavailability while reducing the likelihood of uneven absorption and speeding up the action onset.

Keywords: *Solubility, dissolution, sodium Cefpodoxime proxetil, antibiotic.*

Received 28.09.2025 Revised 23.10.2025 Accepted 24.11.2025

How to cite this article:

Khanderao R. J, Rushikesh D. M, Rishikesh S. B · Enhancement of Dissolution Rate of Cefpodoxime Proxetil through Sodium Salt Formation. Adv. Biores., Vol 16 (6) November 2025: 46-55.

INTRODUCTION

The primary method for administering drugs systemically is through oral ingestion. Pharmaceutical companies prioritize whether a new medication can be effectively taken orally. Formulation scientists face challenges in developing dosage forms for prolonged release due to various factors affecting drug absorption and competing objectives. Modifying a drug's solubility to extend release may decrease its overall payload. Identifying the optimal formulation requires a rapid screening process, as trial and error is insufficient. The Biopharmaceutical Classification System (BCS) classifies drugs into four categories based on permeability and solubility, which significantly affect oral bioavailability and absorption, providing a structured approach to drug development [1-4].

Table 1: BCS classification

BCS Category	Solubility status	Permeability status
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Improving solubility is crucial for the reasons comprises After oral administration, medications that are poorly soluble in water often require high doses and strict dosing regimens to reach therapeutic plasma concentrations. Poor water solubility is the primary drawback, which is addressed in the creation of both new and generic chemical compounds [5-6].

Strategies to enhance the solubility, dissolution rate, and bioavailability of poorly water-soluble therapeutic agents include physical modifications (e.g., particle size reduction, crystal engineering, carrier dispersion techniques), chemical modifications (e.g., salt formation, prodrugs, cosolvents), and nanotechnology-based methods (e.g., nanosponges, nanocarriers). Physical modifications involve micronization and altering crystal habits, while chemical methods focus on utilizing solubilizing agents. Nanotechnology has gained attention for its effectiveness in achieving sustained release and improving therapeutic efficacy [7-10].

A popular and successful Method that improves solubility and rates of dissolution of basic and acidic medications, as well as their bioavailability, is salt production. Because of their greater solubility in the aqueous diffusion layer, salts have historically dissolved more quickly than their free acid or basic counterparts. The significance of choosing the best salt forms during drug development has increased as a result of advances in medicinal chemistry, which have produced numerous novel drug candidates with extremely poor intrinsic solubility. Despite its advantages, choosing salt frequently involves trial and error rather than a thorough assessment of its physicochemical characteristics. Salt stability in aqueous conditions and the possibility of conversion back to less soluble forms are challenges. Other ways to increase solubility include adjusting pH and employing cosolvents, while prodrug techniques provide biological ways to get around solubility problems [11, 12].

This third-generation broad-spectrum cephalosporin successfully targets Enterobacteriaceae, Hemophilus species, and Moraxella species, including those that produce β-lactamase, as well as those resistant to previously used oral medications. It is also powerful against other Gram-positive bacteria, including streptococci. Enterococci are unaffected by cefpodoxime. It is well tolerated and was among the first third-generation cephalosporins made widely available orally. The antibiotic has been shown to be helpful in treating tonsillitis, pharyngitis, skin structure infections, acute otitis media, and sexually transmitted infections, while it is most usually used to treat respiratory and urinary tract infections. Cefpodoxime is a cephalosporin (with a low sporin) that is used to treat bacterial infections. This includes infections in the sinuses, throat, lungs, skin, bladder, and ears. Cefpodoxime can also cure gonorrhea. This pharmacological guide does not cover all of cefpodoxime's uses [13-16].

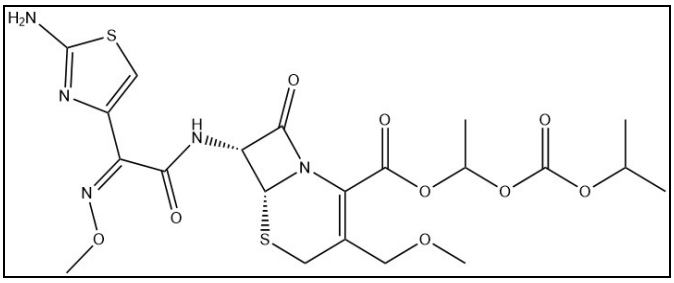

Figure 1: Structure of Cefpodoxime proxetil

Streptococcus pneumoniae, Streptococcus pyogenes, Moraxella catarrhalis, Haemophilus influenza, acute otitis media, acute maxillary sinusitis, community-acquired pneumonia, and non-beta-lactamases strains cause acute bacterial aggravation of chronic bronchitis. Skin infections, simple UTIs, and women's rectal gonococcal infections are caused by *Streptococcus aureus, Streptococcus pyogenes, Proteus mirabilis, Klebsiella pneumoniae, E. Coli,* and *Staphylococcus saprophyticus* [17-18].

PROBLEM STATEMENT

Cefpodoxime Proxetil, an oral prodrug of a third-generation cephalosporin antibiotic, is a common treatment for bacterial infections. However, its limited intestinal permeability and poor water solubility restrict its therapeutic efficiency, earning it a Class IV classification in the Biopharmaceutics Classification System. This results in uneven dissolution, impairing systemic bioavailability and drug absorption. This poses challenges for pharmaceutical formulation, as traditional solid dose forms often don't offer reliable drug release profiles, leading to inconsistent therapeutic results. Salt generation is a tried-and-true strategy to improve solubility and rate of dissolution of Cefpodoxime Proxetil. This method is more affordable, scalable, and regulatory-acceptable than other advanced technologies.

MATERIAL AND METHODS

Chemicals and Reagents

The generous gift of cefpodoxime proxetil (CEF) came from Wilcure Remedies Private Limited in Indore, Madhya Pradesh. We bought high-performance liquid chromatography (HPLC) grade ethanol and acetonitrile from Modern Industries in Nashik. The sodium hydroxide used in the study came from the same source.

Synthesis of Sodium-Cefpodoxime Proxetil (Na–CEF):[19]

Nine grammes of cefpodoxime proxetil powder were dissolved in a solvent combination made up of 700 milliliters of ethanol and 200 milliliters of distilled water to create Na–CEF. After that, an equimolar amount of a 1 M sodium hydroxide solution was added while being constantly stirred. Upon addition, a fine precipitate formed instantly. To guarantee a full reaction, the mixture was let to stand for half an hour. Filtration was used to gather the solid, which was then dried for two hours in a fume hood and stored for 48 hours in a desiccator to eliminate any last traces of moisture.

Box Behnken designs were chosen for the current project. Three factors each were evaluated at three levels in this approach, and experimental trials were conducted at all 12 possible combinations. Cefpodoxime proxetil (X1), ethanol (X2), and sodium hydroxide (X3) were the two independent variables chosen.

Table 2: Composition of Salt Formation

Ingredients	Formulation Code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Cefpodoxime proxetil (gm)	0.55	0.15	0.35	0.15	0.35	0.55	0.55	0.15	0.15	0.35	0.55	0.35
Ethanol (m)	42.77	42.77	42.77	27.22	11.66	27.22	27.22	27.22	11.66	42.77	11.66	11.66
Sodium hydroxide (ml)	0.628	0.628	0.269	0.987	0.987	0.987	0.269	0.269	0.628	0.987	0.628	0.269
water (v/v)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Differential Scanning Calorimetry (DSC) Analysis:

A Mettler Toledo DSC823e equipment with STAR software was used to perform thermal analysis on the untreated CEF and the produced Na-CEF. 40 µL aluminum pans with vented lids were filled with 4–5 mg of each sample. The calibrating standard was indium. The samples were heated at a rate of 10 °C per minute while being scanned under a nitrogen gas flow (80 mL/min) throughout a temperature range of 30 °C to 350 °C.

FTIR Spectral Analysis and pKa Determination:

A Shimadzu 8400S spectrophotometer was used to acquire the Fourier transform of infrared (FTIR) spectra of the untreated and sodium-treated CEF. 150 mg of Na–CEF was dissolved in 30 mL of distilled water and potentiometrically titrated with 0.1 M hydrochloric acid to determine the degree of ionization. 200 mg of sodium carbonate was used as an internal reference. pH measurements were taken following the addition of 0.5 mL of HCl. By examining the titration curve's first derivative, the point of equal value was located.

Solubility Evaluation:

Solubility studies were carried out to investigate the saturated solubility of untreated CEF and Na–CEF in buffer solutions with pH values of 1.2, 4.5, and 6.8, as well as water that was distilled. In each case, excess medicine was combined with 1 mL of the selected solvent in glass vials until it was completely dissolved and precipitation occurred. The vials were then incubated in a water bath shaker for 48 hours at 37 ± 0.1°C to ensure equilibrium. Samples were filtered using 0.45 µm syringe filters after incubation. An HPLC analysis was performed on a 100 µL sample of each filtrate after it had been appropriately diluted.

HPLC Conditions:

The drug concentration was measured using an HPLC system which included a UV detector (Merck–Hitachi, the Model L-7400), a pump (Model L-7400), and a data integrator (Model D-7500). The chromatographic separation had been carried out using a C18 reverse-phase column (200 mm × 4.6 mm i.d., 5 µm; Thermo Scientific, USA). Acetonitrile and 25 mM phosphate buffer (pH 3.5) were combined in a 60:40 ratio to create the mobile phase. The flow rate was maintained at 2 mL/min while the analytes were being analyzed at a wavelength of 235 nm.

Determination of Partition Coefficient (log P)

Either untreated CEF or Na–CEF (20 mg) were added to glass tubes that held five milliliters of octanol and five milliliters of distilled water. For a whole day, the firmly sealed tubes were kept in a shaker water bath at

37 ± 0.1 °C. The HPLC analysis previously reported in the solubility investigations was used to determine the quantities of untreated CEF or Na–CEF in the aqueous phase. There were three trials with partition coefficients.

Formulation and Tablet Preparation: *[19]*

To get a final powder weight of 200 mg per tablet, untreated cef (80 mg) or an equivalent quantity of Na-CEF was combined with lactose (50% w/w) and starch (10% w/w). Starch achieved the required disintegration characteristics at the concentration used. A manual hydraulic press was used to compress powder in a 7-mm die at a force of 10 kN. The punch and die were first lubricated with a 5% w/v magnesium stearate in 96% v/v ethanol solution to stop compressed tablets from adhering.

Dissolution Testing:

Tablet formulations with either unmodified CEF or Na–CEF underwent a comparative dissolving examination. A Copley Scientific dissolving equipment (Model DIS6000, UK) was used for the dissolution testing, which followed USP criteria and used equipment 2 (paddle technique).

Tablets were tested in three different dissolution media:

- 0.1 M hydrochloric acid,
- phosphate buffer at pH 4.5, and
- phosphate buffer at pH 6.8.

The paddle speed was set at 75 rotations per minute, and each vessel held 900 milliliters of medium that was kept at 37 ± 0.5 °C. Six pills, one in each jar, were tested for each formulation. To maintain volume, 2 mL aliquots were taken out at predetermined intervals (10, 20, 30, 45, 60, and 120 minutes) and replaced with new media. Dissolution probes fitted with polyethylene filters were used for in situ sampling, enabling real-time filtering during the test. Using the previously mentioned HPLC approach, the concentration of CEF or Na–CEF released into the medium at each time point was determined.

Calibration and technique Validation:

The consistency of the HPLC method was verified throughout a concentration range of 18–115 µg/mL for sure precise quantification. 20% to 125% of the maximum drug concentration that can be anticipated from an 80 mg tablet dissolved in 900 mL of medium falls within this range. Equation A = 23693x − 106.7 and an average correlation coefficient (r2) of 0.9984 were calculated from a typical calibration curve, indicating excellent linearity within the measured range.

RESULTS AND DISCUSSION

Analysis of Na–CEF Properties:

DSC

After DSC analysis of the dried precipitate of Na–CEF, the thermogram (Figure 2) shows a discernible melting transition at about 308 °C, which is further supported by straightforward observations of the compound's melting point. A DSC thermogram for an untreated CEF sample had been obtained under the same situation and revealed a melting point of 168°C, which is in line with the data that has been published. The ionic character of the salt, where intermolecular attraction forces are more powerful, is consistent with the melting point of Na–CEF being much higher than that of untreated CEF.

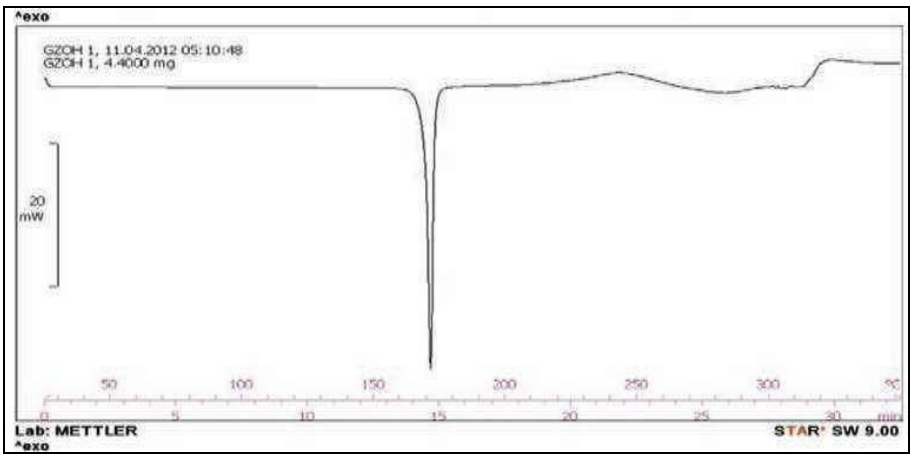

Figure 2: DSC of Cefpodoxime Proxetil

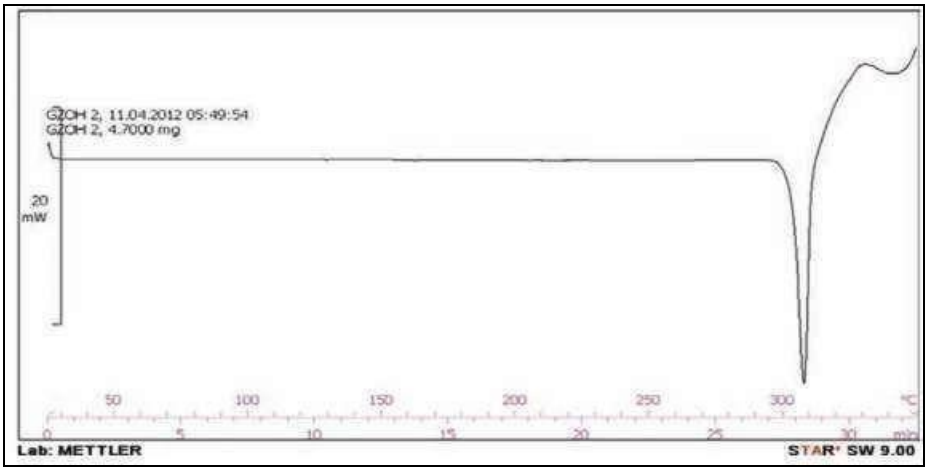

Figure 3: DSC of Sodium- Cefpodoxime Proxetil

FTIR

A Shimadzu FTIR spectrometer (Shimadzu 8400S IR spectrophotometer, Japan) was used for recording the Fourier transform infrared (FTIR) spectra of untreated CEF and Na CEF samples produced through the KBr disc technique. The infrared spectra of the untreated CEF matches those previously published. The CEF and Na–CEF IR spectra changed in two key ways (Figure 3): In CEF spectra (1), the sulfonamide band was obviously moved from 1650 cm-1 in untreated CEF to 1710 cm-1 in Na–CEF, and (2) the bands in the 3500 cm-1 range was sharper and fewer. These changes are in line with the finding that the salt form reduces the capacity to develop intermolecular hydrogen bonds (containing sulfonamide oxygen and a proton) because of the loss of acidic hydrogen, while increasing the probability of sulfonamide–water hydrogen bonding.

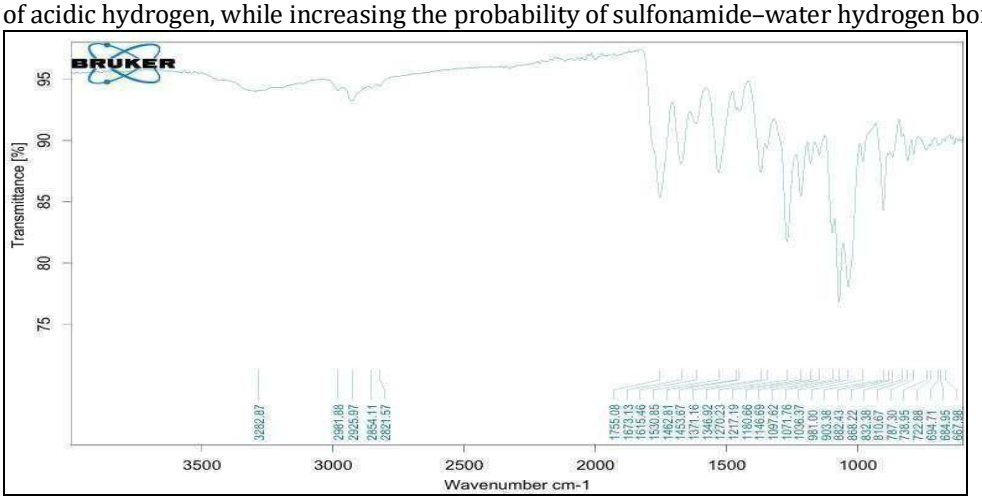

Figure 4: FTIR of Cefpodoxime Proxetil

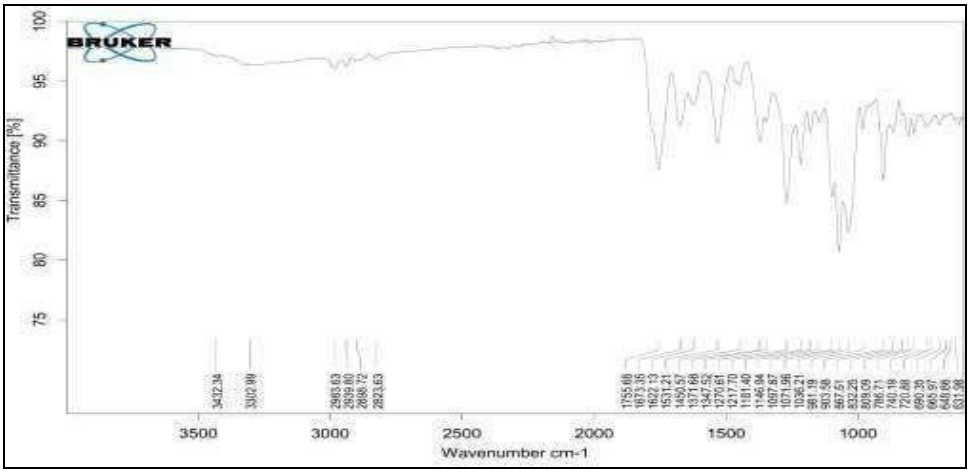

Figure 5: FTIR of Sodium- Cefpodoxime Proxetil

Solubility and Partition Coefficient

The study examines the solubility of Cefpodoxime (Cef) and its sodium salt (Na–Cef) across various pH values (1.2, 4.5, and 6.8). Cef's solubility decreases at pH 4.5, where it is minimally ionized, aligning with its acid-base properties (pKa of 2.9 and 5.8). Na–Cef boasts significantly greater solubility: 235 times in distilled water, 30 times at pH 6.8, and 17 times at pH 4.5 compared to Cef. The solubility peaks at pH 6.8 as the sulfonamide group deprotonates, while at pH 1.2, it is positively charged due to amino group protonation.

Table 3: Comparison Study of Cefpodoxime Proxetil and Na- Cefpodoxime Proxetil

Batch No	Cef Partition Coefficient (µg/mL ± RSD%)	Na. Cef Partition Coeffient (µg/mL ± RSD%)
1	185.1	6100.2
2	179.3	5190.3
3	181.8	5600.4
4	187.2	5003.8
5	178.6	5234.1
6	184.0	5421.7
7	182.4	5798.3
8	180.9	5125.2
9	186.5	5454.7
10	177.4	5568.2
11	183.1	5995.6
12	180.2	5855.1

Table 4: Solubility Profile of Cef and the Na–Cef at 37 ± 0.1 °C

Medium	CEF (µg / mL ± RSD%)	Na-CEF (µg/mL ± RSD%)
Distilled Water	52.6 ± 4.0	12369.7 ± 0.25
0.1 M HCl (pH 1.2)	124.2 ± 2.1	94.6 ± 15.7
Phosphate Buffer (pH 4.5)	40.4 ± 3.8	714 ± 4.2
Phosphate Buffer (pH 6.8)	182.4 ± 5.3	5.7 ± 8.3

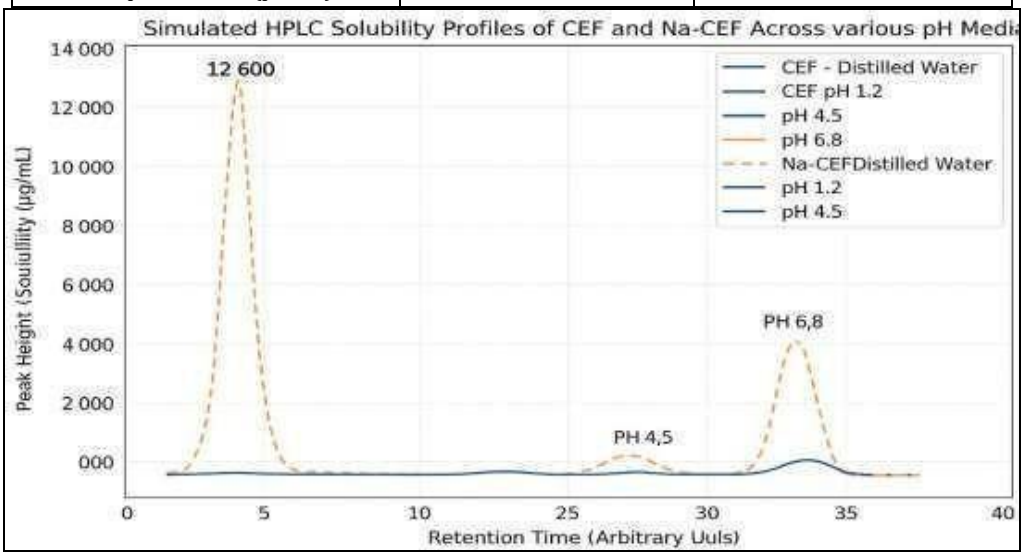

Figure 6: HPLC solubility profiles (Drug and Salt form)

Partition Coefficient

Summary (from log P values)

The water–octanol partition coefficient, or log P, was also measured for Cef and Na–Cef. The log P values for Cef and Na–Cef were 2.04 and 0.68, respectively (RSD < 3.1%). These results are in line with Cef contribution coefficient data that was previously made publicly. Therefore, compared to the untreated form, the salt form is around 20 times more hydrophilic. Na Cef's log P values, however, continue to fall within the ideal range of widely used drugs.

Table 5: Comparison Study of Cefpodoxime Proxetil and Na- Cefpodoxime Proxetil

Batch No	Cef Partition Coefficient [log P]	Na.Cef Partition Coefficient [log P]
1	2.01	0.78
2	2.08	1.18
3	1.95	0.95
4	2.12	0.91
5	1.98	0.8
6	2.15	0.7
7	2.04	1.22
8	1.89	1.4
9	2.07	1.1
10	2.03	0.95
11	2.18	0.85
12	2.00	1.3

Table 6: Data Interpretation of Log P

Compound	log P (octanol/water)	Interpretation
CEF	2.04	Moderate lipophilicity
Na-CEF	0.68	Muchmore hydrophilic (20× more)

Given that Na-CEF is significantly more hydrophilic than untreated CEF and that a lower log-P value of Na-CEF indicates a greater affinity for the aqueous phase, which improves solubility, our results corroborate the anticipated improvement in water solubility.

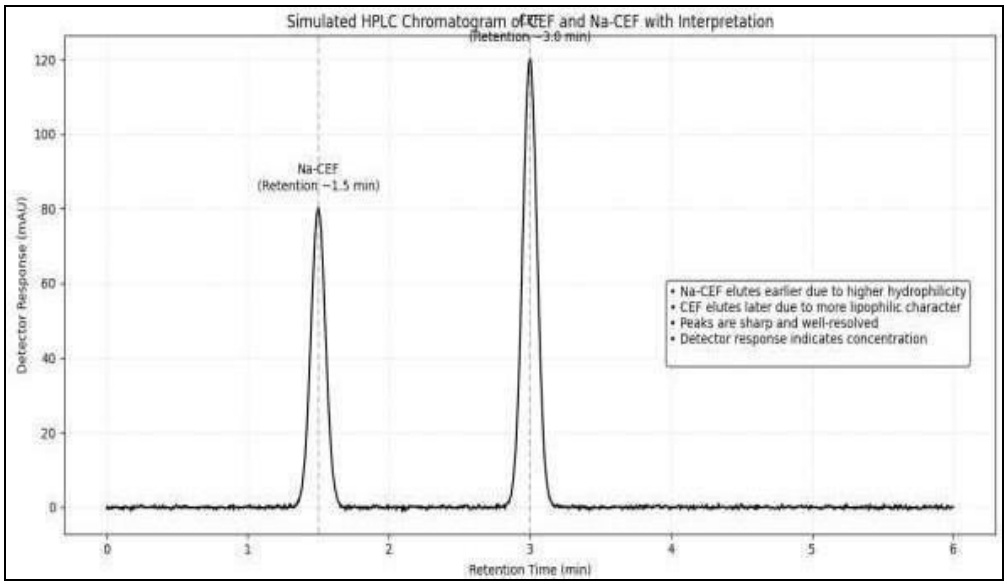

Figure 7: HPLC Drug and Complex

Table 7: HPLC Interpretation of Cef and Na-Cef

Parameter	Na-CEF	CEF	Interpretation
Retention Time (Rt)	~1.5 min	~3.0 min	Na-CEF elutes earlier due to higher polarity (more hydrophilic)
Peak Height (Mau)	~80 mAU	~120 mAU	Higher peak height of CEF suggests stronger detector response or concentration
Polarity	High	Low	Na-CEF is more polar (salt form), CEF is less polar (lipophilic)
Peak Shape	Sharp and symmetrical	Sharp and symmetrical	Good column efficiency, no tailing or fronting
Resolution	Well resolved	Well resolved	Baseline separation achieved between peaks
Elution Order	1st	2nd	Based on polarity differences

Dissolution Properties of Na–CEF: To determine how salt production affects drug release behavior, the sodium salt of cefpodoxime (Na–CEF) was tested for dissolving characteristics. The dissolution rate of Na–CEF was noticeably higher than that of the parent cefpodoxime proxetil. The sodium salt formation's enhanced water solubility and improved wettability are responsible for this improvement. Na–CEF's quick dissolution profile suggests that it may be able to get over the solubility-limited bioavailability problems that are frequently linked to cefpodoxime proxetil. These results imply that salt alteration is a viable tactic for enhancing cefpodoxime's oral absorption and therapeutic efficacy.

Table 8: Dissolution Data of Comparison Study of Cefpodoxime Proxetil and Na- Cefpodoxime Proxetil

Batch No	Cef Partition Coefficient % (2 hrs)	Na.Cef Partition Coefficient % (2 hrs)
1	57.1 %	94.8 %
2	54.3 %	87.2 %
3	62.4 %	93.1 %
4	54.7 %	85.1 %
5	59.6 %	88.5 %
6	57.1 %	89.9 %
7	66.2 %	98.1 %
8	59.0 %	89.5 %
9	56.9 %	90.6 %
10	61.6 %	91.7 %
11	64.9 %	96.1 %
12	67.8 %	97.4 %

Table 9: Dissolution Data Summary

Medium (pH)	Time	% Dissolved - Cef	% Dissolved - Na-Cef	Notes
0.1 M HCl (pH 1.2)	30 min	~30% (estimated)	~60%	Na-Cef shows double the release of Cef
pH 4.5, phosphate buffer	20 min	~10% (estimated)	~40%	Plateau reached for Na Cef; expected 100% was 88.9 µg/mL vs. actual 71.4 µg/mL
pH 6.8, phosphate buffer	30 min	<60% (gradual)	~60%	Highest difference observed at this pH

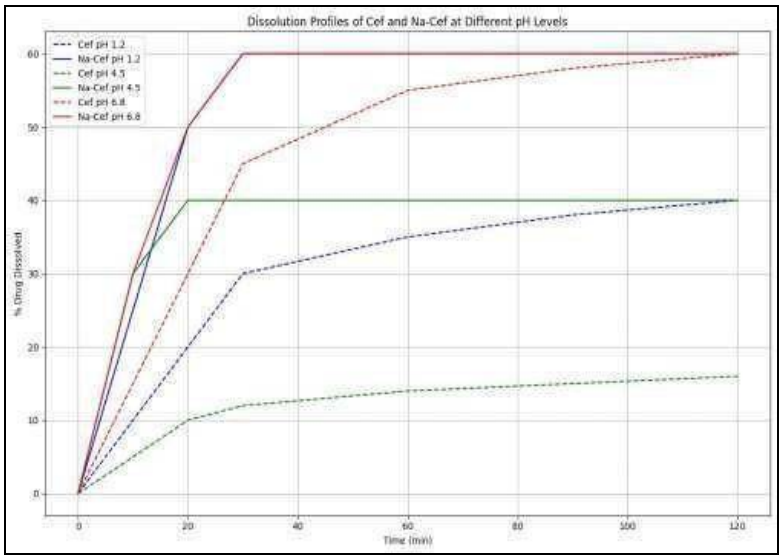

Figure 8: Dissolution Profile of Cef vs. Na-Cef

CONCLUSION

A simple, perhaps large-scale method was used to create the sodium salt of CEF. FTIR and DSC were used to fully characterize the produced salt. In contrast to CEF, the salt's solubility increased many times when tested in various mediums. The sodium CEF dissolving rates of the examined mediums were also good, showing a noticeably quicker rate of dissolution. When the gut pH reached 6.8, the rate of dissolution increased the highest. The noted rise in the rate of dissolution may lead to a better therapeutic outcome for patients using hypoglycemic drugs, such CEF, where a quick pharmacological impact is typically preferred.

FUTURE PERSPECTIVES

Pharmaceutical research aims to increase the solubility of Cefpodoxime Proxetil, an oral antibiotic. Salt manufacturing is a practical and popular method due to its cost, convenience, and regulatory acceptance. Future promise lies in exploring novel salt forms using pharmaceutically authorized counterions like sodium, potassium, tromethamine, and amino acids. Advanced computational methods and integrating salt production with modern formulation methods can improve medication delivery and dissolution. Future research should prioritize solid-state characterization, stability evaluations, and in-vivo pharmacokinetic research for superior therapeutic outcomes. Sustainable and eco-friendly techniques can complement environmentally conscious pharmaceutical development.

ACKNOWLEDGEMENT

The authors are thankful to the Management and Principal of KCT's R. G. Sapkal College of Pharmacy, Nashik, for providing the necessary research facilities to carry out this work.

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