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Nanotechnology-Inspired Approaches for Improving the Stability of Cephradine Dry Suspension: The Role of Pharmaceutical Excipients

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ABSTRACT

Cephradine, a first-generation cephalosporin and β-lactam antibiotic, remains an important therapeutic agent for bacterial infections, particularly in pediatric practice where dry suspensions are preferred. The stability of cephradine dry suspensions is a critical determinant of therapeutic efficacy, patient compliance, and formulation acceptance. Pharmaceutical excipients including suspending agents, preservatives, sweeteners, stabilizers, and flavoring agents play a vital role in maintaining physicochemical stability, bioavailability, and palatability. This review highlights the functional contributions of key excipients, with special emphasis on citric acid as a multifunctional stabilizer, pH modulator, and absorption enhancer. In addition, nanotechnology-enabled strategies are discussed as promising future tools for enhancing cephradine stability. Approaches such as nanoencapsulation, nanostructured stabilizers, and lipid-based nanocarriers can protect β-lactam antibiotics from hydrolysis, improve controlled release, and extend shelf life. By integrating conventional excipient science with nanotechnology perspectives, this review underscores the potential for more robust and patient-friendly cephradine dry suspension formulations.

Keywords: Cephradine, Cephalosporins, β-lactam Antibiotics, Dry Suspension, Excipients, Formulation, Citric Acid, Pharmaceutical Additives, Drug Delivery, Nanotechnology, Nanocarriers, Drug Stability, Nanoformulation.

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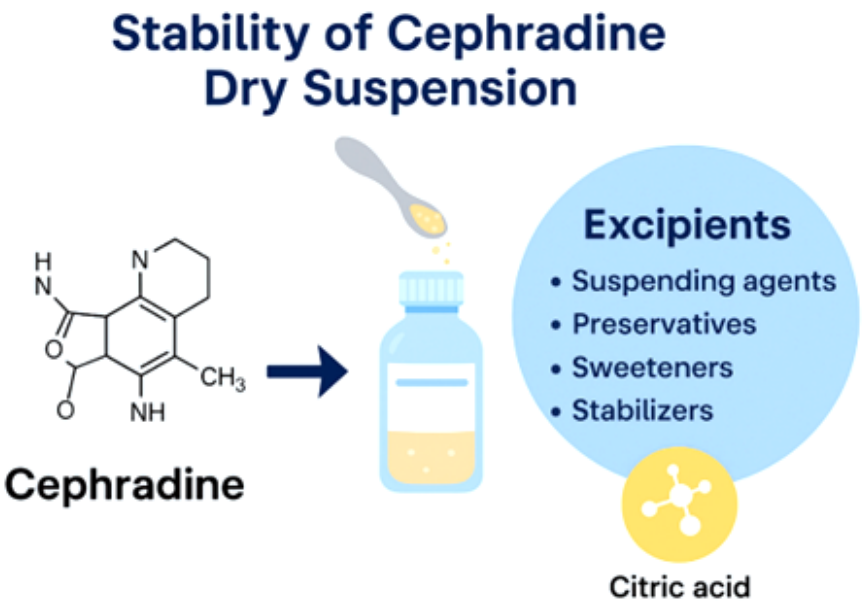
GRAPHICAL ABSTRACT



INTRODUCTION

Cephalosporins remain one of the most extensively prescribed classes of β-lactam antibiotics due to their broad-spectrum activity, favorable safety profile, and availability in diverse dosage forms. Among them, cephradine, a first-generation cephalosporin, exhibits potent antibacterial activity against a wide range of Gram-positive and selected Gram-negative pathogens. Its structural features, including a methyl substituent at position 3 and a (2R)-2-amino-cyclohexa-1,4-dien-1-ylacetamido group at the cephem nucleus, are central to its antimicrobial efficacy. Like other β-lactams, cephradine acts by binding to penicillin-binding proteins (PBPs), thereby inhibiting bacterial cell wall synthesis and ultimately leading to cell lysis. Clinically, cephradine is widely employed in the treatment of respiratory, urinary, skin, and soft tissue infections, and it is available in multiple formulations such as capsules, intravenous injections, and oral dry suspensions. The latter holds particular importance in pediatric and geriatric patients, who often face difficulty swallowing solid dosage forms.

The formulation of stable dry suspensions requires careful optimization of excipients, reconstitution properties, and physicochemical stability to maintain therapeutic efficacy. Excipients such as suspending agents, preservatives, sweeteners, and stabilizers ensure not only redispersion and palatability but also protection of the active drug from degradation. Buffering agents like citric acid help maintain pH-dependent stability, while suspending agents prevent caking and sedimentation. Stability remains a critical concern for cephradine, as its β-lactam ring is highly susceptible to hydrolytic degradation. To safeguard efficacy throughout the shelf life, stability assessments typically evaluate reconstitution time, sedimentation volume, viscosity, pH consistency, microbial preservation, and in-vitro drug release. Beyond conventional excipient science, recent advances in nanotechnology provide new strategies for addressing stability challenges in cephradine suspensions. Nanocarriers, nanoscale stabilizers, and nanoencapsulation techniques have demonstrated the ability to shield β-lactam antibiotics from hydrolysis, enhance bioavailability, and enable controlled or targeted delivery. Nanosized excipients such as fumed silica or nanocellulose further improve flow properties and reduce degradation risks, complementing traditional formulation approaches.

This review therefore provides a comprehensive overview of cephradine dry suspensions, emphasizing the role of pharmaceutical excipients, stability considerations, and quality evaluation in line with pharmacopeial standards. By integrating conventional formulation knowledge with nanotechnology-enabled perspectives, it highlights current challenges, emerging solutions, and future directions for designing stable, effective, and patient-friendly cephradine suspensions.

Antibiotics (β-lactam)

Antibiotics are extensively used in the ROY. During the past year's antibiotics consistently occupied the number one position in the country's pharmaceutical imports. Antibiotics represent 14 - 24 % of the total expenditure of pharmaceutical supplies as described in the official annual reports. The SBDMA registration records for pharmaceutical products show that, antibiotics are a leading therapeutic category. Ampicillin, amoxicillin, cephalexin, and cephradine are the top four antibiotic constituting 24 %, 34 %, 21 % and 19 %, of the total value of antibiotic imports, respectively.

The four antibiotics are manufactured by 16 - 39 companies consisting of Non-Research Based form the 3rd world (NRB, 61 %), Research Based from developed countries (RB, 30 %), and Local Manufacturing from ROY (LM, 9 %, Al-Mekhlafi, 1998). Extensive use and high demand for antibiotics in the ROY is rather a result of irrational utilization. Irrational utilization of antibiotics involves distribution, dispensing, prescribing and patient's compliance. However, under the present situation, it is rather difficult to assess or evaluate the consumption of this agent and/or relate it to actual needs. Demand, in this situation is to a great extent an artifact of actual needs [1].

Cefradine is a first-generation cephalosporin and broad spectrum beta-lactam antibiotic. β-lactam group of antibiotics are considered as most diverse antibacterial agents that contains beta lactam ring in their structure. Penicillin was the first beta lactam antibiotic and it was extracted from Penicillium notatum [2]. Major classifications are penicillin derivatives (penams), cephalosporins (cephems), monobactams (aztreonam) and carbapenems (meropenem).

These antibiotics are recommended for the treatment and prevention of bacterial infections that are prone to occur. Antibiotics called -lactams are used to prevent and treat infections brought on by bacteria. The majority of -lactam antibiotics function by preventing the bacterial cell wall's production. By interfering with the bacterial cell wall's production, beta-lactams stop bacteria from growing [3,4]. Mechanism of action of beta lactam antibiotics is provided in Figure 1.

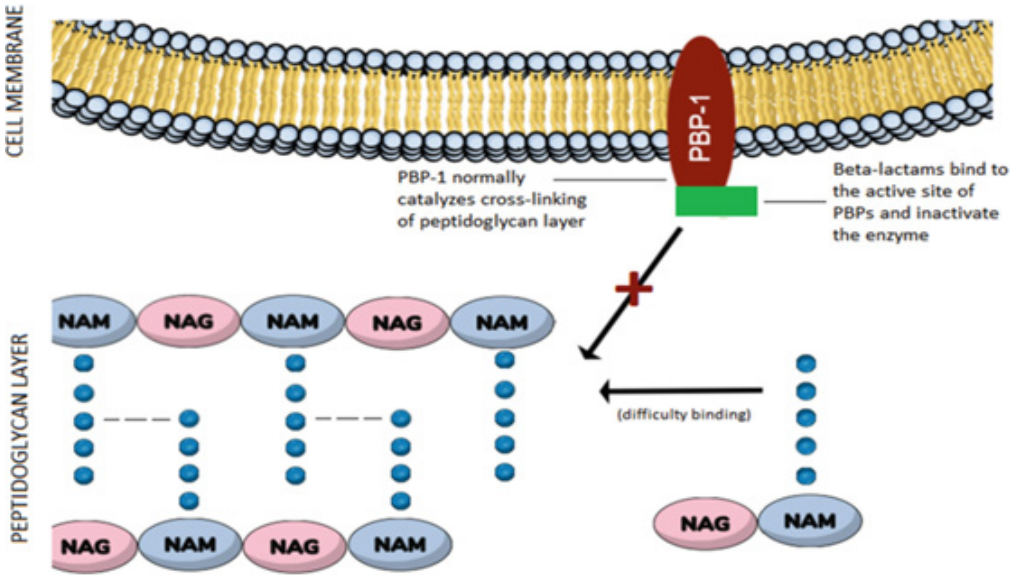


Figure 1. Mechanism of action of beta lactam antibiotics [5].

Among these antibiotics penicillin namely Cephradine is selected as target antibiotics. Increased production of biochemical intermediates that is competitively antagonized by the drug in sensitive cells is also considered as a mechanism of bacterial resistance. Beta lactams are narrow spectrum group of antibiotics and acts as bacteriostatic by preventing the synthesis of peptidoglycan cell wall of bacteria, that is extremely active for the Gram-positive genera like Streptococcus, Gonococcus, & Staphylococcus. Yet, it is difficult for humans or animals to completely metabolize β-lactams, then discharge to the aquatic systems [6] Core structure of beta lactam antibiotics is shown in Figure 2.

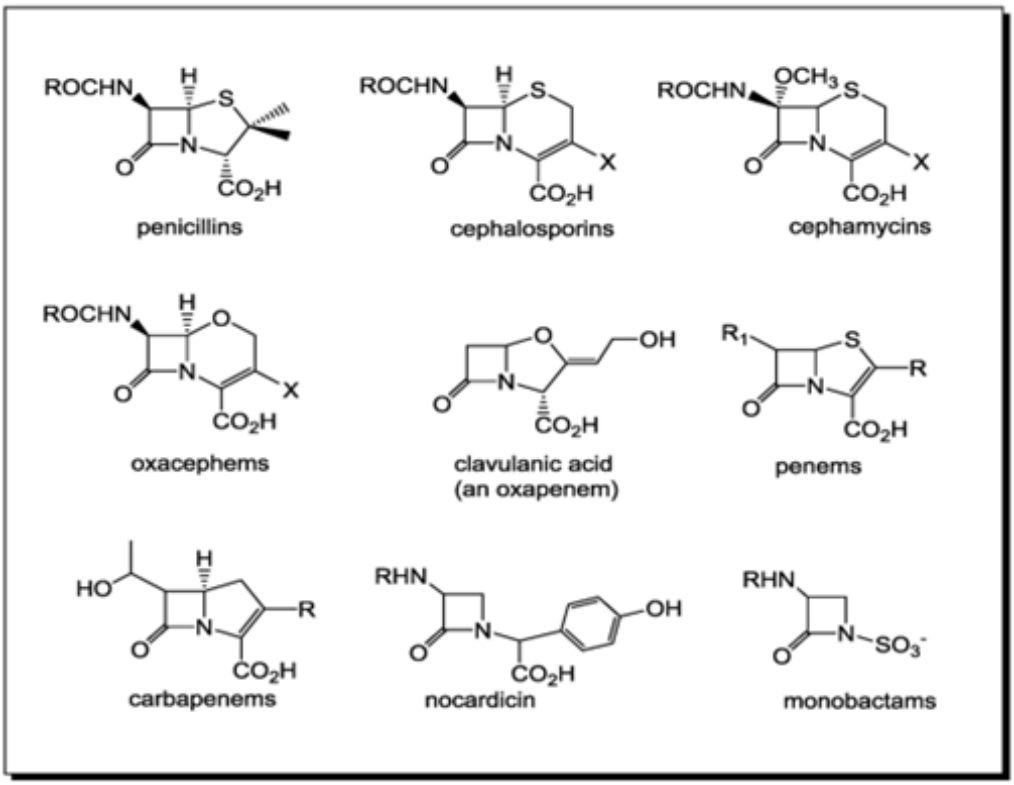


Figure 2. Core structures of beta lactam antibiotics [7].

Cephradine

Cephradine is a first-generation cephalosporin antibiotic that has limited gramme negative coverage but is effective against gramme positive organisms. Cefradine inhibits the third and last step of bacterial cell wall formation by binding to penicillin-binding proteins, which breaks the peptidoglycan cross-linkage and causes cell lysis. This substance is a member of the group of organic substances called n-acyl-alpha amino acids and derivatives. These are substances that have an acyl group attached to the nitrogen atom at the end of an alpha amino acid (or a derivative thereof). Similar to cephalexin in terms of chemistry, pharmacology, and antibacterial properties is cephradine [8].

Structure activity research on cephradine have largely paralleled work in semisynthetic pencillins. Indeed, the primary objective of cephalosporin SAR studies has been the opposite; to increase relatively low intrinsic activity of the natural cephradine as compared to the natural penicillins. Studies involving 7-acyl group modification have been the most profitable source of clinically useful antibiotics. Alterations of this side chain have played a significant role in influencing level and breadth of antibacterial activity. At 3-position variations comprise the second most important type of alteration of the cephradine structure. Indeed, the cephradine that exhibit the highest absorption efficiencies are derivatives of 7-Anhydro Desacetyl Cephalosporic Acid (ADCA) with methyl group at the 3-position.

Measurement of cephradine and other cephalosporin's levels in biological fluids has been described using several analytical methods. Lin et al (2000) used electrophoresis technique in their determinations. The method showed good selectivity and was found to useful for the study of cephalexin stability in pharmaceutical preparations [9-11]. Oral suspension of cephradine is shown in Figure 3.

Figure 3. Cephradine (SNB Pharma. (n.d.). SN-SEF dry suspension (Cephradine). Retrieved August 21, 2025, from: https://snbpharma.com/sn-sef-dry-susp1.

METHODOLOGY

This review was conducted by systematically collecting, screening, and analyzing relevant literature on cephradine dry suspensions, pharmaceutical excipients, and nanotechnology-enabled formulation strategies. A comprehensive search was performed using major scientific databases, including PubMed, ScienceDirect, SpringerLink, Scopus, and Google Scholar, covering the years 2001–2025 to capture both classical and recent advancements. The search was carried out using combinations of keywords such as "Cephradine stability", "Cephradine dry suspension", "β-lactam antibiotics stability", "pharmaceutical excipients", "citric acid stabilizer", "nanocarriers", "nano-enabled drug delivery", and "nanotechnology in antibiotics".

Studies were included if they (i) reported on the formulation, stability, or excipient role in cephradine dry suspensions, (ii) investigated excipient–drug interactions or stabilization mechanisms, or (iii) presented nanotechnology-based strategies for β-lactam antibiotic stabilization. Both original research articles and review papers were considered, while conference abstracts without sufficient data and non-English publications were excluded.

The information was critically reviewed, consolidated, and organized thematically into sections addressing the role of excipients, stability challenges, citric acid as a multifunctional excipient, overall excipient impact, limitations, and emerging nanotechnology perspectives. This methodological approach ensured the inclusion of diverse, relevant, and up-to-date evidence to provide a comprehensive and balanced overview of cephradine suspension stability.

MECHANISM OF ACTION OF CEPHRADINE

Cephradine, a first-generation cephalosporin antibiotic, with a spectrum of activity similar to cefalexin. Cephradine is a beta-lactam antibiotic, just as penicillins. Solubility in lipid is a crucial consideration since the lipoprotein structures that make up the cell membrane serve as semi-permeable lipid membranes. By interacting with certain penicillin-binding proteins (PBPs) present inside the bacterial cell wall, it hinders the third and final stage of bacterial cell wall development as shown in Figure 4. Cephradine probably interferes with an autolysin inhibitor, which therefore causes bacterial cell lysis to occur by the action of autolytic enzymes like autolysins.

It is a compound that is related chemically to helvolic acid and to fusidic acid; asteroid antibiotic elaborated by Fusidium cocuneum. Cephalosporin N (Penicillin N) is an N-acyl derivative of 6-amino penicillanic acid and is inactivated by pencillanase. It has a polar side chain not previously demonstrated in antibiotics, extremely hydrophilic because of the zwitter ionic side chain and yields penicillamine when hydrolyzed [12,13].

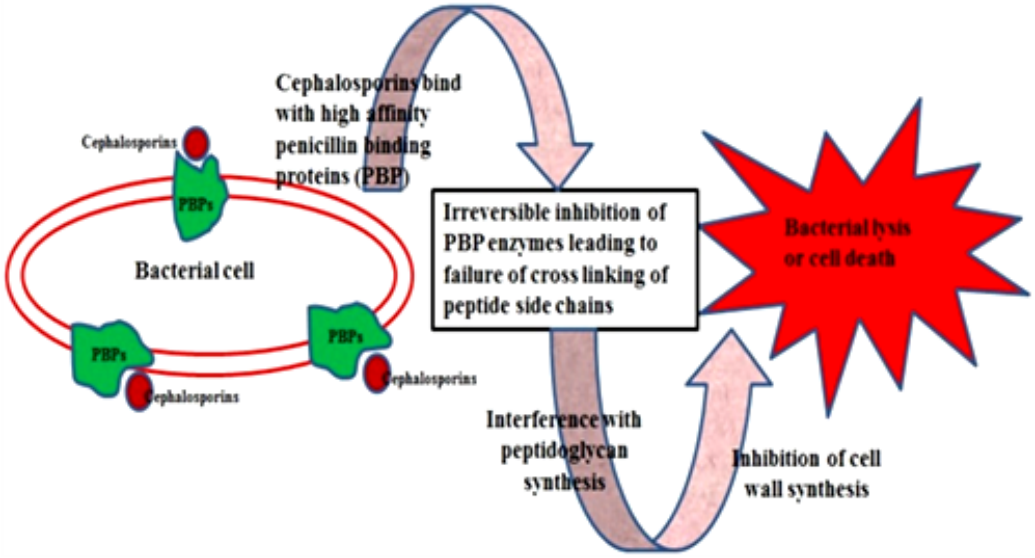


Figure 4. Mechanism of action of Cephradine [14].

CHEMISTRY OF CEPHRADINE

The only cephalosporin derivative that is offered in parenteral and oral dose forms is cephradine. Chemically, it is quite similar to cephalexin (it might be thought of as a partly hydrogenated derivative of cephalexin), and it shares many of the same pharmacokinetic and bactericidal characteristics with cephalexin. Cephradine is a zwitterion, meaning that it has both an acidic and a basic group (the amino function on the acyl side chain) (the carboxyl at the position 4 of the thiazin ring) as shown in Figure 5. Cephradine occurs largely as an inner salt at physiological pH since both groups are present. With exogenous acids or bases, it starts to create a salt on the opposite side of these values.

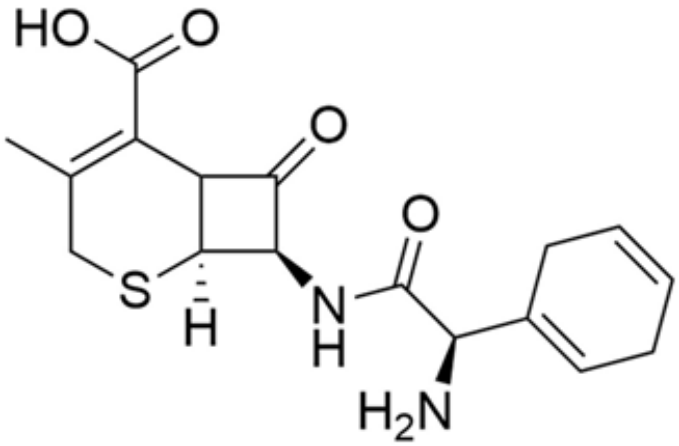


Figure 5. Chemical structure of Cephradine [15].

Cephalosporins are chemically based on the 7-aminocephalosporanic acid (7-ACA) nucleus, which consists of a β-lactam ring fused with a six-membered dihydrothiazine ring. This bicyclic system is more resistant to hydrolysis than the penicillin nucleus, mainly because the dihydrothiazine ring provides steric protection to the strained β-lactam. A characteristic feature is the carboxyl group at position 4 of the thiazine ring, which imparts acidity and enhances water solubility. The variations in activity and stability across different cephalosporins are largely attributed to substitutions at positions 7 and 3 of the nucleus. Modifications at position 7, where the acylamino group is located, strongly influence antibacterial activity and resistance to β-lactamase enzymes. For example, the introduction of methoxy or oxyimino substituents at this site enhances resistance to enzymatic hydrolysis and broadens the antibacterial

spectrum, a hallmark of later generations. Substituents at position 3, such as methyl or heteroaryl groups, primarily affect pharmacokinetic properties, including oral absorption, lipophilicity, and plasma protein binding. In some derivatives, bulky heterocyclic groups at this position extend the half-life, as seen in ceftriaxone [16].

Across successive generations, the chemical modifications become more sophisticated. First-generation cephalosporins generally have simple alkyl or amino side chains, conferring modest stability and narrow activity. Second-generation compounds often incorporate carbamoyl or methoxy groups, which enhance resistance to β-lactamases. The third generation is marked by the addition of oxyimino groups that dramatically increase stability against hydrolysis, particularly from Gram-negative bacterial enzymes. In fourth-generation derivatives, quaternary ammonium-like substituents are found at position 3, increasing polarity and improving penetration into bacterial cells. Fifth-generation cephalosporins, on the other hand, carry unique side chains that enable binding to altered PBPs, such as PBP2a in methicillin-resistant Staphylococcus aureus (MRSA).

Chemically, most cephalosporins are zwitterionic at physiological pH, since they contain both acidic and basic groups. This property influences their solubility, salt formation, and membrane transport. The zwitterionic nature allows them to dissolve well in aqueous environments, which is advantageous for parenteral formulations. Despite this, the strained β-lactam ring remains the most reactive part of the molecule, making the cephalosporins inherently unstable under acidic or basic conditions, a factor that must be considered during formulation and storage [17].

PROPERTIES OF CEPHRADINE

Physical properties of Cephradine

Cephradine is a crystalline powder that ranges in colour from white to cream. It is somewhat soluble in water but insoluble in ether, chloroform, and 96% ethanol. It is freely soluble in propan,1,2-diol and soluble in 70 parts of methanol. Physical characteristics of cephradine metal complexes are given in Table 1.

Table 1. Physical characteristics of cephradine metal complexes

Complex	Colour	Physical State	Melting Point (°C)	Solubility	Remarks
Cephradine–Cu(II)	Greenish-blue	Crystalline powder	235–238	Soluble in DMSO, partially in ethanol	Stable, paramagnetic
Cephradine–Ni(II)	Pale green	Crystalline powder	240–243	Soluble in DMSO, sparingly soluble in methanol	Octahedral geometry
Cephradine–Co(II)	Pinkish	Amorphous solid	230–233	Soluble in DMSO, sparingly soluble in water	High stability constant
Cephradine–Zn(II)	White	Crystalline powder	228–231	Soluble in DMF, insoluble in water	Diamagnetic, thermally stable
Cephradine–Fe(III)	Brown	Amorphous powder	245–248	Soluble in DMSO	Shows ligand-to-metal charge transfer
Cephradine–Mn(II)	Light brown	Crystalline powder	232–236	Soluble in methanol	Octahedral coordination

Pharmacological properties

Cephradine is stable in gastric acid. Cephradine is not absorbed from the stomach but is totally and rapidly absorbed in the upper intestine. It is widely distributed in the tissues and high concentrations are found in all organs especially the liver and the kidney. Cephradine is reported to be about 15 to 20 % protein bound [18].

Interactions of Cephradine with drugs

Interaction of cephradine with the intestinal absorption of D-gluctose is competitive. Both compounds compete for dipeptidase for absorption in the intestine. Concomitant administration of cephalosporin's and aminoglycosides e.g. amikacin may result in an increased risk of nephrotoxicity than use of either drug alone.

Therapeutic Applications of Cephradine

- Cephradine is used to treat infections caused by bacteria.
- Cephradine 500mg for 5 days' course was preferred as prophylactic antibiotic in dental procedures.
- Cephradine fights bacteria in the body.
- Cephradine is used to treat infections caused by bacteria,

including upper respiratory infections, ear infections, skin infections, and urinary tract infections.

- Cephradine may also be used for other purposes not listed in this medication guide [18].

EXCIPIENTS USED IN CEPHRADINE DRY SUSPENSIONS

Excipients play a critical role in the formulation of cephradine dry suspensions by ensuring product stability, palatability, uniformity, and therapeutic efficacy. Since cephradine is a β-lactam antibiotic that is prone to hydrolysis, carefully selected excipients help maintain its stability in the reconstituted form and extend its shelf life. Common excipients used in cephradine dry suspensions include:

Xanthan gum

A natural polysaccharide, xanthan gum is used in medicinal products as a viscosity and suspending ingredient. It serves as a suspending agent, emulsion stabiliser, and foam enhancer in semi-solid, liquid, and topical formulations in a wide range of pharmaceutical applications [19].

Aerosil 200

Fumed silica is amorphous nonporous silica prepared by a flame hydrolysis of SiCl4. Its surface chemistry is hydrophilic due to the presence of hydroxyl or silanol groups (-OH) on the surface. Aerosil R972 was assumed to be associated with its hydrophobic surface property, which might have resulted in reduced moisture uptake. Thus, Aerosil R972 was selected to be the coating agent for manufacturing prototype tablet formulations. The primary particles are nanosized, however, they readily agglomerate such that the average particle size of this grade is about 50μm. It is a widely used excipient, stabiliser and additive in pharmaceuticals, cosmetics, and food products [20-22].

Dried sugar

One significant category of chemicals used in pharmaceuticals is excipients based on sugar. Pharmaceutical actives have a harsh taste; however, sugar-based excipients can help conceal that flavour or at least make the active ingredient more palatable [23,24].

Neotame

Artificial sweeteners are crucial sugar alternatives that are frequently used in food, beverages, and pharmaceutical items to improve flavour without adding extra calories. An artificial sweetener with no calories is called Newtame [25].

Saccharine sodium

Saccharin is an artificial sweetener with effectively no food energy. It is about 550 times as sweet as sucrose but has a bitter or metallic aftertaste, especially at high concentrations. Saccharin is used to sweeten products such as drinks, candies, cookies, and medicines [26]. Saccharin is non-nutritive and is used to add sweetness to beverages and foods without the calories or detrimental effects of consuming sugar. Using artificial sweeteners can help you reduce your consumption of sugar [27].

Sodium benzoate

Additives are widely used for various purposes, including preservation, coloring, and sweetening. The preservatives are added to stop or delay nutritional losses due to microbiological, enzymatic or chemical changes of foods and to prolong the shelf life and quality of foods. Sodium benzoate inhibits the growth of potentially harmful bacteria, mold, and other microbes in food, thus deterring spoilage. It's particularly effective in acidic foods. Therefore, it's commonly used in foods, such as soda, bottled lemon juice, pickles, jelly, salad dressing, soy sauce, and other condiments [28].

Talcum powder

Magnesium silicate (MgSiO3) when hydrated is most commonly known as "talc". In drug formulations it is used as anticaking agent to improve powder flow. Its safety approved by FDA & is compatible with Cephradine. Talc absorbs moisture and reduces friction, thus minimizing sweat production, and preventing fungal infections. Expert says "If you suffer from sweaty feet or have rough patches on your feet, elbows, just rub a bit of antiperspirant powder on those areas [29].

Magnesium Stearate

The most widely used lubricant in the pharmaceutical sector is magnesium stearate (MS), which has a low friction coefficient and low shear strength and already lubricates the mass in tiny amounts [30]. An ingredient called magnesium stearate is typically included in pill form pharmaceuticals. It is viewed as a "flow agent." It keeps the different components from adhering to one another and the equipment used to make the capsules. It enhances the consistency and quality assurance of pill capsules [31].

Colour yellow tartrazine

Food colorants are added to foods and beverages to restore the color lost during processing and to enhance the color of the food or to uniform the color of the final product. Tartrazine is an orange-yellow azo dye used to colour foods, soft drinks and drugs. It is safe for most people, but some are sensitive to it and may suffer adverse reactions [32-34].

Citric acid anhydrous

Citric acid is an organic acid and a natural component of many fruits & fruits juices. it is used as an excipient in pharmaceutical preparations due to its antioxidants properties. It is used as preservative & as acidulant to maintain PH. Citric acid anhydrous is non-toxic and has a low reactivity. Citric acid helps with energy metabolism, the absorption of minerals, and the prevention or treatment of kidney stones [35,36].

Flavour Banana

Banana flavor is added to the formulations specially to make its taste & smell better for children use flavored have no incompatibilities with Cephradine [37].

Flavour orange

The citrus flavour is among the most popular fruit flavors for pharmaceuticals products and beverages. The flavour of orange juice has been studied more than that of any other type of citrus fruit [38].

IRREVERSIBLE ADVERSE EFFECTS OF CEPHRADINE

The severe or irreversible adverse effects of Cephradine, which gives rise to further complications include;

- Most commonly it can cause Diarrhea, nausea and vomiting.
- Allergic Reactions includes Skin rash, shortness of breath, itching and hives.
- It can also cause decrease in white blood cells.
- Other problems associated with Cephradine are unusual bleeding, bruising, unpleasant taste, sore throat and vaginal infection.
- Cephradine produce potentially life threating effects which include thrombophilibitis, anaphylactic reaction which are responsible for the discontinuation of Cephradine therapy.
- The sign and symptoms that are produced after acute over dosage of Cephradine include Indigestion, Nausia, Vomiting, Intense abdominal pain & Convulsions.
- Cephradine interacts with minerals (iron and zinc) and form a complex. This mineral cephradine complex leads to decrease in the absorption of the drug. Vitamins and other compounds also interact with cephradine. Furthermore, the bulk of food and high viscosity leads to retardation of cephradine drug. Besides, the typical Yemeni food (Bread) is made of wheat or sorghum, which can be considered rich in bran and fibers. Such diets usually shorten the residence of the drug and produce large quantities of feces. Consequently it is recommended here, for optimal absorption of cephradine, that the capsule should be swallowed before the administration of common Yemeni food with interval time not less than two hours. This time is enough to prevent interference of common Yemeni food (Al-Sayadeyah) with cephradine absorption.
- It is also associated with several health, social, economical and behavioral problems. Several toxins are known to be used in its cultivation which represents a very serious health hazard [39-46].

ROLE OF CITRIC ACID

Citric acid (CA) is a naturally occurring antioxidant, initially obtained from lemon juice, and widely used as a flavouring agent and preservative in foods such as soft drinks and candies. In pharmaceuticals, it plays multiple roles including stabiliser, preservative, disinfectant, acidulant in mild astringent treatments, and flavour enhancer in syrups, solutions, and elixirs. Beyond its use as an excipient, CA is a versatile natural monomer essential in metabolism regulation, mineralization, neuronal excitation, and renal stone prevention. It contributes to polymer construction with diol monomers via simple, catalyst-free polycondensation, forming ester bonds that allow hydrolytic degradation. Its biocompatibility and role as a cross-linker enhance cell adhesion and desired material properties, while its hygroscopic nature may trigger unwanted autocatalyzed reactions in the presence of moisture. CA is also valuable as a pH modulator, absorption enhancer, and substitute for ligands like chitosan and PEG, with its short chains improving nanoparticle coating. Moreover, CA enhances drug solubility, including glucagon, and supports the formation of nanocarriers and spinel structures as a reducing, coating, and modulating agent. Owing to its multifunctionality,

CA significantly improves drug dissolution, targeted delivery, and absorption, and in specific forms, it even exhibits fluorescence for biomedical applications [47].

Beyond its conventional functions, citric acid has also been employed in nanotechnology as a green reducing and capping agent for nanoparticle synthesis, as well as a coating material for improving the stability and bioavailability of drug-loaded nanocarriers [48-50]. Figure 6 shows pharmaceutical applications of citric acid.

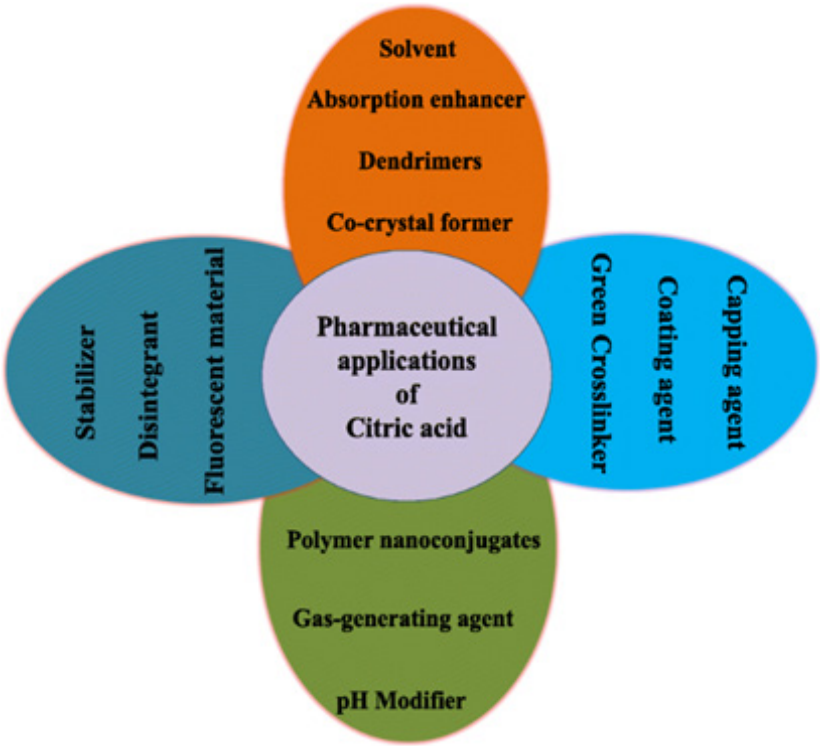


Figure 6. Pharmaceutical applications of citric acid [47].

Effect of Citric acid on Cephradine

By itself, citric acid can effectively stop bacterial growth or improve the antibacterial effects of the antibiotic beta lactam (Cephradine). It has been demonstrated that some organic acids, such as citric and lactic acids, can change how permeable the bacterial outer membrane is. Bacteria may become more sensitive to an antibiotic chemical that by itself is unable to enter deeper bacterial targets by increasing the permeability of their cell walls and plasma membranes. The outer membrane permeability of Gram-negative bacteria is increased when they are exposed to acidic chemicals like citric acid and lactic acid. In light of this, we hypothesised that this impact on permeability would improve the antibacterial effectiveness of antibiotics in the treatment of Gram-negative bacteria [51]. Citric acid's ability to increase changes in outer membrane permeability suggests that it likely enables beta lactam antibiotics to directly act on the inner membrane, interfering with bacterial ion transport activity. Lipopolysaccharide may be involved in bacterial molecular defense against hydrophobic substances, and citric acid has the ability to improve the permeability of bacterial outer membranes [51].

The removal of growth inhibition in a medium in which the acidic pH brought on by citric acid was mitigated demonstrated that the bacterial susceptibility to antibiotics was pH dependant. Contrary to citric acid, none of the other organic acids examined, even under similarly acidic circumstances, enhanced antibiotic activity. These results suggest that citric acid specifically, as well as its function as a weak acid, was necessary for the sensitization of cells to beta lactam antibiotic [52].

As a result, it was anticipated that CA would interact with antibiotics quickly, change their chemical stability, and increase their efficacy all at once. The image depicts the molecular structures of the antibiotic cephradine and CA. These structures exhibit some potential binding sites, such

as carboxylic acid, ketone, and amine in the structure; and a hydroxyl group in addition to the three carboxylate moieties in CA as the counterpart. This combination of antioxidants and antibiotics is suitable for topical preparations, such as pills and capsules. [53].

OVERALL IMPACT OF EXCIPIENTS ON CEPHRADINE FORMULATIONS

Excipients, once regarded as inert additives, have emerged as critical functional components in modern pharmaceutical formulations. In the case of Cephradine dry suspensions, their impact is particularly significant due to the inherent instability of the β-lactam structure and the need to ensure therapeutic consistency after reconstitution. Excipients influence almost every stage of the product's life cycle, from manufacturing and packaging to storage, reconstitution, and patient administration.

For instance, suspending agents such as sodium carboxymethyl cellulose, xanthan gum, or microcrystalline cellulose ensure homogenous distribution of particles upon reconstitution, thereby improving dose uniformity and minimizing sedimentation. Buffering agents play an equally vital role by maintaining the pH within a stable range, preventing hydrolysis of Cephradine during storage. Without suitable stabilizers, the antibiotic may undergo degradation, leading to reduced potency and therapeutic failure [18].

From the patient compliance perspective, sweeteners and flavoring agents are indispensable in pediatric formulations, masking the inherent bitterness of the antibiotic and enhancing acceptance. Furthermore, excipients such as antimicrobial preservatives ensure microbiological safety of the reconstituted suspension during the dosing period. Collectively, excipients are not merely auxiliary components but active contributors that safeguard the stability, bioavailability, and acceptability of Cephradine formulations. Their rational selection and optimization represent a cornerstone of effective formulation design, underscoring their overall impact on the success of Cephradine therapies [18].

Emerging evidence suggests that nanosized excipients, such as fumed silica, nanocellulose, and functionalized nanopolymers, provide enhanced stabilization by improving surface interactions, flow properties, and resistance to degradation, thereby offering additional advantages over conventional excipients.

Table 2. Comparison of Conventional Excipients and Nanotechnology-Enabled Strategies for Improving Stability of Cephradine Dry Suspensions

Approach/Excipient	Conventional Role in Formulation	Nano-Enabled Role/Advantage	Examples/Notes
Citric acid	pH modulation, preservative, stabilizer	Nanoparticle coating, green reducing/capping agent, enhances permeability	Citric acid-coated nanoparticles improve drug stability and bioavailability
Fumed silica (Aerosil 200)	Flow enhancer, anti-caking agent	Used as nanosized stabilizer with high surface area for moisture protection	Nanostructured silica reduces hydrolysis in β-lactams
Polymeric excipients (e.g., xanthan gum, CMC)	Suspending agents, viscosity control	Nano-hydrogels and nanogels provide sustained release and moisture resistance	Polymeric nanocarriers encapsulating antibiotics
Sweeteners (e.g., saccharin, neotame)	Taste masking, palatability	Incorporated in nanosponges or nanoparticle matrices for improved patient compliance	Cyclodextrin nanosponges with sweeteners for oral suspensions
Lipid-based excipients	Solubility enhancement, taste masking	Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) protect drug and allow controlled release	SLNs used for β-lactam encapsulation
Nanostructured stabilizers	Limited protection against degradation	Nanocellulose, nanosilica, and polymeric nanoparticles enhance physical and chemical stability	Prevent caking and aggregation in suspensions

CHALLENGES AND LIMITATIONS

While excipients offer undeniable advantages, their inclusion in Cephradine formulations is not without challenges. The foremost limitation arises from the intrinsic instability of Cephradine. Being a β-lactam antibiotic, Cephradine is highly susceptible to hydrolytic cleavage, and in aqueous systems, even slight variations in pH or excipient interactions may accelerate degradation. This necessitates stringent control of excipient quality and compatibility testing, which can be resource- and time-intensive.

Another major concern relates to drug–excipient interactions. While some stabilizers prolong shelf life, others may inadvertently catalyze degradation pathways. For example, certain reducing sugars used as sweeteners can interact with

amino groups in antibiotics, potentially initiating Maillard-type reactions that compromise both stability and appearance of the formulation. Similarly, hygroscopic excipients increase the risk of moisture uptake during storage, leading to caking, poor flow properties, and loss of reconstitution quality.

On the manufacturing side, the need for uniform powder flow and compressibility remains a challenge, as excipients with high bulk density may segregate from the drug during blending. Post-reconstitution, microbial contamination risk is another limitation, necessitating preservative use, which in turn raises concerns about safety in sensitive populations such as children.

From a regulatory standpoint, differences in pharmacopeial standards across regions complicate the approval process. Some excipients are approved in one jurisdiction but restricted in another, creating difficulties for global harmonization of Cephradine dry suspension formulations. Moreover, the lack of comprehensive databases on excipient–drug interactions further constrains formulation scientists, leading to reliance on empirical methods rather than predictive strategies.

Thus, despite the pivotal role of excipients, these challenges highlight the delicate balance required to optimize formulations without compromising safety, stability, or efficacy. However, the integration of nanotechnology-based stabilizers into cephradine formulations must also consider safety, regulatory, and cost-related challenges, as nanoscale excipients may require specialized testing to ensure their biocompatibility and long-term stability [54,55].

FUTURE PERSPECTIVES

Looking forward, the evolution of Cephradine formulations will likely be driven by advancements in excipient science and technology. The emergence of novel polymeric carriers and cyclodextrin complexes holds promise for stabilizing β-lactam antibiotics by shielding them from hydrolytic attack. Similarly, multifunctional excipients that can simultaneously act as stabilizers, taste-masking agents, and suspending agents could simplify formulations and reduce excipient load.

The application of nanotechnology also offers new horizons. Encapsulation of Cephradine in lipid-based carriers, nanoparticles, or microcapsules could improve stability and modulate release profiles, offering controlled or targeted delivery [56,57]. These technologies may overcome some of the limitations associated with conventional suspensions, particularly in pediatric populations where precise dosing and palatability are critical.

On the analytical front, computational modeling and predictive compatibility tools are expected to reduce reliance on trial-and-error approaches. Molecular docking, thermodynamic modeling, and accelerated stability studies could help identify potential excipient–drug interactions early in development, thereby saving cost and time [58].

Sustainability is another emerging perspective. With growing demand for eco-friendly pharmaceuticals, the use of natural, biodegradable, and renewable excipients will likely gain momentum. Plant-derived polysaccharides and biopolymers can serve as alternatives to synthetic agents, aligning with global trends toward green chemistry and sustainable manufacturing [49,59].

Finally, patient-centered design will remain at the forefront. Formulations tailored to specific populations such as pediatric, geriatric, or patients with swallowing difficulties will emphasize safety, palatability, and ease of administration. With continuous innovation in excipient functionality and regulatory harmonization, the future of Cephradine formulations is expected to move toward more stable, effective, and patient-friendly dosage forms.

Nanotechnology-Enabled Approaches for Cephradine Stability

The integration of nanotechnology into pharmaceutical formulation science has opened new avenues for addressing the stability challenges of β-lactam antibiotics such as cephradine [57]. Conventional excipients provide essential functions in suspension systems, yet their limitations in preventing hydrolysis, improving solubility, and ensuring controlled release highlight the need for advanced solutions. Nanotechnology-enabled approaches offer promising alternatives by providing nanoscale protection and modulation of drug delivery [60].

Encapsulation of cephradine into lipid-based nanocarriers (e.g., solid lipid nanoparticles, nanostructured lipid carriers) can shield the β-lactam ring from hydrolytic degradation while simultaneously enhancing oral bioavailability. Similarly, polymeric nanoparticles and cyclodextrin nanosponges can act as multifunctional stabilizers, offering protection against moisture, controlled release, and improved patient compliance. Nanostructured excipients such as nanosilica and

nanocellulose also demonstrate superior adsorption, flow, and stabilizing capacities compared to their bulk counterparts, thereby reducing the risk of caking and instability in reconstituted suspensions [61].

In addition, nanoscale coatings or surface modifications using citric acid and other biocompatible agents have shown the ability to improve drug stability, enhance permeability, and provide targeted delivery. These strategies not only extend the shelf life of cephradine formulations but also align with the broader pharmaceutical trend toward precision medicine and patient-centered drug design. Incorporating such nanotechnology-enabled strategies into cephradine suspensions could therefore represent a significant step forward in overcoming conventional formulation limitations [62].

CONCLUSION

Excipients are indispensable in determining the stability, performance, and patient acceptability of cephradine dry suspensions. Among them, citric acid stands out as a multifunctional excipient that stabilizes β-lactam structures, regulates pH, and enhances bioavailability. Traditional excipients such as suspending agents, preservatives, and sweeteners complement this role by ensuring homogeneity, microbiological safety, and palatability. However, challenges including drug excipient interactions, hygroscopicity, and formulation-specific instabilities highlight the limitations of conventional strategies. In this context, nanotechnology-enabled approaches offer a transformative perspective. Encapsulation of cephradine in nanocarriers, incorporation of nanostructured stabilizers, and the use of nanoscale excipient coatings could significantly improve resistance to hydrolysis, modulate release kinetics, and extend shelf life. By bridging classical excipient science with emerging nanotechnological innovations, future cephradine formulations can achieve superior therapeutic efficacy, stability, and patient compliance.

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CONFLICT OF INTERESTS

The Authors declare that there is no conflict of interests.

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