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# A REVIEW ON NIOSOMAL SUSPENSION CONTAINING CEFPODOXIME PROXETIL

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**Keywords:**

Cefpodoxime proxetil, Anti-biotic, cephalosporins, Niosomes, Niosomal suspension, Oral liquid dosage form

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**ABSTRACT:** Cefpodoxime proxetil is an oral antibiotic belonging to 3rd generation Cephalosporin category. It has shown its antibiotic activity against both Gram positive and Gram-negative bacteria and has high stability in the presence of β-lactamase except *Enterococci* species. The drug has found its effectiveness in pediatric patients in treating respiratory tract infections. At the present time the most familiar form in which cefpodoxime proxitel is delivered is either oral tablet form or for pediatrics oral dry syrup form. The oral dry syrup form has to be administered twice or thrice a day in order to meet the required dosage regimen. Developing the sustained release formulation for cefpodoxime proxetil probably niosomal suspension can be effective in reducing the dosing frequency along with sustained release and targeted drug delivery. Niosomal suspensions are suspended form of niosomes in an aqueous phase to form liquid dosage form it is called niosomal suspension. It is a potential drug carrier for delivery of drugs orally in liquid form. The niosomal suspensions allow the targeted drug delivery with controlled/sustained release and lead to reduced dose frequency with improved bioavailability and higher therapeutic effectiveness. This could make the formulation most suitable with lesser side effects and higher patient compliance.

**INTRODUCTION:** Niosome is a sustained release dosage type which is designed to sustain a constant level of release of substance in the bloodstream of the patient by releasing the drug over a prolonged period of time maintaining constant blood levels of the drug in the bloodstream increases therapeutic efficacy of the drug [1, 2]. The aim in the design of safe delivery systems is to minimize the frequency of dosing or increase the efficacy of the medication through localization at the site of the operation, to minimize the dose needed or to ensure consistent distribution of the drug [3].

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Ideal drug delivery systems will allow, first, a single dose for the duration of treatment, whether for days or weeks, as with infection, or for the lifetime of the patient, such as hypertension or diabetes [4]. Second, it will send the active agent directly to the site of the operation, reducing the side effects.

The basic goal in the design of the dosage form is to optimize the delivery of drugs in order to calculate the regulation of the therapeutic effect in the face of unpredictable variations in the *in-vivo* environment in which the medication is released [5].

Sustained release mode of drug administration has certain features that have an important impact on the magnitude of the pharmacologic response:

1. It minimizes fluctuation in blood drug concentrations (i.e., between peak and trough).

2. It produces a slow input rate which tends to minimize the body's counteraction to the drug's intervening effect on regulated physiological processes.

3. It provides a continuous mode of drug administration [6].

For many drugs with non-concentration dependent pharmacodynamics, the exposure time, rather than the AUC, is the relevant parameter and it can therefore be optimized by sustained release preparations. Sustained (modified)-release formulation provides higher maximum plasma concentrations with lower inter-patient variability than the conventional, immediate release, twice-daily formulation [7]. Additionally, therapeutic drug levels with sustained release formulations are achieved rapidly and maintained over the course of 24 h, allowing once-daily dosing. The studies have also confirmed good tolerability and safety of sustained-release formulations similar to the immediate-release formulations [8].

**Cefpodoxime Proxetil:** Cefpodoxime proxetil is an oral, broad spectrum third generation antibiotic belonging to the class Cephalosporins. Cefpodoxime has shown its anti-biotic activity against both Gram positive and Gram-negative bacteria and has high stability in the presence of β-lactamase except *Enterococci* species [9, 10]. Cefpodoxime has *in-vitro* activity against *Staphylococcus aureus*, Gram positive bacterial species such as *Streptococcus pyogenes* and *Streptococcus agalactiae* and also against several Gram-negative bacterial species such as *E. coli*, *K. pneumonia*, *Moraxella catarrhalis* and *H. influenzae*. Cefpodoxime proxetil is only well tolerated, 3rd generation cephalosporin that is available in oral form and low concentration of drug is useful in inhibiting most of the respiratory pathogens [11]. Cefpodoxime proxetil has found its therapeutic effectiveness especially in paediatrics against respiratory tract infections (bronchitis and pneumonia), urinary tract infections and in mild to moderate cases of gonorrhoea. Cefpodoxime has shown its activity against *S. pneumoniae* but less when compared to amoxicillin and amoxicillin-clavulanic acid combination [12].

**Molecular Weight:** 557.6 [g/mol]

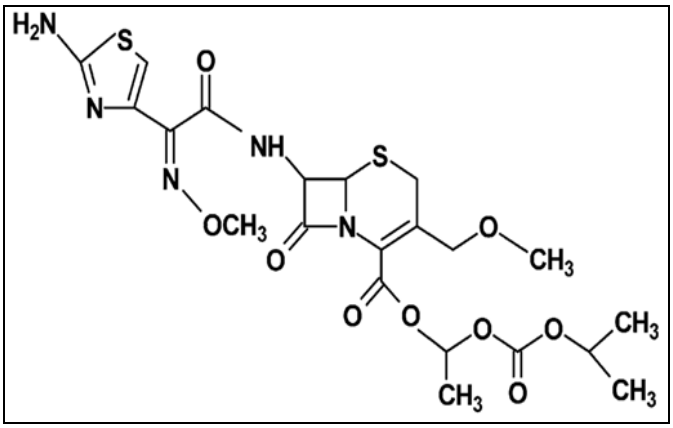
**Molecular Formula:** $C_{21}H_{27}N_5O_9S_2$

**Functional Category:** Anti-bacterial agent

**IUPAC Name:** (RS)-1-(isopropoxycarbonyloxy)-ethyl (+)-(6R, 7R)-7-[2-(2- amino-4- thiazolyl)-2-{(Z) – methoxy - imino} acetamido] – 3 - methoxymethyl -8-oxo-5-thia-1- azabicyclo[4.2.0] oct-2-ene-2-carboxylate

**Description:** Cefpodoxime proxetil is a prodrug of Cefpodoxime and semi-synthetic cephalosporin. It is white to light brownish in colour, with odourless or faint odour. It has good solubility in dehydrated alcohol, acetonitrile, methyl alcohol, slight solubility in ether and water [13].

**Structural Formula:**




**Mechanism of Action:** Cefpodoxime proxetil is a prodrug form of Cefpodoxime. When administered orally, the drug cleaves enzymatically to 2-propanol, $CO_2$ and acetaldehyde. The original form of drug Cefpodoxime gets absorbed rapidly from the gut wall. It reaches the body fluids after absorption exceeding Minimum Inhibitory Concentration (MIC). Then the drug undergoes metabolism process of de-esterification by intestinal esterase. Cefpodoxime acts by inhibiting the bacterial cell wall synthesis and hence works as an effective bactericidal agent. Thereafter, it gets excreted from kidneys unchanged. Also, Cefpodoxime has lower molecular weight which allows the passage of drug through the pores present in the bacterial cell wall. Then, it crosses the periplasmic space and gets bound to Penicillin binding proteins (PBP1 and PBP3) in bacterial cell wall membrane. This binding affects the synthesis of cell membrane and damages the cell [14-16].

**Pharmacokinetics:** Pharmacokinetics describes and predicts the time course of drug concentrations in body fluids.

**Absorption:** Cefpodoxime proxetil in its active form (Cefpodoxime) gets absorbed from the gut wall. The extent of absorption is independent of the food administered. But administration of this drug with other active agent can lead to increase in gastric pH which ultimately reduces the absorption from the gut wall.

**Distribution:** Cefpodoxime distributes rapidly in the body fluids after absorption.

**Excretion:** The drug excretes in the unchanged form from the kidneys.

**Metabolism:** The metabolism of Cefpodoxime proxetil depends on the de-esterification by intestinal esterase. Cefpodoxime acts by inhibiting the bacterial cell wall synthesis and hence works as an effective bactericidal agent.

**Elimination half-life and clearance:** Mean elimination half-life ranges from 1.7 to 3.3 hours in younger patients. The clearance of Cefpodoxime proxetil depends on the age of the patient which is 0.57 L/h/kg in paediatrics and 0.36 L/h/kg in children of age above 5 years.

**Bioavailability:** Cefpodoxime proxetil is a prodrug, which is orally administered cephalosporin with only 50% absolute bioavailability.

**Cefpodoxime Proxetil for Pediatric use:** The drug has found its effectiveness in pediatrics patients in treating respiratory tract infections. At the present time the most familiar form in which cefpodoxime proxetil is delivered is either oral tablet form or for pediatrics oral dry syrup form. The oral dry syrup form has to administered twice or thrice a day in order to meet the required dosage regimen.

Developing the sustained release formulation for cefpodoxime proxetil can be effective in reducing the dosing frequency along with sustained release and targeted drug delivery and also improve the bioavailability of drug. This makes the formulation most suitable with lesser side effects and higher patient compliance.

**Niosomes:** Niosomes are vesicles composed from non-ionic surfactants. Niosomes are microscopic vesicles of nano-range ranging from 10-1000 nm [17-19]. Niosomes are prepared by hydration of synthetic non-ionic surfactants along with incorporation of lipids and cholesterol. Niosomes are microscopic lamellar structures formed on admixture of a non-ionic surfactant, cholesterol, and diethyl ether with subsequent hydration in aqueous media. Niosomes are formulated by self-assembly of non-ionic surfactants in organic solvent (non-aqueous media) as microscopic, spherical, polyhedral, and multi-lamellar structures [20-23].

Several non-ionic surfactants are used in formation of niosomes and these include Spans and Tweens, Polyglycerol alkyl ethers, polyoxyethylene alkyl ethers, glucosyl dialkyl ethers, ester and steroid linked surfactants *etc* [24]. Niosomes are categorised into 3 types based on size and bilayers. These are:

- Small Unilamellar Vesicles (SUV) - 10-100nm.
- Large Unilamellar Vesicles (LUV) – 100-3000nm.
- Multilamellar Vesicles (MLV) [25, 26].

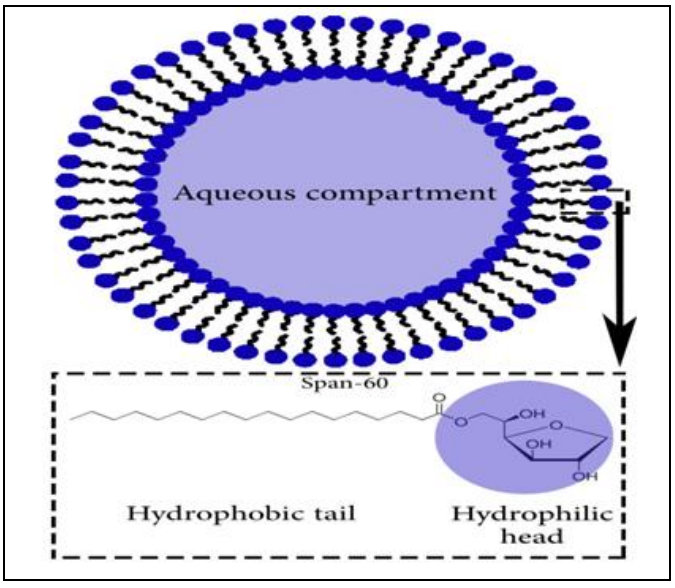



**FIG. 1: STRUCTURE OF NIOSOMES**

Niosomes are vesicular drug delivery systems which are formulated in case of delivery of amphiphilic, hydrophobic or lipophilic drugs [27]. Niosomes have similar structure and activity as that of liposomes but niosomes are highly preferred for following reasons:

- Higher chemical stability.
- Highly suitable for lipophilic drugs or categorically for BCS Class II and IV.
- Easy to manufacture.
- Economical.
- Higher efficacy.
- Doesn't require special handling or storage conditions.
- Précised.
- Promising drug carrier [28].

**Niosomal Suspension:** When the niosomes are suspended in an aqueous phase to form liquid dosage form it is called niosomal suspension. It is a potential drug carrier for delivery of drugs orally in liquid form. The niosomal suspensions allow the targeted drug delivery with controlled/ sustained release and lead to reduced dose frequency with improved bioavailability and higher therapeutic effectiveness [29, 30].

**Advantages of Niosomes/ Niosomal Suspension:**

- Nontoxic and non-immunogenic formulations.
- Improved patient compliance.
- Higher therapeutic efficacy.
- Enhanced oral bioavailability of drug.
- Biocompatible.
- Good carrier option for amphiphilic and lipophilic drugs.
- Controlled and sustained release drug delivery.
- Osmotically active and stable.
- Drug protection against enzymatic metabolism.
- Higher stability.
- Targeted drug delivery.
- Enhanced skin permeability.
- Easy to manufacture, handle, store and transport.
- Can be administered orally, topically as well as through parenteral route [31].

**Components of Niosomes:** The essential components of niosomes are non-ionic surfactants, lipids such as cholesterol and hydration or aqueous medium.

**Non-ionic Surfactants:** The non-ionic surfactants as the name indicates are non charged surfactants which do not have charged groups in hydrophilic heads. Non-ionic surfactants are amphiphilic molecules that consist of 2 regions: Hydrophilic region (water soluble) and Hydrophobic region (lipid soluble) [32-35]. Non-ionic surfactants are used for the preparation of niosomes because of several reasons:

- Non-toxic.
- Stable.
- Biocompatible.

**Lipids:** During the formulation of niosomes, the cholesterol forms hydrogen bond with the hydrophilic head of the non-ionic surfactant. Several properties of niosomes are dependent on the choice and content of cholesterol. The rigidity of the vesicles and stability of the vesicles improves with the increase in cholesterol content and permeability of the vesicles for entrapped drug decreases and hence inhibits leakage from the vesicles. The higher content of cholesterol also enhances entrapment efficiency [36]. Examples of lipids used for niosomes formulation are cholesterol and l-α-Soya phosphatidyl choline.

**TABLE 1: EXAMPLES OF NON-IONIC SURFACTANTS**

| S. no. | Non-ionic surfactant | Examples |
|---|---|---|
| 1 | Alkyl ethers (Alkyl glycerol ethers, Polyoxyethylene glycol alkyl ethers) | Hexadecyl diglycerol ether, Brij 30, 52, 72, 76, 78 |
| 2 | Alkyl esters (Span and Tween) | Span 20, 40, 60, 80, 85 and Tween 20, 40, 60, 80, 85 |
| 3 | Alkyl amides (Glycosides and Alkyl polyglycosides) | C-Glycoside, Octyl-decyl polyglycoside |
| 4 | Fatty alcohols and Fatty acids | Stearyl alcohol, Cetyl alcohol, Myristyl alcohol; Stearic acid, Palmitic acid, Myristic acid |
| 5 | Block copolymer | Pluronic L64, 105 |

**Charged Molecules:** Apart from lipids and non-ionic surfactants, charged molecules are important components of niosomes that increase the stability of niosomes. The charged molecules increase surface charge density and prevent the aggregation of vesicles. Both negatively and positively charged molecules can be used for formulation of niosomes. Appropriate amount of charged molecules (2.5-5 mol %) is important as the higher concentration of charged molecules inhibits the formulation of niosomes [37].

**Method of Preparation:** The method of preparation for niosomes is classified as follow:

**TABLE 2: METHOD OF PREPARATION OF NIOSOMES**

| S. no. | Type of niosomes | Method of preparation |
|---|---|---|
| 1 | Small unilamellar vesicles (SUV) | Sonication method Microfluidization method |
| 2 | Multilamellar vesicles (MLV) | Hand shaking method (Thin film hydration technique) Transmembrane pH gradient technique |
| 3 | Large unilamellar vesicles (LUV) | Ether injection method. Reverse phase evaporation technique |
| 4 | Miscellaneous | Multiple membrane extrusion method. Emulsion method. Lipid injection method |

**Ether Injection Method:** In this method, the non-ionic surfactant along with other additives is added into diethyl ether (organic solvent) and further this solution is injected slowly through needle into aqueous drug solution which is maintained at constant temperature throughout. Consequently, the organic solvent is evaporated using rotary evaporator and single layered vesicles (niosomes) are formed [37-40].

**Hand Shaking Method (Thin Film Hydration Technique):** In this method, all the niosomal components are mixed in organic solvent in a RBF. Then, the organic solvent is evaporated using rotary evaporator and a thin film is obtained inside the walls of RBF. Furthermore, drug aqueous solution is added to RBF and the film is hydrated for specific time with constant shaking. This method of preparation is highly recommended for its ease of application and simplicity. This method allows the formation of multilamellar vesicles (MLV) Niosomes [41-46].

**Transmembrane pH Gradient Method:** In this method of niosome preparation, the non-ionic surfactants and cholesterol are dissolved in organic solvent (chloroform) and then evaporated to form thin film on the walls of RBF. This film is then hydrated by addition of citric acid solution and the resulting mixture is freeze thawed. The above mixture is then hydrated by addition of aqueous drug solution and the pH is maintained in between 7-7.2 [9, 11, 37].

**Reverse Phase Evaporation Technique:** In this method, the niosomes are prepared by dissolving the niosomal components in organic solvent (ether and chloroform) and further adding aqueous drug solution. This mixture is sonicated until the organic solvent evaporates and an emulsion is formed. This method is useful in formulating Large unilamellar vesicles (LUV) [38-40].

**Microfluidization Technique:** This method is performed in an interaction chamber whereby the non-ionic surfactant and drug is interacted at super high velocity. This high-speed impingement allows the formation of précised niosomes. This method is useful in formation of uniform, highly reproducible, small sized, and unilamellar vesicles [41].

**Heating Method:** In this method, the surfactant and cholesterol are hydrated separately in buffer solution and heated upto 120$^{o}$C with constant stirring to dissolve cholesterol. The temperature of above cholesterol mixture is reduced, and both the solutions are mixed together with continuous stirring to form Niosomes [8-11, 38].

**Bubble Method:** In this method, the niosomal components and buffer are added to glass flask. All the components are dispersed at 70$^{o}$C and mixed in homogenizer. Thereafter, the flask is kept in water bath and nitrogen gas is bubbled or passed through the flask in order to form large unilamellar vesicles (LUV) [42-45].

**Sonication Method:** In this method, the niosomal components (surfactant and cholesterol) and aqueous solution of drug are mixed and sonicated at 60$^{o}$C for 3 minutes in order to form niosomes.

This method is useful in formation of uniform sized and small unilamellar vesicles (SUV) [46].

**Multiple Membrane Extrusion Method:** In this method, the niosomal components and diacetyl phosphate are added into chloroform and evaporated to form thin films.

This film is hydrated with aqueous drug solution and the mixture is extruded through polycarbonate membrane to obtain small controlled and uniform sized Niosomes [17-20, 56].

**Emulsion Method:** In this method, oil in water (o/w) emulsion is formed using organic solvent, surfactant, cholesterol and aqueous drug solution. Then, the organic solvent is evaporated resulting in formulation of niosomes in aqueous phase [18].

**Lipid Injection Method:** In this method, the lipid and surfactant mixture is melted and injected into hot aqueous drug solution which is agitated. The drug is further dissolved in above mixture and niosomes are formed. The organic solvent is not used in this method [18].

**Proniosomes:** Proniosomes are dry formulations which are prepared by coating water soluble carriers such as sorbitol and mannitol with surfactant. The proniosomes are prepared because they are highly stable when compared to niosomes.

The proniosomes are hydrated before use to form niosomes. This method allows the formulation of physically stable proniosomes that do not leak, aggregate, and are easier to manufacture, store and transport when compared to Niosomes [17, 18, 57].

**Characterization of Niosomal Suspension**

**Appearance:** Prepared formulation will be visually checked for its colour, clarity and phase separation [57].

**Drug Content:** The drug content of formulation will be determined by diluting 1ml of the formulation with 100 ml methanol, further diluted 5ml to 50ml with methanol followed by analysis with UV-visible spectrophotometer [58].

**Rheological Study:** The viscosity of Niosomal suspension of different formulation will be measured at 10 rpm for 3 min at 25$^{o}$C by Brookfield type rotary viscometer with spindle 63.

**SEM:** The suspension will be determined for the morphology using Scanning Electron microscopy.

**Entrapment Efficiency:** The Niosomal suspension is sonicated and centrifuged, and the drug is separated. Assay is done at optimum wavelength using UV spectrophotometer.

***In-vitro* drug release:** The *in-vitro* drug release study is carried out in two medium: Phosphate buffer and gastrointestinal pH medium [59, 60].

**Activation of Cellophane Membrane:** The cellophane membrane is activated by dipping firstly in hot water and then in ethanol for 1 hour and 30 minutes respectively. Further, the membrane is kept in acetate buffer (pH 4) overnight.

***In-vitro* Drug Release in Gastrointestinal pH Medium:** 3ml of Niosomal suspension is taken on activated cellophane membrane tied to open ended cylinder. The apparatus is kept in 30ml of 0.1N HCl and stirred at 37°C. Samples are withdrawn after 5 minute interval for 2 hours and analysed using UV spectrophotometer.

***In-vitro* Drug Release in Phosphate bBuffer Medium:** The above mentioned procedure is used for determination using phosphate buffer solution pH 7.4.

***In-vitro* Anti-microbial Activity:** The *in-vitro* antimicrobial activity is performed using agar diffusion assay method. The microorganism employed is E. coli. The activity is performed on optimized formulation and plain Niosomal suspension. Petri plate is incubated at 37$^{o}$C for 24h. The sensitivity of test organism to the formulation will be indicated by clear zone of inhibition around the disc and the diameter of the zone of inhibition is measured.

**Stability Studies:** Samples (triplicate) will be placed in flasks and air tightened completely. The samples will be submitted to a thermostable hot air oven at 45 ± 2$^{o}$C for 90 days.

Control samples will be kept at room temperature for the same period of time. The evaluation of the samples are performed initially at time zero and after 15, 30, 60, and 90 days and evaluated for

organoleptic parameters (colour, odor, and appearance) and drug content [61-63].

**CONCLUSION:** In a nutshell to conclude, cefpodoxime proxetil is 3rd generation cephalosporin used as an antibiotic. It has found its effectiveness in the treatment of respiratory tract infection in pediatrics. The oral dry syrup form of drug available in market is therapeutically active but has to be administered twice a day depending on the severity of the disease. Here, the approach is studied that the niosomal suspension of cefpodoxime proxetil could be an effective approach in delivering the drug with sustained or controlled release. The niosomal suspension is an effective approach with appropriate delivery strategies and further research can lead to a novel approach in the antibiotics category.

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**CONFLICTS OF INTERESTS:** Declared None

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