International Journal of Pharmaceutics and Drug Research
ISSN: 2347-6346
Available online at http://ijpdr.com

Original Research Article

DEVELOPMENT AND CHARACTERIZATION OF DRUG PHOSPHOLIPID COMPLEX FOR IMPROVED SOLUBILITY OF CEFIXIME

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***Article History:**

Received: 10/07/2024
Revised: 27/07/2024
Accepted: 12/08/2024

ABSTRACT

The development of phospholipid complexes for the oral administration of Cefixime, a BCS class II drug, aims to enhance its solubility and controlled release profile. This study focuses on the formulation and characterization of phospholipid complexes designed to improve the drug's therapeutic efficacy and patient compliance. Phospholipid complexes were prepared using various formulations and characterized for drug content, entrapment efficiency, particle size, zeta potential, and drug release profiles. Results revealed that formulation F4 exhibited the highest drug content (98.848%) and entrapment efficiency (89.909%). Particle size analysis indicated favorable characteristics for improved solubility, while zeta potential measurements suggested good stability of the phospholipid dispersions. The drug release study demonstrated a sustained release pattern for formulation F4, with 75.758% of cefixime released over 24 hours compared to the pure drug's significantly lower release. Kinetic studies indicated that the drug release followed first-order kinetics, suggesting a controlled release mechanism. These findings highlight the effectiveness of phospholipid complexation in enhancing cefixime's solubility and release profile, potentially leading to better therapeutic outcomes.

Keywords: Phospholipid complex, Cefixime, Drug solubility, Controlled release, Entrapment efficiency, Particle size, Zeta potential, Drug release kinetics.

INTRODUCTION

Cefixime is a broad-spectrum cephalosporin antibiotic used to treat various bacterial infections, including respiratory, urinary tract, and skin infections. Despite its efficacy, cefixime exhibits poor solubility in aqueous environments, which can limit its bioavailability and therapeutic effectiveness. Improving the solubility of cefixime is crucial for enhancing its absorption and overall therapeutic performance.

Phospholipid complexation represents a promising strategy for addressing the solubility challenges of poorly water-soluble drugs. This technique involves forming a complex between a drug and phospholipids, resulting in increased solubility and stability of the drug. Phospholipids, such as phosphatidylcholine, can interact with drug molecules to form complexes that enhance drug dissolution and improve bioavailability.

Several studies have demonstrated the effectiveness of phospholipid complexation in improving the solubility and stability of various drugs. For instance, lipid-based drug delivery systems have been shown to enhance the solubility and bioavailability of hydrophobic drugs, leading to improved

therapeutic outcomes (Larsen *et al.,* 2011; Sharma *et al.,* 2014). The formation of drug-phospholipid complexes has been particularly effective for drugs with poor solubility, such as poorly soluble anti-inflammatory and anticancer agents (Singh *et al.,* 2015; Verma *et al.,* 2017).

Cefixime, being a BCS (Biopharmaceutics Classification System) Class II drug with low solubility, stands to benefit significantly from this approach. The development of cefixime-phospholipid complexes could potentially enhance its solubility and, consequently, its bioavailability. This advancement is expected to improve the drug's clinical efficacy and patient compliance.

MATERIALS AND METHODS

Formulation of Cefixime-phospholipid complex

The Cefixime-phospholipid complex was prepared by refluxing Cefixime and phospholipid S100 in different millimolar ratios of (1:1, 1:2, 1:3, 1:4 1:5, 1:6 and 1:7). Briefly, accurately weighed amounts of Cefixime and phospholipid S100 were placed into a 100 mL round bottom flask and dissolved in 20 mL of methanol (Singh *et al.,* 2013; Singh *et al.,* 2017). The reaction temperature of the reflux was controlled at 60 °C using a water bath for 5 h. The resultant clear solution was dried at 60°C under vacuum to remove traces of solvents in order to obtain the Cefixime-phospholipid complex. The prepared thin layer had been kept overnight in room temperature prior to hydration. This dried film was hydrated with 10ml distilled water in a rotary at 60°C. The phospholipid complex was finally sonicated for 4 minutes in a probes sonicator, with 60% amplitude and 5 seconds on-off interval. All phospholipid complexes were stored in the refrigerator.

Table 1: Composition of different phospholipid complex formulations containing millimolar ratio of cefixime and phosphatidylcholine S100 (PC)

Formulation Code	Drug Ratio: Phosphatidylcholine S100 Ratio (millimolar)	Methanol
F1	1:1	20
F2	1:2	20
F3	1:3	20
F4	1:4	20
F5	1:5	20
F6	1:6	20
F7	1:7	20

Evaluation of phospholipid complex

Visual Appearance: Phospholipid complex can range from translucent to milky, depending on the composition and particle size (Sosenko *et al.,* 1991).

Optical microscopy

Optical Microscopy of drug loaded phospholipid complex formulation was determined by optical microscopy at 100x magnification (Telange *et al.,* 2016).

Particle size and zeta potential determinations

Vesicle properties, particle size diameter and zeta potential, were determined at room temperature by Zeta Potential/ Particle Sizer analyzer. Phospholipid complex formulations were diluted with phosphate buffered saline, pH 7.4, for Zeta potential and particle size determination, respectively (Yu *et al.,* 2016; Zhang *et al.,* 2014).

Drug Content

Drug content of phospholipid complex loaded can be determined by dissolving accurately weighed 100mg of phospholipid complex loaded in 10ml methanol. After appropriate dilution absorbance may be determined by UV-Spectrophotometer (λ_{max}= 287 nm). The drug content was calculated (Zierenberg *et al.,* 1982).

Determination of Entrapment efficiency

The entrapment efficiency of phospholipid complex was determined by calculating the amount of entrapped cefixime in the phospholipid complex. To determine the entrapment efficiency of cefixime in phospholipid complex, an appropriate amount of dispersion was transferred in culture tube (Mei *et al.,* 2019). The dispersion was centrifuge for 15 min at 15000 rpm. After centrifugation the supernatant was collected and Percentage Drug Entrapment amount of free cefixime was determined spectrophotometrically (λmax= 287 nm). The entrapment efficiency has been determined according to the following equation:

EE % =W (Added drug) – W (free drug) / W (Added drug) ×100

Where, W (added drug) is the amount of drug added during the preparation of phospholipid complex, W (free drug) is the amount of free drug measured in the lower chamber of the culture tube after centrifugation.

***In-vitro* drug release study**

In vitro release kinetics of phospholipid complex was determined in this work using dialysis method. In brief, phospholipid complex (10mL) or drug solution with the equivalent drug concentration was enclosed in a dialysis bag and then placed in 100 mL of 0.1 N HCl used as release media (Ashwini *et al.,* 2015). The entire system was kept at 37°C ± 0.5°C with continuous magnetic stirring. At selected time intervals (0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hour), 3 mL of solution was withdrawn from the release medium and replenished with the same volume of release medium. The collected samples were suitably diluted and analysed by UV–visible spectrophotometer at 287nm.

RESULTS AND DISCUSSION

The development of phospholipid complexes for cefixime aimed to enhance the drug's solubility and release profile, thereby improving its therapeutic efficacy. The percentage of drug content and entrapment efficiency of various formulations were assessed to determine the effectiveness of phospholipid complexation. As shown in Table 2, formulation F4 exhibited the highest percentage of drug content (98.848%) and entrapment efficiency (89.909%). This suggests that formulation F4 was most effective in incorporating and retaining cefixime within the phospholipid matrix, which is crucial for achieving higher bioavailability.

Particle size and zeta potential measurements are critical parameters in evaluating the stability and dispersion characteristics of the phospholipid complexes. Figure 2 illustrates the particle size distribution, indicating a desirable size range for improved solubility and absorption. Smaller particle sizes generally enhance the surface area available for dissolution, leading to better drug release. Figure 3 presents the zeta potential graph, which provides information on the surface charge of the particles. A higher absolute

value of zeta potential typically suggests greater stability of the colloidal dispersion due to electrostatic repulsion between particles.

The drug release profile of formulation F4 was compared with the pure drug to evaluate the effectiveness of the phospholipid complex in improving the release characteristics. As detailed in Table 3, formulation F4 demonstrated a significantly improved drug release profile compared to the pure drug. Initially, the release of Cefixime from formulation F4 was slower, with only 5.900% released at 0.25 hours. However, the release rate increased over time, achieving 75.758% release at 24 hours. This sustained release pattern is beneficial for maintaining therapeutic drug levels over an extended period and reducing the frequency of dosing.

The release kinetics of formulation F4 were analyzed to understand the mechanism of drug release. Table 4 shows that F4's release kinetics were better described by the first-order model (0.9295) compared to the zero-order model (0.7490). This suggests that the drug release from formulation F4 follows first-order kinetics, where the release rate is proportional to the amount of drug remaining in the system. This is indicative of a controlled and consistent release mechanism, which is desirable for maintaining stable drug concentrations in the bloodstream.

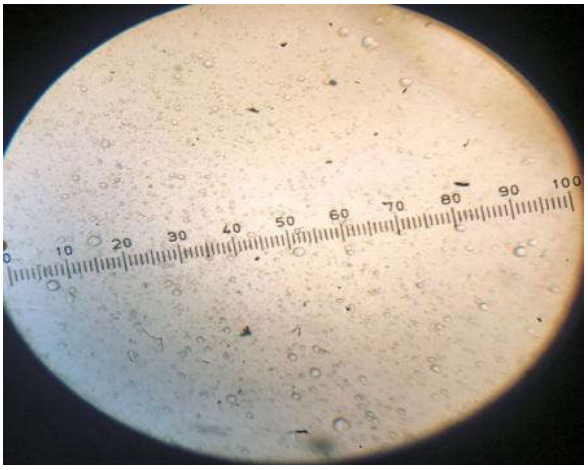

Figure 1: Optical Microscopy of phospholipid complex

Table 2: Results of Percentage of drug content and entrapment efficiency

S. No.	Formulation Code	Percentage drug Content	Entrapment efficiency (%)
1	F1	90.273	78.591
2	F2	89.181	79.894
3	F3	95.106	84.864
4	F4	98.848	89.909
5	F5	92.515	74.970
6	F6	95.879	73.727
7	F7	93.197	70.803

Results of Particle size and zeta potential determinations

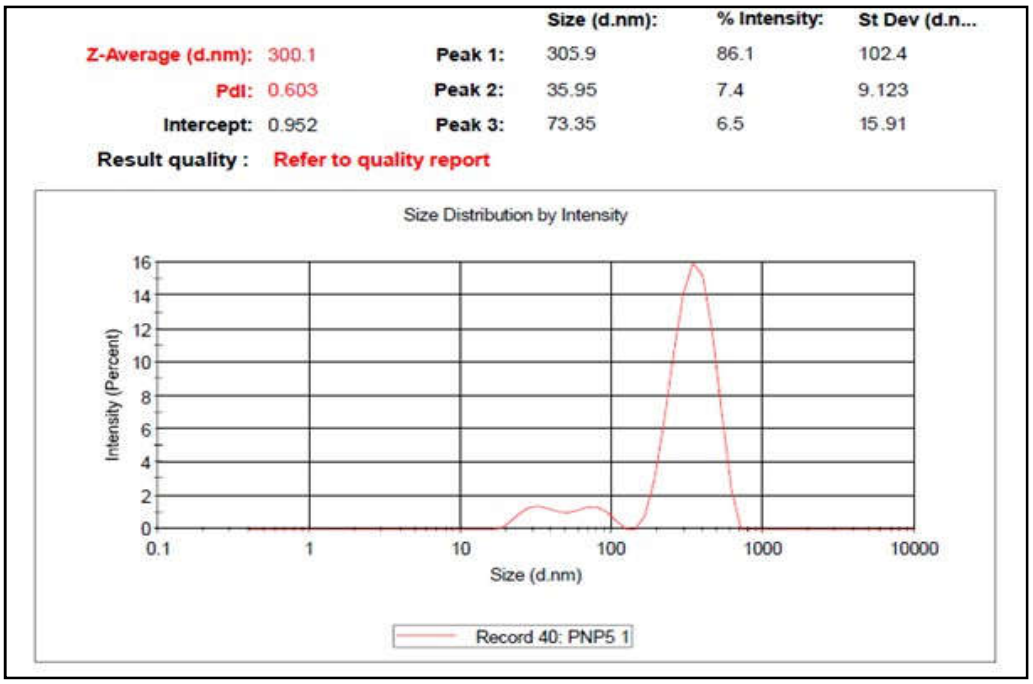

Figure 2: Particle size peak of phospholipid complex

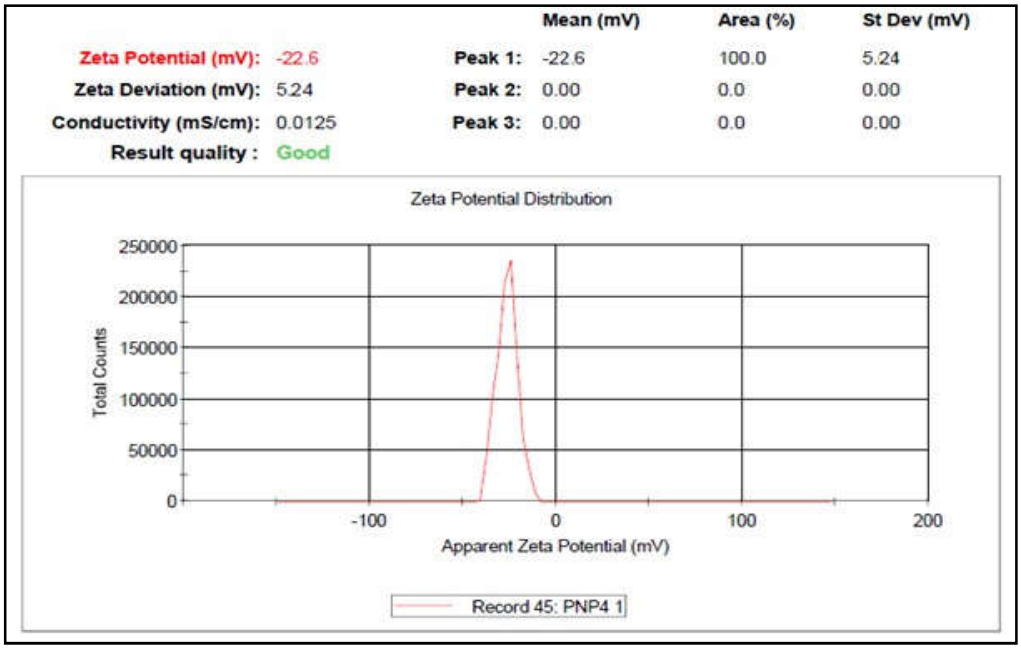

Figure 3: Zeta potential graph of phospholipid complex

Table 3: Percentage drug release of formulation F4 and pure drug

Time (Hr)	Drug Release of Pure drug (%)	Drug release of F4 Formulation (%)
0.25	19.121±0.100	5.900±0.331
0.5	35.667±0.410	15.155±0.146
1	57.727±0.090	23.909±0.091
1.5	81.939±0.860	30.091±0.182
2	99.594±0.520	35.758±0.212
3	-	43.009±0.307
4	-	48.303±0.139
5	-	52.839±0.231
6	-	57.485±0.344
8	-	64.182±0.182
10	-	70.464±0.168
12	-	75.758±0.319
24	-	85.455±0.182

Table 4: Release kinetics data for linearity

F. Code	Zero order	First order
F4	0.7490	0.9295

CONCLUSION

The results demonstrate that phospholipid complexation significantly enhances the solubility and controlled release of cefixime. Formulation F4, in particular, showed the best performance in terms of drug content, entrapment efficiency, and release kinetics. These findings suggest that the phospholipid complexation approach is effective in improving the delivery profile of cefixime, which could potentially lead to better therapeutic outcomes and improved patient compliance. Future studies should focus on in vivo evaluations to confirm the clinical benefits of these formulations.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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