IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF NIOSOMES CONTAINING CEFETAMET PIVOXIL

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Abstract: Cefetamet pivoxil is an oral, broad spectrum third generation antibiotic belonging to class of Cephalosporins. Cefetamet pivoxil 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. This study was aimed at developing and optimizing niosomal formulation of Cefetamet pivoxil in order to improve its bioavailability. in this study, the niosomes of Cefetamet pivoxil will be prepared by using non-ionic surfactant in varied concentration (Span 60) and cholesterol employing thin-film hydration technique. The prepared formulation will be characterized for several parameters such as physical appearance, pH, Scanning Electron Microscopy, Drug content, Drug entrapment efficiency, *in vitro* microbiological study, *in vitro* drug release, and stability studies. From the result of all characterization parameters the in vitro drug release from formulation F4 was found to be optimum. From the release kinetics of formulation F4 it was found that the First order release kinetics was best fitted for niosomes.

Keywords **- Niosomes, Cefetamet pivoxil, Cholesterol, Span 60, Dissolution.**

INTRODUCTION

Sustained Release Drug Delivery System:

Sustained release dosage type is designed to sustain a constant level of release. 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].

Niosomes:

Niosomes are vesicles composed from non-ionic surfactants. Niosomes are microscopic vesicles of nano-range ranging from 10-1000 nm [4-6]. Niosomes are prepared by hydration of synthetic non-ionic surfactants along with incorporation of lipids and cholesterol. . Niosomes are formulated by self-assembly of non-ionic surfactants in organic solvent (non-aqueous media) as microscopic, spherical, polyhedral and multi-lamellar structures [7-10].

Advantages of Niosomes [11, 12]

- Nontoxic and non-immunogenic formulation
- 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 [13]

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

Cefetamet Pivoxil:
Cefetamet pivoxil is an oral, broad spectrum third generation antibiotic belonging to class of Cephalosporins. Cefetamet pivoxil 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. Cefetamet pivoxil has *in vitro* activity against Gram negative bacterial species such as *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella (Branhamella) catarrhalis* and group A *beta-haemolytic streptococci*.

MATERIAL AND METHOD
Cefetamet pivoxil was obtained from Bascham Life Sciences, India; Spans were obtained from S.D. Fine chemicals Ltd, India. Cholestrol, Methanol, Sodium Chloride, Sodium hydroxide, Disodium hydrogen phosphate and HCl were also obtained from from S.D. Fine chemicals Ltd, India.

Evaluation of Raw Materials:
Identification and standardization of drug and other excipients were carried out as per the official procedures mentioned in respective monographs.

Preparation of Niosomes:
Niosomes were prepared using thin film hydration method using nonionic surfactant (span 60) and cholesterol at different concentration. The niosomes were prepared by dissolving varied quantity of Span 60, cholesterol and drug in chloroform and methanol (1:2) solution in a RBF. This mixture was evaporated using Rotary evaporator until a thin film was obtained. Further, this film was hydrated with 20ml of PBS pH 7.4 in a RBF until a suspension was formed and then this niosomal suspension was hydrated at 4^{o}C to obtain niosomes. The obtained niosomes were then dried and stored in desiccators for further characterization. Composition of niosomes is shown in Table 1.

Table 1: **Composition of niosomes**

S. No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Drug (mg)	50	50	50	50	50	50
2	Span 60 (ml)	50	100	150	50	100	150
3	Cholesterol (ml)	50	50	50	25	25	25
4	Chloroform (ml)	50	50	50	50	50	50
5	Methanol (ml)	100	100	100	100	100	100

RESULT AND DISCUSSION:
Organoleptic Properties:
The prepared Niosomes were found to be white, spherical and odorless for all formulations. The results are depicted in Table 2.

Percentage Yield:
The percentage yield of drug loaded Niosomes were calculated using the weight of final product after drying with respect to the initial total quantity of the drug and excipient used for preparation of Niosomes. The results were found to be in the range 91.5-94.3%. The results are depicted in Table 2.

Particle Size Analysis:
The size of Niosomes was determined by using a laser light scattering particle size analyzer and the results are shown in figure 3.2. The particle size of niosomes was found to decrease with increase in concentration of Span 60. The results are shown in Table 2.

Table 2: Characterization of Niosomes (F1-F6) (mean ± S.D., n=3)

Formulation	Appearance	Color	Odor	Percentage Yield (%)	Particle size (µm)
F1	Spherical	White	Odorless	91.5	4.85 ± 0.12
F2	Spherical	White	Odorless	91.7	4.67 ± 0.19
F3	Spherical	White	Odorless	93.6	4.54 ± 0.09
F4	Spherical	White	Odorless	92.7	4.97 ± 0.18
F5	Spherical	White	Odorless	93.1	4.41 ± 0.05
F6	Spherical	White	Odorless	94.3	4.32 ± 0.08

Surface Morphology (SEM analysis):
The shape and surface morphology of Niosomes were studied using Scanning Electron Microscopy (SEM). The photographs of Niosomes are shown in fig. 1.

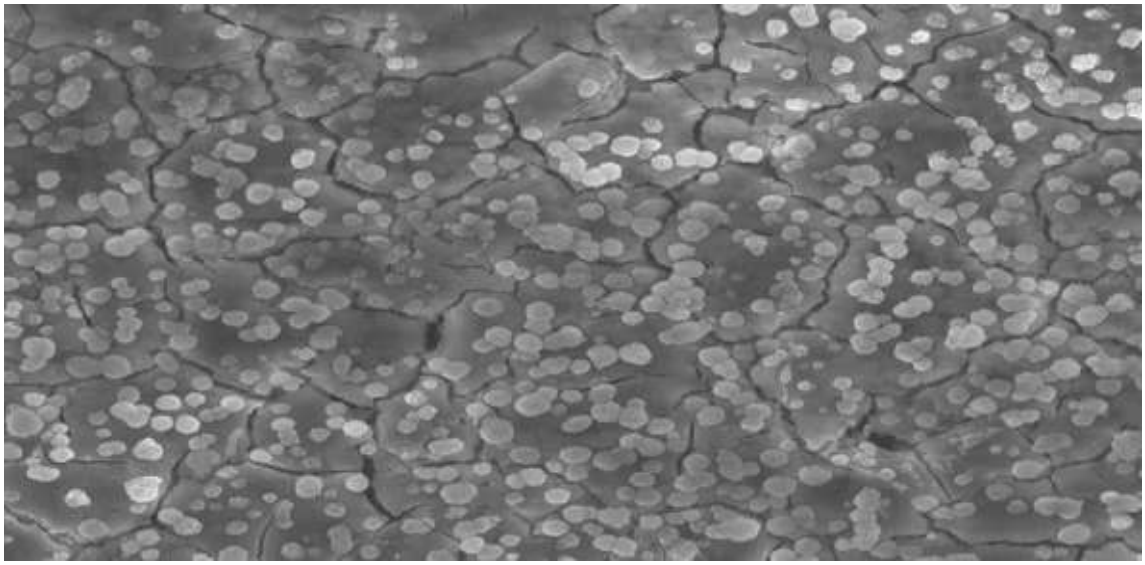

Fig. 1: Photomicrograph of Niosomes

Micromeritic Properties:

A) Angle of repose:
The angle of repose was found in the range of 26.2 to 29.8 which indicated that niosomes have good flow properties. The results are tabulated in Table 3.

B) Bulk density:
The bulk density was found in the range of 0.521 to 0.568 gm/cm^3 which indicated that niosomes have good flow properties. The results are tabulated in Table 3.

C) Tapped Density:
The tapped density was found in the range of 0.528 to 0.588 gm/cm^3 which indicated that niosomes have good flow properties. The results are tabulated in Table 3.

D) Compressibility index:
Compressibility index was found to be in the range of 0.74 to 4.6 for all batches of formulation of Niosomes. The results are tabulated in Table 3.

E) Hausner ratio:
Hausner's ratio was found in between 1.00 to 1.04 for all batches of formulation of Niosomes. The results are tabulated in Table 3.

Table 3: Micromeritic Properties of Niosomes (F1-F6) (mean ± S.D., n=3)

Formulation	Angle of repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
F1	26.8 ± 0.25	0.521 ± 0.02	0.528 ± 0.04	1.32 ± 0.2	1.01 ± 0.02
F2	27.4 ± 0.36	0.535 ± 0.03	0.539 ± 0.03	0.74 ± 0.4	1.00 ± 0.06
F3	28.7 ± 0.74	0.549 ± 0.04	0.576 ± 0.02	4.6 ± 0.7	1.04 ± 0.05
F4	26.5 ± 0.75	0.531 ± 0.02	0.544 ± 0.06	2.38 ± 0.6	1.02 ± 0.04
F5	26.2 ± 0.12	0.542 ± 0.06	0.557 ± 0.03	2.69 ± 0.4	1.02 ± 0.06
F6	29.8 ± 0.56	0.568 ± 0.01	0.588 ± 0.04	3.4 ± 0.7	1.03 ± 0.03

Percentage Moisture Loss:
Drug loaded Niosomes were evaluated for percentage moisture loss. The % moisture loss was minimal in the range 11.5 to 21.2. The results are shown in Table 4.

Degree of Swelling:
The swelling ability of niosomes in physiological media was determined by swelling them in the phosphate buffer solution pH 7.4. The degree of swelling was found to be in the range of 46.2-78.4%. The results are shown in Table 4.

Estimation of Drug Content:
Drug content in the niosomes was estimated by an UV spectrophotometric method based on the measurement of absorbance at 250 nm in phosphate buffer solution pH 7.4. The drug content was found to be in the range of 88.3 to 94.5%. The results are shown in Table 4.

Entrapment Efficiency:
The Entrapment efficiency of Niosomes was calculated and was found to be in the range of 85.11 to 93.4%. The results are shown in Table 4.

Table 4: Characterization of Niosomes (F1-F6) (mean ± S.D., n=3)

Formulation	% moisture loss	Degree of Swelling	Drug Entrapment Efficiency (%)	Drug Content
F1	11.5 ± 0.5	62.3 ± 0.5	88.62 ± 0.94	88.3 ± 0.65
F2	15.6 ± 0.6	55.1 ± 0.6	85.11 ± 0.17	92.5 ± 0.54
F3	17.1 ± 0.3	46.2 ± 0.4	91.35 ± 0.53	93.1 ± 0.48
F4	15.8 ± 0.4	78.4 ± 0.5	93.4 ± 0.44	92.6 ± 0.81
F5	19.6 ± 0.6	72.6 ± 0.6	91.5 ± 0.98	91.6 ± 0.67
F6	21.2 ± 0.8	69.3 ± 0.8	92.6 ± 0.81	94.5 ± 0.88

In Vitro Drug Release Studies:
The release rate of drug loaded niosomes was determined using USP dissolution testing apparatus II (Electro lab, India). The graphical representation of in vitro release data are shown in fig. 2. The rate of drug release is found to be in the order F6 < F5 < F3 < F4 < F2 < F1. The release pattern depends on the surfactant and cholesterol concentration. Although, form the results of all characterization parameters the *in vitro* drug release from formulation F4 was found to be optimum.

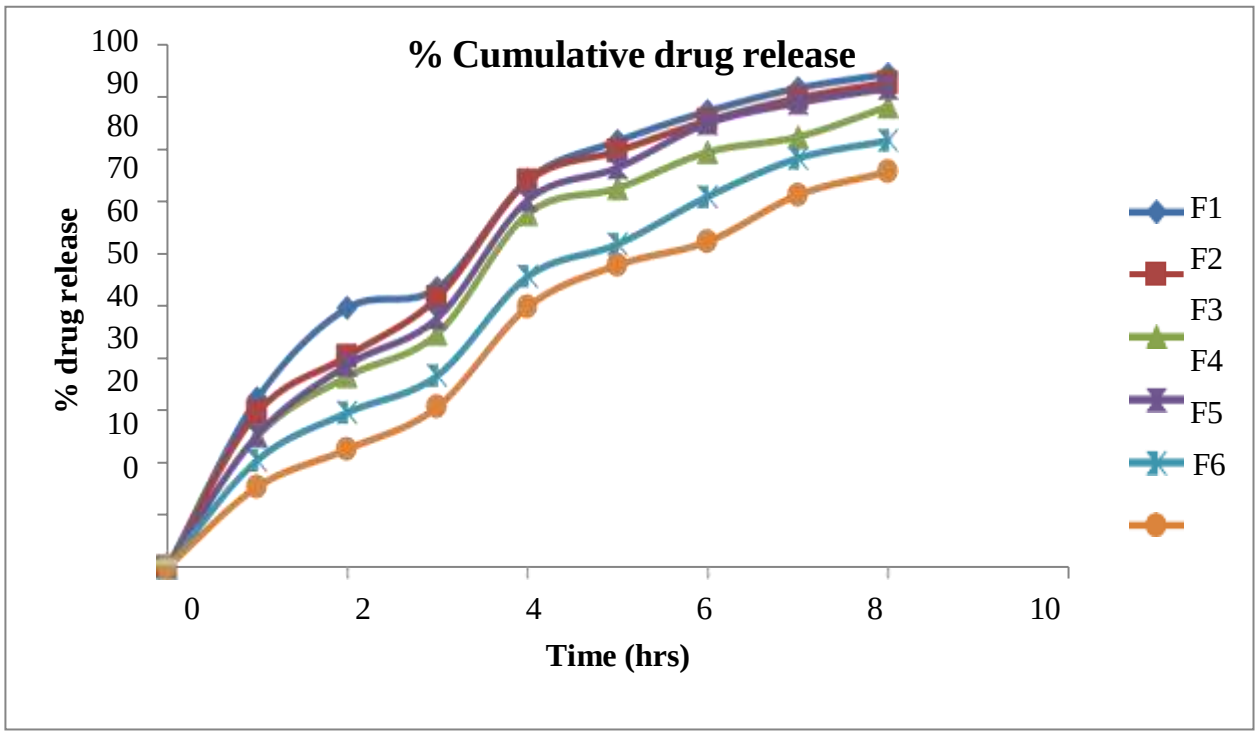

Fig. 2: % Cumulative drug release for Niosomes (F1-F6)

Stability Studies:
The prepared and optimized niosomes (F4) was packed and subjected to stability studies at 45 ± 2ºC for 90 days. Samples were withdrawn at time zero and after 15, 30, 60, and 90 days and evaluated for organoleptic properties (color, odor, and appearance) and drug entrapment efficiency. The results for stability studies are tabulated in Table 5.

Table 5: Results for stability studies

S. No.	Evaluation parameters	Initial	First month	Third month
1	Color	White	White	White
2	Odor	Odorless	Odorless	Odorless
3	Appearance	Spherical	Spherical	Spherical
4	Entrapment Efficiency	93.4 ± 0.44	93.7 ± 0.15	92.2 ± 0.78

Determination of Release Kinetics:

The mathematical models were used to evaluate the kinetics and mechanism of drug release. From the release kinetics of niosomes (Table 6), it was found that the First order release kinetics was best fitted. The correlation coefficient (r^2) was used as an indicator of the best fitting and was found to be highest for First order model kinetic. The mechanisms of drug release are non-Fickian diffusion (anomalous transport) with "*n*" value less than 1. This indicates the drug release depends on swelling and diffusion mechanism of release. Graphical presentation of first order model is shown in fig. 3.

Table 6: Dissolution Characteristics of Drug loaded Niosomes (F4)

Time (hrs)	1	2	3	4	5	6	7	8
Cumulative % drug released	25.3	38.7	47.7	70.22	76.4	84.9	88.8	91.6
% drug remaining	74.7	61.3	52.3	29.78	23.6	15.1	11.2	8.4
Square root time	1	1.414	1.73	2	2.23	2.45	2.64	2.82
Log cumulative % drug remaining	1.87	1.79	1.71	1.47	1.37	1.17	1.05	0.92
Log time	0	0.301	0.477	0.6	0.69	0.77	0.84	0.9
Log cumulative % drug released	1.4	1.59	1.67	1.85	1.88	1.92	1.94	1.96

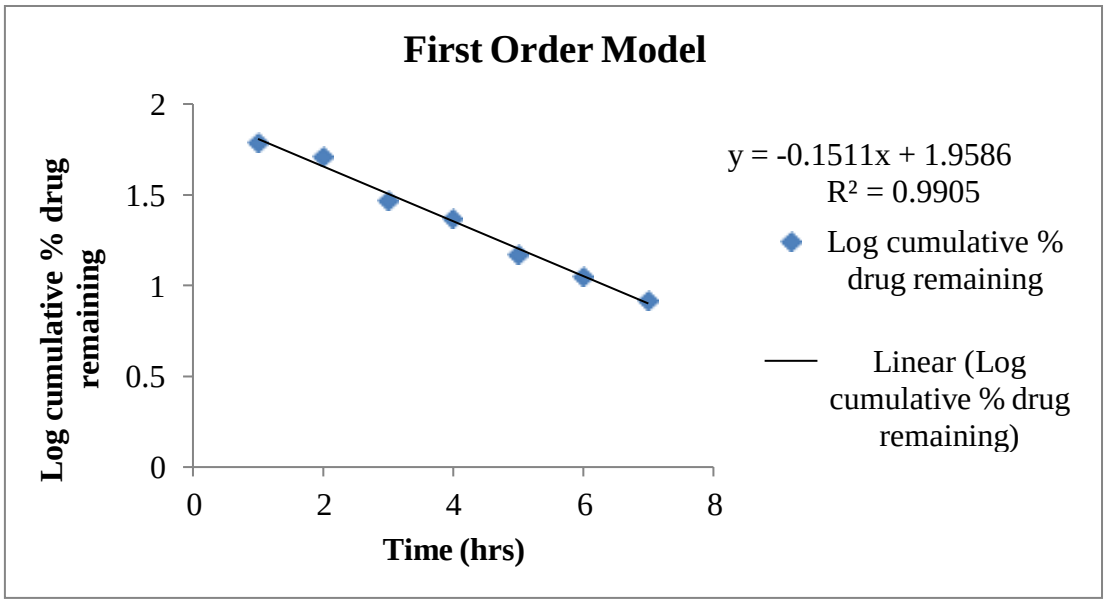

Fig. 3: First order model for Niosomes (F4)

CONCLUSION:

Cefetamet pivoxil is a 3rd generation cephalosporin, an antibiotic used in treatment of various upper respiratory tract infections and urinary tract infections. The organoleptic study showed white, spherical and odorless niosomes. The Scanning Electron Microscopy was conducted showed spherical niosomes. The micromeritic properties for the niosomes were determined in order to find the flow properties. The % moisture loss was minimal in the range 11.5 to 21.2. The degree of swelling was found to be in the range of 46.2-78.4%. The degree of swelling increased when the concentration of cholesterol was enhanced as the higher concentration of cholesterol enhances the rigidity of the niosomes and decreases the swelling ability.

The Entrapment efficiency of Niosomes was calculated and was found to be in the range of 85.11 to 93.4%. The formulation F4 showed highest drug entrapment efficiency. The cumulative percentage drug release from niosomes prepared with drug: cholesterol: surfactant i.e., 1:1:1 ratio showed highest drug release whereas 2:1:6 showed least in vitro drug releases. The amount of cholesterol affects the in vitro drug release. the rate of drug release is found to be in the order F6 < F5 < F3 < F4 < F2 < F1. The release pattern depends on the surfactant and cholesterol concentration. From the release kinetics of formulation F4 it was found that the First order release kinetics was best fitted for niosomes.

In a nutshell to conclude, niosomes play a vital tool in sustaining the drug release, reducing the dosing frequency, improving the patient compliance, improving the pharmacological action, irradiation of infection, improving efficacy of drug, improving the stability of drug and enhancing the bioavailability of drug.

ACKNOWLEDGEMENT:

Authors are thankful to Bascham Life Sciences, India and S.D. Fine chemicals Ltd, India for providing the gift samples of Cefetamet pivoxil and excipients respectively. Authors are also thankful to principal and management of Himalayan Institute of Pharmacy, Kala Amb for providing facilities to carry out the work.

CONFLICT OF INTEREST:

None

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