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Development and evaluation of cefpodoxime proxetil niosomes using various sorbitan esters

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ABSTRACT

Non-ionic surfactant vesicles containing cefpodoxime proxetil were prepared using drug, sorbitan ester and cholesterol in the ratios (by weight) of 1:3:1, 1:6:1, and 1:9:1. The prepared vesicles were characterized for the shape, size, entrapment efficiency, and *in-vitro* drug release and stability studies. The particle size distributions were carried out by optical microscopic technique and spherical shape observed by SEM studies. The drug encapsulation efficiencies varied from 46% to 70%. *Invitro* drug release studies were carried out by using PBS (p^H: 7.4) as a dissolution medium for 24 hours. From the *invitro* studies the span 40 was found to be more satisfactory which exhibit a retarded release of 65.25% for 24 hours, compared than other span series in controlled manner. The stability of vesicles was assessed by storage at 4 ± 1^0C, 25 ± 3^0C and 37 ± 2^0C for one month. The results suggested that the niosomes of cefpodoxime proxetil can be used for controlled release for controlled release drug delivery system.

Keywords: Cefpodoxime proxetil, Non-ionic surfactant, Entrapment efficiency, *In-vitro* drug release Stability studies,

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INTRODUCTION

Controlled release drug products are often formulated to permit the establishment and maintenance of drug concentration at target site for longer intervals of time [1]. One such technique of drug taking is niosomes. These are microscopic lamellar structures formed on admixture of non-ionic surfactant, Cholesterol and diethyl ether (or chloroform) with subsequent hydration in aqueous media [2]. They behave *in-vivo* like liposomes prolonging the circulation of entrapped drug and altering its organ distribution [3].

Niosomes (non-ionic surfactant based vesicles) are formed from the self-assembly of non ionic amphiphiles in aqueous media resulting in closed bi layer structures. These structures are analogous to liposomes and are able to encapsulate solutes are osmotically active and stable. The low cost, greater stability and resultant ease of storage of non-ionic surfactants has leaded the exploitation of these compounds as alternatives to phospholipids4. Niosomes have been used for improving the drug stability of entrapped drug [5], for detection of tumors [6], and to identify the tissue distribution of entrapped harmine [7], nimesulide [8], methotrexate [9], diclofenac sodium[10] and rifampicin [11].

All most all cephalosporins having short biological half lives which may need some novel formulation to maintain its concentration in body in the therapeutic window and to reduce side effects due to over dose [12]. Cefpodoxime proxetil is a third generation broad spectrum antibiotic having a short half life of 2.8 hours. The minimum dose is 200 mg, two times a day. The duration of therapy depends on the disease condition [13]. So in the present study cefpodoxime proxetil was encapsulated in niosomes using different sorbityl esters as surfactants.

MATERIALS AND METHODS

Cefpodoxime Proxetil U.S.P a Gift sample provided by Biochem chemicals, Biochem Pharmaceutical Industries Ltd., Mumbai. Sorbitan mono laurate (Span 20), Sorbitan mono palmitate (span 40), Sorbitan mono oleate (Span 80) of Loba chemical, Mumbai.Tritin x-100 from Nice chemicals, Mumbai.

Preparation of Niosomes

The niosomes were prepared by slight modifications of method reported by Azmin *et al* [14], in drug, surfactant and cholesterol in the ratios shown in table 1 were dissolved in 20 ml of chloroform in evaporating flask of rotary flash evaporator (Super fit apparatus, Mumbai). The flask was rotated at a speed of 140 rpm at 25 mm Hg pressure. The dried film was then hydrated with phosphate buffer saline pH 7.4 for 15 min at 50^{o}C on water bath. This suspension was sonicated for 3x30s to form unilamellar vesicles. The resultant aqueous dispersion of cefpodoxime proxetil niosomes dialyzed exhaustively in Himedia dialysis tubing against 0.9% NaCl as blank to separate the unentrapped drug.

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***In vitro* characterisation of niosomes**

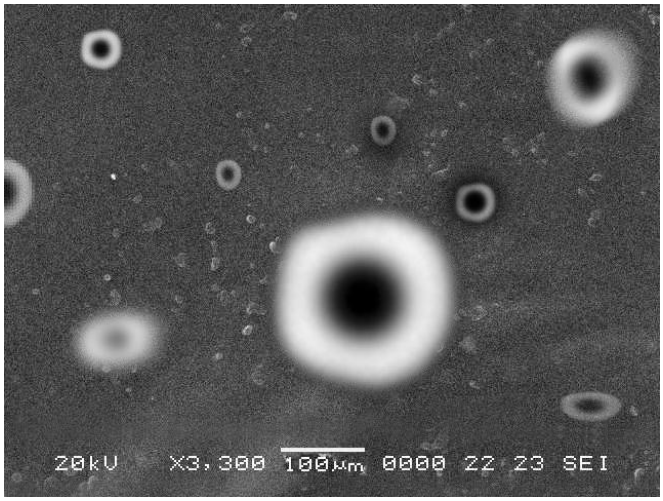

Figure 1 Shape of vesicles by scanning electron microscopy (100X)

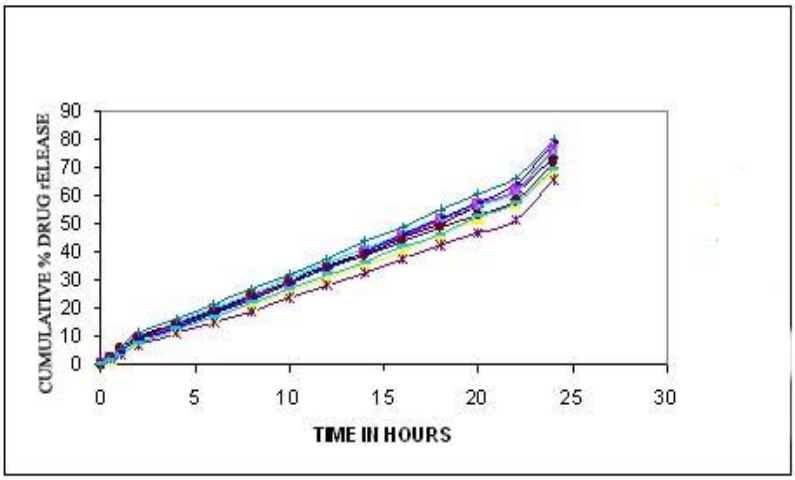

Figure 2 Comparative *in-vitro* dissolution profile formulations containing cefpodoxime proxetil

The shape and size of the niosomes was studied by optical microscope using pre-calibrated eyepiece. The shape of vesicles was further confirmed by scanning electron microscopy (Zeol–JSM 5610). The entrapment efficiencies were further determined by complete disruption of vesicles using Triton X-100. The entrapped cefpodoxime was estimated by digesting a definite quantity of niosomal suspension with 10% triton X-100 for 5min and centrifuging the resultant solution to get clear supernatant. The supernatant was suitably diluted with PBS and drug was estimated by UV spectrophotometric method [15] at 256 nm.

The in vitro drug release rate was determined using Nesselers cylinder of 50 ml , one end of which was sealed using a circular disc of cellophane membrane [16] (Himedia 0.4µm). Measured amount of niosomes was placed in 100 ml of phosphate buffer saline, pH 7.4,

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maintained at 37^{o} C and aliquots were withdrawn at intervals of one hour for 24 hours. At each sampling time, the volume of compartment was maintained with an equal volume of phosphate buffer saline, pH 7.4. The drug in withdrawn samples was estimated by the UV method. The results from release were used for kinetic study [17].

RESULTS AND DISCUSSION

Table 1: Formulations of niosomes containing cefpodoxime proxetil with different ratios of surfactant

Surfactants used	Formulation code	Drug : Surfactant :Cholesterol Ratio	Drug : Surfactant :Cholesterol Weighed(mg)
Span 20	F1	1 : 3 : 1	50 : 150 : 50
Span 20	F2	1 : 6 : 1	50 : 300 : 50
Span 20	F3	1 : 9 : 1	50 : 450 : 50
Span 40	F4	1 : 3 : 1	50 : 150 : 50
Span 40	F5	1 : 6 : 1	50 : 300 : 50
Span 40	F6	1 : 9 : 1	50 : 450 : 50
Span 80	F7	1 : 3 : 1	50 : 150 : 50
Span 80	F8	1 : 6 : 1	50 : 300 : 50
Span 80	F9	1 : 9 : 1	50 : 450 : 50

In this present study, efforts were made to formulate the cefpodoxime proxetil niosomes by thin film hydration technique with various surfactants in different ratios table 1. The sorbityl mono esters (spans) were selected as suitable surfactants due to the lipophilic nature of drug and the surfactants when compared to tweens. The thin film hydration technique was used for all preparations which yielded similar sized niosomes.

The preformulation studies showed better formation of niosomes with span when compared to tween. The particle sizes of formulation were done by optical microscope and the morphology of vesicles was clearly observed by scanning electron microscopy. The niosomal formulations showed an average of 8.348 µm by optical microscopy (45X).

The best formulations were observed by scanning electron micrograpy shows 0.058 m and 0.064 µm respectively for formulation F5 and formulation F3 respectively at 500X magnification.

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Table 2: Particle size and entrapment efficiency of niosomes containing cefpodoxime proxetil

Surfactants used	Formulation code	Average particle size (µm)	% Entrapment efficiency ±S.D*
Span 20	F1	6.14	46.63±0.42
Span 20	F2	8.77	58.49±0.51
Span 20	F3	10.45	68.67±0.34
Span 40	F4	8.38	60.01±0.92
Span 40	F5	9.13	70.72±0.85
Span 40	F6	8.54	64.12±0.45
Span 80	F7	6.64	49.62±0.52
Span 80	F8	7.96	53.24±0.14
Span 80	F9	9.13	57.33±0.26

***Each value is ± SD of three independent determinations**

The entrapment efficiency studies shown better entrapment efficiency in formulation F5 (Span 40,1:6:1) and formulation F3 (Span 20,1:9:1) with 70.72 % and 68.67 % respectively in indirect method and the percentage entrapment efficiency of both formulations were found to be 99.37% and 98.97% respectively by direct method as shown in table 2. The results from entrapment efficiency shows formulation with span 40 and span 20 shows better entrapment efficiency. This may be due to the change in HLB value and change in the phase transition temperature of surfactants. The in vitro drug release studies were done for all formulations up to a constant time of 12h and a comparison on cumulative release with time and with pure drug and formulations were investigated.

Table 3 *In-vitro* drug release study niosomes containing cefpodoxime proxetil

Formulation code	% Drug release in 24 Hours
F1	73.68
F2	76.45
F3	68.2
F4	75.41
F5	65.45
F6	71.82
F7	80.05
F8	78.61
F9	69.50

The pure drug showed 93.88 % of release in 12 hours and all formulations showed an average release of 59.82 % release in 12 hours of time and best formulations of formulation F5 (Span 40, 1:6:1) and formulation F3 (Span 20,1:9:1) showed 51.26 % and 57.37 % of drug release respectively as shown in table 3. The formulations F5 (Span 40, 1:6:1) and F3 (S20, 1:9:1) were selected as best formulations based on the results from entrapment efficiency and the in vitro release studies.

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Table 4. Consolidation chart of kinetic study

Formulation Code	Zero order		First order		Higuchi plot	
	Slope	r^2	Slope	r^2	Slope	r^2
F1	5.093	0.9993	-0.0335	0.9772	5.0085	0.9593
F2	5.1895	0.9986	-0.0343	0.9744	5.1009	0.9964
F3	4.7744	0.9969	-0.0301	0.9720	4.692	0.9943
F4	5.20852	0.9998	-0.0346	0.9848	5.122	0.9986
F5	4.3360	0.998	-0.026	0.9825	4.2615	0.9956
F6	4.8374	0.9998	-0.032	0.9732	4.7572	0.9986
F7	5.4841	0.9995	-0.0382	0.9731	5.393	0.9982
F8	5.4001	0.9973	-0.0361	0.9689	5.306	0.9945
F9	4.8861	0.9989	-0.0309	0.9785	4.8024	0.9966

The kinetics of drug release were studied by taking the cumulative drug release in consideration and plotted in Zero order, First order and Higuchi plots. The results of kinetic study revealed the drug released from the formulations followed by diffusion process which confirmed on comparison of correlation coefficients from the zero order, first order and Higuchi plots. The zero order plots shows a correlation of range from 0.996-0.999 as shown in table 4.

The stability studies for best formulations were done to find out suitable storage condition for the final products, which suggests to store always in refrigerator around 4 ±1° C due to less leakage of drug from those preparations.

The further studies can be carried out by adding any ligand combination or by coating with polymer like poly ethylene glycol for its targeted action and the animal testing are required to study the dose calculation and to study the bio distribution of drug in body.

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