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RESEARCH PAPER

FORMULATION, OPTIMIZATION AND CHARACTERIZATION OF NAPROXEN NIOSOME

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Abstract

Niosomes are vesicular delivery systems which can be formed by aqueous dispersion of non-ionic surfactant films. They are known as analogues of liposomes, and have been used in cosmetic formulations and experimentally as drug carriers. Apart from conventional spherical vesicles, various structures of Niosomes can be formed by varying the vesicle membrane compositions of certain mixed surfactant systems. An effort was made to formulate the Naproxen Niosomes and incorporate the Niosomes into the gel. Formulation F2 (71.98%) showed maximum release while other formulation showed less amount of drug release in 12h. Formulation F5 has highest coefficient of regration (R^2 =0.998) value and follows drug release by first order model. Hence F2 formulation was the optimized one. The optimized formulation F2 was found to follow first order release pattern which was revealed by the linearity shown from the plot of time versus drug release.

Keywords

Niosomes , Naproxen , Dissolution, Proniosome

INTRODUCTION

Niosomes are vesicular delivery systems which can be formed by aqueous dispersion of non-ionic surfactant films. They are known as analogues of liposomes, and have been used in cosmetic formulations and experimentally as drug carriers. Apart from conventional spherical vesicles, various structures of Niosomes can be formed by varying the vesicle membrane compositions of certain mixed surfactant systems. For example, mixtures of hexadecyl diglycerol ether (C16G2): cholesterol: polyoxyethylene 24 cholesteryl ether were previously shown to form spherical, tubular, polyhedral and disk-like vesicles, depending on the molar ratio.[1] Non- ionic surfactant vesicles results from self assembling of hydrated surfactant monomer. Non- ionic surfactant of wide verity of structural types is use full alternatives to phospholipids, in fabrication of vascular system. There is chemical difference between Niosomes and liposome, Niosomes posse's physical properties, similar to liposomes which are formed from phospholipids but as the name indicated Niosomes, non- ionic surfactant vesicles prepared by incorporation of non- ionic surfactant. Niosome also prepared by various ionic amphiphiles such as dicetylphophate stearylamine etc, to achieve a stable vesicular suspension. Non- ionic surfactant forms a verity of aggregates from micelles to large vesicles, which can be used as vehicles for drug delivery.Niosomes are essentially non-ionic surfactant vesicles in which the aqueous solution of solute is enclosed by a bilayer of surfactant macro-molecules.[2,3,4] Naproxen is a potent non- steroidal anti-inflammatory drug, used in the treatment of rheumatoid arthritis, osteoarthritis, acute gout. Naproxen use for niosome preparation because of their adverse effects such as irritation and ulceration of the gastro-intestinal (GI) mucosa by taking orally the Naproxen was incapsulate by niosome to overcome that problem. Naproxen has low aqueous solubility and slow dissolution while orally administration, niosome used for improving aqueous solubility also.

MATERIALS AND METHODS

Naproxen gift sample was obtained from Divis laboratory Ltd., Cholesterol received from HIMEDIA laboratories Pvt. Ltd. And Tween 80, Tween 20 obtained Merck specialities Pvt. Ltd. Mumbai. All Ingredients and solvents used were AR grade.

Section of Surfactants

Surfactants are the backbone of the basic composition of niosome. In the present study the nonionic surfactant of sorbitane esters class were selected. From this class tween 80 and tween 20 were chosen for the preparation of niosome. These surfactants were used in combination with cholesterol.

Method of preparation of niosome

Preparation of Proniosome

Proniosome were prepared by a method modified from Perrett et al. (1991). 50mg of naproxen with surfactant, and cholesterol were mixed with 6 ml absolute ethanol in a wide mouth glass tube. Then the open end of the glass tube was covered with a lid and warmed in a water bath at 60-65°C for 5 min. then 10ml ethanol was added and warmed in water bath for 3 minute. 100µml hot water was added and still warmed on the water bath for about 2 min till the clear solution was observed. The mixture was allowed to cool down at room temperature till the dispersion was converted to proniosomal gel. [22]

Conversion of proniosome to niosome

1ml of proniosome gel was taken and add 5ml water in to it shake and allow to stand for 5 min, and then observed microscopically.[22]

Evaluation of Niosomes

Entrapment Efficiency

The entrapment determined by freeze thawing/centrifugation method. 1 ml Niosomal dispersion was prepared from the proniosomal gel were frozen for 24 hr at -20°C in Eppendorf tubes. The sample were removed from the freezer let to thaw at room temperature then centrifuge at 13000 rpm for 40 mint at 4° C, then 0.2 ml supernatant was analyzed for free naproxen at 330.1 nm after diluted up to 3 ml. The amount of entrapped drug was determined by following formula by subtracting free drug concentration from total drug concentration.[23]

$$EE\ (\%) = C_e / C_t \times 100$$

Were,

EE (%) - % entrapment efficiency

C_e - concentration of entrapped drug

C_t - concentration of total drug

Particle Size

Particle size was determined by binocular microscope. About 50 particles individually were selected random and their size was measured using calibrated ocular micrometer scale average was taken and size distribution range and mean diameter were calculated. Microphotographs were taken by using digital camera.[22, 28]

***In Vitro* Drug Release Study**

The dissolution cell consisted of a hollow glass cylinder (length 14.6 cm and internal diameter 2.5 cm) made up of Borosil glass. One end of the cylinder was covered with got intestine membrane. The dissolution cell was placed in a 50 ml Borosil beaker that served as the receptor cell. The contents of the dissolution cell were agitated with the help of a glass stirrer. The receptor cell contained a magnetic bead and was rotated at a constant speed. The temperature in the dissolution and receptor cells was maintained at 37±2°C, with the help of a thermostat. Two milliliters of each formulation was subjected to release studies. Phosphate buffer (50 ml) pH 7.4 was placed in the receptor cell. 2 ml sample of each formulation was transferred to the dissolution cell. Two milliliter samples were withdrawn from the receptor cell at specified time intervals of 1,2,3,4,5,6,7,8,9,10,11and 12h. At each time immediately after the removal of the sample, the medium was compensated with fresh phosphate buffer (pH 7.4). The samples were analyzed for Naproxen content using a UV spectrophotometer (PC based double beam Systronic UV spectrophotometer 2202) at λmax 224 nm.[27, 28]

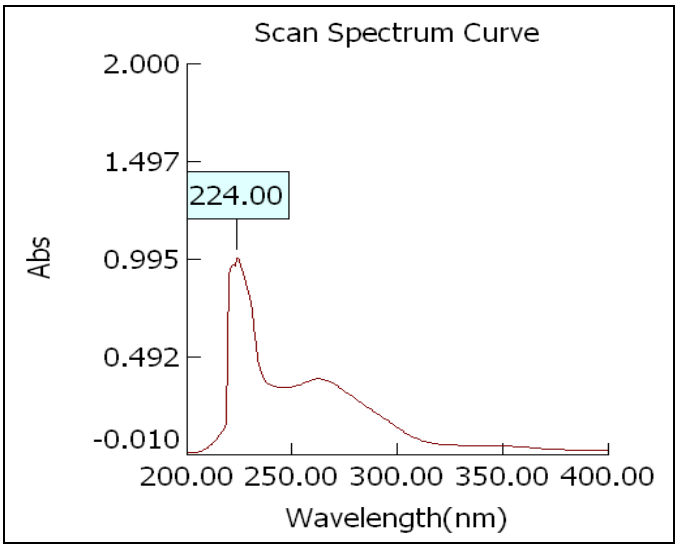

Figure 1 Determination λ max of Naproxen at 224 nm

Release kinetic study

The release data were analyzed mathematically according to the following models.[27]

Zero order equation

$Q_t = Q_0 + K\ t$

First order equation

$\text{Log}\ Q_t = \log Q_0 + K\ t/2.303$

Higuchi order equation

$Q = K\sqrt{t}$

Where,

Q is the amount of drug released at a time (t) and K is the rate constant.

***In vitro* skin permeation**

The skin permeation of naproxen from niosome formulations was determined by using Franz (vertical) diffusion cell. The Wistar rat (7–9 weeks old) skin was mounted on the receptor compartment with the stratum corneum side facing upwards into the donor compartment. The donor compartment was filled with the niosome formulation. A 20 ml pH 7.4 phosphate buffer was used as receptor medium to maintain a sink condition. The available diffusion area of cell was 2 cm^2. The receptor compartment was maintained at 37±2°C and stirred by a magnetic bead at 500 rpm. At appropriate time intervals, 2 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh receptor solution. The samples were analyzed by UV-spectrophotometer for naproxen contents.[22]

The cumulative amount of Naproxen permeated into the receptor compartment was plotted against time to obtain a percentage permeation profile.

RESULTS AND DISCUSSION

Formulation of Niosomes

Based on the optimized parameters, Niosomes were prepared by varying the cholesterol and surfactant in different ratios. Each formulation was evaluated for percentage of drug entrapment and for their cumulative drug release.

Table 1: Different batches of niosome

Code	Cholesterol (mg)	Drug (mg)	Tween 80 (mg)	Tween 20 (mg)
F1	50	50	100	100
F2	50	50	50	150
F3	50	50	150	50

F4	50	50	75	125
F5	50	50	125	75

Figure 2 : Microphotograph of niosome at 40x magnification

Entrapment efficiency and particle size

The entrapment efficiency was performed to estimate the actual amount of drug being entrapped. Maximum percent drug entrapped in F1 and lowest percent in F5. Increases in the concentration of cholesterol did not show any influence in entrapment efficiency. Amount of drug not increases the entrapment of drug (Table 2).

Particle size was performed by ocular light microscope the average of the niosome was found between the ranges of 3.81 – 4.14 µm (Table no. 16). The main factor affecting the size of niosome is cholesterol and HLB of surfactant. F5 having highest average Particle size. Noisomes are spherical in shape.

Table 2 : Entrapment efficiency and particle size of Niosomes

Formulation Code	Entrapment Efficiency (%)	Mean Particle Size (µm)
F1	75.24	3.93±1.81
F2	74.59	3.81±1.82
F3	67.55	4.14±1.80
F4	74.02	3.84±1.82
F5	65.91	4.11±1.83

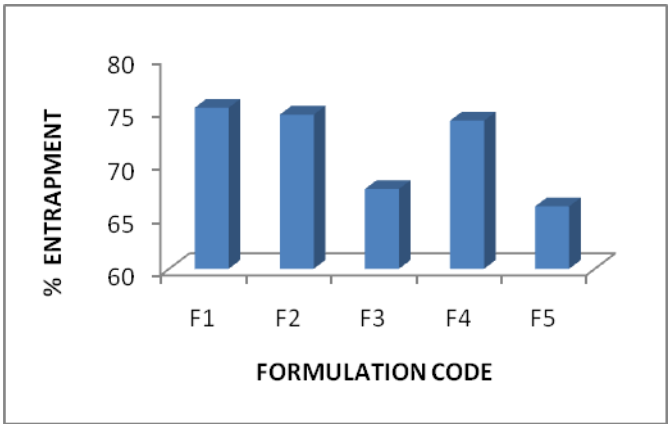

Figure 3 : Entrapment efficiency of niosome formulation

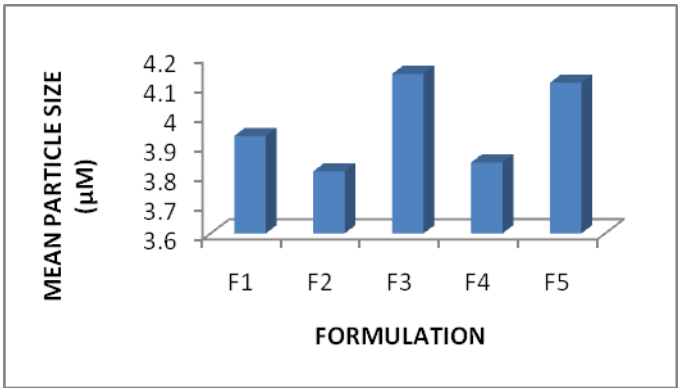

Figure 4 : Mean particle size of formulation

7.4.2 *In Vitro* release study

Under perfect sink condition, the drug release rate depends on concentration of cholesterol and surfactant. Drug release behavior of Naproxen was studied in phosphate buffer (pH 7.4) at 37±2°C. The curve was obtained after plotting the cumulative amount of drug released from each formulation against time. Formulation F2 (71.98%) showed maximum release while other formulation showed less amount of drug release in 12h. Formulation F5 has highest coefficient of rgration (R^2 =0.998) value and follows drug release by first order model.

To predict the release pattern of Naproxen from Niosomal formulation batches (F-1 to F-5) correlation coefficient and rate constant (Table-4) was calculated for zero order, first order and higuchi order kinetics. The study of drug release kinetics showed that majority of the formulations governed by first order kinetic model.

Table 3 : %cumulative drug release of niosome

Time	F1	F2	F3	F4	F5	Control
0	0	0	0	0	0	0
1	7.44	6.83	6.51	5.14	6.4	6.61
2	12.23	13.25	11.26	10.82	13.42	15.62
3	20.20	19.65	17.18	17.04	19.50	28.24
4	28.46	27.69	24.30	22.72	26.84	45.21
5	35.65	35.22	31.70	29.49	31.72	63.89
6	41.50	42.85	37.33	37.06	36.29	78.09
7	48.15	50.44	42.67	43.90	40.26	97.01
8	52.41	57.68	46.23	47.61	44.22	
9	57.20	61.00	50.08	52.48	50.02	

10	61.72	64.87	53.93	56.54	53.68	
11	66.51	67.45	57.78	61.68	56.73	
12	70.24	71.98	62.52	65.20	60.39	

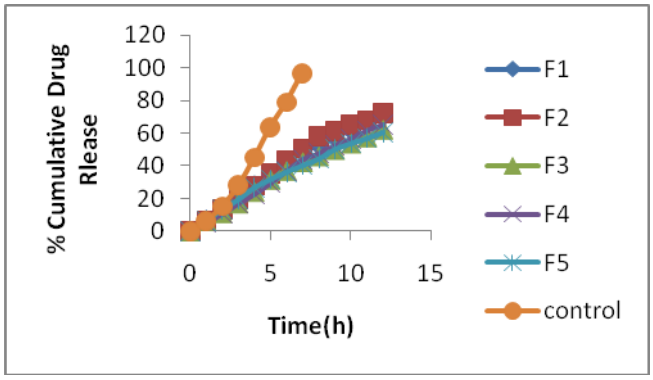

Figure 4 : %CDR Vs TIME graph for naproxen release

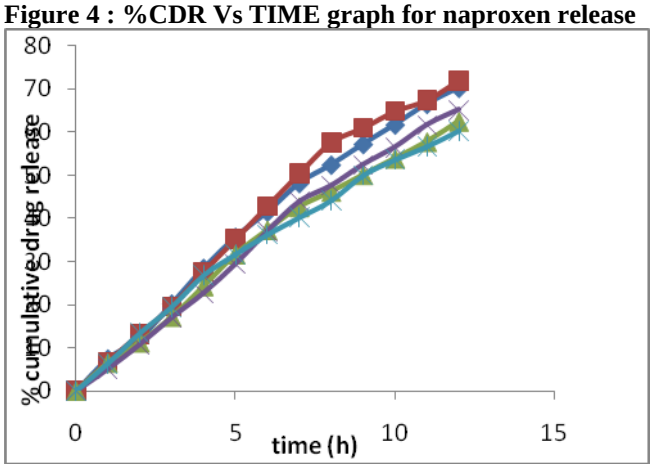

Figure 5: zero order release kinetic of naproxen

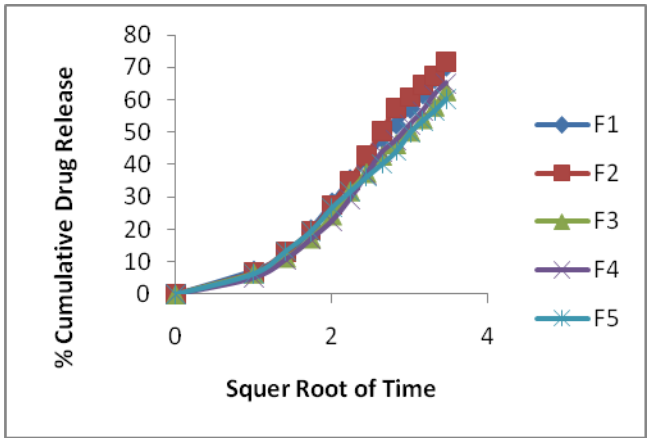

Figure 6: first order release kinetic of naproxen

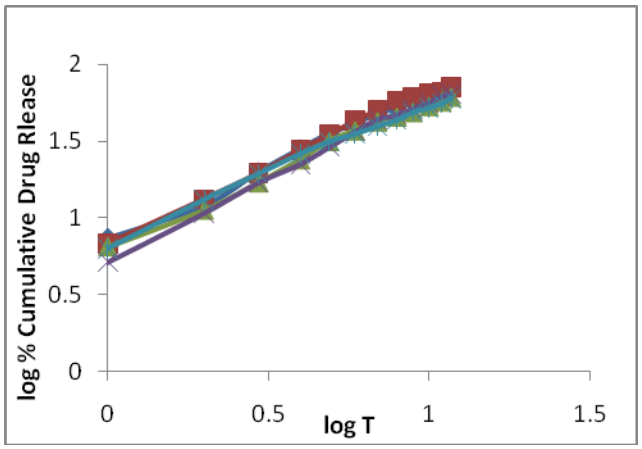

Figure 7 : Higuchi order release kinetic of naproxen

Table 4 : value of rate constant (k) and coefficient of regration (R^2)

Formulation Code	Zero order model		First order model		Higuchi order model	
	K	**R^2**	**K**	**R^2**	**K**	**R^2**
F1	2.48	0.988	0.030	0.995	20.30	0.949
F2	2.33	0.983	0.028	0.992	20.80	0.942
F3	3.12	0.987	0.040	0.997	18.06	0.948
F4	2.90	0.993	0.036	0.995	18.84	0.934
F5	3.30	0.986	0.042	0.998	17.45	0.962

CONCLUSION

An effort was made to formulate the Naproxen Niosomes and incorporate the Niosomes into the gel. Formulation F2 (71.98%) showed maximum release while other formulation showed less amount of drug release in 12h. Formulation F5 has highest coefficient of rgration (R^2 =0.998) value and follows drug release by first order model. Hence F2 formulation was the optimized one. The optimized formulation F2 was found to follow first order release pattern which was revealed by the linearity shown from the plot of time versus drug release.

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