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Research Article

CHARACTERIZATION, OPTIMIZATION AND FORMULATION OF NIOSOME CONTAINING NAPROXEN

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ABSTRACT

Niosomes are vesicular delivery systems which can be formed by aqueous dispersion of non-ionic surfactant films. An effort was made to formulate the Naproxen Niosomes and incorporate the Niosomes into the gel. Formulation F2 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 and found more productive.

Keywords: Niosomes, Dissolution, Liposomes, Naproxen

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.[1] Naproxen has low aqueous solubility and slow dissolution while orally administration, niosome used for improving aqueous solubility also.

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of mild to moderate pain, fever, inflammation and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, injury, menstrual cramps, tenditis, bursitis and the treatment of primary dysmenorrhea.[2]

MATERIALS AND METHODS

Preformulation Studies

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of Preformulation studies is to develop a portfolio of information about the drug substance, so that this information useful to develop different dosage forms. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.

Organoleptic Characteristics of Naproxen

The color, odor, and taste of the Naproxen were characterized and recorded using descriptive terminology.

Melting Point of Naproxen

Melting point is the temperature at which the pure liquid and solid exist in equilibrium. In practice, it is taken as equilibrium mixture at an external pressure of 1 atmosphere; this is sometimes known as normal melting points. The naproxen were taken in Thiele's tube and the temperature was recorded when naproxen complete melted.

Solubility Study of Naproxen

The solubility of Naproxen was tasted in various common solvents. A definite quantity (10 mg) of drug was dissolved in 10 ml of each solvent at room temperature. The solubility was observed only by visual inspection.

Determination of Moisture Content and Loss on Drying

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The moisture in a solid can be expressed on a wet-weight or dry-weight basis. On a wet-weight basis, the water content of material is calculated as percentage of the wet solid, whereas on the dry weight basis, the water is expressed as a percentage of the weight of the dry solid.[3]

Determination of Partition Coefficient

The partition coefficient is defined as the ratio of un-ionized drug distributed between the organic and aqueous phase at equilibrium.The partition coefficient was measured of naproxenlipophilicity and an indication of its ability to cross the biological membrane.The partition coefficient of naproxen was determined in n-octanol: water. 10-10 mg Naproxen was accurately weighted and added to 10ml octanol and 10ml water. The mixture was shaken using mechanical shaker for 24 hours until equilibrium was reached phases were separated by separating funnel and the aqueous phase and oil phase was analyzed after appropriate dilution.

FORMATION OF NIOSOME

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 80and 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***

Proniosomes 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. [5]

- ***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.[5]

EVALUATION OF NIOSOMES

Entrapment Efficiency

The entrapment of niosome prepared by "formation of niosome from pronisome" method was 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.[6]

$$EE\ (\%) = C_e/C_t X100$$

Were,
EE (%) - % entrapment efficiency
C_e - concentration of entrapped drug
C_t - concentration of total drug

Particle Size

Particle size of the niosome 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.[5, 7]

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 λmax224 nm.[7, 8]

RESULTS AND DISCUSSIONS

Preformulation Study

Organoleptic Characteristics

Organoleptic Characteristics was visually determined which was compliance with the standard.

Table 1: Organoleptic characteristic of naproxen

Sr.no	Properties	Standard	Observed
1	Appearance	White crystalline	White crystalline
2	Odor	Odorless	Odorless
43	Taste	Bitter	Bitter

Melting Point of Naproxen

Melting point was determined by Thiele's tube method.Melting point of naproxen was found to be in the range of 154°C which was in compliance with the official value.

Solubility of Naproxen

Solubility of naproxen in different solvents was performed, the study indicate the affinity of naproxen toward non-aqueous solvents.

Table 2: Solubility of naproxen in different solvents

Sr.No.	Solvent	Solubility
1	Methanol	Soluble
2	Ethanol	Soluble
3	Acetone	Practically Insoluble
4	Distilled water	Insoluble
5	PBS pH (7.4)	Soluble
6	Chloroform	Practically insoluble

Determination of Moisture Content and Loss on Drying

The moisture content and loss on drying was determined by following formula,

Weight of water = weight of wet sample – weight of dry sample

% MC = Weight of water / Weight of dry sample ×100

And

% LOD = Weight of water / Weight of wet sample ×100

Percent loss on drying and moisture content was found to be 0.7% and 0.704% respectively.

Determination of Absorbance Maxima

The naproxen shows the absorbance maxima at 305.6 nm in ethanol when the 10 µg/ml solution was scanned at 200-400nm.

Preparation of Calibration Curve of Naproxen

- **In ethanol**

In this study Calibration curve was plotted Concentration Vs Absorbance by preparing dilution between the ranges of 2µg/ml-12µg/ml. Absorbance was determined range "between" 0.078 to 0.443.

- **In pH 7.4 phosphate buffer**

In this study Calibration curve was plotted Concentration Vs Absorbance by preparing dilution between the ranges of 2µg/ml-10µg/ml. Absorbance was determined range "between" 0.056 to 0.249.

Determination of Partition Coefficient

Concentration of the water and octanol dilution was calculated by the linear equation of the calibration curve of naproxen, and the value of partition coefficient was found to be 4.02.

Table 3: Partition Coefficient

Solvent	Absorbance at 330.1 nm	Concentration (µg/ml)
n-octanol	0.638	8.01
Water	0.566	1.99

Optimization of Process Variable

The preparation procure was accordingly optimized and validated on the basis of following process variable

Table 4: Effect of temperature

Temperature	Cholesterol (mg)	Tween 80 (mg)	Tween 20 (mg)	Drug (mg)	% Entrapment
40°C -60°C	50	100	100	50	Not Formed
Above 80°C	50	100	100	50	Color change

Table 5: Effect the concentration of cholesterol and drug

Sr. no.	Cholesterol (mg)	Tween 80 (mg)	Tween 20 (mg)	Drug (mg)	% Entrapment
1	50	100	100	100	68.26
2	100	100	100	50	69.03

EVALUATION OF NIOSOME

Entrapment efficiency and particle size

Table 6: 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

In Vitro release study

Table 7: % cumulative drug release of noisome

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	-

Table 8: 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

DISCUSSION

Pre formulation study

The naproxen identified by white crystalline color, and bitter in test which is compliance with standard value of naproxen, its show starting melting at 154°C which was between the range, Solubility of naproxen in different solvents was performed, the study indicate the affinity of naproxen toward non-aqueous solvents. The solubility of naproxen was show in solvent like ethanol, methanol, dichloromethane and 7.4$_P$H phosphate buffer system and insoluble in Distilled water. %Moisture content and loss on drying was found to be 0.704 and 0.70 respectively. Value of partition coefficient was found to be 4.02.

In ethanol, the determined absorbance show linear absorption and value of the coefficient of Regration was found to be R^2 = 0.998 and equation of line was found to be Y = 0.037x+0.004. In phosphate buffer calibration curve of Naproxen show straight-line with coefficient of Regration R^2 =0.998 was found and equation of line was found to be Y = 0.024x+0.003.

Preparation of niosome

Out of many method of preparation of niosome "formation of niosome from proniosome" was selected. Cholesterol and tween 80 and tween 20 were used in niosome formation. Different concentration of surfactant was used for preparation of niosome. Temperature was maintained between 60-70°C. Below 40°C Temperature the niosome was not formed and above temperature 80°C the formulation changes in color before formation of proniosomal gel.

Particle size and shape

Particle size was performed by ocular light microscope the average of the niosome was found between the ranges of 3.81 – 4.14 µm. The main factor affecting the size of niosome is cholesterol and HLB of surfactant. F5 having highest average Particle size. Niosomes are spherical in shape.

Entrapment efficiency

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.

In vitro Release

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 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.

CONCLUSION

Aim of the present study was to formulate and characterization of niosome naproxen by using cholesterol, surfactant like Tween 80, Tween 20. Preformulation study of the drug (naproxen) was donning. The naproxen was Identified by solubility, melting point, absorption maxima (lambda max) etc. FT-IR study was carried out to check possible interaction between the drug component and surfactant used for niosome formulation, which confirmed that, no interaction was found between them. Naproxen niosome was prepared by "Niosome formulate from proniosome".

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