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Formulation and Characterization of Naproxen Containing Niosomes: A Research

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HUMAN

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ABSTRACT

The proposed study was carried out with the aim to assess the formulation and characterization of niosome based on naproxen it is used for 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.

INTRODUCTION

Niosomes are vesicular delivery systems which can be formed by aqueous dispersion of non-ionic surfactant films[1]. They are known as analogues of liposomes, and have been used in cosmetic formulations and experimentally as drug carriers[1]. Niosomes are essentially non-ionic surfactant vesicles in which the aqueous solution of solute is enclosed by a bilayer of surfactant macromolecules[2,3,4].

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[5,6,7].

MATERIALS AND METHODS

Materials

Naproxen is purchased from Divis Laboratory Ltd. Cholesterol is purchased from HIMEDIA Laboratories Pvt. Ltd. Tween 20 and tween 80 from Merck specialities Pvt. Ltd. and Ethanol from Jiangsu Huaxi International Trade Co. Ltd.

Methods

Preformulation Studies

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

Preparation of Proniosome

Proniosomes were prepared by a method modified from Perrett et al. (1991). 50 mg 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 10 ml ethanol was added and warmed in water bath for 3 minute. 100 µml 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[8,9,10].

Conversion of proniosome to niosome

1 ml of proniosome gel was taken and add 5ml water into it, shake and allow to stand for 5 min, and then observed microscopically[8,11,14].

RESULTS

Preformulation Study

Organoleptic and solubility parameter

Organoleptic & solubility parameter was visually determined which was compliance with the standard in **Table No. 1 & 2.**

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.

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 200-400 nm in **Graph 1.**

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 2 – 12 µg/ml. Absorbance was determined in the range "between" 0.078 to 0.443 **in Table No. 3 and Calibration Curve 1.**

- **In pH 7.4 phosphate buffer**

In this study Calibration curve was plotted Concentration Vs Absorbance by preparing dilution between the ranges of 2 – 10 µg/ml. Absorbance was determined in the range "between" 0.056 to 0.249 **in Table No. 4 and Calibration Curve 2.**

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 in **Table No. 5.**

Excipient and Active Compatibility Studies by FT-IR Spectroscopy

By comparing IR spectra of pure drug and drug with excipients it was observed that the drug is compatible with selected surfactant and co-surfactants.

Comments for compatibility: All IR spectra of pure compound and its composition with excipients in formulation are same. This indicates that there was no structural change caused by excipients **[Table No. 6 and Fig. 1].**

Optimization of Process Variable

The procured preparation was accordingly optimized and validated on the basis of following process variable **[In Table No. 7 and 8].**

Formulation of Niosomes:

It is shown in Table No. 9.

Evaluation of Niosome

1. Entrapment efficiency and particle size was shown in Table No. 10.
2. *In Vitro* release study was shown in Table No. 11.
3. Release kinetics shown in Table No. 12 13 14 ,15,16,17.
4. Skin Permeation Study was shown in Table No. 18.

DISCUSSION AND CONCLUSION

Pre-formulation study

The naproxen identified by white crystalline color, and bitter in taste which is compliant with standard value of naproxen, it started melting at 154°C which was between the range. Solubility of naproxen in different solvents was performed, the study indicates the affinity of naproxen toward non-aqueous solvents (Table No.8). The solubility of naproxen was better in solvents like ethanol, methanol, dichloromethane and pH 7.4 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.

The drug was identified by FT-IR spectra shown in (Figure 1). FT-IR spectra of mixture of drug and surfactant were shown there was no interaction between them. The absorption maxima were determined by using UV/Visible spectrophotometer in PBS pH 7.4 medium, found at 330.1 nm (Fig. No. 1).

In ethanol, the determined absorbance show linear absorption and value of the coefficient of Regression was found to be R^2 = 0.998 and equation of line was found to be Y = 0.037x + 0.004 (Curve 1). In phosphate buffer calibration curve of Naproxen shows straight-line with coefficient of Regression was found to be R^2 = 0.998 and equation of line was found to be Y = 0.024x + 0.003 (Curve 2).

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 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 range of 3.81 – 4.14 µm (Table No. 10). The main affecting factor for the size of niosome is cholesterol and HLB of surfactant. F5 having highest average Particle size. Noisomes 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. Increasing in the concentration of cholesterol did not show any influence in entrapment efficiency. Amount of drug did not increase the entrapment of drug (Table 10).

Skin irritation study

F1 formulation was used for performing skin irritation test. Erythema was not seen when animal observed for 14 days. It indicates that there is no irritation produced by formulation.

***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 12 h. Formulation F5 has highest coefficient of regression (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 17) 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.

Skin permeation

The amount Naproxen niosomes by skin permeation was similar, but much higher than that from the free drug (Fig. 11 and Table 18).

The formulation of control group was Naproxen suspended in the same solvent of proniosome formulation. Flux of Tween 20 and Tween 80 Naproxen Niosomes were similar, but much higher than free drug formulation (control) (Table 18). Surfactant in formulation always acts as a permeation enhancer; however, the enhancement ratio of Niosomes was shown in (Table No. 19).

F3 formulation showed maximum permeation flux of Naproxen and control formulation showed minimum permeation. (Table No. 19) the Figure No. 11 shows the permeation of drug was enhanced by surfactant present in Niosomes.

***In vivo* study**

Vascular permeability assay is a model of first stage inflammatory reaction. In vascular permeability assay, mediators of inflammation, released following stimulation, leads to dilation of arterioles and venules and increased vascular permeability (Eun-Hee Park, 2007). Naproxen at the oral doses of 120 mg/kg showed an inhibition of 43.73% in vascular permeability. From this finding, it is assumed that acute inflammatory effect of naproxen arises from its protection on the release of inflammatory mediators at the first stage. Result of vascular permeability studies revealed that Niosome shows significant ($p<0.05$) inhibition of inflammation.

The innervation of the cornea is provided by a relatively small number of primary sensory neurons located in the trigeminal ganglion. The majorities corneal fiber (poly model nociceptors) activate by near noxious mechanical energy, but they respond to heat, exogenous chemical irritants and to a large variety of endogenous chemical mediator released by damage corneal tissue. Therefore, these extensive nociceptive innervations of cornea make it suitable for studying pain and pain killer drug in trigeminal system. Trigeminal nucleus responds vigorously when applied hypertonic solution of 5M NaCl in corneal surface. Naproxen dose of 50 µl shows 51.55 % (%MPE) decreased in number of eye wiping.

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Table 1: Organoleptic characteristic of naproxen

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

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

Table 3: Concentration and Absorbance data for calibration curve

Sr. No.	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	2	0.078
3	4	0.161
4	6	0.224
5	8	0.295
6	10	0.384
7	12	0.443

Table 4: Concentration and Absorbance data for calibration curve

Sr. No.	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	2	0.056
3	4	0.102
4	6	0.151
5	8	0.193
6	10	0.249

Table 5. Partition Coefficient

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

Table 6. Interpretation of FTIR spectra of naproxen

Bonds	Standard (/cm)	Observed (/cm)
O-H stretch	3600-3500	3421.41
C=o stretch	1750	1740.39
C-O stretch	1100	1076.62
C=C stretch	1650-1550	1569.68

Table 7. 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 8: 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

Table 9: 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

Table 10: 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

Table 11:% cumulative drug release of niosome

Time	F11	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 12: Release kinetic parameter of formulation F1

Time (h)	Root T	Log T	%CDR	%CDRt	Log %CDR	Log %CDRt
0	0	0	0	100	0	2
1	1	0	7.44	92.56	0.87	1.96
2	1.41	0.30	12.23	87.77	1.08	1.94
3	1.73	0.47	20.20	79.80	1.30	1.90
4	2	0.6	28.46	71.54	1.45	1.85
5	2.23	0.69	35.65	64.35	1.55	1.80
6	2.44	0.77	41.50	58.50	1.61	1.76
7	2.64	0.84	48.15	51.85	1.68	1.71
8	2.82	0.9	52.41	47.59	1.71	1.67
9	3	0.95	57.20	42.80	1.75	1.63
10	3.16	1	61.72	38.28	1.79	1.58
11	3.31	1.04	66.51	33.49	1.82	1.52
12	3.46	1.07	70.24	29.76	1.84	1.47

Table 13: Release kinetic parameter of formulation F2

Time (h)	Root T	Log T	%CDR	%CDRt	Log %CDR	Log %CDRt
0	0	0	0	100	0	2
1	1	0	6.83	93.17	0.83	1.96
2	1.41	0.30	13.25	86.75	1.12	1.93
3	1.73	0.47	19.65	80.35	1.29	1.9
4	2	0.6	27.69	72.31	1.44	1.86
5	2.23	0.69	35.22	64.78	1.54	1.80
6	2.44	0.77	42.85	57.15	1.63	1.75
7	2.64	0.84	50.44	49.56	1.7	1.69
8	2.82	0.9	57.68	42.32	1.76	1.62
9	3	0.95	61.00	39.00	1.78	1.58
10	3.16	1	64.87	35.13	1.81	1.54
11	3.31	1.04	67.45	32.55	1.82	1.51
12	3.46	1.07	71.98	28.02	1.85	1.44

Table 14: Release kinetic parameter of formulation F3

Time (h)	Root T	Log T	%CDR	%CDRt	Log %CDR	Log %CDRt
0	0	0	0	100	0	2
1	1	0	6.51	93.49	0.81	1.97
2	1.41	0.30	11.26	88.74	1.05	1.94
3	1.73	0.47	17.18	82.82	1.23	1.91
4	2	0.6	24.30	75.70	1.38	1.87
5	2.23	0.69	31.70	68.30	1.50	1.83
6	2.44	0.77	37.33	62.67	1.57	1.79
7	2.64	0.84	42.67	57.33	1.63	1.75
8	2.82	0.9	46.23	53.77	1.66	1.73
9	3	0.95	50.08	49.92	1.69	1.69
10	3.16	1	53.93	46.07	1.73	1.66
11	3.31	1.04	57.78	42.22	1.76	1.62
12	3.46	1.07	62.52	37.48	1.79	1.57

Table 15: Release kinetic parameter of formulation F4

Time (h)	Root T	Log T	%CDR	%CDRt	Log %CDR	Log %CDRt
0	0	0	0	100	0	2
1	1	0	5.14	94.86	0.71	1.97
2	1.41	0.30	10.82	89.18	1.03	1.95
3	1.73	0.47	17.04	82.96	1.23	1.91
4	2	0.6	22.72	77.28	1.35	1.88
5	2.23	0.69	29.49	70.51	1.46	1.84
6	2.44	0.77	37.06	62.94	1.56	1.79
7	2.64	0.84	43.90	56.10	1.64	1.75
8	2.82	0.9	47.61	52.39	1.67	1.71
9	3	0.95	52.48	47.52	1.71	1.67
10	3.16	1	56.54	43.46	1.75	1.63
11	3.31	1.04	61.68	38.32	1.79	1.58
12	3.46	1.07	65.20	34.80	1.81	1.54

Table 16: Release kinetic parameter of formulation F5

Time (h)	Root T	Log T	%CDR	%CDRt	Log %CDR	Log %CDRt
0	0	0	0	100	0	2
1	1	0	6.4	93.6	0.80	1.97
2	1.41	0.30	13.42	86.58	1.12	1.93
3	1.73	0.47	19.50	80.50	1.29	1.90
4	2	0.6	26.84	73.16	1.42	1.86
5	2.23	0.69	31.72	68.28	1.50	1.83
6	2.44	0.77	36.29	63.71	1.55	1.80
7	2.64	0.84	40.26	59.74	1.6	1.77
8	2.82	0.9	44.22	55.78	1.64	1.74
9	3	0.95	50.02	49.98	1.69	1.69
10	3.16	1	53.68	46.32	1.72	1.66
11	3.31	1.04	56.73	43.27	1.75	1.63
12	3.46	1.07	60.39	39.61	1.78	1.59

Table 17: Value of rate constant (k) and coefficient of regression (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

Table 18: Cumulative amount release of niosome by skin permeation

Time (hrs.)	Cumulative Amount of Drug Release (µg)					
	F1	F2	F3	F4	F5	Control
0	0	0	0	0	0	0
1	20.83	22.21	28.81	17.77	24.84	19.16
2	40.10	39.49	47.39	40.62	42.99	28.33
3	64.33	61.71	76.20	63.47	60.19	41.66
4	80.20	79.81	101.30	92.24	80.26	52.50
5	105.26	97.91	119.88	111.71	100.32	66.66
6	117.80	116.83	144.05	128.64	117.52	75.00
7	138.68	138.23	158.92	144.72	131.86	91.66
8	159.57	157.15	178.43	165.03	149.06	104.16
9	182.96	181.01	200.74	184.49	161.48	120.00
10	201.34	204.05	213.75	203.96	182.50	135.83
11	221.39	220.51	226.76	221.73	218.81	151.66
12	246.46	242.72	237.91	242.89	236.01	167.50

Table 19: Flux and Enhancement ratio of niosome

Sr. No.	Formulation Code	Flux(µg/cm^2/h)	Enhancement Ratio
1	F1	20.32 ± 0.53	1.46
2	F2	20.14 ± 0.73	1.44
3	F3	23.36 ± 2.43	1.67
4	F4	20.72 ± 1.29	1.48
5	F5	19.94 ± 1.82	1.43
6	Control	13.91 ± 1.72	-

Table 20: Treatment of the groups and leakage of Evans blue dye (*A*630)

Group no.	Treatment	Abs. of Evans blue
1	1% Evans blue + 1% AA	0.129
2	1% Evans blue	0.041
3	1% Evans blue +1% AA + Niosome	0.070[a]

a- $p<0.05$ as compared to vehicle treated group

Table 21: Comparison group of different of mice

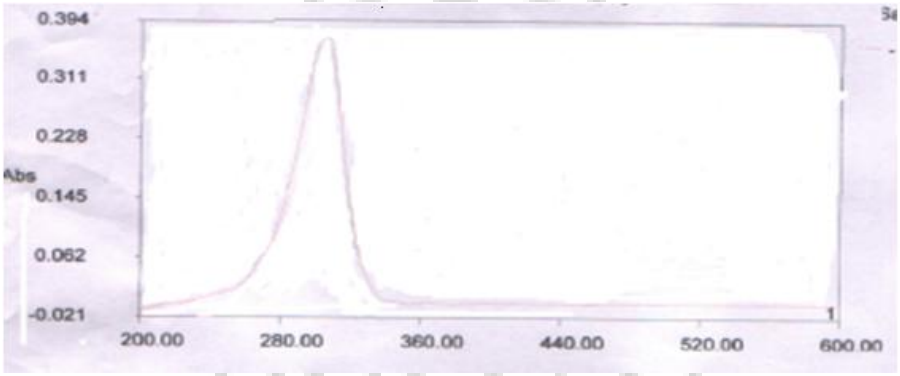
Comparison	Difference in mean	P<0.05
1 vs3	0.088	Yes
1 vs2	0.059	Yes
2 vs3	0.029	Yes

Trigeminal neuralgia test (Nociceptive tests)

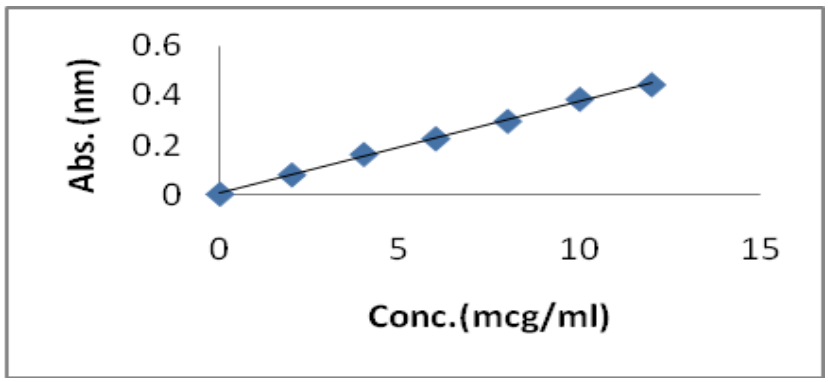
Table 22: Average eye wiping

Group no.	Treatment	Eye wiping (avg.)
1	Control (5M NaCl)	5.16
2	Treatment	2.50[a]

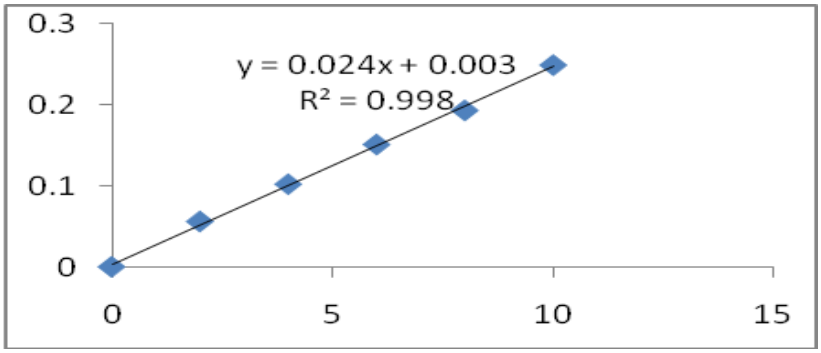
a- p < 0.05 as compared to control group



Graph 1: Absorbance Maxima of Naproxen



Curve 1: Calibration Curve of Naproxen in ethanol



Curve 2. Calibration graph of naproxen in phosphate buffer

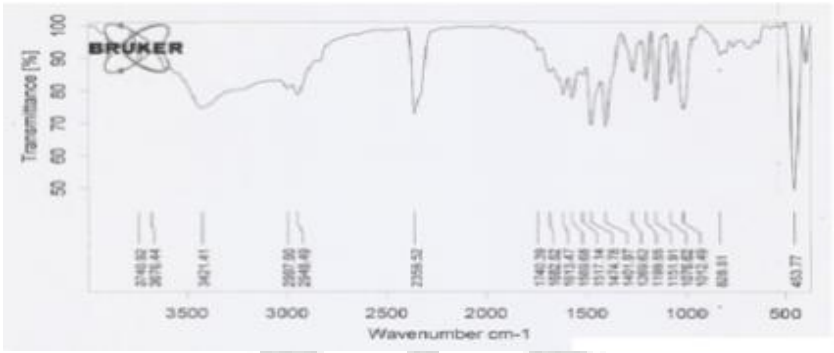


Figure 1. IR Spectra of naproxen

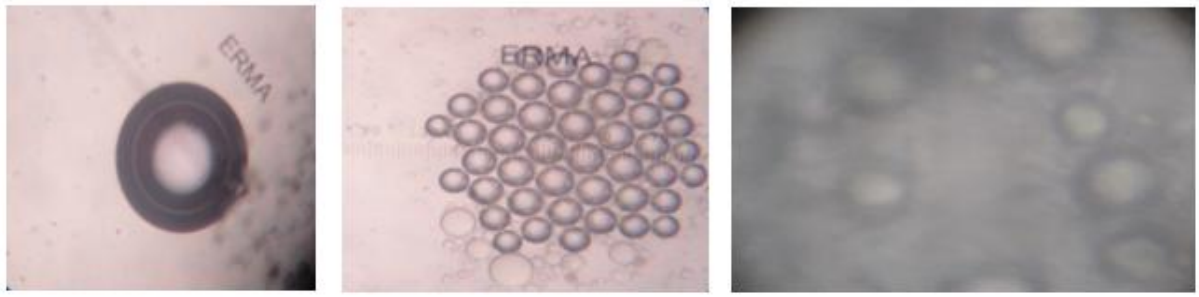


Figure 2, 3, 4 Microphotograph of single Niosome at 10x and 40x magnification

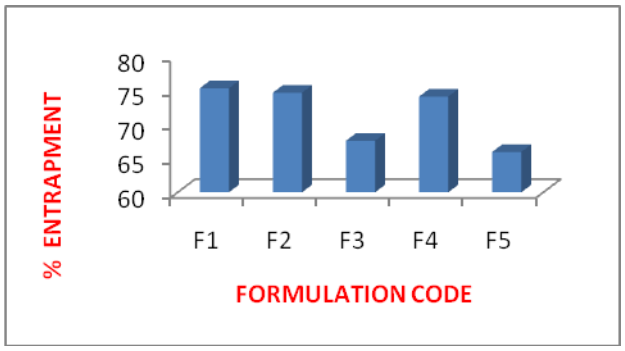


Figure 5. Entrapment efficiency of niosome formulation

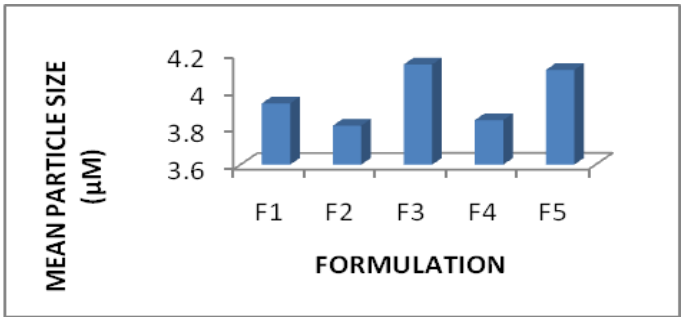


Figure 6. Mean particle size of formulation

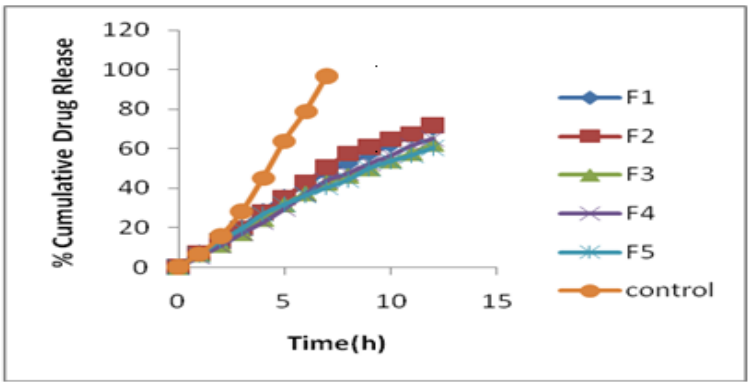


Figure 7: % CDR Vs TIME graph for naproxen release

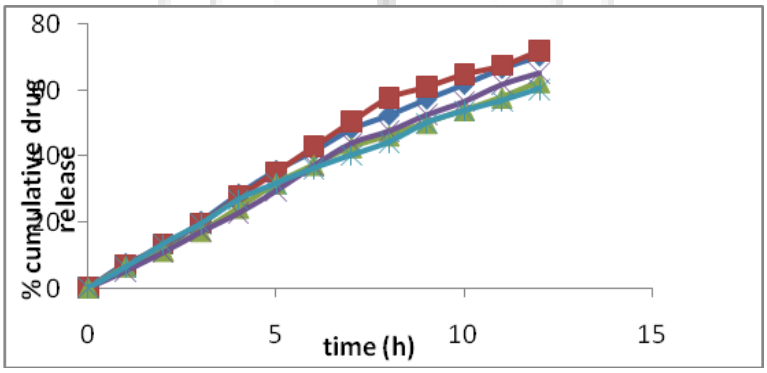


Figure 8: Zero order release kinetic of naproxen

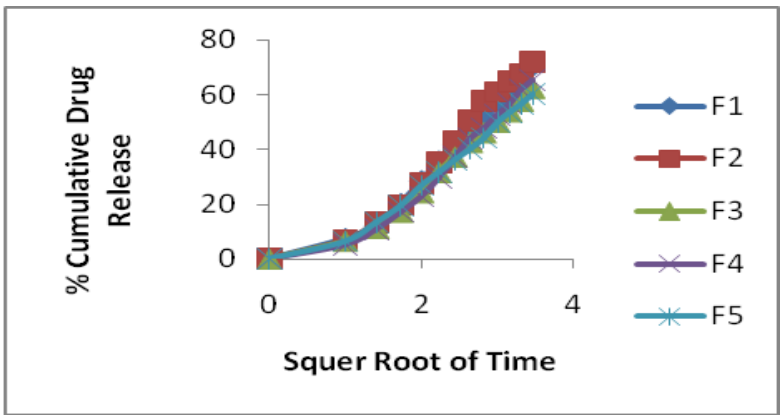


Figure 9: First order release kinetic of naproxen

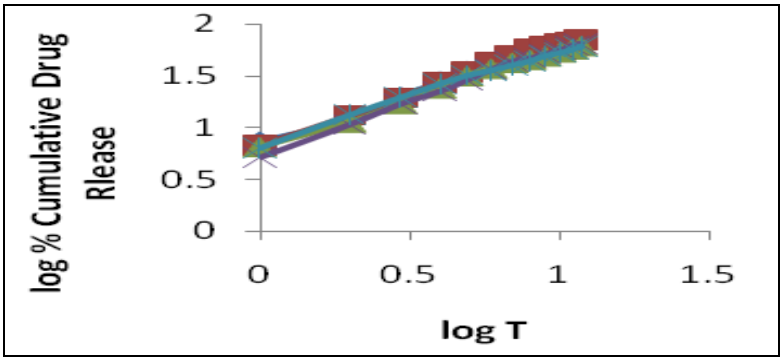


Figure 10: Higuchi order release kinetic of naproxen

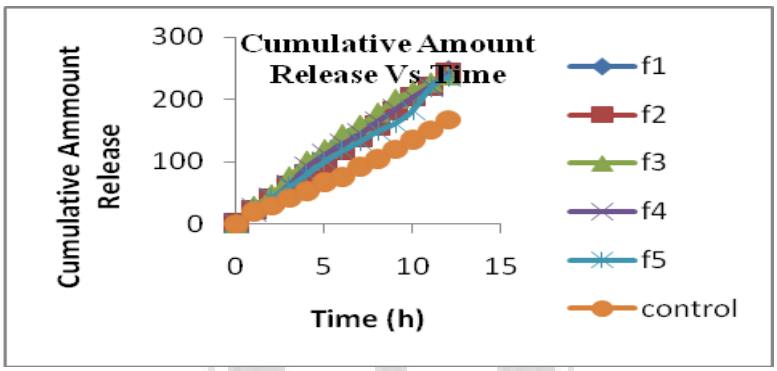


Figure 11 % Cumulative amount of drug release of naproxen by skin permeation

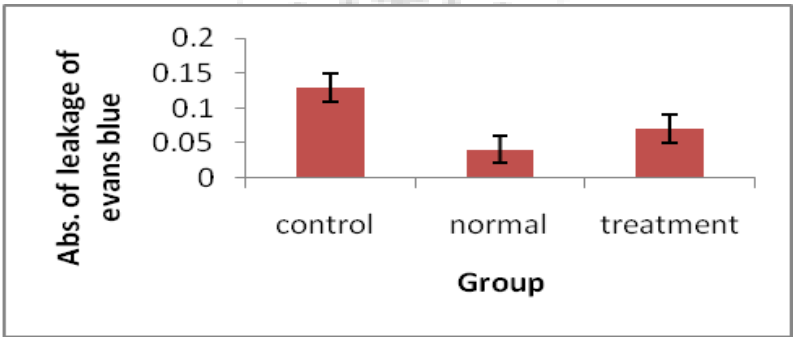


Figure 12: Vascular permeability of Evans blue dye in mice in different groups

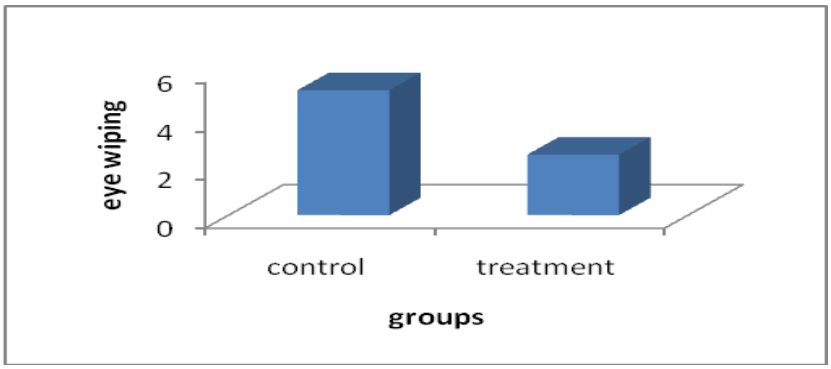


Figure 13: Eye wiping in rats in different groups