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Niosomes: A prominent tool for transdermal drug delivery

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ABSTRACT

Now-a-days a tremendous research work is going on to overcome the barrier properties of the skin. Recently niosomes have been reported for enhanced delivery of drugs. Niosomes are globular submicroscopic vesicles composed of nonionic surfactants. Meloxicam is used as model drug in the present study. Meloxicam entrapped niosomes were prepared by Thin film hydration technique using Nonionic surfactants (Span-80, Span-60, Tween-80 and Tween-60), Cholesterol and drug in different ratios. The prepared niosomes were characterized for size, shape, entrapment efficiency, *In-Vitro* drug release and *In-Vivo* performance. The niosomes appeared as round in shape and size range was found to be 1.54 – 2.64µm. Among all formulations $FS80_4$ shows high entrapment efficiency and consistent drug release pattern. *In-Vivo* anti inflammatory activity of niosomal gel prepared with $FS80_4$ was studied and compared with anti inflammatory activity of conventional meloxicam gel adopting Carrageenan induced rat paw edema method. The studies were demonstrated that niosomal gel was shown better pharmacological activity than the conventional meloxicam gel. Based on the results it was concluded that niosomal preparation offers more advantages than the conventional preparation.

Keywords: Meloxicam, Niosomes, Non-ionic surfactants (spans, tweens),Gel.

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INTRODUCTION

In recent years many researchers substantiating that vesicular structures [1] such as liposomes, niosomes, transferosomes, etc are acting as best carriers for administration of drugs across the skin. Liposomes exhibit certain disadvantages such as – their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable. Apart from these disadvantages, recently researchers proved that the liposomes are incapable to penetrate deeper layers of the skin [2]. Transferosomes also have different disadvantages like expensive, tedious manufacturing process and chemical instability [3].

Niosomes are globular submicroscopic structures and are prepared using nonionic surfactants such as Tweens, Spans etc. [4]. Niosomes has different advantages like

- They are osmotically active and stable, as well as they increase the stability of entrapped drug.
- Handling and storage of surfactants requires no special conditions.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- The surfactants are biodegradable, biocompatible and non-immunogenic.
- They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.
- Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.

Meloxicam is a non-steroidal anti-inflammatory agent (NSAIDs), has been widely used in the treatment of rheumatoid arthritis, osteoarthritis. These vesicular structures acts as carriers for drugs and helps to overcome the barrier properties of the skin. The present study involves the preparation and characterization of meloxicam entrapped niosomes and finding the drug carrier qualities of the niosomes.

MATERIALS AND METHODS

Meloxicam was obtained as a gift sample from Cadila Pharmaceuticals, India. Tween-80, tween-60, span-80 and span-60 produced from S.D Fine Chemicals, India. Cholesterol produced from Loba Chemicals Ltd, India. Other materials and solvents used were of analytical grade.

Preparation and characterization of meloxicam entrapped niosomes

Different niosomal formulations were prepared by slight modification of Thin film hydration technique [5]. Formulations were prepared using non-ionic surfactants (Tween-80, Tween-60, Span-80 and Span-60), Cholesterol and Drug (meloxicam) in different ratios as given in Table.1

Accurate amounts of surfactant and cholesterol were taken in a round bottom flask. The mixture of cholesterol and surfactant was made to dissolve in15ml of chloroform. From the resulting solution, chloroform was then evaporated at temperature not exceeding 50^0C with intermittent vortexing until a thin layer of solid admixture deposited on the walls of the flask. Then the film was hydrated with phosphate buffer pH 7.4 until a good dispersion of mixture was obtained. The dispersion consists of meloxicam entrapped niosomes and some amount of un-entrapped meloxicam.

The un-entrapped meloxicam was separated from meloxicam entrapped niosomes by dialysis method. [6]

Characterization of prepared niosomes [7]

The resulting meloxicam entrapped niosomes were characterized for size, shape, entrapment efficiency, *In-Vitro* drug release and *In-Vivo* activity.

Size and shape of niosomes

The prepared niosomes size and shape was studied using SEM and Optical microscopic (using 45x magnification) techniques. The studies revealed that niosomes are in round in shape and the size was found to be in the range of 1.54-2.64 µm. The sizes of all niosomes of different formulations are given in Table.1. SEM photograph of meloxicam entrapped niosome is given in Figure 1.

Entrapment efficiency of niosomes

The prepared niosomes entrapment efficiency was determined by subtracting the un-entrapped drug from the total amount of drug used for the preparation of niosomes. The amount of the un-entrapped drug was determined by means of dialysis method. The amount of drug dialyzed was determined spectrophotometrically at 354 nm. The entrapment efficiencies of all formulations were given in Table.1.

In-Vitro drug release from niosomes [8]

In-Vitro drug release was studied by subjecting the 2 ml of niosomal suspension for exhaustive dialysis using 900 ml of phosphate buffer pH 7.4 maintained at 37 ± 1^0C and stirred continuously at 100RPM on magnetic stirrer. Samples of 10 ml were withdrawn and replaced with fresh buffer at regular intervals of 1 hr for 10 hrs and then at the end of every 24 hrs until whole encapsulated drug were released from formulation. The samples were analyzed spectrophotometrically after suitable dilutions at 354 nm and the percentage of drug release was calculated taking the estimated amount of the encapsulated drug as 100 %. The results were graphically given in Figures 2-5.

Preparation of meloxicam standard and meloxicam entrapped niosomal gels [9]

1%w/w meloxicam niosomal gel and 1%w/w meloxicam standard gel were prepared by uniformly mixing the niosomal suspension containing Meloxicam and Meloxicam equivalent to 1%w/w of Meloxicam in to a gel base composed of carbopol (1.5% w/w), glycerin (10 %w/w), triethanol amine (1% w/w) and water (86.5% w/w).

In- Vitro Diffusion Studies of the Gels [10]

The receptor compartment of the Franz diffusion cell was filled with 15ml of phosphate buffer pH 7.4 with a magnetic bead and was stirred continuously at 100 rpm using a magnetic stirrer.

Dehaired skin of anaesthetized male albino rats weighing between 200-250 gms was separated from the adhering tissues. Circular section of suitable diameter were cut to place in the diffusion cell and washed well with Phosphate buffer pH 7.4. This was placed between the donor and receptor compartments of Franz diffusion cell.

Diffusion studies were carried out by placing 1gm of gel in the donor compartment at 37±1^0C. 5ml of samples are withdrawn through the sampling port and replaced with fresh buffer at 1, 2, 3, 4, 5, 6, 7, 8, 9, and 24hrs. After suitable dilutions, the absorbance was measured spectrophotometrically at 354nm. The procedure was performed in triplicate and the average percentage of the drug released was calculated.

The results were given in Table 2. *In-Vitro* drug diffusion data of standard gel and niosomal gel is graphically represented in Figure 6.

In- vivo characterization

In-vivo anti-inflammatory activity was evaluated on the basis of the inhibition of the volume of the hind paw edema induced by phlogistic agents. For present study 1% w/v carrageenan solution in 0.9% w/v was used as phlogistic agent [11].

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Selection of animals

White albino rats of either sex weighing between 190-200 gms were selected for study. The animals were divided in to three groups, each consisting of six rats. Each group was treated as follows.

Group I was treated with plain gel base without drug to account for the effect of gel base, Group II was treated with meloxicam standard gel and Group III was treated with $FS80_4$ gel. Study was conducted by complete cross over design.

Group I……Control
Group II……Standard
Group III…….. Test

Procedure

The animals were fasted over night and all groups were treated by applying 1 gm of gel on the left paw of the rats, with respective gels. The area of application was occluded with bandages and it was left in place for 2 hrs. The dressing was then removed and the gel remaining on the surface was wiped off with cotton. The animals were then injected with 0.1 ml of 1% w/v of carrageenan solution in plantar region of left hind paw and the paw volume was measured after 1hr, 2hr, 4hr, 4hr, 5hr, 6hr, 7hr, 8hr and 10 hr using mercury plethysmometer. The right paw served as a reference non-inflamed paw for comparison.

The percentage difference between right and left paw volumes was taken as percent edema produced. The percent edema produced with test samples were subtracted from percent edema produced in control group to obtain percent edema inhibition by respective groups.

Percent inhibition of edema is directly proportional to the anti-inflammatory activity. The results were given in Tables 3 & 4. The results were graphically represented in Figure 7.

RESULTS AND DISCUSSION

The prepared niosomes were appeared as discrete and round in shape. Mean particle size range of niosomes prepared by thin film hydration technique was determined by means of SEM and optical microscopic techniques and the range particles size found to be 1.54 – 2.64µm for all formulations.

The entrapment efficiency of niosomes was measured by dialysis method. The highest and least entrapment of meloxicam as 99.82% and 74.20% was shown by the $FS80_4$ and $FT60_3$ formulations. Maximum entrapment of drug was seen with $FS80_4$, $FS60_3$, $FT80_2$ and $FT60_1$ for Span-80, Span-60, Tween-80 and Tween-60 formulations respectively.

The *In-Vitro* release profile of all formulations was studied using dialysis membrane as semi permeable membrane. After 24 hrs, about 97.3%, 95.9%, 98.6%, 98.0%, 97.7%, 99.6%, 99.0%, 99.0%, 96.9%, 98.4%, 96.9%, 96.3%, 98.8%, 99.4%, 98.5% and 97.6% of meloxicam was released from formulations $FS80_4$, $FS80_3$, $FS80_2$, $FS80_1$, $FS60_4$, $FS60_3$, $FS60_2$, $FS60_1$, $FT80_4$, $FT80_3$, $FT80_2$, $FT80_1$, $FT60_4$, $FT60_3$, $FT60_2$, and $FT60_1$ respectively.

Among all formulations $FS80_4$ was selected as best formulation because of its highest entrapment efficiency and consistent release profile of meloxicam. 1% meloxicam niosomal gel was prepared by using the $FS80_4$ formulation equivalent to 1% w/w of meloxicam in carbopol gel and evaluated by comparing with the 1% w/w standard meloxicam gel.

The *In-Vitro* release profile of the $FS80_4$ gel and standard meloxicam gel were studied using dehaired abdominal skin of the male albino rats. The *In-Vitro* diffusion studies of meloxicam niosomal gel and standard meloxicam gel showed 100.9 % and 96.3 % of meloxicam linear release, after 24 hrs, respectively.

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Table 1: Formulation codes and particle size and entrapment efficiency of niosomes of different formulations

S. No	Formulation Code	Surfactant:Drug:cholesterol	Particle size (µm) Mean±SD	Percentage of Drug Entrapped±SD
1	$FS80_1$	0.5:1:1	1.54 ±0.06	99.66 ±0.12
2	$FS80_2$	1:1:1	1.59 ±0.06	99.72 ±0.20
3	$FS80_3$	1.5:1:1	1.97 ±0.06	99.74±0.10
4	$FS80_4$	2:1:1	1.57 ±0.04	99.82 ±0.15
5	$FS60_1$	0.5:1:1	2.64 ±0.05	99.62 ±0.12
6	$FS60_2$	1:1:1	2.54 ±0.05	99.68 ±0.14
7	$FS60_3$	1.5:1:1	2.32 ±0.05	99.70 ±0.33
8	$FS60_4$	2:1:1	2.41 ±0.09	99.69 ±0.14
9	$FT80_1$	0.5:1:1	2.43 ±0.05	78.05 ±0.69
10	$FT80_2$	1:1:1	2.35 ±0.07	79.35 ±0.53
11	$FT80_3$	1.5:1:1	2.21 ±0.068	74.95 ±0.83
12	$FT80_4$	2:1:1	2.19 ±0.06	75.70 ±0.53
13	$FT60_1$	0.5:1:1	2.08 ±0.07	78.35 ±0.49
14	$FT60_2$	1:1:1	2.24 ±0.05	76.55 ±0.40
15	$FT60_3$	1.5:1:1	2.14 ±0.09	74.20 ±0.34
16	$FT60_4$	2:1:1	2.02 ±0.07	74.45 ±0.44

Table 2: *In-Vitro* drug diffusion of meloxicam from standard and niosomal gels

S. No	Time (h)	Percentage of drug diffused±SD	
		Standard gel	Niosomal gel
1	1	15.0±0.53	16.3±0.66
2	2	21.8±1.87	22.4±0.98
3	3	27.8±1.13	29.9±1.41
4	4	33.2±1.15	42.7±0.98
5	5	51.6±2.00	54.1±1.40
6	6	64.9±1.21	69.3±1.21
7	7	71.4±0.98	76.1±1.11
8	8	77.9±1.21	82.9±1.14
9	9	84.6±1.25	89.8±0.36
10	10	92.1±1.31	96.7±1.37
11	24	96.3±1.55	100.9±2.51

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Table 3: *In-Vivo* evaluation of anti-inflammatory activity (Mean reduction in edema)

S. No	Time (h)	Group-I Mean±SEM (ml)	Group-II Mean ±SEM (ml)	Group-III Mean±SEM (ml)
1	1	2.42±0.13	2.03±0.22	2.15±0.18
2	2	2.36±0.05	1.60±0.10	1.85±0.23
3	3	2.25±0.18	1.42±0.14	1.47±0.29
4	4	2.11±0.10	1.51±0.28	1.25±0.18
5	5	1.98±0.82	1.38±0.12	1.19±0.11
6	6	1.94±0.14	1.46±0.16	0.80±0.26
7	7	1.75±0.18	1.21±0.08	0.62±0.24
8	8	1.64±0.05	1.32±0.14	0.52±0.13
9	10	1.49±0.10	1.19±0.21	0.46±0.16

Table 4: *In-Vivo* evaluation of anti -inflammatory activity (Percentage edema inhibition Vs Time)

S. No	Time (h)	Percentage edema inhibition	
		Group II	Group III
1	1	16.23±0.91	11.21±1.22
2	2	32.18±1.15	21.65±1.06
3	3	36.82±0.70	34.81±1.39
4	4	28.41±0.76	40.62±1.27
5	5	30.1±1.61	39.76±1.45
6	6	24.63±0.57	58.54±1.10
7	7	30.75±0.77	64.72±1.62
8	8	19.44±0.20	68.14±0.85
9	10	19.87±0.25	68.82±1.30

Figure 1: SEM photograph of meloxicam entrapped niosomes

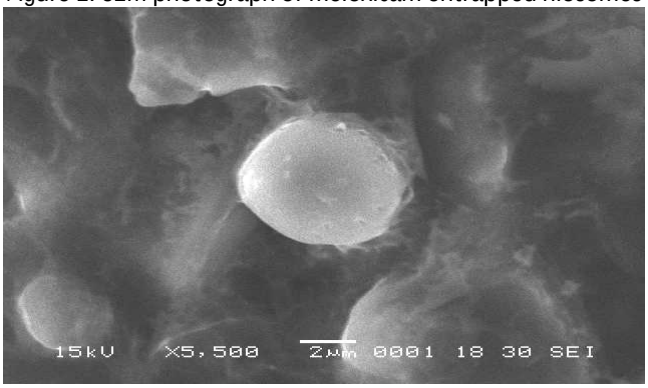

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Figure 2: *In-Vitro* drug release from niosomes prepared with Span-80

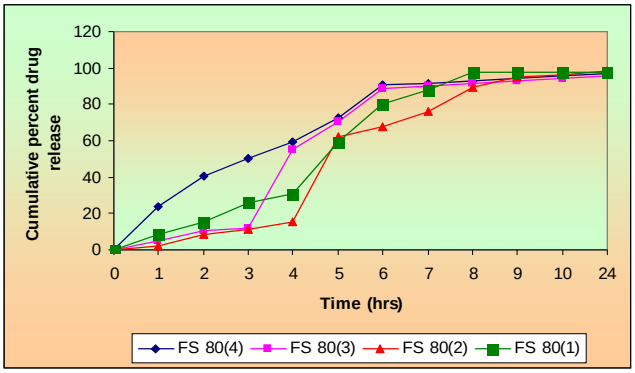

Figure 3: *In-Vitro* drug release from niosomes prepared with Span-60

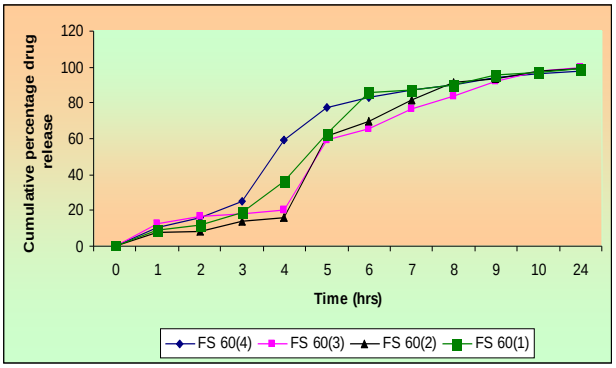

Figure 4: *In-Vitro* drug release from niosomes prepared with Tween-80

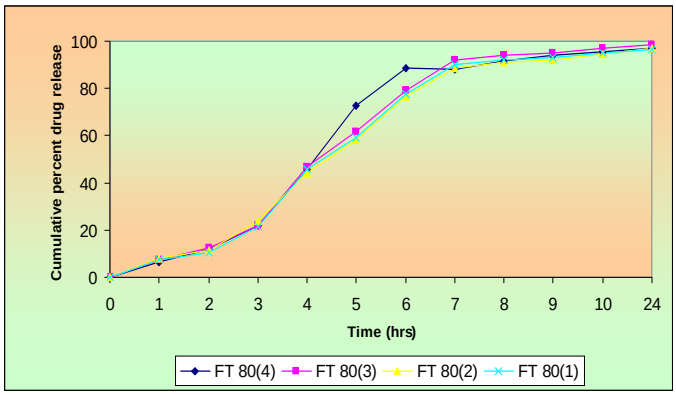

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Figure 5: *In-Vitro* drug release from niosomes prepared with Tween-60

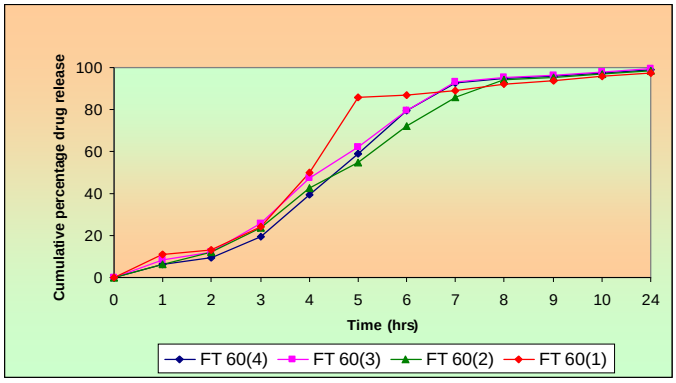


Figure 6: *In-Vitro* drug release from Standard and niosomal meloxicam gels through the rat skin

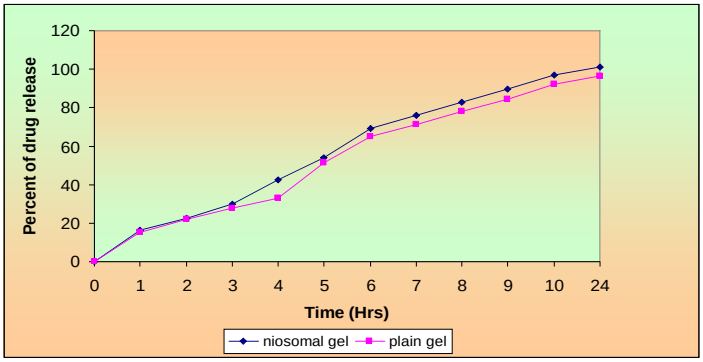
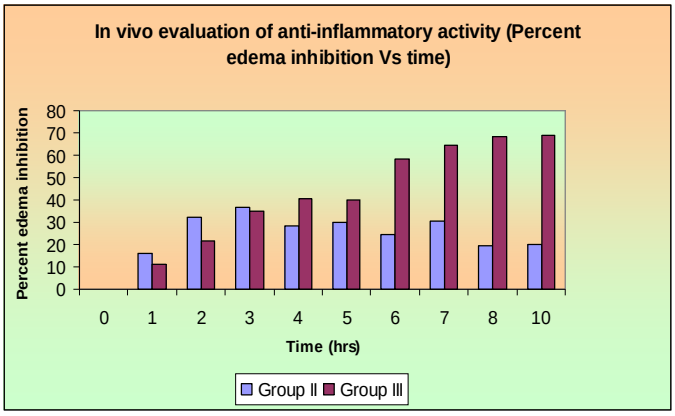


Figure 7: *In-Vivo* evaluation of anti inflammatory activity (Mean percent edema inhibition Vs Time)



Initially (up to 3hrs), in group-II percent of inhibition in edema was high and then the percent of inhibition in edema was reduced significantly with time up to 10 hrs. In case of group-III, initially (up to 3 hrs) the percent reduction in edema was less when compared with the percent reduction in edema in group-II but the percent of reduction in edema was linear up to 10 hrs. In group-II and group-III, the total reduction in edema by the meloxicam standard and niosomal gel was found to be 19.87% and 68.82% respectively, after 10 hrs.

The meloxicam niosomal gel showed better pharmacological activity when compared with the conventional meloxicam gel this due to the penetration capability of niosomes into the deeper layers of the skin and shown better results than the conventional meloxicam gel.

CONCLUSIONS

The results concluding that the preparation process and storage of niosomes easy and these niosomes will show sustained drug delivery activity. Because of this the niosomes is prominent tool (drug carrier) for transdermal delivery of drugs. The concept of incorporation of the drugs in niosomes for administration of drugs through the skin may become popular in coming future.

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