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Formulation and Evaluation of Mefenamic acid Niosomal Gel

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Research Article

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ABSTRACT

The present study was to formulate and evaluate mefenamic acid niosomal gel by using two different surfactants (span 20 and span 80). Estimation of mefenamic acid was done in methanol spectrophotometrically at 285 nm. The preformulation studies include identification, melting point, pH, calibration and drug excipient compatibility studies were carried out. Niosomes were prepared by thin film hydration method using different ratios of drug: surfactant (1:1,1:2,1:3,1:4,1:5). Niosomal gel was prepared using carbopol 940, triethanolamine and distilled water up to 10 ml. All the niosomal gel formulations were evaluated for drug content, entrapment efficiency, rheological properties, *in-vitro* release. Visually gels were sparkling and transparent. The results were obtained with MA5 formulation containing span 80 and cholesterol because of the entrapment efficiency and high localization in the stratum corneum than the span 20. However, niosomes prepared by thin film hydration method were more uniform and small in size which is essential for skin penetration. The *in-vitro* drug release revealed the formulations followed by slow sustained release of the drug for 24 hrs.

INTRODUCTION

Niosomes are bilayered microscopic lamellar structures with a size range between 10-10000 nm. They are formed by self-association of non-ionic surfactants in aqueous phase. They are spherical in shape and consists of lamellar (unilamellar and multilamellar) structures. Encapsulation of the drugs in niosomes improves the drug permeation. They can encapsulate both hydrophobic and hydrophilic drugs. Hydrophilic drugs can be delivered by adsorbing on the surface of the bilayer or by entrapping the drug in aqueous core of particle; hydrophobic drugs are delivered by encapsulating the drug into bilayer of non-ionic surfactants. Niosomes are composed of non-ionic surfactants, lipids and polymers where surfactants act as penetration enhancers and lipids are used to provide rigidity and proper

shape [1]. Niosomes are obtaining much attention because of their advantages like physical and chemical stability, content uniformity, low cost, convenient storage and various surfactants are available forniosomal formulations. A Niosomal formulation minimizes drug degradation, inactivation of drug after administration and prevents side effects. Niosomal gel formulations are used in treatment of various diseases like arthritis, gout, psoriasis and antifungal infections [2].

MATERIALS AND METHODS

Mefenamic acid, Cholesterol, span 20, span 80 and carbopol 940 from research lab, Preparation of Mefenamic acid niosomes: Mefenamic acid niosomes were prepared by thin film hydration method by using two different surfactants (span 20 and span 80). A mixture of either span 20 or span 80 and cholesterol are weighed accurately and then the accurately weighed amount of drug was added to the lipid mixture [3]. All ingredients were then dissolved in 10 ml of methanol and then organic solvent was removed by the rotary evaporation under reduced pressure on a water bath at 60°C. Then the deposited film was then hydrated with 10 ml of phosphate buffer of pH 7.4. Preparation of Niosomal gel 1.5 g of carbopol 940 powders was dispersed into 10 ml of water and vigorously stirred and allowed to hydrate for 24 hrs. Then the dispersion was neutralized with triethanolamine to adjust pH (6.8). Appropriate amount of niosomes containing mefenamic acid was then incorporated into gel base with continuous stirring until homogenous formulation was achieved (Table 1) [4].

Table 1. Composition of different Niosomal aqueous dispersion.

Ingredients (mg)	MA1	MA 2	MA3	MA 4	MA 5	MA 6	MA 7	MA 8	MA 9	MA 10
Mefenamic acid	100	100	100	100	100	100	100	100	100	100
Span 20	100	--	150	--	200	--	250	--	300	--
Span 80	--	100	--	150	--	200	--	250	--	300
Cholesterol	50	50	50	50	50	50	50	50	50	50
Methanol	20	20	20	20	20	20	20	20	20	20
Phosphate Buffer	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Evaluation of niosomal gel

Formulated gel was evaluated for their physico-chemical properties, *in-vitro* release studies and drug content and drug entrapment studies [5].

Clarity: The clarity of various formulations was determined by visual inspection under black and white background [6].

Measurement of pH: The pH of Mefenamic acid gel formulation was determined by using digital pH meter 1 gram of gel was dissolved in 100 ml of distilled water. The measurement of pH of each formulation was done in triplicate and average values were calculated [7].

Homogeneity: All developed gels were tested for homogeneity by visual inspection after the gels have been stored in the container for their appearance and presence of any aggregate [8].

Rheological Characterization: The rheological studies of samples were carried out with Brookfield digital viscometer (LV DV-E model) using S-18 spindle number [9,10]. The developed formulations were poured into the small sample adaptor of the Brookfield viscometer and the angular velocity increased gradually from 0.5 to 100 rpm.

Drug content: Niosomes equivalent to 20 mg were taken into a standard volumetric flask. They were lysed with 25 ml of methanol by shaking for 15 min [11]. The clear solution was diluted to 100 ml with methanol. Then 10 ml of this solution was diluted to 100 ml with phosphate buffer 6.8. Aliquots were withdrawn and the absorbance was measured at 285 nm and drug content was calculated from the calibration curve [12].

The drug content was determined by using following equation

Drug content=(concentration × volume taken) × conversion factor

Scanning electron microscopy: Scanning Electron Microscopy (SEM) is used to determine the surface morphology of niosomal gel with polymer (roundness, smoothness and formation of aggregates).

Entrapment efficiency: To 0.5 g of niosomal gel weighed in a glass tube, 10 ml of the aqueous phase (phosphate buffer pH 6.8) were added; the aqueous suspension was then sonicated [13]. Niosomes containing Mefenamic acid was separated from unentrapped drug by centrifugation at 9000 rpm for 45 min at 4°C. The supernatant was recovered and assayed spectrophotometrically using Shimadzu UV spectrophotometer at 285 nm. The encapsulation efficiency was calculated by the following equation [14.15].

% Encapsulation efficiency=(amount of entrapped drug/total drug added)*100

***In vitro* diffusion studies:** The *in vitro* diffusion study of prepared gel was carried out in Franz diffusion cell using through an egg membrane. 14 ml of phosphate buffer was taken in as receptor compartment, and then 1 gm Mefenamic acid gel was spread uniformly on the membrane. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37 ± 0.50°. The solution on the receptor side were stirred by externally driven Teflon coated magnetic bars at predetermined time intervals, pipette out 5 ml of solution from the receptor compartment at specified time intervals for up to 24 hrs and immediately replaced with the fresh 5 ml phosphate buffer. The cumulative % release of drug was calculated against time [16].

Stability study: To determine the stability of the formulation one should first know the stability of the drug and the vesicles, studies were carried to evaluate total drug content at room temperature (27 ± 2°C) and refrigeration temperature (4 ± 2°C). Samples were collected for every 2 weeks and absorbance was seen at 285 nm in U.V spectrometer.

RESULTS and DISCUSSION

Solubility studies

The solubility of drug in the water was found to be insoluble and slightly soluble in ethanol. Better solubility was found to be in methanol (Table 2) (Figures 1-4) .

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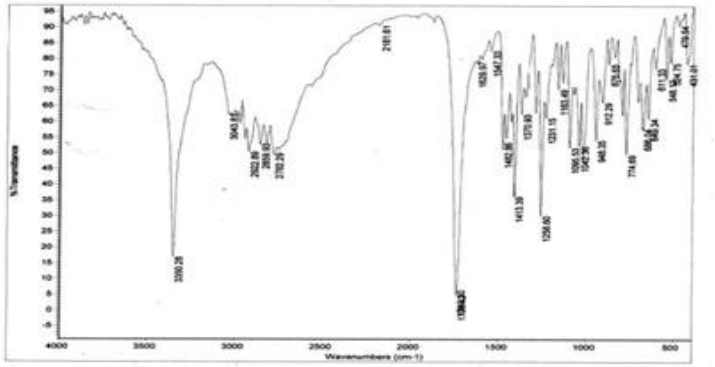
Table 2. Table showing the Solubility of Mefenamic acid (API) in various solvents.

Solvents	Solubility
Water	Insoluble
Methanol	Soluble
Ethanol	Slightly soluble

Fourier transforms infrared study

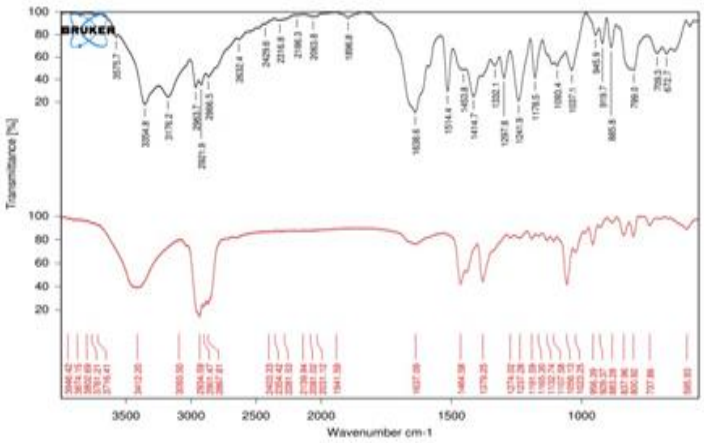
FT-IR Spectrum of pure drug-mefenamic acid

Figure 1. FT-IR Spectrum of pure drug-mefenamic acid in kbr.



FT-IR Spectrum of Mefenamic acid and Cholesterol

Figure 2. FT-IR spectra of mefenamic acid and cholesterol.



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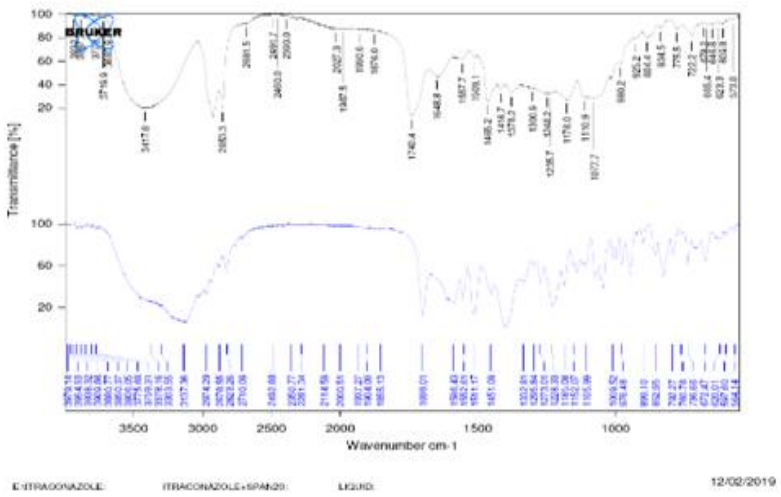
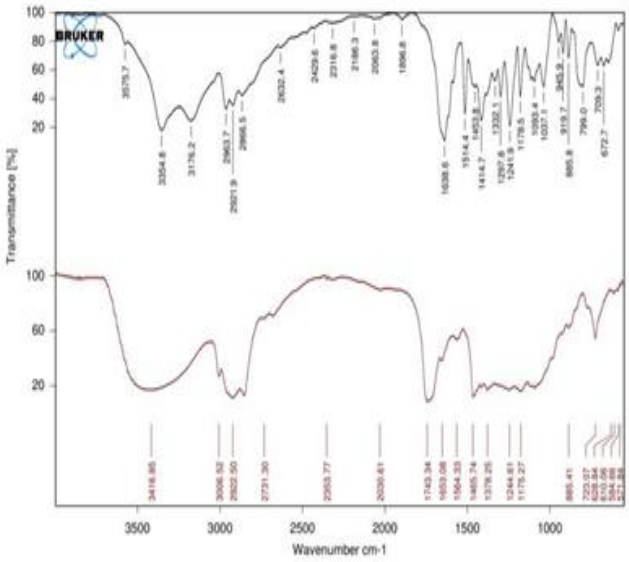
FT-IR Spectrum of mefenamic acid and span 20

Figure 3. FT-IR Spectra of mefenamic acid and span 80.



FT-IR Spectrum of mefenamic acid and span80

Figure 4. FT-IR Spectra of mefenamic acid and span 80.



Size and shape analysis: Microscopic analysis was performed under different magnification to visualize the vesicular structure, lamellarity and to determine the size of niosomal preparations (Figures 5 and 6).

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Scanning electron microscope

Figure 5. Scanning electron microscopes and Optimized niosomal gel.

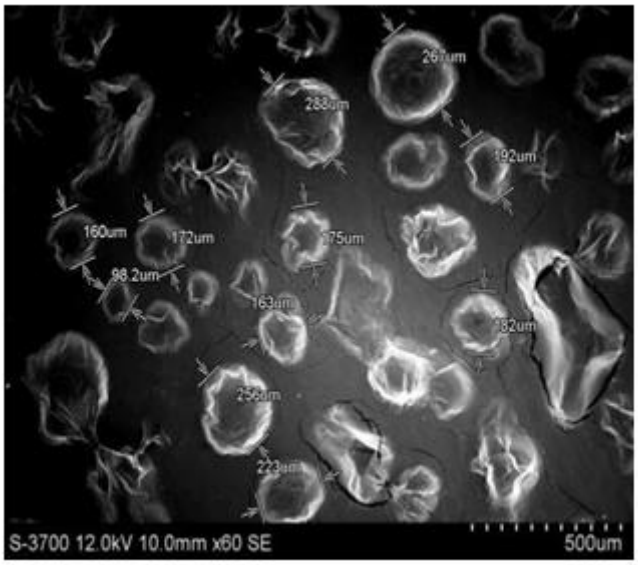
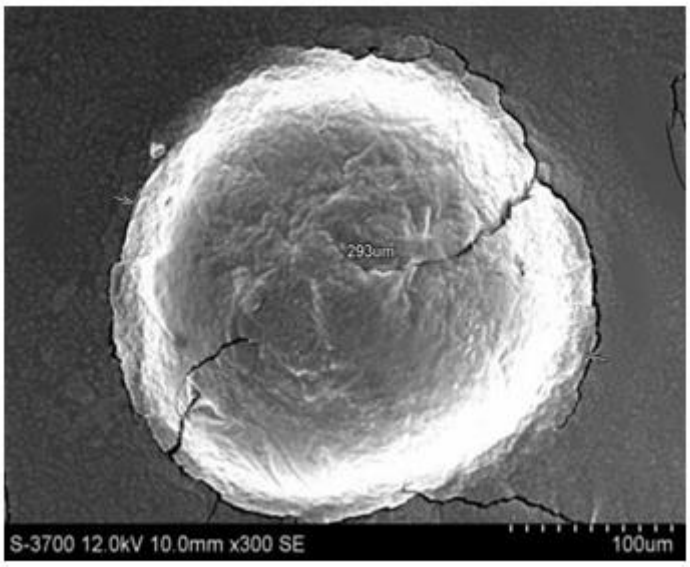


Figure 6. Optimized niosomal gel.



Entrapment efficiency: Once the presence of vesicles was confirmed in the Niosomal system, the ability of vesicles for entrapment of drug was investigated by ultra-centrifugation. Ultra-centrifugation was the method used to separate the niosomal vesicles containing drug and un-entrapped or free drug, to find out the entrapment efficiency. The maximum entrapment efficiency of niosomal vesicles was determined by ultracentrifugation.

Drug content: Drug content of niosomal formulations was determined. The results obtained shows 93.18- 97.82% drug content in the formulations. The results obtained are shown in Table 3.

Table 3. Percent drug entrapped and percent drug content in niosomes.

Formulation	% Entrapment efficiency	% Drug content
MA1	81.12 ± 0.32	93.18 ± 1.52
MA2	82.42 ± 1.2	94.20 ± 0.91
MA3	81.28 ± 0.54	94.19 ± 0.74
MA4	83.19 ± 0.23	94.28 ± 1.15
MA5	89.16 ± 0.71	97.82 ± 0.51
MA6	89.48 ± 0.81	97.27 ± 0.81
MA7	89.16 ± 0.45	96.64 ± 1.41
MA8	86.43 ± 1.21	96.12 ± 1.32
MA9	88.74 ± 1.28	96.28 ± 1.11
MA10	89.46 ± 0.71	96.78 ± 1.31

Clarity: Niosomes containing gels were found to be sparkling and transparent were found to be translucent and white viscous. All gels were free from presence of particles.

PH value: The value of pH of topical niosomal gels was measured by using digital pH meter at the room temperature. The pH of all topical Niosomal gels was found to be in the range of 6.5 ± 0.03 to 6.8 ± 0.02.

Homogeneity: All developed (MA1,3,4,5,6,8,9,10) showed good homogeneity with absence of lumps. The developed preparations were much clear and transparent.

Viscosity measurement: The viscosity of various formulated Mefenamic acid gels was measured using a Brookfield viscometer. The rheological behavior of all formulated gels systems was studied. In gel system, consistency depends on the ratio of solid fraction, which produces the structure to liquid fraction. Viscosity of various formulated gels was found in range of 1760 to 2120 centipoises (Table 4).

Table 4. Viscosity of the developed gel.

Formulation code	Viscosity (cps)
MA1	1760
MA2	1783
MA3	1756
MA4	1794

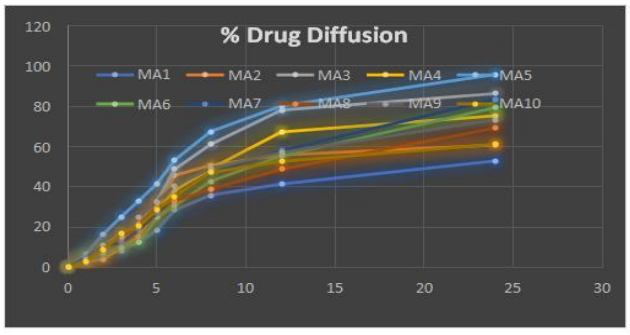
MA5	2120
MA6	1953
MA7	1908
MA8	1819
MA9	1810
MA10	1698

In *vitro* drug diffusion studies: *In vitro* drug release studies were carried out on dissolution test apparatus Franz diffusion cell. These release studies revealed that, the order of release was found to Table 5 (Figure 7).

Table 5. In-*Vitro* drug release of niosomal gel formulations.

Time in hrs	MA1	MA2	MA3	MA4	MA5	MA6	MA7	MA8	MA9	MA10
0	0	0	0	0	0	0	0	0	0	0
1	3	2.5	5.3	4.1	6.5	5.5	4.8	3.4	3.8	2.7
2	6.5	4.1	10.5	9.9	16.5	7.3	10.5	9.9	10.8	8.8
3	8.2	9.7	17	12.9	25.1	9.8	12.4	14.7	14.9	16.9
4	12.4	15.2	21.6	18.5	33.1	12.3	18.8	21.4	24.9	20.6
5	18.5	29.7	32.9	28.4	41.6	24.8	26.7	30	32.4	28.7
6	28.4	45.7	48.7	38	53.2	30.6	35.2	32.9	40.5	35.1
8	35.9	50.6	61	48.9	67.5	42.7	46.8	38.8	49.2	47.2
12	41.3	55.7	78.2	67.2	80.2	55.3	58	48.7	57	52.7
24	52.8	60.7	86.3	75.2	95.7	79.3	83.5	69.2	73.2	61.1

Figure 7. Graph showing *in vitro* drug release for niosomal formulations.



Based on the mefenamic acid nisomal gel drug release MA5 showed maximum drug release 95.7% upto 24 hrs it was selected as optimized formulation (Table 6).

Stability studies

Table 6. Loss in percentage drug during stability studies.

Formulation code (MA5)		Percentage of drug release
Initial	4 ± 2°C	96.3
	27 ± 2°C	96.2
After 2 weeks	4 ± 2°C	96.6
	27 ± 2°C	96.1
After 4 Weeks	4 ± 2°C	95.9
	27 ± 2°C	95.5
After 6weeks	4 ± 2°C	94.9
	27 ± 2°C	94.4
After 8 weeks	4 ± 2°C	94.5
	27 ± 2°C	94.2

CONCLUSION

Recently derived niosomal system can deliver drug molecules into and through the skin. In the present study an attempt was made to formulate and evaluate niosomal system of Mefenamic acid. Estimation of mefenamic acid was done in methanol spectrophotometrically at 285 nm. Niosomes were prepared by thin film hydration method and are evaluated for their appearance, pH, drug content, rheological properties, and drug entrapment study and *in-vitro* release. Visually gels were sparkling and transparent. Promising results were obtained with MA5 formulation containing Span 80 and cholesterol because of the highest entrapment efficiency and high localization in the stratum corneum than the Span 20. However Niosomes prepared by thin film hydration method were more uniform and small in size which is essential for skin penetration. The invitro drug release revealed the formulations followed by slow sustained release of the drug for 24 h.

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