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Formulation of Diclofenac Sodium Niosomes as Oral Drug Delivery System

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ABSTRACT

Diclofenac sodium (DF) niosomes was formulated by sonication method using various proportions of tween 40, span 40 and cholesterol. Each formulation (F1, F2 and F3) was evaluated for vesicle size, drug entrapment efficiency, release of drug, osmotic and rheological properties. F1 with high surfactant level 20 µmol % of each surfactant tween 40 and span 40 has high entrapment efficiency (90.1%), high retention for DF during storage at 4˚C, 304 nm vesicle size and 96% release for 12 hours. All formulations have shear thinning flow and membrane rigidity due to presence of cholesterol in their bilayer membrane. Hence, using niosomes as an oral drug delivery system for DF is feasible approach.

Keywords: DF; entrapment efficacy; niosomes; Vesicle diameter and Diclofenac.

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INTRODUCTION

The oral route is usually preferred by most patients. Thus, many studies are conducted to evaluate orally active formulations that may provide potential plasma level[1]. Moreover, controlled and sustained release formulations are designed to produce a longer effect in comparison with conventional oral dosage forms. The encapsulation of drugs in niosomes can decrease drug metabolism and increase drug level in blood circulation. Consequently, the use of niosomes can alter the bio-distribution of drug to provide a potential targeting and sustained release effect[2]. DF or sodium 2-[(2, 6-dichlorophenyl) amino] phenyl acetate, is a broadly used non-steroidal anti-inflammatory drug for the treatment of inflammatory conditions such as rheumatoid arthritis, osteoarthritis and ankylosing spondilytis[3]. The purpose of this study is to develop a suitable niosomal formulation of DF with an optimal encapsulation efficiency and drug release extended over a prolonged period with avoiding its side effect of gastric mucosal damage.

MATERIALS AND METHOD

Chemicals

Cholesterol was obtained from Croda Chemicals Ltd. (East Yorkshire, UK). Diclofenac sodium, Tween 40 and Span 40 from sigma-Aldrich (Gillingham,UK). Phosphate buffered saline (PBS) was obtained from Lonza Wokingham Ltd. (Berkshire, UK).

Preparation of noisome encapsulated DF

Diclofenac niosomes were prepared using sonication method. The surfactants /chlolestrol concentrations (Table1) were used in the preparation of niosomal formulations. All the components were added in phosphate buffer pH 6.8 (5-8 mL). The samples were sonicated for 5 min using a Probe Sonicator[4].

Determination of Vesicle Diameter

The size of formulations was determined using a Nano ZS® (Malvern, UK) at 25°C. Three drops of each formulation were suspended in 2.5 ml of PBS, pH 7.4. The suspension was added to a cuvette of capillary cells (Malvern, Worcestershire, UK) to measure size. The measurements were taken on the same day that entrapment efficiency was determined for the samples[5].

Encapsulation efficiency study

F1, F2 and F3were characterized on the basis of drug entrapment efficacy. Each formulation was pelleted by ultra centrifuging at 60000 rpm for an hour using an XL-90 ultracentrifuge (Beckman Optima, Greenbelt, Maryland, USA). Pellets were disrupted by addition of 1ml isopropanol[5]. The resultant solution was diluted with the PBS. Samples were analyzed for their entrapment efficiency

by spectrophotometer at 424 nm[6]. Entrapment efficiency was calculated using the following equation:

$$\% \text{ Entrapment } = \frac{\text{Gem in pellets (mg)}}{\text{Initial Gem (mg)}} \times 100$$

***In Vitro* Release Studies**

In vitro release was studied using a dialysis membrane of 5 cm (Himedia dialysis membrane, 12,000-14,000 molecular weight cut-off) and analysis by UV method. Niosomes containing entrapped DF obtained after centrifugation of 2 ml of the formulation were resuspended in 1 ml of PBS, pH 7.4, and used for the release study. The dialysis membrane was soaked in warm water for 10 min, one end was sealed with a clip, the niosome preparation or free DF solution was pipetted into the bag. The dialysis bag was placed in a beaker containing 200 ml of PBS, pH 7.4, at 37±2°C. The medium was stirred by means of magnetic stirrer at a constant speed (100 rpm)[7]. Sample of 5 ml was withdrawn at every 24 hours for 8 days and replaced the medium, so that the volume of diffusion medium was maintained constant at 200 ml. The samples were measured spectrophotometrically at 424 nm[6].

Osmotic characteristics

The effect of osmotic shock on niosomal formulations was investigated by monitoring the change in vesicle diameter after incubation of niosome suspensions in media of different tonicity: 1 M NaCI (hypertonic), 0.9% NaCl (normal) and 0.5% NaCl (hypotonic). Suspensions were incubated in these media for 3 h and the change in vesicle size was measured by a Nano ZS® (Malvern, UK)[7].

Determination of rheological properties

The flow properties of niosomal formulations were performed at 25ºC using a Carri-Med CSL2-100 Rheometer T.A. Instruments (Leatherhead, Surrey, UK). The diameter of the stainless steel geometer was 6 cm and the gap between the geometer and lower stationary plate of rheometer was 1mm. Samples were applied to the plate and allowed to equilibrate for 2 min prior to analysis. Rheograms were formed under stress by regularly increasing the shearing rates from a zero value to a 1000(1/s) value in 60 seconds, and were then returned from the 1000 (1/s) rate to the zero rates in another 60 seconds. In each of the studies, three rheograms were performed[8].

Statistical analysis

Each value was expressed as the mean ±SD. One way ANOVA tests were conducted for the obtained results.

RESULTS AND DISCUSSION

Various niosomal formulations (Table1) were prepared by the sonication method. The size of the prepared vesicles ranged between 304 to 901 nm (Table2). From the presented data, it is apparent that increasing the amount of cholesterol content from 40 to 60 µmol%, increased the size of vesicles significantly ($p<0.05$). Varshosaz *et al.*, study was also showed that the increase in the amount of cholesterol caused an increase in the size of vesicles[9].

Table 1: Various niosomal formulations

Formulations	Diclofenac sodium (mg/ml)	Cholesterol (µmol %)	Tween 40 (µmol %)	Span 40 (µmo %)
F1	50	40	20	20
F2	50	50	15	15
F3	50	60	10	10

Table 2: Particle size of formulations and their encapsulation efficiency percentage

Formulations	Vesicle size (nm)	Encapsulation efficiency%
F1	304±0.12	90.14±2.01
F2	606±0.32	81.23±1.23
F3	901± 0.15	73.45±2.12

Note: Mean ±SD, n=3

DF encapsulation efficiencies in F1, F2 and F3 are also shown in table (2). The amount of DF entrapped in the vesicles increased significantly ($p<0.05$) with an increase in surfactants content. These data are in agreement with results of previous study, indicating a higher entrapment efficiency of drug with increasing the surfactant content[10] whereas the concentrations of cholesterol seem to have no effect on the encapsulation of DF. Results of DF release from niosomes are shown in figure (1). The rate of release of DF from loaded vesicles was slower than that from DF solution as a control. The results showed that approximately 85% of DF was released within 60 min from the control solution, whereas the release of diclofenac from F1, F2 and F3 was 96, 75 and 45% respectively. Of these the DF loaded vesicles yielded the slowest rate of release. These results indicate that, by noisomes, it is possible to sustain of the DF for 12 hours.

Table 3: Percentage retention of DF in niosomes at various temperatures

Formulations	4ºC	25ºC	37ºC
	Amount of drug retained (%) After 30 days		
F1	93±0.5	92±0.1	42.2±0.1
F2	91±0.2	90±0.6	41.1±0.5
F3	90±0.1	89±0.3	40.3±0.5

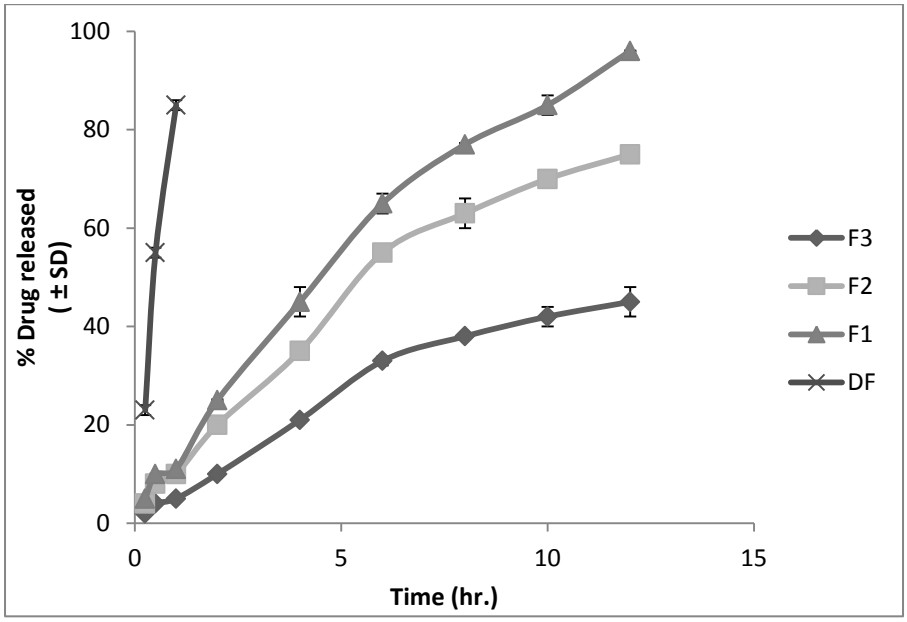

Figure 1: DF release from niosomal formulations

Stability results, as shown in Table (3), indicate that niosomes gives good protection for DF, at under refrigerated conditions and room temperature (25ºC).

Formulations were treated with hypotonic (0.5% NaCl), hypertonic (1 M NaCI), or normal saline (0.9% NaCl) solutions. In hypotonic solution, vesicle size was not increased significantly in formulations due to the rigidity of these vesicles which contain cholesterol as constituent in their bilayer membranes. In hypertonic solution, all the formulations shrank uniformly. Formulations incubated with saline showed same size of vesicles incubated with PBS (Table 4).

Table 4: Osmotic properties of niosomal formulations

Formulations	PBS	Hypotonic 0.5% Nacl	Normal 0.9% Nacl	Hypertonic % Nacl
F1	304nm±0.12	325 nm±0.21	305nm±0.1	shrunk
F2	606nm±0.32	630 nm±0.15	606nm±0.18	shrunk
F3	901nm ± 0.15	921 nm± 0.4	1105nm±0.32	shrunk

In the present study, DF loaded niosomes showed shear thinning flow and their viscosity increased with increased in cholesterol content. Previous studies have shown that the flow features of vesicle formulations are dependent on their composition. For example, paroxetine liposomes, prepared using soya lecithin, cholesterol and drug at different weight ratios, exhibited shear thinning flow behaviour, where there was a decrease in viscosity when the shear rate was increased and this is ideal for oral delivery[11]. Meanwhile, rifampicin liposomes prepared using phosphatidylcholine, cholesterol and oleic acid showed Newtonian behaviour, where the viscosity is independent on shear stress and this is ideal for pulmonary delivery [12].

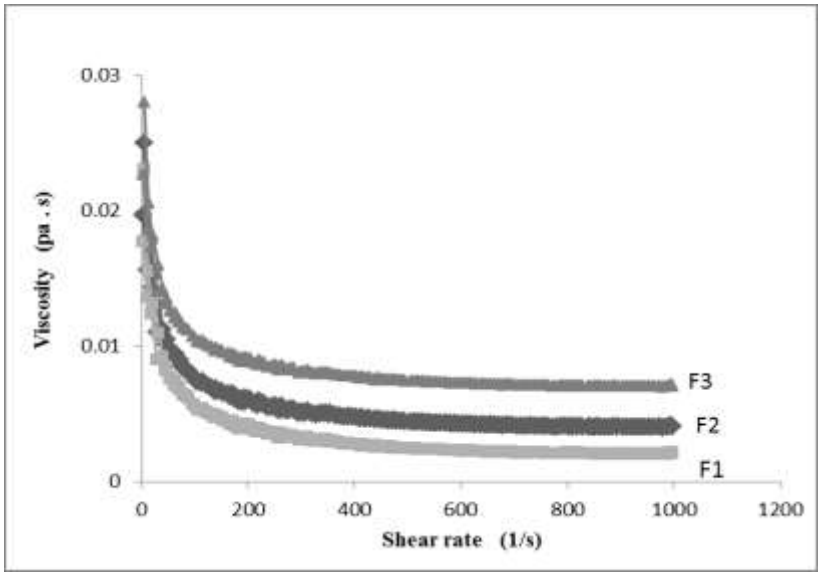

Figure 2: Viscosity and rheological properties of niosomal formulations

CONCLUSION

Niosomal vesicles sustained DF release for a longer time in comparison with free DF. The increase in the amount of cholesterol caused an increase in the size, rigidity and viscosity of DF-niosomes. Niosomes formulated with higher content of tween 40 and span 40 entrapped larger amounts of DF.

REFERENCES

1- Gupta S, Moulik SP. Biocompatible microemulsions and their prospective uses in drug delivery. JPS J Pharma Sci 2008;97: 22-45.

2- Sankhyan A, Pawar P. Metformin loaded non-ionic surfactant vesicles: optimization of formulation, effect of process variables and characterization. DARU J Pharma Sci 2013s; 21(1): 7.

3- SHAJI J, Patole, V. Development of a novel floating pulsatile system for chronotherapeutic release of diclofenac sodium. J Pharm Bio resources. 2008; 4(1):32-38.

4- Dahiya NK, Rao R, Nanda S. Preparation and evaluation of ramipril niosomes prepared using sonication method. Acta Pharmaceutica Sciencia 2011; 53 (3): 441-446.

5- Alsaadi M, JL, Italia AB, Mullen Ravi Kumar MN, Candlish AA, Williams RA, Shaw CD.. The efficacy of aerosol treatment with non-ionic surfactant vesicles containing amphotericin B in rodent models of leishmaniasis and pulmonary aspergillosis infection. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2012; 160 (3): 685-91.

6- Zupančič-Božič, Damjana, Franc V, Franc K. Optimization of diclofenac sodium dissolution from sustained release formulations using an artificial neural network. European J Pharma Sci 1997;(5): 163-169.

7- Ruckmani, Kandasamy, and Veintramuthu, S. Formulation and Optimization of Zidovudine Niosomes. AAPS PharmSciTech. 2010; 11 (3): 1119-1127.

8- Jones, David, S., Michelle, S., Lawlor, and David, W. Examination of the flow rheological and textural properties of polymer gels composed of poly (methyl vinylether maleic anhydride) and poly (vinylpyrrolidone): Rheological and mathematical interpretation of textural parameters. J Pharma Sci 2002; 91 (9): 2090-2101.

9- Varshosaz J, Abbas P, Val-iollah H, Abdolhossein N. Development and Physical Characterization of Sorbitan Monoester Niosomes for Insulin Oral Delivery. Drug Delivery. 2003;10 (4): 251-262.

10- Uchegbu IF, Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharma1998; 172 (1-2): 33-70.

11- Mohamed, AN, Randa T, El Rehem A, Mohammed YS. Formulation and evaluation of dispersed paroxetine liposomes in gel. J Chemical Pharma Res 2012;4:2209-2222.

12- Manca M, Sinico C, Maccioni A, Diez O, Fadda A, Manconi M. Composition Influence on Pulmonary Delivery of Rifampicin Liposomes. Pharmaceutics, 2012a; 4:590-606.