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**Universal Journal of Pharmaceutical Research**  
 An International Peer Reviewed Journal

ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

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## RESEARCH ARTICLE

# FORMULATION AND EVALUATION OF ETODOLAC NIOSOMES BY MODIFIED ETHER INJECTION TECHNIQUE

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### Article Info:



#### Article History:

Received: 6 August 2016  
 Reviewed: 10 September 2016  
 Accepted: 8 October 2016  
 Published: 15 November 2016

#### Cite this article:

Chioma ED. Formulation and evaluation of etodolac niosomes by modified ether injection technique. Universal Journal of Pharmaceutical Research 2016; 1(1): 1-4.

<http://doi.org/10.22270/ujpr.v1i1.R1>

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### Abstract

**Objectives:** Niosomes are non-ionic surfactant based multilamellar or unilamellar vesicles with aqueous solution of solute that is enclosed by a membrane. Etodolac is an indole acetic acid derivative with half-life of 4 to 7 hrs. It is used for the treatment of Rheumatoid arthritis. Whenever used orally, it has many systemic side effects, so it is not preferred orally. The aim of present study was to develop niosomes of Etodolac to avoid all drawbacks associated with it like first pass metabolism and side effects.

**Methods:** In present study four niosomes formulations of Etodolac were successfully developed by modified ether injection technique using different nonionic surfactant i.e. Span 20, Span 40, Tween 20, Tween 40 and cholesterol. Formulations were evaluated for different parameters like particle size, entrapment efficiency, *in-vitro* release, stability studies.

**Results:** Niosomes formulations of batch N3 shows maximum mean particle diameter i.e. 2.46  $\mu\text{m}$ . The entrapment efficiency of the niosomes was between 66.52-78.32%. The entrapment efficiency was found to be higher with the batch N4 (78.32%). The cumulative percent drug release after 10 hrs of the Etodolac niosomes in between 40.59-78.55%. 68.5% for N1, 50.49% for N2, 40.59 for N3 and 78.55 for N4. Accelerated stability studies for 12 weeks revealed that the Etodolac niosomes formulations of batch N4 were stable at up to 45°C.

**Conclusion:** Study concludes that Etodolac can be delivered by niosomes dosage form effectively and all limitations associated with it can be avoided.

**Keywords:** Cholesterol, Etodolac, *in-vitro* release, modified ether injection method, niosomes, stability studies surfactants.

## INTRODUCTION

The main aim of any novel drug delivery system is to provide a therapeutic amount of drug to reach to the desired site in the body and then maintain the required drug concentration to produce therapeutic effect<sup>1</sup>. Niosome is a class of molecular cluster formed by self-association of non-ionic surfactants in an aqueous phase<sup>2</sup>. Niosomes are non-ionic surfactant based multilamellar or unilamellar vesicles in which an aqueous solution of solute is enclosed by a membrane. Niosomes are promising vehicle for drug delivery and being non-ionic; and Niosomes are biodegradable, biocompatible non-immunogenic and exhibit flexibility in their structural characterization. The first niosome formulations were developed and patented by L'Oreal in 1975. Niosomes serve as drug depot in the body which releases the drug in a controlled manner through its bilayer providing sustained release of the enclosed drug<sup>3</sup>.

Etodolac is a nonsteroidal anti-inflammatory drug of COX-2 inhibitor class used for osteoarthritis, rheumatoid arthritis, gout, rheumatoid arthritis and traumatic injury. It produces therapeutic effects by inhibition of prostaglandin synthesis<sup>4</sup>. Due to extensive first pass metabolism it has low bioavailability. Since its terminal half life is 4-7 hrs and hence frequent dosing is required. Frequent oral use of Etodolac leads to serious gastrointestinal disturbance such as ulcer, stomach, or intestinal bleeding and chest pain which may be harmful. Gastrointestinal side effects produced by NSAIDs are either due to direct contact or indirect effect of the drug on the gastrointestinal mucosa. All these associated problems may be avoided by coating of polymer by avoiding release of drug in gastrointestinal tract<sup>5</sup>. Hence, by considering all mentioned points, in present work niosomes of Etodolac have been formulated and evaluated on different parameters to avoid all problems and to improve its oral bioavailability<sup>6</sup>.

## MATERIALS AND METHODS

Etodolac was received as gift sample from Neimeth International Pharmaceuticals, Span 20, Span 40, Tween 20, Tween 40 and Cholesterol (Mopson Pharmaceutical Ltd).

### Formulation development by modified ether injection technique

Niosomes containing Etodolac were prepared by modified ether injection technique using nonionic surfactant and cholesterol at different concentrations (Table 1). For it, Cholesterol and surfactant were dissolved in 6 ml diethyl ether mixed with 2 ml methanol containing weighed quantity of Etodolac.

**Table 1: Compositions of the Etodolac niosomes Formulations.**

Formulation code	Surfactant	Drug: surfactant: cholesterol (mg)
N1	Tween 20	100:100:100
N2	Tween 40	100:200:100
N3	Span 20	100:100:100
N4	Span 40	100:200:100

The resulting solution was introduced by means of micro syringe into 20 ml of solution of phosphate buffer (pH 7.4). The solution was stirred continuously on magnetic stirrer and temperature was maintained at 60-65°C. While the lipid solution was injected slowly into aqueous phase, it causes vaporization of ether, resulting in spontaneous vesiculation and formation of niosomes<sup>7</sup>.

### Evaluation of formulations

#### Particle size

Vesicle size determination was carried out by means of an optical microscopy with a calibrated eyepiece micrometer. About 200 niosomes were measured individually, average was taken, and their size range, mean diameter were calculated<sup>8</sup>.

#### Entrapment efficiency

The percentage entrapment efficiency of the vesicles was determined by freeze thawing centrifugation technique. Niosomal suspension was filled in drop tubes and stored at -20°C in a refrigerator for 24 hours. The niosomal suspension was centrifuged at 1500 X G rpm for 30 minute. Supernatant containing untrapped drug was withdrawn and diluted with water methanol mixture, then measured UV spectrophotometrically at 278 nm against water methanol mixture as standard<sup>9</sup>. Entrapment efficiency was calculated by using following equation:-

$$\%EE = \frac{T_a - T_b}{T_a} \times 100$$

Where; %EE=Entrapment efficiency, Ta=Total amount of drug in suspension, Tb=drug in supernatant

### In-vitro drug release

The *in-vitro* permeation of Etodolac from niosomal formulation was studied using locally fabricated diffusion cell. The *in-vitro* diffusion of the drug through egg membrane was performed<sup>10</sup>. It was clamped carefully to one end of the hollow glass tube of 17 mm (area 2.011 cm<sup>2</sup>) (dialysis cell) this acted as donor compartment. 100 ml of phosphate buffer saline PBS 7.4 was taken in a beaker which was used as a receptor compartment. The known quantity was spread uniformly on the membrane. The donor compartment was kept in contact with the receptor compartment and the temperature was maintained at 37±0.1°C. The solutions of the receptor side were stirred by externally driven Teflon-coated magnetic bars.

At predetermined time intervals, sample was withdrawn and replaced by 4 ml of PBS. The drug concentrations in the aliquot were determined at 278 nm against appropriate blank. Drug release data was normalized by converting the drug concentrations in solution to a percentage of cumulative drug release and was shown graphically.

### Stability study

Stability studies carried out by storing the prepared niosomes of Etodolac at various temperature conditions like refrigeration on (2-8°C) room temperature (25±0.5°C) and elevated temperature (45±0.5°C) for a period of 12 weeks. Drug content and variation in the average vesicle diameter were periodically monitored<sup>11</sup>. ICH (International Conference on Harmonisation) guidelines suggests stability studies for dry niosomes powder meant for reconstitution should be studied for accelerated stability at 75% relative humidity as per international climatic zones and climatic conditions.

### Statistical analysis

Experimental results were expressed as mean±SD. Student's *t*-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at *p*<0.05.

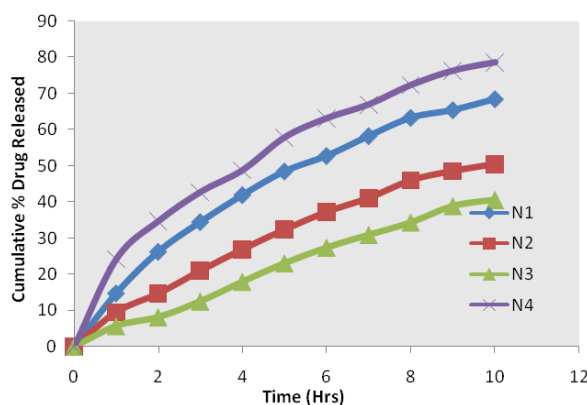
## RESULTS AND DISCUSSION

A successful attempt was made to formulate four formulations of Etodolac niosomes formulations by modified ether injection technique using nonionic surfactant and cholesterol at different concentrations. The pure drug shows sensitivity to light and moisture.

**Table 2: Properties of Etodolac niosomes.**

Formulation Code	Average mean diameter of non sonicated niosomes (µ m) <sup>a</sup>	% Entrapment efficacy <sup>a</sup>	Viscosity (Centipoise)
N1	2.37±0.08	66.52±0.22	2.421
N2	2.41±0.14	68.21±0.23	2.318
N3	2.46±0.09	73.40±0.12	2.329
N4	2.28±0.11	78.32±0.13	3.388

<sup>a</sup>Average ± SD of three determination

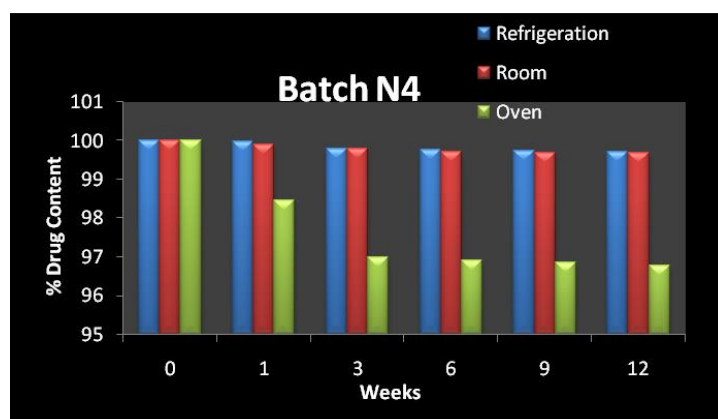


**Figure 1: Percentage of drug released from Etodolac niosomes.**

Therefore formulating it into niosomes can solve this problem to a large extent. The mean particle diameter of the Etodolac was between 2.28-2.46  $\mu\text{m}$  for all twelve formulations. Particles of all formulations were smooth, oval and discrete. Niosomes formulations of batch N3 shows maximum mean particle diameter i.e. 2.46  $\mu\text{m}$ . The entrapment efficiency of the niosomes was between 66.52-78.32%. The entrapment efficiency was found to be higher with the batch N4 (78.32%), which may have an optimum surfactant cholesterol ratio to provide a high entrapment of Etodolac. The *in-vitro* permeation of Etodolac from niosomal formulation was studied using locally fabricated diffusion cell. The cumulative percent drug release after 10 hrs of the Etodolac niosomes in between 40.59-78.55%. 68.5% for N1, 50.49% for N2, 40.59 for N3 and 78.55 for N4.

The formulation containing Tween showed less drug release compared with the preparation containing span. This may be due to the larger size of the vesicles and less lipophilic nature of the Tween, which makes it

more difficult for these vesicles to penetrate or fuse with skin whereas, the inclusion of span which is more lipophilic than Tween further increased the lipophilicity of the drug leading to better penetration. Rapid drug leakage was observed during the initial phase. However, after that a slow release occurred. This could be because the drug is mainly incorporated between the fatty acid chains in the lipid bilayer of niosomal vesicles which leads to rapid ionization and release upon dispersing niosomes in large buffer (pH 7.4) volumes until reaching equilibrium. Stability studies revealed that the niosomes kept at room temperature ( $\sim 25^\circ\text{C}$ ) and 40-75% RH showed the maximum stability. The values of drug content and *in-vitro* studies were close to that of the initial data with only slight variations suggesting that it has an acceptable shelf life. It should be stored in a cool, dry place. Niosomes formulations of Etodolac of batch N4 shows good stability at refrigeration and room temperature in comparison to other.



**Figure 2: Stability study of Etodolac niosomes of batch N4 at different temperature.**

## CONCLUSIONS

At present scenario, many researchers are working for transporting the drug molecules to the desired site in the biological systems. The role of the drug delivery system is not only limited to a drug package just meant for convenience and administration but to bring a required change in therapeutic efficacy and safety by carrying the drug molecules to the desired site in the most convenient manner. In present study four

Etodolac niosomes formulations were successfully developed by using different surfactants i.e. Span 20, Span 40, Tween 20, Tween 40 by modified ether injection method. Accelerated stability studies for 12 weeks revealed that the Etodolac niosomes formulations of batch N4 were stable at up to  $45^\circ\text{C}$ . The stability study of the optimized formulation showed satisfactory characteristics without being drastically influenced. Based on particle size morphology, *in-vitro* release and stability studies, it can

be concluded that formulation N4 was an optimum formulation. However, future experiments should explore the suitability of niosomes with wide variety of drugs having designed drawbacks for improved and effective intended therapy. So, that niosomes are represented as promising drug carriers and promising drug delivery module.

#### ACKNOWLEDGEMENTS

Author extends her thanks and appreciation to the Ahmadu Bello University, Zaria Kaduna, Nigeria to provide necessary facilities for this work.

#### AUTHOR'S CONTRIBUTION

**Chioma ED:** Writing original draft, review, methodology, data curation, literature survey, editing.

#### DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

#### CONFLICT OF INTEREST

The author has declared that there is no conflict of interest related to this paper.

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