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# Development and Evaluation of Etodolac-Loaded Niosomal Gel for Sustained Drug Release

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**ABSTRACT**: Niosomes, vesicular systems formed from non-ionic surfactants, offer benefits such as enhanced stability, controlled drug release, and improved skin penetration. This study aimed to formulate and evaluate niosomal gels for etodolac, a nonsteroidal anti-inflammatory drug, to achieve sustained drug release and enhanced topical application. The study involves the preparation of niosomal suspensions with varying concentrations of surfactants (Span 60) and cholesterol, followed by incorporation into a gel base of carbopol 934. The formulation was evaluated for physical appearance, viscosity, pH, irritancy,drug content and diffusion studies. The optimized formulation (F4) demonstrated good homogeneity, spreadability and a pH range suitable for skin application. It showed sustained drug release of 83.8% at the end of 6 hours in diffusion studies, demonstrating better performance compared to the marketed Etodolac gel. Entrapment efficiency for the optimized formulation was 77%, and the gel was non-irritant based on the HET-CAM assay. In conclusion, this study suggests etodolac loaded niosomal gel was successfully developed and can be a promising strategy for providing localized and sustained drug delivery, minimizing systemic side effects and enhancing patient compliance.

**KEYWORDS:** Etodolac, Niosomes, Sustained release, Topical gel, NSAID

## I. INTRODUCTION

Topical drug delivery systems are increasingly being recognized as effective alternatives to traditional oral or systemic drug administration. By delivering medication directly to the site of action, these systems can provide targeted therapeutic effects thereby minimizing unwanted side effects throughout the body. Among the various topical delivery options, niosomal gels have attracted considerable interest in recent years[1]. These gels are based on niosomes tiny vesicles (Figure 1) formed from non-ionic surfactants and cholesterol,which are capable of encapsulating both water-soluble and fat-soluble drugs[2]. This unique structure allows niosomal gels to enhance the penetration of drugs through the skin and to release their contents in a controlled and sustained manner.

Etodolac is a selective COX-2 inhibitor that is widely used to relieve pain and inflammation in conditions such as arthritis. Despite its clinical usefulness, Etodolac's effectiveness is often limited by its low bioavailability when given in conventional oral forms, mainly due to extensive first-pass metabolism in the liver[3]. This means that much of the drug is broken down before it can reach the bloodstream and exert its therapeutic effect. Developing a niosomal gel formulation of Etodolac can offer a promising solution to various challenges. Such a gel can improve the drug's stability, enhance its penetration through the skin, and provide sustained release, which may result in more consistent and effective symptom relief with fewer side effects[4-10].

This study aims to develop and evaluate an Etodolac-loaded niosomal gel with the goal to optimizing its therapeutic performance and making it easier for patients to use.

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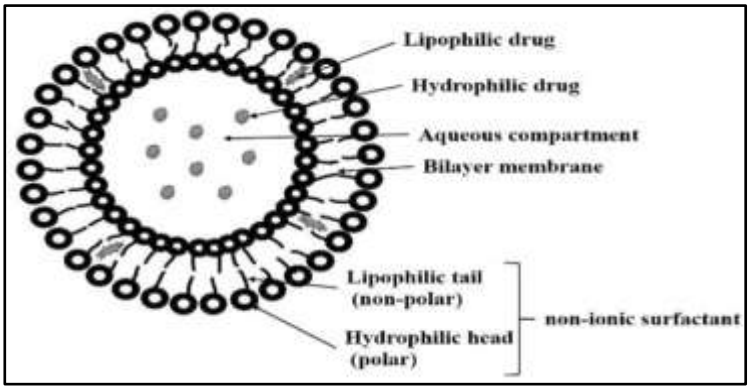


Figure 1: Structure of niosomes

## II. EXPERIMENTAL

### 2.1 Materials

Etodolac was obtained as a gift sample from IPCA Laboratories. Carbopol 934, cholesterol, Span 60, glycerin, ethanol, soy lecithin, phosphate buffer, triethanolamine, and methylparaben were procured from certified suppliers.

### 2.2 Formulation Development:

Niosomal Suspension: A specified quantity of Etodolac, Span 60, and cholesterol was dissolved in ethanol and heated at 60-70°C. Phosphate buffer was added to form a milky suspension. The suspension was pulse sonicated using probe sonicator for 10 mins (two cycle of 5 minutes each with 5 minutes break between the cycle).

Niosomal Gel Preparation: The suspension was incorporated into a carbopol-based gel, with glycerin and methylparaben,which was added for consistency and preservation. The pH was adjusted with triethanolamine [11-15]. Figure 2 shows the image of the formulated gel.

Figure 2: Image of the formulated gel

### 2.3 Evaluation parameters[16-21]:

The formulated gel was evaluated for the following parameters

i. Physical appearance and clarity: The prepared gels were inspected visually for their colour and transparency. All the prepared gel formulations were tested for homogeneity by visual inspection after the gels had been set in the container.

ii. Viscosity: The measurement of the viscosity of the prepared gel was done using a Brookfield digital viscometer.

iii. Measurement of pH: The pH of various gel formulations was determined using a digital pH meter. 1 gram of gel was dissolved in 100 mL of distilled water and used for the measurement.

iv. Spreadability: 1 g gel was placed within a circle of 1 cm diameter pre-marked on a glass tile over which a second glass tile was placed. A weight of 500 g was allowed to rest on the upper glass tile for 1 minute. The increase in the diameter due to the spreading of gels was noted. An average of triplicate readings was taken.

v. Calibration curve of Etodolac

The standard calibration curve was prepared by plotting the absorbance values of Etodolac standard

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solutions, prepared at concentrations ranging from 2 ppm to 12 ppm, against their corresponding concentrations. The absorbance was measured at 278 nm.

vi. Drug Content: 0.1g of gel was dissolved in a 7.4 pH phosphate buffer and the volume was made up in a volumetric flask (10 ml). The solution was filtered with a whattman filter paper and the absorbance was measured after dilutions.

$$\% \textbf{ Drug content} = \left[\frac{\textbf{drug content (mg)}}{\textbf{drug present in 0.1g}} \times \textbf{100}\right]$$

vii. Diffusion: The diffusion studies were carried out using Franz Diffusion cell. The receptor compartment contained phosphate buffer 7.4. A weighted quantity of 0.1g gel was applied on themembrane and was placed between the donor and receptor compartments and clamped inplace. The diffusion cell was placed on the magnetic stirrer and the rpm was set between 500to 600. Aliquots were withdrawn from the side arm at the specific time intervals. Theabsorbance was determined spectrophotometrically at 278 nm. The cumulative % drug released was calculated. A graph ofcumulative % drug released v/s time was plotted.

viii. Entrapment Efficiency: Entrapment efficiency of niosomal formulations wasdetermined by the centrifugation method. 1mL niosomal suspension was poured into astopper test tube in the set of 10 and centrifuged by using a microcentrifuge at rpm 13,000for 60 minutes and then filtered by using Whatman filter paper to obtain a clear fraction. Theclear fraction was used for the quantification of free drug by measuring its absorbance at278 nm. The encapsulation efficiency was calculated using the formula:

**Entrapment Efficiency (%):** $\left[\frac{C_t - C_f}{C_t} \times 100\right]$

where $C_t$ is the concentration of the total drug and $C_f$ is the concentration of the unentrappeddrug.

ix. CAM Assay: A Chorioallantoic membrane (CAM) assay was performed to test the irritancy of the gel on a 10-day-old chicken embryo. The eggshell over the air sack and the inner shell membrane were removed carefully. The gel was gently applied on the CAM and the egg was observed for 5-10 minutesto assess the occurrence of any vascular injury, haemolysis, or coagulation. The time taken for haemorrhage, lysis, and coagulation was noted and the following formula was used to calculate theIrritancy Score (IS).

**IS= [(301-H)/300*5] + [(301-L)/300*7] + [(301-C)/300*9]**

where, H =Haemorrhage time
L =Lysis time
C =Coagulation time

## III. RESULTS AND DISCUSSIONS

1.1 Optimizationof formulation.

Different niosomal formulations were prepared using a nonionic surfactant (Span 60) and cholesterol at different concentrations. The initial formulation, designated F1, incorporated the active pharmaceutical ingredient(API) etodolac and excipients including carbopol, cholesterol, Span 60, and ethanol. However, F1 exhibited high viscosity attributable to an elevated concentration of carbopol,which restricted drug diffusion. To mitigate these challenges, modifications were undertakenin subsequent formulations. Formulation F2 was characterized by a reduction in carbopolcontent, whereas Formulation F3 involved a modification in the quantities of cholesterol andSpan 60 thereby enhancing the membrane stability of the vesicles and resulting in a better release. Finally,formulation F4 was identified as the superior composition,demonstratingsustained release and good entrapment efficiency.Various trial formulations for niosomal gel development are shown in Table 1.

Table 1: Optimization of niosomal gel

| **Name of ingredients** | **Formulation code** | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |

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| | | | | |
|---|---|---|---|---|
| Drug | 0.01g | 0.1g | 0.1g | 0.2g |
| Carbopol 934 | 0.2g in 10ml | 0.1g in 10ml | 0.1g in 10ml | 0.1g in 10ml |
| Cholesterol | 0.025g | 0.025g | 0.05g | 0.1g |
| Span 60 | 0.25g | 0.25g | 0.5g | 1g |
| Glycerine | 5ml | 2ml | 2ml | 1ml |
| Ethanol | 0.5 ml | 0.5 ml | 0.5 ml | 1 ml |
| Soy Lecithin | 0.05g | 0.05g | 0.1g | 0.2g |
| Phosphate Buffer | 1ml | 1ml | 1ml | 1ml |
| Triethanolamine | q.s | q.s | q.s | q.s |
| Methyl Paraben | q.s | q.s | q.s | q.s |

3.2 **Evaluation of formulation:**

pH: F4 showed a desired range of pH between 5 - 6 for maintaining the natural acidity of the skin.

Viscosity: The formulation F4 was found to have a viscosity comparable to a standard marketed formulation.

Standard Calibration Curve of Etodolac: Standard calibration curve plots were found linearover the concentration range of 2 -12 ppm for Etodolac [Figure 3] and the correlationcoefficient ($R^2$) was found to be 0.9977.

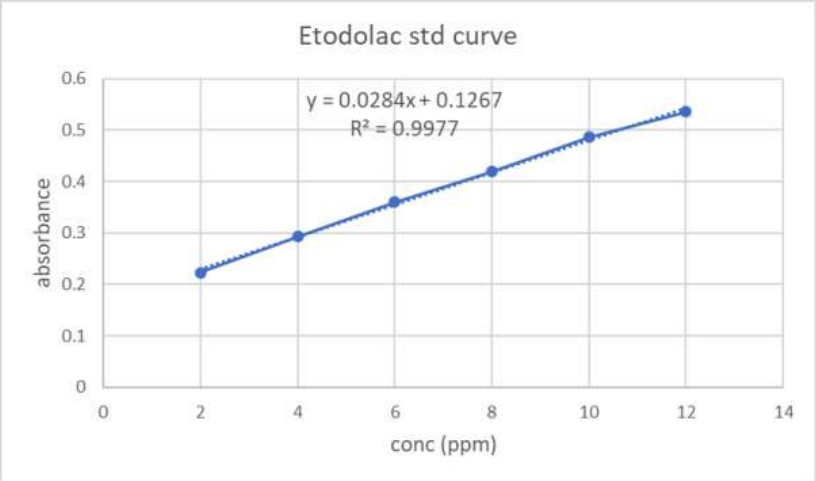


Figure 3. Standard calibration curve

Drug Content: The average drug content and % drug content was found to be 1.93 mg and 96.5 % w/w.

Diffusion Studies: Diffusion studies were conducted on F1, F2, F3 & F4 formulations along with a marketed formulation (Etova gel 2% w/w). For F1 the average % drug release was found to be 16.4% after 4 hrs. For F2 the average % drug release was found to be 26.3% after 6 hrs, for F3 the average % drug release was found to be 59.39% and the diffusion studies for F4 showed an average % drug release of 94.5% at the end of 6 hours [Figure 4], whereas the plain marketed formulation of Etodolac showed drug release of 39.2% at the end of 5 hours and then started to decline as showed in Figure 5. These results indicate that F4 provides a superior and more sustained drug release

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compared to formulations F1, F2, F3, and the marketed formulation.

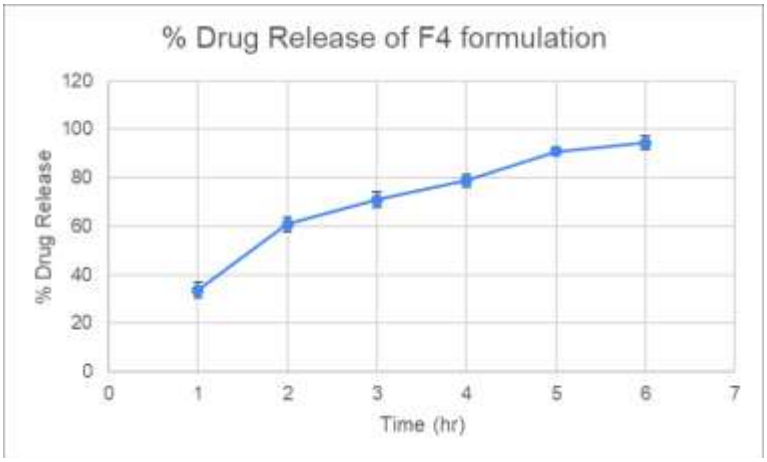


Figure 4. % drug release profile of F4 formulation

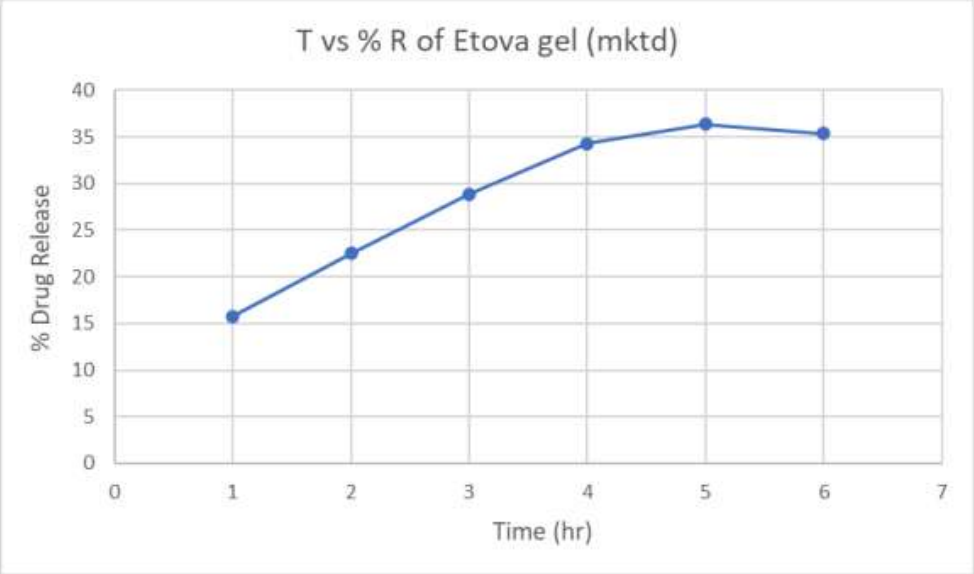


Figure 5. % drug release profile of Etova gel (Marketed Formulation)

Entrapment Efficiency:Entrapment efficiency was determined bycentrifuging the niosomal suspension at 13000 rpm for 60 minutes to obtain the clearsupernatant. The formulation F4 showed the highest entrapment efficiency of 77% indicating the presence of an optimum concentration of surfactant & cholesterol.

HET CAM Assay: HET CAM Assay was performed on all the formulations by applying the formulation directlyon the embryo. Figures 6 and 7illustrate the observations of the CAM assay.After applying the F2, F3 & F4 formulations on chorioallantoic membranes (CAM), novascular lysis, no haemorrhage, and no coagulation was seen. Based on the irritation index(0.07), it can be concluded that none of the formulations showed irritation.

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Figure 6. The embryo pre-application

Figure 7. The embryo post-application

## IV. CONCLUSION

The present study demonstrates that the niosomal gel formulation of Etodolac, F4, offers significant advantages for topical drug delivery. Encapsulation of Etodolac in niosomes resulted in improved drug delivery characteristics, including enhanced and sustained release. The F4 formulation exhibited better skin permeation compared to the conventional marketed gel and had optimal physical properties such as homogeneity, spreadability, and a desirable pH range of 5–6.51. The drug content in F4 was high (96.5%), and it achieved the highest entrapment efficiency (77%) among all formulations tested. In diffusion studies, F4 provided a sustained drug release profile in comparison to F1, F2, F3 formulations, and the marketed product. Additionally, all formulations were non-irritant, with irritancy scores ranging from 0 to 0.9.

These findings suggest that the formulation of Etodolac niosomal gel represents a promising approach for the effective topical delivery of Etodolac.

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