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FORMULATION AND EVALUATION OF KETOROLAC TROMETHAMINE-LOADED NIOSOMAL GELS FOR ENHANCED TOPICAL DRUG DELIVERY

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Keywords:

Niosomal gel, Ketorolac Tromethamine, Topical drug delivery, Span 60, Controlled release

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ABSTRACT: This study focuses on the formulation, characterization, and evaluation of Ketorolac Tromethamine-loaded niosomal gels intended for topical drug delivery. Niosomes were prepared using span 60 and cholesterol in varying ratios by thin-film hydration method, and the optimized niosomal dispersion was incorporated into different hydrogel bases including Carbopol 971P, Xanthan gum, HPMC, and Eudragit S100. The prepared gels were evaluated for physical appearance, pH, viscosity, spreadability, drug content, and *in-vitro* drug release. Vesicle sizes ranged from 226.4 nm to 694.8 nm with PDI values indicating uniform distribution, while zeta potentials confirmed good stability. Drug content across formulations ranged between 93.5% and 98.4%. The calibration curve of Ketorolac Tromethamine showed a λ_{max} at 323 nm with excellent linearity ($R^2 = 0.998$). *In-vitro* release studies demonstrated significantly higher drug release from niosomal gels compared to plain gels, indicating enhanced permeation and controlled release behavior. Among all formulations, the hydrogel H4 containing a combination of Carbopol and Xanthan gum at 1:2% showed superior physicochemical properties, sustained drug release over 12 hours, and optimal spreadability and swelling index. Based on these findings, formulation H4 was concluded to be the most effective for delivering Ketorolac Tromethamine topically through a niosomal gel platform.

INTRODUCTION: Topical drug delivery systems have gained prominence due to their ability to deliver drugs directly to the site of action, minimizing systemic side effects and enhancing patient compliance. Ketorolac Tromethamine, a non-steroidal anti-inflammatory drug (NSAID), is widely used for pain and inflammation management. However, its short half-life and gastrointestinal side effects limit its oral use. Niosomes, non-ionic surfactant-based vesicles, offer a promising approach for encapsulating drugs and enhancing their skin permeation and stability.

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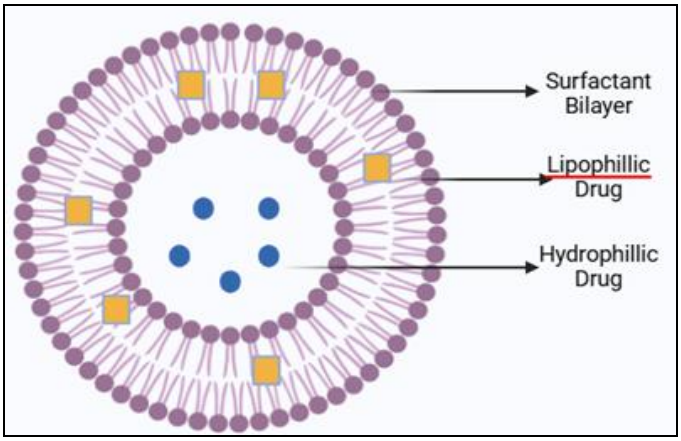

FIG. 1: STRUCTURE OF NIOSOME

Combining niosomes with hydrophilic gels results in niosomal gels, providing the advantages of controlled release and increased residence time. This study aims to develop and evaluate niosomal gels of Ketorolac Tromethamine using different polymers to improve its topical delivery [1-4].

MATERIALS AND METHODS:

Materials: Ketorolac Tromethamine was obtained as a gift sample from Reddys laboratories, Span 60, cholesterol, Tween 80, Carbopol 971P, Xanthan gum, HPMC (15cps), and Eudragit S100 were used as received. All other reagents were analytical grade.

Determination of λ_{max} and Calibration Curve: The λ_{max} of Ketorolac Tromethamine was determined using UV-Visible spectrophotometry. A stock solution (100 µg/mL) was prepared in distilled water and scanned between 200–400 nm. The λ_{max} was found at 323 nm. Calibration curves were constructed in the concentration range of 1–5 µg/mL with excellent linearity ($R^2 = 0.9954$) [5-9].

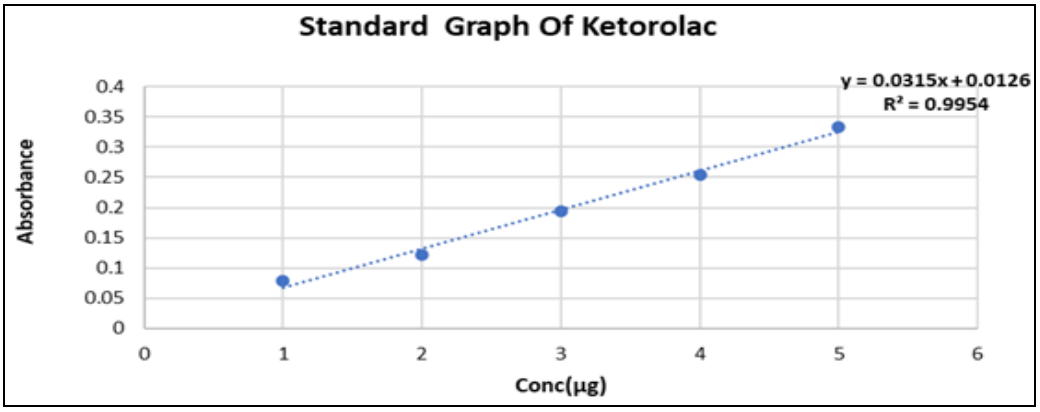

FIG. 2: CALIBRATION CURVE OF KETOROLAC TROMETHAMINE

FTIR Studies: This mixture is compressed using a mechanical press to form a transparent pellet, which is then analyzed in the infrared spectral range of 400 to 4000 cm^{-1}.

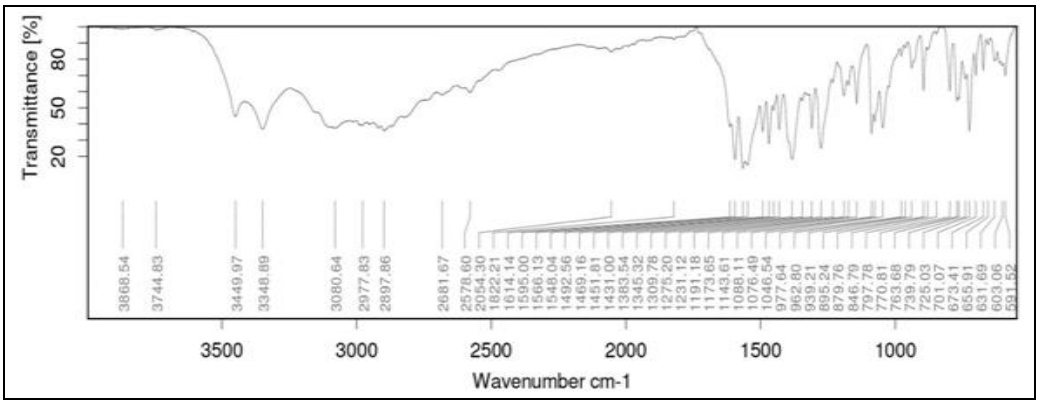

FIG. 3: FTIR OF KETOROLAC TROMETHAMINE PURE DRUG

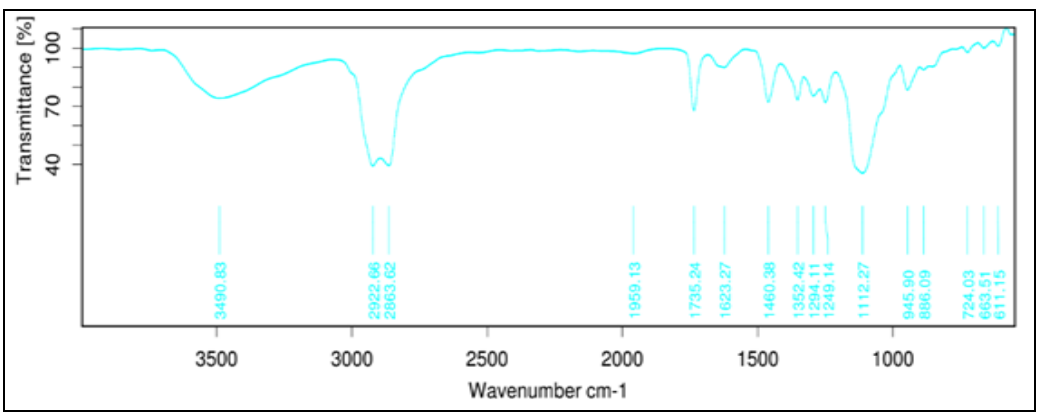

FIG. 4: FTIR SPECTRUM OF OPTIMIZED NIOSOMAL GEL

Formulation of Nanoemulsions: Niosomes were prepared using the thin-film hydration method. Initially, non-ionic surfactants such as Span 60 or Tween 80 and cholesterol were accurately weighed and dissolved in chloroform in a clean round-bottom flask. The flask was then attached to a rotary evaporator and the organic solvent was evaporated under reduced pressure at a controlled temperature of 60°C, rotating at 1000 rpm for 45 minutes. This process resulted in the formation of a thin lipid film along the inner wall of the flask. After complete removal of the solvent, a preheated aqueous phase (typically phosphate buffer) was added to the dried film to hydrate it, which led to the formation of multilamellar niosomal vesicles. The hydration process was carried out with gentle rotation or agitation until the entire film was dispersed into a niosomal suspension. To reduce the size and improve uniformity, the resulting niosomal dispersion was subjected to sonication using a probe or bath sonicator, producing small, stable, and homogenous vesicles suitable for drug delivery [10-16].

Characterization Studies: Niosomes were characterized for vesicle size, zeta potential, Polydispersity index (PDI), and drug content. Gel formulations were evaluated for pH, spreadability, extrudability, swelling index, and *in-vitro* drug release using Franz diffusion cells [17-20].

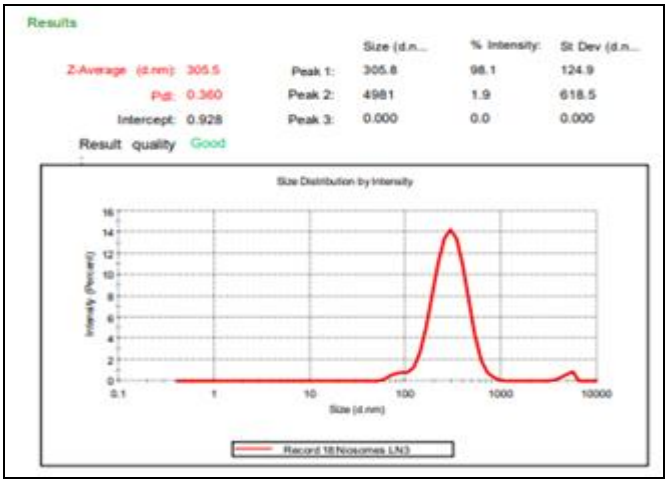

FIG. 5: PARTICLE SIZE AND PDI OF N3 FORMULATION

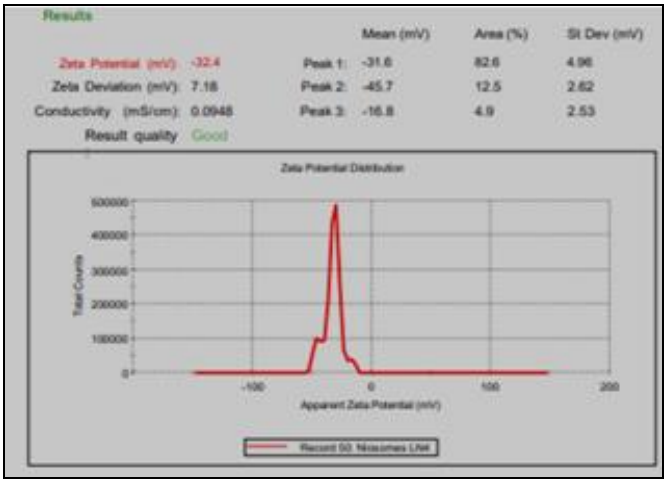

FIG. 6: ZETA POTENTIAL OF N3 FORMULATION

RESULTS AND DISCUSSION: The optimized niosomal formulation (LN4) had a vesicle size of 225 nm, a zeta potential of –32.4 mV, and a PDI of 0.12, confirming good uniformity and stability. Drug content was 98.35 ± 1.23%. Among gel formulations, H4 (Carbopol and Xanthan gum in 1:2 ratio) showed optimal pH (7.4), highest swelling index (169.0 ± 0.78), and excellent spreadability. *In-vitro* release studies revealed a sustained release of 99.6% over 12 hours for H4, compared to burst release in other formulations. The release kinetics followed Higuchi model with non-Fickian diffusion, confirming controlled release.

TABLE 1: EVALUATION OF KETOROLAC NIOSOMAL GEL FORMULATIONS

Formulation	pH	Spreadability (g.cm/sec)	Extrudability	Swelling Index	Mean % Drug Release ± SD
H1	7.01±0.8	18.7±0.3	+	84.0±0.76	96.3±0.32 (1hr)
H2	6.95±0.9	23.11±0.71	+ +	98.9±0.97	98.2±0.25 (1hr)
H3	6.64±0.3	18.18±0.3	+ + +	115.5±0.62	98.2±0.25 (2hr)
H4	6.9±0.4	25.3±0.5	+ + +	169.0±0.78	99.3±0.3 (12hr)
H5	7.5±0.5	28.33±0.6	+ + +	172.8±0.61	98.0±0.3 (4hr)
H6	7.11±0.3	27.0±0.8	+ +	78.2±0.59	97.9±0.3 (4hr)
H7	7.04±0.4	19.6±1.0	+ +	69.0±0.49	98.8±0.35 (2hr)
H8	6.51±0.6	24.0±1.0	+ +	98.3±0.66	98.7±0.4 (1hr)
H9	7.05±0.3	19.4±0.6	+ + +	94.9±0.74	98.6±0.48 (1hr)
H10	7.08±0.5	23.9±0.4	+ +	96.5±1.0	95.5±0.4 (2hr)
H11	6.41±0.4	15.4±0.22	+	109.7±0.67	99.5±0.45 (6hr)
H12	6.53±0.3	17.11±0.9	+	112.2±0.57	98.6±0.6 (6hr)

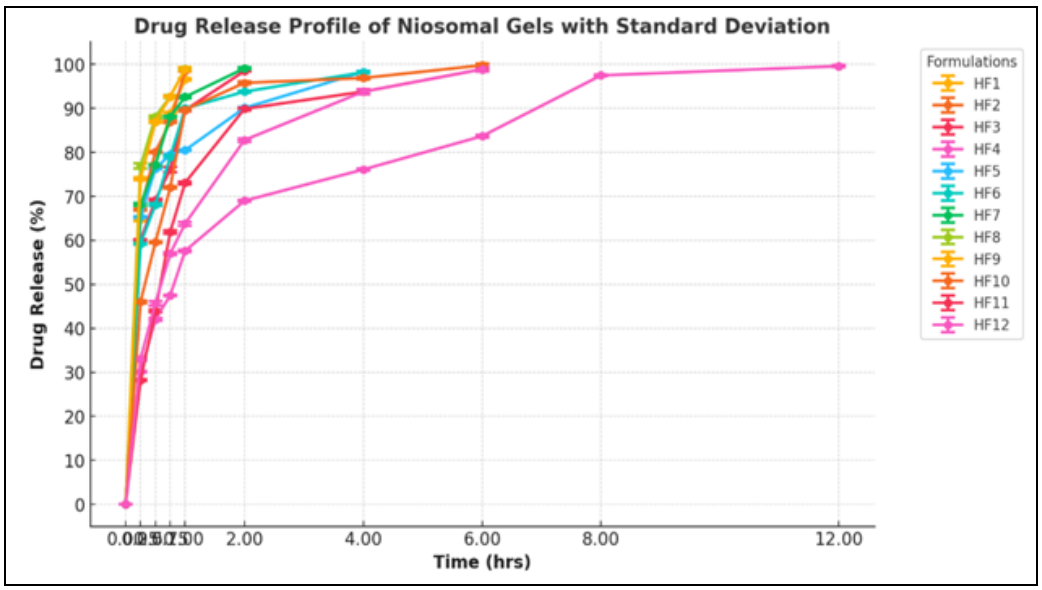

FIG. 7: DRUG RELEASE OF KETOROLAC TROMETHAMINE NIOSOMAL GEL FORMULATIONS

The study successfully developed a niosomal gel formulation of Ketorolac Tromethamine that offers enhanced stability, prolonged drug release, and improved topical application properties. Among all, formulation H4 emerged as the most promising candidate with optimal physicochemical and performance attributes. Further *in-vivo* studies are recommended to establish clinical efficacy.

Niosomal formulations were prepared using the thin-film hydration method, utilizing non-ionic surfactants (Span 60 and Tween 80) along with dicalcium phosphate. A total of four niosomal formulations (N1 to N4) were developed and characterized for vesicle size, polydispersity index (PDI), zeta potential, and drug content. Among them, H4 exhibited the most desirable physicochemical properties with a vesicle size of 225 nm, zeta potential of –32.4 mV, a low PDI of 0.12 indicating uniform size distribution, and high drug content of 97.55 ± 1.23%, suggesting excellent encapsulation efficiency [21-23].

The optimized niosomal formulation (N3) was then incorporated into twelve hydrogel matrices using polymers such as Carbopol 971P, Xanthan gum, HPMC, and Eudragit S100 individually and in combinations. These gels (coded H1 to H12) were subjected to comprehensive evaluation, including physical appearance, pH, spreadability, extrudability, swelling index, and *in-vitro* drug release studies. All gels showed acceptable pH levels ranging from 6.4 to 7.5, indicating their compatibility with skin application. Spreadability and swelling index values varied based on polymer type and concentration, with H4 (Carbopol and Xanthan gum in a 1:2 ratio) exhibiting optimal values, ensuring ease of application and enhanced hydration capability.

In-vitro drug release studies were conducted using Franz diffusion cells and phosphate buffer pH 7.4 as the diffusion medium. The data revealed a biphasic drug release profile in most formulations: an initial burst release followed by sustained release. H4 demonstrated the most controlled and extended drug release pattern-99.6% over 12 hours-compared to other formulations that released the drug within 1-6 hours. This sustained release behavior is advantageous in maintaining therapeutic drug levels at the site of action for prolonged periods, reducing dosing frequency, and improving patient compliance [24-27].

Drug release data from H4 best fit the Higuchi model, suggesting a diffusion-controlled mechanism. The niosomal gel also followed non-Fickian (anomalous) diffusion kinetics, indicating the involvement of both drug diffusion and polymer relaxation mechanisms.

In conclusion, the study successfully demonstrated that niosomal gels of Ketorolac Tromethamine, especially those based on a combination of Carbopol and Xanthan gum, provide an effective strategy for enhancing topical delivery of the drug. These formulations offer multiple benefits including improved drug stability, extended

release, and increased skin retention. Among all, H4 was identified as the most promising formulation based on its favorable physicochemical characteristics, optimal drug release profile, and rheological behavior. Future work may focus on scaling up this formulation, conducting *in-vivo* anti-inflammatory and pharmacokinetic studies, and evaluating long-term stability to facilitate its clinical application.

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CONFLICT OF INTEREST: Authors declare no conflict of interest.

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