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DEVELOPMENT AND EVALUATION OF PRONIOSOMES AS DRUG CARRIERS FOR TRANSDERMAL DELIVERY OF KETOROLAC TROMETHAMINE

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ABSTRACT

Ketorolac tromethamine is a drug with narrow therapeutic index and short biological half-life. This study was aimed at developing and optimizing proniosomal formulation of ketorolac tromethamine in order to improve its bioavailability. The prepared proniosomal gel formulations were evaluated and the effect of the varying composition of non ionic surfactant and cholesterol in various formulations were studied, such as vesicle shape, zeta potential, entrapment efficiency, and *in- vitro* drug release study. The presence of cholesterol made the proniosomes more stable with high drug entrapment efficiency and retention properties. The highest entrapment efficiency was observed with sodium cholate 88.17 ± 0.95 as compared to those formulation prepared with span60 and with sodium deoxycholate. Formulation F1 (LCI-I), zeta potential value was observed -20.0 mV, which is a measure of net charge of proniosomes which made them stable, by preventing aggregation. Formulation F1 which prepared by sodium cholate, showed highest drug release of 94.048 % after 24 hrs as compared to formulation F6 (LDCI-3) and F9 (LSI-3) which were prepared by sodium deoxycholate and sapn60 showed lowest drug release of 76.35% and 69.12%.

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INTRODUCTION:

Development of a new drug molecule is expensive and time consuming. Improving safety efficacy ratio of "old" drugs has been attempted using therapeutic drug monitoring (TDM) of formulation based on novel drug delivery systems. Proniosomes are based on dry formulation of water soluble carriers that are coated with surfactant. It forms niosomal dispersion immediately during the rehydration to before use on agitation in hot aqueous media within minutes[1]. Proniosomes are physically stable during the storage and transport. Drug encapsulated in the vesicular structure of proniosomes prolong the existence of drug in the systematic circulation and enhances the penetration into target tissue and reduce toxicity. Due to the limited amount of water present, these systems behave as viscous phases. When compared with conventional formulations, generally show a better control of blood levels, a reduced incidence of systemic toxicity, no hepatic first-pass metabolism and a higher compliance [2,3]. These 'proniosomes' minimize problems associated with niosome base formulation such as physical stability like aggregation, fusion and leaking, and provide additional convenience in transportation, distribution, storage, and dosing. The focus of this research work is to bring out different aspects related to proniosomes preparation, characterization, entrapment efficiency, *in vitro* drug release and *in vitro* permeation studies.

METHOD OF PREPARATION:

The proniosomes were prepared by rotatory flask method by dissolving cholesterol and various types of surfactants (span60, sodium deoxycholate and sodium cholate) in different concentration in alcohol and thin film was formed along the sides of the flask by continuous vortexing. Drug was dissolved in 10ml of phosphate buffer saline (PBS) pH.7.4 and added to the thin film and then sonicated for 5 min. The proniosomal suspensions were formed, and then these suspensions kept at 4^{o}C.

Table 1: Optimization of Proniosomal Formulation

Batch	Formulations	Surfactant: Lipid: Alcohol Ratio (w/w)	PBS pH 7.4 (ml)
F1	LCI-1	2.1:0.3:9	10
F2	LCI-2	1.71:0.3:7	10
F3	LCI-3	0.9:0.3:4	10
F4	LDCI-1	2.1:0.3:9	10
F5	LDCI-2	1.71:0.3:7	10
F6	LDCI-3	0.9:0.3:4	10
F7	LSI-1	2.1:0.3:9	10
F8	LSI-2	1.71:0.3:7	10
F9	LSI-3	0.9:0.3:4	10

C: Sodium Cholate, **D:** Sodium Deoxycholate, **I**: Isopropanol **L:** Lipid**, S**: Span60

Characterization

Determination of Zeta Potential: The zeta potential of the selected batch of proniosomal formulation was determined at 25ºC using Zetasizer (Malvern Instruments). 4 Proniosomal suspension was diluted 100 times with double-distilled water and voltage was set at 50 or 100 V and electrodes were placed in dispersion for the measurement of zeta potential.

Scanning Electron Microscope: The sizes of the vesicles were measured by scanning electron microscopy 5. Small amount of proniosomal suspension was placed on the specimen stub, coated with carbon and then with gold vapor using Hitachi vacuum evaporator. The samples were examined under scanning electron microscope, and then photographed.

Entrapment Efficiency: The entrapment efficiency was determined after separating the unentrapped drug. Proniosomes (100mg) was hydrated with 10 ml of phosphate buffer saline (pH 7.4) manual shaking for 5 minutes, to form PN dispersion. For the separation of unentrapped drug the PN dispersion was centrifuged at 15000 rpm for 30 minutes at 20^0C and analyzed by UV spectroscopy at 322 nm. The entrapment efficiency was calculated using the formula:

$$\% \text{ Entrapment efficiency} = \frac{\text{Total Drug} - \text{drug in supernatant liquid}}{\text{Total drug}} \text{ X } 100$$

***In vitro* Drug Release**: The release of Ketorolac Tromethamine from proniosomal gel was determined using membrane diffusion technique. The proniosomal gel equivalent to 1mg of Ketorolac Tromethamine was placed in a dialysis bag tied to glass tube acting as a donor compartment. The glass tube was placed in a beaker containing 50ml of phosphate buffer (pH7.4), acting as a receptor compartment. The whole assembly was fixed in such a way that the lower end of tube containing gel was just touching the surface of diffusion medium. The temperature of receptor medium was maintained at 37 ± 05°C and was agitated at the speed of 100 rpm using magnetic stirrer. Aliquots of 3ml sample were withdrawn periodically and after each withdrawal same volume of medium was replaced. The collected sample was analyzed by UV spectrophotometer using phosphate buffer (pH 7.4) as blank.

RESULTS AND DISCUSSION:

Determination of Zeta potential: - The formulation F1, which was subjected to Zeta potential analysis, had a zeta value of -20.0 mV, which is a measure of net charge of proniosomes. High surface charge provides sufficient electrostatic repulsion between the vesicles, which made them stable, by preventing aggregation. Negative charge leads to rapid blood clearance.

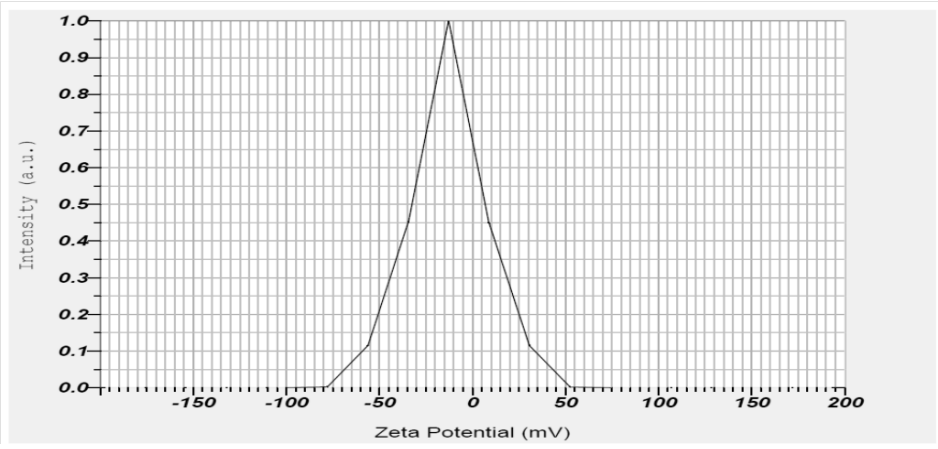

Figure 1: Zeta Potential Analysis

By Scanning Electron Microscope (SEM): Scanning electron microscopy for the selected formulation F1was carried out. The results are shown in the following SEM photograph.

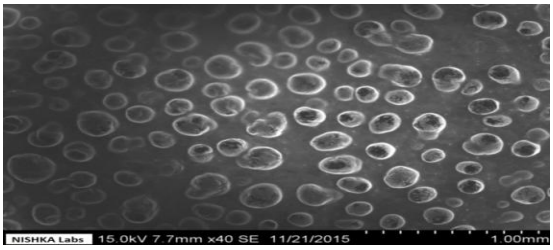

Figure 2: Proniosomes observed under SEM

Entrapment Efficiency: Entrapment efficiency is the percentage fraction of the total drug incorporated into the Proniosomes. As shown in figure no.03. Formulation LCI-1 (88.17 ± 0.95) exhibited very high entrapment efficiency. This could be explained on the basis that the highly lipophilic portion of the drug is expected to be housed almost completely within the lipid bilayer of the proniosomes.

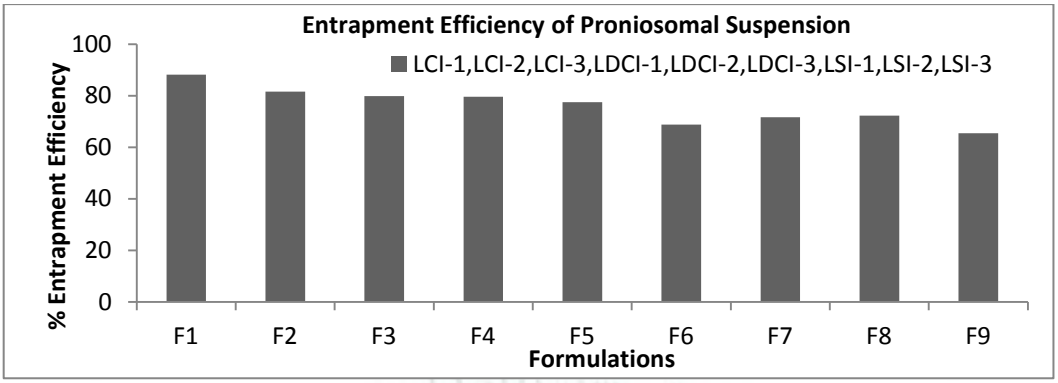

Figure 3: Entrapment Efficiency of Proniosomal Suspension

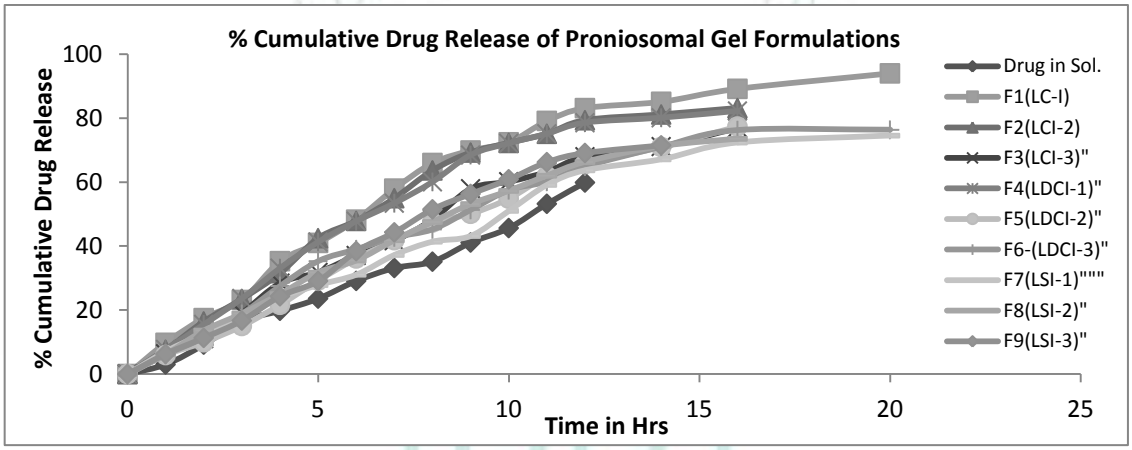

Figure 4: % Cumulative Drug Release of Gel Formulations

***In Vitro* Drug Release of Proniosomal Gel:** Formulation F1 showed highest drug release of 94.011 % in 24 hrs and formulation F9 showed lowest drug release of 71.789 % in 16 hrs (Figure 4). After incorporation of proniosomal vesicles into gel base they show significant delayed in *in-vitro* drug release in 24 hours as compared to proniosomal suspension

CONCLUSION:

The results of the present investigation showed that the problems associated with the transdermal delivery of KT could be overcome by incorporating it into the new PN drug carrier, proniosomes. Among the nine PN formulations developed for transdermal delivery of KT, LCI-1 (F1) showed promising higher entrapment efficiency, showed highest drug release of 94.048 % after 24 hrs as compared to formulation F6 (LDCI-3) and F9 (LSI-3) which were prepared by sodium deoxycholate and sapn60 showed lowest drug release of 76.35% and 69.12%.

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