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Formulation and Characterization of Ketorolac Tromethamine Encapsulated Niosomes for Transdermal Drug Delivery

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ABSTRACT

Objective: The aim of the study was to formulate and evaluate Ketorolac Tromethamine Niosomal gel to reduce the gastrointestinal toxicities associated with oral administration. **Materials and Methods:** The Niosomes were prepared by Hand Shaking Method using Sodium Deoxycholate, Sodium Cholate and Span 60 as surfactant and dicetyl phosphate and stearyl amine as charge inducers. **Results:** The niosomes containing Sodium Deoxycholate and Cholesterol at 1:1 was showed highest entrapment efficiency 83.11±0.093%. After incorporation of Niosomal vesicles into gel base they show significant reduction in *In-vitro* drug release in 8 hours as compared to Plain Gel. Niosomal gel (F2) formulation was showed zero order kinetics and the mechanism of drug release was diffusion. The lower flux value of niosomal gel indicates its prolonged drug release. The permeability coefficient of plain gel, marketed gel and niosomal gel were found to be 2.48 ±0.00038, 3.18 ±0.00005 and 2.01 ± 0.00001 cm $.h^{-1}.10^{3}$. Diffusion coefficient of plain gel, marketed gel and niosomal gel were found to be 4 ±0.00001, 4.7 ±0.00001 and 2.9 ± 0.00001 $cm^{2}.h^{-1}.10^{-4}$. **Conclusion:** the results of the niosomal gel formulations showed maximum *in-vitro* drug permeation. Niosomes may be a promising vehicle for transdermal delivery of Ketorolac Tromethamine.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are those systems which when applied to the skin delivers the drug at a controlled rate to the systemic circulation. The advantages include reduced side effects, improved patient compliance, and longer duration of action, and avoidance of the first-pass metabolism. [1] They have a direct effect on the permeability of skin barriers. [2] These enhancers include compounds that interact with the lipid matrix of the stratum corneum to alter its nanostructure and thereby increase permeability. Enhancers can increase drug diffusivity through skin proteins. [3] Niosomes are non-ionic surfactant vesicles having a bilayer structure i.e. multilamellar or unilamellar enclosed in aqueous solutions of solutes and lipophilic components formed by self-assembly of hydrated surfactant monomers.[4] Niosomes on comparing to phospholipids vesicles show higher physical and chemical stability with greater availability of surfactant classes and lower cost. They can entrap both lipophilic and hydrophilic drugs in the vesicular membrane and aqueous layer. [5] They are less toxic because of their non-ionic nature and improve the therapeutic index of the drug by restricting its action to target cells and are a promising vehicle for drug delivery. [6]

Niosomal gel is a nanometric system embedded in a gel. Nanometric systems have a greater surface area, which is useful for the application of drug substances for homogeneous drug release.[7] Conventional dosage forms absorbed dose is less than 5% but in niosomal gel form absorption of the administered drug is increased.[8] Topically applied niosomes can increase the longer action on the skin (epidermis and stratum corneum) while reducing the drug absorption systemically. [9]

Ketorolac tromethamine (KT) is a non-steroidal agent with moderate anti-inflammatory and potent analgesic activity. KT works by competitive blocking of the enzyme cyclooxygenase (COX) which is involved in the production of various chemicals in the body, some of which are known as prostaglandins. The drug is administered orally in divided multiple doses for short-term management of post-operative pain (10 mg q.i.d. as oral tablets) and intramuscularly (30 mg q.i.d.by IM injection). This frequent dosing results in unacceptability by patients due to the short half-life (4–6 h) of the drug. Therefore, an alternative mode of delivery of the drug is required. To maintain the drug blood levels of KT for an extended period transdermal delivery is an attractive route of administration. This shows that the dosage form acting transdermally must allow the drug to penetrate deeply into the skin. KT is hydrophilic in nature and its absorption through the skin is poor. Therefore, to enhance the

transdermal delivery of KT a drug permeation enhancer likes Dimethyl Sulphoxide was used. The high analgesic activity and low molecular weight of KT make it a good candidate for transdermal delivery. [10], [11]

MATERIALS AND METHODS

Materials

Ketorolac Tromethamine was obtained as a gift sample from Piramal Healthcare Ltd, Pithampur (M.P.). Sodium Cholate, Sodium Deoxycholate, Cholesterol, and Span 60 were purchased from Loba Chemie, Mumbai. Dicetyl Phosphate (DCP) was purchased from Sigma Aldrich, Mumbai. Stearylamine was purchased from Sisco Research Lab, Mumbai. Chloroform and Methanol were of analytical grade.

Method of preparation of niosomes

The niosomes were prepared by handshaking method by dissolving cholesterol, Stearyl amine or Dicetyl Phosphate and surfactant in chloroform: methanol mixture [Table No. 1] and the thin film was formed along the sides of the flask by continuous vortexing, and the thin lipid film was kept overnight in a desiccator to remove the residual solvents. Then the thin lipid film was hydrated with 10 ml of phosphate buffer saline (PBS) pH 7.4 containing drug and the niosomal suspension was allowed to stand at room temperature for a limited period to achieve the complete swelling of the lipid film to obtain the niosomal suspension and then sonicated (Ultra sonicator, Leelasonic) for 5 min. The niosomal suspension was kept refrigerated at 4^{o}C. [12]

Table No. 1: Formulations of Ketorolac Tromethamine niosomes

Formulations	Drug (mg)	Cholesterol (mg)	Surfactant (mg)	DCP (mg)	SA (mg)	Chloroform: Methanol (ml)
F1NaDC	50	50	25	5	-	1:1
F2NaDC	50	50	50	-	5	1:1
F3NaDC	50	50	75	5	-	1:1
F4NaC	50	50	25	5	-	1:1
F5NaC	50	50	50	-	5	1:1
F6NaC	50	50	75	5	-	1:1
F7S60	50	50	25	5	-	1:1
F8S60	50	50	50	-	5	1:1
F9S60	50	50	75	5	-	1:1

NaDC- Sodium Deoxycholate, **NaC-** Sodium Cholate, **S60-** Span 60.

Preparation of niosomal gel and plain gel

Carbopol 940 1% w/v solution was allowed to swell in distilled water for 3-4 h. 2 ml of niosomal suspension was added into carbopol 940 containing glycerin, methylparaben and then it was properly mixed by mechanical stirring. Then Dimethyl Sulphoxide was added as a penetration enhancer. Triethanolamine was added to adjust pH. Niosomal gel was sonicated for 15 min and kept overnight to remove air bubbles. [13], [14] For the preparation of Plain gel equivalent to 20 mg of drug was added into Carbopol 940 containing Glycerin, Methylparaben and then it was properly mixed by Mechanical Stirring. Then Dimethyl Sulphoxide (DMSO) was added as a penetration enhancer. Then Triethanolamine was added to adjust pH. The plain gel was sonicated for 15 min and kept overnight to remove air bubbles. [15], [16]

Evaluation of Niosomes

Fourier Transform Infrared (FTIR) Spectroscopy

The physical mixture of drugs with excipients was identified by FTIR. Fourier-transform infrared spectroscopy (FT-IR) was performed by using the potassium bromide disc method. Over the range of 4,000.00 - 650.00 cm^{-1}, the samples were scanned in an inert atmosphere. Infrared spectroscopy was done for cholesterol, surfactant, pure drug, and physical mixture of drug with excipients was used and was mixed separately with IR grade KBr. The discs were prepared by applying 15000 lb pressure in a hydraulic press. [17]

Vesicle shape by Scanning Electron Microscope

The size of the vesicles was measured by scanning electron microscopy. A small amount of niosomal suspension was placed on the specimen stub. Coated with carbon and then with gold vapor using Hitachi vacuum evaporator. The samples were examined under a scanning electron microscope and then photographed. [18]

Determination of Zeta Potential

The zeta potential of the selected batch of niosomal formulation was determined at 25ºC by using Zetasizer (Malvern Instruments). Niosomal 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. [19]

Entrapment efficiency

Niosomes were separated by centrifugation at 5,000 rpm for 90 min at 20°C. They were settled in the form of pellets. The supernatant having unentrapped drug was separated and analyzed by UV spectroscopy (Shimadzu UV-1800 Japan) at 322 nm. [20], [21] the entrapment efficiency was calculated using the formula:

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

Evaluation of Niosomal Gel

Physical appearance and homogeneity

The physical appearance and homogeneity of the prepared gels were tested by visual observations after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Clarity

The clarity of various formulations was determined by visual inspection under black and white background and it was graded as turbid: +, clear: ++, very clear (glassy): +++. [22]

Viscosity

The measurement of viscosity of the prepared niosomal gel was done with Brookfield Viscometer (DV-E). 10 g of the gel was taken into a beaker and the spindle was dipped into the gel formulation, viscosity of the gel formulation was measured by rotating the spindle 96 at 10 rpm. [23]

Measurement of pH

The pH measurement of the gel was performed in triplicate by using a digital pH meter. Before pH measurements, the pH meter was calibrated and readings were taken by dipping the glass electrode into the gel formulations. [24]

Spreadability

The spreadability of gel formulations was determined by placing 0.5 g gel within a circle of 1 cm diameter pre-marked on a glass slide over which a second glass slide was placed. A weight of 500 g was allowed to rest on the upper glass slide for 5 min. The increase in the diameter due to the spreading of the gels was determined. [25]

$$S = \frac{mxL}{t}$$

Where,

S: Spreadability,

m: the mass of the gel formulation,

L: length travel by upper slide,

t: time.

Drug content

Standard preparation

The standard solution was prepared with 50 mg of Ketorolac Tromethamine dissolved in 50 ml of phosphate buffer pH 7.4 in a 50 ml volumetric flask. Then, 1 ml of this solution was taken and transferred into100 ml of a volumetric flask, diluted up to 100 ml with phosphate buffer pH 7.4.

Sample preparation

5 mg of niosomal gel was dissolved into a 100 ml of volumetric flask and was shaken well for a few minutes until it was completely mixed. The solution in the volumetric flask was then made up to 100 ml with phosphate buffer pH 7.4. The resulting solution was filtered using Whatman filter paper and 1 ml of filtered solution was taken and transferred into a volumetric flask of 10 ml and volume was made up to the mark with phosphate buffer pH 7.4. The solution was analyzed for drug content by using UV Spectrophotometer (Shimadzu-1800, Japan) at 322 nm. The percentage of drug content was calculated by using the following formula. [26]

$$\%\ Drug\ Content = \frac{SampleAbsorbance}{StandardAbsorbance} X \frac{StandardDilution}{SampleDilution} X\ 100$$

Extrudability

The extrusion of the gel from the tube is important during its application and for patient acceptance. This study is useful in explaining whether the gel is removing from the collapsible tube during application in a proper manner or not. Gels with high consistency may not extrude from the tube whereas, low viscous gels may flow quickly, and hence suitable consistency is required to extrude the gel from the tube. The formulation was filled into collapsible aluminum tubes. The tubes were pressed to extrude the 0.5 cm ribbon of the gel in 10 seconds and then extrude ability of formulations was checked. [27]

***In-Vitro* Drug Release**

The release of Ketorolac Tromethamine from Niosomal Gel was determined by using the membrane diffusion technique. The Niosomal Gel equivalent to 1 mg of Ketorolac Tromethamine was placed in a Dialysis bag (Hi-media, Mumbai) was tied with a glass tube that acts as a donor compartment. The glass tube was placed in a beaker containing 50 ml of phosphate buffer (pH 7.4), acting as a receptor compartment. The whole assembly was kept in such a way that the lower end of the tube containing gel was just touching the surface of the diffusion medium. The temperature of the receptor medium was maintained at 37 ± 5°C and the speed of 100 rpm was maintained using a magnetic stirrer (Remi Motors, Mumbai). Aliquots of 3 ml sample were withdrawn at 1, 2, 3, 4, and 8 hrs, after each withdrawal same volume was replaced by receptor medium. The withdrawn sample was analyzed spectrophotometrically (Shimadzu-1800, Japan) at 322 nm using phosphate buffer (pH7.4) as blank. [28], [29]

Drug Release kinetics

To investigate the mechanisms of Ketorolac Tromethamine released from the Niosomal Gel, the release data were analyzed mathematically according to different kinetic models such as zero order kinetics, first-order kinetics, Higuchi's model, Korsmeyer-Peppas model, and Hixson Crowell model. [30]

***In-vitro* permeability study**

A skin permeation study was performed using a Franz diffusion cell with an effective diffusion area of 2.669 cm^2. The experiment was carried out using freshly killed goat dorsal skin obtained from the local slaughterhouse and stored at - 18°C in the Ringer solution. The skin was first flushed with a physiological solution at room temperature for 2 h to remove any skin content, the skin was shaved using a hand razor to remove subcutaneous tissue and the dermis side was wiped with isopropyl alcohol to remove adhering fat. The cleaned skin was washed with distilled water. A circular piece of skin about 3 cm diameters was sandwiched between the donor and receptor compartment of the vertical diffusion chamber and 1 gm drug-loaded niosomal gel was added to the mucosal side. In the donor compartment, the formulation was placed in intimate contact with the skin. The receptor compartment was filled with phosphate buffer pH 7.4, kept at a constant temperature of 37±5ºC, and stirred by a magnetic stirrer (Remi Motors, Mumbai). At appropriate intervals (1, 2, 3, 4, 5, 6, 7, 8 hrs), 3 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh receptor medium. Samples were analyzed by UV Spectrophotometer (Shimadzu-1800, Japan) at 322 nm using phosphate buffer pH 7.4 as blank. [31], [32]

Occlusion studies

25 gm of water was taken in a beaker which was covered and sealed with Whatman filter paper, served as a reference sample. 200 mg of sample was spread evenly with a spatula on the filter surface. The samples were stored at 32°C and 50–55 % RH for 48 hrs. The samples were weighed after 48 hrs which showed the water loss due to evaporation at each time (water flux through the filter paper). The occlusion factor F was calculated according to the following equation:

$$F = \frac{A - B}{A} X\ 100$$

Where,

A is the reference without water loss,

B is the water loss with the sample.

An occlusion factor 0 means no occlusive effect compared to the reference and 100 is the maximum occlusion factor. [33]

Stability Study

A stability study of Niosomal Gel was performed for 1 month. A sufficient quantity of the niosomal gel formulations was sealed in a collapsible aluminum tube in triplicate and stored at refrigerated temperature (2–8°C) and room temperature (25±2°C). The sample was withdrawn after one month and analyzed for drug content, Physical appearance, Homogeneity. [34], [35]

RESULTS AND DISCUSSIONS

Fourier Transform Infrared (FTIR) Spectroscopy

The IR spectrum of pure Ketorolac Tromethamine shows a peak at 3536.40 cm^{-1}which is attributed to N-H and NH_2 stretching and peaks at 1479.18 cm^{-1} are due to C=C aromatic stretching, peak at 1317.75 cm^{-1} is due to -C-N vibrations, peak at 1708.79 cm^{-1} is due to C=O stretch of ester, peak at 1077.81 cm^{-1} is due to -OH bending confirms the presence of an alcoholic group, peaks at 710.649 cm^{-1} and 749.136 cm^{-1} confirms the C-H bending (aromatic) [Figure No. 1, 2, 3, 4 and 5]. Hence, it confirms the structure of Ketorolac Tromethamine and the result indicates that there was no interaction between the drug and excipients used in the niosomal preparation.

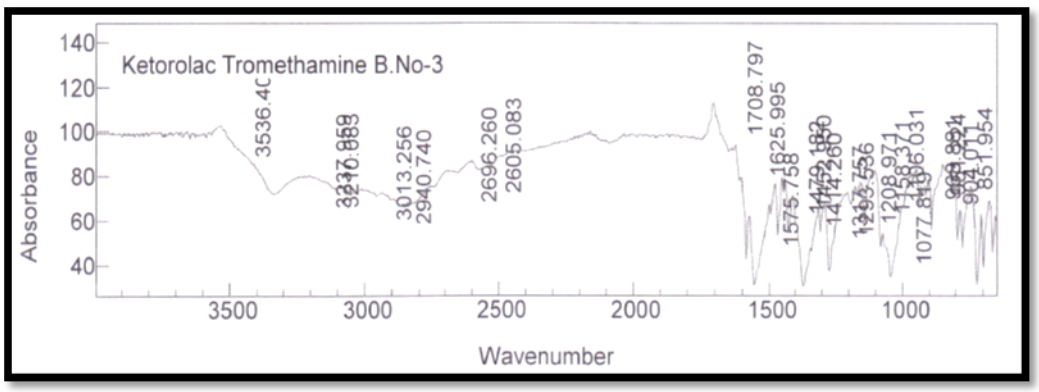

Figure No. 1: IR spectrum of pure Ketorolac Tromethamine

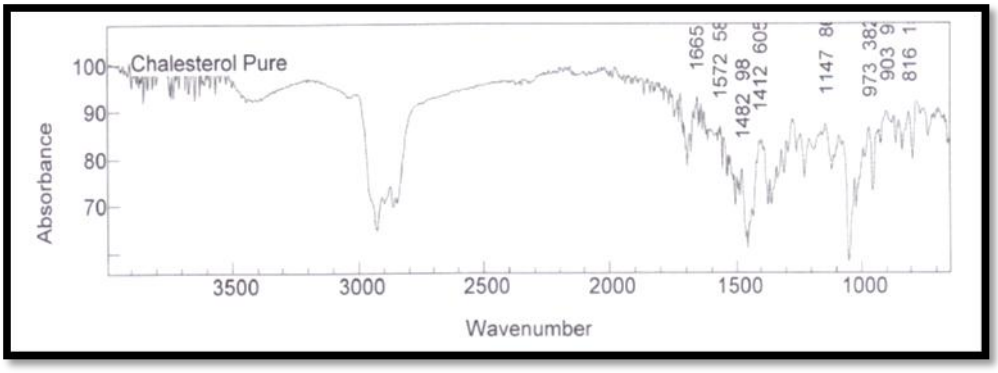

Figure No. 2: IR spectrum of pure Cholesterol

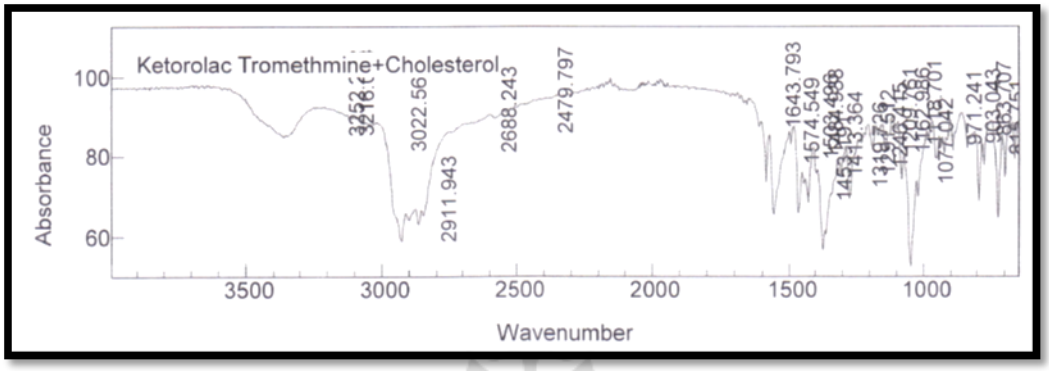

Figure No. 3: IR spectrum of a physical mixture of Ketorolac Tromethamine with cholesterol

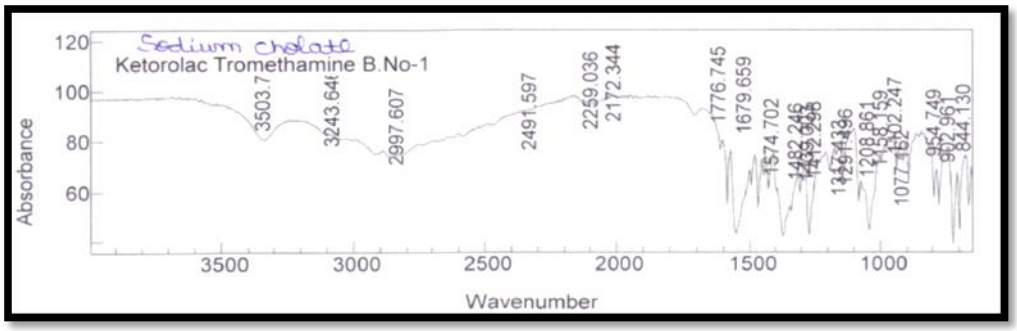

Figure No. 4: IR spectrum of a physical mixture of Ketorolac Tromethamine with Sodium Cholate

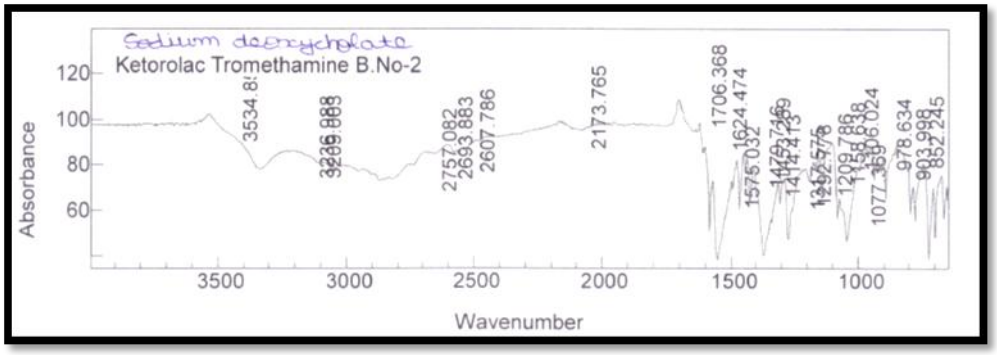

Figure No. 5: IR spectrum of a physical mixture of Ketorolac Tromethamine with Sodium Deoxycholate

Vesicle shape by Scanning Electron Microscope (SEM)

Scanning electron microscopy for the selected formulation F2 was carried out. The results are shown in the following SEM photograph [Figure No. 6].

Determination of Zeta potential

The formulation F2 which was subjected to Zeta potential Analysis had a zeta value of -43.0 mV, which is a measure of the net charge of niosomes. The high surface charge provides sufficient electrostatic repulsion between the vesicles which made them stable, by preventing aggregation. A negative charge leads to rapid blood clearance. This shows that formulation F2 produces stable niosomal suspension [Figure No. 7].

Entrapment Efficiency

The Entrapment Efficiency of the formulations (F1-F3) Sodium Deoxycholate, (F4-F6) Sodium Cholate and (F7-F9) Span 60 was high when the same concentration of the drug and surfactant was used [Table No. 2]. Formulation (F2) showed the highest Entrapment Efficiency of 83.11±0.093 %. Formulation (F9) showed the lowest Entrapment Efficiency of 69.9±0.048 %.

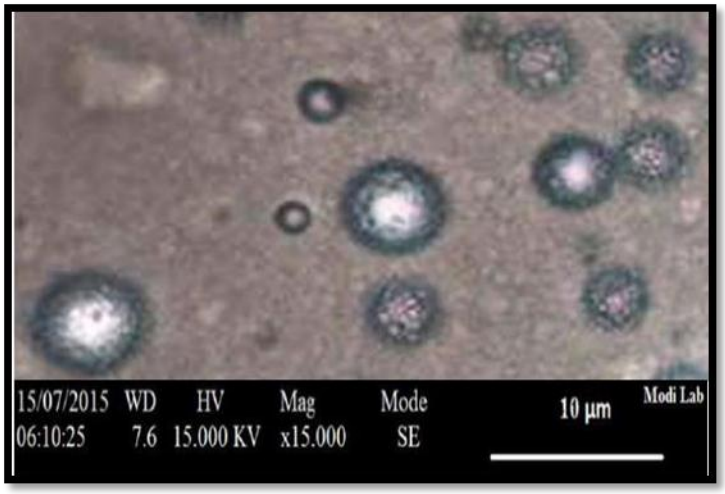

Figure No. 6: Scanning electron microscope image of niosomes

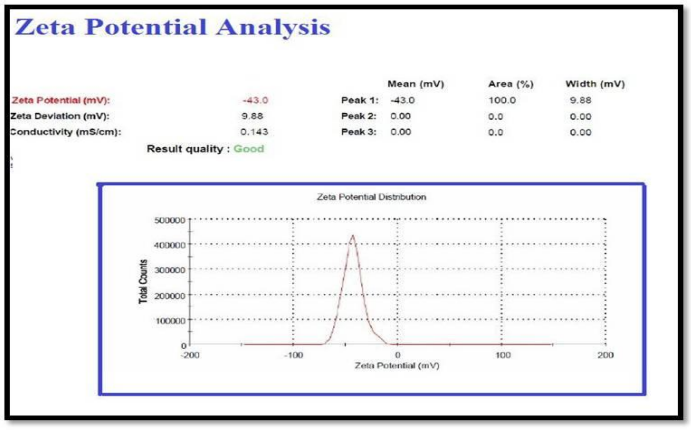

Figure No. 7: Zeta Potential Analysis

Table No. 2: % Entrapment Efficiency of niosomes

Formulation	% Entrapment Efficiency
F1	81.17 ± 0.097%
F2	83.11 ± 0.093 %
F3	70.41 ± 0.049 %
F4	70.58 ± 0.048 %
F5	78.36 ± 0.146 %
F6	72.17 ± 0.049 %
F7	71.31 ± 0.127 %
F8	75.09 ± 0.070 %
F9	69.9 ± 0.048 %

Evaluation of niosomal gel

Physical appearance and homogeneity

All the niosomal gel formulations have a colorless to pale yellow appearance [Table No. 3] and showed good homogeneity with an absence of lumps.

Clarity

All the niosomal gel formulations were found to be transparent and were free from the presence of particles [Table No. 3].

Extrudability

The Extrudability of various formulations was satisfactory, good, and excellent. Gels are easily coming out from the collapsible tube. Formulation F2 showed excellent Extrudability [Table No. 3].

Viscosity

Viscosity was found in the range of 8542 ± 1.632 cps to 10512 ± 1.247 cps [Table No. 4].

Measurement of pH

The pH of all the niosomal gel formulations was in the range of 6.1 ± 0.081-7.0 ± 0.214, which lies in the normal pH range of the skin and would not produce any skin irritation [Table No. 4].

Spreadability

All the niosomal gel formulations showed good spreadability i.e. gel is easily spreadable. Spreadability of niosomal gel was in the range of 3.6 ± 0.216 to 2.5 ± 0.286 g.cm/sec [Table No. 4].

Drug content

Drug content was found in the range between 95.286 ± 1.017 to 98.428 ± 0.511 %. Among all the Formulation (F2) showed maximum drug content of 98.428±0.511 %. The drug

content of all the formulations was within the acceptable range which shows the proper mixing of the drug with the excipients [Table No. 4].

Table No. 3: Evaluation parameters of niosomal gel

Sr. No.	Physical Appearance	Homogeneity	Clarity	Extrudability
F1	Colorless	Good	++	+
F2	Colorless	Good	+++	+++
F3	Colorless	Good	++	+
F4	Pale Yellow	Good	++	+
F5	Pale Yellow	Good	++	++
F6	Pale Yellow	Good	++	+
F7	Colorless	Good	++	+
F8	Colorless	Good	++	+
F9	Colorless	Good	++	++

***In-vitro* drug release of niosomal gel**

Formulation F9 showed the highest drug release of 68.019 % and formulation F2 showed a lesser drug release of 53.418 % in 8 hrs. After incorporation of Niosomal vesicles into gel base they show significant reduction in *In-vitro* drug release in 8 hours [Figure No. 8].

Drug release kinetics

The results obtained for F2 are shown in Table No. 5 and 6. The best fit with higher correlation was found with the Zero-order with the R^2 value of 0.9943 [Figure No. 9] and the mechanism of drug release was diffusion.

Table No. 4: Evaluation parameters of niosomal gel

Sr. No.	Viscosity (cps)	pH	Spreadability (g.cm/ sec)	% Drug Content
F1	10412 ± 1.632	6.5 ± 0.163	3.2 ± 0.124	98.292 ± 1.403
F2	10227 ± 2.054	6.6 ± 0.163	3.2 ± 0.081	98.428 ± 0.511
F3	9192 ± 2.054	6.3 ± 0.169	2.7 ± 0.047	98.224 ± 1.393
F4	9840 ± 1.632	6.1 ± 0.081	2.5 ± 0.081	95.286 ± 1.017
F5	10340 ± 1.247	6.3 ± 0.329	2.5 ± 0.286	96.857 ± 0.255
F6	10224 ± 0.816	7.0 ± 0.214	2.5 ± 0.124	95.901 ± 0.579
F7	10512 ± 1.247	7.0 ± 0.205	3.6 ± 0.216	97.404 ± 1.008
F8	8542 ± 1.632	6.6 ± 0.205	3.0 ± 0.163	97.540 ± 0.885
F9	10095 ± 0.816	6.9 ± 0.124	2.9 ± 0.249	97.131 ± 0.931

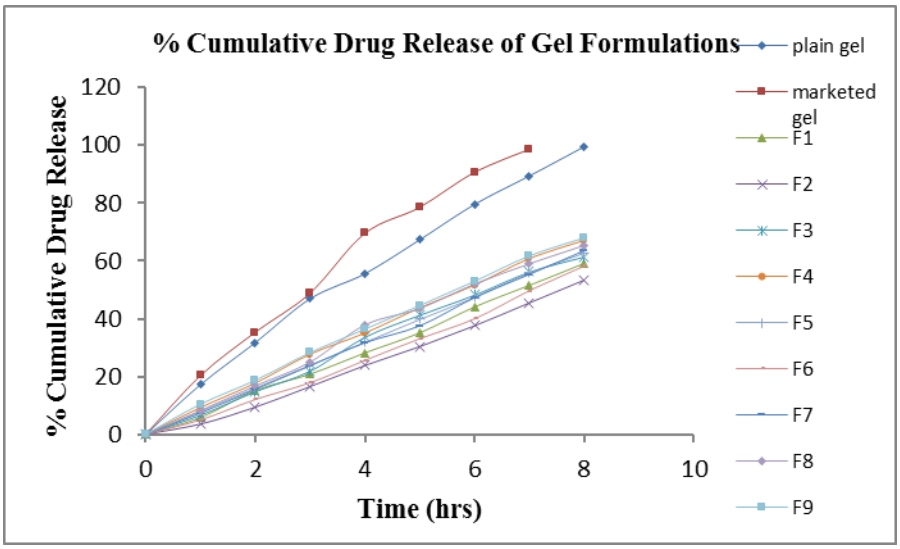

Figure No. 8: % Cumulative drug release of gel formulations

***In-vitro* Permeability study**

The results of *in-vitro* permeation are shown in [Figure No. 10]. The flux values of plain gel, marketed gel, and niosomal gel were found to be 2.758 ± 0.071, 3.181 ± 0.051, and 1.987 ± 0.034 µg/cm^2.hr resp. The lower flux value of niosomal gel indicates its prolonged drug release behaviour as compared to plain and marketed gel. The permeability coefficient of plain gel, marketed gel and niosomal gel were found to be 2.48 ± 0.00038, 3.18 ± 0.00005 and 2.01 ± 0.00001 cm.h^{-1}.10^3. Diffusion coefficient of plain gel, marketed gel, and niosomal

gel was found to be 4 ± 0.00001, 4.7 ± 0.00001, and 2.9 ± 0.00001 $cm^2.h^{-1}.10^{-4}$. The enhancement ratio was found to be 0.72044 ± 0.041 [Figure No. 10].

Table No. 5: Kinetic Release study of Ketorolac Tromethamine Niosomal gel (F2)

Time (hrs)	% CRD	Log % CRD	% drug remaining	Log % drug remaining	√time	Log time	W_0-W_t
0	0	0	100	2	0	0	0
1	3.529	0.54765	96.471	1.98439	1	0	0.05528
2	9.378	0.97211	90.622	1.95723	1.414	0.15	0.14988
3	16.543	1.21861	83.457	1.921462	1.732	0.238	0.27152
4	23.835	1.37721	76.165	1.881755	2	0.301	0.4027
5	30.4	1.482873	69.6	1.842609	2.236	0.349	0.52816
6	37.608	1.57528	62.392	1.79512	2.449	0.388	0.67538
7	45.54	1.658393	54.46	1.736077	2.645	0.422	0.85118
8	53.418	1.727687	46.582	1.668218	2.82	0.45	1.04349

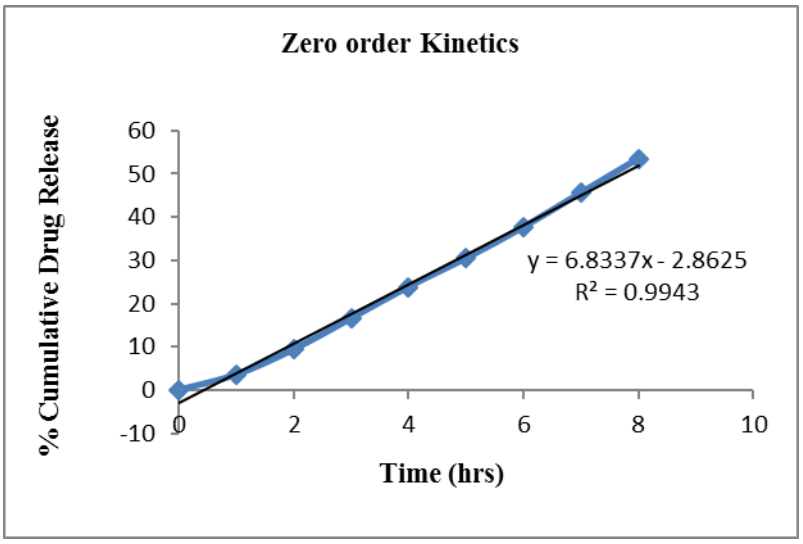

Figure No. 9: Zero Order (% Cumulative Drug Release vs. time)

Table No. 6: Kinetic Release profile of (F2) formulation

Sr. No.	Kinetics Model	Regression Coefficient
1.	Zero Order	0.9943
2.	First Order Kinetics	0.9707
3.	Higuchi Equation	0.8678
4.	Korsmeyer –Peppas Equation	0.9235
5.	Hixson Crowell Cube root law	0.9811

Occlusion studies

The ability of niosomal gel to reduce the Transepidermal loss of water was evaluated by *in vitro* occlusivity test. Plain Ketorolac Tromethamine gel, Marketed Ketorolac Tromethamine gel and the Ketorolac Tromethamine Niosomal gel had an occlusivity factor of 66.290 ± 0.0142, 80.949 ± 0.0971and 82.373 ± 0.0967 respectively. Niosomal gel reduces more water loss as compared to Marketed and Plain gel [Figure No. 11].

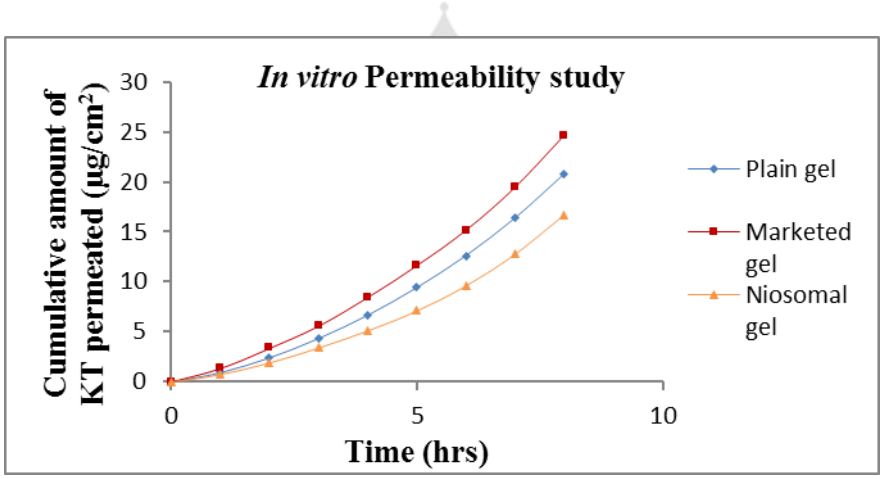

Figure No. 10: Cumulative amount of KT permeated through goatskin

Stability study

The stability of niosomal gel was carried out for 1 month. There was no aggregation, fusion, or disruption of the vesicles during the study period of 1 month and it was found that the prepared formulations were able to retain their multilamellar nature. At refrigerated condition (4±2°C) the niosomal Gel formulation F2 showed 98.909±0.582 %. At room temperature (25±2°C) formulation F2 showed 97.728 ± 0.381% [Table No. 6]. Thus it was found that storage under refrigerated conditions showed greater stability. But in both the storage

conditions drug content was found to be within the specification of 95-105 % throughout the study period of 1 month [Figure No. 12].

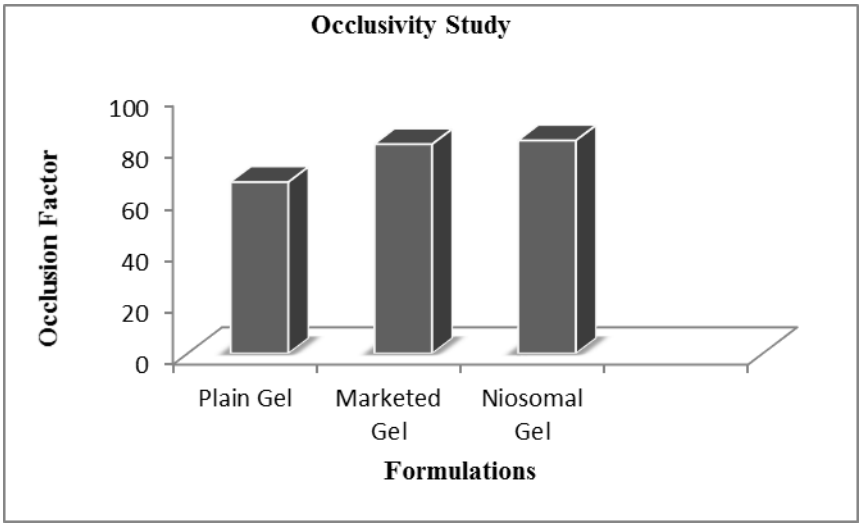

Figure No. 11: Occlusivity study of various gel formulations

Table No. 7: Stability study of niosomal gel at different storage conditions

Parameters	Initial	4^0C	Room Temp.
Colour	colourless	NC	NC
pH	6.6±0.163	6.6±0.163	6.4±0.329
Clarity	Clear	NC	NC
Homogeneity	Good	Good	Good
% Drug Content	98.909 ± 0.582	98.909 ± 0.582	97.728 ± 0.381

NC- No change

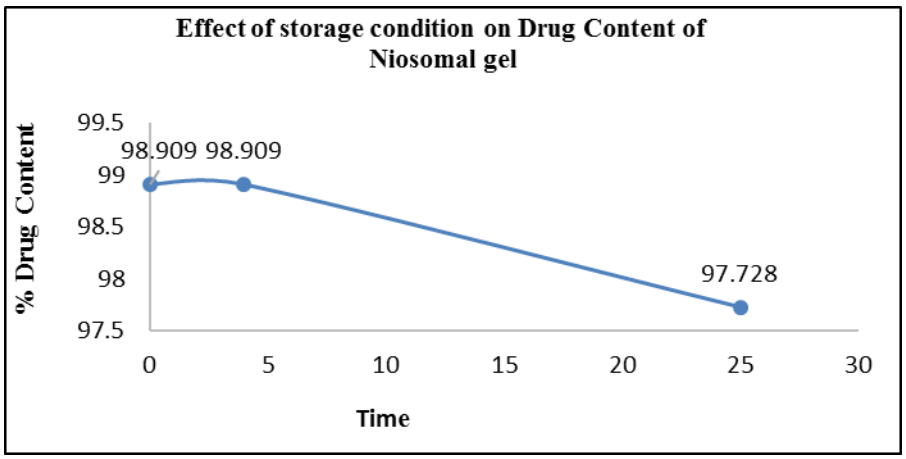

Figure No. 12: % Drug Content after1 month (F2)

CONCLUSION

The niosomal formulations were successfully prepared by handshaking method using cholesterol and sodium deoxycholate, sodium cholate, span 60 as the surfactant. The charge inducers like dicetyl phosphate and stearyl amine were also incorporated in the niosomal formulations. The compatibility of the drug with cholesterol and surfactant was done by FT-IR spectroscopy. This result indicates that there was no interaction between the drug and excipients used in the niosomes preparation. The entrapment efficiency was high when the same concentration of the drug and surfactant was used. The niosomes containing Sodium Deoxycholate and Cholesterol at 1:1 shown highest entrapment efficiency 83.11±0.093%. After incorporation of Niosomal vesicles into gel base they show significant reduction in *In-vitro* drug release in 8 hours as compared to Plain Gel. In drug release kinetics the best fit with higher correlation was found with the Zero-order and the mechanism of drug release was diffusion with the R^2 value of 0.9943. The lower flux value of niosomal gel indicates its prolonged drug release behaviour with sustained therapeutic action as compared to plain and marketed gel. It was also observed that the lipid bilayer of the niosome was rate-limiting in drug permeation. The results indicate that the niosomes can be used as a novel drug delivery carrier for transdermal delivery of Ketorolac Tromethamine for its sustained action.

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