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Research Article

FORMULATION AND EVALUATION OF TRAMADOL HYDROCHLORIDE-LOADED NIOSOMAL GEL BY ETHER INJECTION METHOD

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ABSTRACT

Objective: The primary goal of this study was to develop a topical gel containing tramadol hydrochloride-loaded Niosomes injection technique as the vesicular carrier for site-specific delivery.

Methods: The tramadol hydrochloride-loaded niosomes were created by varying the ratios of nonionic surfactants (Tween 80, Tween 60, Tween 20, Span 20, Span 60, and Span 80) and cholesterol while keeping the drug concentration constant.

Results and Discussion: Each formulation was examined for drug content, entrapment efficiency, mean vesicular diameter, zeta potential, and *in-vitro* drug release tests. Among the six formulations, the N2 formulation containing the drug and Tween 20 demonstrated maximal drug content of 96.7%, entrapment efficiency of 99%, mean vesicular diameter of 319 nm, zeta potential of −28 mV, *in-vitro* drug release of 90.14% in 12 h, and the drug release followed the zero-order with non-fickian diffusion mechanism by ether injection method. As a result, the ether injection approach is an optimal procedure for the synthesis of tramadol hydrochloride niosomes.

Conclusion: By comparing Niosomal gel with plain gel Niosomal gel indicated better results than plain gel.

Keywords: Niosomes, Cholesterol, Span 60, Tween 80, Tramadol hydrochloride, Entrapment efficiency.

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INTRODUCTION

Niosomes are colloidal particles generated by the self-assembly of non-ionic surfactants in an aqueous media, which results in closed bilayer structures. The formation of closed bilayers is not always spontaneous and necessitates the application of external energy like as heat or shearing forces. Niosomes were first identified as a component of the cosmetic business in the 1970s and were utilized in L'Oreal cosmetic formulations. Since then, niosomes have been intensively explored as an alternate drug delivery mechanism to liposomes. Niosomes and liposomes are structurally and functionally comparable in terms of drug entrapment. Niosomes are made up of a non-ionic surfactant bilayer with hydrophilic ends exposed to the aqueous phase on the outside and inside of the vesicle, and hydrophobic chains facing each other within the bilayer [1]. Niosomes, like liposomes, are capable of entrapping both hydrophilic and hydrophobic medicines. Unlike liposomes, the bilayer system of niosomes is composed of uncharged single-chain nonionic surface-active molecules, as opposed to double-liposomal structures. Niosomes as drug carriers have significant benefits over other conventional and vesicular delivery techniques. The key advantages of building niosomal systems include biodegradability, biocompatibility, chemical stability, low production cost, ease of storage and handling, and low toxicity. Niosomes can be administered orally, parenterally, topically, or intravenously, among other methods. In recent years, niosomal formulations have been widely used as a carrier to transport various types of medicines (both synthetic and natural), antigens, hormones, and other bioactive components.

The concept of targeted drug delivery is meant to try to concentrate the drug in the tissues of while lowering the qualifying concentration of the medication in the outstanding tissues. As a result, the medicine is restricted to a tiny area on the targeted spot [2]. Niosomes are contained within vehicles. Surfactant is a non-ionic bilayer active agent. It is a critical system in the vascular structure of an encapsulated medication that helps to decrease toxicity. It is a different type of method of preparation. Niosomes are structurally comparable to liposomes and are also equiactive in drug delivery potential, but their strong chemical strength puts them ahead of liposomes. In both cases, the bilayer is terminated in a non-ionic surfactant in the case of niosomes and phospholipids in the case of liposomes.

Niosomes are atomic lamellar structures with sizes ranging from 10 to 1000 nm that are made up of environmentally friendly, non-immunogenic, and biocompatible surfactants [3].

METHODS

Tramadol hydrochloride was purchased from GVK bioscience Pvt. Limited, india. Cholesterol, Tween60, Tween 20, Span 60, Tween 80, Span80, Span 20, chloroform, ethanol, pH 6.8 buffer and diethyl ether were from SD Fine-Chem. Limited, Mumbai.

Preparation of tramadol hydrochloride niosomes by ether injection method

This procedure allowed for the creation of Niosomes by gradually injecting non-ionic surfactant and cholesterol dissolved in diethyl ether combined with 2 mL ethanol previously holding a weighed quantity of drug. The resultant solution was slowly injected using a micro syringe at a rate of 1 mL/min into 10 mL of hydrating phosphate buffer on a magnetic stirrer, with the temperature kept at 60–65°C. The lipid solution was then progressively introduced into the aqueous phase. Temperature differences between phases resulted in fast ether vaporization and the production of niosomal vesicles.

RESULTS AND DISCUSSION

Tramadol hydrochloride loaded Niosomes using ether injection method optical microscopy

One drop of niosomal dispersion was taken on the glass slide and observed under projection microscope with ×100.

Mean vesicular diameter

A little amount of the improved niosomal formulation was combined with 5 mL of double distilled water and sonicated for 1 h. The material was then tested using a nanoparticle analyzer (HORIBA Nanoparticles SZ-100) to determine particle size [4,5].

The six compositions were all in the nano-size range. N1, N2, N3, N4, N5, and N6 formulations had mean vesicular diameters of 259.3 nm, 319 nm, 240.8 nm, 214.8 nm, 129.8, and 226.7 nm, respectively. N2 formulation had the smallest vesicular diameter of all formulations, measuring 319 nm.

Zeta potential

The improved formulation was tested for zeta potential value to assess its stability. At a temperature of 25°C, the analysis was carried out using double distilled water as the dispersion medium [6].

According to the findings, all formulations were stable. T1, T2, T3, T4, T5, and T6 formulations had zeta potential values of −18.3 mV, −28.4 mV, −26.8 mV, −14.5 mV, −22.4 mV, and −25.4 mV, respectively. T5 formulation had the highest level of stability among all formulations.

Drug content

Suspension of niosomes 1 mL was placed in a 10 mL volumetric flask and filled with methanol and check the absorbance in uv spectroscopy at 271.3 nm [7].

N1, N2, N3, N4, N5, and N6 formulations had drug concentration of 94.7%, 96.7%, 91.2%, 93.8%, 72.2%, and 92.4%, respectively. The maximum drug concentration was observed in formulation N2 with a 1:1 ratio of surfactant to phospholipid of 96.7%.

Entrapment efficiency

After creating the niosomal dispersion, the unentrapped medication was separated by centrifugation in a pH 7.4 phosphate buffer for 45 min at 17,000 rpm. The total amount of entrapped drug was determined using a UV spectrophotometer at 271.3 nm in the resultant solution [8].

$$Entrapment\ efficiency = \frac{Amount\ of\ drug\ taken\ - \ amount\ of\ drug\ in\ \sup erna\tan t}{Amount\ of\ drug} \times 100$$

The percentage of drug entrapment efficiency of N1, N2, N3, N4, N5, and N6 formulations was discovered to be 45.83%, 99%, 77.0%, 67.1%, 68.9% and 88.3% accordingly. The ratio of surfactant to phospholipid utilized to prepare formulation N2 had the highest percentage of entrapment efficiency. Entrapment efficiency was greater in Niosomes produced with a 1:1 ratio of soya lecithin to Tween 20. Entrapment efficiency reduced as lipid concentration increased, which could be ascribed to the fact that increasing surfactant ratio above a particular limit/concentration can disturb the regular linear shape of vesicular membranes.

***In vitro* drug release studies**

The Franz diffusion cell was used to study transferosome drug release *in vitro*. 1 mL of niosomal formulation was put between the donor and receptor compartments on a cellophane membrane holding 50 mL of pH 76.8 buffer. To maintain the sink state, samples were extracted using a micro syringe at regular intervals and fresh buffer was replaced. The absorbance of each sample was measured using a UV spectrophotometer at 271.3 nm, and the *in-vitro* drug release was computed [9,10].

When compared to other formulations, the N2 formulation with a 1:1 ratio of Tween 20 to soya phospholipid demonstrated a sustained release profile of 90.14% up to 12 h. The results of Niosomal formulations showed that the rate of drug release was proportional to the percentage of drug entrapment efficiency [11]. N2 formulation outperformed other Niosomal formulations in terms of prolonged drug release. As a result, it was further improved to be the best Niosomal formulation.

Formulation of niosomal gel

Plain gel (PG) and nano-based gels (N2G) were prepared by simple dispersion technique and evaluated visually for clarity.

Evaluation of niosome loaded gel

Clarity

Plain gel (PG) and nano-based gels (N2G) were prepared by simple dispersion technique and evaluated visually for clarity [12], and the results are shown in Table 3.

The results clearly indicated that all formulations were clear.

pH measurement

The pH values of the formulated plain gel (PG) and nano-based gels (N2G) were determined, and the findings are shown in Table 4.

Homogeneity

All gel formulations were confirmed to be homogeneous and aggregate-free.

Grittiness

All of the formulations were found to be devoid of specific matter and grittiness, which is required for any topical medication [12].

Drug content

The percentage concentration of PG and N2G formulations was assessed. The drug content percentages of PG and N2G

Table 1: Composition of niosomes

Formulation code	Surfactant: Cholesterol ratio	Ethanol: Diethyl ether (mL)	Tramadol hydrochloride (mg)
N1	0.5:1	1:3	50
N2	1:1	1:3	50
N3	1.5:1	1:3	50
N4	2:1	1:3	50
N5	2.5:1	1:3	50
N6	3:1	1:3	50

Table 2: Composition of different formulations of gel

Ingredients	Plaingel	N2 Formulation
Tramadol hydrochloride	50 mg	5 mL
Carbopol	0.25 g	0.25 g
Guar gum	0.05 g	0.05 g
Propylene glycol	5 mL	5 mL
Methyl paraben	0.2 mL	0.2 mL
Propyl paraben	0.1 mL	0.1 mL
Triethanol amine	q. s	q. s
Distill water	10 mL	10 mL

Table 3: Clarity results of PG and N2G formulations

Formulations	Clarity
Plain gel	++
N2G	++

Table 4: PH evaluation of PG and N2G formulations

Formulations	pH
Plain gel	6.3
N2 gel	6.7

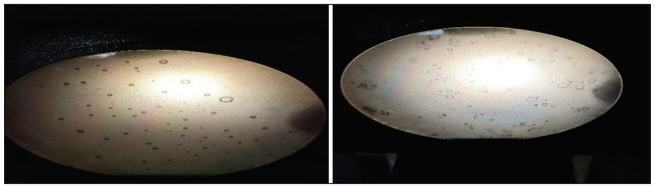

Fig. 1: Photomicrographic images of N2 formulation of tramadol hydrochloride-loaded niosomes prepared by ether injection method

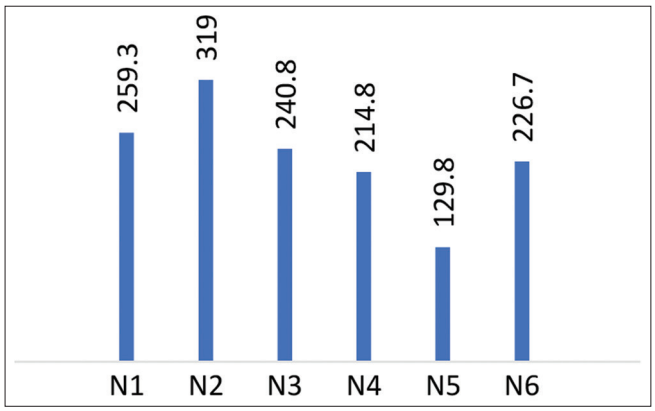

Fig. 2: Comparison of the mean vesicular diameter of six formulations of tramadol hydrochloride-loaded niosomes prepared by ether injection method

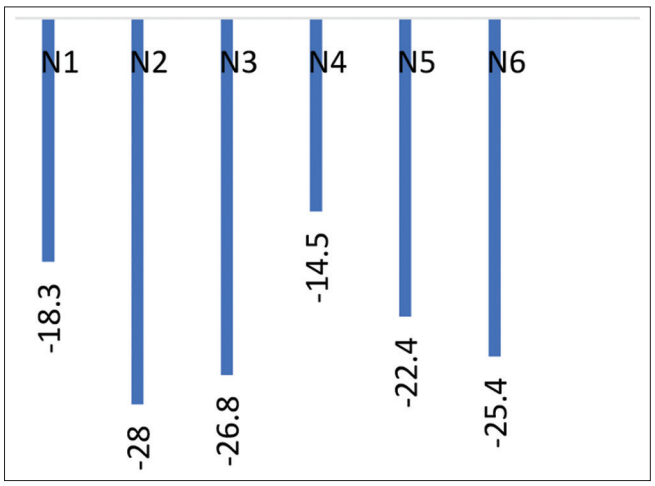

Fig. 3: Comparison of zeta potential values of six formulations of tramadol hydrochloride-loaded niosomes prepared by ether injection method

formulations were determined to be 87.2% and 92.8%, respectively, indicating that N2G formulation had the greatest drug content of 92.8%.

Spreadability

The spreadability of the formulated plain gel (PG) and nano-based gels (N2G) was examined, and the findings are shown in Table 5. N2G formulation has the highest spreadability of 174.50 g cm/s.

***Ex-vivo* diffusion studies**

Drug release studies was done on animal skin to see how much drug is releasing [13].

After 5 and 12 h, the cumulative drug release of PG and N2G formulations was determined to be 99.8% and 90.2%, respectively. The larger drug

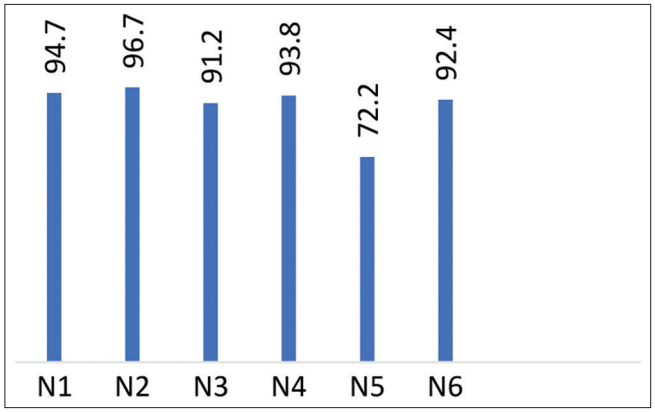

Fig. 4: Comparison of drug content among six formulations of tramadol hydrochloride-loaded niosomes prepared by ether injection method

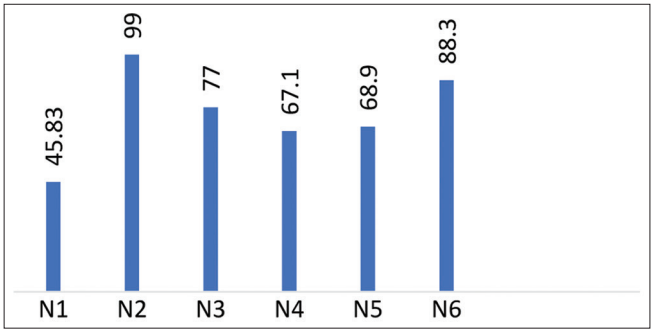

Fig. 5: Comparison of drug entrapment efficiency among six formulations of tramadol hydrochloride-loaded Niosomes prepared by ether injection method

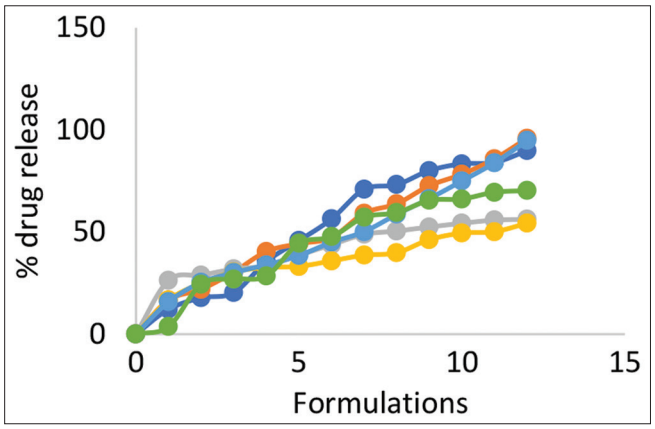

Fig. 6: Comparison of *in vitro* drug diffusion among six formulations of tramadol hydrochloride-loaded niosomes prepared by ether injection method

Table 5: Spreadability results of PG and N2G formulations

Formulations	Spreadability
Plain gel	12.26 g.cm/s
N2 gel	17.450 g.cm/s

concentration and greater entrapment efficiency of theN2G formulation resulted in a more prolonged release compared to other formulations.

The kinetics parameters were determined using several plots, and it was discovered that the best formulation (FN2) used zero order release with a non-fickian diffusion mechanism.

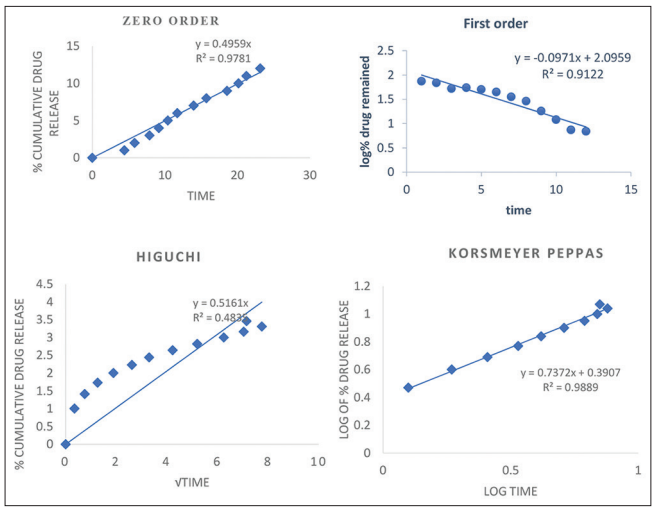

Table 6: Kinetic parameters determined from the in-vitro drug release kinetics plots

Formulation	Zero order	First order	Higuchi	Peppa's	n-value
N2G	0.9939	0.9122	0.9192	0.9889	0.8191

CONCLUSION

Six Niosomes formulations were created using ether injection method procedures and changing the surfactant to phospholipid ratios. All formulations were examined for drug content, entrapment efficiency, and *in vitro* diffusion studies, as well as vesicular diameter and zeta-potential. N2 formulation with surfactant: phospholipid 1:1 ratio was shown to be the optimum formulation. During the Niosomes preparation process, many factors, such as surfactant: phospholipid ratio, hydration temperature, and heating temperature, were tuned. The best Niosomes (N2) formulations were dispersed in 1% Carbopol gel base using a simple dispersion process. The gels were tested for clarity, pH, drug content, spreadability, viscosity, and *in vitro* diffusion. When compared to simple gel and Niosomal (GN2) gels, Niosomal gel produced the greatest results.

AUTHOR'S CONTRIBUTIONS

All the authors have equally contributed.

CONFLICTS OF INTEREST

The authors declares that they have no conflict of interest.

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