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Development And Evaluation of In-Situ Nasal Gel Formulations of Nanosized Transferosomal Triptans

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ABSTRACT

The study's goal was to create an intranasal transferosomal mucoadhesive gel that would increase the bioavailability of zolmitriptan. Reverse phase evaporation was used to create zolmitriptin-loaded transferosomes, which were then characterised for a number of factors, including vesicle diameter, percent entrapment efficiency (%EE), and in vitro release. Carrageenan, poloxamer 188, and carbopol 934 were used in different ratios to create the in-situ gels, which were then evaluated for rheological characteristics, mucoadhesive strength, and gelation temperature. The produced transferosomes showed sustained drug release over 8 hours, mean diameters of 213.7 ± 1.56 to 508.5 ± 3.75, and percent entrapment efficiencies (%EE) ranging from 49.2 ± 1.24 to 94.3 ± 3.87. Using carrageenan as a mucoadhesive polymer, the best formulae were added to Carbopol 934, poloxamer 188, and carrageenan-based in-situ gel. The in-situ gel of zolmitriptan-loaded nano-transferosomes was created as a promising non-invasive drug delivery method based on improving the bioavailability and drug release.

Keywords: *Novel drug delivery, transferosomes, in-situ gel, Nasal drug delivery system*

1. INTRODUCTION

Recently, the vesicular drug-carrier system, transferosome have been reported to increase the transdermal administration of pharmaceuticals, when put onto the skin non-occlusively. Compared to normal liposomes, transferosomes are artificial vesicles that are several orders of magnitude more deformable. By employing surfactants in the right proportion, liposomes can be made more deformable for better drug molecule skin penetration. (1) Transferosomes can squeeze themselves along the stratum corneum's intercellular sealing lipid to get past the barrier to penetration. After being applied to the skin, the ensuing flexibility of transferosome membranes reduces the possibility of total vesicle rupture and enables transferosomes to follow the natural water gradient across the epidermis. (2, 3)

4(S)-4-[3-(2-dimethyl aminoethyl)-1H5-indolyl-methyl] is zolmitriptan. -1,3-oxazolan 2 is a strong and specific agonist of the serotonin (5-HT1B/1D) receptor that constricts the blood vessels in the brain. Additionally, zolmitriptan has been shown to alleviate acute migraine attacks by lowering sterile inflammation linked to antidromic neuronal transmission. (4, 5) At the moment, it is offered as a nasal spray (2.5 mg and 5 mg per dose), an oral disintegrating tablet, and a regular tablet. With first-pass metabolism and quick hepatic and renal clearance, zolmitriptan has a very short half-life of 1-2 hours and an absolute bioavailability of up to 40% for both oral and nasal dosing forms. Because of this, the oral route is inadequate. (6, 7) The administration of zolmitriptan nasal spray produced a faster onset of effect. Clinical data, however, does not indicate any appreciable increase over oral dosing forms in other pharmacokinetic characteristics, such as half-life, bioavailability, and therapeutic gain (8). Therefore, our goal was to develop a nasal gel delivery mechanism for Zolmitriptan that targets the brain in order to overcome the aforementioned disadvantages. The creation of zolmitriptan transferosomes for intranasal delivery to the brain is the main focus of the current study. The blood-brain barrier (BBB) makes it extremely difficult to transfer medications to the brain. (10, 11) Drug delivery to the brain has been improved using a variety of methods.

Drug transport based on nanotechnology is one of these methods. Many medications are delivered to the central nervous system (CNS) via the intranasal route. Drugs do not need to be modified for intranasal administration (12, 13). In situ gelling systems are polymeric liquids that turn into gels when their pH, ion concentration, and temperature vary. They are the best formulations for nasal medication delivery since they are easy to administer and have a longer half-life. (14–17) Finding the right mix of factors to create a product with the best qualities is a problem that pharmaceutical scientists frequently encounter (18). Designing a series of experiments that will accurately measure the response variables, fitting a mathematical model to the data, performing the necessary statistical tests to ensure that the best model is selected, and figuring out the ideal value of independent variables that yield the best response are all included in the optimisation technique (19). Using carbopol 934, PLX 188, and carrageenan, the current study aims to create in situ gels of zolmitriptan

2. MATERIALS AND METHODS

Materials: Zolmitriptan was obtained from Matrix Labs, Hydrabad. Carbopol 934, and Carrageenan were obtained from himedia laboratories, Mumbai and Merck Pvt. Ltd, Mumbai respectively. Polaxmer 188 was obtained from the S.D. Fine chemicals, Mumbai. All chemicals were used as analytical grade.

FT-IR studies: FTIR analyses were performed on the medications and formulations to see whether there would be a drug-excipient interaction. An FT IR spectrophotometer (Bruker FT-IR - GERMANY) was used to perform an FT IR study of the pure medication utilising the K-Br pellet method. Wave numbers ranging from 4000 to 400 cm-1 were used to examine the samples. (20)

Preparation and evaluation of transferosomes: With various adjustments as detailed in the literature, transferosomes were created using the reverse phase evaporation approach. Initially, cholesterol and soy lecithin were collected as lipids in a sanitised beaker. In the same beaker, Tween 80 was then added as a surfactant and dissolved in a 3:1 solvent mixture of diethyl ether and chloroform. Until the thin layer formed, the beaker was left at room temperature for twenty-four hours. After applying an insulin solution (1.40 mg/ml in water) to the thin film, it was sonicated for two minutes at a frequency of 20 KhZ using a probe sonicator (FS-600. Frontline Electronics and Machinery Pvt. Ltd., India). Following that, the film was hydrated using sodium deoxycholate in phosphate buffer saline (pH 7.4) and an edge deactivator. To create transferosomal suspensions, the film was then sonicated for two minutes. (21, 22) As a chemical permeation enhancer, 2% v/v dimethyl sulfoxide (DMSO) was added to each suspension. Following that, several transferosomal suspension formulations were run through Whatman® filter paper (No. 40). After that, these transferosomal solutions were put on 5% w/v methylcellulose gel and kept in a dark, cool environment.

Determination of drug entrapment efficiency: The transferosomal suspensions (total mount) were ultracentrifuged for 30 minutes at 10 °C and 20,000 rpm. A UV–Vis spectrophotometer (Thermo Spectronic UV-1, USA) was used to detect absorbance at 283 nm after 1 ml of supernatant had been centrifuged and diluted with 9 ml of phosphate saline buffer (pH 7.4). (23) The drug entrapment efficiency was calculated as below,

$$DEE=(WT-WF)/WT\times100\%$$

Where, DEE is the drug entrapment efficiency, WT is the total amount of Zolmitriptan in transferosomal suspensions: WF is the free amount of Zolmitriptan that was found in the supernatants.

Potential Analysis: Samples of transferosomal dispersion (100 µL) were diluted with purified water (900 µL) and measured using the dynamic light scattering method using a Malvern Zetasizer (Malvern Instruments Corp; Nano ZS ZEN 3600, Worcestershire, UK) in order to assess the zeta potential, mean diameter, and size distribution curve of the prepared vesicles. Three duplicates of the measurements were made. (24)

In-vitro Release Study of Transferosomes: A dialysis approach, previously recommended in the literature, was used to study the release of zolmitriptan from the produced transferosomes. With a molecular weight cut-off of 12,000 kDa,

transferosomal suspension (10 mg drug equivalent) and triptans solution (10 mg drug equivalent, control) were added to donor compartment dialysis bags. The USP dissolving apparatus type II was used for the release investigation, and the paddle rotation was maintained at 100 rpm. To maintain a sink state, the dialysis bags were completely submerged beneath the surface of 100 mL of SNF, a receptor medium (pH 5.5 at 37ºC). At specific times (0, 0.25, 0.5, 1, 2, 4, and 6 hours), 2 mL of the release medium were sampled and replaced with 2 mL of freshly made SNF. At 283 nm, the collected samples were subjected to UV spectrophotometric analysis (Thermo Spectronic UV-1, USA). Three duplicates of the experiments were conducted. (25, 26)

FORMULATION OF IN-SITU GEL

By adding TF5 to an aqueous mixture of carbopol 940, polaxmer, and carrageenan, the transferosomal gel of zolmitriptan was created. Following precise weighing, Carbopol 940 (0.5, 1.0, 1.5% w/w), PLX 188 (0.5, 1.0, 1.5% w/w), and Carrageenan (0.5, 1.0, 1.5% w/w) were added to distilled water in a beaker. To the solution, propylene glycol (5.6% w/w) was added. Sodium hydroxide was used to bring the gel base's pH down to 5.5 after two hours of stirring at 500 rpm. Using the same composition, a pure drug gel with a strength comparable to the optimised product was created and used for comparative analysis in drug release research. (27, 28)

Table 1: Formulation of in-situ gel

Gel code	Carbapol 934% w/v	PLX 188% w/v	Carrageenan % w/v
TFG1	0.5	1.5	0.5
TFG2	1.0	0.5	1.0
TFG3	1.5	1.0	1.5
TFG4	0.5	1.5	0.5
TFG5	1.0	0.5	1.0
TFG6	1.5	1.0	1.5

Evaluation of formulated gel:

Physical appearance and clarity test: The prepared formulations are visually examined of any foreign particles present.

pH of gel: The human nasal mucosa has a pH between 5 and 6.5. However, it can withstand roughly 4-7.5. To lessen nasal discomfort, the pH of produced formulations should be within the range that the nasal mucosa can tolerate. All formulations' pH values are listed in Table 2. The outcome shows that the pH is within the acceptable range for all formulations. They fall between 6.2 and 6.7. (29)

Measurement of gel temperature: The technique used by Miller and Donovan specified the gelation temperature. A phase transition from a liquid to a gel phase was place in this procedure. The two millilitres of in-situ gel were transferred to a test tube and placed in a water bath, which gradually and steadily raised its temperature. After five minutes of gel equilibration at each setting, the formulation's gelation was assessed. At 90 degrees Celsius, the meniscus would stop moving; this is referred to as the gelation temperature. (30)

Mucoadhesive strength: We employ a modified special balance to measure the mucoadhesive strength, which is the force required to separate the in-situ gel formulation from the nasal mucosa tissue. 50 mg of gel was put on the first glass vial, which was placed beneath the height-adjustable balance, after a small piece of goat nasal mucosa was cut, secured with thread, and kept at 37ºC ±2ºC for ten minutes. To guarantee that the in-situ gel formulation and nasal mucosal tissue made contact, a second vial was secured inverted to the underside of the same balance. Both vials were then adjusted and brought into close contact for five minutes. The strength or tension in weight was then conveyed by putting weight on the other side of the balance until the vials disconnected. (31)

In vitro Release of the Prepared Gel: According to the literature, TFG1-TFG6 formulations were used for the in vitro release investigation in order to examine the release rate of Zolmitriptan from transferosomal containing gel. Briefly, cellophane dialysis tubing (a molecular weight cut-off of 12,000–14,000 kDa, Heidelberg, Germany) was filled with a specific quantity of the formulation under examination (10 mg Zolmitriptan equivalent). In a dissolve flask, the tube was immersed beneath the surface of SNF (300 mL, pH 5.5, rotation speed 75 rpm, and 37±2°C). Spectrophotometric analysis was performed at λmax 283 nm after aliquots (5 mL) were removed and replaced with an equivalent volume of freshly produced SNF (pH 5.5, 5 mL, 37ºC). Three separate runs of the experiment were conducted. The cumulative percentage of

drug penetration was computed and plotted against time. (32)

Stability Study of the Optimized in-situ Gels: To find out how much medication was in the manufactured in-situ gels (TFG2 and TFG4), a stability study was conducted. The gels under examination were stored for three months at 4±2°C, 25±2°C, and 40±2°C with a relative humidity of 75±5% in amber-colored bottles with an aluminium cap. (33)

3. RESULTS AND DISCUSSION

FT-IR Studies: According to published research, the principal peaks of the drug Zolmitriptan were 3461 cm-1, 3367 cm-1, 3187 cm-1, 2924 cm-1, 2848 cm-1, 2256 cm-1, 1766 cm-1, 1576 cm-1, 864 cm-1, and 788 cm-1. The main peaks in the drug peak, both with and without excipients, roughly matched the referral principle peaks. Thus, it can be said that there were no potential interactions between the medicine and the excipients.

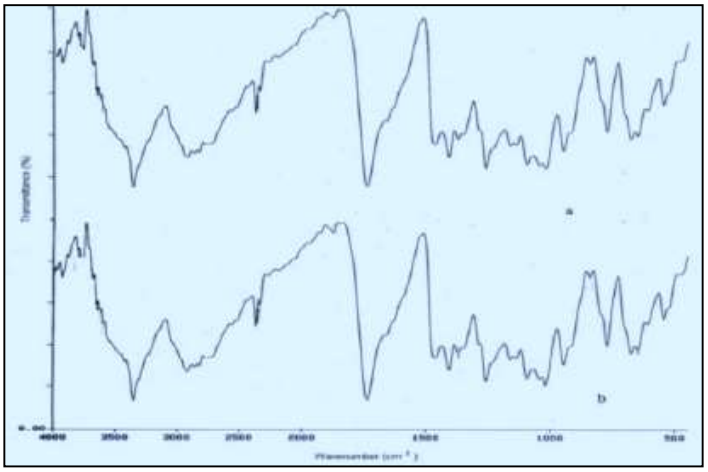

Figure 1: FTIR Spectra of drug and formulation TF5

Evaluation of transferosomes Suspension: Dynamic light scattering (DLS) was used to measure the transferosomes' particle size, size distribution, and zeta potential in aqueous solution. The results are shown in Table 2. The Malvern particle size analyser determined that the average particle size was within the acceptable range of 200–400 nm. The molecular mass of a sample is measured by the polydispersity index (PDI), which is ±. The PDI is the weight average molecular weight divided by number average molecular weight. Good dispersion is indicated by a PDI value less than 0.5. It demonstrates that while particle size grows with increasing lipid content, particle size decreases with increasing surfactant concentration. The stability of the transferosomes and the presence of charge on the vesicular system are both indicated by the zeta potential. A high negative surface charge on transferosomes is indicated by the zeta potential, which in this case was found to be -67±0.012 (±mv). Because of the expected surface repulsion between identical charged particles, this exhibits improved stability and prevents transferosome aggregation. The range of entrapment efficiency was 49.2 ± 1.24 to 94.3 ± 3.87.

Table 2. Experimental evaluation of transferosomes according to the central composite design

S. No.	Formulation code	Entrapment efficiency %	Particle size (nm)	PDI
1	TF1	71.7 ± 2.19	467.5 ± 4.17	0.578 ± 0.02
2	TF2	73.6 ± 1.67	485.2 ± 3.26	0.737 ± 0.01
3	TF3	49.2 ± 1.24	508.5 ± 3.75	0.871 ± 0.02
4	TF4	72.6 ± 2.72	345.6 ± 3.47	0.232 ± 0.04
5	TF5	94.3 ± 3.87	467.4 ± 3.48	0.644 ± 0.05
6	TF6	54.6 ± 2.26	497.3 ± 9.78	0.543 ± 0.03
7	TF7	85.3 ± 1.73	376.3 ± 4.84	0.386 ± 0.06
8	TF8	69.1 ± 2.07	464.2 ± 4.23	0.7533± 0.04

9	TF9	56.6 ± 1.36	213.7 ± 1.56	0.484 ± 0.03
10	TF10	62.6± 2.34	235.7 ± 8.62	0.732 ± 0.02
11	TF11	63.9 ± 1.07	412.8 ± 4.73	0.365 ± 0.08
12	TF12	77.3 ± 1.11	499.7 ± 6.62	0.342 ± 0.01
13	TF13	66.3 ± 1.60	419.5 ± 5.3	0.381 ± 0.08

All values are mean (n= 3) ± standard deviation, PDI: Polydispersity index

In-vitro Drug release study: The kind of polymer utilised, its concentration, and the formulation's viscosity all affect how easily the medicine is released from the formulation. Only the optimised formulation was examined for the drug release profile, depending on the different other evaluation factors. Figure 2 illustrates the in vitro drug release study from TF5, which showed 92% drug release in 8 hours.

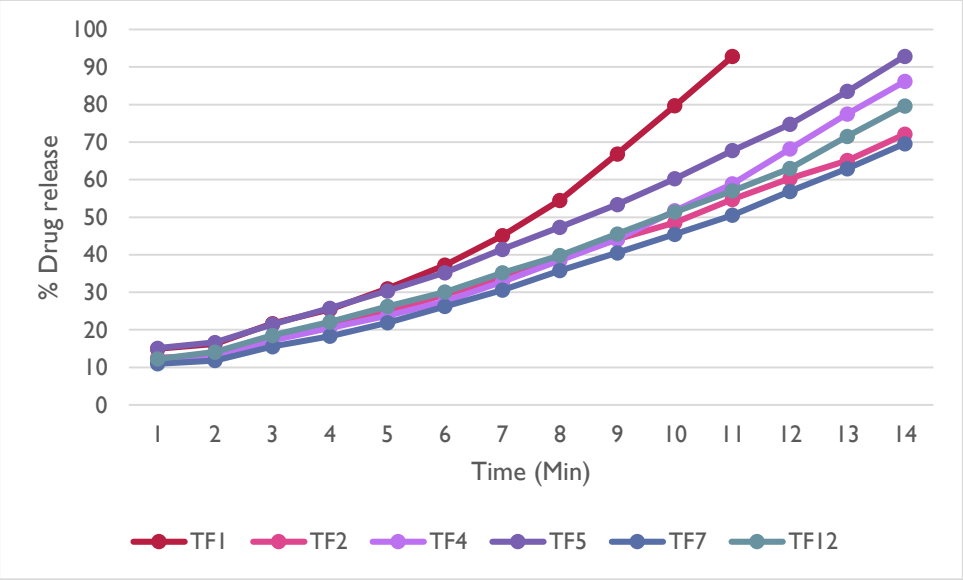

Figure 2: In-vitro Drug release study transferosome

Formulation of gel: Many efforts were made in the current investigation to manufacture the release transferosomal zolmitriptan in-situ gel forming intranasal solution using polymers like carrageenan, PLX 188, and carbopol 934. The new intranasal gel-forming mucoadhesive polymer Carbopol 934 and PLX 188 mixture was utilised as the gelling agent. This polymer turns into gel at body temperature.

Evaluation of Gel:

Appearance: When kept at room temperature, not to exceed 32 °C, all of the created formulation appears transparent in the sol form.

pH: Every formulation fell between 5.02 and 5.43, which is substantially within the range that is designated for nasal formulation.

% Drug content: All the formulations were in the range of 97.12±1.02-98.42±0.12 which is suitable for the novel formulation.

Mucoadhesive force measurement: Over the concentration range of 0.2% to 0.5%, the mucoadhesive force dramatically rose as the concentration of mucoadhesive polymers increased.

Viscosity: The viscosities of 132.65 and 139.6 cps at 100 rpm were demonstrated by the formulation that solely contained TFG1 and TFG4 in solution form. In contrast, the viscosities of formulations TFG2, TFG3, TFG5, and TFG6 were lower at 100 rpm, measuring 111.8, 119.7, 121.4, and 126.6 cps, respectively.

Table 3: Appearance pH gelling capacity and drug content estimation of various formulations

Formulation code	Appearance	pH	Gelling capacity	% Drug content
TFG1	Transparent	7.89	+++	97.19±0.92
TFG2	Transparent &Viscous solution	8.02	++++	98.09±0.83
TFG3	Transparent solution	5.43	+++	97.63±0.21
TFG4	Transparent solution and less viscous solution	5.12	++	98.42±0.12
TFG5	Transparent solution and less viscous solution	5.12	+	97.12±1.02
TFG6	Transparent solution	5.39	+++	98.11±0.69

N=3

Table 4: Mucoadhesive forces of developed formulation

S. NO.	Formulation code	Viscosity (cps)	Mucoadhesive force (dynes/cm2) mean ± SD
1	TFG1	132.65	54.2±1.21
2	TFG2	111.8	51.3±1.08
3	TFG3	119.7	53.1±7.12
4	TFG4	139.6	58.3±5.18
5	TFG5	121.4	60.3±1.03
6	TFG6	126.6	59.7±0.24

N=3

In-vitro drug release of gel formulations: The chosen Transfersomes (TFG1, TFG2, TFG3, TFG4, TFG5, and TFG6) were the subject of an in vitro drug release investigation. The Transfersomes showed a release rhythm of eight hours. 92% of the medication was delivered slowly over the next 8 hours, with 50% of the total amount of doses released during the first 210 minutes. The release profiles of the Transfersomes TFG1 and TFG4 were improved by 8 hours and were 92.8279% and 92.8552, respectively.

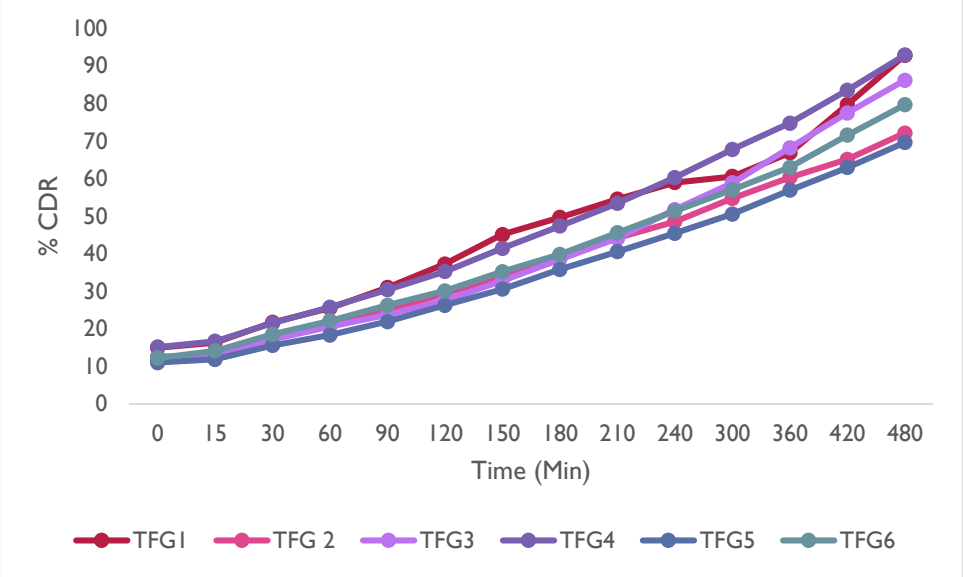

Figure 3: In-vitro drug release of formulation TFG1-TFG6

Stability Study:

At 27 °C and 60% relative humidity, all formulations demonstrated good stability. The drug's stability in the in situ gel formulations was demonstrated by the fact that there were no notable changes in visual appearance or clarity, that the pH stayed constant throughout the stability period, that the drug content did not vary by more than 2%, and that the in vitro release studies showed no discernible changes at the conclusion of the 30-day period.

When made as a solution, a formulation meant for nasal delivery shouldn't exhibit drug precipitation after extended storage. This was accomplished by storing the formulations at standard room temperatures that didn't go above 32 °C. The formulation exhibited settling of the polymers carbopol 934 and PLX 188 when chilled. It also demonstrated the drug's precipitation. This suggested that for ion-activated in situ gels, 4 °C is not the ideal storage temperature. The compositions maintained their gel state for an extended period of time when stored at 45 °C and 75% relative humidity.

4. CONCLUSION

The goal of the current study was to create a nasal in situ gel of zolmitriptan using the in-situ gel forming solution comprising a polymer, carbopol, polaxmer 188, and carrageenan. This gel should help overcome the drawbacks of parenteral and oral administration methods. The in situ gel was prepared using a straightforward and repeatable procedure. The generated transferosomal in-situ gels were successful as a non-invasive nasal medication delivery device based on the comparison indicated above. In the end, it was determined that a promising non-invasive drug delivery method with better patient compliance had been created. The study makes it clear that using transferosomal transdermal gel to administer zolmitriptan is feasible. Because of its straightforward production and easy scale-up, the new transdermal transferosomal formulation may therefore prove to be a promising carrier for zolmitriptan

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