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Ketorolac tromethamine-loaded transferosomal gel Development and Characterization utilizing box-behnken design

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ABSTRACT:

Background: Over the past ten years, vesicular carrier systems like liposomes and niosomes have gotten a lot of attention as a flexible way to carry drugs. The study's goal was to look into the properties and make-up of transferosomal gels that contain ketorolac tromethamine.

Methods: The main goal of this study is to use the Box-Behnken design to make a transferosomal gel with ketorolac tromethamine that can be applied to the skin. The loading, entrapment, and release of the material are affected by the type and amount of lipid, cholesterol, surfactant, and edge activator. The created transferosomes were put through tests to see how well they captured drugs, how well they diffused, and how many vesicles they formed.

Results: We examined the carbopol gel's viscosity, homogeneity, pH, appearance, and drug release in vitro after adding the optimal mixture.At 3348 cm-1, 1379 cm-1, 1387 cm-1, 1047 cm-1, and 798, 780, 730, and 715 cm-1, the FTIR analysis revealed that ketorolac tromethamine was most extensively absorbed. A decrease in trapping efficiency was seen as the concentration of surfactant increased. The combinations released 62.5% of the medication over 8 hours at a 55.01 rate, according to in vitro diffusion experiments.

Conclusion: After numerically optimizing the solutions, we determined that B10 is the optimal formulation. After 8 hours, the drug is released at a rate of 62.5% due to its high entrapment efficiency of 92.0%. Additional research is required to determine vesicle size and zeta potential with the new formulation. Drug diffusion, pH levels, and other properties were examined in a modified gel mixture.

Keywords: Ketorolac tromethamine, transferosomal, gel, box-behnken design

INTRODUCTION:

In its broadest definition, a transfer substance is any supramacromolecular material with the inherent potential to cross a permeability barrier and transport substances from one location to another [1-3]. A transferosome can achieve what it wants by adapting its properties, notably its flexibility, to the specific type and size of pores in a barrier. The lipid spheres, or transferosomes, are incredibly malleable and can pass through narrow openings with ease. In terms of size, it's dwarfed by the particle [2-4].

Very twisted bilayers are made possible in thermodynamic terms by this, which frequently results in a quasimetastable aggregation. Lipid groups in a transfer system can undergo self-modifying reactions when combined properly. Since vesicular transferosomes may have a more malleable shape than conventional liposomes, they are ideal for transdermal delivery [3-5]. In order to cross the barrier and enter the skin, transferosomes push against the stratum corneum's internal sealing lipids. The permeability and pliability of the vesicle allow for this to happen [6].

When the correct quantities of surfactant components are combined, transferosome membranes become malleable. Full vesicles on the epidermis and skin are less likely to form when using the transfer membrane in non-occlusive conditions [4-6]. Because of this, the transferosomes are able to cling to the gradient of water. A typical composite transfersome membrane has remarkable and self-optimizing deformability, which allows an ultra-deformable transfersome to irreversibly alter the membrane's composition in a microscopic pore [5-7].

This is because the hydrophobic outer epidermal layers can be permeated by more meticulously prepared lipid vesicles due to the inherent variations in water concentration among the layers. Unfortunately, this may not be effective with all lipid droplets. Due to the low transdermal osmotic pressure difference [6-8], normal lipid droplets (liposomes) are unable to penetrate the whole stratum corneum of mammals. It is critical to maintain minimal costs for all vesicles in order to maximize their penetration into the epidermis. A adjustment was made to the composition of the lipid bilayer and the transferosomes in order to achieve the most flexible surface for the vesicles [7-9].

One novel non-steroidal anti-inflammatory medicine, ketorolac tromethamine, effectively reduces pain without significantly reducing inflammation. It is believed that pain is alleviated peripherally when prostaglandin synthesis is inhibited. Right now, KT is utilized to alleviate the discomfort of the initial post-operative period. It can be injected into a muscle or taken orally in several little dosages [8-10]. In most cases, the adverse consequences manifest as gastrointestinal bleeding, perforations, or ulcers of the peptic tract. An alternative method of regulated medicine delivery for KT that does not require intrusive procedures is urgently required. This approach has the potential to lessen the severity of esophageal and gastric-related adverse effects while simultaneously increasing the efficacy of treatment through the manipulation of dosage forms and the regulation of drug release [9-11].

Ketorolac tromethamine transferosomal gels were the focus of this investigation on their composition and characteristics.

MATERIALS AND METHODS:

Materials:

Ketorolac tromethamine is offered as a complimentary sample. Tween 80 and phosphatidylcholine were sourced from HiMedi Laboratories in Mumbai. the research lab at Fine Laboratories providing cholesterol. The Mumbai-based company Loba Chemicals Limited supplied the sodium cholate. Everything utilised in this investigation, from solvents to other components, was of laboratory quality.

Pre-formulation study:

Drug and excipient compatibility study:

We looked at the spectra of different mixes of ketorolac tromethamine and other ingredients that have been used before using Fourier Transform Infrared (FTIR) Spectroscopy and potassium bromide (KBr) plates to make the spectra. FTIR research was done to make sure that the medicine and excipients would work together [10-12].

Ketorolac tromethamine transferosome preparation:

Transferosomes were prepared using ethanol injections. Aqueous phase: sodium cholate and ketorolac tromethamine were dissolved in a specific volume of 10 ml of phosphate-buffered saltwater with a pH of 7.4. The clear solution that resulted was then made via sonication. To dissolve the surfactant, cholesterol, and phospholipids, a mixture of chloroform and diethyl ether was utilized. The next step in creating the organic phase was to sonicate the mixture. The dissolved organic solution was added to 10 ml of heated aqueous phase using a 24 gauge needle. The mixture was agitated magnetically and maintained at 65 ℃ for 45 minutes. It was easier to create drug-loaded transferosomes when the excess ether has completely evaporated. When ether evaporates, it forms vesicles [11-13].

Experimental Design:

Using a Box-Behnken design, we examined various amounts of the possession's components, such as lipid content, surfactant volume, and edge activator volume. With values of 1, 0, and -1, each level served as an independent variable. Evaluations of medication concentration, drug distribution, and entrapment efficacy were part of the response (dependent variable). The pharmaceutical content, ex-vivo testing results, entrapment effectiveness, and other characteristics of the formed goods were further studied [12-14].

Numerous permutation combinations were generated by the Design of Experts 12 program. We have the lipid quantity as variable "A," the surfactant quantity as variable "B," and the edge activator quantity as an independent variable "C." Both levels are utilized, albeit one is more challenging. Dosages of 100 mg to 500 mg of lipid are commonly utilized. On one level, you'll find 350 mg of surfactant, whereas on the other, you'll find 50 mg. There are two dosage options for the edge booster: 10 mg and 50 mg [13-15].

Table 1: Experimental runs combinations

Batches	API	P. Choline	T-80	Na Cholate	Cholesterol	Buffer	Organic Phase
B1	10	100	50	10	25	10	5
B2	10	150	100	15	25	10	5
B3	10	250	150	20	25	10	5
B4	10	350	250	25	25	10	5
B5	10	450	300	30	25	10	5
B6	10	500	350	35	25	10	5
B7	10	100	50	10	25	10	5
B8	10	150	100	15	25	10	5
B9	10	250	150	20	25	10	5
B10	10	350	250	25	25	10	5
B11	10	450	300	30	25	10	5
B12	10	500	350	35	25	10	5

In Table 1 you can see the experiment-specific formulas. In the calculations provided, three distinct factors were varied with respect to three distinct quantities. There was no change in the drug accumulation or cholesterol level in 7.4 PBS across all studies.

Evaluation of transferosomes:

Microscopical examination:

Transferosomes were easily observable using an optical microscope.

Entrapment efficacy:

To separate the drug-encapsulating vesicles from the drug that wasn't linked to them, we centrifuged 1.5 ml of the transferosomal mixture four times at 14,000 rpm for 30 minutes at 4°C. In the past, finding free content was done using the transparent percentage. The absorbance was measured at 324 nm after diluting a clear fraction that had been prepared by filtering it using Whatmann filter paper no. 42 [14-16]. If you want to know how effective trapping is, you can utilize this method.

$$E.E.(\%) = \frac{Total\ amount\ of\ the\ drug - Amount\ of\ the\ free\ drug}{Total\ amount\ of\ the\ drug} \times 100$$

Drug content:

To determine the concentration of ketorolac tromethamine in the vesicles, we combined 0.1 milliliters of the transferosomal suspension with 1 milliliters of a 0.1% Triton X-100 solution. To reduce its concentration, five milliliters of the solution was combined with saltwater that had been phosphate-buffered (pH 7.4). Whatmann filter paper no. 42 was used to filter the solution after 1.5 hours. A UV-1800 spectrophotometer was employed to measure absorbance at 324 nm following the appropriate volume of diluting [15-17].

***In-vitro* drug release study:**

$$\text{Drug content} = \frac{amount\ \ of\ drug}{total\ amount\ of\ drug} \times 100$$

The diffusion tests were carried out using a two-sided open-ended cooking tube. Donor vessel: the simmering tube, and receiving vessel: the 250 cc beaker. The donor and recipient compartments were distinguished by the diffusion membrane. As a buffer, a transferosome suspension was introduced. A magnetic bead was utilized to continually agitate the mixture at 50 rpm and 37°C to maintain the pH 7.4 phosphate-buffered saline in the receptor chamber. The same amount of buffer was added to five milliliter samples at regular intervals. Spectrophotometers were calibrated to 324 nm, the optimal wavelength, and samples were examined after correct dilution [16-18].

Transferosomal formulation in gel:

Preparation of Carbopol gel:

To make Carbopol gels, carbopol was mixed with water and triethanolamine was added to dilute it so that the pH level reached 6.8. Before adding Carbopol, the amounts of methyl and propyl paraben were measured out and added to water while shaking constantly until the mixture was smooth. It had distilled water in it and was stirred very hard [19-23].

Table 2: Formulation of transferosomal gel

Sr. No.	Components	Quantity
1.	Optimised formulation	10 ml
2.	Carbopol	2.0%
3.	Glycerine	10%
4.	Triethanolamine	0.5%
5.	Propyl Paraben	0.01%
6.	Propylene glycol	15%
7.	Methyl Paraben	0.02%
8.	D. W.	q.s.

Evaluation of gel:

Spreadability:

Spreadability is important because it shows how the material will behave when it comes out of the tube. One of the slides had twenty grams of weight stuck to it. After making a point, 500 mg of gel was put on the slide across from it. After that, the weighted slide was put on top of the gel-coated slide to press down on the gel. The time was set for one minute and sixty seconds. After one minute, the spreadability was checked again [24-28].

pH:

A portable pH meter is used to measure the pH of the transferosomal gel. One gel grime is mixed with 100 ml of clean water, and then the mixture is left to sit for two hours. Three times, the pH of each mixture is checked, and then the average is found [29-33].

Extrudability:

Extrudability refers to the maximum volume that can be extruded. We measured the extrudability of each combination three times and averaged the results. The extrudability was tested by pouring the gel into a collapsible metal tube and applying pressure. With the weight in grams added, you must remove at least half a centimeter of gel ribbon in ten seconds [34-37].

% Drug content:

A good liquid is mixed with one gram of gel. To make things clearer, the answer is filtered. The UV spectrophotometer checks how much light is absorbed. The usual plot for the drug is made with the same solvent. You can use the absorption value and the standard plot that goes with it to figure out the concentration and make-up of the material [38-40].

Stability:

The novel transferosomal formulation will be physically tested according to ICH standards. For a month, the optimal combination was held at both room temperature and frigid temperatures. The dosage of the medicine was determined by taking samples at 7,14,21, and 28 days [41-43].

RESULTS AND DISCUSSION:

Pre-formulation studies:

Compatibility studies:

Utilizing the potassium bromide pellet technique and FTIR in the 4000-200 cm-1 region, we determined if

ketorolac tromethamine was compatible with other compounds. Ketorolac tromethamine absorption peaks were observed at 3348 cm-1, 1379 cm-1 (C-C stretching), 1387 cm-1 (C-N stretching of secondary amine), 1047 cm-1 (OH stretching), and 798, 780, 730, and 715 cm-1 (CH bending). According to the FTIR spectra, there was no interaction between the excipient and the medicine. This is due to the fact that analysis of the drug and excipient peaks revealed the presence of phospholipids, detergents, and a gelling agent. There was no chemical reaction between the medicine, phospholipids, and lubricant, as shown by the spectra. Therefore, it is safe to claim that excipients do not alter the efficacy of a pure medicine (Figure 1).

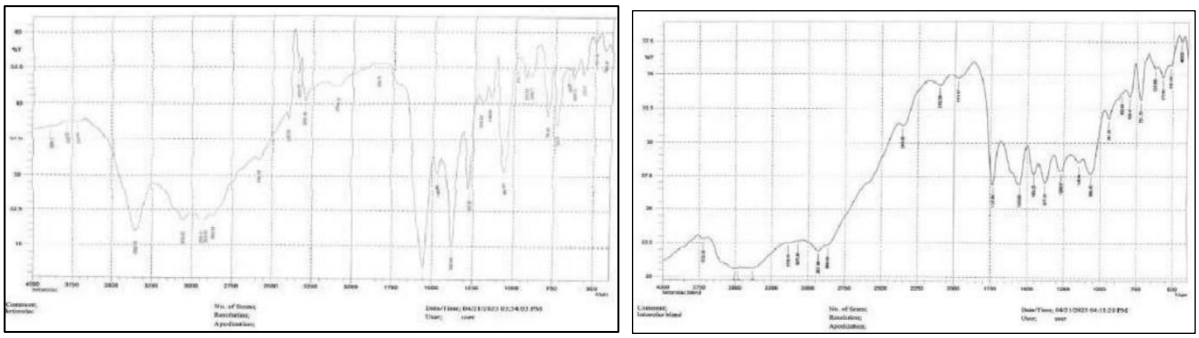

Figure 1: FTIR spectra of the formulation blend (b) and ketorolac tromethamine (a)

Experimental design:

The most effective transferosomes were selected using the Box-Behnken design, a three-factor, three-level statistical method. The transferosomes were synthesized using the ether injection method and evaluated on several factors. The experiment set out to determine the effects of varying process variables, such as lipid (mg), surfactant (mg), and edge activator (mg) concentrations. Using data from seventeen separate tests, the design expert program will create a design matrix. Table 1 displays the outcomes of the twelve combined formulas. The optical microscope makes it possible to observe the three-dimensional graphs of the formulations for both the R1 and R2 reactions. The links between variables and replies, as well as the impact of two factors on a response when they interact, can be explored using these diagrams.

Entrapment effectiveness (R1):

As seen in the 2D counter plot, the entrapment efficacy increased from 85 to 90% and then dropped to 80% when the lipid diffusion was increased to 500 mg. This occurred when the lipid dilution was increased from 100 mg to 500 mg at the center level of factor C. Entrapment efficiency declined with increasing surfactant concentrations. The 3D visualization shows the area with the lowest entrapment efficiency as red. With increasing trapping efficiency, a redder hue was gradually revealed.

Diffusion (R2):

The 2D counter picture shows that drug diffusion goes up as the lipid mixture goes up, peaks, and then goes down as the concentration goes up even more. As the quantity of the surfactant rises, the drug's spread decreases. When the surfactant content was very low, the drug spread the most. Figure shows that the maximum amount of medicine spread was seen near the color red. Higher amounts of lipids and surfactants made the entrapment work better. Also, as the percentage went up even more, drug diffusion went down after going up at first until it reached its highest point. In both two-dimensional and three-dimensional drawings, the relationship between causes and effects is shown by using different colors. The shape of the 2D contour plot comes from the 3D surface plot, which has both color and contour parts. In Figure 2, you can see the 2D and 3D contour plots of a) drug diffusion

studies and b) trapping efficiency studies.

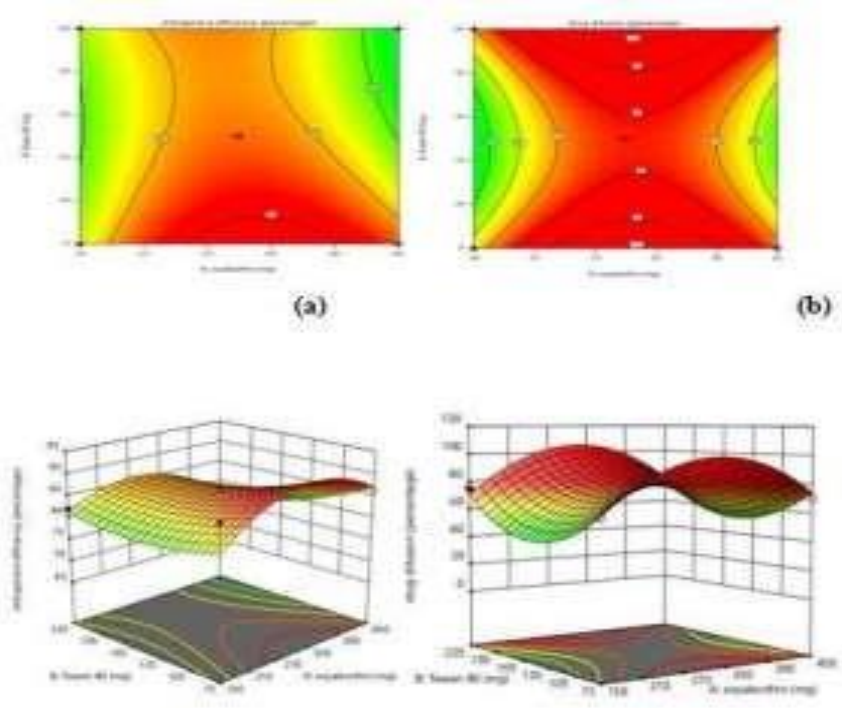

Figure 2: Two- and three-dimensional counter plots showing a) drug diffusion studies b) entrapment efficiency

Selection of optimised formulation:

By using BBD design, the best mixture will be made with a lag time of 4.5 to 6 hours, drug release of 15% to 80% within 8 hours, and entrapment efficiency of 67% to 88%. Number analysis using a desire factor was used to find the best variables. Table 3 shows that 45 mg of sodium chlorate, 75 mg of Tween 80, and 300 mg of soy lecithin are the best composition codes for those ingredients. The numbers here were similar to those in the B10 formulation. To make sure the design was correct, the process formulation was made and tested.

Table 3: Optimised formulation

Sr. No.	Composition	Quantity
1.	API (Ketorolac T.)	10
2.	Tween 80	350
3.	Soya lecithin	250
4.	Na Cholate	25
5.	Cholesterol	25
6.	Organic Phase	5
7.	Buffer (7.4)	10

Characterization of optimized formulation:

The best formulation was determined based on research on drug release, microscopic evaluation, entrapment efficiency, and drug content. Figure 3 presents a microscopic image of the prepared formulation.

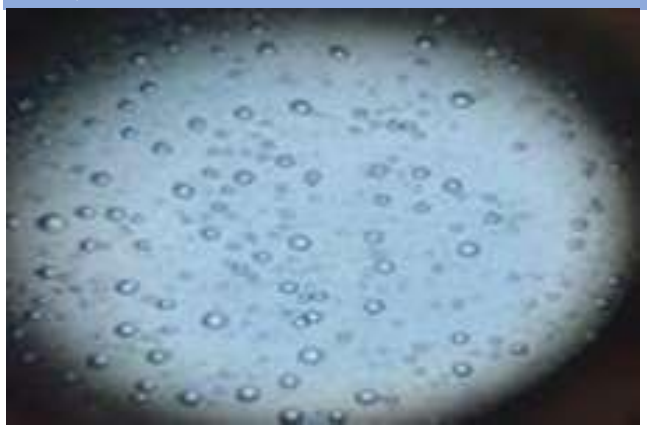

Figure 3: Microscopic image of prepared formulation

Evaluation of drug loaded gel:

The gel is very easy to spread and doesn't shear much, as shown by the 1.5% Carpool spreadability test of 6.2 centimeters. The preparations showed a strong ability to spread. The goo has to come out of the tube in order to be given to patients and accepted by them. It was decided that the mixture could be separated and worked with. Table 4 shows that the pH of 1.5% Carpool was found to be 6.80, which means it can be used on the skin and can be extruded and spread easily. The drug content per 100 mg of gel was found to be 92.0%, which means that the drugs were evenly distributed in the formulas and were loaded efficiently at 92.0%.

Table 4: Evaluation of drug loaded gel

Sr. No.	Evaluated Parameter	Result
1.	Homogeneity	Good
2.	pH	6.80
3.	Drug content	92.0±0.52
4.	Extrudability	Good
5.	Spreadability	6.10±0.24

In-vitro diffusion studies of gel:

Franz diffusion cells and dialysis membranes were used for in vitro diffusion studies. A UV-visible double beam spectrophotometer was used to measure the samples at 324 nm, which is a standard procedure. It was shown in in vitro diffusion studies that the mixtures released 62.5% of the drug over 8 hours at a rate of 55.12 (Figure 4).

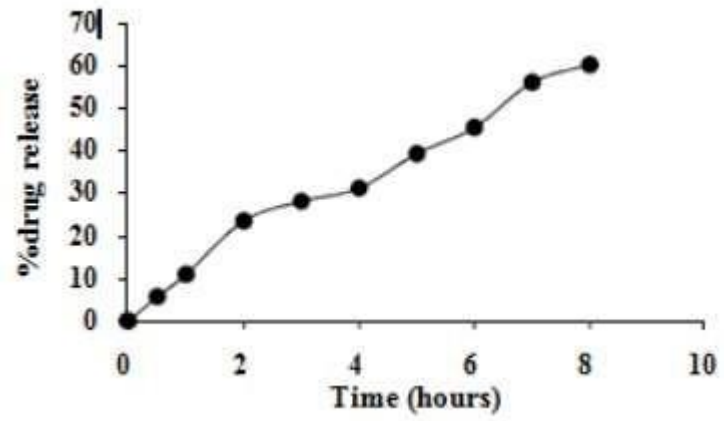

Figure 4: Diffusion studies of gel

Stability study:

The drug in the formulation was reviewed after the stability study's results. It was demonstrated that the mixture was transferosomal and stable throughout the stability assay at different temperatures.

CONCLUSION:

We successfully produced and analyzed transferosomes containing ketorolac tromethamine. According to studies on drug-excipient compatibility, the medicine was compatible with every single excipient. With the help of design software and Box-Menken design, the concentrations of lipid, surfactant, and edge activator were modified. Every Box-Behnken experiment was carefully carried out and assessed for the effectiveness of drug diffusion and trapping. After 8 hours of numerical optimization of the responses, the best formulation, B10, with an entrapment efficiency of 92.0%, begins to release its drug contents at a sustained rate of 62.5%. Using the optimized formulation, additional research into determining vesicle size and zeta potential is necessary. A modified gel formulation was used to assess the drug's diffusion, pH levels, and spreadability.

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Conflict of Interest:

None

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