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FLURBIPROFEN LOADED TRANSFEROSOME DEVELOPMENT AND EVALUATION TO IMPROVE TRANSDERMAL DELIVERY

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Abstract

Numerous joint tissues may be impacted by osteoarthritis, a degenerative joint condition. With over 32.5 million persons affected, it is the most prevalent kind of arthritis. Benefits and drawbacks of traditional drug delivery systems include low solubility and permeability, poor bioavailability, breakdown by GI enzymes, first pass metabolism, need for high doses, and associated drug toxicity. Therefore, the goal of this research is to create a transferosomal gel containing flurbiprofen to treat arthritis. The standard protocol was followed in the formulation and assessment of the prepared gel. According to the results, the F-12 formulation has the highest entrapment effectiveness (73.49%) and the smallest vesicle size (165.58%). The zeta potential of F12 was discovered to be -38.85. Additionally, the optimised gel OTGF1 demonstrated an Extrudability (g) of 185±2.5 g and a Spreadability (g.cm/sec) of 11.15±1.5 g.cm/sec, respectively, according to transferosomal gel evaluation. The measured viscosity of the gel was 32151±8 cps. The estimated percentage of transferosomal gel assay was 98.15±0.32%. The percentage of cumulative drug release at 12 hours was determined to be 92.23. Following the Higuchi model, the r 2 value from the release Kinetics of the optimised gel of transferosomal gel was found to be 0.990. Therefore, it may be said that Transfersomal gel was invented for financial gain in order to increase the stability of drug-carrying vesicles and facilitate topical application.

Keywords: Novel drug delivery system, Osteoarthritis, Rheumatoid arthritis. Transferososme, Flurbiprofen, Transferosomal gel

Introduction

Degenerative joint disease (DJD), also referred to as osteoarthritis, is the most common kind of arthritis. People are more likely to get osteoarthritis as they age. With rare exceptions, changes in osteoarthritis often take place gradually over a number of years. Joint inflammation and injury result in bone alterations, deterioration of tendons and ligaments, and disintegration of cartilage, which cause pain, swelling, and deformity in the joint (Abramoff and Caldera, 2020; Goldring and Otero, 2011).

Rheumatoid arthritis (RA) has a global prevalence of approximately 1%, with women experiencing 2-3 times higher frequency than men. In India, the prevalence ranges from 0.28 to 0.7%, comparable to affluent countries. While RA can affect individuals of all ages, it is most commonly observed in people between 30 and 50 years old. The condition can impact any joint in the body, but it predominantly affects joints like the wrist, knee, proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints.

The wrist is identified as the most commonly affected region in RA. Variations exist in the prevalence of swelling and soreness, with tenderness primarily occurring in major joints such as the elbow, shoulder, and knee. Swelling, on the other hand, is more commonly observed in smaller joints like the metacarpophalangeal joints (Cross et al., 2014; Bullock et al., 2019).

Conventional drug delivery methods have their advantages, but they also come with drawbacks like low solubility and permeability, limited bioavailability, susceptibility to degradation by gastrointestinal enzymes, first-pass metabolism, potential dietary interactions, the need for high doses, and associated drug toxicity. To overcome these challenges, extensive research has led to the development of innovative drug delivery systems known as Novel Drug Delivery Systems (NDDS). These advanced systems offer target-specific activity, require fewer doses, pose lower toxicity risks, exhibit high solubility and permeability, and enhance overall bioavailability (Tarner and Müller-Ladner, 2008; Deshmukh, 2023).

In the realm of transdermal drug delivery, lipid vesicular systems have garnered significant attention due to their superior penetration and permeation abilities upon

topical application. Among these systems, transfersomes stand out as innovative drug carriers with exceptional deformability, allowing them to efficiently transport large molecules across the skin. Transfersomes are nano vesicles or liposomes composed of phospholipids and edge activators such as Tween 80 or Span 80. These components confer high flexibility, enabling the vesicles to change shape and maintain elasticity (Benson, 2006). The objective of this study is to develop a transferosomal gel containing Flurbiprofen for the treatment of arthritis.

Materials and Methods

Chemicals

Soya phosphetidyl choline, Disodium hydrogen phosphate, Di potassium hydrogen orthophosphate, Sodium chloride, Methanol, Ethanol, Chloroform, Carbopol 934p, Methyl paraben, Propyl paraben, Propylene glycol were obtained from S.D fine chemicals. All chemicals used were of laboratory grade.

Preparation of Flurbiprofen loaded Transfersomes

1. Dissolving Soya PC in ethanol: Soya PC is dissolved in ethanol at a concentration of 0.5% to 2% w/v. The exact amount of ethanol used ranges from 5 to 20 ml. This step is carried out in a closed vessel.
2. Heating the mixture: The ethanol solution containing Soya PC is heated to a temperature of 30 ± 1°C using a water bath. This temperature is maintained throughout the process.
3. Addition of distilled water or drug solution: Distilled water or a drug solution in distilled water (at a concentration of 1% w/v) is slowly added in a fine stream to the ethanolic lipid solution. The water or drug solution is also preheated to 30 ± 1°C.
4. Continuous mixing: The addition of water or drug solution is accompanied by continuous mixing using a magnetic stirrer at a speed of 900 rpm. Mixing is continued for 5 minutes to ensure proper dispersion of the components.
5. Cooling: After mixing, the resulting vesicular dispersion is left to cool at room temperature (25±1°C) for 45 minutes. During this time, the vesicles form and

stabilize (Malakar *et al.,* 2012). Different transferosomal dispersions and their composition are shown in table.

Preparation of gel base

1. Dispersion of Carbopol 934: Accurately weigh Carbopol 934 (1% w/v) and disperse it into 80 ml of double distilled water in a beaker. Continuous stirring at 800 rpm is maintained for 1 hour to ensure proper dispersion of Carbopol 934 in water.
2. Addition of propylene glycol: After 1 hour of stirring, 10 ml of propylene glycol is added to the Carbopol 934 dispersion. This helps in enhancing the viscosity and consistency of the gel.
3. Adjustment of gel volume: The volume of the gel is adjusted to a total of 100 ml, likely by adding an additional 10 ml of double distilled water. This step ensures that the gel has the desired volume for further processing.
4. Incorporation of transferosomal preparation: The transferosomal preparation containing Flurbiprofen, corresponding to a concentration of 3% w/w, is incorporated into the gel base. This step is performed to achieve the desired concentration of the drug in the gel base (Ghanbarzadeh *et al.,* 2013).

Optimization of Transfersomes

Optimization of lipid

Table 1: Optimization of lipid concentration

Formulation code	Soya PC (% w/v)	Ethanol	Drug (% w/v)	Average vesicle size (nm)	% entrapment efficiency
F1	0.5	10	1	356.65	75.65
F2	**1**	**10**	**1**	**285.65**	**78.98**
F3	1.5	10	1	310.24	69.98
F4	2	10	1	325.65	65.58

Table 2: Optimization of ethanol concentration

Formulation code	Soya PC (% w/v)	Ethanol	Drug (% w/v)	Average vesicle size (nm)	% entrapment efficiency
F5	1	5	1	285.65	68.85
F6	1	**10**	**1**	**245.85**	**76.65**
F7	1	15	1	265.85	71.12
F8	1	20	1	283.32	69.98

Optimization of drug concentration:

Table 3: Optimization of drug concentration

Formulation code	Soya PC (% w/v)	Drug (% w/v)	Ethanol (ml)	Average vesicle size (nm)	% Entrapment efficiency
F9	**1**	**1**	**10**	**179.98**	**74.45**
F10	1	1.5	10	198.85	69.98
F11	1	2	10	183.32	68.12

Optimization of stirrer time

Table 4: Optimization of Stirrer time

Formulation code	Soya PC: (% w/v)	Drug (% w/v)	Stirrer time (min)	Average vesicle size (nm)	% Entrapment efficiency
F12	**1**	**1**	**5**	**165.58**	**73.49**
F13	1	1	10	145.65	68.85
F14	1	1	15	168.85	63.32

Characterization of Flurbiprofen loaded Transfersomes

Surface charge and vesicle size

The size and size distribution of the vesicles, as well as their surface charge, were determined using the Dynamic Light Scattering method (DLS) on the Malvern Zetamaster, ZEM 5002 instrument in the UK. Zeta potential measurements of the Transfersomes were conducted based on the zeta potential, calculated according to the Helmholtz–Smoluchowsky equation derived from their electrophoretic mobility. Zeta potential measurements were performed using a Zetasizer with a field strength of 20 V/cm in a large bore measurement cell. Samples were appropriately diluted with 0.9% NaCl, adjusted to a conductivity of 50 µS/cm.

Entrapment efficiency

One milliliter of Transfersomes suspension was centrifuged at 15000 rpm for 1 h to allow the separation the entrapped drug from the un-entrapped drug. After removal of the supernatant, the sediment was lysed using methanol and then analyzed spectrophotometrically at 244nm using a UV spectrophotometer (Labindia 3000+).

Characterization of Transfersomes-Containing Gel

Measurement of Viscosity: The viscosity of the prepared topical transfersomes-based gel was determined using a Brookfield viscometer with spindle no. 63 at an optimal speed of 10 rpm, following the method described by Qushawy et al. (2018).

pH Measurements: The pH of the selected optimized formulations was measured using a digital pH meter. Prior to each pH measurement, calibration of the pH meter was performed with buffer solutions of pH 4, pH 7, and pH 9.2. Following calibration, the electrode was immersed into the vesicles until fully covered, as per the procedure outlined by Sharma et al. (2012). The pH of the selected formulation was then measured, and the readings displayed on the digital meter were noted.

Drug Content: Accurately weighed equivalent to 100 mg of topical transfersomal gel was taken in a beaker and 20 ml of methanol was added. This solution was thoroughly mixed and filtered using Whatman filter paper no.1. Subsequently, 1.0 mL of the filtered solution was transferred to a 10 mL volumetric flask, and the volume was adjusted to 10

mL with methanol. This solution was analyzed using a UV-Spectroscope at λmax 244nm, following the method described by Hanpramukkun et al. (2009).

Extrudability Study: Extrudability was assessed based on the quantity of gel extruded from a collapsible tube under the application of a specific load. The extrudability was determined by applying weight to the gel-filled collapsible tube and recording the weight at which gel extrusion occurred, in accordance with the methodology proposed by Jivrani and Patel (2014).

Spreadibility: Spreadibility of the formulation, crucial for ensuring an adequate dose available for absorption through the skin and achieving therapeutic response, was determined using an apparatus consisting of a slide fixed on a wooden block. The upper slide was movable, and one end of the movable slide was tied to a weight pan, as described by Mishra and Biswal (2012). To determine spreadibility, 2-5 g of gel was placed between two slides, and the weight was gradually increased by adding it to the weight pan. The time required for the top plate to cover a distance of 6 cm upon adding a 20g weight was noted, with good spreadibility indicated by a shorter spreading time.

$$Spreadibility\,(g.cm/\sec) = \frac{Weight\,tide\,to\,Upper\,Slide \times Lenth\,moved\,on\,the\,glass\,slide}{Time\,taken\,to\,slide}$$

In Vitro Drug Diffusion Study

The in vitro diffusion study was conducted using a Franz Diffusion Cell, employing an egg membrane as a semi-permeable membrane for diffusion. The Franz diffusion cell comprised a receptor compartment with an effective volume of approximately 60 mL and an effective surface area of permeation of 3.14 sq. cm. A two cm2 size patch was taken, weighed, and then placed on one side of the membrane facing the donor compartment. The receptor medium used was phosphate buffer at pH 7.4. The receptor compartment was surrounded by a water jacket to maintain the temperature at 32 ± 0.5°C. Heat was provided using a thermostatic hot plate with a magnetic stirrer. Stirring of the receptor fluid was facilitated by a Teflon-coated magnetic bead placed in the diffusion cell.

During each sampling interval, samples were withdrawn and replaced with equal volumes of fresh receptor fluid. The withdrawn samples were analyzed spectrophotometrically at a wavelength of 244 nm.

Stability Studies

Stability studies were conducted for drug-loaded transfersomes at two different temperatures: refrigeration temperature (4.0 ± 0.2°C) and room temperature (25-28 ± 2°C) for a duration of 3 weeks. The formulations subjected to stability studies were stored in borosilicate containers to prevent any interaction between the formulation and the container glass. The formulations were analyzed for any physical changes and drug content.

Results and Discussion

The optimization results for various parameters, including lipid, ethanol, and drug concentration, as well as stirrer duration, indicated that the F-12 formulation exhibited the smallest vesicle size of 165.58% and the highest entrapment effectiveness of 73.49%. The zeta potential of F12 was determined to be -38.85. Additionally, the evaluation of the transferosomal gel revealed that the optimized gel, OTGF1, demonstrated Extrudability (g) and Spreadability (g.cm/sec) values of 185±2.5 g and 11.15±1.5 g.cm/sec, respectively. The viscosity of the gel was measured at 32151±8 cps. The transferosomal gel % assay was estimated to be 98.15±0.32%. At 12 hours, the % Cumulative Drug Release was found to be 92.23. The r2 value from the release kinetics of the optimized gel of transferosomal gel was observed to be 0.990, and it followed the Higuchi model.

Table 5: Characterization of Optimized formulation of Transfersomes

Characterization	Average vesicle size (nm)	% Entrapment efficiency	Zeta Potential (mV)
F-12	165.58	73.49	-38.85

Characterization of transfersomes loaded gel

Table 6: Characterization of gel based formulation

Formulation	Viscosity (cps)	Assay* (%)	Extrudability (g)	Spreadability (g.cm/sec)
Optimized Gel OTGF1	3215±18	98.15±0.32	185±2.5	11.15±1.5

***Average of three determinations**

Table 7: *In vitro* drug release study of prepared gel formulation

S. No.	Time (hr)	% Cumulative Drug Release
1	0.5	18.85
2	1	29.98
3	2	43.32
4	4	52.25
5	6	67.74
6	8	79.98
7	12	92.23

Table 8: Release Kinetics of optimized gel of transferosomal gel

Formulation	Zero order	First order	Higuchi	*Korsmeyer*
OTGF1	0.943	0.984	0.990	*0.989*

Conclusion

Transfersomes have demonstrated enhanced efficacy in drug delivery for the management and treatment of osteoarthritis. Flurbiprofen, a key component in osteoarthritis treatment, faces limitations in effectiveness due to challenges in medication reaching the target site. In a bid to augment transfersomes' capabilities in osteoarthritis treatment, nano deformable transfersomes loaded with Flurbiprofen were proficiently formulated, optimized, subjected to physiochemical characterization, and evaluated in vivo. Additionally, a transfersomal gel was developed to enhance the stability of drug-loaded vesicles and facilitate easier application to the skin.

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