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Original Research Article

DEVELOPMENT AND EVALUATION OF FLURBIPROFEN LOADED TRANSFEROSOME TO IMPROVE TRANSDERMAL DELIVERY

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ABSTRACT

Osteoarthritis is a degenerative joint disease that can affect a variety of joint tissues. It is the most common type of arthritis, affecting about 32.5 million adults. Traditional drug delivery systems include benefits as well as drawbacks such as low solubility and permeability, poor bioavailability, degradation by GI enzymes, first pass metabolism, dietary interactions, high dose required, and related drug toxicity. Thus, this study aims to develop transferosomal gel of Flurbiprofen for treating arthritis. The formulation and evaluation of formulated gel was performed as per standard protocol. Results showed that the F-12 formulation has the smallest vesicle size of 165.58% and the highest entrapment effectiveness of 73.49%. F12's zeta potential was found to be -38.85. Furthermore, transferosomal gel evaluation revealed that the optimised gel OTGF1 had Extrudability (g) and Spreadability (g.cm/sec) of 185±2.5 g and 11.15±1.5 g.cm/sec, respectively. The gel's viscosity was measured to be 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 r 2 value from release Kinetics of optimized gel of transferosomal gel was observed to be 0.990 and follows Higuchi model. So, it can be concluded that Transfersomal gel was profitably developed to improve the stability of drug-carrying vesicles and to make it easier to apply to the skin.

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

INTRODUCTION

The most prevalent type of arthritis is osteoarthritis, commonly known as degenerative joint disease (DJD). As people get older, they are more likely to acquire osteoarthritis. Changes in osteoarthritis often occur gradually over several years, with rare exceptions. Inflammation and damage to the joint produce bony changes, degradation of tendons and ligaments, and cartilage disintegration, leading in discomfort, swelling, and joint deformity (Abramoff and Caldera, 2020; Goldring and Otero, 2011).

The global prevalence of RA is estimated to be around 1%, with women experiencing 2-3 times the frequency of men. The prevalence of RA in India ranges from 0.28 to 0.7%, which is comparable to the frequency in affluent countries. RA affects people of all ages, however it is most common in people between the ages of 30 and 50. RA can affect any joint in the body. However, it primarily affects the wrist and knee proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints. The wrist has been found to be the most commonly afflicted region in RA.

There are some variances in the predominance of swelling and soreness, with tenderness happening primarily in major joints such as the elbow, shoulder, and knee, whereas swelling occurs primarily in tiny joints such as the metacarpophalangeal joints (Cross *et al*., 2014; Bullock *et al*., 2019).

Traditional drug delivery systems include benefits as well as drawbacks such as low solubility and permeability, poor bioavailability, degradation by GI enzymes, first pass metabolism, dietary interactions, high dose required, and related drug toxicity. Extensive research has been conducted to overcome these drawbacks, resulting in the development of innovative drug delivery systems (NDDS). These improved systems have target-specific activity, need fewer dosages, have lower toxicity risks, high solubility and permeability, and have increased bioavailability (Tarner and Müller-Ladner, 2008; Deshmukh,2023).

Because of their superior penetration and permeation ability via the skin after topical application, lipid vesicular systems have received a lot of interest in transdermal drug delivery during the last few decades. Transfersomes are innovative drug carriers or drug delivery technologies that are extremely deformable and capable of carrying and transporting big molecules across skin. Transfersomes are ultra-deformable nano vesicles or liposomes made of phospholipids and edge activators such as Tween 80 or Span 80 that permit high flexibility, plasticity of the vesicle shape, and elasticity production (Benson,2006). The aim of this study is to develop transferosomal gel of Flurbiprofen for treating arthritis.

MATERIALS AND METHODS

Chemical and reagent

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 1-4.

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.

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).

Characterization of Flurbiprofen loaded Transfersomes

Surface charge and vesicle size

The vesicles size and size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (Malvern Zetamaster, ZEM 5002, Malvern, UK). Zeta potential measurement of the Transfersomes was based on the zeta potential that was calculated according to Helmholtz–Smoluchowsky from their electrophoretic mobility. For measurement of zeta potential, a Zetasizer was used with field strength of 20 V/cm on a large bore measures cell. Samples were diluted with 0.9 % NaCl adjusted to a conductivity of 50 lS/cm.

Entrapment efficiency

One milliliter of Transfersomes suspension was centrifuged at 15.000 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

Viscosity measurements of prepared topical Transfersomes based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm; viscosity (Qushawy *et al.,* 2018).

pH measurements

pH of selected optimized formulations was determined with the help of digital pH meter. Before each measurement of pH, pH meter

should be calibrated with the help of buffer solution of pH 4, pH 7 and pH 9.2. After calibration, the electrode was dipped into the vesicles as long as covered by the vesicles (Sharma *et al.,* 2012). Then pH of selected formulation was measured and readings shown on display were noted.

Drug Content

Accurately weighed equivalent to 100 mg of topical transfersomal gel was taken in beaker and added 20 ml of methanol. This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 1.0 mL of filtered solution was taken in 10 mL capacity of volumetric flask and volume was made upto 10 mL with methanol (Hanpramukkun *et al.,* 2009). This solution was analyzed using UV-Spectroscope at λ_{max} 244nm.

Extrudability study

Extrudability was based upon the quantity of the gel extruded from collapsible tube on application of certain load. More the quantity of gel extruded shows better extrudability (Jivrani and Patel, 2014). It was determine by applying the weight on gel filled collapsible tube and recorded the weight on which gel was extruded from tube.

Spreadibility

Spreadibility of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response. An apparatus in which a slide fixed on wooded block and upper slide has movable and one end of movable slide tied with weight pan (Mishra and Biswal, 2012). To determine spreadibility, placing 2-5 g of gel between two slide and gradually weight was increased by adding it on the weight pan and time required by the top plate to cover a distance of 6cm upon adding 20g of weight was noted. Good spreadibility show lesser time to spread.

***In vitro* drug diffusion study**

The *In-vitro* diffusion study is carried by using Franz Diffusion Cell. Egg membrane is taken as semi permeable membrane for diffusion. The Franz diffusion cell has receptor compartment with an effective volume approximately 60 mL and effective surface area of permeation 3.14sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A two cm^2 size patch taken and weighed then placed on one side of membrane facing donor compartment. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 32 ± 0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell. During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each sampling. The samples withdrawn are analyzed spectrophotometrically at wavelength of drug 244nm.

Stability Studies

Stability study was carried out for drug loaded Transfersomes at two different temperatures i.e. refrigeration temperature (4.0 ±0. 2°C) and at room temperature (25-28±2°C) for 3 weeks. The formulation subjected for stability study was stored in borosilicate container to avoid any interaction between the formulation and glass of container. The formulations were analyzed for any physical changes and drug content.

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

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

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

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

RESULTS AND DISCUSSION

The results of optimisation for various parameters such as lipid, ethanol, and drug concentration, as well as stirrer duration, revealed that the F-12 formulation has the smallest vesicle size of 165.58% and the highest entrapment effectiveness of 73.49%. F12's zeta potential was found to be -38.85. Furthermore, transferosomal gel evaluation revealed that the optimised gel OTGF1 had Extrudability (g) and Spreadability (g.cm/sec) of 185±2.5 g and 11.15±1.5 g.cm/sec, respectively. The gel's viscosity was measured to be 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 r^2 value from release Kinetics of optimized gel of transferosomal gel was observed to be 0.990 and follows Higuchi model.

CONCLUSION

Transfersomes have been shown to improve drug delivery in the management and treatment of osteoarthritis. Flurbiprofen plays an important role in the treatment of osteoarthritis, although its effectiveness is limited due to medication non-availability at the site of action. To enhance the ability of transfersomes in the treatment and management of osteoarthritis, nano deformable transfersomes of Flurbiprofen were effectively created, optimized, physiochemically characterized, and in vivo evaluated. Transfersomal gel was developed to improve the stability of drug-carrying vesicles and to make it easier to apply to the skin.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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