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FORMULATION AND DEVELOPMENT OF TRANSFEROSOMAL GEL INCORPORATING WITH CHRYSIN FOR TOPICAL APPLICATION

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Abstract:
Skin infection have variable presentations, etiologies and severities. Among the numerous drug delivery systems, vesicles as a drug carrier system have emerged as the preferred vehicle. Transfersomes have been discovered to be one of the most effective drug-delivery methods for topical treatment when compared to conventional topical systems. So, in this study, with the use of a gelling agent as a vehicle for the inclusion of transfersomes the transferosomal gel of chrysin was created for topical administration system. Preparation & evaluation of transferosomal gel was performed as per standard method. Results showed that F-12 formulation have lowest vesicle size of 165.58% with & entrapment efficiency of 73.49%. The zeta potential for F12 was recorded as -38.85. Further, the result of evaluation of transferosomal gel suggested that the optimized gel OTGF1 have Extrudability (g) and Spreadability (g.cm/sec) as 185±2.5 g and 11.15±1.5 g.cm/sec respectively. The viscosity of gel was noted to be 3215±18 cps. The % assay for transferosomal gel was estimated to be 98.15±0.32%. The % Cumulative Drug Release was found to be 92.23 at 12hour. Also, the formulated transferosomal gel was found to be stable for 3 months at 4.0 ±0. 2°C with normal physical appearance & drug content of 95.58&%.

Keywords: *Skin infection, Topical drug deliver, Novel drug delivery system Transferosome, Transferososmal gel*

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INTRODUCTION:

Skin infections which are caused by microbial invasion of the skin and underlying tissues, and depending on the severity of the infection, they can range from mild to severe life-threatening infections manifesting as redness, swelling, pain, and erythema on the entire skin surface. The prevalence of skin infections is rising due to a rise in the number of elderly people, critically ill patients, immunocompromised patients, and the introduction of multi-drug resistance pathogens (Ki *et al*., 2008; Sukumaran and Senanayake, 2016).

The conventional dose form was unable to meet any of these requirements. Oral, topical (skin), transmucosal (nasal, buccal, sublingual, vaginal, ophthalmic, and rectal) and inhalation routes are the most popular. Modified medicine delivery mechanism to improve patient compliance and efficacy of various drug delivery systems are utilised to modify drug release profile, absorption, distribution, and elimination (Kumar *et al*., 2012).
Among the numerous drug delivery systems, vesicles as a drug carrier system have emerged as the preferred vehicle. Lipid vesicles were primarily employed in immune therapy, membrane biology and diagnostic techniques, and genetic engineering.It provides an efficient mechanism for drug delivery to the infection site, resulting in lower drug toxicity and fewer side effects. It lowers therapy costs by increasing medicine bioavailability, particularly in the case of poorly soluble medications, and by lowering dose and dosing frequency, consequently enhancing patient compliance (Sercombe *et al*., 2015).

Transdermal drug delivery devices (TDDS) can improve bioavailability and patient compliance by bypassing first-pass metabolism. Because they are designed for controlled, efficient, and targeted drug delivery, vesicular-based TDDS have received a lot of interest in recent years. Transferosomal-based formulations, one of these delivery systems, have risen in favour due to their ability to meet all of the desired parameters and quality features. Because they include both liposomes (phospholipids and cholesterols) and niosomes (nonionic surfactants; edge activators), transferosomes combine the properties of both. They are hence known as the first generation of elastic liposomes (Tanwar and Sachdeva, 2016; Wokovich *et al*., 2006).
Transfersomes have been discovered to be one of the most effective drug-delivery methods for topical treatment when compared to conventional topical systems. They have ultraflexible bilayer membranes that allow vesicles to be very elastic and malleable. Under nonocclusive conditions, transfersomes can escape from narrow pores in the stratum corneum (one-tenth their own diameter). Furthermore, transfersomes represent multilateral delivery for improving stability and serving as a medication carrier (Jangme and Chavan, 2013).

The main drawback of employing transfersomes topically is their liquid nature. To accomplish this, transfersomes are inserted into an appropriate vehicle while preserving the original structure of the vesicles. It is common knowledge that transfersomes are compatible with gel systems. Also gel can accommodate large amounts of medication (Thakur *et al*., 2018). So, in this study, with the use of a gelling agent as a vehicle for the inclusion of transfersomes the transferosomal gel of chrysin was created for topical administration system. Chrysin have therapeutic advantages. Chrysin has also recently been demonstrated to be a powerful inhibitor of the human immunodeficiency virus (HIV) activation and the aromatase enzyme in models of latent infection. The potential benefits of chrysin as a pharmacological agent are becoming more and more clear. Additionally, through inducing apoptosis in a variety of human and rat cell types, chrysin exhibits anti- inflammatory, antioxidant, and cancer-chemopreventive properties (Mani & Natesan,2018).

MATERIALS & METHODS:

Preparation of Chrysin 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 7.1-7.4.

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.
4. Sonication: The gel is subjected to sonication for 10 minutes using a bath sonicator. This helps in removing any air bubbles present in the gel, ensuring a smooth and homogeneous gel base.
5. pH adjustment: The final pH of the gel base is adjusted to 6.8, likely using an appropriate pH adjuster (e.g., sodium hydroxide or citric acid). This step ensures that the gel base has the desired pH for stability and compatibility with the drug.
6. Incorporation of transferosomal preparation: The transferosomal preparation containing Chrysin, 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 Chrysin 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 278nm 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 This solution was analyzed using UV-Spectroscope at λ_{max} 278nm.

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. 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.

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

***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 278nm.

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.

RESULTS & DISCUSSION:

The result of optimization for various parameters like lipid, ethanol & drug concentration & stirrer time revealed that F-12 formulation have lowest vesicle size of 165.58% with & entrapment efficiency of 73.49%. The zeta potential for F12 was recorded as -38.85. Further, the result of evaluation of transferosomal gel suggested that the optimized gel OTGF1 have Extrudability (g) and Spreadability (g.cm/sec) as 185±2.5 g and 11.15±1.5 g.cm/sec respectively. The viscosity of gel was noted to be 3215±18 cps. The % assay for transferosomal gel was estimated to be 98.15±0.32%. The % Cumulative Drug Release was found to be 92.23 at 12hour. Also, the formulated transferosomal gel was found to be stable for 3 months at 4.0 ±0. 2°C with normal physical appearance & % drug content of 95.58.

Table 5: 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 6: *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 7: Release Kinetics of optimized gel of transferosomal gel

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

Table 8: Stability study of optimized formulation of Transfersomes

Characteristic	Time (Month)					
	1 Month		2 Month		3 Month	
Temperature	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C
Viscosity (cps)	3210	3110	3195	3085	3180	2980
% Assay	98.12	97.65	98.05	96.74	95.58	98.00
Physical Appearance	Normal	High turbid	Normal	High turbid	Normal	High turbid and agglomeration

CONCLUSION:

A current method to TDDS (Transdermal drug delivery system) aims to transport the drug into systemic circulation via Transferosomal gel at a predefined pace utilising skin as a site of administration. Transferosomes, a type of vesicular drug delivery system, have the capacity to increase drug penetration and sustain the drug for a longer amount of time, decreasing the dose and dosing frequency of the pharmaceuticals and improving patient compliance. The improved formulation makes use of Chrysin to potentially be used in skincare or therapeutic interventions. To assess the pharmacokinetics, biodistribution, and therapeutic efficacy of the Chrysin- loaded transfersome gel formulation in pertinent animal models or human individuals, additional in vivo investigations are advised.

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