Available online on 20.08.2022 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Formulation and Characterization of Novel Transfersomes Gel for Enhance TDDS of Losartan Potassium

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Article Info:

Article History:

Received 21 June 2022
Reviewed 04 August 2022
Accepted 11 August 2022
Published 20 August 2022

Cite this article as:

Khan R, Jain PK, Khare B, Jain M, Thakur BS, Jain A, Jain AP, Formulation and Characterization of Novel Transfersomes Gel for Enhance TDDS of Losartan Potassium, Journal of Drug Delivery and Therapeutics. 2022; 12(4-S):96-100

DOI: http://dx.doi.org/10.22270/jddt.v12i4-s.5525

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Abstract

A transferosome is the first generation of an elastic liposome prepared from phospholipids and edge activators. An edge activator is often a single-chain surfactant with a high radius of curvature that destabilizes the lipid bilayers of vesicles and increases the deformability of the bilayers, thereby making the vehicle ultra-deformable. Losartan potassium is an orally active angiotensin-II receptor antagonist used in the treatment of hypertension due to mainly blockade of AT1 receptor. It is freely soluble in water, slightly soluble in acetonitrile, and soluble in isopropyl alcohol. The aim of the present study was to investigate the potential of transfersomal gel formulations for transdermal delivery of losartan potassium by reverse phase evaporation method. Characterization of transfersomes gel performed by vesicle size, pH measurements, drug content, entrapment efficiency, in vitro drug diffusion study, spreadability and stability study. In the formulations pH is found to be around 6.8 to 6.9, pH is found in the range of 6 which is compatible with skin. In the formulations spreadability is found to be around 6.75 to 10.11 g m cm/sec. The prepared gel containing losartan potassium-loaded transfersomal formulation was optimized and can be use for topical preparation. The results were obtained which showed that transfersomal gel was a promising candidate for transdermal delivery with targeted and prolonged release of a drug. It also enhances skin permeation of many drugs.

Keywords: Transferosome gel, Losartan potassium, Antihypertensives, Reverse phase evaporation method

INTRODUCTION

Nanotechnology involves fabrication of nanoscale structures which are observed visibly under high resolution. These molecular assemblies are especially designed for attaining their target functions[1]. Based on their critical packing parameter and hydrophilic lipophilic balance (HLB), these molecules are self-assembled to various morphologies including micelles, sheets and vesicles (liposomes, transferosomes, exsosomes, niosomes etc.) [2]. Furthermore, these vesicular formulations had been more exploited in the field of transdermal drug delivery[3]. They offer many advantages over conventional delivery systems like bio-compatibility, non-toxicity and ability to modify drugs' bioavailability[4]. In addition to the utilization of vesicular carriers for transdermal drug delivery, nano transfection approaches (TNT) have been recently introduced for topical and controllable delivery of reprogramming factors across the skin. These approaches allow delivery of controlling factors by applying intense and highly focused electric field using arrayed nano-channel. Hence, TNT can deliver the cargo to skin in rapid and non-invasive manner[5]. In this manuscript, the strategy of using transferosome s as a vesicular nano-carrier has been selected and investigated for efficient transdermal delivering of drugs and bypassing their oral problems. Transferosomes are ultra-flexible vesicles with a bilayer structure. They can penetrate the skin easily and overcome the barrier function by squeezing through the intracellular lipid of the stratum corneum[6]. After application of Transferosomes on the skin, they move from the dry stratum corneum to a deep hydrated layer according to the osmotic gradient. The presence of surfactant in their structure helps in solubilizing the lipid in stratum corneum and permits high penetration of the vesicles[7]. Losartan potassium is an angiotensin II receptor antagonist with anti hypertensive activity. It belongs to class 1 of Biopharmaceutical Classification System (BCS). It is readily absorbed from the GI tract following oral administration but the bioavailability is about 33% due to substantial first-pass metabolism. Peak plasma concentration occurs at about 1hr after an oral dose and has short terminal elimination halflife is about 1.5 to 2hrs respectively, thereby requiring two to three times daily dosing in large number of patients, which often leads to non-compliance[8]. Thus, there is a strong clinical need and market potential for a dosage form that will deliver losartan potassium in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance. In the present investigation, we attempted to develop and optimize transferosomal gel containing losartan potassium for improved transdermal permeation.

EXPERIMENTAL

Materials

Losartan Potassium was obtained as a gift sample from Cadila Pharmaceutical LTD, Ahemdabad. Phospholipid was purchased from Himedia Laboratory, Mumbai. Ethanol, chloroform, cholesterol, tween 80 and carbopol-934 purchased from CDH chemical Pvt. Ltd. New Delhi. Dialysis membrane of Mol Wt cutoff 1200 was purchased from Himedia Laboratory, Mumbai. Demineralized and double distilled water was prepared freshly and used whenever required. All other reagents and chemicals used were of analytical grade.

Characterization of drug sample

Organoleptic properties

The drug sample was examined for its appearance colour, odors.

Solubility

The solubility parameter of Losartan potassium was determined by adding excess amount of drug in the solvent (water) at 37oC and kept for 3 days for equilibrium in shaking incubator. Equilibrium solubility was determined by taking supernatant and analyzing it on U.V. spectrophotometer.

Partition coefficient

The partition coefficient is defined as the ratio of unionized drug distributed between the organic and aqueous phase at equilibrium.

$$Po/w = [Co/Cw] \text{ equilibrium}$$

Where Po/w is the partition coefficient of drug

Co is the concentration of drug in octanol

Cw is the concentration of drug in phosphate buffer

Calibration curve of losartan potassium in water

Precisely weighed amount of Losartan potassium (100 mg) was dissolved in small quantity of water then volume made up to 100 ml (1000ug /ml). From this solution 1ml of sample was taken and volume was made up to 10 ml to obtain a solution of (100ug /ml). Appropriate aliquots from above stock solution were taken and volume was made up to 10 ml with water, so as to get solutions with drug concentrations of range 2 to 20µg/ml. These solutions were then analyzed using UV spectrophotometer and curve was plotted in between absorbance v/s concentration.

Fourier transform infrared (FTIR) analysis

The FT-IR spectrum of Losartan potassium was recorded using FTIR spectrophotometer (Shimadzu 84005) using KBr through diffuse reflectance attachment cell. Infrared spectrum of any drug or compound gives information about the groups present in that particular drug .FTIR has done by Bruker FTIR ATR (Attenuated total reflection) Technique .FTIR is an analytical tool which is used for identification of unknown sample.

Method of preparation

Transferosomes contain losartan potassium were prepared by reverse phase evaporation method with some modification as described[9]. At first, specified amount of lipids (soya lecithin and cholesterol) and losartan potassium were taken in a clean beaker. Then Tween 80 as surfactant was poured in the same beaker and dissolved in a solvent mixture of ether and chloroform in the ratio of 1:1. The ratio of lipids and surfactants was maintained in all the formulations. The beaker was kept at the room temperature for 24 hr until the thin film was formed. Then, the resulting thin film was resuspended with 2 ml of phosphate buffer saline (pH, 7.4) and sonicated by a probe sonicator and for 5 min at room temperature. The film was hydrated using sodium deoxycholate as edge deactivator in 2 ml of phosphate buffer saline (pH, 7.4) and then further sonicated for 10 min to obtain highly deformable vesicles as transferosomal suspensions containing losartan potassium. Various formulated transferosomal suspensions were passed through Whatman filter paper (No. 40). Then, these transferosomal suspensions containing losartan potassium was transferred to 4% w/v methylcellulose gel. The formulated transferosomal gels were stored in cool and dark place.

Table 1: Composition of formulation

S. N.	Formulation code	Drug (mg)	Surfactant	PC: Cholesterol (mg)	Diethyl ether : chloroform
1.	F1	20 mg	Tween 80 (0.5%)	1:1	1:1
2.	F2		Tween 80 (1%)	1:2	
3.	F3		Span 80 (0.5%)	1:1	
4.	F4		Span 80 (1%)	1:2	

Characterization

Vehicle shape

The surface morphology was examined by Scanning electron microscope (Novanano SEM 450, FEI Netherland). It is used to determine the shape, size and surface morphology of the transferosomes. Suspension was made to Photomicrographs of the Losartan potassium loaded transferosomes using the SEM.

Determination entrapment efficiency

Transferosome entrapped Losartan potassium was estimated by centrifugation method. The prepared transfersome were placed in centrifugation tube and centrifuged at 14000 rpm for

30 minute. The supernatant (1ml) was withdrawn and diluted with phosphate buffer (pH 7.4). The unentrapped losartan potassium was determined by UV spectrophotometer .The samples from the supernatant were diluted 100 times before going for absorbance measurement. The free losartan potassium in the supernatant gives us the total amount of unentrapped drug. Encapsulation efficiency is expressed as the percent of drug trapped.

% Entrapment =Total drug-Diffused drug/Total drug×100

Drug content

Take 1.0 gm of a transfersomes gel formulation was taken in 100 ml volumetric flask which contains 25 ml of ethanol and allow stand sonication for 15 min. Later this solution was placed in a centrifugation tube and centrifuged at 14000 rpm for 30 minutes. The clear solution was diluted to 100 ml with methanol. Then 10 ml of the solution was diluted to 100 ml with phosphate buffer (pH 7.4). Aliquots were withdrawn and drug content was calculated for losartan potassium by using UV spectrophotometer.

PH value of topical transferosome gel

The value of pH of topical transfersome gels was measured by using a digital pH meters (Lab India Sab 5000 pH meter) at the room temperature.

In vitro drug release studies through a cellophane membrane

Each transfersomal gel formulation was subjected to *in vitro* drug release studies using a cellophane membrane. The cumulative amount of drug release was calculated for each formulation. The maximum release was also due to optimum surfactant concentration because at this concentration the surfactant molecule gets associated with the phospholipid bilayer resulting in better partitioning of the drug, and resulted in higher drug release from the vesicles. In vitro release study of topical losartan potassium transfersomes were carried out for 48 hours by using by modified Franz diffusion cell using cellophane membrane in (pH 7.4) phosphate buffer maintained at 37±0.5°C temperature and stirred by a magnetic bar at 100 rpm under sink condition. Gel (2. 0g) was kept on membrane in donor compartment. The contents were stirred using magnetic stirrer at 100 rpm and aliquots each of 5 ml were withdrawn from the release medium at time intervals of 0, 0.25 ,0.50 1, 2, , 4, 6, 8, 12, 24, and 48 hrs. Withdrawn samples were replaced by` equal volumes of same fresh medium. Losartan potassium release (%) of cellophane membrane from different gel formulations was calculated.

Spreadability

It was determined by wooden block and glass slide apparatus. A ground glass slide was fixed on the block and an excess of formulated gel (2.0 g) was placed on it. Gel was sandwiched by using another glass slide which was provided with hook. Weight (100 g) was placed upon the upper slide for 5 minutes to remove entrapped air and to form a uniform thin gel layer between slides. The weight was removed and the excess gel from the edges was scrapped off. The two slides in positioned were fixed to a stand without slightest disturbance and in such a way that only the upper slide to slip off freely by the force of weight tied to it. A 2 .0 g weight was tied to upper slide carefully. The time taken for the upper slide (movable) to travel the distance of 6 cm and separate away from the lower slide (fixed) under the direction of weight was noted. The determinations were carried out in triplicate and the average of three reading was recorded.

Spreadability was then calculated by using the Formula: S = M.L/ T

Where, S = Spread ability, M = Weight tide to the upper slide, L = Length of a glass slide

T = Time taken to separate the slide completely from each other.

RESULTS AND DISCUSSIONS

Solubility of losartan potassium was freely soluble in water, slightly soluble in chloroform, soluble in ethanol and methanol. The melting point and partition coefficient of losartan potassium was 258-262ºC and 3.75 ± 0.06. λ_{max} of losartan potassium was found to be 204 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 2-20µg/ml Fig.1. Identification of losartan potassium was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification Fig.2. The surface morphology was examined by Scanning electron microscope (Novanano SEM 450, FEI Netherland). It is used to determine the shape, size and surface morphology of the transferosomes. Suspension was made to Photomicrographs of the losartan potassium loaded transferosomes using the SEM. Results are shown in Fig 3. The higher % entrapment efficiency (EE) of losartan potassium in transfersomes was found to be F2 (1:2) with increase in surfactant amount this is due to the possible increase in solubilization of drug due to the limiting amount of surfactant and hence increase entrapment efficiency. The higher % entrapment efficiency (EE) of (1:2), so were prepared topical transferosome in this formulation. The EE% of in the vesicles was in the range of 82.07 Table 2. Drug content was found within the range of (F1) 81.22 ± 1.2 (F2) 83.53± 1.1 Table 3. The pH of all topical transfersomal gels was found to be in the range of 7.4±0.02 to 7.4±0.08. In vitro release from the transferosome was studied, which showed good sustaining action over a period of 48 hours. The drug release (F1, F2, F3, F4) 80.53 ± 0.05, 93.23 ± 0.05, 82.08± 0.04, 85.58 ±0.03 respectively Table 4. Spreadability studied of F1to F4 formulation that was raise the concentration of carbopol 934 so enhance the viscosity of losartan potassium loaded transferosome. In the formulations spreadability is found to be around 6.75 to 10.11 g m cm/sec Table 5.

Table 2: Entrapment efficiency of different formulation

S.N.	Surfactant	Molar ratio PC: Cholesterol	Formulation code	Entrapment Efficiency Percent
1	Tween 80	1:1	F1	81.62 ± 0.074
2		1:2	F2	82.07 ± 0.021
3	Span 80	1:1	F3	74.31± 0.033
4		1:2	F4	75..90 ± 0.012

Table 3: Percent drug content of formulations

S. N.	Formulation code	Drug content (%)
1.	F1	81 .22± 1.2
2.	F2	83.53± 1.2
3.	F3	76. 11± 1.1
4.	F4	77.23 ± 1.5

Table 4: Percentage cumulative drug release from transferosomes formulation

Time (hr)	Percentage Drug permeated			
	F_1	F_2	F_3	F_4
0	0	0	0	0
0.25	11.84± 0.01	14.69 ± 0.03	10.31 ± 0.03	9.94± 0.02
0.50	24.57± 0.02	23.05±0. 01	22.19± 0.02	20.52± 0.06
1	40.27± 0.01	45.11± 0.01	43.33 ± 0.04	40.21 ± 0.05
2	57.81± 0.06	66.17 ± 0.03	69.34± 0.02	60.61 ± 0.01
4	61.04 ± 0.07	74.92 ± 0.05	70.63 ± 0.01	62.51 ± 0.02
6	70.69 ± 0.01	81.11 ± 0.06	71.92 ± 0.02	64.54 ± 0.06
8	74.61± 0.02	83.92 ± 0.03	73.99 ± 0.01	70.11± 0.02
12	75.58 ± 0.03	85.59 ± 0.02	75 .59 ± 0.01	77.05 ± 0.05
24	77.25 ± 0.04	88.48 ± 0.04	76.58 ± 0.03	79.58 ± 0.03
48	80.53 ± 0.05	**93.23 ± 0.05**	82.08 ± 0.04	85.58 ± 0.03

Table 5: Spreadability of formulation

S.N.	Formulation code	Spreadability (gm.cm/sec)
1.	**F1**	10.11± 0.022
2.	**F2**	10.00± 0.711
3.	**F3**	8.00± 0.360
4.	**F4**	6.75± 0.260

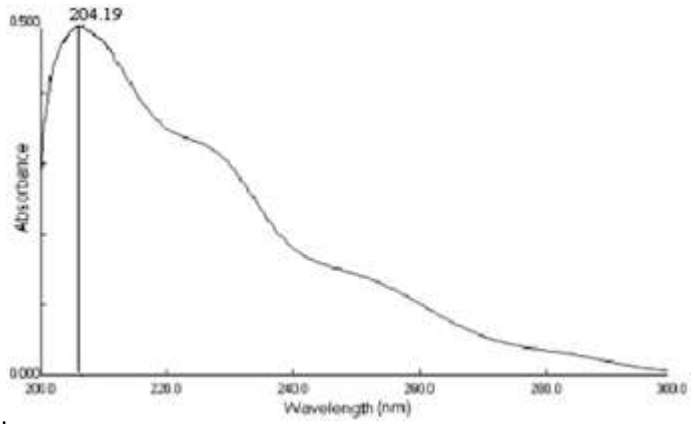

Figure 1: UV spectroscopy of losartan potassium (λ_{max} 204.19)

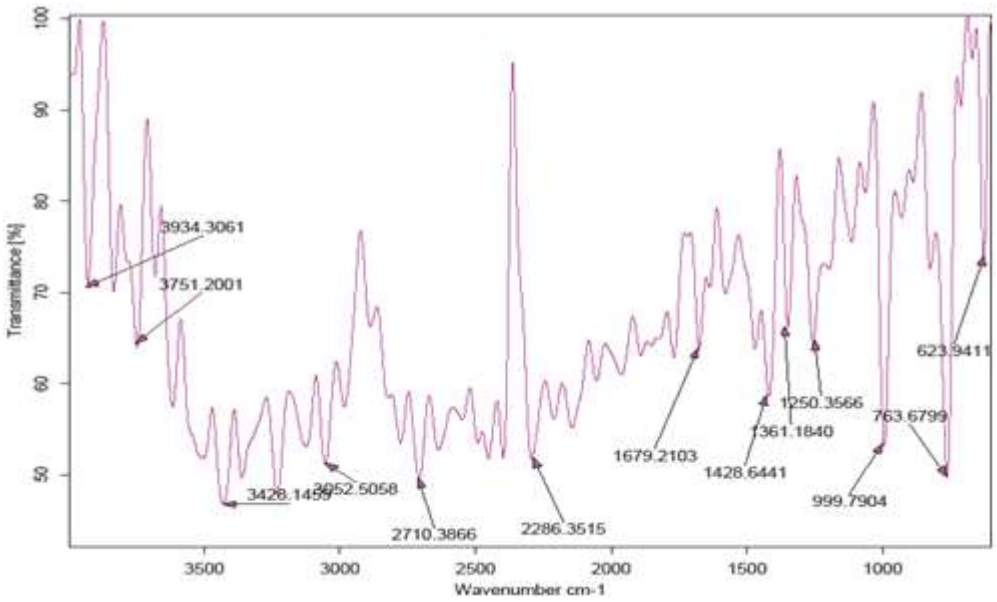

Figure 2: IR Spectra of losartan potassium

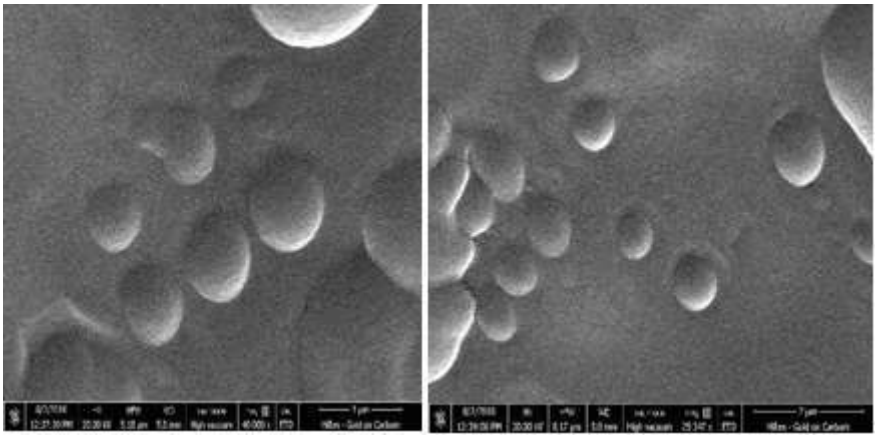

Figure 3: Optical Photomicrographic image of (a) F_1 formulation (b) F_2 formulation.

CONCLUSION

The result of the present study showed that ultraflexible lipid vesicles transferosome prolongs the release transdermal delivery. Transferosomes were prepared by reverse phase evaporation method using various ratio of soya lecithin to surfactant was optimized. Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at a predetermined and controlled rate. The Antihypertensive drug of losartan potassium is an angiotensive receptor blockers used for long time treatment of hypertension; it is freely soluble in water. The result of the present study showed that deformable lipid vesicles, transferosome improve the transdermal delivery.

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