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PREPARATION OF LOSARTAN POTASSIUM LOADED ETHOSOMES FORMULATIONS

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ABSTRACT

The present investigation attempted to prepare and evaluate the finasteride ethosomes for transdermal drug delivery. The ethosomal formulations were developed using different concentrations of ethanol (20-60%) and soya lecithin (1-5%). *In-vitro* release studies of formulation containing 30% ethanol and 3% soya lecithin showed highest % drug release (82.66%) with highest transdermal flux.The entrapment efficiency and drug content of optimized formulation were found to be 85.32% and 99.5% respectively. Scanning Electron micrographs revealed that the formed vesicles were spherical in shape with uniform size. It was also observed that concentration of the ethanol had profound influence on entrapment efficiency. The drug release from the formed vesicles was found to follow first order kinetics with higuchi diffusion mechanism. The transdermal delivery of finasteride could be potentially enhanced when they were formulated into ethosomes. This ethosomal drug delivery was found to be promising than could be a nanogel.

Keywords: *Finasteride, ethosomes, Scanning electron microscopy, transdermal delivery, Zeta potential.*

Introduction

As compared with the oral drug delivery system, transdermal drug delivery system provides various advantage such as inhibits the gastrointestinal side effects, removes the first pass metabolism of the oral drugs etc. However, the transdermal drug delivery system also suffers with the one major limitation i.e. the stratum corneum; a layer of the skin forms the barrier for the permeation of various drugs and it allows only the permeation of lipophilic drugs or the drugs, which have molecular weight less than 500 Dalton (Gangwar et al., 2010; Kumar et al., 2010).Transdermal drug delivery system (TDDS) showed promising result in comparison to oral drug delivery system as it eliminates gastrointestinal involvement and first pass metabolism of the drug.The skin acts as a major target as well as a principle barrier for topical/ transdermal drug delivery. Stratum corneum (SC) permits only the lipophilic drugs having molecular weight < 500 daltons [1] and acts as a barrier. Many approaches have been attempted to overcome this property of skin,

includes the use of chemical enhancers like surfactants, organic solvents, physical enhancers such as iontophoresis, sonophoresis, microneedles, electroporation etc. and various methods have been assessed to increase permeation and amongst them the best is lipid vesicles can modulate barrier property of SC [2,3]. Vesicles act as carrier systems, able to transport large molecular weight drugs into the skin or even into the systemic circulation [4].Conventional liposomes have been generally reported as carriers of drugs with minimal diffusion into deeper tissues, due to their large size and lack of flexibility [5,6]. After meticulous research over the decades led to the development of a new class of lipid vesicles that are shows ultra-elastic property and were considered as ethosomes. Touitou *et al*., (1998) discovered lipid vesicular systems embedding

ethanol in relatively with higher concentration [7]. Ethosomes are surfactants and water [8]. These were show augmented permeation through the skin due to the escalated fluidity of SC lipids [9,10].Further, due high flexibility of ethosomal membranes by excessethanol, these are squeezed into the skin their self through pores,became much smaller than their actual size. Ethosomes are soft,flexible vesicles and considerable dosage forms can efficiently load higher quantities of drug, permeate in depth to the skin than conventional liposomes [11-13].

Finasteride is a type-II 5α-reductase inhibitor, *N*-(1,1-dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene, (5α, 17β)carboxamide [14] and is used in the treatment of androgenicalopecia and as surgical alternative for benign prostatic hyperplasia.The oral bioavailability of finasteride is 65%, mean half-life is 4.5 hand 8h in men 18-60 and 70 years of age respectively. In this study,transdermal drug delivery system of ethosomes was designed and developed with finasteride. Effects of various excipients on the incompatibility, entrapment efficiency, drug release, percutaneous absorption, stability studies were evaluated.

Material and Method

Losartan Potassium was attained as a gift sample from Mepro Pharmaceutical Ltd Ahmedabad, India. Soya lecithin, ethanol, Tween80 and propylene glycol were purchased from Sigma Aldrich Chemie, USA, Eudragit RS100 and Eudragit RL100 was obtained as a gift sample from Evonik industries, India. Methocell K 100M was obtained as a gift sample from Colorcon Goa, India. All other reagents and solvents were of Analytical grade. Distilled water was used throughout the study.

3.3.1. Preparation of Losartan Potassium loaded Ethosomes

Ethosomes were prepared by the method which is described by Touitou et al. To prepare ethosomes all ingredients were weighed in different concentration ratio as described in Table 3.3. Firstly, the drug and soyalecithin were dissolved in ethanol and propylene glycol and then it was placed on magnetic stirrer with continuous stirring at 700rpm at a temperature of 30°c. Then add distilled water as a fine stream to the above solution in a closed vessel. The mixture is stirred untill a milky white suspension was formed. The prepared ethosomes were subjected to the probe sonication at 4°c in 3 cycles of 5 minutes and 5 minute rest between

each cycle (for total 15min). The prepared ethosomes was stored in vials in refrigerator at 4°C until use for further characterization. Composition of Losartan potassium loaded ethosomes is tabulated in **Table 3:**

Composition of Losartan potassium loaded ethosomes

Material	EF 1	EF 2	EF 3	EF 4	EF 5	EF 6	EF 7	EF 8
Losartan Potassium (%w/w)	1	1	1	1	1	1	1	1
Soyalecithin (%w/w)	2	2	2	3	3	3	4	4
Ethanol (%w/w)	30	35	40	30	35	40	30	35
Propylene glycol (%w/w)	1	1	1	1	1	1	1	1
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Preparation of ethosomal patch

To prepare the ethosomal patch firstly the polymer Eudragit RL 100 and methocell K100M in the ratio 1:2 were dissolved in Methanol: di chloro methane DCM ratio 1:1 with continuous stirring on magnetic stirrer for 1 hour. Then add 5 ml of losartan potassium loaded ethosome to the swollen polymer under continuous stirring at 1000rpm for half hour then add glycerin to enhance the permeation of the patch. Then the resulting solution was poured on to the glass petri dish and spread the solution uniformly on plate. The petri dish was kept at room temperature for 12 hour to dry the patch. The dried patches were stored in Aluminium foil for further characterization.Same procedure was followed for the polymer Eudragit RS 100.

Characterization of ethosomes

Particle Size, Polydispersity index (PDI) and Zeta Potential

Particle size and size distribution were determined by using malvern zeta sizer nano ZS which is based on the principle of dynamic light scattering (DLS). For the measurement of size and size distribution the sample were diluted 1 in 10 ml with Phosphate buffer saline (PBS) 6.8. Measurements were carried out at 25 °C. PDI determines the size distribution pattern of the particles present in the ethosomal suspension. PDI value near to 0.45 indicates that the particle show homogeneous or narrow distribution. By using the principle of phase analysis light scattering (PALS) and Doppler velocimetry by malvern zeta nano ZS Zeta potential was determined. In this system, a current is applied across a pair of electrodes at either end of a cell containing the particle dispersion. Particles thus get charged and attracted to the oppositely charged electrode and their velocities are measured. Zeta potential values away from -30mV or + 30mV are considered as a stable formulation (Ravi et al.,

2012).

Result and Discussion

Particle Size, Polydispersity index (PDI) and Zeta Potential

The particle size and polydispersity index (PDI) were determined malvern zeta sizer nano ZS and the results were show in **Table 3.5**. All the formulation shows a particle size ranging from 112.2±1.3 to 288.1±1.2 with PDI ranging from 0.219±0.5 to 0.456±0.7. Formulation EF 1 to EF 3 with constant soyalecithin concentration (2%) and increased ethanol concentration show a particle size of 143.2±1.2, 168.03±0.8,230.2±1.0 with PDI of 0.333±0.2, 0.412±0.6, 0.456±0.5. Formulation EF 4 to EF 6 with constant soyalecithin concentration i.e. 3% and increased ethanol concentration from 30 % to 40% show a particle size of 122.6±1.2 nm, 112.2±1.3 nm and 204.6±1.6 nm with PDI of 0.383±0.6, 0.456±0.7, 0.263±0.5 whereas formulation EF 7 and EF 8 with high soyalecithin concentration i.e. 4% show a particle size of 288.1±1.2 nm and

225.6±1.8 nm with PDI of 0.284±0.4 and 0.245±0.9**.** Zeta potential helps to determine the stability of the ethosomes which was determined by using Phase analysis light scattering principle in malvern zeta sizer. The results of zeta potential were shown in Table 3.3. Formulation EF 1 to EF 3 with constant soyalecithin concentration i.e. 2% and increased ethanol concentration shows a zeta potential value of -36±0.9 mV, -42±0.6 mV, -35±0.7 mV. Formulation EF 4 to EF 6 with constant soyalecithin concentration i.e. 3% and increased ethanol concentration show a zeta potential of -48±0.5 mV, -59±0.8 mV and -32±0.1 mV whereas formulation EF 7 and EF 8 with highest soyalecithin concentration show a zeta potential value of -29±0.2 mV and -27±0.6 mV. The results obtained from the particle size, PDI and zeta potential shows that particle size gets decreased when ethanol concentration was increased upto 35 % but on further increasing the ethanol concentration i.e. 40 % a decrease in the particle size was observed, same was observed in case of zeta potential value that on increasing the ethanol concentration after 40 % thus results in decreased in zeta potential value indicating that the formulation will not remain stable for longer duration of time.Further it was also observed that particle size decreased when soyalecithin was usedin the 2 % concentration but on increasing the soyalecithin concentration i.e. 3% and

4% an increase in particle size was seen similarly in case of zeta potential values.Among all the formulation EF 5 with optimum concentration of lipid (3%) and ethanol (35%) was considered as an optimized formulation. The results were found according to the results obtained by Ravi et al., 2012.

Table 5: Characterization of Losartan potassium loaded ethosomes

Characterization	EF 1	EF 2	EF 3	EF 4	EF 5	EF 6	EF 7	EF 8

Particle size (nm)	143.2±1.2	168.03±0.8	230.2±1.0	122.6±1.2	112.2±1.3	204.6±1.6	288.1±1.2	225.6±1.8
PDI	0.333±0.2	0.412±0.6	0.219±0.5	0.383±0.6	0.456±0.7	0.263±0.5	0.284±0.4	0.245±0.9
Zeta potential (mV)	-36±0.9	-42±0.6	-35±0.7	-48±0.5	-59±0.8	-32±0.1	-29±0.2	-27±0.6

Conclusion

Ethosomes have the capability to entrap both the lipophilic and hydrophilic drug. In this work ethosomes were prepared by the method described by Touitou, firstly lipid and drug was dissolved in ethanol and propylene glycol on a magnetic stirrer with continuous stirring and then distilled water was added in a fine stream and the mixture was kept on stirring untill the milky suspension was obtained and then the prepared ethosomes were subjected to probe sonication to reduce the size of the vesicles.Losartan potassium (LP) is an angiotensin II receptor antagonist used for the treatment of hypertension. The drug Posses extensive first-pass metabolism i.e. 67% and has a biological half-life of 2hr which is very short and requires a higher dose frequency which makes it an ideal candidate for the transdermal drug delivery system.In the first study, ethosomes were prepared by varying the concentration of lipid and ethanol then the prepared ethosomes were incorporated into the Eudragit RS 100 and Eudragit RL 100 patch. The most noteworthy finding of the research work was the precise particle size, zeta potential, high encapsulation of drug and maximum release of drug in 72 hr. Prepared transdermal patch show low moisture content with maximum effect in the *in-vivo* study and maximum stability at 4oC /60±5RH. The optimized Eudragit RL 100 ethosomal patch show maximum effect for the treatment of hypertension. The results obtained from this research work were safe, effective and efficient for the transdermal delivery of losartan potassium. Based on this work, furthermore work is needed to bring ethosomal transdermal patch into its clinical realization.

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