Formulation and evaluation of losartan potassium ethosomal gel

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ABSTRACT

Clinically liposomal systems were found to be effective, at forming drug reservoir in the upper layers of the skin for local skin therapy. Recently, it was found that Ethosomal carriers were phospholipid vesicular systems having relatively high concentrations of alcohol, enhances dermal and transdermal delivery of both lipophilic as well as hydrophilic molecules. In the present work Ethosomal gels loaded with Losartan Potassium were designed to improve the patient compliance by reducing the frequency of dosing and the adverse drug reactions of Losartan Potassium. A novel vesicular carrier i.e. Ethosomes containing Losartan Potassium using different concentrations of ethanol and Soy lecithin by cold method, caused its size reduction by sonication. Potassium is a potent anti-hypertensive drug (Angiotensin II (AT1) receptor blocker) and a hydrophilic agent has limited transdermal permeation. In the cold method; lecithin was used as the vesicle forming agent and Poly glycol, Ethanol were used as skin permeation enhancers. The size of the ethosomes was optimized by varying the concentration of lecithin and ethanol. The prepared ethosomes were evaluated for compatibility with the excipients, vesicular size, shape, entrapment efficiency, stability, skin irritation; wash ability, optimum pH, drug content, uniformity and in-vitro drug permeation. Microscopic examinations suggested that ethosomes are soft, malleable and spherical vesicles with a smooth surface. Among the formulations, the EF4 containing 3% lecithin and 30% ethanol emerged to be the overall best formulation based on the *in-vitro* drug release. Skin irritation study revealed that the system is free of irritation.

Key words: Ethosomes, Losartan potassium, gel.

1. INTRODUCTION

Losartan potassium is best suitable for the treatment of hypertension through oral administration and it has adverse effects like allergic reactions, dizziness, palpitation, shortness of breath etc. In ethosomal system the adverse reactions can also be reduced by the use of penetration enhancers, by improving the skin permeation properties.

Objective: To design Ethosomal gel containing Losartan potassium using ethanol and phospholipid by cold method, sonication for size reduction of vesicles. It is best suitable for the treatment of hypertension. It has some limitations of high dose (25-100mg) due to its poor intestinal absorption (30-35%), elimination half-life (2-2.5 hours).

2. EXPERIMENTAL METHODS

Analytical methods: Scanning of model drug (Losartan potassium), preparation of pH 6.8 phosphate buffer and preparation of calibration curve.

Preparation of losartan potassium ethosomes (by cold method[1]): 100mg of Losartan Potassium was dissolved in 6ml of water in a vessel and cholesterol was added to it with vigorous stirring. Propylene glycol was also added during stirring. The contents were heated to 30^{o}C. In another closed vessel, soy lecithin was dissolved in ethanol with continuous stirring and heated to 30^{o}C. When both the solutions reached to same temperature slowly ethanol solution was added drop wise in the center of vessel containing drug mixture. Then the stirring was continued for another 10min in a covered vessel. Water was added to adjust the volume to 20ml. The vesicle size of ethosomal formulation can be decreased to desire extent using sonication[2] or extrusion method. Finally, the formulation was stored under refrigeration. Ethosomes were formed spontaneously by this process.

The best achieved Ethosomal vesicle suspension formula EF4 was incorporated into Carbapol gel of (1.5%). The specified amount of Carbapol-934 powder was slowly added to pure water and kept at 100^{0}c for 20min. Triethanolamine was added to it drop wise. Appropriate amount of formula EF4 containing Losartan Potassium was then incorporated into gel-base. Sufficient water was finally added with other formulation ingredients with continuous stirring until homogenous formulation was achieved.

Composition of different Ethosomal formulations:

Table.1. Formulation table of Ethosomal formulation

Ethosomal Formulation (EF)	Lecithin (mg)	Propylene Glycol (mg)	Ethanol (mg)	Cholesterol (mg)	Drug (mg)	Water (mg)
EF1	2	10	20	0.05	100	Q.s
EF2	3	10	20	0.05	100	Q.s
EF3	4	10	20	0.05	100	Q.s
EF4	3	10	30	0.05	100	Q.s
EF5	3	10	40	0.05	100	Q.s
EF6	3	10	50	0.05	100	Q.s
EF7	-	10	30	0.05	100	Q.s

Characterization of ethosomal gel: The gel is characterized for surface morphology, organoleptic characters, wash-ability, spread-ability, pH measurement, drug content and drug uniformity, skin irritation test and skin permeation studies were performed and in-vitro kinetics were reported.

3. RESULTS AND DISCUSSION

Ethosomal suspension was slightly yellowish in color which are non-greasy and smoothly applied has spread-ability of 6.25cm/s. The shape of the ethosomes was nearly spherical. The average diameter of optimized formulation (EF_4) was 5.062micrometers. The entrapment efficiency of EF4 was 79.62%. Ethosomes (EF4) containing 30%w/w shown the drug release of 75.62% in 1440min

In – vitro cumulative % drug release profile for Losartan Potassium Ethosomes:

Table.2. In – vitro cumulative % drug release profile for Losartan Potassium Ethosomes

	Cumulative % drug release								
Time	**EF1**	**EF2**	**EF3**	**EF4**	**EF5**	**EF6**	**EF7**	**EF4G2**	**F4G4**
0	0	0	0	0	0	0	0	0	0
30minutes	14.52	17.5	12.09	18.09	11.39	10.01	11.21	17.82	8.46
2hours	25.62	31.52	23.26	32.51	20.21	18.09	23.62	22.31	15.31
4 hours	30.1	38.3	28.21	39.42	25.22	22.31	29.72	28.81	19.71
6 hours	33.08	42.52	32.71	46.42	30.09	27.69	33.32	32.71	23.04
8 hours	38.62	47.81	37.21	49.31	36.21	30.03	37.29	37.61	25.31
10 hours	40.07	54.32	39.05	56.51	37.02	33.61	40.25	41.62	28.32
12 hours	43.62	58.5	43.02	60.41	42.3	37.32	47.91	46.32	33.13
14 hours	49.3	61.32	48.05	63.21	46.31	40.65	52.41	50.02	37.04
16 hours	52.41	64.92	51.51	66.72	49.85	43.32	52.56	57.42	39.21
18 hours	59.32	69.07	58.37	71.46	57.31	48.32	52.56	60.21	40.32
20 hours	66.02	75.41	66.42	76.32	65.21	52.09	52.56	66.32	43.01
22 hours	70.52	78.2	70.31	82.31	68.71	56.31	52.56	72.02	45.32
24 hours	76.89	82.31	73.62	86.42	72.09	63.21	52.56	75.62	47.62

EF4 - optimized ethosomal suspension formulation; EF7- free drug solution; EF4G2-optimized ethosomal gel formulation; F4G4-Ethosomal gel formulation with free drug

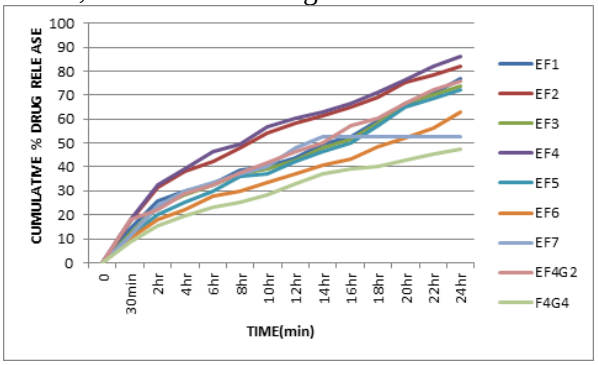

Figure.1. Dissolution profile of Losartan Potassium Ethosomes

4. CONCLUSION

By encapsulating Losartan potassium into ethosomes the frequency of dosing can be reduced as they cause the delivery of drug for almost 24hrs. Finally, it can be said that many drugs such as NSAIDS, anti HIV agents, etc have the scope to be incorporated into ethosomes and thereby enhancing their activity.

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