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FORMULATION AND INVITRO EVALUATION OF ETHOSOMAL GELS CONTAINING POSACONAZOLE AS THE MODEL DRUG

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ABSTRACT

The method described by Touitou et al., (2000) was employed with little modification for the preparation of various ethosomal formulations containing different concentration of ethanol (30 % to 50 %) with sonication . The techniques used were simple and reproducible. The prepared ethosomes were spherical and discrete in shape. However ethosomes prepared by sonication method were more uniform and small in size which is essential for skin penetration. While comparing the entrapment efficiency, ethosomes containing 30% w/w ethanol and prepared by soncation showed highest value respect to all other formulation; so it is concluded ethosomal prepared by sonication and containing 30 % w/w IPA as the best formulation considering all other aspects Increase in the polymer concentration led to increase in, % Drug entrapment efficiency, Particle size. The *invitro* drug release decreased with increase in the polymer and copolymer concentration.Among all formulations P6 shows Maximum drug release in 1440 min when compared with other formulations. Analysis of drug release mechanism showed that the drug release from the formulations followed the Non fickian diffusion mechanism and follows First order kinectics.Based on the results of evaluation tests formulation coded P6 was concluded as best formulation.

KEY WORDS: Ethosomes , Sonication , Transdermal ,Entrapment , Stability

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INTRODUCTION

Optimization of drug delivery through human skin is important in modern therapy. Recently, the transdermal route vied with oral treatment as the most successful innovative research area in drug delivery.Transdermal delivery is an important delivery route that delivers precise amount of drug through the skin for systemic action. Improved methods of drug delivery for biopharmaceuticals are important for two reasons; these drugs represent rapidly growing portion of new therapeutics, and are most often given by injection. Discovery of new medicinal agents and related innovation in drug delivery system have not been only enabled the successful implementation of novel pharmaceutical, but also permitted the development of new medical treatment with existing drugs. Throughout the past two decades, the transdermal patches has become a proven technology holding the promise that new compound could be delivered in a safe and convenient way through the skin. Since the first transdermal patch was approved

in 1981 to prevent nausea and vomiting associated with motion sickness, the FDA has approved through the past 22 years more than 35 transdermal patch products spanning 13 molecules. Transdermal route offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, and most importantly, it provides patient convince. But one of the major problems in transdermal drug delivery is the low penetration rate through the outer most layer of skin. Liposomes were discovered in the early 1960's by Bangham and colleagues and subsequently became the most extensively explored drug delivery system. In early 1960's a great knowledge of vesicle derivatives have been tested for their abilities. Most experiments, however, have centered on liposomes, since derivations only add to their basic properties. Vesicles are closed, spherical membrane that separate a solvent from the surrounding solvent. Possible use of liposomes in topical drug delivery vehicles for both water and lipid soluble drug has been investigated. While it has been suggested that the external envelop of a liposomes would allow it to pass through lipophilic skin, most researches show that liposomal vesicles become trapped within the top layer of the stratum corneum cells2. Generally liposomes are not expected to penetrate into viable skin, although occasional transport processes were reported1. This behavior is useful both for local treatment of skin disorders and for cosmetic formulations. Specific drug accumulation at the site of action and decreased systemic drug absorption can impart increased efficiency as well as decreased side effect to a compound applied topically (1-5).

The increasing need to deliver medication to patients efficiently with fewer side effects and improved compliance has accelerated the pace of invention of new drug delivery system. Revolutionary drug delivery technology is extended to transdermal route apart from oral. The ability to increase the transdermal permeation can be valuable aid when oral administration of drug is associated with problems. Hence there is a need to modify route of administration for better absorption of the drug. The transdermal route of administration may be better suited. Transdermal penetration of Posaconazole cannot be increased by niosomes or liposomes because of its size and rigid character of lipid layer. Recent advancement to increase permeation by reducing the size of carrier and making the lipid layer malleable gave novel drug carrier "Ethosomes" which has shown its effectiveness to increase skin penetration of drugs to several folds then that of simple cream, liposomal carrier and hydroalcoholic solutions[8] .Hence there is a need for preparation of Posaconazole ethosomes for enhanced penetration through the skin, thereby reducing dose, minimizing frequency of administration and adverse affects, hence better patient compliance. These advantages of Posaconazole ethosomal gel includes avoidance of first pass metabolism, predictable and extended duration of action, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in the blood levels, and most important, it provides patient convenience.

MATERIALS AND METHODS

Preparation of Posaconazole Ethosomes (By Cold Method)

Preparation of Posaconazole ethosomes was followed by method suggested by Touitou et al., with little modification. The ethosomal system of Posaconazole comprised of 3-5 % phospholipids, 30-50 ml Ethanol, 2ml of propylene glycol, 0.01g of cholesterol and aqueous phase to 100 % w/w. Posaconazole 2g was dissolved in IPA in a covered vessel at room temperature by vigorous stirring (Table-1). Propylene glycol was added during stirring. This mixture was heated to 30^0 in a separate vessel and was added to the mixture drop wise in the center of the vessel, which was stirred for 5min at 700rpm in a covered vessel the vesicle size of ethosomal formulation can be decreased to desire extend using sonication or

extrusion method. Finally, the formulation is stored under refrigeration .Ethosomes were formed spontaneously by the process (6-8)

Table -1 Composition of different ethosomal formulations

Ethosomal formulation	Lecithin (Soya lecithin%)	Ethanol (ml)	PEG (ml)	Drug (g)	Cholesterol(g)	Water
P_1	3ml	30ml	2ml	2g	0.01g	100ml
P_2	4ml	30ml	2ml	2g	0.01g	100ml
P_3	5ml	30ml	2ml	2g	0.01g	100ml
P_4	3ml	40ml	2ml	2g	0.01g	100ml
P_5	4ml	40ml	2ml	2g	0.01g	100ml
P_6	**5ml**	**40ml**	**2ml**	**2g**	**0.01g**	**100ml**
P_7	3ml	50ml	2ml	2g	0.01g	100ml
P8	4ml	50ml	2ml	2g	0.01g	100ml
P9	5ml	50ml	2ml	2g	0.01g	100ml

Preparation of Posaconazole ethosomal gel

The best achieved ethosomal vesicles suspension, was incorporated into carbopol gel (1%, 1.5%, 2% w/w).The specified amount of carbopol 934 powder was slowly added to ultrapure water and kept at 100^0c for 20min. tri ethanolamine was added to it drop wise. Appropriate amount of formula P-6 containing Posaconazole (1.5% w/w was then incorporated into gel-base. Water q.s was added with other formulation ingredients with continuous stirring until homogenous formulation were achieved (G-1, G-2 and G-3). Gel containing free Posaconazole was prepared by similar method using 1.5% carbopol (Table-2).

Table-2 Composition of different ethosomal gel formulation

Gel formulation	Posaconazole ethosomal suspension(ml)	Carbopol 934(%)	Triethanolamine (ml)	Phosphate buffer (pH 6.8)
G-1	20ml	1	0.5	q.s
G-2	**20ml**	**1.5**	**0.5**	**q.s**
G-3	20ml	2	0.5	q.s

***In-Vitro* Release Studies**

Drug Release Study from Dialysis Membrane

The skin permeation of Posaconazole from ethosomal formulation was studied using open ended diffusion cell specially designed in our laboratory according to the literates. The effective permeation area of the diffusion cell and receptor cell volume was 2.4 cm and 200 ml respectively. The temperature was maintained at 37 ± 0.5°C. The receptor compartment contained 200 ml of pH 6.8 buffer and was constantly stirred by magnetic stirrer at 100 rpm. Prepared dialysis was mounted between the donor and the receptor compartments. Ethosomal formulation was applied to the dialysis membrane and the content of diffusion cell was kept under constant stirring then 5 ml of samples were withdrawn from receptor compartment of diffusion cell at predetermined time intervals and analysed by spectrometric method at 260

nmafter suitable dilution. The receptor phase was immediately replenished with equal volume of fresh pH 6.8 buffer. Triplicate experiments were conducted for drug release studies (9).

RESULTS AND DISCUSSION

Ethosomal formulations composed of phospholipid, drug and ethanol were prepared using the method detailed in last chapter materials and methods and also according to literature with little modification. Ethosomal suspension obtained with sonication were slight yellowish in colour and hazy in appearance. Different characteristics of ethosomes and the effect of sonication were further evaluated and results are reported under the characterization (Fig-1).

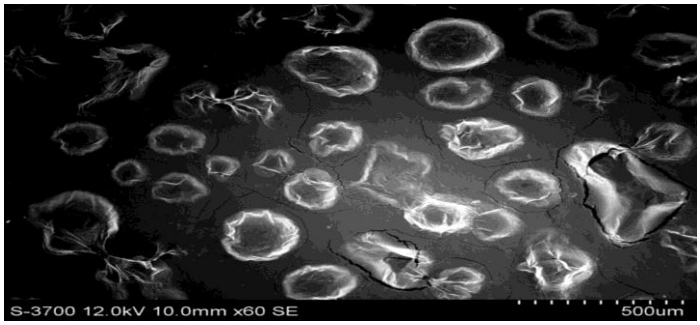

Fig-1 Scanning electron microscope image

The maximum entrapment efficiency of ethosomal vesicles as determined by ultracentrifugation was 87.2% for ethosomal formulation containing 40% ethanol (F6).As the ethanol concentration increased from 30% to 50% w/w, there was increase in the entrapment efficiency and with further increase in the ethanol concentration (>40% w/w) the vesicle membrane becomes more permeable that lead to decrease in the entrapment efficiency. Results of entrapment efficiency also suggest that 5% phospholipid is optimal concentration for entrapment efficiency and hence increased or decreased in concentration of phospholipid reduces the entrapment efficiency of vesicles (Table-3).

Table-3 Drug entrapment efficiency of Posaconazole Ethosomal Gel

Formulation code	Entrapment efficiency(%)
P1	72.0
P2	76.7
P3	78.4
P4	79.8
P5	81.2
P6	87.2
P7	80.1
P8	83.6
P9	84.2

From the table-4, it was confirmed that the P4, P5, P6, P7, P8, and P9 of ethosomal gel release theory up to 24 hrs. And also from the table, it was also confirmed that the formulation (P6) showed maximum drug release up to 24hrs (Fig-2).

Table-4 *In-vitro* cumulative % drug release profile for Posaconazole Ethosomes

Time (hrs)	P1	P2	P3	P4	P5	P6	P7	P8	P9
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
0.08	30.7	4.2	6.52	3.5	6.47	6.2	4.8	3.16	2.4
0.16	48.4	15.06	12.9	8.2	14.6	16.5	11.09	10.1	9.8
0.25	60.47	24.2	28.6	17.9	23.1	28.4	27.4	26.7	25.9
0.5	67.1	32.04	42.4	29.4	36.8	42.1	34.14	33.3	32.01
1	78.1	67.5	62.2	36.01	42.6	56.2	41.7	38.8	35.68
2	86	84.1	75.3	49.2	58.5	62.7	54.5	50.2	49.2
4	100.1	93.2	89.4	56.1	66.9	68.6	62.7	59.8	57.5
6		100	100.9	62.77	72.5	73.4	69.8	68.4	64.7
12				72.4	79.2	86.6	76.2	73.3	71.8
24				76.9	89.4	95.2	89.12	79.9	76.9

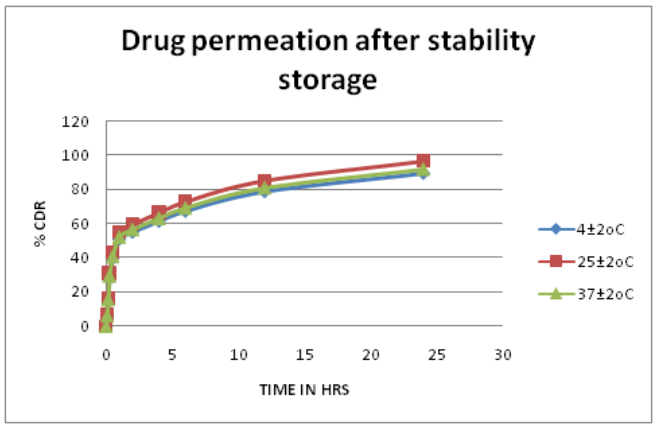

Fig-2 Graph showing dissolution profile for formulations P6 after storage at different temperatures

CONCLUSION

The results of this investigation indicate that Ion gelation method can be successfully employed to fabricate Posaconazole acids ethosomal gels. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymer used. Ethosomal gels containing carbopol and ethanol and phospholipids had a least size range of 613µm. Increase in the polymer concentration led to increase in, % Drug entrapment efficiency, Particle size. The *invitro* drug release decreased with increase in the polymer and copolymer concentration. Among all formulations P6 shows Maximum drug release in 1440 min when compared with other formulations. Analysis of drug release mechanism showed that the drug release from the formulations followed the Non fickian diffusion mechanism and follows First order kinectics. Based on the results of evaluation tests formulation coded P6 was concluded as best formulation

REFERENCES

1. Barry BW. Novel mechanism and devices to enable successful transdermal drug delivery. *European J Pharm Sci* 2004; 14: 101 - 114.

2. Jain N, Talegonkar S, Jain NK. New ways to enter the blood stream: Emerging strategies in transdermal drug delivery. *The Pharma Review*. Sep - Oct 2004; 41-60.
3. Jain NK. *Advances in controlled and novel drug delivery*. 1ed, New Delhi: st CBS publication; 2001; 428 - 451.
4. Jain S, Bhandra D, Jain S and Jain NK. *Transfersomes- A novel carrier for effective transdermal drug delivery. Controlled and novel drug delivery* 1 st Edition. CBS publishers and distributors new Delhi 1997: 426 - 451.
5. Vyas SP, Khar RK. *Controlled drug delivery concepts and advances*. Vallabh prakashan New Delhi. First Edition 2002: 173 - 243.
6. Spotswood LS, Clyde SC, Lowell SE, Earn RK, Steve M and Kenneth AA. . Antimicrob *Agent Chemother* 1984 May ; 25 (5): 553 - 555.
7. Shaw M, King Mary, Jannifer MB, Banatvala JE, John RG and Michael RK. Failure of acyclovir cream in treatment of recurrent herpes labialis. *Brit Med J* 1985 July; 291: 7 - 9.
8. Freeman DJ, Sheth NV and Spotswood LS. Failure of carvedilol Ointment to penetrate Human skin. *Antimicro Agent Chemother* 1986 May; 29 (5) : 730 - 732.
9. Spruance SL, Freeman DJ and Sheth MV. Comparison of foscarnet cream, Acyclovir cream, and acyclovir oitment in the topical treatment of experimental cutaneous Herpes simplex virus Type 1 infection. *Antimicrob Agent chemother* 1986 July; 30 (1); 196 - 198.