INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

FORMULATION AND INVITRO EVALUATION OF OXICONAZOLE TOPICAL ETHOSOMAL GEL

CH.N.V.Durga*, M.Sneha, CH.Parvathi, K.Venkateshulu, K.Syambabu

Department of Pharmaceutics, JITS College of Pharmacy, Kalgampudi, Andhra Pradesh,India.

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 (20 % to 50 %) with sonication . The techniques used were simple and reproducible. The prepared ethosomes were spherical and discrete in shape. Howeverethosomes prepared by sonication method were more uniform and small in size which is essential for skin penetration. While comparing the entrapment efficiency, ethosomes containing 20% 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 20 % w/w ethanol as the best formulation considering all other aspectsIncrease in thepolymerconcentrationledto increase in,%Drugentrapment efficiency, Particle size. The *invitro* drug releasedecreased with increase in thepolymer and copolymerconcentration.Among all formulations F2 shows Maximum drug release in 1440 min when compared with other formulations.Analysis ofdrug release mechanism showedthatthedrug release fromthe formulations followed the Non fickian diffusion mechanism and follows zero order kinectics.Based on the results of evaluation tests formulation codedF2 was concluded as best formulation.

Key Words: Ethosomes , Sonication , Transdermal ,Entrapment , Stability

Author for correspondence
CH.N.V.Durga,
Department of Pharmaceutics,
JITS college of Pharmacy,
Kalgampudi, Andhra Pradesh, India.
Email id: chinthadurga1994@gmail.com.

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 [1].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 [2].The vesicles have been well known for their importance in cellular communication and particle transportation for many

years. Researchers have understood the properties of vesicle structures for use in better drug delivery within their cavities, that would allow to tag the vesicle for cell specificity. Vesicles would also allow to control the release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and would be able to release just the right amount of drug and keep that concentration constant for longer periods of time. One of the major advances in vesicle research was the finding a vesicle derivative, known as an ethosomes.Ethosomal carriers are systems containing soft vesicles and are composed mainly of phospholipid (Phosphotidyl choline; PC), ethanol at relatively high concentration and water. It was found that ethosomes penetrate the skin and allow enhanced delivery of various compound to the deep strata of the skin or to the systemic circulation [3, 4].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 Oxiconazole 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 Oxiconazole ethosomes for enhanced penetration through the skin, thereby reducing dose, minimizing frequency of administration and adverse affects, hence better patient compliance. These advantages of Oxiconazole ethosomalgel 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 Oxiconazole Ethosomes (By Cold Method)

Preparation of Oxiconazole ethosomes was followed by method suggested by Touitou et al., with little modification [5,6].The ethosomal system of Oxiconazole comprised of 2-4 % phospholipids, 20-40 % isopropyl alcohol, 10 % of propylene glycol, 0.005g of cholesterol and aqueous phase to 100 % w/w. Oxiconazole 0.10 g was dissolved in IPA in a covered vessel at room temperature by vigorous stirring. 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[29] or extrusion[30] method. Finally, the formulation is stored under refrigeration[7].

Preparation of Oxiconazole 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 IF-2 containing Oxiconazole (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 Oxiconazole was prepared by similar method using 1.5% carbopol.

Table-1 Composition of different ethosomal gel formulation

Gel formulation	Oxiconazole 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

Drug Release Study from Dialysis Membrane

The skin permeation of Oxiconazole 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 210 nm after 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 [8].

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.Microscopic analysis was performed under different magnification to visualize the vesicular structure, lamellarity and to determine the size of ethosomal preparations (Fig-1).

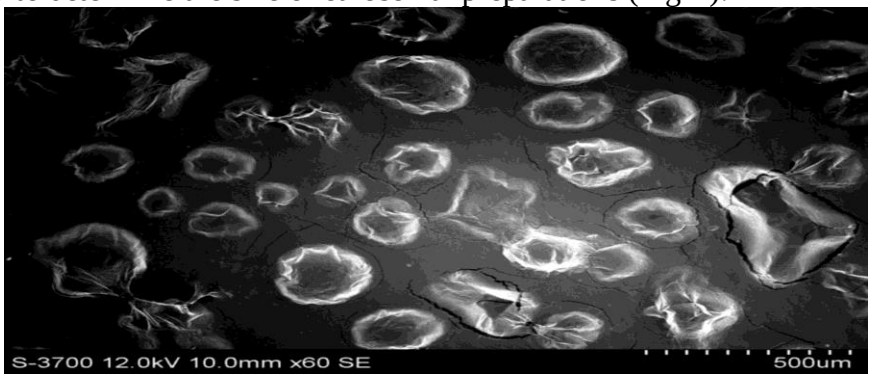

Fig-1 Scanning electron microscope image

The maximum entrapment efficiency of ethosomal vesicles as determined by ultracentrifugation was 87.4% for ethosomal formulation containing 40% ethanol (F9).As the IPA concentration increased from 20% to 40% 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 4% phospholipid is optimal concentration for entrapment efficiency and hence increased or decreased in concentration of phospholipid reduces the entrapment efficiency of vesicles.From the table-2, it was confirmed that the F1, F2, F3, F4, F6, F7 of ethosomal gel release theory up to 24 hrs. And also from the table, it was also confirmed that the formulation (F6) showed maximum drug release up to 24hrs.

Table- 2In-vitro cumulative % drug release profile for OxiconazoleEthosomes

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.08	39.6	3.6	4.57	0.75	5.42	6.26	3.6	2.31	1.46
0.16	53.3	10.08	11.8	6.26	13.5	15.95	10.08	9.42	8.4
0.25	60.44	25.2	26.04	19.68	27.15	30	25.2	24.4	22.97
0.5	67.1	32.04	33.02	28.48	35.68	41.68	32.04	31.24	30.01
1	77.3	75.5	67.1	33.02	41.68	53.3	38.7	37.02	35.68
2	89.3	87.11	77.3	42.6	55.5	57.7	52.4	49.7	47.1
4	100.2	92.6	89.3	49.7	62.22	64.4	58.6	55.5	53.5
6		100.8	100.9	57.77	68.5	70.6	65.7	64.4	62.22
12				67.1	78.2	82.6	75.5	73.3	70.6
24				72.44	88.4	93.7	87.11	78.2	75.5

The stability studies were carried out according to the procedure described in the section of chapter. The results are shown in the fig-2.

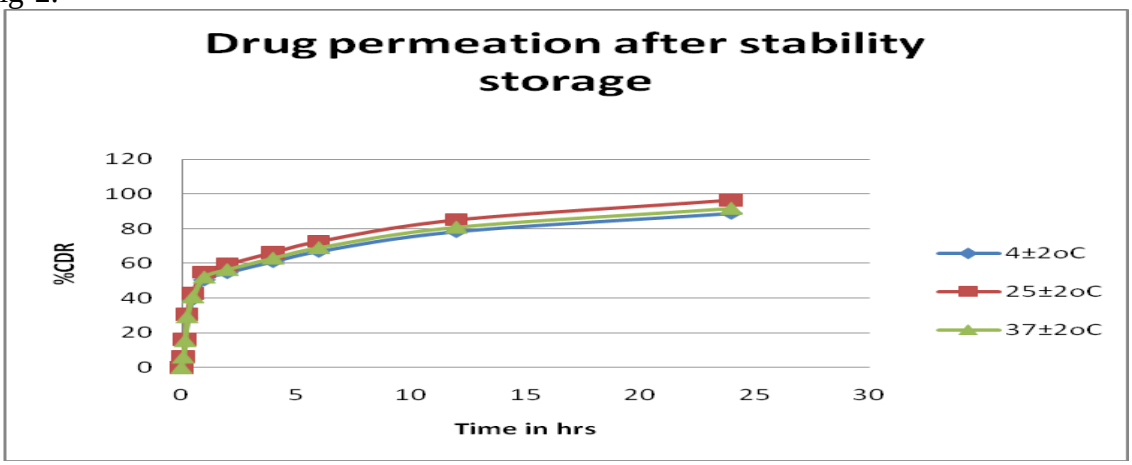

Fig-2 Graph showing dissolution profile for formulations F6 after storage at different temperatures

CONCLUSION

The results of this investigation indicate that Ion gelation method can be successfully employed to fabricate Oxiconazole acids ethosomal gels. FT-IR spectraof the physical mixture revealed thatthedrug 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 thepolymerconcentrationledto increase in,%Drugentrapment efficiency, Particle size. The *invitro* drug releasedecreased with increase in thepolymer and copolymerconcentration.Among all formulations F2 shows Maximum drug release in 1440 min when compared with other formulations.Analysis ofdrug release mechanism showedthatthedrug release from the formulations followed the Non fickian diffusion mechanism and follows zero order kinectics.Based on the results of evaluation tests form ulation codedF2 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. Tuitou E, Godin B, and Weiss C. Enhanced delivery into and across the skin by Ethosomal carriers. Drug
7. Dev Research 2000; 50; 406 - 445.
8. Tauitou E, Dayan N, Bergelson L, Godin B and Eliaz M. Ethosomes – novel vesicular carrier for enhanced delivery: characterization and skin penetration properties. J Con Release 2000; 65: 403 - 418.
9. Jain S, Umamaheshwari RB, Bhadra D and Jain NK. Ethosomes: A novel vesicular carrier for enhances transdermal delivery of a Anti HIV agent. Indian J Pharm Sci 2004; 66 (1): 72 - 81.