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DESIGN AND IN-VITRO CHARACTERIZATION OF CICLOPIROX ETHOZOMES

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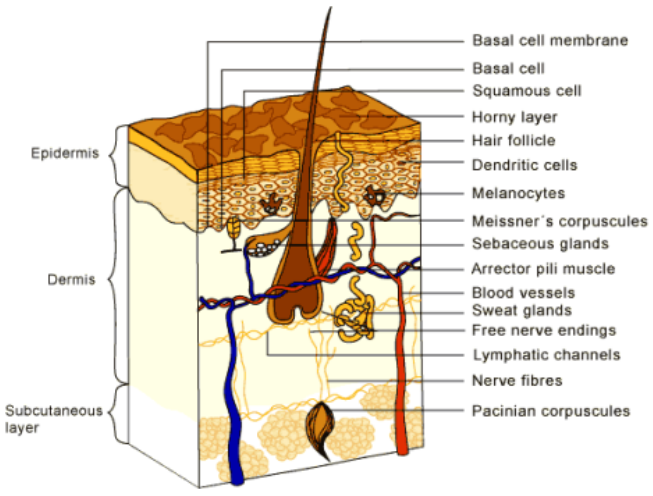
ABSTRACT

Ciclopirox ethosomes were prepared using the cold method reported by Touitouetal.(2000) with little modification. Studies were performed on ethosomes containing 20%, 30%, 40% and 50%w/w ethanol with sonication. Using the same microscopic method and special software "particle size analysis", size of vesicle was determined for sonicated ethosomes respectively. Vesicular size was found to be in the range of 3.23 – 5.79 µm. After confirm existence of vesicles and their size, drug entrapped by vesicular system was evaluated by ultra-centrifugation. Sonicated ethosomes containing 50% w/w ethanol showed higher value i.e., 95.21%.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. The size of vesicles were found to be in the range of 3.26 µm –5.79 µm sonicated ethosomes.

Keywords: Ciclopirox, ethosomal, ultra-centrifugation, ethanol, particle size analysis

1. 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.

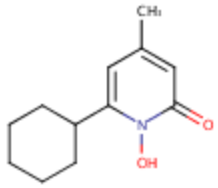


2. REVIEW OF LITERATURE

In the early 1990s, a greater knowledge was gained on vesicles and many types of vesicles and vesicular derivatives have been tested for their abilities for transdermal drug delivery. Most experiments however have centered on liposomes, since derivatives only add to their basic properties. Novel Vesicular Carrier – Ethosomes. Classic liposomes are of little or no value as carriers for transdermal delivery because they do not deeply penetrate the skin, but rather remain confined to the upper layer of stratum corneum[2]. Only specially designed vesicles were shown to be able to allow transdermal delivery. Ethanol is known as an efficient permeation enhancer[3]. Touitou et al., 2000, discovered lipid vesicular system emboding ethanol in relatively high concentrations, which was named as ethosomes[7]. Horwitz et al.,[4] (1999) evaluated the efficiency of 5 % ACV in a novel liposomal carrier (ethosome) in comparison with that of a commercial 5 % ACVcream (zovirax cream) and that of drug free vehicle in the treatment of recurrent herpes labialis in a armed, double blind, randomized clinical study and found the time to crusting with the ethosomal acyclovir (1.6 days) significantly shorter than the time with the acyclovir cream (4.3 days) and the time with the drug free vehicle (4.8 days); in this arm. Touitou et al.,[7] (2000) described a novel carrier for enhanced skin delivery, the ethosomal system, that was composed of phospholipid, ethanol and water. The skin permeation of ethosomal components, ethanol and phospholipid, was demonstrated in diffusion cell experiments Ethosomal systems were composed of soya phosphotidyl choline 2%, ethanol 30% and water were shown by electron microscopy to contain multilamellar vesicles.

3. DRUG PROFILE

Name: Ciclopirox
Description: Ciclopirox olamine (used in preparations called Batrafen, Loprox, Mycoster, Penlac and Stieprox) is a synthetic antifungal agent for topical dermatologic treatment of superficial mycoses. It is most useful against Tinea versicolor. [Wikipedia]
Structure:



Weight: Average: 207.2689
Monoisotopic: 207.125928793
Chemical Formula: $C_{12}H_{17}NO_2$

4. AIM AND OBJECTIVE

The purpose of the present investigation is aimed at: To prepare and evaluate Ciclopirox ethosomal containing different concentration of ethanol and phospholipids by sonication for size reduction of vesicles. Designed Ciclopirox ethosomal are characterized for Size and shape, Entrapment efficiency, Release study. The effect of sonication also studied on the characteristics of Ciclopirox ethosomal.

To formulate ethosomal gel, To characterize the prepared formulation using cold method, To carryout various evaluation parameters which includes vesicular shape and surface morphology, vesicular size, size distribution, drug content, entrapment efficiency. To carry out *in vitro* drug diffusion study of ethosomal gel.

5. MATERIALS AND METHODS

5.1 MATERIALS

Chemicals and Materials

Chemicals	Manufactured by
Ciclopirox	Chandra labs
Soya lecithin	Research lab fine chem. Industries(Mumbai)
Propylene glycol	Research lab fine chem. Industries(Mumbai)
Alcohol	Jiangsu Huaxi International Trade Co.Ltd (CHINA)
Cholesterol	Virat lab(Mumbai).
Carbopol-934	Research lab fine chem. Industries(Mumbai)
Triethanol amine	Research lab fine chem. Industries(Mumbai)
Ultrapure water	Cortex laboratories (Hyderabad)

5.2 Equipment's

Instruments and company

Instruements	Company
Electronic weighing balance	Scimadzu corporation (JAPAN).
Uv.spectrophotometer	Schimadzu 1800(.JAPAN).
Magnetic stirrer	REM elektro technik limited.vasai (INDIA)
Refrigerator	Allwyn(INDIA).
Sonicator	SISCO Scientific Instruments sales Corporation, Thana, Mumbai
pH meter	EI
Scanning electron microscope	Scimadzu corporation (JAPAN).
FTIR	Scimadzu corporation (JAPAN).
Humidity chamber	SISCO Scientific Instruments sales Corporation, Thana,Mumbai

6. METHODOLOGY

6.1 ANALYTICAL METHODS
STANDARD CURVE
SCANNING OF CICLOPIROX

Ciclopirox 10 mg pure drug was dissolved in methanol and was diluted to give concentration of 10µg/ml and was scanned between 220 mm and 300 mm for the determination of λ. The wavelength of 226 nm was selected as for λ_{max}. The same was used for further analysis of drug solution and absorbance of final standard solution was measured at 226 nm.

Preparation of pH 7.4 phosphate buffer

Dissolve 2.38g disodium hydrogen phosphate, 0.19g potassium dihydrogen and 8g of sodium chloride in distilled water and then make up 1000ml with distilled water.

Preparation of standard calibration curve of Ciclopirox[8]

Principle: The Ciclopirox exhibits peak absorbance at 226 nm in methanol.

Instrument used: Shimadzu-1800 UV Spectrophotometer, Japan.

Procedure

Preparation of standard solution

Standard stock solution of Ciclopirox was prepared in methanol. 100 mg of Ciclopirox was accurately weighed into 100ml volumetric flask and dissolved in small quantity of methanol .The volume was made up with 7.4pHPhosphate buffer to get a concentration of 1000µg/ml (SS-I). From this 10ml solution was withdrawn and diluted to 100ml to get a concentration of 100µg/ml (SS-II).

Preparation of working standard solutions

Further, from (SS-II) aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8 ml and1ml were pipetted into 10ml volumetric flasks. The volume was made up with pH6.8 Phosphate buffer to get the final concentrations of 2,4,6,8 and 10µg/ml respectively. The absorbance of each concentration was measured at 226 nm.

The data are compiled in Table.

λ max: 226nm.

Beer's range: 2-10µg/ml.

The concentration was calculated using the following formula with $R^2 = 0.999$.

PARAMETERS	CICLOPIROX
Wavelength(nm)	226
Beer's Law limit(ppm)	2-10
R2 value	0.9999
Regression equation(6.8 pH buffer)	Y=0.03214x+0.05319
R2 value	0.996

6.2 PREPARATION OF CICLOPIROX ETHOSOMES (BY COLD METHOD)

Preparation of Ciclopirox ethosomes was followed by method suggested by Touitou et al., with little modification.[7] The ethosomal system of Ciclopirox comprised of 2-5 % phospholipids, 20-50 % ethanol, 10 % of propylene glycol, 0.005g of cholesterol and aqueous phase to 100 % w/w. Ciclopirox 0.25 g was dissolved in ethanol in a covered vessel at room temperature by vigorous stirring. Propylene glycol was added during stirring.

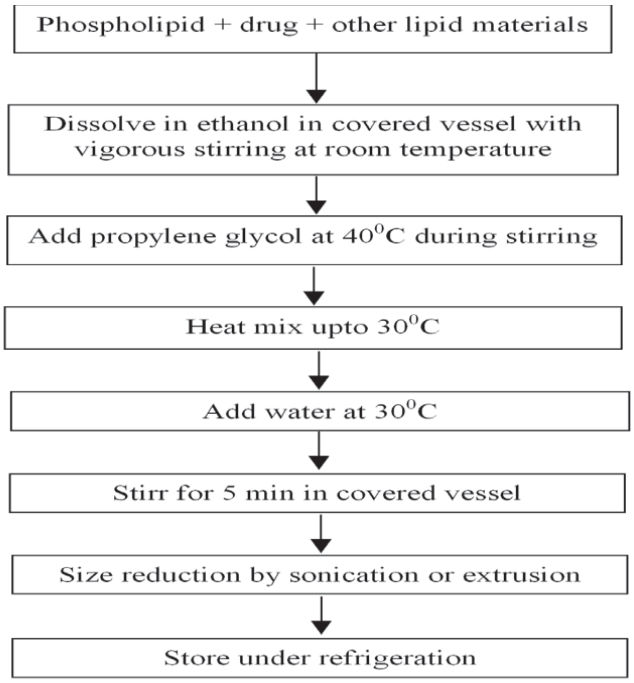


Fig 1: Cold method for the preparation of ethosomes

Preparation of Ciclopirox ethosomal gel

The best achieved ethosomal vesicles suspension, formula EF-2 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 dropwise. 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 Ciclopirox was prepared by similar method using 1.5% carbopol.

6.3 IN-VITRO RELEASE STUDIES

1. Drug Release Study From Rat Skin

The skin permeation of Ciclopiroxfrom ethosomal formulation was studied using Franz 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 20 ml respectively. The temperature was maintained at 37 ± 0.5°C.

2. In-vitro release kinetics (Harris shoaib et al., 2006)[29]

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:

- Zero - order kinetic model – Cumulative % drug released versus time.
- First – order kinetic model – Log cumulative percent drug remaining versus time.
- Higuchi's model – Cumulative percent drug released versus square root of time.
- Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

3. Zero order kinetics

Zero order release would be predicted by the following equation:

$$At = A_0 – K_{0t}$$

Where,

At = Drug release at time't'

A_0 = Initial drug concentration.

K_0 = Zero- order rate constant (hr-1)

4. First order kinetics

First - order release could be predicted by the following equation:

$$\text{Log } C = \log C_0 – K_t / 2.303$$

Where,

C = Amount of drug remained at time't'

C_0 = Initial amount of drug.

K = First - order rate constant (hr^{-1}).

Mechanism of drug release

Table 1: Diffusion exponent and solute release mechanism for cylindrical shape

S.No	Diffusion	Exponent(n) Overall solute diffusion mechanism
1.	0.45	Fickian diffusion
2.	0.45<n<0.89	Anomalous (non-Fickian) diffusion
3.	0.89	Case-II transport
4.	n>0.89	Super case-II transport

7. RESULTS AND DISCUSSION

7.1 ANALYTICAL STUDY

Solubility studies of Ciclopirox

Table 2: Solubility parameters

Solvent	**Ciclopirox**
Water	Sparingly Soluble
Methanol	Soluble
Ethanol	soluble
Chloroform	Insoluble
DMSO	Soluble
0.1N Hcl	Soluble
pH 6.8 buffer	Soluble

Ciclopirox spectrum gave a highest peak at 212.5 nm and same was selected for further evaluations.

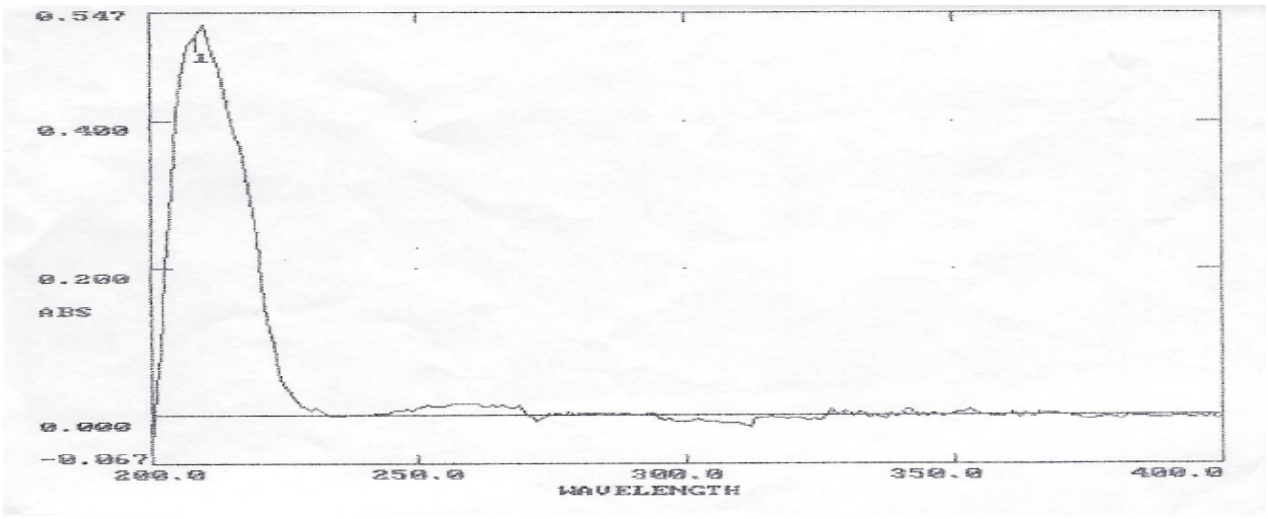


Fig 2: UV Spectrum for Ciclopirox at 212nm

8.2 Standard Calibration Curve

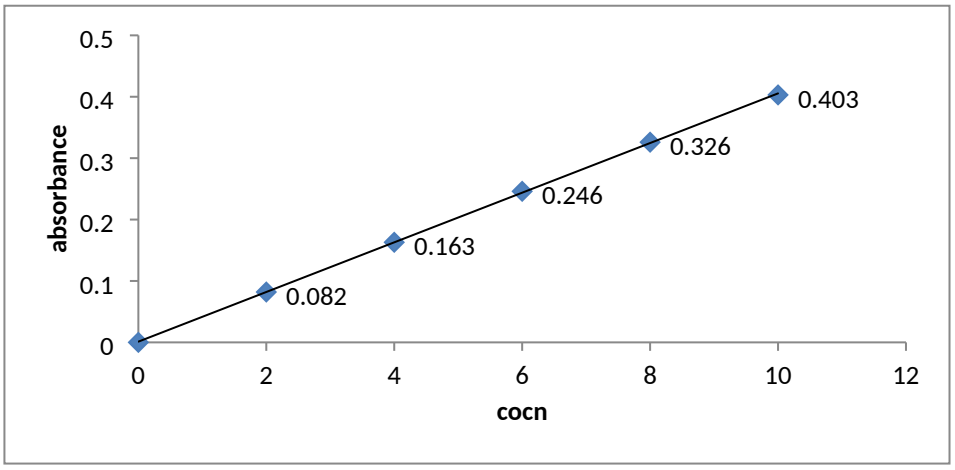


Fig 3: Calibration curve of Ciclopirox graph

SIZE DISTRIBUTION OF CICLOPIROX ETHOSOMAL FORMULATIONS

Table 8: Evaluations of Ciclopirox Ethosomal Gel

Formulation code	Entrapment efficiency (%)	Drug content (%)	P^H	viscosity(cps) at 10 rpm	Spreadability (g.cm/sec)
EF1	81.21	98.6	6.6	18124	16.84
EF2	85.63	99.3	6.7	22776	15.92
EF3	87.51	98.6	6.6	20460	17.01
EF4	89.23	98.3	6.6	13359	15.10
EF5	85.12	95.3	6.7	12107	19.38
EF6	92.52	95.6	6.8	18723	18.41
EF7	93.61	99.7	7.0	16590	20.30
EF8	95.21	97.2	6.7	17421	17.62
EF9	83.21	98.1	6.8	15421	17.21
EF10	85.07	97.3	6.8	14321	18.18
EF11	88.23	96.4	6.7	15234	18.26
EF12	90.23	96.5	6.6	14231	17.25

(n=3)

9. SUMMARY

Transdermal route offers several potential advantages over conventional routes. These advantages 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 pharma-cological response, avoiding the fluctuation in the blood levels, and most important. It provides patient convenience.

But one of the major problem for efficient drug delivery is low penetration rate. While optimizing the topical drug delivery, vesicular system (liposomes and niosomes) appears as upcoming development. Recently advancement in liposomes was done and result obtained “Ehosomal system” which showed topical delivery with higher transdermal flux and higher skin deposition as it is attractive and has desirable advantages.

10. CONCLUSION

It is well known that if drug molecules presenting any difficulties in its solubility and bioavailability along the GI tract, are candidates for other routes of administration and if the site of action for drug candidate is subdermal, effective penetration enhancers are required to provide the drug molecule deeper into skin tissue for optimized therapeutic delivery of drug. It is generally agreed that classic liposomes are of little or no value as carriers for transdermal drug delivery because they do not penetrate the skin.

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