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EFFECT OF FORMULATION VARIABLES ON THE RELEASE OF CICLOPIROX OLAMINE TOPICAL GELS

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ABSTRACT

Topical gels of Ciclopirox olamine were prepared using two different gelling agents (viz, Carbopol and hydroxypropylmethylcellulose). Formulations were evaluated for pH, rheological behavior, drug content and in vitro drug diffusion. Formulations of both the gelling agents appeared to be Nonnewtonian and pseudo plastic. Drug content was found to be high (>98%) and uniform in gels. Effect of solvents, propylene glycol and ethanol on the release of drug from the gels was studied. Drug release from the gels increased with increase in the concentration of propylene glycol up to 10%. However, drug release decreased with further increase in the concentration of the propylene glycol to 20%. In case of carbopol gels, drug release increased with the addition of ethanol. However, in case of hydroxypropylmethylcellulose gels, addition of ethanol decreased the release of ciclopirox olamine. The release of Ciclopirox olamine from the gels followed the Higuchi model. It can be concluded that propylene glycol acts as a good solvent in carbopol and hydroxypropylmethylcellulose based Ciclopirox olamine gels.

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INTRODUCTION

Ciclopirox olamine (CPO) is a hydroxypyridone anti-mycotic drug known chemically as 6-cyclohexyl- l-hydroxy-4-methylpyridin-2-(lH)-one. It is available commercially as a 1% aqueous topical cream preparation (Batrafen®) intended for skin and nail fungal infections[1].The drug is usually available as its ethanolamine. Pharmacological studies on animals have shown that the compound is not expected to produce serious toxicological systemic effects at the doses used in local therapy [2].

The same study on laboratory animals also revealed favorable therapeutic index with no prohibitive mutagenicity or carcinogenicity.CPO has

been shown to possess antimicrobial activity against a broad range of microorganisms including Candida spp [3]. Fungicidal activity in fresh human skin samples was ranked as follows: ciclopirox olamine cream 1% > ciclopirox olamine lotion 1% > naftifine cream 1% > oxiconazole cream 1% > bifonazole creams 1% [4].

Results of preclinical and clinical pharmacokinetic studies have been reviewed earlier. Recent publications have extended the observations that the topical application of ciclopirox olamine results in concentrations of drug that exceed the MICs for sensitive organisms throughout the epidermis and at the level of the dermis . Mucositis and pharyngitis secondary to fungal infection are common. [5] Candida species are reported to be present in the normal oral flora of from 40% to 60% of the population.[6] Candida albicans is most common in the normal flora and most frequently implicated as the pathogen in oropharyngeal and Systemic infection.[7] Oropharyngeal candidiasis can be the source of regional and systemic dissemination, particularly in granulocytopenic and immunosuppressed patients. In these patients, reduced or absent Signs and symptoms of inflammation make diagnosis difficult, [8] .

Ciclopirox olamine demonstrates a broad spectrum of activity that includes yeast, fungi, and various gram-positive and gram-negative bacteria [9]. This agent is a substituted pyridone topical antifungal unrelated to the azoles and demonstrating a broad spectrum of activity not only against yeasts and fungi but also against various gram-positive and gram-negative bacteria [10].The agent is fungicidal and appears to exert its effect through accumulation inside fungal cells and alteration of transmembrane transport of ions and amino acids, leading to loss of membrane integrity [11]. Ciclopirox seems to penetrate hard keratin well, and one open study showed a significant response of onychomycosis to topical therapy with this agent [12] .

MATERIAL AND METHODS

Materials:

Ciclopirox olamine –Model drug ,Carbopol 940, propylene glycol, triethanolamine and HydroxypropylMethylcellulose were purchased from S.D.Fine.Chem.Pvt. Ltd., Mumbai.

Methods:

Preparation of gel:

Ciclopirox olamine gel formulations were prepared using carbopol 940 and hydroxypropylmethyl cellulose as gelling agents. Gelling agent was dispersed in a small quantity of distilled water and then stored overnight to ensure complete hydration. Ciclopirox olamine in a suitable solvent (propylene glycol or ethanol) was added to the dispersion. Other excipients (methyl paraben and propyl paraben) were also added slowly with continuous stirring. In carbopol gels, pH of the vehicle was brought to neutral by using TEA (Triethanolamine). The final weight of the gel was adjusted to 30 gm with distilled water. Entrapped air bubbles were removed by keeping the gels in vacuum desiccators.

Table No 1: composition of the carbopol and hydroxypropylmethylcellulose gels.

Ingredient(mg)	CPOC1	CPOC2	CPOC3	CPOC4	CPOC5	CPOC6
Ciclopirox olamine	300	300	300	300	300	300
Carbapol	250	250	250	_	_	-
Hydroxypropylmethylcellulose	_	_	_	900	900	900
Pluronic F-127	50	70	100	50	70	100
Methyl paraben	20	20	20	20	20	20
Prophyl paraben	30	30	30	30	30	30
Propylene glycol	_	2.5	5	_	2.5	5
Alcohol	_	_	5	_	_	5
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s
Distil water	Upto 30g	Upto 30g	Upto 30g	Upto 30g	Upto 30g	Upto 30g

EVALUTION OF IN SITU GEL:

Determination of pH:

The pH of the gel was determined using a calibrated Digital pH meter. The readings were taken for average of 3 samples.

Gelling Capacity:

The gelling capacity of the formed gel was determined visual inspection and the different grades were allotted as per the gel integrity, weight and rate of formation of gel with respect to time.

Viscosity Studies:

The rheological studies were carried out using Brookfield programmable DVII+Model pro II type (USA). The viscosity of in situ gel and the solution were determined at different angular velocities(0,10,20,30,40….to 100 rpm) average of two reading were used to calculate the viscosity. Evaluation was conducted in triplicate.

Drug Content Determination:

Drug content of gel was determined by dissolving accurately weighed 1gm of gels in 0.1N NaOH. After suitable dilution absorbance was recorded by using UV- visible spectrophotometer (UV – 1700, Shimadzu, Japan) at 298 nm. Drug content was determined using slope of standard curve. The drug content was determined by using following equation:

Drug Content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor

Spreadability study of Topical gel:

Spreadability was determined by apparatus suggested by *Mutimer et al* (1956) [13] .which was suitably modified in the laboratory and used for the study. It consists of a wooden block, which was provided by a pulley at one end. By this method, spreadability was measured on the basis of 'Slip' and 'Drag' characteristics of gels [14]. A ground glass slide was fixed on this block. An excess of gel (about 2 gm) under study was placed on this ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the gel between the slides. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 80 gms. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better Spreadability [16-17].

Spreadability was then calculated using the following formula:

$$S = M \times L / T$$

Where, S = is the spreadability,

M = is the weight in the pan (tied to the upper slide),

L = is the length moved by the glass slide and

T = represents the time taken to separate the slide completely from each other.

Extrudability Study of Topical Gel :

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow one such apparatus is described by *wood et al* [13].

In the present study, the method adopted for evaluating gel formulation for extrudability was based upon the quantity in percentage of gel and gel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of gel in 10 seconds. More quantity extruded better was extrudability. The measurement of extrudability of each formulation was in triplicate and the average values are presented [14]. The extrudability was than calculated by using the following formula[14].

Extrudability = Applied weight to extrude gel from tube (in gm) / Area (in cm2)

In vitro permeation study:

Procedure

Ciclopirox olamine release from the gels was examined through a cellophane membrane using a modified Keishery-Chein cell. Prior to study, cellophane membrane was soaked in diffusion medium for 4 h and then placed on the support screen of the diffusion cell assembly. All the joints were properly sealed with adhesive tape to avoid the penetration of diffusion medium. Aqueous solution of phosphate buffer pH- 7.4 was used as

the receptor medium and 1gm of the test gel was placed on the donor side. The receptor medium was kept at 37 ± 0.5°C. At predetermined time intervals, 5 ml sample was taken from the receptor compartment and replaced with the same volume of fresh phosphate buffer pH-7.4 was Absorbance of the solutions was measured spectrophotometerically at 298nm.

Table No 2: Evaluation parameters of Ciclopirox olamine topical gel

Formulation	pH	Viscosity (cps)	Extrudibility (gm/cm2)	Spredibility (gm.cm/sec)	Drug content (mg/1g of gel)	(Higuchi model) R2
CPOC1	5.8	5420	15.95	13.56	10.1	0.9805
CPOC2	6.0	6100	16.46	14.66	10	0.9839
CPO3	6.0	6200	17.52	14.52	10.2	0.9816
CPOH4	5.9	5800	14.01	12.79	10.05	0.9707
CPOH5	6.0	6200	15.23	12.12	10.09	0.9859
CPOH6	9.9	6600	16.11	11.90	10.2	0.9957

RESULT AND DISCUSSION:

When all the formulations were subjected to physical examination, the gels appeared to Be translucent suggesting that the drug was not completely solubilized rather dispersed/suspended in the gel matrix. In order to neutralize the carbopol gels and

adjust the pH of the gel compatible with the normal pH of the skin (pH 6-7), triethanolamine was used. All the systems showed non- Newtonian flow and exhibited

pseudoplastic behavior, suggesting that gels do not flow at low shear stress and room temperature. The drug content analysis of the formulations showed that the drug content was high (>96%) In the present study, effect of propylene glycol alone and in combination with ethanol was evaluated in two different vehicles.

The transport behavior of Ciclopirox olamine was investigated In vitro. The influence of propylene glycol on the penetration of drug from the carbopol and hydroxypropylmethylcellulose gelling agents through the cellophane membrane was examined and the release profiles are presented in **Fig.1 and 2.**

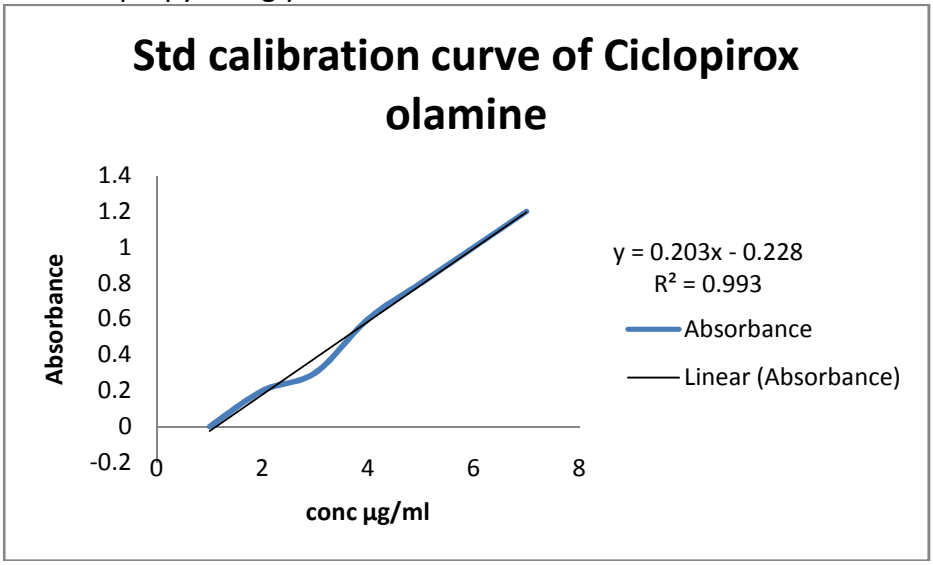

Figure No 1: Standard calibration curve of Ciclopirox olamine in phosphate buffer ph 7.4.

Table 4: *In vitro* Drug Diffusion Study:

Time (hr.)	CPOC1	CPOC2	CPOC3	CPOH4	CPOH5	CPOH6
1	22	23	23.5	21.6	22	16
2	38	39	42	38	38.5	34.6
3	60.1	60	64	62	62.1	59
4	72.1	71	74	71	71.6	70
5	80	82	83.2	79	81	78
6	91	92	95.9	92	91	94

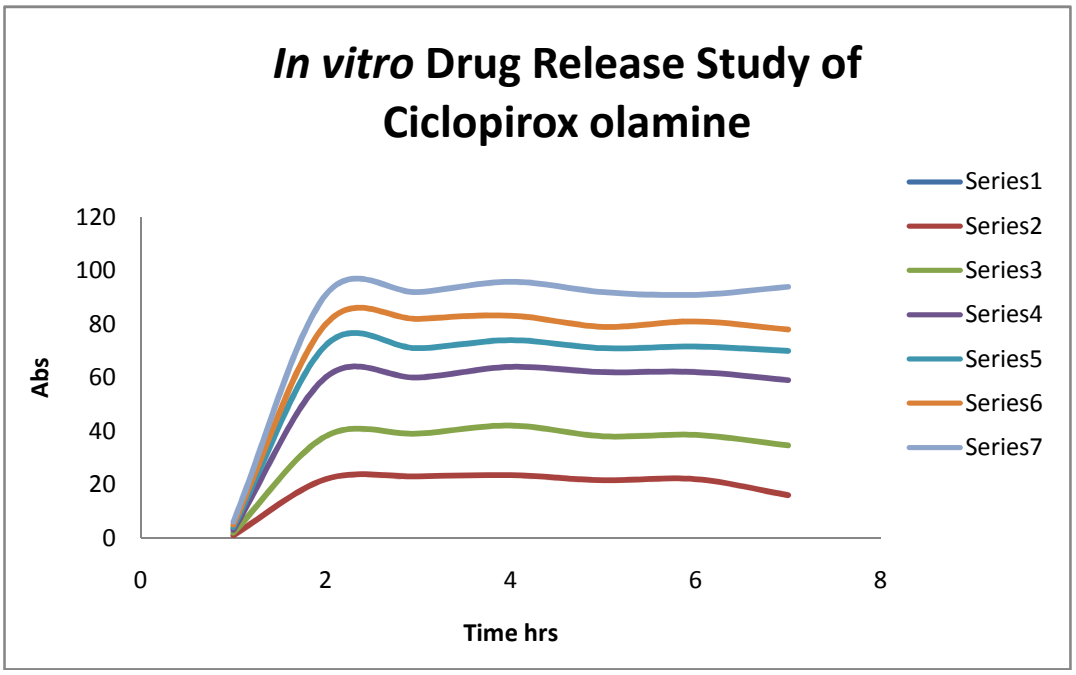

Figure No2: In-vitro Drug Release Study of Ciclopirox olamine

It is reported that propylene glycol has a greater effect on the penetration of drugs when it is used in combination with ethanol.18 19,apart from all discussion ethanol acts as best cosolvent in carbapol gel and propylene glycol in hydroxyprophylmethylcellulose gel and they increase drug release. pH of gel formulation was acidic because of addition of triethanolamine and triethanolamine also acts as a penetration enhancer , viscosity of formulation is good but due to high concentration of pluronic F-127 and carbapol having high viscosity (CPOC3) and pluronic F-127 also acts as a penetration enhancer so that they give good drug release(CPOC3 ,CPOH6).

CONCLUSION :

Ciclopirox olamine topical gels were developed using carbopol and hydroxypropyl Methylcellulose as gelling agents. The effect of cosolvents, propylene glycol and ethanol on the in vitro release of Ciclopirox olamine was studied. The concentration of propylene glycol in formulations was found to be critical in deciding the release of the drug. Ethanol acted as cosolvent in carbopol gels and enhanced the drug release. Whereas, addition of ethanol to the hydroxypropyl methylcellulose gels, decreases the drug release. From the above study we have concluded that the topical gel prepared having good viscosity, spreadability, extrudability .

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