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RESEARCH ARTICLE

Formulation & evaluation of voriconazole ointment for topical delivery

Rajesh Asija*, Prem Chand Dhaker, Nitin Nama

Department of pharmaceutics, Maharishi Arvind Institute of Pharmacy, Mansarovar, Jaipur. Rajasthan, 302020-India.

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ABSTRACT

The studies were conducted with an object to develop a desired ointment for treatment of fungal infection like eczema itching, purities'. Main objective of this study is to formulate the ointment with different ointment bases having good consistency, diffusion, antifungal and antiseptic properties. To assess the efficacy of formulations assay, spread ability, permeability, drug release, uniformity, viscosity, diffusivity, stability, and other physical characteristics were evaluated. The ointment base was prepared and formulation of ointment was done by incorporating the active ingredients in most effective ratio in the base by fusion method. The PEG ointments were prepared with changing the type of the liquid PEG (low molecular weight). Then, the viscosity and the voriconazole release from the prepared formulations were studied.

Keywords: Voriconazole, Polyethylene glycols, Antifungal activity.

INTRODUCTION

Topical products for the treatment of dermatological diseases include a wide choice of vehicles ranging from to semisolids preparations are creams, gels, ointments, pastes, aerosols and solutions. Ointments are topical formulations that offer better patient compliance and hence become more acceptable to patients. It is a semisolid dosage form that contains < 20% water and volatiles and > 50% hydrocarbons, waxes or polyethylene glycols as the vehicle for external application to the skin. The delivery of drug through the skin has long been a promising concept because of the ease of access, large surface area, wide exposure to the circulatory and lymphatic system, and noninvasive nature of the treatment. This is true whether the bioavailability desired is systemic or local. Ointments are homogeneous, semisolid preparations intended for external application to the skin or mucous membranes. Topically applied dermal and transdermal delivery systems could replace needles required to administer many of the new biologics-based drugs and vaccines, in addition to other advantages such as avoiding first-pass metabolism, gastric degradation and frequent dosing.

ADVANTAGES OF TOPICAL DRUG DELIVERY SYSTEMS:

- Avoidance of first pass metabolism.
- Easy to apply.
- Avoid of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time etc.
- Achieve of efficacy with decrease total daily dosage of drug by continuous drug input.
- Maintain in drug levels.
- Easily remove the medications, when needed.
- A large area of application in comparison with buccal or nasal cavity.
- Selectively to a specific site.

SKIN

Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. This research is concern with all detail information regarding rational approach to topical formulation, aim of topical permeation and basic components of topical drug delivery systems. Absorption of ointment through the skin depends on a number of factors, the important of which are concentration, time of contact, solubility of drug, and physical condition of skin layer and part of the body exposed[1].

FACTORS INFLUENCING ABSORPTION

Absorption of ointment through the skin depends on a number of factors:

- Concentration
- Duration of contact
- Solubility of medication
- Physical condition of the skin
- The amount of hair on the skin.

MEDICAL USE OF SKIN ABSORPTION

Dermal application of a medication or chemical allows treatment to be localized, unlike injection. Some medications to be more effective (or are more efficient)

using the dermal route of administration. Some ingest drug are heavily metabolized by the liver and may be inactivated, but using a dermal application bypass this metabolism step allowing more parent compound to enter the peripheral circulation. The drug is absorbed well through the skin it may be used as a means of systemic medication. Dermal dosage forms include: lotions, ointments, creams, liniments, braces, dusting powders, aerosols, and transdermal patches.

OINTMENT

Ointment is a topical medication applied on the body surface. ointments is defines as a homogeneous, viscous, semi-solid preparation with more viscosity, that is used for external application. Ointment ingredient which serve a protective, antifungal or prophylactic purpose when applie on the skin or mucous membranes. Medicated ointment are use for the treatment of infection, inflammation and antifungal activity. However, non-medicated ointments are commonly used due to their emollient/lubricating properties.

TYPES OF OINTMENTS BASES

The medicated stuff or the ingredients present inside the ointment is actually the main base of ointments. There are ointment bases:

1. **Hydrocarbon bases.**

e.g. hard paraffin and paraffin, microcrystalline wax and ceresine.

2. **Absorption bases.**

e.g. wool fat, beeswax.

3. **Water soluble bases.**

e.g. PEG 200, 300, 400.

4. **Emulsifying bases.**

e.g. Emulsifying wax, Vegetable oils like as coconut oil, sesame oil, olive oil, almond oil and peanut oil[2].

METHOD OF PREPARATION

Two type of method for preparation of ointments.

1. Mechanical method: This method also called trituration method. The quantity of ointment is not more than 50g, white porcelain or marble ointment should be used in conjunction with a flexible steel spatula. A steel spatula should not be used as medicament may react with the metal. the substance react with metal such as mercury compounds, tannic acid, salicylic acid and iodine[3].

2. Fusion method: Ointment containing hard paraffin, beeswax, emulsified wax, wool alcohol are prepared by melting ingredients in a porcelain dish over a water bath. In this process higher melting point substance should be melted first and add then other ingredients of the bases in order of their melting point[3].

MATERIALS AND METHOD FOR RESEARCH WORK

Materials

Voriconazole was procured from Jaipur pharmaceutical works. PEG400 and PEG600 was procured from Maharishi Arvind Institute of Pharmacy, mansarovar, Jaipur. All other chemicals were used of analytical grade and without any further chemical modification.

Method

The ointment containing voriconazole was prepared by a fusion method. The specified concentration of polyethylene glycol (PEG) 4000 was melted in a porcelain dish over a boiling water bath. PEG 400 or PEG 600 was heated to decrease order temperature and added to the melted PEG 4000. The mixture was then removed from heat and stirred. Then, voriconazole (5% w/w) dissolved in 20% propylene glycol (which is slightly heated) was added to the PEGs mixture and stirred until congealing. The excipients were taken according to drug weight. The different forms of ointment preparation together with their compositions are given in following tables:

Table 1: Compositions of various ointment preparation of voriconazole

Formulation	F1	F2	F3	F4	F5	F6	F7	F8
Drug	5	5	5	5	5	5	5	5
PEG 4000	20	20	20	20	20	20	20	20
PEG 400	10	20	30	40	-	-	-	-
PEG 600					10	20	30	40
Methanol	2	2	2	2	2	2	2	2
Propylene glycol	20	20	20	20	20	20	20	20
Methyl paraben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Propyl paraben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

EVALUATION OF OINTMENT

Fourier transforms infra red spectroscopy (FTIR):

The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for formulation. The FTIR spectra of voriconazole was done and given in Fig. 1

Physical Examination:

The Prepared ointment formulations were inspected visually for their colour, homogeneity, consistency.

Determination of pH:

2.5gm Ointment sample was taken in 100 ml dry beaker, 50 ml water was added to it. Beaker was heated on water bath maintained at about 60ºC to 70ºC for 10 minutes, cooled to room temperature, and then centrifuged at 3000 rpm for 10 minutes. The pH of water extract was measured by using pH meter. The pH measurements were done by using a digital type pH meter by dipping the glass electrode into the ointment formulation.

Measurement of viscosity:

The viscosity of the prepared ointment formulations was determined using BrookField viscometer DV-III ULTRA (Brookfield Engineering laboratories, USA) using spindle no. 64. The viscosity was measured in centipoises (cps) at 10 rpm for 1 minute and temperature 25ºC using 20 gram sample[4].

Spreadability:

The spreadability is expressed in terms of time in seconds taken by two slides to slip off from ointment, placed in between two slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability of ointment. The spreadability was calculated by using the following formula.

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

Where, M = weight tied to upper slide

L = length of glass slides

T = time taken to separate the slides

Extrudability:

Extrudability test is the measure of the force required to extrude the material from a collapsible tube when certain amount of force has been applied on it in the form of weight. In the present study the quantity in percentage of ointment extruded from the tube on application of certain load was determined. The extruadibility of prepared ointment formulations was calculated by using following formula.

$$\text{Extrudability} = \frac{\text{Amount of ointment extruaded from the tube} \times 100}{\text{Total amount of ointment filled in the tube}}$$

***In-vitro* Drug release study:**

The *in vitro* release of voriconazole from the prepared formulations was studied using dialysis method. 1 gram sample of each formulation was accurately weighed and placed on a semi permeable cellophane membrane immersed in phosphate buffer pH 7.4 for 24 hours. The loaded membrane (donor compartment) was firmly stretched over the lower open end of a glass tube of 2.5 cm internal diameter and made watertight by rubber band. The tube was then immersed in a beaker containing 25 ml of phosphate buffer pH 7.4 which is the release medium (receptor compartment). The system was maintained for 3 hours at 37 ± 0.5ºC in a thermostatic shaking water bath at 50 rpm. Samples of 5 ml were withdrawn at intervals of 1, 2, 3, 4, 5, and 6 hours. The volume of each sample was replaced by the same volume of fresh buffer (kept at the same temperature) to maintain constant volume[4].

***In vitro* antifungal activity:**

Agar cup-plate method was adopted for this study. The *in vitro* antifungal activity of the selected voriconazole formulations; PEG ointment against isolates of *Candida albicans* (as a representative Yeast fungus) and isolates of *Trichophyton Mentagrophyte* (as a representative Dermatophyte fungus) was studied. A single isolate of each fungus was picked from the agar slab culture to prepare spores suspensions in sterile water and was adjusted to be 1×106 spores/ml. One ml of the spores' suspension was mixed with Sabouraud agar (15-20 ml) in sterile Petri dish (9 cm in diameter) and the agar plates were allowed to solidify. After solidification, a single well was made in each agar plate using a porer of size 1 cm and filled with an accurately weighed 0.5 gm of each formula (either medicated or plain). The plates were incubated at 25± 1ºC for 3 days (for Candida isolates) and 8 days (for Trichophyton isolates) and then they were examined for the inhibition zone diameter which is an indicator for the antifungal activity. The mean value of the inhibition zone diameter from three plates was calculated[4].

Release kinetics of selected formulation:

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models represent Zero order, First order, Higuchi model and Peppas model.

RESULTS AND DISCUSSION

Fourier transforms infra red spectroscopy (FTIR):

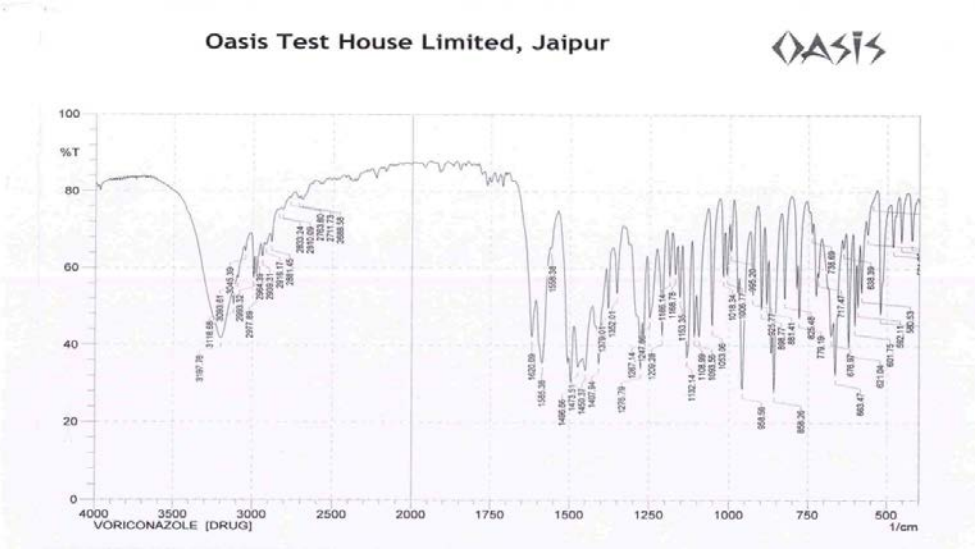

Figure 1: IR spectra of Voriconazole

Physical Appearance:

Ointment formulations were white viscous preparation with a smooth homogeneous texture. Show Physical Appearance discussed in Table 2.

Table 2: Physical Appearance

S. No.	Formulation Code	Colour	Homogeneity	Consistency
1	F1	White	Good	++
2	F2	White	Excellent	+++
3	F3	White	Excellent	+++
4	F4	White	Excellent	+++
5	F5	White	Poor	+
6	F6	White	Poor	++
7	F7	White	Good	++
8	F8	White	Good	+++

Determination of pH:

The pH of the ointment solution was measured with the help of pH meter. 0.5g of ointment was dissolved in 50ml of distilled water and stored for two hours. The measurement of pH each formulation was done in triplicate.

Table 7.3: pH of ointment

S. No.	Formulation Code	pH*
1	F1	6.36±0.3
2	F2	6.27±0.1
3	F3	7.09±0.6
4	F4	6.53±0.5
5	F5	6.09±0.18
6	F6	7.2±0.23
7	F7	7.12±0.4
8	F8	6.8±0.9

Rheological Study:

The viscosity is illustrated according to the change in type of fatty alcohol and concentration and the molecular weight of the liquid polyethylene glycol (for PEG ointments). found that increasing the concentration of the emulsifying agent in the ointments formulation led to increased viscosity of the formulation. In case of PEG ointment formulations, the viscosity was increased with increasing the molecular weight of the liquid PEG used. So, F8 containing PEG 600 exhibited higher viscosity over F4 containing PEG 400.

Table 7.4: viscosity of ointment

S. no.	Formulation Code	Viscosity (CP) *
1	F1	29,840±7.3
2	F2	32,646±16.4
3	F3	33,284±22.8
4	F4	34,028±17.7
5	F5	37,416±9.5
6	F6	37,996±11.3
7	F7	39,728±22.4
8	F8	41,176±18.5

Spreadability:

Pharmaceutical semisolid preparations include ointments, cream, emulsion, gel, and rigid foams. Their common property is the ability to cling to the application surface for a reasonable period of time before they are washed off or worn off. They usually serve as vehicles for topically applied drugs, as emollients, or as protective.

Table 7.4: spreadability of ointment

S. No.	**Formulation Code**	**Spreadability***
1	F1	28.49±0.7
2	F2	36.31±0.58
3	F3	39.54±1.39
4	F4	42.38±0.75
5	F5	18.7±1.04
6	F6	22.15±1.39
7	F7	29.64±0.94
8	F8	32.87±1.8

Extrudability:

Ointments were filled into collapsible tubes after formulating them. The extrudability of the formulation has been checked.

Table 7.5: Extrudability of ointment

S. No.	Formulation Code	Extrudability
1	F1	Easily Extrudable
2	F2	Easily Extrudable
3	F3	Easily Extrudable
4	F4	Easily Extrudable
5	F5	Easily Extrudable
6	F6	Easily Extrudable
7	F7	Easily Extrudable
8	F8	Easily Extrudable

***In-vitro* drug release study:**

In-vitro drug release testing, a measure of release of the active pharmaceutical ingredient (API) from the drug product matrix in controlled laboratory environment, is a key evaluation in drug development and quality control. It involves subjecting the dosage form to a set of conditions that will induce drug release and quantitating the amount of drug released under those conditions. In development, it is an essential test in assessing differences between prototypes, predicting the timeframe of API release, and modeling in vivo behavior.

Table 7.6: *In-vitro* release of ointment

Formulation	% CDR (6hr)*	Drug content*
F1	72.38±1.14	96.1±0.46
F2	86.108±1.04	98.2±0.73
F3	89.722±0.75	98.7±0.39
F4	91.014±1.09	99.6±0.48
F5	63.079±0.95	95.3±0.35
F6	69.256±1.29	95.8±0.95
F7	78.871±1.26	96.3±0.57
F8	82.201±1.05	97.5±0.64

Release kinetics of optimized formulation (F4)

The data were treated according to zero order, first order, higuchi model and korsmeyer peppas pattern for kinetics of drug release during dissolution process. The regression equation of optimized formulation F4 were find out according to zero order equation 0.935 first order equation 0.034 and higuchi model 0.997 respectively. These value clearly indicate that the formulation showed to be best expressed by higuchi kinetics. It was follow the higuchi release pattern.

Table 7.6: Data of release kinetics

Form.	Zero order		First order		Higuchi		Korsmeyer peppas	
	R^2	K_0(-) (1/S)	R^2	K_1(-) M/L.S	R^2	K_H	R^2	N
F4	0.935	13.91	0.034	0.122	0.997	37.16	0.523	0.76

CONCLUSION:

Voriconazole ointment were successfully formulated using the mixture of PEG 4000, PEG 400, PEG 600 and propylene glycol for delivery of drug to produce local effect. Ointment could increase the drug permeability across the skin and fast release of the drug could be successfully achieved. The obtained results showed that the PEG ointment formulations exhibited better voriconazole release formulation. For PEG ointments, the nature of the base itself may be adjunctive to the efficacy of the used antifungal agent. So, PEG ointments could be a promising topical antifungal drug.

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