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FORMULATION AND EVALUATION TEST OF VORICONAZOLE GEL

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ABSTRACT

The studies were conducted with an object to develop a desired gel for treatment of fungal infection. Voriconazole is a triazole antifungal medication that is generally used to treat serious, invasive fungal infections. These are generally seen in patients who are immunocompromised, and include invasive candidiasis, invasive aspergillosis, and certain emerging fungal infections. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. Carbopol based gel formulations with Voriconazole were made. The formulation study was aimed to keep all other ingredients constant and only change in Carbopol 940 concentrations. Gel formulations were characterized for Physical Evaluation, Rheological Studies. The results were found satisfactory for all the parameters studied.

KEYWORDS: Voriconazole, Carbopol 940, gel, gel forming agents, topical delivery, antifungal activity.

INTRODUCTION

Voriconazole is a triazole antifungal medication that is generally used to treat serious, invasive fungal infections. These are generally seen in patients who are immunocompromised, and include invasive candidiasis, invasive aspergillosis, and certain emerging fungal infections.[1] Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth. Patients often forget to take their medicine, and even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, bypassing the gastrointestinal (GI) tract would obviate the GI irritation that frequently occurs and avoid partial first-pass inactivation by the liver. Further, steady absorption of drug over hours or days is usually preferable to the blood level spikes and troughs produced by oral dosageforms.[2] There are various skin infections caused by fungus. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Antifungal compounds works by exploiting differences between mammalian and fungal cells to kill the fungal organism without dangerous effect on host. Voriconazole is an imidazole antifungal derivative and used for the treatment of local and systemic fungal infection. A wide variety of vehicles ranging from solid to semisolids and liquid preparations are available for topical treatment of dermatological disease as well as skin care. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and Skin as topical route.[3] There is various medicated products that are applied to the skin. Such products are referred as topical or dermatological products. There are various Hydrophilic polymers such as Carbopol 940, hydroxyl propyl methyl cellulose (HPMC), Sodium alginate that are used in topical gel delivery system.[4] Based on molecular fraction these polymers are used concentration between 1-5 % in topical formulation.

Information on Gel

Gels for dermatological use have several favorable properties such as being thixotropic, Greaseless, easily spreadable, easily removed, emollient, non-staining, compatible with severalexcipients and water soluble or miscile.[5-6] The USP defines gel as a semisolid system consisting of dispersion made up of either small inorganic particles or large organic molecules enclosing an interpenetrated by liquid. The inorganic particles form a three dimensional structure. Gels consist of two phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved into the continuous phase.[7] Fungal infections are very common and can be topical as well as systemic. Treatment of fungal infection includes medicines like Voriconazole, fluconazole, ketoconazole, clotrimazoleand grisofulvin.[8]

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 exposed1.

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.

MATERIALS AND METHODS

Voriconazole, Carbopol 940, Benzyl alcohol, Oleic acid, Glycerin, Triethanolamine.

Preparation of Gel Base

Purified water was taken and Carbopol 940 was added and allowed to soak for 24 hours. To this, required amount of drug (1 gm.) was dispersed in water and then Carbopol 940 was then neutralized with sufficient quantity of triethanolamine. Glycerin as a moistening agent and oleic acid as a penetration enhancer and benzyl alcohol as a preservative were added slowly under continuous stirring until the homogenous gel was formed. Formulation of various batches is shown in the Table 1.

Table 1: Formulation Table for Voriconazole gel preparation

Sr. No	Ingredients	F1	F2	F3	Role
1	Voriconazole	1gm	1gm	1gm	Active
2	Carbopol 940	1.5gm	2.5gm	3.5gm	Gelling Agent
3	Benzyl alcohol	2	2	2	Preservative
4	Oleic acid	1	1	1	Permeation Enhancer
5	Glycerin	20	20	20	Humectant
6	Triethanolamine	3	3	3	pH adjusting agent
7	Water	q.s	q.s	q.s	vehicle

Evaluation[9-21]

1) Physical Evaluation[9]

The gel formulations of Voriconazole were evaluated for organoleptic characteristics, Color, Odor, Phase separation, Occlusiveness, and Washability etc.

2) pH Determination

The pH of the gel formulations was determined using digital pH meter 10 (3310, Jenway, UK). The reported pH values are from the average of 3 times. Results are shown in Table 2.

3) Spreadability

A sample of 0.1 g of each formula was pressed between two slides (divided into squares of 5 mm sides) and left for about 5 minutes where no more spreading was expected (De Martin and Cussler, 1975; Lucero et al., 1994; Vennat et al., 1994; Contreras and Sanchez, 2002). Diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability. The results obtained are average of three determinations.

4) Extrudability Study[11 & 12]

The extrudability of gel formulations were determined by filling gel in the collapsible tubes. The extrudability was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel.

5) Homogeneity[13] and Grittiness

The gel formulations of Voriconazole were subjected for the critical tests like homogeneity and grittiness in the gel.

6) Gel Strength

An accurate weighed quantity of 30 g of gel was placed in a 50 mL graduated measuring cylinder and was allowed to form gel in a water bath at 37°C. By applying 50 g weight to the gel with the help of a cylinder, the time taken by the cylinder to sink 5 cm down through the gel was measured.[14]

7) Drug Content

A specific quantity of developed gel was taken and dissolved in 100 mL of phosphate buffer of pH 5.5. The volumetric flask containing gel solution was shaken for 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered using 0.45 µm filter. After suitable dilution drug absorbance was recorded by using UV-visible spectrophotometer (UV – 1700, Shimadzu,) at λ max 255 nm using phosphate buffer (pH 6.8) as blank.

8) Rheological Studies

The viscosity of the different gel formulae was determined at 24°Cusing rotational Brookfield viscometer of cone and plate structure with spindle CPE-41 andCP-52.[10] The apparent viscosity was determined at shear rate 40 sec-1. The flow index wasdetermined by linear regression of the logarithmic form of the following equation:

$\tau = k\ \gamma\ n$…….Equation (1)

Where "τ" is the shear stress, "γ" is the shear rate, k is the consistency index, and n is the flowindex. When the flow is Newtonian n=1, if n>1 or n<1, shear thickening or

shear thinning is indicated, respectively. Evaluation was conducted in triplicate.

9) Drug Release Kinetic Study

The data obtained from the in vitro release experiments were analyzed using linear regression method according to the following equations

a- Zero – order equation

$Q = k_o t$

Where Q is the amount of drug released at time t and k 0 is the zero – order release rate.

b-First – order equation

c- $In (100 – Q) = In 100 – k_1 t$

Where Q is the percent of drug release at time t and k 1 is the first – order release rate constant.

d- Higuchi's equation

$Q = k t^{½}$

Where Q is the percent of drug release at time t and k is the diffusion rate constant.[16]

RESULTS AND DISCUSSION

1) Physical Evaluation

All the three gel formulations of Voriconazole were evaluated fororganoleptic characteristics, Color, Odor, Phase separation, Occlusiveness, and Washabilityetc. And found acceptable with respect to the evaluated physical evaluation. The results are given inTable 2.

Table No. 2- Physical Evaluation of Voriconazole Gel Formulations.

Sr.no	Formulation Code	Color	Odor	Phase Separation	Washability	Occlusiveness
1	F1	White to off white	Odorless	No	Washable	No
2	F2	White to off white	Odorless	No	Washable	No
3	F3	White to off white	Odorless	No	Washable	No

2) pH: The pH values of all the three formulations were in range of 5.5 - 7 which is considered acceptable to avoid the risk of irritation upon application to the skin.[17 & 18] The results are tabulated in Table No.3

Table No. 3- The pH details of Voriconazole Gel Formulations

Sr. No.	Formulation Code	pH
1	F1	5.5
2	F2	5.9
3	F3	6.5

3) Spreadability: The spreadability results showed that the formulated gels of Carbopol gelswere most effective i.e. they showed best results for spreadability. The results of spreadability are shown in Table No. 4

Table No. 4: The details of Spreadability of Voriconazole Gel Formulations

Sr.no.	Formulation code	Diameter
1	F1	5.4
2	F2	5.3
3	F3	5.2

4) Extrudability

The results for extrudability showed that Carbopol based gels were in acceptable limits. The results of Extrudability are shown in Table No. 5.

Table No. 5- The details of Extrudability of Voriconazole Gel Formulations

Sr.no.	Formulation code	Extrudability
1	F1	++
2	F2	++

5) Homogeneity and Grittiness

Almost all the formulations were found to be homogeneousand none of the formulations showed grittiness. The results of Homogeneity and Grittinessare shown in Table No. 6.

Table No. 6- the details of Homogeneity and Grittiness of Voriconazole Gel Formulations

Sr.no.	Formulation code	Homogeneity	Grittiness
1	F1	Yes	No
2	F2	Yes	No
3	F3	Yes	No

6) Gel Strength

It has been observed that gel strength increased with the increase in the concentration of Carbopol polymer in the formulation. If comparison is made among the formulations, F3 formulation showed higher gel strength than F1. The reason can be attributed to the higher concentration of Carbopol present in F3 formulation as it has a tendency to increase the gel strength. The results obtained for strength test of all the formulations are mentioned in Table No. 7

Table No. 7- Details of the Gel Strength of Voriconazole Gel Formulations

Sr.no.	Formulation code	Gel Strength
1	F1	86.8 ± 0.58
2	F2	92.8 ± 0.72
3	F3	103.6 ± 1.23

7) Drug Content

The drug content in the gel formulations were evaluated in order to understand if the drug is distributed uniformly in the Gel system. The results for drug content for the all

gel formulation revealed that the drug content and the distribution of drug are satisfactory. All the formulations gave satisfying results for the percentage drug content. The % drug content is shown in Table No. 8.

Table No.8- The % drug content of Voriconazole Gel Formulations

Sr.no.	Formulation code	Drug Content
1	F1	98.8
2	F2	98.1
3	F3	99.2

8) Rheological Studies: The rheological behavior of the prepared formulae showed shearthinning flow indicating structural breakdown of the existing intermolecular interactions between polymeric chains. The different rheological parameters are given in Table 9.

9) Kinetics of Drug Release: The release data analysis was carried out using the various kinetic models i.e. using cumulative % drug release vs. time (zero order kinetic model); log cumulative % drug remaining vs. time (first order kinetic model) and cumulative % drug release vs. square root of time (Higuchi model).[19-21] The R^2 values are tabulated in the Table No. 10. All formulae showed best fitting to Higuchi model kinetics.

Table No. 9- Details of the Rheological Properties of Voriconazole Topical Gels

Sr. No.	Formulation code	Coefficient of determination (R^2)	Flow Index (n)	Viscosity (centipoise)(η)	Flow Behavior
1	F1	0.9421	0.1356	2458	Shear Thinning
2	F2	0.9513	0.1124	2565	Shear Thinning
3	F3	0.9656	0.0921	2717	Shear Thinning

Table No.10- Details of the Kinetics of drug release of Voriconazole Gel Formulations

Sr. No.	Formulation code	Correlation Coefficient [R^2]	
		Zero Order	First Order
1	F1	0.988	0.998
2	F2	0.929	0.972
3	F3	0.884	0.965

CONCLUSION

The physical evaluation of various formulations was successfully carried out. Most of the formulations were easily spreadable. The appearance of formulations ranged from translucent to white. The pH of all the formulations was found to be in the range of 5.5 to 7.0. Almost all the formulations were found to be homogeneous and none of the formulations showed grittiness. The results for extrudability and spreadability showed that Carbopol gels were in acceptable limits.The results for the drug content of all the formulations were acceptable. Thus, the objective of the present work of formulation and evaluation of Voriconazole topical gel has been achieved with overall satisfactory results for the test parameters evaluated.The rheological properties were found satisfactory. The viscosities of Carbopol gels ranged from 1900 to 2500 centipoises (cP). Among the three gel formulations, 3.5%Carbopol 940P showed decreasing order of drug release against 2.5% and 1.5% Carbopolconcentration. The reason for the decreased drug release with increase in Carbopol concentration because polymer concentration increases, viscosity increases. All gel formulations containing penetration enhancer (Oleic acid) was used. From the above results it can be concluded that the 1.5% cabrbopol gel was suitable for topical application.

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