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Formulation and Characterization of "Novel Anti Fungal Drug Candidate" in Gel Dosage Form

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ABSTRACT

Voriconazole is a second-generation azole antifungal agent indicated for use in the treatment of fungal infections including invasive aspergillosis, esophageal candidiasis, and serious fungal infections. Voriconazole works principally, by inhibition of fungal cytochrome P-450-mediated 14 alphalanosterol demethylation, an essential step in fungal ergosterol biosynthesis. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. The intention of presenting in gel formulations is for better patient compliance and to reduce the dose of drug and to avoid the side effects like liver damage and kidney damage associated with oral dosage forms. A gelling agent, Carbopol-940 based Voriconazole topical formulations were made. The formulation study was aimed to keep all other ingredients constant and only change in concentrations of Gelling agent, Carbopol-940. Gel formulations were characterized for Physical Evaluation, pH, Spreadability, Extrudability, Gel Strength, Homogeneity and Grittiness, *in-vitro* drug release and drug release kinetic study. The results were found satisfactory for all the parameters studied.

INTRODUCTION

Transdermal drug delivery gives many important advantages such as it is easy for application, protect the active compound from gastric and enzymatic degradation, simple to terminate the therapy if undesired side effect occurs[1]. Skin is a natural barrier, and only few drugs can penetrate through it easily in sufficient quantity[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 works by exploiting differences between mammalian and fungal cells to kill the fungal organism without untoward effect on the 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 are 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.

Brief Information on Gel

Gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removed, emollient, non-staining, and compatible with several excipients and water soluble or missile[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, Clotrimazole and Griseofulvin[8].

MATERIALS AND METHODS

Voriconazole, Carbopol 940, Benzyl alcohol, Oleic acid, Glycerine, 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

Sl.No.	Ingredients	VF1	VF2	VF3
01	Voriconazole	1 gm	1 gm	1 gm
02	Carbopol 940	1 gm	2 gm	3 gm
03	Benzyl alcohol	2 mL	2mL	2 mL
04	Oleic acid	1 mL	1 mL	1 mL
05	Glycerine	20 mL	20 mL	20 mL
06	Triethanolamine	3 mL	3 mL	3 mL
07	Water	Q.S.	Q.S.	Q.S.

Q. S. – Quantity Sufficient.

EVALUATION

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} 256 nm using phosphate buffer (pH 6.8) as blank.

8) *In Vitro* Drug Release:

The *in vitro* drug release from gel formulations was studied across cellophane membranes using modified Keshery Chien diffusion cell[15]. The receptor compartment was filled with the mixture of Phosphate buffer of pH 5.6 maintained at 37 ± 0.5°C with constant magnetic

stirring. Accurately weighed quantity of gel was placed on the donor compartment. The samples (1 mL) was collected from the receptor compartment at predetermined time interval and replaced by equal volume of fresh receptor solution to maintain constant volume allowing sink condition throughout the experiment. The amounts of Voriconazole in the sample were analyzed at 256 nm against appropriate blank.

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:

$$In\ (100 - Q) = In\ 100 - k_1 t$$

Where Q is the percent of drug release at time t and k_1 is the first – order release rate constant.

c- Higuchi's equation:

$$Q = k\ t^{1/2}$$

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 for organoleptic characteristics, Color, Odor, Phase separation, Occlusiveness, and Washability etc. and found acceptable with respect to the evaluated physical evaluation. The results are given in Table 2.

Table No. 2: Physical Evaluation of Voriconazole Gel Formulations

S. No.	Formulation Code	Color	Odor	Phase Separation	Wash-ability	Occlusiveness
1	VGF1	White to off white	Odorless	No	Washable	No
2	VGF2	White to off white	Odorless	No	Washable	No
3	VGF3	White to off white	Odorless	No	Washable	No

2) **Extrudability:** The results for extrudability showed that Carbopol based gels were in acceptable limits. The results of Extrudability are shown in Table No. 3.

Table No. 3: The details of Extrudability of Voriconazole Gel Formulations

S. No.	Formulation Code	Extrudability
1	VGF1	++
2	VGF2	++
3	VGF3	+

++ Very Good, + Good

3) **Spreadability:** The spreadability results showed that the formulated gels of Carbopol gels were 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

S. No.	Formulation Code	Diameter [cm]
1	VGF1	5.3
2	VGF2	5.2
3	VGF3	5.1

4) **Homogeneity and Grittiness:** Almost all the formulations were found to be homogeneous and none of the formulations showed grittiness. The results of Homogeneity and Grittiness are shown in Table No. 5.

Table No. 5: The details of Homogeneity and Grittiness of Voriconazole Gel Formulations

S. No.	Formulation Code	Homogeneity	Grittiness
1	VGF1	Yes	No
2	VGF2	Yes	No
3	VGF3	Yes	No

5) **pH:** The pH values of all the three formulations was 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. 6.

Table No. 6: The pH details of Voriconazole Gel Formulations

S. No.	Formulation Code	pH
1	VGF1	5.6
2	VGF2	6.4
3	VGF3	6.8

6) **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. 7.

Table No.7: The % drug content of Voriconazole Gel Formulations

S. No.	Formulation Code	Drug Content
1	VGF1	98.6
2	VGF2	97.8
3	VGF3	98.8

7) ***In Vitro* Drug Release:** The *in-vitro* drug release studies clearly performed on dialysis membrane reveal that the drug Voriconazole is released to a satisfactory extent. The results clearly indicate that the higher the concentration of Carbopol, the lesser is the release and the higher concentration of polymers might be retarding the release of the drug while the drug is released to a greater extent in the dialysis membrane. Formulation VGF1 was able to give good release over a period of time when tested in the dialysis membrane. The % drug release is shown in Table 8 whereas the graphical representation of % drug release is shown in Figure No. 1.

Table No. 8: The % drug released across the dialysis membrane for all 3 formulations

Sl. No.	Time Points [in Minutes]	Formulation Codes & % Drug Release		
		VGF1	VGF2	VGF3
1	30	23	19	17
2	60	40	33	29
3	90	56	48	36
4	120	70	62	52
5	150	83	76	60
6	180	92	85	72
7	210	97	88	78

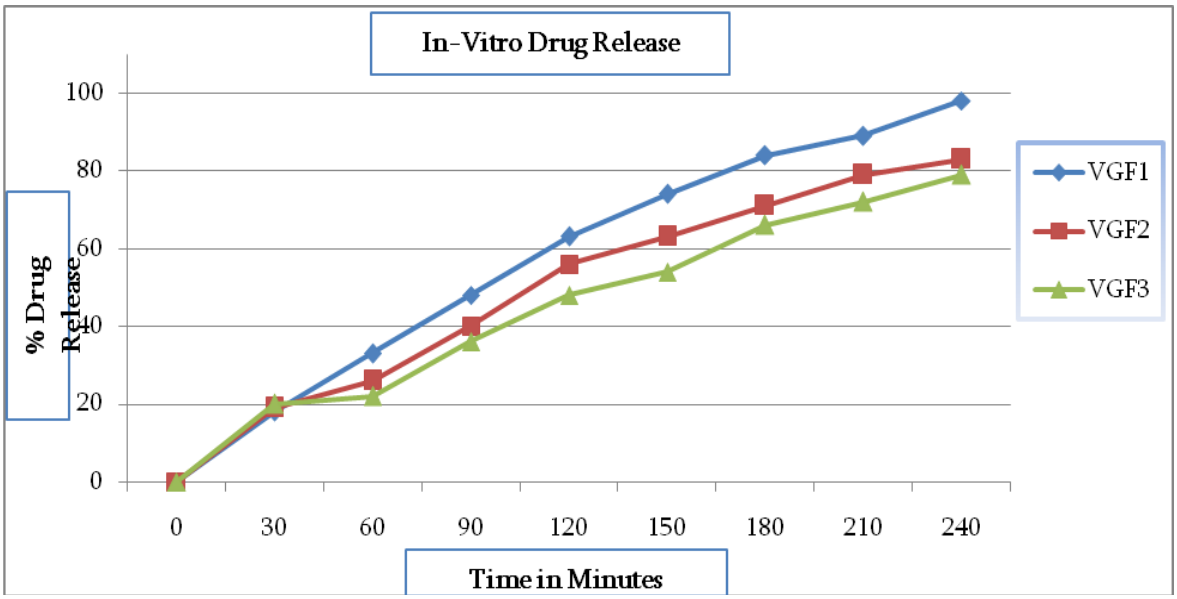

Figure No. 1: Graphical representation of *in vitro* drug release of Voriconazole Gel Formulations

8) 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, VGF3 formulation showed higher gel strength than VGF1. The reason can be attributed to the higher concentration of Carbopol present in VGF3 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. 9

Table No. 9: Details of the Gel Strength of Voriconazole Gel Formulations

Sl. No.	Formulation Code	Gel Strength
1	VGF1	88.6 ± 0.58
2	VGF2	94.8 ± 0.72
3	VGF3	102.8 ± 1.27

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. 10: Details of the Kinetics of drug release of Voriconazole Gel Formulations

Sl. No.	Formulation Code	Correlation Coefficient [R^2]		
		Zero Order	First Order	Diffusion
1	VGF1	0.968	0.9978	0.9972
2	VGF2	0.889	0.972	0.9892
3	VGF3	0.874	0.965	0.9891

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. The *in vitro* release studies of the formulations also gave acceptable results. 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. Among the three gel formulations, 3% Carbopol 940P showed decreasing order of drug release against 2% and 1% Carbopol

concentration. 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% cabrbopol gel was suitable for topical application.

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