EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 7
216-221
Year: 2020

# A REVIEW ON "NOVEL ANTI FUNGAL GEL FORMULATION"

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**Article Received on 24/04/2020** **Article Revised on 15/05/2020** **Article Accepted on 06/06/2020**

**ABSTRACT**
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, Sensitivity Test, Skin Irritation Test, In-vitro drug diffusion through animal membrane for the optimized formulation and in-vitro antifungal activity. The results were found satisfactory for all the parameters studied.

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

## INTRODUCTION

Voriconazole (VFEND®, Pfizer) is a new wide-spectrum, second-generation triazole antifungal drug that is structurally related to fluconazole (Diflucan®, Pfizer).[1] Voriconazole has a replacement of one triazole moiety of fluconazole by a fluoropyrimidine grouping with an additional alpha methylation.[2] This structural modification has led to a more potent compound with fungicidal activity against Aspergillus species.[2] As with other triazole antifungals, the primary mechanism of action is the inhibition of fungal cytochrome P-450–dependent 14α-lanosterol demethylation.[3] Voriconazole is indicated for the primary treatment of invasive aspergillosis (IA) and for the treatment of serious fungal infections caused by Scedosporium apiospermum and Fusariumspecies in patients who are intolerant of, or whose condition is refractory to, other therapies.[3]

Voriconazole is rapidly absorbed after oral administration and reaches maximum plasma concentrations (Cmax) within two hours in normal, healthy, fasting volunteers.[2,3] The oral bioavailability is estimated to be 96% after administration in healthy subjects, and switching from intravenous (IV) to oral voriconazole is appropriate when it is clinically indicated.[3] Consuming a high-fat meal decreases the drug's bioavailability, and administering voriconazole with food alters the time to maximum plasma concentration from one hour to 2.5 hours.[3] Steady-state trough plasma concentrations are obtained within one day following a loading dose and within five days without a loading dose.[3] Voriconazole is metabolized by the cytochrome P-450 hepatic enzymes CYP2C19, CYP2C9, and CYP3A4. It is eliminated by hepatic metabolism, and less than 2% of the dose is excreted unchanged in the urine.[3]

### Pharmacokinetics

The pharmacokinetic parameters of voriconazole are nonlinear and display a disproportionate elevation of serum concentrations with increasing doses.[3, 4] Concentrations of the drug increase up to eight-fold after multiple doses because of a saturation of its own metabolism.[4]

### Pharmacogenomics

CYP2C19 exhibits genetic polymorphism and is extensively involved in the metabolism of voriconazole.[3,4] Voriconazole levels may increase four-fold in patients who are poor metabolizers of CYP2C19 substrates.[3,4] Approximately 20% of those of Asian ancestry and 3% to 5% of whites are poor metabolizers and have predictably higher voriconazole concentrations. 3–5 Currently, no studies have definitively correlated voriconazole concentrations with adverse drug reactions (ADRs), although increased concentrations of this drug have been associated with ADRs.[2,3]

### Brief Information on Gel

A gel is a semi-solid that can have properties ranging from soft and weak to hard and tough.[5][6] Gels are defined as a substantially dilute cross-linked system,

which exhibits no flow when in the steady-state.[7] By weight, gels are mostly liquid, yet they behave like solids due to a three-dimensional cross-linked network within the liquid. It is the crosslinking within the fluid that gives a gel its structure (hardness) and contributes to the adhesive stick (tack). In this way, gels are a dispersion of molecules of a liquid within a solid medium. The word *gel* was coined by 19th-century Scottish chemist Thomas Graham by clipping from *gelatine.* Three types of gels.*[8]*

**Hydrogel**

A hydrogel is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium. A three-dimensional solid results from the hydrophilic polymer chains being held together by cross-links. Because of the inherent cross-links, the structural integrity of the hydrogel network does not dissolve from the high concentration of water.[9] Hydrogels are highly absorbent (they can contain over 90% water) natural or synthetic polymeric networks. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content. As responsive "smart materials," hydrogels can encapsulate chemical systems which upon stimulation by external factors such as a change of pH may cause specific compounds such as glucose to be liberated to the environment, in most cases by a gel-sol transition to the liquid state. Chemomechanical polymers are mostly also hydrogels, which upon stimulation change their volume and can serve as actuators or sensors. The first appearance of the term 'hydrogel' in the literature was in 1894.[10]

**Organogels**

An **organogel** is a non-crystalline, non-glassy thermoreversible (thermoplastic) solid material composed of a liquid organic phase entrapped in a three-dimensionally cross-linked network. The liquid can be, for example, an organic solvent, mineral oil, or vegetable oil. The solubility and particle dimensions of the structurant are important characteristics for the elastic properties and firmness of the organogel. Often, these systems are based on self-assembly of the structurant molecules.[11][12] (An example of formation of an undesired thermoreversible network is the occurrence of wax crystallization in petroleum.[13]).

Organogels have potential for use in a number of applications, such as in pharmaceuticals,[14] cosmetics, art conservation,[15] and food.[16]

**Xerogels**

A **xerogel** /ˈzɪərəʊˌdʒɛl/ is a solid formed from a gel by drying with unhindered shrinkage. Xerogels usually retain high porosity (15–50%) and enormous surface area (150–900 $m^2/g$), along with very small pore size (1–10 nm). When solvent removal occurs under supercritical conditions, the network does not shrink and a highly porous, low-density material known as an *aerogel* is produced. Heat treatment of a xerogel at elevated temperature produces viscous sintering (shrinkage of the xerogel due to a small amount of viscous flow) and effectively transforms the porous gel into a dense glass.

**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.**

| SI.No | Ingredients | Role | VGF1 | VGF2 | VGF3 |
|---|---|---|---|---|---|
| 01 | Voriconazole | Active | 1 gm | 1 gm | 1 gm |
| 02 | Carbopol 940 | Gelling Agent | 1 gm | 2 gm | 3 gm |
| 03 | Benzyl alcohol | Preservative | 2 ml | 2 ml | 2 ml |
| 04 | Oleic acid | Permeation Enhancer | 1 ml | 1 ml | 1 ml |
| 05 | Glycerin | Humectant | 20 ml | 20 ml | 20 ml |
| 06 | Triethanolamine | Ph adjusting agent | 3 ml | 3 ml | 3 ml |
| 07 | Water | Base/Vehicle | Q.S. | Q.S. | Q.S. |

**Evaluation**

**1) Physical Evaluation[17]**: The gel formulations of Voriconazole were evaluated for organoleptic characteristics, Colour, Odour, Phase separation, Occlusiveness, and Wash ability etc.

**2) Rheological Studies:** The viscosity of the different gel formulae was determined at 25°C using rotational Brookfield viscometer of cone and plate structure with spindle CPE-41 and CP-52.[18] The apparent viscosity was determined at shear rate 40 $sec^{-1}$. The flow index was determined by linear regression of the logarithmic form of the following equation:

$$\tau = k\,\gamma\,n \quad \text{.....Equation (1)}$$

Where "τ" is the shear stress, "γ" is the shear rate, k is the consistency index, and n is the flow index. 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.

**3) Sensitivity Test**:

A drop of diluted suspension of the tested gel (1:1) and another drop of saline (control) were put on two corresponding spots of the arms of three human volunteers. After ten minutes, the spot was investigated for any erythema, wheel or any allergic reaction.

**4) Skin Irritation Test[19 & 20]:** As the formulation was intended for dermal application, skin irritancy should be tested. Skin irritation tests were conducted in rabbits to determine irritancy after single application of Voriconazole gel. The back of rabbits after depilation was used in this experiment. About 0.5 g of Voriconazole gel was applied on two different rabbits and then the applied area was covered with gauze and adhesive bandage. The formulation was removed after 24 h and the exposed skin was graded for formation of enema and erythema. Scoring was repeated 72 h later. Based on the scoring, the formulation was graded as 'non-irritant', 'irritant,' and 'highly irritant.'

The total scores for irritation test were calculated using the following equation:

$$\text{Average irritation scores} = \frac{(\text{Erythema reaction scores} + \text{Edemareaction scores})}{\text{Time interval } (h)}$$

**5) Ex-Vivo [In-Vitro] Diffusion Study[21]**

The abdominal skin of Albino mice, weighing 20 – 25 gm of 8 – 10 weeks old was shaved using razor and cleaned the skin with hot water cotton swab. 5 gm of gel was applied uniformly to skin. The skin was mounted between the compartments of the Frantz diffusion cell with stratum corneum facing the donor compartment. Reservoir compartment was filled with 100 mL Phosphate buffer of pH 6.8. The study was carried out at 37 ± 1°C and speed was adjusted until the vortex touches the skin and it carried out for 4½ h. 5 ml of sample was withdrawn from reservoir compartment at 30 min interval and the drug content was measured. Each time the reservoir compartment was replenished with the 5 mL volume of Phosphate buffer pH 6.8 solution to maintain constant volume.

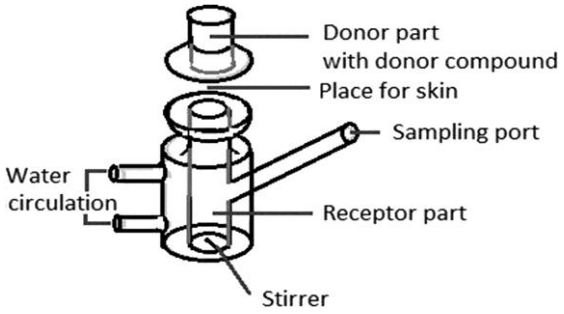


**Figure No. 1: Franz diffusion cell with skin mounted between compartments.**

**6) In Vitro Antifungal activity[21]**

Weighed 16.25 gm of sabouraud dextrose agar was transferred in a 500 ml conical flask and 250 ml of purified water and some amount of heat is applied to dissolve it completely. After sterilizing for 15 min at 121°C at 15 lb pressure in autoclave for about 20 min, cooled it at room temperature. The fungal strain (Candida albicans) was dispersed in the medium and then the medium was poured it into three petridishes allowed it cool at room temperature until it solidifies and then three cups are bored in each petridish with the help of sterile steel bore of 6 mm. Then calculated concentration of the standard drug (Voriconazole), gel formulation (F1) and placebo gel were placed in the bores and incubated the petriplates for 72 h at 37°C in incubators. The zone of inhibition was observed and calculated.

## RESULTS AND DISCUSSION

**1) Physical Evaluation**: All the three gel formulations of Voriconazole were evaluated for organoleptic characteristics, Colour, Odour, Phase separation, Occlusiveness, and Wash ability 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.**

| Sr.No. | Formulation codes | Colour | Odour | Phase Separation | Wash ability | Conclusiveness |
|---|---|---|---|---|---|---|
| 1 | VGF1 | White to off white | Odourless | No | Washable | No |
| 2 | VGF2 | White to of white | Odourless | No | Washable | No |
| 3 | VGF3 | White to off white | Odourless | No | washable | No |

**2) Rheological Studies**: The rheological behavior of the prepared formulae showed shear thinning flow indicating structural breakdown of the existing intermolecular interactions between polymeric chains. The different rheological parameters are given in Table 3.

**Table No. 3: Details of the Rheological Properties of Voriconazole Topical Gels.**

| Sr.No | Formulation Codes | Coefficient of determination ($R^2$) | Flow Index(n) | Viscosity (centipoise)($\eta$) | Flow Behavior |
|---|---|---|---|---|---|
| 1 | VGF1 | 0.9291 | 0.2350 | 1918 | Shear Thinning |
| 2 | VGF2 | 0.9315 | 0.2156 | 2159 | Shear Thinning |
| 3 | VGF3 | 0.9487 | 0.1354 | 2458 | Shear Thinning |

**3) Sensitivity Test:** The formulated Voriconazole gel formulations of all three caused no irritation or sensitivity to the skin when subjected to sensitivity test.

**4) Skin Irritancy Study:** This test is one of the important test parameter which needs to be evaluated for the topical application dosage from. Average response scores of skin irritation for single application. From the results it indicates that all the gel formulations have low skin irritation. The details of the index is shown in Table 4.

| Formulation | Primary Irritation Index | | |
|---|---|---|---|
| | 24 hrs. | 48hrs. | 72 hrs. |
| VGF1 | 0.051 | 0.0973 | 0.092 |
| VGF2 | 0.048 | 0.0922 | 0.089 |
| VGF3 | 0.050 | 0.0944 | 0.097 |

**5) Ex-Vivo [In-Vitro] Diffusion Study**: The release studies clearly reveal that the drug Voriconazole is released to a lesser extent from the animal skin [mice] when compared to the cell membrane. The results clearly indicates that the higher the concentration of Carpool, lesser is the release as the higher concentration of polymers might be retarding the release of the drug while the drug is released to a greater extent in the cell membrane. Though the VGF1 was able to give good release over a period of time when tested in the cell membrane, however, the same showed lesser release because of skin thickness and also the polymer concentration. The % drug diffusion is shown in the Table 5 and also the graphical representation of % drug diffusion is shown in the Figure No. 2.

**Table No. 5: The % drug diffused across the mice skin for all 3 formulations.**

| SI No. | Time Points (in Minutes) | Formulation Codes & % Drug Diffused | | |
|---|---|---|---|---|
| | | VGF1 | VGF2 | VGF3 |
| 1 | 30 | 14 | 11 | 11 |
| 2 | 60 | 22 | 19 | 17 |
| 3 | 90 | 34 | 31 | 28 |
| 4 | 120 | 45 | 42 | 34 |
| 5 | 150 | 54 | 48 | 41 |
| 6 | 180 | 66 | 55 | 49 |
| 7 | 210 | 72 | 61 | 56 |
| 8 | 240 | 79 | 67 | 61 |

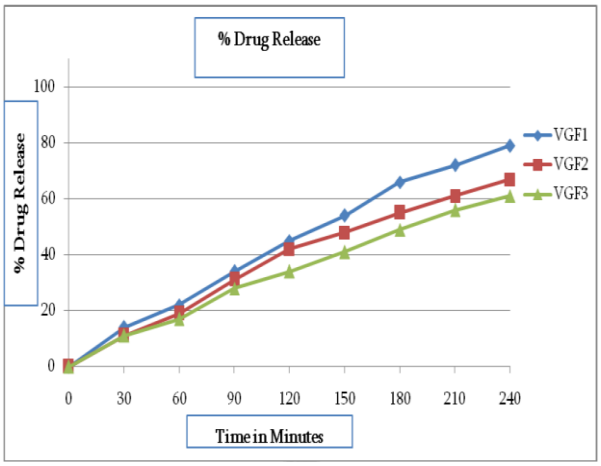


**Figure No. 2: Graphical representation of % drug diffused of all 3 formulations across mice skin.**

**Antifungal Study**

In the antifungal study, the fungi used were Candida albicans. The studies were carried for the optimized formulation [VGF1] and zone of inhibition observed at F1 is 6.2 mm2, placebo gel as 0 mm2 and the pure drug, Voriconazole possess a zone of inhibition 7.4 mm2. The study indicated that the results are satisfactory. The details of the zone inhibition are shown in the Table 6. The graphical representation of antifungal activity is shown in the Figure No. 3. The photographic images of VGF1, Placebo and pure drug substances are shown in the Figure No. 4, 5 & 6 respectively.

**Table No. 6: Reported Zone of Inhibition in mm2 for Placebo, Pure Drug & Optimized Formulation.**

| Sr.No | Formulation | Zone of Inhibition ($mm^2$) |
|---|---|---|
| 1 | Placebo gel | 0 |
| 2 | Pure Drug (Voriconazole) | 7.4 |
| 3 | VGF1 | 6.2 |

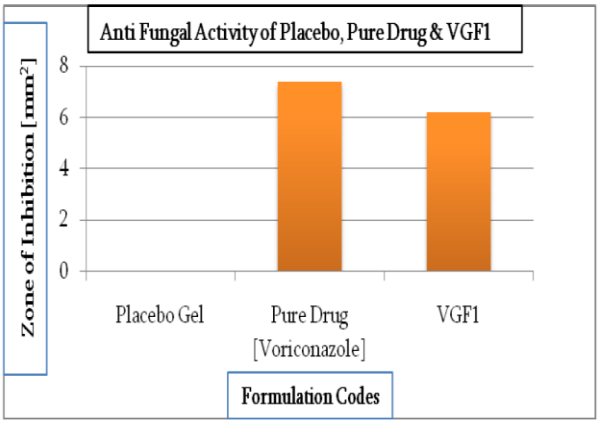


**Figure No. 3: The graphical representation of antifungal activity of Placebo, Pure Drug & VGF1.**

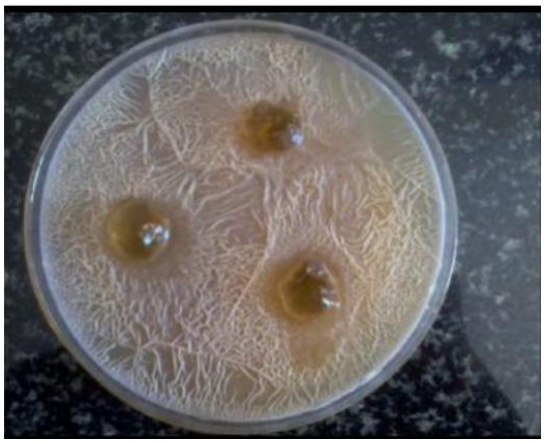

***Figure No. 4: VGF1 Formulation Zone Inhibition.***

**Figure No. 5: Zone Inhibition Placebo Gel Formulation.**

**Figure No: 6 Zone Inhibition of Pure Drug [Voriconazole].**

## CONCLUSION

The physical assessment of various formulations was successfully carried out. The appearance of formulations was translucent to off white. The gel formulation showed no sensitivity and no skin irritation. The rheological properties were found satisfactory. The viscosities of Carbopol gels ranged from 1900 to 2500 centipoises (cP). It can be concluded that gel formulations showed acceptable physical properties and drug diffusion study. Among all the three gel formulations, Carbopol 940 having 1% concentration showed the promising results with respect to % drug diffused. Being optimized formula, the VGF1 was subjected to % drug diffusion and antifungal activity which showed promising results. Further, in the Carbopol gel formulations, the % drug diffusion was decreased with increase in Carbopol concentration because of viscosity increases with increase in polymer concentration. From the above results it can be concluded that the Voriconazole Gel formulation VGF1 was suitable for topical application.

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