ORIGINAL ARTICLE

Preparation and evaluation of topical span 60-based oleogel of voriconazole

Hiba Muneer Fysal[1], Hanan Jalal Kassab[2]

[1]Ministry of Health, Baghdad, Iraq, [2]College of Pharmacy, University of Baghdad, Baghdad, Iraq

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ABSTRACT

Voriconazole (VOR) is a triazole antifungal agent; it blocks the synthesis of ergosterol, available in the market orally and intravenously, but, not without various side effects. The aim of this study is development and characterization of VOR oleogel for the topical treatment of skin fungal infection to avoid the drug's systemic side effects that are associated with oral and IV routes. The gelator Span 60 (S) was added at different concentrations to different oils (oleic OO, grapeseed GO, and sesame oil SO) to obtain the minimum gelation concentration, the prepared formulas were subjected to various evaluation tests, and the optimum formula was checked for antifungal effect, and subjected to viscosity, and texture analysis. The optimized formula, Span60 with SO 14SSO, showed 100% drug release, good antifungal activity, and acceptable transition temperature. The study of viscosity demonstrated the pseudo-plastic shear thinning behavior. A Fourier-transform infrared study showed that the drug and excipients did not significantly interact. 14SSO might be a promising topical treatment option for skin fungal infections.

Key words: Antifungal, gelator, sesame oil, Span 60

INTRODUCTION

Topical delivery of drugs helps to avoid the first-pass effects, irritation in the gastrointestinal tract, and degradation of the drug due to metabolism that is associated with oral administration.[1] Gels are patient friendly topical semisolid preparation, they are basically liquid trapped in a three dimensional (3D) solid gelator.[2] Oleogel (OG) the liquid is an oil entrapped in a self-assembly gelator, to form a viscoelastic system.[3] It has a multitude of advantages, such as ease of manufacture. The popularity of OG is increasing due to its ability to penetrate the layers of skin, and ability to accommodate medication which is soluble in liquid oils such as voriconazole (VOR)[4] furthermore, fatty acids and essential oils have permeation-enhancing impact, which may be the reason why OG has a high permeability through the skin. In addition, the safety of the oils employed in OG adds to their potential as a promising topical medication delivery vehicle.[5] Cutaneous fungal infection is a common worldwide disease.[6] VOR, an azole antifungal, has a broad spectrum of antifungal activity and is effective on strains resistant to other antifungal agents. It is a second-generation triazole available in both intravenous and oral formulations.[7] However, administration through these routes is associated with several side effects such as hepatotoxicity, joint or muscle pain abdominal pain, unusual tiredness or weakness, and vision change.[8] Furthermore, its intravenous administration is reported to cause heart rhythm problems.[9] Therefore, there is a need for a VOR topical delivery system for skin fungal infections to overcome the limitations and side effects.[10] OG exhibits

Address for correspondence:
Dr. Hiba Muneer Fysal,
Ministry of Health, Baghdad, Iraq.
E-mail: hiba.abd2200@copharm.uobaghdad.edu.iq

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superior skin penetration without a chemical catalyst, making it an effective vehicle for lipophilic medications. These drug delivery systems can achieve controlled delivery of drugs and enhance the performance of drug safety, stability, and efficacy.[11] This research aimed to develop an OG formulation of VOR using Span 60 (S) as a gelator with several oils as a solvent.

MATERIALS AND METHODS

Materials

VOR was a kind gift from Sama Alfayhaa for the Pharmaceutical Industry/Iraq, Span 60 was purchased from Alpha Chemika/India, and oils were supplied from Loba Chemie/India.

Preparation of oleogel

The saturation solubility of VOR in various mediums was determined using the shaking flask method.[12] The blank OG was prepared to find the minimum gelation concentration (MGC) of the gelator in each of the selected oils, and this was done by using the specific quantity of span 60 in the vials, then the weight was completed to 1 g with the oil, followed by incubation of the vial in a water bath at 85°C for 30 min clear solution is achieved, to ensure the gelator solubility in oil. The OG vials were allowed to cool to the room temperature. The vials were then inverted to ensure OG formation. Solid (gel) OG is obtained when there is no flow in the OG. The OGs that passed this test were selected for drug-loading, by inclusion of 1% w/w of the drug to the chosen quantity of the oils and then, the gelator was added with stirring for 40 min at 85°C.[13]

Transition temperature

The vials containing VOR OGs were placed in a water bath at 24°C. Subsequently, the temperature increased every 15 min by 2°C until it reached 85°C. After every 15 min, the vials were inverted to observe the movement of the OG formulation. The gel-sol point is the moment when the OG begins to flow. Then the temperature decreased every 15 min by 2°C until it reached 24°C to measure the gelation points.[14]

Fourier-transform infrared analysis

The Fourier-transform infrared (FTIR) spectra of OG were examined using an FTIR instrument (Model, Alpha-e, Bruker, Germany).[15] The result was graphed using Origin Lab software 24.

In vitro release study

A thin film of 1 g of medicated OGs, containing 10 mg of VOR, was placed onto a watch glass of 7 cm diameter. A stainless-steel mesh was utilized to cover the sample. It was placed at the base of a 500 mL dissolution jar containing citrate phosphate buffer pH 5.5 in the USP Type II dissolution apparatus. A control containing a solution of 10 mg of VOR in the selected oil was used alongside the release experiments of OGs to make comparisons with the OGs. The *in vitro* release study was performed at 34°C ± 0.5°C and rotated at 75 rpm. To keep the sink condition, samples of 5 mL were taken out at 1, 2, 3, 4, 5, 6, 7, and 8 h and replaced with an equivalent amount of new buffer solution; then filtered the sample with a 0.45 filter syringe and spectrophotometrically analyzed for VOR at its λmax 256 nm.[16] The best formula was further studied.

Viscosity studies

The selected VOR OG was rotated at 5, 10, 30, 50, 100, and 200 rpm upward and downward using spindle number R6 (Myr, Spain), allowing a 2-min rotation period before reading.[17]

Texture analyzer

A texture study of the prepared OG was performed using a TA: XT, plus texture analyzer (Stable Micro Systems Ltd. Godalming, Surrey, UK). The sample cups used to store the samples have an internal diameter of 5 cm. The samples have a thickness of 3.0 ± 0.3 cm. The texture analyzer's probe had a diameter of 1 cm and a load cell of 5 kg, specifically a 1″spherical probe (*P*/1S). The velocity at which the probe entered the sample was 2 mm/s. The depth of penetration reached a maximum of 1 cm. The firmness and cohesiveness of the sample were quantified, and the resulting plots of force versus penetration depth were obtained. This test assesses the uniformity of semisolid medicinal products.[18]

Antifungal-sensitivity test

Broth macro dilution test was used, *Candida albicans* was prepared as a fungal suspension with a concentration of 1.5 × 108 fungus cells per mL (0.5 McFarland scale adjusted standardized microbial suspension). Mix an equal amount of fungal suspension, with the selected formula, and with the blank OG as a control (without VOR) separately, and put the mixture in the incubator for 15 min. Then, transfer 100 mL from the mixture above in a tube containing incubation sterilized nutrient liquid medium; then incubated for 24 h.[18,19]

Statistical analysis

The measurements were carried out in triplicates and subjected to the statistical analysis. One-way ANOVA was performed using GraphPad Prism 8.0.1. The similarity factor was employed in the *in vitro* release analysis utilizing the DD solver program.

RESULTS

Oleic acid oil (OO), grape-seed oil (GO), and sesame oil (SO) were selected based on their high-solubilizing capacity for the Voriconazole. The MGC of Span 60 was found to be 27wt%, 12wt%, and 14wt% in the OO, GO, and SO, respectively.

Subsequently, the VOR was added into three OGs, starting with the lowest concentration of Span 60 those oils had gelled. OG formulations are shown in Table 1. The gel-sol transition temperature increased as the concentration of the span60 increased. Ultimately, temperatures at which the OGs experienced a phase change from a Solid (gel) to a liquid (sol) form were higher than the typical temperature of the body. ANOVA test showed that there is no significant difference between the formulas ($P < 0.05$). The results are listed in Table 2. The controllable release and release ratios of VOR were closely linked with the structure of the organic oils. The release profiles of VOR show typical sustained release behavior; as the concentration of the span 60 OG increases, the release percentage of the drug decreases. Because the oil is known to prevent the release of the hydrophobic medication, the control has been developed. The control VOR oily solution showed nonsimilar release with a similarity factor ($f2 < 50$) in comparison with the respective OGs. The 14SSO formula showed 100% release at 8 h, as shown in Figure 1a-c. FTIR analysis is done for the lowest span 60 concentration formula of the selected oils utilized in our investigation. The 3700–3200 cm^{-1} wavenumber range showed a large peak in all OG formulations. Pure VOR and OG formula FTIR spectra were identical. The C–N peak around 1128.5 cm^{-1}, the–OH peak stretching at 3189.9 cm^{-1}, and the C–F peak at 1403.89 cm^{-1} were retained in all the formulations, as shown in Figure 2.

Table 1: The Oleogel names and composition

Formulation name	VOR % (w/w)	Span 60% (w/w)	Oil up to l g
27SOO	1	27	OO
30SOO	1	30	OO
32SOO	1	32	OO
12SGO	1	12	GO
14SGO	1	14	GO
16SGO	1	16	GO
14SSO	1	14	SO
16SSO	1	16	SO
18SSO	1	18	SO

SO: Sesame oil, GO: Grape-seed oil, OO: Oleic acid oil, VOR: Voriconazole

Table 2: Results present the T sol-gel, T gel-sol, for voriconazole oleogel

Oleogel	T sol-gel °C±SD*	T gel-sol °C±SD
27SOO	32.33±0.53	40.33±0.73
30SOO	30.33±0.57	41.33±0.57
32SOO	29.66±1.15	43.66±0.75
12SGO	32.26±0.53	41.06±0.53
14SGO	30.26±0.20	41.13±1.15
16SGO	28.26±0.55	41.06±0.53
14SSO	30.81±0.57	39.66±0.73
16SSO	29.81±1.15	41.66±0.73
18SSO	28.81±0.27	43.33±0.55

SO: Sesame oil, GO: Grape-seed oil, OO: Oleic acid oil, SD: Standard deviation

From the results above, especially the *in vitro* release profile; the 14SSO formula was used as a selected formula for further study.

As shown in Figure 3, the Viscosity behavior of the 14SSO formula showed the non-Newtonian pseudo-plastic shear thinning type of flow which is characterized by viscosity reductions with rising shear rates. When the rate of shear was reduced, there was an incomplete reversal of the structure, resulting in the formation of a small open hysteresis loop. Figure 4 illustrates the results of the texture analyzer test, where the highest force recorded as a graph peak quantifies the firmness of the sample (105 g). The region covered by the positive section of the graph represents the level of consistency in the samples. The graph negative force peak represents the adhesive force of the sample; the moderate negative value indicates the moderate stickiness of the sample. The region below the negative portion of the graph is referred to as adhesiveness, which represents the amount of energy needed to separate the probe from the sample. The antifungal study showed that there is no growth in the tubes treated with a mixture of the fungus and the 14SSO formula, and the appearance of the growth of fungus in the tube results from the treatment of blank OG with the fungi. The result is illustrated in Figure 5.

DISCUSSION

The differences in the MGC of the gelator in oils might be related to the different solubility of the span 60 in the oils or maybe to the differences in oil viscosity.[20] The formation of the OG occurred by crystallization of the span 60, causing its molecules to self-assembly as the temperature decreased. This could be attributed to the interaction between the span60 hydrophobic parts, resulting in the formation of a network of three-dimensional structures. The oil was then immobilized within this structure, with drug molecules trapped within the solid OGs.[21] When the temperature increased above the transition temperature, the bond between self-assembled structures was completely broken, causing the collapse of the networked structure; this resulted in the gelled system transitioning into a liquid state and being able to flow freely.[22] The result indicates that the OGs maintained their solid state when applied topically to the skin. These results are consistent with the findings of the span OG investigation.[23] The *in vitro* release percentage and the low rates of drug release can be attributed to the formation of dense 3D networks resulting from increasing concentrations of the gelator. In other words, the VOR has to diffuse through the oil and gelator to be released from the OG. On the other hand, the OG of OO show the slowest and less percentage of release of the VOR drug than SO and GO based OG, this may result from the higher concentration of span60 needed to form the OG as shown in the MGC study. The control release behavior belongs to the OG scaffold rather than the properties of the oil. The

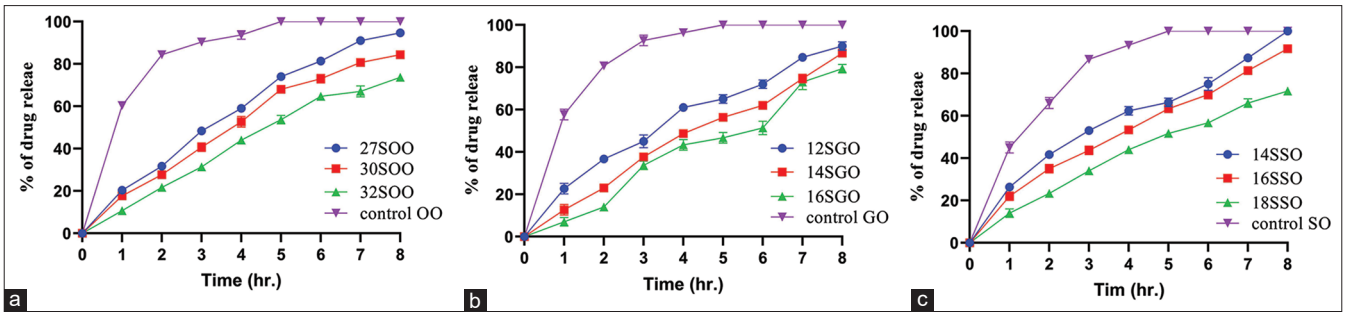

Figure 1: (a-c) The results of the voriconazole oleogel with oleic acid oil, grape-seed oil, and sesame oil, respectively, as percentage of *in vitro* dissolution of the drug, in citrate phosphate buffer (pH 5.5), at 34°C

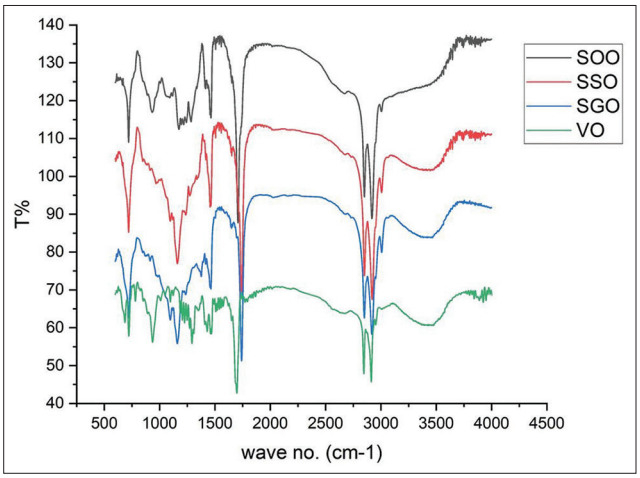

Figure 2: Fourier-transform infrared of voriconazole drug and span60-based Oleogel formulas

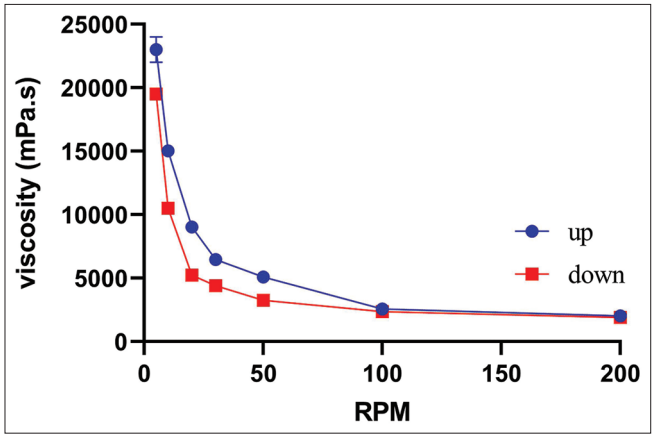

Figure 3: Viscosity of 14SSO formula

exceptional solubilizing activity of the OGs constituents, such as span60 and SO, was responsible for this notable increase in drug release from the 14SSO formula.[24]

This outcome is consistent with the outcome obtained from cinnarizine OG with varying quantities of the gelator.[25] The FTIR analysis peaks of the OG formula indicated that no irreversible interactions were established between the drug and excipients. The viscosity finding demonstrated that the gelling material's disorganized molecules align their long axes in the flow direction when the shear stress is increased. Viscosity and the material's internal resistance are both decreased by this orientation.[26] This thixotropic behavior of OG is a desirable characteristic of pharmaceutical preparations to deliver an initially thick product as a thinner, easily spreadable material. The same trend of results was found in azithromycin OG.[5] Hysteresis is a typical characteristic of gels; completely recovering the initial apparent viscosity was accomplished after some time, and this could be related to the gel architecture's disturbance.[27] The texture analyzer result indicates that the 14SSO OG has moderate viscosity with good adhesive and firmness properties for better skin permeation for topical application.[18] Samples with moderate hardness are less difficult to remove from the container or to spread on the skin. Adhesiveness helps predict the topical skin residence time. Cohesiveness reflects the internal forces that must be overcome to spread the product on the surface of the skin; this parameter is related to the elasticity of the sample.[28] The antifungal evaluation indicates that VOR OG was able to inhibit the growth of the microorganism. On the other hand, the non-medicated OG showed a growth of fungus. This implied that the antimicrobial activity of the 14SSO is because of the existence of the VOR drug in the formula rather than the OGs constituents.

CONCLUSIONS

The organogelator Span 60 gave good gelation to the oils OO, GO, and SO. The selected OG formula 14% of span 60 with SO achieved the 100% of drug release in 8 h, good antifungal activity, and suitable firmness and cohesiveness texture, serving as a good candidate for VOR topical formulation.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

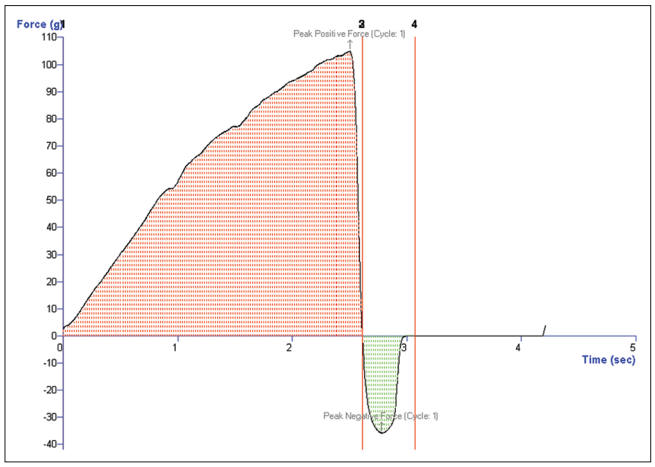

Figure 4: Graph of oleogel texture determination

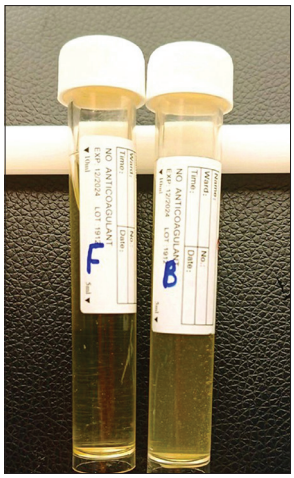

Figure 5: The antifungal activity of voriconazole (VOR) in on *Candida albicans* for F (14SSO) formula and B blank Oleogel (without VOR)

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