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Microsponge based drug delivery system of voriconazole for fungal infection: formulation development and *In-vitro* evaluation

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ABSTRACT

The plan behind the present research work was to develop a microsponge based dosage form for modified delivery of voriconazole prepared by quasi-emulsion solvent diffusion method using polymer Ethylcellulose with two factors drug-polymer ratios and surfactant concentration, these two factors influences micro particles and physical properties. The characterization techniques followed for the formed microsponges were DSC, FT-IR, SEM and particle size analysis, along with morphology, drug loading, *in-vitro* drug release data. DSC and FT-IR data discloses that there were no chemical interactions between drug and polymer used. The drug-polymer ratio and surfactant concentration showed notable impact on drug content, encapsulation efficiency and particle size, SEM micrographs revealed that microsponges formed were spherical in shape with porous surface, and had 119.47 µm mean particle size. The microsponges were then loaded in carbopol gel followed by *ex vivo* drug deposition, primary skin irritancy study, *in vivo* antibacterial activity and *in-vitro* drug release study; which depicted that microsponges with drug-polymer ratio of 1:3 were more capable to give extended drug release of 93.79.±0.06 % at the end of 24 h, better in contrast to conventional formulation. Hence, the developed microsponge based formulation of voriconazole would be a hopeful, promising alternate to conventional therapy for the fungal treatment.

Keywords: Voriconazole, Microsponge, Particle size, Entrapment efficiency, *ex vivo* drug deposition primary skin irritancy

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INTRODUCTION

Drug delivery through skin is a powerful technique for local as well as systemic administration of biological response modifiers. The topical administration evades gastric irritation and hepatic first pass metabolism evident from oral treatment. The topical delivery recommends a sustained release of drug at the site of application as well as termination of therapy by removal of the formulation in case where toxic effects are noticed.

The barrier function of skin in transdermal drug delivery is due to the outermost layer of the skin, the stratum corneum encompass a vascular dead keratinized cells[1]. As a result, diverse methodologies are adapted to achieve desired therapeutic activity from a topical formulation. One such methodology is microsponge-based delivery systems (MDS)

Voriconazole is a low molecular weight synthetic triazole antifungal drug for the treatment of superficial and systemic fungal infections. Voriconazole has confirmed activity against aspergillosis, candida infections, scedosporium apiospermum and fusarium spp., the oral and parenteral administration of voriconazole repeatedly produces injection site reactions and allergic reactions. The oral administration of voriconazole is reported to interact with a number of medicines, which include rifampicin, rifabutin, carbamazepine, quinidine and ergot alkaloids[2-4]. These issues might be overwhelmed by adopting novel approach of voriconazole.

MDS gives guarantee of drug localization on skin surface and inside epidermis without entering in systemic circulation in greater extent; in this manner decreasing systemic and local cutaneous adverse effects. MDS likewise recommend preference of programmable release and are biologically protected. In addition, this innovation shows moderately a lot of benefits via drug entrapment by means of better formulation flexibility, reduced side effects, improved elegance and better stability[5-8].

Thus, taking into consideration the benefits of MDS, the objective of this current investigation was aspired to formulate and evaluate voriconazole microsponge loaded carbopol gel for its promising effects over extended period of time.

MATERIAL AND METHODS

Materials

Voriconazole, ethyl cellulose 50 cps, polyvinyl alcohol, carbopol 934 triethanolamine, disodium hydrogen phosphate, potassium dihydrogen phosphate, triethyl citrate and ethyl acetate were used.

Methodology

Preformulation studies

(a) Drug – Excipients compatibility studies by DSC

DSC studies were carried out using Mettler-Toledo DSC 821e instrument equipped with an intercooler (Mettler-Toledo, Switzerland). Indium and zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed in aluminium crucibles and heated at a constant rate of 10◦ C/min over a temperature range of 25–300◦C. Inert ambiance was continued by purging nitrogen gas at flow rate of 50 mL/min[9].

Formulation of voriconazole microsponge

The voriconazole microsponges were prepared by quasi emulsion solvent diffusion procedure with internal and external phases[10]. To prepare the internal phase, different concentrations of drug: polymer ratios were dissolved in ethyl acetate 20 ml. In this procedure, ethyl acetate was a proficient solvent for dissolving both the drug and the polymer. The external phase, which included the emulsifying agent dissolved in 80 ml of distilled water, was placed in the vessel, and stirred at 1000 rpm, and then the internal phase was slowly added into the stirring external phase. The mixture was then stirred at 1000 rpm for 8 h at room temperature to remove the ethyl acetate from the reaction flask. The formed microsponges were filtered through filter paper with a pore size of 0.45 µm, washed with distilled water and dried at room temperature for further use.

Table 1: Formula of voriconazole microsponges

F.Code	Drug (mg)	Polymer (mg)	Ethyl Acetate (ml)	Triethyl citrate (ml)	PVA (%w/v)	Water (ml)
VZM1	100	50	20	2	0.75	80
VZM 2	100	100	20	2	0.75	80
VZM 3	100	150	20	2	0.75	80
VZM 4	100	200	20	2	0.75	80
VZM 5	100	250	20	2	0.75	80
VZM 6	100	300	20	2	0.75	80
VZM 7	100	150	20	2	0.45	80
VZM 8	100	150	20	2	0.6	80
VZM 9	100	150	20	2	0.9	80
VZM10	100	150	20	2	1	80

Evaluation of voriconazole microsponges

Production yield

The production yield of voriconazole microsponges was determined by using formula mentioned below [11].

$$\% \text{ of Production yield} = \frac{\text{Practical Mass of microsponges}}{\text{Theoritical Mass (Polymer+Drug)}} \text{ X } 100 \quad (1)$$

Drug content and Encapsulation efficiency

Exactly weighed amount (100 mg) of microsponges containing drug was kept in 100 ml phosphate buffer solution (pH 7.4) for 12 h with constant stirring. Filtered samples (using 0.45 lm membrane filter) were analyzed at 276 nm next to blank using UV spectrophotometer (Pharmaspec 1700, Shimadzu, Japan). Evaluation of drug content and encapsulation efficiency for all batches were completed using following expressions

$$\text{Drug content (\%)} = \frac{Mact}{Mms} \text{ X100} \quad (2)$$

$$\text{Encapsulation Efficiency} = \frac{Mact}{Mthe} \text{ X } 100 \quad (3)$$

Where *Mact* = actual Voriconazole content in weighed quantity of microsponges,

Mms = weighed quantity of microsponges and *Mthe* = theoretical Voriconazole content in microsponges [11].

Scanning electron microscopy (SEM)

For evaluating morphology and surface topography, the formulated microsponges were examined under scanning electron microscope (LEO 440i, UK) operating at 5 kV. Using double adhesive tape, samples were mounted on a metal stub and coating with platinum/palladium alloy under vacuum was done[12].

Particle size analysis

Particle size analysis of prepared microsponges was carried out using particle size analyzer (Malvern Mastersizer Hydro 2000, Malvern, UK). Microsponges were dispersed in double distilled water before running sample in instrument to ensure that light scattering signal (as indicated by particles

count per second) is within the sensitivity range of instrument[13].

Preparation of Voriconazole microsponge gel

0.5 g of Carbopol 937 was taken and was uniformly dispersed in beakers containing sufficient quantity of water and was allowed to hydrate overnight. In another beaker, drug containing microsponge formulations was dispersed in propylene glycol and methanol. Ingredients like methyl paraben, sodium Meta bisulphite and disodium edetate were dissolved in water and added to the drug solvent system. Triethanolamine was added to adjust pH to 6.5–7.5. Gels prepared were degassed by ultra-sonication. Formulations of microsponges containing voriconazole were characterized for pH using pH meter, viscosity using a Brookfield digital viscometer (Viscometer VR 3000), spreadability and drug content[14]. Quantities of the ingredients were mentioned in Table 2.

Table 2: Composition of Voriconazole microspongic gel formulation

S.No	Ingredients	Quantity (%w/w)
1	Drug Loaded Microsponges	1
2	Propylene Glycol	40
3	Methanol	8
4	Methyl Paraben	0.15
5	Sodium Meta Bisulphite	0.10
6	Disodium Edetate	0.10
7	Carbopol 934	1.00
8	Triethanolamine	Q.S
9	Water	100

Characterization of Voriconazole loaded microsponge gel

The prepared voriconazole microsponge loaded gel was subject to different physical evaluations studies like; colour, pH, viscosity, spreadability[15].

***In vitro* release studies of Voriconazole loaded microsponge gel**

In vitro release studies were performed by artificial dialysis membrane. For this testing, a vertical Franz diffusion cell with a surface area of 2.54 cm^2 and a reservoir capacity of 20 ml was used. The artificial membrane was firmly positioned between the two halves of the diffusion cell. The receptor compartment contained phosphate buffer (pH 5.4), and its temperature maintained at 37 ± 0.5^0C and stirred constantly by magnetic stirrer. A predetermined amount of formulated gel (2.7 mg) containing 1 mg of voriconazole was placed on the donor side. A total of 2 ml of the sample was withdrawn from the receptor compartment at definite time intervals and replaced with an equal volume of fresh receptor fluid. The aliquots were correctly diluted with the receptor medium and analyzed by an UV spectrophotometer. Measurements were performed in triplicate and their means were reported[16].

Primary skin irritation studies

Primary skin irritation studies of the voriconazole microspongic gel and plain gel were performed using nine male Wister rats. The experimental protocols for the animal study were approved by the Animal ethics committee of the department. (1358/ac/10/CPCSEA). Hair present on the back of each rat was removed using a depilatory and an area of 4 cm^2 was marked. Nine rats were randomly assigned to three experimental groups of three rats each. Group I served as a control, group II was treated with voriconazole plain gel, group III was treated with Voriconazole microspongic gel. 10 mg of sample were applied to each rat (2.5 kg^{-1} body mass) to groups I, II and III every day. The skin was cleaned before application of each dose and the reactions (erythema and edema), were scored after 1, 3, 5 and 7 days, as per the Draize patch test. The selection criteria for the Draize test and skin irritation score scale is shown in Table 3.

The primary irritation index (PII) was calculated using following Equations. The results of triplicate measurements and their means were reported[17].

PII ¼ Average scores X variable factors

Whereas average scores = Σ Erythema grade* + Σ Edema grade*/Number of animals*at 1, 3, 5 and 7 day and variable factor = types of skin X time of reading.

Table 3: Skin irritation score scale.

Grading	Description of irritant response
0	No reaction
+	Weakly positive reaction (usually characterized by mild erythema across most of the treatment site)
++	Moderate positive reaction (usually distinct erythema, possibly spreading beyond the treatment site)
+++	Strongly positive reaction (strong, often spreading erythema with edema)

In vitro antifungal study of voriconazole loaded microspongic gel

In vitro antifungal test was determined by Sabouraud dextrose agar disk diffusion method employing the 'cup–plate technique' using sterilized Petri dish. Voriconazole plain gel (1 mg/ml), voriconazole microspongic gel (1 mg/ml) and pure voriconazole as a standard (1 mg/ml) prepared in DMSO and were placed into cups of size 8 mm, then into wells of a Sabouraud dextrose plate previously seeded with the test organism of *Candida Albicans* MTCC 1637. After allowing diffusion of the solution for 2 h, the plates were incubated at 27^{0}C for 48 h. The zone of inhibition measured around each cup was compared with that of the standard. The results of triplicate measurements and their means were reported[18].

Ex *vivo* drug deposition study

The ex vivo skin deposition study was carry out using tape stripping technique. On the day of the trial, rats were randomly assigned to three experimental groups of five rats each. Hair was removed from the back of each rat by using depilatory (Anne French) and an area of 2 cm^2 was marked. Voriconazole plain gel (VLG) and voriconazole microsponge (VLMSG) formulations containing 1 mg equivalent of VL were applied on the skin and smoothly distributed on the marked area of different groups. At the end of 12 h, the skin surface of each group of animal was carefully washed with double distilled water and wiped with a cotton swab in order to take away excess formulation. The SC was removed by tape stripping with 15 pieces of adhesive tape. Tapes containing the SC were immersed in 5 ml methanol, vortex stirred for 2 min, filtered using a 0.45-µm membrane and analyzed for VL content by UV spectrophotometry. UV spectroscopy was selected as the method for determination as it is universal, cheap, rapid and easy to use and also has moderately high sensitivity. The amounts of drug detected in SC are indicative of drug deposition in the skin. Measurements were performed in triplicate and their means were reported[19].

In vivo antifungal activity of voriconazole loaded microspogic gel

Wister rats, weighing 200g were used to compare the efficacy of developed-loaded microsponge formulations with that of plain gel using surgical wound model infected with *Candida spp*. The surgical wound model was adapted as previously described by McRipley and Whitney[20]. Briefly; superficial surgical wounds were produced on the back of mice by making a longitudinal midline incision 2.3 ± 0.2 cm in length and extending down to the panniculus carnosus. A contaminated suture was inserted through the skin to infect the wound and secured by knotting and formulation was administered topically 0.1 ml/rat. Treatment was initiated at 4 h after surgery and continued for further 3 days. On day 5 after surgery, 16–20 h after the last topical application, the animals were killed by diethyl ether asphyxiation. A 1 x 2 cm area of skin, including the wound, was excised and homogenized in 1 ml of saline solution. The homogenates were serially diluted, plated on agar plates, and incubated at 37°C. After 24 h, the number of colony forming units (CFU) per wound was counted. Bacterial counts were expressed in terms of mean ± SD.

Accelerated stability studies

The prepared voriconazole microspongic gel were packed in aluminium collapsible tubes (5 g) and subjected to stability studies at 5^{0}C, 25^{0}C/60 % RH, 30^{0}C/65 % RH, and 40^{0}C/ 75 % RH for a period of 3 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles[21].

RESULTS AND DISCUSSION

In this experiment, voriconazole containing ethyl cellulose microsponges have been formulated and loaded into gel base which was check-up as topical carriers for the modified release for fungal infection. The impact of the drug: polymer ratio and emulsifier concentrations were studied on production yield, drug content, entrapment efficiency and mean particle size. The emulsion solvent diffusion method was opting to make microsponge because of its ease in manufacturing at large scale, cost effectiveness, reproducible and commercial purpose. To meet out the objective of this study we have chosen ethyl acetate as solvent because it has an ability to dissolve drug and polymer.

Differential Scanning Calorimetric Analysis (DSC)

DSC thermograms of pure drug and physical mixtures of drug and excipients are shown in Figure 1. The pure drug, voriconazole showed an endothermic peak at 130.03^{0}C and the physical mixture of drug and excipients showed endothermic peaks at 129.03^{0}C respectively. In this case, melting endotherm of drug was well protected with minor changes in terms of shifting in the temperature of the melt. It is recognized that the quantity of material used, particularly in drug-excipient mixtures, could influence the peak enthalpy. Thus, this slight change in the melting endotherm of drug could be due to the combination of drug and excipient, which lowered the purity of the constituent in the mixture, and this, might not necessarily point out potential incompatibility[22].

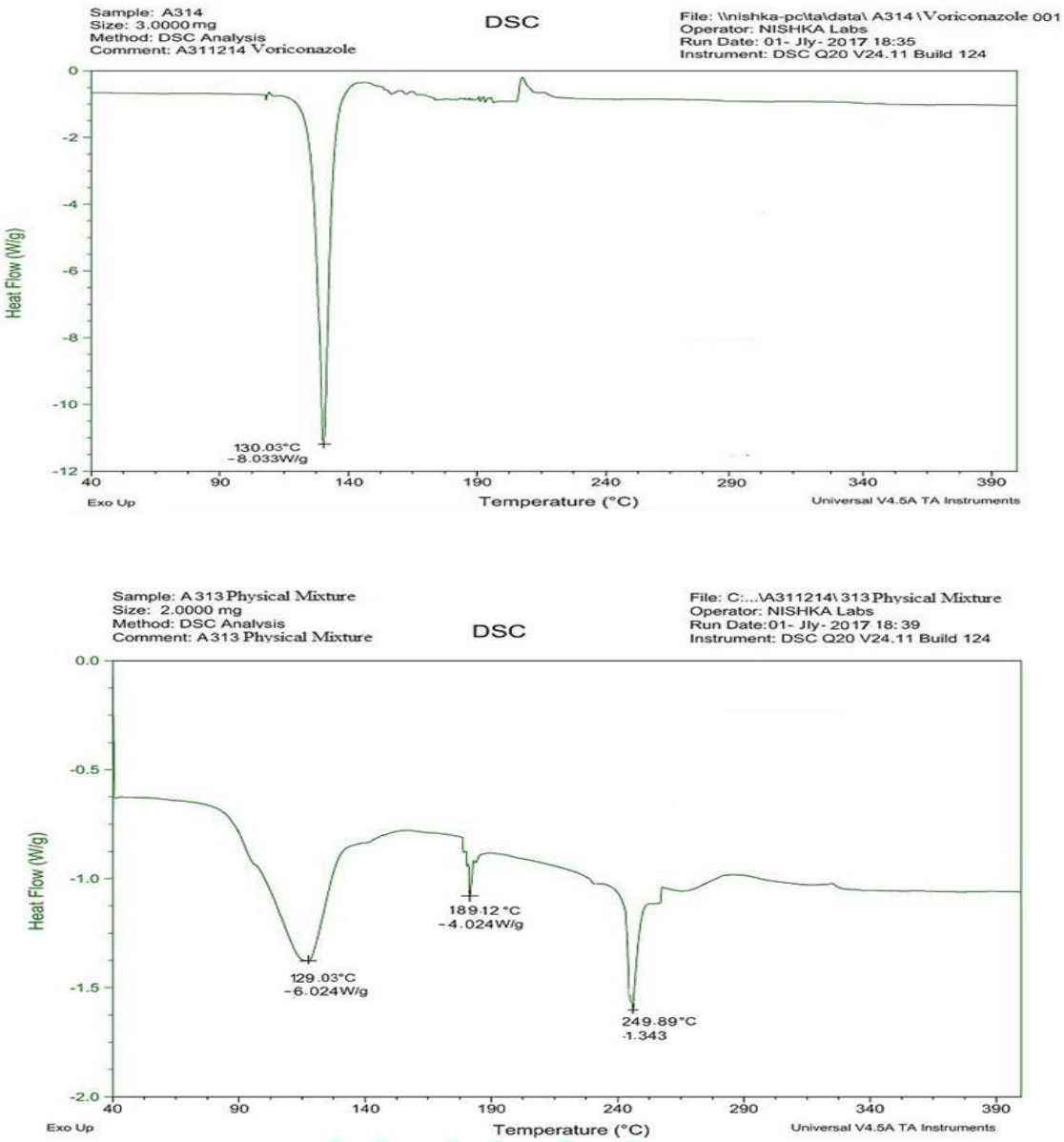

Figure 1: DSC thermograms of (A) Pure voriconazole and (B) Physical mixture of voriconazole PVA and EC

Production yield, drug content and encapsulation efficiency

The results of production yield, drug content and encapsulation efficiency of microsponges were described in Table 4 Production yield of voriconazole was significantly impacted by drug: polymer proportion and concentration of the surfactant. Increase in the drug: polymer ratio resulted into increased production yield. When drug: polymer ratio was 1:1 (VZM1) the production yield was very low, i.e. 20.18% while for drug: polymer ratio 1:3 (VZM6) it was 78.12%. Besides this drug polymer ratio, surfactant concentration also has impact on production yield when the surfactant concentration was 0.75% w/v the production yield was increased (VZM1-VZM6). As the concentration of surfactant reduced from 0.75% to 0.45% (VZM7-VZM8) yield was noticeably reduced to 26.28% and 36.11%. The production yield was drastically reduced from the formulations VZM9-VZM10 due to high concentration of surfactant (0.9%-1%) the reason for the less production yield may be due to the development of unreasonable foam and evaporation of the drugs while preparing microsponges.

The drug loading efficiency did not reach 100% at all ratios of drug: polymer used. This could be due to dissolution of drug in the solvent or in the aqueous phase. The outcome of encapsulation efficiency shows that, the higher drug loading efficiency was attaining at lower drug: polymer ratios. Additionally surfactant concentration also a vital part in encapsulation efficiency, utilization of higher amount of surfactant in the formulations of VZM9 and VZM10 caused great drug payloads and it influences the production yield. The entrapment efficiency of voriconazole microsponges was noted in the range of 58.10% to 92.10% individually. Based on the above results we considered VZM3 as optimized formulation and it was evaluated.

Table 4: Production yield, drug content and encapsulation efficiency of voriconazole microsponges.

F.Code	Production yield (%)	Drug content (%)	EE (%)
VZM1	20.18±0.11	46.07 ± 0.21	92.10±0.01
VZM2	35.48±0.21	29.00 ± 0.23	87.22±0.03
VZM3	50.15±0.28	21.22 ± 0.17	83.20±0.07
VZM4	62.11±0.02	19.05 ± 0.05	79.24±0.04
VZM5	69.08±0.05	16.25 ± 0.08	76.16±0.01
VZM6	78.12±0.01	14.05 ± 0.05	69.12±0.06
VZM7	26.28±0.01	12.15 ± 0.17	58.10±0.02
VZM8	36.11±0.12	10.10 ± 0.11	66.30±0.03
VZM9	19.40±0.11	10.00 ± 0.12	70.31±0.01
VZM10	18.54±0.19	9.13 ± 0.19	71.15±0.04

Scanning electron microscopy (SEM)

SEM images of voriconazole-loaded microsponges as shown in Figure 2. It shows that the microsponges were uniform, spherical in shape, and porous. No drug crystals were observed visually. The pores were created may be due to by diffusion of solvent ethyl acetate from surface of microsponges.

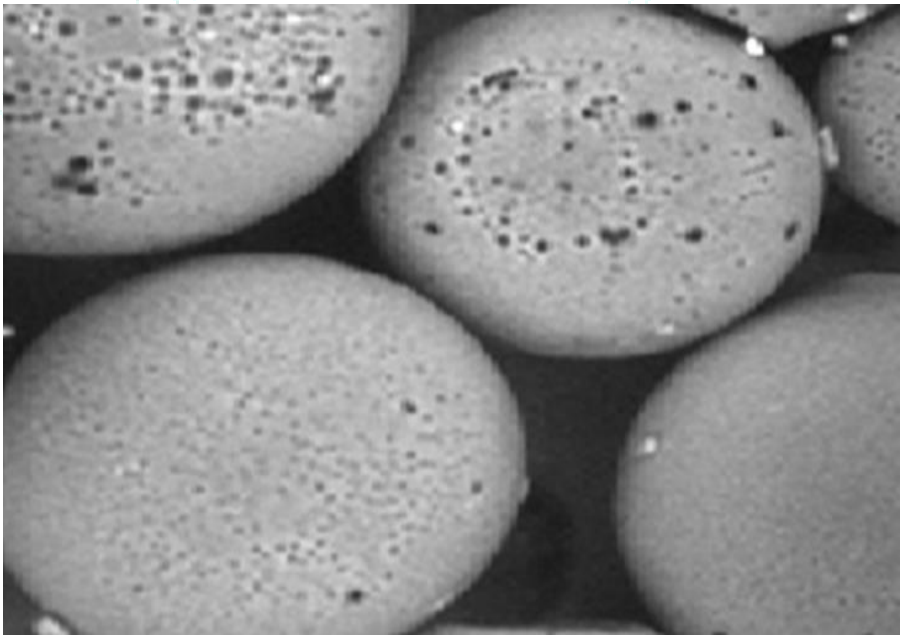

Figure 2: Scanning electron microscopy (SEM)

Particle size analysis

Using the laser light-scattering technique, a particle size distribution map by volume of the voriconazole microsponge was determined, which illustrate that the specific area, surface diameter and diameter by volume of the particles were 0.123 m^2/g, 48.68 µm and 70.08 µm, respectively. The particle size distribution of (0.1), d (0.5), d (0.9) and d (1) were 29.25 µm, 65.06 µm, 119.47 µm and 177.23 µm and the particle uniformity was 0.569. Figure 3.

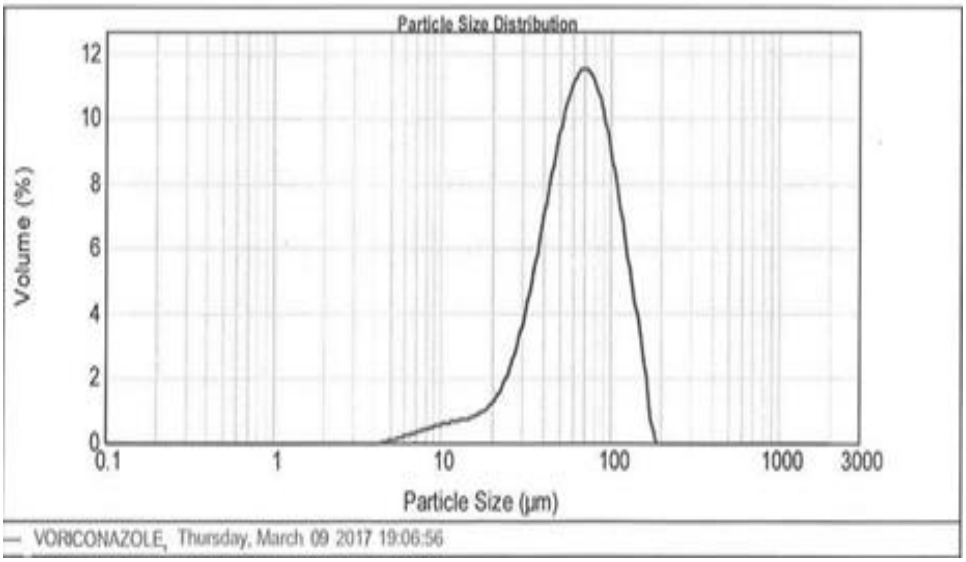

Figure 3: Particle size Characterization of Drug loaded microsponge

Characterization of voriconazole loaded microsponge gel

In vitro release studies of voriconazole loaded microsponge gel

The impact of the composition and vehicle in the formulation was investigated using an artificial cellophane membrane with phosphate buffer (pH 5.4). Being a topical preparation, the release medium was adjusted to the pH of the skin (i.e., pH 5.4). The *in vitro* release profiles of voriconazole from microsponge (VZMG3) and plain voriconazole gel (SVG) are shown in Figure 4. The obtained results indicated that voriconazole plain gel released 94.15% of drug within 2 hrs, whereas voriconazole loaded microsponges extended the drug release up to 24 hrs with 93.79%.

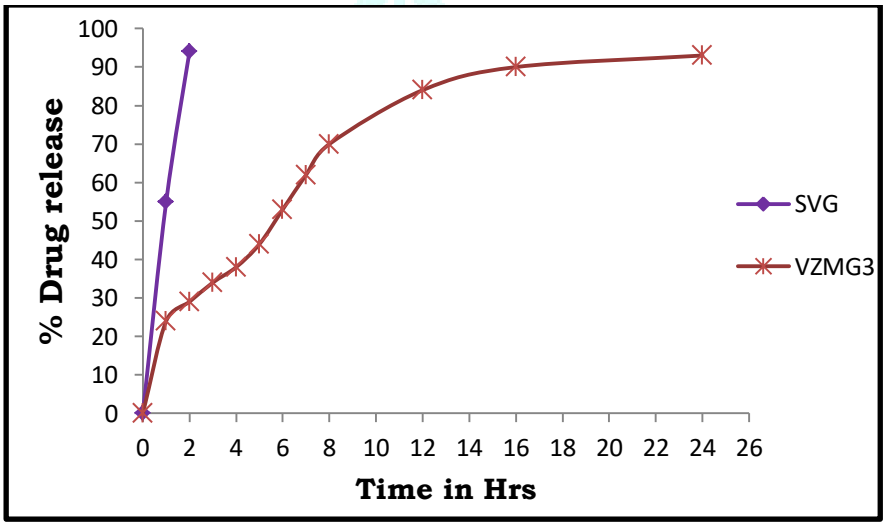

Figure 4: *In vitro* release studies of voriconazole plain gel and voriconazole microsponge gel

Evaluation of voriconazole microspongic gels

The prepared voriconazole loaded microsponge gels were inspected visually for their color, texture and appearance. All formulations were transparent, viscous and good homogeneity without lumps. The pH values of all prepared formulations were found in the range of 6.5–7.1, which is supposed to be suitable to pass up the threat of nuisance on application to the skin. The microsponge loaded carbopol gel was thicker than the gel loaded with plain drug. The viscosities of VZMGs were observed to be 24,210 to 46,730 cPs. The spreadability was observed to be in the range of 6.30 to 11.31g cm/s which is demonstrating that spreadability of k microsponge gel was great. The results were depicted on Table 5.

Table 5: Evaluation of voriconazole microsponge loaded carbopol gel.

F.Code	Visual inspection	pH	Spreadability	Viscosity
VZMG1	Transparent	6.9±0.01	6.30±0.04	24,210±0.79
VZMG2	Transparent	6.6±0.01	8.40±0.38	28,630±1.26
VZMG3	Transparent	6.8±0.03	11.31±0.31	33,520±1.64
VZMG4	Transparent	6.5±0.01	10.09±0.43	39,540±1.65
VZMG5	Transparent	6.8±0.02	10.07±0.59	42,630±1.15
VZMG6	Transparent	7.2±0.04	7.70±0.58	46,730±1.20
VZMG7	Transparent	7.0±0.01	11.24±0.39	35,710±1.15
VZMG8	Transparent	7.1±0.01	11.20±0.04	35,260±1.08
VZMG9	Transparent	6.3±0.02	10.08±0.29	35,580±1.12
VZMG10	Transparent	6.2±0.03	10.21±0.34	35,450±1.14

Skin irritation studies

The overall scores for erythema and edema of the rats at the 1st, 3rd, 5th and 7th days were performed. The PII was calculated based on the sum of the scored reactions divided by 48 (four scoring intervals multiplied by two test parameters multiplied by three rats). Voriconazole microsponge did not produce erythema and was a non-irritant (PII: 0.00), whereas voriconazole plain gel exhibited some erythema and a PII of 0.04 and 0.06, indicating scarcely noticeable irritation on to the rat skin Figure 5.

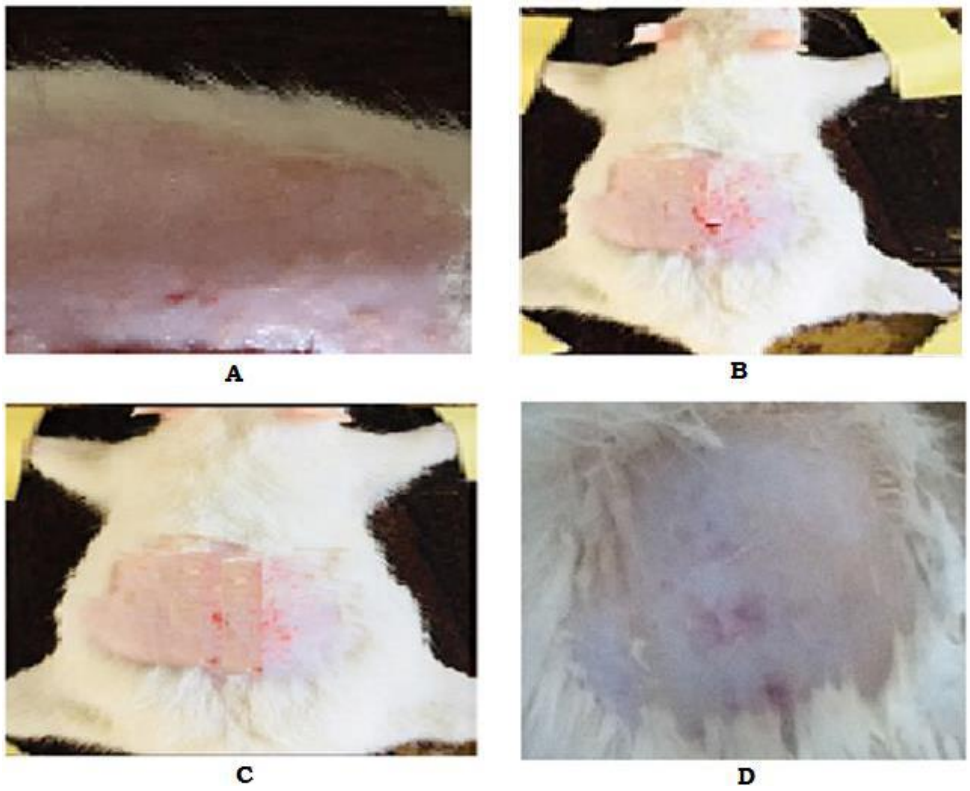

Figure 5: Skin irritation study (a) Control (b) Plain Fluconazole gel (c) Placebo (d) Voriconazole loaded microspongic gel

***In vitro* antifungal study of voriconazole loaded microspongic gel**

The remarkable differences in antifungal activity were observed between VLMSG, VLG and control formulations (DMSO). VLMSG produced 1.9±0.07 mm of zone of inhibition but there were no zone of inhibition was seen with disk containing DMSO and plain gels against *Candida Albicans*. Figure.6

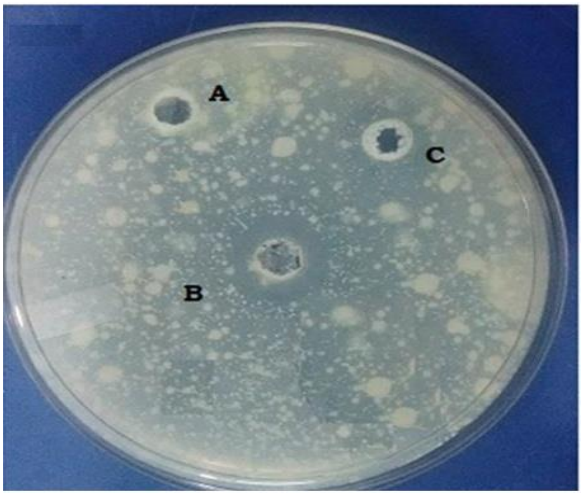

Figure 6: *In vitro* antifungal studies (A) Plain gel (B) Voriconazole microsponge gel (C) Control

Ex *vivo* drug deposition study

For successful topical medication treatment requires adequate quantity of medication taken-up by skin over a specific timeframe for maximal therapeutic activity. The drug extraction efficiency showed that 228.68 µg and 57.45µg of voriconazole by tape stripping method, from which their depositions were calculated. The amount of VL deposited in the skin (sc) from VLMSGS was 126.48±3.24g/cm² which was 3fold greater than that of VLG 40.8±3.11g/cm² at the end of 24h. This demonstrated that the microsponges enhanced the drug residence period on skin. Figure.7

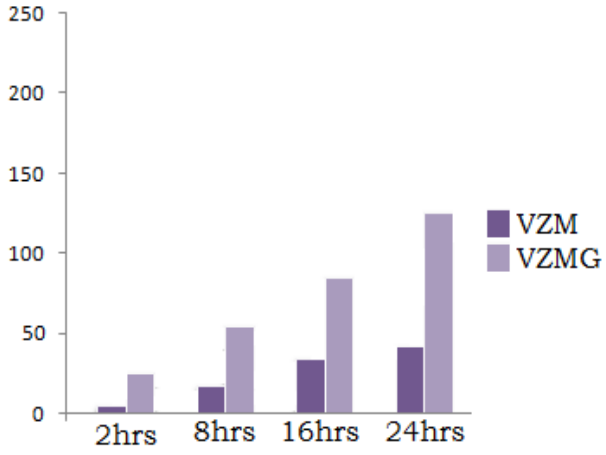

Figure 7: *In vivo* drug deposition of VZM & VZMG

***In vivo* antifungal activity of voriconazole loaded microspogic gel**

VLMG gel (once daily); VLG gel (three times a day) administered topically compared with untreated control groups. During the treatment period the bacterial counts were observed, VLMG gel formulation significantly reduced the mean bacterial counts 3.18 ± 0.22 as compared with VLG 2.51±0.13 log10 CFU/wound Figure. 8. At the same time, there was no difference has been observed in untreated group. Therefore, the results proved that microsponge formulations extensively different from normal gel preparations.

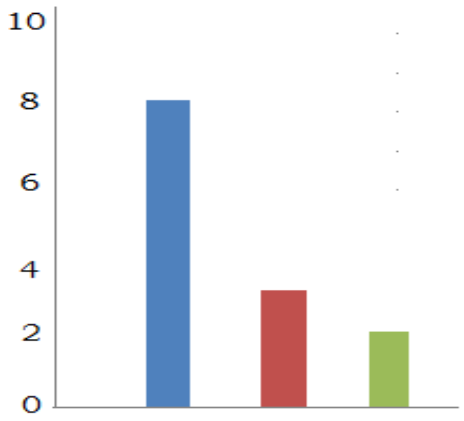

Figure 8: Wound healing property of VZMG against *Candida spp*. mean ± SD (n = 3)

Accelerated stability studies

The developed VZ-loaded microsponge formulation was found to be stable upon storage for 3 months. No major changes were noticed in their physical properties and drug release profiles.

SUMMARY CONCLUSION

Voriconazole microsponge was formulated using the quasi emulsion solvent diffusion method and characterized as an effective carrier for the topical delivery of the drug. The properties of the developed system were greatly influenced by the drug: polymer ratio. The prepared microsponge gel formulation confirmed controlled release of the drug. The primary skin irritation tests exposed that microsponge gel formulation was non-irritant. In addition, voriconazole engaged antifungal activity on encapsulation in microsponges. The microsponges confirmed to be a potential carrier for voriconazole in topical fungal treatment. The formulations showed excellent maintenance of drug on to the skin, which representing microsponge gel is a good drug delivery system as compared with plain gel. The microsponge-based gel formulations will have significantly advanced part in treatment of primary and secondary fungal skin infections.

Conflicts of interest

The authors declare no conflict of interest.

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