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DEVELOPMENT OF VORICONAZOLE MICROSPONGE BASED TOPICAL DELIVERY FORMULATION

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ABSTRACT
Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, etc. to control the delivery rate of active agents to a predetermined site in human body. The study aimed towards formulation development and evaluation of polymeric micro sponges consisting of noncollapsible structures with porous surface through which active ingredients are released in a controlled manner

Preparation of Voriconazole microsponges is done by quasi emulsion solvent diffusion method followed by preparation of microsponge Voriconazole gel. Charactization of Voriconazole microsponges is done by various physical parameters e.g. Particle size (Microscopy), Morphology and Surface topography, Characterization of pore structure, Loading efficiency and production yield, Drug content, Compatibility studies, Resiliency as well as by In vitro drug release studies e.g. drug release study, release kinetics, In vitro anti-microbial study etc. This system has been utilized for the improvement of performance of topically applied drug. MDS technology is now being presently used in cosmetics, over-the-counter(OTC) skin care, sunscreens and prescription products.

KEYWORDS: *Polymeric Microsponges (PMS), Voriconazole, Microsponges delivery systems (MDS),*

INTRODUCTION[1-3]

Today more and more developments in delivery systems are being integrated to optimize the efficacy and cost effectiveness of the therapy. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, and liposome etc. To control the delivery rate of active agents to a predetermined site in human body has been one of the biggest challenges faced by drugindustry. The Micro sponge delivery system fulfils these requirements. Microsponges consisting of noncollapsible structures with porous surface through which active ingredients are released in a controlled manner. Microsponge polymers possess the versatility to load a wide range of actives providing the benefits of enhanced product efficacy. To avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle. Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period. MDS technology is now being presently used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. MDS is ideal for skin and personal care products. They can absorb large amounts of excess of skin oil, while retaining an elegant feel on the skin's surface. The technology is currently employed in almost number of products sold by major cosmetic and toiletry companies worldwide.

MATERIALS AND METHODS

METHODOLOGY PREFORMULATION STUDY[09-18]

Organoleptic Properties

a. **Colour:** A small quantity of the drug was taken on butter paper and viewed in well- illuminated place.
b. **Taste and odour**: Very less quantity of the drug was used to get taste with the help of tongue as well as smelled to get the odour.

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Melting Point

Melting point of Voriconazole was determined by capillary method using Melting point apparatus.Here, the capillary tube was filled by pressing the open end gently into Voriconazole (pure drug) sample by tapping the bottom of the capillary on a hard surface so that the drug pack down into the bottom of the tube. When the drug packed into the bottom of the tube, the tube was placed into the slot. Make sure the unit is plugged in and set to zero, and then turn it on. The temperature were noted when the drug start to melt and the drug till complete melt.

Solubility profile

The sample was qualitatively tested for its solubility in various solvents. It was determined by shaking 10.0 mg of drug sample in 10.0 ml of different solvents in small bottle with the help of mechanical shaker for 30 min and the time required to disappear the sample completely was recorded.

Partition Coefficient: The partition coefficient of Voriconazole was determined by shaking flask method in n-octanol: Phosphate buffer 7.4. 10 mg of drug Voriconazole was added into 50 ml each of n-octanol and Phosphate buffer 7.4. The mixture was shaken for 24 hours until equilibrium was reached. Phases were separated in a separating funnel and the aqueous phase was filtered through 0.2µ filter, suitably diluted and amount of Voriconazole in aqueous phase was determined by measuring the absorbance at 225 nm using UV spectrophotometer. The partition coefficient ($P_{o/w}$) of Voriconazole was calculated from the ratio between the concentration of Voriconazole in organic (C_{oil}) and aqueous phase
($C_{aq.}$) using following equation. $P_{o/w} = (C_{oil}/C_{aq.})$ equilibrium

Ultraviolet Absorbance spectra STANDARD GRAPH OF Voriconazole

A precise, sensitive and accurate method for estimating Voriconazole was developed using UV visible spectrophotometer

Preparation of pH 7.4 Phosphate Buffer

Placed 50.0 ml of 0.2 M potassium dihydrogen phosphate in a 200ml volumetric flask, added the specified volume of 39.1 ml of 0.2 M sodium hydroxide and then added water to make up the volume.

0.2M Potassium dihydrogen phosphate: Dissolved 27.218 gm of potassium dihydrogen phosphate in distilled water and diluted with distilled water to 1000ml.

0.2M sodium hydroxide solution: Dissolved 8 gm of sodium hydroxide in distilled water and diluted with distilled water to 1000ml.

Procedure for UV spectroscopic method

The drug Voriconazole was solubilized in negligible amount of methanol and volume was made up by pH 7.4 Phosphate Buffer. A concentration of 10µg/ml was prepared and the absorption maximum (λ-max) was determined by scanning the drug solution within the range of 200 nm to 400 nm using a UV- Visible Spectrophotometer. The drug exhibited a λ-max at 225nm.

Preparation of Standard Solution

50 mg of the drug was accurately weighed into a 50 ml volumetric flask, which was dissolved in negligible amount of methanol and made up to the mark using pH 7.4 Phosphate Buffer to get 1000 µg/ml solution and was used as a standard stock solution (SS).

Working Standard I

From SS 5ml was pipette out into another 50 ml volumetric flask and was further diluted up to the mark with pH 7.4 Phosphate Buffer to get in 100 µg/ml
solution (WS1) and was used to prepare further dilutions.

Working Standard II

From WS-I, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5 and 4.0ml was pipette out into separate 25ml volumetric flask and was diluted to the mark with pH 7.4 Phosphate Buffer to get a concentration range of 2 to 16µg/ml. These solutions were scanned and the absorbance was measured at 225nm against blank (pH 7.4 Phosphate Buffer: methanol=4:1). The absorbance values thus obtained were plotted against the respective concentration to obtain the standard calibration graph. The procedure was repeated three times and the average values of absorbance were calculated. The data obtained was statistically evaluated to obtain the standard

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deviation of the said values and regression coefficients were calculated and the results are shown in Table.

Interference of Additives/Compatibility Testing

A 100 mg quantity Voriconazole was weighted and solubilized in negligible amount of methanol and volume was made up by pH 7.4 Phosphate Buffer (100 ml). Similarly 150 mg of powder blend containing 100 mg drug and 50 mg of polymer (Eudragit S 100) was dissolved in the respective solutions as above. Similarly 50 mg of polymer blend containing no drug (placebo) were dissolved in the respective solutions. All flasks were kept for 45 minutes in ultrasonic bath. Later solutions were filtered. Filtered solutions were diluted 100 times and the absorbances were measured at corresponding wavelength to verify the interference of additives.

Preparation of micro sponges

Voriconazole Microsponges were prepared by quasi-emulsion solvent diffusion method. To prepare the internal phase, Voriconazole was dissolved in 10 ml of dichloromethane: ethanol (1:1) mixture to dissolve both the drug and the polymer (Eudragit S 100) and to this add 20% by weight dibutyl phthalate as a plasticizer. The external phase containing 200 ml of 1% (w/v) PVA in water. The external phase was placed in the vessel with propeller stirrer rotating at 600 rpm, to this add slowly internal phase. The system was thermally controlled at 25^0 C in a water bath. Agitations up to 30 min permit the formation of microsponges and continue stirring for 8h to get desired rigid microsponges. After 8h stop stirring filter the rigid micro sponges through the filter paper (Whatmann filter paper
0.45 µm), washed with distilled water and dried at room temperature.

Voriconazole microsponges were prepared using various drug: polymer ratios i.e. 1:1, 1:1.25, 1:1.5, 1:7.5,1:2 keeping stirring rate of 600 rpm constant, The formula of various microsponge are shown in table.

Table 2: Micro sponge Formulations (Both Internal & external phase) INTERNAL PHASE

Formulation					
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**
Voriconazole (%w/v)	2%	2%	2%	2%	2%
Drug: Polymer	1:1	1:1.25	1:1.5	1:7.5	1:2
DCM (ml)	5	5	5	5	5
Ethanol (ml)	5	5	5	5	5
Di butyl phthalate (ml)	0.5	0.5	0.5	0.5	0.5

Table 3: **EXTERNAL PHASE**

Formulation						
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
PVA (mg)	100	100	100	100	100	100
Water (ml)	200	200	200	200	200	200

Characterization of Microsponges

Production/Percentage yield: The dried microsponges of each batch are weighed separately and percentage yield is calculated by using following equation:-

$$\text{Percentage yield} = \frac{\text{Practical weight}}{\text{Theoretical weight}} \times 100$$

Entrapment efficiency (EE)/Loading efficiency (%): 100 mg of microsponges were accurately weighed. They were powdered and extracted with 100 ml of methanol. Further it was serially diluted with pH 7.4 phosphate buffers. The resulting solution was analyzed for Voriconazole drug content by measuring absorbance in a UV-spectrophotometer at 225 nm using pH 7.4 phosphate buffer as blank. The studies were carried out in triplicate. The actual drug content and EE were calculated as given below:

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- **Actual drug content (%) = (Mact/Mms)*100**
- **Entrapment effciency(%)= (Mact/M_{the})*100**

Where M_{act} is the actual amount of Voriconazole in weighed quantity of microsponges, M_{ms} is the weighed quantity of microsponges, and M_{the} is the theoretical amount of Voriconazole in microsponges.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) is an electron optical imaging technique that provides photographic images and elemental information. SEM is useful for characterizing the morphology and size of microscopic specimens with particle size as low as nano meter to deca meter. The sample is placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. Interaction of the electron beam with the specimen produces a variety of physical phenomena that, when detected, are used to form images and provide elemental information about the specimens. Micro sponges were fixed on aluminum studs and coated with gold using a sputter coater SC 502, under Vacuum [0.1 mm Hg]. The Microsponges were then analyzed by scanning electron microscopy (SEM) [Model JSM-840 A, Joel. Japan].

In Vitro dissolution studies: The release of Voriconazole from microsponge was investigated in pH 7.4 phosphate buffer as a dissolution medium (900 ml) using USP type I apparatus. A sample of microsponge equivalent to 100 mg of Voriconazole was taken in the basket. A speed of 50 rpm and temperature of 37 ± 0.5^0 c was maintained throughout the experiment. At fixed intervals, aliquots (5 ml) was withdrawn and replaced with fresh dissolution media. The concentration of drug released at different time intervals was then determined by measuring the absorbance using Double beam UV spectrophotometer at 225 nm against blank. The studies were carried out in triplicate.

Preparation of optimized microsponge gels

Dissolve accurately weighed quantity of carbopol 934 in 10ml distilled water to this add solvent blend comprising of methanol: PEG 400 which is previously contained 100mg of optimized microsponge with constant stirring. To the whole mixture add drop wise triethanolamine until transparent gel was obtained. Stirring was stopped to escape entrapped air; further formed gel was stored in a air tight container for further study.

Table 4: Microsponge Incorporated Gel Formulations

S.No.	Ingredients	F-3 Gel
1	Optimized microsponge (mg) (equivalent to 100mg of (Voriconazole)	117
2	Carbopol 934 (mg)	100
3	Distilled water (ml)	10
4	Methanol (ml)	2
5	Poly ethylene glycol	2 drops
6	Tri ethanol amine	4-5 drops

In Vitro diffusion studies: The release of Voriconazole from optimized microsponge gels were determined using membrane diffusion technique. The microsponge gels equivalent to 100 mg of Voriconazole was used for the diffusion study. The gel was taken in a glass tube having a diameter 2.5 cm with an effective length of 8 cm that was previously covered with soaked osmosis cellulose membrane, which acts as a donor compartment. The glass tube was placed in a beaker containing 100 ml of phosphate buffer pH 7.4, which acts as receptor compartment. The whole assembly was fixed in such a way that the lower end of the tube containing gel was just touched (1-2mm deep) the surface of diffusion medium. The temperature of receptor medium maintained at 37±100C and the medium was agitated at 100 rpm speed using magnetic stirrer. Aliquots of 5ml sample were withdrawn periodically and after each withdrawal same volume of medium was replaced. The collected samples were analysed at 225 nm in Double beam UV-VIS spectrophotometer using phosphate buffer 7.4 as blank.

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Kinetic Modeling

Data obtained from in-vitro release studied was evaluated to check the goodness of fit to various kinetics equations for quantifying the phenomena controlling the release from microspheres. The kinetic models used were zero order, first order, and Higuchi and Korsmeyer-peppas model. The goodness of fit was evaluated using the correlation coefficient values (R^2).

The results of in-vitro release profile obtained for all the formulations were plotted in kinetic models as follows,

1. Cumulative of drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining to be absorbed versus time (First order model)
3. Cumulative amount of drug release versus square root of time (Higuchi model)
4. Log cumulative drug released versus log time (Korsmeyer-Peppas model)

Zero Order Kinetics: It describes the system in which the drug release rate is independent of its concentration.

$Q_t = Q_o + K_o t$ (1)

Where

Q_t= Amount of drug dissolved in time t

Q_{os} = Initial amount of drug in the solution, which is often zero and K_o = zero order release constant.

If the zero order drug release kinetic is obeyed, then a plot of Q_t versus t will give a straight line with a slope of K_0 and an intercept at zero.

First Order Kinetics

It describes the drug release from the systems in which the release rate is concentration Dependent.

$\log Q_t = \log Q_o + kt/ 2.303$ (2)

Where

Q_t = amount of drug released in time t.

Q_o = initial amount of drug in the solution k = first order release constant

If the first order drug release kinetic is obeyed, then a plot of $\log (Q_o - Q_t)$ versus t will be straight line.

With a slope of kt/ 2.303 and an intercept at t=0 of $\log Q_o$

Higuchi Model

It describes the fraction of drug release from a matrix is proportional to square root of time.

$M_t / M_\infty = kt^{1/2}$ (3)

Where

M_t and M_∞ are cumulative amounts of drug release at time t and infinite time,

and k = Higuchi dissolution constant reflection formulation characteristics. If the Higuchi model of drug release (i.e. Fickian diffusion) is obeyed, then a plot of M_t / M_∞ versus $t^{1/2}$ will be straight line with slope of k.

Korsmeyer-Peppas model (Power Law)

The power law describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation.

$Mt / M\infty = kt^n$ (4)

$\log [M_t / M_\infty] = \log k + n \log t$ (5)

Where M_t and M_∞ are cumulative amounts of drug release at time t and infinite time (i.e. fraction of drug release at time t),

k = constant incorporating structural and geometrical characteristics of CR device,

n = diffusion release exponent indicative of the mechanism of drug release for drug Dissolution.

To characterize the release mechanism,

The dissolution data $\{M_t / M_\infty < 0.6\}$ are evaluated.

A plot of $\log \{Mt / M\infty\}$ versus log t will be linear with slope of n and intercept gives the value of log k. Antilog of log k gives the value of k.

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Table1 5: Interpretation of diffusion release mechanisms

n	Mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous(Non-Fickian) diffusion
0.89	case II transport
Above 0.89	Super case II transport

Skin Irritation Study

Albino Rabbits (2-2.5kg) of either sex were used for testing of skin irritation. The animals were maintained on standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was shaved from back of rabbits and area of 4cm^2 was marked on both the sides. One side served as control while the other side was test. Prepared optimized microsponge gel was applied (500 mg/rabbits) twice a day for 7 days and the site was observed for any sensitivity and reaction if any, was graded as 0, 1, 2, 3 for no reaction, slightly patchy erythema, slightly but conflict or moderate patchy erythema, severe erythema with or without edema respectively.

RESULT AND DISCUSSION

Organoleptic Properties

The sample drug Voriconazole was found to be white crystalline through visual inspection which is in accordance with I.P

Table 6

TEST	Specification/limits	Observations
Color	white, crystalline powder	white, crystalline powder
Taste	Tasteless	Tasteless
Odour	odourless	Odourless

Solubility Profile

The solubility of Voriconazole was determined in different solvents. The drug was found to be more soluble in organic solvents.

Table 7

S.No.	Solvent	Solubility
1	Dichloromethane	Freely Soluble
2	Chloroform	Soluble
3	Methanol	Soluble
4	Ethanol (95%)	sparingly soluble
5	Water	Practically insoluble
6	Ether	Slightly soluble

Melting Point

Melting point of the sample drug Voriconazole was found to be 151 °C which is in accordance with IP.

Table 8

Test	Specification /limit	Observation
Melting point	148-152ºc	151°c

***the study conducted in triplicate Partition Coefficient**

The partition coefficient of Voriconazole was determined in n-octanol: distilled water and log P value was found to be 4.2

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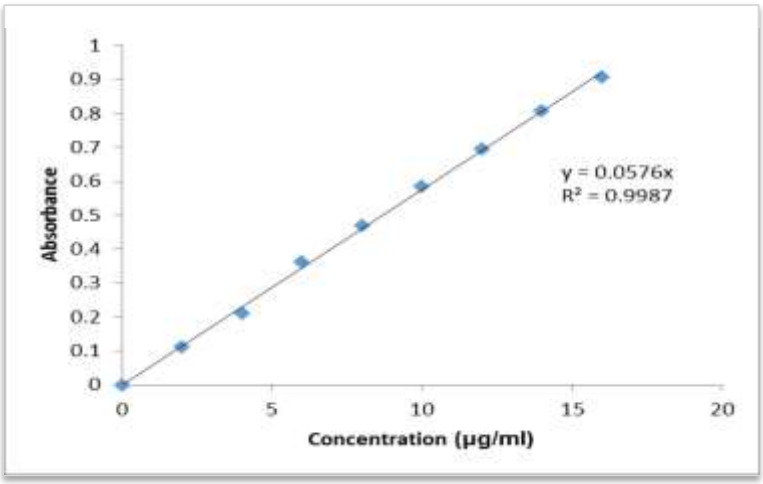
Table 9

Test	Specification / limits	Observations
Partition Coefficient	n-Octanol: distilled water	4.2

***the study conducted in triplicate Ultraviolet absorbance spectra**

STANDARD CURVE OF Voriconazole IN PHOSPHATE BUFFER pH 7.4
Graph-1



Interference of Additives/Compatibility Testing

The results of UV spectroscopic analysis indicated that there was no chemical interaction between the drug and the additives as the physical mixture of polymers and drug exhibited absorption nearly similar to those of the pure drug sample.seen in Table -19.

Table 10

Formulations	Absorbance of solutions			Interference Yes / No
	Polymer blend with drug	Placebo	Pure drug	
F1	0.586	0.003	0.585	No
F2	0.585	0.001	0.585	No
F3	0.586	0.004	0.585	No
F4	0.584	0.003	0.585	No
F5	0.586	0.004	0.585	No

Preparation of Voriconazole microsponges by quasi-emulsion solvent diffusion method:

Free flowing powder particles of Voriconazole Microsponge Delivery System were also obtained by quasi-emulsionsolvent diffusion method with Eudragit S100in dichloromethane: ethanol (1:1) mixture. In quasi-emulsion solvent diffusion method, the formation of the microsponges could be by the rapid diffusion of dichlormethane (good solvent for the polymer and drug) into the aqueous medium, might reduce the solubility of the polymer in the droplets, since the polymer was insoluble in water. The instant mixing of the dichlormethane and water at the interface of the droplets induced precipitation of the polymer, thus forming a shell enclosing the dichlormethane and the drug. The finely dispersed droplets of the polymer solution of the drug were solidified in the aqueous phase via diffusion of the solvent.

The method seems to be promising for the preparation of Voriconazole microsponges with being easy, reproducible, rapid method. Microsponges using drug:Eudragit ratio 1:1.5 (F3) was further investigated for drug release after entrapment in carbopol 934 gels. The formulation F3 was chosen as the optimized formulation for drug release because of its highest entrapment efficiency.

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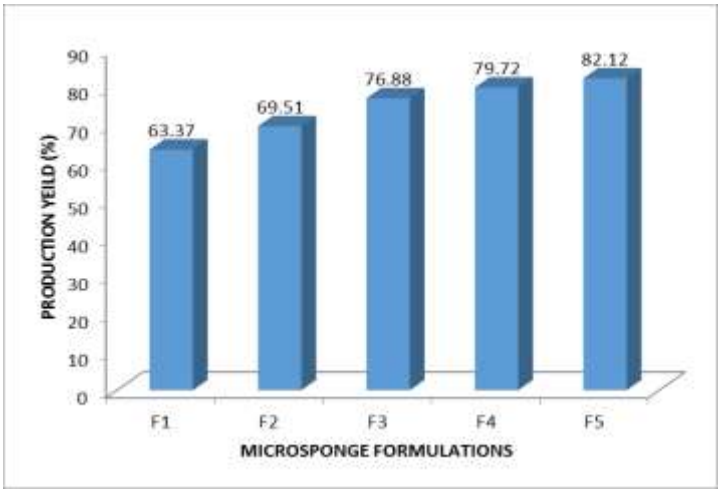
Characterization of microsponges Production/Percentage yield (%)

The production yield of Voriconazole microsponge formulations are givenin Table20. Production yield calculated for all microsponges ranged from 63.37 to 82.12. The readings are mean of three different measurements ±SD. It was found that production yield increases with increase in drug: polymer ratio.



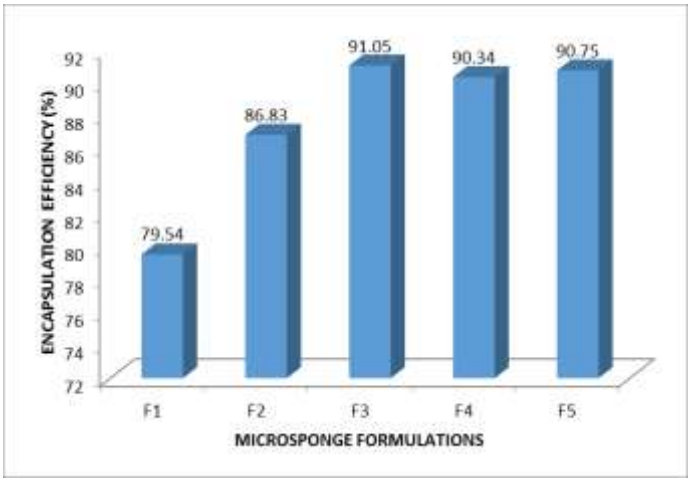
Graph-2: Production/Percentage yield (%):

Encapsulation efficiency/Loading efficiency (%)

The loading efficiency of Voriconazole microsponge formulations are given in Table21 The loading efficiency calculated for all microsponges ranged from 79.54 to 91.05 %. The highestloading efficiency was found for the formulation F3 where a greater amount of drug was encapsulated. The highest loading efficiency, greater the amount of drug was encapsulated. It is indicated that Voriconazole /Eudragit S 100 ratio (1:1.5) had the optimum capacity for drug entrapment. With further increase in drug/polymer ratio from 1:1.5 to 1:2, no significant change in loading efficiency was observed.

Table 11: Encapsulation efficiency/Loading efficiency (%)

Formulation	Drug: Polymer Ratio	Theoretical drug content (%)	Actual drug content (%)	Encapsulation Efficiency (%)
F1	1:1	50	39.77	79.54
F2	1:1.25	44.44	38.59	86.83
F3	1:1.5	40	36.42	91.05
F4	1:1.75	36.36	32.85	90.34
F5	1:2	33.33	30.25	90.75



Graph 3: Encapsulation efficiency/Loading efficiency (%): Scanning electron microscopy

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The SEM photographs of the microsponges are shown in Fig. SEM images showed the microsponges are porous and spherical in shape. No intact drug crystals are seen visually and inner structure was porous in nature with void spaces. The pores were induced by the diffusion of the solvent from the surface of the microsponges.

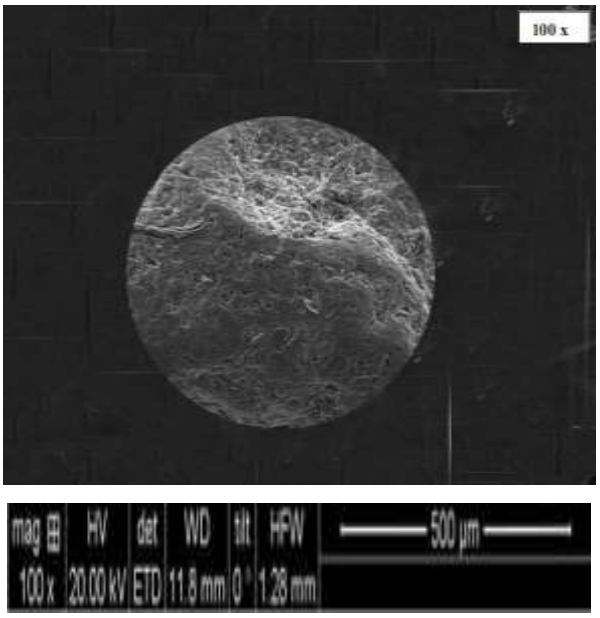

Figure 1: SEM photograph of F-3 microsponge formulation

In vitro dissolution studies

It was observed as the concentration of eudragit was increased, the percent release of ketokonazole decreases. The increase in eudragit concentration leads to the increased density of polymer matrix into the microspoges which result in an increased diffusional path length. This may decrease the overall drug release from polymer matrix.

Drug Release Kinetics of Voriconazole Microsponge Zero order release kinetics

Table 12: Zero order release kinetic data of Voriconazole Microsponge

Time (hr)	% Cumulative Release				
	F1	F2	F3	F4	F5
0	0.0	0.0	0.0	0.0	0.0
1	02.02 ± 0.14	1.92 ± 0.13	1.94 ± 0.08	01.09 ± 0.08	01.03±0.10
2	04.93 ±0.03	3.95 ± 0.17	4.96 ± 0.09	04.86 ± 0.08	02.97 ± 0.02
3	10.84± 0.09	12.84 ± 0.16	15.42 ± 1.06	13.82 ± 0.07	17.33 ± 0.48
4	20.08± 0.45	25.34 ± 2.38	26.14 ±1.11	19.52 ± 0.93	29.44 ± 0.42
5	27.35± 0.66	37.69 ± 1.62	40.54 ±1.05	30.75 ± 0.91	40.16 ± 0.45
6	38.06± 0.77	46.50 ± 1.05	51.25 ± 0.66	35.60 ± 1.32	52.00 ± 0.42
7	45.43 ± 1.33	58.01 ± 0.55	65.56 ± 1.00	43.14 ± 0.57	59.64 ± 0.80
8	54.80 ± 0.74	71.34 ± 0.56	76.00 ± 1.17	51.07 ± 1.95	67.38 ± 0.42
9	63.33 ± 0.70	77.35 ± 0.49	83.32 ± 1.22	57.19 ± 1.02	75.44 ± 0.82
10	75.39 ± 0.66	81.96 ± 0.35	86.30 ± 1.70	65.70 ± 0.64	78.89 ± 0.79
11	88.13 ± 1.23	84.76 ± 0.53	87.28 ±1.36	77.40 ± 0.45	80.38 ± 0.96
12	92.26 ± 1.20	90.31 ± 2.11	89.19 ± 1.05	85.11 ± 0.73	82 .66 ± 0.95

 # All the values are expressed as mean ± standard deviation (n=3)

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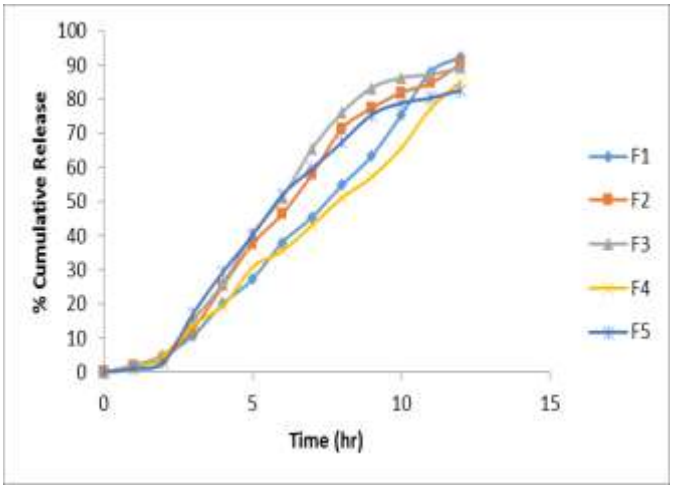
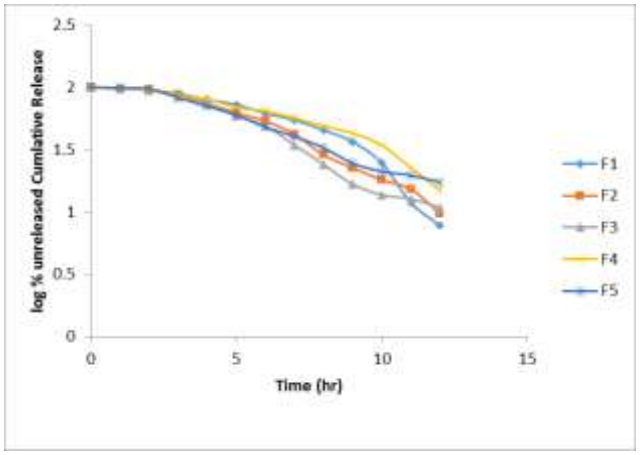


Graph 4: Zero order release kinetics profile of Voriconazole Microsponge

First Order Release Kinetics

Table 13: First order release kinetic data of Voriconazole Micro sponge

Time (hr)	Log % Cumulative drug remain to be Released				
	F1	F2	F3	F4	F5
0	2	2	2	2	2
1	1.9911	1.9915	1.9914	1.9952	1.9955
2	1.9780	1.9824	1.9779	1.9783	1.9869
3	1.9501	1.9403	1.9272	1.9354	1.9173
4	1.9026	1.8730	1.8684	1.9056	1.8485
5	1.8612	1.7945	1.7742	1.8404	1.7769
6	1.7919	1.7283	1.6879	1.8088	1.6812
7	1.7369	1.6231	1.5370	1.7548	1.6059
8	1.6551	1.4572	1.3802	1.6895	1.5134
9	1.5643	1.3550	1.2221	1.6315	1.3902
10	1.3911	1.2562	1.1367	1.5352	1.3244
11	1.0744	1.1829	1.1044	1.3541	1.2926
12	0.8885	0.9863	1.0338	1.1728	1.2390



Graph 5: First order release kinetics profile of Voriconazole Micro sponge

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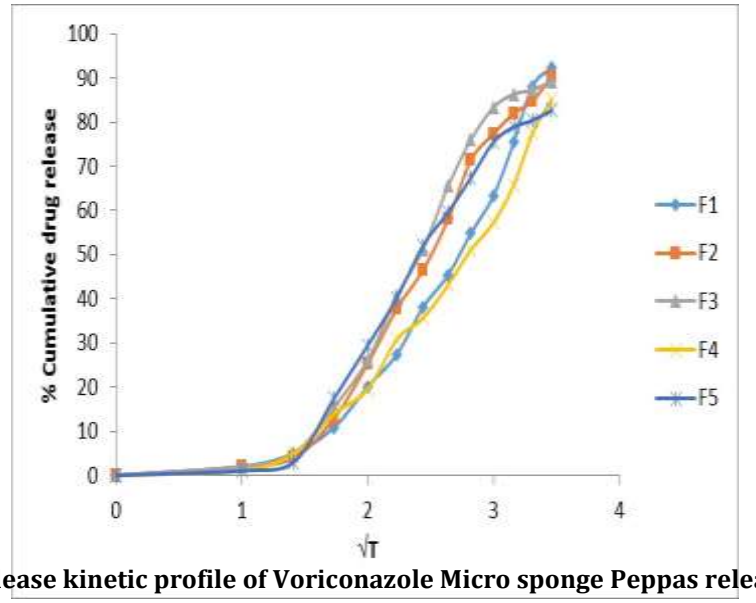
Higuchi Release Kinetics

Table 14: Higuchi release kinetic data of Voriconazole Micro sponge

√T	% Cumulative Release				
	F1	F2	F3	F4	F5
0	0.0	0.0	0.0	0.0	0.0
1.00	02.02 ± 0.14	1.92 ± 0.13	1.94 ± 0.08	01.09 ± 0.08	01.03±0.10
1.41	04.93 ±0.03	3.95 ± 0.17	4.96 ± 0.09	04.86 ± 0.08	02.97 ± 0.02
1.73	10.84± 0.09	12.84 ± 0.16	15.42 ± 1.06	13.82 ± 0.07	17.33 ± 0.48
2.00	20.08± 0.45	25.34 ± 2.38	26.14 ±1.11	19.52 ± 0.93	29.44 ± 0.42
2.23	27.35± 0.66	37.69 ± 1.62	40.54 ±1.05	30.75 ± 0.91	40.16 ± 0.45
2.44	38.06± 0.77	46.50 ± 1.05	51.25 ± 0.66	35.60 ± 1.32	52.00 ± 0.42
2.64	45.43 ± 1.33	58.01 ± 0.55	65.56 ± 1.00	43.14 ± 0.57	59.64 ± 0.80
2.82	54.80 ± 0.74	71.34 ± 0.56	76.00 ± 1.17	51.07 ± 1.95	67.38 ± 0.42
3.00	63.33 ± 0.70	77.35 ± 0.49	83.32 ± 1.22	57.19 ± 1.02	75.44 ± 0.82
3.16	75.39 ± 0.66	81.96 ± 0.35	86.30 ± 1.70	65.70 ± 0.64	78.89 ± 0.79
3.31	88.13 ± 1.23	84.76 ± 0.53	87.28 ±1.36	77.40 ± 0.45	80.38 ± 0.96
3.46	92.26 ± 1.20	90.31 ± 2.11	89.19 ± 1.05	85.11 ± 0.73	82 .66 ± 0.95



Graph 6: Higuchi release kinetic profile of Voriconazole Micro sponge Peppas release kinetics

Table 15: Peppas release kinetic data of Voriconazole Microsponge

Log T	Log % Cumulative Release				
	F1	F2	F3	F4	F5
0	0.0	0.0	0.0	0.0	0.0
0	0.3053	0.2833	0.2878	0.0300	0.0128
0.301	0.6928	0.5965	0.6954	0.6866	0.4727
0.477	1.0350	1.1085	1.1880	1.1405	1.2387
0.602	1.3027	1.4038	1.4173	1.2904	1.4689
0.698	1.4369	1.5762	1.6078	1.4878	1.6037

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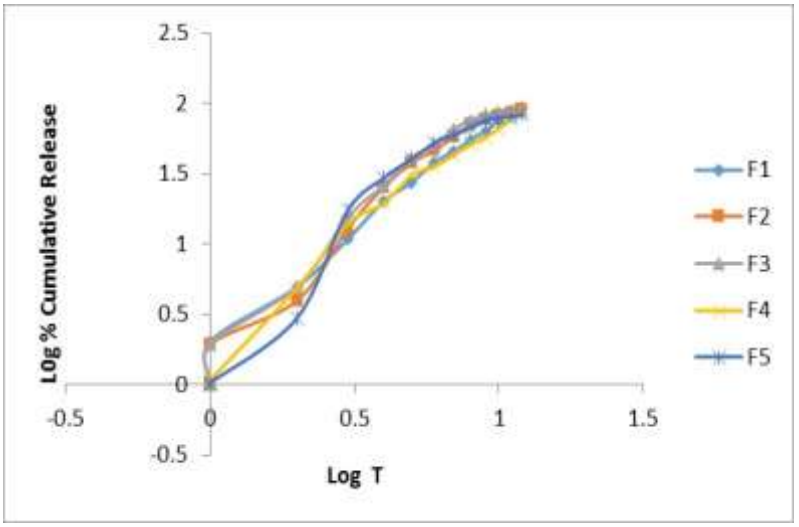
0.778	1.5804	1.6674	1.7096	1.5514	1.7160
0.845	1.6573	1.7635	1.8166	1.6348	1.7755
0.903	1.7387	1.8533	1.8808	1.7081	1.8285
0.954	1.8016	1.8884	1.9207	1.7573	1.8776
1.0	1.8773	1.9136	1.9360	1.8175	1.8970
1.041	1.9451	1.9281	1.9409	1.8887	1.9051
1.079	1.9650	1.9557	1.9503	1.9299	1.9172



Graph 7: Peppas release kinetic profile of Voriconazole Microsponge

Kinetic Modeling of Microsponge formulations

In vitro drug release data of all the Microsponge formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in table.

Table 16: Kinetic Modeling of Microsponge formulations

Formulation	Zero order kinetic Data	First order kinetic data	Higuchi Matrix kinetic data	Peppas kinetic data		Best fit model
	Regression coefficient (r^2)	Regression coefficient (r^2)	Regression coefficient (r^2)	Regression coefficient (r^2)	n-value	
F1	0.9899	0.9590	0.9361	0.8751	0.6223	Zero order
F2	0.9761	0.9668	0.9717	0.9679	0.5803	Zero order
F3	0.9555	0.9701	0.9654	0.9668	0.5910	First order
F4	0.9954	0.9047	0.9595	0.7884	0.6129	Zero order
F5	0.9561	0.9877	0.9782	0.9298	0.5114	First order

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The results suggest that, the drug was released by mixed order kinetics. The R^2 values of Zero order of the above 5 formulations were in the range of 0.9555 to 0.9954. Similarly the R^2- Value of first Order were in between 0.9047 to 0.9877 (as shown in table)

Among the 5 formulations some formulations F1, F2 and F4 release the drug by zero order kinetics and some are F3 and F5 release by first order kinetics.

To ascertain, the drug release mechanism the in-vitro release data were also subjected to Higuchi's diffusion equation, the R-values of all the formulations of Higuchi's equations were 0.9361 and above (as shown in table). It suggests that the Higuchi diffusion plots of all the formulations were fairly linear and we can conclude that the drug released by Higuchi's diffusion mechanism.

The formulations are also treated to Peppas plots by taking log percent versus log time. Irrespective of polymer level, the prepared Microsponge formulations showed non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation, $0.5<n<0.89$. Thus, it was proposed that these formulations delivered their active compound by coupled diffusion and erosion.

In Vitro diffusion study of optimized microsponge gel formulation

The optimized formulation F3 of microsponge was incorporated into carbopol 934 gels and evaluated for primary skin irritation test and diffusion studies. Summarized in table.

Table 17 In vitro diffusion study of optimized microsponge gel formulation

Time (hrs)	√T	Log T	% CR	Log % CR	% CDR	Log % CDR
0	0	0	0	0	100.0	2.0
1	1	0	01.03	0.0128	98.97	1.9955
2	1.414	0.301	02.97	0.4727	97.03	1.9869
3	1.732	0.477	17.33	1.2387	82.67	1.9173
4	2.0	0.602	29.44	1.4689	70.56	1.8485
5	2.236	0.698	40.16	1.6037	59.84	1.7769
6	2.449	0.778	52.00	1.7160	48.00	1.6812
7	2.645	0.845	59.64	1.7755	40.36	1.6059
8	2.828	0.903	67.38	1.8285	32.62	1.5134
9	3.0	0.954	75.44	1.8776	24.56	1.3902
10	3.162	1.0	78.89	1.8970	21.11	1.3244
11	3.316	1.041	80.38	1.9051	19.62	1.2926
12	3.464	1.079	82 .66	1.9172	17.34	1.2390

T = Time, CR = Cumulative release, CDR = Cumulative drug retained

Kinetic Modeling of optimized Microsponge gel formulation

The R^2 values of optimized Micro sponge gel formulation suggests that the drug was released by first order kinetics with non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation, $0.5<n<0.89$.

Table 18: Kinetic Modeling of optimized Microsponge gel formulation

Formulation	Zero order kinetic Data	First order kinetic data	Higuchi Matrix kinetic data	Peppas kinetic data		Best fit model
	Regression coefficient (r^2)	Regression coefficient (r^2)	Regression coefficient (r^2)	Regression coefficient (r^2)	n-value	
F3 Gel	0.9451	0.9824	0.9554	0.9769	0.6515	First order

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Skin Irritation Study

Skin irritation studies of optimized Microsponge gel formulation shows that there was no sign of erythema or edema after application on rabbits and the results were shown in Table that indicates the prepared optimized Microsponge gel formulation was free from significant skin irritation. summarized in table-19.

Table 19: Results for possible score for skin irritation

TEST	SKIN REACTION	SCORE
Erythema	Very slight erythema	0
	Well defined erythema	0
	Moderate to severe erythema	0
	Severe edema	0
Edema	Very slight erythema	0
	Well defined erythema	0
	Moderate to severe erythema	0
	Severe edema	0

SUMMARY AND CONCLUSION

Delivery via polymer systems has been proposed to be the prevailing in the type of controlled drug delivery devices both in present and future. For scientific as well as economic reasons, such delivery systems have potential advantage which include enhanced therapeutic response, predictable rate of release and extent of absorption, topical retention and improved patient acceptance. In the present work a topical polymeric micro sponge formulation of a locally acting anti fungal agent, Voriconazole was developed using quasi-emulsion solvent diffusion method. The idea behind developing a topical polymeric micro sponge delivery system was to deliver Voriconazole in a sustained release patternfor an extended period of time to reduce frequency of application and improve patient compliance.

Voriconazole (KTZ) is a broad spectrum antifungal agent active against a wide variety of fungi and yeasts. It is readily but incompletely absorbed after oral dosing and is highly variable. Topically it is used in the treatment of candidal or tinea infections of the skin. Encapsulation of KTZ in microsponge gel may increase the half life providing prolonged drug delivery and minimize the commonly occurring side effects.

Production yield and loading efficiency: Production yield and loading efficiency Were calculated for all the micro sponge formulations. Production yield calculated for all micro sponges ranged from 63.37 to 82.12. It was found that production yield increases with increase in the concentration of polymer.

The loading efficiency calculated for all microsponges ranged from 79.54 to 91.05 %. The highest loading efficiency was found for the formulation F3 where a greater amount of drug was encapsulated. The highest loading efficiency, greater the amount of drug was encapsulated. It is indicated that Voriconazole /Eudragit S 100 ratio (1:1.5) had the optimum capacity for drug entrapment. With further increase in drug/polymer ratio from 1:1.5 to 1:2, no significant change in loading efficiency was observed.

Scanning electron microscopy: SEM images showed the micro sponges are porous and spherical in shape.

In vitro dissolution studies: It was observed as the concentration of eudragit was increased, the percent release of Voriconazole decreases. The increase in eudragit concentration leads to the increased density of polymer matrix into the microspoges which result in an increased diffusional path length. This may decrease the overall drug release from polymer matrix. The cumulative % drug release of micro sponge formulation after 12 hrs was found out to be- **F1:92.26, F2: 90.31, F3: 89.19, F4: 85.11, F5: 82 .66.**

Among the 5 formulations some formulations F1, F2 and F4 release the drug by zero order kinetics and some are F3 and F5 release by first order kinetics. To ascertain, the drug release mechanism the in-vitro release data were also subjected to Higuchi's diffusion equation, the R-values of all the formulations of Higuchi's equations were 0.9361 and above. It suggests that the Higuchi diffusion plots of all the formulations were fairly linear and we can conclude that the drug released by Higuchi's diffusion mechanism.

The formulations are also treated to Peppas plots by taking log percent versus log time. Irrespective of

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polymer level, the prepared Micro sponge formulations showed non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation, $0.5<n<0.89$. Thus, it was proposed that these formulations delivered their active compound by coupled diffusion and erosion.

The R^2 values of optimized Micro sponge gel formulation F3 suggests that the drug was released by first order kinetics with non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation, $0.5<n<0.89$.

Skin irritation studies: Skin irritation studies of optimized Microsponge gel formulation shows that there was no sign of erythema or edema after application on rabbits.

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