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Span 80 - Tween 80 Based Fluid - Filled Organogel for Topical Delivery of Fluconazole

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ABSTRACT

Organogels are generally formed by immobilization of various liquids within 3-dimensional network, formed by self assembly, formed of molecules called as gelators. Different compositions of organogels were prepared by varying the concentrations of the organogelators Span 80 and Tween 80 was added to improve the gel stability. The formulated organogels were characterized by visual inspection, gel-sol transition studies, pH, microscopic analysis, rheological studies, drug content analysis and *in-vitro* drug release study. The microscopy of the organogels suggested that a three-dimensional network of aggregates gelator is responsible for immobilising the solvent. The drug release profile of all the formulations were subjected to various kinetic models and the mechanism of drug release were found to be non-fickian diffusion controlled process. As the concentration of Span 80 increased, there was a proportionate decrease in drug release pattern. The pH range of the organogels was simulated to the skin pH conditions and all the formulations were able to restrict the growth of fungal infection efficiently as comparable to the other product. Based on the results, the developed organogels can be used as an efficient drug carrier for the topical delivery of Fluconazole.

KEYWORDS: Organogel, Fluconazole, Span 80, Tween 80, Anti-fungal, Topical delivery.

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INTRODUCTION

Gels are the semisolid viscoelastic systems. They are said to be the systems easy to identify then to define. We use many gels in our day to day life, such as soaps, shampoo, toothpaste, hair gel and cosmetics, as well as contact lenses and gel pens etc. Gel can either be natural gel or artificial or synthetic gel.

The gels can be dried and obtained in solid form. Depending upon the method of drying gels may be classified as either aerogel (formed by replacing the liquid phase with air), cryogel (obtained by freeze drying), and xerogel (obtained by using conventional drying method). [1]

There are 2 major types of gels, i) Hydrogels and ii) Organogels. The classification is based on nature of liquid, that the gel immobilizes. Hydrogels contains high amount of water in there composition. Whereas gels in which, the immobilized liquid is organic solvent are termed as organogels.

Organogels are generally formed by immobilization of various liquids within 3-dimensional network, formed by self assembly of fibers, formed of molecules called as gelators.[2]

Chemical gels are thermally irreversible whereas gels formed by weak non-covalent interactions (physical gels) are reversible.[1]

A minimum concentration of gelator required to gel the solvent is known as Critical gelation concentration (CGC). Below CGC concentration the resulting system exhibits flow properties and behaves as a liquid. [3]

Organogels do have some advantages over conventional drug delivery system, which includes longer shelf-life, no need of sophisticated instruments, less chances of batch to batch variations, ease of preparation and thermo-reversible nature of the organogels-based formulations. [4]

❖ *Properties of organogels*

In the present section, attempts will be made to discuss about the various physicochemical properties of the Organogels.

- **Viscoelaticity**: The organogels behaves like a solid at lower shear rates and hence shows an elastic property. As the shear stress is increased, the physical interacting points amongst the fiber structures start getting weakened until the shear stress is high enough to disrupt the interactions amongst the fiber structures, when the organogels starts flowing.
- **Non-birefringence**: Organogel of not allowing the polarized light to pass through its matrix is regarded as non-birefringent.

- **Thermoreversibility**: As the organogels are heated up above a critical temperature, the organogels loses its solid matrix like structure and starts flowing.
- **Thermostability:** The organogels are inherently thermostable in nature.
- **Biocompatibility**: Initially, organogels were developed using various non-biocompatible organogels which rendered the organogels non-biocompatible of late, research on organogels using various biocompatible constituents has opened up new dimensions for the use of the same in various biomedical applications. [5]

❖ *Advantages of Organogels*

- **Template vehicle:** Span 80 and Tween 80 based Organogels provide opportunities for incorporation of wide range of substances with diverse physicochemical characters viz., chemical nature, solubility, molecular weight, and size etc.
- **Process Benefits:** Self-assembled supramolecular arrangement of surfactant molecules makes the process very simple and easy to handle.
- **Structural/ Physical Stability**: Structural integrity of organogels is maintained for longer time periods.
- **Chemical Stability:** organogels are moisture insensitive and being organic in character also resists microbial contamination.
- **Topical Delivery Potential:** They enhance the skin penetration and transport of the molecules.
- **Safety:** Use of biocompatible, biodegradable and non-immunogenic materials makes them safe for long-term applications.[6]

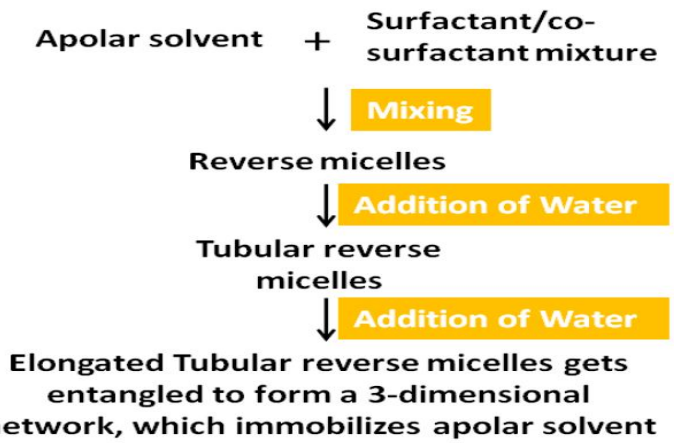

Figure 1: Method of formation of organogels by fluid-filled mechanism.

Fluconazole remains one of the most frequent prescribed triazole because of its excellent bioavailability, tolerability, and side-effect profile. More than 80 % of ingested drug is found in the

circulation, and 60 to 70% is excreted in the urine. Only 10% of fluconazole is protein bound. Skin infection: e.g. foot fungus (usually smelly but not life threatening, sometimes becomes serious), ring worms. [7]

The Spans 80 (Sorbitan Monooleate) is a range of mild non-ionic surfactants providing formulating benefits in a number of Home Care applications. Croda's Span 80 materials have long-standing food and pharmacopoeia approval with a safe history of use.

Span 80 is light yellow viscose oily liquid. Span 80 is insoluble in water and soluble in organic solvents. It is water/oil type emulsifier. [8, 9]

As non-ionic, Spans 80 offer many advantages over ionic surfactants including increased stability, formulating flexibility and wider compatibility. They are stable in mild acids, alkalis and electrolytes and do not react with ionic ingredients or actives. By combining Spans 80 at different ratios, formulators are able to produce systems with a wide HLB range to emulsify most oils and waxes. Certain Spans 80 are also highly effective solubilisers, dispersing agents and wetting aids. [10]

Tween 80 (polysorbate 80) ($C_{64}H_{124}O_{26}$) is a common excipient and solubilizing agent used in the pharmaceutical industry. Polysorbate 80 (also known as polyoxyethylene-sorbitan-20 mono-oleate, or Tween 80) is used in the pharmaceutical and cosmetic industry in lotions, medical preparations (e.g., vitamin oils, vaccines, and intravenous preparations) and as an excipient in tablets. [11]

Tween 80 offer many advantages over ionic surfactants including increased stability, formulating flexibility and wider compatibility. They are stable in mild acids, alkalis and electrolytes and do not react with ionic ingredients or actives. By combining Span 80 and Tween 80 at different ratios, formulators are able to produce systems with a wide HLB range to emulsify most oils and waxes. Certain Spans and Tweens are also highly effective solubilisers, dispersing agents and wetting aids. [10]

Sunflower oil is mainly triglycerides (fats), typically derived from the fatty acids linoleic acid (with is doubly unsaturated) and oleic acid. [12]

A ternary phase diagram has three components. The three components are usually compositions of elements. This type of diagram is three-dimensional but is illustrated in two-dimensions for ease of drawing and reading. Instead of being a rectangular plot, it is a triangle. Ternary phase diagrams are needed so that three components can be compared at once. [13]

EXPERIMENT

❖ *Material*

Fluconazole was purchased from SGPTC Pvt. Ltd., Amritsar, Punjab, India. Span-80 was purchased from Thomas baker (chemicals) Pvt. Ltd., Mumbai, India. Tween 80 was purchased from Thomas baker (chemicals) Pvt. Ltd., Mumbai, India. Edible refined sunflower oil (SO) was purchased from the local market.

❖ *Methods*

A. Preparation of organogel

Surfactant mixtures of span 80 and tween 80 were prepared so as to have span 80: tween 80 ratios of 1:1 (OS-organogels), 2:1 (3O-organogels) and 1:2 (OT-organogels). Specified amounts of the surfactant mixtures were added to specified volume of sunflower oil in 15-ml culture bottles kept on Vortex Shaker. The above mixture was vortexing for 10 min. Subsequently, water was added drop by drop to the surfactant–oil solution with the use of a burette until the formation of organogel or until the total fraction of water has reached 80% of the volume of the surfactant–oil–water mixture. Based on the composition of the surfactant–oil–water mixture, the systems either formed gelled structures or remained as a liquid mixture. A ternary phase diagram was plotted to find the area of the gelation. Software was used to plot the ternary plot. [14]

Table 1: Formula table of Optimize Formulation

S. No.	Ratio (Oil: Surfactant Mixture)	Sunflower oil		Surfactant Mixture				Water added
				Span 80		Tween 80		
		mg	ml	mg	ml	mg	ml	ml
OS-5	5:5	495	0.550	247.5	0.250	247.5	0.233	0.4
OS-6	6:4	594	0.660	198	0.200	198	0.187	0.3
OS-7	7:3	693	0.770	148.5	0.150	148.5	0.140	0.5
3O-5	5:5	495	0.550	330	0.333	165	0.156	0.5
3O-6	6:4	594	0.660	264	0.266	132	0.124	0.4
OT-4	4:6	396	0.440	198	0.200	396	0.374	0.3
OT-5	5:5	495	0.550	165	0.167	330	0.311	0.3

B. Evaluation studies

- **Organoleptic evaluation**

Freshly prepared organogels samples were observed for their colour, odour, appearance and texture.

- **Gel-Sol transition studies**

Organogels were incubated at various temperatures in the range of 30°C and 70°C in a constant temperature water bath. An increment of 5°C was made after 5 min incubation at previous temperature. Samples were analyzed by inverted test-tube method after each incubation period. The temperature at which samples started flowing was recorded as gel-sol transition temperature (Tg). [15]

- **pH Determination**

The pH of formulated organogels was determined using pH meter. 2 g of gel was stirred in distilled water to get a uniform suspension. Volume was made up to 40 ml. The electrode was immersed in organogel - distilled water suspensions and readings were recorded on pH meter. [16]

- **Rheological evaluation**

Viscosities of the formulated organogels were determined using Brookfield Viscometer (Model: DV-1 Prime, Brookfield Engineering Lab., Inc., USA). Spindle no. 6 was used for organogels and the spindle speed of 2 rpm at 25° C.

- **Microscopic studies**

A microscopic study of an Electronic Microscope or Fluorescent Microscope was used for analyzing the microstructure of the organogels. Attempts were made to understand the mechanism of the organogel formation by varying the proportions of organogel and analyzing their microstructures.

- **Drug content**

Each formulation of 5oomg was dissolved in 10 ml methanol. The solution was filtered through 45µ membrane (whatman filter paper), 1ml of the above filtrate was pipette out and diluted to 10ml with methanol. The absorbance was measured at 261 nm, using double beam UV visible spectrophotometer. [17]

- ***In-vitro* dissolution studies**

Egg membrane: The membrane was treated with 0.1N HCl few minutes, so that the acid reacts with the calcium and aids the removal of the outer shell of the egg membrane. The reaction is indicated by the appearance of bubbles. Finally the separated membrane was washed with distilled water for several times.

A two-compartment cell was used for the drug release study. The compartments were separated by a dialysis membrane (egg membrane). Accurately weighed 1 g of the organogel samples (OS-5, OS-6, OS-7, 3O-5, 3O-6, OT-4 & OT-5), containing 1% (w/w) fluconazole and marketed formulation of fluconazole (gel). The donor compartment contained 1g of fluconazole loaded organogels while the receptor compartment contained 32 ml of 7.4 pH buffer which was maintained at 100rpm and 37°C. 1ml sample was withdrawn at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hour time interval. This withdrawn sample was analysed using UV-visible spectrophotometer (Shimadzu UV 1800) at λ_{max} of 261 nm after appropriate dilution.

- **Drug release kinetics**

The release kinetic was studied by various kinetic models as zero order plot, first order plot, higuchi plot and korsmeyer-peppas. In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release. To analyse the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted into Zero order, First order, Higuchi matrix, Korsmeyer-Peppas. By comparing the R^2-values obtained from the above equations, the best-fit model was selected. [18]

RESULT AND DISCUSSION

- ***Preparation of the organogels***

The organogels were prepared by dissolving the surfactant mixture in sunflower oil followed by the addition of water. With the initial addition of water, the mixture turned into a white turbid solution. As further amount of water was added, the samples either formed a gelled structure or remained as turbid solution. The samples were regarded as organogels if the surfactant–sunflower oil–water mixture did not flow when the culture bottles were inverted.

Ternary phase diagrams were prepared for the OS, 3O and OT type organogels. Each arm of the phase diagram represents the proportion of a particular component. The formation of the organogel was dependent on the concentration of all the three components, viz. surfactant mixture, sunflower oil and water. From the experimental results, it can be concluded that the composition of the surfactant mixture played an important role in governing the phenomenon of gelation as can be visualized from the area of gelation in the ternary phase diagram.

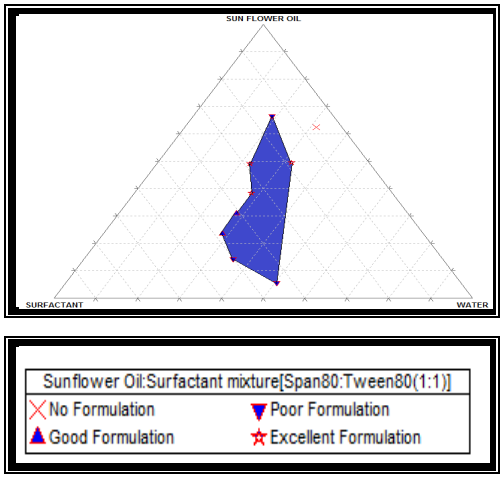

Figure 2: Pseudo-ternary phase diagrams of OS organogel.

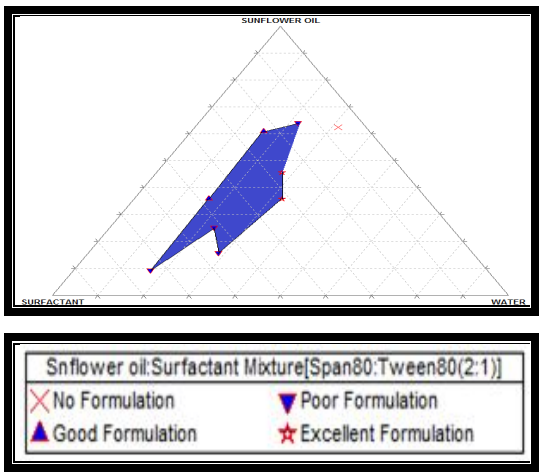

Figure 3: Pseudo-ternary phase diagrams of 3O organogel.

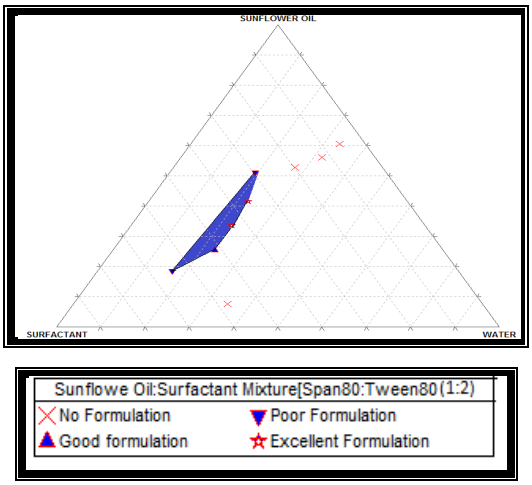

Figure 4: Pseudo-ternary phase diagrams of OT organogel.

- ***Identification of pure drug (FT-IR spectra)***

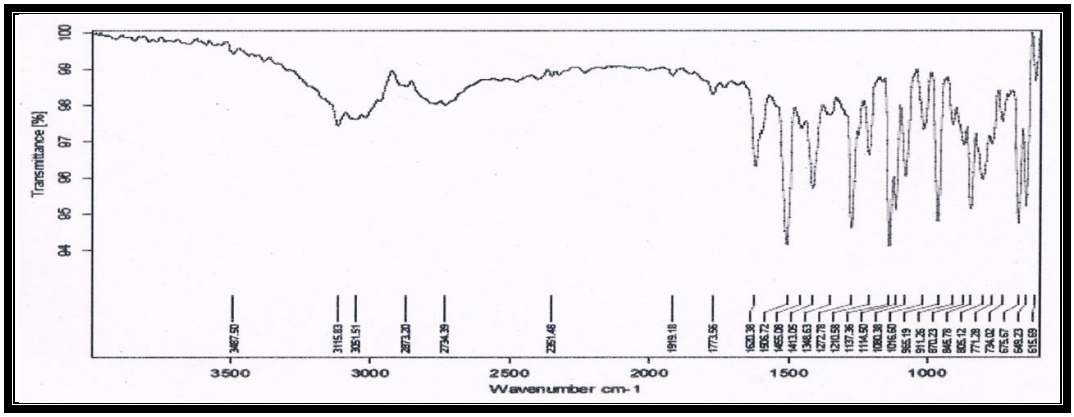

Figure 5: FT-IR Spectra of fluconazole drug.

Pure fluconazole has characteristic IR peaks at 3487.50 cm^{-1}[OH Stretching], 2873.20cm^{-}

^{1}[CH_2 Stretching], 3051.51 cm^{-1} [CH Aromatic Stretching], 1620.38 cm^{-1}[C=N Stretching], 1455.08[CH Aromatic bending]$cm^{-1}$and 1080.38[C-F Stretching]cm^{-1}.

- ***Drug- excipients compatibility study***

The IR spectrum of ternary mixtures of API with Excipients (Span 80, Tween 80 and Sunflower oil) were interpreted and identified.

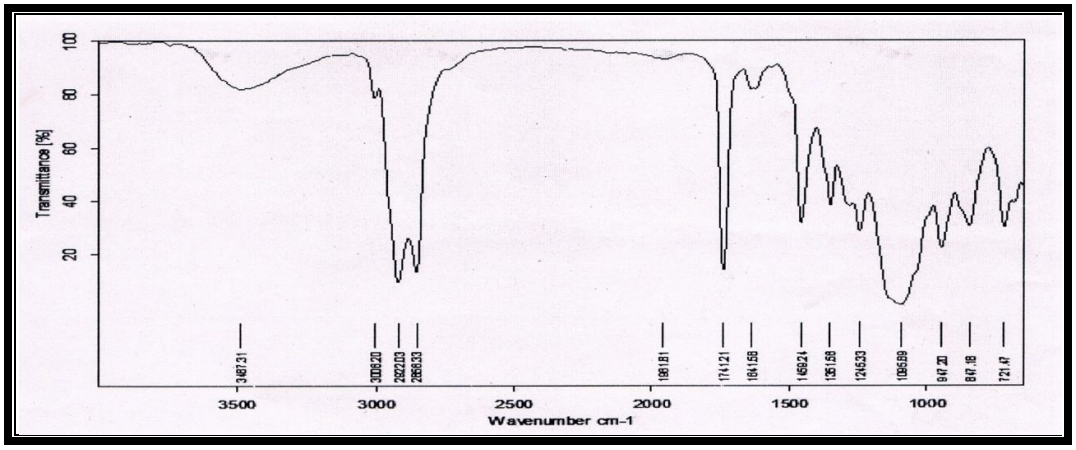

Figure 6: FTIR spectra of pure drug +Excipients.

The IR spectrum of API and mixtures of API with excipients were interpreted and identified. The main absorption bands of the drug were present in the mixtures with same degree of sharpness and position indicating that there is absence of physical and chemical interactions among both active component and the excipients.

Mixtures of API has characteristic IR peaks at 3487.71 cm^{-1}[OH Stretching], 2856.33cm^{-1}[CH_2 Stretching], 3006.20 cm^{-1} [CH Aromatic Stretching], 1641.58 cm^{-1}[C=N Stretching], 1459.24[CH Aromatic bending]$cm^{-1}$and 1095.89[C-F Stretching]cm^{-1}.

- **Organoleptic evaluation**

Table 2: Organoleptic Properties of optimize formulation.

S. No.	Formulation	Colour	Odour	Appearance	Texture
1.	OS-5	pale yellow	slight odour	pale yellow oily gel	Uniformity
2.	OS-6	pale yellow	slight odour	pale yellow oily gel	Uniformity
3.	OS-7	pale yellow	slight odour	pale yellow oily gel	Uniformity
4.	3O-5	pale yellow	slight odour	pale yellow oily gel	Uniformity

5.	3O-6	pale yellow	slight odour	pale yellow oily gel	Uniformity
6.	OT-4	pale yellow	slight odour	pale yellow oily gel	Uniformity
7.	OT-5	pale yellow	slight odour	pale yellow oily gel	Uniformity

- **Gel-Sol transition studies**

A. OS organogel at 65°C

B. 3O organogel at 70°C

C. OT organogel at 60°C

Figure 7: Gel–sol transition temperatures of optimize organogels formulation.

The organogels were subjected to increasing temperatures starting from 30°C. An increment of 5°C was made after 5 min incubation at the previous temperature. The samples were considered to have undergone gel–sol transition when they started to flow (determined by inverted test tube method). The gel-to-sol transition temperatures were found to be at 65°C, 70°C and 60°C for OS, 3O and OT organogels, respectively. As the temperature is increased, there is a corresponding increase in the surface free energy with a subsequent increase in the mobility of the self-assembled structures formed by the gelators. With further increase in the temperature, the interaction amongst the self-assembled structures gets abolished, and hence results in the disruption of the networked structure, which causes the system to flow freely.

- ***pH Determination***

Table 3: pH of optimize organogel formulation.

S. No.	Formulation	pH Mean±S.D.
1.	OS-5	6.8±0.10
2.	OS-6	6.8±0.06
3.	OS-7	6.7±0.09
4.	3O-5	6.5±0.15
5.	3O-6	6.4±0.12
6.	OT-4	6.6±0.09
7.	OT-5	6.7±0.03

- ***Rheological evaluation***

- **Table 4: Viscosity of optimize organogel formulation.**

S. No.	Formulation	Viscosity (Centipoise) Mean±S.D.
1.	OS-5	17231±95
2.	OS-6	17479±93
3.	OS-7	17655±101
4.	3O-5	18546±73
5.	3O-6	18842±82
6.	OT-4	16037±68
7.	OT-5	15814±59

The viscosity profile of the organogel showed an elastic phase followed by a non-elastic phase. The presence of the elastic phase may be attributed to the elastic nature of sorbitan ester organogels. In this region, the physical interactions amongst the gelator molecules are stronger and the applied shear is not able to dislodge the gelator molecules involved in the formation of the gelled structures via fluid-filled microstructures. As the applied shear is increased, the hydrophobic interactions are not able to keep the fluid-filled microstructures together. This results in the transition of the system from the gelled phase to the free-flowing liquid phase, marked by the disruption of the 3-dimensional networked structures.

- ***Microscopic studies***

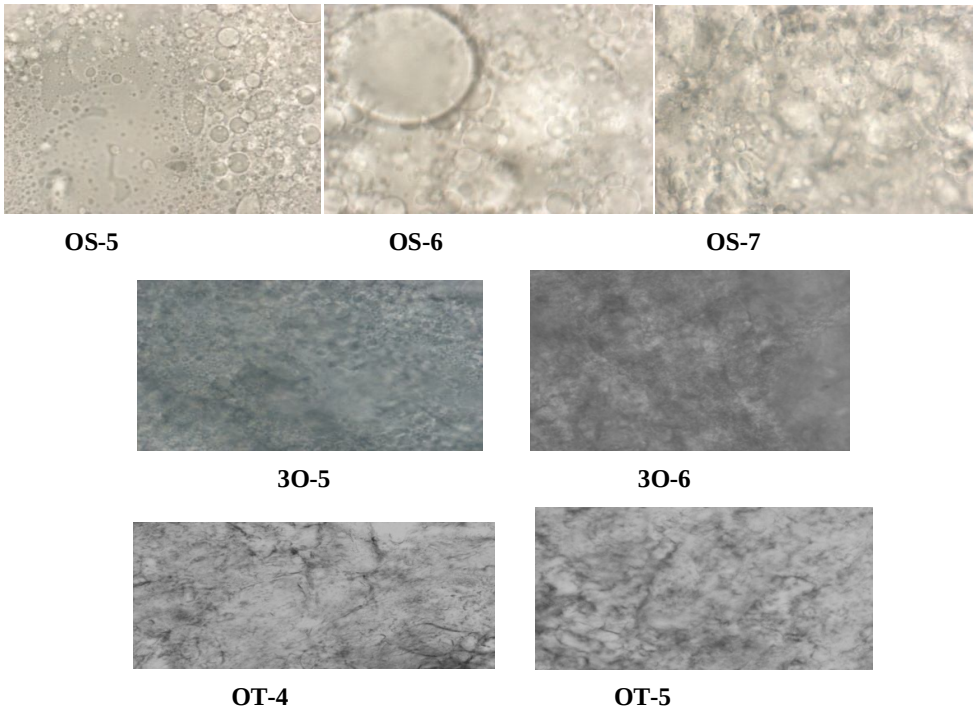

Figure 8: Fluorescence microscope study of optimize organogel formulation.

The micrographs indicated the presence of aggregated granular structures which lead to the formation of a 3-dimensional network structure. The apolar fluid phase remained entrapped within this gelled network. With the increase in the concentration of surfactant mixture, there was a corresponding increase in the 3-dimensional networked structure as visualized under light microscope.

- ***Drug content %***

Table 5: Drug content of optimize organogel formulation.

S. No.	Formulation	Drug content % Mean±S.D.
1.	OS-5	98.23±0.026
2.	OS-6	97.04±0.029
3.	OS-7	97.57±0.021
4.	3O-5	96.09±0.023
5.	3O-6	98.14±0.016
6.	OT-4	98.95±0.019
7.	OT-5	99.52±0.020

- ***%CDR of all optimized organogel formulation and marketed formulation***

Table 6: *In vitro* drug release studies of all optimized organogel formulation and marketed formulation.

Time (hr)	OS-5 Mean±S.D.	OS-6 Mean±S.D.	OS-7 Mean±S.D.	3O-5 Mean±S.D.	3O-6 Mean±S.D.	OT-4 Mean±S.D.	OT-5 Mean±S.D.	Marketed formulation Mean±S.D.
0	00	00	00	00	00	00	00	00
0.5	03.733± 0.25	04.495 ± 0.022	02.971± 0.021	03.733± 0.023	06.019± 0.033	06.781± 0.026	08.304± 0.031	12.038 ±0.037
1	13.754± 0.038	15.302 ± 0.045	16.016± 0.033	17.564± 0.043	20.683± 0.026	17.659± 0.037	17.707± 0.042	33.747 ±0.045
2	24.847± 0.034	24.157 ± 0.061	25.657± 0.026	28.776± 0.036	30.467± 0.053	29.633± 0.043	29.681± 0.038	51.552 ±0.063
3	35.512± 0.047	34.797 ± 0.037	36.345± 0.043	38.797± 0.043	40.537± 0.038	40.440± 0.059	42.012± 0.029	62.262 ±0.072
4	45.723± 0.055	47.271 ± 0.042	46.581± 0.028	49.104± 0.054	49.367± 0.024	50.795± 0.046	53.938± 0.049	71.733 ±0.048
5	56.221± 0.042	58.578 ± 0.029	54.816± 0.032	58.174± 0.022	59.959± 0.047	59.912± 0.038	66.197± 0.061	75.347 ±0.051
6	67.004± 0.036	70.195 ± 0.036	59.457± 0.025	64.433± 0.035	67.790± 0.051	69.267± 0.047	76.504± 0.054	77.485 ±0.039
7	79.597± 0.041	79.835 ± 0.053	64.955± 0.021	67.788± 0.047	76.574± 0.029	77.335± 0.041	86.312± 0.046	78.100 ±0.041
8	84.142± 0.032	83.619 ± 0.048	72.095± 0.021	74.238± 0.049	75.667± 0.027	87.119± 0.053	93.309± 0.051	80.190 ±0.032
9	85.712± 0.026	85.164 ± 0.031	78.640± 0.019	78.545± 0.033	77.712± 0.028	89.521± 0.029	95.878± 0.032	80.757 ±0.029
10	85.733± 0.021	84.400 ± 0.026	83.042± 0.016	80.638± 0.019	78.233± 0.031	91.161± 0.024	96.923± 0.018	81.276 ±0.037

In vitro drug release studies were carried out for OS-5, OS-6, OS-7, 3O-5, 3O-6, OT-4, OT-5 and marketed formulation, employing Franz diffusion cell apparatus. The release rate of drug from organogel systems depends on the drug partition coefficient and drug solubility in the oil and aqueous phases. OT-5 organogel showed maximum percentage of drug release at the end of 10 hr, followed by the release of the drug from OS-5, OS-6, OS-7, 3O-5, 3O-6, and OT-4 organogels and marketed formulation [figure 7.30].

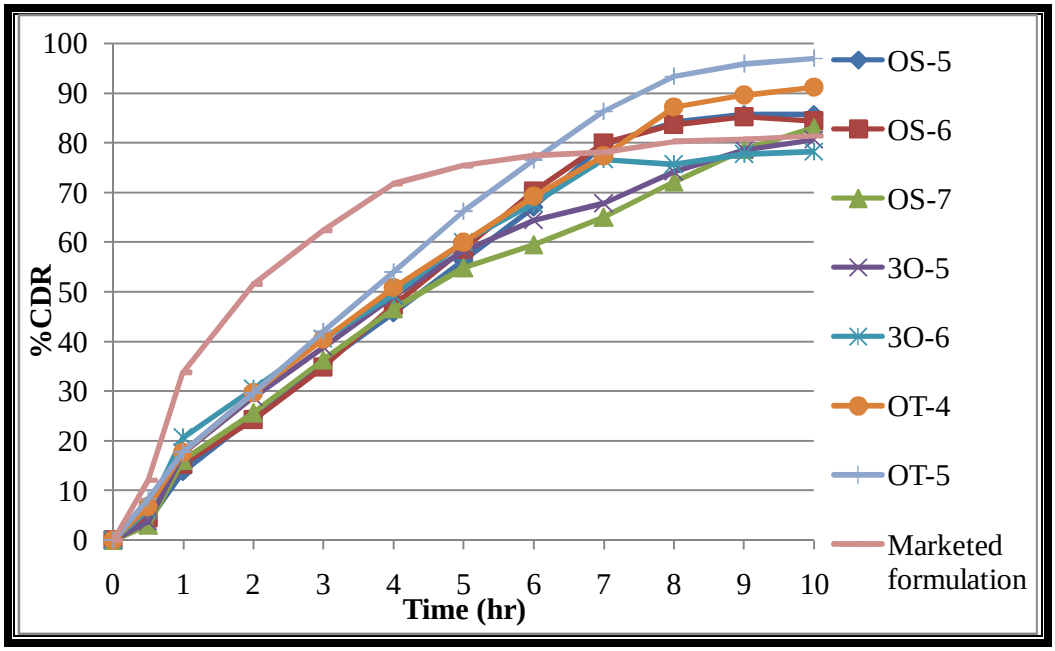

Figure 9: *In vitro* drug release studies of optimized organogel formulation and marketed formulation.

The order of % cumulative drug release was

OT-5> OT-4> OS-5> OS-6> OS-7> marketed formulation> 3O-5> 3O-6.

- **Comparative *in-vitro* drug release study of marketed formulation v/s OT-5**

Table 7: *In vitro* drug release studies of marketed formulation v/s OT-5.

Time (hr)	OT-5 Mean±S.D.	Marketed formulation (Gel) Mean±S.D.
0	0	0
0.5	8.304±0.031	12.038±0.037
1	17.707±0.042	33.747±0.045
2	29.681±0.038	51.552±0.063
3	42.012±0.029	62.262±0.072
4	53.938±0.049	71.733±0.048
5	66.197±0.061	75.347±0.051
6	76.504±0.054	77.485±0.039
7	86.312±0.046	78.100±0.041
8	93.309±0.051	80.190±0.032
9	95.878±0.032	80.757±0.029
10	96.923±0.018	81.276±0.037

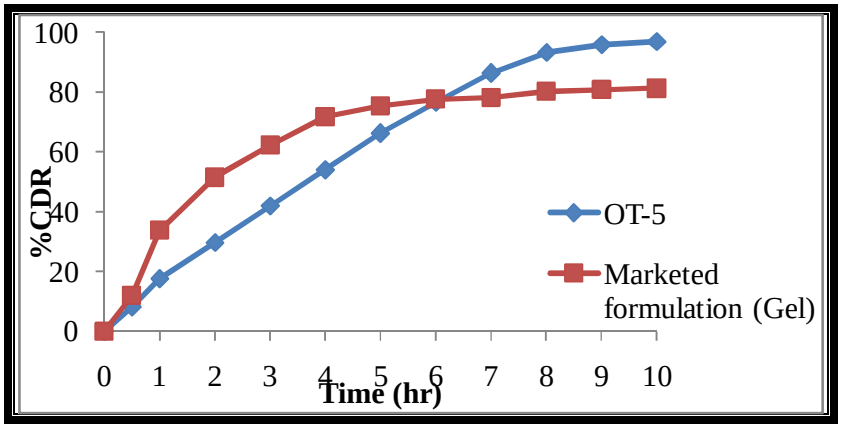

Figure 10: *In vitro* drug release studies of marketed formulation v/s OT-5.

%CDR OT-5 organogel was found to be better than marketed formulation (gel).

- **Drug release kinetics**

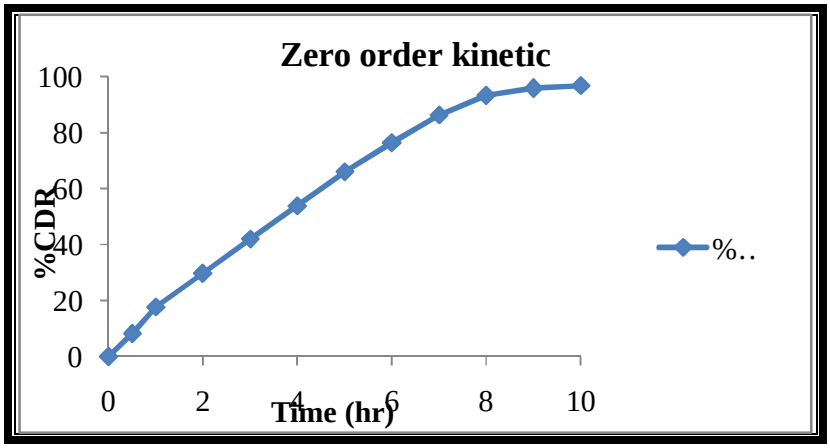

Figure 11: Zero order plot for drug release kinetics for OT-5.

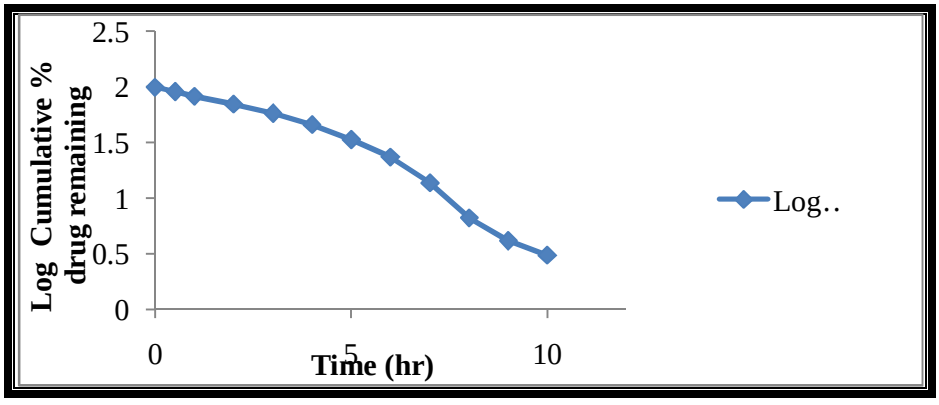

Figure 12: First order plot for drug release kinetics for OT-5.

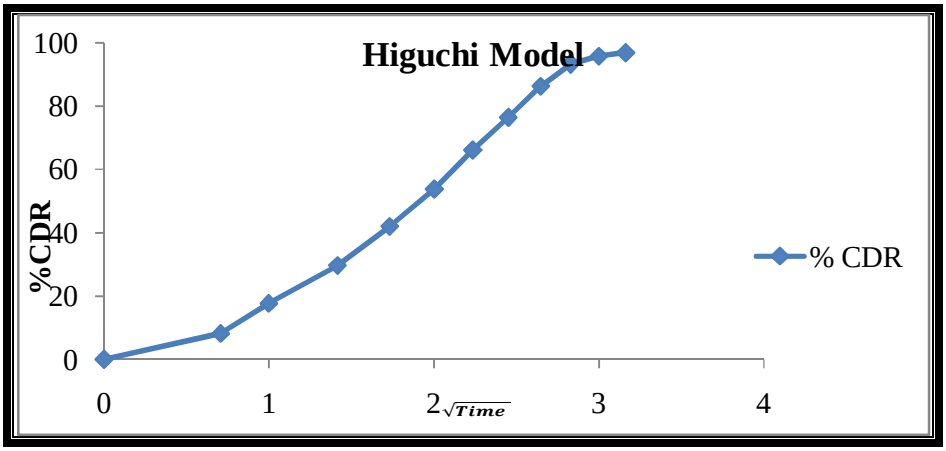

Figure 13: Higuchi model plot for drug release kinetics for OT-5.

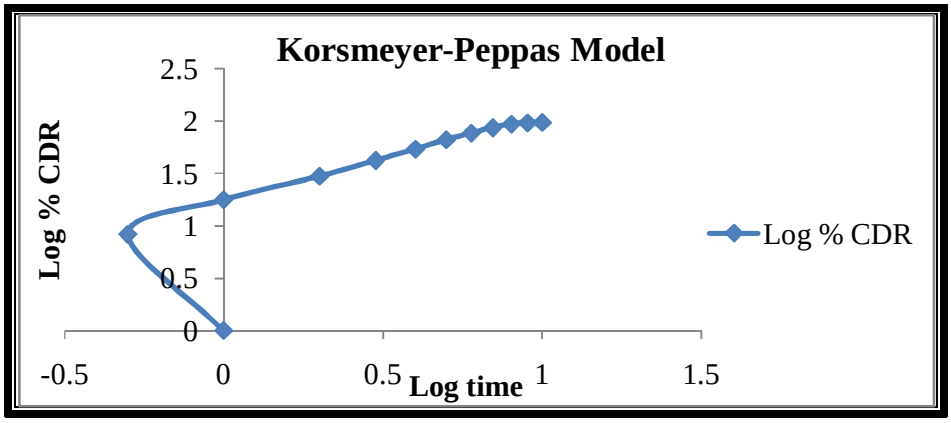

Figure 14: Korsmeyer-Peppas Model plot for drug release kinetics for OT-5.

Table 8: Drug release kinetic equation parameter of fluconazole organogel (OT-5).

Formulation	Zero order		First order		Higuchi		Korsmeyer - peppas	
	R^2	K_O	R^2	K_f	R^2	K_h	R^2	N
OT-5	0.965	10.205	0.951	-0.344	0.971	35.405	0.694	1.140

The calculated regression coefficients for zero order, first order and higuchi models and korsmeyer were shown in Table no.8. It was found that the in vitro drug release fluconazole organogel was best explained by higuchi equation as the plot showed the highest linearity. Therefore the release pattern seems to fit higuchi model.

CONCLUSION

This study reports the successful development of novel span 80–tween 80 mixture based organogels. The gels were developed by fluid-filled mechanism. The developed organogels were found to be stable in nature and were able to sustain heat shocks for prolonged period. The drug release study from the organogels indicated diffusion-dependent release. Since the organogels were prepared using FDA approved components, the organogels are expected to be biocompatible. Based on the preliminary studies, it seems that the span 80–tween 80 mixture based organogels may be tried as a drug carrier for transdermal bioactive agent delivery. Optimized formulation OS-5, OS-6, OS-7, 3O-5, 3O-6, OT-4 and OT-6. From among all the developed formulation, OT-5 shows better drug diffusion. The release rate of drug from OT-5 formulation is best fitted to Higuchi matrix model. Drug release profile of OT-5 organogel was found to be better than marketed formulation. Hence from the above results we can conclude that it is possible to formulate organogel of fluconazole drug using sunflower oil, span 80-tween80 polymer for treatment of various fungal infections.

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