INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Research Article

Formulation and Evaluation of Surfactants Based Ocular Drug Delivery System of Antifungal Drug

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ARTICLE INFO

Published: 28 July 2026
Keywords:
ocular Drug delivery system, surfactants, antifungal drug, vesicles, voriconazole
DOI:
10.5281/zenodo.21662278

ABSTRACT

Ocular drug delivery is the most challenging tasks for the pharmaceutical researchers. To retain a therapeutic level of the drug at the site of action for a prolonged duration is major obstacle. Due to unique anatomy and physiology, the eye presents challenges for delivery of pharmaceuticals.

INTRODUCTION

The structure of eye is divided into two main parts that are anterior segment and posterior segment. Approximately one-third portion of the eye is occupied by anterior segment whereas the residual portion is occupied by the posterior segment. Anterior portion includes cornea, aqueous humor, conjunctiva, iris, ciliary body and lens whereas back of the eye or posterior segment of the eye consists of sclera, choroid, neural retina, retinal pigment epithelium, optic nerve and vitreous humour. [1,2]

Ideal characteristics required to optimize ocular drug delivery systems:

1. It should have good corneal penetration.
2. It should possess prolonged contact time of drug with corneal tissue.
3. There should be simplicity in instillation and removal for the patient.
4. It should be non-irritating to eye.

Routes of Ocular Drug Delivery

1. Topical route
2. Peri ocular route

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

It includes subconjunctival, subtenon, retrobulbar, and peribulbar administration

3. intravitreal route

VESICULAR DRUG DELIVERY SYSTEM

In novel drug delivery system, the vesicular drug delivery system (VDDS) has become popular due to its benefits such as improved bioavailability and reduced dose frequency. It gives prolonged and controlled action at the corneal surface by preventing the metabolism of the drug from the enzymes present at the tear/corneal epithelium

PREPARATION OF SURFACTANT BASED VESICLES

They can be prepared by theethanol injection method.

Dissolve drugin ethanol in water bath at 70 ˚C
↓
Quickly inject this resultant solution into preheated aqueous phase containing the EA(Tween80)
↓
Stir continuously on a magnetic stirrer at 1000 rpm for 15 min at 70 ˚C
↓
Cool at room temperature to get drug-loaded surfactant based vesicular dispersion[14]

- Uveitis
- Diabetic retinopathy

FUNGAL INFECTIONS

Fungal infections are mostly responsible for ocular morbidity and blindness. Fungi are subdivided into yeasts and molds. For treatment of ocular fungal infection antifungal agents are required. [16]

MATERIALS AND METHODS

Materials:-

A. Drug: Voriconazole

B. Chemicals: Chemicals and reagents used for the preparation of buffers, solutions and other experimental purposes are listed in table.

List of chemicals used in formulation of eye drops

Sr. No	Chemicals	Manufacturer/ Supplier
1	Tween 80	S. D. Chemical Center, Mumbai.
2	Span80	
3	Ethanol	
4	Voriconazole	Cipla lab, Mumbai

All the other reagent sused were of analytical gradeand were used as procured.

C. Instruments: Instruments and equipments used.

List of Equipment's used

Sr. No.	Name of Equipment	Manufacturer
1	Weighing Balance	Adventurer-Ohaus
2	Melting Point Apparatus	Chemiline (CL726)
3	pH Meter	Microprolabmate
4	Magnetic Stirrer	Remi Scientific Instruments, Mumbai
5	UV-Visible Spectrophotometer	Shimadzu, Japan
6	ATR-FTIR Spectrophotometer	Bruker, Alpha
7	Stability Chamber	Thermolab
8	Binocular Microscope	Lawrence and Mayo
9	Differential Scanning Calorimeter	Perkin Elmer 4000
10	Zeta Analyzer	Horiba Nanoparticles Analyzer SZ-100
11	Particle Size Analyzer	Horiba Nanoparticles Analyzer SZ-100

Method:-

Preformulation studies

Characterization of drug

1. **Description:** The sample was analyzed for its nature, colour and odour.

2. **Melting Point:** Melting point of Voriconazole was determined by micro-controlled based melting point apparatus (Chemiline-CL 726). Taking a pinch of Voriconazole into a capillary tube, closed at one end. Then the capillary was inserted in bath of silicone oil which was heated in controlled manner with the help of electrical heating coil. The temperature which made drug sample transparent was noted as melting point temperature. Average of triplicate readings was noted and compared with the literature value. [26]

3. **Differential Scanning Calorimetry (DSC):** DSC was performed in order to assess the thermal behavior of the drug. It measures heat flow in and out of both sample and reference during control temperature. About 1 mg of the sample was sealed in the aluminium pan and heated at the rate of 10°C/min, covering a temperature range of 30°C to 35°C under nitrogen atmosphere, at flow rate of 20 ml/min. [27]

4. **FTIR Spectroscopy:** IR study was carried out to check purity of drug. It was determined by Fourier Transform Infrared spectrophotometer. The IR spectrum of Voriconazole was recorded using Fourier transform infrared spectroscopy (FTIR) to check its purity. The spectrum was recorded over the wave number of 4000 to 400 cm-1. [28]

5. **UV spectroscopy**:

- **λ max determination [29]**

Accurately weighed 100 mg of drug was dissolved in 100 ml of ethanol to form stock-I (1000µg/ml).10 ml ofsolution was with drawn from stock-I added to 100 ml of volumetric flask. The volume was made to 100 ml using ethanol to form stock-II (100 µg /ml). Then 1 ml from stock-II was withdrawn and added to 10 ml volumetric flask. The volume was adjusted to 10ml using ethanol to prepare final solutions (10µg/ml). The UV spectrum was recorded in range of 200-400 nm using UV spectrophotometer. The ƛ max was determined by scanning solution of 10µg/ml against blank solution..

- **Calibration Curve of Voriconazole [29]**

➢ **Preparation of Primary stock solution:**

Accurately weighed 100mg of voriconazole was added in to 100 ml volumetric flasks. Then small amount of ethanol was added to dissolve the drug and then volume was made to 100 ml with the methanol (diluents). The concentration of standard stock solution was 1000 µg/ml.

➢ **Preparation of Secondary stock solution:**

Transferred 1 ml from the above standard stock solutions in to 10 ml volumetric flasks and diluted up to the mark with diluent toget working secondary stock solution having concentration of 100µg/ml.

➢ **Preparation of diluted concentration:**

From the secondary stock solution 1, 1.2, 1.4, 1.6, 1.8, 2, 2.2, 2.4 ml were transferred to 10ml volumetric flasks and final volume was made to 10ml with methanol to prepared solution in concentration range of 10-24 µg/ml. The absorbance of each dilutions were measured at λ max 255 nm using methanol as ablankand standard

curve was plotted between concentration (µg/ml) on X-axis and absorbance on Y-axis. The calibration curve follows equation of straight line,

$$Y = mx + C$$

Where, Y=absorbance m=slope x=concentration C=constant

6. **Drug Excipient Interaction Study:** Drug-excipient interaction study was performed by FTIR and DSC studies. IR was determined by Fourier Transform Infrared Spectrophotometer (FTIR-410,Jasco, Japan). The spectra were scanned over wavelength region of 4000 to 400 cm-1 at resolution of 4 cm-1. [28] For DSC study, about 1mg of the sample was sealed in the aluminum pan and heated at the rate of 10˚C/min, covering a temperature range of 30˚C to200˚C under nitrogen atmosphere, at flow rate of 20 ml/min. [27]

Characterization of excipients

1. **Saponification value:**

Saponification value is number of mg of potassium hydroxide necessary to neutralize the free acids and to saponify esters present in 1gm of substance. 2 gm. of substance under examination was accurately weighed into 200ml flask of borosilicate glass fitted with reflux condenser. Then in this flask 25ml of 0.5M ethanolic KOH and little pumice powder was added.All this material was boiled under reflux on water bath for 30min. 1ml of phenolphthalein solution was added and this whole solution was titrated with 0.5M HCl (a). Blank titration was carried out (b).

Saponification value was determined by using formula-

$$\text{Saponification Value} = 28.05 \times (b-a)/W$$

Where, W- Weight in gm of substance [30]

2. **Acid value:**

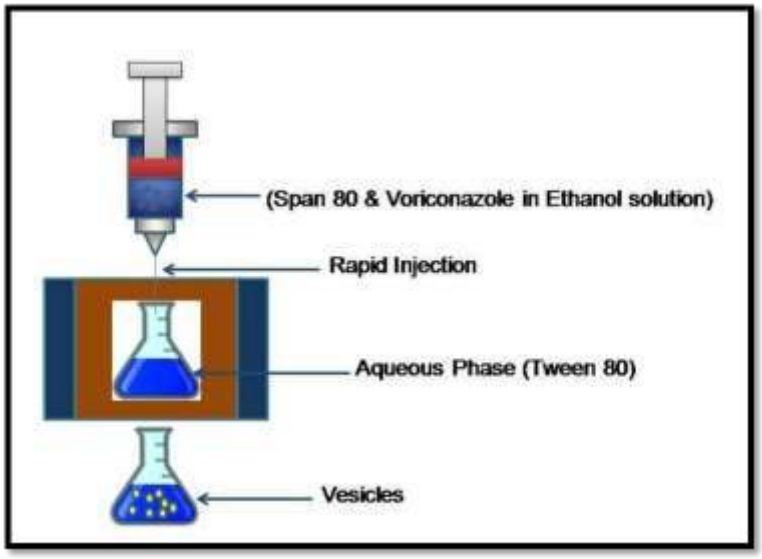
Acid value is the number which express in milligrams. The amount of potassium hydroxide necessary to neutralize the free acids present in 1 gm of the substance. 10 g of the substance under examination was accurately weighed into 50ml flask of a mixture of equal volume of ethanol (95 %) and ether previously neutralized with 0.1 m potassium hydroxide to phenolphthalein solution. If the sample does not dissolve in the cold solvent connect flask with the reflux condenser and warm slowly with frequent shaking until the sample dissolve. Add 1 ml of phenolphthalein solution and titrate with 0.1 KOH until the solution remains faintly pink after shaking for 30 seconds. Acid value was determined by using formula-

$$\text{Acid value} = 5.61 \times n/W$$

Where, n= the number of ml of 0.1 M KOH required. W=the weighting of the substance[30]

Preparation of surfactant based vesicles:

Surfactant based vesicles containing Span 80 and edge activator (EA) Tween 80 were prepared by ethanol injection method. Voriconazole and span 80 were dissolved in ethanol. The solution so prepared is then transferred rapidly into the preheated tween 80 and vigorously stirred on the magnetic stirrer at high speed 1000 rpm/ min. Voriconazole was used at a concentration of 10 mg/ml for the preparation of vesicles. [12,14]



Ethanol injection method for formulation of Surfactants Based Ocular Drug Delivery system of voriconazole.

Design of experiment

A 32 full factorial design was chosen in which concentration of tween 80 (X1) and concentration spans 80 (X2) were used as 2 factors and experimental trials were performed at all 9 possible combinations.

Amount of variables in 32 factorial design batches-

Coaded Values	Actual Values	
	X1:(Conc of Span 80)	X2:(Conc of Tween 80)
-1	10 %	70 %
0	20 %	80 %
1	30 %	90 %

Responses:

Y1=Total drug content

Y2=Corneal Permeability Studies (CADD/cm2)

A32 full factorial experimental design layout

Formulation batches	Coded values	
	X1	X2
F1	1	1
F2	1	-1
F3	1	0
F4	0	0
F5	0	-1
F6	0	1
F7	-1	0
F8	-1	1
F9	-1	-1

Composition of surfactant based vesicles of voriconazole

Formulation batch		Ingredients			
	Voriconazole (mg)	Span80 (%)	Tween80 (%)	Ethanol (ml)	Water (ml)
F1	100	30	90	q. s	q. s
F2	100	30	70	q. s	q. s
F3	100	30	80	q. s	q. s
F4	100	20	80	q. s	q. s
F5	100	20	70	q. s	q. s
F6	100	20	90	q. s	q. s
F7	100	10	80	q. s	q. s
F8	100	10	90	q. s	q. s

F9	100	10	70	q. s	q. s

EVALUATION OF FORMULATION

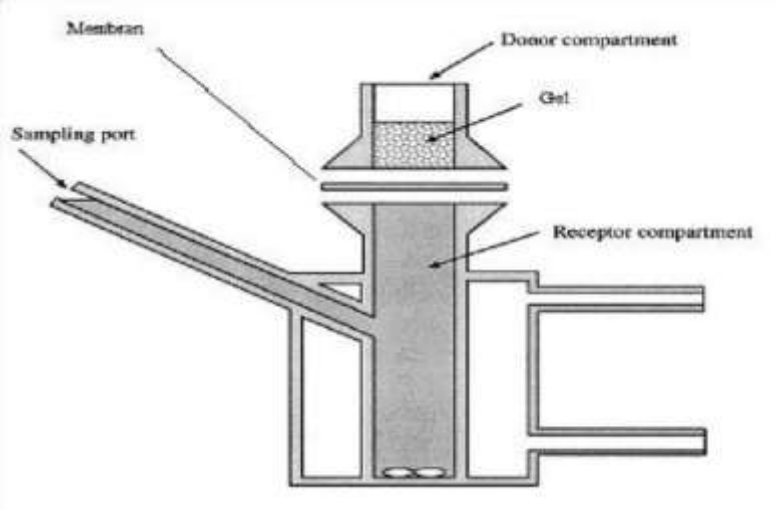
- **Total drug content:**

Isopropyl alcohol was chosen as a suitable solvent for disrupting the prepared vesicles. Aqueous dispersion (1 ml) was disrupted using sufficient quantity of isopropyl alcohol and the absorbance was recorded at 255 nm. [12]

% Drug content= actual drug content/ Theoretical drug content *100

- **Corneal Permeability Studies:**

Study is performed on a Franz diffusion cell assembly.



Franz diffusion cell

Drug permeation studies were carried out by using freshly excised goat cornea. Goat whole eye balls were transported from the local butcher shop to the laboratory in cold (4°C) normal saline within 1 hour of slaughtering of the animal. The cornea was carefully excised along with 2 to 4 mm of surrounding sclera tissue and was washed with cold normal saline till the washing was free from proteins. The receptor compartment of an all-glass modified Franz diffusion cell was filled with 40 mL freshly prepared normal saline solution (pH 7.4) and all air bubbles were expelled from the compartment. Freshly excised cornea was fixed between clamped donor and receptor compartments in such a way that its epithelial surface faced the donor compartment.The corneal area available for diffusion was 2.26 cm^2. An aliquot (1 mL) of test solution was placed on the cornea and the opening of the donor cell was sealed with a glass cover slip. The receptor fluid was kept at 37°C with constant stirring using a Teflon-coated magnetic stir bead.

Permeation study was continued for 180minutes and samples were withdrawn from receptor and analyzed for voriconazole content by measuring absorbance at 255nm in a spectrophotometer.[25]

- **Morphology:**

Vesicles were characterized by using optical microscope for structural attributes such as uniformity of size, shape and physical stability

characteristics i.e. aggregation and/or irregularity. [12]

- **Vesicular size determination and Zeta potential measurement:**

Particle size analysis was carried out by using Horiba Nanoparticle Analyzer SZ- 100 instrument. SZ-100 uses the technique of dynamic light scattering to determine particle size. During testing, temperature was maintained at 25^0 C. Sample was placed in sample holder. [12] Zeta potential of formulation can be measured by zeta meter. Zeta potential analysis was determined by using Horiba Analyzer SZ-100 instrument. [14]

- **Stability Study:**

Stability studies were carried out for optimized formulation. For stability studies the optimized formulations were stored at temperature 4˚C-8˚C and 25˚C for a period of 2 months. Sample was analyzed for the change in appearance and aggregation. [12]

RESULTS AND DISCUSSION

Preformulation studies

Characterization of drug

1) Description:

Drug sample was found to be odourless, solid, white crystalline powder**.**

2) Melting point:

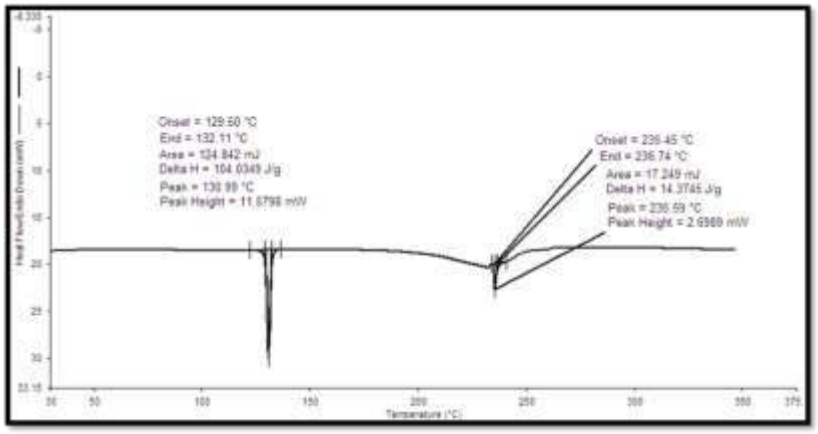
Melting point of Voriconazole was found to be in range of 127-130°C which complies with that given in the literature. [18]

Melting point of drug

Sr. No	Observed melting point	Average Melting Point
1	127-130ºC	127-130ºC
2	128-131ºC	
3	127-130ºC	

3) Differential Scanning Calorimetry:

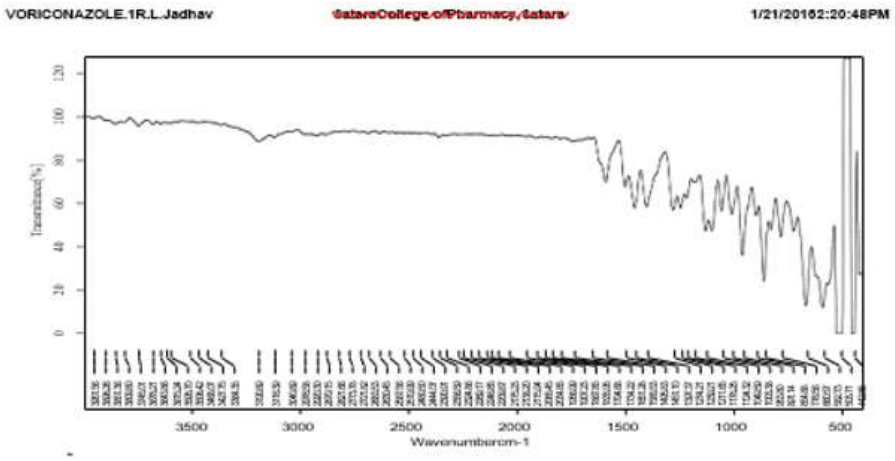
According to the thermogram, a sharp endothermic peak was observed at 130.99 ºC which corresponds to the melting point of pure drug. Such an endothermic peak was also reported for standard drug material near to the melting range. [27] This indicated that Voriconazole drug was in pure form.



DSC thermogram of pure drug

4) FTIR Spectroscopy:

The infrared spectrum of Voriconazole was recorded and spectral analysis was carried out is shown in Fig-9.2



FTIR Spectrum of Voriconazole

- **Pure Voriconazole peaks are shown in table no. 9.2**

IR interpretation of Voriconazole

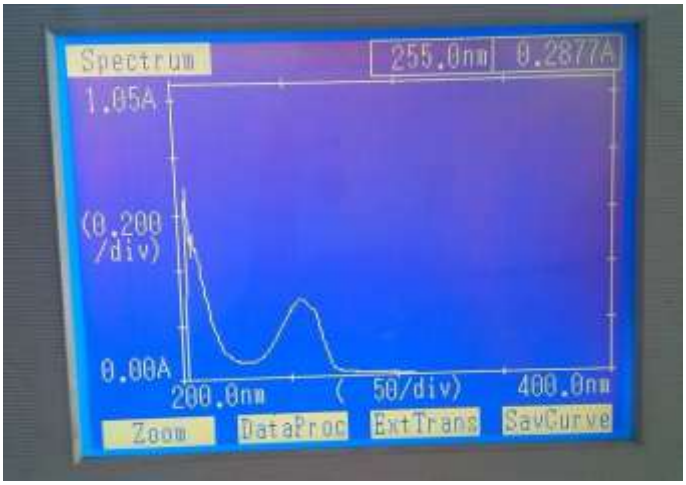
Sr. No	Functional Groups Associated	Standard Wave Number (cm^{-1})	Observed Wave number (cm^{-1})
1	C=C	1600, 1475	1585, 1451
2	C-N	1350-1000	1049
3	C=N	1690-1640	1647
4	O-H	3400-2400	3190
5	C-F	1400-1000	1397

In IR study, it was found that all the important characteristic peak were present, which confirmed the purity of drug sample.

5) UV spectroscopic study

λ max Determination-

The λ max value of Voriconazole was found to be 255 nm in ethanol.



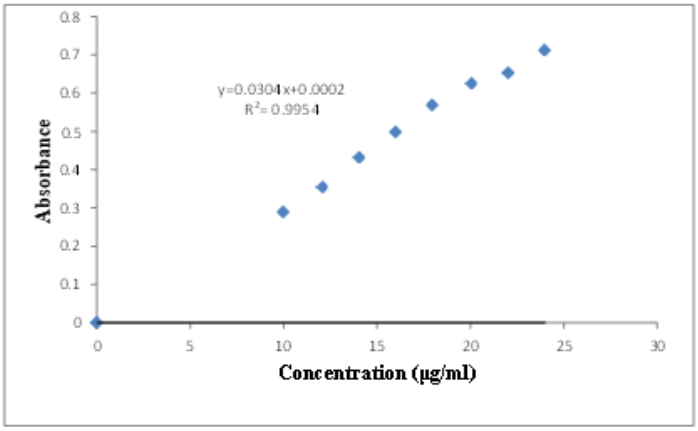
UV Spectrum of Voriconazole

Calibration Curve of Voriconazole in ethanol-

The standard calibration curve for Voriconazole in ethanol was plotted by using following results of absorbance at various concentrations.

Observations for calibration curve of Voriconazole.

Sr.no	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.2898
3	12	0.3543
4	14	0.4321
5	16	0.4982
6	18	0.5687
7	20	0.6254
8	22	0.6532
9	24	0.7132



Calibration Curve of Voriconazole in ethanol

Parameters of Calibration Curve of Voriconazole in ethanol

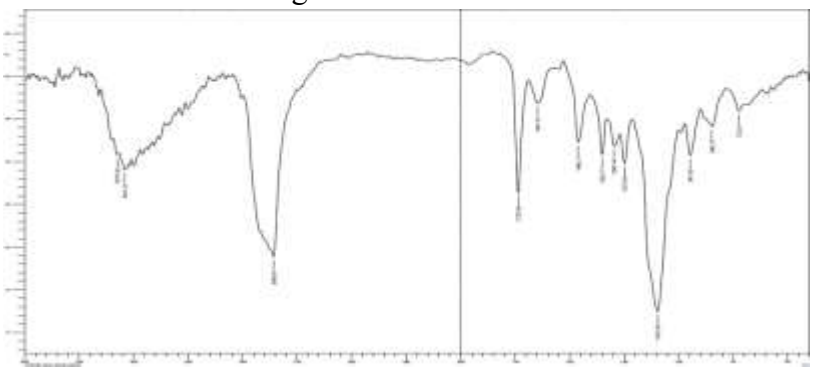
Sr. No	Parameter	Value
1	λmax	255 nm
2	Slope (m)	0.0304
3	Intercept(c)	0.0002
4	Linearity Range	10-24µg/ml.
5	Correlation Coefficient(r2)	0.995

6) Drug excipient interaction study:

This study was carried out to check for any possible interaction between the drug and excipient. Drug – excipient interaction study was performed by FTIR and DSC study.

- **FTIR Spectrum-**

From FTIR study, it was found that the peaks found in pure drug and formulation are similar. Thus incorporation of drug in surfactants did not change the position of its functional groups. This indicated that there was no interaction between drug and excipients.



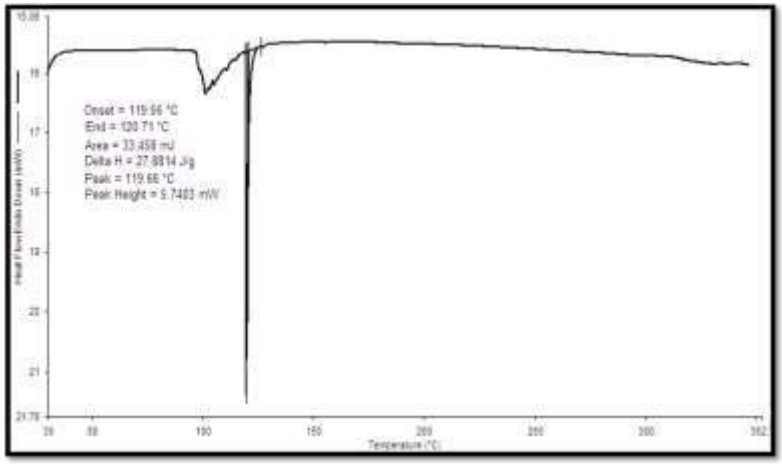
FTIR spectra of Surfactants Based Ocular Drug Delivery system of Voriconazole

IR interpretation of optimized formulation

Sr. No	Functional Groups Associated	Standard Wave number (cm^{-1})	Observed Wave number (cm^{-1})
1	C=C	1600, 1475	1550, 1460
2	C-N	1350-1000	1097
3	C=N	1690-1640	1651
4	O-H	3400-2400	2858
5	C-F	1400-1000	1350

- **DSC Thermogram-**

According to thermogram, peak was observed at 119.66°C which is at low temperature compared to thermogram of pure drug (130.99 °C). This shifting of peak may be due to presence of surfactants which encapsulates the drug by forming vesicles.



DSC thermogram of Optimized formulation

Characterization of excipients (span80 and tween80)

1) Saponification value-

Saponification value was determined by using formula-

$$\text{Saponification value} = 28.5 \text{ x } \frac{(b - a)}{w}$$

$$\text{Saponification value span 80} = 28.5 \text{ x } \frac{(20.5 - 10.5)}{2}$$

=140.25

Saponification value of span 80 was found near to standard value (145-160) and it confirmed the purity of span 80.

$$\text{Saponification value Tween 80} = 28.5 \text{ x } \frac{(20.5 - 16.2)}{2}$$

=60.30

Saponification value of tween 80 was found near to standard value (45-55) and it confirmed the purity of tween 80.

2) Acid value-

Acid value was determined by using formula-

$$\text{Acid value} = 5.61 \frac{n}{w}$$

Where, n= the number of ml of 0.1 M KOH required.

W= the weighting of the substance.

Acid value for Span 80 =

$$\text{Acid value} = 5.61 \frac{15.6}{10}$$

$$=8.75$$

Acid value of span 80 was found near to standard value (less than 8) and it confirmed the purity of span 80.

Acid value of tween 80 =

$$\text{Acid value} = 5.61 \frac{2.5}{10}$$

$$=1.40$$

Acid value of tween 80 was found tobe complied with standard value and it confirmed the purity of tween 80.

Evaluation of surfactant-based formulation

1. **Drug content**

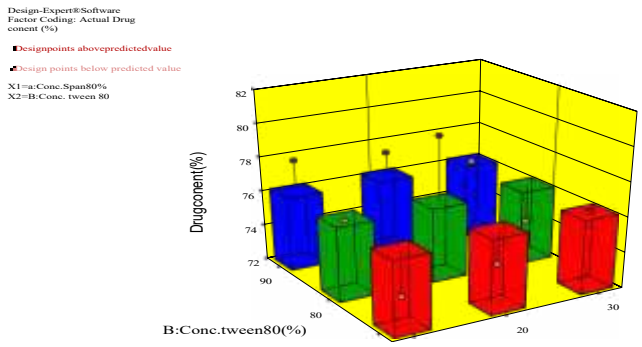
Drug content of all the batches of formulation was calculated. Drug content was calculated by using formula

%Drug content =actual drug content/The oretical drug content X 100

The result was found in the range of 73.72-80.03%. The drug content of the F4 formulation was found to be higher i.e., 80.03% based on the calibration curve. All the values of formulation are shown in table no 9.6.

Drug content of all batches of formulation

Sr. No	Formulation Batch	Drug content (%) ± SD (n= 3)
1	F1	76.26±0.0124
2	F2	76.41±0.0152
3	F3	74.11±0.0100
4	F4	80.03±0.0152
5	F5	77.42±0.0100
6	F6	77.68±0.0152
7	F7	76.21±0.0200
8	F8	78.10±0.0152
9	F9	73.72±0.0200



Response 3D Surface plot for Drug Content(%)

The relationship between the response and variables can be directly visualized from the response surface plot. The response surface plot was generated using Design Expert 10 software and was presented in figures 9.7. This was used to observe the effect of independent variables on the % drug content. From plot it was observed that batch F4 containing 20:80 (Span 80: Tween 80) shows higher drug content (80.03%).

2. **Corneal Permeability Studies:**

Goat corneas were used to study the permeation across the corneal membrane. In the study, cumulative amount of drug diffused per unit area (CADD/ cm2) for all formulation was calculated. The CADD/ cm2 of all formulations were quoted in table no. 9.7 and 9.8. Percent cumulative

amount of drug diffusion (CADD %) were quoted in table no. 9.9 and 9.10.

Amount of drug diffused per unit area for formulation Batch F1to F5

Time (min)	CADD/ cm^2±SD(n=3)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
30	0.63±0.03	0.68±0.01	0.05±0.01	1.08±0.06	0.01±0.01
60	0.73±0.06	0.88±0.01	0.07±0.0	3.10±0.09	0.03±0.01
90	0.78±0.06	1.27±0.06	0.43±0.07	3.20±0.03	0.27±0.01
120	1.14±0.01	2.22±0.04	1.64±0.07	3.38±0.02	0.80±0.01
150	2.47±0.01	2.71±0.07	1.72±0.01	4.12±0.15	1.33±0.03
180	2.97±0.06	3.23±0.05	2.48±0.04	4.22±0.02	1.68±0.01

Amount of drug diffused per unit area for formulation Batch F6 to F9

Time (min)	CADD/cm^2±SD(n=3)			
	F6	F7	F8	F9
0	0	0	0	0
30	0.02±0.02	0.42±0.33	0.82±0.36	0.80±0.01
60	0.24±0.09	0.59±0.04	1.71±0.02	0.85±0.03
90	0.68±0.01	0.71±0.01	2.31±0.06	1.07±0.03
120	1.38±0.07	2.45±0.14	2.55±0.02	1.40±0.02
150	1.70±0.01	2.64±0.02	3.22±0.01	2.23±0.03
180	2.43±0.07	2.72±0.04	3.54±0.01	3.35±0.06

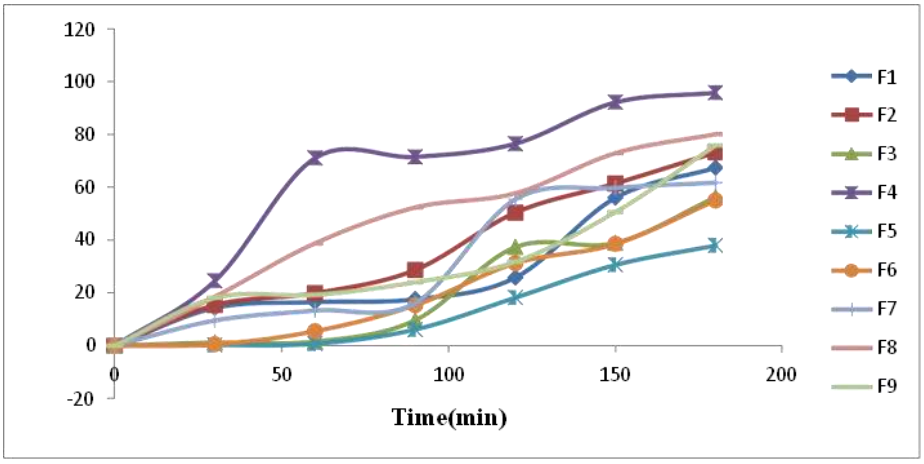
Percent cumulative amount of drug diffused for formulation Batch F1 to F5

Time (min)	CADD %± SD (n= 3)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
30	14.33±0.07	15.40±0.02	1.20±0.01	24.56±0.13	0.23±0.01
60	16.53±0.13	19.93±0.02	1.56±0.005	71.10±0.01	0.73±0.005
90	17.60±0.13	28.70±0.13	9.66±0.15	71.53±0.05	6.13±0.02
120	25.80±0.01	50.43±0.09	37.36±0.15	76.53±0.03	18.20±0.01
150	56.06±0.01	61.46±0.15	38.93±0.1	92.20±0.14	30.60±0.05
180	67.40±0.14	73.23±0.12	56.23±0.08	95.83±0.04	37.96±0.005

Percent cumulative amount of drug diffused for formulation Batch F6 to F9

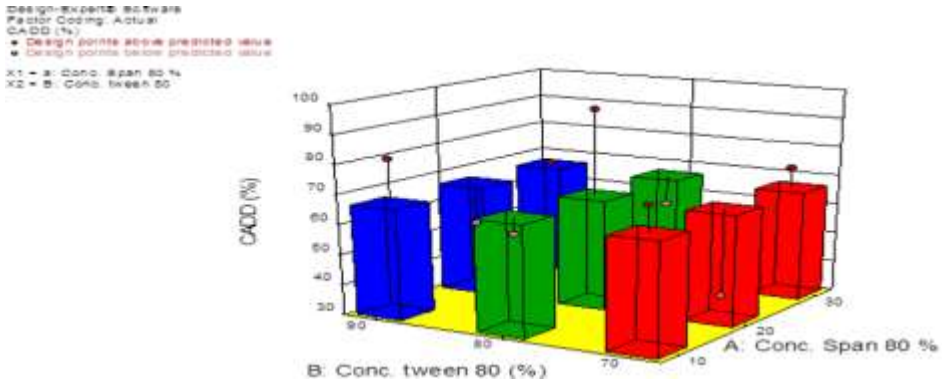
Time (min)	CADD%± SD(n= 3)			
	F6	F7	F8	F9
0	0	0	0	0
30	0.53±0.04	9.56±0.75	18.60±0.14	18.13±0.01
60	5.50±0.21	13.33±0.80	38.80±0.51	19.26±0.06
90	15.33±0.01	16.20±0.02	52.36±1.36	24.03±0.04
120	31.26±0.16	55.50±0.31	57.76±0.49	31.80±0.03
150	38.53±0.01	59.80±0.04	72.96±0.15	50.63±0.06
180	55.03±0.14	61.76±0.08	80.16±0.05	75.90±0.13

Following graph represent the comparative drug diffusion profile of all the formulation batches.



Comparative drug diffusion profile of F1- F9

From graphical presentation it was found that batch F4 gives maximum cumulative drug diffusion.



Response 3D Surface plot for CADD (%)

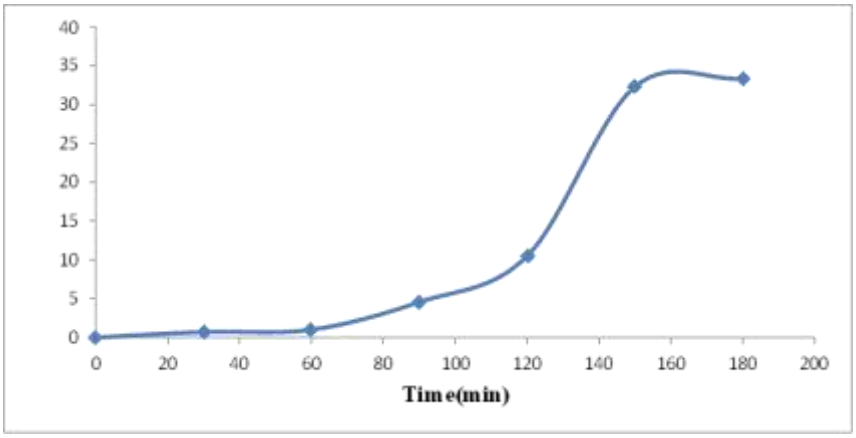
The response surface plot was generated using Design Expert 10 software and was presented in Figures 9.9. The plot shows that batch F4 gave maximum CADD% compared to other formulation batches. The reason behind better permeability of the F4 batch may be the ratio of surfactants, i.e., Span 80: Tween 80 (20:80). Span 80 at a concentration of 20% solubilised the drug, and Tween 80 at 80% concentration performed the role of edge activator, which helped the drug to pass through the corneal barrier. Above or below the 20:80 ratio, surfactants may fail to perform their role as solubiliser and edge activator.

Corneal Permeability Study by Using Saline pH 7.4 Solution

The drug (Voriconazole) was dissolved in pH 7.4 solution. By using this solution, the corneal permeability study was carried out to compare the diffusion rate with formulation batches. Table No. 9.11 shows the values of CADD/cm² and CADD% by using saline pH 7.4 solution.

Amount of Drug Diffused per Unit Area and % Cumulative Amount of Drug Diffused from Saline pH 7.4 Solution

Sr. No	Time (min)	CADD/cm^2 ± SD (n=3)	CADD % ± SD (n= 3)
1	0	0	0
2	30	0.03±0.01	0.70±0.01
3	60	0.04±0.01	1.00.±0.01
4	90	0.2±0.05	4.56±0.11
5	120	0.46±0.01	10.50±0.1
6	150	1.43±0.05	32.30±0.10
7	180	1.46±0.12	33.30±0.27



CADD% in saline pH 7.4 solution

From study it was found that in saline pH 7.4 solution CADD % was 33.30±0.27.

From overall corneal permeability study it was found that surfactant based formulation gave more drug diffusion compared to saline pH 7.4 solution. Among all batches, formulation batch F4 found to be giving maximum drug release i.e., 95.83±0.04.

By studying drug content and corneal permeability of all batches, batch F4 was taken as optimized batch and used for further studies.

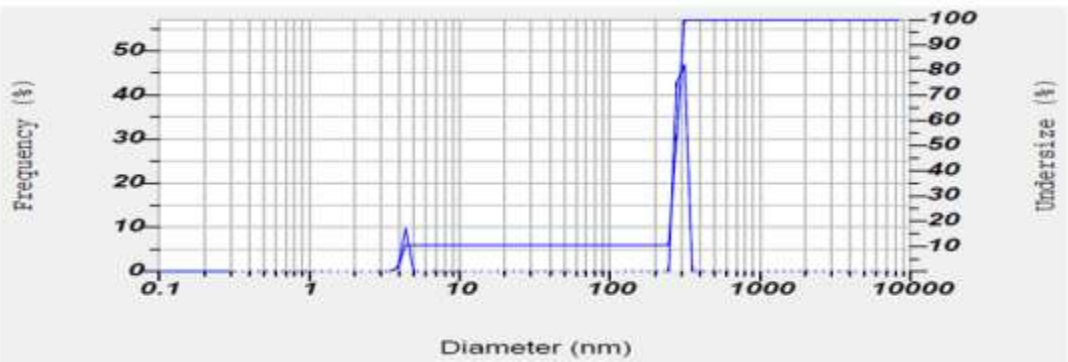
3. Morphology

For an initial characterization of the vesicles, Voriconazole surfactant based formulations were observed microscopically. Optical observation indicated the vesicles were small in size, round in shape and no aggregation was observed in the formulation.

Optical microscopy of optimized formulation batch 4

4. Particle size analysis-

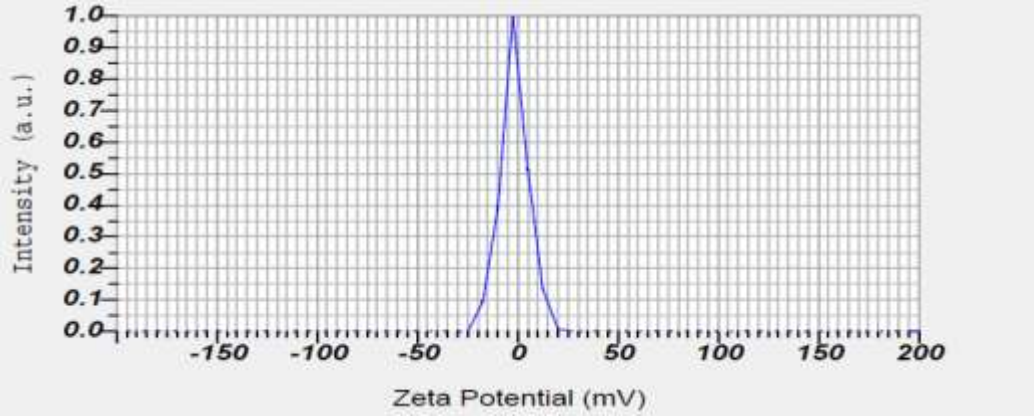
The mean particle size of formulations should be in range of nanometer to micron. The optimized batch of surfactant based vesicles was used for particle size determination. The average particle size of optimized formulation was found to be 251.1 nm, which lies in standard range. Dispersity index was found to be 2.37. Therefore, formulation was found to be polydisperse in nature.



Graph of particle size of optimized batch (F4)

5. Zeta potential analysis

Measurement of Zeta potential is very important parameter in determination of stability of formulation. Highly negative or highly positive zeta potential indicates good physical stability. Value > ±20 is essential for effective stability and decrease aggregation. Zeta potential of optimized formulation was found to be -1.6 mV which was not according to standard range.



Graph of zeta potential of optimized batch (F4)

6. Stability Study

Optimized formulation was subjected to stability studies as per the literature search. Stability of vesicles is studied by studying aggregation/ irregularity and appearance of vesicles over a period of 2 months storage. Table no. 9.12 shows result of stability studies.

Observation of stability studies

Condition for stability	Duration	Appearance	Aggregation
Refrigeration (4˚C -8˚C)	0 day	Clear solution	No
	15 days	Clear solution	No
	30 days	Clear solution	No
	60 days	Clear solution	No

Ambientroom temperature (25˚C)	0 day	Clear solution	No
	15 days	Clear solution	No
	30 days	Clear solution	No
	60 days	Clear solution	No

Extent of drug aggregation in refrigerator and at ambient room temperature (25˚C) was significantly low. Hence, the formulation can be refrigerated or stored at room temperature for use.

CONCLUSION

Surfactant based vesicles of Voriconazole containing Span 80 and edge activator (EA) Tween 80 were prepared by ethanol injection method and evaluated.

Purity of drug and excipients were confirmed by pre-formulation testing. Purity of drug was confirmed from calibration curve, melting point and analytical method. IR and DSC studies indicated excipients used in formulation were compatible with drug.

By using 3^2 full factorial design, surfactant-based vesicles of Voriconazole were prepared in which concentration of tween 80 and concentration span 80 were used as 2 factors and experiments were performed. The response surface plot was generated using software. This was used to observe the effect of independent variables on the % drug content and corneal permeability. From plot it was observed that formulation batch F4 containing 20:80 (Span 80: Tween 80) showed better corneal permeability (95.83±0.04 %) performed on goat's eye and higher drug content (80.03±0.0152 %) among all formulated batches.

When optimized batch is compared with normal saline pH 7.4 solution it found that newly developed surfactant-based formulation gives increase in corneal permeability.

In stability study,it was found that extent of drug aggregation upon storage in refrigerator and at ambient room temperature was significantly low. Hence the formulation is stable in nature.

Therefore, from the present study it can be concluded that surfactant based ocular drug delivery systems shows good permeability for topical ocular delivery of Voriconazole and it can be used to deliver drugs to the posterior segment of the eye.

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HOW TO CITE: Harsha Kamble, Shweta Nagtilak, Dr. Naga Potnuri, Ananda Waghmode, Formulation and Evaluation of Surfactants Based Ocular Drug Delivery System of Antifungal Drug, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 5442-5459. https://doi.org/10.5281/zenodo.21662278