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Formulation and Evaluation of Ketoconazole Nanoemulsion Gel for Topical Delivery

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ABSTRACT

The aim of present investigation was to develop nanoemulsion gel of ketoconazole for topical delivery and comparison with the marketed preparation. Ketoconazole, BCS class II antifungal agent with broad spectrum activity is a poorly soluble and highly permeable drug. Due to its poor solubility, it is incompletely absorbed after oral dosing and bioavailability varies. The drug efficacy of topical formulation can be limited by instability due to its poor solubility in the vehicle and low permeability. Therefore, to overcome these shortcomings of conventional system nanoemulsion have been used as drug carrier in topical treatment of fungal infection, especially in dermatology**.** Pseudo-ternary phase diagram was constructed on triplot software to identify nanoemulsion area using different concentrations of oil, Smix (surfactant and co- surfactant) and water. 2% Carbopol 980 as gelling agent and 0.5% DMSO as permeation enhancer was used in topical gel formulation. The formulations was characterized on the basis of pH, drug content, viscosity and *in-vitro* diffusion study. The optimized formulation was found to have pH 7.4 and drug content 98.90%. *In-vitro* diffusion study of nanoemulsion gel showed 80.375% release within 8 hrs. Drug release of ketoconazole nanoemulsion gel when compared with marketed formulation showed 80.375% release within 8 hrs as compare to 52.125% for marketed preparation (Ketoconazole cream 2%, H&H Pharmaceutical). So, it is concluded that by incorporating ketoconazole nanoemulsion in topical gel provided sustained release along with improved solubility and permeability.

Keywords: Topical Delivery, Permeability, Permeation Enhancer, *In-vitro*, Diffusion Study.

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INTRODUCTION

Topical drug delivery is the system used to ensure that the drug get into the body and reach the area where it is needed. Topical route of administration is a localized system for delivery of drug in the body through ophthalmic, rectal, vaginal and skin as topical routes. These preparations are applied on to the skin surface for providing local or systemic effect[1]. Fungal disease is ubiquitous in the world and antifungal medication account for sales of more than US$ 1 billion annually. Most fungal disorder is relatively benign but can become life threatening in immune compromised or malnourished population. The main stay of management of fungal infection and dermatophytes associated with skin and nail injuries has been oral and topical antifungal[2]. Ketoconazole is a broad spectrum imidazole antifungal agent marketed as creams and tablets. It interacts with 14-demethylase, a cytochrome P-450 enzyme and inhibits ergosterol synthesis and increased fungal cellular permeability and is used against a wide variety of fungi and yeasts. It is readily but incompletely absorbed after oral dosing and is highly variable. The major drawback of this drug is its low aqueous solubility. Increasing the water solubility of insoluble or slightly soluble compounds is a major concern for pharmaceutical researchers. It is effective topically for the management of cutaneous, candidiasis and tinea infections of the skin. Ketoconazole belongs to BCS class II i.e. poorly soluble and highly permeable drug[3]. Due to poor solubility, it is incompletely absorbed after oral dosing and bioavailability varies among individuals. Thus intravenous administration becomes necessary if high drug concentration is required but this causes discomfort and patient incompliance. Various conventional topical doses forms of ketoconazole are available in the market such as cream and gel, however, side effects are associated with ketoconazole therapy such as burning at application site, several allergic reaction (rash, itching and swelling of mark, face lips or tongue) blister, irritation, pain and redness. Therefore, to overcome these shortcomings of the conventional system the novel drug delivery system (NDDS) plays a crucial role. Nanoemulsions have been widely used as drug carrier in topical treatment of diseases, especially in dermatology. They are capable to incorporate a variety of hydrophilic and hydrophobic drugs, to enhance the accumulation of drug at the administration site and to reduce side effects. Nanoemulsion can provide sustained and/or controlled release of entrapped drug. Nanoemulsion system allows for a high accumulation of drug in the skin, with relatively low permeation flux as compared to the conventional topical forms. It has been shown that nanoemulsions are fairly compatible with gels and are used as carriers for the incorporation of drug for topical delivery[4]. The ketoconazole nanoemulsion gel was prepared. So, the objective of

the present research work was to formulation and evaluation of ketoconazole nanoemulsion gel for topical delivery for improving the solubility and bioavailability of drug.

Material and methods

MATERIALS AND METHOD

Ketoconazole was obtained as a gift sample from Heliox Pharma Pvt. Ltd. Myritol ®318 was purchased from BASF Care Creations. Kolliphor HS 15 was sourced from BASF the chemical company. PEG200, Potassium Dihydrogen Phosphate was purchased from Qualikems Fine Chem Pvt. Ltd. DMSO, Triethanolamine were purchased from Fisher Scientific. Carbopol 980 was sourced from Lubrizol Advanced Material Europe. Sodium hydroxide was obtained from Avarice Laboratories Pvt. Ltd. All chemicals and solvents were of analytical grade. Freshly double distilled water was used in the experiments.

Determination of organoleptic properties

The physical identification of ketoconazole was done by checking its physical appearance i.e. colour, odour, taste and state. Weighed quantity of ketoconazole as drug was taken and viewed in well illuminated place. Very less quantity of drug was smelled to get the odour.

Determination of Melting point

Melting point of the drug was determined by using capillary method. Drug was filled into capillary tube by sealing its one end at the height of 3 mm from the closed end. The capillary was introduced into the digital melting point apparatus and the point at which the drug starts melting was noted until the entire samples get melted.

Identification of drug by FTIR and UV- Visible spectroscopy

Fourier transforms infrared spectral spectroscopy (FTIR): The pure drug was mixed with IR grade potassium bromide in a ratio of (1:100) and pellets were prepared by applying 10 metric ton of pressure in shimadzu hydrophilic press. The pellets were then scanned over range of 4000-400 cm^{-1} in FTIR spectrometer. FTIR spectrum of ketoconazole showed the presence of the peaks which complies with the reference spectra.

UV-Visible spectroscopy:

10 mg of drug (Ketoconazole) was accurately weighed on calibrated digital weighing balance and was transferred to 100 ml volumetric flask. Small quantity of methanol was added to dissolve the drug. The volume was made up to 100 ml using methanol to prepare stock solution of 100µg/ml. From the above solution, 1ml solution was pipetted into 10 ml volumetric flask and volume was

made up to 10 ml with Methanol. Using a double beam UV-visible spectrophotometer, absorbance maxima was determined.

Preparation of Standard Calibration Curve of Ketoconazole in methanol

10 mg of drug (Ketoconazole) was accurately weighed from calibrated digital weighing balance and was transferred to 100 ml volumetric flask. Small quantity of methanol was added to dissolve the drug. The volume was made up to 100 ml using methanol to prepare stock solution of 100µg/ml. From the stock solution 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0 ml of solution was pipetted into 10 ml volumetric flasks and volume was made up to 10ml to form concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20µg/ml with methanol. The absorbance was measured with the help of UV Spectrophotometer at 243nm by taking methanol as reference solution. All study done in triplicate (n=3) with the same instrument.

Preparation of Standard Calibration Curve of Ketoconazole in 10% methanolic phosphate buffer PH 7.4

10 mg of drug (Ketoconazole) was accurately weighed from calibrated digital weighing balance and then it dissolved in small quantity of methanol. This solution was transferred to 10ml volumetric flask. The volume was made up to 10 ml with methanol up to the mark. The above solution was then transferred in 100ml volumetric flask. The volume was made up with phosphate buffer pH 7.4 up to prepare stock solution 100µg/ml. From the stock solution 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0 ml of solution was transferred into 10 ml volumetric flasks and volume was made up to 10 ml to form concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20µg/ml with 10% methanolic phosphate buffer pH 7.4. The absorbance was measured with the help of UV Spectrophotometer at 286nm by taking 10% methanolic phosphate buffer pH 7.4 as reference solution. All the study was done in triplicate (n=3) with the same instrument.

Determination of partition coefficient:

Partition coefficient was determined by taking excess amount of ketoconazole in 10 ml mixture of n-octanol and water (1:1) in a separating funnel. The system was shaken intermittently for 30 mins and kept undisturbed for overnight to achieve equilibrium. Then the two phases were separated and centrifuge at 10000 rpm for 15 minutes. After centrifugation, the concentration of ketoconazole in both phases was determined by measuring the absorbance at 243 nm on UV-Visible spectrophotometer.

The partition coefficient is commonly determined by shake flask method and calculated by formula:

$$P\ (o/_W) = C1\ (oil)/\ C2\ (water)$$

Where, C1 (oil) = Conc. of solute in organic phase.

C2 (water) = Conc. of solute in aqueous phase.

P (o/w) = Partition coefficient

Log P = log (o/w)

Determination of drug-excipients compatibility study

Drug and excipient compatibility studies were conducted to determine the compatibility of the excipients with the drug for the preparation of formulation. The FTIR spectrum was recorded by using FTIR after preparing potassium bromide disk. The finely ground drug powder and excipients powder were mixed with powdered potassium bromide and the mixture was pressed with a specific hydraulic compression. The prepared KBr pellet was then observed under Fourier transform infrared spectrometer (FTIR) and the spectrum of drug and excipients was recorded and compared.

Formulation development

Pseudo-ternary Phase Diagram

Pseudo-ternary phase diagram involve plotting the three components i.e surfactant: co-surfactant (Smix), oil and water each of them representing an apex of triangle. Ternary mixtures with varying compositions of the components were formed. For any ternary mixture formed, the total of surfactants, co-surfactants and oil concentrations always added to 100%. The required amount of the three components were weighed accurately and then sonicated for 3 minutes. Add ketoconazole, 20 mg in the mixture. The mixture was then gently heated at 45–50ºC and vortex to form homogenous mixture. To this mixture distilled water was added drop by drop until a transparent solution was formed. The surfactant and co-surfactant was varied in mass ratios 1:1, 1:2, 2:1, 3:1, 1:3. The different concentration ratios of oil and mixture of surfactant and co-surfactant were taken as 0.5:9.5, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. Ternary mixtures were formed in these ratios and then quantity of water (up to 5ml) forming transparent solution was plotted with other components in the pseudo-ternary phase diagram[5].

Optimization of nanoemulsion

Determination of % Drug Content

The mixture (Nanoemulsion) was centrifuged at 10000 rpm for 15min, 0.2ml (2µg/ml) of supernatant was taken and diluted with methanol (if necessary). Absorbance was measured at 243nm by UV Spectrophotometer. Concentration of ketoconazole was determined using standard curve equation and % drug content was calculated[6].

Determination of % transparency and drug precipitation

Formulations of different ratio were selected on the basis of ternary phase diagram. Transparency study was done to find out the maximum % transparency and drug precipitation between oil, Smix (surfactant and co-surfactant) and water containing 2% drug.

(* Nanoemulsion is a clear transparent system when diluted with distilled water).

CHARACTERIZATION AND EVALUATION OF OPTIMIZED NANOEMULSION

From the pseudo-ternary plot it was observed that there is more than one nanoemulsion formulation showing transparency. For optimization, following parameters were analyzed for each ternary mixture.

Determination of pH

Important parameter of nanoemulsion evaluation is pH determination. The excipients used in the formulation decide the pH of the final preparation and hence the route of administration. The pH of the formulation was measured using digital pH meter. Results were taken in triplicate to reduce the error[6].

Centrifugation

This parameter characterized to check the physical stability of formulation. The nanoemulsion system was centrifuged at 5000 rpm for 10 minutes to determine whether the system shows signs of creaming or phase separation. The system was observed visually for appearance[6].

Droplet size distribution and Zeta potential of ketoconazole nanoemulsion

Droplet size was determined by photon correlation spectroscopy (PCS) it analyses the fluctuations in light scattering due to Brownian motion of the droplets using a Zeta-sizer (Zeta-sizer ver. 7.01, Malvern Instruments). The ketoconazole nanoemulsion formulation (0.1 ml) was dispersed in water in a 50 ml volumetric flask, mixed thoroughly with vigorous shaking and light scattering was monitored at 25 °C[5]. The surface charge was determined using a Zeta-sizer at 25˚C by measuring the zeta potential of the nanoemulsion formulation. Suitable dilution of nanoemulsion formulation was done with distilled water.

Preparation of nanoemulsion gel (%w/w)

Nanoemulsion gel was prepared by using gelling agent and penetration enhancer. The gel bases were prepared by dispersing 0.5%, 1%, 2% carbopol 980 in distilled water separately with constant stirring at a moderate speed using mechanical shaker. The dispersion was left overnight. The pH of all formulations was adjusted to neutral using triethanolamine. Ketoconazole is hydrophobic drug. To formulate drug loaded nanoemulsion, it has to be first dissolved in oil phase. After dissolving the drug completely, surfactant and co-surfactant mixture (Smix) was added. Transfer aqueous solution in oil phase with continuous stirring and keep it at room temperature for 24 hrs. The

obtained nanoemulsion was then incorporated into gel bases with gentle stirring to obtain the nanoemulsion gel under room temperature[7].

Optimization of Nanoemulsion gel

Different concentration of nanoemulsion gel was optimized on the basis of the pH and % drug content.

Measurement of pH

pH of various gel formulations was determined by using digital pH meter. 1g of gel was dissolved in 100 ml distilled water and stored for 2 hrs. The measurement of pH of each formulation was done in triplicate to avoid error[8].

Determination of % drug content

1g of nanoemulsion gel was mixed with 100 ml of suitable solvent. Aliquots of different concentration were prepared by suitable dilutions after filtering the stock solution and absorbance was measured. Drug content was calculated using the equation obtained by linear regression analysis of calibration curve[8].

Characterization and Evaluation of Optimized Nanoemulsion Gel

Determination of viscosity

Viscosity of nanoemulsion gel was determined by using Brookfield viscometer. 20 gm of nanoemulsion gel was filled in a 25 ml beaker and the viscosity was measured by using Spindle number S64.

In vitro Diffusion studies

The diffusion studies of the prepared gel were carried out in Franz diffusion cell through a cellophane membrane. Gel sample (0.5g) was taken in cellophane membrane and the diffusion studies were carried out at 37 ± 1 C° using 250 ml of (25%) methanolic phosphate buffer (pH 7.4) as the dissolution medium. 1ml of each sample was withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 hrs and each sample was replaced with equal volume of fresh dissolution medium in order to maintain sink condition. Samples were analyzed by UV-visible spectrophotometer at 243 for drug content[8].

Kinetic modelling and mechanism of drug release

The correlation coefficient of the zero order, First model, Korsmeyer & peppas and Higuchi's plot model was compared with the final selected optimized nanoemulsion gel[9].

RESULTS AND DISCUSSION

Organoleptic properties

Organoleptic properties of ketoconazole was found to be as per I.P monograph.

Table 1: Organoleptic Properties of ketoconazole

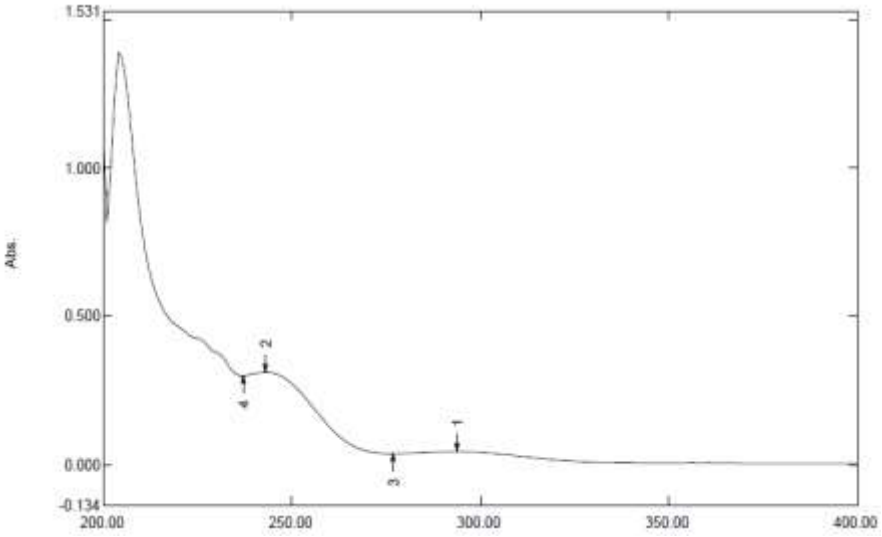
S. No.	Test	Specification	Observation
1.	Colour	White	White
2.	Odour	Odourless	Odourless
3.	Appearance	Powder	Powder

Melting point analysis

The melting range of ketoconazole was observed to be 146-150° C which complies with reported melting range i.e. 148-152^{o} C (146 ^{o} C).

Identification of drug through UV-visible Spectroscopy

Determination of Absorption Maxima (λ_{max}) of ketoconazole as pure drug in Methanol



No.	P/V	Wavelength	Abs.	Description
1	↑	294.00	0.045	
2	↑	243.00	0.313	
3	↓	277.00	0.038	
4	↓	237.00	0.301	

Figure 1: Absorbance maxima (λmax) of ketoconazole

The *λmax* of ketoconazole was determined in methanol by scanning the drug in range of 200-400 nm. Observed wave length was found to be 243 nm, thus the procured drug sample of ketoconazole complies with the reference spectra.

Standard calibration curve of ketoconazole in methanol

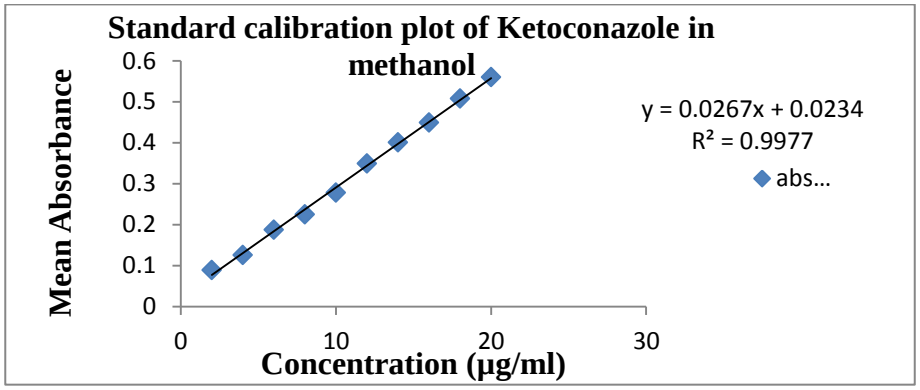


Figure 2: Standard calibration curve of ketoconazole in methanol

Standard Calibration Curve of ketoconazole in 10% methanolic phosphate buffer pH 7.4

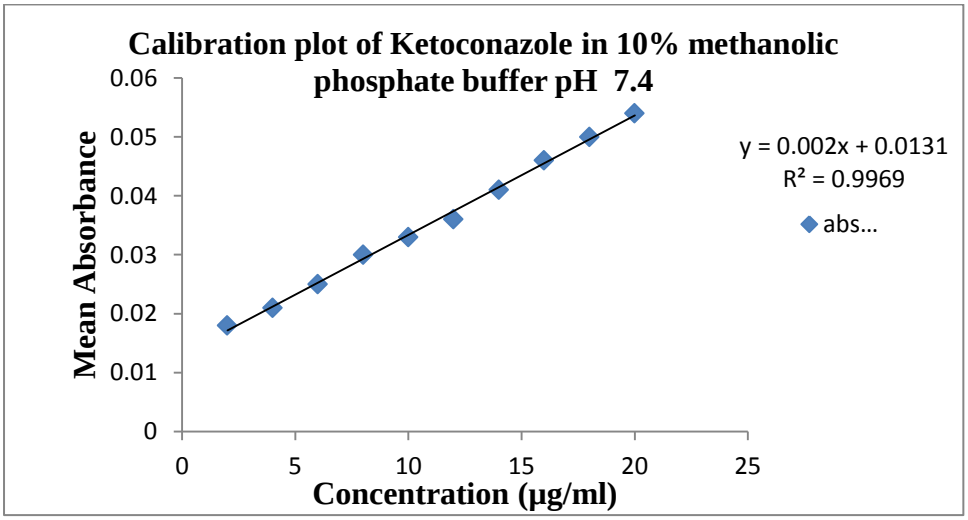


Figure 3: Standard calibration curve of ketoconazole in 10% methanolic phosphate buffer pH 7.4

Partition Co-efficient

Partition co-efficient value of ketoconazole was observed as 4.00 which showed that ketoconazole is lipophilic in nature.

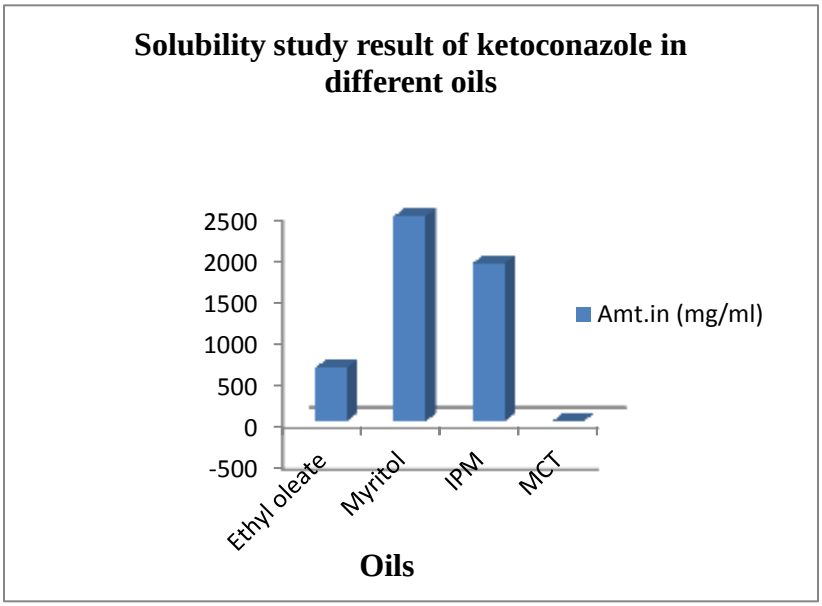
Determination of solubility in various solvents (oils, surfactants and co-surfactants)

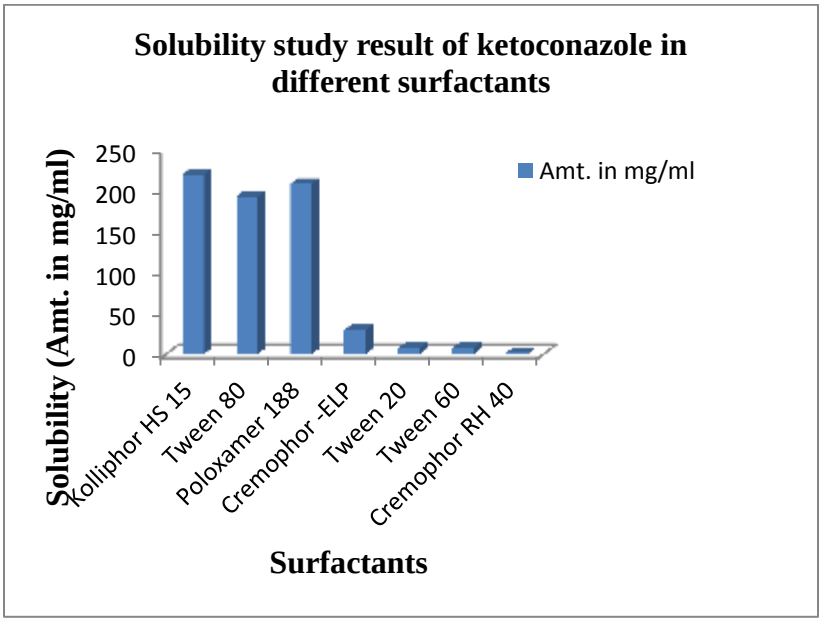
Table 2: Solubility data of ketoconazole in different oils, surfactants and co-surfactants

S. No.	Oils	Solubility (mg/ml)
1.	Ethyl Oleate	646.15384
2.	Myritol 318	2476.9230
3.	IPM	1911.5384
4.	MCT	-0.3076
S. No.	Surfactants	Solubility (mg/ml)
1	Kolliphor HS 15	219.2307
2	Tween80	192.3076

3	Poloxamer 188	207.6923
4	Cremophor ELP	29.3461
5	Tween20	7.1153
6	Tween60	7.3076
7	Cremophor RH40	1.4615

S. No.	Co-surfactants	Solubility (mg/ml)
1	PEG 200	538.4615
2	Propylene glycol	288.4615
3	Iso propyl alcohol	26.9230
4	Ethanol	7.0769
5	Glycerin	8.3461
6	PEG 400	2.3461





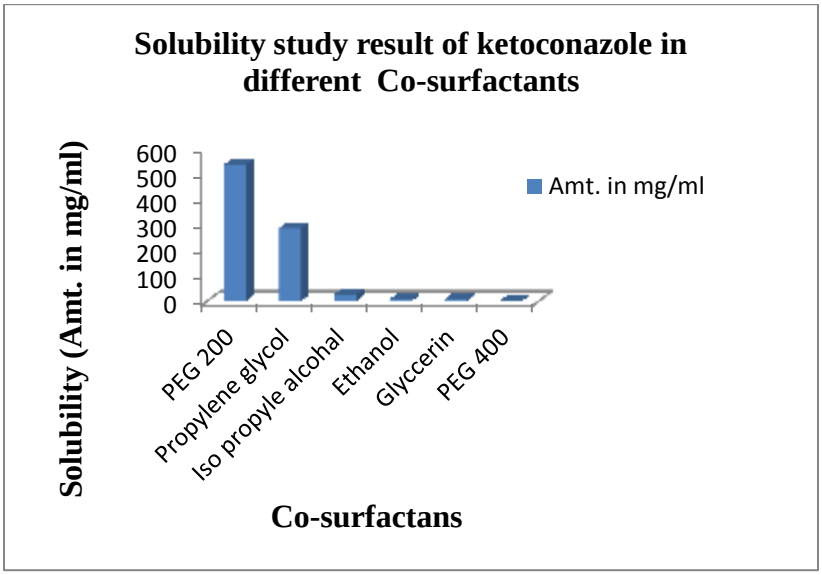


Figure 4: Solubility study in different oils, surfactants and co-surfactants

Determination of drug-excipients compatibility study

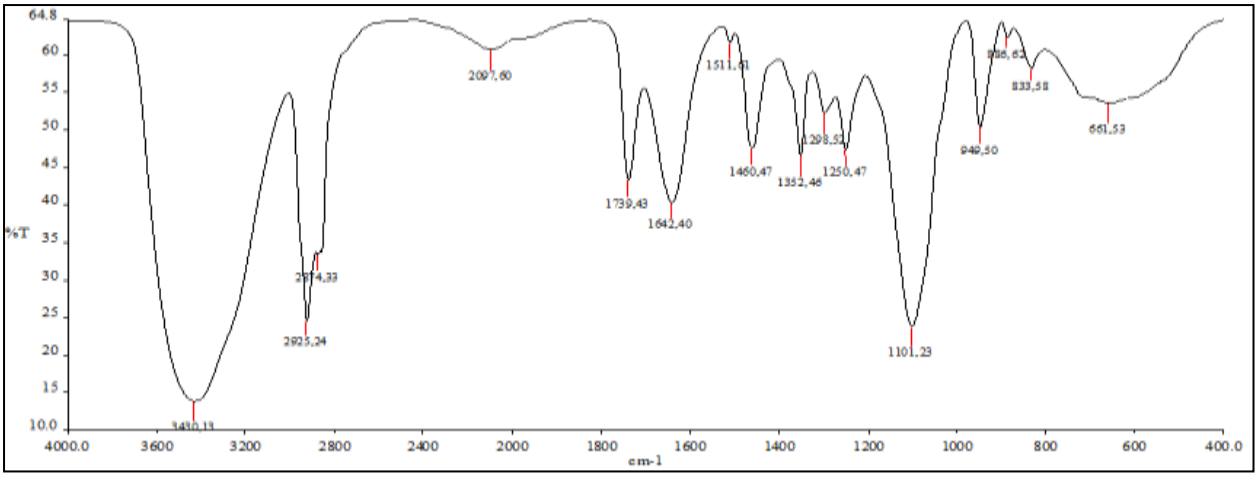


Figure 5: FTIR of Nanoemulsion

The peaks observed in FTIR of mixture of ketoconazole and excipients at 3430,13 cm^{-1}, 2925,24 cm^{-1}, 1642,40 cm^{-1}, 1450,47 cm^{-1} , 1250.47 cm^{-1}, 1101,23 cm^{-1}, and 833,58 cm^{-1}, 661,53 cm^{-1}. There was no major shifting in the frequencies of above said functional groups of which indicates that there was no chemical interaction between ketoconazole and excipients which were used in the formulation.

Optimization of nanoemulsion formulation

Determination of % Drug content

The selected formulation for determining drug content was diluted with sufficient methanol and absorbance was measured at 243nm by UV spectrophotometer. Concentration of drug was determined using standard curve equation.

Table 3: Determination of % Drug content

% Drug content	99.98%

Transparency and drug precipitation

The prepared formulation was diluted upto 5ml with water and observed visually for the transparency and drug precipitation.

Table 4: Transparency and drug precipitation

Observation	Transparent and drug not precipitated

Characterization and evaluation of optimized nanoemulsion

Determination of pH

The pH of the formulation was determined using digital pH meter. Formulation of ketoconazole nanoemulsion was taken in beaker containing 10 ml of water and pH was determined. Results were taken in triplicate and the average was determined.

Table 5: Determination of pH

S.No	Set 1	Set 2	Set 3	Mean	±SD
	7.4	7.3	7.4	7.3	0.057

Centrifugation

Ketoconazole nanoemulsion formulation was diluted with distilled water. Nanoemulsion was centrifuged (Remi Laboratories, Mumbai, India) at 1000 rpm for 15 minute and observed for any change in homogeneity.

Table 6: Phase separation and precipitation

Phase Separation	Not seen
Precipitation	Not seen

Droplet size distribution and Zeta potential

The droplet size of optimized nanoemulsion formulations was found to be Z-Average 627.5 nm as shown in the figure 6. The zeta potential of optimized nanoemulsion formulations was found to be -15.4mV.

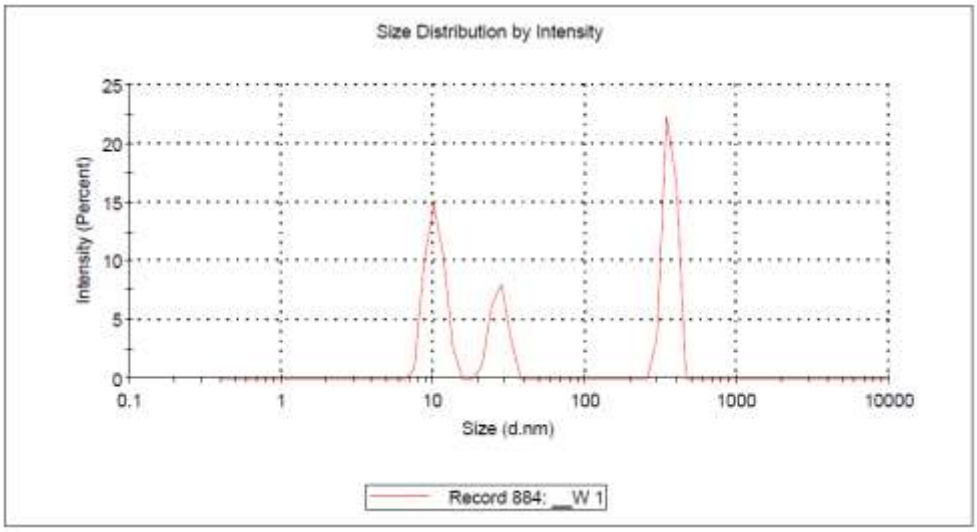


Figure 6: Droplet size distribution curve of the nanoemulsion

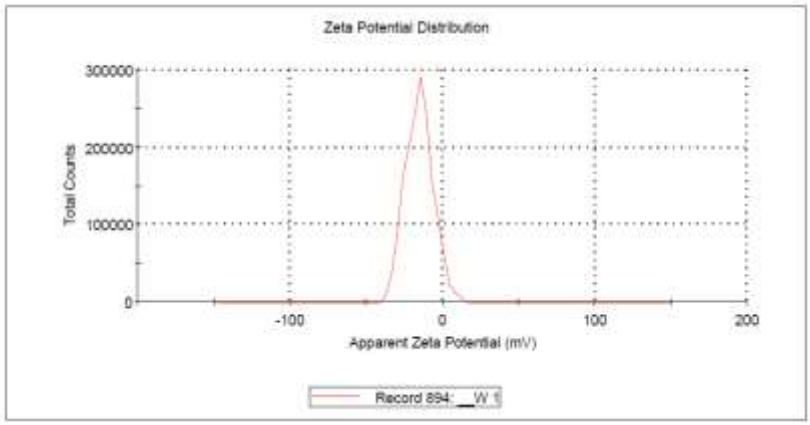


Figure 7: Zeta potential curve of the nanoemulsion

Preparation of nanoemulsion gel (%w/w)

From the literature, polymers carbopol 980 was considered in preparation of gel. Carbopol 980 was selected for further studies due to formation of transparent gel formation.

Table 7: Preparation of nanoemulsion gel (5gm)

Formulation Code	% Carbopol 980	Carbopol 980 (g)	Water (g)	Optimized Nanoemulsion (g)
RC1	0.5	0.025	3.975	1
RC2	1	0.05	3.95	1
RC3	2	0.1	3.9	1

Carbopol 980 was taken in beaker and weighed quantity of water was added and kept for overnight. Nanoemulsion containing ketoconazole was loaded in the gel and pH was maintained to 7.4 by using triethanolamine.

Optimization of different concentration of nanoemulsion gel

Determination of % Drug content and pH

The different concentration of nanoemulsion gel was optimized on the basis of pH and % drug content.

Table 8: Determination of % Drug content and pH of nanoemulsion gel

S.No.	Formulation code	% Carbopol 980	% Drug content	pH
1	RC1	0.5	90.71	7.2
2	RC2	1	95.55	7.0
3	RC3	2	98.90	7.4

From the table 8 it can be concluded that the concentration of RC3 was selected for the formulation of nanoemulsion gel.

Characterization and evaluation of nanoemulsion gel

Determination of viscosity

Viscosity of nanoemulsion gel was determined by spindle no. S 64 by varying % Torque.

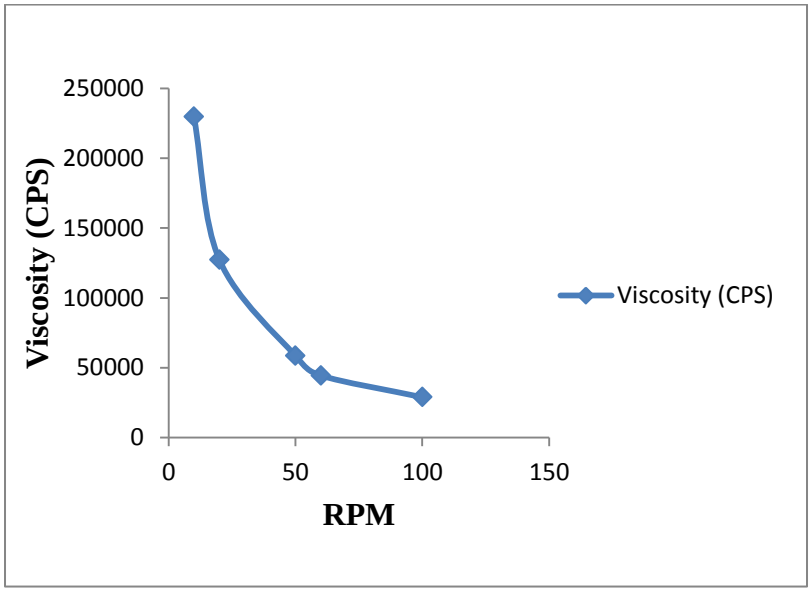


Figure 8: Viscosity of nanoemulsion gel

***In-vitro* Diffusion studies**

Optimized nanoemulsion gel containing 2% polymer concentration and 0.5% DMSO as permeation enhancer showed the sustained release of ketoconazole from the formulation. After 8 hrs, nanoemulsion gel shows drug release of 80.375 %. The release profile of ketoconazole from nanoemulsion gel is shown in figure 9 and data shown in table 9.

Table 9: Percentage (%) Cumulative drug release (CDR) of optimized nanoemulsion gel and marketed formulation.

S. No.	Time (min)	% CDR of Nanoemulsion gel with permeation enhancer (0.5% DMSO)	% CDR of marketed formulation (ketoconazole Cream 2% of H&H Pharmaceutical)
1	30	3.75	7.5
2	60	7.625	15.25
3	120	19.125	19.5
4	180	28.125	27.625
5	240	39.375	32.25
6	300	55.625	37.5
7	360	64.875	41.875
8	420	78.125	50.625
9	480	80.375	52.125

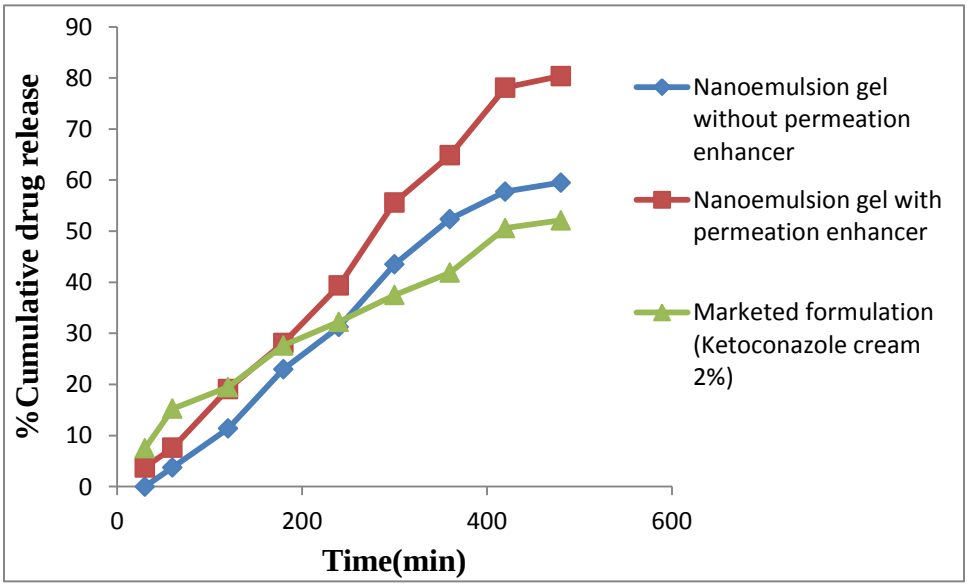


Figure 9: Percentage Cumulative drug release of optimized nanoemulsion gel and marketed formulation (Ketoconazole cream 2%, H&H Pharmaceutical)

Kinetic modelling and mechanism of drug release

The correlation coefficient of the Korsmeyer & peppas model was found to be 0.997, slightly higher when compared with the Zero order, First model and Higuchi's plot for final selected optimized nanoemulsion gel. Hence, the release of drug from the preparation followed Korsmeyer & peppas model.

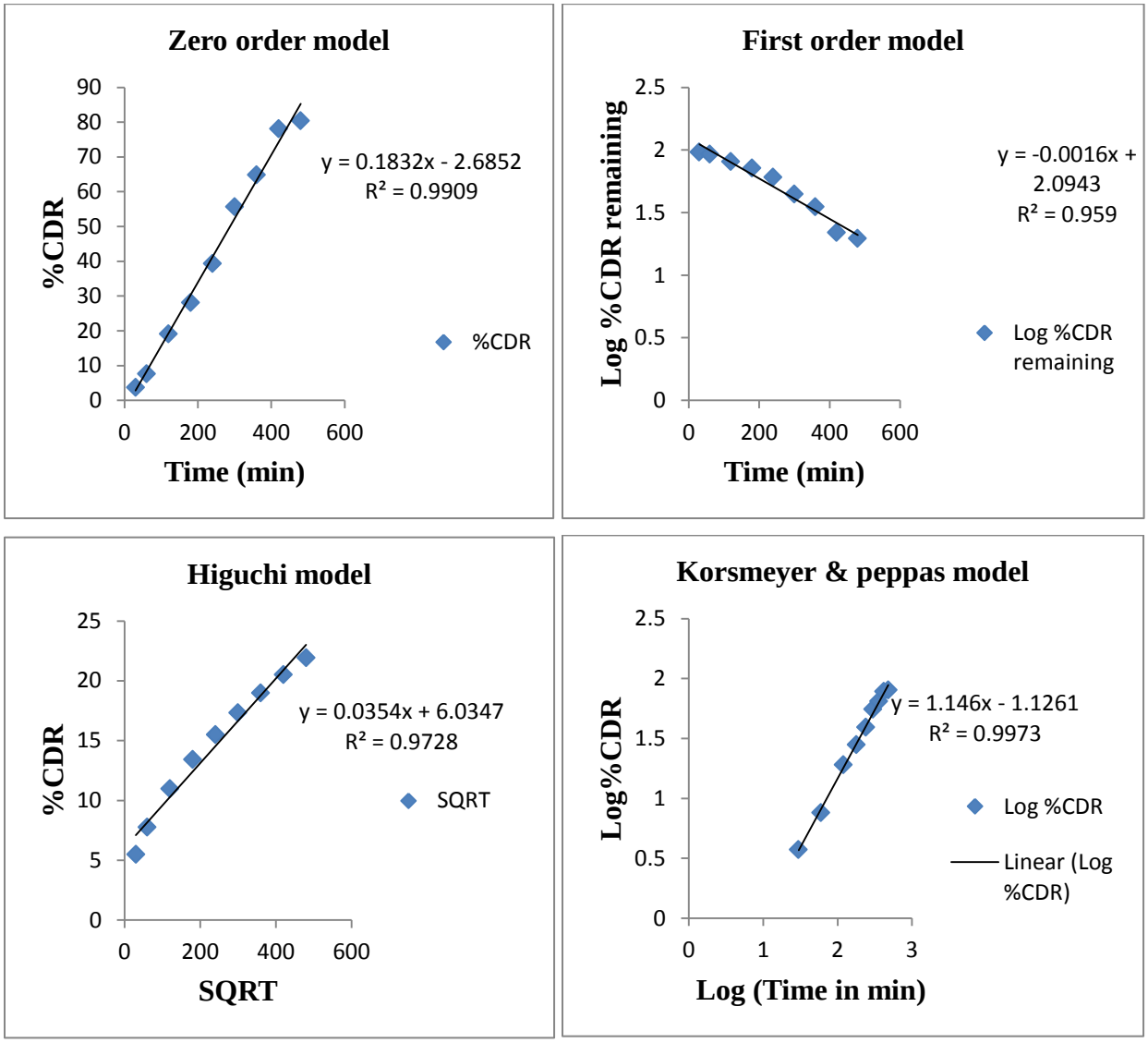


Figure 10: Various kinetic models applied for determination of release mechanism of Ketoconazole from nanoemulsion gel

CONCLUSION

The present work concluded that Ketoconazole nanoemulsion based gel formulation was successfully prepared by the aqueous titration method. Now a days, nanoemulsion based gels are more acceptable for the topical drug administration. Myitol 318 (Oil), Kolliphor HS-15 (surfactant) and PEG200 (Co-surfactant) was successfully used as a suitable carrier system for incorporating ketoconazole for topical drug delivery. Myritol 318, Kolliphor HS 15 are well-suited with the PEG 200 and helps in solubilising the drug in the formulation of nanoemulsion. Various formulations were prepared as per the composition and drug loaded nanoemulsion was incorporated into gel containing 2% of carbopol 980 and 1% of DMSO as permeation enhancer. Formulated gel was futher studied for % drug release. The developed system when compared with

marketed formulation (Ketoconazole 2% w/w, H&H Pharmaceutical) might be able to release the drug in sustained pattern and might reduce the frequency of administration and improves the patient compliance.

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