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FORMULATION AND EVALUATION OF NANOEMULSION FOR SOLUBILITY ENHANCEMENT OF KETOCONAZOLE

Ravi Shankar[*1], Vishnu Tiwari[1], Chandra Prakash Mishra[1], Chandra Kala Singh[1], Dharampal Sharma[2], Sandhya Jaiswal[3]

[1*]Department of Pharmaceutics, Rajasthan Pharmacy College, Bhankrota, Jaipur (Raj.) - 302026, India.
[2]Department of Pharmaceutics, Oniosome Healthcare Pvt. Ltd., Phase 8B, Mohali - 160071, Punjab, India.
[3]Department of Pharmaceutics, A.S.B.A.S.J.S. Memorial College of Pharmacy, Affiliated to Punjab Technical University, Bela (Ropar) -140111, Punjab, India.

ABSTRACT

The aim of present research was to design and develop Nanoemulsion of ketoconazole for solubility enhancement. Ketoconazole is an imidazole antifungal agent with broad spectrum activity. It belongs to BCS class II i.e. poorly soluble and highly permeable drug. Due to its poor solubility, it is incompletely absorbed after oral dosing and bioavailability varies among individuals. 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 nanoemulsions have been designed. Nanoemulsion was formulated by aqueous titration method using myritol 318 as oil, kolliphor HS 15 as surfactant and PEG 200 as co-surfactant. 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. The formulations were evaluated for thermodynamic stability test such as droplet size, zeta potential, drug content, transmission electron microscopy and FTIR. The optimized formulation contains droplet size 627.5nm and zeta potential -15.4mv. *In-vitro* diffusion study of nanoemulsion showed 86.33 % release within 5hrs. Hence, it is concluded that nanoemulsion enhances the solubility of ketoconazole.

KEYWORDS

Nanoemulsion, Solubility, Pseudo ternary phase and Anti-fungal.

Author for Correspondence:
Ravi Shankar,
Department of Pharmaceutics,
Rajasthan Pharmacy College,
Bhankrota, Jaipur (Raj.) - 302026, India.

Email: ravipharma50@gmail.com

INTRODUCTION

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 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.

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. Due to poor solubility, it is incompletely absorbed after oral dosing and bioavailability varies among individuals. To overcome these shortcomings novel drug delivery system (NDDS) plays a crucial role.

Nanoemulsions have been widely used 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. They are considered to be in the range of 100 nm to 1000nm. Various effects such as surface area and area to volume ratio and many other physical properties get magnified when reduced to nanoscale. Most of the current research works in almost all technical and biomedical fields is based on nanosize. Nanoemulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and co-surfactant molecules having a droplet size of less than 1000 nm. The ketoconazole nanoemulsion was prepared. The optically clear and low-viscous formulation with enhanced solubility and minimum droplet size diameter would pose a definite promise in improving the significance of poorly soluble drug[1-10]. So, the objective of the present research work was to formulate nanoemulsion of ketoconazole for improving the solubility and bioavailability of drug.

MATERIAL AND METHODS

Materials

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. Triethanolamine were purchased from Fisher Scientific. 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.

Methods[11-24]

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

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.

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 100 µg/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 10 ml to form concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 µg/ml with methanol. The absorbance was measured with the help of UV Spectrophotometer at 243nm by taking methanolas 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 10 ml volumetric flask. The volume was made up to 10 ml with methanol up to the mark. The above solution was then transferred in 100 ml volumetric flask. The volume was made up with phosphate buffer pH 7.4 up to prepare stock solution 100 µg/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 20 µg/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 ofketoconazolein10 ml mixture of n-octanol and water (1:1) in a separating funnel. This 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:

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

Where, C1 (oil) =Conc. of solute in organic phase.
C2 (water) = Conc. of solute in aqueous phase.
P (o/w) = Partition coefficient
LogP=log (o/w)

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

Excess amount of drug (100 mg) in 3 ml of selected oils (Ethyl Oleate, Oleic Acid, IPM, Myritol 318, MCT), surfactants (Cremophor-RH40, Kolliphor-ELP, Tween80, Tween60, Tween20, Kolliphor - HS15) and co-surfactants (Glycerin, Propylene Glycol, Ethanol, PEG 400, PEG 200, Propanol, n-Butanol) was taken in stopper vials and was then, fixed by vortex mixer.
The mixture vials were kept at 37±1ºC in a water bath shaker for 72 hr. The equilibrated samples were removed from shaker and centrifuged at 5000 rpm from 15 min. The solubility profile of drug in oil, surfactant and co-surfactant was determined from the supernant layer of centrifuge sample. 1 ml accurately and diluted with methanol up to 10 ml. The concentration of ketoconazole was then quantified by UV spectrophotometer at 243 nm. Solubility of Ketoconazole in different oils, surfactants, and co-surfactants were calculated with the help of standard calibration curve of drug in methanol.

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 5 ml) forming transparent solution was plotted with other components in the pseudo-ternary phase diagram.

Optimization of nanoemulasion

Optimization of oil and Smix concentration range was done for preliminary study. The concentration range of oil and Smix was determined based on water up take in the formulation and the % transparency from ratio 2:1 was found to be 6.74 % w/w for oil, 61.73 % w/w for Smix and 31.53 % w/w for water.

Determination of % Drug Content in nanoemulsion

The mixture (Nanoemulsion) was centrifuged at 10000 rpm for 15 min, 0.2 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.

Determination of % transparency and drug precipitation of nanoemulsion

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 are more than one nanoemulsion formulations 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.

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.

Droplet size distribution and Zeta potential of ketoconazole nanoemulsion

Droplet size was determined by photon correlation spectroscopy (PCS) it analyzes 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.

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.

Transmission Electron Microscopy (TEM)

TEM was performed to analyze the morphology and structure of the formed nanoemulsion droplets. This is capable of point to point resolution. For carrying out the study, a drop of the nanoemulsion was deposited on the copper grid film and studied after drying.

RESULTS AND DISCUSSION

Organoleptic properties

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

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).

The R^2 value obtained from the standard plot between concentrations vs. absorbance close to one which indicated the linearity. The standard regression equation was found to be y = 0.002 x + 0.013.

Partition Coefficient

Partition coefficient 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)

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.

Formulation development

Pseudo -ternary Phase Diagram

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.

Transparency and drug precipitation

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

Characterization and evaluation of optimized nanoemulsion

Determination of PH

The pH of the formulation was determinate 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.

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.

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 No.8. The zeta potential of optimized nanoemulsion formulations was found to be -15.4mV as shown in the Figure No.9.

Transmission Electron Microscopy (TEM)

TEM was performed to analyze the morphology and structure of the formed nanoemulsion droplets.

Optimized nanoemulsion shows drug release of 98.57 %. The release profile of ketoconazole from nanoemulsion is shown in Figure No.10 and data shown in Table No.10.

Table No.1: Organoleptic Properties of ketoconazole

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

Table No.2: Interpretation of FTIR of Ketoconazole as pure drug

S.No	Functional Groups Stretching	Observed value(cm^{-1})
1	C-H (Aromatic)	3119,46
2	C-H (Methyl)	2831,33
3	C=O (Amide)	1646,12
4	C=C	1511,11
5	C=N	1442,20
6	C-N	1245,12
7	C-O	1106,27
8	C-Cl	815,22 ,664,35

Standard Calibration Curve in methanol

Table No.3: Absorbance of different dilution of drug at 243 nm in methanol

S.No	Concentration (µg/ml)	Absorbance				
		Set 1	Set 2	Set 3	Mean	±SD
1	2	0.090	0.089	0.088	0.089	0.0010
2	4	0.128	0.127	0.125	0.126	0.0015
3	6	0.188	0.192	0.186	0.188	0.0030
4	8	0.226	0.223	0.226	0.225	0.0017
5	10	0.279	0.281	0.276	0.278	0.0025
6	12	0.350	0.352	0.345	0.349	0.0036
7	14	0.402	0.404	0.399	0.401	0.0025
8	16	0.451	0.450	0.448	0.449	0.0015
9	18	0.509	0.511	0.506	0.508	0.0025
10	20	0.561	0.562	0.558	0.560	0.0020

Table No.4: Absorbance of different dilution of drug at 286 nm in 10% methanolic phosphate buffer (pH 7.4)

S.No	Concentration (µg/ml)	Absorbance				
		Set 1	Set 2	Set 3	Mean	±SD
1	2	0.020	0.018	0.018	0.018	0.001
2	4	0.022	0.024	0.019	0.021	0.002
3	6	0.027	0.026	0.024	0.025	0.001
4	8	0.031	0.033	0.028	0.030	0.002
5	10	0.035	0.032	0.034	0.033	0.001
6	12	0.037	0.039	0.034	0.036	0.002
7	14	0.039	0.043	0.042	0.041	0.002
8	16	0.047	0.047	0.046	0.046	0.0005
9	18	0.053	0.048	0.049	0.050	0.002
10	20	0.055	0.057	0.052	0.054	0.002

Table No.5: 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	Isopropylealcohal	26.9230
4	Ethanol	7.0769
5	Glycerin	8.3461
6	PEG 400	2.3461

Table No.6: Determination of % Drug content

S.No	Formulation code	Drug content
1	R9	99.98

Table No.7: Transparency and drug precipitation

S.No	Formulation code	Observation
1	R9	Transparent and drug not precipitated

Table No.8: Determination of pH

S.No	Formulation code	pH				
		Set 1	Set 2	Set 3	Mean	±SD
1	R9	7.4	7.3	7.4	7.3	0.057

Table No.9: Phase separation and precipitation

S.No	Formulation Code	Phase Separation	Precipitation
1	R9	Not seen	Not seen

Table No.10: Percentage (%) Cumulative drug release (CDR) of optimized nanoemulsion

S.No	Time (min)	Percentage (%) CDR of nanoemulsion
1	0	0
2	30	62.25
3	60	66.57
4	120	70.97
5	180	78.07
6	240	83.83
7	300	86.33

Identification of ketoconazole as pure drug by Fourier transforms infrared spectral spectroscopy

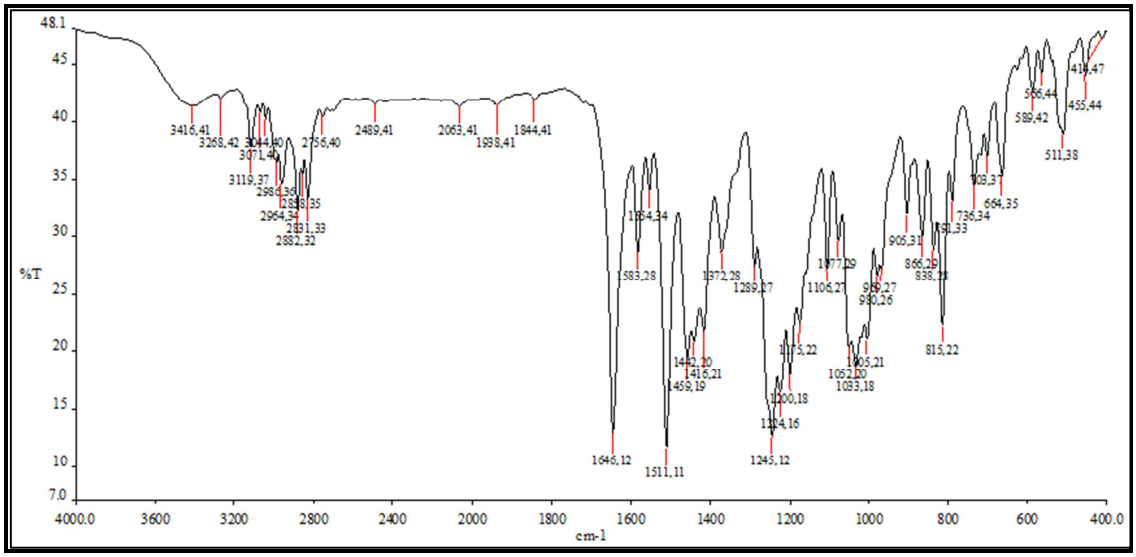


Figure No.1: FTIR Spectrum of Ketoconazole as pure drug

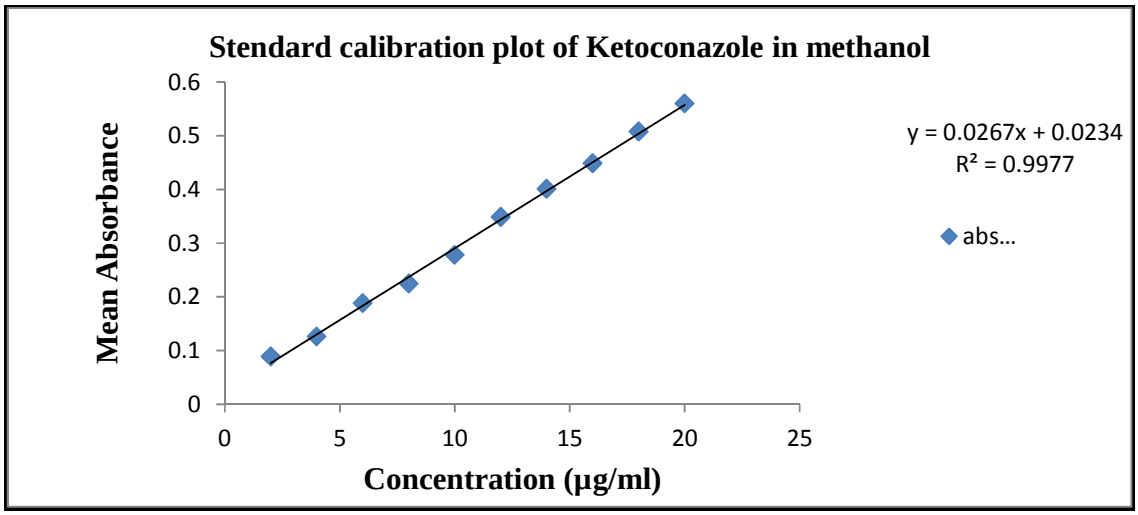


Figure No.2: Standard calibration curve of ketoconazole in methanol

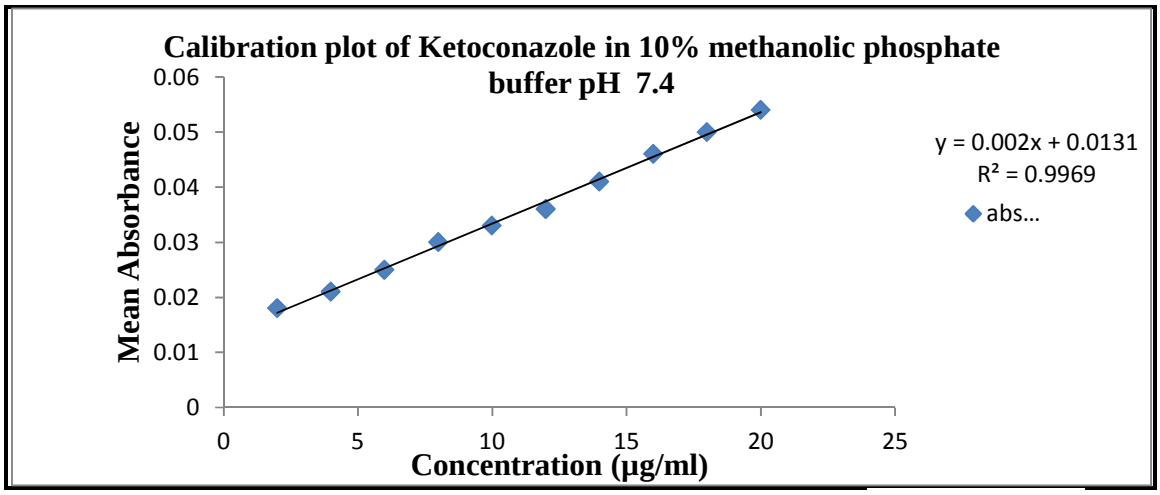
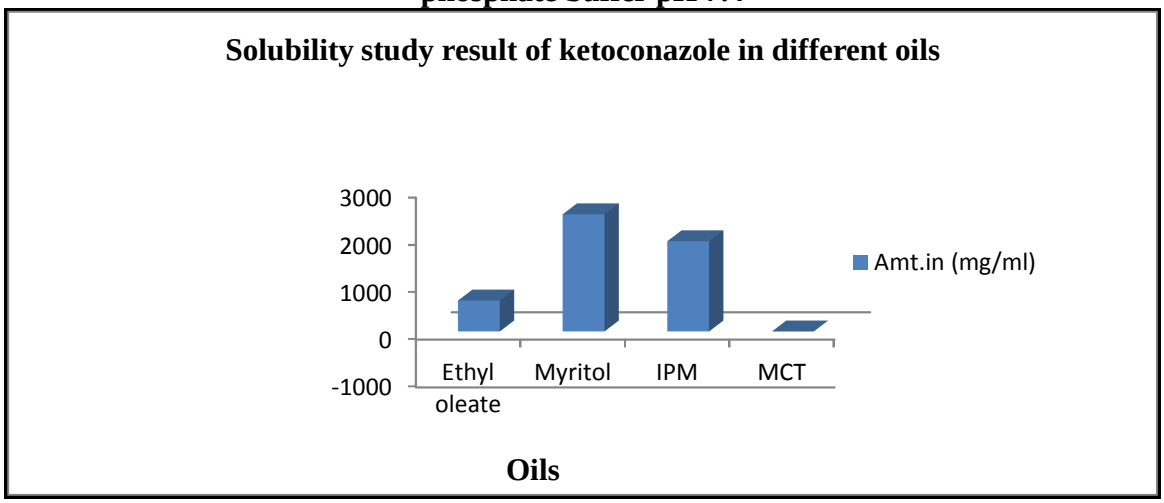
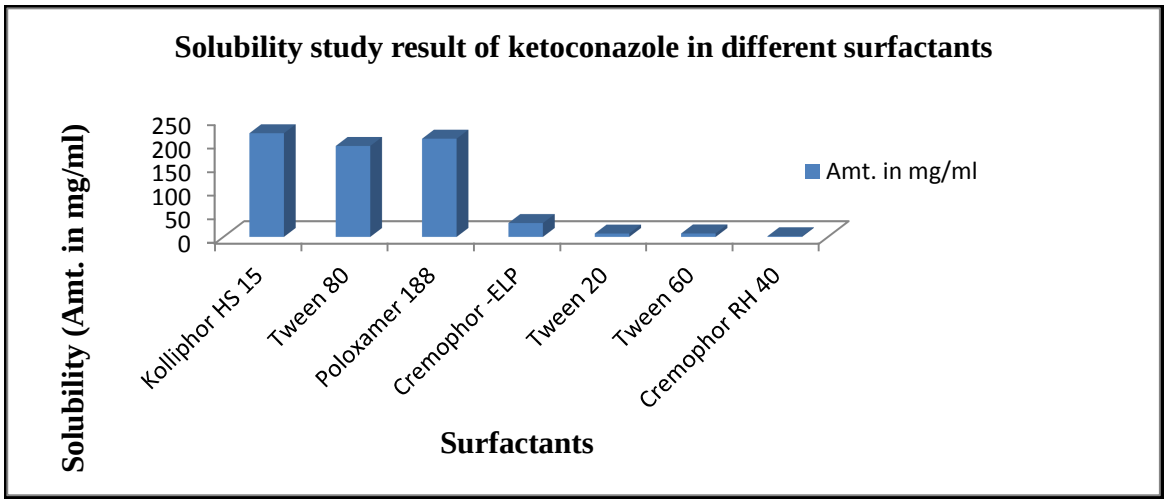


Figure No.3: Standard calibration curve of ketoconazole in 10% methanolic phosphate buffer pH 7.4





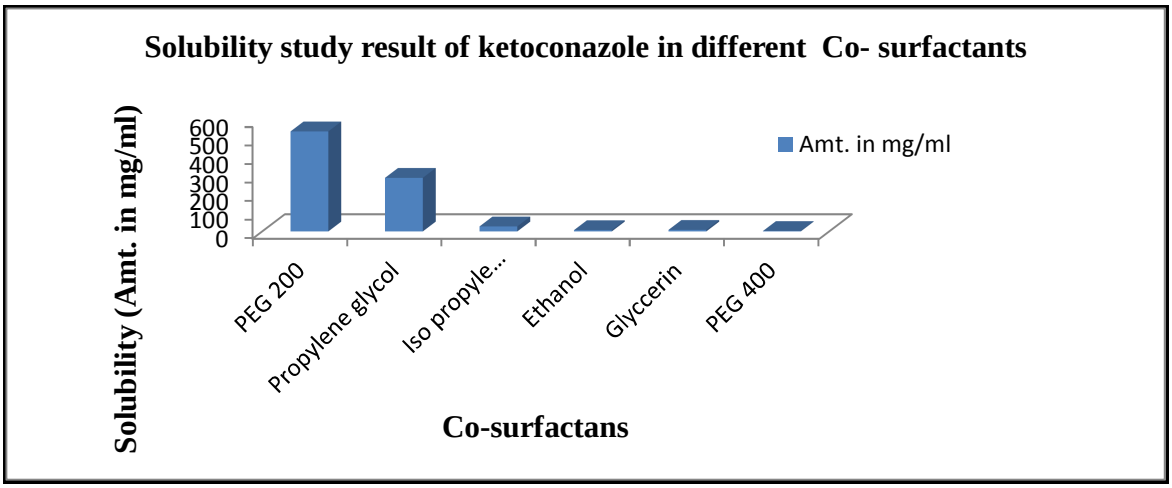


Figure No.4: Solubility study in different oils, surfactants and co-surfactants

Determination of drug-excipients compatibility study

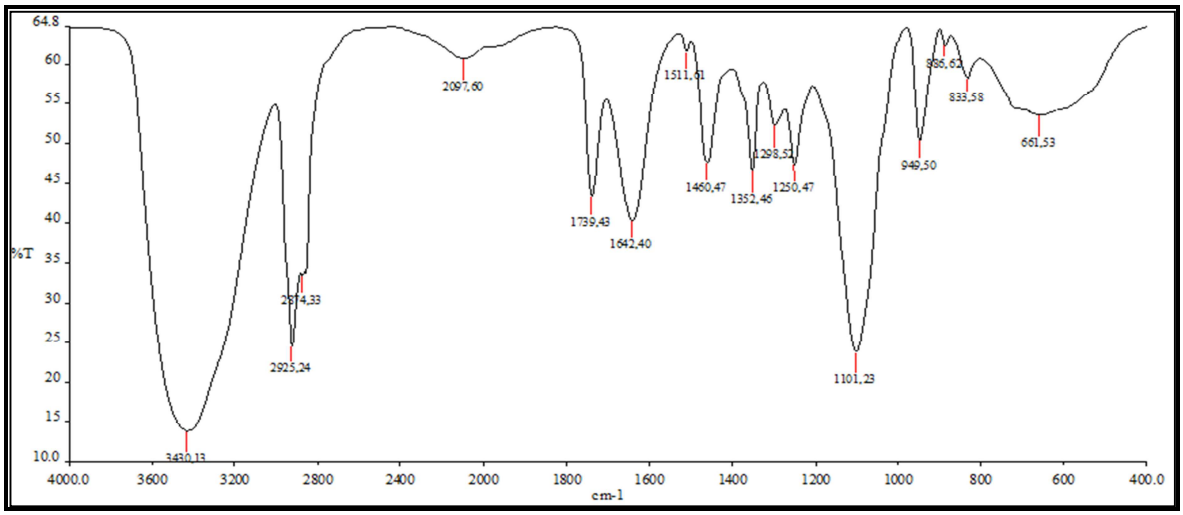
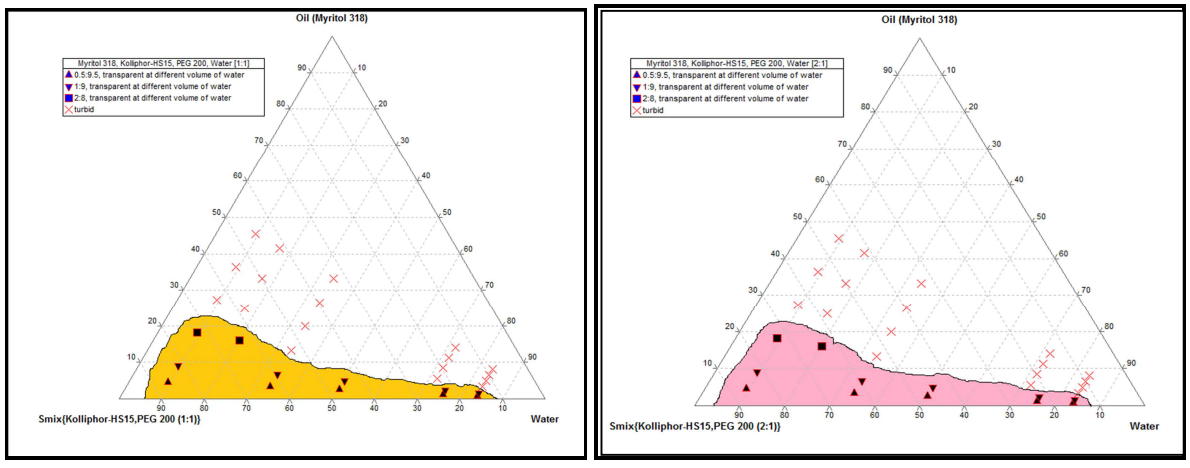


Figure No.5: FTIR of nanoemulsion formulation R9



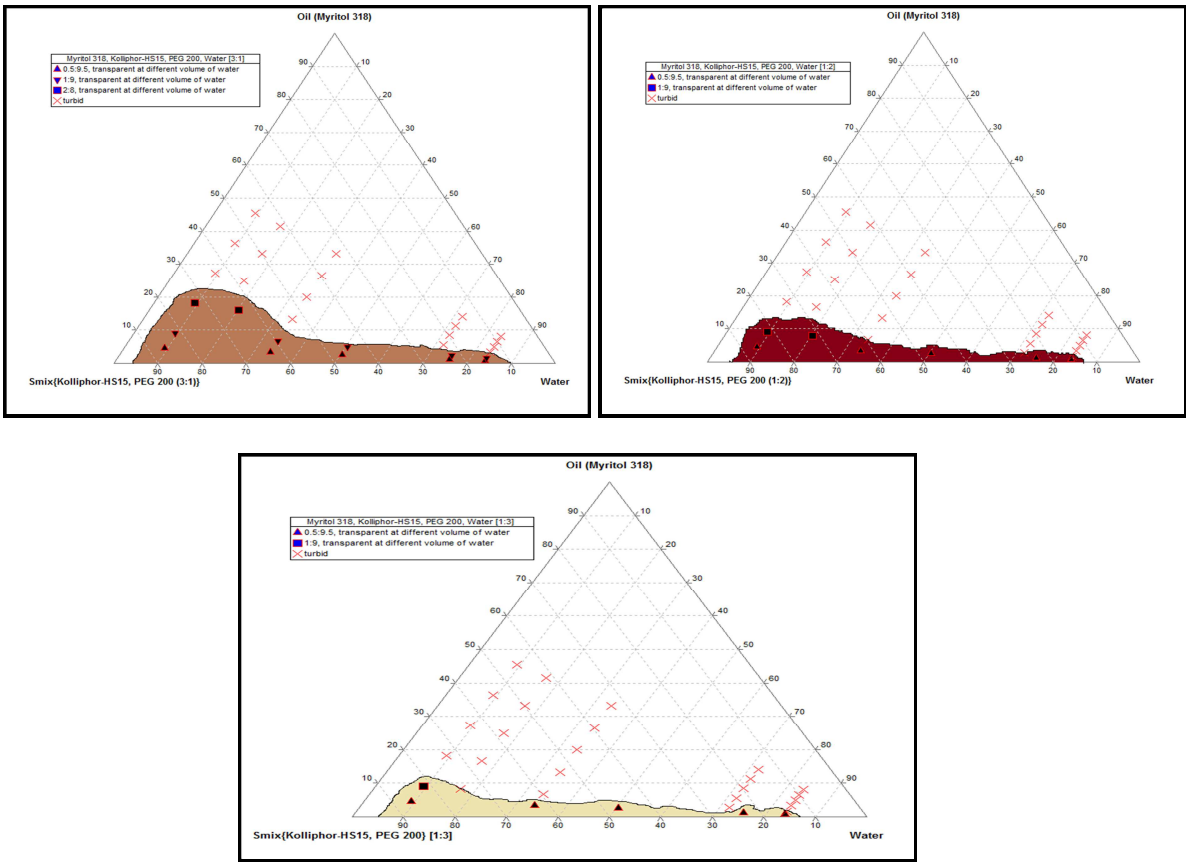


Figure No.6: Pseudo ternary phase diagram with various ratios of surfactant-co-surfactant at 1:1, 2:1, 3:1 and 1:2, 1:3 weight ratio of Kolliphor HS 15 to PEG200 mixture

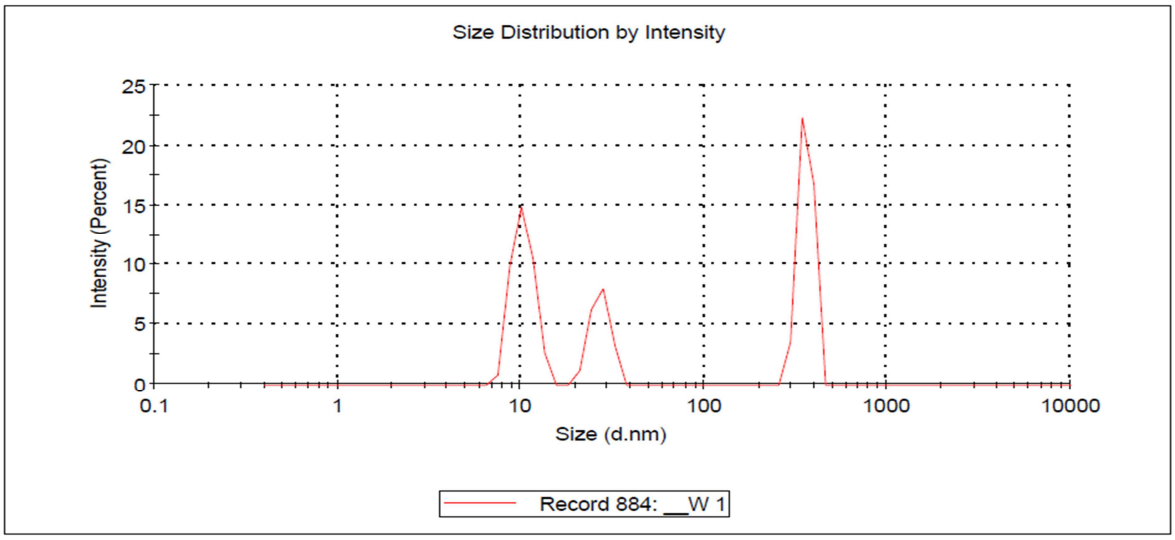


Figure No.7: Droplet size distribution curve of the nanoemulsion formulation R9

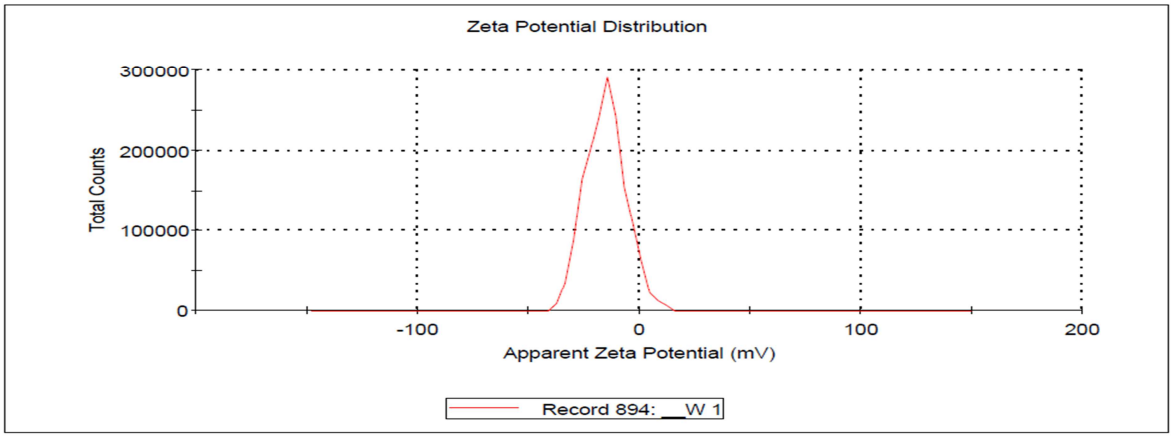


Figure No.8: Zeta potential curve of the nanoemulsion formulation R9

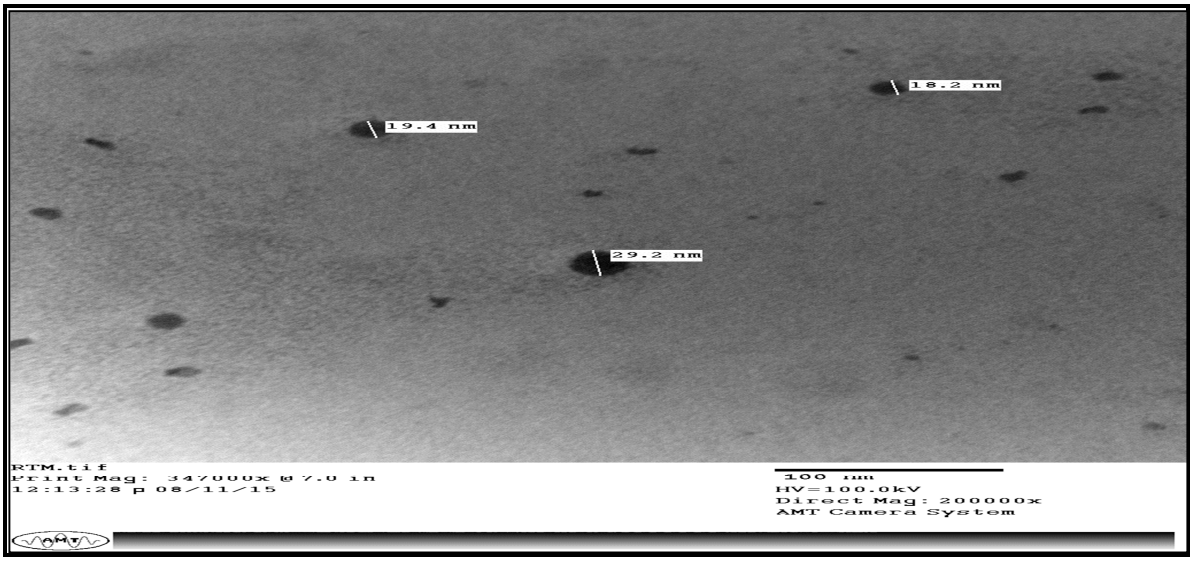


Figure No.9: TEM of ketoconazole loaded nanoemulsion formulation R9

***In-vitro* Diffusion studies**

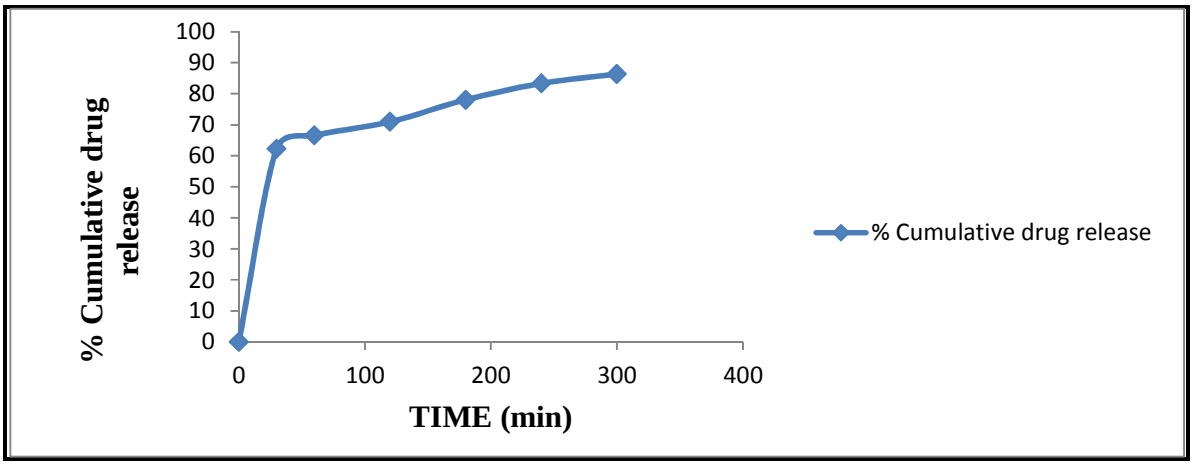


Figure No.10: Percentage Cumulative drug release of optimized nanoemulsion

CONCLUSION

The present work concluded that Ketoconazole nanoemulsion formulation for solubility enhancement was successfully prepared by aqueous titration method. Now a day, nanoemulsionas carrier systems are more acceptable in drug delivery system. Myitol 318 (Oil), Kolliphor HS-15 (surfactant) and PEG200 (Co-surfactant) was successfully used as a suitable carrier system for incorporating ketoconazole. Myritol 318, Kolliphor HS 15 are well-suited with the PEG 200 and helps in solubilising the drug in the formulation of nanoemulsion. Hence it is concluded that Myitol 318 based nanoemulsion for ketoconazole can be further studied for topical application in the treatment of fungal diseases and work need to be performed towards the area of drug administration.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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