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Formulation and Evaluation of O/W Nanoemultion of Ketoconazole

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Abstract: ***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 ergo sterol synthesis and increased fungal cellular permeability and is used against a wide variety of fungi and yeast .Nano technology scales up to one billionth of a meter Generally, they are considered to be in range of 100nm to 1000nm. Ketoconazole Nano emulsion drug delivery system is known to improve dissolution characteristics of a poorly water soluble drug since they maintain the drug in a dissolution characteristics of a poorly water soluble drug since they maintain the drug in solubilized state. Using the optimized Nano emulsion of ketoconazole loaded were prepared. The prepared liquid Nano emulsion are subjected to thermodynamic stability testing and zeta potential due to their characteristics size and properties which included kinetic stability; they are effective L solubilizing the drug and transferring them to words the target areas. It is characterized for droplet size, ze potential, viscosity, in vitro drug release study we performed.***

Keywords: Ketoconazole,14-demethylase, cytochrome P-450 enzyme

I. INTRODUCTION

Various effect Such as surface area and area to volume ratio and many other physical properties get magnified when reduced to Nano scale Most of the current research work in almost all technical and biomedical field is based on Nano size Nano emulsions are thermodynamically stable transparent (translucent) dispersion of oil and water stabilized by an interfacial film of surfactant and co surfactant molecules having a droplet size of less than 1000 nm. Ketoconazole is Antifungal drug often used in the treatment of fungal infection of skin such as athlete's foot, jock itch, ringworm, candidiasis, and seborrhea. It has pH dependent solubility and permeability.

The drug has a half-life of 1 to 2 hours. Because of its short biological half-life the drug has to be administered frequently. Furthermore oral Ketoconazole causes irritation in gastric mucosal membrane and possess a bitter taste and after taste. Therefore present work aims at designing novel Nano sponges as carriers for topical delivery of Ketoconazole which minimizes its gastro intestinal side effects and provides consistent drug levels at application site for longer period of time. Nano emulsion, which is categorized as multiphase colloidal dispersion, 15 generally characterized by stabilized and clarity. Nano emulsion are thermodynamically stable dispersions of two immiscible liquid (oil and water) which are stabilized using a surfactant co-surfactant molecules.

They may be either transparent or translucent and have a droplet size of 5- 200nm. They are well tolerated orally on the skin and mucus membrane when used to deliver topically active drug. Nowadays increasing loading enhancing drug solubility, and bioavailability are there most important advantages encouraging the uses of Nano emulsion as drug delivery carriers' Nano emulsion is form of delivery for a drug that is difficult to dissolve and has side effects when administered orally by increasing the penetration of drug through the skin. Nano emulsion comprise safe surfactant with or without - other emulsifier to improve stability, oil (natural/ synthetic/semi-synthetic) and co surfactant Q.

II. METHODOLOGY

A. Method Of Preparation

Several methods have been suggested for the preparation of nanoemultion.The basic objective of nanoemultion preparation to achieve the droplet size range 100- 600 nm and another is to provide stability condition. Formation of nano emultion system required High amount of energy. This energy can be provider either by mechanical equipment or the chemical potential inherent within the component.

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1) High Pressure Homogenization

This technique makes used of high pressure homogenizer piston homogenizer to produce nanoemulsion of extremely low particle size (up to 1 nm), during this process, several force, such as hydraulic shear. Intense turbulence and cavitation, act together to yield nanoemulsion with extremely small droplet size. The resultant product can be subjected to high pressure homogenization until nanoemulsion with desired droplet size and polydispersity index is obtained. The production of small droplet (submicron) requires application of high energy several procedures may applied to enhance the efficiency of emulsification when producing nanoemulsion. The emulsion is preferably prepared. at high volume faction of the disperse phase and diluted afterwards. however, very high phase volume ratio may result in coalescence during emulsification, but more surfactant could be added to create a smaller reduction in effective surface tension and possibly coalescences. Surfactant mixture that show more reduction in surface is dissolved in the disperse phase rather than the continuous phase; this often leads to smaller droplets. It may be useful to emulsify in steps of increasing intensity, particularly with emulsion s having highly viscous disperse phase.

Effect of homogenization pressure : It should be form 100 to 150 bars. The higher the pressure the lower is the particle size obtained.

No. of Homogenization cycles: The higher the homogenization cycles the smaller is the particle size obtained. The cycles are carried out in 3,40 10 cycles. The number of cycles is analysed by polydispersity index of drug after each cycles.

DIAGRAM OF HIGH PRESSURE HOMOGENIZER:-

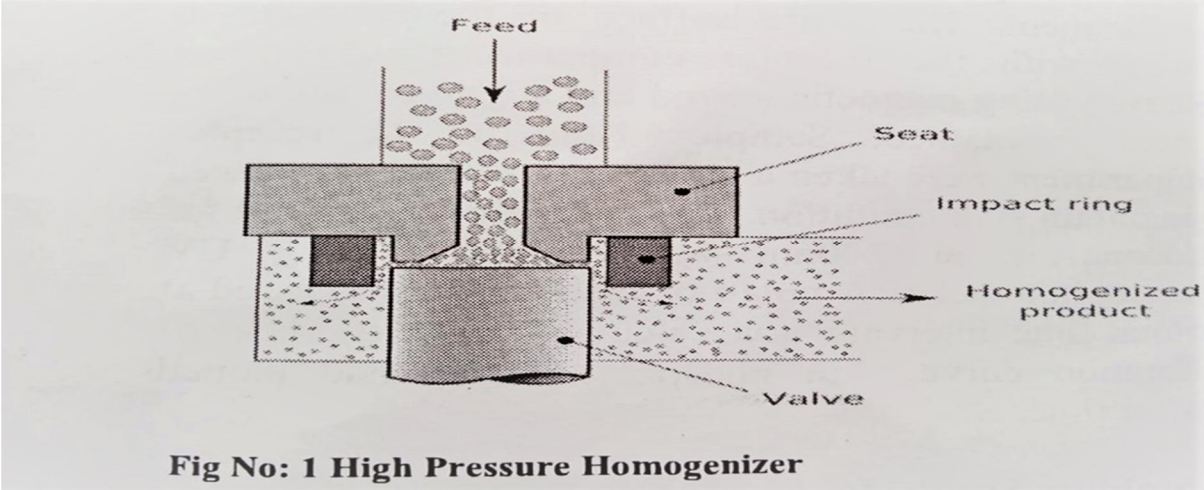


Fig No: 1 High Pressure Homogenizer

2) Phase Titration Method

Nanoemulsion are prepared by the spontaneous p emulsification method (phase titration method) and can be depicted with the help of phase diagram Construction of phase diagram is useful approach to study the complex serious of interaction that can occur when different component are mixed Nanoemulsion are formed along with various association structure. (including emulsion, micelles, lamellar hexagonal, cubic, and various gel and oily dispersion depending on the chemical composition and concentration of each compone. Preparation of Nanoemulsion It was prepared by mixing with the isopropyl myristate to form oily phase, it was enriched by the addition of surfactant and co-surfactant mixture, finally nanoemulsion was formed. Pseudo- ternary phase diagram study Tween 80 and ethanol were used as surfactant and co- surfactant respectively.t The understanding of their phase equilibrium and demarcation of the phase boundaries are essential aspect of the study as quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is often constructed to find the different zone including nanoemulsion zone in which each corner of the diagram represents 100% of the particular component. The region can be separated into w/o or o/w nanoemulsion by simply considering the composition that is whether it is oil rich or water rich. Observation should be made carefully so that the metastable system is not included.

3) Sonication Method

Sonication method is another best way to prepare nanoemulsion. In this method the droplet size conventional emulsion or even micro emulsion are reduced with the help of sonication mechanism. This method is not suitable for large batches of nanoemulsion can be prepared by this method.

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4) Phase Inversion Method

In this method fine dispersion is obtained by chemical energy resulting of phase transitions taking place through emulsification path. The adequate phase transition are produced by varying the composition at constant temperature at constant composition, phase inversion temperature (PIT) Method was introduced by shinoda et al. based on the changes of solubility of polyoxyethylene - type surfactant with temperature. This surfactant becomes lipophilic with increase in temperature due to dehydration of polymer chain. but at low temperature, The surfactant monolayer has a large positive spontaneous curvature forming oil swollen micelle solution phase.

B. Evaluation of Nano emulsion

The Nano emulsion was evaluated for the following characteristics:

1) *Optical transparency:* The formulation was determined by inspecting the sample in clear and transparent container under the presence of light against reflection into the eyes
2) *Viscosity Measurement:* The viscosities of Nano emulsion were measured using a Brookfield rotational viscometer at 24.9 at 10rpm.
3) *Phase Separation:* Nano emulsion system subjected to centrifugation at 3000rpm for a period of 2 hour and examined for any evidence of phase separation
4) *Determination of ₚH:* A 10% dispersion of formulation was prepared in distilled water and pll was determined by pH meter which was prior standardized with standard buffer of pl 4 and pH 7.
5) *Measurement of Globule Size:* The average globule size of the Nano emulsion was determined by Zetasizer Nano-ZS (Malvem Instrument,UK) Measurement were carried at angle of 90 at 25c Nano emulsion was diluted with double distilled water to ensure that the light scattering intensity was within the instruments sensitivity range. All the measurement was carried out at 25c The polydispersity index of the formulation was determined by the same instrument. The width of the size distribution was indicated by the polydispersity index (P.1)
6) *Measurement of Zeta Potential:* The zeta potential was determined to verify stability of nanoemulsion due to charge interaction. Zeta potential was measured by using Zetasizer Nano-ZS (Malvern instrument, UK). The measurement was performed a 25c.
7) *Drug Content:* A define volume of formulation was taken in a 10ml volumetric flask and diluted with ethanol. Absorbance of the resultant solution was sonicated for 3 min at ambient temperatures and the absorbance of the resultant solution was measured at à maxof 240nm against blank.
8) *In Vitro Diffusion Study:* In vitro diffusion was carried out by modified Franz diffusion cell. A glass cylinder with both ends open 10 cm height 3.7cm outer diameter and 3.1cm inner diameter was used as diffusion cell a shep mucosa was fixed to one end of the cylinder with the aid of an to result as a diffusion cell. 1 ml of Nano emulsion was taken in the cell and cell was immersed in a beaker containing 100ml of pH 6.8 as receptor compartment. The entire surface of the cell was in contact with the receptor compartment which was agenized using magnetic stirred and a temperature of 37 c was maintained. Samples 10ml of the receptor compartment were taken and with same amount replaced to maintain sink condition. The sample was analyzed for ketoconazole at 240nm against blank using UV Spectrophotometer. Amount of ketoconazole released at a various time intervals was calculated with the help of calibration curve with phosphate buffer and plotted against time.
9) *Stability Studies:* The nanoemulsion were subjected to stability study at 37°C for 1 month respectively. The sample were evaluated for transparency drug content, pH and in vitro drug realest every one month for three month period.

III. RESULT AND DISCUSSION

Solubility study:

Result of solubility study of drug in oil, surfactant, co surfactant are shown in table Ketoconazole solubility study data:

Table No:- 1,2 and 3 for Solubility study .

Sr.No	Oil	Solubility(mg/ml)
1	Arachise oil	8.8
2	Seaseam oil	8.9
3	Oleic acid	49.23
4	Castor oil	9.2
5	Soyabean oil	7.2

Sr.No	Surfactant	Solubility(mg/ml)
1	Tween 20	32
2	Span 20	38
3	Tween 80	28
4	Campul PG8	18.32

Sr.No	Surfactant	Solubility(mg/ml)
1	PEG400n	44
2	Ethanol	28
3	Isopropylene Glycol	32
4	PEG20	30

Construction of Pseudo-Ternary Hase Diagram:
Surfactant was blended with co surfactant in fixed weight ratio (1:1, 1:2, 2:1) Aliquots of each surfactant mixture (Smix) were then mixed with oil at room temperature 25C For each phase diagram, the ratio of oil to the Smix was varied at 9:1, 82, 7:3, 6:4, 5.5.46 3.7. 2.8, 19 (w/w) Water was added drop wise to each oil Mix mixture under the vigorous stirring After equilibrium the sample were visually checked and determined to clear nanoemulsion. For the determination of existence zone of Nanoemulsion, pseudotermary phase diagrams were constructed using water titration method. To constructed pseudotemary phase diagrams, the oil phase was mixed with different ratio of surfactant and co-surfactant and mixtures was titrated with distilled water until turned turbid. Examine cach and every point I detailed and note it down Pseudo ternary phase diagrams were drawn by using data obtain in aquasc titration method as shown in figure. The amount of water added to give water the water to the oil and Smix mixture, visual observation were made as shown in figure The ratio of surfactant and co surfactant were used for the titration.

IV. COMPOSITION OF FINAL NANOEMULTION

Table no:-04

Sr. No	Ingredient	% w/w
1	Seaseam oil	10ml
2	Tween 80	35ml
3	Ethanol	35ml
4	Water	20ml

Table no:-05

Sr. No	Test	Nanoemultion
1	pH	5.10+-0.46
2	Viscosity	248.3+-0.67
3	Globule size	122.0
4	Zeta potential	-32.9mv
5	Optical transparency	Transparent
6	Drug content	88.85+-0.75
7	Phase separation	No phase separation

V. CHARACTERIZATION OF NONAEMULSION: THE RELEASE PROFILE OF KETOCONAZOLE

1) In vitro drug release study:

Table no:-06

Times in min.	ME1	ME2	ME3
5	15.25±0.54	13.52±60	11.75±0.64
10	19.65±0.78	19.47±0.60	20.54±0.63
15	25.45±0.66	24.63±0.64	28.12±0.67
20	29.02±0.55	30.84±0.67	35.75±0.65
25	36.83±0.65	36.63±0.64	41.95±0.75
30	40.65±0.63	42.14±0.60	49.35±0.77
35	47.12±0.55	49.82±0.67	54.15±0.64
40	52.88±0.67	54.37±0.59	60.52±0.38
45	57.78±0.65	60.46±0.41	66.74±0.76
50	64.61±0.59	65.91±0.69	71.03±0.96
55	71.43±0.61	71.73±0.44	78.13±0.64
60	78.46±0.58	76.12±0.52	53.09±0.5

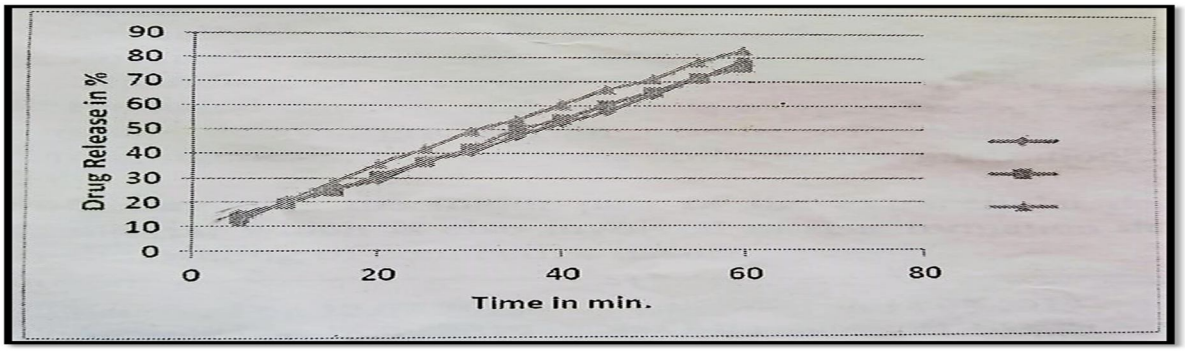


Fig 2:- IN VITRO DRUG RELEASE

2) Stability Study

The nanoemulsion were subjected to stability study at 37°C for 1 month respectively. The sample were evaluated for transparency. drug content, pH, and in vitro drug release every month for three months period shown in table.

Table of stability study

Table no:-07

Sr. No.	Observations	Before accelerated stability study	After accelerated stability study (30 Days)
1	Visual appearance (Transparency)	Transparent	Transparent
2	Drug content (±)	88.85 ± 0.77	88.56 ± 0.64
3	pH(±)	5.10±0.47	5.18±0.64
4	In Vitro drugs release (±)	83.09±0.56	83.6±0.50

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VI. CONCLUSION

The following conclusion can be drown form the present study:

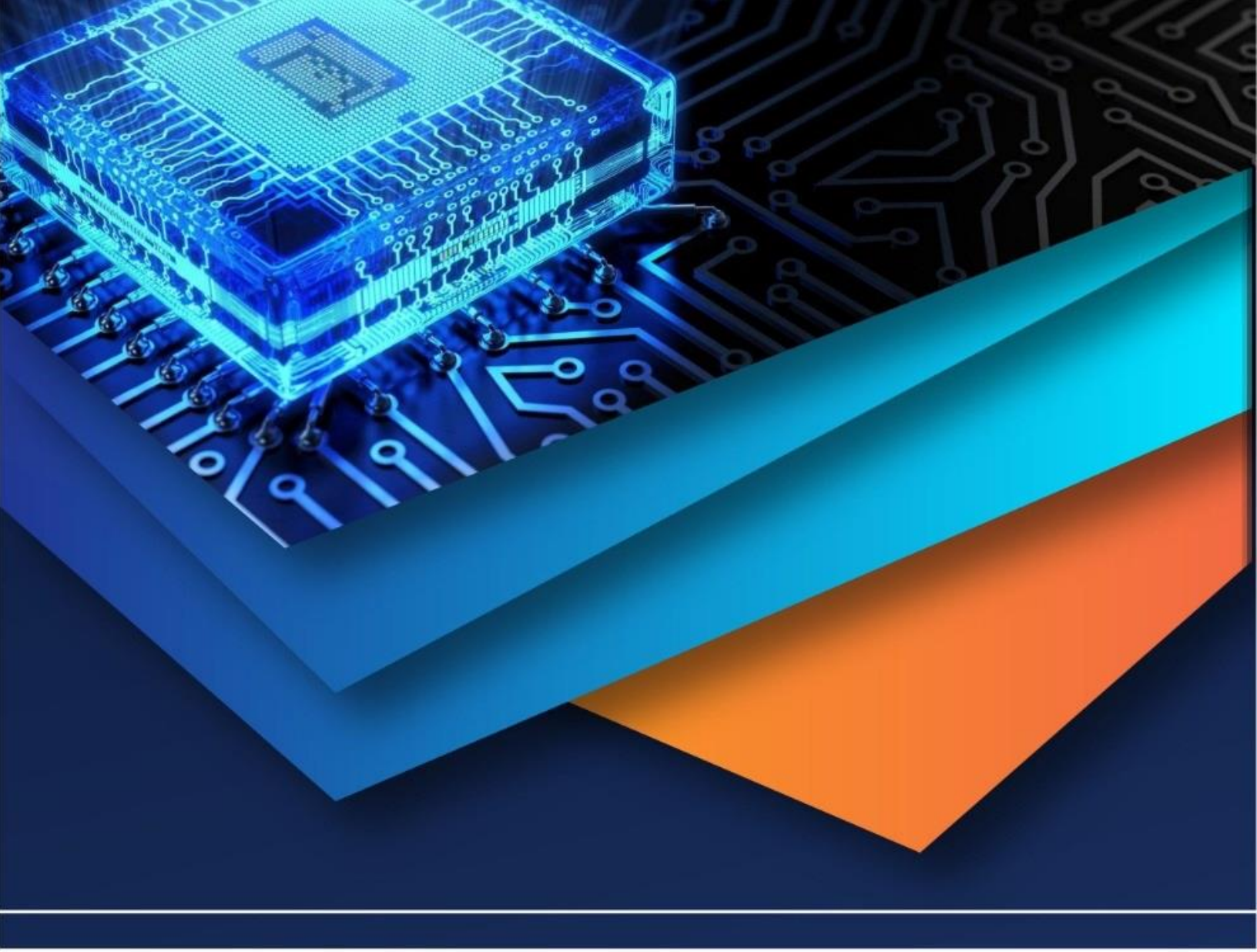
1) Solubility analysis aided the selection of suitable sea scam oil as a oil phase, tween 80 as a surfactant, ethanol as co surfactant.
2) From the pseudo ternary phase diagram construction, it aided to find the proper construction of sea seam oil as oil, tween 80 as a surfactant, ethanol as a co surfactant and aqueous phase.
3) Globule size of optimized Nano emulsion (NE3) was found to be 122nm.
4) Drug content of optimized Nano emulsion (NE3) was Found to be 88.85%.
5) Drug release study showed that, developed Nano emulsion formulation (NE3) give higher percentages of drug release 83.09% in 60 min.
6) Stability studies indicated that prepared Nano emulsion formulation did not show any significant change in physical appearance, drug

Content, turbidity or phase separation in case of formulation NE3 up to 3 month Finally, it can be summarized and concluded that the Nano emulsion of ketoconazole can be one of promising tool in improve bioavailability, increases the rate of absorption due to the small globule size and by avoiding first pass metabolism and direct transport into systemic circulation.

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