JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

"FORMULATION AND EVALUATION OF O/W NANOEMULTION OF KETOCONAZOLE"

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Abstract

Many of strategies are described to show enhancement in the penetration of the low molecular weight drug and several of which have been successfully employed in commercial system in this study, nanoemulsion drug delivery system a mixture containing surfactant, co surfactant and oil, were prepared nanoemulsion solubility studied was determined in various oils for selection of oil phase, surfactant ,co-surfactant with distilled water being the aqueous phase. Various oil in water nanoemulsion prepared by the water titration method. This property composition of the excipients as well as concentration in was dependent on the well as their individual te mixture. The transparent emulsification are was identified by constructing pseudo phase ternary phase diagram. Excipients evaluated in nanoemulsion drug delivery system. Tween 80 as surfactant, ethanol as co surfactant and seaseam oil as oil. All the excipients showed a tendency to form a nanoemulsion with varying degree of efficiency. A particular nanoemulsion mixture comprising of tween80, ethanol, and seaseam oil was selected and optimized for the purpose for delivering a model drug.

Keywords :- Ethanol, Seaseam oil, Ketocanazole .

Introduction

Nanotechnology scales up to one billionth of a meter Generally, they are considered to be in range of 100nm to 1000nm. Various effect 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 work in almost all technical and biomedical field is based on nanosize Nanoemulsions 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 athletes foot, jock itch, ringworm, candidiasis, 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 Ketoconazolecauses irritation in gastric mucosal membrane and possess a bitter taste

and aMost 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 dermatologyfter taste.

MATERIAL AND EQUIPMENTS :

A) Chemical :-

Ketoconazole, seasum oil, tween 80 , Oil mix (Ttertiary phase) , phosphate buffer ethanol surfactant co-surfactant .

B) Equipment :-

High pressure homogenizer, distilled water, beaker, magnetic stirrer, container, vortex mixture, UV-VFS Spectrophotometer , pH meter, Chemical software (to view phase diagram) , volumetric Flask.

Zetasizer Nano ZS (Maevent intstrument UK) It is Used to determine average globule size of of nanoemulsion.)

METHODOLOGY AND EXPERIMENTAL WORK :

METHODOLOGY:

1.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.

A. 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 :

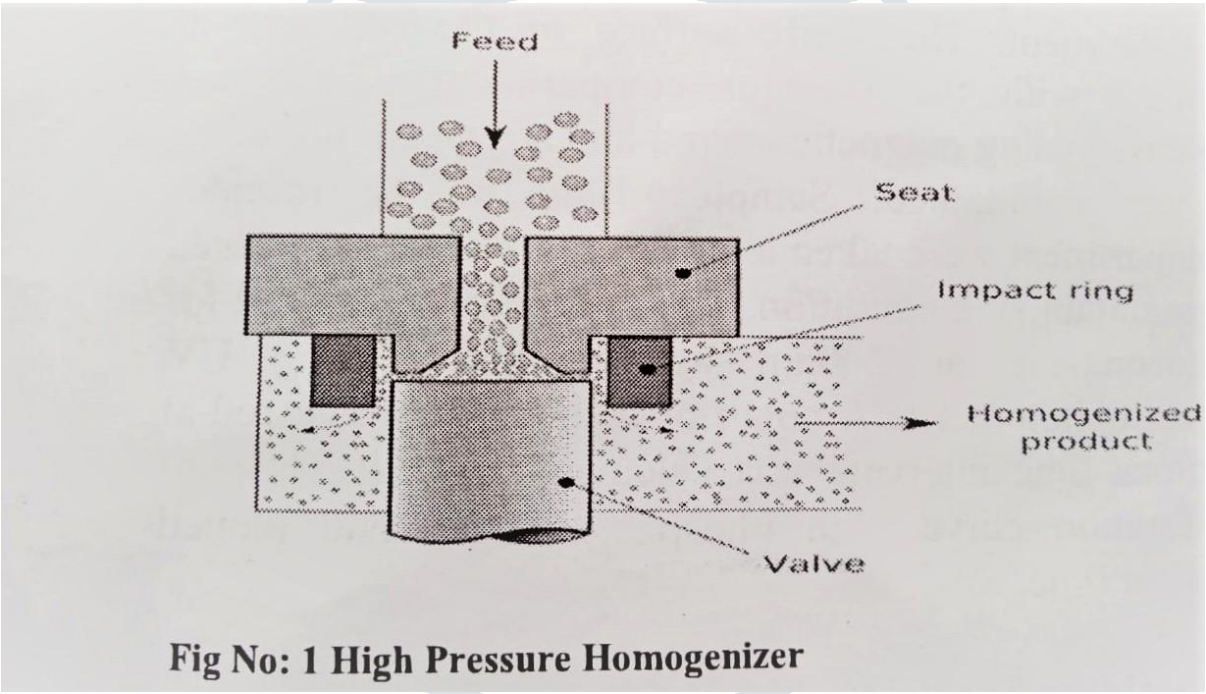


Fig No: 1 High Pressure Homogenizer

b. 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.

c. 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.

d. 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.

RESULT AND DISCUSSION:

Solubility study:

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

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.

Composition of final nanoemultion :

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

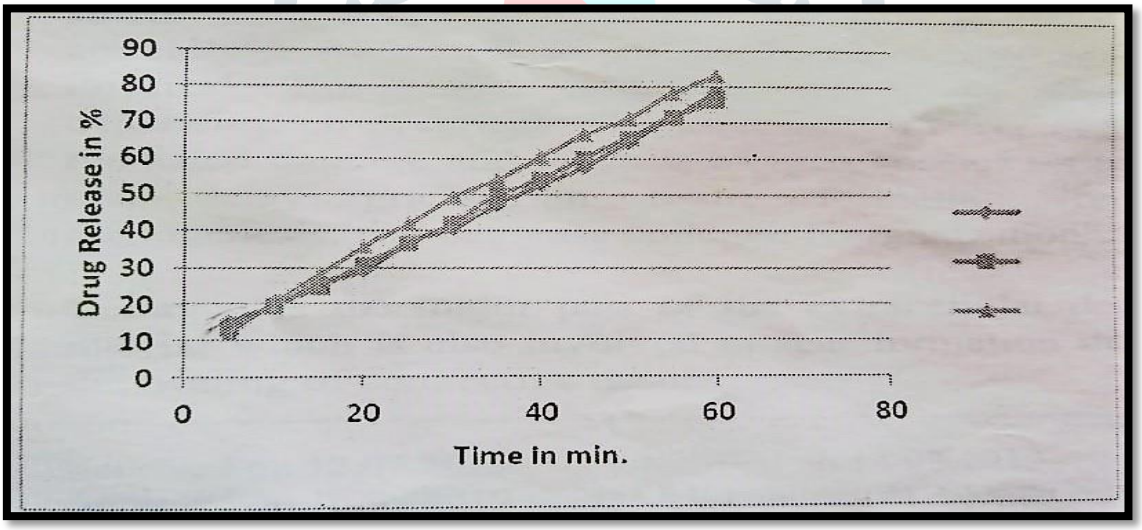
Sr. No	**Test**	**Nanoemultion**
1	pH	5.10+-0.46
2	Viscosity	248.3+-0.67
3	Globule size	122.0
4	Zeta potential	-32.9mv
5	Optical transparency	Transparent
6	Drug content	88.85+-0.75
7	Phase separation	No phase separation

CHARACTERIZATION OF NONAEMULSION: THE RELEASE PROFILE OF KETOCONAZOLE:

In vitro drug release study:

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

IN VITRO DRUG RELEASE



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 :

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

CONCLUSION:

Many of strategies are described to show enhancement in the penetration of the low molecular weight drug and several of which have been successfully employed in commercial system in this study, nanoemulsion drug delivery system a mixture containing surfactant, co surfactant and oil, were prepared nanoemulsion solubility studied was determined in various oils for selection of oil phase, surfactant ,co-surfactant with distilled water being the aqueous phase. Various oil in water nanoemulsion prepared by the water titration method. This property composition of the excipients as well as concentration in was dependent on the well as their individual te mixture. The transparent emulsification are was identified by constructing pseudo phase ternary phase diagram. Excipients evaluated in nanoemulsion drug delivery system. Tween 80 as surfactant, ethanol as co surfactant and seaseam oil as oil. All the excipients showed a tendency to form a nanoemulsion with varying degree of efficiency. A particular nanoemulsion mixture comprising of tween80, ethanol, and seaseam oil was selected and optimized for the purpose for delivering a model drug.

ketoconazole nanoemulsion 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 nanoemulsion of ketoconazole loaded were prepared. The prepared liquid nanoemulsion wer 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 th target areas. It is characterized for droplet size, ze potential, viscosity, in vitro drug release study we performed.

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