IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

SOLUBILITY ENHANCEMENT OF ITRACONAZOLE BY SELF-EMUSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Oral route is the most convenient route for drug administration. More than 40% of new chemical entities exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery. Improving oral bioavailability of low poorly water soluble drugs using Self Nano emulsifying Drug Delivery System (SNEDDS)possess significant potential.

The nanoemulsion was characterised by measuring Transmission Electron Microscopy, Particle Size distribution Analysis, Zeta Potential Analysis.

To optimize formulation of SNEDDS is a potential alternative oral dosage form for improving oral absorption of Itraconazole.

SNEDDS formulation has significantly increased the absorption rate when compared to the pure drug. Thus, this SNEDDS should be an effective oral dosage form for improving oral bioavailability of lipophilic drug Itraconazole. The Lipid-based drug delivery system is extensively reported within the literature for enhancing drug solubility, permeability, and bioavailability. A considerable majority of novel pharmacologically active constituents produced in recent drug discovery programs are lipophilic and poorly soluble, posing a significant problem for pharmaceutical researchers enhancing the oral bioavailability of such drug molecules. Self-Nanoemulsifying Drug Delivery Systems (SNEDDS), are the viable oil-based approaches for drugs that exhibit low dissolution rate and inadequate absorption. Ever since the progress of SNEDDS, researchers have been focusing on the challenges of BCS Class II and Class IV Drugs for enhancing water Solubility of poorly water-soluble drugs. SNEDDS is a Validate method for enhancing the

solubility and bioavailability of lipophilic compounds. It's the isotropic mixture of oil, surfactant, co-surfactant molecules and it also contains co-solvent molecules. Which spontaneously form oil-in-water nano emulsion of approximately 200 nm or less in size upon dilution with water under gentle stirring. Its Drug delivery system which possesses thermodynamically and kinetically stability. The physicochemical properties, drug solubilisation capacity considerably regulate the selection of the SNEDDS components. The compositions of the SNEDDS are often optimized with the assistance of phase diagrams. Further optimization of SNEDDS can be done with the help of statistical experimental design.

Keywords : Self-Nanoemulsifying Drug Delivery, System, Poorly Water Soluble drugs,Oral Bioavailability,Itraconazole,Surfactant, Co-surfactant,Poor Bioavailability.

INTRODUCTION

Low oral bioavailability of drugs as a consequence of their low water solubility is a growing challenge to the development of new pharmaceutical products. One of the most popular approaches of oral bioavailability and solubility enhancement is the utilization of lipid-based drug delivery systems. Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) are regarded as pre-concentrated nanoemulsion or as an anhydrous form of the nanoemulsion. Self-Nanoemulsifying Drug Delivery system (SNEDDS) is an isotropic mixture of the natural or synthetic oil, surfactants and co-surfactants and alternatively, Aqueous media were followed by one or more hydrophilic solvents and co-solvents/surfactant's ability to generate fine oil-in-water (O/W) nano-emulsions under mild agitation conditions[1]. The size range of globules in the Self-Nanoemulsifying Drug Delivery System is less than 100nm when dispersed in water[2]. Recent years Self-Nanoemulsifying Drug Delivery System (SNEDDS), Self-Micro Emulsifying Drug Delivery System (SMEDDS) and self-emulsifying drug delivery systems (SEDDS) is employed to enhance the aqueous solubility of BCS Class II and Class IV Drugs which are having poorly water-soluble in nature. Nanoemulsion is a colloidal particulate system which disperses in two immiscible liquids; either oil in water phase (O/W) or water in oil phase (W/O) in the submicron size. In terms of their size, there is no definite standard regarding their particle size. Shah et al, 2010 proposed that nanoemulsion is an emulsion system with particle size distribution from 50 nm to 1000 nm. Whereas Shakeel, et al, 2008 said that nanoemulsion is a transparent emulsion system and consist of the dispersion of oil and water and surfactant as a stabilizer, usually has 50 - 500 nm [2] or between 20-200 nm particle size.[3] Normally, the average of the nanoemulsion size varies from 10 to 1.000 nm.[4]

MATERIAL AND METHOD:

Itraconazole (ITZ), Poly Ethylene Glycol (PEG) 200, Castor Oil, Tween 80, Ethanol, Distilled Water. The Self Nanoemulsifying Drug Delivery System is prepared by using high pressure homogenizer as well as ultrasonic equipment which is expensive. The Stability of nanoemulsion is also affected by Temperature and pH[1,2].

The methods are:

i. High energy methods: It consists of High Pressure Homogenization, High-Shear Stirring, Ultrasonic Emulsification, Micro fluidization [3-7].

ii. Low energy methods: It consists of spontaneous Nano-emulsification, Phase inversion methods and its components like Phase inversion temperature, Phase inversion composition

Method of Preparation of Self emulsifying drug delivery system:

It is prepared using High energy method like It consists of High Pressure Homogenization It's important method for preparation of self- Nanoemulsifying drug delivery system having the surfactant/co-surfactant ratio and oil/ surfactant/co- surfactant ratio was selected From the Pseudo ternary phase diagram. Different concentrations of oil, surfactant, and Co-surfactant were used to process a number of series of the formulation. The oil and surfactant were weighed in appropriate proportions, and the drug was dissolved in this mixture, which was then stored at room temperature.

Table 1 : Formulation of Self Emulsifying Drug Delivery System

Sr. No.	Ingredients	B1F1	B1F2	B1F3	B1F4
1	Itraconazole	300mg	300mg	300mg	300mg
2	PEG200	5ml	5ml	5ml	5ml
3	Tween 80	5ml	10ml	15ml	20ml
4	Castor Oil	6ml	8ml	10ml	12ml
5	Ethanol	5ml	5ml	5ml	5ml
6	Distilled Water	79ml	72ml	65ml	58ml

CHARACTERISATION:

1. **Determination of pH:**

   The pH was measured using a pH meter.The instrument was checked and calibrated against standard pH 4.0 and 8.0.The electrode was thoroughly rinsed after every individual sample in order to avoid errors due to electrode oil contamination.

2. **Viscosity:**

   The viscosity of the nanoemulsion was measured using Brookfield viscometer using spindle 62.The speed was kept 100 RPM. The spindle was directly immersed into the nanoemulsion and viscosity was measured and values was recorded in centipoise.

3. **Particle Size Analysis:**

   The particle size distributions were performed to observe the distribution of particles in the nanoemulsion. This test was performed using a Particle Size Analyzer (Zetasizer Nano ZS, Malvern Instrument). This instrument is appropriate to measure the globule size from 3 nm to 3 um.

4. **Drug Content:**

   Drug content of Nanoemulsion was determined by UV spectrophotometer. Milliliter of Nanoemulsion was diluted to 100 ml with 0.1 N methanolic HCl and sonicated for 10 min. Then the solution was filtered and diluted suitably with 0.1N methanolic HCL. The absorbance of the resulting solution was measured spectrophotometrically at 260 nm.

5. **TRANSMISSION ELECTRON MICROSCOPY (TEM):**

   Morphology of microemulsion globules obtained after water dilution of optimized ITZ SNEDDS was assessed by Transmission electron microscopy. The obtained image is presented in Figure. The observations confirm the ability of optimized ITZ SNEDDS to produce uniformly distributed, spherical shaped oil globules of nano size. This observation of the TEM image is in agreement with results obtained from globule size analysis.

6. **Stability Test**:

   The stability of the nanoemulsion was assessed by monitoring the changes in the particle sizes distribution of the nanoemulsion during 3 months. The nanoemulsions were stored at room storage condition and the Particle Size distribution was measured by using Zetasizers Nano ZS (Malvern Instrument).

Result and Discussion:

1. **Determination of pH:**

   The pH values of all Nanoemulsions were determined and they were within the range of 4.0 to 8.0. As the pH value lies in the normal pH range of the skin, it may not produce any skin irritation.

2. **Viscosity:**

   Brookfield viscometer is used to test the nano-emulsion's rheological properties. This viscosity determination conforms to whether the system is water/oil or oil/water. If the system has low viscosity, then it's o/w type of the system and if high viscosities then it's w/o type of the system[21].

3. **Particle Size Analysis:**

   The nanometric size range of the particles is retained even after 100 times dilution with water which demonstrates the system is compatible with excess water. The particle size distributions were performed to observe the distribution of particle in the nanoemulsion. This test was performed using a Particle Size Analyzer. The figure is follow 1:

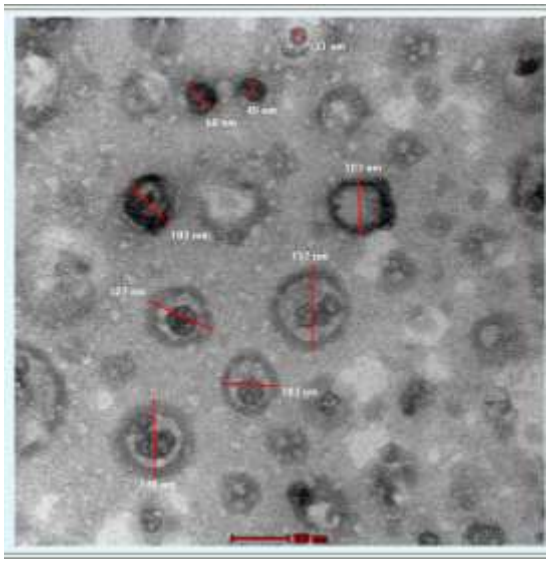

Fig 1. Particle Size Analyser image of B1F4-ITZ Self Nanoemulsifying Drug Delivery System (SNEDDS)

4. **Zeta Potential Analysis:**

Zeta Potential is used to identify the charge of the droplets. In conventional SNEDDSs, the charge on an oil droplet is negative due to the presence of free fatty acids. Higher the Negative charge more, will be the stability of the nano-emulsion. Zeta potential is a crucial indicator to determine the stability of ITZ-SNEDDS; where a stable colloidal dispersion is within the range of -10 mV and +10 mV while zeta potential value of nano-dispersions greater than 30 mV and lesser than -30 mV are considered highly cationic and anionic. The zeta potential value of ITZ-SNEDDS obtained was -20.2mV which is considered neutral and stable as the sample is monodispersed (single peak) corresponds to a single component zeta potential value in the ITZ-SNEDDS [14]. The figure is below:

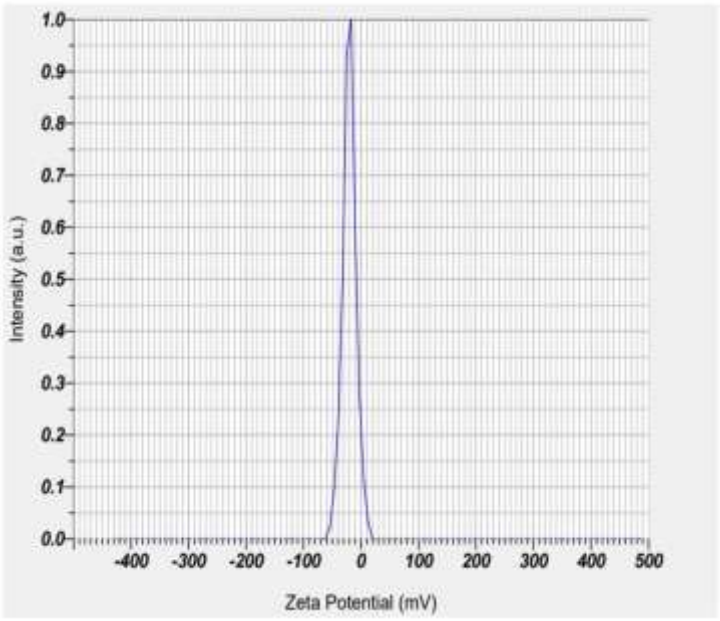

Fig 2: The Zeta Potential of Itraconazole containing Self Nanoemulsifying Drug Delivery System.

5. **Drug Content:**

The calibration curve of ITZ in 0.IN methanolic HCI was plotted. The regression equation was used for calculating drug content of the formulation. The drug content of all Nanoemulsion formulations was found to be in the range of 98-102%.

6. **TRANSMISSION ELECTRON MICROSCOPY (TEM):**

The TEM was used because it determines or helps to analyse the morphology and structure of the formed nano-emulsion droplets, TEM is performed. This allows point to point resolution. Transmission electron microscopy (TEM) was performed to elucidate the shape, size and homogeneity of the nanoparticles. As depicted in Fig. 3. ITZ-SNEDDS were in the nano-size range; relatively uniform in shape, existed as spherical particles and had a small size distribution.

The result of batch is as below:

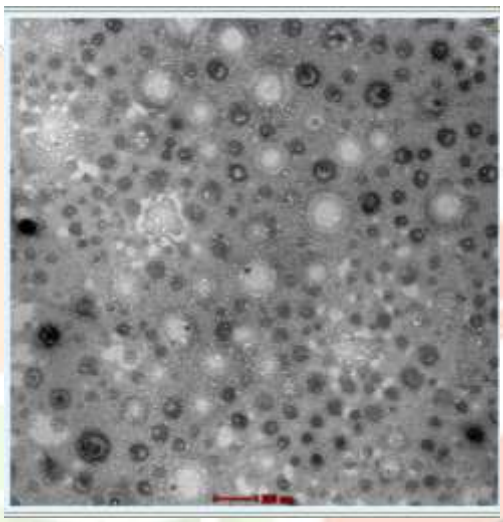

Fig 3: Transmission Electron Microscopy (TEM) image of B1F4-ITZ Self Emulsifying Drug Delivery System

7. **Stability Test**:

The stability of the nanoemulsion was assessed by monitoring the changes in the particle sizes distribution of the nanoemulsion during 3 months. The nanoemulsion was stored at room temperature.

Table 2.. Results of qualitative and quantitative test of Nanoemulsions

FORMULATION	pH	Drug Content	%Transmittance	Viscosity(cps)
B1F1	6.89	98.25	96.55	8.83
B1F2	7.0	98.80	97.86	10.33
B1F3	7.10	99.35	98.85	14.66
B1F4	7.30	100.65	99.02	20.50

Conclusion:

A SNEDDS containing a poorly water-soluble drug, Itraconazole, was formulated for oral administration. The ITZ Nano-Emulsion was formulated using PEG200,Tween 80,Castor Oil, Ethanol, Distilled Water. The components and their ratio ranges for the formulation of SNEDDS were obtained by Viscosity,% Transmittance, Drug Content and droplet size analysis. The formulations were found to be stable for three months. The above results indicated potential application of ITZ towards Nanoemulsion. Itraconazole nanoemulsion is successfully prepared using castor oil as the oil phase. It is suggested that castor oil can be used as a good oil phase in nanoemulsion formulation.

Acknowledgement:

The authors are thankful to Mr.Vikas Mishra Ji Cipla Ltd. Haridwar ,Uttrakhand, India for providing a gift sample of Itraconazole. The corresponding author gratefully acknowledged the Principal to D.S.T.S. Mandal's College of Pharmacy, Solapur,.

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