Itraconazole Self-Nano Emulsifying Drug Delivery System for Enhancement of Solubility

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**Abstract**

The main objective of formulation is to enhance the bioavailability of the drug within the body. Some of the challenging subjects associated with poorly water-soluble drugs concern solubility and bioavailability factors. To overcome these problems, new technologies, such as lipid-based drug delivery systems including micro or nano emulsifying drug delivery system, have obtained importance in recent years, due to their enhanced solubility and bioavailability in the gastrointestinal tract. Such systems are solubilized within the lipid excipients or mixed with oils or surfactants/co-solvents to facilitate the solubility and absorption rate, which can enhance the bioavailability of the targeted drug. The research was targeted to develop a self-Nano Emulsifying drug delivery system (SNEDDS) for oral bioavailability enhancement of BCS II antifungal drug Itraconazole. Nano Emulsions are emulsions that are significantly less than 100 nm in droplet size. SNEDDS formulation can be obtained through phase diagram approach. Pseudo Ternary phase diagrams were constructed, using Chemix software, to optimize the concentrations of excipients. Thermodynamic stability studies were satisfactory. Robustness to dilution did not exhibit phase separation and drug precipitation. TheAmong 4 formulations, B1F3 formulation showed more than 95% of drug content and were considered superior and subjected to droplet size analysis and zeta potential measurement. Droplet size ranged from 120 nm to 505 nm. The Nano size was obtained for formulation. The zeta-potential results indicated the range -35 mV. Based on all evaluation tests, formulation B2F3 was chosen as the best. Thus, this self-Nano Emulsifying drug delivery system should be an effective oral dosage form for improving oral bioavailability of lipophilic drug Itraconazole.

**Keywords:** Lipid, Solubility, Oral bioavailability, SNEEDS-Self Nano Emulsifying Drug Delivery System, Itraconazole

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1. **Introduction**

Nanoemulsion are colloidal dispersions with a size range of 20-400nm [1] and consists of an oil phase, aqueous phase, surfactant and co surfactant at appropriate ratios. Unlike coarse emulsions micronized with external energy, Nanoemulsion are based on low interfacial tension. This is achieved by adding a co-surfactant, which leads to spontaneous formation of a thermodynamically stable nanoemulsion. [2] The term ‘Nanoemulsion’ is often used to designate emulsions with the internal phase droplets smaller than 1000nm. It is a appeared as a novel drug delivery system which allows sustained or controlled release of drug, biological active ingredient. [4] The Nanoemulsions are also referred as mini emulsions, ultrafine emulsions and submicron emulsions. [4] Phase behavior studies have shown that the size of the droplets is governed by the surfactant phase structure (bicontinuous micro emulsion or lamellar) at the inversion point induced by composition. The term ‘Nanoemulsion’ refers to a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water stabilized by an interfacial film of surfactant molecules. Nanoemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and water phase in combination with a surfactant. The dispersed phase droplet size is about 5 nm-200 nm and should...
have very low oil/water interfacial tension. Co-surfactant is used in many cases in addition to the surfactant, the oil phase and the water phase.

Itraconazole is the triazole antifungal agent used for cure of local and systemic fungal infection. Itraconazole is an acutely selective inhibitor of fungal cytochrome P-450 sterol C-14-α demethylation. The consequent loss of normal sterols correlates with the accretion of 14-α-methyl sterols in fungi and may be liable for the fungistatic activity of Itraconazole3–4. Compared with other conventional antifungal agents, Itraconazole has a reduced amount of nephrotoxicity than Amphotericin B and has wider spectrum of activity and well tolerated than other triazoles like fluconazole, ravuconazole, and posaconazole5–6. Itraconazole is indicated for the treatment of fungal infections like blastomycosis, histoplasmosis, including chronic cavitary pulmonary disease and disseminated non-meningeal histoplasmosis, aspergillosis.

The major advantages of nanoemulsion as drug delivery systems include increased drug loading, enhanced drug solubility and bioavailability, reduced patient variability, controlled drug release, and protection from enzymatic degradation. The nanoemulsion of natural products are used for several purposes. Three types of Nanoemulsion are most likely to be formed depending on the composition.

2. Materials And Methods
Itraconazole (ITZ), Poly Ethylene Glycon (PEG) 200, Tween 20, Ethanol, Distilled Water. Itraconazole nanoemulsion were prepared by titration method using Castor oil, PEG 200 as cosurfactant and tween 20 as surfactant and purified water as continuous phase. Oil phase were mixed with Smix and titrated with Distilled water. Distilled Water was added to drug loaded internal phase in dropwise manner under continuous stirring. The compositions which are optically clear have been evaluated further by constructing pseudo ternary phase diagrams.

Methods:
The schematic representation of the method of preparation of nanoemulsion is depicted below.

1. High energy approaches:
   a) High Pressure Homogenization,
   b) High-Shear Stirring,
   c) Ultrasonic Emulsification,
   d) Microfluidization

2. Low Energy Approaches:
   a) spontaneous Nano-emulsification,
   b) Phase inversion methods components
      i. Phase inversion temperature,
      ii. Phase inversion composition

Method of Preparation of Nanoemulsion
The formulations were prepared by incorporation of Itraconazole in an ethanol and Castor oil solution. Tween 20 and PEG 200 were added to the distilled water respectively and a water solution was prepared. Oil solution was added to water solution at room temperature. The final mixture was mixed by vortexing until a transparent solution was obtained. The formulation was homogenized using a high-speed homogenizer and finally Itraconazole nanoemulsion was characterized.

Formulation Table

Table 1: Formulation table of Self Nano Emulsifying Drug Delivery System

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
</tr>
<tr>
<td>PEG200</td>
<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
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<tr>
<td>Tween 20</td>
<td>5ml</td>
<td>10ml</td>
<td>15ml</td>
<td>20ml</td>
</tr>
<tr>
<td>Castor Oil</td>
<td>6ml</td>
<td>8ml</td>
<td>10ml</td>
<td>12ml</td>
</tr>
<tr>
<td>Ethanol</td>
<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
</tr>
<tr>
<td>Distilled Water</td>
<td>79ml</td>
<td>72ml</td>
<td>65ml</td>
<td>58ml</td>
</tr>
</tbody>
</table>
Characterization

pH Determination
pH was determined by using digital pH meter. The range for preparation it is between 6.0 - 8.0. The nanoemulsion were immersed in pH meter. The electrode was previously washed with distilled water and calibrated. The pH value determination monitoring the pH value is important for determining the nanoemulsions' stability because pH changes indicate the occurrence of chemical reactions that can compromise the quality of the final product.

Viscosity
Viscosity was determined using Brookfield viscometer using spindle no. 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.

Particle Size
Average particle size and size distribution of selected batches of Nanoemulsion was determined by using SAGLOSOFT Micro-Imaging Swoftware version-2. The optimized batch B2F3 were evaluated by using Transmission Electron Microscope Analyzer.

Percentage Drug Content
Accurately weighed quantities of nanoemulsion were mixed with of 0.1N methanolic HCL. The filtrate was analyzed spectrophotometrically at 260 nm for drug content against 0.1N methanolic HCL. Corresponding drug concentrations in the samples were calculated from the calibration plot generated by regression of the data. Drug content was calculated as detected amount of Itraconazole with respect to theoretical amount of drug used for the preparation of nanoemulsion.

Zeta Potential
The nanoemulsion was measured by photon correlation spectroscopy using a Malvern Zetasizer. Samples were diluted appropriately with the aqueous phase of the formulation. The measurements were carried out at 25 ºC. The samples were analyzed.

Transmission Electron Microscope (TEM)
The morphology of the resulting nanoemulsion droplets was studied using transmission electron microscopy. The SNEDDS B2F3 sample were dispersed in distilled water (1000-fold dilution) to produce nanomulsion, stained for 30 seconds with 2 percent (w/v) phospho-tungstic acid, and observed on 400-mesh copper grids with films.

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

3. Result and Discussion

pH Determination
The pH values of all Nanoemulsions were determined and they were within the range of 6.0 to 8.0. As the pH value lies in the normal pH range of the GI tract, it may not produce any GI irritation.

Viscosity
Viscosity was determined using Brookfield viscometer using spindle no. 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.

Particle Size Analysis
The morphological examination of drug nanoemulsion was performed by transmission electron microscope respectively. For TEM, the nanoemulsion were redispersed in water and placed on a Cu grid and then the grid was inserted into the TEM column for examination.
Fig 1: Particle Size Analyser image of B2F3-ITZ Self Nano Emulsifying Drug Delivery System (SNEDDS)

**Percentage Drug Content**
Drug content of Nanoemulsion was determined by UV spectrophotometer. Milliliter of Nanoemulsion was diluted 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.

**Zeta Potential**
Zeta potential of droplets produce from formulations is observed with negative charge irrespective of the dilution medium and it was in the range of -35 mV. B2F3 was selected as optimized SNEDDS of ITZ and evaluated for further studies. ITZ S-SNEDDS on their globule size and zeta potential analysis is provided in below fig. 2.
Fig.2: The Zeta Potential of B2F3 Itraconazole containing Self Nano Emulsifying Drug Delivery System

Transmission Electron Microscope
Morphology of nanoemulsion globules obtained after 1000 folds water dilution of optimized ITZ S-SNEDDS was assessed by Transmission electron microscopy. The obtained image is presented in Figure 3, the observations confirm the ability of optimized ITZ SNEDDS to produce uniformly distributed, spherical shaped oil globules of nano size. This observation of TEM image is in agreement with results obtained from globule size analysis.

Fig 3: Transmission Electron Microscopy (TEM) image of B2F3-ITZ Self Emulsifying Drug Delivery System

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

Table 2: Results of qualitative and quantitative test of Nanoemulsion

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Ph</th>
<th>Drug Content</th>
<th>% Transmittance</th>
<th>Viscosity (Cps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2F1</td>
<td>7.23</td>
<td>98.00</td>
<td>97.45</td>
<td>8.95</td>
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<tr>
<td>B2F2</td>
<td>7.34</td>
<td>98.75</td>
<td>98.34</td>
<td>11.33</td>
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<tr>
<td>B2F3</td>
<td>7.45</td>
<td>99.46</td>
<td>98.65</td>
<td>13.66</td>
</tr>
<tr>
<td>B2F4</td>
<td>7.85</td>
<td>100.35</td>
<td>98.74</td>
<td>20.65</td>
</tr>
</tbody>
</table>

4. Conclusion
A SNEDDS containing a poorly water-soluble drug, Itraconazole, was formulated for oral administration. The ITZ Nano-Emulsion was formulated using PEG200, Tween 20, Castor Oil, Ethanol, and Distilled Water. The components and their ratio ranges for the formulation of SNEDDDS were obtained by Viscosity, % Transmittance, Drug Content and droplet size analysis. The formulations were found to be stable for 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.
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References: