

FLUCONAZOLE: A SIMPLE NANOEMULSION DRUG DELIVERY SYSTEM

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ABSTRACT

Fluconazole, an inhibitor of cytochrome P450 enzyme is found hydrophobic with dissolution related problems and also fungistatic in action. On the account of few physico-chemical disadvantages, we worked on a novel cinnamon oil based nanoemulsion drug delivery system. The drug-loaded formulation used cinnamon oil, tween 80 and water at a ratio of 6:18:76 v/v and was checked for various parameter of the internal system including conductivity, droplet size and polydispersity index. The surfactant concentration was reduced to a great extent using sonicator as high energy method at a laboratory scale; that would help in the reduction of gastrointestinal irritation. Also sonication helps in the breakdown of coarse emulsion to fine droplets (nanoemulsion). The particle size reduction to about 67 ± 2.13 nm as determined by dynamic light scattering technique would enable easy permeation through capillaries. Thus we propose that the formulated system would serve as excellent oral drug delivery system for fluconazole.

Keywords: Fluconazole, Dynamic light scattering, Cinnamon oil, Drug delivery system, Solubility.

INTRODUCTION

Fluconazole is a triazole antifungal drug used to treat superficial and systemic fungal infections [1]. Although fungi and human cells are eukaryotic and are similar at biological level, this drug adroitly differentiates between these two. This drug works by inhibiting fungal cytochrome P450 enzyme 14 α -demethylase and thereby preventing the formation of essential component of cytoplasmic membrane of fungi [2]. The mammalian demethylase is less sensitive to fluconazole when compared to the fungal demethylase. Fluconazole is active against a wide spectrum of fungal species that include *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Epidermophyton*, *Histoplasma*, *Microsporum* and *Trichophyton*. This drug has prolonged half-life, good bioavailability of about 90% and easy absorption after oral administration and hence distributed widely in different sites of the body [3, 4]. This drug is fungistatic when administered in low dosage and this leads to the incomplete destruction of fungi that result in the emergence of resistant strains [5]. Fluconazole is an inhibitor of cytochrome P450 particularly the isozyme CYP2C9. Hence, in theory, this drug decreases the metabolism and therefore increases the concentration of drugs metabolized by this enzyme. Fluconazole is hydrophobic and poses dissolution related problems [6]. Anaphylaxis, liver damage, hormonal imbalance, skin allergies, prolonged QT intervals are some common side effects. Fluconazole is majorly eliminated by urine, and hence, patients with impaired renal function are at a risk of over dosage. This drug is unprotected against bodily chemicals and has high potency of drug interactions. Hence, there is a need for the design of novel drug delivery system to enhance the solubility and to reduce the drug interaction so as to improve the efficacy of this drug.

In recent years, the application of nanoemulsion in the pharmaceutical field has gained increasing interest. This is due to

the presence of compartmentalized hydrophobic and hydrophilic domains that facilitates the incorporation of polar and non-polar compounds. These nanoemulsions have low interfacial tension, greater solubilization of organic compounds, small droplet size, high surface area and good thermodynamic stability [7]. Fine oil droplets empty rapidly and promote wide distribution of the drug throughout the intestine, and thereby, minimizes irritation frequently encountered with extended contact of the drug and gut wall [8]. The structures in nanoemulsions are much smaller than the wavelength of the visible light, so most nanoemulsions are optically transparent even at large loadings. They reduce the drug interactions and have potential to deliver drugs that are prone to enzymatic hydrolysis in gastro-intestinal tract [9]. These emulsions are prepared by applying continuous mechanical shear to the continuous phase in order to break the larger droplets of the dispersed phase into smaller ones. To significantly deform a droplet, one has to overcome Laplace pressure which is inversely proportional to the droplet size [10]. Thus, for the preparation of nanoemulsions, higher shear is to be applied which requires higher energy methods like ultrasonic agitation. These nanoemulsions are kinetically unstable and hence pose a big problem during the storage of formulation for long time. The ostwald ripening is the main problem associated with the unacceptability of nanoemulsion formulations. The suppressing ostwald ripening can be easily achieved by choosing a very insoluble liquid for the dispersed phase [11]. In our study, we initially assessed the highest solubilization capacity, in order to reduce the dosage concentration and also to improve the efficacy of the drug. Hence, we aimed at designing and characterizing biologically acceptable novel cinnamon oil based nanoemulsion system as drug delivery vehicle for fluconazole with minimum components. Our study is explained as a simple schematic representation in Fig. 1.

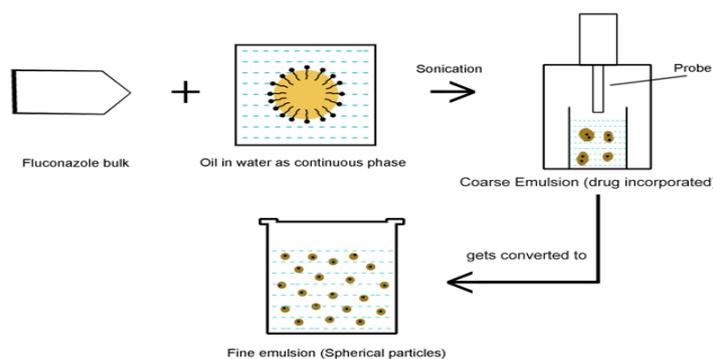


Fig. 1: Schematic representation of a new drug delivery system for fluconazole

MATERIALS AND METHODS

Chemicals

Fluconazole was obtained from Morepen Laboratories Private Limited (Parwanoo, Himachal Pradesh, India). Tween 80 (Bioxtra) and cinnamon oil was obtained from Sigma Aldrich, India. Peppermint oil and castor oil were obtained from Hi Media, India. For all experiments, ultrapure water (Cascada™ Biowater System, Pall Corporation, USA) with a resistivity of not less than 18.2 MΩ cm was used. Other reagents used were of analytical reagent grade.

Solubility

Due to the lipophilicity of fluconazole, the drug was checked for its solubility in various oils using the basic conventional equilibration method. The concentration of drug in these oils were determined using double beam UV-Visible spectrophotometer (UV-Vis Systronics-2201) after diluting appropriately with carbinol at 276 nm.

Drug-incorporated nanoemulsion formulation

Owing to the highest and complete solubilization of fluconazole in cinnamon oil as obtained from the solubility studies, the drug was initially dissolved in cinnamon oil and kept overnight to ensure complete solubilization and later centrifuged to separate the supernatant for analysis or preparation. This was followed by the addition of surfactant and water at a ratio of 6:18:76 v/v, and thus, a coarse emulsion were formed as the first step. This was then kept for sonication (Ultrasonics, USA) of 750 W (probe diameter=13 mm), as this method uses high energy, it is capable of conversion of coarse emulsion into a fine emulsion i.e., nanoemulsion (we followed the protocol of Vijayalakshmi et al, 2013 for our preparation method) [12].

Stability studies

- Centrifugation: The formulation was centrifuged at 3500 rpm for 30 min to ensure physical stability.
- Heating cooling cycle: Six cycles between refrigerator temperature of 4 °C and 45 °C for 48 h was examined.
- Freeze thaw cycle: Three freeze-thaw cycles between -21 °C and +25 °C was also checked.

Conductivity measurement

The electrical conductivity (σ) of our formulation was checked quantitatively using conductivity meter (Elco CM 180). The measurements were performed in triplicates.

Droplet size distribution and polydispersity index

The droplet size and polydispersity index of our formulation was determined by dynamic light scattering (DLS) – 90 Plus Particle Size Analyzer (Brookhaven Instruments Corp., Holtsville, New York, USA). The measurements were carried out in triplicates and the average results were reported in this paper.

RESULTS

Solubility study

The solubilization potential of fluconazole in various oils has been depicted clearly in Table 1.

Table 1: Solubility of fluconazole (mean \pm S. D., n=3) in different oils

Oils	Solubility (mg/ml)
Peppermint oil	12.57 \pm 0.46
Castor	4.18 \pm 0.04
Cinnamon oil	64.41 \pm 1.34

Stability

The drug-loaded cinnamon oil based nanoemulsion system have passed through all three stages of stress tests and was found to resist stress under extreme temperatures i.e., the sample experienced no phase separation, flocculation or coalescence.

Conductivity

The conductivity of our drug-loaded formulation as determined by conductivity meter was recorded to be 0.129 \pm 0.06 μ S/cm.

Droplet size and polydispersity index measurement

The mean droplet size of our formulation was recorded to be 67 \pm 2.13 nm as measured by dynamic light scattering technique. The polydispersity index was found to be 0.181 \pm 0.14; this confers more uniformity in size distribution and homogeneity.

CONCLUSION

Nanoemulsions are the most promising mode of drug delivery system that captured the attention of many pharmaceutical scientists due to its tiny nano-sized droplets that are spherical and also exhibit good kinetic stability. Hence, considering its unique advantages, we formulated a cinnamon oil based nanoemulsion system for the antifungal drug, fluconazole that showed enhanced solubilization with reduced toxicity.

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