Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 3, 2013

Research Article

ENHANCING THE SOLUBILITY OF FLUCONAZOLE USING A NEW ESSENTIAL OIL BASED MICROEMULSION SYSTEM

M. JOYCE NIRMALA[a], SRINIVAS ALLANKI[b], AMITAVA MUKHERJEE[a], N. CHANDRASEKARAN[a,*]

[a]Centre for Nanobiotechnology, VIT University, Vellore, [b]Department of biotechnology, Indian Institute of Technology Madras, Chennai, India. Email: nchandrasekaran@vit.ac.in, nchandra40@hotmail.com

Received: 22 Jun 2013, Revised and Accepted: 30 July 2013

ABSTRACT

Among the azole antifungal agents, fluconazole acts best on many fungal pathogens like *Blastmoyces dermatitidis*, *Microsporum*, *Cryptococcus neoformans* and *Candida albicans*. Fluconazole is fungistatic rather than being fungicidal and hence causes resistance of certain fungi. This drug is found to be poorly aqueous insoluble but possess good bioavailability. Hence, we tried to improve on the solubility using a new lipophilic environment as the drug is highly lipophilic. Our novel microemulsion drug delivery system for fluconazole was formulated using cinnamon oil, tween 20 and water (5:25:70 v/v) without any high-energy methods. The optimized formulation was checked for various parameters to demonstrate the internal state of the system. Cinnamon oil based drug-incorporated system (F5) showed higher solubility, hydrodynamic diameter of 10–45 nm and good stability. Also, the surfactant concentration was found to have a direct relation to stability and viscosity. Moreover, the system due to the presence of cinnamon oil may have additional influence on the efficacy against certain pathogens. Thus, our novel formulation has added advantage in serving as best drug delivery agent for fluconazole.

Keywords: Cinnamon oil, Microemulsion, Fluconazole, Drug delivery system, Solubility.

INTRODUCTION

Fungi are identified to be a cause of serious infection with increased frequency during the past two decades. Fungal diseases seem most dangerous as they are often caused by fungi that are most commonly found in the environment. Azole antifungal drugs inhibit the enzyme lanosterol 14 α-demethylase that is necessary to convert lanosterol to ergosterol. Depletion of ergosterol in fungal membrane disrupts the structure and many functions of fungal membrane leading to inhibition of fungal growth [1]. Fluconazole [2, 4-difluoro-(alpha), (alpha) 1-bis (1H-1, 2, 4-triazol-l-ylmethyl) benzyl alcohol] belongs to the subclass of synthetic triazole antifungal agent. It works on many fungi like *Blastmoyces dermatitidis*, *Microsporum*, *Cryptococcus neoformans* and mainly on *Candida albicans.* In 1980s, yeasts (particularly *C. albicans*) were the most common causative agents of invasive mycoses [2]. Fluconazole is fungistatic rather than fungicidal and therefore is a cause for resistance of certain fungi like *C. albicans* [3]. Though the bioavailability is as high as 90%, the plasma protein binding is very low (12%). The drug is metabolically stable with renal excretion accounting for nearly 80% of the elimination as unchanged drug [4].

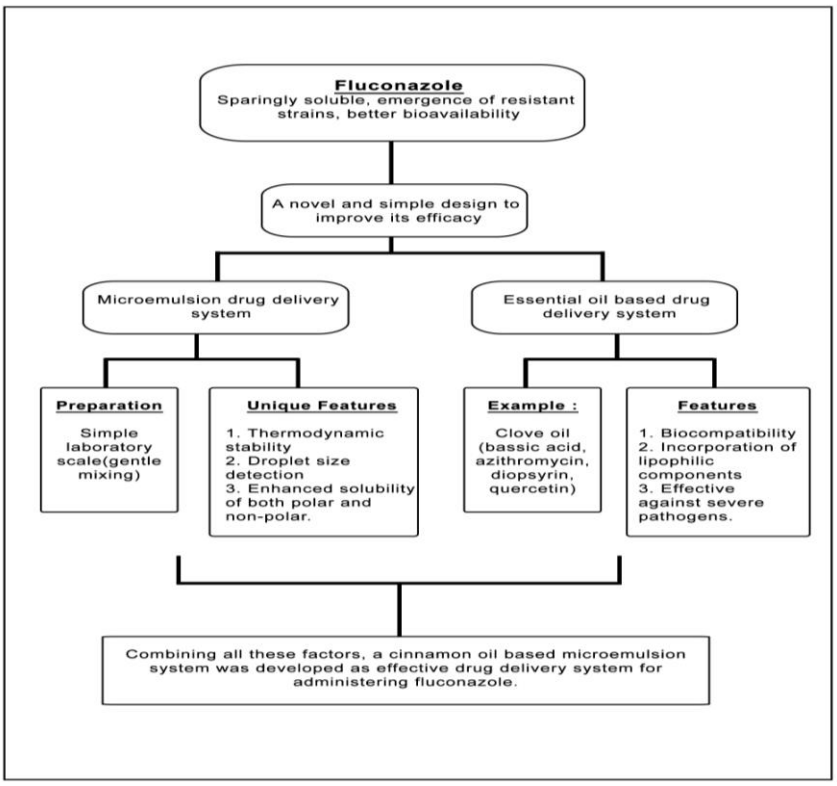

Fig. 1: Detailed study of fluconazole drug delivery system.

MATERIALS AND METHODS

Chemicals

Fluconazole was obtained from Morepen Laboratories Private Limited (Parwanoo, Himachal Pradesh, India). Tween 20 (Bioxtra) and cinnamon oil was obtained from Sigma Aldrich, India. Peppermint oil, castor oil and olive 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

The solubility of fluconazole in various lipophilic environments was determined by conventional equilibration method. The concentration of drug was analyzed using double beam UV–Visible spectrophotometer (UV–Vis Systronics-2201) after appropriate dilution with carbinol at 276 nm.

Microemulsion technique

Based on the highest solubilization of fluconazole in cinnamon oil, a minimum fixed concentration of the drug was loaded into the oil core (5%) and allowed to stand overnight for solubilization to occur. Followed by, addition of bio-based surfactant (tween 20) and water. After thorough mixing, the drug was completely encapsulated in the oil phase with no leakage into the water phase.

Stability

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 solubilization of water phase in the selected oily mixture was monitored quantitatively by measuring the electrical conductivity (σ) using conductivity meter (Elco CM 180). The measurements were performed in triplicates.

Viscosity

The viscosity of the microemulsion formulation was determined as such without dilution using Brookfield Viscometer (LVF model)-UL-Adapter with spindle set, Spindle # 2 at 25 ± 1 °C. Viscosity measurement was carried out in triplicates.

Droplet size

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

RESULTS

Solubility study

The lipophilic system plays an important role in maintaining the drug in its solubilized state. The solubilization potential of fluconazole in various oils are shown in Table 1.

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

Oils	Solubility (mg/ml)
Peppermint oil	1.58 ± 0.06
Olive oil	1.57 ± 0.05
Castor	1.07 ± 0.09
Cinnamon oil	140.41 ± 2.53

Microemulsion formation

The drug was solubilized in cinnamon oil initially. Optically clear, transparent and easily flowable microemulsion system was formed within few seconds, followed by, the addition of tween 20 and water respectively (5:25:70 v/v). This was done by gentle mixing with hand to bring the components together. The system was then subjected to characterization.

Stability

The drug-loaded cinnamon oil based microemulsion system was found physically stable for a period of one year with no phase separation, flocculation or coalescence. The formulation passed through all three stress tests and therefore said to demonstrate good thermodynamic stability.

Conductivity

The conductivity of the microemulsion system as determined by conductivity meter was 0.279 µS/cm. The conductivity study was based on percolation theory and this study clearly explains that our drug-loaded system was of oil-in-continuous type.

Viscosity

The viscosity of the drug-loaded system was 21 cPs as determined by viscometer. With increase in the surfactant concentration, the water molecules get trapped into the cross-linking portions of surfactant molecule. Therefore, the surfactant concentration has a positive correlation with the viscosity readings.

Droplet size

The droplet size diameter of the formulation was found to be in the range of 10–45 nm as measured by dynamic light scattering technique. Our result more or less coincides with our previous report of clove oil microemulsion encapsulation of the same drug. The size distribution analysis was taken without dilution as the microstructure may get altered.

CONCLUSION

Cinnamon oil based microemulsion is a novel drug delivery system for fluconazole with unique importance such as droplet size reduction, high solubilization potential and their applications as antimicrobials that would further enhance the activity of the drug with this new system.

ACKNOWLEDGEMENT

The authors thank the management of VIT University, Chancellor, for providing facility to carry out our research.

REFERENCES

1. Sheehan D, Hitchcock C and Sibley C. Current and Emerging Azole Antifungal Agents. Clin Microbiol Rev. 1999; 12: 40–79.
2. Nucci M and Marr KA. Emerging Fungal Diseases. Clin Infect Dis. 2005; 4: 521–6.
3. Rex JH, Rinaldi MG and Pfaller MA. Resistance of Candida species to fluconazole. Antimicrob Agents Chemother. 1995; 39: 1–8.
4. Brammer KW, Farrow PR and Faulkner JK. Pharmacokinetics and Tissue Penetration of Fluconazole in Humans. Clin Infect Dis. 1990; 12: 318–326.
5. Lawrence MJ and Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Deliver Rev. 2000; 45: 89–121.
6. Nirmala G, Padmini R and Rashmi M. Microemulsions For Topical Use– A Review. Ind J Pharm Edu Res. 2011; 45: 103–110.
7. Nirmala MJ, Mukherjee A and Chandrasekaran N. Improved efficacy of fluconazole against candidiasis using bio-based microemulsion technique. Biotechnol Appl Bioc. 2013; 00: 01–13.
8. Nirmala MJ, Mukherjee A and Chandrasekaran N. A bio-based approach in designing an oral drug delivery system for fluconazole. Int J Pharm Pharm Sci. 2013; 5(1): 273-275.

9. Sonia K, Anupama D. Microemulsion based Transdermal Drug delivery of Tea Tree Oil. Int. J. Drug Dev & Res. 2011; 3: 191–198.
10. Shinoda K and Saito H. The Stability of O/W Type Emulsions as Functions of Temperature and the HLB of Emulsifiers: The Emulsification by PIT- method. J. Colloid Interface Sci. 1969; 30: 258–263.
11. Singh HB, Srivastava M, Singh AB and Srivastava AK. Cinnamon bark oil, a potent fungitoxicant against fungi causing respiratory tract mycoses. Allergy. 1995; 12: 995–999.