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Research Article

AZITHROMYCIN: ESSENTIAL OIL BASED NANOEMULSION DRUG DELIVERY SYSTEM

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ABSTRACT

Azithromycin has a substantial potency against both gram-positive and gram-negative organisms due to the presence of a nitrogen atom in its ring. Due to bulky nature of the drug, it has limitations in the porin pathway and a very low bioavailability. Hence, we tried to work on a novel cinnamon oil based nanoemulsion drug delivery system for azithromycin using sonication technique at laboratory scale. Cinnamon oil, tween 80 and water were prepared at a ratio of 6:18:76 v/v to produce fine droplets in the range of 68.39 ± 2.19 nm after a sonication period of 30 min. Also, the polydispersity index confers better stability of the system as it recorded a lower value. Cinnamon oil was mainly chosen as it enhances the solubility to greater extent in azithromycin as it is highly lipophilic in nature. Moreover, the surfactant concentration was reduced greatly compared to other microemulsion systems. Hence, this system would be more efficient with mild or no toxic effects.

Keywords: Cinnamon oil, Surfactant concentration, Azithromycin, Nanoemulsion, Solubilization

INTRODUCTION

The macrolide antibiotic class is based upon the structure of erythromycin, the natural macrolide isolated from *Streptomyces erythreus.* Azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin) is a semi-synthetic macrolide antibiotic chemically related to erythromycin and clarithromycin [1]. It differs chemically from erythromycin by having an extra positive charge created by the presence of methyl-substituted nitrogen in the 15-membered macrolide ring. This results in substantially increased potency against Gram-negative bacteria. Azithromycin is stable at gastric pH and has an absolute bioavailability of approximately 37 percent following oral administration [2]. It acts by interfering protein synthesis in bacteria. Due to differences in the way proteins are made in bacteria and humans, it does not interfere with human protein synthesis. It binds to 50s rRNA subunit of 70s bacterial ribosome's, therefore, inhibits RNA-dependent protein synthesis. The peak plasma concentrations are achieved within 2 to 3 h [3]. It is absorbed when given orally to produce modest serum concentrations, but has very high tissue concentration due to its high penetration power and makes it sustain for a number of days [4]. In humans, it can be used in treating respiratory, skin, sexually transmitted diseases and pediatric otitis media infections [5]. Studies show that hydrophilic antibiotics below a certain size limit can cross the outer membranes of gram-negative bacteria through the water-filled channels of porins [6–7]. However, azithromycin is bulky and has a molecular weight of 747 that exceeds the exclusion limit of porins, suggesting that, it would not be efficiently taken up through the porin pathway [8].

So, due to the bulkiness, lipophilic properties and comparatively low bioavailability of azithromycin, its efficacy is lowered. To improve its efficacy, we tried to administer it through a newly famous nanoemulsion drug delivery system. Nano-emulsions (ultrafine emulsions or mini-emulsions) consist of very small emulsion droplets (< 300nm), commonly oil droplets in water. They are generally formulated through high-energy methods using specific devices like ultrasound generators or high pressure homogenizers that are able to supply enough energy to increase the water/oil interfacial area for generating nano-sized uniform droplets. Low-energy methods also allow the formulation of nano-emulsions, but by spontaneous emulsification without requiring any device or energy [9]. A characteristic feature of nanoemulsions is their kinetic stability. The major difference between microemulsions and nanoemulsions is that the former are thermodynamically stable, while the latter are not [10]. The oil used in this study is cinnamon oil (*Cinnamomum zeylanicum*). Experiments were already done in administering the same drug through essential oil based microemulsion system using clove oil [11,12]. But the morphology of droplets in nanoemulsion is uniform and perfectly spherical unlike microemulsion. In this study, we have reduced the surfactant concentration to a greater limit as increase may influence gastro-intestinal irritation. Our study is explained in simple terms using a flowchart in Fig. 1.

MATERIALS AND METHODS

Chemicals

Azithromycin was obtained from Aurobindo Pharma Limited, Hyderabad, India. Tween 80 (Bioxtra) and cinnamon oil was obtained from Sigma Aldrich, India. Eucalyptus 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 azithromycin's solubility in various oil systems were checked using the basic conventional equilibration method. The concentration of drug in the oil system were determined using double beam UV–Visible spectrophotometer (UV–Vis Systronics-2201) after diluting appropriately with ethanol at 215 nm.

Nanoemulsion formulation

The drug showed its highest solubilization in cinnamon oil, hence, the drug was dissolved in the oil and kept overnight and then centrifuged to ensure complete solubilization. Followed by addition of surfactant and water at a ratio of 6:18:76 v/v, and thus, a coarse emulsion were formed. This preparation was kept for sonication (Ultrasonics, USA) of 750 W (probe diameter=13 mm). This method uses high energy converting coarse emulsion to a nanometer ranged formulation i.e., nanoemulsion. In our lab, the blank counterparts of the system, i.e., drug-unloaded nanoemulsion system was standardized previously (the same methodology has been followed in this chapter) [13].

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 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) - 90Plus 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.

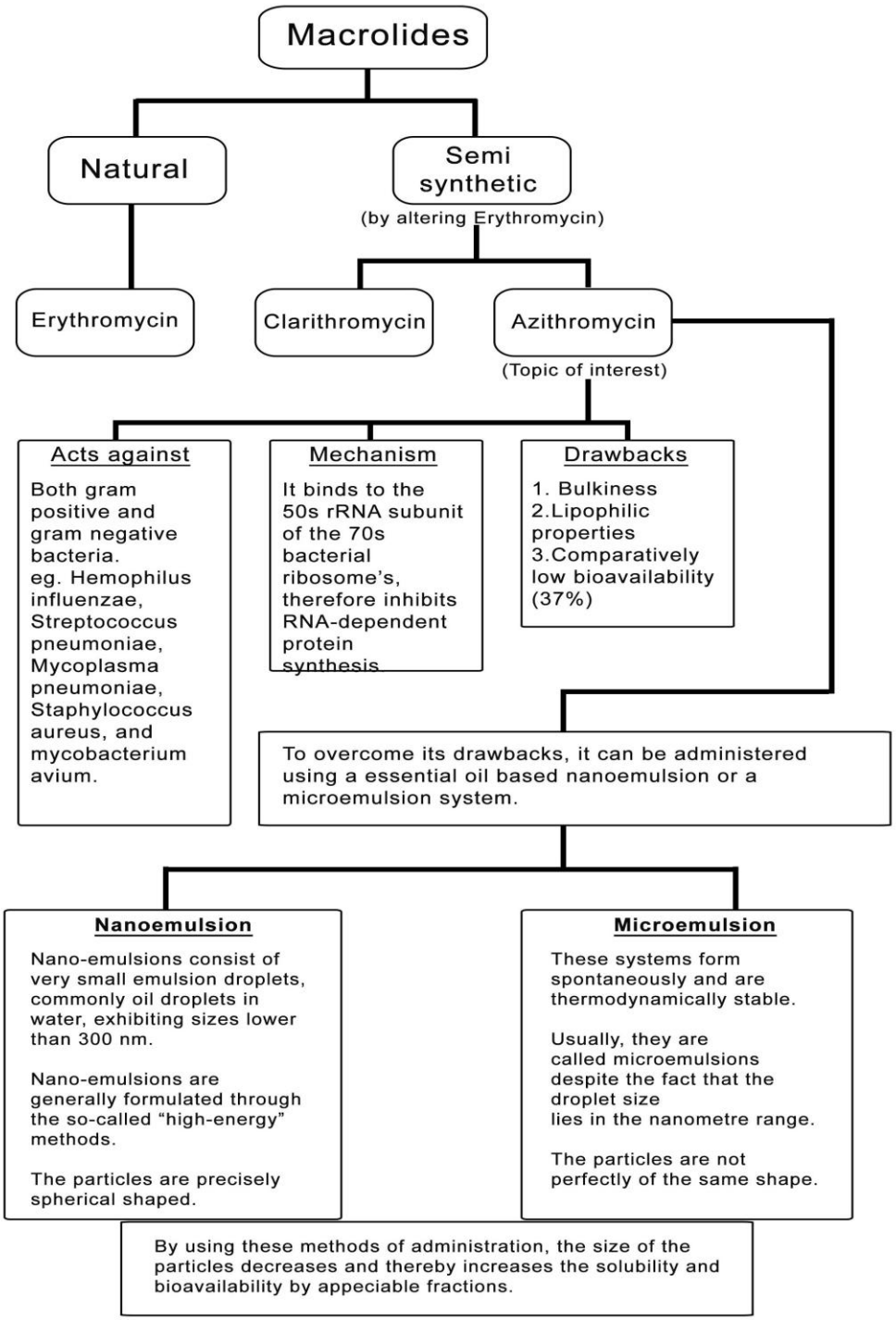

Fig. 1: Simple flowchart representation of our study plan for azithromycin

RESULTS

Solubility study

The solubilization capacity of azithromycin in different lipophilic system owing to the lipophilic nature of the drug is clearly depicted in Table 1.

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

Oils	Solubility (mg/ml)
Eucalyptus oil	0.66 ± 0.03
Olive oil	0.02 ± 0.01
Cinnamon oil	64 ± 2.45

Stability

The drug-loaded cinnamon oil based nanoemulsion system of ours have undergone all three stages of stress tests and was found to exhibit better stability i.e., the sample experienced no phase separation, flocculation or coalescence.

Conductivity

The conductivity of the nanoemulsion system as determined by conductivity meter was recorded to be 0.130 ± 0.13 μS/cm.

Droplet size and polydispersity index measurement

The mean droplet size of our formulation was recorded to be 68.39 ± 2.19 nm as measured by dynamic light scattering technique. The polydispersity index was found to be 0.158 ± 0.07; this confers more uniformity in size distribution and their stability.

CONCLUSION

The nanoemulsion drug delivery system for azithromycin was developed using cinnamon oil, tween 80 and water. This system has reduced the surfactant concentration as compared to the microemulsion system to a greater extent using ultrasonication technique that may further influence in the reduction of gastrointestinal irritation.

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