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Research Article

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

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ABSTRACT

Ramipril is a good angiotensin converting enzyme (ACE) inhibitor. This drug is found to be poorly aqueous insoluble due to its lipophilic nature. But the efficacy of the drug directly depends on the solubility. Hence, we tried to improve on the solubility using a new lipophilic environment. Our novel microemulsion drug delivery system for ramipril was formulated using cinnamon oil, tween 20 and water (6:30:64 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 9-48 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 ramipril.

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

INTRODUCTION

By many surveys and estimates, up to 40 percent of new chemical entities (NCEs) discovered by the pharmaceutical industry today and many existing drugs are poorly soluble or lipophilic compounds. The lipophilic nature of many drugs leads to poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality. In recent years, much attention has focused on lipid-based formulations to improve the oral bioavailability of poorly water soluble drug compounds. The most popular approach is the incorporation of the active lipophilic component (drug) into inert lipid vehicles such as oils, surfactant dispersions, microemulsions, nanoemulsions, self-microemulsifying formulations, emulsions and liposomes. Most of these methods increase surface area of the drugs to improve solubilization behaviour, as well as permeation [1]. We worked on one such drug, Ramipril, which exhibits similar pharmacodynamic properties to captopril and enalapril. Like enalapril, it is a prodrug that is hydrolyzed after absorption forming the active metabolite ramiprilat which has a long elimination half-life and permits once daily administration [2–3]. The renin angiotensin system (RAS) plays a significant physiological role in maintaining blood pressure and fluid balance in the human body. Ramipril [(2S, 3aS, 6aS)-1[(S)-N-[(S)-carboxy-3- phenylpropyl] alanylocta-hydrocyclopenta[b] pyrrole-2- carboxylic acid, 1-ethyl ester], an effective inhibitor of angiotensin converting enzyme (ACE), prevents the conversion of AT I (Angiotensin I) to AT II. It is effective in patients suffering from hypertension, myocardial infarction, stroke, congestive heart failure and also acts as an antiproteinuric agent in children with chronic renal failure [4]. Being a highly lipophilic compound (log p octanol/water, 3.32), pose few drawbacks like relatively low oral bioavailability of 28–30% due to its poor aqueous solubility. This may result in dissolution related problem and low absorption and therefore the efficacy may be greatly reduced [5].

Due to the drawbacks stated above such as low solubility and low oral-bioavailability, we tried to design an essential oil based microemulsion system as a drug delivery vehicle. A microemulsion typically consists of oil, surfactant and water in required and optimized proportions. These are clear, stable and isotropic mixtures [6]. Microemulsions can be formed upon simple mixing of the components and do not require high energy conditions. The advantages of using a microemulsion are spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, improved drug solubilization of hydrophobic drugs and bioavailability [7]. There are many essential oils that can be used to make microemulsions. For eg., clove oil, mustard oil, tea tree oil, coconut oil, cinnamon oil (*Cinnamomum zeylanicum*) [8–11]. We carried on this study using cinnamon oil, as ramipril showed good solubility in it. A detailed study of ramipril and administering it using a novel essential oil based microemulsion drug delivery system is shown in Fig.1.

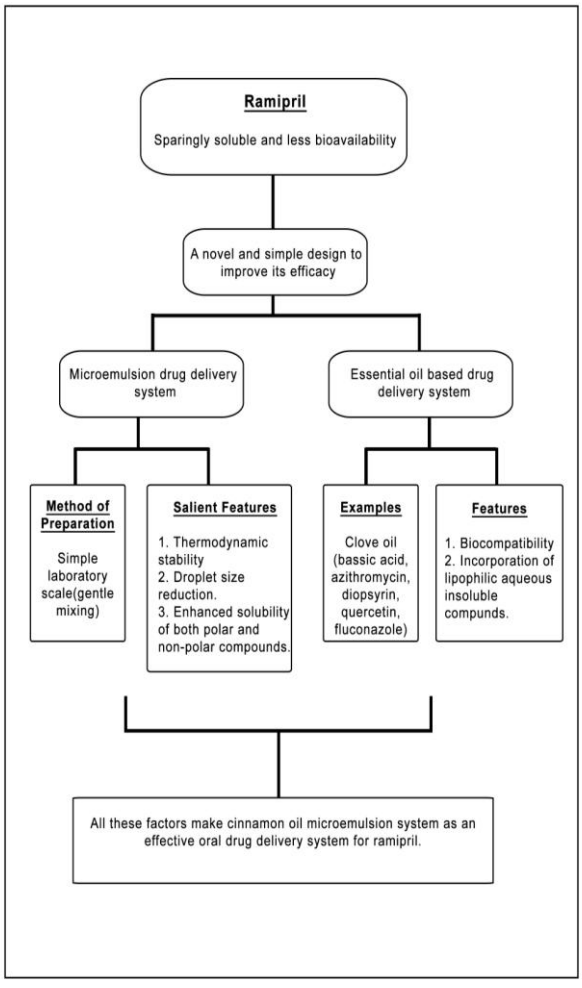

Fig. 1: Detailed study of ramipril drug delivery system.

MATERIALS AND METHODS

Chemicals

Ramipril 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 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 ramipril in various lipophilic environments was determined by conventional equilibration method. A double beam UV–Visible spectrophotometer (UV–Vis Systronics-2201) was used for the analysis of concentration of drug. The required readings were taken after appropriate dilution with methanol at 210 nm.

Microemulsion technique

Based on the highest solubilization of ramipril in cinnamon oil, a minimum fixed concentration of the drug was loaded into the oil core (6%) 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

Using Brookfield Viscometer (LVF model)-UL-Adapter with spindle set, Spindle # 2 at 25 ± 1 °C, viscosity measurements was carried out in triplicates. The readings were taken without dilution.

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 drug is maintained in the solubilized state due the lipophilic system used. The solubilization potential of ramipril in various oils are shown in Table 1.

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

Oils	Solubility (mg/ml)
Peppermint oil	0.014 ± 0.02
Olive oil	0.067 ± 0.04
Cinnamon oil	80.25 ± 0.04

Microemulsion formation

Initially, the drug was solubilized in cinnamon oil. Optically clear, transparent and easily flowable microemulsion system was formed within few seconds. Then we added tween 20 followed by water (6:30:64 v/v). This was done by gentle mixing with hand to bring the components together. The system was then subjected to characterization.

Stability

Without any phase separation, flocculation or coalescence, the drug-loaded cinnamon oil based microemulsion system was found physically stable for a period of one year. The formulation is said to demonstrate thermodynamic stability, as it passed through all three stress tests.

Conductivity

The conductivity of the microemulsion system as determined by conductivity meter was 0.283 µS/cm. The conductivity study was based on percolation theory and this study clearly explains that our drug-loaded system was of oil-in-water continuous type.

Viscosity

As determined by viscometer, the viscosity of the drug-loaded system was 32 cPs. 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

As measured by dynamic light scattering technique, the droplet size diameter of the formulation was found to be in the range of 9–48 nm. This result almost 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 ramipril with high solubilization potential and droplet size reduction. Thus, improved bioavailability would enhance the activity of the drug with this new system.

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