ABSTRACT

The main purpose of this work was to develop a microemulsion formulation for enhancing the bioavailability of isotretinoin. A Captex-355®, based microemulsion formulation with Cremophor EL® as surfactant and ethanol as cosurfactant was developed for oral delivery of isotretinoin. Phase behavior and solubilization capacity of the microemulsion system were characterized, and in vitro oral absorption of isotretinoin from the microemulsion was investigated. A single isotropic region, which was considered to be a bicontinuous microemulsion, was found in the pseudoternary phase diagrams developed at various Cremophor EL: Ethanol: Captex-355 ratios. With the increase of Cremophor EL concentration, the microemulsion region area and the amount of water and Captex-355 solubilized into the microemulsion system increased; however, the increase of ethanol percentage produced opposite effects. The microemulsion system was also investigated in terms of other characteristics, such as interfacial tension, viscosity, pH, refractive index, in vitro diffusion and droplet size analysis. Isotretinoin, a poorly soluble drug, displayed high solubility in a microemulsion formulation using Captex-355 (5%), Cremophor EL (28%), Ethanol (7%), and water (60%). The in vitro diffusion study revealed an increase of bioavailability (38.56 times) after in vitro drug diffusion analysis of the microemulsion formulation as compared with the commercially available soft gelatin capsules.

Key Words: Microemulsion, nonionic surfactant, conductivity, interfacial tension, droplet size
INTRODUCTION

Isotretinoin, a synthetic retinoic acid derived from retinoids, is the most widely used for treatment of severe recalcitrant cystic acne. It is effective in the treatment of keratinization disorders, cutaneous T-cell lymphoma, leukoplakia; prevention of skin cancer in patients with xeroderma pigmentosum.

In this study the use of a microemulsion to improve the extent of absorption and the overall bioavailability was investigated. This novel drug delivery system has been reported to improve the rate and extent of absorption of lipophilic drugs. Microemulsions are homogeneous, transparent, thermodynamically stable dispersions of water and oil, stabilized by a surfactant, usually in combination with a cosurfactant (typically a short-chain alcohol). As pharmaceutical drug delivery systems, microemulsions have many advantages, including clarity, high stability, and ease of preparation.

In the present study, a microemulsion was prepared using the non-ionic surfactant, (Cremophor EL), Ethanol (as cosurfactant), Captex 355, and water. Pseudoternary phase diagrams were constructed to find out the zone of microemulsion at different ratios of surfactant to cosurfactant (eg. 4:1 and 3:1). The effect of formulation variables on different physicochemical characteristics such as globule size, electroconductivity, and viscosity was studied. An ex vivo diffusion study was performed using rat duodenum, and the pharmacokinetics of the optimized microemulsion were evaluated by administering it orally to rats. The absolute and relative bioavailability was calculated after intravenous injection of a commercially available formulation (Accutane, Roche, US) and oral administration of a commercial soft gelatin capsule (Sotret, Ranbaxy, US), respectively.

MATERIALS AND METHODS

Materials

Cremophor EL (macrogol/glycerol ricinoleate 35) was gift of BASF, Germany, Ethanol, and Captex 355 (medium-chain triglyceride) was gift of Abitec corp. Isotretinoin was a gift from Ranbaxy Laboratories Ltd. (Tonsa, India). Analytical-grade sodium bicarbonate, High Performance Liquid Chromotography (HPLC)-grade hexane, ethyl acetate, glacial acetic acid and methylene chloride was purchased from (Rankem, India). All other chemicals used were of analytical reagent grade and used as received without further purification. Double-distilled water was used throughout the study.

Preparation of Microemulsion Formulation

Liquid microemulsions were prepared by dissolving Cremophor EL in Ethanol. Isotretinoin and Captex 355 were then dissolved, followed by gentle mixing with distilled water. The monophasic formulations were formed spontaneously at room temperature. The final concentration of isotretinoin in the microemulsions was 1%.

Construction of Phase Diagrams

Pseudoternary phase diagrams were constructed to examine the formation of oil in water microemulsions using 4 components: oil, surfactant, cosurfactant, and aqueous phase system. The 4-component system consisted of (1) a medium-chain fatty acid–based triglyceride (Captex 355); (2) a cosurfactant (Ethanol); (3) a surfactant (Cremophor EL); and (4) double-distilled water (aqueous phase). Pseudoternary
phase diagrams were constructed keeping the ratio of Cremophor EL and Ethanol constant and varying the remaining 2 components. For convenience, the phase diagrams were constructed by drawing “water dilution lines” representing increasing water content and decreasing surfactant-cosurfactant levels. The water was titrated along dilution lines drawn from the surfactant-cosurfactant apex (100% surfactant-cosurfactant) to the opposite oil side of the triangle. The line was arbitrarily denoted as the value of the line intersection with the oil scale (eg, 20:80, 30:70). If turbidity appeared followed by a phase separation, the samples were considered to be biphasic. If clear and transparent mixtures were visualized after stirring, the samples were considered monophasic. The samples were marked as points in the phase diagram. The area covered by these points was considered to be the microemulsion region of existence.

Physicochemical Evaluation

1 Particle Size Measurements
2 Viscosity
3 Electroconductivity Study
4 Refractive Index and Percent Transmittance
5 In vitro Intestinal Permeability Studies
6 In vivo Absorption Study
7 HPLC Analysis of Plasma Sample
8 Pharmacokinetic Data Analysis
9 Statistical Analysis

CONCLUSION

The study demonstrates that the microemulsion formulation can be employed to improve the bioavailability of a poorly absorbed drug. The ratio of Cremophor EL: Ethanol: Captex 355 played a major role in formulating the microemulsion. The optimum microemulsion formulation contained Captex 355 (5%), Cremophor EL (28%), Ethanol (7%), and water (60%), which was a transparent and less viscous system. After oral administration in rats, the microemulsion showed an absolute bioavailability of 29.7%, which is 14.6 times higher than that of commercially available soft gelatin capsules (Accutane and Sotret).

REFERENCES:

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