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Phase Behaviour of Microemulsion Systems Containing Short-Chain Alcohols as Co-Surfactant

Kosürfaktan Olarak Kısa Zincirli Alkol Içeren Mikroemülsiyon Sistemlerin Faz Hareketleri

Gülten Kantarcı[1], H. Yeşim Karasulu[2], Işık Özgüney[2] and Tamer Güneri[2]

University of Ege, Faculty of Pharmacy, Departments of [1]Pharmaceutical Biotechnology [2]Pharmaceutical Technology 35100 Izmir, Turkey

Abstract

The purpose of this study was to develop several microemulsion (w/o) formulations and to examine the effects of different types of alcohols as co-surfactants. Phase diagrams were constructed at 25°C to investigate the phase behaviour of systems containing water, soy-bean oil, surfactants (S) (Brij 58, Span 80) and co-surfactants (Cos) (ethanol, isopropyl alcohol, 1-butanol, 1-propanol). Comparing the phase diagrams, it was seen that the microemulsion region for all co-surfactants examined was much larger when 1-butanol was used. To investigate the possibility of loading drug in microemulsion systems, diclofenac sodium was employed as a model compound.
It was proposed that, microemulsion systems could be used as peroral and topical drug carriers. Therefore, microemulsion formulations containing appropriate amounts of water were suggested as optimal microemulsion formulation for loading hydrophilic drugs and microemulsions containing 6:1 (S/Cos) ratio of ethanol and 4:1(S/Cos) ratio of isopropyl alcohol were selected as the optimal formulations.

Key words: w/o microemulsions; phase diagrams; effect of cosurfactants; Brij 58; Span 80; diclofenac sodium

Introduction

In the past twenty-five years, microemulsions have been the focus of worldwide extensive research due to their importance in a variety of technological applications (Park *et al.*, 1999, Paul *et al.*, 1997, Phee *et al.*, 2001).Microemulsions, which form spontaneously upon mixing appropriate proportions of water, oil, surfactant and a sparingly water-soluble alcohol, are appropriate systems for the solubilization of both water-soluble and oil insoluble compounds.

Microemulsions may constitute an important component of pharmaceutical formulations of drug combinations that otherwise would be insoluble in other systems. Several drug

groups, including steroids, β-blockers, non-steroidal anti-inflammatory agents, and other drugs of different hydrophobic/hydrophilic balances have been incorporated into microemulsion systems (Olivera *et al.*, 1997). Microemulsions are expected to be easy to administer for children and people who have difficulty in swallowing solid dosage forms. Besides, they offer several benefits for peroral administration including increased absorption benefits and clinical potency and decreased toxicity (Ho *et al.*, 1996).

The majority of microemulsions are produced in the presence of co-surfactants of which the most commonly used are low molecular weight alcohols (Comelles *et al.*, 1996, Lawrance *et al.*, 2000, Park *et al.*, 1999). Microemulsions have been used mainly for peroral delivery of peptides and have also been reported as drug carriers for topical, dermal, transdermal and pulmonary administrations of drugs. Microemulsions have also great potential as i.v. vehicles for sparingly soluble substances by virtue of their high solubilization capacity (Corswant *et al.*, 1998).

In the present work, the phase properties of pseudo-ternary systems containing polyethylene alkyl ethers and sorbitan esters as non-ionic surfactants and a new w/o microemulsion formulation were developed and optimized for peroral and transdermal delivery. The main aim of this paper was to compare the influence of the type of co-surfactant on the phase properties.

Materials and Methods

Materials: Soybean-oil was purchased from Sigma Chemicals Ltd. Brij 58, Span 80, absolute ethanol, isopropyl alcohol, 1-propanol and 1-butanol were obtained from Merck-Co., Inc.

Preparation of w/o microemulsions: Soybean-oil was used as the oil phase and Brij 58 and Span 80 were the surfactants. Absolute ethanol, isopropyl alcohol, 1-propanol and 1-butanol were used as co-surfactants. To investigate the microemulsion formation regions, phase diagrams were constructed by titration of a series of surfactant/co-surfactant (S/Cos) mixtures with water at 25°C. The boundaries of the microemulsion domains were determined for different values of the surfactant/co-surfactant (w:w) ratios. The surfactant/co-surfactant weight ratios of 1/1, 2/1, 3/1, 4/1, 5/1 and 6/1 were used and Span 80: Brij 58 weight ratio was 9:1.

For the microemulsion formulations, surfactants were mixed and melted at 60°C, then added to the appropriate amount of soybean oil. Co-surfactant was added into this mixture and the obtained mixture was named as mixture A. Phase studies were carried out by titrating slowly with distilled water while stirring mixture A with a stirring bar using a magnetic stirrer (IKA Labortechnik) (9 rpm) until turbidity was observed. Pseudoternary phase diagrams were constructed to obtain the components, and their concentration ranges that can result in large existence areas of microemulsions. The ideal surfactant:co-surfactant weight ratios and microemulsion areas were detected by the aid of phase diagrams drawn using a computer programme developed in the Computer Center, Faculty of Pharmacy, University of Ege. The optimum microemulsion formulation was developed using the gravity center of the microemulsion formation area. Diclofenac sodium was dispersed in the microemulsion by stirring at the last stage.

Droplet size determinations: Optimum microemulsion formulations were selected, and the sizes of the droplets in the microemulsions were determined using Zeta Seizer (Malvern HPPS).

Results and Discussion

Non-ionic surfactants are generally used in pharmaceutical and cosmetic products. They are compatible with the other three classes of surfactants and retain this utility over a broad range of pH values. Therefore, non-ionic surfactants Brij 58 and Span 80 were selected to prepare the microemulsions.

In preliminary studies, stable microemulsions could not be prepared by using Brij 58 and Span 80 alone or in a mixed form and co-surfactant is needed besides surfactants (Comelles *et al.*, 1996). It was reported that the surfactants that are too hydrophilic or lipophilic are inappropriate for the formation of microemulsions, even with the aid of co-surfactants. Therefore, Span 80 and Brij 58 were studied with 9:1 ratio and a HLB value of 5.44 was obtained.

As shown in Figs. 1 and 2, when ethanol and isopropyl alcohol were used as co-surfactants, the existence area of the microemulsion became enlarged as S/Cos ratio increased.

The distribution of alcohols is dependent on their partition coefficients. Most probably, more hydrophilic alcohols distribute mainly in between the aqueous and the interfacial layers. The hydrophobic alcohols would be expected to distribute primarily between the oil and the interfacial layer (Ho *et al.*, 1996). Comparing the phase diagrams, it was observed that the microemulsion regions for all co-surfactants examined were much larger when 1-butanol was used. Since the solubility of 1-butanol was intermediate in water, it was expected to partition preferentially toward the interfacial layer. As a result, the increased number of butanol molecules at the interface increases the flexibility of the interface and the addition of short-chain alcohols as co-surfactants was able to reduce interfacial free energy and tension by their incorporation into the interfacial layer.

Microemulsion formulations containing appropriate amounts of water were suggested as optimal microemulsion formulations for loading drugs. Hence, microemulsions contain 6:1 S/Cos and 4:1 S/Cos ratios for ethanol and isopropyl alcohol respectively, were selected as optimal for this aim, and their droplet sizes were measured and diclofenac sodium was loaded into these microemulsions. On addition of diclofenac sodium, no opalescence was observed, indicating that these systems retained their stability when the drug was added.
The mean droplet diameters of these microemulsions without diclofenac sodium but with 4:1(S/Cos) ratio of isopropyl alcohol and 6:1 (S/Cos) ratio of ethanol were determined as 11.7 and 13.34 nm, whereas with diclofenac sodium these were 9.19 and 10.96 nm respectively.

The particle size distributions of microemulsion formulations with and without diclofenac sodium are shown in Fig 5. The mean droplet size of microemulsions loaded diclofenac sodium decreased when compared to the mean droplet size of microemulsions without

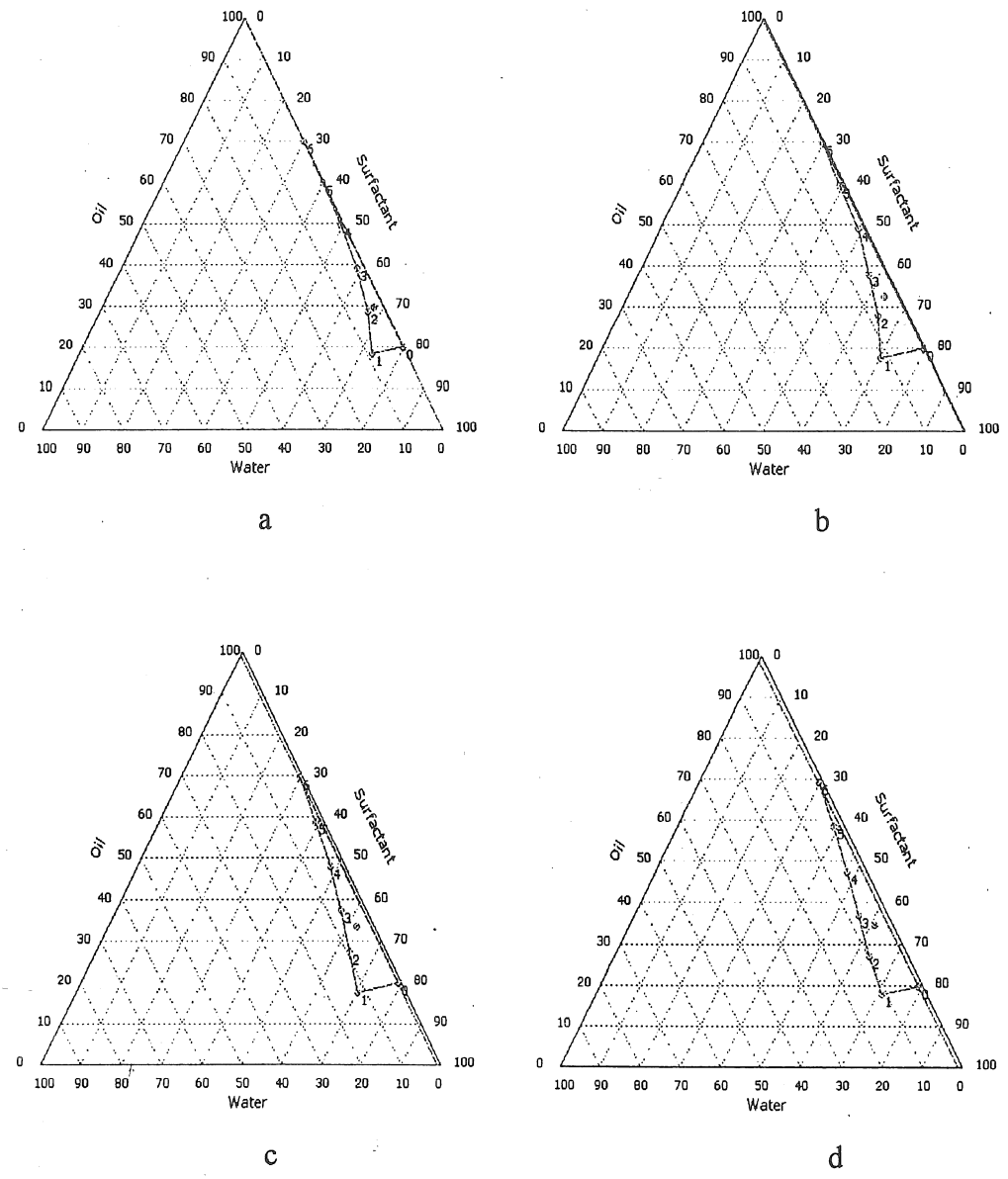


Fig.1. Phase diagrams of microemulsion systems containing soybean oil/water/ surfactant / EtOH (a) 3:1 S/Cos (b) 4:1 S/Cos (c) 5:1 S/Cos (d) 6:1 S/Cos

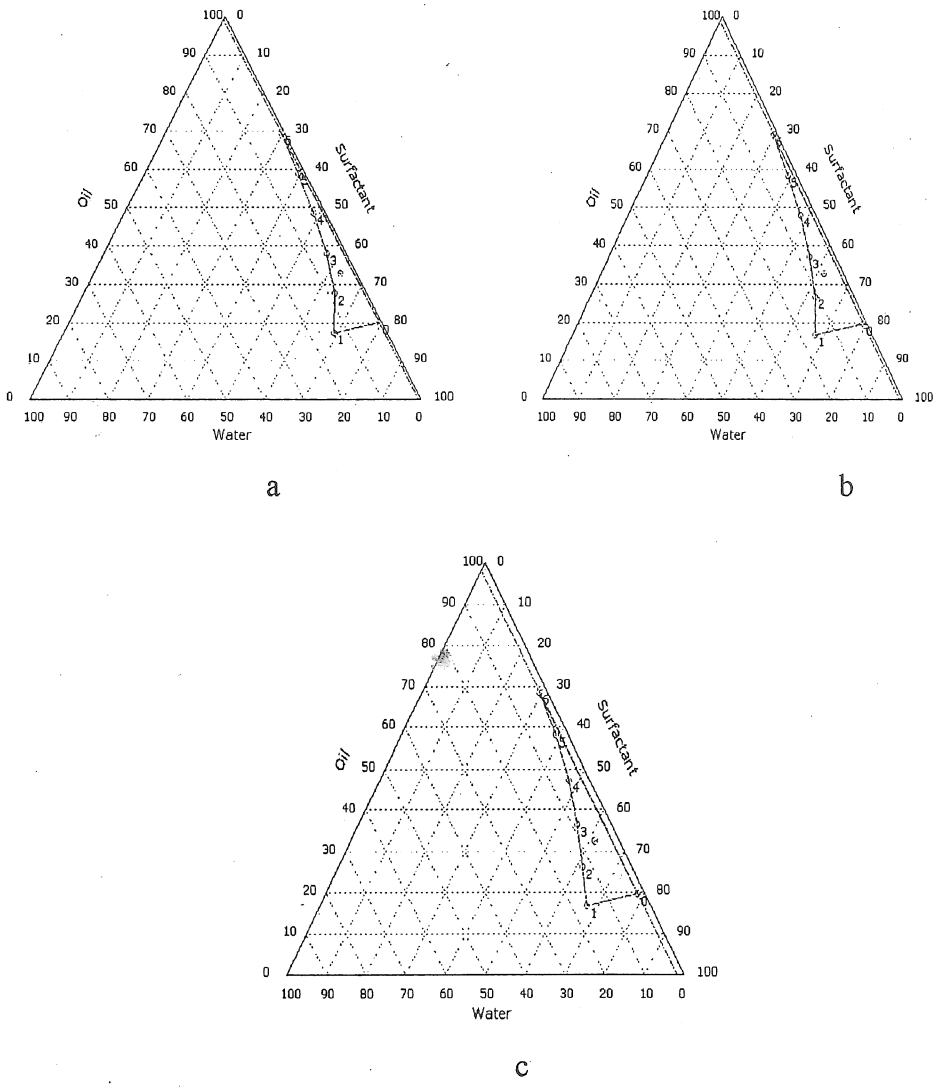
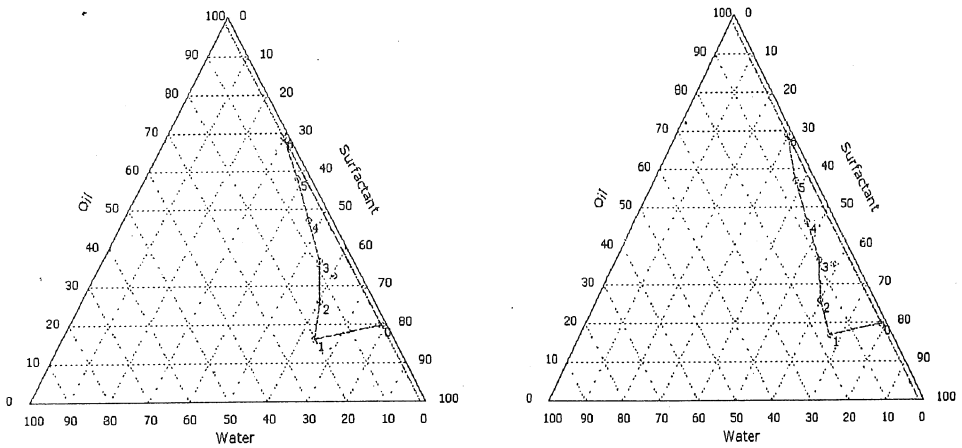
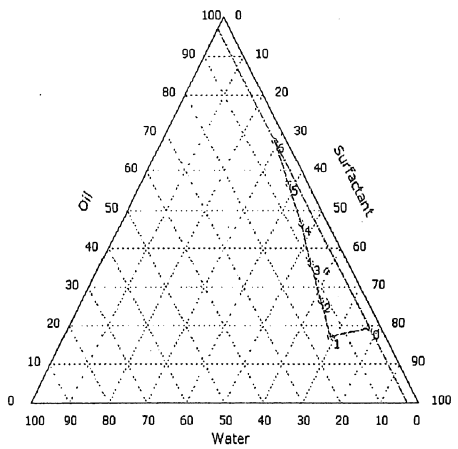


Fig.2. Phase diagrams of microemulsion systems containing soybean oil/water/ surfactant / isopropyl alcohol (a) 3:1 S/Cos (b) 4:1 S/Cos (c) 5:1 S/Cos



a

b



c

Fig.3. Phase diagrams of microemulsion systems containing soybean oil/water/ surfactant / butanol (a) 3:1 S/Cos (b) 4:1 S/Cos (c) 5:1 S/Cos

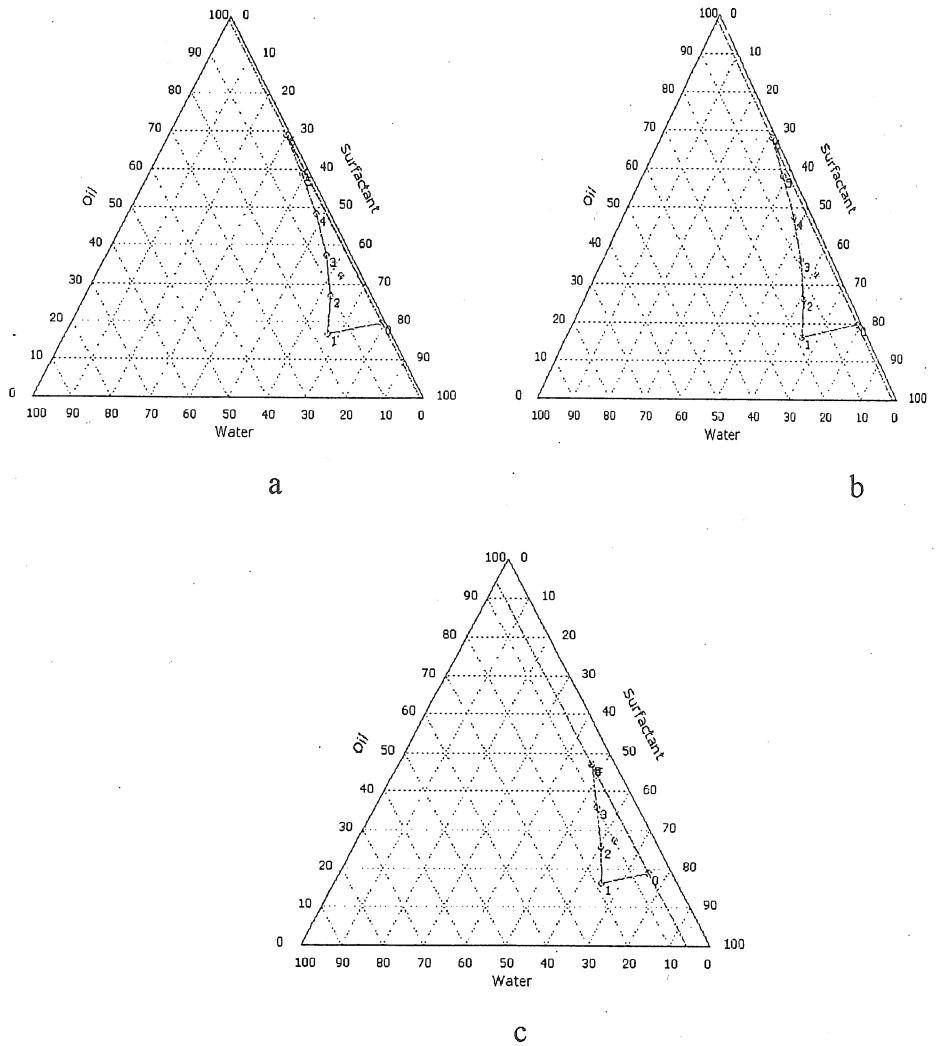


Fig.4. Phase diagrams of microemulsion systems containing soybean oil/water/ surfactant / propanol (a) 3:1 S/Cos (b) 4:1 S/Cos (c) 5:1 S/Cos

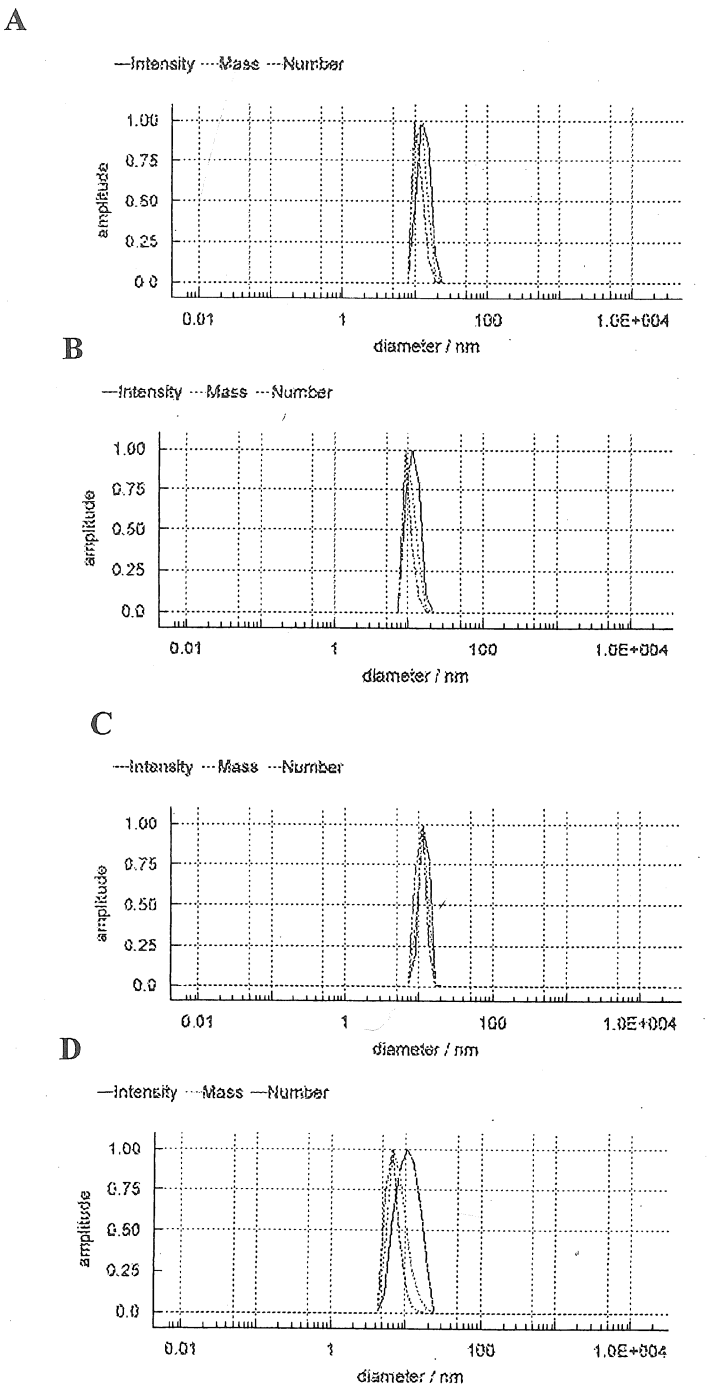


Fig. 5 The droplet size distribution of microemulsions prepared with **A**) ethanol **B**) ethanol and loaded diclofenac sodium **C**) isopropyl alcohol **D**) isopropyl alcohol and loaded diclofenac sodium acted

drug. Currently, it was not clear by which mechanism the droplet size decreased. However, the two possibilities considered can be: a) A certain portion of undissolved drug could have as an emulsifying agent by the deposition of drug particles at the interface of the microemulsion b) By the deposition of drug at the interface of the microemulsion, the reduced motility of the surfactant was thought to decrease the particle size of drug-loaded microemulsions as was demonstrated previously (Park *et al.*, 1999).

Özet

Bu çalişmanin amaci çeşitli (s/y) mikroemülsiyon formülasyonlari geliştirmek ve kosürfaktan olarak çeşitli alkol tiplerinin etkilerini araştirmaktir. faz diyagramlari, su, soya yağı, sürfaktan (s) (brij 58, span 80) ve kosürfaktan (cos) (etanol, izopropil alkol, 1-butanol, 1-propanol) içeren sistemlerin faz davranişlarini incelemek için 25°c de çizildi. faz diyagramlarinin incelenmesi sonucunda, araştirilan kosürfaktanlar arasinda en geniş mikroemülsiyon bölgesini 1-butanolün verdiği bulundu. Mikroemülsiyon sistemlerine ilaç yükleme olasiliğini araştirmak için , diklofenak sodyum model madde olarak seçildi. mikroemülsiyon sistemler, peroral ve topikal ilaç taşiyici sistemler olarak önerilmişlerdir. bu nedenle, hidrofilik ilaçlari yüklemek için en uygun miktarda su içeren mikroemülsiyon formülasyonlari optimal formülasyonlar olarak önerilir. bu yüzden 6:1 (s/cos) etanol ve 4:1(s/cos) izopropil alkol kullanilarak hazirlanan mikroemülsiyon formulasyonlari optimal formülasyonlar olarak seçilmiştir.

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