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Assigning the components of a Self-Nanoemulsifying Drug Delivery System (SNEDDs) of Deferasirox

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1. Introduction

Deferasirox (DFR) is an oral tridentate iron chelator effective for reduction of body iron in iron-overloaded patients with transfusion-dependent anemias [1]. It is a highly lipophilic molecule (log P: 3.52) which is classified as BCS Class II drug substance [2].

Self-nanoemulsifying drug delivery systems (SNEDDs) are isotropic mixtures of drug, oil and hydrophilic surfactants and co-surfactant/co-solvents. In recent years, SNEDDs gained more attention in the solubility enhancement of lipophilic molecule hence enhancing their oral bioavailability. The selection of appropriate components in the SNEDDs formulation is crucial for development of a successful formulation.

The goal of this work is to select and to screen appropriate components for the optimization of DFR loaded SNEDDs formulations. In this respect, different SNEDDs formulations were prepared and pseudo-ternary phase diagrams were constructed.

2. Materials and Methods

2.1. Materials

Deferasirox (Sanovel İlaç A.Ş., Turkey) Labrafac Lipophile WL1349, Labrafac PG, Peceol, Transcutol, Labrasol ALF, Labrafil M2125, Maisine, Gelucire 44/14 and Gelucire 48/16 were gifted from Gattefosse (France). Kolliphor PS20, Kolliphor PS60, Kolliphor PS80, Kolliphor CS12 and Kolliphor HS15 were gifted from BASF (Germany). All other chemicals were of analytical grade.

2.2. Solubility study

The saturation solubility of DFR in different oils, surfactants, and co-surfactants were determined by using shake flask method; an excess amount of DFR was added to 1 ml of each of vehicle in Eppendorf tube, then stirring by using a vortex mixture to facilitate solubility of drug, sealed vials were kept on orbital shaker at 37.0 ± 0.5 °C for 48 hours to attain equilibrium, the equilibrated sample was centrifuged at 5,000 rpm for 15 min. Solution was appropriately diluted and UV absorbance values were measured at wavelength 245 nm. Concentration of dissolved drug was calculated by using standard equation previously prepared.

2.3. Construction of Pseudo-Ternary Phase diagrams

Surfactant and co-surfactant were mixed (Smix) in different weight ratios (1:1, 1:2, 2:1, 3:1, 4:1), for each phase diagram, specific Smix ratio was mixed with oil in different ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1). The all oil/Smix mixtures were titrated in a separated glass vials with purified wa-

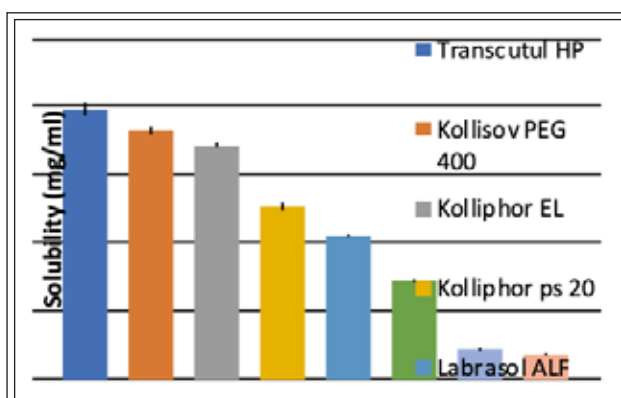


Figure 1 Solubility of DFR in different oils, surfactants and co-surfactants

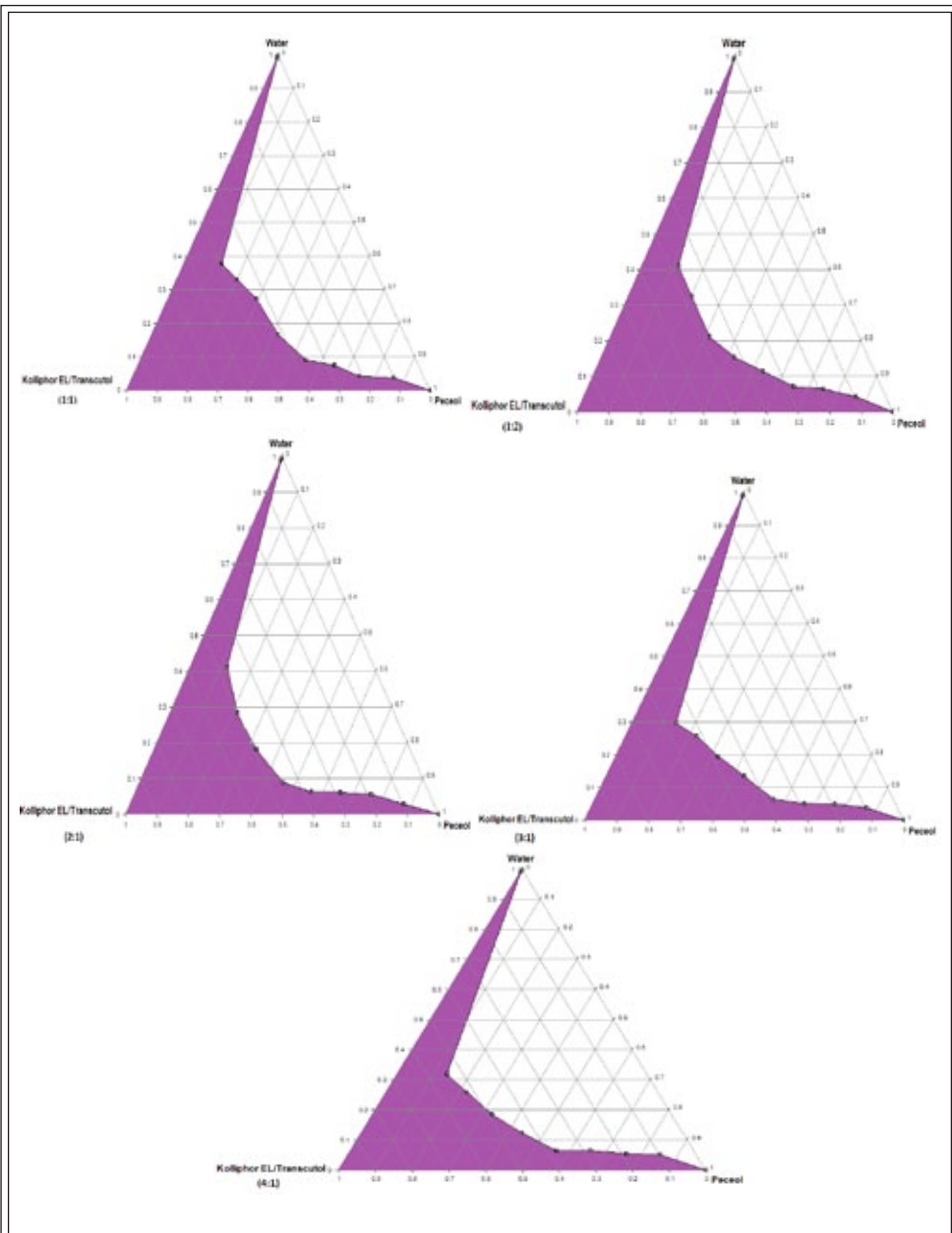


Figure 2 Pseudo-Ternary Phase diagrams of Peceol, Kolliphor EL and Transcutol at Smix ratios (1:1, 1:2, 2:1, 3:1 and 4:1. The colored region represents the nanoemulsion formation region.)

ter drop by drop and vortexed at room temperature, observations by naked eye for any turbidity or phase changes were reported and the weight of the water recorded. Pseudo-Ternary Phase Diagrams were constructed by using Prosim Ternary phase diagram software (Strategie, Cedex, France)

2.4. SNEED Formulations formation assessment

For checking nanoemulsion formation; each oil and Smix ratio previously prepared for pseudo-ternary diagram preparation was evaluated for

the formation of nanoemulsion by diluting 50 mg of each mixture to 50 ml with purified water and checked visually for the formation of nanoemulsion (3). Mixtures that showed nanoemulsion formation; stable and transparent dispersions were subjected for droplet size measurement and Polydispersity index (PDI) by using Zetasizer Nano ZS (Malvern Instrument)

3. Results

3.1. Solubility study

The solubility of DFR in different oils, surfactants and co-surfactants are shown in *Figure 1*. DEF has the highest solubility in Peceol as oil, Kolliphor EL as Surfactant and Transcutol HP as co-surfactant, which were chosen for further investigations.

3.2. Pseudo-ternary phase diagrams

The importance of pseudo-ternary phase diagram construction is

to identify the appropriate concentrations of oil (Peceol), surfactant (Kolliphpor EL) and cosurfactant (Transcutol HP) for the formulation of stable SNEDDs formulation.

The curves show that increasing surfactant proportion in Smix led to increase the region of nanoemulsion formation.

3.3. SNEED Formulations formation assessment

As shown in Table 1, five combinations showed droplet size less than 30 nm and PDI less than 0.3,

Table 1 Droplet size and PDI for candidate combinations

Combination : (Peceol, Kolliphor EL, Transcutol HP (w/w%))	Droplet size (nm)	PDI
P1(10%, 45%, 45%)	20.46	0.149
P2 (10%, 30%, 60%)	21.49	0.201
P3 (10%, 60%, 30%)	15.71	0.042
P4 (10%, 67.5%, 22.5%)	15.30	0.152
P5 (10%, 72%, 18%)	15.31	0.1

means that these combinations can be self emulsified under dilution and will be the candidates for uploading DEF.

4. Conclusions

The components of SNEEDs of DFR were identified and five successful combinations were prepared by using Peceol, Kolliphor EL and Transcutol HP. These five combinations will be upload-

ing with DFR and subjected for characterization and stability tests.

5. Acknowledgements

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