W4061

Understanding capsule compatibility with lipid-based formulations: 1. Microstructural formulation changes with aqueous dilution and comparison to percolation theory

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BACKGROUND

Lipid-based formulations (LBFs) have become a key technology for oral delivery of poorly-soluble drugs [1] but are also important delivery systems for low-dose drugs or labile compounds such as peptides [2,3]. Depending on the given delivery task, a formulation scientist may select from different types of formulations. An example of LBFs are systems comprising mixtures of surfactant and oil, i.e. self-emulsifying drug delivery systems (SEDDS), that result in a fine emulsion upon aqueous dispersion *in situ*. Lipid-based formulations are commonly filled in soft or hard shell capsules [4]. When designing the formulation and the final dosage form, it is essential to foresee potential interactions between the fill mass and the capsule shell material, as these can lead to problems during manufacturing and long term stability. One of the key factors to consider is the extent of water exchange between the formulation and the shell. For instance, swelling of formulation colloids can lead to creation of aqueous channels that are expected to damage the capsule shell. It is therefore crucial to have a better understanding of how water affects the LBF microstructure to further the advancement of capsule compatibility knowledge.

PURPOSE

To study the formation of continuous water channels in lipid-based formulations (LBFs) and modeling of the microstructural changes using percolation theory.

METHODS

LBFs were prepared by mixing each of the PEGylated surfactants, Kolliphor EL or Tween 80, with medium-chain triglycerides, Miglyol 812, at a ratio of 60:40 (w/w). Increasing amounts of water (volume fraction, ϕ_w = 0–0.18) were then added to the mixtures. These blends were analyzed by means of conductivity, water activity, time-domain nuclear magnetic resonance (TD-NMR) and diffusing wave spectroscopy (DWS). Conductivity and water activity (a_w) were measured at 25ºC using a Metrohm 856 conductometer and a *Lab*Master-aw (Novasina AG), respectively. A benchtop TD-NMR (minispec mq20, Bruker) was employed to characterize different water fractions in the sample by means of their ^{1}H spin-lattice relaxation time *T1*. A standard inversion recovery pulse sequence was used and the results obtained were fitted using a biexponential decay function. Two populations of water (free and bound) were differentiated in the sample. DWS measurements were performed with a ResearchLab (LS Instruments AG) in transmission mode. These measurements allowed the assessment of the microrheological properties of the formulations, i.e., storage (G') and loss (G'') moduli and dynamic viscosity (η'). The results were modeled using percolation theory. First, the experimental critical exponent, q, was determined using a slope of a regression line from the results plotted on a double-logarithmic plot. Using this value, the following power law was fitted to the triplicate results

$$X = X_0 + S(\phi_w - \phi_{wc})^q$$

where X_0 corresponds to the experimental baseline value, S is a proportional constant, ϕ_w is the volume fraction of water and ϕ_{wc} is the critical volume fraction of water that corresponds to the threshold. From this fitting, the different percolation thresholds were obtained for the two systems investigated.

RESULTS AND DISCUSSION

For both LBF systems studied, the addition of water led to changes in the microstructure of the formulations that were clearly observed with conductivity, water activity and DWS measurements.

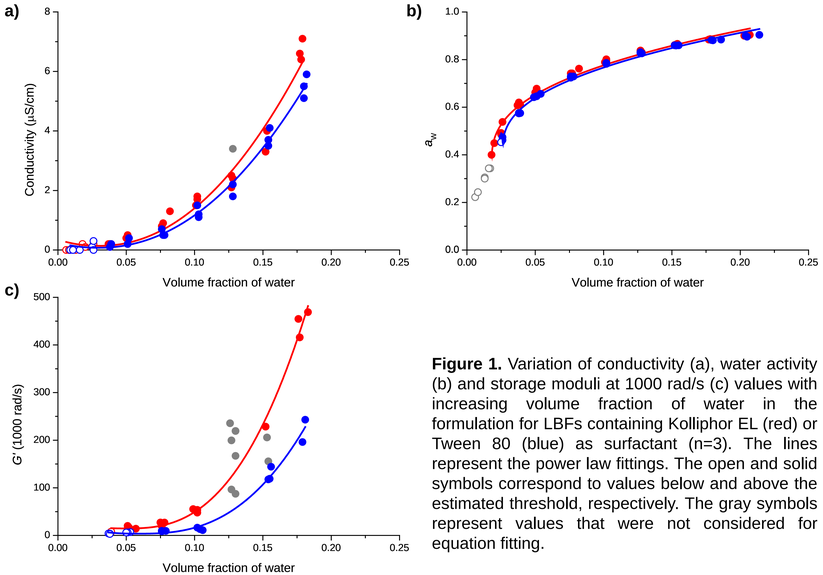


Figure 1. Variation of conductivity (a), water activity (b) and storage moduli at 1000 rad/s (c) values with increasing volume fraction of water in the formulation for LBFs containing Kolliphor EL (red) or Tween 80 (blue) as surfactant (n=3). The lines represent the power law fittings. The open and solid symbols correspond to values below and above the estimated threshold, respectively. The gray symbols represent values that were not considered for equation fitting.

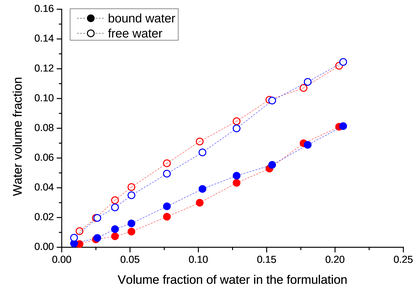
The results were modeled according to percolation theory and thresholds were identified for the formation of continuous water channels (ϕ_{wc} ~ 0.02–0.06). Thresholds were found to vary slightly depending on the physical property studied and they were slightly lower for the system containing Kolliphor EL. A new theoretical model for water activity based on percolation theory was also successfully introduced.

Table 1. Critical exponents in three dimensions and thresholds estimated for the two lipid-based formulations (LBF) in the presence of increasing amounts of water according to different parameters.

Surfactant in LBF	Tween 80		Kolliphor EL	
	Critical exponent	Estimated threshold	Critical exponent	Estimated threshold
Conductivity	μ = 2.10 ± 0.14[a]	ϕ_{wc} = 0.029 ± 0.005	μ = 2.10 ± 0.05[a]	ϕ_{wc} = 0.030 ± 0.007
Water activity	φ = 0.42 ± 0.02[b]	ϕ_{wc} = 0.026 ± 0.000	φ = 0.39 ± 0.03[b]	ϕ_{wc} = 0.018 ± 0.000
Elastic modulus	f = 2.64 ± 0.25[a]	ϕ_{wc} = 0.059 ± 0.007	f = 2.67 ± 0.16[a]	ϕ_{wc} = 0.050 ± 0.007

[a]The experimental exponents obtained were very similar to the universal critical exponents reported in the literature [5,6].
[b]Although no critical exponent has been reported for water activity, it is interesting to note that the empirical exponent obtained was very similar to the exponent for the strength of the infinite or percolating cluster [6].

RESULTS AND DISCUSSION



Moreover, the bound and free water fractions in the formulations could be differentiated with TD-NMR. This approach permits quantification of the relevant water fraction in the formulation that is directly available to interact with the capsule shell.

Figure 2. TD-NMR results of bound and free water fractions, as a function of the total volume fraction of water in the formulation. The LBFs contained Kolliphor EL (red) or Tween 80 (blue).

CONCLUSIONS

This mechanistic study demonstrated the importance of understanding the microstructural changes occurring in lipid-based formulations with increasing amounts of water. Since the formation of continuous water channels in the formulation is a likely determinant for capsule shell compatibility, such microstructural studies would help to predict and understand potential incompatibility issues.

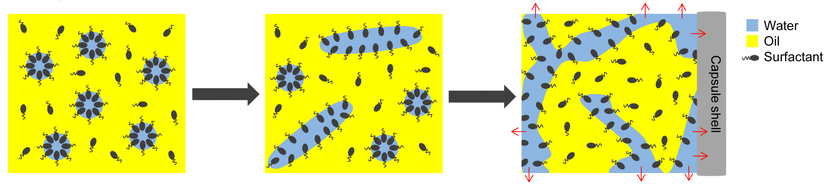


Figure 3. Schematic representation of the microstructural transitions occurring in lipid-based formulations with increasing amounts of water. The red arrows represent the potential transfers of water between the continuous channels and the capsule shell.

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