MOLECULAR WATER INTERACTION IN LIPID-BASED FORMULATIONS AND CAPSULE COMPATIBILITY

INTRODUCTION

Lipid-based formulations (LBF) have become increasingly important for oral delivery of poorly-soluble drugs [1]. These delivery systems typically improve solubility, dissolution and absorption of these challenging drugs. An example of LBF are systems comprising mixtures of surfactant and oil, the so-called self-emulsifying drug delivery systems (SEDDS), that result in a fine emulsion upon aqueous dispersion *in situ*.

Lipid-based formulations are commonly filled in both, soft and hard shell capsules [2]. Although soft capsules have been widely used for this purpose, liquid-filling of hard capsules provides an attractive alternative dosage form [3, 4].

When designing the formulation and the final dosage form, it is very important to foresee potential incompatibility issues between the fill mass and the capsule shell material. One of the key factors to consider is the extent of water exchange between the formulation and the shell. Hygroscopic formulations can remove water from the capsule shell leading to brittleness, whereas formulations with relatively high amounts of water may lead to over-hydration of the shell with its consequent capsule softening.

In this study, we investigated the phase behaviour of the LBF system, Kolliphor EL and Miglyol 812 (60:40, w/w). When diluted 1:100 (v/v) in water, this forms emulsions with a droplet size of ~90 nm, and is thus classified as a self-nanoemulsifying drug delivery system (SNEDDS). The present study aimed at a better understanding of how water interacts with the formulation and possible effects on capsule compatibility by using time domain nuclear magnetic resonance.

EXPERIMENTAL SECTION

MATERIALS

Kolliphor® EL (Macrogolglycerol ricinoleate) was provided by BASF (Germany) and medium-chain triglycerides, Miglyol 812, were obtained from the local supplier Hänseler (Switzerland). The reagent for coulometric Karl Fischer titration, Hydranal Coulomat-E, was purchased from Sigma-Aldrich (Switzerland). Before using, Kolliphor EL was dried in a vacuum oven for 48h at 50°C, to eliminate removable residual water.

DETERMINATION OF RESIDUAL AMOUNTS OF WATER

To determine the initial amount of water in the components and thus to know the exact amount of water in the initial formulations, coulometric Karl-Fisher (KF) titration (831 KF Coulometer, Metrohm, Switzerland) was performed. In this method, a sample of known weight of the dried surfactants was injected into the KF solution and the amount of water determined.

LIPID-BASED FORMULATION PREPARATION

LBFs were prepared by mixing the surfactant with oil (60:40, w/w) and increasing amounts of water were added to the mixtures.

CONDUCTIVITY MEASUREMENTS

Conductivity was measured using a Metrohm 856 conductometer fitted with a 5-ring Pt1000 conductivity measuring cell and a Pt100 temperature sensor (Metrohm, Switzerland).

WATER ACTIVITY DETERMINATION

Water activity (a_w) measurements were performed using a LabMaster-aw (Novasina, Switzerland). The a_w is defined as the ratio of the vapour pressure of the water on the surface of the sample to that of pure water. This value equals the relative equilibrium humidity (%) of the sample.

TIME DOMAIN ^{1}H NUCLEAR MAGNETIC RESONANCE (TD-NMR)

Water fractions in the sample were characterized by means of their ^{1}H spin-lattice relaxation time T1 with a benchtop time domain nuclear magnetic resonance instrument (minispec mq20, Bruker, Germany). The samples were equilibrated at room temperature before measuring. A standard inversion recovery pulse sequence ([RD - 180° - IR - 90° - RDT - asd]NS)N was used, where RD is the recycle delay (1000 msec), IR is an incremented inversion recovery delay interval (first pulse separation: 5 msec; final pulse separation: 2000 msec), RDT is the delay for receiver dead time (0.03 msec), and asd is the sampling window (0.03 msec). The number of scans for signal averaging is represented by NS (=8) and N is the number of collected data points. The results obtained were fitted using a biexponential decay function, allowing the distinction between two populations of water in the sample.

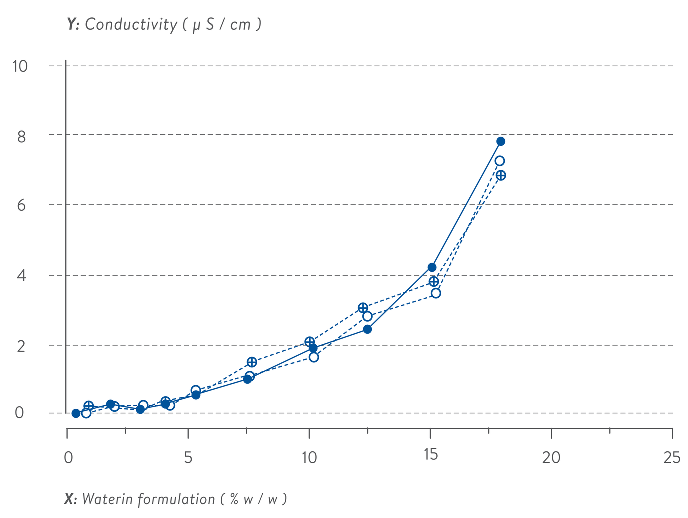
RESULTS AND DISCUSSION

Figure 1 shows that the conductivity remained almost negligible for samples with low water content. When approaching 5% (w/w) of water in the formulation, a pronounced increase in the conductivity was observed. As the conductivity of oil is negligible, this increase seems to correspond to the formation of water continuous channels in the formulation (**Figure 2**). This could indicate, for the given system, that encapsulation of samples with water content above 5% may harm the capsule shell.

Figure 3 shows that above 5% (w/w) water in the formulation, the water activity becomes higher than 0.60. Relative humidity values above ca. 60% have been reported to lead to softening of the hard capsule shell [5].
These findings of water activity were therefore in agreement with the results of conductivity measurements regarding potential capsule shell softening using formulations containing water amounts above 5% (w/w).

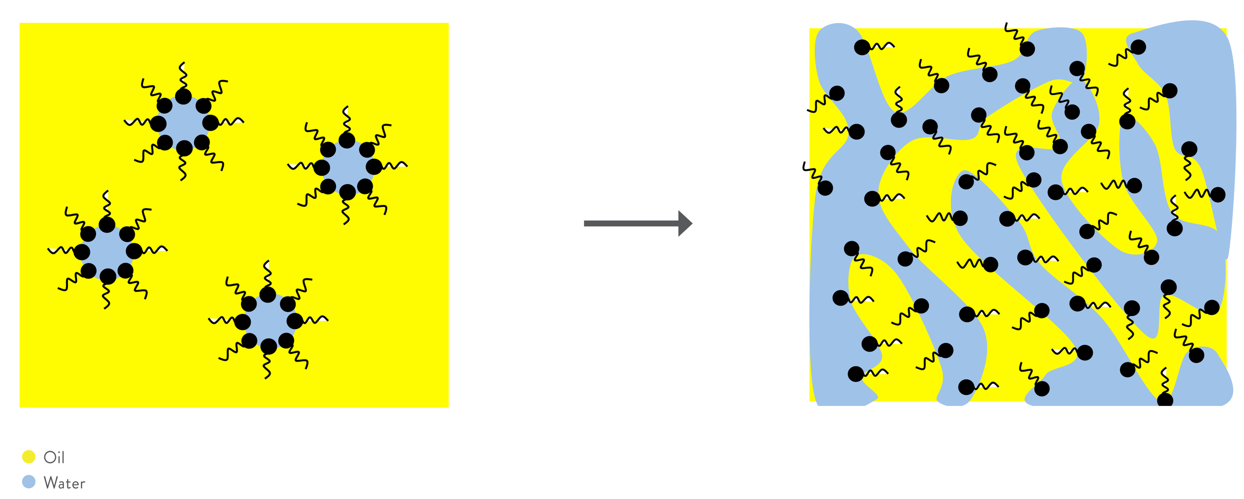
Using TD-NMR, it was further possible to differentiate between different populations of water, i.e. bound and free (i.e. bulk) water fraction [6]. This approach permits quantification of water in the formulation that is directly available to interact with the capsule shell. As can be seen in **Figure 4a**, for a sample with 5% water, only approximately 4% is free to interact with the shell and potentially lead to compatibility problems. It can also be seen in **Figure 4b** that as the water in the formulation increases, the relative amount of bound water also increases.

Figure 1



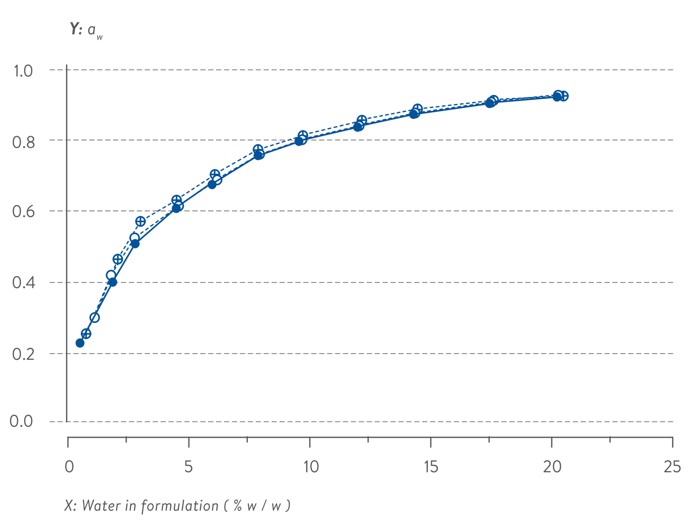
Variation of conductivity values with rising amounts of water in the formulation.

Figure 2



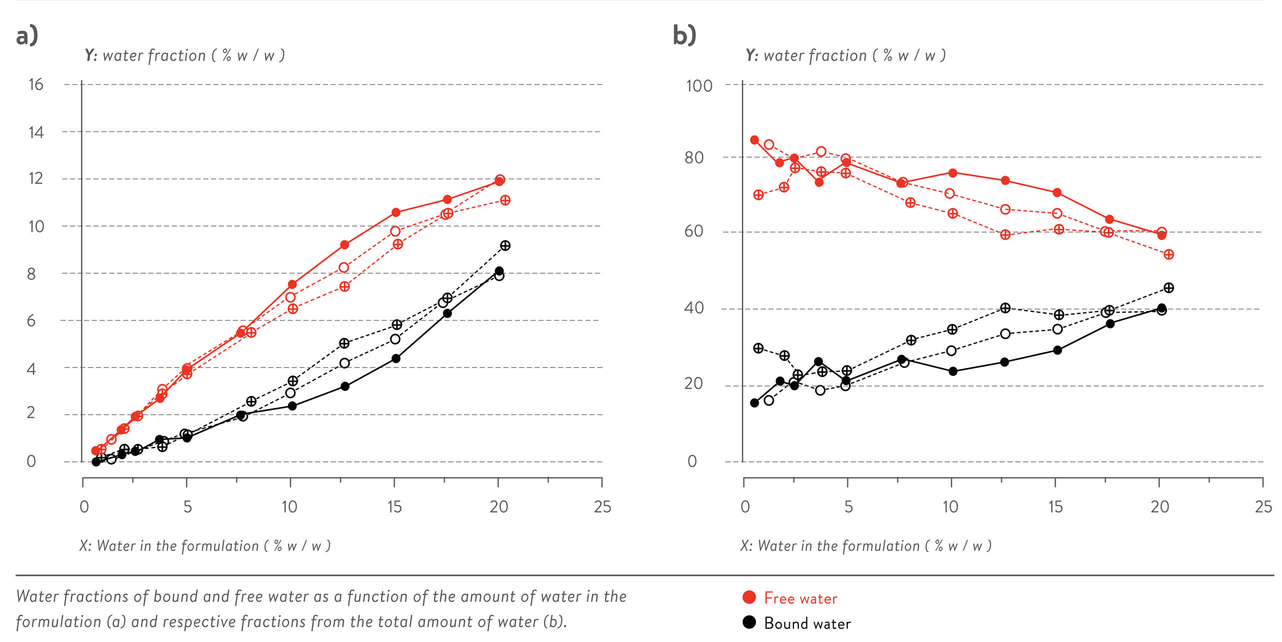
Schematic representation of the formation of water continuous channels as the water amount in the formulation increases.

Figure 3



Water activity values with increasing concentrations of water in the formulation.

Figure 4



Water fractions of bound and free water as a function of the amount of water in the formulation (a) and respective fractions from the total amount of water (b).

CONCLUSIONS

The results obtained indicate that different types of water exist in a lipid-based formulation containing increasing amounts of water, which could be differentiated regarding capsule compatibility. In the system studied, 5% (w/w) was identified as the potential concentration to trigger changes in the capsule shell. Further research will include mechanical testing of capsules to determine compatibility with water levels determined using these methods.

ACKNOWLEDGMENTS

The authors would like to thank Qualicaps Europe S.A.U., Tillotts Pharma AG and the University of Applied Sciences and Arts Nortwestern Switzerland for financial support.

REFERENCES

[1] Kuentz, M. Lipid-based formulations for oral delivery of lipophilic drugs, Drug. Discov. Today Technol. 9, e97-e104 (2002).
[2] Jannin, V; Musakhanian, J; Marchaud, D. Approaches for the development of solid and semi-solid lipid-based formulations. Adv Drug Del Rev. 60, 734–46 (2008).
[3] Niederquell, A; Kuentz, M.; AAPS PharmSciTech. 12, 323-330 (2011)
[4] Nagata, S; Tochio, S; Compatibility between liquid and semi-solid excipients and HPMC capsules. Poster, C.R.S. Annual Meeting, Seoul (2002).
[5] Cole, E.T. Liquid filled and sealed hard gelatin capsules. Bull. Tech. Gattefossé 92, 67-77 (1999).
[6] Blinc, R.; Zupančič, I; Zidanšek, A. and Slak, J. Proton spin-lattice relaxation time of hydrated gelatin. Appl. Magn. Reson. 12, 61-68 (1997).

University of Applied Sciences and Arts Northwestern Switzerland, Institute of Pharma Technology, Muttenz, Switzerland: Alexandra Machado, Martin Kuentz / Qualicaps, Nara, Japan: Tohru Kokubo / Tillotts Pharma AG, Switzerland: Roberto Bravo, Claudio Scialdone / Qualicaps Group and School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, UK: Brian Jones / Qualicaps, Madrid, Spain: Gabriela Dujovny. alexandra.machado@fhnw.ch

Qualicaps® Engineered to perform

ZERIA GROUP TILLOTTS PHARMA

n|w University of Applied Sciences and Arts Northwestern Switzerland