Qualicaps

Case Study

Influence of water in lipid-based formulations on mechanical properties of hard-shell capsules

A microstructural study of water effects in lipid-based pharmaceutical formulations for liquid filling of capsules. European Journal of Pharmaceutical Sciences 90 (2016) 64–75

Authors: Alexandra H. E. Machado[1], Tohru Kokubo[2], Gabriela Dujovny[3], Brian Jones[3], Claudio Scialdone[4], Roberto Bravo[4], Martin Kuentz[1]

1 University of Applied Sciences and Arts Northwestern Switzerland, Institute of Pharma Technology, Muttenz, Switzerland; **2** Qualicaps® Co. Ltd., Japan; **3** Qualicaps® Europe S.A.U, Spain; **4** Tillotts Pharma AG, Switzerland

Objectives

With the collaboration of Qualicaps® Europe S.A.U. Spain, Tillotts Pharma AG Switzerland and the University of Applied Sciences and Arts Northwestern Switzerland, a project was undertaken to understand how microstructural changes in lipid-based formulations (LBFs), due to the presence of water, affect compatibility with capsule shells, by comparing differences between gelatin and HPMC capsules using mechanical texture analysis.

Background

Hard-shell capsules are an important alternative to soft-shell capsules for the encapsulation of liquid and semi-solid formulations for the pharmaceutical industry, one that allows in-house development and manufacturing, from early preclinical phase, through scale-up up to industrial runs. Formulation design of liquid-filled hard capsules should consider potential interactions between the fill mass and the capsule shell material. One of the key aspects is the extent of water exchange between formulation and capsule, as it can lead to unacceptable changes in mechanical behavior of the hard capsules, e.g. brittleness or softening. It is therefore highly important to understand how the presence of water or hydrophilic components in LBFs will affect the capsule shell. This will provide guidance for formulators and optimize the time and costs associated with compatibility tests.

FORMULATION DESIGN OF LIQUID-FILLED HARD CAPSULES SHOULD CONSIDER POTENTIAL INTERACTIONS BETWEEN THE FILL MASS AND THE CAPSULE SHELL MATERIAL

In colaboration with:

TILLOTTS PHARMA ZERIA GROUP

n|w University of Applied Sciences and Arts Northwestern Switzerland

Investigation

LBFs were prepared by mixing either of two PEGylated surfactants, Kolliphor EL and Tween 80, with medium-chain triglycerides, Miglyol 812, at a ratio of 60:40 (w/w). Increasing amounts of water (volume fraction, $\varnothing w$ = 0–0.18) were then added to the mixtures.

In the first experiment, size 0 gelatin (Quali-G™) and HPMC (Quali-V®) capsules (Qualicaps® Europe S.A.U.) were filled with the different formulations containing increasing amounts of water and were stored in open vials at 25°C / 60% RH for 4 months. Capsule stiffness was determined using a texture analyzer, by compressing capsules with a platen up to a 1.2 mm displacement at a speed of 0.2 mm/s *Figure 1*.

In a second set of experiments, size 0 gelatin and HPMC capsule caps were immersed in different formulations for 2 weeks at 25°C, after which they were removed and carefully cleaned. The mechanical capsule properties, i.e., elastic stiffness and elongation at break, were assessed using a texture analyzer (tensile rig, force in tension mode at a speed of 0.5 mm/s *Figure 2*).

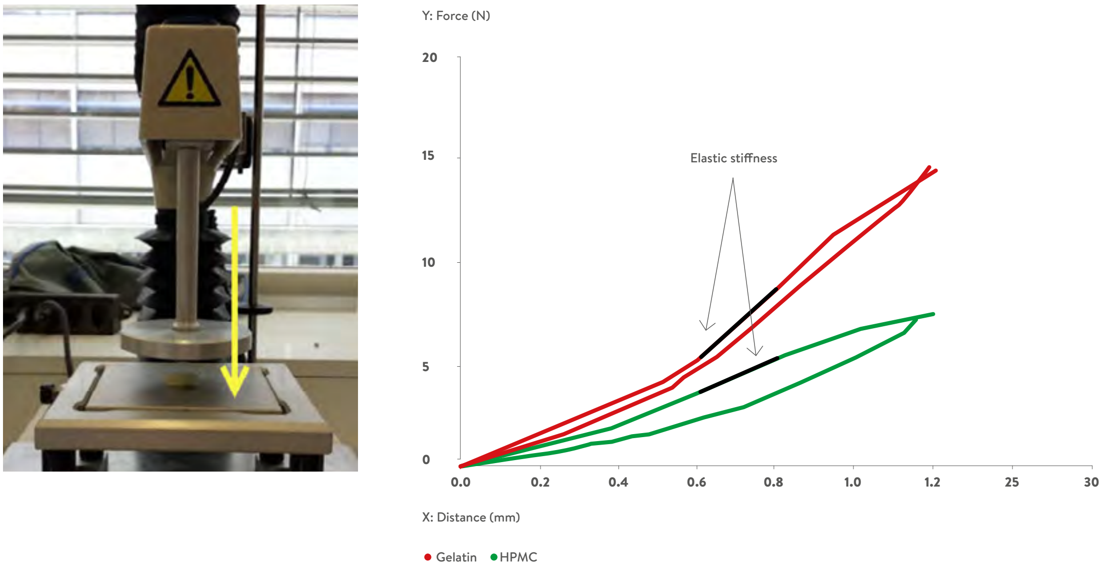

Figure 1 Texture analysis method for force in compression. The elastic stiffness was determined as secant in the linear region of the curve.

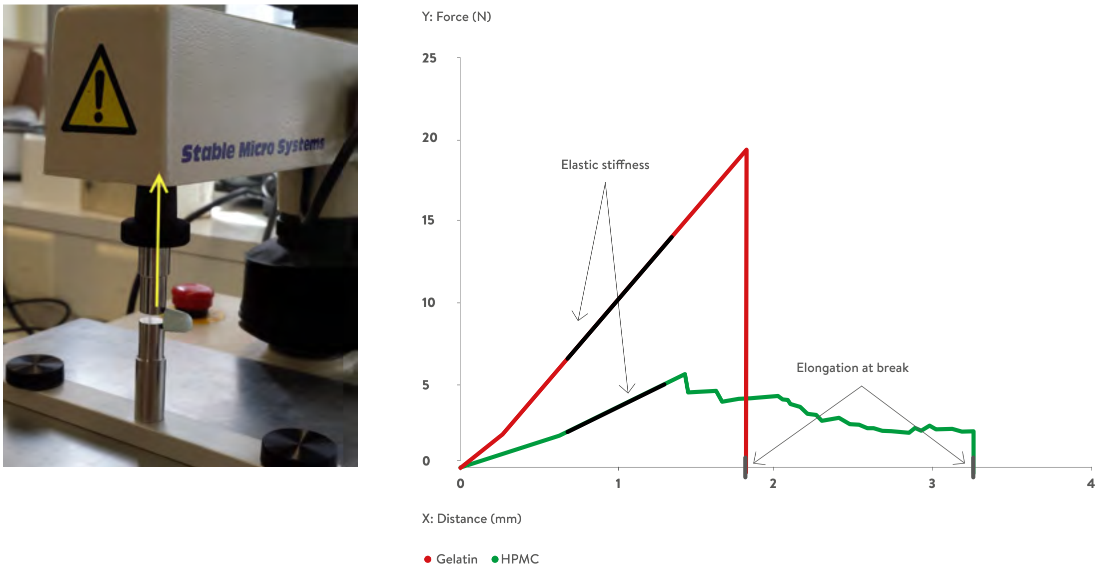

Figure 2 Texture analysis method for force in tension. The elastic stiffness was determined as secant in the linear region of the curve and the elongation at break as the distance traveled by the rod until the cap was split.

Results

Data obtained from the compression of filled capsules stored in open vials showed that neither gelatin nor HPMC capsules exhibited marked mechanical changes with increasing amounts of water in the formulation. These results indicate that, when stored at mild conditions, capsules were not significantly visually deformed by formulations with water contents of øw = 0.15–0.18 (corresponding to initial water activity values of 0.8-0.9) *Figure 3*. It is important to note that the ratio of free to bound water in the formulations may play a major role.

The second set of experiments focused on the formulation-capsule shell interface. Mechanical results obtained for capsule caps immersed in formulations clearly showed that gelatin capsules were affected by the water content of the formulation, with considerable softening being observed for øw > 0.04 *Figure 4*. These results were similar for formulations containing either Tween 80 or Kolliphor EL as surfactants and could be correlated with the thresholds determined in part 1 of this work for water channel formation. Interestingly, HPMC capsules were found to be comparatively less sensitive and less affected by the presence of these continuous channels in the formulation.

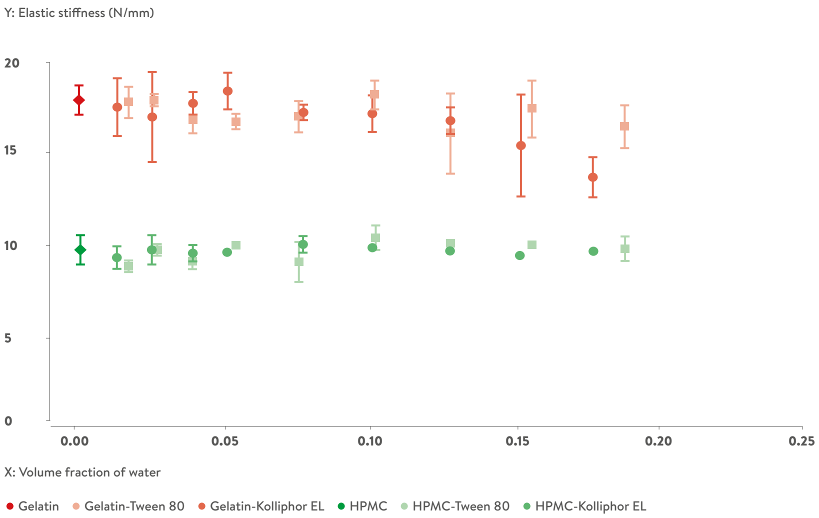

Figure 3 Elastic stiffness for gelatin and HPMC capsules liquid-fille with formulations containing either Kolliphor EL or Tween 80 as sufactant and increasing amounts of water. The results obtained for the empty capsules at the same conditions are also shown for comparison (n=3).

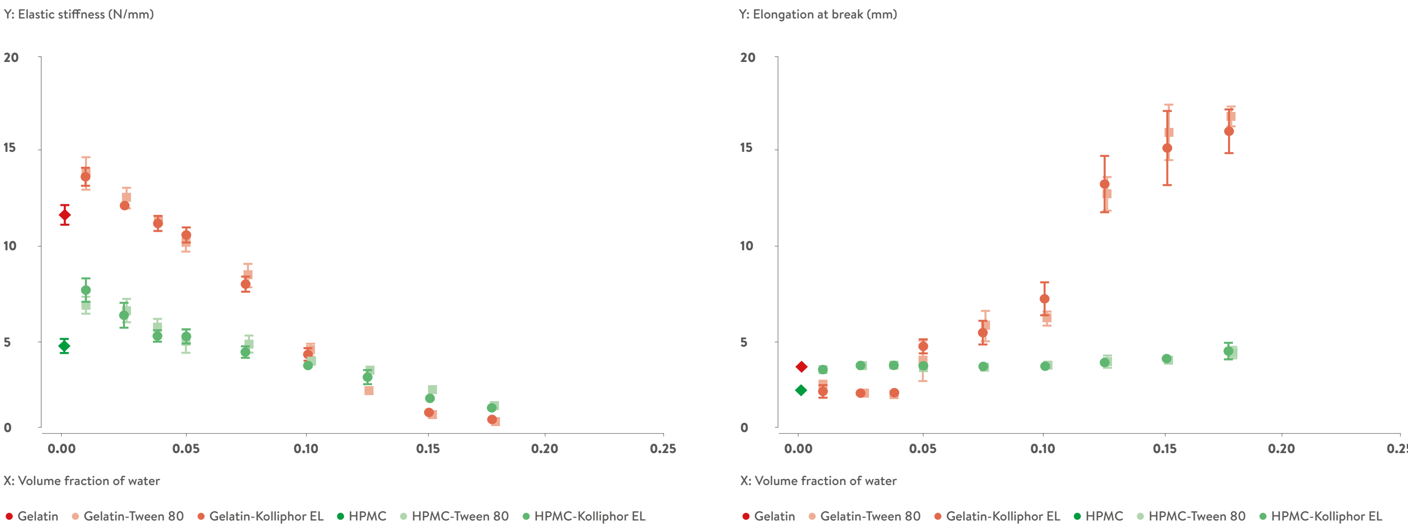

Figure 4 Elastic stiffness and elongation at break for gelatin and HPMC capsules caps immersed in formulations containing either Kolliphor EL or Tween 80 and increasing amounts of water. The results obtained for the empty caps at the same conditions are also shown for comparison (n=5).

Conclusion

Knowledge of the microstructural changes in lipid-based formulations (e.g. formation of water channels) is helpful for pharmaceutical scientists to overcome shell incompatibility and therefore to design quality into the final dosage form. Overall, HPMC capsules proved to be less affected by the presence of water in formulations than gelatin capsules. Furthermore, the method of storage and analysis of the mechanical properties of capsules was shown to be of critical relevance for compatibility assessment.