W4062

Understanding capsule compatibility with lipid-based formulations: 2. Assessment of mechanical properties of gelatin and HPMC capsules after equilibration with formulations

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BACKGROUND

Hard-shell capsules are becoming an important alternative to soft-shell capsules for the encapsulation of liquid and semi-solid formulations [1]. These capsules are particularly attractive for the pharmaceutical industry due to the availability of equipment for liquid-filling and sealing. This allows the development and manufacturing in-house, from early preclinical phase, through scale-up up to production-scale. Moreover, hard-shell capsules allow higher filling temperature, have a lower moisture content and do not require the addition of plasticizers as their soft-shell counterparts [2,3]. 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 shell changes in hard gelatin capsules, e.g. brittleness or softening [4,5]. It is therefore highly important to understand how the presence of water or hydrophilic components in the lipid-based formulations (LBFs) will affect the capsule shell. This will provide guidance for formulators and optimize the time and costs associated with compatibility tests.

PURPOSE

To understand how microstructural changes in LBFs due to the presence of water affect compatibility with capsule shells by comparing differences between gelatin and HPMC capsules using mechanical texture analysis.

METHODS

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, ϕ_w = 0–0.18) were then added to the mixtures. In the first experiment, size 0 gelatin 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 25ºC / 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).

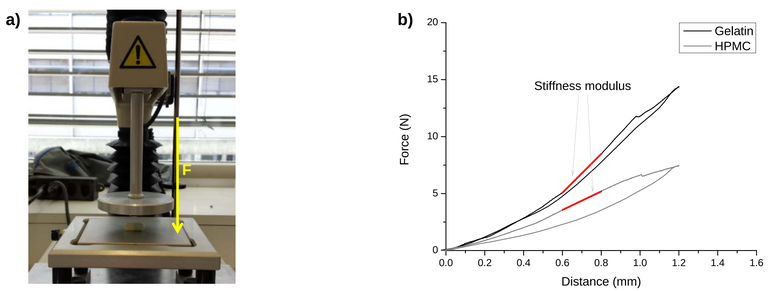

Figure 1. Texture analysis method for force in compression (a). The stiffness modulus was determined as secant in the linear region of the curve (b).

METHODS

In a second set of experiments, size 0 gelatin and HPMC capsule caps were immersed in different formulations for 2 weeks at 25ºC, after which they were collected 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).

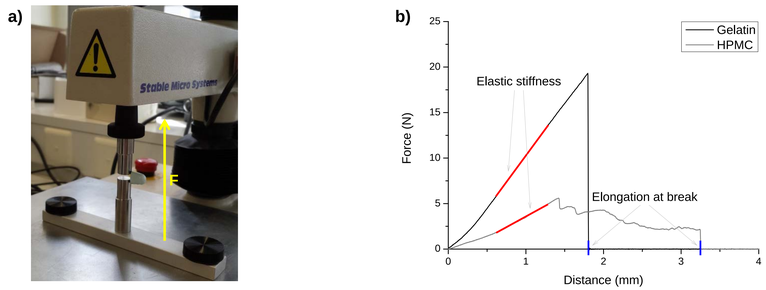

Figure 2. Texture analysis method for force in tension (a). The elastic stiffness was determined as secant in the linear region of the curve and the elongation at break as the distance traveled by the rod until the cap was completely broken (b).

RESULTS AND DISCUSSION

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 damaged by formulations with water contents of ϕ_w = 0.15–0.18 (corresponding to initial water activity values of 0.8-0.9). It is important to note that the ratio of free to bound water in the formulations may play a major role.

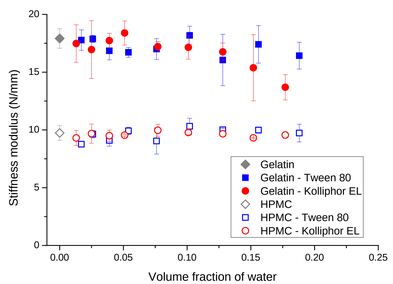

Figure 3. Stiffness modulus for gelatin and HPMC capsules liquid-filled with formulations containing either Kolliphor EL or Tween 80 as surfactant and increasing amounts of water. The results obtained for the empty capsules at the same conditions are also shown for comparison (n=3).

ACKNOWLEDGEMENTS

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RESULTS AND DISCUSSION

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 ϕ_w > 0.04. 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 [6]. Interestingly, HPMC capsules were found to be particularly robust and comparatively less affected by the presence of these continuous channels in the formulation.

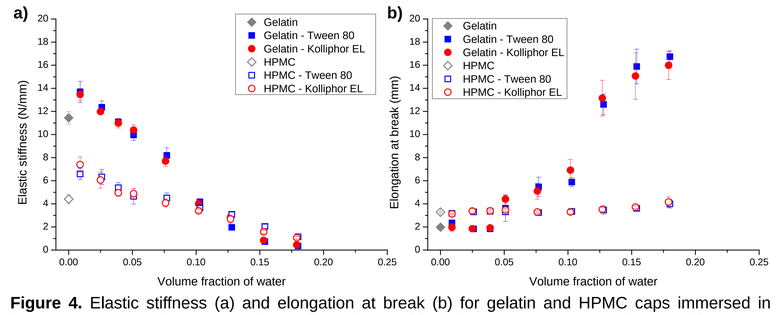

Figure 4. Elastic stiffness (a) and elongation at break (b) for gelatin and HPMC caps immersed in formulations containing either Kolliphor EL or Tween 80 and increasing amounts of water. The results obtained for the empty caps at the same conditions are also shown for comparison (n=5).

CONCLUSIONS

It was shown that 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 sensitive to the presence of water in formulations than gelatin capsules. Furthermore, it was shown that the method of storage and analysis of the mechanical properties of capsules is of critical relevance for compatibility assessment.

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