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Determination of the optimal amount of water in liquid-fill masses for hard gelatin capsules by means of texture analysis and experimental design

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Abstract

The aim of this study is to use texture analysis as a non-destructive test for hard gelatin capsules filled with liquid formulations to investigate mechanical changes upon storage. A suitable amount of water in the formulations is determined to obtain the best possible compatibility with the gelatin shell. This quantity of water to be added to a formulation is called the balanced amount of water (BAW). Texture profiling was conducted on capsules filled with hydrophilic polymer mixtures and with formulations based on amphiphilic masses with high HLB value. The first model mixture consisted of polyethylene glycol 400 and polyvinylpyrrolidon K17 with water and the second type consisted of caprylocaproyl macrogol glycerides (Labrasol®) with colloidal silica (Aerosil® 200) and water. The liquid-fill capsules were investigated by measuring changes on mass and stiffness after storage under confined conditions in aluminium foils. Capsule stiffness was investigated als as a parameter in a response surface analysis to identify the BAW. Polyvinylpyrrolidone did not show a great influence on the BAW in the range of 10–12% (w/w) for the first model mixture. Capsules with the less hydrophilic Labrasol® formulations, however, kept their initial stiffness after storage best with only half of that amount, i.e. 5–6% (w/w) of water in the compositions. From this study it can be concluded that texture profiling in the framework of an experimental design helps to find hydrophilic or amphiphilic formulations that are compatible with gelatin capsules. Short-term stability tests are meaningful if capsule embrittlement or softening is due to water equilibration or another migration process that takes place rapidly. Long-term stability tests will always be needed for a final statement of compatibility between a formulation and hard gelatin capsules.

Keywords: Texture analysis; Hard gelatin capsules; Liquid-fill; Compatibility testing; Experimental design; Optimisation

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1. Introduction

The filling of liquid and semisolid masses into hard gelatin capsules provides a variety of formulation options to a formulator in pharmaceutical industry. The drug can be dissolved in oily or non-oily bases, or alternatively suspensions can be administered by this route.

Poorly water soluble compounds can show higher oral bioavailability in a liquid-filled hard gelatin capsule compared to a conventional capsule formulation (Erlich et al., 1999). This agrees with Shelley (1996) who earlier reported a similar finding of improved oral bioavailability using soft gelatin capsules.

Broer (1978) and Cuine´ et al. (1978) established the basis for liquid-filled hard gelatin capsules and later Walker et al. (1980) described adaptation of equipment for large-scale filling.

The capsules can be sealed as an additional step. Development of new sealing technologies for hard gelatin capsules (Cade´ et al., 1987; Cole,1999) contributed to the rising interest of the pharmaceutical industry. There are some aspects of this dosage form that make it preferable even to soft gelatin capsules. For example the development, scale-up and manufacture of liquid-filled hard gelatin capsules can be done in-house and Cole (1999) listed a number of further positive characteristics of this dosage form.

The compatibility between the fill mass and the gelatin shell of the capsules is in most cases not critical for lipidic formulations. However, compatibility can become an issue when using large amounts of amphiphilic or hydrophilic excipients. Such formulations may dehydrate the gelatin shell leaving the capsule brittle if its water content falls below about 10% or other formulations may soften the capsules if the water content of the gelatin shell increases to 17–18% (w/w) (Cole, 1999). The decrease in capsule stiffness can be observed also under humid storage conditions or if the water activity of the formulation is rather high.

Water is a potent plasticiser for gelatin. The Flory interaction parameter of water with gelatin is little lower than 0.5 and even small amounts of water decrease the glass transition temperature of gelatin (Tomka, 1983). This molecular interaction causes stiffness changes in the gelatin.

Low molecular weight polyethylene glycols (PEG) are known to take up water from gelatin shells. For this reason Walters et al. (1992) reported that such hygroscopic excipients in great quantities should be avoided in hard gelatin capsules. Yet, if a water migration process originates the incompatibility between the formulation and the capsule, it should be possible to overcome this problem by adjustment of the initial water concentration in the formulation (Cole, 1989; Bowtle, 1998). The water in a liquid-fill mass, for which gelatin capsules do not change their mechanical properties under storage, is called the balanced amount of water (BAW). This quantity is hard to determine, as it is part of a complex water diffusion process between the formulation, the shell, and the humidity in the environment. The BAW is therefore a relative value depending on given storage conditions and is a compromise between embrittlement and softening of the capsules. Careful monitoring of the capsule stiffness is necessary to identify the appropriate initial water concentration.

The conventional methods to assess embrittlement of capsules are based on the resistance of the specimen to a defined impact (Cade´ and Madit, 1996; Kontny and Mulski, 1989). The capsules can either break under the mechanical stress or stay intact. A considerable number of capsules have to be tested in this way, which is often a major problem in early development phase due to the very limited amount of substance available. Besides, the method is not sensitive enough to accurately study the influence of a formulation parameter on capsule stiffness.

In the present paper a non-destructive texture analysis is presented that measures the change of individual capsule stiffness upon storage. This technique is applied in the framework of a statistical design to determine the BAW for two different model formulations. The first system is based on mixtures of hydrophilic polymers (PEG 400 and PVP K17) with water, whereas the second type consists mainly of an amphiphilic excipient (Labrasol®) with a high HLB value together with colloidal silicon dioxide (Aerosil® 200) and water.

2. Materials and methods

The first mixture type consisted of a low molecular weight polyethylene glycol (PEG), Polyglykol400® (Clariant GMBH, Frankfurt), and polyvinylpyrrolidone (PVP) as Povidone K17® (BASF, Ludwigshafen). Labrasol® (Gattefosse´, France) a caprylocaproyl macrogol-8-glycerides was the main part of the other mixtures. This amphiphilic excipient has an HLB value of about 14. It was mixed together with a thickening agent, colloidal silicon dioxide, Aerosil® 200 (Degussa, Frankfurt). The compositions of all formulations are listed in Table 1.

The formulations were manually filled into the capsules and were not sealed. The capsules were stored in small hermetically sealed aluminium foils (simulating aluminium blisters) at 25 °C and 60% relative humidity (RH) for two weeks in the study with PEG 400 containing formulations and for one week with the Labrasol® mixtures. The storage period was shorter for the latter study because a week is in most cases a sufficient time to reach the equilibrium of the water.

All capsules were numbered so that changes of weight and stiffness were measured individually. Testing was performed with filled capsules at ambient conditions.

The characterisation of capsule stiffness was obtained from texture profiles using a texture analyser TA-XT2i (Stable Microsystems, England). Licaps® capsules, size zero (Capsugel, France) were compressed with a platen up to 1.2 mm displacement, which corresponds to a reversible range of the strain. The testing speed was 0.2 mm/s. A line was fitted to a defined range of the profile as a secant from which the slope was taken as a stiffness modulus in N/mm. Consequently, the change of initial capsule stiffness upon storage was calculated.

The experiments were planed and conducted using multilevel factorial designs (4^2 and 3^2, respectively) from which the response surfaces of capsule stiffness changes was calculated using a software package Statgraphics® Plus V5.0 Quality and Design (Manugistics, USA).

Table 1

Hydrophilic and amphiphilic model compositions

No.	Water % (w/w)	PVP K17% (w/w)	PEG 400 % (w/w)
Hydrophilic model			
1	0	0	100.0
2	0	2.5	97.5
3	0	5.0	95.0
4	0	7.5	92.5
5	12.5	0	87.5
6	12.5	2.5	85.0
7	12.5	5.0	82.5
8	12.5	7.5	80.0
9	25.0	0	75.0
10	25.0	2.5	72.5
11	25.0	5.0	70.0
12	25.0	7.5	67.5
13	37.5	0	62.5
14	37.5	2.5	60.0
15	37.5	5.0	57.5
16	37.5	7.5	55.0

No.	Water % (w/w)	Aerosil % (w/w)	Labrasol % (w/w)
Amphiphilic model			
1	0	0	100
2	0	1.5	98.5
3	0	3.0	97.0
4	7.5	0	92.5
5	7.5	1.5	91.0
6	7.5	3.0	89.5
7	15.0	0	85.0
8	15.0	1.5	83.5
9	15.0	3.0	82.0

3. Results and discussion

The first model system investigated displayed similar changes of capsule weight for the different amounts of PVP K17 in PEG 400 (Fig. 1A). The initial amount of water in a formulation proved to be the most dominant factor for the change of the mass. However, the changes take place in a range of ±2% that is accepted for hard gelatin capsules (Cade´ and Madit 1996). Certainly the total mass change of the dosage form is limited by the hermetic closure of the aluminium blister. The capsules could take up considerably more water if they were open stored and weight changes would then possibly exceed the limitations by far.

From Fig. 1A, it can be inferred that capsules of all four compositions with no added water increased a little their mass. The capsules with 12.5% (w/w) initial water content, however, showed a slight decrease of weight. This change is more pronounced for the formulations of 25% (w/w) water content and is maximal with the compositions of 37.5% (w/w) water. Based on these results, there seems to exist a specific amount of water in a formulation for which the total weight of the capsules remains unchanged at given storage conditions.

The applied storage time was at least one week for all formulations. This should be long enough for the water

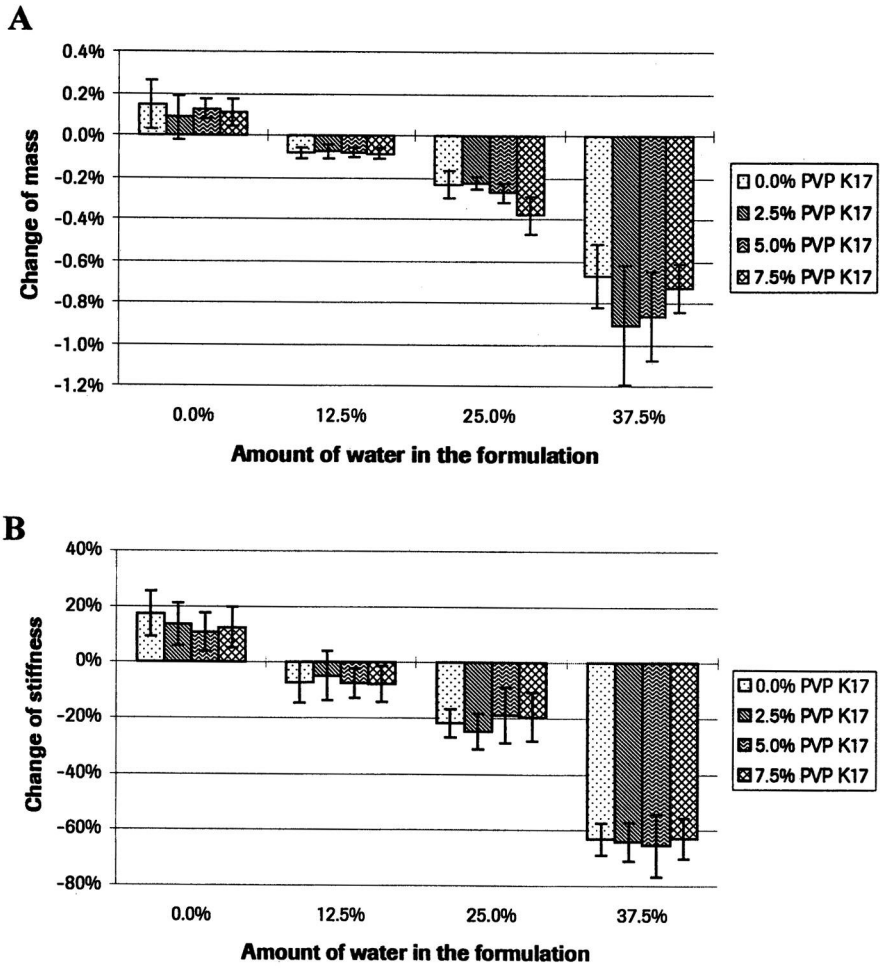

Fig. 1. The change of Licaps® (A) weight (%) and (B) stiffness (%) related to different amounts of water added to mixtures of PEG 400 with varying amounts of PVP K17% (w/w).

equilibrium to be attained since this process is expected to take from hours to a few days depending on the type of formulation (Bowtle, 1998).

Textural profiles are characteristic for the type of capsule investigated. The Licaps® underwent a reversible strain on the lateral side of the capsules where the force almost linearly increased up to a displacement of about 0.6 mm. The slope of a fitted line in this range provided a measure of stiffness. Unlike a Young's modulus of elasticity, this stiffness value does not exclusively characterise a material property but depends also on the geometry of the capsule, especially on the cap/body overlap. Additional factors can potentially influence this value, i.e. the fill-mass, strain region in which the slope of the line is fitted, strain rate, as well as the temperature, and relative humidity during the measurement. Hence, relative measurements were performed before and after storage of the same capsules. This procedure allows the measurement of individual capsule changes avoiding variability due to different initial stiffness values.

The absolute values of the stiffness, determined directly after filling of the capsules, varied from 15 to 22 N/mm. Texture profiling was repeated with the capsules after storage and the stiffness changes were calculated. The results for the mixtures of PEG 400 with PVP K17 are shown in Fig. 1B. Considering the water in the various compositions, the capsule stiffness changes displayed a similar behaviour to their corresponding mass changes. One may even speculate that a BAW could be determined solely based on mass changes of the capsules. Yet, the relevant parameter is the stiffness change because using the mass change as a surrogate marker for a stiffness difference is basically problematic. Mechanical alterations of gelatin capsule are not necessarily reflected by total weight changes, so that a validation of the method would be necessary for every formulation type. Texture profiling also provides additional information compared to a simple monitoring of capsule weight changes.

As a result, the observed mass changes of the capsules should be taken as a confirmation of the assumption that water transfer is the origin of stiffness changes in the capsules investigated. In Fig. 1B, it can be seen that mixtures without any water displayed an increase of stiffness, which is due to the water uptake by the gelatin shell. The capsule becomes stiffer, which makes it prone to brittlenesss. Such rather moderate changes of capsule stiffness are quantitatively hard to assess by other methods than texture analysis. The conventional brittleness tester, where a defined impact is released onto the capsules, is suitable for quality control, but less adequate for development purposes.

Capsules with 12.5% (w/w) initial water content exhibited a softening of the shell. This decrease of capsule stiffness was greater with 25% (w/w) water, and further most softening exhibited the capsules with an original water content of 37.5% (w/w).

These latter capsules were soft enough for a simple mechanical assessment by palpation. Some of these capsules were slightly deformed and the absolute stiffness values were all below 10 N/mm for these units with 37.5% (w/w) water. Thus, a high water activity of the formulation leads to a considerable water migration into the shell where the plasticiser effect is evident.

Results obtained indicate that there must exist a BAW in the formulation that leaves the gelatin shell mechanically unaltered. A mathematical modelling of the data is needed to find this optimal water content. A multilevel factorial design allows the calculation of the coefficients of a second order model according to Eq. (1) (Lewis et al., 1999):

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{12} X_1 X_2 + \varepsilon \qquad (1)$$

X_1 is the water content, X_2 represents the amount of PVP K17 in the formulation and ε contains the residuals. The determined coefficients are listed in Table 2 and the r^2 value adjusted for the degree of freedom was 0.968 for the PEG/PVP mixture type. Fig. 2 shows a plot of the corresponding response surface for the stiffness changes for the variables water and PVP K17. Only a part of the experimental region is shown in order to highlight the plane of zero stiffness changes. The intersection line with the response surface is marked with dots in Fig. 2 and corresponds to formulations for which the capsules did not change mechanically upon storage. Therefore compositions with about 10–12% (w/w) water depending on the amount of PVP K17 have to be considered as

Table 2

Coefficients for the change of stiffness calculated for the two model systems according to Eq. (1)

Coefficients	First model[a]	Second model[b]
r^2 (adjusted)	0.968	0.983
β_0	14.283	9.1792
β_1	–0.7184	0.8066
β_2	–1.1702	–6.9372
β_{11}	–0.0357	–0.3519
β_{22}	0.0895	1.840
β_{12}	0.0217	0.1167

[a] X_1: effect of water; X_2: effect of PVP K17.

[b] X_1, Effect of water; X_2: effect of Aerosil® 200.

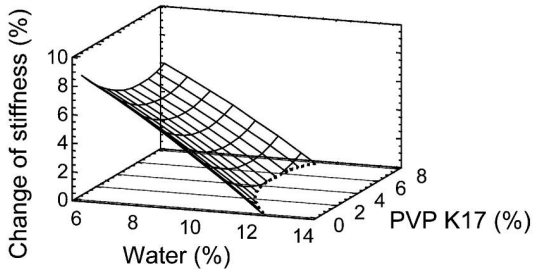

Fig. 2. A part of the response surface, i.e., the change of initial stiffness as a function of the initial water concentration and amount of PVP K17% (w/w) in mixtures of PEG 400.

optimal for the Licaps® closed in aluminium foils. The influence of PVP K17 on the BAW was found to be rather small and can practically be neglected. Yet, it should be kept in mind that for other formulation types some excipients might significantly affect the BAW.

A closer look at the response surface in the present example is also interesting regarding the aspect of the robustness of the formulation. Small changes of a selected composition should not greatly affect capsule properties. Thus, formulations with 12 ±1% (w/w) water resulted in stiffness changes over a rather small range of ±2%. The extent of mechanical capsule changes in vicinity of the BAW is therefore not considered to be relevant for handling operations such as deblistering.

The amphiphilic model mixture of Labrasol®, Aerosil® 200 and water displayed a similar pattern of capsule weight changes as previously observed for the hydrophilic model system (Fig. 3A). As the filling mass is less hydrophilic, one could expect that a lower BAW than in the previous example would be necessary. The weighing results showed a mass increase for the capsules without water added to the formulations. On the other hand, an initial water content of 7.5 and 15% (w/w) resulted in a loss of capsule weight. This decrease of weight was maximal for formulations with the highest water content, but the changes were generally small because of the confined environment in the aluminium foil.

Texture profiling of the capsules with the amphiphilic mixtures gave similar results in a range of 15–22 N/mm. Considering the stiffness of the capsules with formulations containing only Labrasol® and Aerosil® 200, a slight increase was observed (Fig. 3B). The formulations with 7.5 and 15% (w/w) initial water content exhibited a softening.

However, there was a great difference in the amount that the stiffness changed. At a water level of 7.5% (w/w) a marginal stiffness change occurred that could only be assessed by a very sensitive method like texture analysis, whereas the softening of the capsules with 15% (w/w) water was even apparent by manual inspection. The absolute stiffness values of these capsules were all below 10 N/mm just as it was the case with the first model mixtures at the highest water concentration of 37.5% (w/w).

The experimental data for the Labrasol® formulations constitute a three level factorial design from which the response surface of stiffness change was calculated. The determined coefficients from the model Eq. (1) are listed in Table 2. A $r2$ value adjusted for the degree of freedom of 0.983 was obtained for this model. Since only a part of the entire response surface is reproduced in Fig. 4, the curvature is increased in comparison to a view of the entire experimental region that was investigated. Yet, the graph shows clearly for which formulations the stiffness changes are expected to become zero. A 4–6% (w/w) water addition, depending on the amount of Aerosil® 200, is expected to represent optimal formulations regarding their compatibility with Licaps® (dotted line, Fig. 4).

4. Conclusions

A new technique to analyse mechanical changes of capsules was presented based on a non-destructive texture analysis. The change in Licaps®, capsules mass and stiffness was monitored to assess the compatibility of model formulations with the gelatin shell. The suitable amount of water, to be added to a formulation in view of capsule compatibility, was particularly focussed. Depending on the water activity in the formulations, the Licaps®, capsules became either brittle or they softened. Accordingly it was evident that there exists an optimal water concentration, i.e. a BAW. Since the analytical method provides a quantitative measure of capsule stiffness changes it is possible to inspect this property as a response surface obtained from an experimental design. The concepts presented are useful because hydrophilic or amphiphilic liquid-fill formulations are often thought to be incompatible with gelatin capsules and are therefore refused. Yet, in many cases a good compatibility could be achieved by adding a BAW to the composition and by using tightly closed aluminium blisters. One should of course bear in mind that there are compatibility problems that can not be revealed in a short-term test.

The migration of polyols or other excipients can also exert a plasticiser effect on gelatin capsules. The equilibration time for such a diffusion process may take much longer than for water.

This happens for example in case of a glycerol containing formulation in which capsules may soften even though a BAW was used. From these considerations long-term stability tests should alwaysbe initiated.

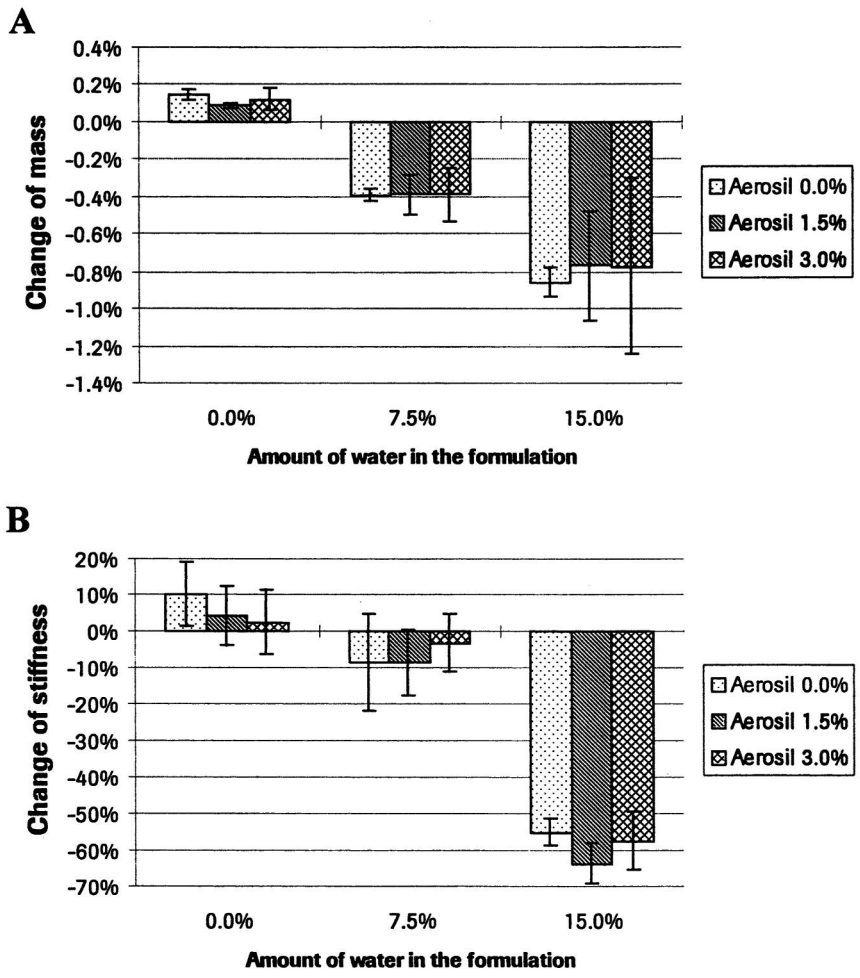

Fig. 3. The change of Licaps® (A) weight (%) and (B) stiffness (%) related to different amounts of water added to mixtures of Labrasol® with varying amounts of Aerosil® 200% (w/w).

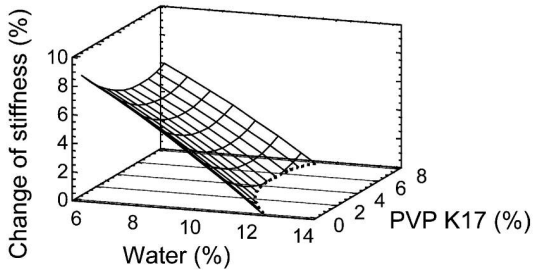

Fig. 4. A part of the response surface, i.e. the change of initial stiffness as a function of the initial water concentration and amount of Aerosil® 200% (w/w) in mixtures of Labrasol®.

The use of texture profiling in combination with a statistical design provides a valuable tool for the development of liquid-fill formulations. The possible interaction of water with other formulation components can be studied as well as the robustness of a composition in relationship to capsule mechanical changes. All information is gathered with a simple analytical technique and comparatively few experiments are required in the framework of a statistical design so that only limited time resources are needed. Industrial scientists could therefore use the methods presented to improve their liquid-fill masses for hard gelatin capsules.

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