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International Journal of Pharmaceutics 324 (2006) 128–135
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Use of texture analysis to study hydrophilic solvent effects on the mechanical properties of hard gelatin capsules

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Received 14 October 2005; received in revised form 31 May 2006; accepted 1 June 2006
Available online 13 June 2006

Abstract

The aim of this work was to explore texture analysis for quantitative evaluation of the effect of hydrophilic solvent systems used as capsule fills on the mechanical properties of hard gelatin capsules. For this purpose, a texture analyzer (Stable Micro Systems, model TA.XT Plus) equipped with a capsule separating rod fixture was used. The tests were conducted in a tension mode. Elastic stiffness, tensile force and elongation at break were determined from the experimental stress–strain curve in order to quantitatively describe both brittleness and softening of capsules. In this paper, it has been demonstrated that the effect of various hydrophilic solvent (i.e. propylene glycol (PG), polyethylene glycol 400 (PEG 400), ethanol) mixtures on the mechanical properties of hard gelatin capsules can be easily monitored using texture analysis. Significant counteractive effects between PG and PEG 400 or ethanol on the integrity of capsule shells were discovered in this study. Texture analysis is found to be a convenient tool for studying formulation compatibility. It can be invaluable in early screening studies of liquid filled hard gelatin capsules.

Keywords: Texture analysis; Hard gelatin capsules; Mechanical properties; Hydrophilic solvents; Experimental design

1. Introduction

Bioavailability of poorly water soluble drugs can be improved by liquid or semi-solid filled capsule formulations (e.g. Sandimmune®, Neoral® and Agenerase®). The formulations can be filled into either soft or hard gelatin capsules. In comparison to soft gelatin capsules, hard gelatin capsules offer several advantages including simplified manufacture and in-house scale-up, higher filling temperature and no addition of plasticizers (other than water) to the capsule shell (Cole, 1999). The impact of liquid filling materials on mechanical properties of hard gelatin capsules still must be considered when developing liquid fill formulations. Small amounts of hydrophilic solvents including propylene glycol (PG), polyethylene glycol 400 (PEG 400) and ethanol are often used in liquids which are filled into hard gelatin capsules in order to improve the solubility or dissolution of the drug. It is known that such solvents may cause either brittleness or softening of the gelatin shell. Depending on the composition of a liquid formulation, it may take a long time (e.g. several months) before one can visually observe changes (i.e. leaking or deformation) in the mechanical properties of the capsules. There is a need for development of a convenient and sensitive technique which can be used to detect minor changes to the capsules in a short period of time even when the capsules still appear acceptable visually. Such a method would be invaluable in early formulation screening.

In the past, various methods have been employed to assess the mechanical properties of hard gelatin capsules. Brittleness of capsules has been determined based on their resistance to applied impact (Cadé and Madit, 1996). In this test, the capsules either break or stay intact when they are hit or compressed by certain mechanical stress. This method is not suitable for evaluating capsules when the capsules become soft rather than brittle. Tensile testing machines have been widely used to study the mechanical properties of polymers. However, these studies have focused on gelatin films (Kellaway et al., 1978) or ribbons (Vemuri, 2000) rather than the intact capsule shells.

A non-destructive texture analysis was described by Kuentz and Rothlisberger (2002) for determination of the optimal amount of water in liquid-filled hard gelatin capsules. Textural profiles were generated when capsules were compressed with a platen up to a certain displacement (Fig. 1a). Because the

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doi:10.1016/j.ijpharm.2006.06.017

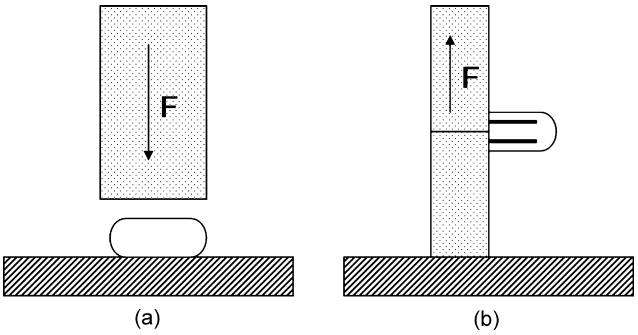

Fig. 1. Comparison of two test modes of texture analysis: (a) force in compression and (b) force in tension.

applied force increased linearly with the displacement, stiffness of capsules can be defined by the slope of a fitted line in the reversible linear range. The potential advantage of this method is that the capsules can be re-analyzed at later time points, which is advantageous especially in an early development stage where little drug material is available and capsules must be hand filled. However, the prerequisite is that the properties of capsules will not be affected by the analysis. Sometimes the moisture content of capsule shells may quickly change when the samples are pulled from stability chambers and exposed to ambient environment. In addition, the stiffness value depends on not only mechanical properties of the capsule but also capsule geometry and the fill mass. If the capsules become soft rather than brittle, the compression test will encounter more difficulties due to deformation of the capsules, i.e. change in capsule geometry.

In the present paper, a new texture analysis method is described. With this technique, the filled material is removed prior to measurement and the intact empty capsule shell is mounted to a separating rod fixture (Fig. 1b). Afterwards, the test is conducted in a "force in tension" mode in contrast to compression mode which is commonly used to evaluate hard shell capsules. In the previous texture analysis method, the probe interacts with the capsule outside surface which is not geometrically homogenous (i.e. body, cap and banding or sealing site). However, the probe in the current method is only in contact with the inner surface of the empty capsule body which always has a standard dimension. Therefore, only changes to the capsule shell itself are detected. Using this method, it is possible to quantitatively profile some mechanical properties of hard gelatin capsules with a wide range of properties. Thus, the effect of various hydrophilic solvent systems on the mechanical properties of hard gelatin capsules can be easily monitored using the current technique. Furthermore, significant interactions (counteractive effects) between PG and PEG 400 or ethanol are found in this study.

2. Materials and methods

2.1. Materials

Cremophor® EL was obtained from BASF. Captex® 355 was provided by Abitec.

Absolute ethanol was from AAPER alcohol and chemical. Propylene glycol (PG) was purchased from Sigma and polyethylene glycol (PEG 400) was from Union Carbide. Hard gelatin capsules (Licaps™, size 00, white opaque) were used as received from Capsugel.

2.2. Water sorption isotherm of hard gelatin capsule

The water sorption isotherm of empty hard gelatin capsules was generated by incubating the capsules with saturated salt solutions in desiccators at 25 °C. The relative humidity in the desiccators was maintained at 6.4, 11.7, 21.6, 32.8, 40.0, 57.5, 68.9, 74.2, 84.3 and 93.7% through the use of saturated salt solutions (LiBr, LiCl, CH_3COOK, $MgCl_2$, CrO_3, NaBr, KI, $NaNO_3$, KCl and KNO_3). After atleast 20 days, water content in the capsules was determined using loss on drying (LOD) as described by Berntsson et al. (1997). The thermogravimetric analysis was conducted using a TGA Q500 (TA Instruments Inc., New Castle, DE) with heat and hold test option (heating rate: 20 °C/min; isothermal temperature: 105 °C; isothermal time: 16 h). Three capsules were used per test. The capsules were cut into small pieces to be loaded onto the TGA pan. Typically the sample size was approximately 15 mg. The hard gelatin shells exposed to various relative humidities and of known water content were also evaluated by the texture analysis method described below.

2.3. Texture analysis

Individual hydrophilic solvents, i.e. ethanol, PG and PEG 400, or their mixtures with Cremophor® EL were manually filled into hard gelatin capsules which were not sealed.

All capsules were completely filled in order to keep the same contact area between different fill materials and the inner surface of the shells. The capsules were sealed in aluminum pouches under ambient conditions and stored at 25 or 40 °C for 1 week or 12 days. After storage, the capsules were emptied and cleaned by removing the filled material and wiping the inner wall with a cotton applicator before analysis using the texture test.

The mechanical properties of hard gelatin capsules are studied using a TA.XT Plus Texture Analyzer (Stable Micro Systems, UK). The instrument is equipped with a 30 kg load cell fitted with a TA-227 separating rod fixture (Fig. 1b). The TA-227 has two short rods of 3 mm diameter each, protruding horizontally from the fixture. The starting position for the two rods is 1 mm apart. The hard gelatin capsules are mounted onto the pair of rods. The tests are conducted using a "return to start" test option with a "force in tension" mode. The probe travels upwards at a speed of 0.5 mm/s until the capsules are pulled apart. The applied force is recorded as a function of distance. Different parameters (elastic stiffness, tensile force and elongation at break) are calculated with software Texture Exponent 32.

2.4. Experimental design

The combinatorial effects of hydrophilic solvents on the mechanical properties of capsules were studied by texture

Table 1
Experimental design and results of combinatorial effect of hydrophilic solvents on mechanical properties of hard gelatin capsules after 12 days at 40 °C

Run order	Ethanol % (w/w)	PG % (w/w)	PEG 400 % (w/w)	Elastic stiffness (N/mm)	Tensile force (N)	Elongation at break (mm)
1	30	0	0	165.7	253.6	5.2
2	0	30	0	14.3	28.2	11.3
3	0	0	30	181.4	279.2	4.6
4	15	15	0	178.6	274.5	4.8
5	15	0	15	178.9	291.7	5.0
6	0	15	15	183.3	313.6	5.0
7	20	5	5	177.9	292.7	5.0
8	5	20	5	159.1	198.7	4.5
9	10	10	10	181.0	308.7	5.0
10	5	5	20	181.4	313.9	5.0
11	30	0	0	165.7	252.1	5.1
12	0	0	30	181.3	302.8	4.8
13	0	30	0	9.0	30.4	13.5
14	15	0	15	178.9	297.5	5.0
15	0	15	15	182.8	311.2	5.0
16	15	15	0	177.3	269.8	4.9
Empty capsule[a]	–	–	–	172.4	221.9	4.3
Empty capsule	–	–	–	173.1	229.2	4.4
Captex® 355	–	–	–	172.2	227.2	4.4
Cremophor® EL	–	–	–	176.1	238.5	4.4

[a] Measured at time 0.

analysis. The experiments were planned by a mixture design using a software package Design-Expert V6.0.6 (Stat-Ease Inc., Minneapolis, MN). The three components studied were: ethanol (A), PG (B) and PEG 400 (C). The total concentration of the three components comprises 30% for each run, yielding 100% with Cremophor® EL as the remaining component. Mechanical properties of hard gelatin capsules were used as responses. The compositions of all the formulations and results of analysis are listed in Table 1.

3. Results and discussion

3.1. Mechanical properties of hard gelatin capsules as a function of moisture content

It is well known that water content is critical for maintaining the structural and mechanical properties of gelatin (Kozlov, 1983), and it has been shown that the structural and mechanical properties of hard gelatin capsules are a function of relative humidity (Bond et al., 1970). Therefore, in order to demonstrate that the proposed texture analysis method could be used to characterize both brittle as well as soft capsules, representative samples were generated by exposing empty shells to controlled humidity conditions. Samples which were stored under the same condition and for the same length of time were analyzed for water content by TGA, and for elastic stiffness, tensile force and elongation at break by texture analysis.

Fig. 2 shows the water vapor sorption isotherm generated for the empty hard gelatin shells exposed to controlled humidity conditions. The data are fitted to the GAB equation:

$$W = \left[W_m C_g K \left(\frac{P}{P_0}\right)\right] \times \left[\left(1 - K\left(\frac{P}{P_0}\right)\right)\left(1 - K\left(\frac{P}{P_0}\right)\right) + C_g K\left(\frac{P}{P_0}\right)\right]^{-1} \quad (1)$$

where W is the amount of water sorbed to a solid component (weight of water/weight of solid), P/P_0 the relative humidity, W_m the amount of sorbed moisture associated with all primary binding sites for that component and C_g and K are constants

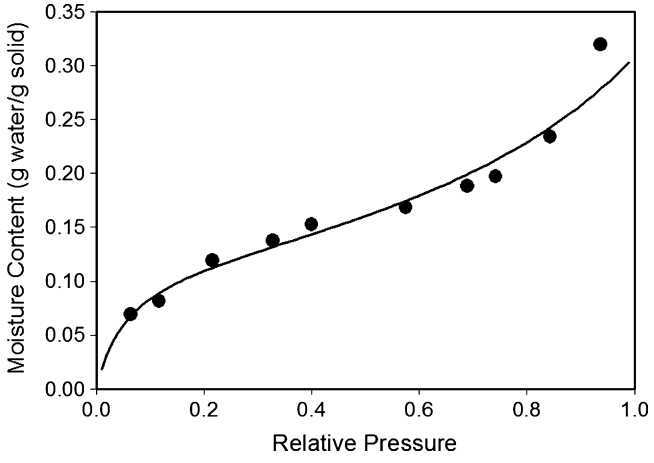

Fig. 2. Water vapor sorption isotherm and fit to GAB equation for empty hard gelatin capsules exposed to controlled humidity conditions. GAB values: $W_m = 0.1191$; $C_g = 28.7$; $K = 0.621$.

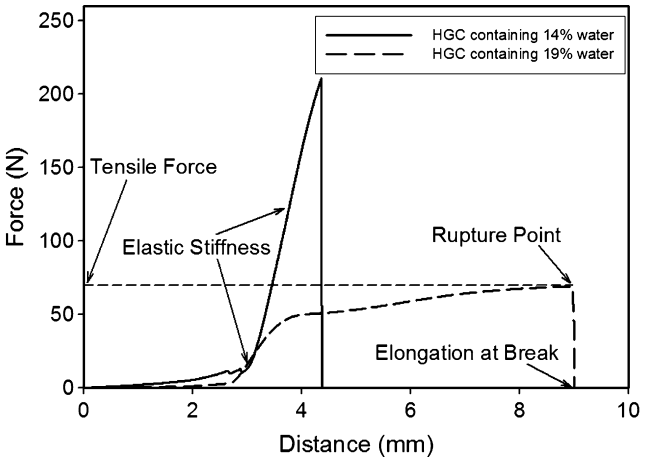

Fig. 3. Typical force–distance profile of hard gelatin capsules by texture analysis.

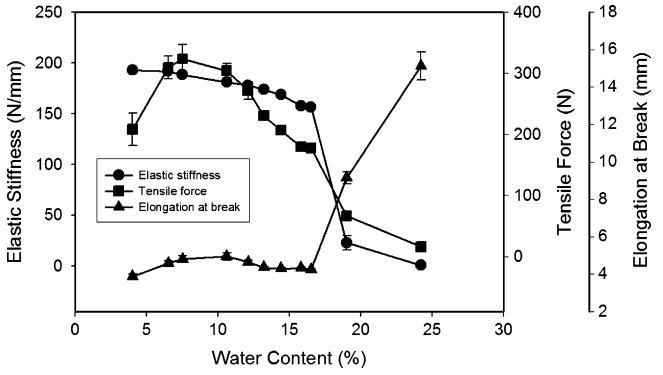

Fig. 4. Mechanical properties of hard gelatin capsules as a function of water content.

related to the free energy of sorption. The parameters (Fig. 2) for the hard gelatin capsules used in this study are similar to those reported by Kontny and Mulski (1989), i.e. $W_m = 0.0874$, $C_g = 10.6$ and $K = 0.775$. This demonstrates that exposing the hard gelatin shells to various controlled humidity conditions is a successful means of generating shells containing different amounts of water.

Fig. 3 shows a typical force–displacement diagram obtained by texture analysis for the empty hard gelatin capsules containing 14 and 19% water, respectively. The water content was determined by TGA, as described in Section 2. Three important parameters, elastic stiffness (slope of linear region of the curve), tensile force (force applied at rupture point) and elongation at break (deformation when a capsule is broken), were derived. In this study, the elastic stiffness and tensile force were not normalized by the cross-section area of gelatin shell since the capsules obtained from the manufacturer are very uniform and the difference in dimension is negligible. Capsules containing 14% water exhibited greater elastic stiffness and higher tensile force than those containing 19% water, which indicates that the higher level of moisture softened the capsules. Therefore, hard gelatin capsules containing 19% water accommodated more plastic deformation before the rupture point was reached.

Commercial hard gelatin capsules typically contain 13–16% moisture. When water content falls below 10%, the capsules become brittle and will easily fracture (Bond et al., 1970). If water content rises above 18%, the capsules soften and distort. Fig. 4 shows that the mechanical properties of empty hard gelatin capsules, as measured using texture analysis, are a function of gelatin shell water content. As may be seen, both elastic stiffness and tensile force decrease when capsules become softer due to increasing water content. Also, elongation at break increases dramatically (plastic deformation) when capsules contain more than 18% water. Conversely, lower moisture content in hard gelatin capsules will result in an increase in elastic stiffness as well as tensile force. When water content drops below 8%, the capsules become so brittle that the tensile force and elongation at break start decreasing. Within the optimal water content range (13–16%), the elastic stiffness and tensile force values range from 157 to ~174 N/mm and 177 to ~230 N, respectively. These data demonstrate that the current texture analysis method can quantitatively characterize mechanical properties of hard gelatin capsules as a function of water content.

3.2. *Effects of individual solvents*

To investigate the effect of hydrophilic solvent systems on mechanical properties of hard gelatin capsules, three solvents, i.e. ethanol, PG and PEG 400, were selected and first studied individually. These hydrophilic solvents are often used in liquid filled capsule formulations to help solubilize the drug. It is known that at the 100% level, they are incompatible with hard gelatin capsule shells (Cole, 1999).

Fig. 5a–c summarizes the effect of each hydrophilic solvent on the integrity of the hard gelatin capsule shells. Captex® 355, a medium chain triglyceride, was chosen as the control for the study since it has been demonstrated to exhibit good compatibility with hard gelatin capsules. As expected, all the studied mechanical properties (i.e. elastic stiffness, tensile force and elongation at break) of capsules filled with Captex® 355 are within the same range of values as empty capsules containing 13–16% moisture. This shows that the handling of capsules (i.e. removing fill materials and cleaning the capsule wall, as described in Section 2.3) has no impact on the mechanical properties of capsule shells. In contrast to Captex® 355, all the hydrophilic solvents have significant effects on the studied mechanical properties of capsules. The presence of ethanol and PG result in lower elastic stiffness and tensile force of the capsules, thus, softening and weakening the capsules. Small molecule alcohols migrate into the capsule shell and replace the chemisorbed water which stabilizes the triple helical structure of gelatin (Moreton and Armstrong, 1998). It was also observed that capsules filled with PG exhibited much lower elastic stiffness and tensile force as well as shorter elongation at break than those filled with ethanol. Indeed for PG, the measurement had to be conducted after the capsules were filled for only 1 min. Otherwise the capsules would become too fragile to be tested.

In contrast to ethanol and PG, capsules filled with PEG 400 became harder and tougher with an increase of all parameters. This is due to the hygroscopicity of PEG 400 which extracts water out of the shell and causes brittleness of hard gelatin

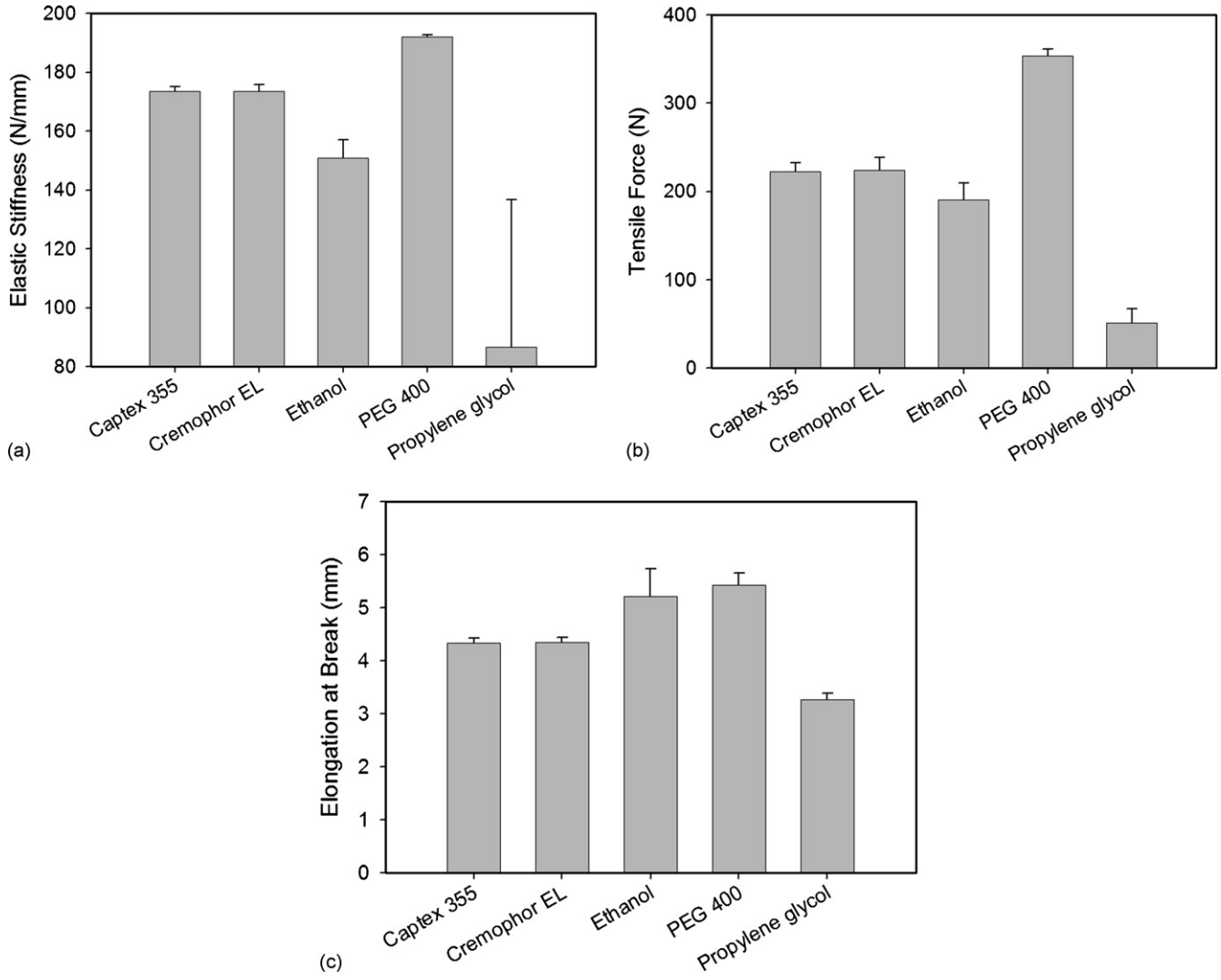

Fig. 5. Mechanical properties of hard gelatin capsules filled with the indicated solvent and stored for 1 week at 25 °C: (a) elastic stiffness; (b) tensile force; (c) elongation at break. For PG, the measurements were taken after 1 min due to rapid softening of the capsules. Samples filled with ethanol also softened, but not to the same extent. Samples filled with PEG 400 remained hard.

capsules, as described by Walters et al. (1992). Overall, the above results agree with findings observed and published by other researchers.

3.3. Combinatorial effects of hydrophilic solvents

A model system containing combinations of all three solvents was studied by means of the texture analysis. The goal was to firstly, demonstrate that the new method is sensitive enough to monitor changes to mechanical properties of capsule shells upon small variations in the formulation composition, and secondly, to study interactions among different hydrophilic solvents with respect to their effect on the capsules. Thus, an experimental design study (Table 1) was conducted. In this study, Cremophor® EL was used as the filler because it is miscible with all the hydrophilic solvents and formed homogenous systems within the studied range. Furthermore, Cremophor® EL has been shown to have minimal effect on the capsules so that it will not interfere with the hydrophilic solvents in the current study. All the capsules were stored at 40 °C for 12 days in order to accelerate the interaction between filled materials and capsules.

Capsules filled with Captex® 355 or Cremophor® EL exhibited nearly identical properties to empty capsules (Table 1). Thus, the changes observed in this study are mainly due to the effects of the hydrophilic solvents in the formulation. The effects of combined hydrophilic solvent systems on mechanical properties of hard gelatin capsules were statistically analyzed using Design-Expert software. The probability value (p-value) was chosen to be the standard level of 0.05 for determination of statistical significance. The software provides several tests, e.g. “lack of fit”, “RootMSE”, “Predicted R-squared” and “PRESS” (Predicted Residual Sum of Squares), to identify the most appropriate model for each response. A quadratic model was selected for both elastic stiffness and elongation at break. However, a special cubic model was found to be the best for tensile force. Also, transformation (inverse square root) was applied to elastic stiffness in order to achieve insignificant lack-of-fit. The following are the equations which, based on the Design-Expert data

analysis, best predict the changes in the mechanical properties of hard gelatin capsules filled with solvents for the formulations listed in Table 1:

$$\frac{1}{\sqrt{Y_1}} = \beta_1 A + \beta_2 B + \beta_3 C + \beta_{12} AB + \beta_{13} AC + \beta_{23} BC \quad (2)$$

$$Y_2 = \beta_1 A + \beta_2 B + \beta_3 C + \beta_{12} AB + \beta_{13} AC + \beta_{23} BC + \beta_{123} ABC \quad (3)$$

$$Y_3 = \beta_1 A + \beta_2 B + \beta_3 C + \beta_{12} AB + \beta_{13} AC + \beta_{23} BC \quad (4)$$

where Y_1, Y_2 and Y_3 represent each response elastic stiffness, tensile force and elongation at break; A, B and C represent the content of individual components: ethanol (component 1), PG (component 2) and PEG 400 (component 3), respectively. In these equations, β represents the coefficient for the associated model term, e.g. β_1 is the estimated coefficient for A and

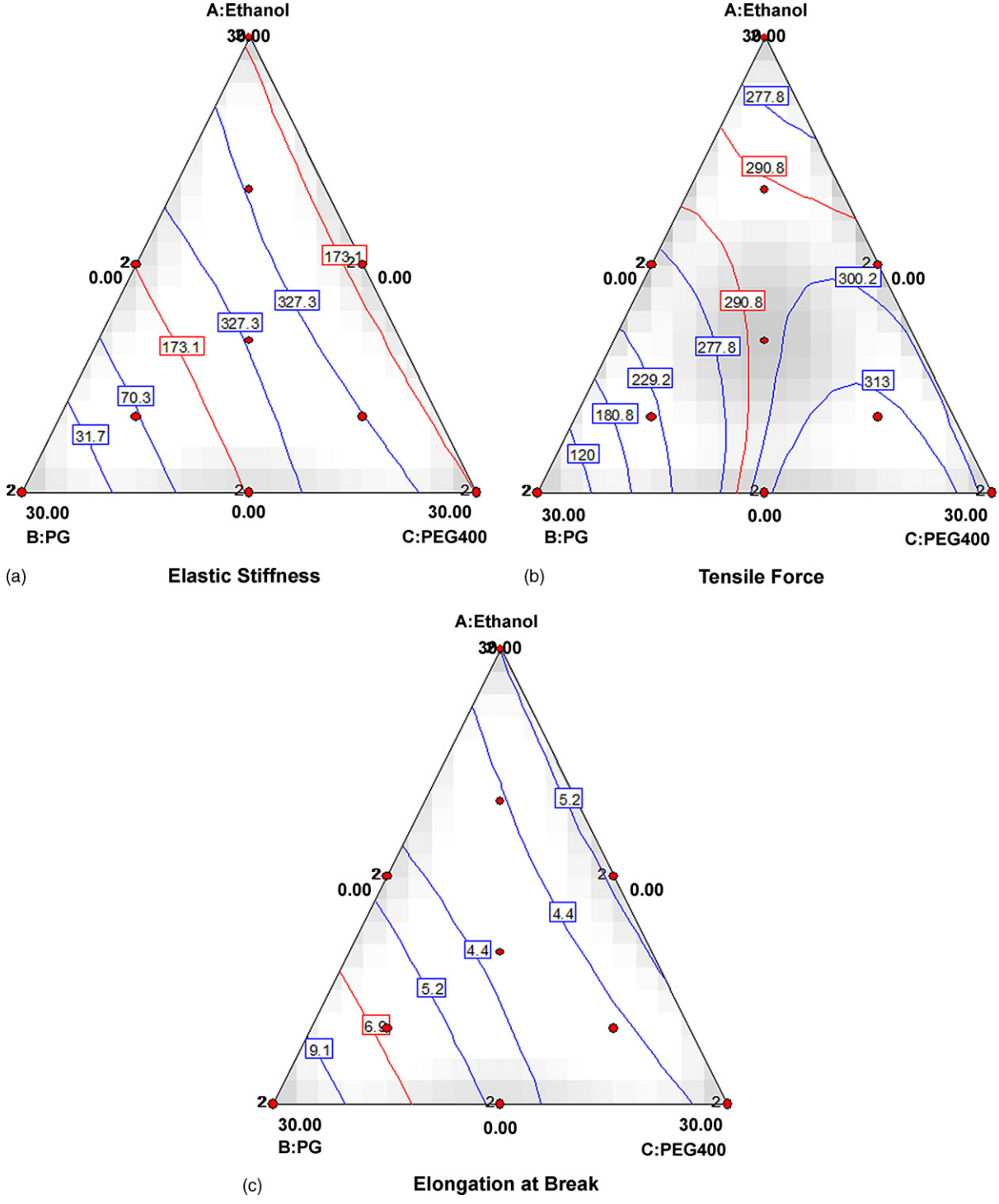

Fig. 6. Contour plot of combinatorial effects of ethanol, PG and PEG 400 on mechanical properties: (a) elastic stiffness; (b) tensile force; (c) elongation at break of hard gelatin capsule (X_1 = ethanol; X_2 = PG; X_3 = PEG 400).

Table 2
Parameter estimates for β in Eqs. (2)–(4)

Component	Elastic stiffness (Y_1)		Tensile force (Y_2)		Elongation at break (Y_3)	
	Coefficient estimate	p-value	Coefficient estimate	p-value	Coefficient estimate	p-value
A	0.08	N/A	253.67	N/A	5.22	N/A
B	0.29	N/A	26.33	N/A	12.10	N/A
C	0.08	N/A	291.05	N/A	4.83	N/A
AB	−0.44	0.0002	519.82	<0.0001	−15.47	0.0004
AC	0.03	0.7321	92.49	0.0339	1.31	0.6723
BC	−0.44	0.0002	603.01	<0.0001	−14.09	0.0009
ABC			−793.78	0.0229		

A, ethanol; B, PG; C, PEG 400.

β_{12} represents an interaction coefficient between A and B. The coefficients for each model and their tests of significance are summarized in Table 2. In a mixture design, it is not meaningful to look at the effects of the individual components since the levels of the components depend on one another. The component combinations which had significant effects on the responses are: AB and BC with p-values smaller than 0.05. These combinations indicated interactions between PG and ethanol or PEG 400. The analysis implied that PG is a critical factor for the mechanical properties of hard gelatin capsules filled with the model system. A delicate balance between PG and ethanol or PEG 400 is required to optimize the compatibility of formulations containing these hydrophilic solvents.

Contour plots of different responses (elastic stiffness, tensile force and elongation at break) are shown in Fig. 6a–c for selected factors (A: ethanol; B: PG; C: PEG 400). Each corner of the plot represents 30% of one of the factors, e.g. corner A = 30% ethanol, 0% PG and 0% PEG 400. The points on the three side lines of the triangle represent two component systems. For example, the points on the line joining A and B represent systems containing ethanol and PG with 0% PEG 400. Any point inside the triangle represents all possible combinations of the three components. The contour lines give predicted values of the response. As shown in Fig. 6a, there are two contour lines which read 173.1 N/mm for predicted elastic stiffness. The contour line close to line AC represents systems containing very low levels of PG. The other contour line corresponds to systems containing approximately 15% PG. Moving toward corner B (i.e. increasing levels of PG), the elastic stiffness decreases significantly.

These plots also demonstrate that the mechanical properties of the hard gelatin shells are significantly influenced by the level of PG present in the formulation. With increasing levels of PG, the elastic stiffness and tensile force decrease, and the elongation at break increases significantly. There seems to be an optimal ratio between PG and ethanol as well as PEG 400 for each response. For example, capsules containing approximately 15% PG had very similar elastic stiffness to that of empty capsules (173.1 N/mm). Similarly, when about 20% PG was in the formulation, tensile force was close to that of empty capsules (229.2 N). Elongation at break was the same as that of empty shells (4.4 mm) as long as the PG content was between 5 and 10%. Systems containing more than 20% PG exhibited significant plastic deformation. Meanwhile, the ratio between ethanol and PEG 400 was shown to be insignificant with respect to its impact on the capsules. These data suggest that the maximum concentration of PG in the model formulation should not exceed 20% in order to minimize the impact on mechanical properties of hard gelatin capsules.

According to these models, the compatibility of formulations containing hydrophilic solvents with hard gelatin capsules could be potentially optimized by selecting the appropriate combinations of these solvents. For example, some solvents, such as PEG 400, can harden the capsules, while others, such as PG and ethanol, exhibit plasticizing characteristics. Therefore, it is postulated that the overall changes to the capsules might be minimized by means of the counteractive effect between these two types of solvents when they are both present in the formulation.

Although the texture analysis method is very sensitive in terms of monitoring small changes of the mechanical properties of hard gelatin capsules over a short period of time, long term stability is still required in order to definitively address the compatibility. This is because the mechanical changes of capsules are typically caused by the diffusion of certain ingredients into capsule shells. Such diffusion processes may take place within various timeframes depending on the properties of filled materials as well as other factors such as storage temperature, environmental humidity, etc. For example, it generally takes about 1–2 weeks for water exchanges between fill mass and the capsule shell. But for other excipients with lower diffusion coefficients (e.g. low molecular weight PEG), a much longer time might be required in order to reach the equilibrium. The process may become even more complicated when the water equilibrium is influenced and accompanied by the migration of other hydrophilic excipients. Therefore, the described method should not be used to replace a long term stability study, but can serve as a useful screen for ranking formulations in the early development process.

4. Conclusion

The texture analysis method described herein has been demonstrated to be a convenient tool for quantitative characterization of the mechanical properties of liquid-filled hard gelatin capsules. Solvents and interaction between solvents which play a major role in capsule shell instability, such as the interaction

between PG and ethanol, can be identified from a mixture design of experiments, in which the fill composition is varied, and the responses are the mechanical properties of the capsule shells obtained from texture analysis. The technique is sensitive enough to differentiate between slightly modified formulations with respect to their effect on capsule integrity, and should therefore provide a useful tool for formulation screening prior to the initiation of long term stability studies.

Acknowledgement

The authors would like to thank Ms. Janet Hinderliter for her assistance.

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