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Time Domain ^{1}H NMR as a New Method to Monitor Softening of Gelatin and HPMC Capsule Shells

Martin Kuentz, Benno Rothenhäusler and Dieter Röthlisberger
F. Hoffmann-La Roche Ltd., Pharmaceutical and Analytical R & D, Basel, Switzerland

ABSTRACT Defined mechanical properties are an essential requirement for any pharmaceutical dosage form and this is particularly important in the case of liquid-filled capsules. Changes in the mechanical properties may be induced by exposure of the capsules to humidity or by a shift of the water equilibrium that typically occurs when hydrophilic or amphiphilic fill masses are used, for example, in self-emulsifying drug delivery systems. This study aims to characterize the softening of empty hard gelatin and hydroxypropyl methylcellulose (HPMC) capsules by means of mechanical tests, a Bareiss hardness test, and a stiffness test using a texture analysis method. A benchtop time domain NMR method is applied in addition to characterize the physico-chemical state of water in the capsule shells and to correlate this with the results of the mechanical tests. Hardness and stiffness measurements resulted in corresponding values, showing a softening for both capsule materials in a humid environment, which was most pronounced beyond 60% relative humidity. The capsules made of gelatin exhibited in general higher stiffness and hardness values compared to the HPMC capsules. The physico-chemical state of water in the capsule shells, as probed by a time domain NMR method, was interpreted in terms of a population balance model. Three different water populations were identified that differ in their molecular mobility, as indicated by their characteristic spin-lattice relaxation times, *T1*. The most loosely bound water fraction dominated in the capsule shells in the range beyond 60% relative humidity. Numerical correlation of the data led to a heuristic equation between the NMR-derived fraction of loosely bound water in the capsule shells and their mechanical stiffness and hardness. Adequate models were obtained for both capsule types, gelatin, and HPMC. Mechanical measurements of pharmaceutical capsules are generally destructive and time consuming. Testing is usually performed in an analytical laboratory, off-line from the manufacturing process, and involves only a small number of samples. Based on the here presented correlation between mechanical stiffness measurements and benchtop time domain NMR data, the latter method may be used as a nondestructive alternative for mechanical testing. This study also opens the possibility to investigate liquid-filled capsules and to establish a process analytical technology (PAT) during manufacturing.

KEYWORDS Liquid filled capsules, Gelatin, HPMC, Hardness, Texture Analysis, Time domain NMR

Address correspondence to M. Kuentz, University of Applied Sciences, Northwestern Switzerland, Institute for Pharma Technology, Gründenstr. 40, CH- 4132, Muttenz, Switzerland; Fax: +41-61-467-47-01; E-mail: martin.kuentz@fhnw.ch

INTRODUCTION

Liquid-filling of hard capsules has become increasingly important for the pharmaceutical industry (Rowley, 2004). The pioneering work of Broer (1978) and Cuiné et al. (1978) established the basis for liquid-filling in hard gelatin capsules and later Walker et al. (1980) adapted the process to large scale filling. Traditionally, capsules are banded. A more recent sealing technology (Cadé et al., 1987) works by lowering the melting point of gelatin by microspraying moisture into the area between the capsule's body and cap. Nowadays this liquid encapsulation by microspray is a commercial process that is available at different production scales known as LEMS™ (Capsugel Division, Pfizer) technology. Thus, in-house development and manufacture of small batches is possible, which is an advantage of hard gelatin capsules compared to soft gelatin capsules (Cole, 1989).

A different liquid-fill capsule technology is used in the case of HPMC capsules (LEMS™ Capsugel Division, Pfizer, Colmar, France) (Ogura et al., 1998), for example, Qualicaps™ by Shionogi Ltd. (Japan). In contrast to the gelatin hard capsules there is only one sealing technology available that is based on a banding process. There is filling and banding equipment available for different batch sizes, covering the needs of industrial drug product development and production as well.

In all liquid-fill capsule technologies, the mechanical properties of the shell play a pivotal role for handling and processing of the dosage form. Softening of the capsule shells may lead to a variety of technical problems during manufacturing. Mechanical shell properties may be altered by an unbalanced amount of water (Kuentz & Röthlisberger, 2002). The amount of water in the capsule shell is defined by the environmental humidity as well as by the hygroscopicity of a fill mass in a coupled equilibrium. Hard gelatin capsules are for example known to exhibit brittleness under dry conditions (Kontny & Mulski, 1989) or softening under high humidity (Cole, 2003). HPMC capsules are known to be less prone to brittleness than gelatin at low relative humidity (RH) (Ogura et al., 1998), but show a softening similar to gelatin capsules under high humidity. It is noteworthy, that brittleness or softening may also origin from migration of other excipients than water.

There are different methods to characterize the mechanical capsule properties. A common method is to expose the capsules to a defined impact load and to summarize the number of broken units (Ogura et al., 1998; Cadé & Madit, 1996). This method is suitable to find the mechanical threshold for capsule brittleness, but is less appropriate to assess the softening of capsules. The loss of capsule hardness may be measured by the Bareiss test (Bareiss Testing Instruments, Oberdischingen, Germany) or more thoroughly by means of a texture analysis method (Kuentz & Röthlisberger, 2002).

The present article focuses on the softening of capsules made of gelatin and HPMC. In particular, we elucidate the role of water during softening. Figure 1 provides a simplified scheme how the water content is associated with different physical states of the polymeric materials. Capsules can be viewed as solid polymer matrices with some water inclusions at the different humidities. It is assumed that the water inclusions reduce the density of physical polymer cross-links (Kuijpers et al., 1999) and thereby lead to a softening of the capsule shell. Once the form stability is lost, the polymer materials may be even viewed as a gel As the material of the capsule shell is changing with water content, the physico-chemical state of the water itself may change as well. Here we used a time domain (TD) NMR method to assess the water in the samples in terms of a population balance model as was previously suggested by Blinc et al. (1995) and Lamisovsky et al. (1997) for gelatin and collagen. In accordance with the arguments provided by Zografi and Kontny (1986) for celluloses, starches, and other polymeric materials, we assumed that water exists in the sample in three distinct populations: as tightly bound, loosely bound, and intermediately bound water. There is a practical and theoretical need to better understand the role of water in the softening of pharmaceutical capsules. Such basic knowledge may lead to the development of a nondestructive analytical technique (process analytical technology, PAT) that could find application during capsule manufacturing and subsequent processing.

MATERIALS AND METHODS

Materials

Gelatin capsules were purchased as Licaps™ (Capsugel, Pfizer Division, Colmar, France) and HPMC capsules were purchased as Qualicaps™ (Shionogi Ltd., Japan) size

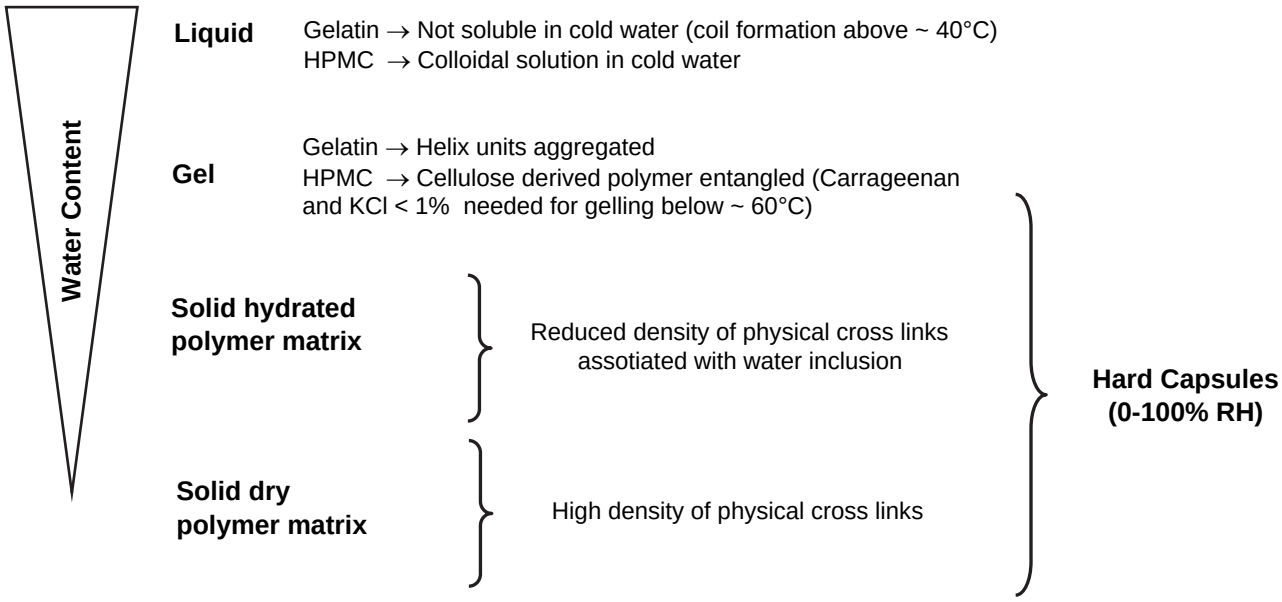

FIGURE 1 **Physical State of Polymer Systems According to Water Content.**

0. All capsules used in the mechanical tests were initially dried under vacuum for 60 h (water loss was gravimetrically measured to check the equilibrium) to have defined water uptake in the following adsorption step, where the capsules were transferred to desiccators of 0%, 6%, 12%, 33%, 57.6%, 75.3%, 84.3%, and 100% relative humidity and stored for 1 week at room temperature for equilibration.

Capsule Stiffness and Hardness Testing

The hardness of Licaps™ and Qualicaps™ was measured using a Bareiss U73 tester (Bareiss Testing Instruments Ltd., Oberdischingen, Germany). A cylindrical plate sensor was used to compress a capsule at a constant compression rate up to 2 mm displacement during 20 sec. The maximum compression force for each individual capsule was recorded (N= 5). The force resolution was 0.2 N and the measuring range was set to 0–20 N.

The characterization of capsule stiffness was obtained from texture profiles using a texture analyzer (TA-XT2i; Stable Microsystems Ltd., Godalming, UK). Licaps™ of size zero (Capsugel, Pfizer Division, France) were compressed with a plate up to 1.2 mm displacement without leaving the regimen of elastic deformation. The testing speed was 0.2 mm/sec and a line was fitted in a defined range of the profile as a secant from which the slope defined a stiffness modulus in units of N/mm. Finally, the change of initial capsule stiffness upon storage was calculated as previously described (Kuentz and Röthlisberger, 2002).

Dynamic Vapor Sorption

Gelatin and HPMC capsules were cut into small peaces of 2–5 mm using a laboratory scale shredder mill (IKA A10, IKA Ltd., Staufen, Germany) and subsequently dried until 0% water exchange was recorded by a microbalance. Water sorption isotherms (adsorption and desorption) for gelatin and HPMC capsules were determined by dynamic vapor sorption at 20°C (DVS1, Surface Measurement Systems Ltd., Alperton, UK). Both materials show a significant hysteresis between the adsorption and desorption branch of the isotherm. We therefore chose to prepare all moisture levels in the samples for stiffness analysis and TD-NMR in the adsorption mode starting from dry material. We used the measured adsorption isotherm of each material also for the linear interpolation of moisture levels expressed in terms of weight percent (TD-NMR) to moisture levels expressed in terms of relative humidity for the correlation of stiffness data with the appearance of particular water populations in the sample.

Time Domain NMR Analysis

Preparation of Capsules for NMR Experiments

Ten capsules were used in each experiment. The capsules were cryo-milled using a laboratory scale shredder mill (IKA A10; IKA Ltd., Staufen, Germany) and

cut into small pieces of approximately 2–5 mm. The pieces were then filled into NMR glass tubes (pctub 18.0; Bruker, Rheinstetten, Germany) and dried under vacuum at room temperature for 60 h. The weight of the dry samples was recorded. The samples were then remoisturized to a predefined level within the sealed NMR glass tubes for 13 days at 20°C by means of a humidifying tube insert that contained the required amount of water. The actually reached moisture level within the samples was confirmed by weighing after the humidifying device has been removed from the tubes. The sample tubes were sealed again and stored at 20°C for not longer than 24 h until the samples were examined by TD-NMR.

Determination of Water Fractions

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 (TD-NMR) instrument (minispec mq20, Bruker, Rheinstetten, Germany). Temperature was constant at 20°C during all measurements. We used a standard inversion recovery pulse sequence $\{[RD - 180° - IR - 90° - RDT - ADS]_{NS}\}_N$, 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 *ADS* 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 various inversion recovery traces $S(t)$ that we obtained from gelatin and HPMC capsules at various moisture levels were fitted in parallel for all using a triexponential decay function:

$$S_s(j,t) = M1_s(j)\left(1 - 2\exp\left(\frac{-t}{T1_{1s}}\right)\right) + M2_s(j)\left(1 - 2\exp\left(\frac{-t}{T1_{2s}}\right)\right) + M3_s(j)\left(1 - 2\exp\left(\frac{-t}{T1_{3s}}\right)\right) \quad (1)$$

where *j* indicates the moisture level in the sample and the index *s* stands for either gelatin or HPMC capsules. The amplitudes $M1_s(j)$, $M2_s(j)$, and $M3_s(j)$ are proportional to the three populations of water in the sample *s*, at a particular moisture level *j*, characterized by the relaxation times $T1_{1s}$, $T1_{2s}$, and $T1_{3s}$. The total moisture content by weight in a sample, $M_s(j)$ may be calculated as:

$$M_s(j) = \alpha_s\left(M1_s(j) + M2_s(j) + M3_s(j)\right) \quad (2)$$

where α_s is a scaling factor that is obtained by comparison of the total NMR amplitude as given by Eq. (2) with the water content of the sample as obtained from the sorption isotherm.

RESULTS AND DISCUSSION

Gelatin and HPMC capsules were first characterized by their water sorption isotherms. As the conformation of the polymer chains depends on the sorption or desorption history (Zografi & Kontny, 1986), all capsules used in this study were first dried before they were equilibrated at varying humidities. Figure 2 shows the adsorption branch of the isotherms at 20°C for both materials. According to the Brunauer classification (Dörfler, 1994) the isotherm of HPMC represents a type III isotherm, whereas the one observed from gelatin would have to be categorized as type II. Both isotherms may be interpreted in terms of multilayer sorption where different water populations are involved having distinct sorption energies.

The HPMC capsules adsorbed less water than the gelatin capsules at given humidities, which was in good agreement with published data from Nagata (2001), who also used Karl Fisher methodology.

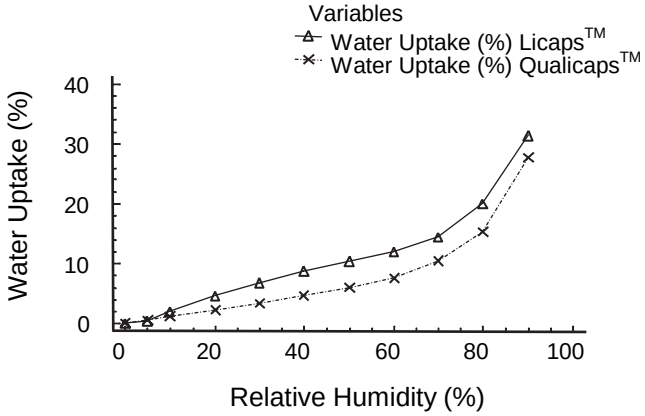

FIGURE 2 **Water Uptake in (%) From Dynamic Vapour Sorption Measurements of Gelatin (Licaps™) and HPMC (Qualicaps™) Capsules.**

The two capsule types were studied using two different mechanical tests. A texture analysis was conducted in which the entire compression force versus displacement curve was obtained. The stiffness was here determined in the linear range, that is, the reversible strain. On the other hand, the Bareiss U 73 hardness test is a typical quality control method for capsules. A single force is measured after a defined compression has been applied. Figure 3 displays the results of the tested gelatin capsules for stiffness (N/mm) and for the Bareiss hardness (N) as a function of the relative humidity. Both mechanical properties exhibit a similar pattern. This could be expected, since both texture analysis and Barreis test were performed within the elastic portion of the force–displacement curves.

Figure 3 shows that stiffness and hardness below 40% relative humidity (RH) do not greatly change on the average. It is known that dry conditions below 25% RH can lead to brittleness (Kontny & Mulski, 1989; Cadé & Madit, 1996) if the elastic region of the force–displacement curve is left. On the other hand, a loss of both stiffness and hardness occurred at higher relative humidities than 60% (Fig. 3) and the softening was here also palpable.

The stiffness and hardness values for the HPMC capsules (Fig. 4) were generally lower than the values obtained from the gelatin shells. Again softening was observed at higher relative humidity, being most pronounced above 60% RH. The softening appeared unacceptable in view of capsule processing and of later handling by the patient.

The phenomenon of capsule softening in the presence of water is still not fully understood. Tomka and Signer (1975) and later Zografi and Kontny (1986) proposed a mechanism for the uptake of water by swellable polymers. According to their view, a polymeric material has disordered voids of varying size and shape. At low relative humidity water is tightly bound within those voids where the water molecules fit well and where hydrogen bonding occurs. At higher humidity levels, water becomes increasingly incorporated into the polymer, which leads to swelling and the polymer chains become gradually more separated from each other. The binding energy of these water molecules may be decreased thereby. However, the number of potential binding sites increases as the number of contact points between the polymer segments decreases. At even higher relative humidity, one might expect the occurrence of a type of water, viewed as bulk or loosely bound water. This model was first applied to gelatin (Tomka, 1983) assuming as a first approximation only two water subsystems. Later three water subsystems were considered for cellulose (Zografi & Kontny, 1986). Time domain NMR analysis has been shown to be a suitable technique for probing the water subsystems with regard to the molecular mobility of the respective water protons according to their characteristic spin-lattice relaxation time *T1*. The molecular mobility of the more tightly bound water should thereby be reduced (Katzhendler, 2000). Up to three water subsystems have been identified by TD-NMR in highly hydrated gelatin matrices (Lamisovsky et al., 1997). These subsystems differed according to their binding energies and correspondingly displayed characteristic spin-lattice relaxation times *T1*. Whereas the relaxation time *T1* is considered as characteristic and constant for a certain water subsystem or population, the amount of water in that population may change, as the sample is exposed to different levels of

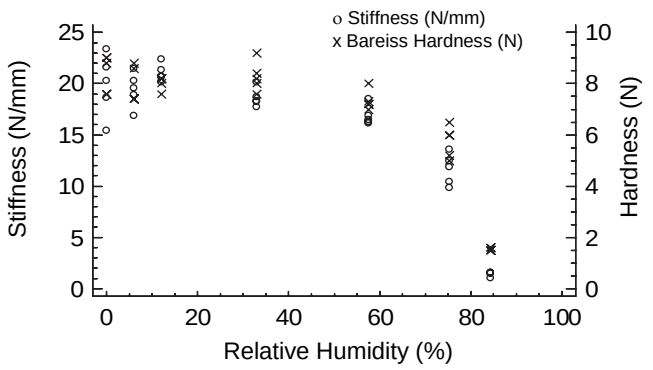

FIGURE 3 **Stiffness (N/mm) and Bareiss Hardness (N) of Hard Gelatin Capsules (Licaps™) as a Function of the Relative Humidity (%).**

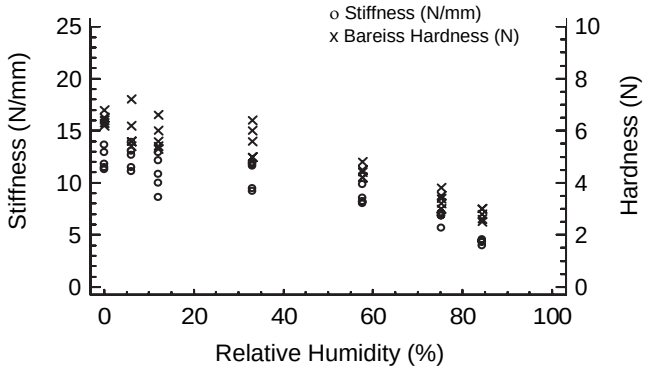

FIGURE 4 **Stiffness (N/mm) and Bareiss Hardness (N) of HPMC Capsules (Qualicaps™) as a Function of the Relative Humidity (%).**

humidity. Here we also followed this so-called population balance approach as outlined by Blinc et al. (1995) and Lamisovsky et al. (1997) in our evaluation of the TD-NMR signals, although our focus is on polymer systems in the low hydration regimen. It should be mentioned, however, that an alternative theoretical approach is debated in the physical literature, where the water populations in a sample may exhibit varying relaxation times depending on the water content (Vackier et al., 1999).

We achieved best fitting results for the various inversion recovery traces when we assumed a three population model according to the three exponential terms given in Eq. (1). Thus, we obtained a set of three characteristic spin-lattice relaxation times, $T1_x$ for each capsule material, gelatin, and HPMC. The parameter fitting Eq. (1) provided for Licaps^{TM} subsystems with: $T1_1$= 60.0 msec, $T1_2$ =1.7 msec, $T1_3$= 120.1 msec, and for the HPMC capsules: $T1_1$= 34.1 msec, $T1_2$=2.5 msec, $T1_3$= 179.5 msec. These subsystems can be viewed as corresponding to water fractions having a characteristic molecular mobility and hence distinct sorption energy. The amount of water by weight in each subsystem was obtained from Eq. (1) and by comparison with the sorption isotherm (Eq. 2). Labels were assigned to each subsystem according to the molecular mobility of the water, that is, the *M1* fraction was named as "loosely bound" water or bulk water, *M2* as bound water, and *M3* represents the amount of "tightly bound" water.

Figure 5 gives the amount of water in the different water populations in gelatin capsules as a function of the relative humidity. As the humidity is increased, the first populated subsystem consists of tightly bound water, *M3*. Surprisingly we find that this water population disappears again at higher humidity levels beyond about 40% RH. This could indicate a structural change of the whole polymer matrix, where the corresponding binding sites of the tightly bound water disappear during the swelling process. The water subsystems *M2* and *M1* appeared only above a threshold of about 10% RH and increased continuously as humidity was increased. Most dominating was the loosely bound water at higher relative humidity, which was also expected from the model of Gál, Tomka and Signer (1976), keeping in mind that this is a population balanced view. The loosely bound water appears to prevail in the range of polymer swelling and hence also in the softening of the shells. Due to this dominating character the *M1* fraction seems to be most important for hardness and stiffness of gelatin capsules.

Figure 6 shows the three water populations *M1*, *M2*, and *M3* as a function of the relative humidity in HPMC capsules. The first populated subsystem consists again of tightly bound water at low humidity levels. Interestingly, the tightly bound water fraction *M3* increased slightly under very dry conditions until saturation is reached at about 60–70% RH, followed by a slight further increase at the highest humidity. The behavior of the tightly bound water, *M1*, showed the most noticeable difference of this polymer in comparison with gelatin. The water population *M2* appeared at similar threshold humidity as in gelatin capsules and also increased continuously. Higher threshold humidity than with gelatin was observed for the loosely bound water, *M1*, that started to increase

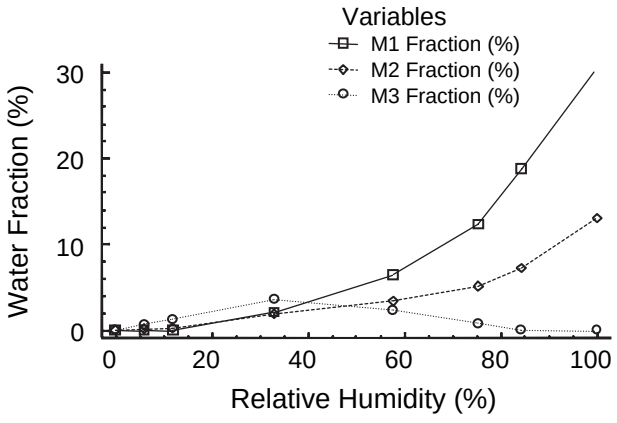

FIGURE 5 **Determined Water Fractions From Time Domain NMR in (%) as a Function of the Relative Density for Gelatin Capsules (Licaps^{TM}).**

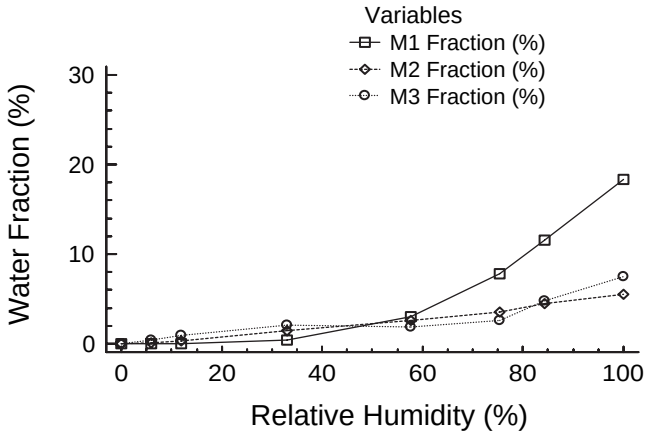

FIGURE 6 **Determined Water Fractions *M1*, *M2*, and *M3* From Time Domain NMR in (%) as a Function of the Relative Density for HPMC Capsules (Qualicaps^{TM}).**

beyond 30–40% RH. As expected, the *M1* population prevailed again in the high humidity range. It appeared that for both polymer capsules the *M1* water population contributed the most to the softening effect.

We therefore further focused on finding a correlation of the mechanical stiffness with the *M1* water subsystem in HPMC and gelatin capsules (using StatgraphicsPlus® v.5.0, StatPoint, Herndon, VA, USA). A simple linear model did not adequately fit the experimental data from both capsule types and therefore a second order polynomial equation was chosen as a heuristic fitting function:

$$S = a + bM1 + cM1^2 \tag{3}$$

where S is the stiffness (N/mm), $M1$ is the amount of loosely bound water with spin-lattice relaxation time $T1_1$, and a, b, and c are constants.

A very good fitting adequacy was attained with an R^2 value of 0.945 and Fig. 7 shows the model including the confidence bands and prediction limits for gelatin capsules. The decline of stiffness with rising *M1* was very well explained by the model and the fitted constants are provided in Table 1. The goodness of fit can also be inferred from the low *P*-value being even smaller than 10^{-3}. Model validity was also confirmed by comparing the lack of fit with the pure error (Table 1).

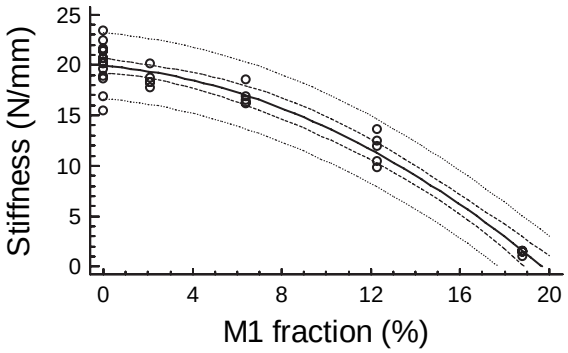

FIGURE 7 **Gelatine Capsules: Polynomial Regression Model With 95% Confidence and Prediction Limits of the Stiffness (N/mm) as a Function of the Water Fraction *M1* (%).**

Figure 8 shows the decline of stiffness in HPMC capsules as a function of the M1 water subsystem. Here we find a different curvature as compared to the corresponding relationship in gelatin capsules (Fig. 7). The stiffness of HPMC capsules was generally lower than the corresponding values for gelatin. However, the stiffness changes relative to the initial value was less marked for capsules of HPMC than for those made of gelatin. The residual stiffness can be found in HPMC capsules even at the highest humidity levels. This explains the good mechanical robustness of HPMC capsules in this humidity range.

The model for the HPMC capsules is displayed in Table 2 and the adjusted R^2 value indicates that an adequate portion of the variance is explained by the model, which was also reflected by the corresponding *P*-value. An analysis of the residuals showed again no significant lack of fit (Table 2).

It can be summarized that adequate models of the capsule stiffness were found for both polymers as a function of the loosely bound water, *M1*, alone. The other water populations might contribute to stiffness as well, but their importance for the softening is limited and they can be neglected in a first approximation. The amount of loosely bound water *M1* in the sample as obtained from TD-NMR relaxation measurements could therefore hold as a surrogate marker for mechanical stiffness of capsules of gelatin and HPMC.

We further investigated the relationship between *M1* and the Bareiss hardness using the second order polynomial model analogues to Eq. (5). The hardness as a function of *M1* resulted in a similar relationship

TABLE 1 **Gelatin Capsules (Licaps™) Polynomial Regression Model:Stiffness (N/mm)=19.92 – 0.196*M1 – 0.0415*M1^2, R^2 (adj.) 0.945**

Analysis of variance with lack of fit					
Source	SS	DF	MS	*F*-Ratio	*P*-Value
Model	1439.0	2	719.48	292.8	0.000
Residual	78.640	32	2.4575		
Lack of fit	4.0555	2	2.0278	0.82	0.452
Pure error	74.585	30	2.4862		
Total (corr.)	1517.6	34			

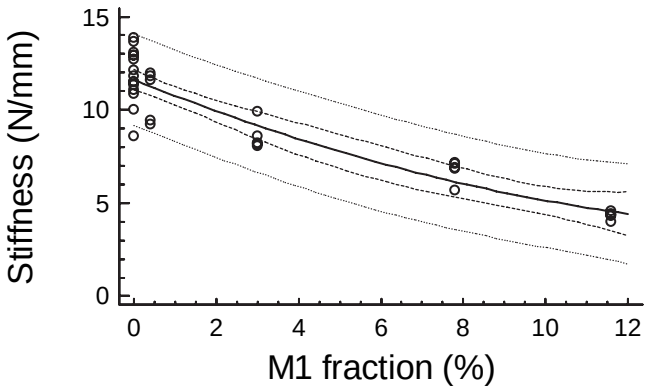

FIGURE 8 **HPMC Capsules:Polynomial Regression Model With 95% Confidence and Prediction Limits of the Stiffness (N/mm) as a Function of the Water Fraction *M1* (%).**

TABLE 2 **HPMC Capsules (Qualicaps™) Polynomial Regression Model:Stiffness (N/mm)=11.63 – 0.895*M1+0.0245*M1^2, R^2 (adj.) 0.845**

Analysis of variance with lack of fit					
Source	SS	DF	MS	*F*-Ratio	*P*-Value
Model	263.02	2	131.51	93.8	**0.000**
Residual	44.865	32	1.4020		
Lack of fit	5.6283	2	2.8142	2.15	**0.134**
Pure error	39.237	30	1.3079		
Total (corr.)	307.88	34			

as shown by Fig. 7 and the adjusted R^2 of the model yielded 0.949, without indication of an existing lack of fit. An acceptable second order model was also obtained with the hardness data of HPMC capsules, and analogous to the stiffness in Fig. 8, a similar curvature was obtained with a mathematical function of the *M1* values. The adj. R^2 was 0.877 and the model validity was again supported by an absent lack of fit. These analogous findings were expected, since stiffness and hardness correlated quite well with the relative humidity as discussed before (Figs. 3 and 4). The mechanical parameters mark a softening of capsules with rising humidity. This loss of capsule stiffness and hardness can therefore be viewed as the result of a swelling process that the polymer matrix undergoes and loosely bound water plays a key role here. The effect might be an indirect one, as a rise of bulk water is accompanied by a divergence of polymer chains and thus loss of binding points in the matrix. The physico-chemical nature of the two polymer matrices is, however, not the same for gelatin and HPMC capsules, as shown by the different curvature of hardness or stiffness as function of *M1*. There is certainly more experimental work needed to elucidate the relationship between spin-lattice relaxation signals and the structure of the different polymer matrices during their interaction with water in more detail (Blinc et al., 1995). However, from a technological viewpoint it is a finding of practical importance that NMR relaxivity data can be correlated with capsule stiffness or hardness. This could finally lead to a fast, noninvasive and nondestructive test for these mechanical parameters during pharmaceutical manufacturing of capsules. Further applied research should also be conducted using liquid-filled capsules, where water migration between fill mass and capsule shell often induces mechanical changes such as softening.

CONCLUSION

Hard gelatin and HPMC capsules were tested in view of their softening behavior with rising humidity. Herein capsule stiffness and hardness were determined and correlated with data obtained from time domain NMR. The latter method indicated that adsorbed water existed in the capsules in the form of three distinct subsystems characterized by their corresponding spin-lattice relaxation times: tightly bound water, bound water, and loosely bound water. The amount of loosely bound water, *M1*, could successfully be correlated with stiffness as well as with hardness for both capsule types. It is interesting that tightly bound water, *M3*, showed a qualitatively different behavior in gelatin as opposed to HPMC. This might indicate different underlying swelling processes. The presented TD-NMR method provides a better mechanistic understanding of the interaction of water with polymer capsules and their softening and, in addition, provides a surrogate parameter for capsule hardness or stiffness measurements.

A next research step could be to study filled capsules either with granules or liquid-filled masses. For the latter systems, a coupled equilibrium of water exchange between fill mass, capsule shell, and environment exists. Such liquid-filled capsules often exhibit a softening at lower humidities than one could expect for the shell material alone, which causes technical problems during manufacture and storage. The TD-NMR data are also here expected to be a surrogate marker of the shell softening that arises from water.

Better monitoring during the capsule manufacturing process is also in line with the current requirements of

the regulatory authorities that foster development of innovative process analytical controls. The pharmaceutical quality should be rather built in the product than just tested in the following production. However, there is additional research needed to bring this idea to industrial reality.

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