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Gelatin capsule brittleness as a function of relative humidity at room temperature

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Summary

The pharmaceutical literature cites many examples which indicate that hard gelatin capsule brittleness is a function of moisture content. Likewise, brittleness can be correlated with relative humidity. In this study, brittleness of empty capsules was noted at relative humidities below 40%. Mexitil capsules exhibited a similar profile, suggesting that relative humidity in the vapor phase is an important factor that can be monitored and controlled. It is known that moisture will redistribute between the various components in a given system until a single relative humidity is attained in the vapor phase. Thus, a priori prediction of the value of this thermodynamic variable for known conditions will allow prediction of capsule brittleness. For a closed system, the final value is intimately dependent upon the affinity of the various materials for water. As such, the sorption–desorption moisture transfer (SDMT) model, which is based on isotherms for the respective materials, was employed to estimate the final relative humidity for the Mexitil/gelatin capsule system. Results are presented that demonstrate the general applicability of the SDMT model for predicting the incidence of brittleness problems, as well as selecting optimal initial loss on drying (LOD) values for the empty gelatin capsules and the formulation to ensure the absence of brittleness.

Introduction

The viscoelastic properties of gelatin capsules are markedly dependent upon moisture content and temperature. Under ambient temperature conditions, a minimum quantity of sorbed moisture is necessary to act as a plasticizer and maintain the capsules in a pliable state. However, too much sorbed moisture can induce swelling and cause the capsules to become sticky and adhere to one another. Hence, an intermediate moisture content range is desirable to provide optimal handling properties.

Empty gelatin capsules have a tendency to gain or lose moisture as environmental conditions change. Generally, as relative humidity is increased (under constant temperature) or temperature decreased (at constant relative humidity), moisture uptake (sorption) will occur. Conversely, decreasing relative humidity (at constant temperature) or increasing temperature (at constant relative humidity) will lead to a moisture loss (desorption). Such changes in environmental conditions can occur during storage, filling, and packaging, potentially altering the properties of the capsules.

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Another factor that warrants serious consideration, and one upon which the current paper is based, is the transfer of moisture between gelatin capsules and the contents of the capsules. Consider filling "overdried" formulation into capsules. Transfer of moisture from the capsules to their contents will occur and, if enough moisture is lost, will render the capsules brittle. At the opposite extreme is filling "wet" formulation into capsules. In this situation, moisture transfer to the capsules will occur, and if enough moisture is sorbed, capsule swelling and stickiness will be induced.

Several studies have appeared in the pharmaceutical literature demonstrating the transfer of water from gelatin capsules to their contents. Strickland and Moss (1962) showed transfer to pentobarbital sodium. Bond et al. (1970) described similar phenomena to cephalexin and Bell et al. (1973) to sodium cromoglycate. Ito et al. (1969) demonstrated that water-insoluble excipients with high sorptive capacities (i.e., Avicel and corn starch) are also involved in moisture transfer between materials in this dosage form.

The present study addresses the following unresolved questions concerning gelatin capsule brittleness under constant temperature conditions. What is the critical relative humidity (and related water content) for gelatin capsules below which brittleness occurs? Can the relative humidity that exists in a closed container of capsules and formulation be predicted if one knows the weight of the capsules and formulation, and the initial moisture contents of each? Subsequently, can such predictive capability be utilized in conjunction with the critical relative humidity of brittleness to rationally select the optimal initial moisture levels of both the capsule and formulation to inhibit the capsule from drying out?

Materials and Methods

Mexitil granulation[1] was prepared by typical pharmaceutical manufacturing procedures. Mexitil contains the active drug mexiletine HCl, colloidal silicon dioxide, corn starch, and magnesium stearate. The gelatin capsules[2] were used as received.

Water vapor uptake isotherms

All water vapor uptake isotherms were generated gravimetrically. The sorption isotherm for Mexitil was obtained using a Cahn electrobalance[3], sorption rack, and procedures similar to those employed in previous work (Zografi et al., 1988; Kontny, 1985; Grandolfi, 1987). In essence, about 0.4 g of formulation were initially dried under heat (100 °C) and at a pressure of approximately 0.005 mm Hg. Upon return of the sample to 20 °C and isolation from the vacuum pumps, the isotherm was generated by first exposing the sample to the lowest relative humidity until constant weight was attained. This weight was recorded, and the relative humidity was measured using an oil manometer which had previously been calibrated against relative humidities (obtained from the literature) of known saturated salt solutions. The second and subsequent sorption points were measured in a similar manner by gradually increasing the relative humidity to higher values.

Isotherms for the empty gelatin capsules were generated using desiccators containing saturated salt solutions in the bottoms of the containers. Individual isotherm points were obtained by placing 10 capsules from their original storage containers into a weighing boat, obtaining their initial (total) weight and placing them in the appropriate desiccator. Subsequent weighings were taken until constant sample weights were attained. Generation of the capsule isotherm in this manner provided a representative isotherm in terms of practicality for this material since capsules are usually used with an initial moisture content of greater than 10%. This procedure is in contrast to more classical isotherm generation in which the solid is initially dried to very low moisture levels (approaching 0%). In this manner, potential hysteresis

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[1] Boehringer Ingelheim Pharmaceuticals, Inc.

[2] Capsugel.

[3] Model 2000, Cahn Instruments, Division of Ventron Corp.

effects (York, 1980) were minimized since the isotherm for the desorbing species (gelatin capsules) was effectively generated beginning from the "storage" state. Dry weights were estimated by taking similar samples from their original sample containers and conducting loss on drying (LOD) determinations using a Compu-Trac Moisture Analyzer [4] with temperature rising to 145 ° C. The initial moisture content was then subtracted from the initial sample weight to provide an estimate for the dry capsule weights.

Brittleness testing

Capsules (empty or containing formulation) were equilibrated in desiccators containing various saturated salt solutions prior to brittleness testing. All brittleness testing was carried out according to the following procedure. The capsule to be tested was placed on a flat surface. Force was uniformly applied to the capsule using the bottom of a beaker. Capsules were evaluated for brittleness based on the following criteria: brittle - capsules shattered into pieces; non-brittle - capsules deformed with force but did not shatter. Forty capsules were equilibrated at each relative humidity and evaluated for brittleness.

Moisture transfer studies

Equipment and procedures used for moisture distribution studies were similar to those described elsewhere (Zografi et al., 1988; Grandolfi, 1987). In essence, the system had high vacuum drying capabilities (i.e., forepump [5] and diffusion pump [6], temperature control (20 ° C), and pressure measurement [7]). All headspace volumes were determined via helium [8] gas expansions and associated pressure measurements [9].

Mexitil and empty gelatin capsule samples were placed in separate compartments. Mexitil was dried under heat (90 ° C) and dynamic vacuum ($< 1 \times 10^{-4}$ mmHg). The headspace volume in this cell was determined at this point. The gelatin capsules were exposed to dynamic vacuum pull for about 30 s to evacuate air from the system and were then isolated. With the remainder of the system evacuated, water vapor of the desired relative pressure (using temperature-controlled saturated salt solutions) was exposed to the gelatin sample until no further change in the vapor pressure occurred. Equilibrium was verified by isolating the saturated salt solution from the system and monitoring vapor pressure in the headspace above the capsules, again assuring no further change in vapor pressure. Following a similar procedure for the Mexitil, the two compartments were equilibrated together until an equilibrium pressure was attained. This pressure was then converted to relative pressure by dividing by P_0 (17.535 mmHg at 20 ° C (Weast, 1986–87)). When multiple data points were generated on the same sample, experiments were always conducted in a manner similar to that used to generate the isotherms (i.e., increasing relative pressure for Mexitil, decreasing relative pressure for gelatin capsules). To avoid potential uncertainties associated with hysteresis, the headspace volume in the gelatin capsule compartment was obtained only after all distribution studies were completed for that material.

Results

Capsule brittleness studies

Fig. 1 shows the effect of relative humidity on capsule brittleness of empty gelatin capsules. Capsules stored at relative humidities less than about 40% exhibit brittleness, whereas those stored at higher relative humidities are not brittle. Hence, capsule brittleness can be related to the relative humidity to which the capsules are exposed. Brittleness phenomena were not investigated above 84% relative humidity as the gelatin sorbs considerable moisture in this range (Bell et al., 1973; York, 1980). This induces swelling and alters the physical properties of the capsule to a very elastic nature.

Provided that equilibrium relative humidity is an indicator for capsule brittleness, gelatin cap-

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[4] Model MA-5A, Compu-Trac, Inc.

[5] Model 1402, Sargeant-Welch.

[6] Model VMF-20, CVC Products, Inc.

[7] Ionization gauge and controller, Granville-Phillips.

[8] Presto.

[9] Barocel pressure sensor and electronic manometer, Datametrics, Inc.

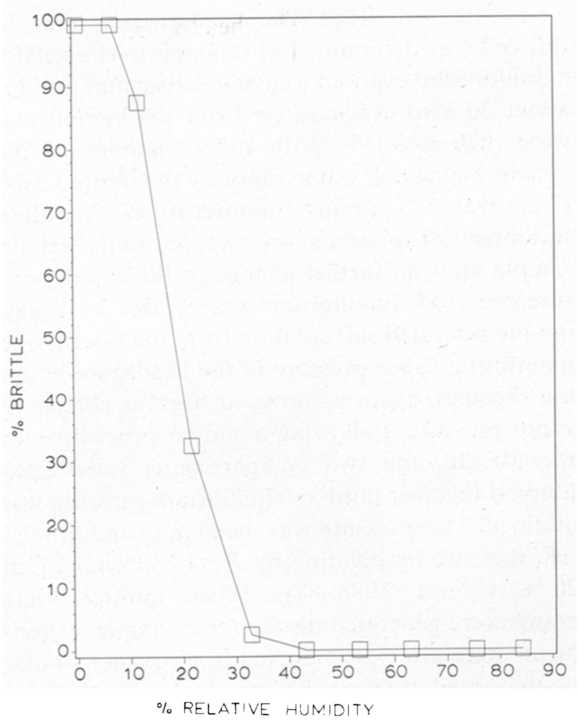

Fig. 1. Brittleness of empty gelatin capsules as a function of relative humidity.

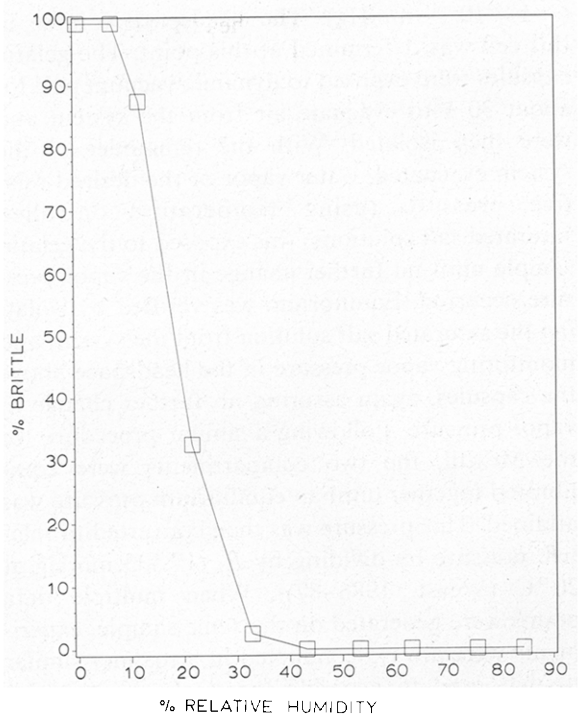

Fig. 2. Brittleness of Mexitil capsules as a function of relative humidity.

sules containing solid material should exhibit a similar brittleness profile to that observed for empty capsules. Fig. 2 illustrates that this is indeed the case for Mexitil-filled capsules. The slight apparent difference in the brittleness of Mexitil-filled capsules relative to empty capsules is not deemed significant due to the inherent difficulties in conducting brittleness testing on filled capsules.

Water sorption isotherms

Water sorption isotherms for the empty gelatin capsules and Mexitil formulation are presented in Fig. 3. Since this study focused on moisture transfer from gelatin capsules to Mexitil formulation as a whole, and not to individual components of the formulation, a single isotherm was generated for Mexitil. Note that both isotherms are similar in shape (i.e., sigmoidal) but differ in the amounts sorbed at a given relative humidity. For comparison purposes, consider the amounts of moisture taken up at 50% relative humidity. Empty gelatin

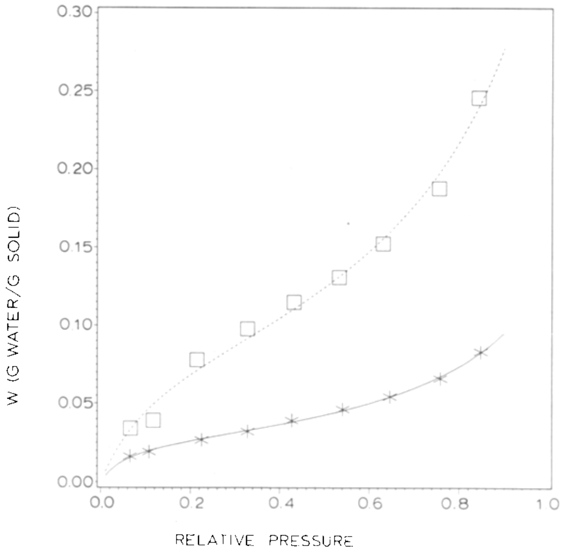

Fig. 3. Moisture uptake isotherms and GAB fits for empty gelatin capsules and Mexitil formulation. □□□, Gelatin capsules; ***, Mexitil; ———, GAB Mexitil; ------, GAB gelatin capsules. Mexitil GAB values: $W_m = 0.0274$, $C_g = 21.2$, $K = 0.800$. Gelatin capsule GAB values: $W_m = 0.0874$, $C_g = 10.6$, $K = 0.775$.

capsules sorb about 13% while Mexitil only sorbs about 4.5% moisture. The affinity for water of all the individual materials (i.e., gelatin and the components of Mexitil) accounts for this difference. Also shown are the GAB fits (see below) to the respective isotherms obtained via non-linear regression/least squares fitting techniques using a computer. Fit is very good for both materials over the entire relative humidity range.

The GAB equation (Guggenheim, 1966; Anderson, 1946; De Boer, 1968) is a 3 parameter extension of the Brunauer, Emmett and Teller equation and has been shown to fit water uptake data very well over a wide relative humidity range (Van den Berg, 1981; Kontny, 1985). In Eqn. 1,

$$W = \left\{ W_m C_g K(P/P_0) \right\} \times \left\{ (1 - K(P/P_0)) \times (1 - K(P/P_0) + C_g K(P/P_0)) \right\}^{-1} \qquad (1)$$

P/P_0 = relative humidity/100; P is water vapor pressure; P_0 is the saturated water vapor pressure at the temperature of the system; W_m is the amount of sorbed moisture associated with all primary binding sites for that component; while C_g and K are constants related to the free energy of sorption.

Discussion

Gelatin capsule brittleness is expected to occur, then, if the relative humidity of the surrounding environment falls below about 40% at ambient temperature. This might occur in a closed system where other materials with a strong affinity for water are present that have been initially equilibrated at lower relative humidity conditions (i.e., formulation, desiccant, packaging materials). To avoid this potential problem we only have to adjust the initial moisture contents of the formulation and capsule such that the equilibrium relative humidity is greater than 40%.

The sorption–desorption moisture transfer (SDMT) model (Zografi et al., 1988) predicts a priori the final relative humidity in a closed system of several materials of varying moisture contents. Zografi et al. (1988), have shown the general utility of the SDMT model to predict the final equilibrium relative pressure in binary and ternary systems consisting of various combinations of microcrystalline cellulose, corn starch, gelatin capsules, and silica gel. In essence, the SDMT model accounts for all water initially in a system (i.e., in the vapor phase and sorbed to each component), and based on mass balance and mathematical expressions for the sorption isotherms for each component and their dry masses, predicts the equilibrium relative pressure for that system. The current work utilizes the GAB equation to fit the isotherms for gelatin capsules and Mexitil, although other expressions fitting the data also could be employed. The final SDMT equation

$$(P/P_0)^5 + C_1(P/P_0)^4 + C_2(P/P_0)^3 + C_3(P/P_0)^2 + C_4(P/P_0) + C_5 = 0 \qquad (2)$$

is a fifth order polynomial that is solely a function of P/P_0. Expressions for C_1–C_5 are available in Appendix 1 to Zografi et al. (1988). Solving this fifth order polynomial for P/P_0 (between 0 and 1) provides an estimate of the equilibrium relative pressure in the system following transfer of moisture between components.

Table 1 presents results of a moisture transfer study for gelatin capsules initially equilibrated at a given relative humidity and Mexitil independently equilibrated at another relative humidity. Values calculated for the equilibrium relative humidity using the SDMT model are also presented, as are moisture contents for each material calculated using the GAB equation. In addition, Table 1 shows the effect of varying the masses of gelatin capsules and Mexitil, as well as varying the headspace volumes. In all cases, agreement between theory and experimental results is very good, demonstrating the utility of the SDMT model for predicting the final relative humidity for this system. This demonstrates the applicability of the SDMT model to systems in which one component (e.g., the formulation) consists of several individual solids. This extension of the model makes this approach even more useful to the pharmaceutical formulator.

TABLE 1

Predicted vs experimental moisture transfer between Mexitil and gelatin capsules

Expt.	Initial					Final					
	Gelatin capsules		Mexitil		M_T (g H_2O)	%RH		Moisture content (g/g)			
	%RH	Moisture content (g/g)	%RH	Moisture content (g/g)		Exptl.	Pred.	Gelatin capsules		Mexitil	
								Exptl.	Pred.	Exptl.	Pred.
1	37.0	0.0992	11.0	0.0202	0.445	21.4	21.0	0.0710	0.0702	0.0269	0.0267
2	38.4	0.102	23.3	0.0279	0.149	29.0	29.9	0.0850	0.0866	0.0308	0.0313
3	44.7	0.114	7.3	0.0165	0.439	18.4	20.5	0.0649	0.0692	0.0252	0.0264
4	47.2	0.118	33.1	0.0329	0.624	37.0	39.4	0.0992	0.104	0.0350	0.0363
5	44.8	0.114	44.8	0.0393	0.680	44.7	44.8	0.113	0.114	0.0393	0.0393
6	56.2	0.138	0.0	0.000	0.0951	11.1	13.3	0.0477	0.0534	0.0202	0.0219
7	55.8	0.137	12.2	0.0212	0.151	27.5	32.9	0.0823	0.0919	0.0301	0.0328
8	55.6	0.137	24.2	0.0284	0.170	33.7	39.8	0.0933	0.104	0.0332	0.0365
9	56.2	0.138	33.0	0.0329	0.183	38.4	44.5	0.102	0.113	0.0357	0.0392
10	55.3	0.136	44.7	0.0392	0.731	47.2	49.4	0.118	0.123	0.0408	0.0422
11	55.1	0.135	55.1	0.0462	0.803	55.3	55.1	0.136	0.135	0.0463	0.0461

Experiments 1, 3–5, 10, 11 used samples with capsule masses of 2.34 g and Mexitil masses of 10.48 g. Initial capsule headspace volume = 61.07 ml; initial Mexitil headspace volume = 116.32 ml. Experiments 2, 6–9 used samples with capsule masses of 0.68 g and Mexitil masses of 2.65 g. Initial capsule headspace volume = 62.82 ml; initial Mexitil headspace volume = 121.62 ml. (Exception: initial Mexitil headspace volume in Expt. 2 = 709.70 ml).

The practical utility of the SDMT model is that it can be used a priori to adjust the formulation and/or the gelatin capsule initial moisture contents to obtain a system in which the final relative humidity is in the desirable range (e.g., between 40% and 60%). For example, consider the Mexitil capsule system. The capsule might have an initial moisture content between 10% and 15%. What initial moisture level should the formulation be dried to in order to attain a desirable relative humidity and avoid brittleness?

Fig. 4 shows the calculated relative humidities (from Eqn. 2) that would result for a system in which 40 kg of granulation of a given moisture content is filled into 8 kg of gelatin capsules with initial moisture content from 10% to 15% at 20 ° C. GAB values used are noted in Fig. 3. It is assumed that the headspace volume is 20% of the volume of a storage drum (75 cm in height by 55 cm in diameter). For this system, where the formulation is dried initially to 1–2% moisture content, brittleness would always be induced in these capsules since the final relative humidity generated is below 40%. On the other hand, formulation dried to 4%

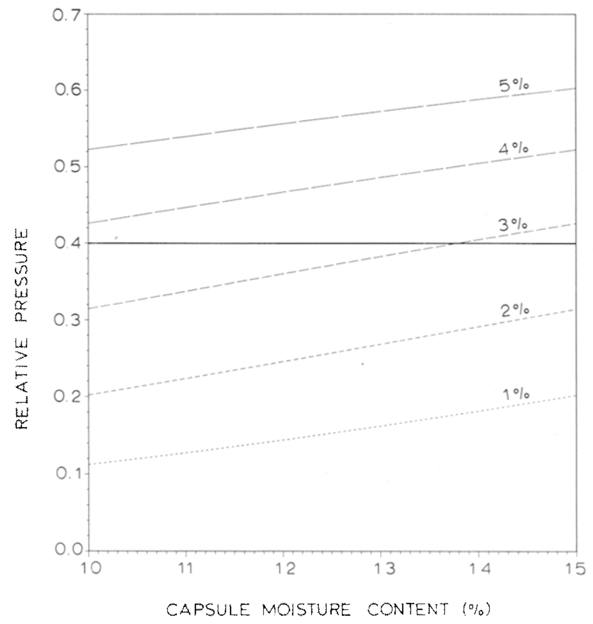

Fig. 4. Final SDMT-predicted relative pressure as a function of initial empty gelatin capsule moisture contents for initial Mexitil formulation moisture contents of 1%, 2%, 3%, 4% and 5%. Solid line at relative pressure of 0.4 corresponds to minimum acceptable relative pressure necessary to avoid capsule brittleness.

or 5% will not induce brittleness problems when filled into capsules since the final relative humidity will be greater than 40%. Formulation dried to 3% will have brittleness problems if the initial capsule moisture content is less than about 14%, but will not become brittle if the initial capsule moisture content is greater than this value.

This analysis clearly demonstrates that (ideally) a given formulation and capsule should initially be brought to the same ultimately desired relative pressure to minimize moisture transfer and avoid capsule brittleness.

In this light, water sorption isotherms for individual formulations provide an extremely useful tool in establishing target LOD values for processed granulations and other materials.

Conclusions

(1) Brittleness of both empty gelatin capsules and formulation-filled capsules becomes prevalent at relative humidities below about 40%.

(2) Initial moisture contents and masses of all components are important in establishing the final equilibrium relative humidity in a given capsule system.

(3) The SDMT model allows accurate prediction of the equilibrium relative pressure (humidity) in a system consisting of gelatin capsules and Mexitil formulation (consisting of several components) initially equilibrated to given moisture contents. This relative pressure can be readily related to capsule brittleness.

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