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The Influence of Disintegrant Level and Capsule Size on Dissolution of Hard Gelatin Capsules Stored in High Humidity Conditions

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ABSTRACT

Six batches of hard gelatin capsules were manufactured to explore the effect of disintegrant level and capsule fill porosity on the dissolution behavior of encapsulated dosage forms after exposure to high humidity. Size 0 capsules filled with powder blends containing 10 and 25% disintegrant dissolved faster than size 2 capsules filled with identical powder blends after storage under direct high humidity exposure. Interestingly, the trend was reversed when these identical products were exposed to high humidity but stored in, and protected by, a high density bottle-polypropylene container/closure system. It is hypothesized that capsules filled with a highly compacted powder blend, which are directly exposed to high humidity form a water layer at the gelatin-powder blend interface that inactivates the disintegrant.

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INTRODUCTION

Recent experiences in this laboratory indicate that high humidity can adversely affect the disintegration and resultant drug release from hard gelatin capsules (HGC). This occurrence is of practical and clinical significance as a commercial product, if improperly packaged, could be exposed to high humidity throughout the world. For instance, Martin (1) demonstrated how humid storage conditions destroyed the clinical efficacy of phenytoin capsules. Others have shown this to be true from an ***in vitro*** viewpoint for chloramphenicol capsules (2-3), tetracycline capsules (3), nitrofurantoin capsules (4), and capsules containing either water-insoluble or relatively water-soluble agents (5). Murthy, et. al. (5) demonstrated how storage conditions could adversely affect the performance of hard gelatin capsule products. These workers evaluated four different dye systems in the hard gelatin capsule shells in conjunction with three powder blends. Murthy, et. al. (6) in later work, reported that the effects of adverse storage conditions could be overridden by testing the products in dissolution media containing enzymes. Georgarakis, et. al. (7) studied the influence of ampicillin particle size, lubricant content, lubricant mixing time, and storage humidity on ampicillin dissolution. Their work indicated that dissolution of hard gelatin capsules containing a very small particle size of ampicillin was the most adversely affected by high humidity storage conditions. Unfortunately the capsule fill weight for that set of capsules was approximately 60% that of the acceptable dissolving capsules, which may have altered the porosity. It has also been reported that the powder fill moisture content can also have an adverse effect on drug release (8). For instance, the lower the moisture content of the maize starch-drug powder blend the slower the drug release.

There are several possible ways to overcome the adverse effects that high humidity has on capsule dissolution. Among those are the use of very water vapor-impermeable packaging systems or the addition of disintegrants to the hard gelatin capsule fill powder blend. Botzolakis has been the most prolific in the area of evaluating the role of disintegrants in the powder fill of hard gelatin capsules (9-12). In Botzolakis' earlier work (9), the effect of three types of disintegrants on the dissolution and disintegration characteristics of various capsule formulations was studied. The authors concluded that disintegrants are most useful in conditions where the drug is either poorly soluble or when there may be wetting problems due to the level of lubricant used in the formulation. Botzolakis (10) also evaluated the role of several disintegrants in hard gelatin capsules containing an insoluble drug with either soluble (e.g. anhydrous lactose) or insoluble (e.g. dicalcium phosphate) diluent. Croscarmellose sodium type B, in low levels, was more effective than croscarmellose sodium type A in soluble capsule fill matrices. Botzolakis and Augsburger (11-12) in two sets sophisticated experiments, evaluated the mechanism of action and the swelling efficiency of disintegrating agents in hard gelatin capsules. However, they did not extend their work to evaluate the utility of disintegrants in hard gelatin capsules that were exposed to high humidity conditions. Khan and Rhodes (13) have evaluated the water sorption by disintegrants and the results on *in vitro* performance. But very little has been done in evaluating the water vapor sorption and subsequent permeation through hard gelatin capsules (14-15).

Since *in vitro-in vivo* correlations have been established with some therapeutic agents, it becomes very critical to formulate a capsule dosage form which will adequately perform, regardless of how the capsule dosage form was stored (light, high humidity, etc). Therefore, the purpose of this work was to evaluate if disintegrant could overcome the adverse effects of high humidity exposure on two sizes of hard gelatin capsules containing identical fill weights. Hard gelatin capsules containing 0, 10 or 25% disintegrant were tested in 0.1N HCl and deionized water to characterize the dissolution behavior of the capsule formulations.

EXPERIMENTAL SECTION

Chemicals

Acetaminophen, USP (Lot 0048985E984, Mallinckrodt, St. Louis, MO), crosscarmellose sodium Type A, NF (Lot T713, FMC, Philadelphia, PA), calcium phosphate dibasic unmilled, USP (Lot 6438, Stauffer Chemical Co., Shelton, CT), magnesium stearate, NF (Mallinckrodt, St. Louis, MO), sodium hydroxide, NF (Lot 5367KBAH, Mallinckrodt, St. Louis, MO), hydrochloric acid solution 12M (Lot 3560KVTM-A, Mallinckrodt, St. Louis, MO or Lot A48042, Baker, Phillipsburg, New Jersey), opaque blue size #2 hard gelatin capsule shells (Lot J8CT30, Elanco, Indianapolis, IN), and opaque blue size #0 hard gelatin capsule shells (Lot G7EH34, Elanco, Indianapolis, IN) were used as received.

Capsule Manufacture

The formulation, which was similar to that used by Botzolakis (1982) was composed of acetaminophen, croscarmellose sodium Type A, unmilled calcium phosphate dibasic, and magnesium stearate. The first three components were blended in a low shear mixer according to the formulation ratios given in Table 1. Magnesium stearate was subsequently added to the powder blend and mixed three minutes in a Hobart. The three powder blends (15 kg) were subdivided into7.5 kg quantities and filled into either size #0 or #2 blue opaque capsules using an H & K capsule filling machine (Bosch Packaging Machinery Division, Piscataway, NJ). An given powder blend, an identical fill weight was filled into the two capsule sizes to provide powder fills of varying porosity. For instance, the 400 mg fill weight in the size 2 capsules was the maximum obtainable fill weight for that size of capsule, while the same fill weight loosely occupied the size 0 capsules. The six batches were labeled as B0-0 (blend with 0% disintegrant in a size #0 hard gelatin capsule), B10-0 (blend with 10% disintegrant in a size #0 hard gelatin capsule), and so on. The average capsule fill weights (n=20) for the six batches were monitored every fifteen minutes during the one hour filling process as an in

TABLE I

COMPOSITION OF THE FORMULATIONS USED IN THE STABILITY STUDIES

Capsule Formulation*	Capsule Size	Ingredient	Amount (mg/capsule)
B0-x	0 or 2	Acetaminophen, USP	40.0
		Croscarmellose sodium, NF+	-
		Calcium phosphate dibasic, USP	356.0
		Magnesium stearate, NF	4.0
		Total	400.0
B10-x	0 or 2	Acetaminophen, USP	40.0
		Croscarmellose sodium, NF+	40.0
		Calcium phosphate dibasic, USP	316.0
		Magnesium stearate, NF	4.0
		Total	400.0
B25-x	0 or 2	Acetaminophen, USP	40.0
		Croscarmellose sodium, NF+	100.0
		Calcium phosphate dibasic, USP	256.0
		Magnesium stearate, NF	4.0
		Total	400.0

* - Bxx-x designates disintegrant level(e.g. 0, 10, 25%) and capsule size(0 or 2), respectively

\+ - Type A

process check. Content uniformity of the powder blends (n=9) and the six capsule formulations (n=20) was also evaluated.

Powder Moisture Determination

The contents of nine capsules were emptied onto the aluminum pan of a moisture analyzer (Computrac Inc., Tempe, AZ). The percent of moisture loss on drying was then determined using a temperature setting of 105°C.

Dissolution

Dissolution studies were performed on a set of six capsules, which were wrapped with stainless steel coils as shown by shape #2 in a recent article (16). All dissolution tests were conducted according to the USP XXII/NF XVII Apparatus II (17). A dissolution apparatus (Hanson Research, Northridge, CA) equipped with USP paddles was used in conjunction with a rotation speed of 50 rpm. The dissolution medium was 900 ml of either 0.1N HCl or deionized water maintained at 37° C. Sampling was performed at 11.3, 24.4, 37.5 and 60.0 minutes by an automated system and analyzed at 244 nm using an ultraviolet (UV) spectrophotometer (Model HP-8451A, Hewlett-Packard, Palo Alto, CA). The UV absorbance values were then compared to a standard calibration curve.

Stability Studies

All capsules were packaged in a container/closure system comprised of HDPE bottles and polypropylene caps lined with SG100 inner seals. The SG100 inner seal was activated by heat induction to allow water vapor transmission through only the surface area of the bottle. Capsules were stored at either room temperature (controls) or in a humidity chamber (37° C/80% RH). Negative controls were set up by placing the capsules in petri dishes and exposing the dosage forms to the conditions in the humidity chamber.

RESULTS AND DISCUSSION

Characterization of powder blends

The average content uniformity and standard deviation of the powder blends were 92.2 ± 3.9, 97.5 ± 1.5, and 94.6 ± 3.5 percent of the theoretical acetaminophen content for the batches containing no disintegrant (B0), 10% disintegrant (B10), and 25% disintegrant (B25), respectively. The means (n=9) and standard deviations were calculated from the drug content analysis of three samples withdrawn from either the top, middle, or bottom layer of the powder blends.

Characterization of capsule powder blend

The percent label strength and initial moisture content for the filled capsules are shown in Table II. The initial moisture content based upon a weight loss on drying measurement for the powder blends were 1.0%, 1.1%, and 1.2% for powder blends B0, B10, and B25, respectively. However, after three months of being stored in petri dishes exposed to 37° C/80% RH, the LOD values were 0.8, 3.0, and 9% for the powder filled into size 0 capsules for batches B0-0, B10-0, and B25-0, respectively. The size 2 capsules had a slightly smaller increase in moisture content as their values were 0.7, 1.9, and 7.7% at three months after the same exposure for batches B0-2, B10-2, and B25-2, respectively.

TABLE II

CHEMICAL CHARACTERIZATION OF HARD GELATIN CAPSULE BATCHES

Batch	Label Strength(SD)*	Percent Loss On Drying
B0-0	91.4 (0.8)	1.0%
B10-0	96.3 (1.3)	1.1%
B25-0	97.3 (0.8)	1.2%
B0-2	91.6 (1.5)	1.0%
B10-2	97.3 (1.2)	1.1%
B25-2	98.3 (0.9)	1.2%

* Average and standard deviation based upon the contents of 20 capsules.

Influence of disintegrant and capsule size on the initial dissolution of acetaminophen hard gelatin capsules

There are some interesting trends with respect to the *in vitro* dissolution profiles for the six batches. The hypothesis for the work at hand is that a disintegrant works by absorbing the dissolution media into its domain and, due to a swelling phenomena, internal pressure is built up within the matrix of the dosage form. This internal pressure then causes the dosage form to disintegrate. Obviously, the action of the disintegrant will be voided if the powder bed is either not compressed (e.g. powder filled into size 0 HGC in this study) or if the matrix yields elastically to the swelling (18).

Figure 1a demonstrates the effect of capsule size and disintegrant level on the dissolution process in 0.1N HCl at the initial storage time point. As expected, an increase in disintegrant level will increase the dissolution rate. Although not of statistical significance, the size 0 capsules containing disintegrant (B10-0 and B25-0) dissolve slightly slower in 0.1N HCl than the size 2 capsules containing disintegrant (B10-2 and B25-2). Presumably, these results are due to the dominance of high disintegrant concentrations over porosity effects. Powder blends without disintegrant filled into size 0 capsules (B0-0), dissolved significantly faster than the same powder blend filled into size 2 capsules (B0-2), due to the increased porosity and

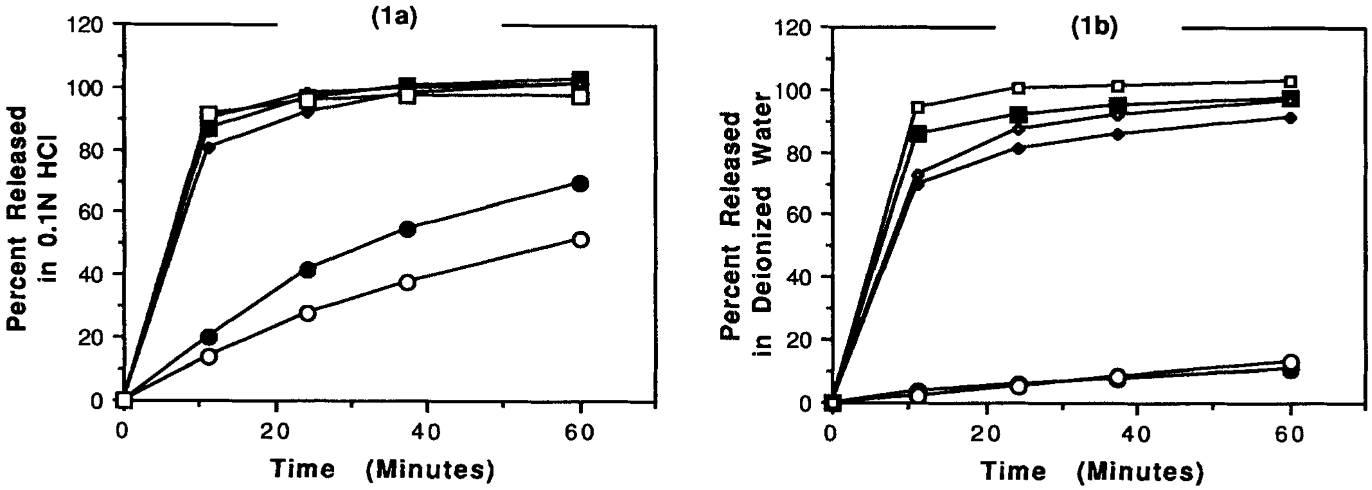

Figure 1.
The influence of capsule size (closed symbol, size 0; open symbol, size 2) and disintegrant level (o, ● -0%; ◊ , ♦-10%; □, ■-25%) on acetaminophen release in 0.1 N HCl (la) and deionized water (1b)

immediate surface area of the powder blend available for dissolution. Similar results have been shown by Shah, et. al. (19) by altering the number of tamps to fill a hard gelatin capsule or by increasing the compression force. Our dissolution results for the size 2 capsules without disintegrant are very similar to the work by Botzolakis (9).

Figure 1b illustrates that at the initial time point all batches dissolve in deionized water at a rate proportional to the disintegrant content and, more importantly, at a rate inversely proportional to capsule fill capacity. Due to the fact that the small capsule size yields a denser compact, size 2 capsules dissolve slightly faster than size 0 capsules. However, when the dosage form does not contain disintegrant in the formulation (B0-0 and B0-2), the release of drug in deionized water is significantly reduced and no difference was observed between the size 0 and 2 capsules. Increasing the croscarmellose sodium concentration from 0 to 10% significantly enhances the dissolution of this insoluble powder fill in both dissolution media. If one compares the dissolution profiles of capsules containing no disintegrant tested in both dissolution media, it is obvious that the capsule matrix dissolves faster in the acidic media. This is due to the solubility of dibasic calcium phosphate, which is governed by the K_{sp} value, since acetaminophen solubility is unaffected by pH. For instance, at low pHs there will be virtually no $HPO_4^{=}$ species available as indicated below (20), thereby allowing more Ca^{++} ion to be solubilized.

$$K_{sp}=[Ca^{++}]\,[HPO_4^{=}]=1 \times 10^{-7}$$

Influence of room temperature storage condition on dissolution of hard gelatin capsules stored in sealed bottles

Figures 2a and 2b illustrate four months of room temperature storage does not affect the dissolution profiles of either size 0 or 2 hard gelatin capsules with 0 and 25% disintegrant in water. In fact, if the two plots are superimposed they are indistinguishable within a formulation set (e.g. same level of disintegrant). The size 0 and size 2 capsules containing 10% disintegrant are not shown because their dissolution profiles are very similar to the profiles of capsules containing 25% disintegrant. Capsules tested in 0.1N HCl also showed the same profiles at four months as they did initially and therefore ware not illustrated.

Influence of high humidity storage conditions on dissolution of hard gelatin capsules stored in sealed bottles

Figure 3a clearly shows that disintegrant level reduces the influence of high humidity exposure on size 0 capsules tested in 0.1N HCl dissolution media. Note, those capsules were in high density polyethylene bottles in combination with aluminum heat seals. Batch B0-0, which did not contain disintegrant, showed a slight decrease in dissolution after 4 months of storage. Figure 3b illustrates the effect of high humidity exposure on the dissolution profiles of size 2

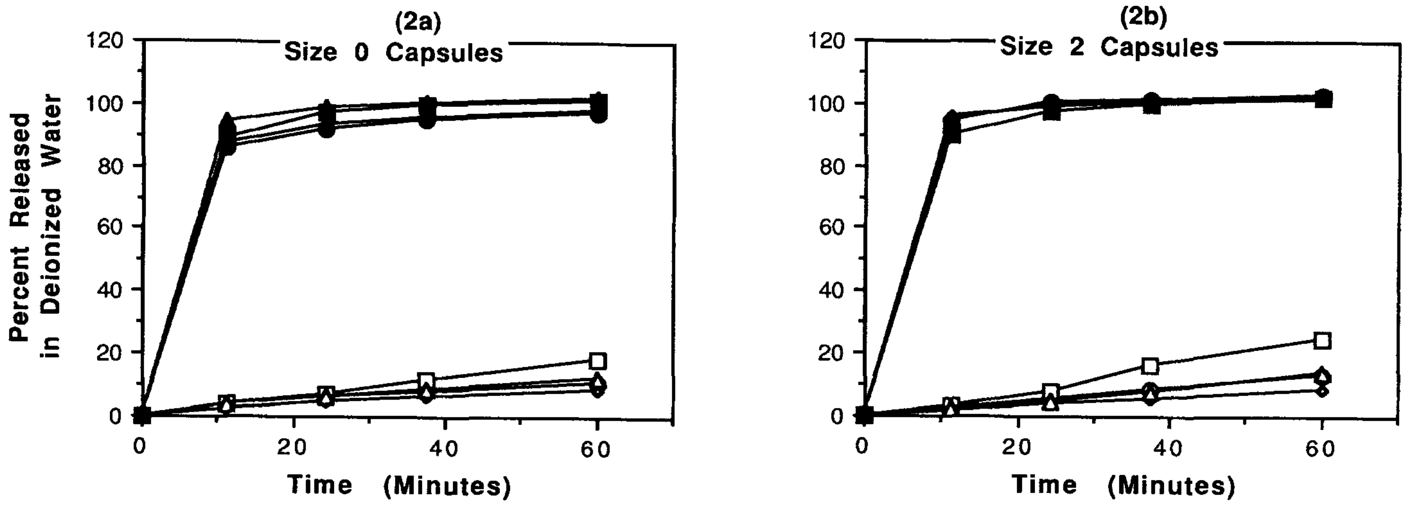

Figure 2.

The influence of capsule size and disintegrant level (open symbol, 0%; closed symbol, 25%) on acetaminophen release from capsules stored at room temperature (o, ● -0 months; ◊ , ♦- 1 month; □ , ■ -3 months; Δ , ▲ - 4 months). Figures represent acetaminophen dissolution in deionized water for size 0 (2a) and size 2 (2b) capsules.

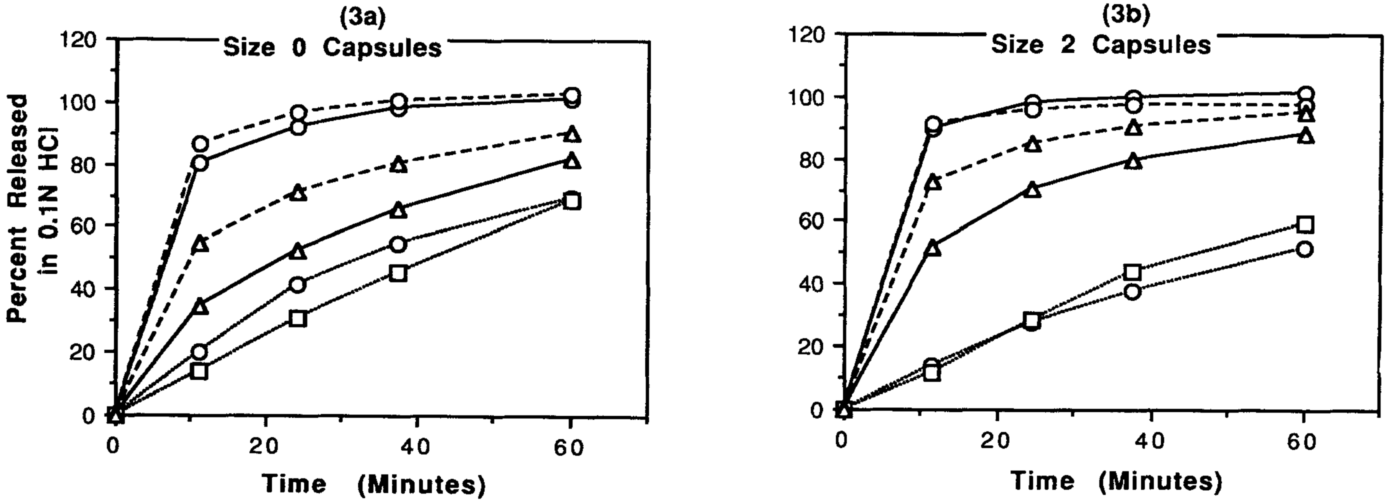

Figure 3.

The influence of capsule size and disintegrant level (dotted line, 0%; solid line, 10%; dashed line, 25%) on acetaminophen release from capsules stored in a container-closure system exposed to high humidity (o, 0 months; □, 4 months; Δ , 4.5 months). Figures represent acetaminophen dissolution in 0.1 N HCl for size 0 (3a) and size 2 (3b) capsules.

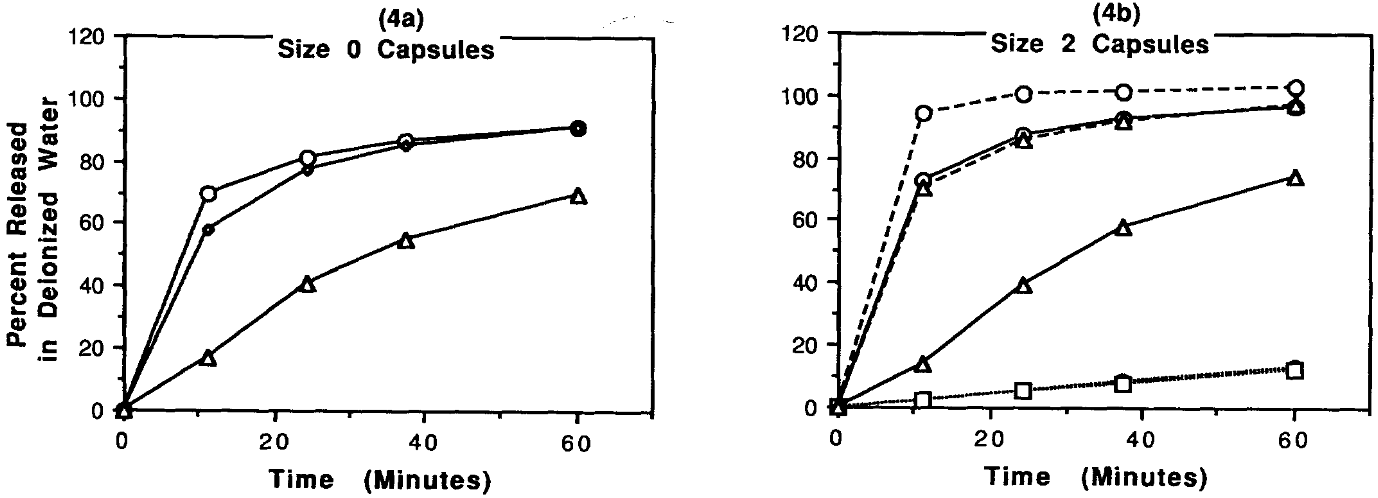

Figure 4.

The influence of capsule size and disintegrant level (dotted line, 0%; solid line, 10%; dashed line, 25%) on acetaminophen release from capsules stored in a container-closure system exposed to high humidity (o, 0 months; ◊ , 2 months; □ , 4 months; Δ , 4.5 months). Figures represent acetaminophen dissolution in deionized water for size 0 (4a) and size 2 (4b) capsules.

capsules stored in sealed bottles. In Figures 3a and 3b, the reduction in a dissolution profile due to storage is inversely proportional to disintegrant level. For instance, B10-0 showed a greater decrease in dissolution with storage than capsule batch B25-0. For size 2 capsules, the dissolution results at the 60 minute time point for the formulation containing 25% disintegrant (B25-2) was virtually unchanged with storage time. However at 11 minutes there was a difference of about 20% between the two storage time points. By comparing Figures 3a and 3b it becomes obvious that the size 2 capsules containing disintegrant are not as adversely affected as the size 0 capsules containing disintegrant when protected from direct exposure to high humidity. However, these differences are not significant. Size 0 capsules without disintegrant demonstrated better in vitro dissolution performance in 0.1N HCl than size 2 capsules, presumably due to increased powder surface area and porosity.

Figure 4a shows how the dissolution profile in water of size 0 capsules containing 10% disintegrant is affected by 2 and 4.5 month storage times. Figure 4b illustrates the effects of high humidity storage on bottled size 2 capsules for all three formulations. When the profiles of B10-2 in Figure 4b are compared with those of Figure 4a, no obvious difference can be seen between the two capsule sizes as a function of storage time.

Influence of high humidity storage conditions on dissolution of hard gelatin capsules stored in petri dishes

Figures 5a and 5b illustrate the influence of 3 months of storage under severe humidity conditions on capsule dissolution profiles in 0.1N HCl. Quite remarkably, both figures demonstrate that capsules containing 25% disintegrant show large decreases in dissolution at early sampling points. For instance, 85% or more of the total dose had dissolved within 15 minutes for the inital storage time point sample but the amount released decreased to less than 25% after three months of high humidity storage in a petri dish. Additionally, Figure 5a shows that size 0 capsules appear to dissolve slightly, but not significantly faster than the size 2 capsules in 0.1N HCl (Figure 5b). Figures 6a and 6b show the dissolution profiles of the size 0 and 2 capsules, respectively, in deionized water after 0 and 3 months of high humidity storage in a petri dish. From these two figures it becomes apparent that deionized water is much more discriminatory than 0.1N HCl with respect to detecting differences due to capsule size and disintegrant level. Figure 6a shows the same large difference at the 15 minute time point between the 0 and 3 month storage conditions for size 0 capsules containing disintegrant. The 60 minute values differ by 25% or less between the 0 and 3 month storage samples for the formulation containing 25% disintegrant. Figure 6b clearly shows that the size 2 capsule formulations are more dramatically affected at all dissolution time points when comparing the 0 month and 3 month storage time points. A comparison of Figures 5a-6b shows the level of disintegrant decreases the dissolution differences between the two capsule sizes after three months of high humidity exposure. These differences being independent of the dissolution media used. In all cases where capsules have been directly exposed to high humidity storage conditions

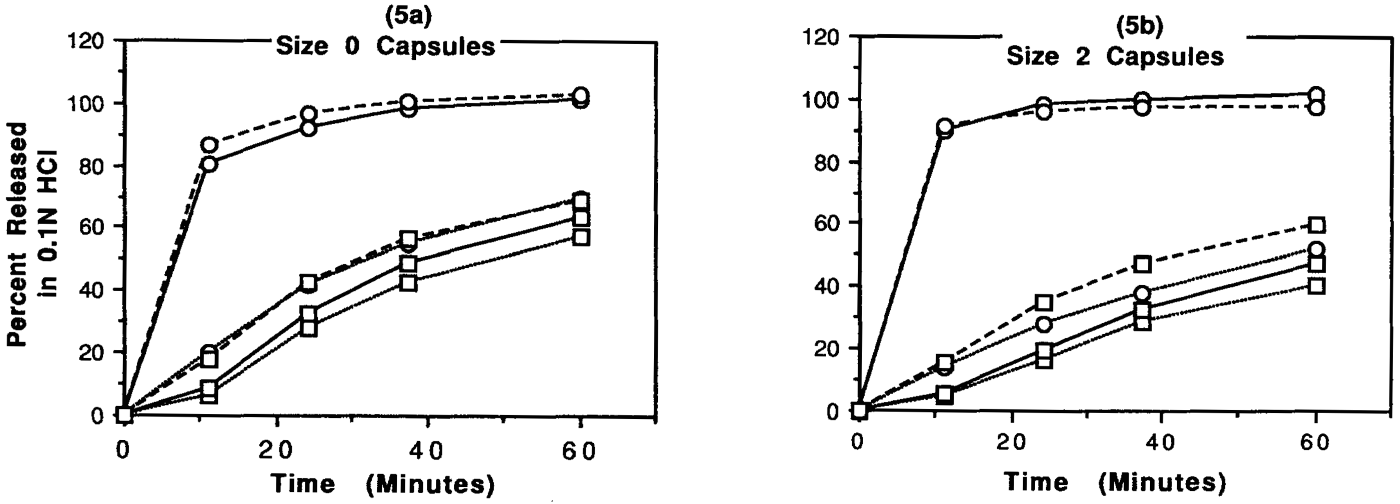

Figure 5.
The influence of capsule size and disintegrant level (dotted line, 0%; solid line, 10%; dashed line, 25%) on acetaminophen release from capsules stored in an open petri dish exposed to high humidity (o, 0 months; □, 3 months). Left and right figures represent acetaminophen dissolution in 0.1 N HCl for size 0 (5a) and size 2 (5b) capsules.

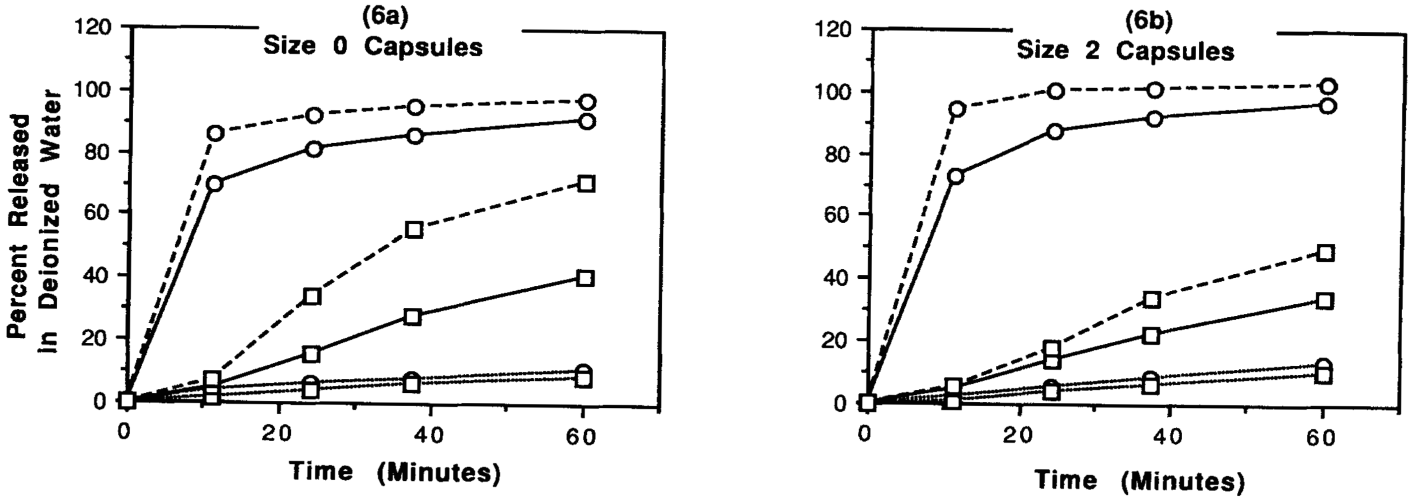

Figure 6.

The influence of capsule size and disintegrant level (dotted line, 0%; solid line, 10%; dashed line, 25%) on acetaminophen release from capsules stored in an open petri dish exposed to high humidity (o, 0 months; □, 3 months). Left and right figures represent acetaminophen dissolution in deionized water for size 0 (6a) and size 2 (6b) capsules.

the size 0 capsules outperform the size 2 capsules. Since there is not a great deal of difference between the two sizes of capsules with respect to water pickup (see section on **Characterization of Capsule Powder Blend**), it is possible this phenomena may be due to the way the moisture is distributed. For instance, a moisture or water layer could be forming at the gelatin-calcium phosphate matrix interface in the size 2 capsules resulting in inactivation of the surface disintegrant. Hence, in size 0 capsules where there is no compaction and therefore high porosity, the disintegrant may still be functional enough due to the distribution of the water vapor to aid in breaking up any agglomerates which may have formed due to the high humidity exposure. Interestingly, this observation is opposite that seen when capsules are stored in sealed bottles.

CONCLUSION

Two capsule sizes were filled with identical amounts of powder blend containing 0, 10 or 25% disintegrant (e.g. croscarmellose sodium). Due to the insoluble nature of the capsule fill matrix it is obvious that the release profiles for the two capsule sizes containing no disintegrant are unchanged even when subjected to adverse humidity conditions. Size 2 capsules filled with a powder blend containing disintegrant and stored in sealed bottles are only moderately affected by high humidity compared to size 0 capsules filled with the powder blend containing disintegrant. On the other hand, direct exposure of the two capsule sizes shows that the size 0 capsules are less adversely affected by high humidity due to the increased surface area and more even distribution of moisture throughout the capsule fill matrix.

This work demonstrates the impact of incorporating a disintegrant into the powder fill of a hard gelatin capsule exposed to high humidity. This work also has shown how the capsule formulations containing 10 or more percent of disintegrant can withstand the stress of a high humidity storage condition presumably due to the more porous nature of capsule fill.

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