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RESEARCH ARTICLES

Role of Binders in Moisture-Induced Hardness Increase in Compressed Tablets and Its Effect on *In Vitro* Disintegration and Dissolution

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Abstract □ The role of commonly used binders in the moisture-induced hardness increase in compressed tablets containing lactose as a major excipient was studied. Tablets compressed from granulations containing different binders at different moisture levels increased in hardness after overnight exposure to ambient room conditions. The results suggest that this hardness increase is related linearly to the amount of moisture loss from the tablets after compression. The magnitude of the hardness increase is related to the type and concentration of the binder used in wet granulation. The moisture-induced hardness increase in tablets prepared from granulations containing different binders had no effect on the tablet disintegration time and *in vitro* drug dissolution.

Keyphrases □ Binders—role in moisture-induced hardness increase in compressed tablets, disintegration, dissolution, *in vitro* □ Disintegration—of compressed tablets following moisture-induced hardness increase, role of binders, *in vitro* □ Dissolution—of compressed tablets following moisture-induced hardness increase, role of binders, *in vitro*

Recent studies (1, 2) discussed the hardness increase induced by partial moisture loss in compressed tablets prepared by wet granulation. Tablets compressed from granulations containing moisture levels above 2% increased in hardness during storage at ambient room conditions. When the granulation moisture levels during compression were below 2%, tablet hardness did not increase during storage at ambient room conditions. However, when these tablets were equilibrated under accelerated humidity and then exposed to ambient room conditions, tablet hardness increased due to partial moisture loss. Moisture-related hardness increases did not decrease *in vitro* drug dissolution.

The exact mechanism by which moisture affects tablet hardness is not understood fully. Previous results (1) suggested that a possible mechanism was the recrystallization of the soluble drug and/or soluble excipient in the void spaces caused by the moisture loss. Obviously, the physical properties of the drug–excipient combinations play a major role.

Since binders impart cohesiveness to the tablet and ensure tablet strength after compression, investigation of their role in the moisture-induced hardness increase is important. In this study, the tablets compressed from granulations containing the most commonly used binders at different moisture levels increased in hardness due to partial moisture loss during overnight exposure to ambient room conditions. The data suggest that the hardness increase is related linearly to the amount of moisture loss after compression. The magnitude of the hardness increase is related to the type and concentration of binder used in wet granulation. The moisture-related hardness increase in tablets prepared from granulations containing different binders did not affect the tablet disintegration time and *in vitro* drug dissolution.

EXPERIMENTAL

Materials—Acacia[1], povidone[2], starch[3], lactose[4], gelatin[5], and magnesium stearate[6] were USP grade, and salicylic acid[6] was analytical reagent grade. Methylcellulose[7], hydroxypropyl methylcellulose[8], hydroxypropylcellulose[9], and ethylcellulose[10] were used as received.

Granulation—The material was prepared by wet granulation. Lactose and salicylic acid were mixed in geometric proportions on a piece of glassine paper and then in a small planetary mixer[11] for 3 min. The granulating solution was added with mixing and was mixed for ~5 min. The wet granulation was passed through a No. 12 mesh screen and dried in trays in a forced-air drying oven at 50°. One-half of the granulation was dried to ~3% moisture, and the other half was dried until the moisture reached below 1%.

[1] J. T. Baker Chemical Co., Phillipsburg, NJ 08865.
[2] G.A.F. Corp., New York, N.Y.
[3] Staley Manufacturing Co., Decatur, Ill.
[4] Lactose regular, Foremost Food Co., San Francisco, CA 94104.
[5] Sigma Chemical Co., St. Louis, MO 63178.
[6] Mallinckrodt Chemical Works, St. Louis, MO 63160.
[7] Methocel, A-15 premium, Dow Chemical Co., Midland, Mich.
[8] Type 60 HG premium, Dow Chemical Co., Midland, Mich.
[9] Type HF, Hercules, Wilmington, Del.
[10] Ethocel, premium, Dow Chemical Co., Midland, Mich.
[11] Kitchen Aid model K5-A, Hobart Manufacturing Co., Troy, Ohio.

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Table I—Tablet Formulations (Milligrams of Ingredient per Tablet)

Ingredient	Formulation													
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Salicylic acid	19	19	19	19	19	19	19	19	19	19	19	19	19	19
Lactose	311.1	311.1	311.1	311.1	311.1	311.1	311.1	316.1	301.1	291.1	311.1	316.1	301.1	291.1
Starch	38	38	38	38	38	38	38	38	38	38	38	38	38	38
Magnesium stearate	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9
Acacia	10	—	—	—	—	—	—	—	—	—	—	5	20	30
Ethylcellulose	—	10	—	—	—	—	—	—	—	—	—	—	—	—
Gelatin	—	—	10	—	—	—	—	—	—	—	—	—	—	—
Hydroxypropylcellulose	—	—	—	10	—	—	—	—	—	—	—	—	—	—
Hydroxypropyl methylcellulose	—	—	—	—	10	—	—	—	—	—	—	—	—	—
Methylcellulose	—	—	—	—	—	10	—	—	—	—	—	—	—	—
Povidone	—	—	—	—	—	—	10	5	20	30	—	—	—	—
Starch	—	—	—	—	—	—	—	—	—	—	10	—	—	—

These granulations then were screened separately through a No. 16 mesh screen, and appropriate proportions were mixed to obtain the desired moisture levels. Starch and magnesium stearate then were blended with the granulation. The granulation was stored in tightly closed jars; the moisture content was determined prior to compression.

The granulating solutions were prepared in the usual fashion. The solvent was water except for the ethylcellulose solution, in which 95% ethanol was used. Starch paste was prepared by boiling the water and mixing with starch.

Compression—Tablets were compressed with a single-punch machine[12] to a targeted hardness of 6 Strong–Cobb units. The punches and die were 0.95 cm in diameter and flat faced. The tablet weight was 380 mg.

Moisture Determination—The granulation moisture was determined with a moisture balance[13] by exposure to a 125-w IR lamp for 1 hr at the 70-v setting. The percent weight loss on drying was read directly from this instrument. The tablets were ground with a mortar and pestle, and the same procedure for moisture determination was followed.

Hardness Determination—Initial hardness was determined immediately after compression. The tablets were placed on open trays, exposed to ambient room conditions (23°, 25–50% relative humidity), and allowed to equilibrate and reach maximum hardness. For each hardness determination[14], 10 tablets were tested and the mean was calculated.

Disintegration Time—The disintegration apparatus consisted of a basket–rack assembly and a 1-liter beaker as described in the USP. The beaker containing 900 ml of distilled water was maintained at 37° in a constant-temperature water bath. The disintegration times of the individual tablets were noted, and the mean of six tablets was calculated.

***In Vitro* Dissolution**—The dissolution apparatus was the same as described previously (1). It consisted of a 1-liter beaker and a stirrer driven by a synchronous motor at 120 rpm. The beaker containing 600 ml of distilled water was maintained at 37° in a constant-temperature water bath. A stainless steel paddle, 2.5 × 7.6 cm, was centered at the end of a stainless steel shaft and was used as a stirrer. The distance between the bottom of the beaker and the bottom of the stirrer was maintained at 1.8 cm.

At zero time, a tablet was dropped into the stirred dissolution medium. Then, 5-ml samples were withdrawn at appropriate time intervals and filtered through a 0.80-μm pore size filter paper. The absorbance[15] of the salicylic acid in the solution was measured at 303 nm. Three tablets were run for each determination.

RESULTS AND DISCUSSION

To study the role of binders in the moisture-induced hardness increase

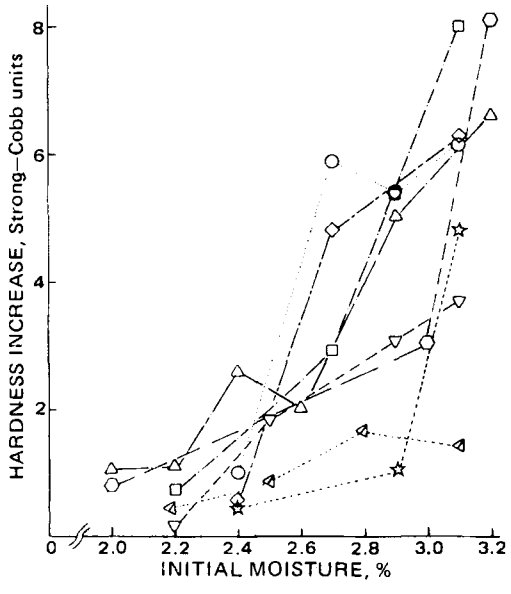

Figure 1—*Effect of binders on hardness increase induced by partial moisture loss in compressed tablets prepared by wet granulation. Key: ○, hydroxypropyl methylcellulose; △, ethylcellulose; ▽, hydroxypropylcellulose; □, povidone; ◇, methylcellulose; ○, gelatin; ☆, acacia; and ▲, starch.*

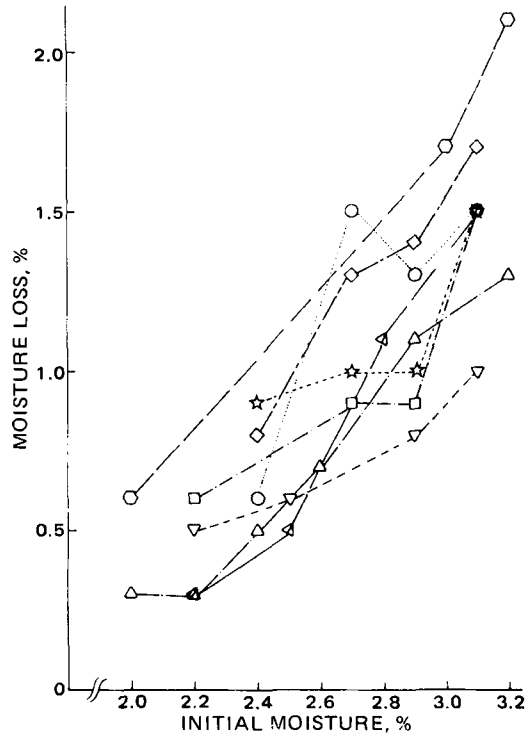

Figure 2—*Effect of binders on moisture loss inducing hardness increase in compressed tablets prepared by wet granulation. Key: ○, hydroxypropyl methylcellulose; △, ethylcellulose; ▽, hydroxypropylcellulose; □, povidone; ◇, methylcellulose; ○, gelatin; ☆, acacia; and ▲, starch.*

[12] Stokes model F4.
[13] Cenco, Central Scientific Co., Chicago, IL 60623.
[14] Heberlein hardness tester, Heberlein and Co., AG, Switzerland.
[15] Unicam recording spectrophotometer, SP 1800, Pye Unicam Ltd., Cambridge, England.

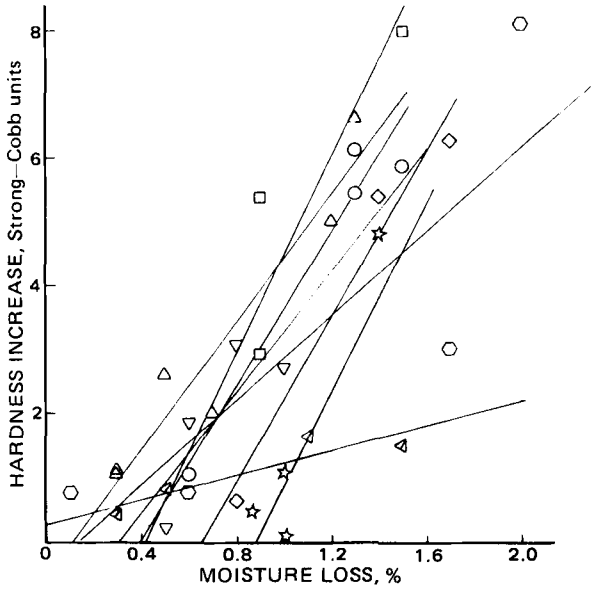

Figure 3—*Relationship between hardness increase and percent moisture loss in compressed tablets prepared by wet granulation using different binders. Equations of the regression lines and correlation coefficients (r) are: ○, hydroxypropyl methylcellulose, y = −2.348 + 5.932x, r = 0.968; △, ethylcellulose, y = −0.486 + 4.95x, r = 0.961; ▽, hydroxypropylcellulose, y = −1.49 + 4.74x, r = 0.819; □, povidone, y = −3.266 + 7.72x, r = 0.930; ◇, methylcellulose, y = −4.386 + 6.54x, r = 0.982; ☆, acacia, y = −6.45 + 7.236x, r = 0.970; ▲, starch, y = 0.32 + 0.9055x, r = 0.886; and ○, gelatin, y = −0.45 + 3.29x, r = 0.855.*

in compressed tablets, lactose was chosen as a major excipient since it is commonly used in tablets. The salicylic acid, starch, and magnesium stearate percentages were kept constant in the formulations studied (Table I).

The granulations containing 2–3.2% moisture and different binders at the 10-mg tablet level were compressed into tablets at a targeted initial hardness of 6 Strong-Cobb units. Above a 3.1% initial moisture level, it was not possible to compress the povidone, methylcellulose, hydroxypropyl methylcellulose, acacia, hydroxypropylcellulose, and starch granulations into tablets because of picking and sticking to the punches.

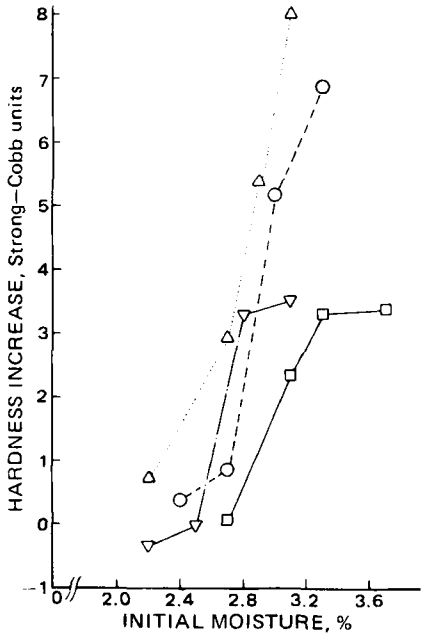

Figure 4—*Effect of the povidone concentration on the hardness increase induced by partial moisture loss in compressed tablets prepared by wet granulation. Key: ○, 5 mg/tablet; △, 10 mg/tablet; ▽, 20 mg/tablet; and □, 30 mg/tablet.*

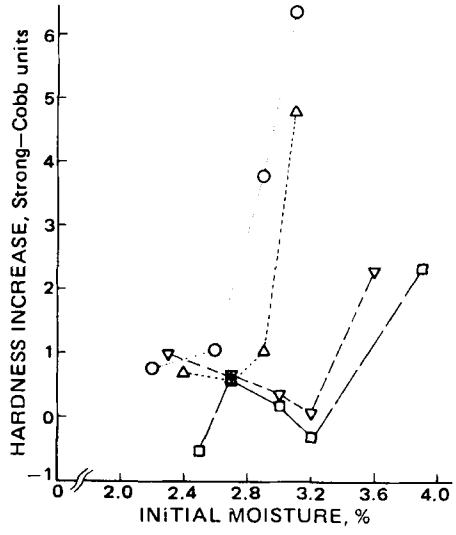

Figure 5—*Effect of the acacia concentration on the hardness increase induced by partial moisture loss in compressed tablets prepared by wet granulation. Key: ○, 5 mg/tablet; △, 10 mg/tablet; ▽, 20 mg/tablet; and □, 30 mg/tablet.*

Tablet hardness was determined again after overnight exposure to ambient room conditions.

The results of the hardness increase *versus* the percent initial moisture are given in Fig. 1. The tablets prepared with different binders that contained a higher moisture content showed large hardness increases, with the exception of starch, which showed a small hardness increase. The magnitude of the hardness increase at a given moisture content depended on the binder.

Plots of the percent moisture loss *versus* the initial moisture are shown in Fig. 2. The tablets prepared with different binders showed an increased moisture loss after overnight exposure to ambient room conditions as the moisture content during compression was increased. The differences in the moisture loss with the binders used in this study were due to the modification of the equilibrium moisture level in the tablets by the binder.

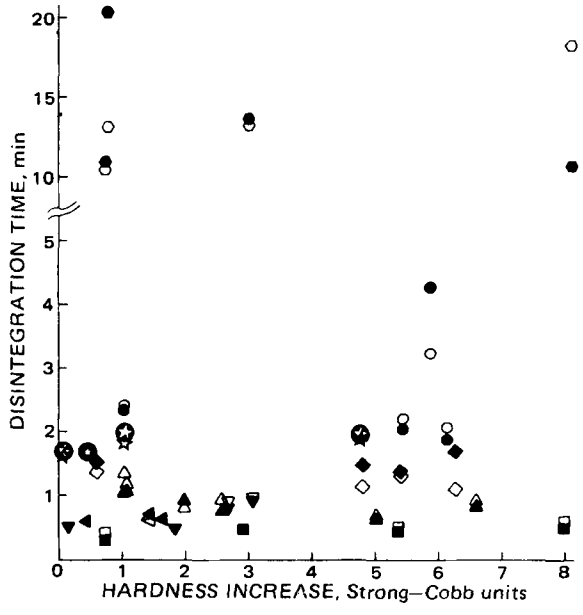

Figure 6—*Role of binders in tablet disintegration time as a function of hardness increase induced by partial moisture loss in compressed tablets prepared by wet granulation. Open symbols give the disintegration time before the hardness increase, and closed symbols give the disintegration time after the hardness increase. Key: ○, ●, hydroxypropyl methylcellulose; △, ▲, ethylcellulose; ▽, ▼, hydroxypropylcellulose; □, ■, povidone; ◇, ◆, methylcellulose; ☆, ✪, acacia; ○, ●, gelatin; and ◁, ◀, starch.*

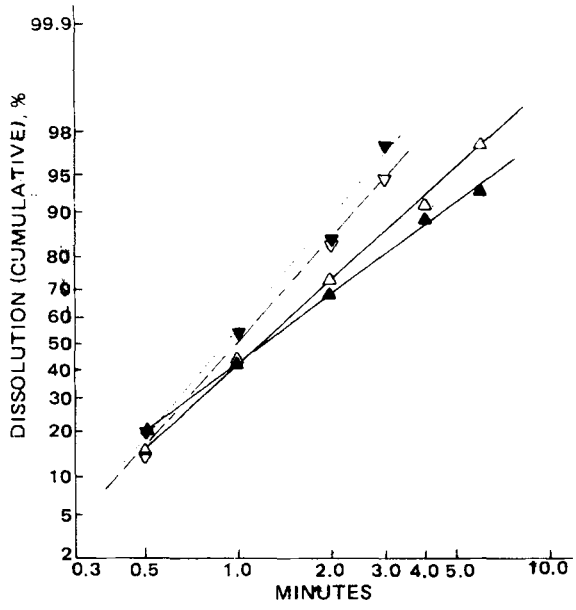

Figure 7—*Percent dissolution* versus *time plots on log probability paper showing the linear relationship. Open symbols give dissolution results before the hardness increase, and closed symbols give dissolution results after hardness increase. Key:* △, *ethylcellulose, initial moisture = 3.2%, and* ▽, *hydroxypropylcellulose, initial moisture = 3.1%.*

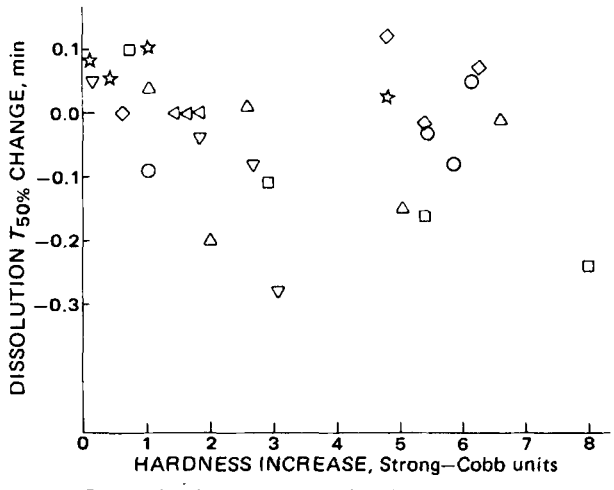

Figure 8—*Role of binders on* in vitro *dissolution as a function of the hardness increase induced by partial moisture loss in compressed tablets prepared by wet granulation. Key:* ○, *hydroxypropyl methylcellulose;* △, *ethylcellulose;* ▽, *hydroxypropylcellulose;* □, *povidone;* ◇, *methylcellulose;* ○, *gelatin;* ☆, *acacia; and* ◁, *starch.*

Figure 3 gives the relationship between the hardness increase and the percent moisture loss that occurred after the tablets were exposed to ambient room conditions. The tablets containing different binders had a reasonably linear relationship between the hardness increase and the percent moisture loss. These results indicate that the hardness increase in tablets mainly occurred due to the partial moisture loss after compression. Some of the solution of the soluble excipients and/or drug is forced into the void spaces between the compressed granules when the moisture in the granulation exceeds a certain level. Recrystallization of the excipients and/or drug from the saturated solution results in the formation of bridges at the point of contact, leading to a hardness increase.

The strength of the crystalline bridges depends not only on the amount of water-soluble excipient and/or drug deposited in the void spaces but also on the crystallization rate. Any change in the formulation such as the replacement of one binder with another would change the crystallization rate of the drug–excipient solution. This crystallization rate change would modify the size and number of crystalline bridges formed in the void spaces, resulting in different hardness increases.

Any change in the formulation would change the moisture sorption properties of the tablets and the magnitude of the hardness increase. For example, a formulation containing 66% water-insoluble drug, 18% lactose, 10% starch, 5% povidone, and 0.2% magnesium stearate (1) caused greater hardness increases compared to Formula G in this study, which contained about 82% lactose.

Changes in the binder concentrations in the tablet formulations also would change the moisture sorption properties. Two binders, povidone and acacia, were selected to investigate the influence of the binder concentration on the moisture-induced hardness increase. The amount of binder per tablet varied from 5 to 30 mg. The lactose amount was adjusted to keep the total weight per tablet constant. Figure 4 gives the effect of povidone concentration on the hardness increase induced by partial moisture loss. The maximum moisture-induced hardness increase was seen with 10 mg of povidone/tablet. With 20 and 30 mg of povidone/tablet, the hardness increase occurred at higher moisture levels and was less pronounced. With 5 mg of povidone/tablet, the hardness increase was slightly less pronounced compared to the 10-mg of povidone/tablet level at the same initial moisture content.

The effects of the acacia concentration on the hardness increase are shown in Fig. 5. As the amount of acacia in the formulation was increased, a higher initial moisture in the granulation was needed to increase hardness. In agreement with the povidone data (Fig. 4), the effect was less pronounced at higher acacia concentrations.

Physical properties of the drug–excipient combination were changed by changing the binder concentration. The granulations containing 10 mg of povidone/tablet could not be compressed at 3.5% moisture, while the formulation containing 30 mg of povidone/tablet were compressed easily at 3.7% moisture without picking or sticking. However, on equilibration at ambient room conditions, the moisture content of all povidone tablets essentially was the same. Similarly, the granulations containing lower acacia concentrations could not be compressed above 3.2% moisture; at 30 mg of acacia/tablet, the granulation containing 3.9% moisture easily was compressible.

The small hardness increases at higher binder concentrations due to the moisture-related effect could be explained by the crystallization rate decrease of the excipient–drug solution in the voids, which, in turn, results in the formation of fewer crystalline bonds, imparting lower additional strength to the tablet.

The role of binders in tablet disintegration time as a function of hardness increase induced by partial moisture loss is illustrated in Fig. 6. Tablets prepared from most binders did not show an increase in the disintegration time resulting from a moisture-induced hardness increase. However, tablets prepared by wet granulation with gelatin solution had an increased disintegration time in one case, when hardness increased only slightly, but the disintegration time decreased when the hardness increased by about 8 Strong–Cobb units. These results indicate that the hardness increase resulting from partial moisture loss in lactose-based tablets does not affect the tablet disintegration time.

Percent dissolved *versus* time profiles were generated for tablets prepared with different binders at 10 mg of binder/tablet and containing initial moisture levels of 2–3.2% before and after the hardness increase. The data from these tests were plotted on logarithmic probability graph paper (3), and the median ($T_{50\%}$) was obtained from the line. Figure 7 shows linear percent dissolved *versus* time plots. The dissolution median change was obtained by subtracting the dissolution median after the hardness increase from the dissolution median before the hardness increase (Fig. 8). The percent dissolved *versus* time profiles for tablets containing gelatin as a binder at 10 mg of gelatin/tablet and containing different initial moisture levels were not generated. It is obvious from the data given in Fig. 8 that the hardness increase induced by partial moisture loss from lactose-based tablets containing different binders had no effect on drug dissolution.

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