Hardness Increase Induced by Partial Moisture Loss in Compressed Tablets and Its Effect on *In Vitro* Dissolution

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Abstract □ The hardness increase induced by partial moisture loss in compressed tablets was studied. Several factors such as the type and percentage of the excipient, the water solubility and hygroscopicity of the excipient or drug, and the influence of frequently used binders were investigated. The results indicate that the tablets increased in hardness by the recrystallization of the soluble excipient or the soluble drug in the void spaces. This recrystallization occurred because of the moisture loss after expulsion of the solution of the excipient or drug in the void spaces on compression. The large increase in hardness induced by the partial moisture loss did not decrease *in vitro* dissolution appreciably. This result was clearly different from the hardness increase caused by higher compression loads in the absence of a moisture-induced effect, which showed a decrease in the *in vitro* dissolution as the hardness was increased.

Keyphrases □ Tablets, compressed—effect of partial moisture loss on hardness and *in vitro* dissolution □ Hardness—compressed tablets, effect of partial moisture loss □ Dissolution, *in vitro*—compressed tablets, effect of partial moisture loss □ Dosage forms—compressed tablets, effect of partial moisture loss on hardness and *in vitro* dissolution

It is generally recognized that the granulation moisture content should be adjusted to an optimal range to obtain desirable compaction properties. The optimal range, however, depends on the nature and absorptivity of the drug and excipients. Therefore, it is imperative that the beneficial effects of moisture such as the improvement in compaction properties, alleviation of static charge, and improved cohesion to reduce demixing and the deleterious effects such as the reduction in flow rate and sticking of material to punches are balanced.

BACKGROUND

To study the mechanism by which moisture in powders increases compaction, sodium chloride, a cubic crystalline material capable of being compressed directly to form coherent compacts without added excipients, was used (1, 2). It was concluded that the increase in strength of the compacts on drying of the remaining moisture was due to recrystallization at the crystal boundaries and in the voids.

In a similar study (3), the effect of moisture on the flow and compression properties of phenacetin, acetaminophen, and dextrose monohydrate without the addition of excipients was reported. These results suggested that the increase in strength of the compacts on drying was in the same order as their solubility. It was concluded that substances with low water solubility would show little, if any, increase in compact strength due to the loss of moisture on drying.

Naproxen, a nonsteroidal anti-inflammatory agent, has very low water solubility. The tablet formulation contains about 66% drug, 10% starch, 18% lactose, and 0.2% magnesium stearate. The wet granulation is carried out with a povidone solution in methanol–water. An unusual increase in hardness of these tablets was noticed recently in this laboratory, a few hours after manufacturing. Preliminary investigations suggested that this increase was related to the moisture content of the granulation.

This paper discusses the hardness increase phenomenon in compressed tablets induced by the partial moisture loss during equilibration under ambient room conditions. The effects of drugs, excipients, and binders on the moisture-induced hardness increase were examined and related to *in vitro* dissolution. The data suggest that the increase in hardness of compressed tablets, induced by the partial moisture loss, has very little effect on the *in vitro* dissolution of the drugs studied. Since the moisture-induced hardness increase in compressed tablets does not affect *in vitro* dissolution, a test indicative of *in vivo* bioavailability, an upper limit on stability hardness would be unnecessary and meaningless.

EXPERIMENTAL

Materials—Sodium benzoate[1], starch[2], povidone[3], lactose[4], magnesium stearate[1], dextrose[5], acacia[5], and hydroxypropyl methylcellulose[6] were all USP grade. Microcrystalline cellulose[7] and methanol were NF grade. FD&C Yellow No. 5[8] was used as a coloring agent. Naproxen[9] and naproxen sodium[9] were at least 99% pure. All other chemicals were analytical reagent grade, unless otherwise indicated.

Granulation Preparation—The granulations were prepared by wet granulation. The powders, except magnesium stearate, were mixed in a small planetary-type mixer[10] for 5 min. The granulating solution was added while 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° until the desired moisture level was reached. The dry granulation was screened through a No. 14 mesh screen and mixed with magnesium stearate in a mixer for 2 min. At the end of mixing, the granulation was stored in tightly closed glass jars; the moisture content was determined prior to compression.

The granulating solutions were prepared in the usual fashion. The dye was first dissolved in water and mixed with the cosolvents, if required. The binder was then added and mixed until dissolved. Starch paste was prepared by boiling the water and then mixing with the dye and starch.

Compression—Tablets were compressed with a single-punch machine[11] to a targeted hardness of 10 Strong–Cobb units. The punches and die were 0.95-cm diameter and flat faced. The tablet weight was adjusted to contain 200 mg of active drug. An instrumented single-punch machine[11] was used for a compression load *versus* hardness experiment.

Moisture Determination—The granulation moisture was determined with a moisture balance[12] by exposure to a 125-w IR lamp for 15 min at the 90-v setting. The weight loss on drying, in percent, was read directly from this instrument. The tablets were first ground with a mortar and pestle, and the same procedure for moisture determination was followed.

Hardness Determination—The initial hardness was determined immediately after compression. The tablets were placed in open trays exposed to ambient room conditions (20°, 35–40% relative humidity) and in "filled to capacity and tightly closed" glass bottles. The samples stored in open trays were allowed to equilibrate and reach maximum hardness. For each hardness determination[13], 10 tablets were tested and the mean was calculated.

***In Vitro* Dissolution**—The dissolution apparatus consisted of a 1-liter beaker and a stirrer driven by a synchronous motor at 120 rpm. The beaker, containing 600 ml of 0.1 *M* phosphate buffer (pH 7.4), was maintained at 37° in a constant-temperature water bath. For naproxen sodium and sodium benzoate, the dissolution medium was distilled water.

[1] Mallinckrodt Chemical Works, St. Louis, MO 63160.
[2] Staley Manufacturing Co., Decatur, Ill.
[3] G.A.F. Corp., New York, N.Y.
[4] Lactose Regular, Foremost Food Co., San Francisco, CA 94104.
[5] J. T. Baker Chemical Co., Phillipsburg, NJ 08865.
[6] E-15 Premium, Dow Chemical Co., Midland, Mich.
[7] FMC Corp., American Viscose Division, Marcus Hook, Pa.
[8] Warner Jenkinson Manufacturing Co., St. Louis, Mo.
[9] Syntex Research, Palo Alto, CA 94304.
[10] Kitchen Aid, model K5-A, Hobart Manufacturing Co., Troy, Ohio.
[11] Stokes model E.
[12] Cenco, Central Scientific Co., Chicago, IL 60623.
[13] Heberlein hardness tester, Herberlein and Co., AG, Switzerland, or Stokes hardness tester, F.J. Stokes Machine Co., Philadelphia, Pa. The Stokes hardness tester was only used where the Heberlein hardness tester went off scale; hardness was converted to Strong–Cobb units by running a correlation between the two instruments.

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Table I—Tablet Formulations

Formulation	Ingredients as Percent of Total Tablet Weight[a]												Tablet Weight, mg
	Naproxen	Naproxen Sodium	Sodium Benzoate	Starch	Lactose	Microcrystalline Cellulose	Dextrose	Povidone	Acacia	Hydroxypropyl Methylcellulose	Methanol	Water	
A	65.79	—	—	10.00	18.72	—	—	5.26	—	—	10.26	10.26	380
B	73.96	—	—	10.07	9.82	—	—	5.92	—	—	10.26	10.26	338
C	70.51	—	—	10.00	14.00	—	—	5.26	—	—	10.26	10.26	355
D	59.25	—	—	9.96	25.83	—	—	4.73	—	—	10.26	10.26	422
E	65.79	—	—	10.00	23.98	—	—	—	—	—	—	20.52	380
F	65.79	—	—	10.00	21.98	—	—	—	—	2.00	10.26	10.26	380
G	65.79	—	—	10.00	18.98	—	—	—	5.0	—	—	20.52	380
H	65.79	—	—	10.00	—	—	18.72	5.26	—	—	10.26	10.26	380
I	65.79	—	—	10.00	—	18.72	—	5.26	—	—	10.26	10.26	380
J	—	65.79	—	10.00	—	18.72	—	5.26	—	—	—	20.52	380
K	—	—	65.79	10.00	—	18.72	—	5.26	—	—	10.26	10.26	380

[a] The percentage of magnesium stearate was 0.20 and the percentage of FD&C Yellow No. 5 was 0.03 in all formulations.

A stainless steel paddle, 2.5 × 7.6 cm, was mounted in the middle of a stainless steel shaft and used as a stirrer. The distance between the bottom of the beaker and the bottom of the stirrer was kept constant at 2.5 cm.

At zero time, a tablet was dropped into the stirred dissolution medium. Then 1-ml samples were withdrawn at 5-min intervals and filtered through a medium sintered-glass funnel. The absorbance[14] of the naproxen samples was measured at 332 nm after appropriate dilution. The absorbance of sodium benzoate was measured at 275 nm. Each time point represented the mean of three determinations.

RESULTS AND DISCUSSION

Several tablet formulations were prepared (Table I). Tablets were compressed from granulations containing different moisture contents; they were obtained by drying the wet granulation in a forced air convection oven at 50° to desired moisture levels, mixing with the lubricant, equilibrating in tightly closed containers, and determining moisture contents. No apparent change in moisture content was observed due to compression. After compression and after exposure to ambient room conditions, the tablets were tested for hardness and for *in vitro* dissolution. The difference between the mean hardness before and after exposure to ambient room conditions represented an increase in hardness induced by the partial moisture loss.

The results of hardness increase induced by the partial moisture loss from naproxen tablets, using Formulation A (Table I), are given in Fig. 1. At and below 2% moisture, the tablet hardness did not increase on equilibration. Above 2% moisture, hardness increased as the moisture content increased. An increase in hardness of about 24 Strong–Cobb units occurred at 3.5% moisture. Above 4% moisture, cohesion of the granulation inside the hopper prevented uniform filling in the die. Moreover, the moisture content of the granulation reduced the contact between the die walls and the granulation on compression and caused excessive water lubrication effect.

The *in vitro* dissolution of the tablets after compression and after hardness increase, as a function of the initial moisture content, is also given in Fig. 1. A large increase in hardness at 3 and 3.5% moisture did not affect the *in vitro* dissolution at 5 and 10 min. This result suggests that the hardness increase of these tablets induced by the partial moisture

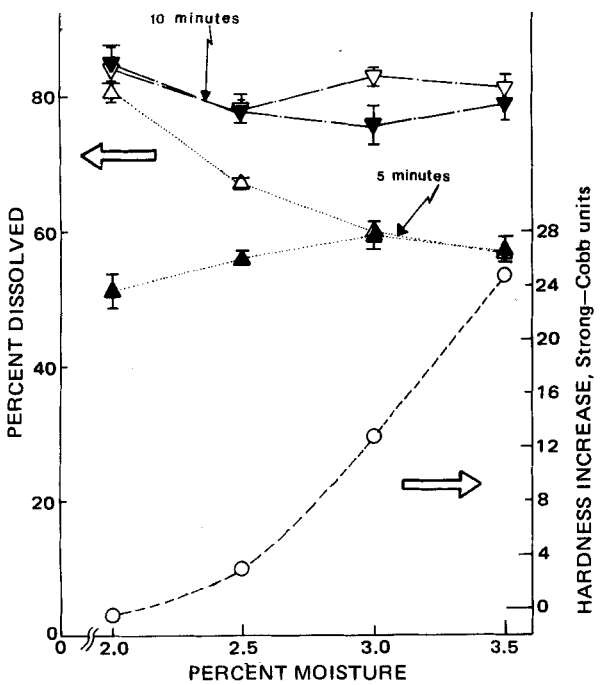

Figure 1—*Effect of hardness increase induced by partial moisture loss on dissolution of naproxen tablets (Table I, Formula A). Key: ○, hardness* versus *percent moisture plot; △ and ▽, dissolution of tablets immediately after compression; and ▲ and ▼, dissolution of tablets after hardness increase. Vertical lines represent standard deviations; the absence of vertical lines indicates that the standard deviation was too small to be shown.*

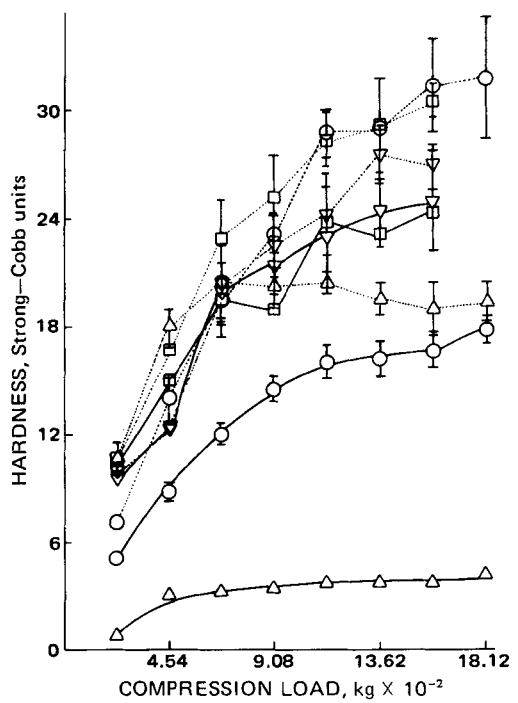

Figure 2—*Effect of compression load on hardness of naproxen tablets (Table I, Formula A) at different moisture contents. Key: —, compression load* versus *hardness profiles immediately after compression; . . . . , compression load* versus *hardness profiles after exposure to ambient room conditions; ▽, 2.0% moisture; □, 2.3% moisture; ○, 3.2% moisture; and △, 4.0% moisture. Vertical lines represent standard deviations; the absence of vertical lines indicates that the standard deviation was too small to be shown.*

[14] Unicam recording spectrophotometer.

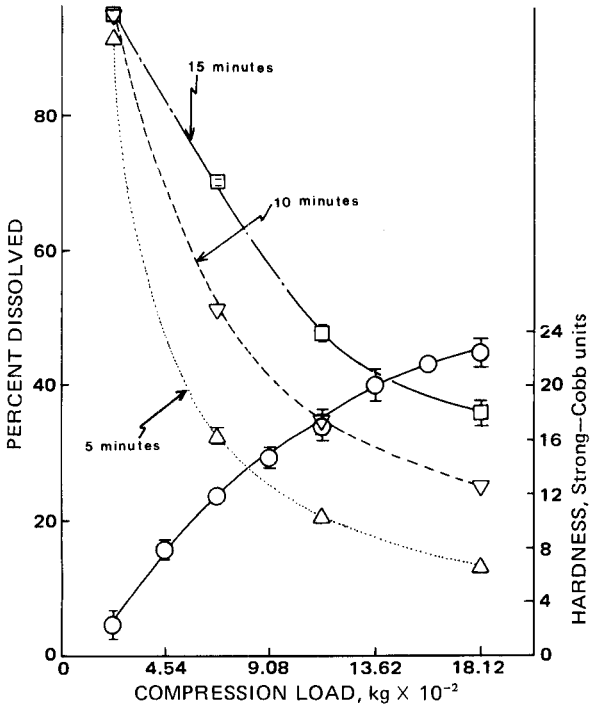

Figure 3—*Effect of compression load on hardness and* in vitro *dissolution of naproxen tablets compressed to contain 0.2% moisture. Key:* ○, *hardness* versus *compression load profile; and* △, ▽, *and* □, *dissolution at various time points* versus *compression load profiles.*

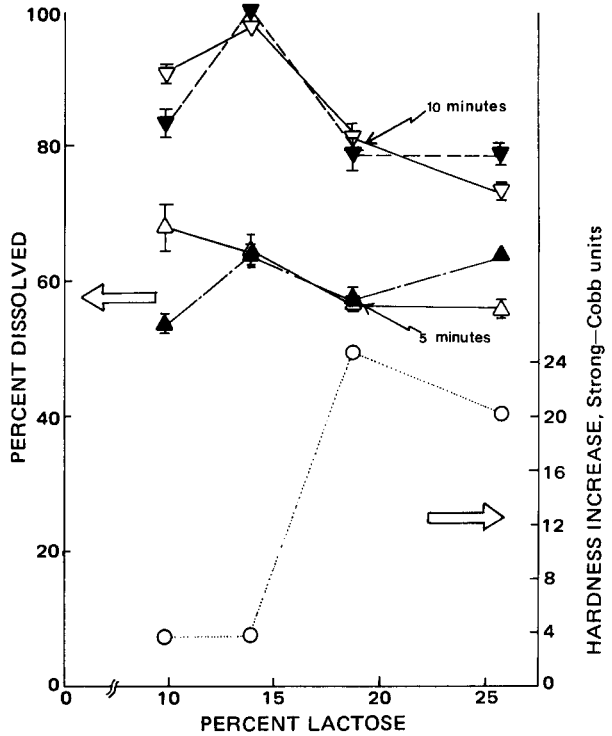

Figure 4—*Effect of percent lactose in naproxen tablets on hardness increase induced by the partial moisture loss and* in vitro *dissolution. The moisture content of the granulation was 3.5%. Key:* ○, *percent lactose* versus *hardness increase plot;* △ *and* ▽, *dissolution of tablets immediately after compression; and* ▲ *and* ▼, *dissolution of tablets after hardness increase. Vertical lines represent standard deviations; the absence of verticle lines indicates that the standard deviation was too small to be shown.*

loss has no effect on *in vitro* dissolution. At a moisture content where no increase in hardness occurred, the *in vitro* dissolution at 5 min was lower after equilibration at ambient room conditions than initially. However, the *in vitro* dissolution under both conditions was the same at 10 min.

The relationship between hardness and compression load of the tablets prepared from Formulation A containing varying moisture content is given in Fig. 2. The hardness of the tablets containing varying moisture content increased as the compression load increased. At all compression loads, as the moisture content increased, the hardness of the tablets decreased. Under normal conditions, as the compression load increases, the porosity of tablets decreases. In the presence of moisture, the void spaces in the tablets probably become filled with the solution of the water-soluble excipient. This phenomenon is dependent on the moisture content and the applied compression load.

At higher moisture contents, as the compression load increases, the liquid driven out of the void spaces forms a continuous film at the die wall. This film acts as a lubricant and results in reduced contact between the tablet granulation and the die wall. The compression load *versus* hardness profile before exposure to ambient room conditions at 4% moisture illustrates this point. It was not possible to compress tablets of reasonable hardness from the granulation containing 4% moisture, even at high compression loads. However, when the moisture content was reduced to 3.2%, the hardness increased as the compression load increased. This result was due to the reduced amount of expelled liquid after filling the void spaces, thus allowing higher contact between the tablet granulation and the die wall. These data reaffirm the importance of controlling the moisture content of the granulation to optimize compression properties.

Figure 2 also gives the compression load *versus* hardness profiles after the tablets were exposed to ambient room conditions. At 2% moisture, a significant increase in hardness did not occur, even at higher compression loads. However, at 2.3% moisture, higher compression loads resulted in hardness increases after equilibration under ambient room conditions. Around compression loads greater than 1000 kg, a small increase in moisture content resulted in some expulsion of saturated solution in the void spaces, which, upon recrystallization, resulted in increased tablet strength. This phenomenon of increased tablet strength after exposure to ambient room conditions was observed at lower compression loads as the moisture content increased.

The granulations from Formulation A were dried to contain 0.2% moisture, and tablets were compressed at different compression loads. Plots of the compression load, hardness, and *in vitro* dissolution are given in Fig. 3. As the compression load increased, the tablet hardness increased and the percent drug dissolved decreased. The hardness increase caused by the compression load in the absence of a moisture-induced effect must be clearly distinct from the hardness increase caused by the partial moisture loss after compression. The data in Fig. 3 indicate that tablets compressed at very low moisture content increased in hardness as the compression load increased and show a remarkable decrease in *in vitro* dissolution. However, the results in Fig. 1 show that the tablets compressed at higher moisture contents, *i.e.*, above 2%, increased in hardness after exposure to ambient room conditions. The increase depended on the initial moisture content and did not decrease *in vitro* dissolution.

Apparently, granulations containing moisture above a certain level, on compression, force solution of the soluble excipient and binder into the void spaces. Recrystallization of the dissolved excipient from the binding solution results in the formation of bridges at the point of contact, resulting in an increase in hardness. Under these circumstances, one should expect a dependence of the hardness increase on the percent of water-insoluble excipient in the formulation containing a water-insoluble drug.

In Formulation A, lactose was varied (Formulations B–D) at a moisture content where it was known that hardening would occur. The plot of the percent lactose *versus* the hardness increase induced by the partial moisture loss (Fig. 4) confirms the importance of the percentage of water-soluble excipient in the formulation. The maximum hardness increase occurred at lactose concentrations that allowed optimum recrystallization in the void spaces, thus giving strength to the tablets. The results of the *in vitro* dissolution *versus* lactose percentage are also given in Fig. 4. Similar *in vitro* dissolution before and after exposure to ambient room conditions reaffirms that the hardness increase induced by the partial moisture loss has no effect on the *in vitro* dissolution.

For a water-insoluble drug, the excipient may play an important role in the moisture-induced hardness increase and *in vitro* dissolution of the drug. In Formulation A, lactose was replaced by microcrystalline cellulose (Formulation I). The results of the hardness increase and *in vitro* dissolution as a function of the initial moisture percentages are given in Fig. 5. Since microcrystalline cellulose is insoluble in water, no excipient

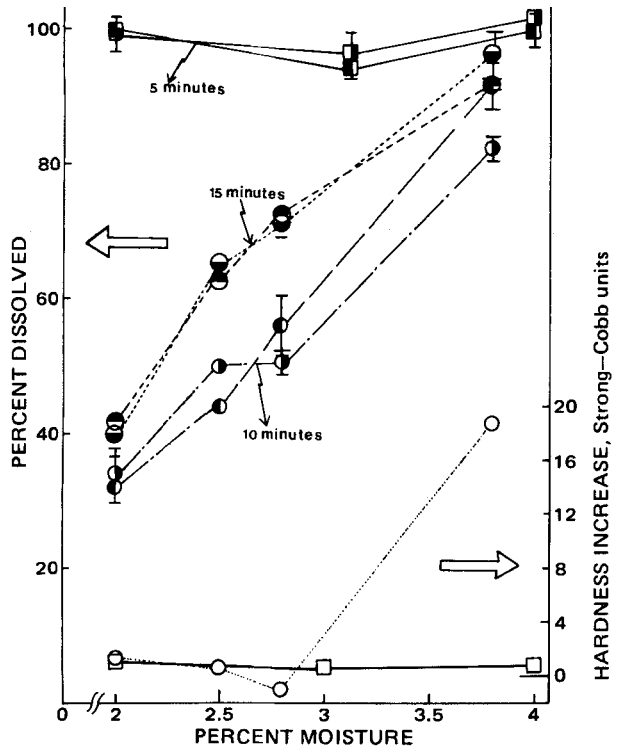

Figure 5—*Effect of excipients on hardness increase induced by the partial moisture loss and* in vitro *dissolution of naproxen tablets. Key:* ○ *and* □, *effect of dextrose and microcrystalline cellulose on moisture-induced hardness increase, respectively;* ◨, ◑, *and* ◓, in vitro *dissolution of tablets immediately after compression; and* ◧, ◐, *and* ◒, *dissolution of tablets after hardness increase. Vertical lines indicate standard deviations; the absence of vertical lines indicates that the standard deviation was too small to be shown.*

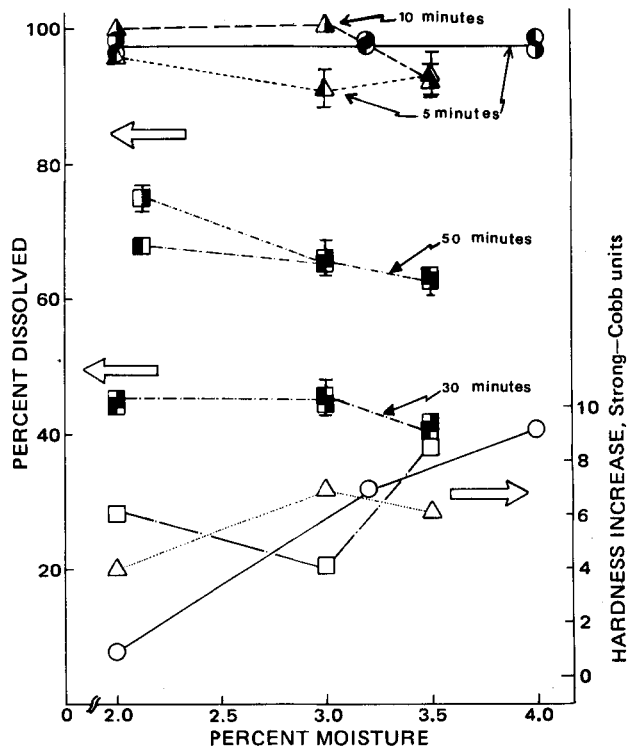

Figure 6—*Effect of binders on hardness incease induced by the partial moisture loss and* in vitro *dissolution of naproxen tablets. Key: circles, starch paste; squares, acacia solution; triangles, hydroxypropyl methylcellulose solution;* ○, □, *and* △, *hardness increase* versus *percent moisture plots;* ◑, ◨, *and* ▲ in vitro *dissolution immediately after compression; and* ◐, ◧, *and* ◭, in vitro *dissolution after hardness increase. Vertical lines represent standard deviations; the absence of vertical lines indicate that the standard deviation was too small to be shown.*

recrystallization was expected and no increase in hardness occurred. This study confirms that when povidone is used as a binder in these formulations, it does not increase tablet strength because it does not crystallize. The replacement of lactose by microcrystalline cellulose also decreased disintegration time, resulting in rapid *in vitro* dissolution. Almost 100% of the drug dissolved at the end of 5 min.

The results of the effect of the replacement of lactose by dextrose (Formulation H) in Formulation A are given in Fig. 5. The hardness of the tablets with an initial moisture percentage of 3.8 increased after room temperature exposure. The granulation containing moisture between the last two data points was not tested. Therefore, the moisture-induced hardness increase probably started anywhere between these two data points. The hardened tablets showed a small decrease in *in vitro* dissolution.

The percent drug dissolved increased as the moisture content at the time of compression increased. The amount of moisture in the granulation affected drug dissolution by its effect on disintegration time. The average disintegration time for 2% moisture-containing tablets was 17 min, compared to the 7 min for the 3.8% moisture case. Although the hardness of 3.8% moisture-containing tablets after exposure increased significantly, the disintegration time did not change. The decrease in disintegration time and the increase in *in vitro* dissolution as a function of moisture content suggest that as the moisture contents increase, saturated solution of dextrose filled the void spaces on compression, thus allowing the liquid to penetrate into the tablets and resulting in an increase in *in vitro* dissolution.

Another parameter that may have considerable bearing on the phenomenon of hardness increase induced by moisture is the choice of binders used in the wet granulation procedure. The strength of the crystalline bridges depends not only on the amount of water-soluble excipient deposited in the void spaces between water-insoluble drug but also on the crystallization rate. Besides povidone (Formulation A), other frequently used binders such as starch paste (Formulation E), hydroxypropyl methylcellulose (Formulation F), and acacia (Formulation G) were investigated. The results of the hardness increase as a function of moisture content at the time of compression are given in Figs. 1 and 6.

At 2% moisture, the largest hardness increase occurred with acacia, while starch paste and hydroxypropyl methylcellulose did not cause a significant increase. At higher moisture contents, povidone caused a larger increase in hardness compared to other binders. The *in vitro* dissolution before and after exposure to ambient room conditions for all binders was similar (Figs. 1 and 6). However, considerable differences in the dissolution rate with different binders are evident. Starch paste and hydroxypropyl methylcellulose gave excellent *in vitro* dissolution, while acacia slowed the dissolution rate considerably (Fig. 6). These differences in dissolution rate are directly related to the effect of binders on disintegration time.

To confirm that the phenomenon of hardness increase induced by moisture is not specific to naproxen, a water-soluble compound, sodium benzoate and a water-insoluble excipient, microcrystalline cellulose, were studied (Formulation K) (Fig. 7). This formulation could be compressed at higher moisture contents. The hardness increase induced by the partial moisture loss occurred at a higher moisture content. Dissolution before and after exposure to ambient room conditions changed only slightly.

Obviously, if the water-soluble drug or the water-soluble excipient in the granulation does not recrystallize in the void spaces on compression, the moisture-induced phenomenon of hardness increase would not occur (Fig. 8). The granulations contained a soluble drug, naproxen sodium, and an insoluble excipient, microcrystalline cellulose. Naproxen sodium absorbs water, and the percentage of water absorbed is proportional to the relative humidity of the surrounding atmosphere. The hardness increase did not occur after storage under various conditions. *In vitro* dissolution also remained similar after overnight drying at 80°.

CONCLUSION

The results of this study suggest that the tablet hardness increase induced by partial moisture loss occurs because of recrystallization of water-soluble excipients or a water-soluble drug that is expelled into the void spaces on compression. The extent of the hardness increase depends on the specific combination of the drug and excipients, and their physical

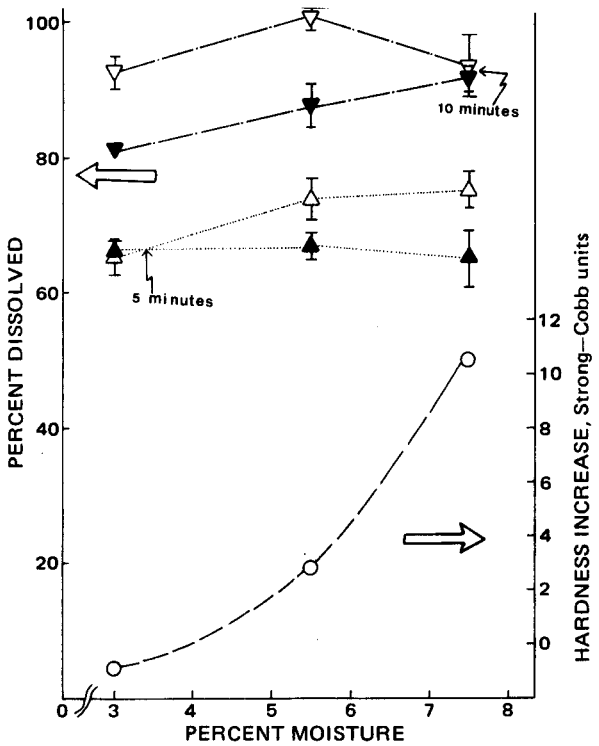

Figure 7—*Effect of hardness increase induced by the partial loss of moisture on the* in vitro *dissolution of compressed tablets prepared from sodium benzoate and microcrystalline cellulose. Key:* ○, *hardness increase* versus *percent moisture plot;* △ *and* ▽, in vitro *dissolution immediately after compression; and* ▲ *and* ▼, in vitro *dissolution after hardness increase. Vertical lines represent standard deviations; the absence of vertical lines indicates that the standard deviation was too small to be shown.*

properties such as aqueous solubility, crystalline properties, and hygroscopicity. These data indicate that this phenomenon could be avoided by careful selection of excipients. No significant decrease in *in vitro* dissolution occurs as a result of the hardness increase induced by the moisture content. However, in the absence of the moisture-induced phenomenon, when moisture contents of the granulations are low, hardness produced by the use of higher compression induces a considerable decrease in *in vitro* dissolution.

Specifications for the hardness of compressed tablets are generally established for two unrelated reasons. A minimum hardness limit is needed to ensure that the tablets resist chipping, abrasion, and breakage during packaging, storage, transportation, and handling prior to use. A maximum hardness limit for tablets is intended to ensure proper dissolution of the drug.

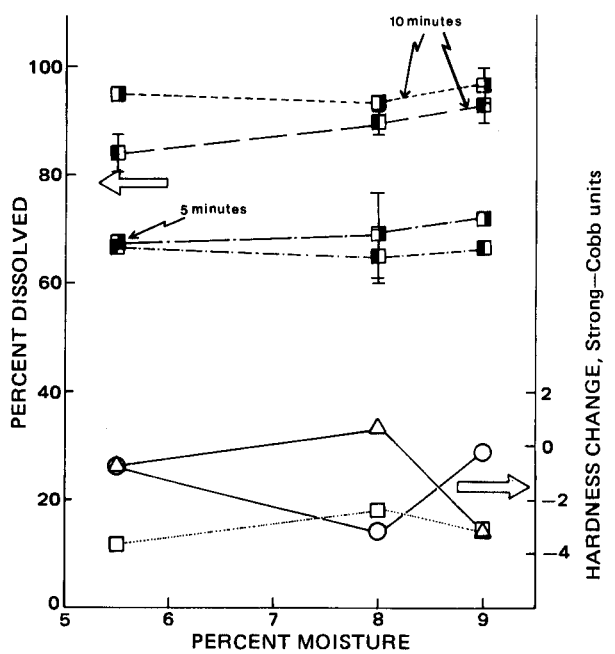

Figure 8—*Effect of moisture on hardness and* in vitro *dissolution of naproxen sodium tablets containing microcrystalline cellulose. Key:* ○, *change in hardness after exposure to ambient conditions;* △, *change in hardness after exposure in a desiccator;* □, *change in hardness after overnight drying at 80°;* ■, in vitro *dissolution immediately after compression; and* ◧, in vitro *dissolution after overnight drying at 80°. Vertical lines represent standard deviations; the absence of vertical lines indicates that the standard deviation was too small to be shown.*

Since the important parameter, *in vitro* dissolution of the tablets, is related to the moisture content of the granulation and the hardness of the tablets at the time of compression, an *in vitro* dissolution specification would ensure that the tablets did meet the moisture and hardness requirements as well. Therefore, it is recommended that the moisture content of the granulation and the initial hardness of the tablets be used as in-process controls. A lower limit of hardness should be established to ensure resistance of the tablets to abrasion, *etc.*

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