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MOISTURE, HARDNESS, DISINTEGRATION AND DISSOLUTION INTERRELATIONSHIPS IN COMPRESSED TABLETS PREPARED BY THE WET GRANULATION PROCESS

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ABSTRACT

Interrelationships among moisture, hardness, disintegration and dissolution in compressed tablets were studied by compressing tablets from granulations prepared by the wet granulation process containing low moisture levels. Hardness, disintegration and dissolution of these tablets did not change on exposure to ambient room conditions. After equilibration under high humidities, a decrease in tablet hardness occurred which depended linearly on tablet hardnesses at the time of compression. After overnight exposure to ambient room conditions, the softened tablets increased in hardness and this increase greatly exceeded the initial hardnesses. The magnitude of hardness increase was independent of the hard-

nesses at the time of compression. Increased tablet hardnesses resulted in an increase in the disintegration time, although in vitro dissolution of the drug remained unaffected. The results suggest that moisture gain and subsequent loss on storage under varying humidity conditions could account for major increases in hardness of compressed tablets in storage.

INTRODUCTION

The physical effects of moisture in the tablet manufacturing processes such as mixing, granulation, drying, flow into the die, compression and ejection from the die have been reviewed by Griffiths (1). Adverse effects on tablet hardness were reported as a result of aging tablets in conditions of high humidity (2-3). The effect of storage at specified temperature and humidity on properties of directly compressible tablet formulations indicated (4-5) that the evaluation of tablet hardness was not a reliable measure of physical aging of tablets. It was concluded that tablet aging is a complex problem, the causes of which are not fully understood.

Recent studies (6) in our laboratories indicated that moisture content of the granulation at the time of compression plays an unusually important role in the hardness increase phenomenon of compressed tablets. Two types of phenomena relating moisture content of the granulation at the time of com-

pression to tablet hardness and in vitro dissolution were observed (6);

1) Tablets compressed from granulations with high moisture content increased in hardness after storage. The important factors in the moisture induced hardness increase were the drug and excipient combinations in a formulation and their physical properties, such as aqueous solubility, crystalline properties and hygroscopicity. The magnitude of this increase was related to the percent moisture in the granulation at the time of compression. It was established that this moisture related hardness increase in the tablet formulations containing a high percentage (66%) of drug had no effect on in vitro dissolution.

2) The second phenomenon, interrelating moisture, hardness, and in vitro dissolution, occurred in tablets compressed from granulations with low moisture content. These tablets did not increase in hardness on storage. However, in vitro dissolution of the drug was strongly dependent on initial hardnesses.

This paper discusses the second phenomenon by equilibrating tablets under accelerated humidity conditions and subsequently exposing to ambient room conditions. These storage conditions resulted in large increases in tablet hardnesses which increased disintegration time and did not affect the in vitro

dissolution of the drug. The data suggest that moisture gain and subsequent loss on storage under varying humidity conditions could account for major increases in hardness of compressed tablets on storage

MATERIALS

Lactose, starch, povidone, magnesium stearate were all USP grade. Methanol was NF grade. FD&C Yellow #5 or FD&C Yellow #6 were used as coloring agents. Naproxen (Syntex Research, Palo Alto, California 94304) was at least 99% pure. All other chemicals were analytical reagent grade unless otherwise indicated.

METHODS

Granulation Preparation

The granulations were prepared by wet granulation. The powders, except magnesium stearate, were mixed in a small planetary-type mixer (Kitchen Aid, Model K5-A, The Hobart Manufacturing Co., Troy, OH 45373) for five minutes. The granulating solution was added while mixing and mixed for five minutes. The wet granulation was passed through a #12 mesh screen and dried in trays in a forced air drying oven at 50°C until the desired moisture level was reached. The dry granulation was screened through a #14 mesh screen and mixed with magnesium stearate in a mixer

for two minutes. 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 cosolvent. The binder was then added and mixed until dissolved.

Compression

Tablets were compressed by means of a single punch machine (Stoke Model E) to targeted hardnesses. The punches were standard concave and the diameter of the die and punches was 1.11 cm.

Moisture Determination

The granulation moisture was determined by the three commonly used methods, Cenco moisture balance (Central Scientific Co., Chicago, IL 60623), Karl Fischer reagent, USP and loss on drying, USP. The granulations of Formulation A (Table 1) were dried to contain different moisture levels ranging from approximately 1% to 7% and sealed in tightly closed containers. In the moisture balance method the granulations were exposed to a 125-W infrared lamp for 15 minutes at a heat control setting of 90. The weight loss on drying, in percent, was read directly from this instrument. The conditions for the loss on drying method were 90°C for 5 hours. Based on the results of these methods, the moisture balance method was used throughout this investigation.

TABLE 1.

FORMULATIONS USED IN THIS STUDY

Formulation	Ingredients	Mg/Tablets
A*	Naproxen	250
	Povidone, USP	20
	Starch, USP	38
	Lactose, USP	71.12
	FD&C Yellow #5	0.12
	Magnesium stearate, USP	0.76
B*	Lactose, USP	320
	Starch, USP	38
	Povidone, USP	20
	FD&C Yellow #6	0.08
	Magnesium stearate, USP	1.9

*The granulation solvent was methanol, NF 31 mg/tablet and purified water 39 mg/tablet.

The tablets were ground with a mortar and pestle and the same procedure for moisture determination was followed.

Hardness Determination

Initial hardnesses were determined immediately after compression. The tablets were placed in open trays exposed to different humidities in dessicators containing saturated salt solutions at 20° and 37°C. At appropriate time intervals, samples were taken

out for hardness, disintegration and dissolution determinations. Samples were also exposed to ambient room conditions (20°C, 35-45% relative humidity) until maximum hardnesses were reached. Hardnesses were determined by the Heberlein hardness tester (Heberlein and Company AG, Switzerland). The Stokes hardness tester (F.J. Stokes Machine Co., Philadelphia, PA) was only used where the Heberlein hardness tester went off the scale and hardnesses were converted to Strong Cobb units by running a correlation between the two instruments. For each hardness determination, ten tablets were tested and mean and standard deviations calculated.

Disintegration

The USP method for uncoated tablets was used. The time of disintegration for each tablet was noted. Mean and standard deviations of six tablets were calculated.

Dissolution

The dissolution method was exactly the same as reported previously (6). The apparatus consisted of a one liter beaker and a stirrer driven by a synchronous motor at 120 rpm. The beaker, containing 600 ml of 0.1M phosphate buffer at pH 7.4, was maintained at 37°C in a constant temperature water bath. A stainless steel paddle, 2.5 x 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. The absorbance (Unicam SP 1800 ultraviolet spectrophotometer, Pye Unicam Ltd., Cambridge, England) of the naproxen samples was measured after appropriate dilution at 332 nm.

RESULTS AND DISCUSSION

For determining moisture contents in the granulations, three commonly used methods were evaluated. The results of the moisture balance method and the titrimetric method gave good correlation (correlation coefficient - 0.997) and a positive Y intercept value. The lactose in the granulation is in the monohydrate form. The partial or full inclusion of the water of crystallization in the moisture contents determined by the titrimetric method, accounts for the higher moisture content values. An excellent correlation between the moisture balance method and the loss on drying method (correlation coefficient = 0.99990 and slope = 1.006) was obtained. A small negative Y intercept indicates slightly higher moisture content values by the moisture balance method compared to the loss on drying method.

Since the moisture determination method in the granulations should not include the water of crystallization of the excipient(s) or the drug, either the loss on drying method or the moisture balance method would be suitable for the purpose of this study.

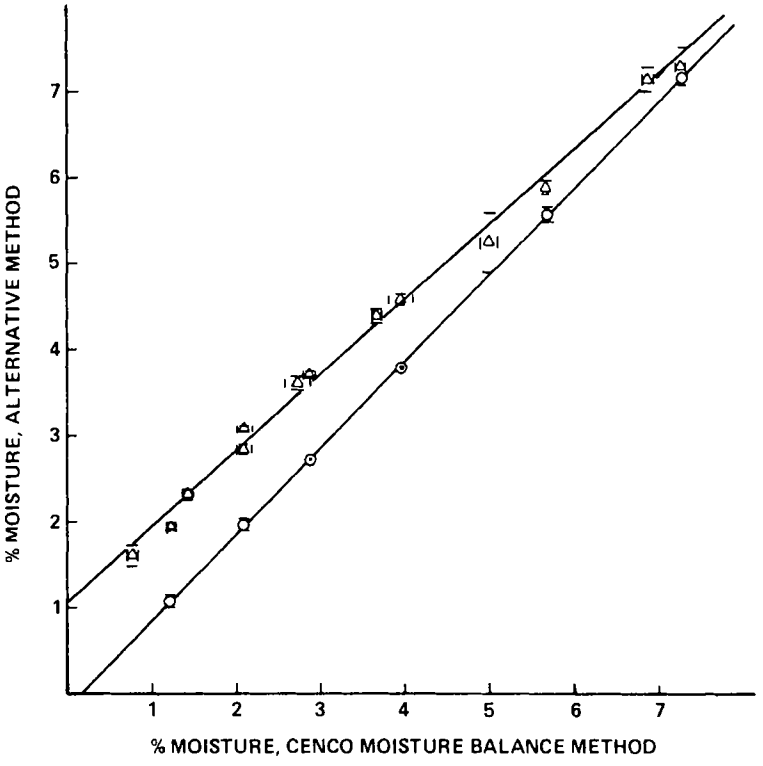

FIGURE 1:

Correlation between percent moisture in the granulation of Formulation A determined by the moisture balance method and by the titrimetric method or by the loss on drying method.

KEY: △, titrimetric method: the linear regression line is Y = 1.093 + 0.874X; correlation coefficient = 0.997; ○, loss on drying method: the linear regression line is Y = -0.16273 + 1.00633X; correlation coefficient = 0.99990. The data points are averages of three results and the lines are the standard deviations.

Because of the good reproducibility, simplicity and ease of use, the moisture balance method was used throughout this investigation for the moisture content determinations.

The granulation for Formulation A (Table 1) was dried to low moisture content (1.4%). Tablets were compressed to a hardness of about 12 Strong Cobb units. As expected from the results of the previous study (6), tablet hardness (Figure 2) and *in vitro* dissolution of the drug (Figure 4) did not

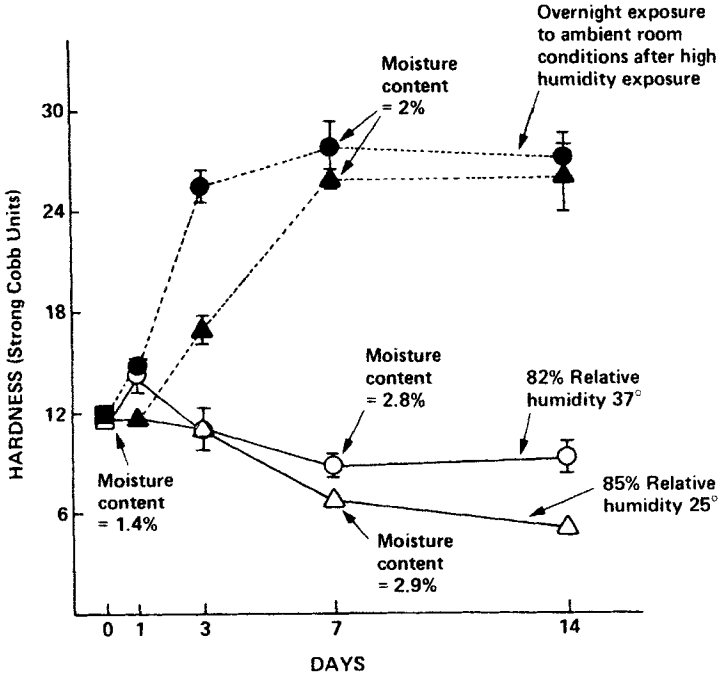

FIGURE 2:

Effect of storage on hardness of tablets prepared from granulation of Formulation A with low moisture content.

KEY: □, initial hardness; △, hardness after exposure to 85% relative humidity at 25°C; ○, hardness after exposure to 82% relative humidity at 37°C. Solid data points represent an overnight exposure to ambient room conditions after corresponding high humidity storage. Data points are averages of ten tablets and vertical bars are the standard deviations.

change after overnight exposure to ambient room conditions.

These tablets were then exposed to 85% relative humidity at 25°C and 82% relative humidity at 37°C. Samples were taken out of the humidity chambers at appropriate time intervals for immediate determination of the moisture content, disintegration time and *in vitro* dissolution of the drug from the tablets. The tablet samples equilibrated at high humidities were subsequently exposed overnight to ambient room conditions. The moisture content, hardness, disintegration and *in vitro* dissolution of the exposed tablets were again determined.

Figure 2 gives the plots of the tablet hardness versus the number of days of exposure to accelerated humidity conditions. The open data points are the results of the hardnesses determined immediately after removal from the humidity chambers. As expected, the tablet hardnesses decreased after storage at high humidities, resulting from a gain in the moisture contents. After seven days, the moisture contents of the tablets were 2.8% at 37°C (82% relative humidity) and 2.9% at 25°C (85% relative humidity). When those tablets were then exposed to ambient room conditions, the moisture content dropped to 2.0% resulting in considerable increases in hardness values, as shown by the solid data points in Figure 2. The

hardness increases reached a maximum value after seven days storage under accelerated humidity conditions and subsequent overnight exposure to ambient room conditions.

These results indicate that the moisture related effect on tablet hardness is not limited to the moisture content of the granulations at the time of compression, as reported earlier (6). The moisture gain followed by the moisture loss on storage may also induce an increase in tablet hardness. As discussed earlier (6), one of the mechanisms by which tablets increase in hardness is by the dissolution of some of the soluble excipient(s) at high humidities and then recrystallization by the partial loss of that water under normal storage conditions.

Important parameters which could be affected by the moisture related hardness increase in compressed tablets are the disintegration time and in vitro drug dissolution. The plots of the disintegration time of Formulation A tablets, as a function of the accelerated humidity storage time, are given in Figure 3. The results suggest that the tablet disintegration time increased after storage under accelerated humidity conditions and subsequent overnight exposure to ambient room conditions. Similar to the increase in tablet hardness, disintegration time increase also reached a plateau value in about one week.

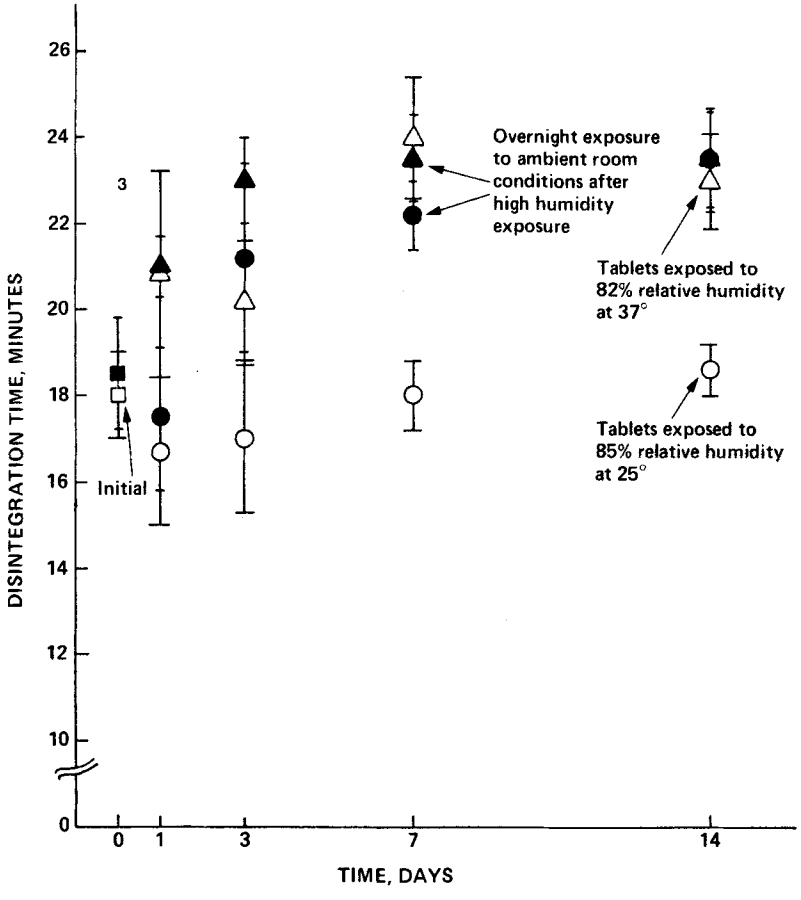

FIGURE 3:

Effect of storage on disintegration time of tablets prepared from granulation of Formulation A with low moisture content.

KEY: □, initial disintegration time; ○, disintegration time after exposure to 85% relative humidity at 25°C; △, disintegration time after exposure to 82% relative humidity at 37°C. Solid data points represent an overnight exposure to ambient room conditions after corresponding high humidity exposure. Data points are averages of six tablets and vertical bars are the standard deviations.

Figure 4 and Figure 5 give the percent drug dissolution at five minute and fifteen minute time points as a function of the storage time under accelerated humidity conditions. The results clearly show that the moisture related hardness increases in these tablets did not change the *in vitro* drug dissolution.

The hardness of the tablets at the time of compression in Figure 2 to Figure 5 was around 12 Strong Cobb units. To study the effect of initial hardness on hardness changes after storage, tablets were compressed at various hardnesses from granulation containing low moisture content. These tablets were equilibrated under 85% relative humidity at 25°C for one week and subsequently exposed overnight to ambient room conditions. Figure 6 gives the plots of the initial hardness versus changes in hardness of these tablets after storage. The tablet hardnesses obtained immediately after one week equilibration under 85% relative humidity at 25°C decreased linearly as the hardness at the time of compression increased. When the softened tablets were then exposed overnight to ambient room conditions, hardnesses increased and these increases did not appear to depend on the hardnesses at the time of compression.

The granulation of the Formulation B, containing 84% lactose (Table 1), was dried to contain low moisture content (0.8%). The tablets were compressed

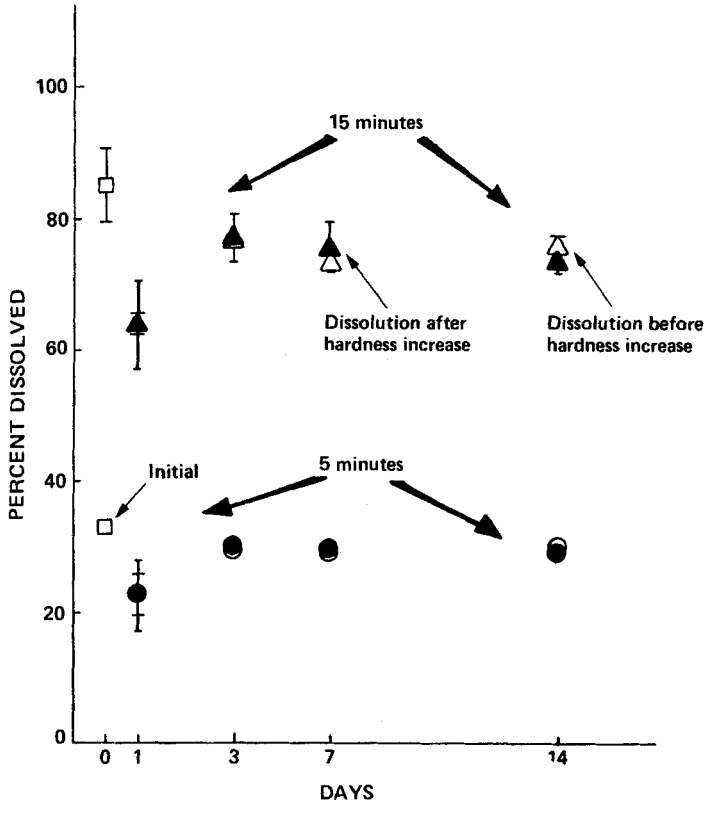

FIGURE 4:

Effect of storage on in vitro dissolution of naproxen in tablets prepared from Formulation A granulation with low moisture content.

KEY: □, initial dissolution; ○, △, dissolution after exposure to 85% relative humidity at 25°C; ●, ▲, dissolution after overnight exposure to ambient room conditions after high humidity exposure. Data points are averages of three results and vertical bars are the standard deviations.

at various initial hardnesses and then equilibrated at accelerated humidity conditions for seven days and subsequently exposed overnight to ambient room conditions. The plots of the initial hardness versus

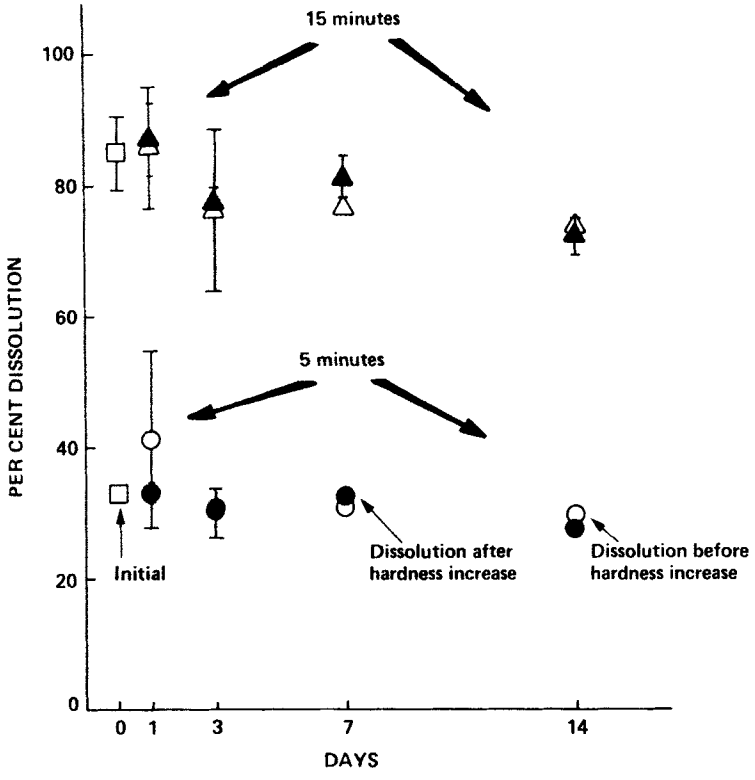

FIGURE 5:

Effect of storage on in vitro dissolution of naproxen in tablets prepared from Formulation A granulation with low moisture content. KEY: □, initial dissolution; ○, △, dissolution after exposure to 82% relative humidity at 37°C; ●, ▲, dissolution after overnight exposure to ambient room conditions after high humidity exposure. Data points are averages of three results and vertical bars are the standard deviations.

changes in hardness after storage are given in Figure 7. Under both humidity conditions, the tablet hardness decreased linearly as the hardness at the time of compression increased due to the moisture gain.

The moisture content of the tablets after equilibration under 85% relative humidity at 25°C was 2.8% and after equilibration under 82% relative humidity at 37°C was 3.0%. When these tablets were exposed to ambient room conditions, the moisture contents dropped to 1.9% and 1.8% respectively, resulting in large increases in tablet hardness. Similar to the Formulation A tablets, the increases in tablet hardness did not depend on the hardness at the time of compression. Comparisons of the results of Figure 6 and Figure 7 indicate that larger increases in hardness occurred by the substitution of the water insoluble drug with a water soluble excipient in the formula.

The mean disintegration time of Formulation B tablets after compression ranged from 3.03 to 5.37 minutes. As the initial hardness of the tablets increased, the disintegration time increased. Figure 8 (a) gives the increase in the disintegration time versus initial hardness plots resulting from seven days equilibration under 85% relative humidity at 25°C and subsequent overnight exposure to ambient room conditions which resulted in the hardness increases. These results indicate that as the initial hardnesses increased, storage under accelerated humidity conditions resulted in increases in the disintegration time. However, increases in the disintegration time due to moisture related hardness increases were small.

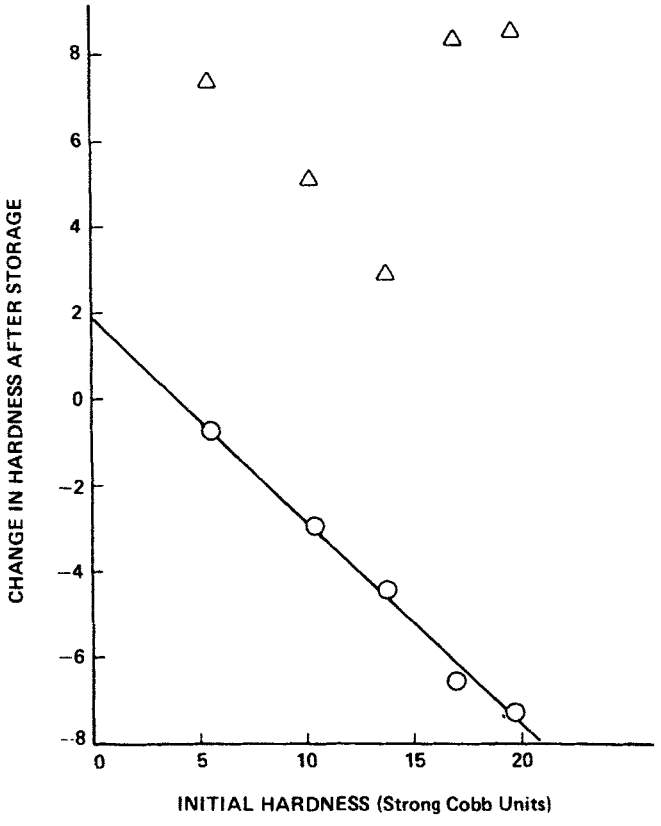

FIGURE 6:

Effect of the tablet hardness at the time of compression on changes in hardness after storage.

KEY: ○, 7 day storage under 85% relative humidity at 25°C the equation of the regression line is Y = 1.884 - 0.479X (correlation coefficient = 0.996); △, tablets exposed overnight to ambient room conditions after accelerated humidity storage.

Figure 8(b) gives the increases in the disintegration time versus initial tablet hardness plots caused by the seven days equilibration under relative humidity at 37°C. In agreement with the 85% relative humidity data, the hardness increases due to storage

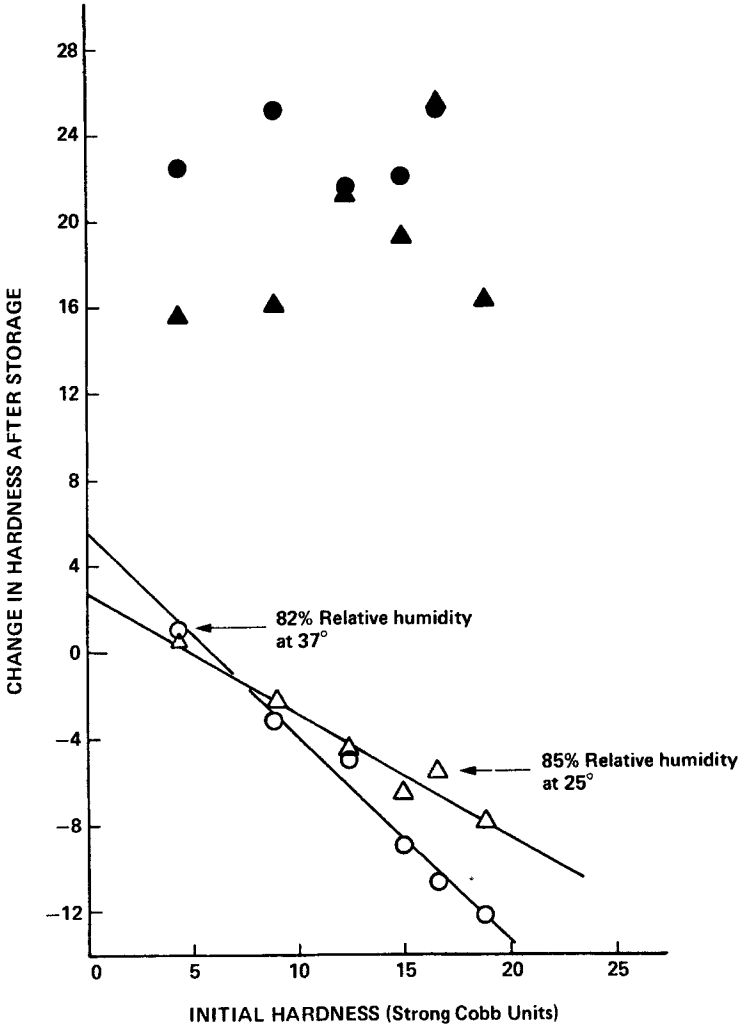

FIGURE 7.

Effect of the tablet hardness at the time of compression on changes in hardness after storage.

KEY: △ , 7 day storage under 85% relative humidity at 25°C; the equation of the regression line is Y = 2.724 - 0.5613X (correlation coefficient = 0.9772); ○ , 7 day storage under 82% relative humidity at 37°C; the equation of the regression line is Y = 5.642 - 0.9476X (correlation coefficient = 0.9933). The solid data points are the increase in hardnesses of corresponding tablets after an overnight room condition exposure.

under 82% relative humidity at 37°C and subsequent overnight exposure to ambient room conditions resulted only in small changes in the disintegration time.

The smaller changes in the disintegration time of Formulation B tablets compared to Formulation A tablets caused by the moisture related effect on hardness, appears to be due to the differences in solubility of the formulation compositions in the disintegration medium.

CONCLUSION

To elucidate our understanding of the role of moisture on tablet hardness and its subsequent effect on important tablet parameters, most commonly used excipients like lactose and starch with and without a water insoluble drug were used. The data suggests that moisture plays a significantly important role in controlling hardness of compressed tablets, after storage. Tablets prepared from granulations with low moisture content may gain moisture from high humidity exposures and increase in hardness as a consequence of the partial loss of the gained moisture, after storage. Such hardness increases do not decrease the *in vitro* dissolution of the drug; the disintegration time is only slightly increased depending upon the solubility of the drug and excipients in the disintegration medium. The data suggest that the magnitude of the moisture related hardness increase depends on the

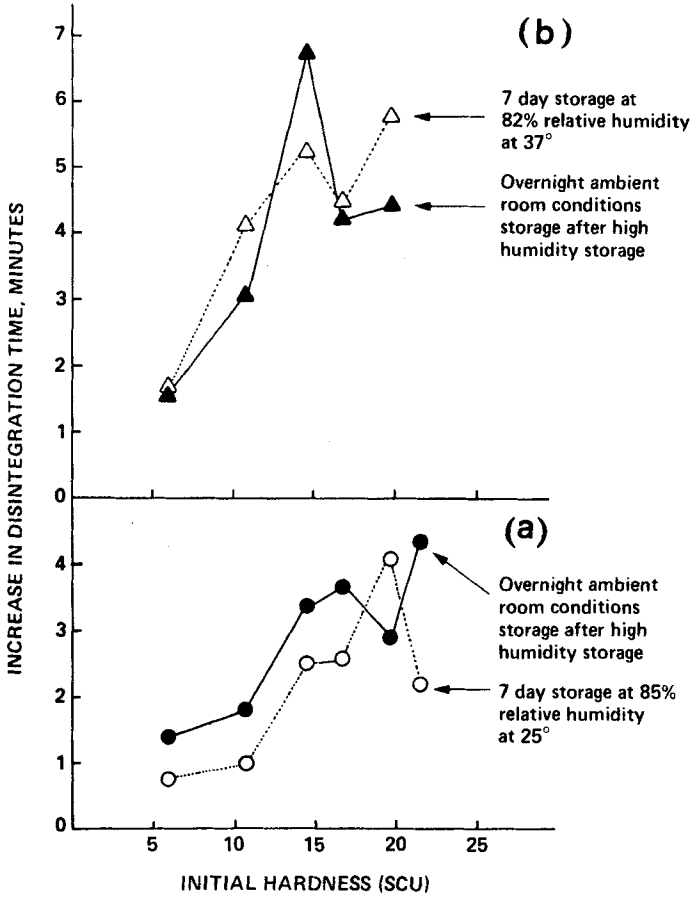

FIGURE 8.

Effect of the hardness at the time of compression on increase in the disintegration time of Formulation B tablets after storage.

KEY: ○, 7 day storage under 85% relative humidity at 25°C;
△, 7 day storage under 82% relative humidity at 37°C.
The solid data points are the results of the disintegration time after hardness increased.

physical properties of the drug and/or excipient combinations.

The exact mechanism by which moisture controls tablet hardnesses is not fully understood. It is

possible that binders play an important role in the moisture related hardness increase phenomenon. Undoubtly, additional studies directed specifically to the effect of binders and their role on hardness increase in compressed tablets are required. It is hoped that further work directed in this vein would be helpful in understanding the role of moisture on important tablet parameters.

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REFERENCES

1. R.V. Griffiths, Manufacturing Chemist and Aerosol News, 40, 29(1969).

2. E. El-Kalek and A.A. El-Kader, J. Pharm. Sci., V.A.R. 5, 117(1964).

3. G.E. Reier and R.F. Shangraw, J. Pharm. Sci., 55, 510(1966).

4. S.T. Horhota, J. Burglo, L. Lonski and C.T. Rhodes, J. Pharm. Sci., 65,1746(1976).

5. J. M. Lausier, Chia-Whei Chiang, H.A. Zompa and C.T. Rhodes, J. Pharm. Sci., 66, 1637(1977).

6. Z.T. Chowhan, L. Palagyi, J. Pharm. Sci., in press.