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COMPARATIVE STUDY OF DISINTEGRATING AGENTS IN TIARAMIDE HYDROCHLORIDE TABLETS

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ABSTRACT

The water sorption properties of some commonly used disintegrants (i.e., starch, sodium starch glycolate, croscarmellose sodium, crospovidone and alginic acid) were studied to correlate the disintegration and physical mechanical properties of tiaramide hydrochloride tablets containing 5% of these disintegrants. With the exception of alginic acid, disintegration time of tablets decreased with the increase in water sorption properties of the disintegrants. When exposed to high humidity (100% RH at 35°C), tablets containing two high water-sorbing disintegrants, e.g., croscarmellose sodium and crospovidone, exhibited a marked decrease in hardness. When these tablets were dried after exposure to humidity, the hardness remained lower than the initial values. It is possible that high water affinity of the disintegrants disrupts the interparticulate bonds inside the tablets. However, such a decrease in interparticulate bond may not be observed if the disintegrant also acts as a binder in the presence of water. For example, the hardness of tablets containing another high water-sorbing disintegrant, sodium starch glycolate, increased when these tablets dried after exposure to high humidity. Unlike croscarmellose sodium and crospovidone, sodium starch glycolate also increased the disintegration time if tablets were previously exposed to high humidity.

Studies of the moisture absorption and drying cycle may be very important in evaluating environmental effects of tablets containing high water-sorbing disintegrants.

INTRODUCTION

While at first glance it would seem simple to formulate a tablet of a very water-soluble drug, there are, in fact, many inherent problems. Tablets containing high concentrations of water-soluble drugs normally tend to erode, rather than disintegrate, which may result in slow disintegration and possible gastrointestinal irritation as has been reported with potassium chloride.[1] To prevent these problems, a rapidly disintegrating tablet is preferred.

Although many mechanisms of action of disintegrants (such as water sorption, swelling, wicking, and deformation) have been variously hypothesized, stated and debated,[2-5] data will be presented to show that the water sorption capacity of a disintegrant plays an important role in the disintegration of tablets.

Because tiaramide hydrochloride, a water-soluble nonsteroidal anti-inflammatory agent, has desirable physical mechanical properties (e.g., no binding agent is necessary for preparing a tablet) and is not hygroscopic, the disintegration of tiaramide hydrochloride tablets may be easily related to the absorption of fluid by a disintegrant in the tablets.[6] Therefore, this drug was chosen as a model drug to evaluate the water sorption properties of various disintegrants such as starches, celluloses and other macromolecules and their disintegration action in the tablets.

Since the most effective disintegrants are highly hydrophilic, tablets containing even small amounts of these ingredients may soften when exposed to high humidity. Therefore, the physical properties of tablets were measured before and after exposure to humidity. The role of compression

forces on the tablet disintegration were also evaluated, because tablet porosity decreases as compression pressure increases and may hinder penetration of fluid into tablets[7,8] and slow down the disintegration. Nevertheless, literature[9, 10] suggests that some newer "superdisintegrants" such as croscarmellose sodium and sodium starch glycolate were fairly insensitivie to increases in compression force.

EXPERIMENTAL

Materials - Tiaramide hydrochloride (Fujisawa Pharmaceutical, Osaka, Japan) was at least 98% pure. Starch (corn starch: National Starch & Chemical, Bridgewater, NJ) sodium starch glycolate (Explotab: Edward Mendell, Carmel, NY), croscarmellose sodium (Aci-Di-Sol: FMC, Philadelphia, PA), crospovidone (Polyplasdone XL: GAF, New York, NY), alginic acid (Satialgine H8: Edward Mendell, Carmel, NY), and magnesium stearate were from a single lot and used as received.

Granulation Preparation - Tiaramide hydrochloride powder was granulated in a small Hobart planetary mixer using purified water. Granulating fluid was added while mixing and was mixed for 8 minutes to produce a mass of proper consistency. The wet mass was passed through a #8 mesh screen and dried in trays in a forced air oven at 50°C until the moisture of the dried granules was below 0.3%. The dried granules were sized through a #16 mesh screen. The granulation was divided into portions and mixed with the same concentration of various disintegrants (5% by weight of the drug for comparing the efficiency of the disintegrants) and magnesium stearate. Except for starch, which normally requires a higher concentration to be effective, the quantities used for all disintegrants were within the normal use range. Each tablet contained tiaramide hydrochloride 220.4 mg (equivalent to 200 mg tiaramide base), disintegrant 11.0 mg, and magnesium

stearate 1.8 mg. A control tablet contained tiaramide hydrochloride and magnesium stearate only.

Compression - Since the Stokes single punch press was not instrumented, the tablets were compressed to a target hardness of 10 ± 1 Strong Cobb (S.C.) units using 0.313 cm round standard tooling. The tablet weight was adjusted to 233.2 mg. These tablets were used for physical property evaluations before and after exposure to humidity. The tablets were also compressed on a Carver hydraulic press, using the same size punches, with compression forces ranging from 682 to 1,818 kg (1,500 to 4,000 lbs) gauge pressures. These tablets were used to investigate the physical properties of tablets as a function of compression forces.

Hardness - Hardness of the tablets was determied using a Schleuniger hardness tester. Each hardness value reported is based on an average of 10 tablets.

Disintegration - The disintegration time of the tablets in purified water 37 ± 2°C was determined by means of a modified USP apparatus with 40 mesh stainless steel screen. Disks were not used for better visual observation of table disintegration. The reported disintegration time for each sample of tablets represented an average time for 6 individual tablets. Since tiaramide hydrochloride is highly water soluble (190 mg/mL at 37°C), measurement of disintegration time using a 40 mesh screen may provide a qualitative indication of the dissolution rate of tablets; the drug in the disintegrated particles smaller than 40 mesh was found to be rapidly soluble in the medium.

Determination of Moisture Sorption of Disintegrants - The method was similar to that used by Kornblum and Stoopak.[11] Ten grams of each

disintegrant was accurately weighed and evenly distributed in a 60 mm tared glass dish. A sample of tiaramide hydrochloride was used as a control. The sample was placed in a desiccator containing purified water in its reservoir. The desiccator was then stored in an oven maintaining constant temperature at 35 ± 0.5°C (100% R.H. at 35°C). At various time intervals, the amount of water absorbed was calculated from the weight difference.

Physical Properties of Tablets After Exposure to Humidity Cycling – About 150 tablets containing the various disintegrants and the control tablets (containing no disintegrant) were placed and touching each other in a 60 mm tared glass dish and exposed to 35°C/100% RH. At various time intervals (after day 1, 3 and 7), the tablets were removed for determination of their physical properties. To minimize exchange of water vapor between the tablets and atmosphere, the tablets were stored in small covered vials until testing. In order to study the effect of environmental changes (moisture and drying) on the physical properties of tablets, the tablets were dried at 55°C in an oven for 24 h after 7 d of moisture exposure. The physical properties of these tablets were then examined.

RESULTS AND DISCUSSION

The water sorption behavior of these disintegrants and of tiaramide hydrochloride, as a function of time, is shown in Fig. 1. At the end of 7 d, croscarmellose sodium exhibited the highest water sorption, 35% of its own weight, followed closely by crospovidone and sodium starch glycolate. Alginic acid and starch had water uptake values of 12–16% while tiaramide hydrochloride exhibited no water sorption at all. Two groups of disintegrants can be classified from the magnitude of water

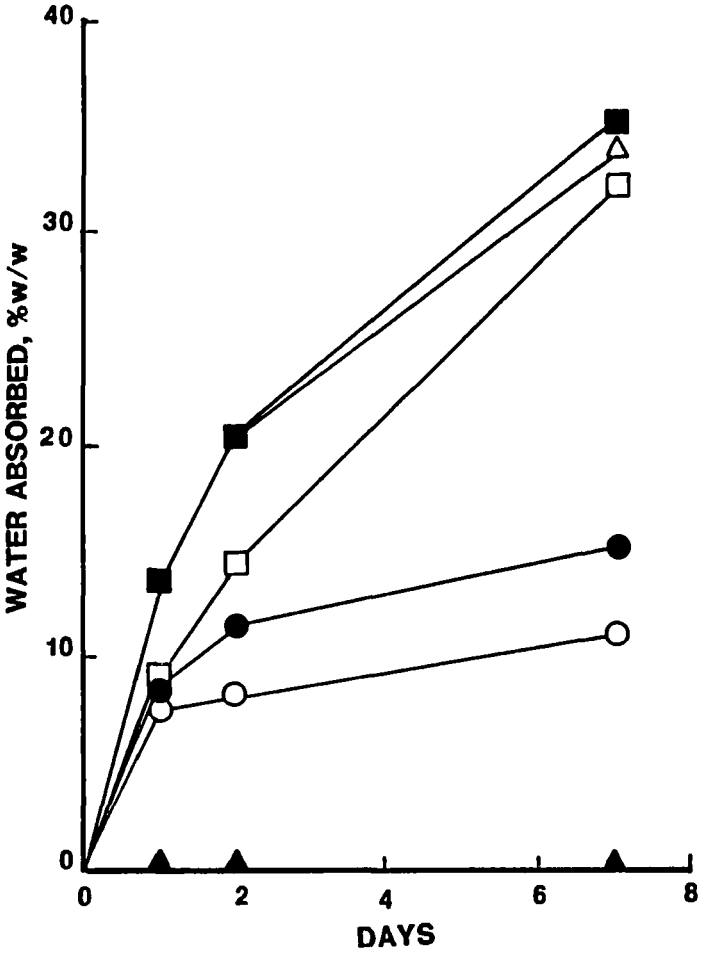

Figure 1 *Water sorption profile for disintegrants and tiaramide* hydrochloride. Key: (▲) tiaramide hydrochloride; (○) starch; (□) sodium starch glycolate; (■) croscarmellose sodium; (△) crospovidone; (●) alginic acid.

sorption: high sorption - croscarmellose sodium, crospovidone, and sodium starch glycolate with water sorption values of 32-35% in contrast to those with moderate sorption - alginic acid and starch with 12-16% of water uptake.

Since water sorption is preliminary to swelling, it is not surprising that the data in Fig. 1 is in direct agreement with the maximum swelling of disintegrants as given by Gissinger and Stamm.[12]

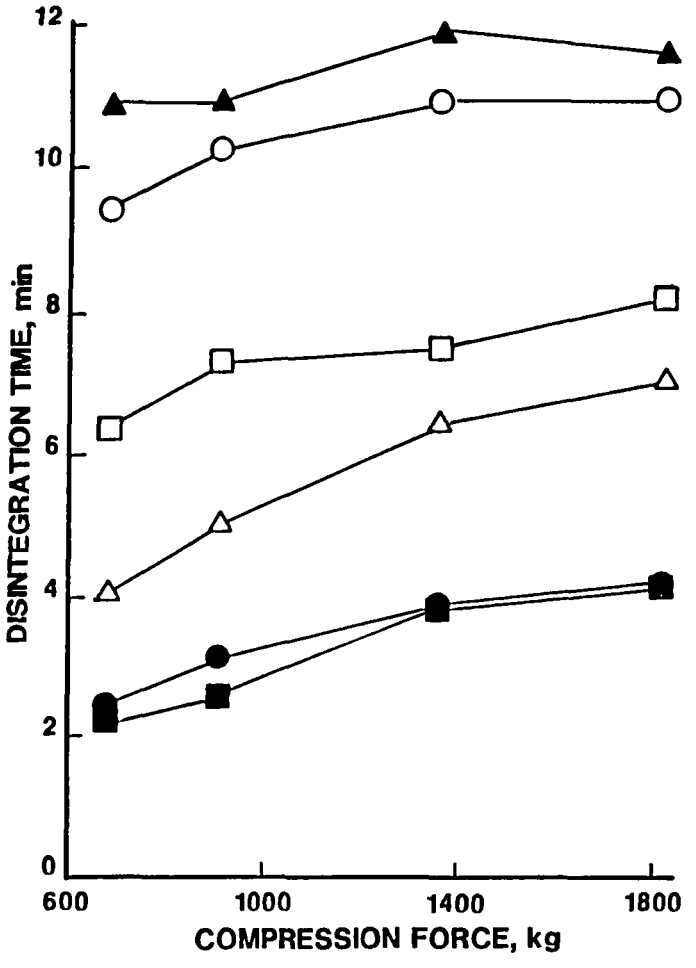

Figure 2 Effect of compression force on disintegration time of tiaramide hydrochloride tablets. Key: (▲) control (containing no disintegrant); (○) starch; (□) sodium starch glycolate; (■) croscarmellose sodium; (△) crospovidone; (●) alginic acid.

Figure 2 shows the disintegration time of tablets produced on a Carver hydraulic press at different compression forces. A distinct rank order of the efficiency of these disintegrants in the tablets is consistently demonstrated across a normal range of compression pressures: croscarmellose sodium and alginic acid had the best disintegrating property, followed by crospovidone, sodium starch glycolate, starch and the control tablets. A

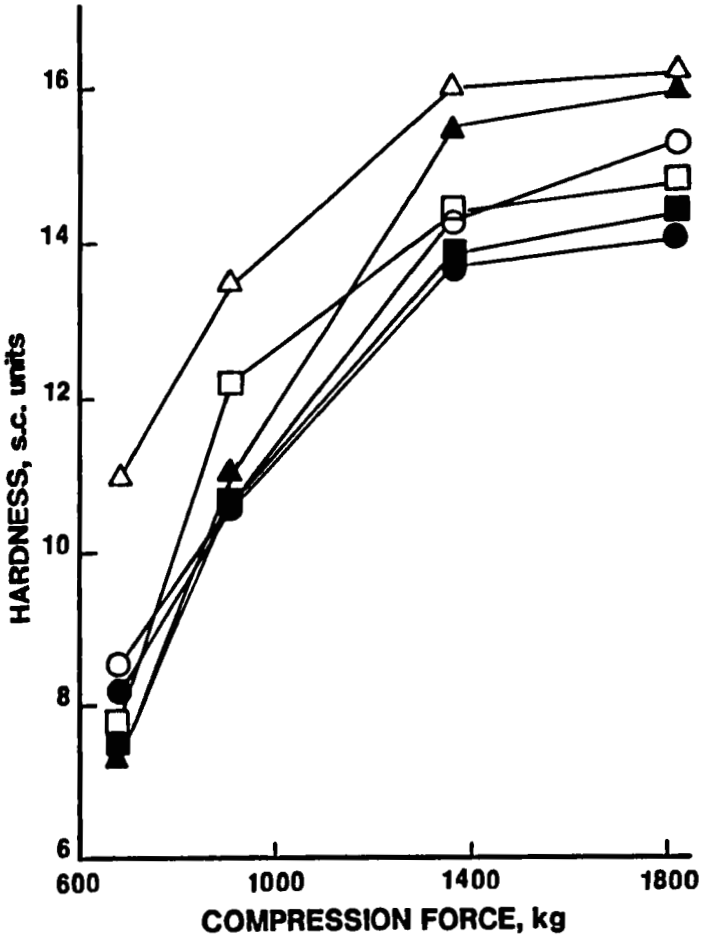

Figure 3 Effect of compression force on hardness of tiaramide hydrochloride tablets. Key: (▲) control; (○) starch; (□) sodium starch glycolate; (■) croscarmellose sodium; (△) crospovidone; (●) alginic acid.

similar rank order for these disintegrants in insoluble calcium phosphate tablets was also found by Gissinger and Stamm.[12] The control tablets without disintegrant eroded rather than disintegrated. As compressional forces increase, tablets normally become more dense and consequently less porous, with particle-to-particle bonds becoming stronger. The phenomenon is reflected in an increase in tablet hardness (Fig. 3). The effect of

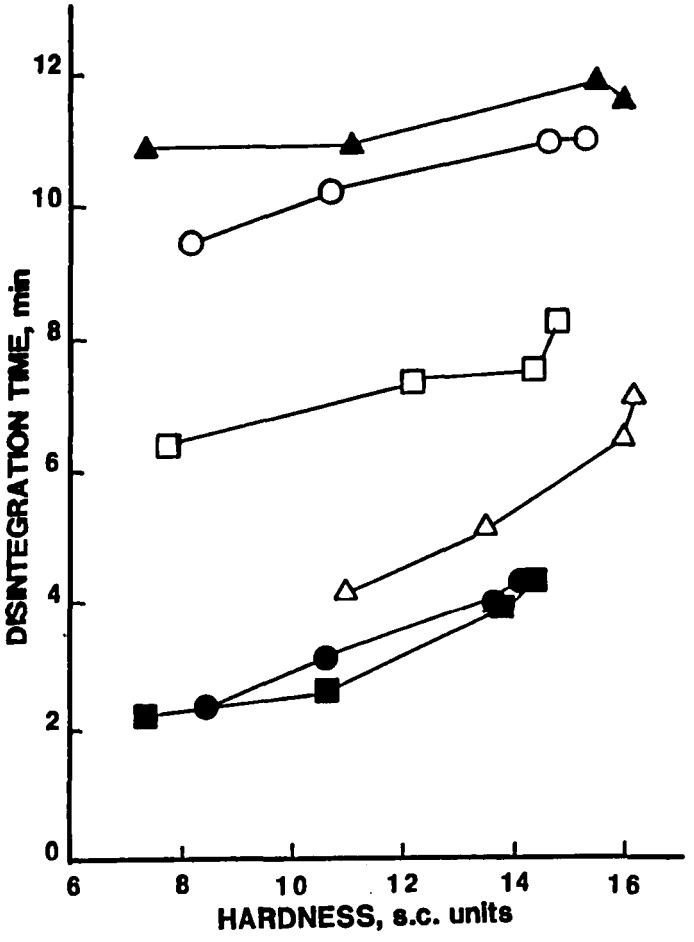

Figure 4 Effect of hardness on disintegration time of tiaramide hydrochloride tablets. Key: (▲) control; (○) starch; (□) sodium starch glycolate; (■) croscarmellose sodium; (△) crospovidone; (●) alginic acid.

hardness on the disintegration time of the tablets is illustrated in Fig. 4. The disintegration time increased slightly as compression forces as well as tablet hardness increased.

Alginic acid, which had moderate water sorption, was found to be a very effective disintegrant for tiaramide hydrochloride tablets as was croscarmellose sodium in the high water uptake class. There appeared to

be no particular correlation existing between water sorption of alginic acid and disintegration time. Nevertheless, with the exception of alginic acid, the efficiency of these disintegrants ranks well with their water uptake (Fig. 2).

The tablets containing crospovidone had the best mechanical strength (Fig. 3); this disintegrant is also used as a dry binder.[13] All other disintegrants had some deteriorating effect on compressibility of the drug when the compression force is beyond 1,200 kg.

The effect of storage (100% relative humidity at 35°C) on the relative changes in tablet hardness compared to the initial values is demonstrated in Fig. 5. The use of relative hardness allows direct comparison of trends in tablet strength after they were exposed to humidity. In such a comparison, the initial hardness of tablet becomes unity. Tablets containing high water sorption disintegrants (croscarmellose sodium, crospovidone, and sodium starch glycolate) showed marked decreases in hardness (about 50%) after they were stored in a high humidity atmosphere. The reduction in the strength of these tablets, prepared with disintegrants having a high affinity for moisture, can be related to the slow absorption of moisture by the disintegrant, initiating swelling and bond disruption.[13] Gissinger and Stamm[12] reported that these 3 disintegrants demonstrated a maximum swelling ability within 15 minutes in water, although it should be noted that immersion swelling in minutes may not be predictive of moisture sorption behavior in days.

The hardness of control tablets and tablets containing alginic acid showed a slight increase initially and then decreased as exposure to humidity was extended (Fig. 5). The slight increase in hardness after 1 d exposure could have been partially due to a moisture gain which might improve the cohesion of a tablet.[15] A rough surface appeared on tablets containing alginic acid after prolonged exposure to humidity. There was no change in appearance in the tablets containing other disintegrants.

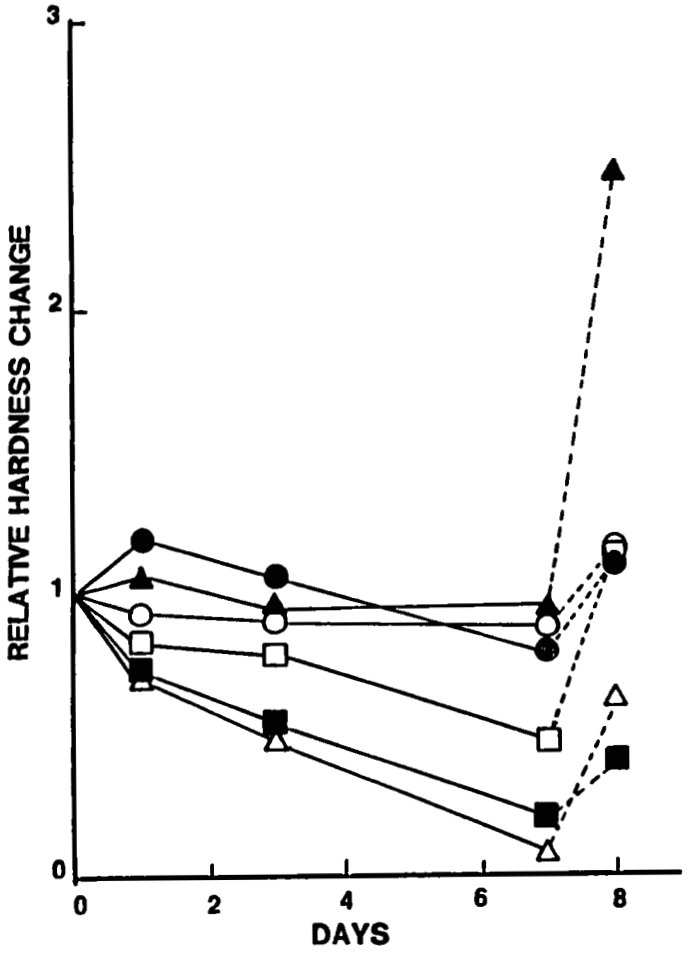

Figure 5 Relative hardness change of tiaramide hydrochloride tablets after exposure to humidity (——) and drying (---). Key: (▲) control; (○) starch; (□) sodium starch glycolate; (■) croscarmellose sodium; (△) crospovidone; (●) alginic acid.

After 7 d exposure to humidity, the hardness of the control tablet was essentially equivalent to the initial hardness due to negligible water sorption.

When the control tablets were dried, their hardness increased sharply due to recrystallization of drug from the interparticulate surface liquid films which helped to increase the strength of tablets.[16] Rees and

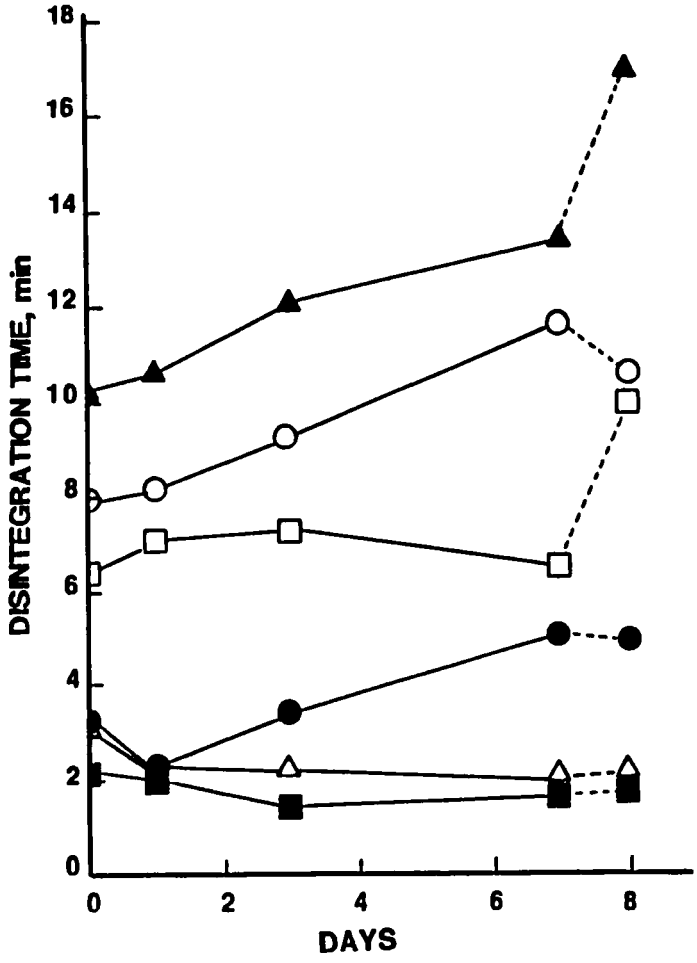

Figure 6 Disintegration time of tiaramide hydrochloride tablets after exposure to humidity (——) and drying (---).
Key: (▲) control; (○) starch; (□) sodium starch glycolate; (■) croscarmellose sodium; (△) crospovidone; (●) alginic acid.

Shotton[17] also observed an increase in hardness of a sodium chloride compact, stored at 100% R.H. and dried, despite its small moisture sorption. Even though increases in hardness were noticed for tablets dried for 24 h, the hardness of dried tablets containing croscarmellose sodium or crospovidone was lower than the initial hardness because the high affinity to moisture of these disintegrants might have caused the

disruption of the tablets' interparticulate bonds. On the other hand, the hardness of dried tablets containing high water uptake sodium starch glycolate became higher than their initial hardness because this disintegrant also has binding properties according to Khan and Rhodes.[18]

The disintegration times of tablets after exposure to humidity and drying is depicted in Fig. 6. The disintegration time of tablets containing high water sorption croscarmellose sodium and crospovidone were only slightly decreased after exposure to humidity. The tablets containing moderate water sorption starch and alginic acid showed an increase in disintegration times because the disintegration action was reduced by moisture which resulted in a loss of absorption and swelling ability. This can be substantiated by the decrease in disintegration times of dried tablets which contained dried disintegrants. The disintegration times of tablets containing sodium starch glycolate changed insignificantly after exposure to humidity. However, when they were dried, the disintegration time increased due to the binding property of this disintegrant.

CONCLUSION

At the same concentration level studied, croscarmellose sodium and alginic acid had the best disintegrating property, followed by crospovidone, sodium starch glycolate and starch for tiaramide hydrochloride tablets. The studies showed that the hardness of tablets containing high water sorption disintegrants decreased drastically when exposed to high humidity. The effect of exposure to moisture and drying cycles should be investigated when developing a tablet containing a high concentration of a water soluble drug because the environmental effects may markedly change the physical properties of tablets.

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