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Report

Intrinsic Dissolution Rates of Tablet Filler-Binders and Their Influence on the Dissolution of Drugs from Tablet Formulations

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Intrinsic dissolution rates were determined for different grades of commonly used calcium salt fillers and lactose. Typical tablet formulations of low-dose drugs were studied to determine the influence of this property on drug dissolution.

KEY WORDS: intrinsic dissolution rate; lactose; calcium salt; tablet filler; drug dissolution; rotating disk method.

INTRODUCTION

Dissolution of a drug from its formulation is influenced not only by its own physical-chemical properties, but also by the properties of the inert excipients in the formulation. With the development of increasingly potent drug molecules, the inert excipients can constitute as much as 95% of the formulation. Therefore, solid dosage forms must be developed with due consideration of the physical-chemical properties of the excipients.

Lactose is widely used as a soluble diluent in the tablet and capsule dosage forms. It is commercially available in the anhydrous as well as the hydrous forms and both forms are accepted as U.S.P.-grade lactose. Either one of the forms is often arbitrarily selected for use in formulation. However, the hydrate and anhydrous forms may be expected to possess different physical properties such as intrinsic dissolution rate.

Similarly, a number of calcium salts are used as diluents in solid dosage forms and also as sources of calcium in geriatric patients. These salts dissolve in gastric fluid by reaction with the hydrochloric acid. Thus, the normal differences in the pH of gastric fluid could influence the dissolution rate of the drug formulated with these salts and would most certainly influence the release of calcium from these salts. This has significant connotations in the formulation of many drug products but particularly dietary supplements. The objective of this study was to determine the intrinsic dissolution rates of lactose and calcium salts used as tablet fillers and to determine their influence on drug dissolution.

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EXPERIMENTAL

Materials

1. Lactose U.S.P., anhydrous (Sheffield Products, Memphis, Tennessee).
2. Lactose U.S.P., hydrous, fine crystalline powder (Foremost Foods Company, Foremost-McKesson, Inc., San Francisco, California).
3. Lactose U.S.P., hydrous (HMS Lactose, Extra Fine Crystals, Mutchler Chemical Company, Inc., Westwood, New Jersey).
4. Lactose U.S.P., spray dried, hydrous (Foremost-McKesson, Inc., San Francisco, California).
5. Lactose, U.S.P., Fast Flo, hydrous (Foremost Foods Company, Foremost-McKesson, Inc., San Francisco, California).
6. Lactose, hydrous, (Tablettose, Fallek Chemical Company, New York).
7. Milled dicalcium phosphate, dihydrate (Stauffer Chemical Company, Industrial Chemicals Division, Westport, Connecticut).
8. Milled dicalcium phosphate, anhydrous (Stauffer Chemical Company, Industrial Chemicals Division, Westport, Connecticut).
9. Calcium sulfate, NF XII (British Gypsum, England).
10. Tricalcium phosphate (Tri-Tab, Stauffer Chemical Company, Industrial Chemicals Division, Westport, Connecticut).

Equipment

A six-vessel automated dissolution test apparatus modified to use the rotating disk method has been described elsewhere (1). The specially designed disk preparation assembly was used to prepare nondisintegrating disks of pure lactose or calcium salts.

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Intrinsic Dissolution Test (IDR)

Nondisintegrating disks of the fillers were immersed in 500 ml of dissolution medium and rotated at 150 rpm.

Deaerated distilled water was the dissolution medium for the lactose dissolution studies. For the calcium salts, the medium was freshly prepared 0.1 or 0.01 *M* hydrochloric acid solution in deaerated water. The ionic strengths of the acid solutions were adjusted to 0.25 *M* using potassium chloride. All dissolution studies were conducted at 37 ± 0.2°C. At appropriate sampling times, all disks were removed simultaneously by raising the motor drive and blotted dry.

The amount of lactose dissolved was determined by the iodometric back-titration procedure as recommended in the Swiss Pharmacopeia (2) with some modifications to adjust for the quantities of lactose involved in this study (Figs. 1 and 2). The amount of calcium dissolved was determined by the complexometric back-titration procedure recommended in the British Pharmacopeia (3). The intrinsic dissolution rate (IDR) test was conducted in triplicate.

Influence of Ionic Strength on the IDR of Calcium Salts

The influence of change in the ionic strength and concentration of the dissolution medium on the intrinsic dissolution rate of each calcium salt was studied. IDR tests were carried out using 0.1 *M* hydrochloric acid solutions having a pH of 1.0 and an ionic strength of 0.1 *M*. The effect of change in the ionic strength was studied using 0.1 *M* hydrochloric acid solutions having an ionic strength of 0.25 *M*, adjusted using potassium chloride. The pH of this solution was 1.0.

To study the influence of patient variables such as reduced gastric acidity, dissolution rates were also determined in 0.01 *M* hydrochloric acid solutions having an ionic strength of 0.25 *M*, adjusted using potassium chloride. The pH of this solution was 2.0.

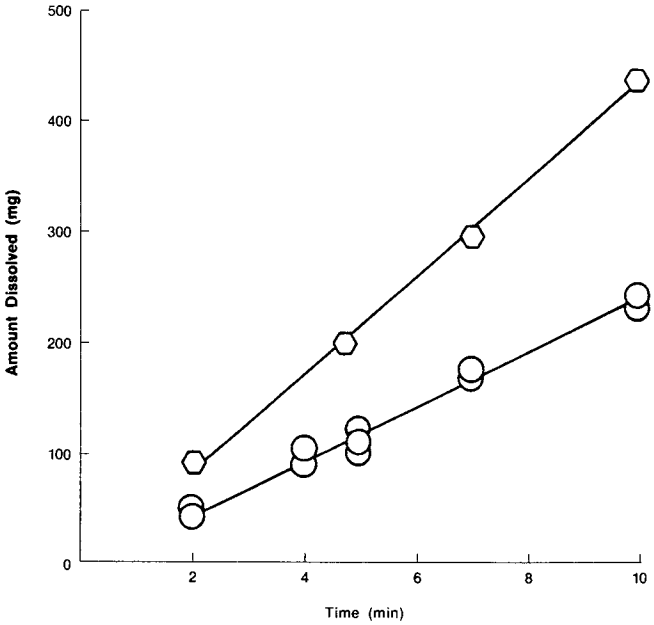

Fig. 1. Dissolution of anhydrous lactose U.S.P. and hydrous lactose U.S.P. (spray dried) from a disk surface of 2.00-cm² area rotated at 150 rpm in distilled water (37°C). (⬡) Anhydrous lactose (IDR = 21.9 mg/min/cm²). (○) Hydrous lactose, spray dried (IDR = 12.4 mg/min/cm²).

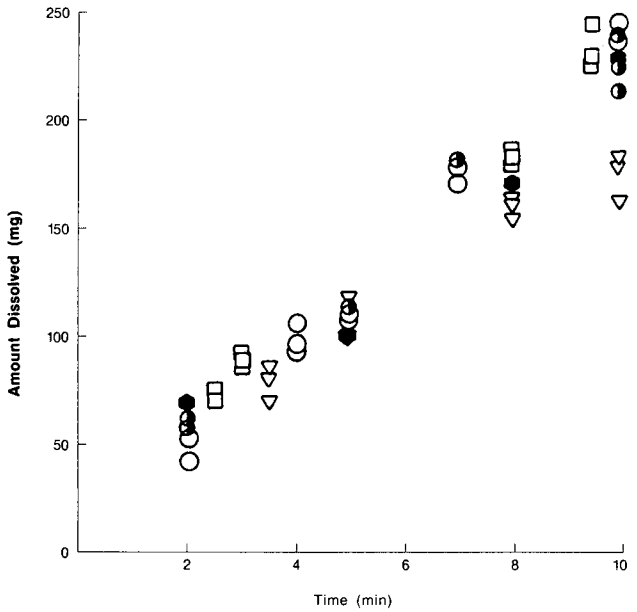

Fig. 2. Dissolution of different hydrous lactose samples from the disks of 2.00-cm² area rotated at 150 rpm in distilled water (37°C). (○) Lactose U.S.P., spray dried, hydrous. (◑) Lactose U.S.P., Fast Flo, hydrous. (●) Lactose USP, hydrous, powder. (▽) Tablettose, hydrous, lactose. (□) Lactose U.S.P., hydrous, EFC.

Dissolution of Drugs from Filler Disks

In a nondisintegrating disk made using a blend of a low-dose drug and a filler, the particles of the drug are physically occluded by the filler. Thus, the dissolution rate of the drug from such a matrix will be influenced by the dissolution rate of the diluent itself.

For this study, chlorpheniramine maleate and hydrochlorothiazide were selected as examples of drugs having widely differing solubilities. Each drug was mixed with different samples of tablet diluents. The mixtures contained either 60 mg chlorpheniramine maleate (CPM) per g mix or 80 mg hydrochlorothiazide (HCTZ) per g mix. These proportions were chosen to maintain a low drug-to-excipient ratio. The blends were then used to prepare disks for dissolution studies.

Almost no dissolution of either drug could be detected from blends with calcium compounds. Dissolution of both drugs from blends with lactoses could be determined satisfactorily. Sample plots of the dissolution are shown in Figs. 6 and 7.

Preparation of Typical Direct Compression Tablet Formulations Containing Lactose

Hydrochlorothiazide was formulated into typical direct compression tablet formulations containing either direct tableting-grade anhydrous lactose U.S.P. or Fast Flo lactose U.S.P. as diluent, Starch 1500 as the disintegrating agent, and magnesium stearate as the lubricant. The formulas are shown in Table I.

The tablet weight was maintained at 250 mg for all for-

Table I. Formulations of Direct Compression Tablets Containing Lactose

Ingredient	Amount for 2000 tablets (g)
(1) Hydrochlorothiazide	25.0
Starch 1500 (8%)	40.0
Anhydrous lactose, U.S.P.	430.0
Magnesium stearate (1%)	5.0
(2) Hydrochlorothiazide	25.0
Starch 1500 (8%)	40.0
Fast Flo lactose, U.S.P.	430.0
Magnesium stearate (1%)	5.0

mulations. The drug was premixed with the disintegrant and the diluent. Lubricant was added to this and the powders blended in a 2-qt-size V-shaped blender (Model LB-3974, The Patterson-Kelly Co., Inc., East Stroudsburg, Pennsylvania) for 10 min without the intensifier bar. Flat-face tooling (5/16 in.) was used to compress tablets on a Stokes RB-2 rotary tablet press instrumented to measure the compression force and the ejection force. Samples of the tablets compressed at six different pressures were collected in each case. This facilitated the selection of samples from each formulation having similar tablet hardnesses for use in the dissolution test. However, it was not possible to obtain tablets of the two formulations having comparable hardnesses and similar disintegration times.

Preparation of Typical Direct Compression Tablet Formulations Containing Calcium Salts

Direct compression tablet formulations were prepared using commercially available directly compressible calcium salt diluents: dicalcium phosphate dihydrate (Di-Tab) and tricalcium phosphate (Tri-Tab). Ac-Di-Sol was used as the disintegrant and a combination of stearic acid and magnesium stearate for lubrication.

Hydrochlorothiazide was used as the model drug of low water solubility. Three hundred-milligram tablets were prepared in the same manner as described earlier for lactose. The formulas are shown in Table II.

Table II. Formulations of Direct Compression Tablets Containing Calcium Salts

Ingredient	Amount (g)
(1) Hydrochlorothiazide	40.0
Ac-Di-Sol	10.0
Tri-Tab	730.0
Stearic acid (80 mesh)	16.0
Magnesium stearate (80 mesh)	4.0
(2) Hydrochlorothiazide	40.0
Ac-Di-Sol	10.0
Di-Tab	730.0
Stearic acid (80 mesh)	16.0
Magnesium stearate (80 mesh)	4.0
(3) Hydrochlorothiazide	40.0
Ac-Di-Sol	40.0
Tri-Tab	700.0
Stearic acid (80 mesh)	16.0
Magnesium stearate (80 mesh)	4.0

Dissolution of Hydrochlorothiazide from Tablets

The general procedure for the U.S.P. dissolution test (Method II) using the paddle stirrers and 900 ml of fluid (4) was followed.

Tablet samples having an average tablet hardness of approximately 6 kp were used in all dissolution tests.

RESULTS AND DISCUSSION

Studies on Lactose

Dissolution of Lactose Disks

The anhydrous lactose (U.S.P.) dissolved nearly twice as fast as the samples of hydrous lactose (Figs. 1 and 2). For example, the intrinsic dissolution rate of the anhydrous lactose (U.S.P.) sample from the plots is 21.9 mg/min/cm^2 and that of Fast Flo hydrous lactose (U.S.P.) is 10.9 mg/min/cm^2. The intrinsic dissolution rate of spray-dried hydrous lactose (U.S.P.) is 12.4 mg/min/cm^2; that of hydrous lactose (U.S.P.) powder, 10.3 mg/min/cm^2; and that of hydrous lactose (U.S.P.) extra fine crystals, 10.8 mg/min/cm^2. The rate could not be calculated in the case of Tablettose hydrous lactose from the slope of the plot in Fig. 2 because this plot is not a straight line as indicated by the F test for the linearity of the regression function. However, the plot overlaps the region of the plots for all of the other hydrous lactose samples. The results show that all hydrous lactose samples obtained from different sources dissolve at nearly the same rate. The IDR of anhydrous lactose, U.S.P., however, is distinctly different from the IDR values of the hydrous lactose samples.

Although hydrous lactose dissolves slower than the anhydrous lactose, both types of lactoses are classified as "freely soluble" in water. The significance of the results of the intrinsic dissolution rate tests must be viewed in light of this fact. It is generally observed that the disks containing a soluble filler tend to dissolve rather than disintegrate. Thus, the dissolution rate of the drug may be influenced by the intrinsic dissolution rate of the filler.

Dissolution of Drugs from Lactose Disks

The effect of different intrinsic dissolution rates of the two types of lactose on the dissolution rates of drugs was assessed by studying the dissolution of the drugs from blends with lactose. The nondisintegrating disks simulated the situation where the drug particles are surrounded by the diluent (lactose) particles. The dissolution medium must dissolve the diluent particles surrounding the drug particles before fresh particles of the drug become accessible to the medium. Therefore, the faster-dissolving anhydrous lactose may be expected to allow faster dissolution of the drug blended with it.

The results in Figs. 6 and 7 show that both chlorpheniramine maleate and hydrochlorothiazide dissolved faster from blends with anhydrous lactose. The linearity of most of the plots indicates that the disks remained intact. These facts seem to support the hypothesis that a soluble diluent could influence the dissolution rate of a drug from nondisintegrat-

ing or poorly disintegrating tablets by physically occluding the drug particles from the dissolution medium.

Dissolution of Hydrochlorothiazide from Lactose Tablets

Samples having similar hardnesses around 6 kp were used. The disintegration time of the anhydrous lactose tablets was 4 to 6 min, whereas that of the hydrous lactose tablets was less than 1 min. The dissolution of the drug from the anhydrous lactose tablets is somewhat slower than from the hydrous lactose tablets for about 8 min (Fig. 8). However, at 10 min, the amount of the drug dissolved from the anhydrous lactose tablets is more than that from the hydrous lactose tablets.

The results of these experiments with disintegrating tablets indicate that the influence of the intrinsic dissolution rate of the diluent on the dissolution rate of the formulated drug is confounded by the differences in the efficiency of the disintegrant in breaking up the tablets containing different diluents. However, some hint of the diluent effect may be obtained from the length of time required for the complete release of the drug from each type of formulation. The differences in the dissolution rate of a drug from the formulations containing the two types of lactoses are not likely to be physiologically significant. Therefore, it would be inappropriate to select anhydrous lactose over the hydrous type simply because of its higher intrinsic dissolution rate. Other factors such as their flow properties, their compressibilities, and the physical stability of their compacts must be considered in conjunction with their intrinsic dissolution rates.

Studies on Calcium Fillers

Dissolution of the Diluent Disks

The total acidity of the gastric juice in adults is reported to be in the range of 5 to 118 mEq per liter (6). These values correspond to the pH range of about 0.9 to 2.3. Thus, pH's of the selected concentrations of the dilute hydrochloric acid solutions lie in this range. In fact, the original plan of work included use of the more dilute hydrochloric acid solutions having higher pH values. The results of such studies in the more dilute acid solutions would be useful in predicting the effect of decreased acid secretion in the patients having achlorhydria. These proposed studies were abandoned for reasons discussed later.

Dissolution of the calcium salts results in the formation of new ionic species in the dissolution medium. However, the ionic strengths of the dissolution media were adjusted to 0.25 *M* using potassium chloride to assure that the change in the ionic strength would be negligible. The concentrations of different electrolytes in the gastric juice vary considerably (6), although the range for the overall ionic strength is not reported. The results of the dissolution tests in the hydrochloric acid solutions with and without potassium chloride were useful in interpreting the influence of the electrical environment in the dissolution medium.

Effect of the Ionic Strength of the Dissolution Medium

Figure 3 shows the amounts of different calcium salts dissolved in the pH 1.0 hydrochloric acid (ionic strength, 0.10 *M*). Anhydrous and dihydrate dicalcium phosphates dissolve at nearly the same rate. Tricalcium phosphate dissolves slower and calcium sulfate ranks as the slowest dissolving of the four calcium salts. When these dissolution rates are compared with the dissolution rates in pH 1.0 HCl solutions having an ionic strength of 0.25 *M* (Fig. 4), the rank order of the salts remain the same. Thus, a change in the ionic strength of the medium does not influence the rank order of the materials. A comparison of the intrinsic dissolution rates also reveals that the ionic strength does not influence the intrinsic dissolution rate significantly (Table III). There is a trend of somewhat higher dissolution rates in solutions of acid of higher ionic strength. This might be explained by the evidence that a higher ionic strength of a reaction medium tends to increase the rates of the reactions which result in production of oppositely charged ionic species (7). Based on these observations, changes in the concentrations of electrolytes in the gastric fluid are not expected to influence the dissolution of calcium salts significantly.

Effect of the pH of the Dissolution Medium

Dissolution of the same salts in pH 2.0 HCl solutions (ionic strength, 0.25 *M*) occurred much more slowly (Table IV, Fig. 5). The concentration (0.01 *M*) of the pH 2.0 solution is 10 times lower than the concentration (0.1 *M*) of the pH 1.0 solution. Thus, the rates at which the salts react with

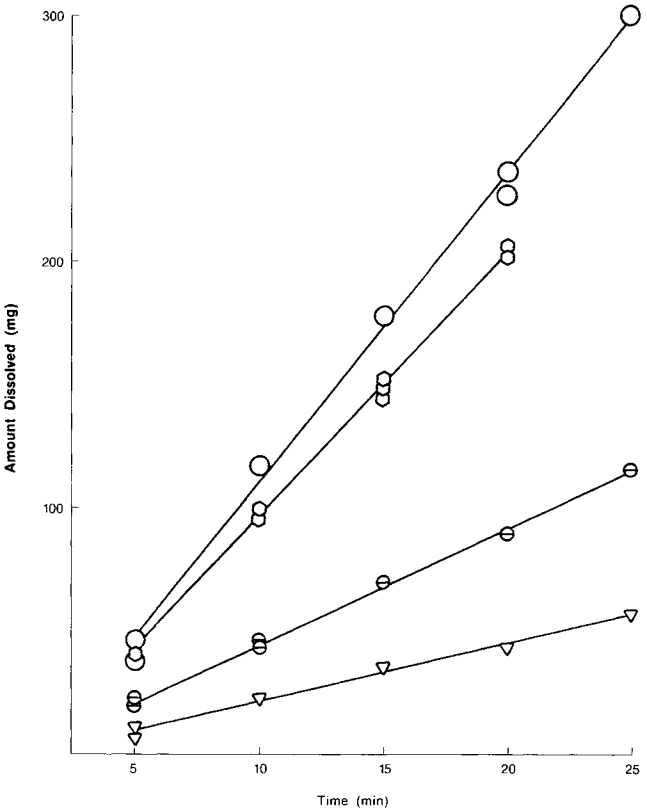

Fig. 3. Dissolution of calcium salt diluents from the disks rotated at 150 rpm in 0.1 *M* HCl solution (ionic strength = 0.1 *M*, pH 1.0). (○) Dicalcium phosphate dihydrate. (⊖) Tricalcium phosphate. (⬡) Anhydrous dicalcium phosphate. (▽) Calcium sulfate dihydrate.

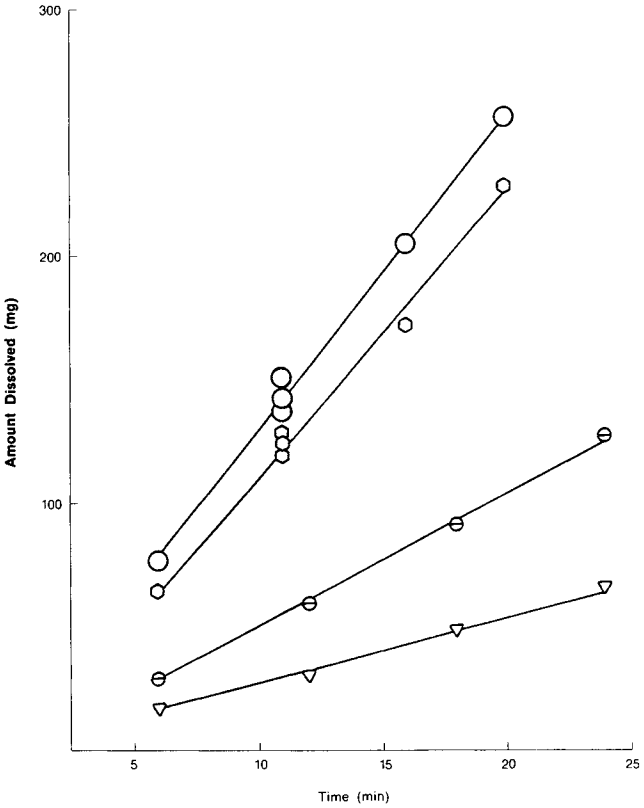

Fig. 4. Dissolution of calcium salt diluents from the disks rotated at 150 rpm in 0.1 *M* HCl solution (ionic strength = 0.25 *M*, pH = 1.0). (○) Dicalcium phosphate dihydrate. (⊖) Tricalcium phosphate. (⬡) Anhydrous dicalcium phosphate. (▽) Calcium sulfate dihydrate.

the acid are much slower and consequently the dissolution rates of the salts in pH 2.0 solutions are much lower. The amounts of calcium dissolving in these cases are very small and the variability is greater at pH 2.0 than at pH 1.0. The rank order is different at pH 2.0 from that at pH 1.0. This probably is due to the fact that calcium sulfate dihydrate is slightly soluble in water, whereas tricalcium phosphate is almost insoluble in water (7).

Dissolution of Hydrochlorothiazide from the Tablets Containing Calcium-Type Diluents

Hydrochlorothiazide is a low-dose, slightly soluble drug. A standardized procedure for the dissolution test of hydrochlorothiazide tablets is described in the U.S.P. (4). This drug has been successfully used earlier in our laboratory to study the comparative *in vitro* drug release from various tablet and capsule formulations. In an elaborate study on the dissolution of thiazides, Augsburger (9) noted that the dissolution of hydrochlorothiazide from some marketed tablet formulations showed prolonged dissolution times in water as compared to dilute hydrochloric acid. The author surmised that the marketed formulations which released the drug slowly perhaps contained calcium salt fillers which exhibit pH-dependent solubility. Therefore, to investigate the effects of different calcium fillers on the dissolution rate of the formulated drug, hydrochlorothiazide seemed to be an appropriate choice (Fig. 8).

When dissolution tests were conducted using nondisin-

Table III. Intrinsic Dissolution Rates of Calcium Salts at 150-rpm Disk Velocity in the Solutions Containing 0.1 *M* Hydrochloric Acid

Material	mg diluent/min/cm² at ionic strength 0.25 *M*	0.10 *M*
Dicalcium phosphate dihydrate	6.37	6.27
Anhydrous dicalcium phosphate	5.75	5.37
Calcium sulfate dihydrate (Terra Alba)	1.36	1.15

Table IV. Intrinsic Dissolution Rates of Calcium Salt Diluents from the Disks Rotated at 150 rpm in pH 2.0 HCl-KCl Buffer Containing 0.01 *M* HCl (Ionic Strength = .25 *M*)

Material	Intrinsic dissolution rate (mg diluent/min/cm²)
Dicalcium phosphate dihydrate	0.90
Anhydrous dicalcium phosphate	0.69
Tricalcium phosphate	0.30
Calcium sulfate dihydrate	0.75

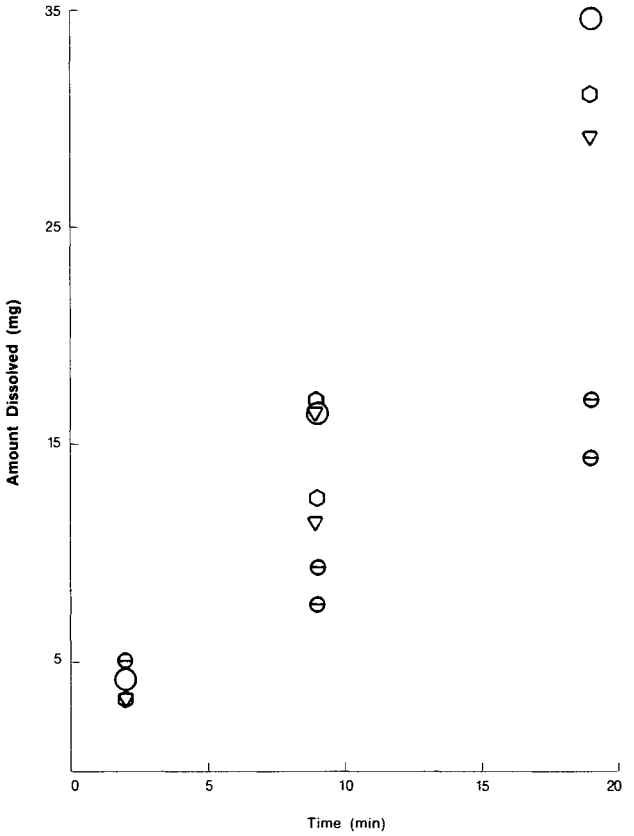

Fig. 5. Dissolution of calcium salt diluents from the disks rotated at 150 rpm in pH 2.0 HCl-KCl buffer containing 0.01 *M* HCl (ionic strength = 0.25 M). (○) Dicalcium phosphate dihydrate. (⊖) Tricalcium phosphate. (⬡) Anhydrous dicalcium phosphate. (▽) Calcium sulfate dihydrate.

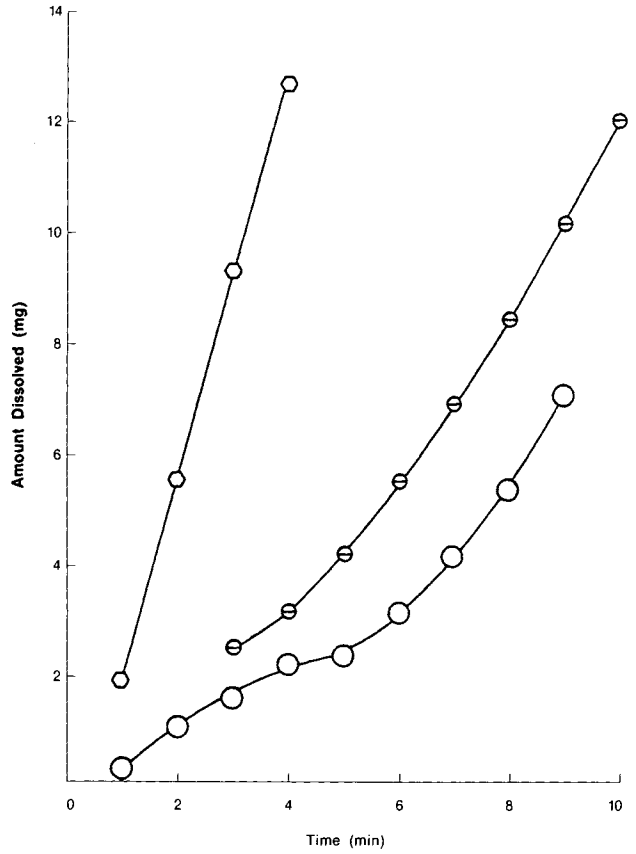

Fig. 6. Dissolution of chlorpheniramine maleate from the nondisintegrating disks prepared using blends of the drug with the lactose samples. (○) Anhydrous lactose, U.S.P. (⊖) Fast Flo lactose. (○) Hydrous lactose, U.S.P. powder.

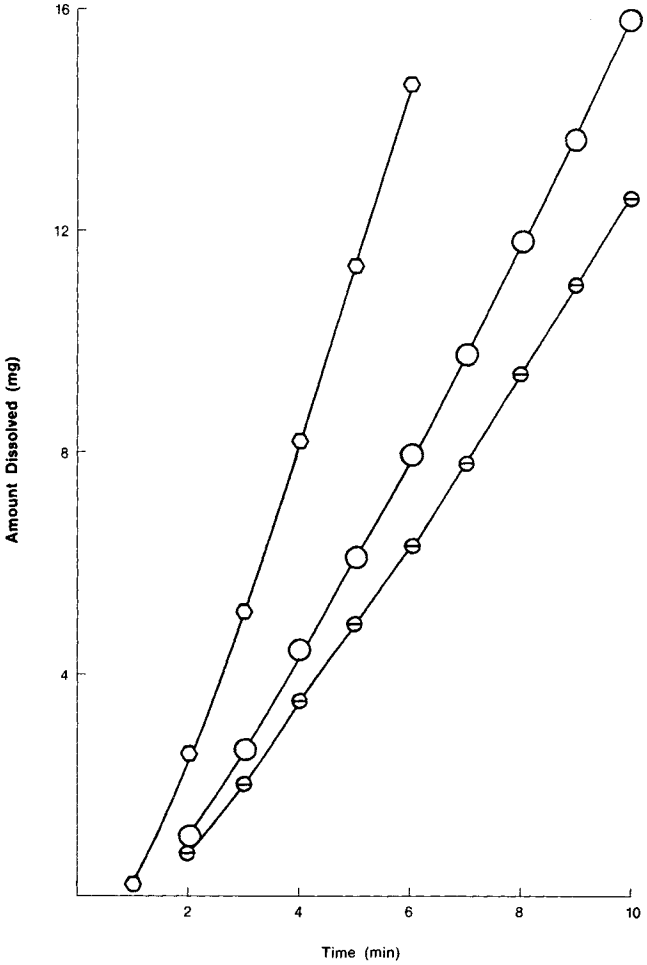

Fig. 7. Dissolution of hydrochlorothiazide from the nondisintegrating disks prepared using blends of the drug with the lactose samples. Symbols same as in Fig. 6.

tegrating disks prepared from blends of the drug with the calcium salts, almost no dissolution of the drug could be detected due to the limited surface area of the drug available for dissolution.

In order to evaluate the influence of calcium salt fillers on the dissolution of hydrochlorothiazide from tablet formulations, similar hydrochlorothiazide tablet formulations containing 1.25% AcDiSol and either Di-Tab or Tri-Tab as fillers were compared (Fig. 9). Dissolution of the drug from the formulation containing Tri-Tab was much slower than from the formulation containing Di-Tab (Formulas 1 and 2). This is attributable, at least in part, to the slower disintegration of the Tri-Tab formulation (disintegration time of about 30 min) in comparison with the disintegration of the Di-Tab formulation (disintegration time of approximately 30 sec). Therefore, a faster-disintegrating Tri-Tab formulation was made using 5% Ac-Di-Sol as the disintegrant. These tablets (Formula 3) disintegrated in approximately 30 sec and could be compared with the Di-Tab formulations containing 1.25% Ac-Di-Sol. Figure 9 shows that the dissolution of hydrochlorothiazide from the new Tri-Tab formulation is still significantly slower than from the Di-Tab formulation, although their disintegration times are similar. Thus, the order of dissolution rates of hydrochlorothiazide from the formulations parallels the rank order of the IDRs of the diluents used.

For the hydrochlorothiazide formulations, it may be hypothesized that the fillers form a physical barrier between the drug particles and the dissolution medium. This barrier is removed faster in the case of the filler having a higher intrinsic dissolution rate. Therefore, dissolution of the drug occurs faster from the Di-Tab formulations than from the Tri-Tab formulations.

The implications of these data in terms of the bioavailability of the calcium salts themselves when used as calcium supplements is of even greater concern. Dicalcium phosphate has been used for many years as a nutritional supplement and more recently tricalcium phosphate has been introduced for the same purpose because of its higher calcium load. While these salts would appear to dissolve at pH 1, the decrease in solubility even at a pH level of 2 is 10-fold. As many geriatric patients are achlorhydric and may have gastrointestinal pHs as high as 4–6, the use of phosphate salts may not be advisable. These conclusions must be tested further both *in vitro* and *in vivo*.

SUMMARY AND CONCLUSIONS

Anhydrous lactose dissolves approximately twice as fast as hydrous lactose. All samples of the commercially available tableting-grade hydrous lactoses used in these ex-

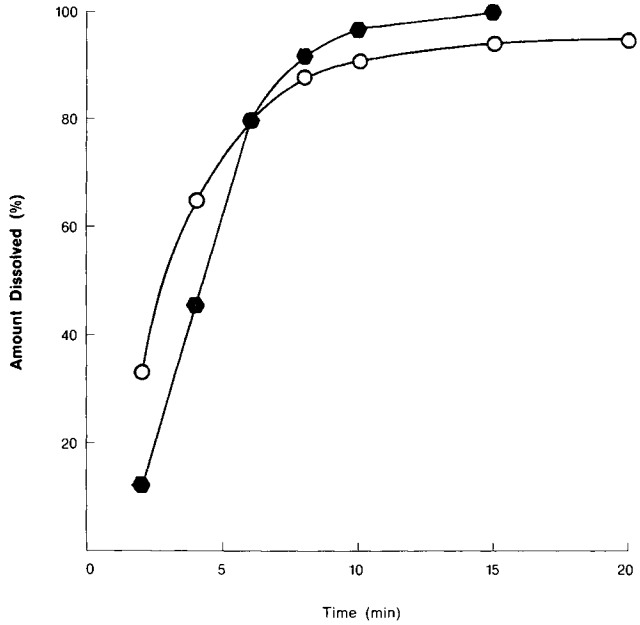

Fig. 8. Dissolution of hydrochlorothiazide from direct compression tablets containing lactose as the diluent (average tablet hardness of approximately 6 kp). (●) Anhydrous lactose, U.S.P. (○) Fast Flo hydrous lactose, U.S.P.

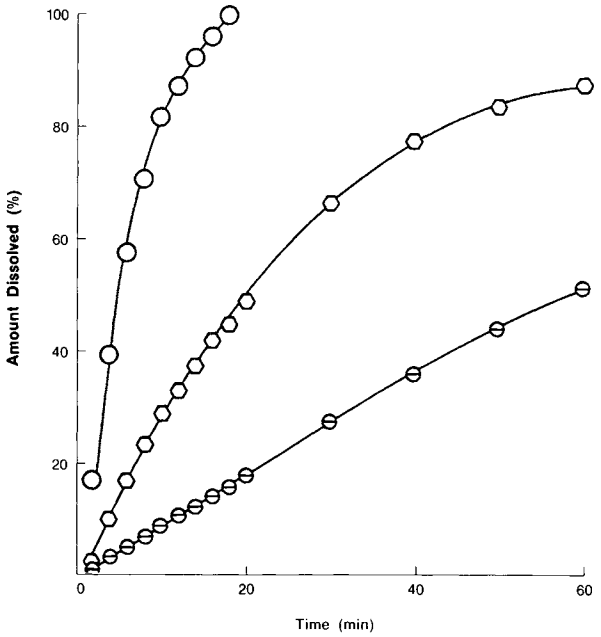

Fig. 9. Dissolution of hydrochlorothiazide from the directly compressed tablets containing dicalcium phosphate dihydrate (DiTab) or tricalcium phosphate (TriTab) as diluent (tablet hardness, approximately 6 kp). (⊖) Tri-Tab + 1.25% Ac-Di-Sol, d.t. = 30 min. (○) Tri-Tab + 5% Ac-Di-Sol, d.t. = 30 sec. (○) Di-Tab + 1.25% Ac-Di-Sol, d.t. = 30 sec.

periments dissolved at nearly the same rates. Although drugs dissolved faster from anhydrous lactose than from hydrous lactose disks, no significant differences were observed from typical tablet formulations containing a disintegrant. It appeared that the advantage of higher dissolution rate of anhydrous lactose was compensated by the poorer disintegration of the tablets. Since both types of lactoses are freely soluble, the differences in their effects may not be of any physiological significance.

Dicalcium phosphates (anhydrous and dihydrate), tricalcium phosphate, and calcium sulfate dihydrate were also studied using the nondisintegrating disks and direct compression formulations. The calcium salts seem to dissolve predominantly by reaction with hydrochloric acid. The anhydrous and dihydrate forms of dicalcium phosphate dissolve at nearly the same rate. Tricalcium phosphate dissolves more slowly than the dicalcium phosphates. Calcium sulfate dihydrate was the slowest dissolving of the four compounds studied. All compounds dissolved nearly eight to nine times more slowly when the pH of the hydrochloric acid solution was changed from pH 1.0 to pH 2.0. The amounts dissolved at pH 2.0 were very small.

The decrease in the dissolution rates at higher pH indicates that if these salts are administered as sources of calcium, the availability of calcium may be low in patients having hypochlorhydria. Also, when these salts are used as diluents in tablet formulations, the rate and extent of drug release may be significantly controlled by the pH of the gastric fluid.

The dissolution rate of hydrochlorothiazide from the direct compression formulations containing dicalcium phosphate dihydrate (Di-Tab) was faster than that from the formulation containing tricalcium phosphate (Tri-Tab). Thus, the filler having a higher intrinsic dissolution rate permitted faster drug release than the filler having a lower intrinsic dissolution rate. These results indicate that for formulation excipients, the intrinsic dissolution rate of the filler may be as important as its compressibility and physical stability.

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