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Effect of Intergranular *versus* Intragranular Cornstarch on Tablet Friability and *In Vitro* Dissolution

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Received March 22, 1982, from the *Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA 94304.* Accepted for publication August 18, 1982.

Abstract □ The effect of blending dry cornstarch *versus* wet granulation with the drug and other excipients on friability and *in vitro* dissolution of a ticlopidine hydrochloride tablet formulation was studied. The friability of the tablets was reduced by wet granulating cornstarch with the drug and other excipients compared with the dry blending. The dissolution rate and the tablet-to-tablet variability was improved by incorporating cornstarch in the wet-granulation stage. The lactose placebo tablets, which were wet granulated with either a binder solution or without a binder, also showed reduced tablet friability due to the incorporation of cornstarch in the wet-granulation step. Examination of the tablet cross sections under the scanning electron microscope indicated clumping of starch grains when starch was blended in the dry form. Starch grains were well embedded in the other materials of the tablet and not readily visible when starch was wet granulated with the other excipients. This results in better bonding, fewer weak points, and better homogeneity of the starch disintegrator within the tablet, which accounts for better friability and improved dissolution.

Keyphrases □ Ticlopidine hydrochloride—tablet friability, *in vitro* dissolution, effect of inter- *versus* intragranular cornstarch □ Cornstarch—inter- *versus* intragranular, effect on tablet friability and *in vitro* dissolution, ticlopidine hydrochloride □ Dissolution—*in vitro*, ticlopidine hydrochloride, effect of inter- *versus* intragranular corn starch, friability

Starch USP is a common excipient in compressed tablets, both as a disintegrator and as a binder. Cornstarch is one of the most common disintegrating agents used in tablet formulations today. When added in the dry state to the dry granulation, it acts as a disintegrator. In the paste or dry form, when added before wet granulation, its function is that of a disintegrator and binder.

The mechanism of action of starches is not well understood. In aspirin tablets (1) where contact of starch grains was continuous in the interparticle spaces, disintegration was rapid and effective even when void spaces were eliminated. Where contact was not continuous, disintegration was slower, and appeared to depend on the degree of contact between starch grains and aspirin particles and on the size of interparticle spaces. The primary mechanism appeared to be a swelling action. Capillarity *per se* did not appear to have a disintegrating effect. Ingram and Lowenthal (2) could not find any measurable correlations between starch grain damage and disintegration time or between starch swelling and compressional force. Outside of compressional force, the inherent effect of the tablet ingredients was the only factor that appeared to affect disintegration. In a later study, Lowenthal and Burruss (3) discounted pore diameter and porosity of the tablet as a mechanism of action of starch as a disintegrator. A significant swelling of the starch grains was not observed (4) when pressure-deformed grains were moistened with water. Thus, the regaining of the shape of starch grains was apparently not the mechanism of action as a tablet disintegrator. Observations by scanning electron microscope (5) indicated that rupture of the tablet surface occurred where starch agglomerates were found. It was postulated that water hydrates the hydroxyl groups of the starch molecules, causing them to move apart. The slight swelling that occurs is due to a rapid hydration step and a slower sorption step after the addition of water. Channels or pores lined with starch were not evident. The conditions for rapid tablet disintegration were sufficient agglomerates, low pressure, and presence of water.

In wet-granulated tablet formulations, starch is usually added in the dry form prior to compression. This general practice is based perhaps on the swelling theory of the mechanism of action of starch as a disintegrator which is generally discounted. The data in the literature strongly suggest that disintegration is influenced by a wide variety

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Table I—Formulations Used in This Study [a]

Ingredients	Formulation A	Formulation B	Formulation C
Ticlopidine hydrochloride	250.00	—	—
Microcrystalline cellulose	87.35	—	87.35
Lactose	—	337.35	255.85
Citric acid	3.90	3.90	3.90
Starch	39.00	39.00	39.00
Povidone	7.80	7.80	—
Stearic acid	—	—	3.90
Magnesium stearate	1.95	1.95	—

[a] Milligrams of ingredient per tablet.

of factors that are specific only for a given tablet formulation; it is difficult to determine the mechanism of action of starch as a tablet disintegrator.

Recent studies from these laboratories (6) suggested that the friability of compressed tablets was reduced by incorporating 80% cornstarch in the wet-granulation step compared with the dry blending. This paper examines the effects of intragranular *versus* intergranular cornstarch on tablet friability and *in vitro* dissolution.

EXPERIMENTAL

Materials—The drug, ticlopidine hydrochloride[1], was ≥99.0% pure. The excipients used were microcrystalline cellulose[2] NF, povidone[3] USP, citric acid[4] USP, stearic acid[5] powder NF, cornstarch[6] NF, lactose[7] USP, and magnesium stearate[4] NF.

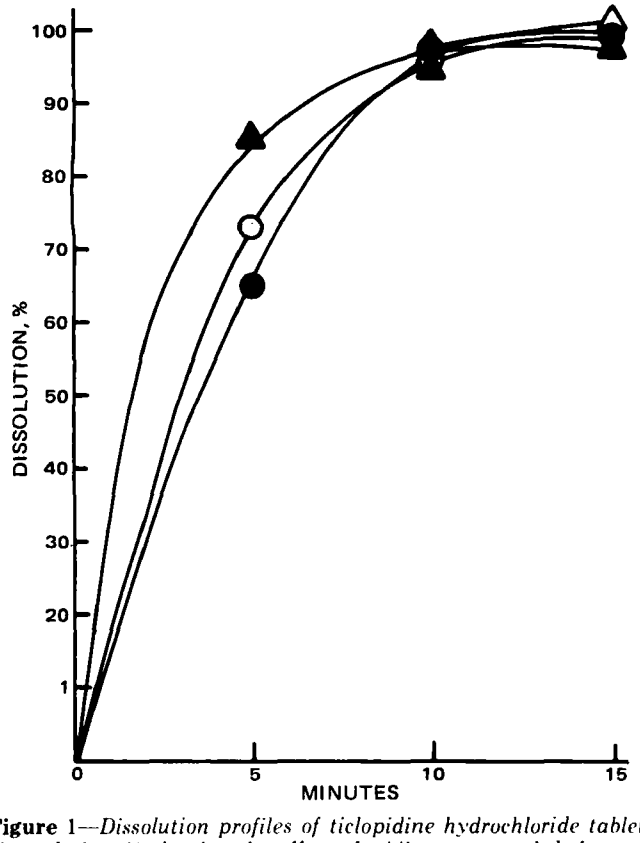

Figure 1—*Dissolution profiles of ticlopidine hydrochloride tablets (formulation A) showing the effect of adding cornstarch before wet granulation* versus *blending it with the dry granulation. The granulation moisture content was 2.1%, and tablet crushing strength was 15 Strong Cobb units. Key: (○) starch dry blended, with extra-deep concave punches; (●) starch dry blended, with standard concave punches; (△) starch wet granulated, with extra-deep concave punches; (▲) starch wet granulated, with standard concave punches.*

[1] 5-(o-Chlorobenzyl)-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine hydrochloride; Sanofi Research Co., New York, NY 10019.
[2] Avicel pH 101; FMC Corp.
[3] GAF Corp., New York, NY 10020.

Table II—Effect of the Addition of Starch During Wet Granulation or Blending with the Dry Granulation on Friability of Tablets Compressed with Standard Concave Punches [a]

Punch	Tablet Friability, % Starch Blended with Dry Granulation	Tablet Friability, % Starch Wet Granulated with Other Materials
Standard concave	0.27	0.0925
Extra-deep concave	0.135	0.0165

[a] Using formulation A with a granulation moisture of 2.1% and tablet crushing strength of 15 Strong Cobb units.

Granulation—The formulations used in this study are given in Table I. The drug and the appropriate excipients were mixed together in a small, planetary mixer for 10 min. Citric acid and povidone in formulations A and B and citric acid alone in formulation C were dissolved in water. These solutions were used to granulate the powder mixture. After 10 min of mixing, the granulation was passed through a 1.4-mm aperture and dried in a forced-air oven at 50° until the desired moisture levels were obtained. The dried granulation was forced through a 1.2-mm aperture screen. The lubricant and the disintegrator were blended with the granulation for 5 min. The granulations were stored in tightly closed, glass bottles. The moisture content of the final granulation was determined prior to compression.

Compression—The compression was carried out by means of a single-punch tablet machine[8]. The punches and die were 10.32 mm in diameter. Standard concave and extra-deep concave punches were used for compression. The target compression weight was 390 mg/tablet. The tablet crushing strength was determined[9] immediately after compression. For each determination, 10 tablets were tested and the mean was calculated.

Granulation Moisture—The granulation was exposed to a 125-W

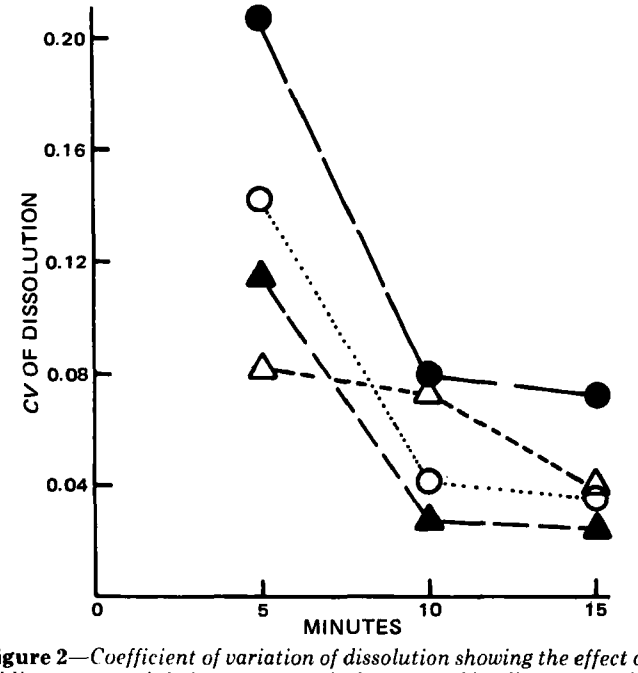

Figure 2—*Coefficient of variation of dissolution showing the effect of adding cornstarch before wet granulation* versus *blending it with the dry granulation (formulation A). The granulation moisture content was 2.1%, and the tablet crushing strength was 15 Strong Cobb units. Key: (○) starch dry blended, with extra-deep concave punches; (●) starch dry blended, with standard concave punches; (△) starch wet granulated, with extra-deep concave punches; (▲) starch wet granulated, with standard concave punches.*

[4] Mallinckrodt, Inc., St. Louis, MO 63147.
[5] Emery Industries, Inc., Cincinnati, OH 45232.
[6] Staley Manufacturing Co., Decatur, Ill.
[7] Regular Grade; Foremost Co., San Francisco, CA 94104.
[8] Stokes Model F4.
[9] Schleuniger-2E Hardness Tester; Vector Corp., Marion, IA 52303.

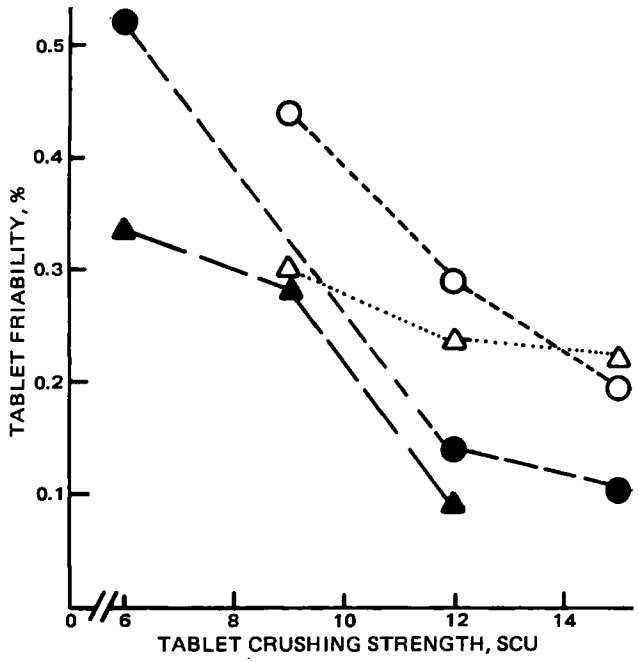

Figure 3—*Effect of adding cornstarch during wet granulation* versus *blending with the dry granulation on friability of placebo tablets (formulation B). The granulation moisture content was 2.0%. Key: (○) starch dry blended, with standard concave punches; (●) starch dry blended with extra-deep concave punches; (△) starch wet granulated, with standard concave punches; (▲) starch wet granulated, with extra-deep concave punches.*

IR lamp for 15 min at a 90-V setting in a moisture balance[10]. The percent weight loss on drying was read directly from the instrument.

Tablet Friability—A Roche-type friabilator was used. Twenty tablets were brushed with a soft, camel's hair brush to remove all adhering particles. After accurate weighing, the tablets were placed in the drum. The drum was rotated for 4 min (100 revolutions), the tablets were removed, brushed to remove adhering particles, and accurately weighed. The test was carried out in duplicate, and the mean percent friability was calculated.

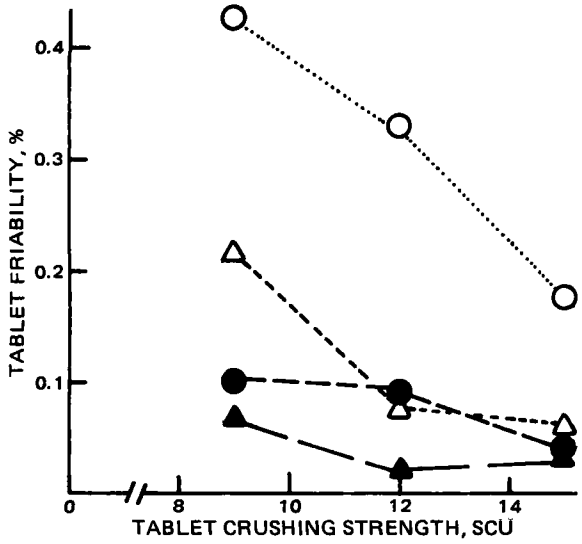

Figure 4—*Effect of adding cornstarch during wet granulation* versus *blending with the dry granulation on friability of placebo tablets (formulation C). The granulation moisture content was 2.0%. Key: (○) starch dry blended, with standard concave punches; (●) starch dry blended, extra-deep concave punches; (△) starch wet granulated, with standard concave punches; (▲) starch wet granulated, with extra-deep concave punches.*

[10] Cenco Central Scientific Co., Chicago, IL 60623.

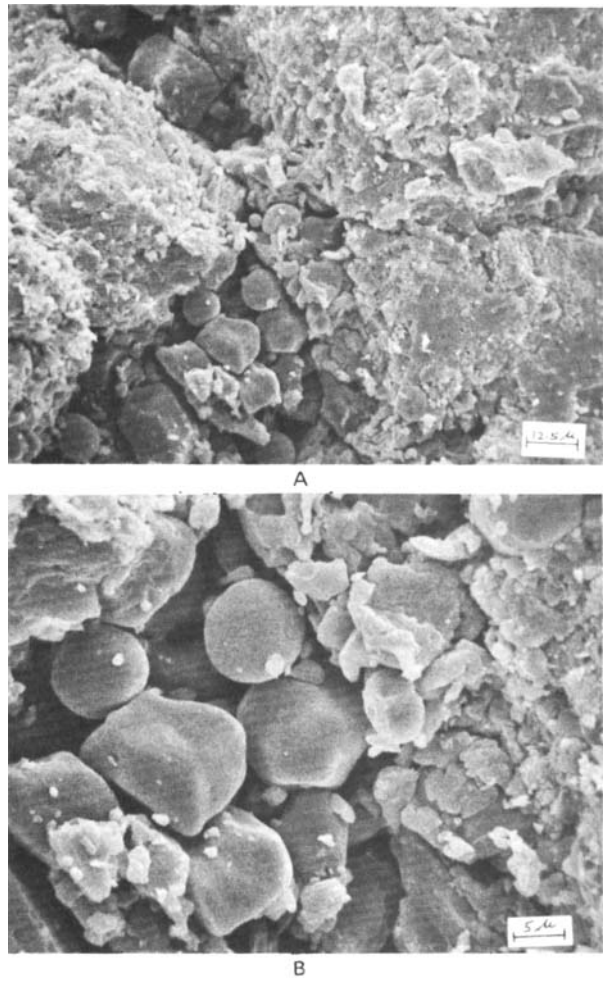

Figure 5—*Cross-sectional view of ticlopidine hydrochloride tablets compressed with the standard concave punches using formulation A. Starch was dry blended. Key: (A) ~800× (original magnification); (B) ~2000× (original magnification).*

***In Vitro* Dissolution**—The *in vitro* dissolution was determined by the USP Method II as reported earlier (6). For each determination, six tablets were tested. This apparatus consisted of USP paddles driven by a multiple-spindle drive with a variable-speed control[11]; round-bottom, plastic resin kettles[12] measuring 1 liter; and a water bath. The dissolution

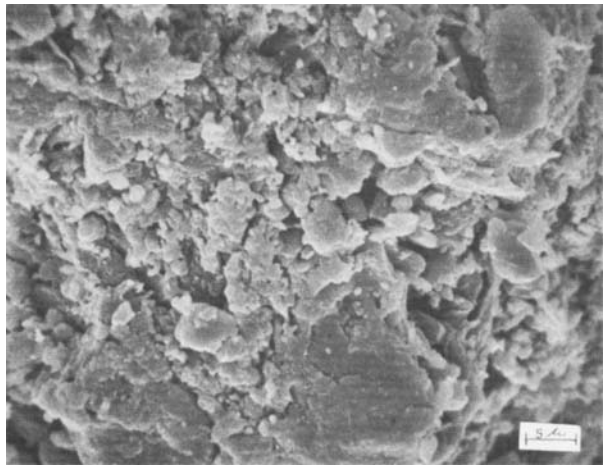

Figure 6—*Cross-sectional view of ticlopidine hydrochloride tablets compressed with the standard concave punches using formulation A. Starch was wet granulated [~2000× (original magnification)].*

[11] Model 72R; Hanson Research Corp., Northridge, Calif.
[12] Elanco, Indianapolis, Ind.

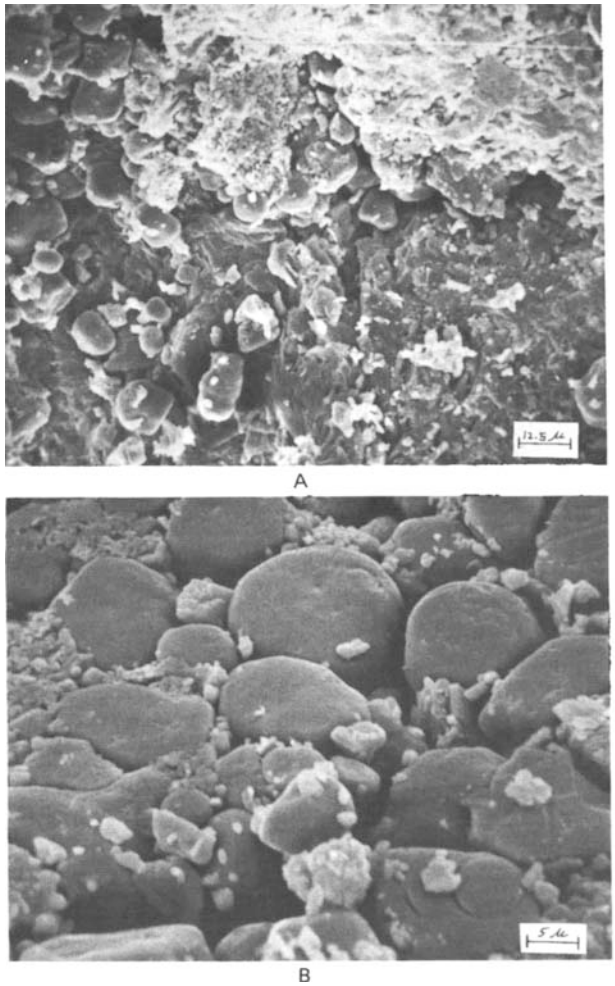

Figure 7—*Cross-sectional view of ticlopidine hydrochloride tablets compressed with the extra-deep concave punches using formulation A. Starch was dry blended. Key: (A) ~800× (original magnification); (B) ~2000× (original magnification).*

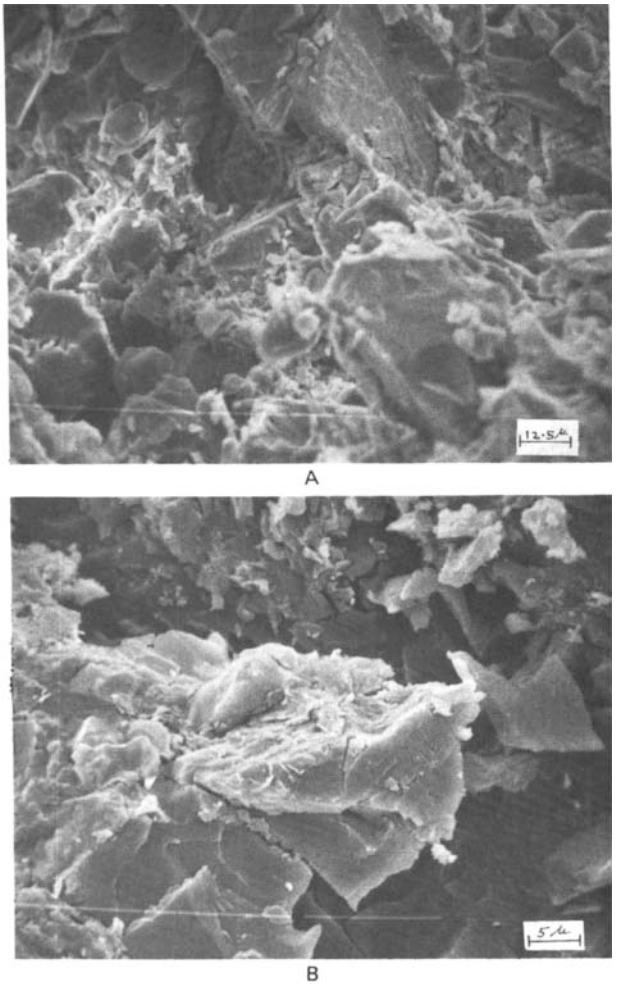

Figure 9—*Cross-sectional view of the placebo tablets compressed with extra-deep concave punches using formulation B. Starch was (A) dry blended or (B) wet granulated [~2000× (original magnification)].*

medium was 700 ml of deaerated water equilibrated at 37° and stirred at 50 rpm. The dissolved drug was analyzed by recording the absorbance at 236 nm, using an automated monitoring system consisting of a peristaltic pump[13], 1-mm spectrophotometer flow cells, and automatic sample changer/spectrophotometer[14]. The absorbances were plotted on a recorder every minute until complete dissolution was achieved. The dissolution apparatus was calibrated using USP dissolution calibrator tablets (prednisone, 50 mg). The mean dissolution and the standard deviations were within the required range.

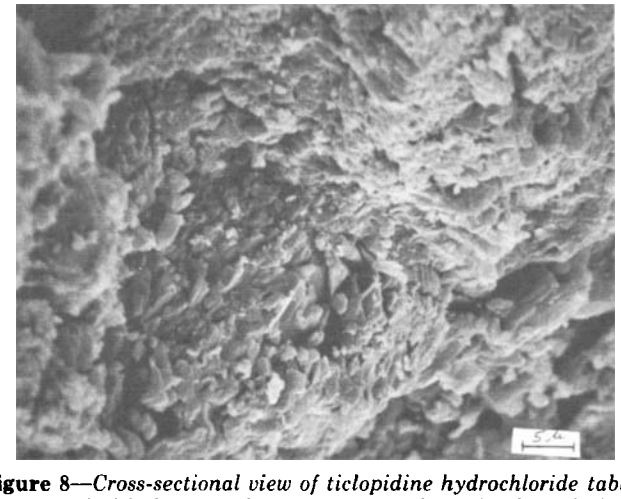

Figure 8—*Cross-sectional view of ticlopidine hydrochloride tablets compressed with the extra-deep concave punches using formulation A. Starch was wet granulated [~2000× (original magnification)].*

Scanning Electron Micrographs—Cross sections of the tablets were obtained by cutting tablets axially with a sharp razor blade. The tablet cross sections were mounted on cylindrical specimen stubs with double-stick tape[15] with the inner side surface up. Surface conductivity on the tablet sample was obtained with a silver paste in a vacuum evaporator. The samples were viewed at an oblique angle of 30° in a scanning electron microscope[16]. The photographs were taken using self-developing film[17].

RESULTS AND DISCUSSION

The results of the friability of ticlopidine hydrochloride tablets (formulation A) are given in Table II. The starch was either added during the wet-granulation process or blended in the dry form with the dry granules. The tablet crushing strength and the granulation moisture were both controlled in these studies[18]. The compression was carried out with standard concave and extra-deep concave punches. The results indicate that the friability of the tablets compressed from granulations in which starch was incorporated in the wet-granulation process was lower compared with the friability of the tablets containing starch in the dry-blended form. Extra-deep concave punches showed a much larger effect

[13] Model 1210; Haryard Apparatus, Millis, Mass.
[14] Model 25; Beckman Instruments, Fullerton, Calif.
[15] Scotch Tape; Minnesota Mining and Manufacturing Co., St. Paul, MN 55101.
[16] SEM Model Alpha-9; International Scientific Instruments, Inc., Santa Clara, CA 95050.
[17] Type 52 Polapan; Polaroid Corp.
[18] Data to be published.

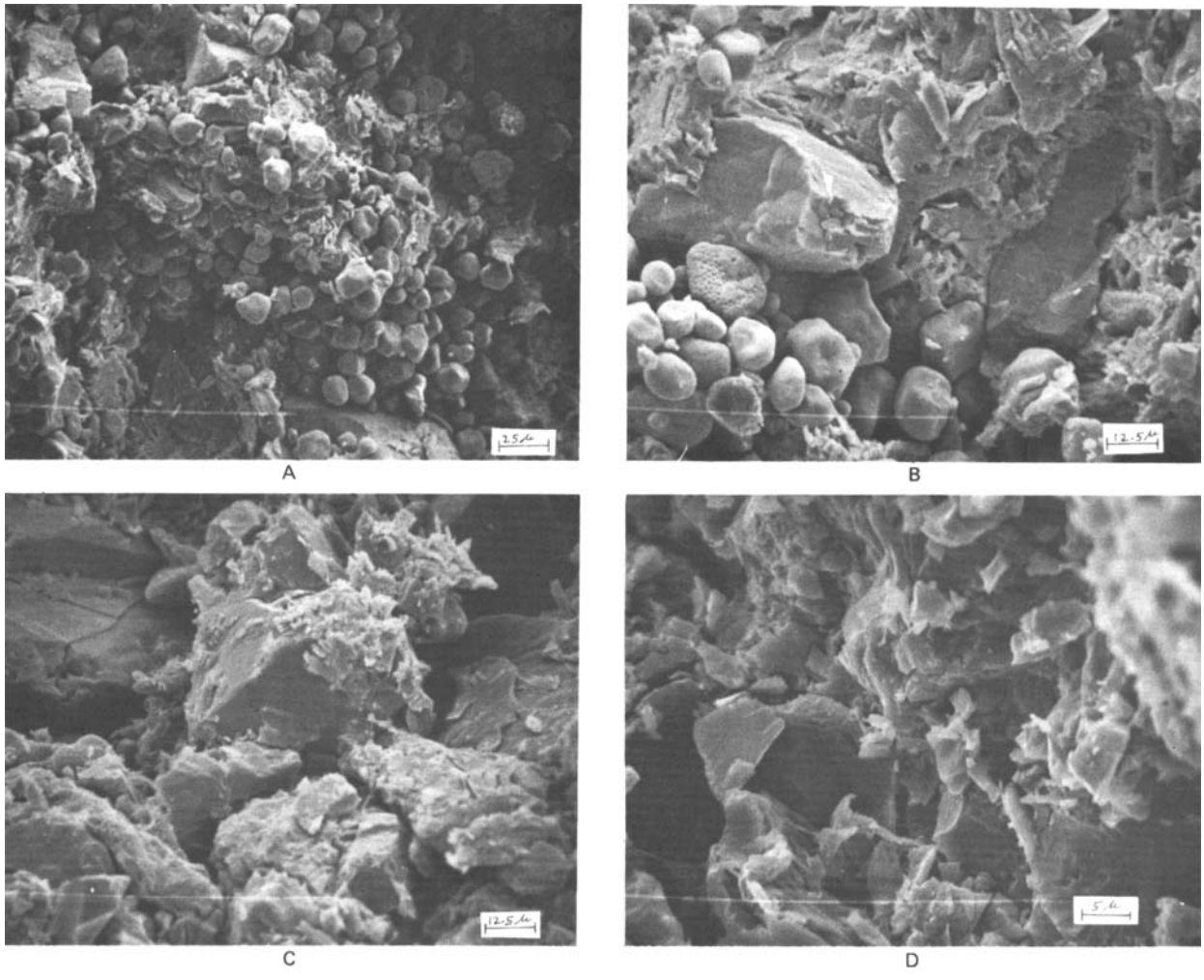

Figure 10—*Cross-sectional view of the placebo tablets compressed with the standard concave punches using formulation C. Key: (A) Starch was dry blended [~400× (original magnification)]; (B) starch was dry blended [~800× (original magnification)]; (c) starch was wet granulated [~800× (original magnification)]; (D) starch was wet granulated [~2000× (original magnification)].*

in reducing tablet friability compared with the standard concave punches as a result of the differences in processing starch.

Figure 1 gives the dissolution profiles of ticlopidine hydrochloride tablets (formulation A) resulting from granulations in which starch was either blended in the dry form or wet granulated with the drug and other excipients. For both punch tip geometries, the initial dissolution rate of the tablets compressed from granulations containing starch in the wet-granulation stage was higher compared with the tablets that were compressed from granulations containing starch in the dry form.

The coefficients of variation (CV) of these tablets as a function of the dissolution time are given in Fig. 2. At all time points studied, the dissolution coefficient of variation of standard convex tablets was smaller for tablets containing starch in the wet-granulated form compared with the tablets containing starch in the dry-blended form. The dissolution coefficient of variation of extra-deep convex tablets compressed from granules containing wet-granulated starch was smaller only at the 5-min time point. At later time points, the punch tip geometry effects discussed earlier (6) override, at least in part, the starch-processing effects.

Placebo tablets (formulations B and C) were compressed with both punch tip geometries to confirm the nonspecificity of the effect on tablet friability caused by the mode of the addition of starch. The results of the friability of formulation B placebo tablets at various crushing strengths under controlled granulation moisture are given in Fig. 3. The tablets compressed with the granulation containing wet-granulated starch were less friable compared with the tablets compressed from granulations containing starch in the dry-blended form. At higher crushing strengths, these differences were small. This was true with both punch tip geometries. In agreement with an earlier report (6), the friability of extra-deep convex tablets was smaller than the friability of standard convex tablets.

Granulations were made without a wet binder (formulation C) to study the influence of the mode of the starch addition on tablet friability. Figure 4 gives the results of the tablet friability at various crushing strengths at a controlled moisture content. For both punch tip geometries, the friability of the tablets compressed from granulations containing wet-granulated starch was smaller than the tablets compressed from granulations containing starch in the dry-blended form. The friability of the extra-deep convex tablets was much smaller than the friability of the standard convex tablets.

These results suggest definite advantages of incorporating starch as a disintegrator in the wet-granulated part of the formulation of tablets containing soluble drugs and/or soluble major excipients for improving tablet friability and *in vitro* dissolution. It is also important to point out that the wet granulations containing starch must be dried below 60° to prevent gelatinization of the starch.

To investigate the mechanism by which the incorporation of starch in the wet granulation improved tablet friability and *in vitro* dissolution, a scanning electron microscope was used to examine the cross sections of the tablets. Figure 5 is a cross-sectional view of ticlopidine hydrochloride tablets (formulation A) containing starch in the dry-blended form compressed with the standard concave punches. Starch grains, mostly deformed, appeared in clumps with some loose, fine granules. The clumping of the starch grains was not observed when cross sections of the tablet containing starch as a part of the wet granulation were examined (Fig. 6). The starch grains were well distributed in the drug–excipient granules showing good contact with the powders.

Because of the dependence of the axial and radial movement of the powders on punch tip geometry, cross sections of the extra-deep convex tablets were examined to study its effect on the distribution of starch granules within the tablet. Clumps of starch grains with some loose, fine granules were observed (Fig. 7) when starch was dry blended with the dry granules. Starch did not appear to adhere to itself or to the other materials

in the tablet. This results in weaker points within the tablets and fine cracks around the agglomerates. Higher tablet friability and higher tablet-to-tablet variability in dissolution could be explained as resulting from clumping of starch grains and weaker points around these agglomerates. The cross-sectional view of the tablet compressed from granules containing starch in the wet-granulation stage is shown in Fig. 8. No clumping of the starch grains was seen. The materials were well distributed in the tablet matrix. Comparisons of the two punch tip geometries revealed no major differences in the distribution of starch resulting from the differential particle movement during compression (compare Figs. 5 and 6 with Figs. 7 and 8).

Figure 9 gives cross-sectional views of the placebo tablet compressed with the standard concave punches (formulation B). Tablets containing dry-blended starch showed only a few starch grains (Fig. 9A) compared with the largely fused lactose (Fig. 9B) for tablets compressed from wet-granulated starch.

The cross-sectional views of the tablets compressed from formulation C without a wet binder are shown in Fig. 10. Similar to ticlopidine hydrochloride tablets, clumping of starch grains was observed when starch was dry blended (Fig. 10A and B). Starch grains do not adhere to themselves or to the other materials in the tablet. This is in contrast to the case when starch was wet granulated with other excipients using water (Fig. 10C and D). Agglomerates or even isolated starch grains were not observed. The starch was well embedded in the soluble excipient, lactose, which on drying crystallized out.

In conclusion, this study suggests that the tablet friability and *in vitro* dissolution improved by incorporating starch in the wet-granulation stage of formulations containing a soluble drug and/or a soluble major excipient. This improvement in tablet friability and *in vitro* dissolution is due to a better bonding, fewer weak points, and better homogeneity of the disintegrator, starch, within the tablet.

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Application of the Ammonia Gas-Sensing Electrode: Determination of Drugs Having a Carbothionamido Group by Decomposition with Acid

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Abstract □ A method to determine drugs having a carbothionamido group using an ammonia gas-sensing electrode is described. To obtain analytical accuracy, the effect of factors that influence the potential is also discussed. Ethionamide or prothionamide was refluxed with 20% HCl to give ammonium chloride, hydrogen sulfide, and a carboxylic acid. The ammonia, which evolved at pH > 11, was determined. A linear calibration plot was obtained within the drug concentration range of 2×10^{-5}–1×10^{-2} *M*.

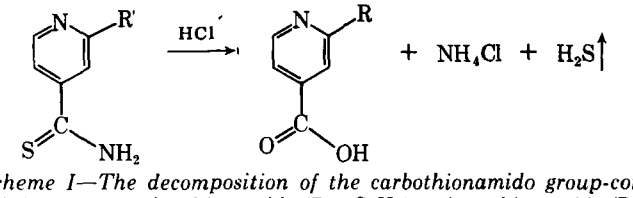
Keyphrases □ Ammonia gas-sensing electrode—determination of carbothionamido groups, acid decomposition of ethionamide and prothionamide □ Ethionamide—carbothionamido group, determination using ammonia gas-sensing electrode, acid decomposition □ Prothionamide—carbothionamido group, determination using ammonia gas-sensing electrode, acid decomposition

In recent years, the development of gas-permeable membrane electrodes has led to their widespread use in the analytical field (1). Although electrodes that use immobilized enzymes on the membrane are employed for the determination of organic and biological compounds, few applications to drug analysis have been reported in the literature, and no pharmacopeia has yet introduced their use for assays. Therefore, a previous paper (2) described procedures for the determination of drugs having a carboxyamido group (ethenzamide, niacinamide, pyrazinamide, and salicylamide).

The present paper describes the determination of drugs having a carbothionamido group in an analogous way and describes in detail the operations and handling of the ammonia gas-sensing electrode. The carbothionamido group decomposes into ammonium chloride, hydrogen sulfide, and a carboxylic acid on heating with hydrochloric acid (Scheme I). It may thus be possible to utilize the ammonia gas-sensing electrode to determine the ammonia derived from the ammonium chloride during the decomposition.

EXPERIMENTAL

Apparatus and Reagents—Direct potentiometric measurements were made at 20° in an 80-ml cell equipped with a magnetic stirrer, using a pH/mV meter[1] with a recorder[2] and ammonia gas-sensing electrodes A[3] and B[4]. Ethionamide[5], prothionamide[6], and ammonium chloride[7] were analytical grade or certified quality and were dried *in vacuo* at room temperature for 5 hr. Other chemicals used were reagent grade. Ammonium chloride solutions of 0.001–1 *M* and ammonium chloride solutions of 0.01–0.1 *M* saturated with ammonium picrate were used as internal filling solutions.



Scheme I—The decomposition of the carbothionamido group-containing compounds ethionamide ($R = C_2H_5$) and prothionamide ($R = C_3H_7$).

[1] Model F-7ss, Hitachi-Horiba Instruments, Horiba Co., Kyoto.
[2] Model EPR-22A, Toa-Denpa Co., Tokyo.
[3] Model 5002-05T, Horiba Co., Kyoto.
[4] Model 95-10, Orion Research Inc., Cambridge.
[5] Daiichi Seiyaku Co., Tokyo (lot CA 7921806).
[6] Lederle Japan Ltd., Tokyo (lot CA 7917603; assay, 100.2%).
[7] E. Merck, Darmstadt (lot 0074534; assay, 99.8%).

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