DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(15), 2693-2718 (1987)

AN EVALUATION OF TRICALCIUM PHOSPHATE EXCIPIENTS PARTICULARLY USING INSTRUMENTED ROTARY AND SINGLE STATION TABLET PRESSES

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ABSTRACT

Two direct compression grades of tricalcium phosphate, Tri-Compress[R] (Edward Mendell Co., Inc.) and Tri-Tab[R] (Stauffer Chemical Co.), and a product containing tricalcium phosphate, locust bean gum and citric acid, Loco-Tab[R] (Ingredient Technology Corp.), were studied. Loco-Tab is composed of smaller particles having more irregularly shaped surfaces than the others. It is also less dense and somewhat less flowable than the other materials. None of these excipients lost weight at elevated

temperature and none can be considered to be hygroscopic. Compressibility in formulations was studied using instrumented rotary and single station tablet presses. In all cases, the single station press yielded harder tablets at a given compression force. Dissolution of an insoluble drug was affected to a degree by the press used. Drug dissolution from Loco-Tab formulations was excellent at all tablet hardnesses, a highly desirable property for tablets to be coated using fluidized bed equipment. Loco-Tab would seem to be the calcium phosphate excipient of choice while recognizing that it is not a single entity and that it is acidic, in contrast to the neutral to slightly basic pH of the others.

INTRODUCTION

The most widely used inorganic filler in direct compresion tablet formulation is unmilled dicalcium phosphate dihydrate (1). Direct compression grades of tricalcium phosphate which are claimed to be superior because of their compressibility and anhydrous nature are Tri-Compress and Tri-Tab (2,3). Both conform to the specifications for tribasic calcium phosphate, NF. In addition, a product containing 90-92 per cent tricalcium phosphate, 6-8 per cent locust bean gum and 2 per cent citric acid, known as Loco-Tab, has been reported to be second only to microcrystalline cellulose among the excipients studied (4). All of these tricalcium phosphate products are claimed to have

excellent disintegration characteristics when included in tablet formulations (2-4). Formulations containing Loco-Tab have been reported to need no disintegrating agent (5).

While the compressibility of Tri-Tab alone has been reported (6), the present work was undertaken to examine other physical properties of these materials and to determine the relationships among compression force, tablet hardness and dissolution of a soluble and an insoluble drug from formulations containing them. A second purpose was to compare tablets of these formulations produced by a single station or a rotary machine to ascertain whether the compression-hardness-dissolution relationships differ as a result of fundamentally different compression mechanisms. It has been suggested on a theoretical basis that a rotary tablet press may compress a formulation less satisfactorily than a single station machine (7).

EXPERIMENTAL

The tricalcium phosphate products were examined for the following properties: appearance (macro and microscopic), mean particle size, density, flowability, moisture loss at 50°, pH and hygroscopicity.

The formulations studied for compressibility and dissolution are shown in Table 1. Formulation "A" is a control formulation containing a high proportion of microcrystalline cellulose and no tricalcium phosphate. Formulation "E" contains no

TABLE 1

Formulation Composition
(mg/tablet)

	Formula Designation				
	A	B	C	D	E
Drug	50.00	50.00	50.00	50.00	50.00
Micro-crystalline Cellulose	159.00	119.25	79.50	39.75	---
Fast-Flo Lactose	39.75	39.75	39.75	39.75	39.75
Tri-Tab, Tri-Compress, or Loco-Tab	---	39.75	79.50	119.25	159.00
Magnesium Stearate	1.25	1.25	1.25	1.25	1.25
Total	250.00	250.00	250.00	250.00	250.00

microcrystalline cellulose but allows the evaluation of a tricalcium phosphate product as the major excipient. The other formulations are mixtures of a tricalcium phosphate material and microcrystalline cellulose. None contain a disintegrating agent per se although microcrystalline cellulose has disintegrating properties in addition to binding properties (8). Fast-Flo Lactose^{R} was included in each of the formulations to simulate commercial formulations which often are mixtures of ingredients to facilitate flow and/or compressibility and to reduce cost. The lubricant in each case was magnesium stearate.

Hydrochlorothiazide was studied as an example of an insoluble drug and procainamide hydrochloride as an example of a soluble drug. The 50 mg per tablet level of the latter is recognized to be sub-therapeutic but was chosen only to provide powder in the cylinder after 15 taps and the weight of the powder contained in the cylinder is used to calculate the "tap" density.

Flow. Powder (200 g) was allowed to fall freely from a 410 ml Accofil^{R} Powder Filler cup[13] having an inside diameter of 2 9/16" and a conical bottom portion sloping downward at an angle of 60° with the vertical. The opening at the bottom of the cone is 1/2". Attached to the cup is an air vibrator[14] which is supplied with air at 10 psig during the test. The time required for the powder to empty from the cylinder was a measure of the flow rate.

Loss on Drying. One gram samples of powder were placed in open Petri dishes of 60 mm diameter and weighed after storage at 50° for one month.

pH. Suspensions of the indicated percentage were made in distilled water. After agitation for one hour, the pH was determined .

Hygroscopicity. One gram samples were placed in open 60 mm diameter Petri dishes. These were placed in desiccators containing saturated solutions (with an excess of solute) which produce known humidities. Differences in sample weights reflected moisture gain.

Formulation Manufacture. Batch sizes of 2 kg were manufactured using a planetary mixer[15] as follows. All materials were screened through a #20 mesh screen except for the magnesium stearate which was screened through a #30 mesh screen. The drug was mixed with the Fast-Flo Lactose for three minutes. The tricalcium phosphate product was added and the mixing was continued for another three minutes. The microcrystalline cellulose was added followed by mixing for an additional three minutes. Following addition of the magnesium stearate, the powders were mixed for one minute.

Tablet Compression. Tablets were compressed using 5/16" flat-face tooling on an instrumented (9) Stokes "F" single station machine[16] and an instrumented (10) Manesty "Express" rotary tablet press[17] operated at about 60 tablets per minute per compression station. When the correct weight (250 mg) was obtained, tablets were compressed within four hardness ranges (4-6, 8-10, 13-15, 22-24 SC). Hardness was determined using a Schleuniger-2E[18] tablet hardness tester.

Dissolution. Drug dissolution was determined using USP Apparatus 1 at 50 rpm (0.1N HCl). Analytical methodology was that described in the USP for hydrochlorothiazide tablets and procainamide capsules.

RESULTS AND DISCUSSION

Physical Properties

Physical characteristics of each of the tricalcium phosphate products are summarized in Table 2.

TABLE 2

Physical Characteristics

	Tri-Compress	Tri-Tab	Loco-Tab Lot I	Loco-Tab Lot II
Appearance	White, smooth	Off-white, angular (rough)	Sl. off-white, plate-like, clear crystals	White, plate-like
Mean Particle Size (μ)	288	280	165	195
% Under 100 Mesh	4.0	7.2	42.0	31.2
Fluff Density (g/ml)	0.520	0.758	0.445	0.476
Tap Density (g/ml)	0.555	0.836	0.502	0.536
% Increase from Fluff to Tap	6.7	10.3	12.8	12.6
Flow (g/sec)	>15	>15	4.9	8.3
% Loss at 50°	0	0	0.5	0.8
Color Change at 50°	++	++++	+	+
pH 1% Suspension	6.5	7.0	5.2	5.6
5% Suspension	7.1	7.6	4.9	5.0
20% Suspension	ND[a]	ND[a]	TG[b]	4.5
Moisture Sorption				
RT/75%RH (%)	1.2	2.8	1.6	0.4
RT/83%RH (%)	1.8	5.3	3.1	1.8

[a]Not determined. [b]Thixotropic gel formed.

FIGURE 1

SEM Photomicrograph of Tri-Compress

Tri-Compress was the whitest of the materials followed closely by one of the Loco-Tab lots. The other Loco-Tab lot was somewhat off-white. Tri-Tab was decidedly off-white.

SEM photographs (Figures 1-3) reveal that Tri-Compress is composed mainly of large smooth particles with smaller particles adhering to them. Tri-Tab particles are more angular and have a rougher surface. Loco-Tab has more or less flat "top" and "bottom" surfaces which are relatively smooth with sides that are generally perpendicular, resulting in a thick plate-like shape.

By optical microscopic examination, one of the Loco-Tab lots was observed to contain clear crystals in addition to typical

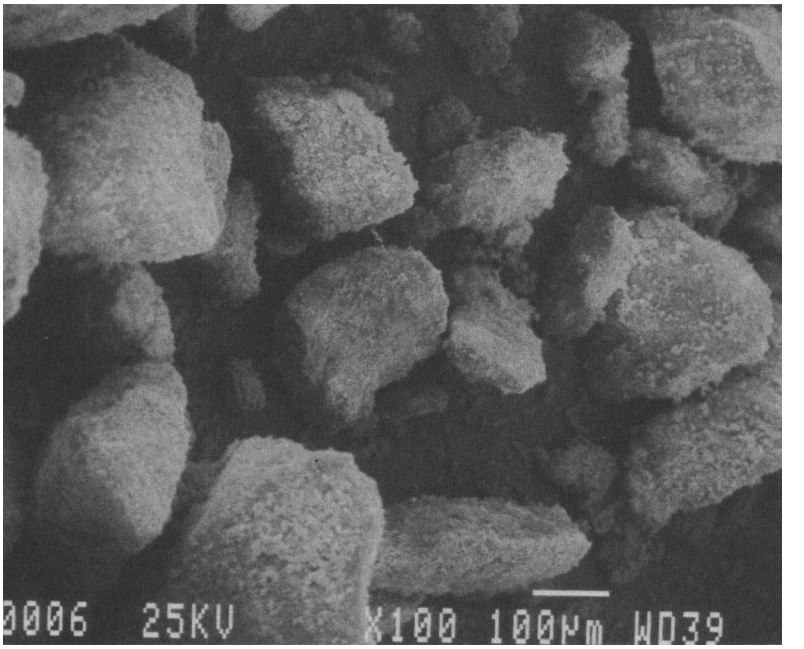

FIGURE 2

SEM Photomicrograph of Tri-Tab

opaque, white particles. These clear crystals were assumed to be citric acid.

Tri-Compress and Tri-Tab were found to have mean particle sizes of 288 and 280 microns respectively. The two Loco-Tab lots had mean particle sizes of 165 and 195 microns. By way of comparison, a lot of Fast-Flo Lactose was found to have a mean particle size of 130 microns. The coarseness of Tri-Compress and Tri-Tab is emphasized by noting the amounts smaller than 100 mesh.

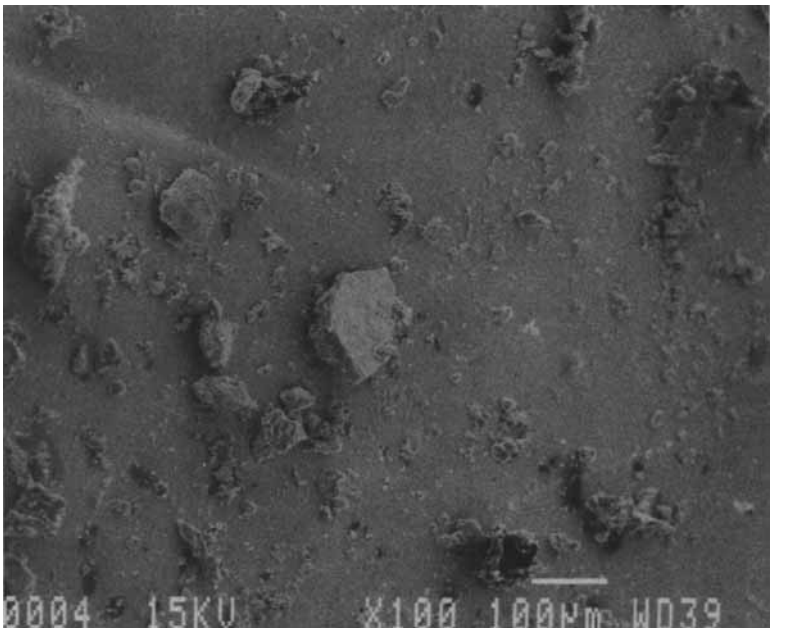

FIGURE 3

SEM Photomicrograph of Loco-Tab

The Loco-Tab lots were less dense than either Tri-Compress or Tri-Tab which is surprising, considering their smaller particle size and the expectation of closer packing. This finding may be attributed to the inherent nature of Loco-Tab as a co-dried product of several constituents or a result of its plate-like shape which prevents closer packing. The lower per cent increase in density of Tri-Compress caused by tapping probably reflects the surface roughness of the particles.

Tri-Compress and Tri-Tab have extremely rapid flow rates which no doubt are related to their high density. As noted,

Loco-Tab particle shape may not be ideal for flowability; nevertheless its flow was found to be satisfactory for direct compression purposes.

Because of the indicated moisture content of Loco-Tab (maximum of 5 per cent determined by loss on drying) (4), samples were placed at 50° in open Petri dishes for one month to estimate the degree to which this moisture might be liberated into a formulated product stored at elevated temperature. Only an insignificant amount of moisture was lost. The plain calcium phosphate excipients were found to lose no weight in the same test. However, Tri-Tab became much darker in color and Tri-Compress became slightly darker while the Loco-Tab samples changed only slightly. Excipient moisture content is an important parameter to be considered in solid dosage forms containing hydrolyzable drugs as it has been shown to affect drug stability (11).

Tricalcium phosphate has been reported to be slightly alkaline, and because of this, its use is not recommended with strong acid salts of weak organic bases or with certain other materials (12). The pH of both Tri-Compress and Tri-Tab suspensions was found to increase with increasing concentration. Loco-Tab suspensions, on the other hand, become more acid with increasing concentration due to the presence of citric acid. At 20 per cent, the lot of Loco-Tab which contained the clear crystals seen by microscopic observation

produced a thixotropic gel which could not be centrifuged to obtain supernatant liquid for pH determination.

Citric acid as a component of Loco-Tab raises the possibility of moisture absorption during high humidity storage. Curiously, Tri-Tab was found to be the most hygroscopic at the conditions studied. Loco-Tab Lot I which contained the clear crystals was more hygroscopic than the one which did not, indicating that the crystals were probably "unreacted" citric acid. Under ordinary conditions, however, Loco-Tab does not adsorb moisture.

Compression Properties

The compression force-hardness profile for Formulation "E" containing hydrochlorothiazide compressed on the rotary machine is shown in Figure 4. Formulation "E" contained about 64 per cent of the calcium phosphate excipient (Table 1). Tri-Compress and the two lots of Loco-Tab were equal in compressibility. Tri-Tab was less compressible as indicated by lower tablet hardnesses at the same compression force. The same relative compression force-hardness profile comparisons resulted for this formulation regardless of the drug in the formulation or whether a single station or a rotary machine was used.

For Formulation "B" containing 16 per cent calcium phosphate excipient and 48 per cent microcrystalline cellulose, equal compression force-hardness profiles were produced for all the calcium phosphate products with either procainamide or

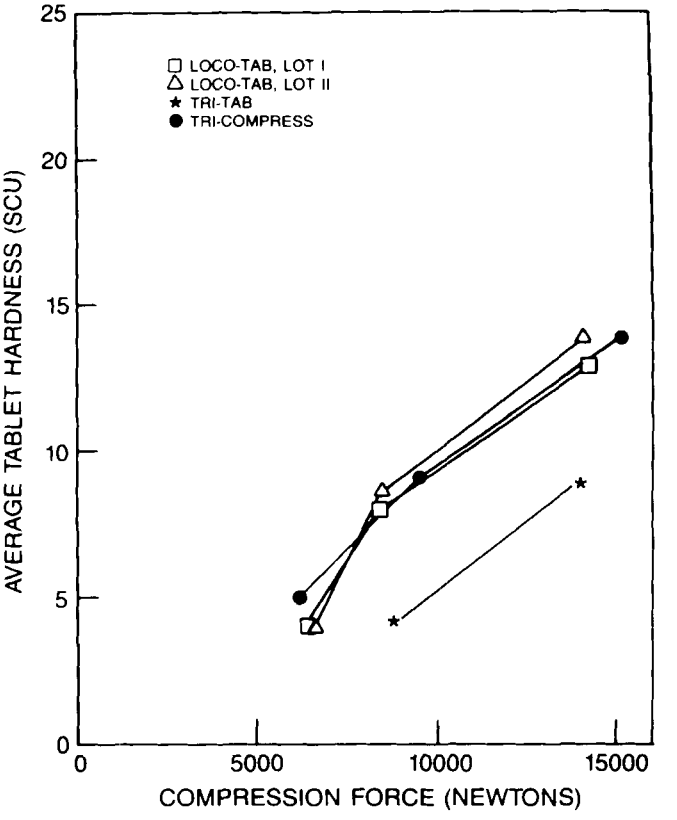

FIGURE 4

Hardness vs. Compression Force: Formulation "E" Containing Hydrochlorothiazide (Rotary Press)

hydrochlorothiazide using the single station press. In the case of the rotary machine, shown in Figure 5, a slightly lower compressibility was observed for Tri-Compress with both drugs at mid to high compression forces.

Increasing the microcrystalline cellulose content increased the compressibility of the formulation as shown in Figure 6 for

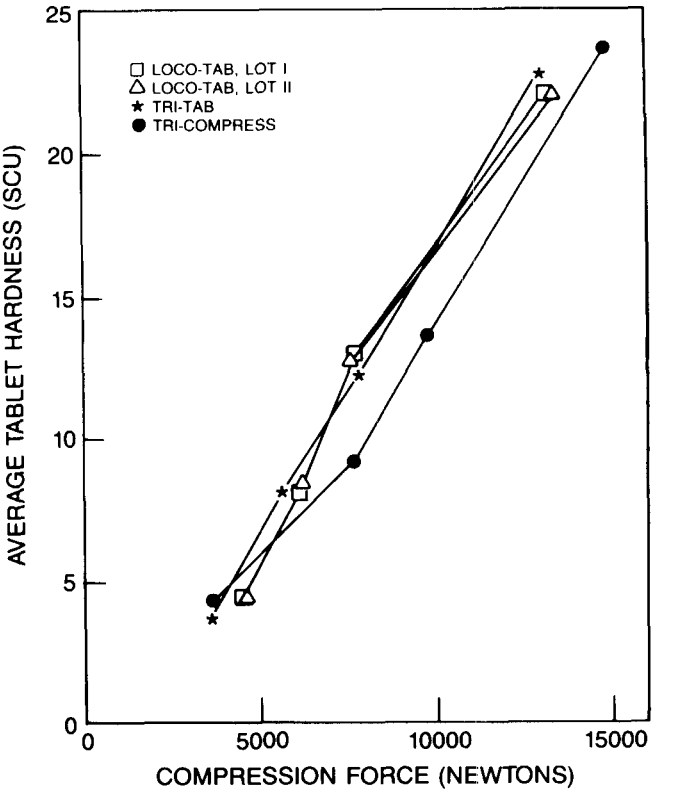

FIGURE 5

Hardness vs. Compression Force: Formulation "E" Containing Procainamide HCl (Rotary Press)

Loco-Tab formulations. However, in this instance, there is little practical difference in compressibility between "A" and "B" indicating that a considerable portion of microcrystalline cellulose can be replaced by this excipient. Indeed, Formulations "C" and "D" yield tablets of high hardness providing opportunity for still further microcrystalline cellulose

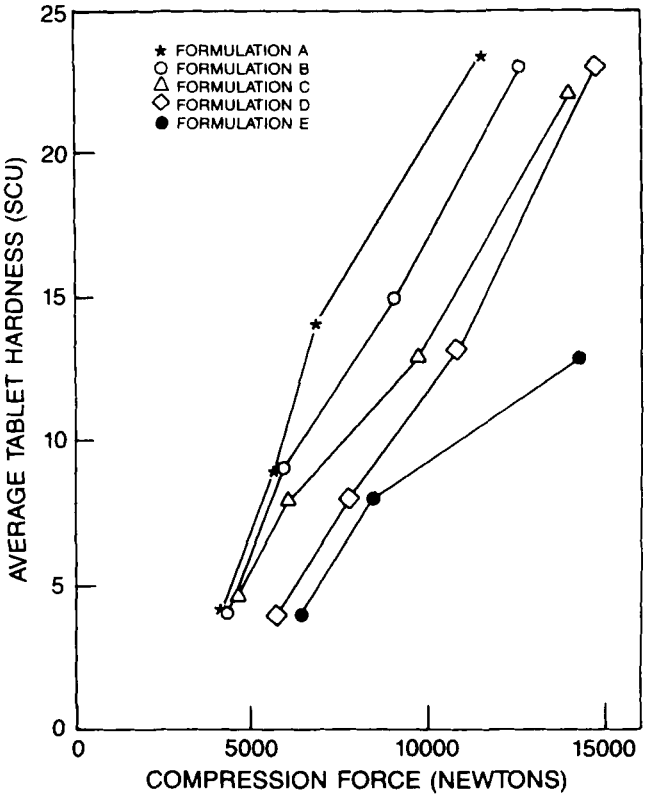

FIGURE 6

Hardness vs. Compression Force: Loco-Tab Lot I and Hydrochlorothiazide (Rotary Press)

replacement. Tri-Compress and Tri-Tab also can be used as replacements for microcrystalline cellulose.

While no relative differences in the compressibility of the tricalcium phosphate formulations were observed as a result of single station or rotary tablet machine use, there were differences in the absolute compression force-hardness profiles depending on the machine type. In every case for Formulation

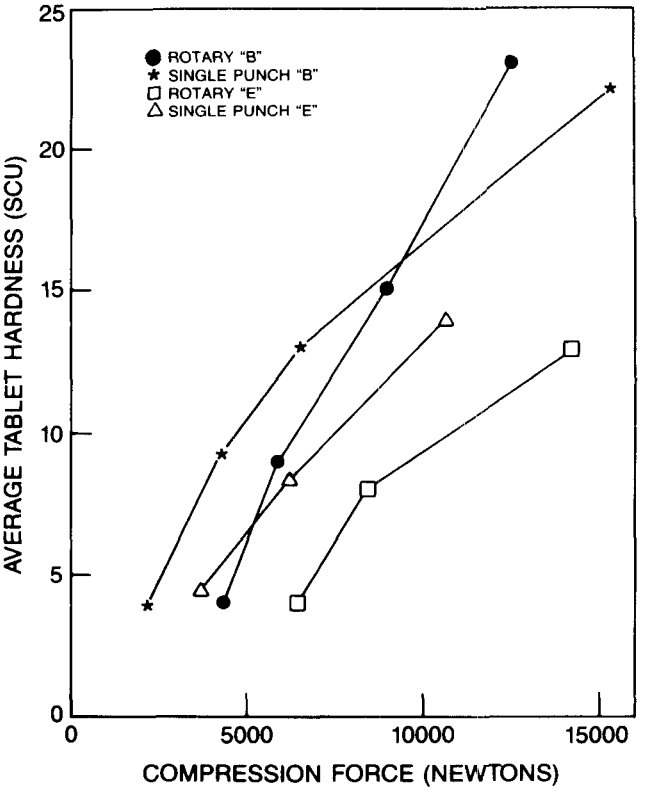

FIGURE 7

Hardness vs. Compression Force: Formulations "B" and "E" Containing Loco-Tab Lot I and Hydrochlorothiazide

"E", no matter which tricalcium phosphate product or which drug was included, a given compression force resulted in harder tablets when the single station machine was used than when the rotary machine was used. The same was true of Formulation "B" prepared from Tri-Compress and either drug throughout the compression force range examined. These observations support the view that single station machines have a longer time of punch/

powder contact than rotary machines and thus more time to allow for plastic deformation (7). It was surprising, therefore, to find that Formulation "B" containing either Loco-Tab (Figure 7) or Tri-Tab and either drug produced a convergence and "crossing over" of the compression force-hardness profiles at higher compression forces. The same was true of Formulation "A" which contained no tricalcium phosphate excipient. Perhaps these observations have to do with the manner in which the tablets break when tested for hardness.

Inclusion of Loco-Tab in Formulation "E" containing hydrochlorothiazide resulted in rapid drug dissolution at all hardnesses when compressed using either tablet press, but rather poor dissolution for tablets of Tri-Compress and Tri-Tab (Figure 8). This observation is particularly striking in light of the tablet hardnesses obtained for the plain tricalcium phosphate excipients. Results for Formulation "E" containing procainamide were comparable indicating that Loco-Tab indeed does have disintegrant properties in addition to binder properties. The other products would require an ingredient to enhance dissolution if used in high concentration as in Formulation "E".

For procainamide tablets of Formulation "B", equivalent hardness-dissolution profiles were found regardless of excipient. However, for hydrochlorothiazide tablets of Formulation "B" (Figure 9) there is more rapid release in going from Loco-Tab to Tri-Tab to Tri-Compress.

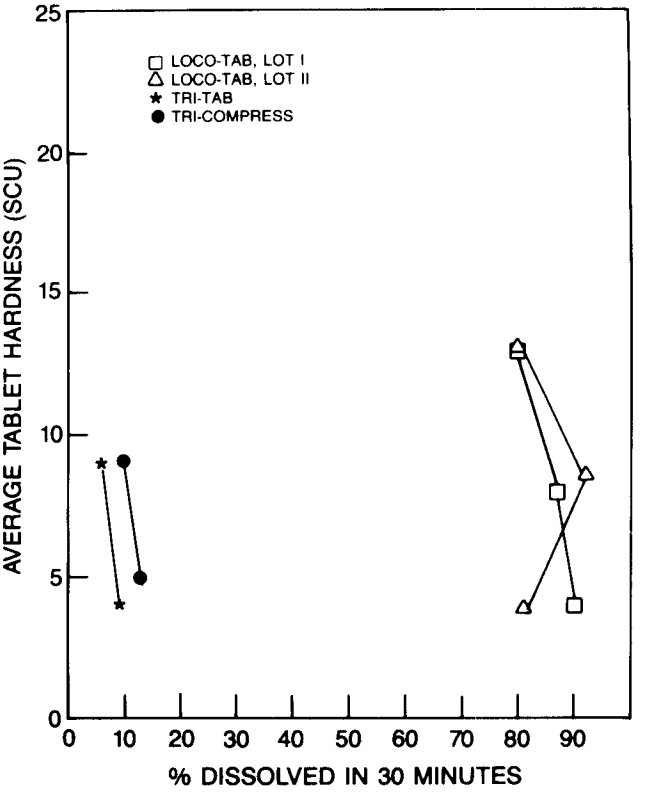

FIGURE 8

Hardness vs. Dissolution: Formulation "E"
Containing Hydrochlorothiazide (Rotary Press)

The dissolution of hydrochlorothiazide as a function of tablet hardness for Formulations "B", "C", "D", and "E" containing Loco-Tab and Formulation "A" compressed using a rotary tablet machine is shown in Figure 10. Formulation "A" has the slowest drug releasing profile. Tablets of this formulation exhibited the typical lamination observed during disintegration of tablets containing high amounts of microcrystalline cellulose.

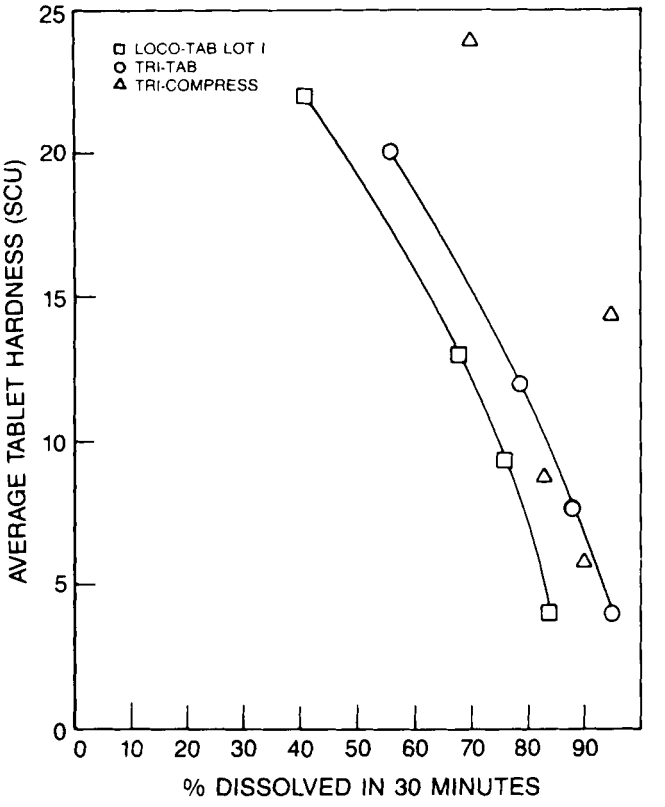

FIGURE 9

Hardness vs. Dissolution: Formulation "B" Containing Hydrochlorothiazide (Single Station Press)

This lamination, or disintegration into layers which resist further disintegration particularly at high tablet hardnesses, results in poor dissolution. In going from "A" to "D", a decreasing amount of lamination occurred. The dissolution of "D" was independent of tablet hardness. These observations were also made in the case of hydrochlorothiazide tablets compressed on the single station machine but not for procainamide tablets.

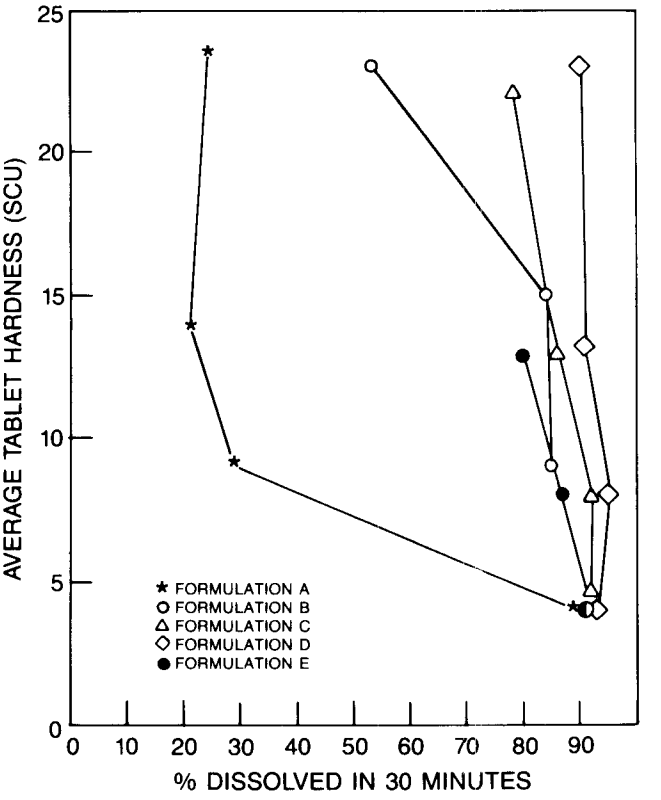

FIGURE 10

Hardness vs. Dissolution: Loco-Tab Lot I and Hydrochlorothiazide (Rotary Press)

Procainamide dissolution was essentially equal for all formulation/excipient combinations regardless of compression equipment used.

Formulations "C" and "D" with Tri-Tab and Tri-Compress were not evaluated but given their somewhat superior behavior to that of Loco-Tab in Formulation "B", there is no reason to believe that tablets of Formulation "C" and "D" also would not be

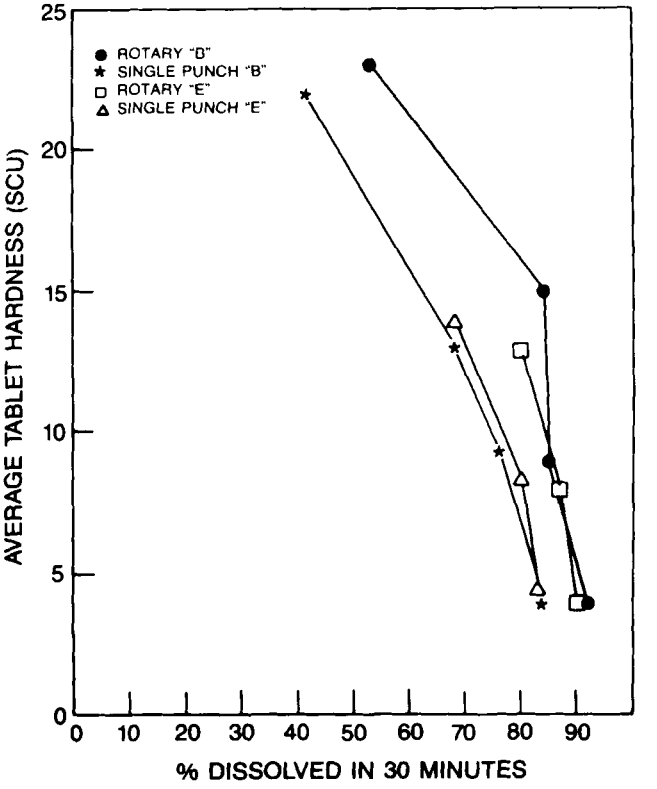

FIGURE 11

Hardness vs. Dissolution: Formulations "B" and "E" Containing Loco-Tab Lot I and Hydrochlorothiazide

rapidly disintegrating as a result of the interruption of the microcrystalline cellulose matrix.

Hydrochlorothiazide dissolution from Formulation "B" and Formulation "E" tablets containing Loco-Tab was more rapid at the same hardness for rotary compressed tablets than for single station compressed tablets (Figure 11). The same was true for

Tri-Compress and Tri-Tab based tablets. When the drug was procainamide, compression machine type made no difference.

It is interesting to speculate on the reasons for these apparent differences in tablet matrix structure as a result of rotary or single station compression which manifest themselves as (a) softer tablets and (b) more rapid dissolution at the same compression force in the case of a rotary machine. As noted above, softer tablets might be a result of insufficient time for plastic deformation. This in itself could lead to faster dissolution since the matrix is less strongly bonded and more easily disrupted by the dissolution medium. Train proposed regions of differing density in a compact resulting from single sided compression (13). A low density region is visualized as being in the top center of the compact while higher density is present at the bottom center. If the density distribution following rotary compression were to be two of Train's visualizations joined such that the top were the mirror-image of the bottom, then a rotary compressed tablet would have regions of low density along both punch/compact interfaces. In such a case, dissolution would be expected to be more rapid due to the fact that two faces of low density are presented to the dissolution medium. Compact fracture (as a measure of tablet hardness) would undoubtedly also be different.

Whatever the explanation for these findings, there are in fact differences in compacts produced by the two types of machines and further studies of a basic nature are needed.

While compressibility and dissolution of the three calcium phosphate products when combined in various ratios with microcrystalline cellulose were nearly always indistinguishable, Loco-Tab appears to offer advantages over the others. When used without microcrystalline cellulose it retains compressibility and has self-disintegrating properties. Loco-Tab would be an ideal excipient for tablets to be coated, particularly using fluidized bed coating equipment where tablet breakage due to attritional forces has been a problem. Its particle size and shape are such that it should be easily mixed and maintained in a mixed state. It resists color development at high temperature. Formulation stability of individual drugs may be improved due to the acid pH of Loco-Tab. The presence of citric acid crystals in one lot but not the other did not affect the reproducibility of dissolution and compressibility data. Lot-to-lot reproducibility for the other materials was not studied.

Loco-Tab possesses characteristics of a tablet filler, binder and disintegrant. It is by no means a new excipient and would seem to have potential for increased application over its current level of use.

ACKNOWLEDGEMENTS

This contribution is based on a thesis submitted by Mr. Bhavesh R. Patel to the Graduate Faculty, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University,

in partial fulfillment of the M.S. in Industrial Pharmacy degree requirements.

A presentation of this material was made at the 36th Academy of Pharmaceutical Sciences Meeting, Industrial Pharmaceutical Technology Section, Minneapolis, MN, 1985.

Financial aid from Ingredient Technology Corporation, Pennsauken, NJ in support of this work is appreciated.

Gratitude is expressed to the Squibb Institute for Medical Research and particularly to those in the Pharmaceutical Research and Development Department who facilitated this industry-university collaborative project. The authors are deeply indebted to Miss B. A. Sarsfield; without her assistance much of the laboratory work could not have been conducted.

FOOTNOTES

[1] Edward Mendell Co., Inc., Carmel, NY 10512. Subsequent to this study Tri-Compress was withdrawn from the market.

[2] Stauffer Chemical Co., Westport, CT 06881

[3] Ingredient Technology Corp., Pennsauken, NJ 08810

[4] Profarmaco, S.P.A., Milan, Italy

[5] Hoechst AG, Frankfurt, Germany

[6] FMC Corp., Philadelphia, PA 19103

[7] Mallinckrodt, Inc., St. Louis, MO 63147

[8] Foremost Whey Products, Baraboo, WI 53913

[9] Structure Probe, Metuchen, NJ 08840

[10] Fisher Scientific Co., Pittsburgh, PA 15219

[11]Available at Squibb Institute for Medical Research, New Brunswick, NJ 08903

[12]Van-Kel Industries, Inc., Edison, NJ 08820

[13]Perry Industries, Green Bay, WI 54303

[14]Martin Engineering Co., Neponset, IL 61345

[15]Hobart Corp., Troy, OH 45374

[16]Pennwalt Corp., Philadelphia, PA 19120

[17]Thomas Engineering, Hoffman Estates, IL 60195

[18]Vector Corp., Marion, IA 52302

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