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EVALUATION OF SOY POLYSACCHARIDE AS A DISINTEGRATING AGENT

PART II: WET GRANULATION

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ABSTRACT

Soy polysaccharide was evaluated as a disintegrating agent in tablets made by wet granulation utilizing both lactose and dicalcium phosphate dihydrate as fillers, gelatin as a granulating agent and hydrochlorothiazide as a model drug. It was found to be more effective than starch but less effective than cross-linked carboxymethylcellulose (Ac-Di-Sol^{R}) at equivalent concentrations. Soy polysaccharide appears to reduce the friability of tablets as concentration increases. Tablets containing either Soy polysaccharide or cross-linked carboxymethylcellulose showed no changes in dissolution profiles after storage under ambient conditions for six months.

INTRODUCTION

The effects of formulation and manufacturing method on tablet disintegration and dissolution are well-known. In making tablets by wet granulation it has been a common practice to add the disintegrating agent both before the formation of granules (intragranularly) and in the final granules (extragranularly). Since the intragranular disintegrant undergoes both wetting and drying during the granulation process it may not be as effective, in equivalent concentrations, as the disintegrant used in tablets made by direct compression and slugging. This has been a problem in some formulations with corn starch and has caused formulators to search for disintegrating agents which are equally effective regardless of the method of tablet production. One of the advantages of some of the newer tablet disintegrants is the fact that the method of manufacture has less of an effect on functionality. For example, this was found to be the case with cross-linked carboxymethylcellulose (1), sodium starch glycolate (2) and cross-linked polyvinylpyrrolidone (3). The object of this work was to compare the effectiveness of soy polysaccharide (Emcosoy^{R}) to both a classical disintegrant (starch) and a super disintegrant (cross-linked carboxymethylcellulose) in tablets made by wet granulation using

both dicalcium phosphate and lactose as prototype tablet fillers.

EXPERIMENTAL

Formulations

All materials used in the tablets were the same as those listed in Part I of this study (4) except for the addition of gelatin[1] which was used as the granulating agent. Tablets were prepared using both lactose (Fast-Flo^{R} Lactose) and dicalcium phosphate dihydrate (Emcompress^{R}) as fillers. The various formulations studied are listed in Tables I and II and are comparable to those used in the direct compression studies with a few exceptions. Cross-linked CMC was used as a control at a 3% level rather

TABLE I

Wet Granulation Tablet Formulations Containing Lactose as a Filler

	% w/w of the ingredient in the formulation number				
Ingredient	1	2	3	4	5
Lactose	95.0	90.0	95.0	93.0	88.0
Cross-linked CMC	3.0	-	-	-	-
Corn starch	-	8.0	-	-	-
Soy polysaccharide	-	-	3.0	5.0	10.0
Gelatin (dry basis)	1.0	1.0	1.0	1.0	1.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0

TABLE II

Wet Granulation Tablet Formulations Containing Dicalcium Phosphate as a Filler

Ingredient	% w/w of the ingredient in the formulation number				
	6	7	8	9	10
Dicalcium phosphate	94.0	89.0	94.0	92.0	87.0
Cross-linked CMC	3.0	-	-	-	-
Corn starch	-	8.0	-	-	-
Soy polysaccharide	-	-	3.0	5.0	10.0
Gelatin (dry basis)	2.0	2.0	2.0	2.0	2.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0

than 2% because prior studies had shown that slightly higher levels were needed to optimize disintegration and dissolution (5).

It was found necessary to use 2% gelatin on a dry weight basis to mass the dicalcium phosphate based formulations while only 1% was required by the lactose formulations. All tablets contained 1% magnesium stearate as a lubricant.

The formulations containing hydrochlorothiazide utilized in the dissolution studies are shown in Table III. All tablets contained equal portions of dicalcium phosphate and lactose. The amount of gelatin binder used on a dry weight basis was 1.5%.

Preparation of Tablets

One thousand (1000) gram batches of tablets were

TABLE III

Wet Granulation Tablet Formulations Containing Hydrochlorothiazide Used for Dissolution and Aging Studies

Ingredient	% w/w of the ingredient in the formulation number		
	11	12	13
Lactose	44.75	45.25	43.75
Dicalcium phosphate	44.75	45.25	43.75
Hydrochlorothiazide	5.0	5.0	5.0
Cross-linked CMC	3.0	-	-
Soy polysaccharide	-	2.0	5.0
Gelatin (dry basis)	1.5	1.5	1.5
Magnesium stearate	1.0	1.0	1.0

prepared for the study by first mixing one-half of the amount of the disintegrant with the drug, if present in the formulation, and the filler in a Twin-shell^{R} blender[2] for 5 minutes. A freshly prepared aqueous solution of gelatin (10% w/v) was used as the granulating fluid. The warm solution was added to the powder blend and mixed by hand. A Kitchen-Aid^{R} mixer was tried for granulating but the filler was found to form lumps and mixing was not uniform. The amount of the granulating agent added was kept constant for all formulations of a particular filler. If any formulation required more wetting, in order to properly mass the powders, water was

added. The wet mass was passed through a #16 mesh screen and tray-dried in a drying oven[3] for 14 hours at 125°F. The dried granulation was passed through a #20 mesh screen. The remaining half of the disintegrant and all of the magnesium stearate were added and blended for 15 minutes in a Twin-shell[R] blender.

Tablets were compressed on an instrumented rotary tablet machine described in Part I of this article and evaluated by methods which were also previously described.

In the case of formulations prepared for the dissolution and aging studies, tablets were compressed at two hardness levels only; low hardness (~6 kg) and high hardness (~13 kg). Tablets retained for the aging study were stored in amber-glass, screw-cap bottles at room temperature (~25°C).

RESULTS AND DISCUSSION

Variation in the Data

In order to provide an indication of the variation in the tablet weight, hardness and disintegration time data, the average coefficient of variation obtained for each formulation over five compression force levels, within the range of compression force reported, is shown in Table IV. In general there were few differences in the variability of each parameter between the formulations. However,

TABLE IV

The Effect of Disintegrant Type and Concentration on the Variability in the Data of Weight, Hardness and Disintegration Times of Tablets Containing Lactose or Dicalcium Phosphate Dihydrate as a Filler

Formulation Number	Compression Force Range (kg)	C.V.* in Weight (%)	C.V. in Hardness (%)	C.V. in Disintegration Times (%)
Lactose				
1	200-900	1.51	10.26	8.21
2	200-850	0.72	6.37	6.90
3	190-640	0.70	3.92	3.88
4	185-600	0.64	4.54	4.20
5	130-660	0.59	5.21	3.22
Dicalcium Phosphate				
6	125-910	0.79	7.57	6.50
7	300-1250	0.80	5.19	10.71
8	195-850	0.53	3.83	8.83
9	180-870	0.44	4.47	7.05
10	200-840	0.43	4.55	15.56

*Coefficient of variation (%) value reported is the average of values obtained at five compression force levels within the range of compression force reported in the table.

the lactose formulations containing cross-linked CMC did show slightly higher variability with respect to weight and tablet hardness (possibly interrelated) than did the other formulations. Tablets of dicalcium phosphate containing 10% soy polysaccharide also had a very high coefficient of variation.

Compressibility

The compressibility profiles for the lactose tablets and the dicalcium phosphate tablets are shown in Figures 1 and 2 respectively. The formulations

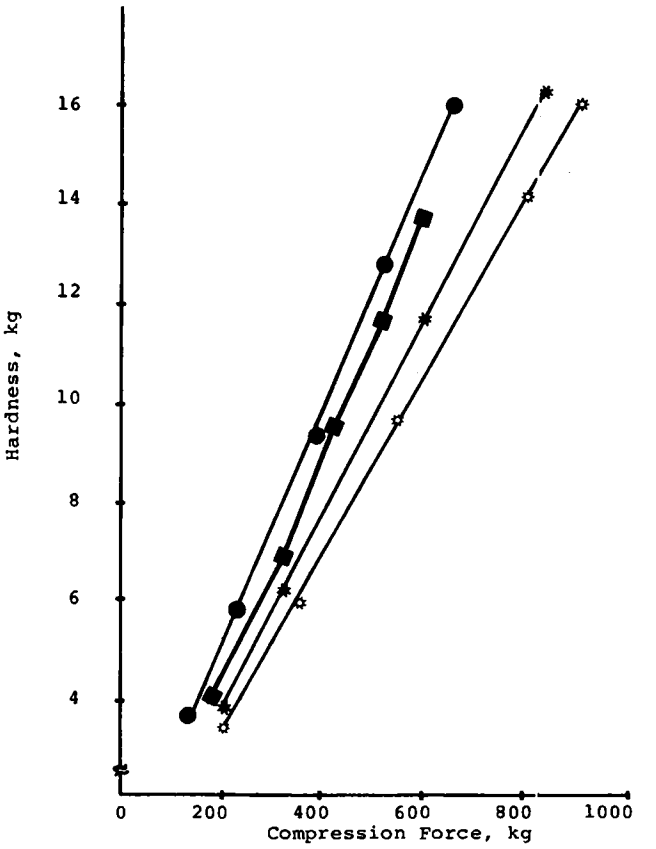

FIGURE 1
The Effect of Disintegrant Type and Concentration on the Hardness of Lactose Tablets Made at Various Compression Forces. Key: ✡, 3% Cross-linked CMC; ✱, 8% Corn starch; ■, 3% and 5% Soy polysaccharide and ●, 10% Soy polysaccharide.

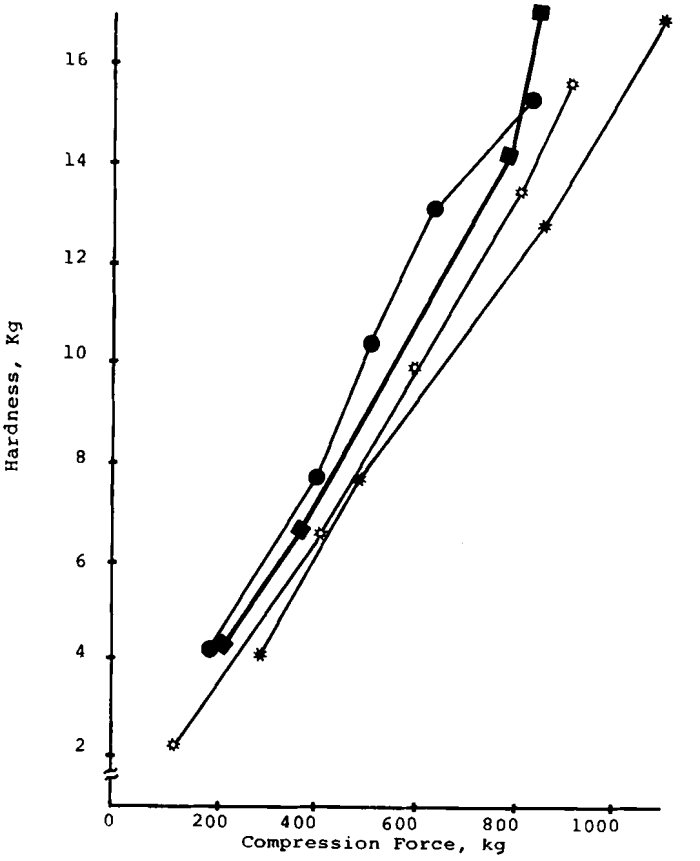

FIGURE 2
The Effect of Disintegrant Type and Concentration on the Hardness of Dicalcium Phosphate Tablets Made at Various Compression Forces. Key: same as in Figure 1.

containing soy polysaccharide seemed to be more compressible than the controls exhibiting higher hardness values at given compression forces. This could indicate some secondary binding effect by the disintegrating agent.

The control tablets containing starch exhibited much better compressibility than did similar direct compression formulations due to the binder effect of the gelatin. However, except for the starch tablets, other formulations produced no harder tablets than did the corresponding direct compression blends. In fact directly compressible lactose (Fast-Flo^{R} Lactose) seems to lose compressibility when wet-granulated. In general it can be stated that all the formulations produced tablets with acceptable hardness levels at reasonable compression forces.

Friability

Friability profiles for the tablets containing soy polysaccharide and the control disintegrants are shown in Figures 3 and 4. The effect of disintegrants on friability was similar to the effect observed on tablet hardness but more pronounced. Increasing levels of soy polysaccharide appeared to reduce friability and all soy polysaccharide formulations had lower friabilities than tablets containing the control disintegrants. Such an effect was previously reported for another super disintegrant -- cross-linked

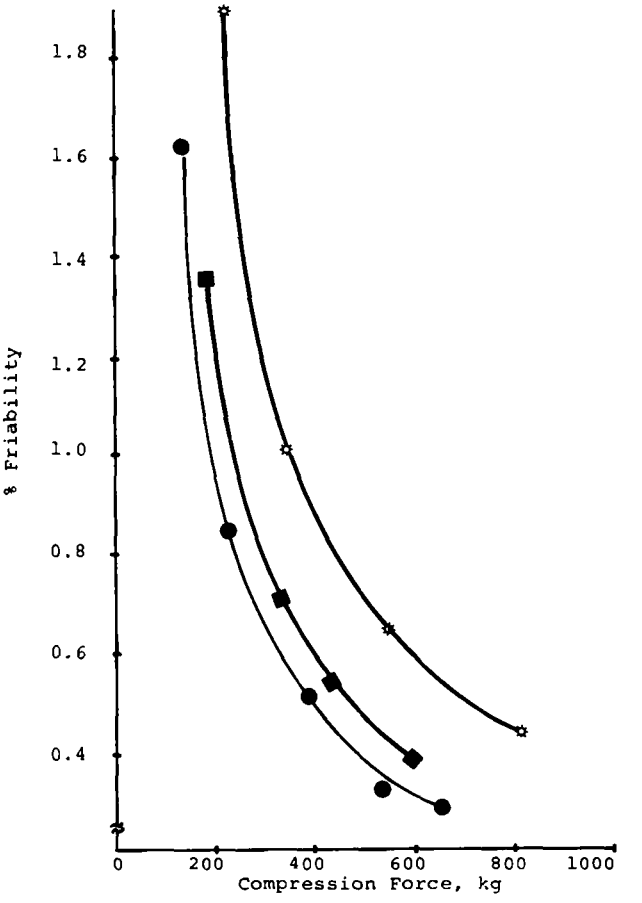

FIGURE 3
The Effect of Disintegrant Type and Concentration on the Friability of Lactose Tablets Made at Various Compression Forces. Key: ✲, 3% Cross-linked CMC and 8% Corn starch; ■, 3% and 5% Soy polysaccharide; ●, 10% Soy polysaccharide.

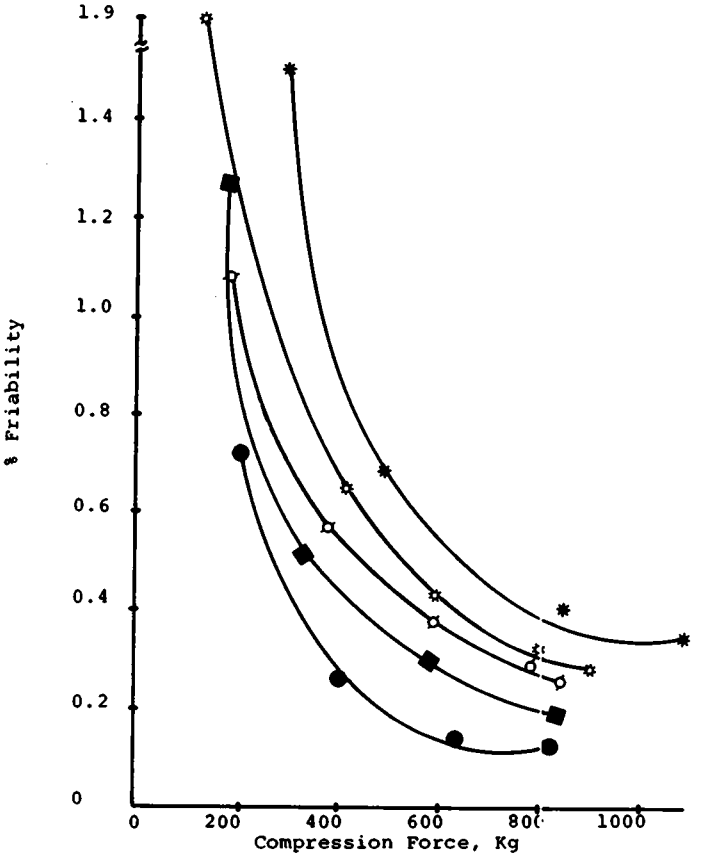

FIGURE 4
The Effect of Disintegrant Type and Concentration on the Friability of Dicalcium Phosphate Tablets Made at Various Compression Forces. Key: ✲ , 3% Cross-linked CMC; ✱ , 8% Corn starch; -o- , 3% Soy Polysaccharide; ■ , 5% Soy polysaccharide and ● , 10% Soy Polysaccharide.

polyvinylpyrrolidone (3). As was seen in the direct compression studies, the tablets containing the 8% corn starch exhibited the lowest hardnesses and highest friabilities.

Disintegration Times

The effect of disintegrant type and concentration on the disintegration times of tablets produced at various hardness levels is shown in Figures 5 and 6. Disintegration times of the lactose tablets were less affected by concentration of the disintegrant or tablet hardness than were the dicalcium phosphate tablets. This is due to the soluble nature of lactose which tends to produce tablets which dissolve from the

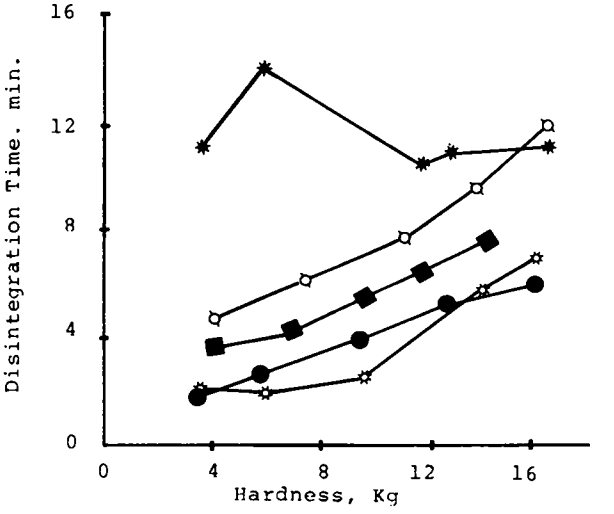

FIGURE 5
The Effect of Disintegrant Type and Concentration on the Disintegration Time of Lactose Tablets at Various Hardness Levels. Key: same as in Figure 4.

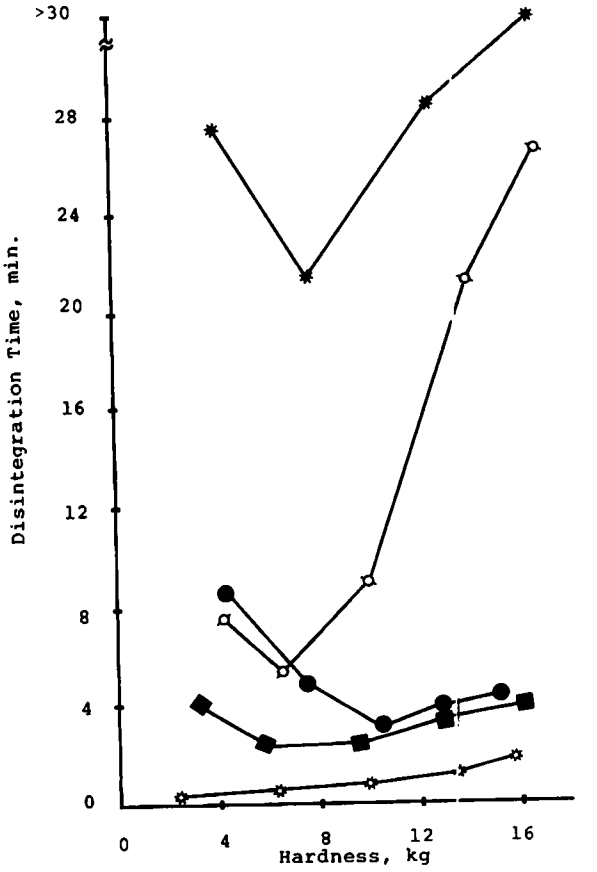

FIGURE 6
The Effect of Disintegrant Type and Concentration on the Disintegration Times of Dicalcium Phosphate Tablets at Various Hardness Levels. Key: same as in Figure 4.

outside inward rather than disintegrate rapidly. Disintegration times tend to increase proportionally with increase in tablet hardness which is typical of tablets made out of soluble components. Lactose tablets containing 3% cross-linked CMC provided similar disintegration profiles to those containing 10% soy polysaccharide. The tablets containing 8% starch gave consistently higher and relatively constant disintegration times at all hardness levels.

Tablets of dicalcium phosphate exhibited a minima in disintegration times with both 8% starch and the soy polysaccharide particularly at the 3% and 10% levels. This minima is characteristic of insoluble tablets containing starch as a disintegrant and has been attributed to a hardness where tablet porosity (water penetration) and starch deformation (swelling) are optimized (6). At lower hardness levels it appears that the 5% soy polysaccharide level might actually be superior to the 10% level but these differences disappear as hardness is increased. While even the 3% soy polysaccharide is more effective than 8% starch there seems to be a significant advantage of going to at least 5% level if tablets are to be compressed at higher hardness values. In all cases 3% cross-linked CMC produced tablets with the shortest disintegration times, all being less than two minutes and comparable to those seen in direct compression formulations.

Dissolution Rates

The dissolution profiles for tablets containing hydrochlorothiazide and equal portions of lactose and dicalcium phosphate as filler are shown in Figure 7. All the points are not shown in the graph for clarity reasons. Dissolution profiles were run on tablets prepared at two hardness levels only; low hardness (~6 kg) and high hardness (~13 kg). Two concentration levels of soy polysaccharide, 2% and 5%, were chosen for study as they represented values both above and below the 3% cross-linked CMC control. As can be seen from the dissolution profiles both hardness level and disintegrant concentration had a significant effect on dissolution rates. Increasing the hardness of the tablets containing 5% soy polysaccharide increased the $T_{60\%}$ from approximately 20 minutes to over 30 minutes. Increasing the level of disintegrant in tablets compressed at the low hardness level, from 2% to 5%, decreased the $T_{60\%}$ from 35 minutes to 20 minutes.

It would appear that levels of at least 5% would be needed in tablets made by wet granulation. However tablets containing only 3% of the cross-linked CMC exhibited better dissolution profiles than tablets containing 5% soy polysaccharide at either hardness level. Of further interest is the fact that tablet hardness did not appear to have any significant effect

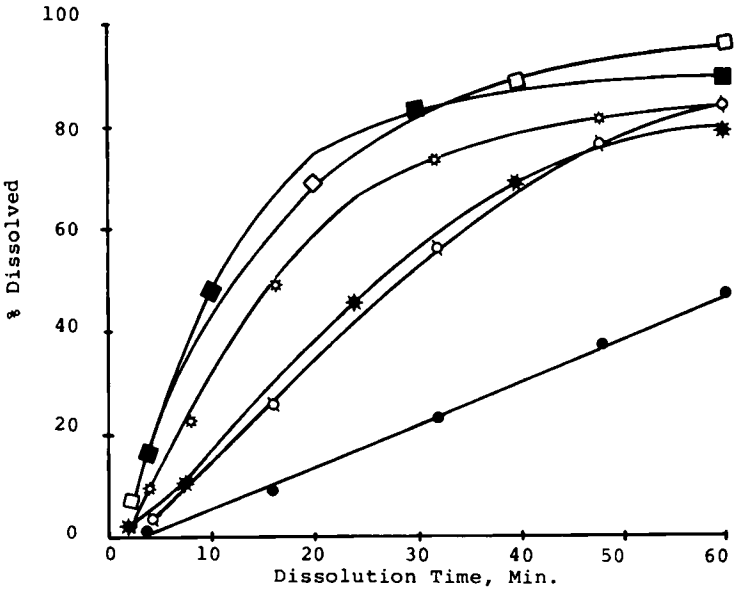

FIGURE 7
The Effect of Disintegrant Type and Concentration and Tablet Hardness on the Dissolution of Hydrochlorothiazide from Tablets Made by Wet Granulation.
Key:

- 2% Soy polysaccharide; tablet hardness = 6 kg
- 2% Soy polysaccharide; tablet hardness = 13 kg
- 5% Soy polysaccharide; tablet hardness = 6 kg
- 5% Soy polysaccharide; tablet hardness = 13 kg
- 3% Cross-linked CMC; tablet hardness = 6 kg
- 3% Cross-linked CMC; tablet hardness = 13 kg

on dissolution of hydrochlorothiazide tablets containing the cross-linked CMC. This can be attributed to the internal wicking of water into the tablet matrix by the cellulose fibers regardless of the degree of tablet porosity resulting from different hardness levels. In general, the effects of disintegrant type, amount and tablet hardness were much more pronounced in tablets made by wet granulation than those made by direct compression.

Effect of Aging on Dissolution Rates

Although it is most common to be concerned about decreases in potency of tablets on aging, changes in dissolution profiles and drug availability can also be of great importance. Increases in disintegration times and decreases in dissolution rates are known to occur in many tablet formulations after aging. Tablets containing 2% and 5% soy polysaccharide and 3% cross-linked CMC compressed to the higher hardness levels (~13 kg) were stored in tightly closed glass containers at room temperature for six months and dissolution profiles redetermined. The results are shown in Figure 8 and again all the points are not shown for clarity reasons. Aging at room temperature appeared to have very little effect on the dissolution of hydrochlorothiazide regardless of the disintegrant type or concentration. These results

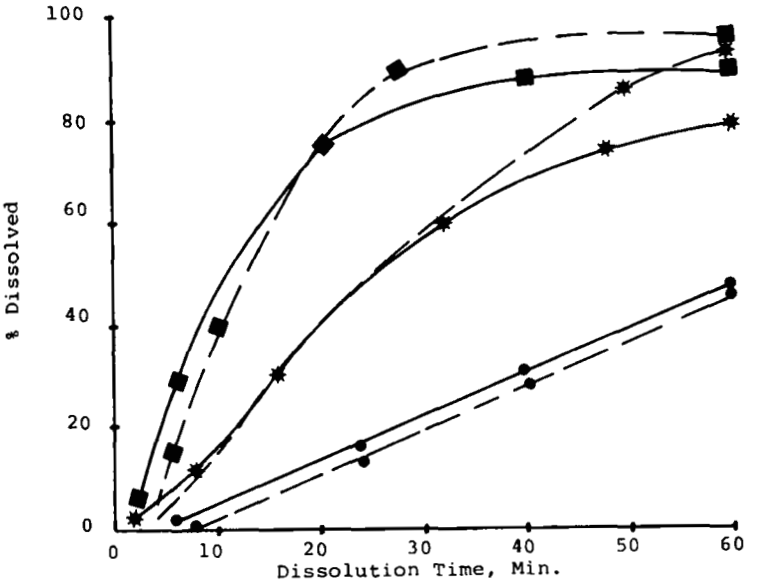

FIGURE 8
The Effect of Aging on the Dissolution Profiles of Hydrochlorothiazide Tablets (hardness=13 kg.) Made by Wet Granulation.
Key:

● 2% Soy polysaccharide
✱ 5% Soy polysaccharide
■ 3% Cross-linked CMC
—— Before Aging (original)
---After Aging

are similar to those seen with the direct compression formulations. Further work is necessary before long term stability can be assured.

SUMMARY AND CONCLUSIONS

Soy polysaccharide performs well as a disintegrant in tablets made by direct compression and its effectiveness closely parallels the best of the super disinte-

grants. In tablets made by wet granulation it appears to be far superior to starch even at lower use levels. However it is not as effective, at equivalent use levels, as cross-linked carboxymethylcellulose.

FOOTNOTES

1. Gelatin U.S.P., 270 Bloom, Lot #722378, J.T. Baker Chemical Co., Phillipsburg, N.J. 08865
2. 10 quart size, Patterson-Kelly Co., Inc., East Stroudsburg, PA 18301
3. Model 1018E, Arthur Cotton Co., Detroit, MI

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