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EVALUATION OF SOY POLYSACCHARIDE AS A DISINTEGRATING AGENT

PART I: DIRECT COMPRESSION

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ABSTRACT

Soy polysaccharide, a group of high molecular weight polysaccharides obtained from soy beans, was evaluated as a disintegrant in tablets made by direct compression using lactose and dicalcium phosphate dihydrate as fillers. A cross-linked sodium carboxymethyl cellulose and corn starch were used as control disintegrants. Parameters studied were compressibility, friability and disintegration times. Dissolution studies were conducted on tablets containing hydrochlorothiazide as a model drug of low water solubility. Soy polysacchardie performs well as a disintegrating agent in direct compression formulations with results paralleling those of cross-linked CMC at the 2% level and superior to corn starch at the 8% level. Dissolution rates of

the drug from tablets were rapid, particularly at the 5% level and were not adversely affected by aging at room temperatures.

INTRODUCTION

During the past five years a number of significant developments have occurred in the field of tablet disintegrants. A review of the various new disintegrating agents was published by Shangraw et al (1). Other reports have appeared in the literature regarding the properties and functionality of new disintegrants such as sodium carboxymethyl starch (2-6), cross-linked polyvinylpyrrolidone (7) and cross-linked sodium carboxymethyl cellulose (8-10). While these new disintegrants have a number of advantages over the traditional corn starch, particularly in lower use concentrations, the search continues for other active materials. The present study is concerned with the evaluation of soy polysaccharide for its potential use as a disintegrant in tablets made by direct compression.

EXPERIMENTAL

Materials

Soy polysaccharide[1] was originally supplied by the Ralston Purina Company but is presently available

1. Ralston Purina Company, St. Louis, MO. 63188

from Edward Mendell under the trade name Emcosoy[2]. Soy polysaccharide is a group of high molecular weight polysaccharides obtained by processing defatted soy beans and it contains mainly the remnants of the cell wall with about 7.5% moisture content. Other materials used were Fast Flo^{R} lactose (modified α-monohydrate lactose)[3], Emcompress^{R} (unmilled dicalcium phosphate dihydrate of a special particle size cut)[2], Ac-Di-Sol^{R} (cross-linked sodium carboxymethyl cellulose)[4], corn starch[5], magnesium stearate[6] and hydrochlorothiazide[7].

Formulations

A list of the formulations used in the disintegration portion of this study can be found in Tables I and II. Control formulations contained either 2% cross-linked CMC or 8% corn starch while the concentration of soy polysaccharide was varied from 1% to 10%.

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2. Edward Mendell Company, Carmel, N.Y. 10512
3. Foremost-McKesson, Inc., San Francisco, CA. 94104
4. FMC Corporation, Food and Pharmaceuticals Division, Philadelphia, PA. 19087
5. Best Foods, Wayne, PA. 19087
6. Amend Drug and Chemical Company, Irvington, N.J. 07111
7. Merck Sharp and Dohme Laboratories, West Point, PA. 18301

TABLE I

Direct Compression Tablet Formulations Containing Lactose

Ingredient	% w/w of the ingredient in the formulation number					
	1	2	3	4	5	6
Lactose	97.0	91.0	98.0	97.0	94.0	89.0
Cross-linked CMC	2.0	-	-	-	-	-
Corn Starch	-	8.0	-	-	-	-
Soy Polysaccharide	-	-	1.0	2.0	5.0	10.0
Magnesium Stearate	1.0	1.0	1.0	1.0	1.0	1.0

TABLE II

Direct Compression Tablet Formulations Containing Dicalcium Phosphate Dihydrate

Ingredient	% w/w of the ingredient in the formulation number					
	7	8	9	10	11	12
Dicalcium Phosphate Dihydrate	97.0	91.0	98.0	97.0	94.0	89.0
Cross-linked CMC	2.0	-	-	-	-	-
Corn Starch	-	8.0	-	-	-	-
Soy Polysaccharide	-	-	1.0	2.0	5.0	10.0
Magnesium Stearate	1.0	1.0	1.0	1.0	1.0	1.0

The formulations containing hydrochlorothiazide are shown in Table III; in this case only cross-linked CMC was used as a control. Hydrochlorothiazide was used as the model drug because of its relatively low water solubility and wide use as a therapeutic agent. Lactose and dicalcium phosphate represent soluble and insoluble fillers while corn starch and cross-linked CMC exemplify the classical and the new super disintegrants respectively.

Preparation of Tablets

Batches of the various formulations (600 g) were prepared by mixing the disintegrant and magnesium stearate (and also hydrochlorothiazide if present in

TABLE III

Direct Compression Tablet Formulations Used for Dissolution and Aging Studies

Ingredient	% w/w of the ingredient in the formulation number		
	13	14	15
Lactose	46.0	46.0	44.5
Dicalcium Phosphate Dihydate	46.0	46.0	44.5
Hydrochlorothiazide	5.0	5.0	5.0
Cross-linked CMC	2.0	-	-
Soy Polysaccharide	-	2.0	5.0
Magnesium Stearate	1.0	1.0	1.0

the formulation) with the filler for 15 minutes in a two-quart size V-blender[8] without using the intensifier bar. Tablets were compressed on an instrumented rotary press[9] at five different compression forces using 5/16" flat-faced tooling. Only one station, producing 25 tablets/min., was used. A polygraph recorder[10] was used to monitor the compression and ejection forces. The tablet target weight was 300 mg. The tablets were collected into screw-capped glass bottles and hardness, weight variation, friability and disintegration time tests were conducted after allowing the tablets to age for at least 24 hours.

Hardness

Hardness of the tablets was determined using a Schleuniger hardness tester[11]. Values used in the plots are an average of 10 determinations.

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8. Patterson-Kelley Company, Inc., East Stroudsburg, PA. 18301
9. Model RB-2, Stokes Division, Pennwalt Corp., Warminster, PA. 18974
10. Model 7702-B, Hewlett Packard, San Diego, CA. 92127
11. Model 2E/1106, Vector Corporation, Hiawatha, IA 52233

Weight Variation

Weights of 20 tablets were determined using a Cahn millibalance[12] and the average and coefficient of variation were calculated.

Friability

A Roche friabilator[13] was employed to determine the friability. The sample size was 20 tablets and test time was four minutes. Percent friability was calculated.

Disintegration

Disintegration times of the tablets were determined in dilute HCl solution (1 in 100) using the U.S.P. XX method. The mean of six determinations for each batch was used in the plots.

Dissolution

The dissolution rate study was conducted utilizing a standard multiple-head dissolution unit[14]. This dissolution equipment features six round bottom flasks each containing 900 ml of dilute HCl solution (1 in 100) maintained at 37°±1°C. Paddles were

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12. Model 7500, Cahn Division, Ventron Instruments Corporation, Paramount, CA. 90701
13. Erweka Model TA3, Chemical and Pharmaceutical Industry Company, New York, N.Y. 10013
14. Hanson Research Corporation, Northridge, CA. 91324

used for agitation and were positioned 2.5 cm from the bottom of the flask and driven at 50 rpm by the multiple-drive unit. The dissolution medium from each flask was continuously filtered through a Millipore^{R} pre-filter (filter type AP) and circulated through a 1.0 mm pathlength flow cell of a spectrophotometer[15]. One tablet was placed in each flask and absorbance was measured at 272 nm at a set interval of two minutes. Absorbance values were recorded simultaneously on a recorder[16]. Dissolution rates were studied at 50 rpm for 60 minutes and then the stirring speed was increased to 150 rpm for about 15-20 minutes to ensure 100% dissolution of hydrochlorothiazide; this value gives an idea of the content uniformity of the batch also. The % hydrochlorothiazide dissolved at a given time was calculated from a standard curve for hydrochlorothiazide at 272 nm.

Aging Study

Tablets were stored for six months at 25°C in screw-capped amber-colored bottles and dissolution tests were repeated on those tablets compressed at the higher hardness level (~ 13 kg).

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15. Model 25, Beckman Instruments, Inc., Silver Spring, MD. 20904
16. Model 24-25 ACC, Beckman Instruments, Inc., Silver Spring, MD. 20904

RESULTS AND DISCUSSION

Variation in the Data

In order to provide an indication of the variability 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 compression force range reported is shown in Table IV. In general there are very few differences in the variability of tablet weight and hardness between formulations. However with lactose as filler, soy polysaccharide at the 5% and 10% levels appears to give less variability in the disintegration times than either starch or cross-linked CMC. On the other hand, with dicalcium phosphate dihydrate as filler, cross linked CMC gives much lower variability in disintegration times than either starch or soy polysaccharide at any level.

Compressibility

The effect of disintegrant type and concentration on the hardness of tablets can be seen in Figures 1 and 2. The presence of soy polysaccharide does not seem to have any significant effect on tablet hardness. The tablet softening effect exhibited by the 8% corn starch in the lactose formulation was not observed either in any soy polysaccharide formulation, regardless of concentration, or in the 2% cross-linked CMC formulation. Corn starch did not have as great a softening

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	100-600	0.30	5.50	4.80
2	200-920	0.39	7.06	4.76
3	100-500	0.28	5.64	7.18
4	100-650	0.34	5.18	4.72
5	100-500	0.28	3.03	2.45
6	150-800	0.31	3.16	2.56
Dicalcium Phosphate				
7	250-1200	0.50	4.78	2.00
8	300-100	0.44	3.54	18.40
9	250-900	0.34	3.02	19.02
10	250-1200	0.31	3.24	7.70
11	250-900	0.44	3.44	7.50
12	150-1000	0.43	3.70	10.10

*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.

effect on dicalcium phosphate tablets as it did on the lactose tablets. This is no doubt due to the differences in the mechanisms by which these two materials deform under pressure. It is important to note, however, that soy polysaccharide did not soften tablets even when employed at higher use levels.

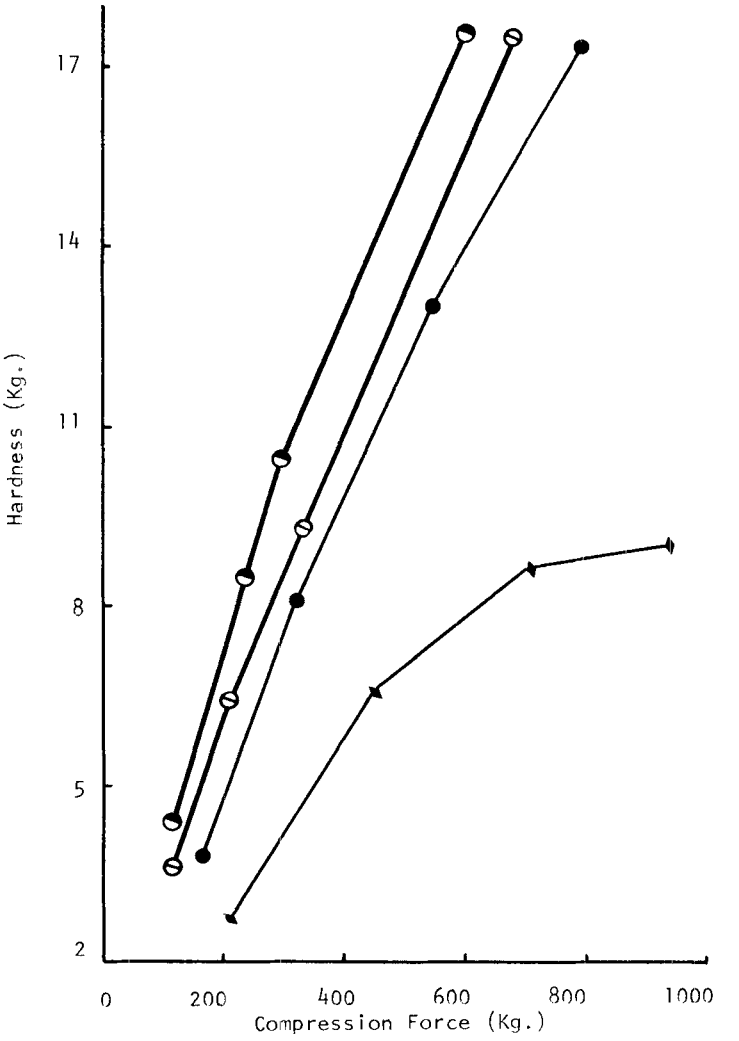

FIGURE 1
The Effect of Disintegrant Type and Concentration on the Hardness of Lactose Tablets Made at Various Compression Forces. Key: ⊖, 2% Cross-linked CMC, 2% Soy Polysaccharide; ♦, 8% Corn starch; ◒, 1% Soy Polysaccharide, 5% Soy Polysaccharide; and ●, 10% Soy Polysaccharide.

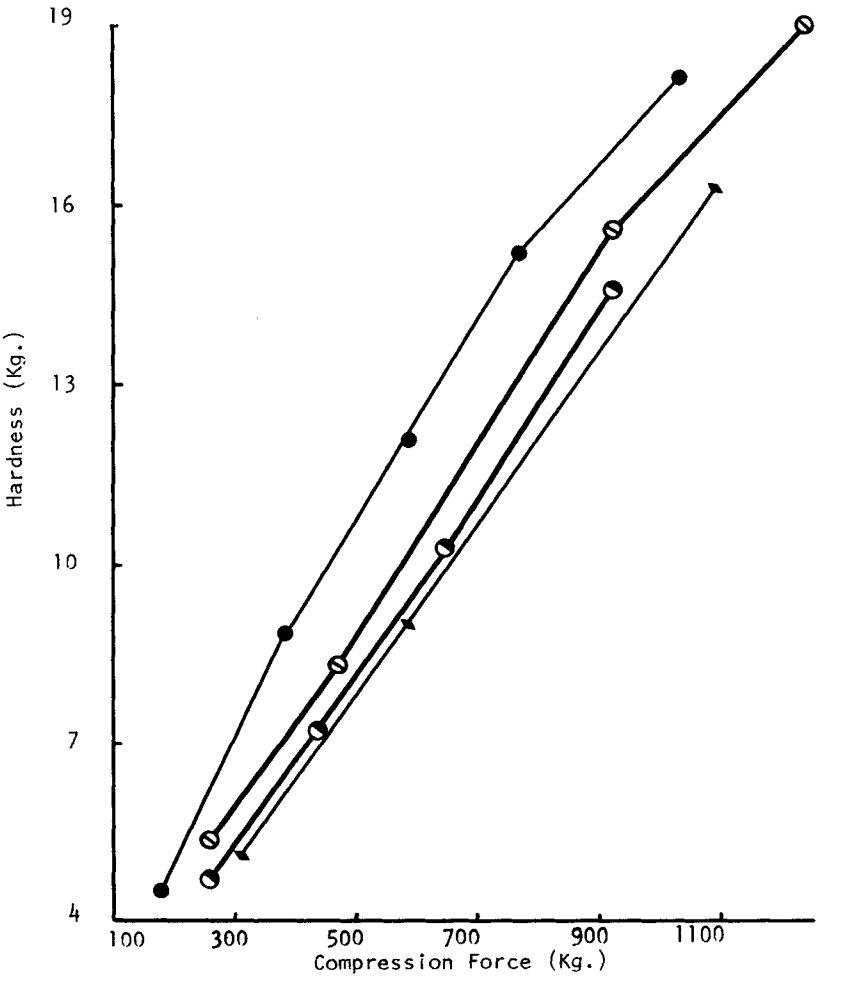

FIGURE 2
The Effect of Disintegrant Type and Concentration on the Hardness of Dicalcium Phosphate Tablets Made at Various Compression Forces. Key: Same as in Figure 1.

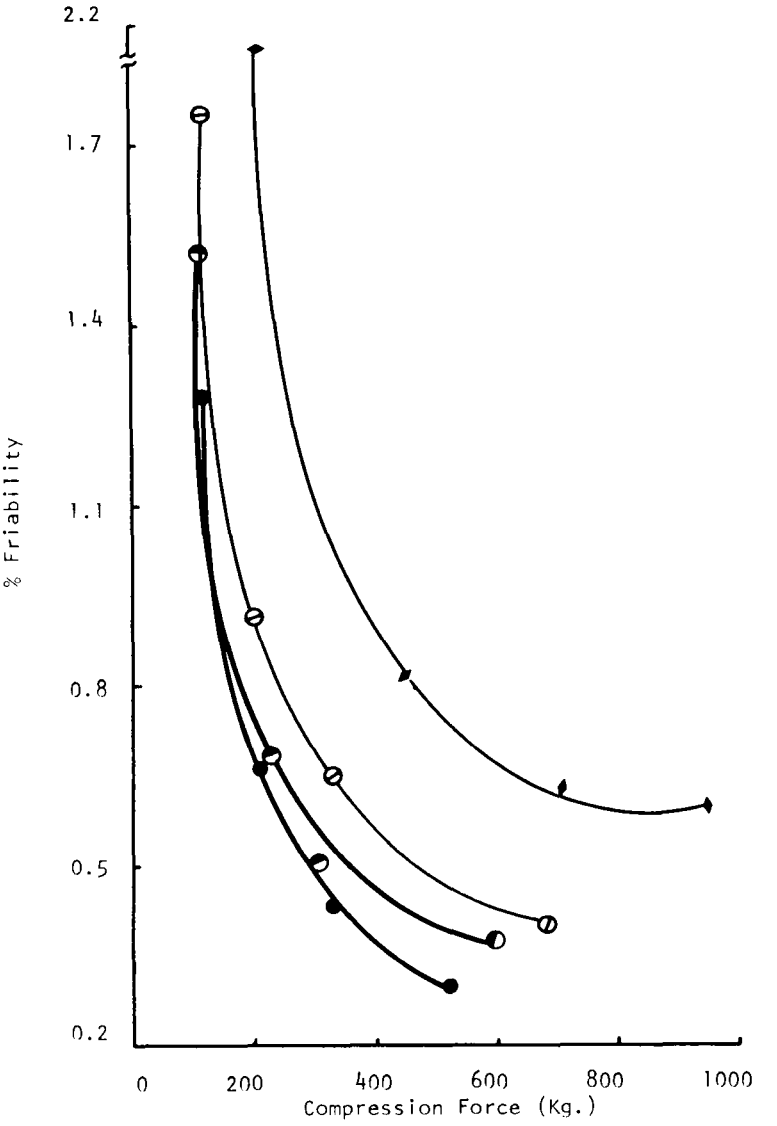

FIGURE 3
The Effect of Disintegrant Type and Concentration on the Friability of Lactose Tablets Made at Various Compression Forces. Key: ♦, 8% starch; ⊖, 2% Cross-linked CMC, ◓, 1% and 2% Soy Polysaccharide, ●, 5% and 10% Soy Polysaccharide.

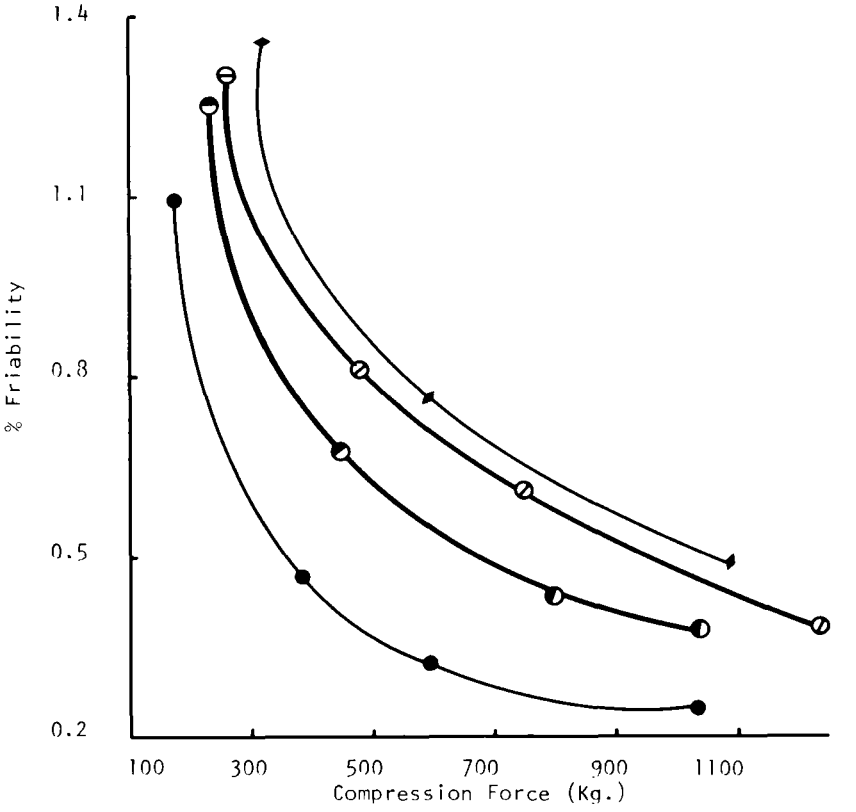

FIGURE 4
The Effect of Disintegrant Type and Concentration on the Friability of Dicalcium Phosphate Tablets Made at Various Compression Forces. Key: ♦, 8% Corn Starch; ⊖, 2% Cross-linked CMC, 1% Soy Polysaccharide; ◓, 2% and 5% Soy Polysaccharide; ●, 10% Soy Polysaccharide.

Friability

The effect of disintegrant type and concentration on tablet friability is shown in Figures 3 and 4. The level of soy polysaccharide had little effect on friability of lactose tablets. Tablets made from all other

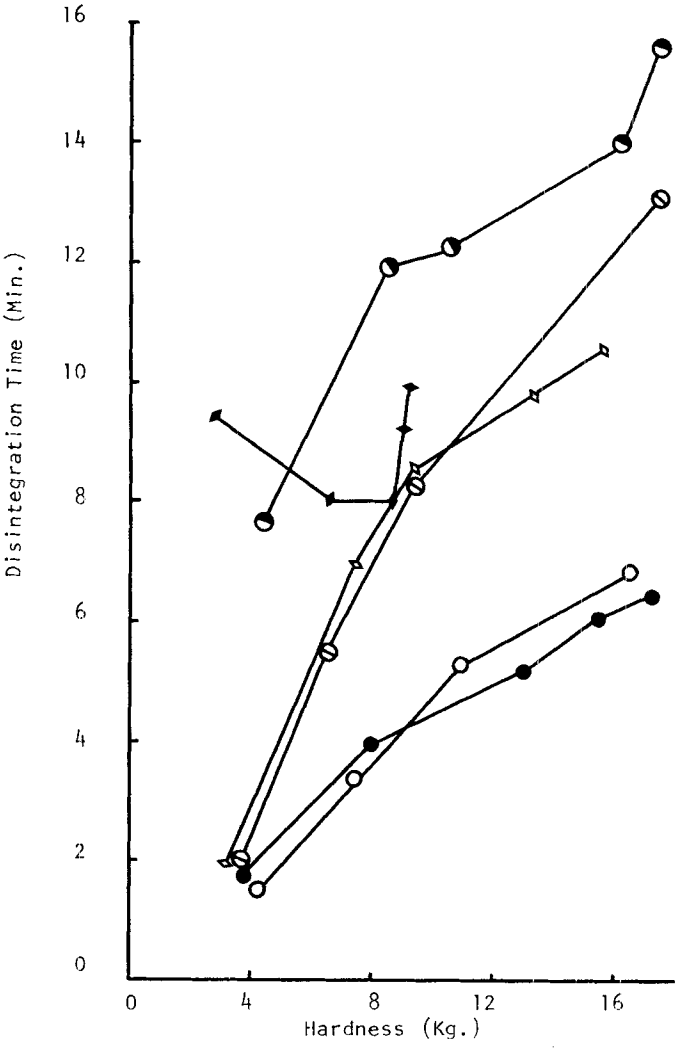

FIGURE 5
The Effect of Disintegrant Type and Concentration on the Disintegration Time of Lactose Tablets at Various Hardness Levels. Key: ⊖ , 2% Cross-linked CMC: ◓ , 1% Soy Polysaccharide; ◊ , 2% Soy Polysaccharide; ○ , 5% Soy Polysaccharide; ● , 10% Soy Polysaccharide; ♦ , 8% Corn Starch.

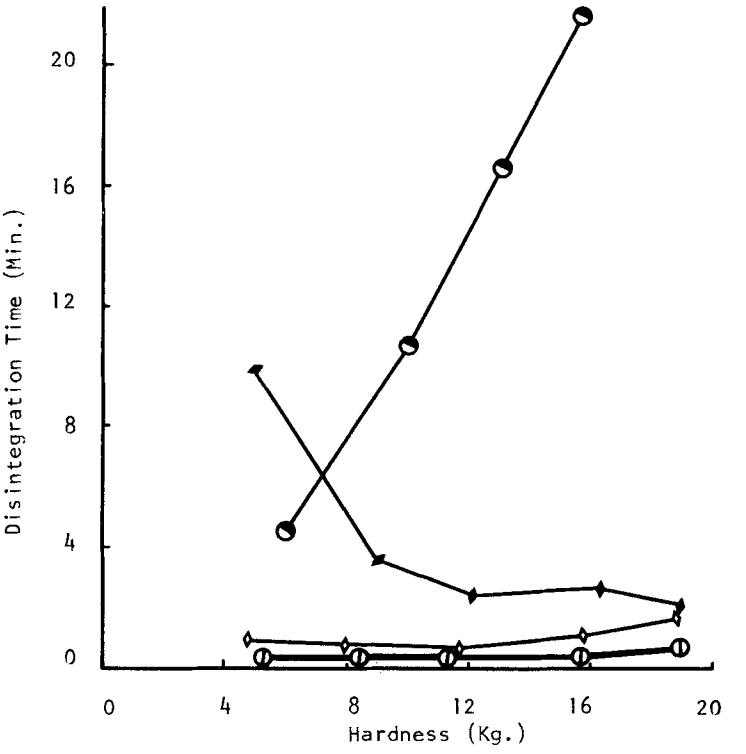

FIGURE 6
The Effect of Disintegrant Type and Concentration on the Disintegration Time of Dicalcium Phosphate Tablets at Various Hardness Levels. Key: ◓, 1% Soy Polysaccharide; ♦, 8% Corn Starch; ◊, 2% Soy Polysaccharide; ⊖, 2% Cross-linked CMC, 5% Soy Polysaccharide and 10% Soy Polysaccharide.

formulations were considerably less friable than those containing starch. Friability of dicalcium phosphate tablets seemed to decrease slightly with increasing concentration of soy polysaccharide indicating that soy polysaccharide may have some dry bonding properties at higher use levels.

Disintegration Times

The effect of disintegrant type and concentration on the disintegration time of tablets made at various compression forces are shown in Figures 5 and 6. The tablets containing 1% soy polysaccharide gave much higher disintegration times than either of the controls. However, at the 2% level, the disintegration times were equivalent to or lower than the controls and no significant differences in disintegration times were noted between the 5% and 10% levels of soy polysaccharide in either the lactose or the dicalcium phosphate tablets. The lactose tablets containing 8% starch gave a somewhat classical hardness-disintegration time profile - initially decreasing to a minimum and then increasing as tablet hardness was increased. Lactose tablets containing either soy polysaccharide or cross-linked CMC exhibited a continuing increase in disintegration time as hardness was increased which is typical of tablets with a soluble filler in which disintegration is dependent primarily on filler dissolution.

All levels of soy polysaccharide and the 2% cross-linked CMC gave extremely low disintegration times in the dicalcium phosphate tablets and were more effective than the 8% corn starch. Unlike starch, tablet hardness had little effect on disintegration times.

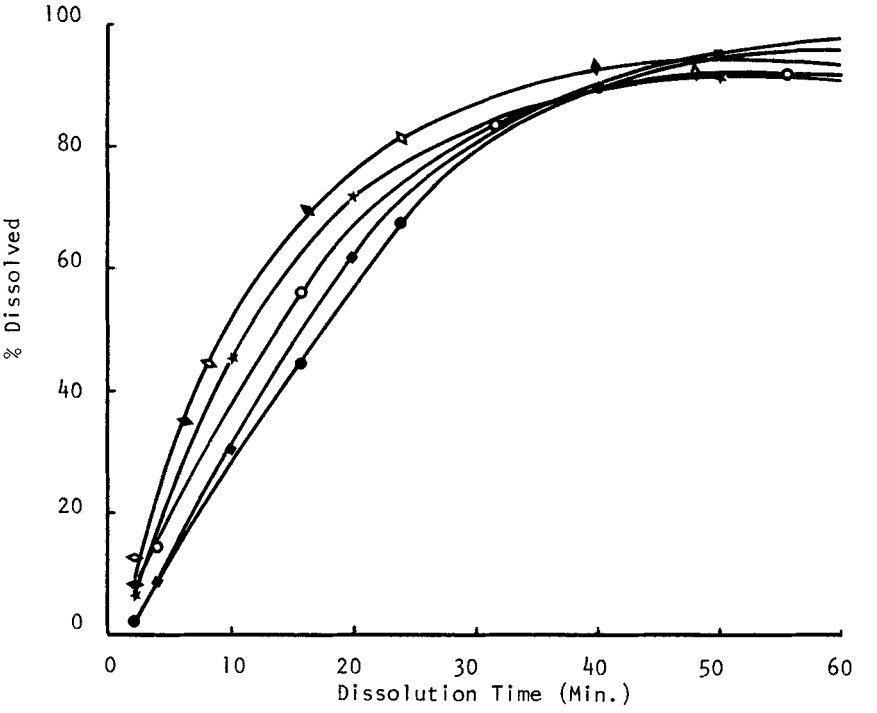

FIGURE 7
The Effect of the Disintegrant Type and Concentration and Tablet Hardness on the Dissolution of Hydrochlorothiazide from Tablets Made By Direct Compression.
Key:

◊ 5% Soy Polysaccharide; Tablet Hardness = 6 kg.
♦ 5% Soy Polysaccharide; Tablet Hardness = 13 kg.
* 2% Cross-linked CMC; Tablet Hardness = 6 kg.
■ 2% Cross-linked CMC; Tablet Hardness = 13 kg.
O 2% Soy Polysaccharide; Tablet Hardness = 6 kg.
● 2% Soy Polysaccharide; Tablet Hardness = 13 kg.

Dissolution Rates

The effect of disintegrant type and concentration on the dissolution of hydrochlorothiazide from tablets compressed at two hardness levels is shown in Figure 7.

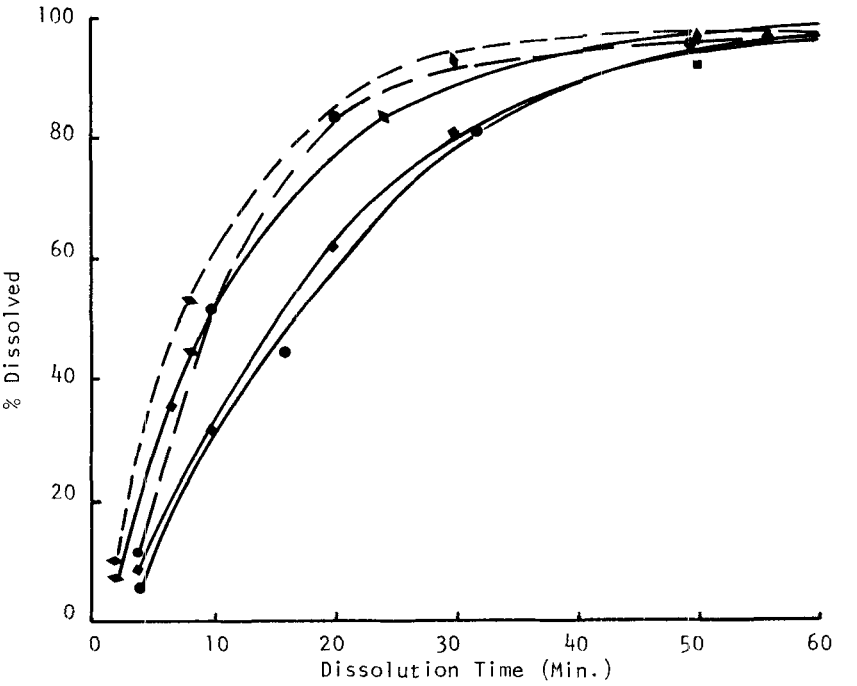

FIGURE 8
The Effect of Aging on the Dissolution Profiles of Hydrochlorothiazide Tablets (Hardness=13 kg.) Made by Direct Compression.
Key:

♦ 5% Soy Polysaccharide
● 2% Soy Polysaccharide
▪ 2% Cross-linked CMC
—— Before Aging (Original)
– – – After Aging

Only a few points are shown for each curve for clarity reasons. The results paralled those seen in the disintegration data. Dissolution rates obtained with 5% soy polysaccharide were only slightly higher than those seen at the 2% level. Cross-linked CMC, at the

2% level, gave dissolution rates which were intermediate between those obtained with 2% and 5% soy polysaccharide. Tablet hardness had a very small effect on dissolution rates irrespective of formulation although the softer tablets containing the soy polysaccharide and cross-linked CMC did exhibit slightly faster dissolution profiles than did the harder tablets.

Effect of Aging on Dissolution Rates

The results obtained in the six month aging study are presented in Figure 8 and only a few points are shown for each curve. These results were somewhat surprising. The tablets made from the soy polysaccharide exhibited faster dissolution profiles after aging than they did originally. The reason for this is difficult to explain but it certainly indicates no loss in disintegrant properties of the soy polysaccharide. Dissolution rates with the cross-linked CMC did not change after aging.

SUMMARY

Soy polysaccharide appears to perform well as a tablet disintegrant in tablets made by direct compression and its effect closely parallels that of cross-linked CMC and is much superior to corn starch even when that substance is used at higher levels. Soy polysaccharide seems to reduce the friability of the tablets, especially at higher

use levels, and it does not adversely affect the dissolution rate of hydrochlorothiazide after aging the tablets for six months under ambient conditions.

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