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THE BINDING AND DISINTEGRANT PROPERTIES OF THE CORN STARCH FRACTIONS: AMYLOSE AND AMYLOPECTIN

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ABSTRACT

Corn Starch USP consists of the two glucose polymers, amylose and amylopectin, whose normal ratio is 27%:73%. This study was initiated to determine whether a variation in this ratio would have any benefit in pharmaceutical granulations. Starch pastes prepared by varying the amylose/amylopectin ratio were used to granulate a dicalcium phosphate system and the resulting tablet properties were evaluated.

Physical mixtures of the polymers and also special hybrid polymer mixtures were studied. Binding and disintegrant properties of the starch fractions do vary with the amylose/ amylopectin ratio and with the degree of starch hydrolysis during the heating (cooking) phase of starch paste preparation. The results of this study give

some indication as to the binding and disintegrant activity of starch and its fractions.

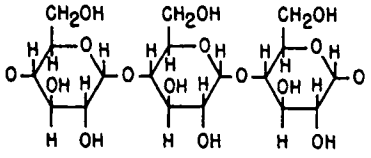
INTRODUCTION

Corn starch is commonly used throughout the pharmaceutical industry in dry powder form as a tablet disintegrant, and in paste form as a binder which facilitates granulation and imparts good compression properties to powder blends.

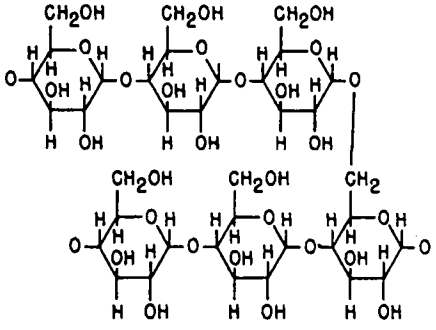
Natural starch consists of two different polymers of glucose, amylose and amylopectin (Figure 1). The amylose molecule is a long, linear chain of anhydroglucose units having a low molecular weight, a high intrinsic viscosity, and a low solution stability in water at ordinary concentrations. The amylopectin molecule is a larger, complex branched chain of tree-like structures with many branches, with a high molecular weight, a fairly high solution stability, and about the same intrinsic viscosity[1].

The relative content of amylose and amylopectin in natural starches varies, depending on the source of the starch. Tapioca starch contains from 17%-21% amylose; potato starch contains from 22%-25%; and corn starch from 22%-30%[1].

Bulletin No. 214, National Starch and Chemical Corporation (2) states the following:



(A)



(B)

Figure 1

(A) Segment of an amylose molecule

(B) Segment of an amylopectin molecule

Current thinking on the architecture of the starch granule indicates that the granule is made up of radially arranged crystallites which are largely amylopectin, with the linear amylose fraction occurring throughout the granule in a disorganized fashion. The associative forces holding the starch crystallites together can be overcome

if sufficient energy is applied. Ordinary heating at 190° to 210°F in water is sufficient to cook ordinary starch.

In theory, the amylose fraction should give starch its binding property because it is a high quality film former; the amylopectin lends viscosity to a starch paste system; it is the thickening agent. Amylopectin alone does not gel, but when the solution is dried it forms a film of poor quality.

The major starch corporations have developed hybrid strains of corn which have varying ratios of the two polymers. This study was designed to determine if better control could be maintained over specific tablet properties such as hardness or disintegration time by adjusting the amylose/amylopectin ratio of the starch paste used for granulating. It would be of interest to the formulator to determine whether these different starch fractions have any advantage over Corn Starch USP in this capacity.

EXPERIMENTAL

Materials

Dicalcium Phosphate Dihydrate USP, Milled[1] and Magnesium Stearate USP[2] were used in all tablet formulations. The starches included Corn Starch, USP[3], Amylopectin[4], Amylose/ Amylopectin 55:45[5], and Amylose/Amylopectin 70:30[6].

Tablet Preparation

Various ratios of amylose and amylopectin were prepared by combining 70:30 mixture[7] with 100% amylopectin in the proper proportions. The ratios studied are shown in Table I. Two controls were also included: one with no starch fraction and one with Corn Starch USP.

The general tablet formula was held constant throughout the study and is as follows:

	Per Tablet
Dibasic Calcium Phosphate Dihydrate USP, Milled	478.15 mg
Corn Starch*	21.85 mg
Magnesium Stearate USP Impalpable Powder	1.25 mg
Tablet Weight	**501.25 mg**

* Added as 15% paste.

Batch sizes of 1 kg were manufactured in a small planetary mixer.[8] The quantity of dicalcium phosphate was held constant at 956.3 g per batch and the quantity of each starch mixture was held constant at 48.5 g or 4.85% of tablet weight. The quantity of water used for the starch paste preparation was also held constant at 275 ml to produce a 15% starch paste. In the one case where no starch was used, the water still remained constant.

TABLE I

Amylose/Amylopectin Ratios Tested

Ratio Amylose/Amylopectin	70:30 Mixture	100% Amylopectin
0/0	0	0
0/100	0	48.5 g.
20/80	13.86 g.	34.64 g.
25/75	17.32 g.	31.18 g.
30/70	20.79 g.	27.71 g.
50/50	34.64 g.	13.86 g.
70/30	48.5 g.	0
Control	Corn Starch USP[a]	

[a] A natural occurring product commercially considered to contain 27% amylose.

After drying, sizing, and lubrication steps, tablets were compressed at a weight of 500 mg on a Hydraulic Press[9] at 2000 lbs. pressure. Punches were 0.9525 cm in diameter (12/32 inch) with a round, flat beveled edge shape.

Testing Procedures

Sieve analyses were carried out on the granulations using a nest of sieves and an electromagnetic sieving machine.[10] Compressibility factor was calculated by the standard formula:

$$\% \text{ Compressibility} = \frac{P - L}{P} \cdot 100 \qquad \text{(Eq. 1)}$$

where P = packed density and
L = loose density.

Densities were measured using a graduated cylinder and a motorized tapping device[11] set to operate for 2000 cycles. The angle of repose was measured for each lubricated granulation using the method of Nelson, (3) where the repose angle ϕ is defined by

$$\phi = \tan^{-1}\left[\frac{h}{r}\right] \qquad \text{(Eq. 2)}$$

in which h is the height and r is the radius of the base of the cone formed by the powder[12]. The flow rate of the granulations was determined by measurement of the time for 60 g of material to flow through a standard aluminum funnel.

Tablet properties measured included individual weights determined on a semi-microanalytical balance[13], individual thickness measurements made on a dial comparator[14], and breaking strength measurements determined on a motorized tester[15]. The disintegration time of six tablets was measured by the method described in USP XVIII.

Pore volume was also determined by using a Mercury Intrusion Porosimeter[16] and from these measurements the mean pore diameter was calculated as described previously. (4)

RESULTS AND DISCUSSION

The first step in the process was the preparation of the starch pastes. Those starch pastes prepared from the polymer mixtures

produced opaque, viscous liquids when heated, rather than the expected firm gels.

During the granulating step with the dicalcium phosphate, all of the amylose/amylopectin mixtures formed a fine granule within five minutes; these fine granules became only slightly more coarse with continued mixing. No distinct differences in granulating properties were observed during processing. This is reflected in Table 2 which lists the physical properties of the granulations.

TABLE 2

PROCESSING PROPERTIES OF AMYLOSE/AMYLOPECTIN GRANULATIONS

Property	Amylose/Amylopectin Ratio 0/0*	0/100	20/80	25/75	30/70	50/50	70/30	70/30[a]	Starch Control[b]
Density (g./ml.)									
Bulk	0.790	0.640	0.670	0.750	0.730	0.780	0.780	0.700	0.660
Tapped	1.039	0.761	0.817	0.903	0.858	0.939	0.987	0.886	0.835
Compression Ratio (%)	23.9	15.9	17.9	16.9	14.9	16.9	20.9	20.9	21.0
Flow Rate (seconds)	1.4	1.4	1.4	1.4	1.4	1.2	2.0	1.6	2.0
Repose Angle	48°40'	38°6'	36°42'	36°42'	35°13'	33°41'	36°42'	36°42'	38°6'
Sieve Analysis (% retained):									
On # 16	0	2	1	1	0	0	0	0	0
30	21.5	65.0	51.0	37.0	41.0	21.5	5.5	8	5
50	33.5	21.5	31.0	49.0	49.0	32.5	14.0	16.5	13.5
100	15.0	5.5	11.0	13.0	8.0	25.5	14.0	18.5	21.0
200	12.0	2.0	3.0	2.0	1.0	14.0	21.0	27.0	41.5
325	10.0	1.5	1.0	1.0	0.5	2.0	8.5	15.0	10.5
Base	8.0	2.5	2.0	1.0	0.5	4.5	37.0	15.0	8.5

* Dicalcium Phosphate Control.

[a] Held at 99°C for ten minutes.

[b] Corn Starch USP.

The dicalcium phosphate control, when granulated with plain water, however, produced a coarse granule within five minutes of mixing. After 10 minutes there were ½" to 3/4" diameter balls which were slightly overwet.

This is also reflected in Table 2 where the dicalcium phosphate control yielded a granulation with a higher density. Other differences are reflected in the compression ratio (23.9%) and the angle of repose ($48^{o}40'$) which indicate that this granulation should have poorer flow characteristics than the others.

The experiment with the 70:30 mixture was repeated and the paste was held at $99^{o}C$ for 10 minutes to improve its gel characteristics, but no obvious change occurred in the paste.

The properties of the resulting tablets are shown in Table 3. In general, the tablet hardness decreases as the level of amylopectin decreases; this was not the expected direction. Amylose was expected to provide the major binding power, but based on these results, the binding appears to be predominately due to the amylopectin.

The disintegration time also decreases as the amylopectin level decreases. Here, again, tablets with more amylopectin exhibit better binding, but the amylose appears to be acting as a disintegrant, and a rather efficient one, even in its intragranular location.

TABLE 3

TABLETTING PROPERTIES OF AMYLOSE/AMYLOPECTIN GRANULATIONS

Property	Amylose/Amylopectin Ratio								
	0/0*	0/100	20/80	25/75	30/70	50/50	70/30	70/30[b]	Starch Control[c]
Weight (mg)	499.7	499.6	499.3	505.2	511.3	507.3	500.3	514.7	497.0
Thickness (mm)	4.16	4.21	4.20	4.25	4.28	4.28	4.27	4.40	4.25
Range	4.11-4.24	4.11-4.29	4.10-4.30	4.14-4.39	4.17-4.42	4.16-4.41	4.19-4.43	4.33-4.52	4.19-4.31
Hardness (kg)	6.8	12.9	10.4	8.1	9.0	7.9	7.0	7.8	8.1
Range	5.3-7.9	11.9-13.8	9.2-12.2	7.7-8.6	8.3-9.7	7.1-8.6	6.4-7.3	7.0-8.8	7.4-9.3
Disintegration Time (min.)[a]	>4 hr	210	128.5	62.5	40.5	1.2	0.25	0.1	0.75
Range	-	-	121.6-135.5	59.2-65.3	27.6-50.3	1.0-1.25	-	-	-
Pore Volume (cc/g)	0.1444	0.1389	0.1379	0.1411	0.1416	0.1436	0.1547	0.1488	0.1605
Mean Pore Diameter (μm)	0.2911	0.3844	0.3722	0.3971	0.3941	0.3661	0.3746	0.3539	0.4395

[a] USP water at 37°C with discs.

[b] Held at 99°C for ten minutes.

[c] Corn Starch USP.

• Dicalcium Phosphate Control.

The porosity, or void volume is not significantly affected by the ratio of amylose to amylopectin. There may be a very slight increase as the level of amylose is increased. The tablet with natural corn starch, however, does exhibit the highest value (0.1605 cc/g).

The mean pore diameter is not affected by the ratio of amylose to amylopectin, but the sample with no starch exhibits the lowest value (0.2911μ).

Because the amylose/amylopectin mixtures were physical mixes for these experiments, it is possible that the results may be anomalous. No degree of mixing can produce the intimate mixtures which are available in natural hybrids.

In Table 3, for example, the 25/75 amylose/amylopectin mixture contains about the same ratio as the natural product, Corn Starch, USP. Yet, the resulting tablets prepared from this mixture did not disintegrate as quickly as those prepared from Corn Starch, USP, although the hardness values are comparable.

Since several hybrids were available and to further substantiate these above indications, another series of experiments were conducted. Three major changes were made: (1) No physical mixtures were utilized to obtain the varying percentages of amylose/amylopectin, so that only four materials were tested (0%, 27%[17], 55%

and 70% amylose); (2) the percentage of starch in the tablet was reduced from 4.85 to 1.3% of the tablet composition (by weight) to determine the effects at a lower starch level; (3) the concentration of starch in the paste was reduced from 15% to 5% to maintain the water content at the previous level. This resulted in the following formula:

	Per Tablet
Dibasic Calcium Phosphate Dihydrate USP, Milled	493.48 mg
Starch*	6.52 mg
Magnesium Stearate USP	1.25 mg
Tablet Weight	**501.25 mg**

*Added as a 5% paste.

The four products were first slurried in cold water and used to granulate the dicalcium phosphate.

The same four products were then treated (heated) as one would normally produce starch paste and the resulting thin paste or thick liquid was used to granulate. The resulting tablet properties from these experiments are shown in Table 4.

For the tablets prepared from granulations with the four starch product slurries, there is no apparent change in tablet

TABLE 4

TABLET PROPERTIES

	Amylose/Amylopectin Ratio							
	Slurries				Pastes			
	0/100	27/73[a]	55/45	70/30	0/100	27/73[a]	55/45	70/30
Tablet Weight (mg)	499	496	495	494	498	500	498	498
Tablet Thickness (mm)	4.20	4.18	4.18	4.21	4.21	4.28	4.23	4.22
Tablet Hardness (kg)	7.24	6.94	7.54	7.16	8.42	8.04	7.36	6.98
Disintegration Time (min.)	0.17	0.15	0.19	0.19	32.37	2.41	0.18	0.27

[a] Corn Starch USP.

hardness or in tablet disintegration time which is rapid in all cases. None of the starch fraction has been tied up as a binder and all is free to act as disintegrant. For comparison the control tablet in the previous experiments exhibited a disintegration time greater than four hours when only water was used.

For the tablets prepared from granulations with the starch suspensions which were heated (cooked) there is a slight trend to a decrease in hardness as the amylose is decreased or an increase in hardness as amylopectin increases (see Figure 2).

There is a definite change in the disintegration characteristics with these starch pastes. The higher amylose content products yield disintegration times as fast as the slurried products. As the

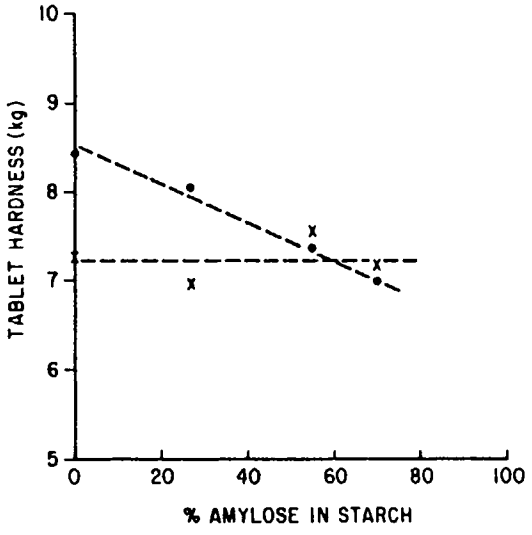


Figure 2

Plot of tablet hardness as a function of the percent amylose in the starch.

Key: X, starch slurry; 0, starch paste

amylose content is reduced, however, the disintegration time increases (see Figure 3).

This comparison indicates, however, that it is not only the lack of amylose that delays disintegration, but the fact that the amylopectin (or at least part of it) is now tied up as the binder. This supports the Remington statement (5) that "starch pastes which are useful as binding agents will generally not be effective as disintegrating agents."

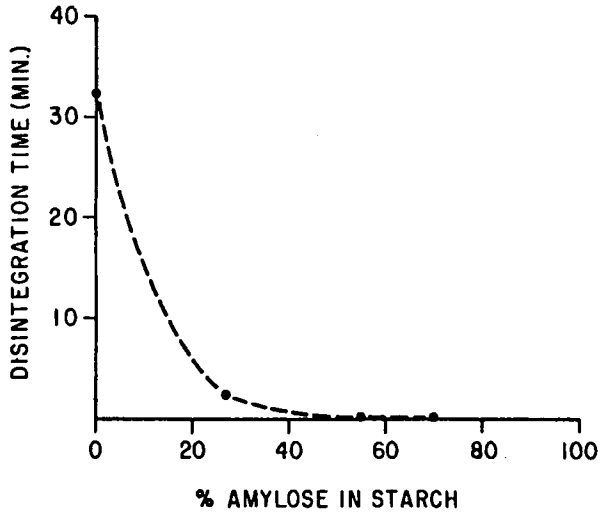


Figure 3

Plot of disintegration time as a function of the percent amylose in the starch paste

It is interesting to note that for the 70% amylose product the same tablet properties are obtained whether the starch fraction is 4.85% (Table 3) or 1.3% (Table 4) of the tablet; and at the 1.3% level the same results are obtained whether the starch is cooked or simply slurried.

The level of amylopectin apparently must approach 5% of tablet weight to get the significant increase in tablet hardness indicated by the 12.9 kg value in Table 3.

This information should be useful to the formulator since very little has been written about the mechanism of starch as a binder

in granulations for tabletting (6, 7). More has been written about its action as a disintegrant than as a binder even though the starch may be included as an intergranular component. (8-21)

Although amylose is the film and gel former and is useful in many situations in that capacity (e.g. food industry), it is apparently not the starch component which imparts binding capacity in pharmaceutical formulations.

Although it is not the primary film former, the branched molecules of amylopectin contribute the gummy or cohesive and tacky properties (22) and thus provide the binding capacity.

The results of these experiments are in agreement with the findings of Manudhane, et al (23) where amylose and amylopectin were added as disintegrants in the dry state. They concluded that amylose was the effective component of starch in terms of its disintegrant effect in these direct compression studies.

Amylose has also been investigated as a dry binder for direct compression by Kwan and Milosovich (24) but obviously does not act as a film former under these conditions. In the form used it functioned as the filler, lubricant and effective disintegrant.

Amylopectin also seems to be an extremely effective disintegrant in this insoluble system if it is not tied up as a binder. The control tablet in Table 3 (no starch fraction) does not disin-

tegrate in four hours while the tablet made with a 5% slurry of 100% amylopectin (where amylopectin represents only 1.3% of the tablet weight) disintegrates in less than one minute. Since the quantity of starch usually recommended as a disintegrant is 5-10% of tablet weight, this is even more surprising.

Increasing the level of 100% amylopectin from 1.3% of the tablet to 4.6% of the tablet does increase the tablet hardness from 8.4 kg to 12.9 kg (see Tables 3 and 4) but because the disintegration time also increases, the formulator would have to counteract this effect with additional disintegrant.

For Corn Starch USP prepared as a paste, tablet hardness is the same whether the level of starch is 4.85 or 1.3% of tablet weight. Disintegration time is decreased slightly by this increase in starch concentration.

At the 1.3% level of Corn Starch USP the hardness and disintegration time are both decreased slightly when the starch is added as a slurry rather than a paste since the amylopectin is not tied up in its binding capacity.

CONCLUSIONS

1. The binding power of starch appears to be provided by the amylopectin fraction; it must be heated to provide the binding power.

2. The amylose fraction of starch seems to be an extremely effective disintegrant.
3. If not tied up as a binder, amylopectin also functions as a very effective disintegrant in this system.
4. The location of starch or its fractions and the cooked or hydrolized state of the starch can dramatically influence tablet properties.
5. The individual starch components or the hybrid mixtures might have application for the formulator if there are special problems relating to tablet hardness, but in general Corn Starch USP provides adequate efficiency and the best properties of both amylose and amylopectin.

ACKNOWLEDGEMENT

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FOOTNOTES

1 Stauffer Chemical Company, Westport, Ct. 06880

2 Mallinechrodt Chemical Works, St. Louis, Mo. 63147

3 A. E. Staley Manufacturing Company, Decatur, Ill.

4 Waxy Maize #1, A. E. Staley Mfg. Co., Decatur, Ill.

5 Amylon or Hylon, National Starch and Chemical Corp., N.Y., N.Y.

6 Amylon VII or Hylon VII, National Starch and Chemical Corp., N.Y., N.Y.

7 70:30 was the most concentrated amylose mixture available commercially.

8 Hobart Manufacturing Co., Troy, Ohio

9 Carver Laboratory Press, Fred S. Carver, Inc., Summit, N.J.

10 Geoscience Inst. Corp., Mt. Vernon, New York

11 Model JEL-ST2, Numec Inst. & Control Corp., Monroeville, Pa.

12 The value of r in this set of experiments was 2.55 cm.

13 Model H20T, Mettler Inst. Corp., Princeton, N.J.

14 Model 282M, B. C. Ames Co., Waltham, Mass.

15 Heberlein Hardness Tester, Cherry Burrell, Park Ridge, Ill.

16 Aminco, American Instrument Co., Bethesda, Md.

17 Corn Starch USP

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