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Intragranular Starch: Comparison of Starch USP and Modified Cornstarch

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Abstract □ Incorporation of starch USP or a modified cornstarch within the granules of several drug formulations was investigated. In general, the formulation containing the modified starch exhibited improved processing characteristics as well as improved tablet properties. A comparison of a granulated and a direct compression formulation of the same ingredients indicated that granulation of an active ingredient is not necessarily detrimental to its (pharmaceutical) availability.

Keyphrases □ Starch—comparison of starch USP and modified cornstarch □ Excipients—comparison of starch USP and modified cornstarch □ Disintegrants—comparison of starch USP and modified cornstarch □ Binding agents—comparison of starch USP and modified cornstarch

Direct compression of pharmaceutical tablets has become an integral part of pharmacy in recent years, and several components have been designed and marketed especially for use in such systems. For example, Manudhane *et al.* (1) discussed the use of a modified cornstarch[1] in direct compression formulas. Starch USP is a common excipient in solid dosage forms, both as a binder and as a disintegrant (2).

When cornstarch, in either of these two forms, is added to a formulation in the dry state (prior to the lubricating step), its use is that of a disintegrant. When it is incorporated into the granule, either as a paste or dry (prior to granulation with some other agent), both the binding property and the disintegrant property may be operative. It is this dual property that is of interest in this study.

This work documents a comparison of starch USP and a modified cornstarch incorporated in the granules of several drug formulations. Their processing properties and their relative pharmaceutical availabilities, as indicated by dissolution measurements, were studied.

EXPERIMENTAL

Materials—Excipients used in preparing the tablets included starch USP, a modified cornstarch[1], microcrystalline cellulose[2], spray-dried lactose[3], and magnesium stearate USP. Active ingredients included acetaminophen[4], ascorbic acid[5], chlorothiazide[5], levodopa[6], methyldopa[5], and probenecid[5].

Tablet Preparation—The active ingredients selected were all at a dosage of 500 mg, and tablet composition was identical for all drugs. The excipients were maintained constant in the experimental plan, although the formulation may not have been ideal for any one of the drugs. Batch sizes remained constant at 1000 tablets.

Granulations of 500 g of each active ingredient and 60 g of either starch USP or the modified cornstarch with a 7.0% starch paste (65°) were processed in a planetary mixer[7]. In all cases, the starch paste was prepared with starch USP. The wet granulations were manually screened through a No. 6 screen and oven dried overnight at 45°. After dry milling[8], the granulations were blended[9]

[1] Sta Rx 1500 starch, A. E. Staley Manufacturing Co., Decatur, Ill.

[2] Avicel PH 101, FMC Corp., American Viscose Division, Newark, Del.
[3] Foremost-McKesson, Inc., San Francisco, Calif.
[4] S. B. Penick & Co., New York, N.Y.
[5] Merck & Co., Rahway, N.J.
[6] Monsanto Co., St. Louis, Mo.
[7] Kitchen Aid model K-45, Hobart Manufacturing Co., Troy, Ohio.
[8] Homoloid, 0.13-cm (0.050-in.) screen.
[9] Patterson Kelley V-blender.

Table I—Granulation Properties

Drug	A, Methyldopa		B, Acetaminophen		C, Ascorbic Acid		D, Chlorothiazide		E, Levodopa		F, Probenecid	
Starch	Modified	USP	Modified	USP	Modified	USP	Modified	USP	Modified	USP	Modified	USP
Loss on drying, %	10.2	10.0	0.8	1.0	1.4	1.7	1.0	1.4	1.0	1.4	0.6	1.4
Sieve analysis, % on screen												
No. 30	12.0	11.8	5.5	1.6	16.2	4.8	4.2	5.6	2.6	3.8	2.2	1.1
No. 50	32.8	37.2	36.2	24.7	37.2	23.3	23.9	10.4	23.7	8.8	15.9	10.7
No. 100	22.8	20.1	35.6	40.3	26.0	35.5	35.5	81.3	28.4	17.1	57.3	14.2
No. 200	15.7	16.4	22.6	32.8	13.5	29.5	30.3	2.7	23.5	27.7	21.5	59.5
No. 325	13.7	10.3	0.1	0.6	5.2	6.4	5.2	—	19.2	30.2	2.9	13.7
Base	3.0	4.2	—	—	1.8	0.5	0.8	—	2.7	12.5	0.1	0.8
Mean granule diameter, μm[a]	385	430	380	300	480	290	290	340	250	135	320	170
Density, g/ml												
Bulk	0.578	0.633	0.459	0.449	0.733	0.695	0.569	0.466	0.614	0.594	0.343	0.325
Tapped	0.770	0.879	0.695	0.736	0.991	1.007	0.769	0.790	0.787	0.848	0.528	0.551
Compressibility, %	24.94	27.99	33.46	38.99	37.92	30.98	26.01	41.01	21.98	29.95	35.04	41.02
Angle of repose	49°38′	53°55′	55°25′	55°25′	48°55′	51°27′	52°18′	58°44′	51°27′	53°08′	56°49′	58°44′
Flow, sec	4	14	14	17	5	16	7	49	8	26	59	68
Flow properties on rotary press	Good	Fair	Good	Poor	Good	Good	Good	No run	Good	Poor	No run	No run

[a] Obtained from graphs of the sieve analysis data.

with 130 g of microcrystalline cellulose and lubricated with 0.6% magnesium stearate.

Tablets were compressed on a rotary machine[10] operating at 20 rpm and equipped with only two sets of capsule-shaped punches, 0.71 × 1.82 cm (9/32 × 23/32 in.), stationed on opposite sides of the die table.

Testing Procedures—Sieve analyses were performed on samples of the milled granulations, using a nest of sieves and an electromagnetic sieving machine[11]. The compressibility factor was calculated using:

$$\text{percent compressibility} = \frac{P - L}{P} \times 100 \quad \text{(Eq. 1)}$$

where P is packed density, and L is loose density. Densities were measured using a graduated cylinder and a motorized tapping device[12] set to operate for 2000 cycles. Loss-on-drying moisture determinations were obtained with a moisture balance[13].

The angle of repose was measured for each lubricated mixture using the method of Nelson (3), where the repose angle ϕ is defined by:

$$\phi = \tan^{-1}\frac{h}{r} \quad \text{(Eq. 2)}$$

in which h is the height and r is the radius[14] of the base of the cone formed by the powder. Flow time was determined by the flow of 60 g of material through a stainless steel funnel with a 1.5-cm opening.

The tablet properties measured included 20 individual weights determined on a semimicro analytical balance[15], 20 individual thickness measurements made on a dial comparator[16], and breaking strength measurements determined on a motorized tester[17]. The disintegration time of six tablets was measured by the method described in USP XVIII.

Dissolution measurements were carried out by the method specified in USP XVIII with a 50-rpm rate of rotation. The dissolution medium was 0.1 N HCl unless noted otherwise.

RESULTS AND DISCUSSION

The various drugs were all treated in the same manner, and comparisons were made between the two formulations of each active ingredient, *i.e.*, one containing starch USP and one containing the modified starch, and not between active ingredients.

The physical properties of the granulations (Table I) showed some differences. In most cases, the formulation containing the modified starch appeared to yield a granulation with a slightly larger mean diameter, indicating more efficient granulation. Correspondingly, the granulations containing starch USP were generally more dense. There was very little difference in the moisture levels between the two granulations of a given drug.

The three factors of compressibility, angle of repose, and time of flow, which should give some indication of flow properties, generally predict that the granulations containing the modified starch will perform better. The lower the compressibility (4) and the lower the response angle (3), the better is the predicted flow.

This was shown to be true in every case where the material flowed sufficiently to produce tablets. With probenecid (Table I), neither granulation would flow well enough to compress a tablet on the rotary machine, even when operated manually. With ascorbic acid, the two formulations seemed to perform equally well. In the other four cases, the formulation containing the modified starch performed better on the rotary machine than its counterpart containing starch.

Although this evaluation is subjective in the case of methyldopa, it is less so with the others. Two of the formulations containing starch USP (Table I, B and E) required that the machine be turned slowly by hand to obtain tablets that did not cap at the take-off bar. The starch USP counterpart of a third (Table I, D) would not flow sufficiently to run at all.

The three formulations that would not flow sufficiently to fill the die cavity yielded repose angles >56° whereas all others were below 56°. Time of flow through a funnel also appeared to give correlation with nonflowability, since the same three formulations gave values of 49 sec or greater.

The physical properties of the resulting tablets (Table II) support this evaluation. The weight control, as indicated by the rela-

[10] Stokes model BB2, modified by removal of the front ejection cam so only one compressing station was used.
[11] Geoscience Instrument Corp., Mt. Vernon, N.Y.
[12] Model JEL-ST2, Numec Instrument & Control Corp., Monroeville, Pa.
[13] Central Scientific Co., Chicago, Ill.
[14] The value of r in this set of experiments was 2.55 cm.
[15] Model H20T, Mettler Instrument Corp., Princeton, N.J.
[16] Model 282M, B. C. Ames Co., Waltham, Mass.
[17] Heberlein hardness tester, Cherry Burrell, Park Ridge, Ill.

Table II—Tablet Properties

Drug	Methyldopa			Acetaminophen			Ascorbic Acid		Chlorothiazide		Levodopa		Probenecid	
Starch	Modified		USP	Modified		USP	Modified	USP	Modified	USP	Modified	USP	Modified	USP
Weight, mg	—[a]	—[b]	—	—[a]	—[b]	—	—	—	—	—	—	—	—	—
Mean[c]	722	710	710	547	550	547	673	711	678	—	681	697	—	—
RSD, %	0.57	2.28	2.38	1.56	1.76	3.55	1.09	1.91	0.97	—	1.13	23.14	—	—
Thickness, mm														
Mean	673	733	659	528	578	525	555	567	583	—	618	597	—	—
RSD, %	0.25	0.22	0.64	0.80	0.34	2.52	0.28	0.58	0.18	—	0.34	0.79	—	—
Hardness, kg														
Mean	13.02	6.32	8.3	6.15	3.45	2.12	12.62	12.72	11.08	—	8.90	8.88	—	—
RSD, %	7.37	15.02	11.69	13.16	16.30	17.83	8.86	10.45	7.96	—	9.56	14.66	—	—
Disintegration time, sec	58	37	58	100	40	148	142	65	35	—	72	62	—	—

[a] Tablets prepared under pressure equivalent to starch USP formulation. [b] Decreased hardness to match starch USP formulation. [c] Although the formulations are identical for all drugs studied, the mean tablet weights differ due to the density differences exhibited by the granulations. The tablet machine fill weight adjustment was not changed during the experiment.

Table III—Tablet Hardness at Equivalent Pressures

Drug	Hardness at Equivalent Pressures, kg	
	Tablet with Starch USP	Tablet with Modified Starch
Methyldopa	7.5	10.5
Acetaminophen	5.0	6.5
Ascorbic acid	5.0	6.5
Chlorothiazide	11.0	15.5
Levoaopa	5.0	8.0
Probenecid	9.5	13.0

tive standard deviation, was always higher for the granulation containing starch USP than for its modified starch counterpart. The other physical properties were adequate in all cases, with the exception of the hardness of the starch USP formulation of acetaminophen which could not be increased.

The ability to lessen the tendency for capping and splitting of the tablet, as mentioned previously, represents a significant advantage of the modified starch. This material apparently acts as a stronger internal binder than starch USP; but if too much binding power is contributed, disintegration and dissolution could be adversely affected. What is required is an internal binder that also has disintegrant properties[18].

The disintegration values (Table II) are all satisfactory, indicating that the additional binding capacity of the modified cornstarch is not detrimental. Moreover, the dissolution profiles show a difference between the two granulations when a comparison was available. As shown in Fig. 1, the release profile of the modified starch formula is consistently higher than that of the corresponding starch USP formula for the five drugs that did yield tablets.

These comparisons were made on tablets of approximately the same hardness values for a given drug. In general, the hardness value for the tablet containing starch USP was the maximum possible; *i.e.*, no additional compression pressure could be applied. For the drugs in Figs. 1*a* and 1*b*, harder tablets were made from the modified starch formulation (13 kg for methyldopa and 6 kg for acetaminophen); the release profiles, although lower with increased pressure, were still higher than those for the corresponding starch USP tablets. In one case (chlorothiazide), the tablet containing starch USP was prepared manually with a hydraulic press[19] to obtain a dissolution comparison.

To illustrate the differences in internal binding power at equivalent pressures, tablets were compressed from each mixture on the manual hydraulic press. The image in this case was a round, flat beveled edge tablet, 1.27 cm (0.5 in.) in diameter. Since the compressional force remained constant at 2000 lb, the comparisons in Table III show that the formulation containing the modified starch for any drug yielded a harder tablet than did the formulation containing starch USP.

As noted, each drug selected for the study was treated in the same manner with regard to formulation, granulation, *etc.* For the one soluble drug in the group, ascorbic acid, the mixture was overwet during granulation as expected. For this reason, the experiment was repeated with a 37% decrease in the quantity of the water used for the starch paste.

Although both formulations performed adequately on the rotary tablet press, the one containing the modified starch appeared superior again. However, no significant difference was observed in the two dissolution profiles (Fig. 2). The formulation containing the modified starch showed no difference from the previous experiment (Fig. 1*c*), and that containing starch USP improved to an equivalent level. This finding appears to indicate that the modified starch formulation is relatively insensitive to this change in processing but that the formulation containing starch USP can be adversely affected by overgranulation.

Direct Compression—The ingredients selected for the experi-

[18] According to the manufacturer's literature, Sta Rx 1500 starch differs from starch USP only from water solubility and particle-size standpoints. It contains a 20% maximum cold water-soluble fraction.

[19] Carver laboratory press, Fred S. Carver, Inc., Summit, N.J.

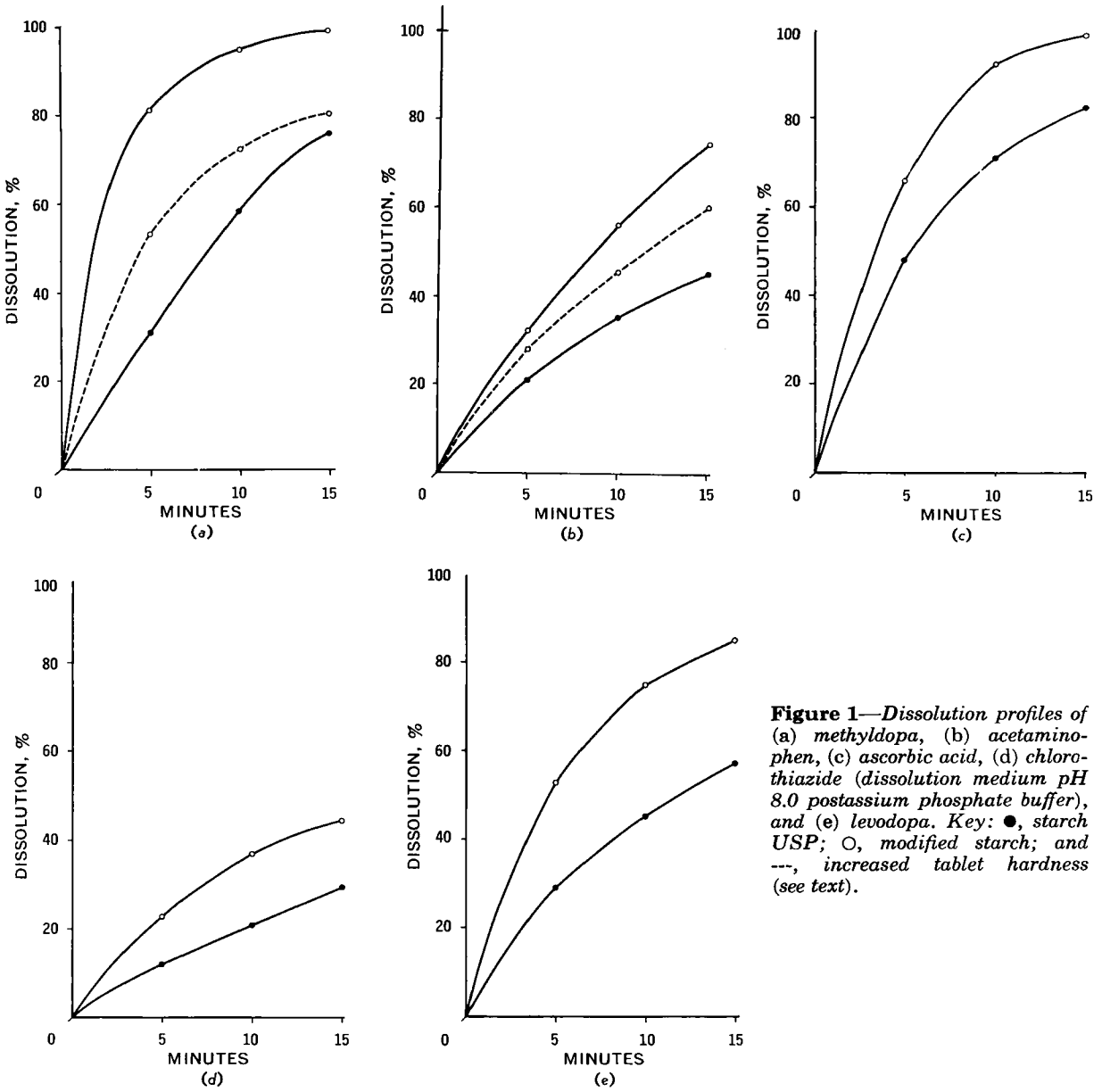

Figure 1—*Dissolution profiles of* (a) *methyldopa*, (b) *acetaminophen*, (c) *ascorbic acid*, (d) *chlorothiazide* (*dissolution medium pH 8.0 postassium phosphate buffer*), *and* (e) *levodopa. Key:* ●, *starch USP;* ○, *modified starch; and* ---, *increased tablet hardness* (*see text*).

mental formulation in this work, as mentioned previously, are marketed mainly as direct compression excipients. It has been proposed that a direct compression formulation is preferable for several reasons, one being that the drug is not bound by granulation and, therefore, its availability should be superior. This formulation was suitable for such an evaluation since the same ingredients could be used both ways. In addition, the percentage of the drug in the formulation was so high that the primary drawback of direct compression formulations, possible lack of content uniformity, was not a concern.

One soluble and one insoluble drug (ascorbic acid and chlorothiazide, respectively) were selected, and the identical formulations were prepared as in the previous section but this time by the appropriate simple mixing techniques in a twin-shell blender[9].

With respect to processing, these direct compression mixtures were inferior in all cases. None would flow well enough on the rotary tablet machine to fill the die even when the machine was operated manually. This result was not completely unexpected when so great a percentage of the formulation was the active ingredient which then controlled the physical properties. The experiment was continued, however, by compressing manually on the hydraulic press.

The dissolution profiles on the resulting tablets (Fig. 3) were not those expected. Although the formulation containing the modified starch for each drug did exhibit a faster release than the starch USP counterpart, each direct compression mixture gave a slower release than its granulated counterpart (Figs. 1*c* and 1*d*). The values for tablet hardness were held constant for the two experiments. Thus, it is not always true that the granulation of an active ingredient is detrimental to its availability.

Soluble Excipient—The effect of including a soluble component in the formulation under study was of interest. For this reason, the two chlorothiazide granulations were prepared as before but were then mixed with a directly compressible lactose rather than the microcrystalline cellulose.

Again, the processing characteristics of the formulation containing the modified starch were superior to the starch USP counterpart. While tablets of 15–16 kg in hardness were prepared from the former, the latter produced only tablets of 4–6 kg on the rotary tablet press.

For dissolution testing, tablets of equivalent hardnesses were prepared by hydraulic press as before. In the case of these lactose formulations (Fig. 4), the one containing starch USP gave a higher release rate than did its modified starch counterpart. The release of the starch USP–lactose formulation was essentially equivalent to that of the starch USP–microcrystalline cellulose formulation, and both were slower than the modified starch–microcrystalline cellulose formulation (Fig. 1*d*).

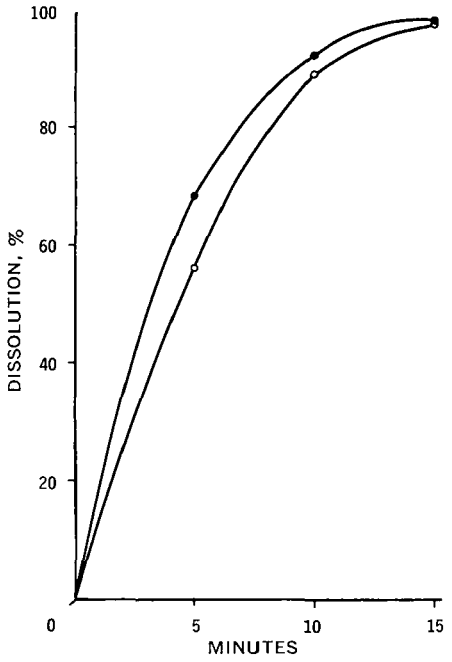

Figure 2—*Release profile for ascorbic acid tablets. Key:* ●, *starch USP; and* ○, *modified starch (see text).*

A possible explanation for the release of the modified starch–lactose formulation being lower than its microcrystalline cellulose counterpart may be that the wicking action of the microcrystalline cellulose allows the dissolution medium to act on the granules quickly, thus bringing into play the properties of the modified starch; in the other formulation, the activity of the solvent is divided between the dissolution of the lactose and the action on the granules. Thus, in the case of a specialized ingredient such as modified starch, it is important to consider the effect of each ingredient in the formulation on the specialized property one is trying to utilize.

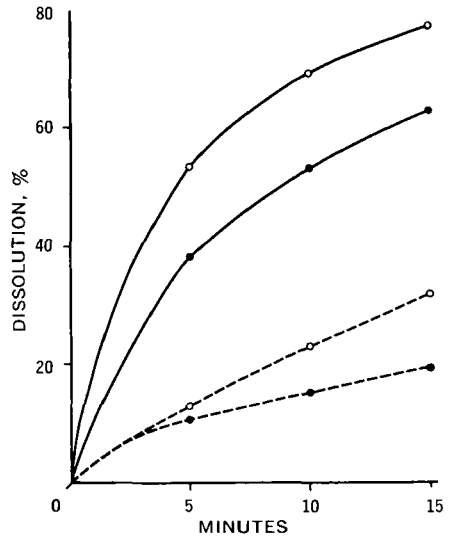

Figure 3—*Release profiles for direct compression formulations. Key:* ●, *starch USP;* ○, *modified starch;* ——; *ascorbic acid; and* ---, *chlorothiazide.*

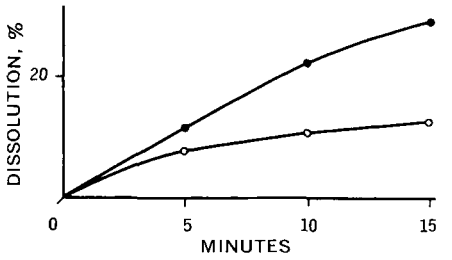

Figure 4—*Dissolution profiles for chlorothiazide formulations containing lactose. Key:* ●, *starch USP; and* ○, *modified starch.*

SUMMARY

Formulations of several drugs were prepared by incorporating either starch USP or a modified starch within the granule and subsequently adding microcrystalline cellulose. In general, for a given drug, the formulation containing the modified starch performed better during processing (flow and weight uniformity) and exhibited a slightly faster release rate (under the conditions of the test) than did its starch USP counterpart. The modified starch mixture produced a harder tablet than the starch USP mixture when compressional force was held constant. The data also indicate that the mixture containing modified starch may be less sensitive to changes in processing, *i.e.*, overgranulating.

When granulated and direct compression mixtures of the same ingredients were prepared, the granulated mixtures performed better with respect to both processing and dissolution testing. Substitution of a soluble component, lactose, for the microcrystalline cellulose did not significantly change the properties of the starch USP formulation but did lower the release rate of the modified starch formulation.

The results of this study show that although modified starch is marketed as a direct compression excipient, it may also be used in the granulation technique with possible improvement in processing properties and pharmaceutical availability as measured by dissolution.

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