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BINDING EFFICIENCIES OF STARCH N.F. AND MODIFIED STARCHES IN FORMULATIONS OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

Active and excipient ingredients were granulated in planetary and high intensity mixers. Compression properties of single and multi-drug formulations were evaluated with an instrumented single punch tablet press interfaced with a digital computer. Dissolution rates were measured using the USP Apparatus #I. Binding efficiency was found directly proportional to granule coarseness and in turn directly proportional to mean work of compression for equally well-lubricated granulations. Some differences were observed between the starches, in the manner of their incorporation (dry or as slurry) and between the single and multi-drug formulations. The formulations containing the pregelatinized starches allowed faster release of a poorly water soluble drug than did those containing starch, N.F.

INTRODUCTION

Starch NF, and pregelatinized starch NF are common excipients in solid dosage forms and may be incorporated both as binders and as disintegrants[1]. The binding efficiency of these materials has been studied extensively[2-8]. Schwartz et al[2], found that, in general, formulations containing pregelatinized starch exhibited better processing characteristics and produced superior tablet properties. In another effort, the same authors[3] studied the binding properties of the corn starch fractions amylose and amylopectin concluding that the binding properties of starch were due to amylopectin with the amylose fraction probably responsible for disintegrant properties. Their final conclusion was that corn starch, NF, (amylose/ amylopectin 27/73), possessed the best properties of both amylose and amylopectin. Other authors[6] have noted that binders with molecular weight >500 possess good binding efficiency.

This work documents a comparison of starch NF and pregelatinized starch NF incorporated in three ways by two mechanical processes into the granules containing a poorly water soluble drug(s).

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[1]National Starch Company

[2]Colorcon, Inc., West Point, Pennsylvania

[3]Merck and Company, Rahway, New Jersey

EXPERIMENTAL

Materials

Excipients in the tablets included starch NF, pregelatinized starch NF[1], pregelatinized starch NF (starch 1500-Colorcon)[2] hereinafter referred to as Starch 1500, mannitol USP, dibasic calcium phosphate USP, red and yellow ferric oxides NF, and magnesium stearate NF. Active ingredients included two drugs lisinopril and hydrochlorothiazide, both of poor water solubility[3].

Manufacturing Method

Three formulations were studied, viz. A - one containing lisinopril at a 20 mg per unit dose; B - one containing hydrochlorothiazide at a 12.5 mg per unit dose and C - a combination of the above two drugs in a 20/12.5 mg dose ratio respectively. Excipients were maintained constant in the experimental plan as were the tablet weights. Batch sizes were also constant at 9800 tablets. Pregelatinized starch NF was incorporated into formulations dry or as a cold-water slurry. Starch NF was added as a paste at 65°C. Granulation took place in planetary or high intensity mixers. The concentration of granulating starch, i.e., starch vs water was constant at 8.33% w/w. All granulations were fluid bed dried at 40°C for approximately one hour. After dry sizing all granulations were further mixed in a 'V' blender with starch N.F. and with 0.67% w/w magnesium stearate. Tablets were compressed on a single station instrumented press operated at speeds of 42 and 64 tablets

per minute. Tooling included either 5/16" round or a modified trapezoidal shaped punch.

Test Methods

Sieve analyses were performed on samples of dry sized granulation. A compressibility factor of each was calculated according to the following equation:

$$\% \text{ compressibility} = P-L/P \times 100$$

where P is packed density, and L is loose density. Moisture contents were determined by a loss on drying method with a moisture balance. Granulation surface area was calculated by dividing the percent retained on a given sieve by packed density, multiplying this result by a mesh factor for each sieve.[9]

Tablet strength, thickness, disintegration time and breaking strength were measured with conventional equipment. Tensile strength was measured with a Schleuniger[4] with special accessories. Dissolution measurements were made with the USP Apparatus I.

RESULTS AND DISCUSSION

Examination of the physical properties of the granulations (Table I) shows that those containing starch NF typically have the lowest apparent bulk density and in one case the largest surface area. This is not entirely surprising since it was noted during the granulation process that these appeared the least wet.

[4]Schleuniger Model 2E-106, Dr. K. Schleuniger and Co., CH-4501, Solothurn, Switzerland.

TABLE I - GRANULATION PROPERTIES

	Formulation A					Formulation B		Formulation C			
Starch	1	2	3	4	N.F.	2	4	2	4	N.F.[5]	N.F.
Loss on Drying %	1.67	1.30	1.28	1.67	1.30	0.70	0.55	1.76	1.83	1.68	1.25
Sieve Analysis % on Screen											
No. 18	2.0	0.0	0.0	0.5	0.5	0.0	0.0	0.6	0.29	1.0	2.0
No. 35	23.0	6.5	12.5	23.0	9.5	8.5	8.5	31.8	17.6	14.5	2.5
No. 60	21.0	13.5	22.5	30.0	17.0	26.0	29.0	34.2	25.9	33.0	31.0
No. 120	22.0	40.5	32.5	20.0	28.5	46.5	32.0	13.5	23.2	32.5	15.0
No. 230	16.0	27.5	16.5	9.0	28.0	8.0	12.0	8.4	13.5	12.0	10.0
Base	18.0	10.5	16.5	16.5	18.0	9.0	18.5	11.4	19.4	12.0	14.0
Surface Area $cm^2/100g$	59171	62792	61447	54235	73831	46052	61976	40465	64391	55949	49114
Density, g/ml											
Bulk	0.746	0.694	0.735	0.758	Q.685	0.746	0.746	0.826	0.735	0.677	0.746
Tapped	0.960	0.847	0.926	0.926	0.877	0.910	0.943	0.974	0.909	0.847	0.943
Compressibility, %	22.9	18.1	20.6	18.1	21.9	18.0	20.9	15.2	19.1	20.0	20.9

1) Pregelatinized Starch NF + Water
2) Pregelatinized Starch NF Slurry
3) Starch 1500 + Water
4) Starch 1500 Slurry
5) Planetary Mixer

The one granulation made in the planetary mixer was less dense and was of lower compressibility than its counterpart made in the high intensity mixer. It also had a larger surface area. The energy creating granulations in the high intensity mixers is believed related to this observation.

The physical properties of the resulting tablets are in Table II. Weight uniformity, tablet thickness, uniformity, hardness and disintegration values were acceptable in all cases.

To determine further if there were any differences in breaking strength among formulations tablets were compressed at equivalent compression pressures in a round configuration from each mixture on a manual hydraulic press. Figures 1, 2 and 3 illustrate the data generated. Formulations containing modified starches yielded a slightly harder tablet than did formulations containing starch, NF. Also, tendency for 'capping' or lamination at exaggerated compressional force (7000 pounds) was not seen in any formulation. At a compression force of 5000 pounds the multi-drug product gave harder tablets than the single drug products; the latter being equivalent to each other.

By plotting hardness vs log compressional force then extrapolating to zero one can obtain a minimum compressional force (F min) for compact formation. Tablets of formulation A prepared by dry addition of pregelatinized starch NF and extemporaneously added water produced tablets having the lowest F min values.

Instrumented press data were obtained with the assistance of a digital computer. Time parameter ratios at approximately

TABLE II - TABLET PROPERTIES

Drug	Formulation A					Formulation B		Formulation C			
Starch	1	2	3	4	N.F.	2	4	2	4	N.F.[5]	N.F.
Weight, mg Uniformity											
Mean	225	228	225	225	224	227	227	228	228	230	231
RSD	0.21	0.19	0.12	0.15	0.11	0.16	0.26	0.27	0.32	0.3	0.38
Thickness, mm											
Mean	3.15	3.15	3.10	3.13	3.12	3.07	3.05	3.14	3.18	3.16	3.17
RSD	0.03	0.03	0.02	0.01	0.02	0.03	0.02	0.04	0.02	0.03	0.04
Hardness, kp											
Mean	16.5	14.6	13.2	15.4	13.9	12.2	11.5	17.3	15.5	15.7	17.5
RSD	2.2	2.2	2.0	1.29	1.21	0.69	1.55	2.54	2.5	2.15	2.27
Mean[6]	5.5	5.2	4.8	5.1	5.1	4.0	4.0	7.0	5.9	5.9	7.2
Disintegration time (min)	2.25	1.25	2.25	2.0	1.5	0.25	0.5	3.0	2.25	2.0	4.25

1) Pregelatinized Starch NF + water
2) Pregelatinized Starch NF Slurry
3) Starch 1500 + Water
4) Starch 1500 Slurry
5) Planetary Mixer
6) Schlueniger Tester with 'Jaws'

(RSD - relative standard deviation)

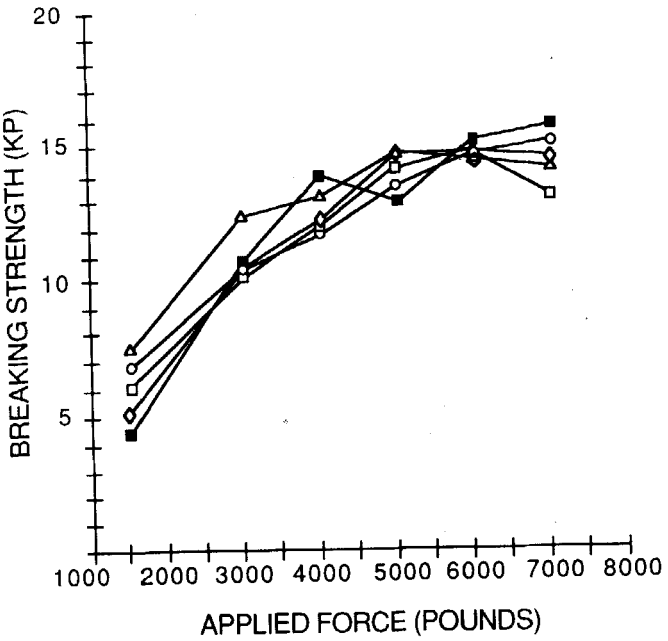

FIGURE 1

Breaking Strength vs Applied Force - Formulation A

Pre-Gel Starch 1551

Starch NF

Pre-Gel Starch 1551 Slurry

Sta-Rx 1500

Sta-Rx 1500 Slurry

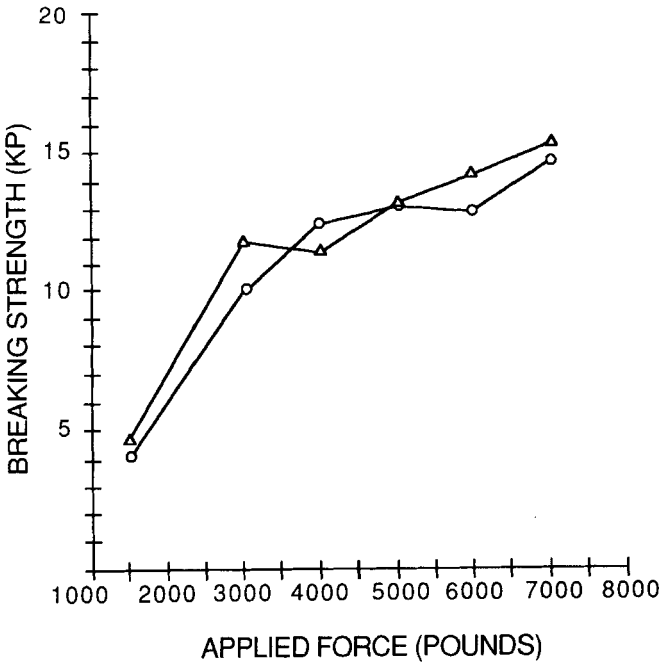

FIGURE 2

Breaking Strangth vs Applied Force - Formulation B

Pre-Gel Starch 1551 Slurry

Sta-Rx 1500 Slurry

equivalent compressional force are shown in Table III. The values, for any parameter for all formulations fall within a narrow range. The effects of increasing compressional force on these ratios, while evident, are relatively small.

The ratio of transmitted force to applied force (coefficient of lubrication[10]) range from 0.86 to 0.98 with a value of 1.0 indicating perfect lubricity. The value 0.82 indicates adequate

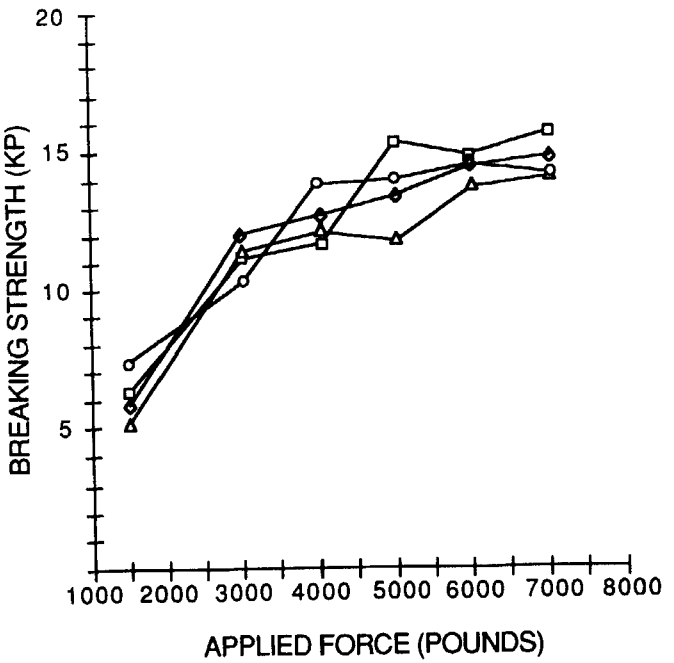

FIGURE 3

Breaking Strength vs Applied Force - Formulation C

Starch NF Planetary

Starch NF High Intensity

Pre-Gel Starch 1551 Slurry

Sta Rx 1500 Slurry

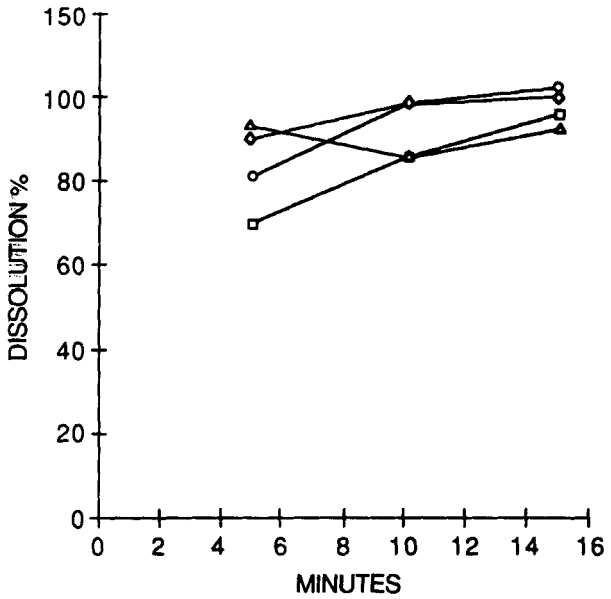

FIGURE 4

Dissolution % (Hydrochlorothiazide) vs Time - Formulation C

Starch NF Planetary

Starch NF High Intensity

Pre-Gel Starch Slurry

Sta-Rx 1500 Starch Slurry

TABLE III - SUMMARY OF KEY PARAMETERS CONCERNED WITH BINDING EFFICIENCIES OF STARCH, N.F. AND MODIFIED STARCHES

I. Formulation A

	Dry-Q.S. With Water To Granulate		Slurry/Paste		
	Pregel Starch	Sta-Rx 1500	Pregel Starch	Sta-Rx 1500	Starch N.F.
1. Granule Surface Area (cm^2/100g)	59,000	61,400	62,700	54,200	73,800
2. Compressibility (%)	22.9	20.6	18.1	18.1	21.9
3. Wc (Joules)	4.06	5.00	4.97	5.01	4.71
4. Lr	0.88	0.93	0.88	0.97	0.86
5. F min (lbs)	399	676	554	485	668

II. Formulation B

	Slurry	
	Pregel Starch	Sta-Rx 1500
1. Granule Surface Area (cm^2/00g)	46,000	61,976
2. Compressibility (%)	18	20.9
3. Wc (Joules)	5.46	5.11
4. Lr	0.97	0.98
5. F min (lbs)	738	783

TABLE III (Continued)

III. Formulation C

	Slurry		Starch, N.F. Paste	
	Pregel Starch	Sta-Rx 1500	High Intensity	Planetary
1. Granule Surface Area ($CM^2/100g$)	40,465	54,390	49,100	55,949
2. Compressibility	15.2	19.1	20.9	20.0
3. Wc (Joules)	5.76	4.2	5.3	4.3
4. Lr	0.97	0.86	0.97	0.87

Wc = Mean work of compression (average of the work expended by the upper and lower punches)

$Lr = \frac{\text{Transmitted Force}}{\text{Applied Force}}$ - (lubrication ratio)

F min = Minimum force for tablet formation - obtained by extrapolation

lubricity compared with a perfect value of 1.0. The area of the force: time curve is a linear function of maximum compression force.

Binding efficiency was directly proportional to the granule coarseness (i.e., smaller granule surface area), which, in turn, was directly proportional to the mean work of compression expended by the upper and lower punches for equally well-lubricated granulations. More work was necessary to compress a coarser and hence harder granule. Finally, a higher binding efficiency was reflected in a lower value of F min.

Higher dissolution rates were obtained for formulations containing modified starches than when starch NF was employed as indicated in Figure 4.

CONCLUSION

Binding efficiency was directly proportional to the granule coarseness which, in turn, was directly proportional to mean work of compression for equally well-lubricated granulations. Some differences were observed between the starches and manner of incorporation (dry or as slurry) and between the single potency and combination products. The rank order of wet binding efficiency was pre-gel starch 1551 (dry)>, Sta Rx 1500 starch (dry), >pre-gel starch slurry, >Sta Rx 1500 starch slurry, > starch NF.

A plot of tablet hardness vs compression force indicated a maximum, (i.e., limiting force) for starch NF only.

The formulations containing the modified starches exhibited a faster release of low water soluble drug than the starch NF

counterparts due to more uniform dispersion of modified starch binders.

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