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Crosslinked starch as a binding agent

II. Granulation in a high shear mixer

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Summary

A high shear mixer was utilized for the evaluation of pregelatinized and pregelatinized-crosslinked waxy-corn starches as binding agents in the wet granulation process. Lactose granules prepared with a high shear mixer showed a larger average size in comparison to granules prepared in a planetary mixer using the same amount of binding solution. The use of pregelatinized or pregelatinized-crosslinked starches as a paste provided larger and less friable granules than when the binder was added in the dry form. The high shear mixer produced granules with lower friability in comparison with those prepared in the planetary mixer. Granule size was influenced by the concentration of the binders while a difference in friability was not observed. No influence was observed for the experimental massing time on particle size distribution and on friability of the granules except when a paste of pregelatinized starch was used as a binder.

Introduction

High shear mixers have recently been attracting increased attention because of their usefulness in the granulation process. With high shear mixers, it is a well-known fact that a granulation process requires less binding solution (Kristensen, 1988) and a shorter processing time than does granulation in conventional mixers (Record, 1980). In the early investigations, the studies were focused on the effects of process variables during granulation in high shear mixers. Record (1980) found that the quantity of binding solution is normally reduced as compared with low speed mixers due to the powerful compacting forces in high shear mixers. Holm et al. (1983, 1984) studied the granulation of lactose and dicalcium phosphate dihydrate in a high shear mixer and found that granule growth was governed by the amount of binding solution, impeller speed and starting material.

In a previous study, Visavarungroj et al. (1990) evaluated the use of thermally modified and/or chemically crosslinked modified waxy-corn starches as binding agents in a conventional wet granulation process. The study indicated that pregelatinized waxy-corn starch and pregelatinized-crosslinked waxy-corn starches were good binding

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agents. The crosslinked-only waxy-corn starches showed no advantage in binding properties over native corn starch or waxy-corn starch. In this study, the same modified starches were evaluated as binding agents in a granulation process using a high shear granulator.

Materials and Methods

Materials

Lactose (Pharmatose, 200M α-lactose monohydrate, DMV, The Netherlands) was used as a diluent in the wet granulation process. The starch samples evaluated as binding agents were the same as those described in a previous paper (Visavarungroj et al., 1990) and are detailed in Table 1.

Methods

Granulation

Wet granulation was performed by using a high shear mixer (Gral 10, Machines Collette, Wommelgem, Belgium) and by adding a binding agent either in the dry form or as a starch paste. Both types of granulations were performed in triplicate for each form of starch. Water was used in one granulation in order to evaluate the binding properties of lactose.

TABLE 1

Modified waxy-corn starches used in this study

Types of starches	Pregelatinized (Pregel.)	Phosphate-crosslinked (Phosp. XL)	Adipate-crosslinked (Adip. XL)
Pregelatinized	+		
Pregelatinized-phosphate cross-linked	+	+	
Pregelatinized-adipate cross-linked	+		+
Crosslinked			
Low level		+	+
High level		+	+

Granulation with starch paste. A 6% w/w starch paste was prepared for all modified waxy-corn starches investigated according to the same method as that described in a preceding paper (Visavarungroj et al., 1990).

Cooled freshly prepared starch paste (250 g) was added to lactose (1.5 kg) and the granulation was performed at an impeller speed of 430 rpm and a chopper speed of 1500 rpm for 8 min. The wet mass was then sieved through a 2.0 mm screen. The granules were dried at 50 °C for 3 h in a hot air tray oven.

Granulation with dry starch. The pregelatinized and pregelatinized-crosslinked starches were used for these experiments. A mixture of lactose (1.5 kg) and each sample (15 g) was dry blended for 10 min at an impeller speed of 430 rpm without using the chopper. Subsequently, 235 ml of water were added and the mixture was massed for 8 min at the same impeller speed and at a chopper speed of 1500 rpm. The wet mass was then sieved through a 2.0 mm screen. The granules were dried at 50 °C for 3 h in a hot air tray oven.

Effects of binder concentration. Three different concentrations (3, 6 and 9% w/w) of pregelatinized and pregelatinized-crosslinked starches were used in the dry form as a binding agent.

Effects of massing time. The influence of massing time on the granules prepared with pregelatinized starch and pregelatinized-phosphate crosslinked starch paste was evaluated. The massing time varied from 2 to 4 and 8 min, respectively.

Granule evaluation. The dry granules were stored in well closed containers and evaluated with respect to the size distribution, average size and friability. The methods employed have been described in a previous study (Visavarungroj et al., 1990).

Results and Discussion

The granule size distribution (Tables 2 and 3) and average granule size data (Table 4) demonstrate that the granulation in a high shear mixer produced a shift in particle size distribution towards coarser granules in comparison to those

TABLE 2

Size distribution of granules (% on sieve ± SD) prepared by using 6% w/w starch paste

Starch	Sieve size (μm)					
	> 1 400	1 400–1 000	1 000–710	710–500	500–250	< 250
Corn	19.9 ± 2.6	40.4 ± 0.6	16.2 ± 0.9	8.9 ± 0.5	12.4 ± 1.6	2.2 ± 0.6
Waxy corn	31.6 ± 0.7	32.7 ± 1.8	12.5 ± 1.3	9.2 ± 0.7	12.4 ± 1.2	1.7 ± 0.8
Pregelatinized	46.2 ± 2.3	25.6 ± 0.6	12.5 ± 1.0	9.4 ± 0.9	6.0 ± 0.6	0.3 ± 0.2
Pregel. Phosp. XL	22.4 ± 3.0	43.7 ± 0.9	15.0 ± 1.2	7.9 ± 0.8	9.4 ± 0.3	1.6 ± 0.2
Pregel. Adip. XL	29.7 ± 2.7	38.7 ± 2.5	13.7 ± 0.6	8.3 ± 0.6	8.5 ± 0.7	1.1 ± 0.3
Phosp. XL-low	28.1 ± 0.4	37.7 ± 1.0	14.9 ± 0.6	8.3 ± 0.6	9.7 ± 0.4	1.3 ± 0.0
Phosp. XL-high	18.4 ± 1.0	41.2 ± 1.8	17.2 ± 0.8	9.0 ± 0.5	11.9 ± 1.2	2.3 ± 0.3
Adip. XL-low	20.3 ± 2.1	39.7 ± 1.9	18.7 ± 1.5	8.8 ± 0.4	10.8 ± 1.3	1.8 ± 0.6
Adip. XL-high	14.8 ± 2.0	43.3 ± 1.0	20.3 ± 0.2	8.5 ± 0.1	11.3 ± 1.2	1.7 ± 0.5

produced by a planetary mixer, using the same amount of binding solution. In particular, the amount of granules larger than 1000 μm was dramatically increased and less fine granules were produced. When no binding agent was used, the granules produced with a high shear granulator were smaller than those in the case of a planetary mixer. This could be attributed to the heat produced by the considerable mechanical strength of the high shear mixer and subsequent evaporation of water during granulation when no binding agent was used (Schaefer, 1988). The granules formed during wet massing without binder were crushed by the action of the chopper.

Only the pregelatinized and pregelatinized-crosslinked starches were used in the granulation process with dry starch. As shown in a previous study (Visavarungroj et al., 1990), the non-pregelatinized starches used in the dry form provided granules of very poor quality. Pregelatinized and pregelatinized-crosslinked starches used in the dry form produced somewhat smaller granules than when a starch paste was added. This can be explained by the fact that the dry starch needed time for swelling before efficient agglomeration of the lactose powder occurred while a starch paste can directly be dispersed and thus assist in the agglomeration.

The friability data (Table 4) show that the use of pregelatinized or pregelatinized-crosslinked starches as a paste yielded less friable granules than those prepared with starches added in the dry form. The lowest values for the friability were obtained for granules prepared with pregelatinized starch. This finding confirms the fact that when a paste was used, the agglomeration and handling strength of lactose granules were improved. In general, a high shear mixer provided granules with a lower friability in comparison with those produced with a planetary mixer. A high shear mixer exerts stronger compacting forces than a planetary mixer, resulting in the more dense granules. With the planetary mixer (Visavarungroj et al., 1990), no difference in friability between granules prepared at different levels of cross-linking of the crosslinked-only starches was observed (about 40–

TABLE 3

Size distribution of granules (% on sieve ± SD) prepared by using 6% w/w dry starch

Starch	Sieve size (μm)					
	> 1 400	1 400–1 000	1 000–710	710–500	500–250	< 250
Pregelatinized	19.1 ± 2.1	40.0 ± 1.2	17.9 ± 0.6	10.7 ± 1.3	10.3 ± 0.4	2.0 ± 0.4
Pregel. Phosp. XL	9.1 ± 0.4	34.3 ± 0.9	32.0 ± 1.7	12.9 ± 1.1	10.0 ± 0.8	1.7 ± 0.9
Pregel. Adip. XL	10.4 ± 0.9	48.3 ± 1.1	22.0 ± 0.7	9.8 ± 2.2	8.5 ± 1.0	0.9 ± 0.1
Water	12.3 ± 0.5	24.9 ± 1.0	18.0 ± 1.0	16.9 ± 0.5	22.3 ± 0.6	5.5 ± 0.2

TABLE 4

Average size (μm ± SD) and friability (% ± SD) of granules prepared by using 6% w/w modified starch

Starch	Average granule size		Granule friability	
	Dry starch	Starch paste	Dry starch	Starch paste
Corn	–	1064.7 ± 29.5	–	40.73 ± 2.93
Waxy corn	–	1140.4 ± 21.6	–	30.82 ± 3.03
Pregelatinized	1063.6 ± 23.8	1278.9 ± 22.7	35.34 ± 2.36	23.66 ± 2.52
Pregel. Phosp. XL	957.5 ± 11.6	1118.7 ± 26.6	38.37 ± 1.39	30.85 ± 3.30
Pregel. Adip. XL	1038.0 ± 19.1	1170.6 ± 16.2	36.85 ± 4.60	29.66 ± 2.86
Phosp. XL-low	–	1146.3 ± 5.0	–	35.23 ± 2.66
Phosp. XL-high	–	1056.7 ± 14.4	–	44.43 ± 3.27
Adip. XL-low	–	1077.1 ± 16.6	–	33.22 ± 2.57
Adip. XL-high	–	1041.9 ± 25.0	–	44.92 ± 1.66
Water	855.8 ± 9.0		68.62 ± 0.64	

45% when used as a paste). With the high shear mixer, the differences in degree of crosslinking resulted in less friable granules at low levels of crosslinking (Table 4). The low-level crosslinked starches produced granules with a friability of 35% as compared to 45% for high-level crosslinking. A difference in swelling properties between these starches might be the cause of such a difference in friability. Highly crosslinked starches showed a lower swelling capacity in comparison with those with a low degree of crosslinking (Wurzburg, 1986).

Tables 5 and 6 list the data on the particle size distribution and average size of granules prepared using different concentrations of dry starches. A low starch concentration produced coarser granules than a high concentration. This could be explained by the fact that pregelatinized starch granules form a viscous gel barrier in contact with water, thereby preventing further swelling. The high shear mixer disrupted this gel-like barrier, allowing the starch granules to swell further and inducing the agglomeration of the lactose powder. With a high concentration of dry starch, more

TABLE 5

Size distribution of granules (% on sieve ± SD) prepared by using different concentrations of dry starch

Starch	Sieve size (μm)					
	> 1400	1400–1000	1000–710	710–500	500–250	< 250
Pregelatinized						
3%	34.0 ± 2.2	33.8 ± 1.0	12.9 ± 0.9	9.7 ± 0.8	8.7 ± 0.8	0.9 ± 0.1
6%	19.1 ± 2.1	40.0 ± 1.2	17.9 ± 0.6	10.7 ± 1.3	10.3 ± 0.4	2.0 ± 0.4
9%	11.9 ± 0.3	42.9 ± 0.6	25.5 ± 0.7	10.8 ± 0.2	8.4 ± 0.8	0.5 ± 0.1
Pregel. Phosp. XL						
3%	15.8 ± 1.4	43.3 ± 1.6	18.6 ± 3.5	11.0 ± 0.6	10.0 ± 0.8	1.3 ± 0.1
6%	9.1 ± 0.4	34.3 ± 0.9	32.0 ± 1.7	12.9 ± 1.1	10.0 ± 0.8	1.7 ± 0.9
9%	2.8 ± 0.0	17.5 ± 0.6	44.4 ± 3.0	25.0 ± 2.3	9.5 ± 0.9	0.7 ± 0.3
Pregel. Adip. XL						
3%	15.8 ± 1.7	37.4 ± 1.4	22.4 ± 0.7	12.4 ± 0.7	10.8 ± 1.4	1.2 ± 0.1
6%	10.4 ± 0.9	48.3 ± 1.1	22.0 ± 0.7	9.8 ± 2.2	8.5 ± 1.0	0.9 ± 0.1
9%	3.8 ± 0.7	21.1 ± 2.3	37.6 ± 0.7	24.9 ± 2.1	11.2 ± 1.1	1.3 ± 0.2
Water	12.3 ± 0.5	24.9 ± 1.0	18.0 ± 1.0	16.9 ± 0.5	22.3 ± 0.6	5.5 ± 0.2

TABLE 6

Average size (μm ± SD) and friability (% ± SD) of granules prepared by using different concentrations of dry starch

Starch	Average granule size	% Friability
Pregelatinized		
3%	1186.5 ± 20.2	33.92 ± 3.90
6%	1063.6 ± 23.8	41.34 ± 2.36
9%	1032.3 ± 5.0	38.48 ± 1.25
Pregel. Phosp. XL		
3%	1053.0 ± 16.3	43.65 ± 1.39
6%	957.5 ± 11.6	42.37 ± 1.39
9%	825.6 ± 13.4	42.88 ± 2.03
Pregel. Adip. XL		
3%	1026.5 ± 26.3	43.51 ± 2.34
6%	1038.0 ± 19.1	37.85 ± 4.60
9%	834.8 ± 22.0	38.97 ± 0.19
Water	855.8 ± 9.0	68.62 ± 0.64

time was needed for the starch particles to swell than in the case of a low starch concentration. No important difference in friability was observed for granules prepared using various concentrations of dry starches (Table 6).

As demonstrated by the results in Tables 2 and 3, no important difference occurred in the properties of granules prepared using starches with a different crosslinking agent. Pregelatinized and pregelatinized-phosphate crosslinked starches were used in the paste form to study the effects of massing time. There was no dramatic influence on granule size distribution (Table 7) and average granule size (Table 8) between granules prepared with pure water or pregelatinized-phosphate crosslinked starch while varying the massing time. This result is in agreement with the data reported by Holm et al. (1984), who found that the granulation of lactose did not appear to be influenced by the processing conditions in a high speed mixer, reflecting presumably a balance between size enlargement and crushing. However, the pregelatinized starch provided coarser granules with less fine particles when the massing time was increased from 2 to 4 and to 8 min, respectively. A possible explanation for this phenomenon might be that pregelatinized starch has a very high bonding strength (lowest friability, Table 8). The size enlargement rate of lactose granules prepared with this starch was higher than the rate of crushing induced by the action of the high shear mixer, resulting in coarser granules when the massing time was increased. No difference in granule friability was observed between granules when the massing time was increased.

In conclusion, using the same amount of modified waxy-corn starches as binding agents, coarser lactose granules were obtained with a high shear mixer than with a planetary mixer. The

TABLE 7

Size distribution of granules (% on sieve ± SD) prepared by using starch paste and varying the massing time

Starch	Sieve size (μm)					
	> 1400	1400–1000	1000–710	710–500	500–250	< 250
Water						
2 min	23.7 ± 2.6	29.7 ± 1.1	20.8 ± 0.8	13.6 ± 1.3	10.2 ± 1.6	2.0 ± 0.3
4 min	24.4 ± 1.1	28.7 ± 0.2	20.1 ± 0.3	13.7 ± 0.3	11.0 ± 0.8	2.1 ± 0.1
8 min	12.3 ± 0.5	24.9 ± 1.0	18.0 ± 1.0	16.9 ± 0.5	22.3 ± 0.6	5.5 ± 0.2
Pregelatinized						
2 min	16.4 ± 0.2	38.2 ± 0.8	19.3 ± 1.2	12.0 ± 0.5	12.3 ± 0.9	1.8 ± 0.1
4 min	36.3 ± 1.9	36.9 ± 2.3	10.1 ± 0.7	7.0 ± 0.3	8.4 ± 0.5	1.3 ± 0.0
8 min	46.2 ± 2.3	25.6 ± 0.6	12.5 ± 1.0	9.4 ± 0.9	6.0 ± 0.6	0.3 ± 0.2
Pregel. Phosp. XL						
2 min	19.1 ± 1.6	38.6 ± 0.4	20.6 ± 0.9	10.0 ± 0.8	9.7 ± 0.4	2.1 ± 0.1
4 min	19.5 ± 1.3	43.0 ± 0.4	18.7 ± 0.4	8.1 ± 0.4	8.9 ± 0.5	1.8 ± 0.1
8 min	22.4 ± 3.0	43.7 ± 0.9	15.0 ± 1.2	7.9 ± 0.8	9.4 ± 0.3	1.6 ± 0.2

TABLE 8

Average granule size (μm ± SD) and granule friability (% ± SD) of granules prepared by using starch paste and varying massing time

Starch	Massing time (min)		
	2	4	8
Average size			
Water	909.8 ±37.3	897.5 ±14.0	855.8 ±19.0
Pregelatinized	1112.7 ±15.6	1221.5 ±17.3	1278.9 ±22.7
Pregel. Phosp. XL	1062.4 ±17.8	1091.3 ±14.1	1118.7 ±26.6
Friability			
Water	63.25 ± 1.60	63.60 ± 0.40	68.62 ± 0.64
Pregelatinized	25.75 ± 2.90	25.75 ± 1.48	23.66 ± 2.52
Pregel. Phosp. XL	36.27 ± 1.23	37.98 ± 1.27	30.85 ± 3.30

use of pregelatinized or pregelatinized-crosslinked starches as a paste yielded coarser but less friable granules than those in the dry form. The high shear mixer provided granules with a lower friability as compared with those produced with a planetary mixer. This study showed that variation in the massing time had no influence on particle size or friability of the lactose granules except when pure pregelatinized starch was used as a binder. Starches that were only crosslinked showed no advantage in binding properties over native corn or waxy-corn starch unless they were pregelatinized. The pregelatinized starch and pregelatinized-crosslinked starches showed potential use as a binding agent in the granulation of lactose by both the conventional process of wet granulation and the granulation in high shear mixer.

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