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Crosslinked starch as binding agent

III. granulation of an insoluble filler

N. Visavarungroj and J.P. Remon

Laboratory of Pharmaceutical Technology, State University of Gent, Harelbekestraat 72, 9000 Gent (Belgium)

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Summary

Pregelatinized waxy-corn starch and pregelatinized-phosphate crosslinked waxy-corn starch were compared with corn starch and waxy-corn starch as binding agents for dicalcium phosphate dihydrate. The modified starches produced higher quality granules in comparison to those prepared with the native corn or waxy-corn starches. Pregelatinized waxy-corn and pregelatinized phosphate-crosslinked waxy-corn starches in the dry form produced granules with similar properties to those prepared by corn or waxy-corn starch pastes. The use of a high shear mixer yielded coarser but less friable granules than those prepared by a planetary mixer. There was no difference in binding properties between pregelatinized waxy-corn starch and pregelatinized phosphate-crosslinked starch.

Introduction

Thermally modified and/or crosslinked modified waxy-corn starches were previously evaluated as binding agents in a conventional and a high shear wet granulation process (Visavarungroj and Remon, 1990; Visavarungroj et al., 1990). The authors reported that pregelatinized and pregelatinized crosslinked waxy-corn starches were good binding agents for the granulation of lactose either in the dry form or as a paste. Purely crosslinked waxy-corn starches showed no advantage in binding properties over native corn starch or waxy-corn starch. By using lactose which is a water-soluble substance as the bulk material in a wet granulation, the strength of granules can be improved due to crystalline bridges formed by recrystallized lactose (Worts, 1972; Veillard et al., 1982). In order to evaluate the binding properties due to pregelatinized waxy-corn starch and pregelatinized crosslinked waxy-corn starch, dicalcium phosphate dihydrate was used as the bulk material in this study.

Correspondence: J.P. Remon, Laboratory of Pharmaceutical Technology, State University of Gent, Harelbekestraat 72, 9000 Gent, Belgium.

Materials and Methods

Materials

Dicalcium phosphate dihydrate (Emcompress, Edward Mendell, New York, U.S.A.) and lactose monohydrate (Pharmatose 200 M, DMV, Veghel, The Netherlands) were used as the bulk material.

The pregelatinized waxy-corn, pregelatinized phosphate-crosslinked waxy-corn, corn and waxy-corn starches were provided by Cerestar (Vilvoorde, Belgium).

Methods

Granulation

Wet granulation was performed in a planetary mixer (Hobart K 45 SS, Troy, OH, U.S.A.) using a K-shaped mixing arm or in a high shear mixer (Gral 10, Machines Collette, Wommelgem, Belgium) and by the addition of the binding agent either in the dry form or as a starch paste. Pure water was used in one granulation in order to evaluate the binding properties of dicalcium phosphate dihydrate. All granulations were performed in triplicate on each sample.

Granulation with dry starch With the planetary mixer, a mixture of dicalcium phosphate dihydrate (900 g) and binder (15 g) was dry blended for 10 min at 80 rpm. Subsequently, 135 ml of water were added and the mixture was granulated for 8 min. In the granulation with the high shear mixer, 2.4 kg of dicalcium phosphate dihydrate and 40 g of starch were mixed for 10 min at an impeller speed of 430 rpm without using the chopper. Subsequently, 360 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 and dried at 50 °C.

In order to compare the influence of pure bulk material, a wet granulation was performed on lactose monohydrate and dicalcium phosphate dihydrate by massing for 8 min in a planetary mixer. Corn, waxy-corn and pregelatinized waxy-corn starches were used as the binding agents for the dry addition method at a concentration of 6% (w/w).

Two different binder concentrations (6 and 10% w/w) and massing times (4 and 8 min) were used for the granulation process on dicalcium phosphate dihydrate.

Granulation with starch paste A 10% (w/w) starch paste was prepared for pregelatinized waxy-corn, pregelatinized phosphate-crosslinked waxy-corn, waxy-corn and corn starches, respectively. Cooled freshly prepared starch paste (150 g) was added to 900 g dicalcium phosphate dihydrate and granulated with the planetary mixer at 80 rpm for 8 min. With the high shear mixer, the granulation was performed on 2.4 kg dicalcium phosphate dihydrate and 400 g starch paste at an impeller speed of 430 rpm and a chopper speed of 1500 rpm for 8 min. Next, the wet mass was sieved through a 2.0 mm screen. The wet granules were dried at 50°C.

Granule evaluation

Sieve analysis The granule size distribution and average granule size were determined in triplicate by sieving through a set of standard sieves (250, 500, 710, 1000 and 1400 μm). The method was previously described by Visavarungroj et al. (1990a).

Granule friability The friability of granules was determined in triplicate by subjecting 10 g of the 250–500 μm fraction together with 200 glass beads (average diameter 4 mm) to falling shocks for 10 min in a friabilator (Erweka type TAP, Erweka, Frankfurt, Germany) set to a speed of 25 rpm (Remon and Schwartz, 1987). After 10 min, the glass beads were removed and all remaining material was placed on a 250 μm screen which was placed on the sieve shaker (Retostat, Germany). The sieve shaker was operated for 15 s. Material remaining on the screen was weighed and the percent friability was calculated.

Results and Discussion

Pregelatinized waxy-corn and pregelatinized phosphate crosslinked waxy-corn starches were compared with corn and waxy-corn starches as binding agents for the granulation of dicalcium phosphate dihydrate. As it was previously demonstrated that purely crosslinked starch did not show any advantage in binding properties over corn or waxy-corn starches and that the type of crosslinking agent did not influence the granule quality (Visavarungroj and Remon, 1990; Visavarungroj et al., 1990), only pregelatinized and pregelatinized phosphate-crosslinked waxy-corn starch were compared with corn and waxy-corn starches in this study.

TABLE 1

Influence of the bulk material on the average size and friability of granules prepared by planetary mixer for 8 min using the dry starch addition method (6% w/w) (n = 3)

Starch	Average size (μm ± SD)	Friability (% ± SD)
Corn		
lactose	811.6 ± 10.1	75.40 ± 3.67
Dicalcium Phosphate	196.6 ± 6.8	76.54 ± 1.13
Waxy-corn		
lactose	776.3 ± 17.1	78.64 ± 3.03
Dicalcium phosphate	197.0 ± 5.4	74.82 ± 2.11
Pregelatinized		
lactose	820.2 ± 11.5	31.93 ± 1.10
Dicalcium phosphate	493.2 ± 9.8	58.28 ± 1.43

Fig. 1 and Table 1 display the size distribution and average size of lactose and dicalcium phosphate granules prepared by the dry addition method using a 6% concentration (w/w) of the different starches under investigation. With lactose monohydrate, the average size of granules was much larger in comparison to dicalcium phosphate dihydrate granules. No difference in granule friability was observed by using corn or waxy-corn starches, which were shown to have poor binding action for either lactose or dicalcium phosphate when used in the dry form (Visavarungroj and Remon, 1990; Visavarungroj et al., 1990). With pregelatinized waxy-corn starch, lactose granules showed lower friability in comparison to those prepared from dicalcium phosphate dihydrate. All these observations supported the fact that the formation of a crystalline bridge by the recrystal-

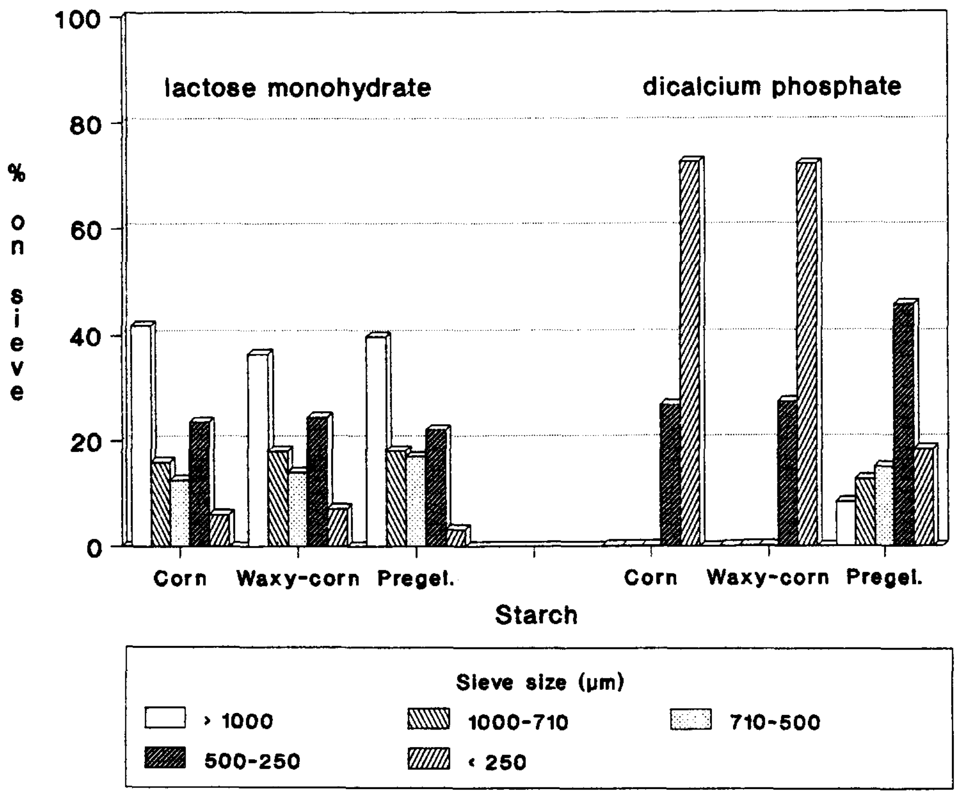

Fig. 1. Influence of the bulk material on the size distribution of granules prepared by planetary mixer for 8 min using the dry starch addition method (*n* = 3).

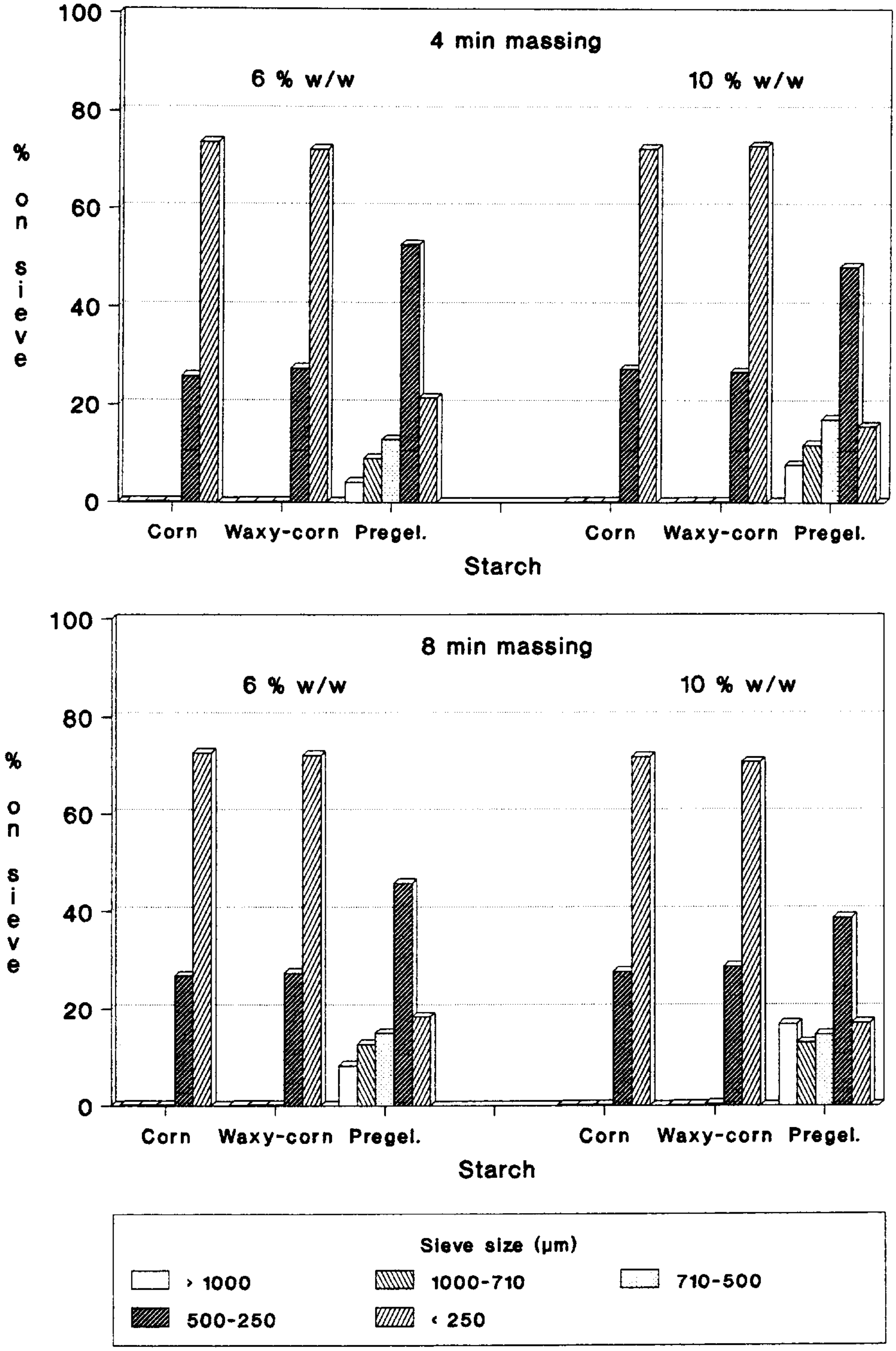

Fig. 2. Influence of binder concentration and massing time on the size distribution of dicalcium phosphate granules prepared by planetary mixer using the dry starch addition method ($n = 3$).

TABLE 2

Influence of binder concentration and massing time on the average size and friability of dicalcium phosphate granules prepared by planetary mixer using the dry starch addition method (n = 3)

Starch	Average size ($\mu m \pm SD$)	Friability ($\% \pm SD$)
4 min massing		
Corn		
6%	193.3 ± 7.2	72.21 ± 1.25
10%	196.8 ± 6.4	76.83 ± 1.70
Waxy-corn		
6%	196.5 ± 5.1	75.26 ± 1.07
10%	195.3 ± 6.0	74.92 ± 1.21
Pregelatinized		
6%	427.7 ± 7.2	65.77 ± 2.05
10%	494.4 ± 6.5	56.45 ± 1.71
8 min massing		
Corn		
6%	196.6 ± 6.8	76.54 + 1.13
10%	199.9 ± 5.0	73.27 ± 0.24
Waxy-corn		
6%	197.0 ± 5.4	74.82 ± 2.11
10%	200.1 ± 6.2	75.17 ± 1.62
Pregelatinized		
6%	493.2 ± 9.8	58.28 ± 1.43
10%	568.1 ± 19.9	43.74 ± 0.93

lized soluble materials is one of the mechanisms of particle bonding and the granules' properties can be improved by using soluble bulk materials (Worts, 1972; Veillard et al., 1982).

Changing the binder concentration or the massing time did not influence the properties of dicalcium phosphate granules prepared with corn or waxy-corn starches (Fig. 2 and Table 2). The average size was about 200 μm and the friability was about 75% in all cases. Using pregelatinized waxy-corn starches as binding agents, coarser dicalcium phosphate granules with lower friability were obtained. Increasing the concentration of pregelatinized waxy-corn starch up to 10% yielded coarser granules with lower friability. On the basis of these results, a concentration of 10% was used for further experiments. In a previous study, it was shown that there was no influence of massing time on particle size distribution and on friability of lactose granules (Visavarungroj and Remon, 1990). In contrast, coarser particles with a lower friability were obtained with dicalcium phosphate as the bulk material and pregelatinized waxy-corn starch as the binder when increasing the massing times from 4 to 8 min. This result is in agreement with data published by Holm et al. (1984) who reported that granule growth during the massing phase depended to a great extent on the starting material. The granulation process of lactose is less critically affected by moisture level and massing intensity. After a short period of massing, the granule size of lactose remained rather constant reflecting presumably a balance between size enlargement and crushing, whereas an increase in granule size was observed for those prepared with dicalcium phosphate dihydrate. The same group of authors pointed out later that the intragranular porosity of dicalcium phosphate granule was reduced by prolonging the massing time which might be the reason for the improvement in the strength of granules (Jægerskon et al., 1984). The friability of dicalcium phosphate granules prepared with 10% pregelatinized waxy-corn starch and granulated for 8 min was about 45% (Table 2), therefore an 8 min massing time was selected for the next study.

Fig. 3 and Table 3 show the size distribution and average size for dicalcium phosphate dihydrate granules prepared with a planetary mixer. Corn and waxy-corn starches used in the dry form produced granules with an analogous size distribution and average size to the case when no binding agent was used. No difference in granule properties was observed when corn or waxy-corn starches were used. The friability of granules prepared from dry corn and waxy-corn starches or without a binding agent was identical at about 75% (Table 3). The granulation using corn or waxy-corn starches in the paste form produced coarser granules with a greater average size in comparison to the dry addition method. In addition, less friable granules were obtained when a starch paste was used. These results showed again the poor binding capacity of corn starch and waxy-corn starch used in the dry addition method. Pregelatinized waxy-corn and pregelatinized phosphate-crosslinked waxy-corn starches used in the dry form produced smaller granules in comparison with a starch paste. This can be attributed to the incomplete dissolution of binding agent and effects of local high

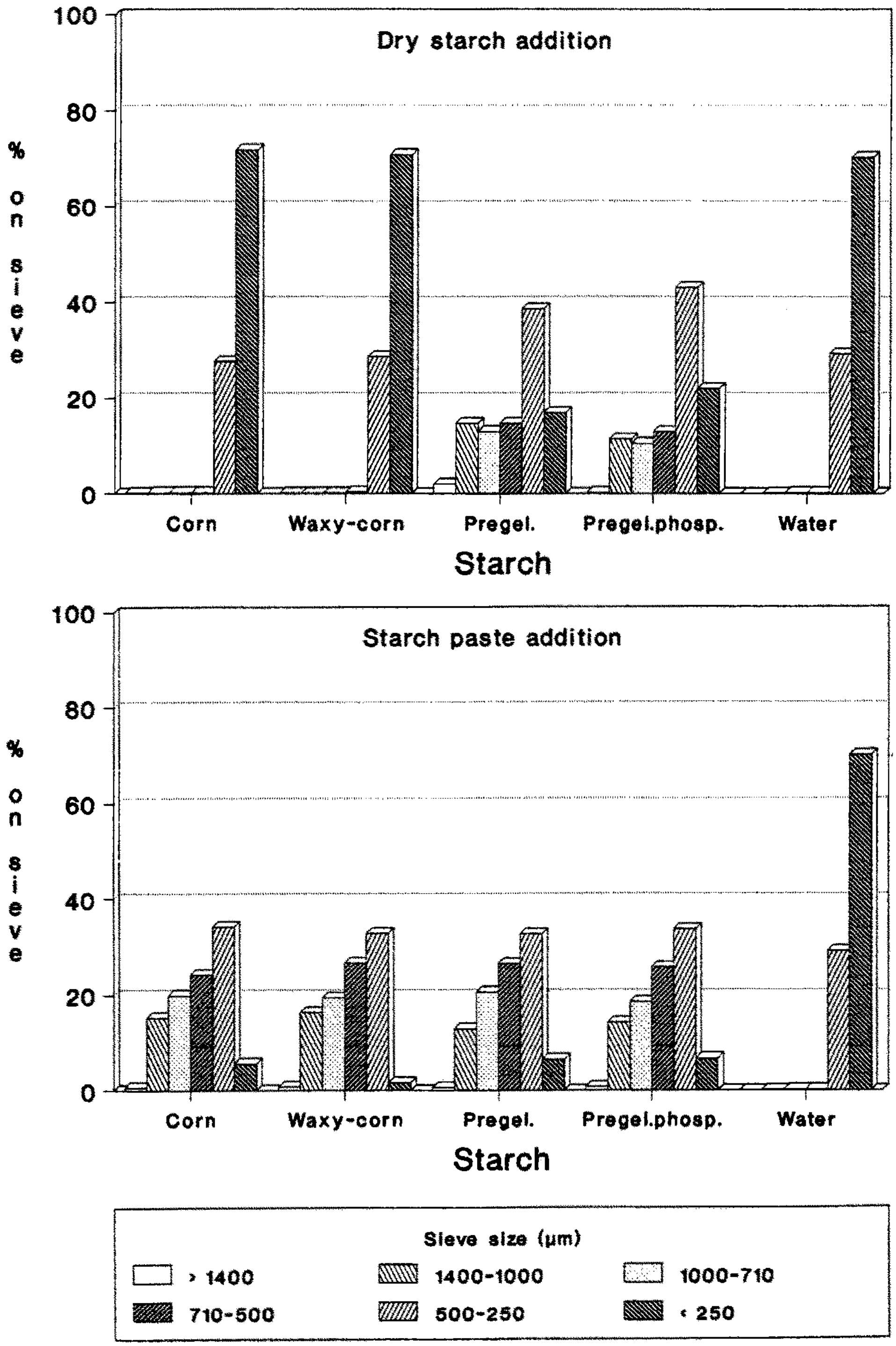

Fig. 3. Size distribution of dicalcium phosphate granules prepared by planetary mixer for 8 min ($n = 3$).

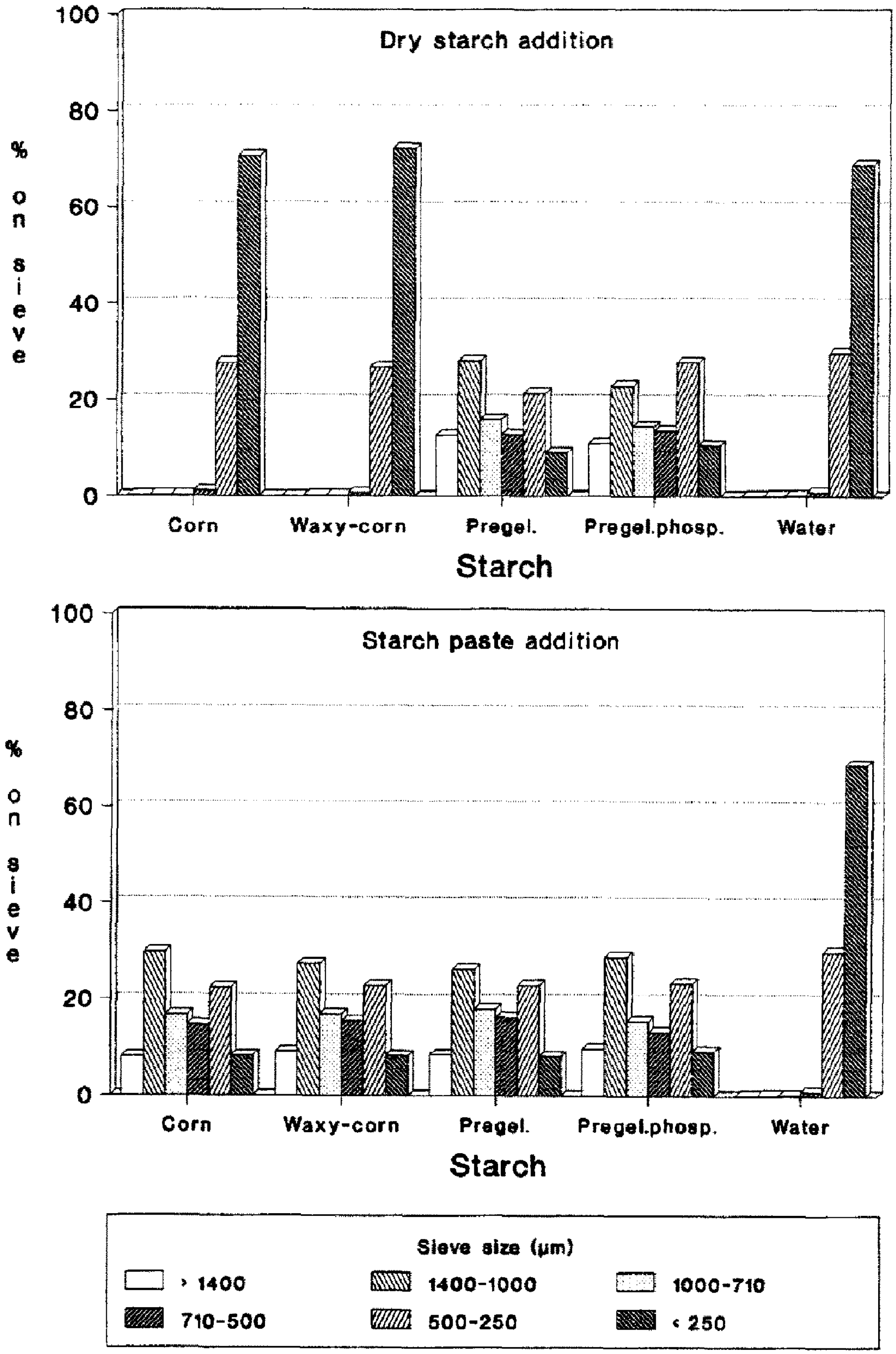

Fig. 4. Size distribution of dicalcium phosphate granules prepared by high shear mixer for 8 min ($n = 3$).

viscosities that opposed the distribution of the binding agent. As a result, pregelatinized waxy-corn and pregelatinized phosphate-crosslinked waxy-corn starches used as a starch paste produced less friable granules than those prepared with the dry addition method. Granules produced with pregelatinized waxy-corn and pregelatinized phosphate-crosslinked waxy-corn starches in the dry form showed similar friability (about 45%) to those prepared with corn or waxy-corn starches in the paste form. There was no difference in friability between granules prepared with pregelatinized waxy-corn and pregelatinized phosphate-crosslinked waxy-corn starches.

The granulation in the high shear mixer induced a shift in particle size distribution towards coarser granules in comparison to those prepared by a planetary mixer for the same granulation time (Fig. 4 and Table 4). As in the planetary mixer process, there was no difference in size distribution, average size and friability between granules prepared with dry corn or waxy-corn starches or without binding agent. No difference in particle size between granules prepared by the dry or paste addition method with the pregelatinized modified starches was observed when the granulation took place in a high shear mixer.

TABLE 3

Average size and friability of dicalcium phosphate granules prepared by planetary mixer for 8 min (n = 3)

Starch	Average size ($\mu m \pm SD$)	Friability ($\% \pm SD$)
Corn		
dry	199.9 ± 5.0	73.27 ± 0.24
paste	647.7 ± 15.4	45.71 ± 1.37
Waxy-corn		
dry	201.8 ± 8.1	75.84 ± 1.67
paste	671.7 ± 12.8	41.65 ± 1.33
Pregel.		
dry	576.9 ± 19.9	47.34 ± 0.93
paste	633.7 ± 13.3	38.42 ± 1.21
Pregel. Phosp. XL		
dry	497.6 ± 7.3	45.52 ± 1.86
paste	635.9 ± 12.3	36.27 ± 1.04
Water	202.5 ± 7.4	76.72 ± 1.07

TABLE 4

Average size and friability of dicalcium phosphate granules prepared by high shear mixer for 8 min (n = 3)

Starch	Average size ($\mu m \pm SD$)	Friability ($\% \pm SD$)
Corn		
dry	205.0 ± 8.2	75.09 ± 1.63
paste	820.6 ± 17.4	40.25 ± 1.02
Waxy-corn		
dry	199.2 ± 6.2	78.23 ± 2.18
paste	818.5 ± 18.4	36.45 ± 2.01
Pregel.		
dry	858.1 ± 26.5	36.60 ± 2.26
paste	806.0 ± 23.2	34.35 ± 2.22
Pregel. Phosp. XL		
dry	781.4 ± 14.5	33.83 ± 3.13
paste	823.8 ± 25.7	33.99 ± 2.04
Water	209.9 ± 6.9	79.97 ± 2.41

This observation was different in comparison with the granulation in the planetary mixer and might be due to intense mixing in the high shear granulator ensuring the dissolution and distribution of the binding agent (Kristensen, 1988). As a result, dry pregelatinized modified starches were wetted, dispersed and swelled, thereby promoting the agglomeration of granules. The high shear granulating process provided dicalcium phosphate dihydrate granules with a lower friability in comparison to those prepared with a planetary mixer. The friability of dicalcium phosphate granules prepared by the modified starches in high shear granulator was about 35% in comparison to about 40–45% in the planetary mixer. This finding is in agreement with the results published in previous studies on lactose granulation (Visavarungroj and Remon, 1990; Visavarungroj et al., 1990). Pregelatinized waxy-corn and pregelatinized phosphate-crosslinked waxy-corn starches used either in the dry form or as a paste produced higher quality granules in comparison with corn starch and waxy-corn starch.

With the planetary granulation, pregelatinized modified waxy-corn starches used in the paste form produced less friable granules than those prepared with the dry addition method. A difference in friability between granules prepared by the dry or paste addition method of these starches was not observed by using the high shear mixer. No difference in friability between granules prepared with pregelatinized waxy-corn starch or pregelatinized phosphate crosslinked waxy-corn starch was observed in a high shear granulator.

In conclusion, using the same amount of pregelatinized modified waxy-corn starches as binding agents, coarser and less friable dicalcium phosphate dihydrate granules were obtained with a high shear mixer than with a planetary mixer. Pregelatinized waxy-corn starch and pregelatinized phosphate-crosslinked waxy-corn starch used either in the dry or paste form produced higher quality granules than did corn starch and waxy-corn starch. There was a difference in particle size distribution between granules prepared in a planetary mixer by the dry or paste addition method of the pregelatinized modified waxy-corn starches. By using the high shear mixer in the granulation process, this difference was not observed. There was no improvement in granule quality by crosslinking the pregelatinized waxy-corn starch.

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