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Crosslinked starch as binding agent

I. Conventional wet granulation

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Summary

Different types of crosslinked waxy-corn starches and pregelatinized-crosslinked waxy-corn starches were evaluated for potential use as a binding agent in a conventional wet granulation process. Lactose granules were prepared by granulation in a planetary mixer using starch as a binding agent in either the dry or paste form. The granules, prepared with dry starch or starch paste, showed no difference in size distribution and average size of granules. The pregelatinized starch used in the paste form gave coarser granules with a greater average size in comparison to other starch modifications. In general, the friability of granules prepared by using dry starch is higher than that when using starch paste. Nevertheless, starches that were only pregelatinized or pregelatinized and crosslinked yielded granules having a similar friability by using either a dry starch or starch paste. The lactose granules prepared by using a paste of pregelatinized-crosslinked starch provided more friable granules with greater friability as compared to only pregelatinized starch paste. No difference in friability was observed between granules prepared with different types of pregelatinized-crosslinked (phosphate and adipate) starches. There was no difference in moisture content between all granules prepared in this study. The pregelatinized starch and pregelatinized-crosslinked starches showed potential use as a binding agent in the conventional wet granulation process. The starches that were crosslinked only showed no advantage in binding properties over native corn starch or waxy-corn starch.

Introduction

Wet granulation is a size-enlargement process by which powder is agglomerated in the presence of a liquid. This method of preparing granules for tabletting was the first procedure to be developed for this purpose and is still the most widely used. It primarily serves to prepare powders for tabletting by conferring upon them the properties of free flow, non-segregation and ease of compressibility. This technique uses a solution, a slurry, or a suspension containing a binding agent which is usually added to the powder mixture to form granules. However, the binding agent may be incorporated in a dry form into the powder, while the granulating liquid can be added later.

Starch has always been one of the most commonly employed granulating agents. It is normally used in the form of starch paste producing tablets which are generally soft and brittle. Common tablet binding agents were compared and it was

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found that starch showed the lowest adhesive strength but also had the least deleterious effect on tablet disintegration rates (Banker et al., 1980)

In this study, thermally modified and/or chemically crosslinked modified waxy-corn starches were investigated in comparison to native corn starch and waxy-corn starch regarding their potential use as a binding agent in the conventional wet granulation process.

Materials and Methods

Materials

Native waxy-corn starch was modified by pregelatinization only, pregelatinization and crosslinking or by crosslinking only. All these modifications were performed by Cerestar (Vilvoorde, Belgium). Table 1 summarizes the different types of modified starches evaluated in this work.

Two types of crosslinks were used: phosphate and adipate. Native starches were crosslinked at both low and high levels. Pregelatinized starches were crosslinked only at a high level. Other samples used were native corn starch and native waxy-corn starch (both from Amylum, Aalst, Belgium). Lactose (Pharmatose, 200 M Lactose, DMV, The Netherlands) was used as a diluent in the wet granulation process.

TABLE 1

Modified waxy-corn starches used in this study

Type of starch	Pregelatinized (Pregel.)	Phosphate-crosslinked (Phosp. XL)	Adipate-crosslinked (Adip. XL)
Pregelatinized	+		
Pregelatinized–phosphate-crosslinked	+	+	
Pregelatinized–adipate-crosslinked	+		+
Crosslinked			
Low-level		+	+
High-level		+	+

Methods

Granulation

Wet granulation was achieved by massing in a planetary mixer (Hobart K45SS, Troy, OH) using a K-shaped mixing arm and by the addition of binding agent either in the dry form or as a starch paste. Both types of granulations were performed in triplicate on each starch sample. Water was used in one granulation in order to evaluate the binding properties of lactose.

Granulation with starch paste. A starch paste containing 6% w/w of pregelatinized, pregelatinized–phosphate-crosslinked, or pregelatinized–adipate-crosslinked starch was prepared by suspending the starches in water using a homogenizer (Silverson Laboratory Mixer Emulsifier, Waterside, Chesham, U.K.) for 5 min. Starches which were not pregelatinized were prepared by initial suspension in an equal amount of cold water to form a slurry. Subsequently, 2–4-times the amount of boiling water was added and the slurry stirred until a transparent paste was obtained that could be diluted with cold water to achieve the desired concentration (Sheth et al., 1980).

Cooled freshly prepared starch paste (50 g) was added to 300 g lactose and granulated at 80 rpm for 8 min. The wet mass was then sieved through a 1.4 mm screen. Granules were dried at 50 °C for 3 h in a hot-air-tray oven.

Granulation with dry starch. A mixture of 300 g lactose and 3 g of each form of modified starch was dry-blended for 10 min at 80 rpm. Subsequently, 47 ml water were added and the mixture granulated for 8 min. The wet mass was then sieved through a 1.4 mm screen. The granules were dried at 50 °C for 3 h in a hot-air-tray oven.

Viscosity of starch paste

Dispersions (6% w/w) of starch or of the modified types in the paste form were prepared as described above. After a 2 h swelling period, the viscosity was measured in triplicate at 25 °C using a rotational viscosimeter (Haake RV12, Karlsruhe, F.R.G.) employing an MVI body at a speed of 256 rpm. All values was read after 10 min.

Granule evaluation

Dry granules were stored in sealed containers and evaluated via the following tests.

Sieve analysis. The granule size distribution and average granule size were determined in triplicate by sieving through a set of standard sieves. Four standard sieves (250, 500, 710 and 1000 μm) were nested in descending order with respect to screen opening. Granules (approx. 100 g) were placed on the upper sieve, and the sieves agitated for 5 min using a sieve shaker (Retostat, F.R.G.). The granule size distribution could be established according to the amount (% w/w) of granules retained on each sieve. The average size (in μm) of granules on any particular sieve was determined by averaging the size of the sieve openings through which the granules passed and that of the sieve upon which granules were retained. The weight retained on each tared sieve was converted to percent retention and multiplied by the average size for that sieve. The sum of these products divided by 100 (percent) yielded the average granule size (Davies and Gloves, 1971).

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, F.R.G.) 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 put on the Retostat sieve shaker. The sieve shaker was operated for 15 s. Material remaining on the screen was weighed and the percent friability calculated.

Moisture content. The moisture content of 5 g lactose granules from each granulation process was determined in triplicate by using a Cenco moisture balance (Central Scientific, Chicago, IL) operating at 100 °C for 15 min.

Results and Discussion

The sieve analysis data revealed no significant difference in either pattern of granule size distribution (Tables 2 and 3) or average granule size (Table 4) for granules prepared using starch or the modified types in the dry form or as a paste, except in the case of the pregelatinized starch paste. Pregelatinized starch used in the paste form yielded granules with coarser particles and a greater average granule size in comparison with other starch modifications. Table 5 lists the viscosities of 6% w/w dispersions of the different types

TABLE 2

Size distribution of granules (% on sieve ± SD) prepared by using the dry starch addition method

Starch	Sieve size (μm)				
	> 1000	1000–710	710–500	500–250	< 250
Corn	41.9 ± 1.1	16.0 ± 0.2	12.6 ± 0.2	23.5 ± 0.8	6.0 ± 0.4
Waxy corn	36.4 ± 2.7	18.0 ± 1.5	14.0 ± 1.3	24.5 ± 0.4	7.1 ± 1.1
Pregelatinized	39.7 ± 1.8	18.1 ± 0.5	17.0 ± 0.4	22.0 ± 1.1	3.2 ± 0.2
Pregel.					
Phosp. XL	36.6 ± 0.5	19.9 ± 1.0	16.7 ± 0.4	23.1 ± 1.4	3.8 ± 0.4
Adip. XL	33.3 ± 4.2	19.5 ± 1.1	17.9 ± 0.8	25.8 ± 2.1	3.5 ± 0.4
Phosp. XL					
Low	34.6 ± 2.3	18.0 ± 1.4	15.0 ± 1.1	26.2 ± 3.5	6.2 ± 0.5
High	36.1 ± 2.0	19.5 ± 1.9	14.8 ± 1.2	23.2 ± 2.4	6.4 ± 0.8
Adip. XL					
Low	38.0 ± 3.0	18.8 ± 0.8	14.7 ± 1.5	22.6 ± 1.9	6.0 ± 0.8
High	32.5 ± 1.6	18.1 ± 0.4	17.7 ± 1.4	26.3 ± 1.9	5.3 ± 0.9
Water	50.9 ± 4.0	19.9 ± 1.1	11.7 ± 1.1	12.6 ± 2.2	4.9 ± 0.5

TABLE 3

Size distribution of granules (% on sieve ± SD) prepared by using the starch paste addition method

Starch	Sieve size (μm)				
	> 1000	1000–710	710–500	500–250	< 250
Corn	38.4 ± 4.0	17.6 ± 1.1	15.5 ± 1.6	23.0 ± 2.2	5.6 ± 0.3
Waxy corn	35.6 ± 3.8	20.4 ± 0.7	17.8 ± 1.6	22.7 ± 1.7	3.5 ± 0.3
Pregelatinized	61.6 ± 3.9	19.4 ± 2.4	10.3 ± 1.5	6.6 ± 0.5	2.1 ± 0.3
Pregel.					
Phosp. XL	38.6 ± 3.1	21.7 ± 1.4	16.5 ± 0.7	19.6 ± 1.4	3.6 ± 0.3
Adip. XL	35.7 ± 1.1	21.7 ± 1.4	17.3 ± 0.3	21.4 ± 1.0	3.9 ± 0.9
Phosp. XL					
Low	27.9 ± 0.6	20.7 ± 0.5	19.4 ± 0.8	27.0 ± 1.2	5.1 ± 0.3
High	28.4 ± 0.9	21.8 ± 0.8	19.1 ± 0.7	26.4 ± 0.7	4.3 ± 0.1
Adip. XL					
Low	23.6 ± 0.6	20.9 ± 0.4	21.1 ± 0.2	30.0 ± 0.6	4.4 ± 0.7
High	28.8 ± 2.4	22.2 ± 1.3	17.3 ± 2.3	26.4 ± 1.5	5.4 ± 0.7

of unmodified and modified starches in the paste form. As can be seen from the data, the viscosity of pregelatinized starch is the lowest. The high viscosity of the starch paste could lead to the insufficient distribution of the paste during granulation, resulting in a smaller granule particle size (Tiamraj and Dingwall, 1978). Nearly all starches, either in the dry form or as a paste, showed a lower average granule size (except the pregelatinized starch paste) than when water was used to granulate lactose. This finding is in agreement with the data reported by Hill (1976) who concluded that the lactose granules had coarser particles when the starch paste used for granulation was diluted.

Granule friability is related to the strength of the granules and their ability to withstand abuse during normal handling. Table 6 lists the friability data for granules prepared by using starch and the modified types in the dry form and as a paste. In the dry form, all types of pregelatinized starches (pregelatinized, pregelatinized–phosphate-cross-

TABLE 4

Average granule size (μm ± SD)

Starch	Dry starch	Starch paste
Corn	811.6 ± 10.1	798.0 ± 26.3
Waxy corn	776.3 ± 17.1	799.0 ± 25.1
Pregelatinized	820.2 ± 11.5	994.9 ± 16.7
Pregel.		
Phosp. XL	801.6 ± 7.8	826.8 ± 17.7
Adip. XL	775.2 ± 28.4	803.6 ± 13.7
Phosp. XL		
Low	765.7 ± 26.1	736.2 ± 6.2
High	785.0 ± 10.2	746.8 ± 8.4
Adip. XL		
Low	797.7 ± 17.2	707.9 ± 6.7
High	758.0 ± 8.2	745.6 ± 19.8
Water	905.1 ± 25.0	

TABLE 5

Viscosity of 6% starch paste (mPa s ± SD)

Starch	Viscosity
Corn	151.81 ± 1.81
Waxy corn	172.50 ± 4.51
Pregelatinized	86.82 ± 0.26
Pregel.	
Phosp. XL	211.38 ± 2.12
Adip. XL	234.38 ± 0.53
Phosp. XL	
Low	358.85 ± 3.84
High	262.35 ± 2.65
Adip. XL	
Low	334.19 ± 3.90
High	271.69 ± 1.49

TABLE 6

Granule friability (% ± SD)

Starch	Dry starch	Starch paste
Corn	75.40 ± 3.67	57.49 ± 2.20
Waxy corn	78.64 ± 3.03	44.96 ± 2.54
Pregelatinized	31.93 ± 1.10	25.17 ± 0.32
Pregel.		
Phosp. XL	36.23 ± 0.73	36.25 ± 3.72
Adip. XL	33.85 ± 3.36	34.54 ± 1.83
Phosp. XL		
Low	77.51 ± 2.25	47.95 ± 0.93
High	81.44 ± 1.26	43.46 ± 0.35
Adip. XL		
Low	75.82 ± 1.96	46.55 ± 3.13
High	78.46 ± 2.67	43.22 ± 2.62
Water	52.67 ± 2.41	

linked and pregelatinized–adipate-crosslinked starch) gave granules with lower friability than that of other samples. This can be explained by the fact that pregelatinization allowed the starches to swell on addition of water during the granulation process. The swollen starches could readily be dispersed, thereby aiding in the agglomeration of lactose particles and improving the bonding strength of granules after drying.

Granules prepared with non-pregelatinized starches, including corn and waxy-corn starches, showed very high friability (> 75% in this study) with no significant difference in friability between all samples. In fact, granules prepared by using water only displayed a lower friability compared to those prepared with non-pregelatinized starches. The addition of water alone during the granulation seemed to yield less friable lactose granules. This can be explained on the basis of lactose being able to dissolve in water during granulation, to recrystallize during drying and to form a crystalline bridge holding the powder particles together. The addition of non-pregelatinized starches to lactose may reduce this effect by restricting the formation of crystalline bridges.

In the paste form, non-pregelatinized starches once again produced granules with greater friability as compared to the pregelatinized and pregelatinized-crosslinked starches. However, granule friability in this case was lower than when they were used in the dry form. This finding supports the theory stating that the use of a binder solution produces granules with better properties as compared to binder in the dry form (Banker et al., 1980). The lactose granules prepared with the pregelatinized-crosslinked starches (phosphate or adipate) as a binding agent showed higher friability than those prepared with purely pregelatinized starch. No difference in friability was observed between granules prepared with the different types of pregelatinized-crosslinked (phosphate and adipate) starches.

The greater binding strength of waxy-corn starch used in the paste form produced granules with lower friability than that of corn starch paste containing 22–30% amylose and 70–78% amylopectin. This result is in agreement with the data of Schwartz and Zelinskie (1978) who concluded that the binding strength of starch appears to be provided by the amylopectin fraction.

There was no difference in moisture content (Table 7) between all granules. The moisture content was about 5% for all granules after drying. As a result of the approximately equal moisture levels for each type of granulation, the influence of moisture upon variations in some granule properties should be minimal.

TABLE 7

Moisture content (% ± SD)

Starch	Dry starch	Starch paste
Corn	5.13 ± 0.21	5.07 ± 0.21
Waxy corn	5.13 ± 0.25	5.27 ± 0.21
Pregelatinized	4.93 ± 0.12	5.13 ± 0.15
Pregel.		
Phosp. XL	5.13 ± 0.12	5.00 ± 0.26
Adip. XL	5.10 ± 0.26	5.13 ± 0.42
Phosp. XL		
low	5.00 ± 0.20	5.23 ± 0.45
high	5.07 ± 0.15	5.13 ± 0.12
Adip. XL		
low	5.03 ± 0.23	5.07 ± 0.42
high	4.90 ± 0.17	5.20 ± 0.26
Water	5.13 ± 0.31	

In conclusion, the preparation of lactose granules with crosslinked starches showed no advantage over the use of corn starch or waxy-corn starch as a binding agent. However, the pregelatinized forms (pregelatinized, pregelatinized–phosphate-crosslinked or pregelatinized–adipate-crosslinked starches) could be used as binding agents, in either the dry or paste form, yielding less friable granules than corn starch or waxy-corn starch. There was no significant difference in granule size distribution, average granule size and friability between granules prepared with pregelatinized–phosphate-crosslinked and pregelatinized–adipate-crosslinked starches. The use of pregelatinized and pregelatinized-crosslinked starches as a binding agent in this study gave higher-quality lactose granules than with corn starch or waxy-corn starch. These pregelatinized starches could be used in a dry form and gave granules with properties similar to those in the case of the paste form. The pregelatinized waxy-corn and pregelatinized-crosslinked starches showed their potential use as a binding agent in the conventional wet granulation process.

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