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AN EVALUATION OF HYDROXYPROPYL STARCH AS DISINTEGRANT AND BINDER IN TABLET FORMULATION

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ABSTRACT

Hydroxypropyl and pregelatinized hydroxypropyl starch were evaluated as disintegrant and binder in tablet formulations. The study showed that the use of pure hydroxypropyl starch showed no advantage as a disintegrant or binder over the actually available tablet ingredients. Pregelatinized hydroxypropyl starch showed some good disintegrating properties and could be used as a binder in wet granulation.

INTRODUCTION

Starch is a multipurpose excipient used in tablet formulation which can be formulated as a filler, a disintegrant or as a binder. Native starch, however, has its limitations in application (1). As a binder in a conventional wet granulation process, it must be converted into a paste. It does not show good compressibility nor flowability for direct compression formulations. The relatively high levels of starch needed as a disintegrant often weakens the tablet structure. Therefore, some food

accepted modified starches with improved properties have been evaluated as tablet excipient, i.e. thermal modified and chemically crosslinked modified starches (2, 3).

Hydroxypropyl starch is one of the modified starches which are normally used in food applications where it provides viscosity stability as a thickening agent and ensures water-holding under low-temperature storage conditions (4). Because of some interesting properties of this chemically modified starch,i.e. the rate of granule swelling in water and the excellent dispersibility in cold water (4), it is interesting to study the use of hydroxypropyl starch as a disintegrant and a binder in tablet formulations.

MATERIALS

Native waxy-corn starch was modified by the hydroxyalkylation technique using propyleneoxide as a reactant to yield hydroxypropyl starch. The resultant modified starch had a degree of substitution (DS) less than 0.09 and included a small amount of phosphate crosslinked starch (0.1% maximum). Pregelatinized hydroxypropyl starch was obtained by drum drying technique after the hydroxyalkylation reaction. Hydroxypropyl modified starches were compared with native corn starch for their binding properties. All starches were obtained from Cerestar (Vilvoorde, Belgium).

METHODS

Disintegrating Agent

Influence of disintegrant concentration - Powder mixtures, containing dicalcium phosphate dihydrate (Emcompress, Edward Mendell, New York, USA) and 2% or 4% of starch sample, were prepared and compressed to a tablet with the hardness of 8 kg (Heberlein) as previously described (2).

Influence of tablet additives - The influence of filler was studied by replacing dicalcium phosphate with lactose monohydrate (Tablettose, Meggel, Wasserburg, Germany). While the influence of lubricant was studied by replacing 0.5% magnesium stearate with 2.0% sodium benzoate (≤180 µm, Laboratoria Flandria, Gent, Belgium). Powder mixtures and tablets were prepared as previously described (2).

Granulating Agent

Granulation - Wet granulation was achieved by massing in a planetary mixer (Hobart K45SS, Troy, OH, USA) or in a high shear mixer (Gral 10, Machines Collette, Wommelgem, Belgium) and by the addition of binding agent either in the dry form or as a paste. Both types of granulations were performed in triplicate on each starch sample and were detailed in a previous study (3, 4).

Granule Evaluation - The dry granules were evaluated for size distribution and friability. The evaluation methods were previously described (3).

RESULTS AND DISCUSSION

Disintegrating Agent

Influence of disintegrant concentration - The dicalcium phosphate tablets formulated with hydroxypropyl starch did not disintegrate within 15 min. These results are similar to formulations with some crosslinked starches. Chemical modifications of starches as hydroxyalkylation with a low DS or crosslinking without pregelatinization yielded starches with poor disintegrating properties (2). The use of 4% pregelatinized hydroxypropyl starch in the formulation induced tablet disintegration within 2 min whereas 2% was still inadequate.

Influence of tablet additives - Changing the filler from dicalcium phosphate to lactose had a great influence on the disintegration time of tablets formulated with hydroxypropyl starch (Table 1). This confirms the results

TABLE 1

Influence of tablet additives (filler and lubricant) on the disintegration time (in s ± SD) of tablets prepared using 4% disintegrant (n = 6).

Additive	Disintegrant	
	Hydroxypropyl starch	Pregel.hydroxy-propyl starch
Filler		
Dicalcium phosphate	>900	125.2 ± 22.1
Lactose monohydrate	24.7 ± 2.5	32.0 ± 1.3
Lubricant		
Magnesium stearate	>900	125.2 ± 22.1
Sodium benzoate	17.8 ± 1.0	39.7 ± 0.8

using crosslinked modified starches as disintegrating agents, where the disintegration time was reduced from more than 15 min to less than 1 min. The disintegration time of dicalcium phosphate tablets formulated with pregelatinized hydroxypropyl starch was reduced from 2 min to 30 s. The differences in disintegration time are not as dramatic with lactose tablets as for dicalcium phosphate tablets. The disintegration time of dicalcium phosphate tablets depends on the action of the disintegrants. Erosion at the outer surfaces of lactose tablets due to the dissolving lactose along with the action of disintegrants cause the lactose tablets to break apart. Due to the different mechanisms involved, only minor differences in disintegration time of lactose tablets using different types of disintegrant were observed.

By replacing magnesium stearate with sodium benzoate, the disintegration time of tablets containing hydroxypropyl starch was reduced from more than 15 min to less than 30 s (Table 1). This effect was also observed for the tablets formulated with pregelatinized

TABLE 2

Particle size distribution (% on sieve ± SD) of granules prepared with 6% w/w dry starch or starch paste by planetary mixer (n=3)

Starch	Sieve size (µm) >1000	1000-710	710-500	500-250	<250
Corn					
- dry starch	41.9±1.1	16.0±0.2	12.6±0.2	23.5±0.8	6.0±0.4
- starch paste	38.4±4.0	17.6±1.1	15.5±1.6	23.0±2.2	5.6±0.3
Hydroxypropyl					
- dry starch	37.2±1.3	19.1±1.6	12.3±1.4	25.6±2.1	5.8±0.8
- starch paste	34.2±0.7	19.2±1.2	14.7±0.6	26.2±1.1	5.7±0.6
Pregelatinized-hydroxypropyl					
- dry starch	32.2±0.1	17.8±0.7	17.3±0.7	29.0±0.4	3.8±0.2
- starch paste	33.7±0.3	17.0±1.5	18.9±0.8	27.0±0.3	3.4±0.4

hydroxypropyl starch where the disintegration time was reduced to 40s.

The results from this study and previous studies (2) did not reveal any difference in disintegrating properties for the different types of chemical modifications. Both types of chemically modified starches, hydroxypropyl or crosslinked starches, without pregelatinization showed a poor disintegrating action. After pregelatinization, which imparted the cold water swellable property of these modified starches, the disintegrating property was improved. Nevertheless, the disintegrating action of this pregelatinized and chemically modified starch was still inferior to the actually available disintegrants.

Binding Agent

The sieve analysis data (Table 2) revealed no influence on the particle size distribution of lactose granules prepared with corn, hydroxypropyl and pregelatinized hydroxypropyl starches as binding agents in a

TABLE 3

Particle size distribution (% on sieve ± SD) of granules prepared with 6% w/w dry starch or starch paste by high shear mixer (n=3)

Starch	Sieve size (μm)				
	>1000	1000-710	710-500	500-250	<250
Corn					
- dry starch	38.7±1.9	19.2±1.1	12.8±0.8	24.7±1.7	4.1±0.4
- starch paste	60.3±2.1	16.2±0.9	8.9±0.5	12.4±1.6	2.2±0.6
Hydroxypropyl					
- dry starch	42.3±1.8	18.3±0.8	15.4±1.3	20.3±0.8	3.6±0.5
- starch paste	58.3±1.6	17.4±1.4	9.5±0.9	11.9±1.3	2.8±0.7
Pregelatinized-hydroxypropyl					
- dry starch	40.0±0.6	34.0±0.4	13.6±0.4	9.9±0.5	2.5±0.2
- starch paste	57.2±1.4	21.5±0.5	7.6±0.7	11.2±1.4	2.4±0.3

TABLE 4

Friability (% ± SD) of granules prepared with 6% w/w dry starch or starch paste by planetary or high shear mixer (n=3)

Starch	Mixer	
	Planetary	High shear
Corn		
- dry starch	75.40 ± 3.67	58.67 ± 1.74
- starch paste	57.49 ± 2.20	40.73 ± 2.93
Hydroxypropyl		
- dry starch	82.46 ± 1.93	61.27 ± 2.13
- starch paste	53.34 ± 2.11	44.38 ± 2.57
Pregelatinized-hydroxypropyl		
- dry starch	35.80 ± 1.42	32.36 ± 3.13
- starch paste	34.41 ± 1.07	30.28 ± 2.67

planetary mixer. Nevertheless, granules prepared with starch paste showed a lower friability in comparison to the dry addition method with an exception of pregelatinized hydroxypropyl starch (Table 4). No difference in granule friability was seen when pregelatinized hydroxypropyl starch was used in the dry or the paste addition method.

Granulation in a high shear mixer produced a shift in particle size distribution towards coarser granules in comparison to granules produced by planetary mixer (Table 3). Especially, the amount of granules above 1,000 μm was increased and less fines were produced. Pregelatinized hydroxypropyl starch produced less friable granules than those produced with corn or hydroxypropyl starch. The high shear mixer provided granules with a lower friability in comparison with granules produced with planetary mixer. Nevertheless, there was no difference in friability between granules binded by pregelatinized hydroxypropyl starch and produced with the two different granulators. The results from this granulation study using hydroxypropyl and pregelatinized hydroxypropyl starch are in good agreement with the finding in previous studies (3, 4). The only chemically modified starches showed no advantage over native corn starch while pregelatinized starches showed their potential use as binding agents. Pregelatinized hydroxypropyl starch gave the same granule quality as those prepared with pregelatinized crosslinked starch. Nevertheless, the pregelatinized hydroxypropyl starch showed an advantage related to the ease of dispersion in comparison to the pregelatinized starches previously tested (3, 4). A pregelatinized hydroxypropyl starch paste was easily prepared by simple stirring in a container whereas pregelatinized crosslinked starch pastes have to be prepared using a homogenizer.

CONCLUSION

Hydroxypropyl starch showed to be a poor disintegrating agent in tablet formulations. The use of 4% pregelatinized hydroxypropyl starch in the formulation was sufficient to disintegrate dicalcium phosphate tablets within 2 min. The disintegration of tablets formulated with hydroxypropyl starch was influenced by the type of filler and lubricant. The quality of lactose granules prepared with hydroxypropyl starch showed no advantage over the use of native corn starch. Pregelatinized hydroxypropyl starch used as binder yielded higher quality granules than did corn or hydroxypropyl starch. The main advantage of using pregelatinized hydroxypropyl starch is the ease of dispersion when a starch paste has to be prepared.

REFERENCES

1. G.S. Banker, G.E. Peck and G. Baley, in "Pharmaceutical Dosage Form : Tablet," vol.1, H.A. Lieberman and L. Lachman, eds., Marcel Dekker, New York, 1980, p.61.
2. N. Visavarungroj and J.P. Remon, Int. J. Pharm., 62, 125 (1990).
3. N. Visavarungroj, J. Herman and J.P.Remon, Int. J. Pharm., 59, 73 (1990).
4. N. Visavarungroj and J.P. Remon, Int. J. Pharm., In press, (1990).