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Crosslinked starch as a disintegrating agent

N. Visavarungroj and J.P. Remon

Laboratory of Pharmaceutical Technology, State University of Ghent, Harelbekestraat 72, 9000, Ghent, Belgium

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Summary

Different types of crosslinked starches and pregelatinized-crosslinked starches were evaluated as disintegrating agents in comparison to potato starch and a number of super-disintegrants such as Ac-Di-Sol, Explotab and Polyplasdone XL. The granule swelling power, and the rate and amount of water uptake of each sample were determined. The influence of disintegrant concentration, tablet hardness and tablet additives was evaluated by measuring the disintegration time of the tablets. Potato starch and the starches that were crosslinked only showed the lowest granule swelling power. In contrast with the considerable swelling power achieved for the pregelatinized or pregelatinized-crosslinked starches, both the rate and amount of water uptake were observed to be low for these forms. Tablets formulated with pregelatinized starches, with or without crosslinking, showed variable and long disintegrating times in comparison to the super-disintegrants. The disintegration time of tablets, using pregelatinized-crosslinked starches, was influenced by the type of filler and the lubricant. No variation in disintegration properties was observed for the different types of crosslinking agents used in starch modification.

Introduction

The term disintegrant is used to refer to a substance that is added to a tablet formula for the purpose of causing the compressed tablet to break apart when placed in an aqueous environment (Gunsel et al., 1980). The function of the disintegrant is to counteract the action of tablet binder and the compression forces used to form the tablet. The stronger the effect of the binder, the more efficient is the disrupting effect required of the disintegrant in order to release the active ingredient into the gastrointestinal fluid.

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

Disintegrants have been attracting an increasing amount of attention as a result of the greater interest in drug dissolution and bioavailability. Many investigations reported were exclusively directed at the elucidation of the mechanism and comparative evaluations of standard, new and modified disintegrants. The initial investigations in this area were concerned primarily with materials that are known to swell when wetted with water. The supposition was that these agents would swell when exposed to gastric fluids and would exert sufficient pressure in the tablet to break it apart into small segments.

Starch is the most common disintegrating agent in use today. It was once assumed that the function of starch as a disintegrant depended on its swelling when wetted. However, it has been shown

that starch does not swell when exposed to water at the temperature found in gastric fluids. It has been suggested that the disintegrating action of starch is not due to swelling but rather arises from capillary action (Curlin, 1955). The activity of starch as a disintegrant has been defined as being involved in formation of intermolecular hydrogen bonding during compression and release in the presence of excess moisture (Ingram and Lowenthal, 1966). Despite a long and proven record as a disintegrant, starch possesses disadvantages when used in direct compression formulation (Shangraw et al., 1981). The relatively high levels required and the lack of compressibility often weaken the tablet structure. Therefore, the development of new disintegrants that are effective at lower levels is of great importance in formulations for direct compression.

In this work, different types of thermally modified and/or crosslinked modified waxy-corn starches were studied regarding their potential use as disintegrating agents in comparison to those commonly used.

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 crosslinking were used: phosphate and adipate. The native starches were crosslinked at both low and high levels. The pregelatinized starches were crosslinked only at a high level. The other disintegrants used were potato starch and super-disintegrants, such as croscarmellose sodium type A (Ac-Di-Sol, FMC, Philadelphia, U.S.A.), sodium starch glycolate (Explotab, Edward Mendell, New York, U.S.A.) and crospovidone (Polyplasdone XL, GAF, New York). Dicalcium phosphate dihydrate (Emcompress, Edward Mendell, New York) and lactose monohydrate (Tablettose, Meggel Milchindustrie, F.R.G.) were used as fillers. Magnesium stearate (≤ 180 μm) and sodium benzoate (≤ 180 μm) (both from Laboratoria Flandria, Ghent, Belgium) were used as lubricants in the tablet formulation.

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 crosslinked	+	+	
Pregelatinized–adipate-crosslinked	+		+
Crosslinked			
Low level		+	+
High level		+	+

Methods

Some fundamental properties, such as mean particle size, granule swelling power, water uptake, and a disintegration test were used to determine the disintegrating action of the modified starches.

Mean particle size The mean particle size of samples was determined microscopically with a calibrated eyepiece (Carl Zeiss Photomicroscope, Carl Zeiss, F.R.G.). The mean particle size of each sample, dispersed in isopropylmyristate (Henkel, Dusseldorf, F.R.G.), was calculated from 50 particles of which the diameters were measured at random.

Granule swelling power The granule swelling power of each sample was examined in triplicate by determining the water retention capacity and swelling capacity. Both tests were performed by using the same procedure as described previously (Visavarungroj et al., 1990).

Water uptake The rate and amount of water uptake of tablets compressed from 1 g of pure sample at 150 MPa with 13-mm flat-face punches (Erweka tablet press type EKO, Frankfurt, F.R.G.) were determined in triplicate as described previously (Visavarungroj et al., 1990).

Disintegration test

Influence of the disintegrant concentration Powder mixtures, containing dicalcium phosphate dihydrate and 2 or 4% of each sample, were mixed for 13 min in a Turbula mixer (type T2A, W.A. Bachofen, Basel, Switzerland). Magnesium stearate (0.5%) was then added and mixing continued for an additional 2 min. The disintegration time of six tablets, weighing 1 g, compressed with 13-mm flat-face punches (Erweka tablet press type EKO) was determined in water by a disintegration test apparatus without disks at 37 °C (Erweka disintegration test apparatus, type ZT3, Offenbach am Main, F.R.G.). All tablets were compressed to a hardness of 8 kg (Heberlein).

Influence of tablet hardness The influence of tablet hardness on the disintegration time was evaluated for tablets containing 4% disintegrant. The tablets were prepared as described above and compressed to achieve a hardness of 4, 8 and 12 kg (Heberlein), respectively. The tablets were then subjected to the disintegration test.

Influence of tablet additives The influence of filler was studied by replacing dicalcium phosphate dihydrate by lactose monohydrate in the formula containing 4% disintegrant and 0.5% magnesium stearate. All the tablets had a hardness of 8 kg (Heberlein).

The influence of lubricants on the disintegration time was studied by replacing 0.5% magnesium stearate with 2.0% sodium benzoate. This study was performed on the formula containing dicalcium phosphate dihydrate as a filler. All tablets had a hardness of 8 kg (Heberlein).

Results and Discussion

Mean particle size Results of particle size analysis are shown in Table 2. The crosslinked-only starches contained very fine particles with a mean diameter of about 10 μm. The pregelatinized starch and pregelatinized-crosslinked starches had a particle size of about 15–20 μm in diameter. The fine particle size can be explained by the fact that these starches were milled to the desired particle size after drying during the pregelatinizing process. The other commonly used disintegrants showed a mean particle size of about 20–30 μm.

TABLE 2

Mean particle size of the disintegrants

Disintegrant	Mean particle size (μm ± SD)
Potato starch	26.11 ± 16.32
Ac-Di-Sol	30.56 ± 42.43
Explotab	24.72 ± 14.33
Polyplasdone XL	22.36 ± 13.47
Pregel. starch	18.24 ± 11.65
Pregel. + Phosp. XL	15.37 ± 13.45
Pregel. + Adip. XL	20.42 ± 10.89
Phosp. XL-low	9.14 ± 2.89
Phosp. XL-high	11.00 ± 4.07
Adip. XL-low	11.54 ± 3.85
Adip. XL-high	11.44 ± 3.78

TABLE 3

Granule swelling power of commonly used disintegrants and modified starches

Sample	Water retention capacity (± SD)	Swelling capacity (± SD)
Potato starch	2.4 ± 0.1	0.8 ± 0.0
Ac-Di-Sol	7.9 ± 0.7	4.3 ± 0.0
Explotab [a]	18.0 ± 2.1	32.0 ± 2.8
Polyplasdone XL	7.9 ± 0.7	1.5 ± 0.0
Pregel. starch	23.8 ± 0.2	[b]
Pregel. + Phosp. XL.	15.3 ± 0.1	6.0 ± 0.2
Pregel. + Adip. XL.	15.7 ± 0.1	10.5 ± 0.2
Phosp. XL.-low	2.3 ± 0.0	0.9 ± 0.0
Phosp. XL.-high	2.2 ± 0.0	0.8 ± 0.0
Adip. XL.-low	2.2 ± 0.0	0.9 ± 0.1
Adip. XL.-high	2.2 ± 0.0	0.9 ± 0.0

[a] Because Explotab showed an excessively high swelling power, only 1 g of the product was dispersed in water.
[b] Cannot be determined due to being highly miscible with water.

Granule swelling power The granule swelling power is defined as the extent of swelling of the starch granules (Wurzburg, 1986). The results (Table 3) are in agreement with previously published data where it was shown that the crosslinked starches do not swell while the pregelatinized-crosslinked starches showed a lower swelling power than the pregelatinized starch (Visavarungroj et al., 1990). For the commonly used disintegrants, potato starch revealed the lowest swelling power,

nearly identical to that of crosslinked starches. Among the super-disintegrants used in this study, Explotab showed the highest water retention and swelling capacity. The pregelatinized starch showed a higher swelling power than the super-disintegrants. The granule swelling power of the pregelatinized-crosslinked starches was lower in comparison with the pregelatinized starch.

Water uptake There was no important difference in the rate and amount of water uptake by potato starch and the cross-linked starches. The rate and amount of water uptake by these samples were very low in comparison to the super-disintegrant. The rate and amount of water uptake by the pregelatinized starches were even lower than those of the crosslinked starches (Fig. 1). The small amount of water uptake by the pregelatinized starch could be explained by the fact that the granules of this type swelled on contact with water, forming a viscous gel barrier, blocking the tablet pores and thus hindering further water uptake (Van Kamp et al., 1986). The type of crosslinking did not influence the water uptake for the pregelatinized-crosslinked (phosphate and adipate) starches. Among the superdisintegrants (Fig. 1), the highest rate and amount of water uptake were found for Explotab. Ac-Di-Sol showed a lower rate and amount of water uptake than Polyplasdone XL. This could be attributed to the partial water solubility of Ac-Di-Sol resulting in a viscous barrier forming during water penetration (Van Kamp et al., 1986).

TABLE 4

Disintegration time (in s, ± SD) of tablets containing dicalcium phosphate dihydrate, 2 or 4% disintegrant and 0.5% magnesium stearate (hardness was 8 kg (Heberlein))

Sample	Disintegrant concentration	
	2%	4%
Potato starch	>1800	>1800
Ac-Di-Sol	14.7± 3.1	10.3± 0.6
Explotab	15.3± 2.0	11.3± 0.6
Polyplasdone XL	38.2±18.1	9.7± 1.2
Pregel. starch	273.3±67.9	369.0±62.5
Pregel. + Phosp. XL.	>1800	93.3±16.2
Pregel. + Adip. XL.	>1800	100.0±16.4
Phosp. XL.-low	>1800	>1800
Phosp. XL.-high	>1800	>1800
Adip. XL.-low	>1800	>1800
Adip. XL.-high	>1800	>1800

Disintegration test

Influence of the disintegrant concentration (Table 4) The dicalcium phosphate dihydrate tablets, formulated with potato starch or crosslinked

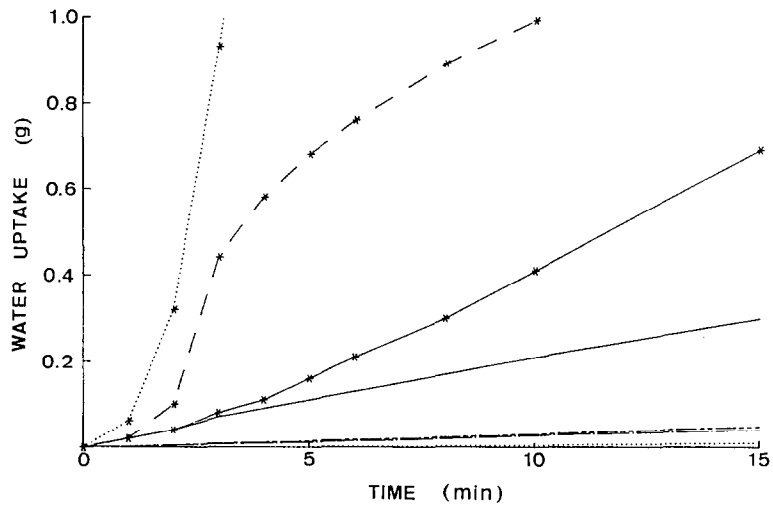

Fig. 1. Water uptake as a function of time for tablets prepared from different types of disintegrants. (———) Potato starch; (*———*) Ac-Di-Sol; (*·····*) Explotab; (*— — —*) Polyplasdone XL; (·····) pregelatinized starch; (–·–·–·–) pregelatinized-phosphate crosslinked starch; (– – – – –) pregelatinized-adipate crosslinked starch.

starches, did not disintegrate within 30 min. These results demonstrate the poor disintegrating character of potato starch and crosslinked starches in these formulas. These non-pregelatinized starches do not swell in water and their mechanism of disintegration is based mainly on water penetration due to capillary action, which developed insufficient internal pressure to induce complete tablet disintegration. In contrast, the use of 2% Ac-Di-Sol, Explotab or Polyplasdone XL appeared to be sufficient to disaggregate tablets in less than 30 s. There was no important difference in the disintegration time between the tablets using different concentrations of Ac-Di-Sol or Explotab. However, increasing the concentration of Polyplasdone XL significantly decreased the disintegration time. This can be explained by the fact that the mechanism of disintegration of Polyplasdone XL was reported to comprise capillary action with a secondary swelling effect (Shangraw et al., 1980). The capillary network of tablets with 4% Polyplasdone XL was improved and absorbed water more rapidly, causing the tablets to disintegrate. Tablets with 2% of the pregelatinized-crosslinked starches as a disintegrator did not disintegrate within 30 min, however, they did disintegrate in about 2 min when the disintegrant concentration was increased to 4%. When 4% of disintegrant was used, no important difference in disintegration time between tablets formulated with starches crosslinked with different crosslinking agents or to various degrees of crosslinking was observed. Tablets using 2% or 4% of the pregelatinized-only starch as a disintegrator showed an average disintegration time of about 5 min but were characterized by considerable variation in disintegration time.

Influence of tablet hardness (Table 5) The tablets using potato starch or the crosslinked-only starches as disintegrants showed poor disintegrating characteristics irrespective of tablet hardness. In contrast, the tablets using super-disintegrants showed very short disintegration times. The differences in tablet hardness for tablets containing Ac-Di-Sol or Explotab as a disintegrant did not reveal any influence on their disintegration time. However, those containing Polyplasdone XL disintegrated more rapidly when the hardness was increased from 4 kg to 8 and 12 kg, respectively. The large variation in disintegration time for tablets formulated with the pregelatinized-only starch was confirmed. By increasing the tablet hardness from 4 to 12 kg, a progressive increase in disintegration time was observed for the pregelatinized starch and pregelatinized-crosslinked starches. This phenomenon could be explained by a progressive decrease in tablet porosity and capillary diameters. A rapid increase in volume and gel formation of the pregelatinized starch inhibits further water uptake. Crosslinking of the pregelatinized starch prevents complete gel formation and swelling which can be seen in reduced

TABLE 5

Disintegration time (in s, ± SD) of tablets containing dicalcium phosphate dihydrate, 4% of disintegrant, and 0.5% of magnesium stearate (hardness was 4, 8 and 12 kg (Heberlein))

Sample	Hardness		
	4 kg	8 kg	12 kg
Potato starch	> 1 800	> 1 800	> 1 800
Ac-Di-Sol	11.0 ± 0.0	10.3 ± 0.6	9.7 ± 0.5
Explotab	11.0 ± 0.0	11.3 ± 0.6	13.0 ± 0.0
Polyplasdone XL	25.7 ± 4.6	9.7 ± 1.2	6.3 ± 0.5
Pregel. starch	261.7 ± 46.4	369.0 ± 62.5	429.7 ± 88.6
Pregel. + Phosp. XL.	112.3 ± 5.4	93.3 ± 16.2	147.0 ± 9.9
Pregel. + Adip. XL.	72.3 ± 8.3	100.0 ± 16.4	124.0 ± 21.4
Phosp. XL.-low	> 1 800	> 1 800	> 1 800
Phosp. XL.-high	> 1 800	> 1 800	> 1 800
Adip. XL.-low	> 1 800	> 1 800	> 1 800
Adip. XL.-high	> 1 800	> 1 800	> 1 800

disintegration times. Nevertheless, in comparison to super-disintegrants, the partially reduced swelling by crosslinking is insufficient to prevent pre-obstruction.

Influence of tablet additives Changing the filler from dicalcium phosphate dihydrate to lactose monohydrate reduced the disintegration time for all formulations containing starch or starch modifications (Table 6). This effect was especially important for potato starch and the crosslinked-only starches. The disintegration time of these tablets was reduced to about 1 min. The disintegration time of the lactose tablets containing the super-disintegrants was longer than for the dicalcium phosphate tablets. This supported the finding of Graf et al. (1982) who stated that the swelling disintegrants retarded water penetration as the solubility of the other tablet ingredients increased, thus prolonging the disintegration time. The swelling particles of super-disintegrants partially filled the void of lactose tablets and thus water could not easily penetrate into the tablets. An additional retarding effect can be expected because of the dissolved lactose making the penetrating water more viscous. In the case of potato starch and the crosslinked starches whose mechanism of disintegration is due to capillary action instead of swelling, the water penetrated rapidly along a capillary network. Also, erosion at the outer surfaces of Tablettose tablets due to the dissolving lactose caused the tablets to break apart.

TABLE 6

Disintegration time (in s, ± SD) of tablets containing dicalcium phosphate dihydrate or lactose monohydrate, 4% disintegrant and 0.5% magnesium stearate (hardness was 8 kg (Heberlein))

Sample	Filler	
	Emcompress	Tablettose
Potato starch	>1800	53.4± 3.0
Ac-Di-Sol	10.3± 0.6	112.0±10.0
Explotab	11.3± 0.6	77.0± 5.2
Polyplasdone XL	9.7± 1.2	32.4± 3.2
Pregel. starch	369.0±62.5	128.6± 8.4
Pregel. + Phosp. XL.	93.3±16.2	41.0± 1.4
Pregel. + Adip. XL.	100.0±16.4	50.6± 0.9
Phosp. XL.-low	>1800	54.4± 5.4
Phosp. XL.-high	>1800	53.0± 5.0
Adip. XL.-low	>1800	53.6± 5.0
Adip. XL.-high	>1800	56.0± 3.8

TABLE 7

Disintegration time (in s, ± SD) of tablets containing dicalcium phosphate dihydrate, 4% disintegrant and 0.5% magnesium stearate or 2.0% sodium benzoate (hardness was 8 kg (Heberlein))

Sample	Lubricant	
	Magnesium stearate	Sodium benzoate
Potato starch	>1800	14.0± 0.8
Ac-Di-Sol	10.3± 0.6	14.0± 0.0
Explotab	11.3± 0.6	20.0± 1.7
Polyplasdone XL	9.7± 1.2	8.0± 1.0
Pregel. starch	369.0±62.5	286.7±81.8
Pregel. + Phosp. XL.	93.3±16.2	32.3± 0.6
Pregel. + Adip. XL.	100.0±16.4	41.0± 1.7
Phosp. XL.-low	>1800	28.3± 5.9
Phosp. XL.-high	>1800	24.7± 2.1
Adip. XL.-low	>1800	23.0± 1.7
Adip. XL.-high	>1800	25.0± 2.0

When magnesium stearate was replaced by sodium benzoate, the disintegration time of dicalcium phosphate tablets was reduced when starch and starch modifications were used (Table 7). The disintegration time of the tablets using potato starch or the crosslinked-only starches was reduced from more than 30 min to less than 30 s. This phenomenon was not observed for the super-disintegrant and was much less pronounced for the pregelatinized-only starch. This can be explained by the fact that magnesium stearate formed a hydrophobic film around the disintegrant particles during the mixing of the tablet ingredients (Bolhuis et al., 1981). The deleterious effect of magnesium stearate seemed to be dependent on the swelling properties of the disintegrants. As the super-disintegrants swell extensively when brought into contact with water, it might be assumed that a small amount of water already destroyed the hydrophobic lubricant film. Consequently, a chain reaction of swelling of the disintegrant was initiated with subsequent penetration of water and disintegration of the tablet. The limited swelling properties of potato starch and the crosslinked starches were insufficient to eliminate the deleterious effect of the hydrophobic film, producing tablets with very long

disintegration times. When magnesium stearate was replaced by sodium benzoate, water easily penetrated into the tablets resulting in a shorter disintegration time.

In conclusion, the crosslinked-only waxy-corn starches showed the same disintegrating properties as potato starch in this study. They revealed the lowest granule swelling power and a poor rate and amount of water uptake. The poor disintegrating character of the tablets containing potato starch or the crosslinked-only starches could be improved by changing the filler or the lubricant. The pregelatinized-crosslinked waxy-corn starches showed better disintegrating properties than the crosslinked-only starches. The tablets containing pregelatinized starch revealed considerable variation and longer disintegration times than those formulated with pregelatinized-crosslinked starches. By increasing the tablet hardness, a progressive increase in disintegration time was observed for the pregelatinized starch and the pregelatinized-crosslinked starches. This phenomenon was not seen for the super-disintegrants. The super-disintegrants showed better disintegrating properties than all starch samples investigated. This study indicates that thermally modified and/or crosslinked modified waxy-corn starches are not superior to actually available disintegrants.

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