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EVALUATION OF MODIFIED RICE STARCH, A NEW EXCIPIENT FOR DIRECT COMPRESSION.

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ABSTRACT

The compression characteristics of modified rice starch (Primotab^{R}ET), a new excipient for the preparation of tablets by direct compression is evaluated. Modified rice starch is an agglomerated rice starch product. It has excellent flowing and disintegration properties. In contrast to other starch-based filler-binders, after mixing with a lubricant, the binding properties were sufficient.

Tablets containing oxazepam as a model drug were prepared with modified rice starch as unique filler-binder or with a blend of equal parts of modified rice starch and a commonly used filler-binder. The tablet

properties show that modified rice starch is a useful product for the preparation of tablets by direct compression. It can be used as a unique filler-binder, or in combination with other excipients such as α-lactose monohydrate or anhydrous lactose. Combinations with microcrystalline cellulose should be avoided because of the poor flowability of the blends and the slow disintegration of the tablets.

INTRODUCTION

Since the late 1960's many excipients have been introduced on the pharmaceutical market as filler-binders for tablets prepared by direct compression. The products are based, among others on starch, cellulose, anorganic calcium salts, polyalcohols, lactose and other sugars. Although starches are cheap and widely available excipients, their flow properties are insufficient for use as directly compressible filler-binders [1]. Special starch products with both improved flow and binding properties as compared with native starch were introduced. Pregelatinized starch is available in a directly compressible quality. It is partially hydrolyzed corn starch and marketed as STARCH 1500^{R} (formerly STA-Rx 1500^{R}). Although it was claimed to have many advantages over starch USP with respect to fluidity and compressibility [2], the flow properties were poor as compared with other filler-binders for direct compression [3]. A major drawback is, however, the dramatical decrease in binding properties during mixing with hydrophobic lubricants such as magnesium stearate [4,5]. Another starch product for direct compression, Amylose, with promising properties for direct compression [6,3] showed a similar extreme lubricant sensitivity with respect to binding properties [4] and was taken out of the market. Although the decrease in crushing strength as an effect of mixing with magnesium stearate was attributed to the plastic behaviour of the starch products during compaction [7], recent investigations showed that also other factors such as distribution and quantity of the lubricant as well as the mechanism of consolidation of the excipient may play a role [8,9].

In an evaluation of several native starches, rice starch proved to have much better compaction properties than potato -, maize - and tapioca starch [1]. Moreover, the binding properties of rice starch proved to be almost insensitive to mixing with magnesium stearate. This in contrast to the other starches. Rice starch exhibited worst flowability, caused by its fine particle size as compared to the other starches. The lack of lubricant sensitivity of rice starch was attributed to its poor flow properties, which would impair the formation of a lubricant film over the particles during mixing with the lubricant.

Granulation of rice starch improved both flow and compaction properties, but also increased the lubricant sensitivity [1]. In another study [8] it was shown that the lubricant sensitivity of starch granulations was dependent, among others, on the granulation method, i.e on the properties of the granules such as bulk density and flowability.

Recently, modified rice starch (Primotab^{R}ET), a new filler-binder for direct compression has been introduced. Modified rice starch is a freely flowing product consisting of aggregated rice starch particles. The present study describes the tabletting characteristics of modified rice starch whereas tablets containing a model drug (oxazepam) are evaluated.

MATERIALS AND METHODS

Materials

Modified rice starch, developed as Era-Tab^{R} by Erawan Pharmaceutical Research and Laboratory Co. Ltd.(Bangkok, Thailand) and marketed as Primotab^{R}ET by Avebe, Foxhol, The Netherlands), was used as a filler-binder. Other filler-binders used were anhydrous ß-lactose (Pharmatose^{R}DCL21) and hydrous lactose 100 mesh (Pharmatose^{R}100M), both from DMV, Veghel, The Netherlands, microcrystalline cellulose (Avicel^{R}PH102) from F.M.C. Corp., Brussels, Belgium and pregelatinized starch (STARCH 1500^{R}) from Colorcon, Orpington, England. Rice starch Ph.Eur. grade was obtained from Chemiefarma, Maarssen, The

Netherlands. The tablets were lubricated with magnesium stearate (Centrachemie, Etten-Leur, The Netherlands). Colloidal siliciumoxide (Aerosil[R]200 from Degussa, Frankfurt a/M, Germany) was added as a glidant. Prior to use, magnesium stearate and colloidal siliciumoxide were sieved through a 210 μm sieve, respectively. Oxazepam (Pharmachemie, Haarlem, The Netherlands) was used as a drug. Before use, all tabletting materials were stored at 20° ± 1° C and 45% ± 5% relative humidity, for at least one week. The other used materials were of analytical quality.

Powder characterisation of modified rice starch

The particle size distribution of modified rice starch was estimated by sieve analysis. On seven sieves with decreasing sieve opening on vibrational sieve machine (Fritsch analysette, Idarsdorff, Germany), 200 g of the product was placed. After 30 min the fraction on each sieve was weighed. The bulk density was measured by pouring a weighed amount of the product into a measuring glass with an internal diameter of 26 mm. The results are the mean of four measurements. The tap density was measured as described in the Deutsche Industrie Norm 53194. The Hausner ratio was calculated as the quotient of tap and bulk density. The results are the mean of 4 measurements.The results of the angle of repose are the mean of two measurements.

The percentage of water was estimated by measuring the loss on drying as described in the USP XXI.

Tablet preparation

Placebo tablets were prepared by mixing modified rice starch with 0.5% w/w magnesium stearate during 5 min in a Turbula mixer (model 2P, W.A.Bachofen, Basle, Switzerland) at a rotation speed of 90 rpm. Tablets of 250 mg were prepared on a single punch tabletting machine (HOKO KJ, Indola, Rijswijk, The Netherlands), at several compression load levels (5, 10, 15 and 20 kN). Modified rice starch tablets without lubricant were prepared in the same way.

For the measurements of the lubricant sensitivity, different filler-binders were mixed with 0.5% magnesium stearate during different time periods in the Turbula mixer at 90 rpm. Both unlubricated and lubricated tablets of 250 mg were compressed in a 13 mm die of a compression device mounted between the plates of a motorized hydraulic press (ESH Testing Ltd, Brierley Hill, U.K.) at 20 kN. The loading rate was 2 kN/s. If necessary, the die was prelubricated by compression of a magnesium stearate tablet.

For tablets containing oxazepam, all ingredients except magnesium stearate were mixed for 15 min in the Turbula mixer at 90 rpm. After addition of 1.0% magnesium stearate, mixing was continued for 2 min. The oxazepam tablets (tablet weight 250 mg) were prepared on a single punch tabletting machine (HOKO-KJ, Indola, Rijswijk, The Netherlands) at 20 kN, using flat 9 mm punches.

Tablet properties

The tablet properties were measured one day after preparation. The crushing strength of the tablets was measured using a Schleuninger instrument, model 2E (Dr.K.Schleuniger, Zurich, Switzerland). The data given are the mean of ten measurements.

The disintegration time was measured, using the Ph.Eur. apparatus, with water of 37°C as a test fluid. The tests were performed without disks. The data given are the mean of six measurements.

The friability was tested in duplicate in a Roche friabilator. Ten tablets were weighed before and after 100 rotations and the removal of dust.

From each batch 20 individual tablets were weighed and the variation coefficient of tablet weight was calculated.

The dissolution rate measurements of oxazepam from tablets were performed according to the USP XX paddle method at 100 rpm. As dissolution medium 900 ml of deareated water (37 ± 0.5 °C) was used. The concentration of oxazepam was measured spectrofotometrically at 236 nm (Ultrospec 4052 TDS, LKB, Zoetermeer, The Netherlands).

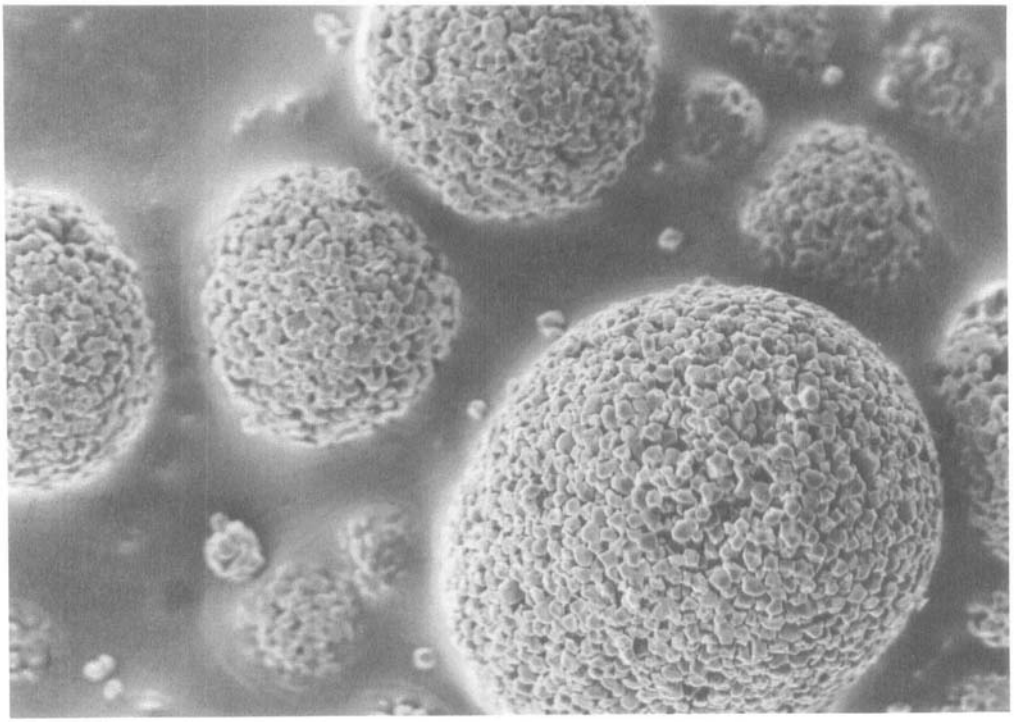

FIGURE 1.
Scanning electron micrograph of modified rice starch.

RESULTS AND DISCUSSION

Powder characterization of modified rice starch

Modified rice starch is a dry, white, odorless, tasteless, insoluble, neutral powder produced by physical modification of rice starch. A scanning electron micrograph (figure 1) shows that it is composed almost entirely of aggregates of rice starch grains with a spherical particle form. The particle size distribution, obtained by sieve analysis (figure 2) shows that the majority of the particles lies between 75 μm and 150 μm. The water content was found to be 11.3%. The bulk density was 553 kg/m^3.

In Table 1, the flow properties of modified rice starch as indicated by angle of repose and Hausner ratio are compared with those of native rice

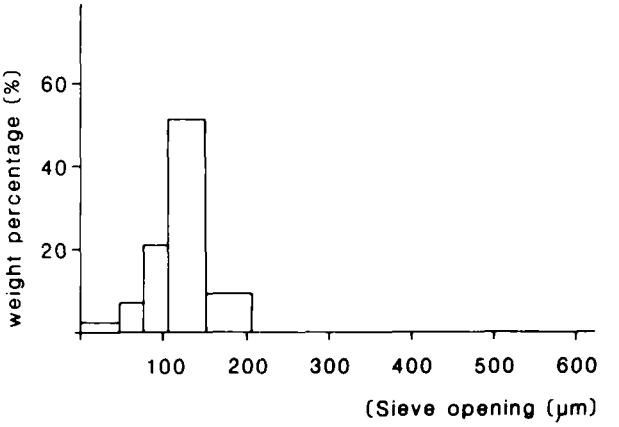

FIGURE 2.
Particle size distribution of modified rice starch

starch and pregelatinized starch. It can be seen that the flow properties of modified rice starch are better than those of the other products, which is an effect of the more favourable particle size of the former.

Compaction characteristics of modified rice starch

Placebo tablets containing modified rice starch only and modified rice starch lubricated with 0.5% magnesium stearate (mixing time 5 min), respectively, were prepared at different compaction load levels using a single punch tabletting machine. Of these batches of tablets the crushing strength and the variation coefficient of tablet weight were measured. Figure 3 shows the crushing strength for both unlubricated and lubricated tablets as a function of the compression load level. It can be seen that the presence of magnesium stearate causes a reduced binding capacity, just as might be expected from the plastic behaviour under compression of starch products (7). However, the reduction in crushing strength is much smaller than that of pregelatinized starch, where zero crushing strength was reached after 10 min of mixing with 0.5% magnesium stearate (5). In

TABLE 1

Flow properties of rice starch and two starch products for direct compression.

	Rice starch	Pregelatinized starch	Modified rice starch
Angle of repose (°)	60.0	33.7	30.5
Hausner Ratio	1.38	1.22	1.14

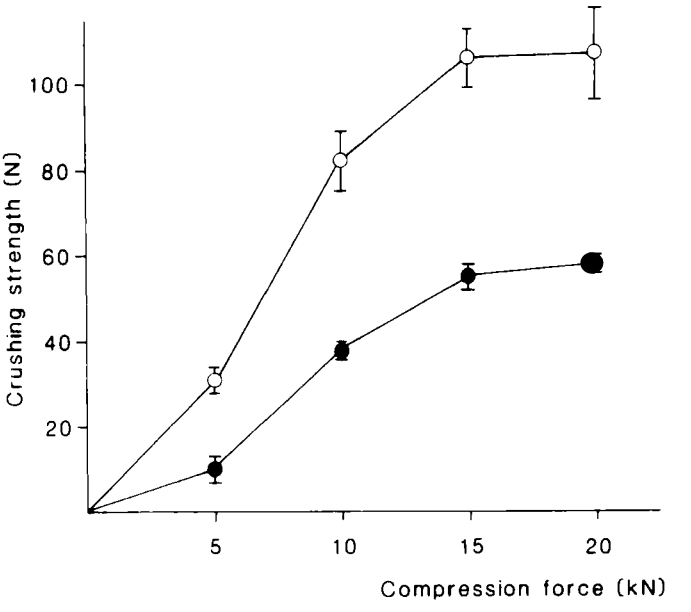

FIGURE 3.

Crushing strength of tablets, compressed from modified starch as a function of the compression force. Open symbols: unlubricated; closed symbols: lubricated with 0.5% magnesium stearate.

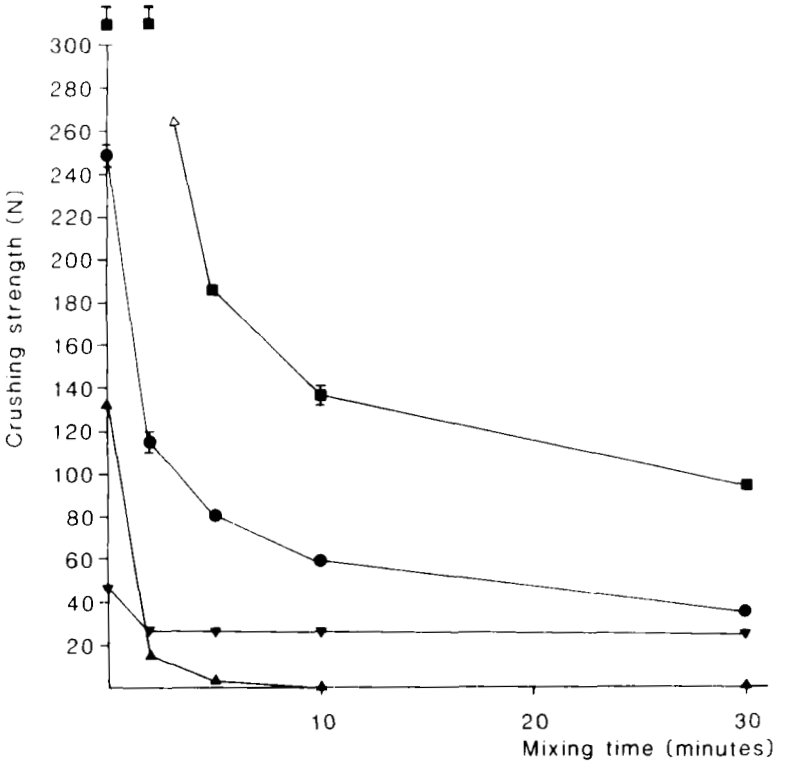

FIGURE 4.

Crushing strength of tablets compressed from different filler-binders as a function ot the mixing time with 0.5% magnesium stearate. Symbols: ■ microcrystalline cellulose; ● modified rice starch; ▲ pregelatinized starch; ▼ α-lactose monohydrate 100 mesh.

contrast to the latter, sufficient binding capacity for modified rice starch is left after lubrication. The variation coefficient of tablet weight of the tablets compressed at 20 kN was 1.2% for unlubricated tablets and 0,5% for tablets containing 0.5% magnesium stearate. These low variation in tablet weight are caused by the excellent flow properties, as was shown earlier in Table 1. The favourable effect of magnesium stearate on powder flow properties were described previously (4).

TABLE 2

Effect of mixing with 0.5% magnesium on the disintegration time of tablets compressed from modified rice starch (0 min mixing time means no lubricant added)

mixing time with lubricant	disintegration time (s)
0 min	128 ± 6
2 min	147 ± 8
5 min	159 ± 11
10 min	158 ± 4
30 min	145 ± 14

In order to study the effect of mixing with a lubricant more in detail, tablets were prepared from modified rice starch and three other commonly used filler-binders after mixing for different time periods with 0.5% magnesium stearate. Figure 4 shows the crushing strength as a function of the mixing time with magnesium stearate. Although a strong decrease in crushing strength can be seen for modified rice starch after prolonged mixing with the lubricant, the effect is much less than found for pregelatinized starch. After 10 min intensive mixing, the tablet hardness is sufficient. Because modified rice starch as such has lubricating properties of its own, in practice tablets with a high concentration of modified rice starch can be prepared with much lower magnesium stearate concentrations than 0.5%.

As hydrophobic lubricants may have a deteriorating effect on tablet disintegration (10), particularly after prolonged mixing with the lubricant (11), the disintegration time of the lubricated tablets was measured. Table

TABLE 3

Formulations for 10 mg Oxazepam Tablets without colloidal silica.

	I (%)	II (%)	III (%)	IV (%)
Oxazepam	4.0	4.0	4.0	4.0
Modified rice starch	90.8	45.4	45.4	45.4
α-Lactose monohydrate 100 mesh	-	45.4	-	-
Anhydrous lactose	-	-	45.4	-
Microcrystalline cellulose	-	-	-	45.4
Sodium starch glycolate	4.0	4.0	4.0	4.0
Magnesium stearate	1.0	1.0	1.0	1.0
Crushing strength (N)	48	56	90	116
Friability (%)	1.1	1.0	0.6	0.4
Tablet weight variation coefficient	0.4	0.7	1.5	3.5
Disintegration time*(s)	185	147	334	688
% Dissolved after 20 min	71	94	83	92

* without disks

2 shows that all tablets disintegrated in between 120 and 150 seconds, even when modified rice starch was mixed prior to compression for 30 min with 0.5% magnesium stearate. This result shows that modified rice starch can reduce the deteriorating effect of hydrophobic lubricants on tablet disintegration (11).

Evaluation of oxazepam tablets

For the evaluation of modified rice starch as a filler-binder in tablets prepared by direct compression, oxazepam (10 mg in a 250 mg tablet) was added as a model drug. In order to study the effect of combination of

TABLE 4

Formulations for 10 mg Oxazepam Tablets with 0.2% colloidal silica.

	I (%)	II (%)	III (%)	IV (%)
Oxazepam	4.0	4.0	4.0	4.0
Modified rice starch	90.8	45.4	45.4	45.4
α-Lactose monohydrate 100 mesh	-	45.4	-	-
Anhydrous lactose	-	-	45.4	-
Microcrystalline cellulose	-	-	-	45.4
Sodium starch glycolate	4.0	4.0	4.0	4.0
Colloidal silica	0.2	0.2	0.2	0.2
Magnesium stearate	1.0	1.0	1.0	1.0
Crushing strength (N)	76	68	109	130
Friability (%)	0.8	0.8	0.5	0.2
Tablet weight variation coefficient	0.2	0.3	0.3	3.0
Disintegration time*(s)	188	129	308	732
% Dissolved after 20 min	78	92	80	85

* without disks

modified rice starch with other filler-binders, tablets were prepared with modified rice starch only and with 50/50 % mixtures of modified rice starch with microcrystalline cellulose, α-lactose monohydrate and anhydrous ß-lactose, respectively. Although modified rice starch has disintegration properties of its own, 4 percent sodium starch glycolate was added as a disintegrant. As colloidal silica may effect both flowability and lubricant sensitivity [12], tablets were prepared without as well as with 0.2% colloidal silica.

Both the oxazepam tablet formulations and the results of the measurements of the tablet parameters are shown in Table 3 for tablets without colloidal silica and in Table 4 for tablets with 0.2% colloidal silica.

Comparing the Tables, it can be seen that the addition of colloidal silica increases the crushing strength for all the tablets examined. This effect is caused by a reduction of the negative effect of magnesium stearate on the binding properties. When colloidal silica is mixed with a tabletting mixture prior to mixing with a hydrophobic lubricant, the lubricant film formation is reduced [12,13]. This effect may be caused by the strong molecular interactions between magnesium stearate and colloidal silica [14].
Next to the effect on crushing strength, the addition of colloidal silica has a favourable effect on relative tablet weight coefficient.

Table 4 shows that tablets containing modified rice starch or mixtures of modified rice starch with one of the lactoses had excellent properties with respect to crushing strength, friability, relative weight standard deviation, disintegration time and drug dissolution rate. Tablets containing equal parts of modified rice starch and microcrystalline cellulose show, on the other hand, a relatively long disintegration time and a high weight variation coefficient, even when colloidal silica is present in the formulation.

In conclusion, modified rice starch, marketed as Primotab^{R}ET, has excellent flow and binding properties. In contrast to other starch based filler-binders the binding properties stay sufficient after mixing with a hydrophobic lubricant. In tablet formulations, it can be used as unique filler-binder, which may be of benifit when drugs like primary amines are tabletted, which are incompatible with lactose because of the reaction of Maillard [15].

Modified rice starch can be combined with other filler-binders such as α-lactose monohydrate 100 mesh or anhydrous ß-lactose. Combinations with microcrystalline cellulose should be avoided because of the poor flowability of the blends and the slow disintegration of the tablets.

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