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Comparative Tableting and Microstructural Properties of a New Starch for Direct Compression

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ABSTRACT

A new directly compressible starch for direct compression marketed as Sepistab® St 200 has been studied in relation with the classical variety for direct compression—Sta Rx® 1500. Flowability of Sta Rx was in general higher. Sepistab showed a weight mean diameter two times higher than Sta Rx. Particle size of Sepistab demonstrated a better fitting to normal distribution. No differences of note were observed in the consolidation mechanism on the basis of the tablet-in-die Heckel method. Binding properties and plasticity of Sepistab were higher. Sta Rx showed more interparticulate and die wall friction during compression. Disintegration of the tablets was absolutely different. Sta Rx showed swelling of the tablet with gel formation and longer disintegration times. On the contrary, Sepistab showed almost immediate disintegration. This different behavior can be partially explained on the basis of the content of amylose as effective disintegrating agent. The microstructure of the tablets was measured by mercury porosimetry. The parameters calculated were the total porosity, median size of pore expressed as radius, and surface area of pores, assuming cylindrical pores. The microstructure of tablets of Sepsitab—with higher porosity, surface area of pores, and median pore radius—can also enhance the water penetration and disintegration of the tablet by breaking the hydrogen bonding which is formed during compression and suddenly released in the presence of water.

INTRODUCTION

The successful application of direct compression excipients in pharmaceutical tableting depends on the development of suitable excipients that are free flowing, highly compressible, physiologically inert, and chemically compatible with the active ingredients (1). Therefore, new excipients might be designed deliberately, on the basis of what present pharmaceutical technology knows to be desirable properties. In this way, Armstrong (2) suggests guidelines for the selection of an appropriate direct compression medium and for the specifications that one might require from a commercial supplier.

One of these direct compression excipients is starch. Numerous papers have been published discussing the particular application of starch. In this sense, Schwartz and Zelinskie (3) discuss the binding and disintegrating properties of corn starch fractions; the individual starch components or the hybrid mixtures might have application for the formulator if there are problems relating to tablet hardness. Manudhane et al. (4) showed that compressible starch can be blended and directly compressed in combination with other filler–binders commonly used in direct compression. However, it is recommended, that a glidant such a 0.25% pyrogenic silica be employed to maximize fluidity. Also the suitability of cocoyam starch (5), both as a binder and as a disintegrating agent, has been studied in the formulation of some tablets.

The studies of consolidation mechanism demonstrated that Sta Rx® 1500 is an excipient with a tendency to deform plastically until a certain applied pressure is exceeded (6).

In this study we compare the powder and particle properties, the tabletability, and the microstructure of tablets compressed of Sta Rx 1500 compressible starch and the new variety for direct compression, Sepistab St® 200.

MATERIALS AND METHODS

In this study two starches for direct compression were used: Starch Sta Rx 1500—batch 920453 (Dr. Esteve, Barcelona, Spain) and Sepistab St® 200–batch 3710 (Seppic, Paris, France).

The methodology used for determining the rheological characteristics of repose angle and compressibility on tamping, was described in detail in earlier studies (7,8). Dynamic angle of repose was measured according to the rotating cylinder method (9) (stainless steel cylinder with an internal diameter of 80 mm). Particle size distributions were determined using high-accuracy mesh sieves of 500, 450, 400, 300, 250, 200, 175, 150, 125, 100, 75, 50, and 25 μm (CISA, Barcelona, Spain) in a vibrator sieve (Retsch, Rheil, Germany). Vibration time was previously adjusted to obtain a constant amount of powder in each sieve. True density of each powder was determined in triplicate with a comparison gas pycnometer (Model Stereopycnometer SPY-3, Quantachrome, Syosset, USA), using helium as inert gas. Excipients were stored under controlled humidity conditions (RH = 40%).

Compression characteristics of the powders were investigated on an instrumented single-punch tablet machine (Bonals AMT 300, Barcelona, Spain) with strain gauges HBM YL6 (HBM, Darmstat, Germany) connected to dynamic amplifiers (NEC San-ei, Tokyo, Japan) and inductive displacement transducers HBM TS-50 connected to digital amplifiers HBM AB12; all channels are attached to A/D converter Metrabyte DAS 16G1 (Metrabyte Corp., MA, USA). The displacement measurements were corrected with the deformation of the punches (10). A quantity of powder to produce tablets of thickness 2.5 mm at zero theoretical porosity was manually filled into the die (12 mm). Flat compacts were prepared at fixed breaking force (40, 60, and 80 newtons) to study the variations of the compression properties of the powders. Also, to investigate the sensitivity to lubrication, similar tablets were made after lubricating the die with a chloroformic solution of stearic acid (5% w/v).

The study of tablet weight variation was performed on an single-punch tablet machine (Bonals, Mod. AMT 300, Spain) running at 30 cycles/min and equipped with a forced feeding system. The weight uniformity of the tablets was determined using an analytical Mettler AE 100 balance (Mettler Instrumentate, Greinfesee, Switzerland) according to European Pharmacopoeia II (12). The tablet breaking force was determined immediately after compression using a commercially available tester (Schleuniger-2E, Dr. K. Schleuniger, Geneva, Switzerland). Friability was evaluated from the weight loss of 10 tablets tumbled 100 revolutions in a Erweka TA-3 (Erweka, Heusenstamm, Germany) friability tester. Disintegration testing (6 tablets) was performed at 37°C in HCl 0.1 N medium using the European Pharmacopoeia II (11) apparatus Erweka ZT-3 (Erweka, Heusenstamm, Germany), without disks.

The microstructure of the tablets was measured by mercury porosimetry (Model Autoscan 33, Quantachrome, Syosset, NY, USA). The pressure range was

from 1 to 33,000 psi, corresponding to a pore radius from 8.6 10^6 to 32 Å. The parameters calculated were: total porosity, median size of pore expressed as radius, and the surface area of pores, assuming cylindrical pores.

RESULTS AND DISCUSSION

Table 1 shows the values of true density, tap density, bulk density, Hausner ratio, compressibility index, static angle of repose, and dynamic angle of repose of both starches. Sta Rx showed lower Hausner ratios and compressibility factors than Sepistab. However, these values of Hausner ratios denote minimum interparticulate frictions (12), and the compressibility factors between 5 and 15 indicate an excellent flow of the powders (13). The dynamic and static angles of repose of Sepistab were higher than those founded for Sta Rx, according to the compressibility parameters of these materials.

Typical parameters of normal distributions are represented in Table 2: weight mean diameter (d_w), standard deviation, and coefficients of variation, kurtosis, and skewness. Sepistab showed a mean diameter in weight higher than Sta Rx. Sepistab exhibits more symmetry around the mean—coefficient of skewness closer to 0—and the height of the size distribution curve was more similar to a normal size distribution—coefficient of kurtosis closer to 0 (14)—than Sta Rx. Hence, the fitting of Sepistab particle size was closer to a normal distribution.

To evaluate the compressional properties of the excipients unlubricated (UN) and with lubrication of the die (L), the average of the following parameters have been calculated from values obtained for tablets at 40, 60, and 80 newtons of breaking force: maximum upper force, ratio between breaking force and mean applied force to compress the tablet, ejection force, work of ejection, residual lower punch force (RLPF), lubrication coefficient (R) defined as the ratio between the maximum lower punch force and the maximum upper punch force during compression, and plasticity (15) expressed as the ratio between apparent net work and applied work. These parameters are shown in Table 3.

The ratios between crushing and mean applied force of the Sepistab were higher than those calculated for Sta Rx. Thus, the binding properties of Sepistab were improved with regard to those founded for Sta Rx. Parameters depending on die wall and interparticulate friction demonstrated higher friction in the Sta Rx. Friction was almost negligible when the Sepistab was compressed with the die wall lubrication previously described. The plasticity (15) of Sepistab was higher in unlubricated and lubricated tablets than the values obtained for Sta Rx. The difference in the plasticity between the starches is even higher with lubrication of the die wall. This is due to the higher expansion during decompression when the die wall has been lubricated. In this latter case, the plasticity of Sta Rx was significant lower.

Table 1

Rheological Parameters (± SD)

Material	True Density (g/cm³)	Tap Density (g/cm³)	Bulk Density (g/cm³)	Hausner Index	Compressibility (%)	Static Angle of Repose	Dynamic Angle of Repose
Sta Rx 1500	1.486 ± 0.008	0.704 ± 0.016	0.596 ± 0.016	1.18 ± 0.02	4.1 ± 0.7	42.9 ± 1.7	39.0 ± 1.0
Sepistab St 200	1.464 ± 0.024	0.785 ± 0.006	0.591 ± 0.017	1.33 ± 0.01	12.4 ± 0.3	51.9 ± 1.0	50.0 ± 2.0

Table 2

Fitting of Particle Size to Normal Distribution

Material	d_w (μm)	Variation	Kurtosis or Excess	Skewness
Sta Rx 1500	99.1 ± 42.6	0.4298	8.349525	1.53860
Sepistab St 200	184.3 ± 121.2	0.6580	-0.39081	0.85640

Table 3

Compressional Properties of the Excipients

Excipient	Die	Maximum Upper Force (N)	Crushing/ Mean Applied Force	Ejection Force (N)	Ejection Work (J)	RLPF (N)	*R*	Plasticity (%)
Sta Rx	UN	18459 ± 4768	$3.52\ 10^{-3} \pm .3\ 10^{-4}$	401 ± 11	2.289 ± .315	365 ± 27	0.808 ± .013	81.1 ± 2.0
1500	L	17205 ± 4621	$3.57\ 10^{-3} \pm .3\ 10^{-4}$	113 ± 15	0.148 ± .021	53 ± 24	0.950 ± .015	73.3 ± 3.1
Sepistab	UN	16818 ± 6680	$3.83\ 10^{-3} \pm .1\ 10^{-4}$	206 ± 44	0.057 ± .018	129 ± 36	0.895 ± .027	82.3 ± 2.1
St 200	L	16062 ± 7834	$3.93\ 10^{-3} \pm .2\ 10^{-4}$	78.8 ± 26	0.019 ± .011	17 ± 5	0.992 ± .008	80.8 ± 3.2

Note. UN: unlubricated; L: lubricated die; *R*: lubrication coefficient.

Results derived, using the Heckel tablet-in-die method (6), from experimental data obtained (N) are shown in Table 4: intercept density of the linear regression (*Da*), density contribution to movement and rearrangement (*Db'*), relative density of precompression (D'_0) , and yield pressure (*Py*). Also, correlation coefficients (*r*) and values of *F* test for significance of regression (*F*) are shown in Table 4. It has been pointed out that plastic deformation is one of the most important factors for producing firm tablets. Thus the yield pressure is not a limit value for plastic deformation although plastic deformation below this pressure cannot complete. The practical importance of this value is that it gives an impression of the ease of the plastic deformation and the softness of the material. Consolidation mechanism on the basis of yield pressure results obtained using the Heckel tablet-in-die method supported the finding of Humbert-Droz et al. (6) for Sta Rx and the finding of Paronen and Juslin (16) for barley, corn, potato and wheat starches—they described these excipients as materials with an extensive plastic deformation. It is interesting to note that the yield pressures of the modified starches under study were lower than those reported by Paronen and Juslin (16), between 109 and 125 MPa, for the starches above mentioned. Consequently, these modified starches are more prone to plastic deformation than natural starches. No significant difference was obtained between values of yield pressure of Sepistab and Sta Rx. Only a small difference in compression behavior was observed in the Db' values, higher in the case of Sta Rx. The values of Db' support the findings of Fell and Newton (17) for crystalline and spray-dried lactose, and of York (18) for four pharmaceutical materials. The rearrangement of particles occurs more with the smaller particle size (Sta Rx) and less with larger particle size (Sepistab).

The study of tablet properties was performed using a eccentric press running at 30 cycles/min and equipped with a forced feeding system. The different tests for unlubricated tablets are represented in Tables 5 and 6.

The coefficient of tablet weight variation of Sepistab was lower. Although Sta Rx showed better rheological

Table 4

Parameters of Heckel Tablet-in-Die Method

Excipient	Die	*Da*	*Db'*	D'_0	*Py* (MPa)	*N*	*r*	*F*
Sta Rx	UN	0.514 ± .033	0.067 ± .009	0.347 ± .000	46.0 ± 4.3	120	0.9887	4611
1500	L	0.432 ± .020	0.062 ± .015	0.348 ± .002	39.6 ± 4.4	119	0.9835	3897
Sepistab	UN	0.382 ± .010	0.028 ± .012	0.351 ± .002	46.0 ± 4.03	115	0.9964	14150
St 200	L	0.385 ± .008	0.030 ± .015	0.352 ± .004	35.7 ± 1.7	117	0.9855	4026

Note. UN: unlubricated; L: lubricated die.

Table 5

Weight Uniformity of Tablets of 40, 60, and 80 Newtons Breaking Force

Excipient	40 Newtons Weight (mg)	40 Newtons *VC* (%)	60 Newtons Weight (mg)	60 Newtons *VC* (%)	80 Newtons Weight (mg)	80 Newtons *VC* (%)	Average *VC* (%)
Sta Rx 1500	378.8 ± 15.3	4.0	379.1 ± 19.2	5.1	346.9 ± 9.4	2.7	3.9
Sepistab St 200	371.1 ± 1.8	0.5	368.9 ± 2.6	0.7	375.1 ± 2.5	0.7	0.6

Table 6

Thickness, Friability and Distinegration Time of the Tablets

Excipient	Thickness (mm) 40 N	Thickness (mm) 60 N	Thickness (mm) 80 N	Friability (%) 40 N	Friability (%) 60 N	Friability (%) 80 N	Disintegration (s) 40 N	Disintegration (s) 60 N	Disintegration (s) 80 N
Sta Rx® 1500	2.61 ± .03	2.44 ± .05	2.28 ± .05	3.17	0.25	3.15	2580± 149	2940 ± 158	2100 ± 67
Sepistab St® 200	2.77 ± .03	2.57 ± .03	2.48 ± .05	3.03	1.60	1.05	2 ± 0	4 ± 0	8 ± 0

properties on the basis of the parameter measured (Table 1), the coefficient of tablet weight variation was higher. In this case, there is no relationship between the rheological parameters and the weight variation. This supports the finding of Fassihi and Kanfer (19) for several pharmaceutical materials, suggesting the measurement of flow properties using the coefficient of tablet weight variation. Our results demonstrated that the relationship between coefficient of weight variation and compressibility index is not clear when this later value is lower than 20%. This fact was previously observed by Fassihi and Kanfer (19), who demonstrated an increase in tablet weight variation with compressibility of powders when powders showed a compressibilities higher than 20%

The tablets compressed under these experimental conditions demonstrated an unacceptable friability (higher than 1%). However, Sepistab showed less friability for tablets made at the same breaking force than Sta Rx. Disintegration of Sepistab was almost immediate. Opposite to this, Sta Rx showed swelling of the tablet, with the formation of a gel layer around the tablet. This fact explains the longer disintegration time (> 1800 sec). Thus, the higher the swelling, the longer disintegration time of the tablets. This behavior of the Sta Rx tablets was previously described by Manudhane et al. (4), finding disintegration time longer than 5 min depending upon compression pressure. However, as is well known, starch could act as a disintegrating agent in lower concentrations. This difference in the disintegration time may be explained on the basis of the percent of amylose (3,4) as the effective component of starch in terms of its disintegrating effect. This differences also confirmed that the swelling of the starch grains is not the mechanism of the tablet disintegration by the starch as has been concluded by several authors (4,20).

The microstructure of the tablets was studied by mercury porosimetry. Total porosity, median pore size in volume, expressed as radius; and pore surface area, assuming cylindrical pores, are shown in Table 7. As expected, these parameters decreased as the strength of the tablet was increased. All these parameters in tablets compressed with the Sepistab were higher than those

Table 7

Microstructure of Tablets at 40, 60, and 80 Newtons Breaking Force

Excipient	Porosity (%)			Median Pore Size (Å × 10^4)			Surface Area (m^2/g)		
	40 N	60 N	80 N	40 N	60 N	80 N	40 N	60 N	80 N
Sta Rx ® 1500	12.86 ± .50	10.93 ± .47	10.38 ± .05	2.22	1.69	1.58	5.73 ± .21	5.37 ± .27	5.32 ± .15
Sepistab St® 200	25.12 ± .76	15.73 ± .33	14.31 ± .25	5.74	4.44	2.22	6.89 ± .33	5.98 ± .56	5.67 ± .21

obtained for Sta Rx at the same breaking force. These results can also partially explain the difference between the disintegration behaviors of the two materials. The microstructure of tablets of Sepistab, with higher porosity and pore radius, can also enhance the water penetration and disintegration of the tablet by breaking the hydrogen bonding which is formed during compression and is suddenly released in the presence of water (20). The differences between the tablets compressed to obtain the same breaking force decreased as the strength of the tablets was increased. Figures 1 and 2 show the pore size distribution of Sta Rx and Sepistab, respectively, at 60 Newtons breaking force tablets. The y-axis scale unit is cc/g 10^{-1} and the x-axis is in logarithmic

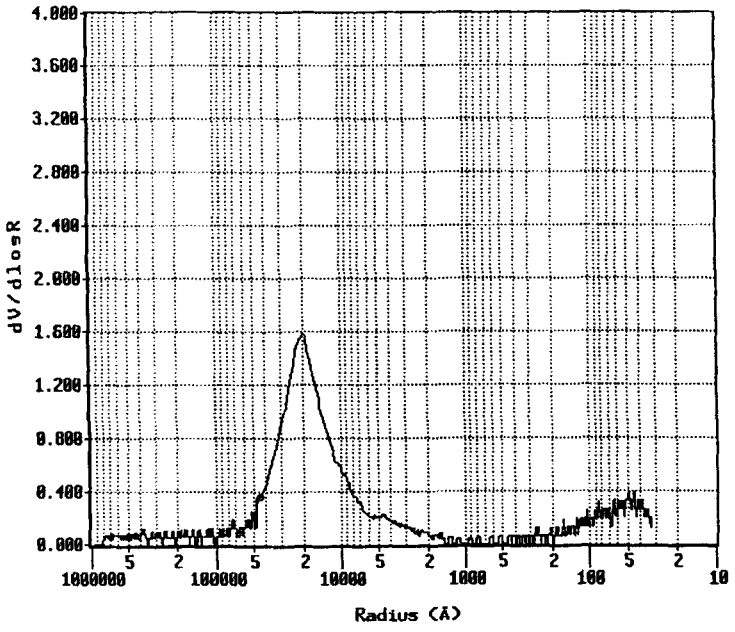

Figure 1. Pore size distribution of Sta Rx tablets at 60 N breaking force.

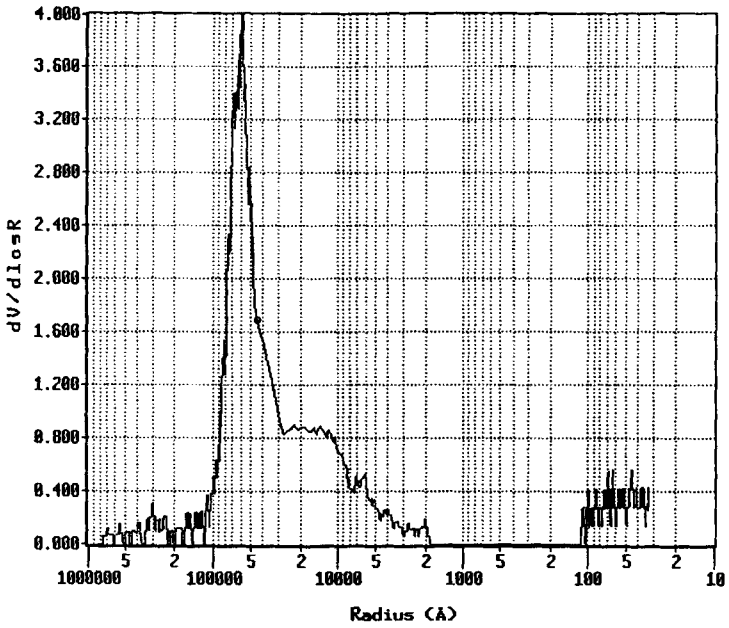

Figure 2. Pore size distribution of Sepistab St tablets at 60 N breaking force.

scale. Mercury volume is normalized by sample weight. The same pattern was observed when pore distribution of the tablets was compared at the other breaking forces.

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