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Commercial pregelatinized starches: ability to settle and rheological evaluation

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The ability to settle and the tribological properties of three samples of pregelatinized starch widely available commercially were investigated with reference to their technological implications. In particular, we evaluated the influence of storage conditions, storage time, moisture content, equipment, handling, and mechanical treatment on the apparent volume, poured density and tapped density, as well as on tests of flow parameters such as basic flowability energy. The results obtained highlight the fact that the technologically relevant behaviour of pregelatinized starches in terms of apparent volume and tribological properties may be influenced not only by relative humidity (RH%) conditions, but also by common pharmaceutical operating practices. In particular, previous mechanical treatment can lead to statistically different behaviour in tests of ability to settle according to pharmacopoeial specifications, depending on both RH% conditioning and the amount of powder, although the materials under investigation all conform to the respective monograph in the Pharmacopoeia. All these aspects are of special interest with regard to the various pharmaceutical formulations which include pregelatinized starch, both on an industrial scale and in small-scale production.

1. Introduction

Pregelatinized starch (PS) is a versatile pharmaceutical excipient noted for its various uses (Te Wierika et al. 1997; Alebiowu and Itiola 2003; Gohil et al. 2004; Martindale 2005). Its traditional uses are as a ligand, disintegrating agent and diluent. Such applications in pharmaceutical formulation or technology depend on the amounts employed and the modalities of use (Lordi and Rowley 2000). At the level of the pharmacopoeias which contain monographs on this material, PS is defined as starch, other than wheat starch, that has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and in either the absence or the presence of heat, and is subsequently dried. It contains no added substances but it may be modified to render it compressible and flowable (European Pharmacopoeia 2004a; US Pharmacopoeia – National Formulary 2005). Furthermore, the botanical source is not indicated in the USP. The preparation of pharmaceutical grade samples is performed without additives and depends on the desired degree of pregelatinization (Singh et al. 2003). Full pregelatinization may be achieved by spreading an aqueous dispersion of unmodified starch over adequately hot surfaces at the temperature at which gelatinization occurs. The manufacture of partially pregelatinized starch is based on the application of mechanical treatment to moistened starch. Levels of gelatinization or modification are not specified in the monographs. Many products corresponding to pregelatinized starch with different degrees of pregelatinization are commercially available (Patindol et al. 2003; Tomasik 2004). These products differ from each other in terms of structural modification and functionality, although they all meet the pharmacopoeial requirements. Examination of samples suspended in glycerin show characteristic forms (eg irregular chunks, thin plates) depending upon the method of drying used during production. Generally, PS contains free amylose (5%), free amylopectine (15%) and unmodified starch (80%) (Lordi and Rowley 2000).

PS is practically insoluble in organic solvents. Its solubility in cold water is proportional to the degree of pregelatinization, ranging from slightly soluble to soluble in the case of fully pregelatinized starch. We highlighted in a previous study that the degree of pregelatinization influences the behaviour of starch in terms of its hygroscopic characteristics, as well as influencing its solubility in cold water (Travagli 2004). Furthermore, recent research has shown how the use of PS contributes to improvements in mixture uniformity, especially in the case of minimum amounts of an API (Hardy et al. 2003; Gohil et al. 2004). Starting from the characteristics reported above, this study reports the poured and tapped densities as well as a rheological evaluation of three commercial samples of PS. The dependence of these parameters on moisture content and operator handling, storage time and mechanical treatment are investigated. The results obtained are of interest at the level of the formulation process in an R&D environment. They can also be used in production departments to ensure uniform behaviour of the different PS samples used in both the technological and formulation fields.

2. Investigations, results and discussion

Table 1 summarizes the principal properties of the three commercial samples.

The behaviour of the various samples in terms of apparent volume with relation to the experimental conditions adopted is summarized in Table 2 (powder quantity: 100.0 g) and Table 3 (powder quantity: 50.0 g). In particular, the ability to settle was assessed by both the differences between apparent volumes $V_{10}-V_{500}$ and V_0-V_{10}. The first difference conforms to that indicated in the pharmacopoeial monographs. The latter has been adopted to give useful information in the formulation field, as in the case of capsule production, where some mechanical stresses are to be expected (Jones 2001; Kachrimanis et al. 2003; Sørensen et al. 2005). As may be seen, there are significant differences among the data. This result reflects a trend observed in a recent study in which the bulk volumes of powders PS1-PS3 were evaluated in the absence and presence of mechanical treatment under different storage conditions with respect to RH% (Travagli 2004). As for as comparison within the same powder type is concerned, different trends are apparent. Among the various possible considerations, the following could be considered the most important: PS1, PS2 and PS3 are not influenced by RH conditions in the absence of previous mechanical treatment either in respect of $V_{10}-V_{500}$ or V_0-V_{10} values. Analogous behaviour was also observed for the 50 g test. The only exception is represented by the $V_{10}-V_{500}$ values of PS2 at 35 RH% and room conditions vs. 76 RH% obtained using 100 g (19.2 ± 0.52 and 20.7 ± 2.2 vs. 28.6 ± 2.3, $P < 0.001$). However, if PS1 and PS2 were treated mechanically by pestle-mortar mixing, statistically different behaviour in $V_{10}-V_{500}$ at 35 RH%, room conditions and 76 RH% was observed. In particular, PS1 gives 9.4 ± 0.64 vs. 14.8 ± 0.84 ($P < 0.001$) and 14.0 ± 1.2 ($P < 0.001$) and PS2 shows 18.4 ± 1.8 vs. 19.8 ± 0.71 (not significant) and vs. 24.0 ± 2.4 ($P < 0.01$). On the basis of these observations, the mechanical treatment of PS powders is an important factor as far as their settling properties are concerned. Furthermore, with respect to the comparison of the different PS samples, analogous behaviour can be seen in PS1 and PS3, except for the $V_{10}-V_{500}$ determination after mechanical treatment (9.4 ± 0.64 vs. 14.6 ± 1.0; $P < 0.001$). On the other hand, PS2 is characterized by a substantial difference (P between 0.01 and 0.001) in all the $V_{10}-V_{500}$ values, both in the absence and the presence of mechanical treatment. These findings were also seen independently of the amount of PS tested (ie 100 g or 50 g). With respect to V_0-V_{10}, however, statistically significant differences were confirmed only at RH% = 76 between PS1 and PS2

Table 1: Principal properties of three commercial samples of pregelatinized starch investigated

	PS1	PS2	PS3
Degree of pregelatinization	partial	partial	partial
Description	white-coloured powder	intensely white-coloured powder	yellow/white-coloured powder
Particle size	medium-fine D10 = 17.0 μm D50 = 72.1 μm D90 = 259 μm	fine D10 = 44.2 μm D50 = 94.3 μm D90 = 151 μm	medium-fine D10 = 23.0 μm D50 = 85.4 μm D90 = 434 μm
Loss on drying (%)	9.9	8.8	12.0
pH (10% w/v, slurry)	5.7	6.0	5.8
Sulfated ash	0.12	0.21	0.15
Botanic characteristics	maize (corn)	maize (corn)	maize hybrid

Table 2: Ability to settle of various PS samples under experimental conditions adopted. Sample amount: 100.0 g

	PS1	PS2	PS3
RH% = 35			
$V_{10}-V_{500}$[a]	13.8 ± 1.0	19.2 ± 0.52	13.8 ± 0.84
$V_{10}-V_{500}$[b]	9.4 ± 0.64	18.4 ± 1.8	14.6 ± 1.0
V_0-V_{10}[a]	4.6 ± 0.95	7.0 ± 1.4	5.6 ± 1.0
V_0-V_{10}[b]	4.2 ± 0.71	7.0 ± 2.1	$5.6 + 0.81$
Poured density[a]	0.6418	0.4869	0.6353
Poured density[b]	0.6274	0.4892	0.6211
Room conditions			
$V_{10}-V_{500}$[a]	13.6 ± 2.1	20.7 ± 2.2	13.5 ± 1.8
$V_{10}-V_{500}$[b]	14.8 ± 0.84	19.8 ± 0.71	13.4 ± 1.5
V_0-V_{10}[a]	4.2 ± 1.3	7.0 ± 2.1	5.1 ± 2.2
V_0-V_{10}[b]	4.6 ± 1.1	6.6 ± 1.0	6.6 ± 1.5
Poured density[a]	0.6498	0.5033	0.6262
Poured density[b]	0.6427	0.4946	0.6211
RH% = 76			
$V_{10}-V_{500}$[a]	15.6 ± 0.90	28.6 ± 2.3	15.4 ± 1.3
$V_{10}-V_{500}$[b]	14.0 ± 1.2	24.0 ± 2.4	14.6 ± 2.2
V_0-V_{10}[a]	4.2 ± 0.71	8.8 ± 2.5	5.4 ± 1.9
V_0-V_{10}[b]	5.4 ± 1.2	9.2 ± 2.8	5.8 ± 2.7
Poured density[a]	0.5754	0.4233	0.5800
Poured density[b]	0.5760	0.4405	0.5862

[a] in absence of mechanical treatment. [b] in presence of mechanical treatment. See text for further explanation.

Table 3: Ability to settle of various PS samples under experimental conditions adopted. Sample amount: 50.0 g

	PS1	PS2	PS3
RH% = 35			
$V_{10}-V_{500}^{a}$	10.4 ± 1.0	13.6 ± 1.1	10.4 ± 0.71
$V_{10}-V_{500}^{b}$	9.8 ± 0.84	14.6 ± 1.0	10.0 ± 0.78
$V_{0}-V_{10}^{a}$	3.4 ± 0.95	6.6 ± 0.90	4.4 ± 0.64
$V_{0}-V_{10}^{b}$	3.6 ± 0.90	4.8 ± 1.5	4.8 ± 0.78
Poured density^{a}	0.6158	0.4780	0.6234
Poured density^{b}	0.6053	0.4854	0.6068
Room condition			
$V_{10}-V_{500}^{a}$	10.0 ± 2.0	13.7 ± 2.6	10.0 ± 2.9
$V_{10}-V_{500}^{b}$	9.8 ± 0.84	13.0 ± 1.2	10.0 ± 1.3
$V_{0}-V_{10}^{a}$	4.1 ± 1.3	5.3 ± 1.8	3.7 ± 2.4
$V_{0}-V_{10}^{b}$	4.6 ± 1.4	4.8 ± 1.3	4.8 ± 1.2
Poured density^{a}	0.6234	0.4878	0.6143
Poured density^{b}	0.6297	0.4836	0.5938
RH% = 76			
$V_{10}-V_{500}^{a}$	7.8 ± 0.78	16.2 ± 0.45	8.6 ± 0.71
$V_{10}-V_{500}^{b}$	8.4 ± 0.64	15.0 ± 0.95	9.6 ± 1.4
$V_{0}-V_{10}^{a}$	4.4 ± 1.0	6.6 ± 0.95	4.6 ± 1.1
$V_{0}-V_{10}^{b}$	3.6 ± 0.95	5.6 ± 1.4	4.4 ± 1.7
Poured density^{a}	0.5631	0.4318	0.5814
Poured density^{b}	0.5695	0.4488	0.5896

[a] in absence of mechanical treatment. [b] in presence of mechanical treatment. See text for further explanation.

(4.2 ± 0.71 and 8.8 ± 2.5; $P < 0.05$) also taking into account the greater standard deviations denoting major variability in the initial phases of settling.

In order to explore more deeply the parameters involved in these experimental results, the rheological properties were evaluated (Conesa et al. 2004). Table 4 summarizes the results for the rheological FT4 characterization of the three commercial samples under investigation (see Experimental, section 3.6.). Fig. 1 shows the energy plot by which the changes in flow energy requirement during repeat testing, ie the Stability Index (SI), were evaluated. It showed that PS1 could be considered the less stable powder because of its increase in energy by 5% over the stability zone. A SI not very near unity (as in the case of PS2 and PS3) is not common for powders that are of a homogeneous nature, as are PS1-PS3. Reasons for this unusual albeit slight instability are numerous, including effects such as de-aeration, segregation, attrition and moisture uptake to name but a few. The most likely of these factors to have caused the 5% increase seen with PS1 could be de-aeration and moisture uptake. Further testing could confirm which factors were actually responsible for the changes observed. As far as the basic flowability energy (BFE) is concerned, these values did not show massive variation. However, because of the excellent stability characteristics of the three samples these differences are sufficient to distinguish them. Furthermore, these absolute BFE values are not absolute indicators of flow properties of the PS samples. They all had quite high bulk densities, suggesting that the interparticulate forces acting are small. Therefore, although the BFE values are high, the cohesiveness is low, and as a result the powders flow very well under gravitational forces. This behaviour is better characterised by means of the compaction and aeration tests, as shown later.

As regards the Flow Rate Index, these samples were fairly similar, ranging from 1.42 to 1.51, relatively low values. This parameter indicates fairly predictable behaviour in most handling and transfer applications, where the flow rate of the powder will no doubt be changing, being sta-

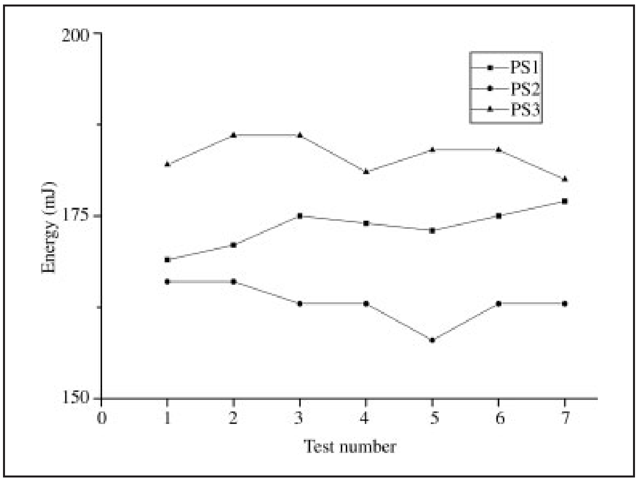

Fig. 1: Basic flowability energy in terms of energy needed to displace the three conditioned and stabilized powders at a given flow pattern (−5° helix) and flow rate ($100\ \mathrm{mm \cdot s^{-1}}$). Sample volume = 25 mL. CV% < 1

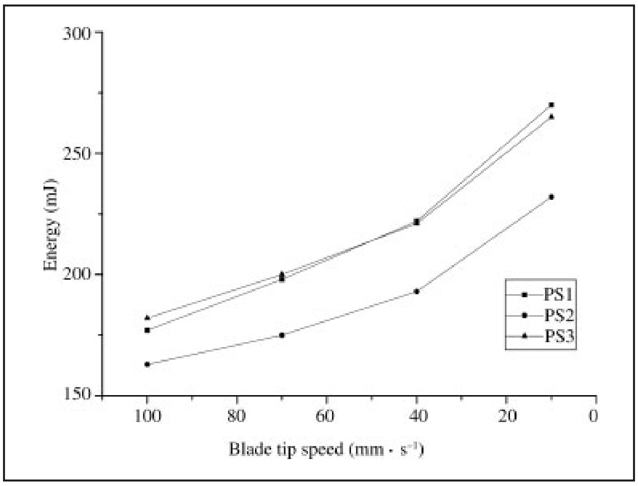

Fig. 2: Effect of flow rate on the three powders, after conditioning and stabilization. Sample volume = 25 mL. CV% < 1

tionary at its most extreme, although PS2 displays lower energy values (Fig. 2).

Consolidation of powders whether produced by storage, vibration during manipulation or direct pressure – as, for example, in capsule plug formation – makes the powders more resistant to flow. The Compaction Index (CI) is an estimate of the increase in energy necessary to flow (Table 4). In general, cohesive powders are more affected by direct pressure than non-cohesive powders due to the presence of the entrained air. The absence of this air in non-cohesive powders results in less significant changes by direct pressure but in a more significant change in energy by tapping, because the strength of the interparticulate forces is overcome by the gravitational forces exerted by tapping, with the particles re-orientating into a highly consolidated bed. PS1-PS3 show a range of sensitivities to both methods and generally conform to the systems described above. Although these powders were all quite sensitive to tapping, none were particularly sensitive to direct pressure. This is because they lack any significant amount of entrained air, which would otherwise be squeezed out on compaction. The particles resist being forced into each other, but will, if given the opportunity to move around, pack themselves quite tightly by means of tapping consolidation. Furthermore, as far as PS1 and PS3 are concerned they appear very similar both in their bulk densities and in their BFE values. However, we can see that there are differences between the two with regard to their interparticulate forces. PS1 has a CI of only 5.9 for tapped consolidation as compared with a CI of 10.5 for PS3 and a CI of 1.9 for direct pressure consolidation as compared with a CI of 1.6 for PS3. What is particularly interesting is that although the CI-tapped of PS3 is twice that of PS1, the Mass Change Ratios (MCR) are exactly the same. So, both powders have consolidated by the same amount volumetrically (ca. 23%), but PS3 has done so in such a way as to increase its resistance to flow by a much larger amount. This relationship is in keeping with the assumption that PS1 is slightly more cohesive than PS3, and so has a higher proportion of entrained air for the particles to move into under light pressure, which is also in agreement with the results previously described in relation to the apparent volume method, in particular as regards the powder RH sensitivities and the number of taps.

The addition of air naturally occurs when powder is moved freely, as in the pharmaceutical technology operation of capsule filling. When aerated, less energy is required to move the powder (Fig. 3). This reduction is described by the Aeration Ratio (AR) which reflects the cohesiveness or stickiness of the powder. In fact, those powders that are particularly cohesive do not allow air to pass through readily and the powder bulk does not became aerated. The resulting reduction in energy, and therefore AR, is small. On the other hand, in freer flowing powders air is able to permeate through the bulk of the powder and the reduction in energy is large. PS1-PS3 show some significant variations in their AR values, although all are aeratable. In particular, PS2 is the least aeratable, with an estimated AR of only 2.9. This suggests quite a cohesive material with stronger interparticulate forces, such a phenomenon being well correlated with the lower bulk density than either PS1 and PS3, and with the results obtained by apparent volume experiments. Although the difference in AR for PS1 and PS3 (7.7 and 6.2, respectively) is slight, it appears to show that PS3 is slightly more cohesive than PS1, and so aerates less readily. Furthermore, the non-correlation between this and the results obtained from the compaction tests suggest that there are different mechanisms dominating powder formation and packing in aeration experiments, from those acting during evaluation of compaction.

In conclusion, the three commercial samples of pregelatinized starch that were examined exhibit different behaviour in terms of apparent volume determination with respect to the various experimental conditions adopted. Firstly, the unexpected but undoubted differences presented by PS2 are remarkable. Among other factors, they may be attributed to the different particle size, as clearly indicated in the product information sheets, where PS2 is described as a fine powder while PS1 and PS3 are bimodally stated to be medium and fine. In fact, the particle size analysis performed by laser diffractometry confirmed that both PS1 and PS3 have a wider size range than PS2 (Table 1). Assuming a similar particle shape for the three samples, the homogeneity of particle size as well as the size classification result in different pouring and settling behaviours. These aspects can be explained by the densification properties being inversely proportional to both homogeneity and size of the particles, the latter being within a certain range of values (Barbosa-Cánovas, 2005). Such properties can also lead to greater sensitivity to taps, in accordance with the homogeneity of the sample (Bos

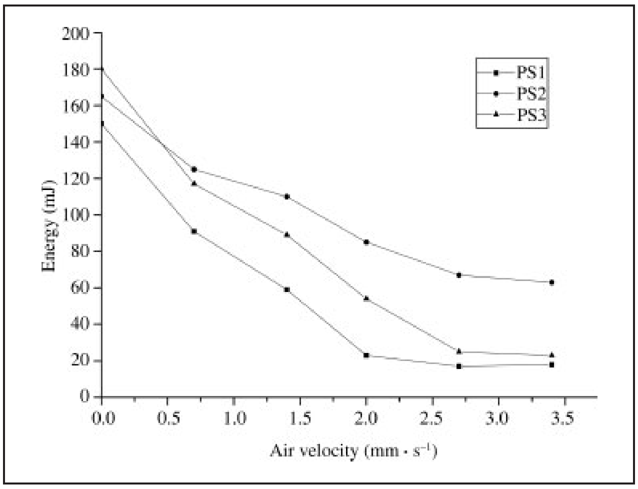

Fig. 3: Influence of aeration on flowability energy. Test helix angle = $-5°$. Blade tip speed = 100 mm · s^{-1}. Sample volume = 25 mL

Table 4: Summary of tribological properties as obtained by FT4 powder rheometer

	PS1	PS2	PS3
Bulk density [kg/L]	0.620	0.532	0.624
Stability index (SI)	1.05	0.98	0.99
Basic flowability energy (BFE) [mJ]	177	163	180
Flow rate index (FRI)	1.51	1.42	1.45
Compacted energy [mJ]			
tapped 100 times	1044	1402	1890
direct pressure (0.2 bar)	336	261	288
Compaction index (CI, Compacted energy/BFE)			
tapped 100 times	5.9	8.6	10.5
direct pressure (0.2 bar)	1.9	1.6	1.6
Mass change ratio (MCR) on compaction			
tapped 100 times	1.23	1.23	1.23
direct pressure (0.2 bar)	1.10	1.08	1.08
Aeration ratio (AR)	7.7	2.9	6.2

et al. 1987). The arrangement by tapping represents an important factor to take into account when PS1-PS3 are used as diluents in a formulation in which other substances, characterized by a different size distribution, are present. Furthermore, the statistical comparison provides evidence for the significant influence of both relative humidity conditions and previous mechanical treatment. So far as the rheological characterization is concerned, they present a widely ranging set of tribological behaviours and they would behave differently in any given pharmaceutical process. How significant these differences are and which of the flowability parameters are most important would depend upon how the materials are handled and processed. Many studies, like recovery from compaction, attrition, and segregation, were not carried out in this investigation. The present study indicates the importance of characterizing apparent volume and flow properties. These data could then be used during formulation in an R&D environment, and for production and predicting performance, eg in advance of starting on each batch, and as a QC tool to ensure that the raw materials always behave the same.

3. Experimental

3.1. *Pregelatinized starch samples*

Three commercially available partially pregelatinized maize starches were tested. They represent pregranulated and free-flowing powders of a grade usable for direct compression and capsule filling. In particular, they were: i) Starch 1500, hereinafter referred to as PS1, batch number IN504527 (2004), a generous gift of Colorcon Limited, Kent, England;. ii) C Pharm DC93000, hereinafter referred to as PS2, batch number AW3824 (2003) and HP3891 (2005), a generous gift of Cerestar France S.A.; iii) Sepistab ST200, hereinafter referred to as PS3, batch number 24510 (2003), a generous gift of Seppic Italia S.p.A.

3.2. *Relative humidity conditioning*

The samples were conditioned as follows: the necessary amounts of the various pregelatinized starches were exposed for at least 24 hours under normal conditions (22 ± 0.5 °C) or at constant relative humidity (RH%) conditions in closed vessels. In particular, saturated aqueous solutions containing large amounts of undissolved sodium chloride (about 75% RH) or calcium chloride hexahydrate (about 35% RH) were used (Moyers and Baldwin 1997). Samples were poured in to glass Petri dishes of appropriate diameter (16 cm and 8 cm for 100 g and 50 g, respectively) with a resulting powder depth between 10.4 and 12.1 mm.

3.3. *Mechanical solicitation*

Mechanical treatment was applied by mortar-pestle mixing. In particular, the pestle was rotated ten times clockwise and ten times anti-clockwise. Undue pressure was not used to avoid compaction of the powder on the bottom of the mortar. A porcelain round-bottomed mortar of adequate capacity and a round-headed pestle were used in order to avoid powder overfilling and to simulate mixing operations.

3.4. *Apparent volume determination*

An apparatus for testing apparent volume (Tap Denser IG/4, Giuliani Tecnologie, Torino, Italy) according to apparent volume monographs (European Pharmacopoeia, 2005b) was used. In particular, a 250-mL graduated (2 mL intervals) glass cylinder was loaded with 100.0 g of powder, unless otherwise stated. Each powder was cautiously poured with the aim of a plastic spoon through a plastic funnel for solids with an opening diameter of approximately 22 mm. After pouring, if the powder was uneven at the top it was carefully levelled, without compacting, using a spatula. The opening was secured with parafilm and the unsettled volume (V_0) was noted. The graduated cylinder was secured in its holder and the appropriate number of taps were given. The number of taps were in agreement with the pharmacopoeial method ($n = 10, 100, 500, 1250, 2500$). At least three determinations were conducted for each trial with the same excipient sample, starting at the beginning of the method. At least three independent trials were run for each material and for each of the experimental conditions employed.

3.5. *Particle size analysis*

Particle size of the PS1 and PS3 samples was determined using a Mastersizer 2000 Laser Diffraction Particle Size Analyser (Malvern Instrument, UK) equipped with a Scirocco 2000 dry powder feeder (Malvern Instrument, UK) at a dispersion pressure of 0.1 bar. For sample PS2, particle size distribution was measured by laser diffraction with a Helos KA/LA (Sympatec GmbH, Germany) equipped with a Rhodos disperser at 1 bar dispersion pressure and at 80% vibration of the Vibri powder feeder with a gap of 2 mm between the powder filler and the Vibri feeder. Results are expressed as D10, D50 and D90, that is the particle diameter for which the fraction of the particles with diameter less than that value represented 10%, 50% and 90% of the overall particle size distribution, respectively. All values were averages of three repetitions (Table 1).

3.6. *Rheological characterization*

Rheological properties of the PS samples were determined using an FT4 Powder Rheometer (Freeman 2006). Reproducibility of data (number of independent experiments = 3) was always within 3%. For the detail of the methodology see the Freeman Technology website (www.freemantech.co.uk). Briefly, the most important flow parameter under investigation was the Basic Flowability Energy (BFE). It represents the energy required to displace a constant volume of conditioned powder at a given flow pattern and flow rate (helix = $-5°$; blade tip speed = 100 mm s^{-1}; sample volume = 25 mL). This value was recorded at the repeat test number 7. As regards the other rheological characteristics, Stability Index (SI) represents stress changes during repeat testing at a constant blade tip speed of 100 mm s^{-1}. The SI was evaluated by the ratio between the values obtained in test numbers 7 and 1. In addition, Flow Rate Index (FRI), Mass Change Ratio (MCR), Compaction Index (CI) and Aeration Ratio (AR) were evaluated as single point measurement, unless otherwise stated. FRI represents the factor by which the flow energy requirement is changed when the flow rate is reduced by a factor of 10, at a blade tip speed reducing from 100 mm $\cdot$ s^{-1} to 10 mm $\cdot$ s^{-1}, in stepd of 30 mm $\cdot$ s^{-1}. MCR on compaction is the change in the sample mass, for a given volume, following consolidation by direct pressure or tapping. As a formula, MCR = mass of consolidated sample (by direct pressure or tapping)/mass of conditioned sample. CI represents the factor by which the BFE is increased when the powder is consolidated by direct pressure, tapping or storage under given conditions. Thus, CI corresponds to the energy of the consolidated sample divided by the BFE. Lastly, AR was evaluated as the factor by which the BFE is reduced by aeration at a given air flow velocity. The aeration investigation uses a sample initially conditioned twice. At this point, air was turned on at the lowest velocity and the sample was again conditioned twice and tested. The air velocity was increased successively and the sample was conditioned once and tested. The latter sequence was repeated until stabilisation.

3.7. *Statistical evaluation*

One-way ANOVA with the Bonferroni post-test (Instat software, version 1.14 GraphPAD Software Inc., San Diego, CA) were used for the statistical analysis of the results. Significance was defined as a P value of less than 0.05.

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