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Packing properties of starch-based powders under mild mechanical stress

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This study reports the ability to settle of commercial pharmaceutical grade starch samples, both native and pregelatinized. The experiments were carried out under different relative humidity (RH%) conditions and the packing properties were evaluated using both official pharmacopoeial monograph conditions and also modified conditions in order to give a deeper knowledge of tapping under mild mechanical stress. The technique adopted, simulating common pharmaceutical operating practices, appears to be useful to estimate some technologically relevant features of diluent powder materials. Moreover, a general mathematical function has been applied to the experimental data; this could be appropriate for adequately describing material settling patterns and offers practical parameters for characterizing starch powders within the context of a pharmaceutical quality system.

1. Introduction

Starch of pharmaceutical grade is a high-polymeric carbohydrate material primarily composed of amylopectin and amylose and characterised by specific properties as stated in the official pharmacopoeial monographs (European Pharmacopoeia 2008a; US Pharmacopoeia – National Formulary 2008a; Martindale 2007). It is usually derived from cereal grains such as corn, wheat and sorghum, or from roots and tubers such as potatoes and tapioca. It includes starch which has been pregelatinized by heating in the presence of water (European Pharmacopoeia 2008b; US Pharmacopoeia – National Formulary 2008b; Martindale 2007). Commercial samples of this material differ from each other in terms of structural modification and functionality, even if they meet all the official requirements. The phenomenon of granular compaction involves the increase of the bulk density of a granular material subjected to shaking, tapping or, more generally, to some kind of external excitation (Bhattachar et al. 2004; Arsenović et al. 2007). Moreover, the physical characteristics of a starch may depend on its methods of preparation. The technologically relevant behaviour of pregelatinized starch (PS) is influenced by common pharmaceutical operating practices. Previous studies have reported a comparison of poured and tapped density by official methods, as well as the rheological behaviour of various commercial samples of PS (Travagli and Zanardi 2007). Starch-based diluent materials are available from a wide range of commercial sources. The development of a technique able to explain some technologically relevant features by focusing on the tapping characteristics of starch samples, whether pregelatinized or not, appears both topical and attractive. To achieve this goal, the number of taps and the modality of imparting them were studied and applied in such a way that the settling capability could give information about the different packing behaviour of raw materials nominally identified as the same. Because of the importance of hy-

Table 1: Principal properties of commercial samples investigated

	S1	PS1	PS2	PS3	PS4[a]	PS5[b]
Degree of pregelatinization	None	Partial	Partial	Partial	Partial	Partial
Particle size	Medium-fine D10 = 15.2 μm D50 = 73.1 μm D90 = 169 μm	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	Medium-fine D10 = 15.3 μm D50 = 72.2 μm D90 = 167 μm	Medium-fine D10 = 11.5 μm D50 = 18.5 μm D90 = 29.5 μm
Loss on drying (%)	13.6	9.9	8.8	12	<14	<14
Sulfated ash	<0.6	0.12	0.21	0.15	<0.5	<0.5
pH	6.9	5.7	6.0	5.8	3–4	6–7.5
Botanic characteristics	Maize	Maize	Maize	Maize, hybrid	n.a.	n.a.

[a] mixture of pregelatinized starch (96.5%), magnesium stearate (1.5%), silicon dioxide (1%), tartaric acid (1%); [b] mixture of pregelatinized starch (97.5%), magnesium stearate (1.5%), silicon dioxide (0.5%), talc (0.5%); n.a. = not available

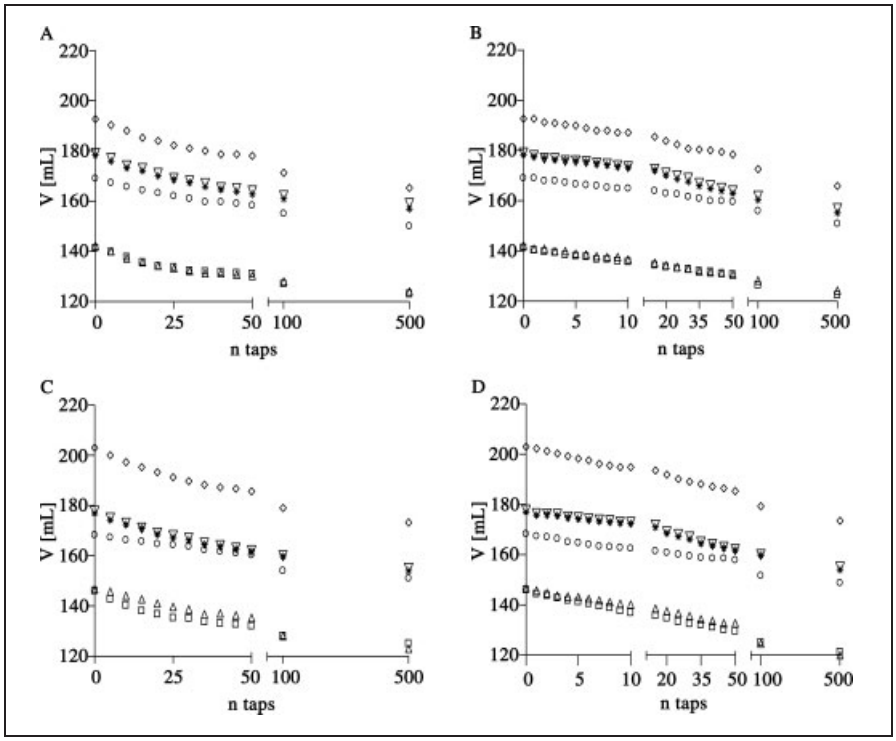

Fig. 1:
Ability to settle of the various samples with respect to tapping modalities and in relation to the experimental conditions adopted (see text for further explanation). A) method a, r. c.; B) method b, r.c.; C) method a, RH = 35%; D) method b, RH = 35%. ○ S1, * PS1, ◇ PS2, PS3, □ PS4, △ PS5

groscopicity, the effect of RH% on the equilibrium properties of the mixture was also experimentally evaluated. The results obtained provide a tool capable of both characterizing the densification pattern and of showing appreciable differences, even where there are apparently negligible differences in the certificate of analysis of commercial starch samples. Finally, the mathematical function employed in the present paper appropriately describes the fairly complex process of settling in powder packing by tapping and provides realistic information about changes in density during compaction. The results obtained are of interest in the "QbD" field (International Conference on Harmonization, 2007), both in an R&D environment and in industrial and small-scale production.

2. Investigations, results and discussion

Table 1 summarizes the principal properties of the commercial samples under investigation. The products presented some differences although they all meet the requirements of pharmacopoeial monographs. All the pure samples considered are from maize as the botanical source, apart from starch-based excipient mixtures where the supplier did not declare the origin. The ability to settle of the various samples in relation to the experimental conditions adopted is shown in Fig. 1. A great variability of the initial apparent volume of the same weight of starch (100 g) poured into a glass cylinder was obtained, ranging from 192.7 ± 0.58 to 141.3 ± 0.57 mL and from 203.0 ± 1.0 to 146.0 ± 0.50 mL, for PS2 and PS4 stored either under room conditions or at RH = 35%, respectively. Both the homogeneity of particle size distribution and the finer dimensional classification explained the behaviour of PS2, while the presence of antifriction agents was responsible for the pattern seen with PS4. The latter argument is confirmed by the values obtained with PS5, with results very close to those for the related composition of PS4. Moreover, the overall settling profiles of PS1 and PS5 appear

Table 2: Ability to settle of the different starch-based samples under experimental conditions adopted

	S1	PS1	PS2	PS3	PS4 (mix)	PS5 (mix)
Room condition						
$V_{10}-V_{500}$[a]	15.7 ± 1.5	10.2 ± 1.1	22.7 ± 0.6	10.2 ± 2.3	14.7 ± 0.6	13.3 ± 0.6
$V_{10}-V_{500}$[b]	14.0 ± 1.0	9.7 ± 1.2	21.0 ± 2.0	9.5 ± 1.3	17.3 ± 0.6	12.3 ± 1.5
$V_{10}-V_{500}$[c]	15.0 ± 1.0	13.6 ± 2.1	20.7 ± 2.2	13.8 ± 0.8	17.0 ± 0.9	17.0 ± 1.0
V_0-V_{10}[a]	3.3 ± 0.6	4.3 ± 1.1	4.7 ± 0.6	3.9 ± 1.8	3.7 ± 0.6	5.0 ± 0.6
V_0-V_{10}[b]	4.0 ± 0.1	4.0 ± 1.0	5.3 ± 1.2	3.7 ± 1.9	5.8 ± 0.6	5.7 ± 0.6
V_0-V_{10}[c]	4.0 ± 1.0	4.2 ± 1.3	6.7 ± 0.9	5.1 ± 2.2	5.3 ± 0.9	4.3 ± 1.0
Poured density	0.5917	0.6297	0.4878	0.5938	0.7076	0.7026
RH = 35%						
$V_{10}-V_{500}$[a]	15.3 ± 0.6	10.5 ± 0.9	24.0 ± 1.0	10.5 ± 1.1	15.3 ± 0.6	21.0 ± 1.0
$V_{10}-V_{500}$[b]	14.0 ± 4.4	10.0 ± 1.4	21.0 ± 2.6	10.1 ± 0.6	16.3 ± 3.7	20.7 ± 2.3
$V_{10}-V_{500}$[c]	20.0 ± 1.0	13.8 ± 1.0	19.2 ± 0.5	13.8 ± 0.8	17.0 ± 1.1	17.0 ± 1.0
V_0-V_{10}[a]	2.0 ± 0.1	3.6 ± 0.5	5.7 ± 0.6	4.7 ± 0.9	5.7 ± 0.6	2.7 ± 0.6
V_0-V_{10}[b]	6.0 ± 2.6	3.3 ± 0.4	8.3 ± 2.6	4.3 ± 0.7	9.4 ± 0.6	6.7 ± 0.6
V_0-V_{10}[c]	3.3 ± 1.1	4.6 ± 0.9	12.0 ± 1.5	5.6 ± 1.0	7.0 ± 1.2	3.7 ± 1.4
Poured density	0.5939	0.6158	0.4780	0.6234	0.6849	0.6818

[a] Method a; [b] method b; [c] method c. See text for further explanation

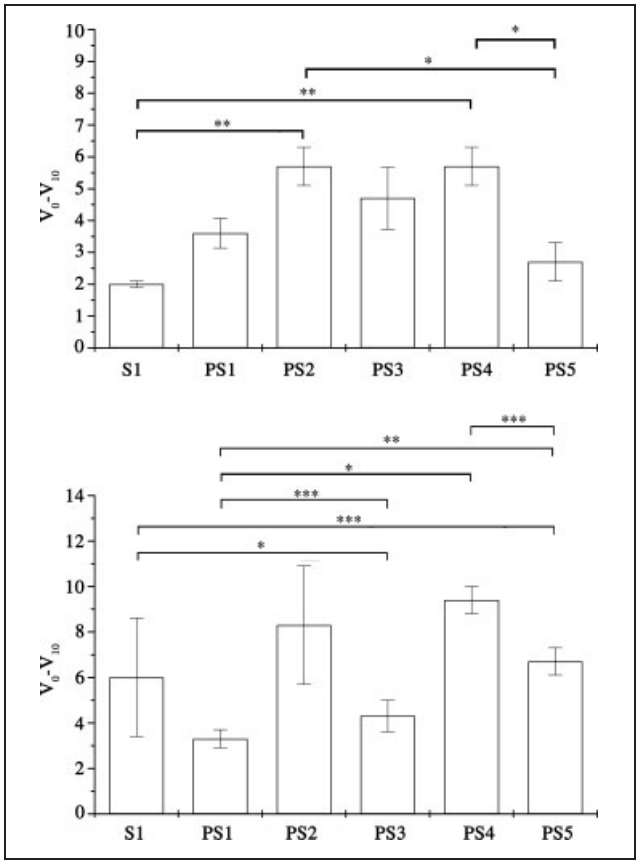

Fig. 2: Statistical analysis of the ability to settle differences (V_0-V_{10}) as obtained by the various samples, at RH = 35%. Method a (top); method b (bottom). See text for further explanation

to be very similar to those of PS3 and PS4, respectively, bearing out the importance of the factors previously described. Table 2 summarizes the differences between apparent volumes after n taps. The modalities between successive taps adopted for both methods a) and b) were able to distinguish the systems, so that the initial state for each tap represents a metastable equilibrium with respect to that obtained with method c), which was adopted for its conformity to the pharmacopoeial monograph, in terms of the tapping modality. No differences between the apparent volume difference $V_{10}-V_{500}$ as obtained by the two methods a) and b) were observed at under different experimental conditions, except for PS4 under room conditions ($P < 0.001$). When the step-by-step tapping modalities and the official monograph method were compared under room conditions, the evolution of the apparent volume differences for the same sample led to significant differences among the data in PS1, PS2, PS5 ($P < 0.001$) and PS3 ($P < 0.05$) as well as in both PS1, PS3 and PS3 ($P < 0.001$) with respect to methods a) and b), respectively. However, if RH = 35% was adopted, all the samples appeared significantly different ($P < 0.001$) in the $V_{10}-V_{500}$ values, except for PS4 with $P < 0.01$ and $P > 0.05$ for methods a) and b), respectively, and for both PS2 and PS4, method b), differences were not significant. A comparison among the ability to settle as determined for the various samples using method a) under room conditions showed significant differences, except for: S1 vs. both PS4 and PS5; PS1 vs. PS3; and PS4 vs. PS5. If RH = 35% was used, the exceptions were reduced to S1 vs. PS4 and PS1 vs. PS3. The latter outcome was expected, in view of the similarity of these samples, as evidenced by previous studies (Travagli and Zanardi 2007). When method b) was adopted, the only non-significant difference was the pair S1 vs. PS5, under room conditions. However, at RH = 35%, greater standard deviations were obtained and statistically significant differences could be found only between S1 vs. both PS2 and PS5 ($P < 0.05$), PS1 vs. both PS2 and PS5 ($P < 0.001$), PS2 vs. PS3 ($P < 0.001$) and PS3 vs. PS5 ($P < 0.001$).

V_0-V_{10} was also investigated to obtain practical information for formulation purposes (Travagli and Zanardi 2007). Even with this evaluation, the proposed methods a) and b) were not statistically significantly different from each other for the same material, except for PS4 at room condition ($P < 0.001$). Statistical significant differences between

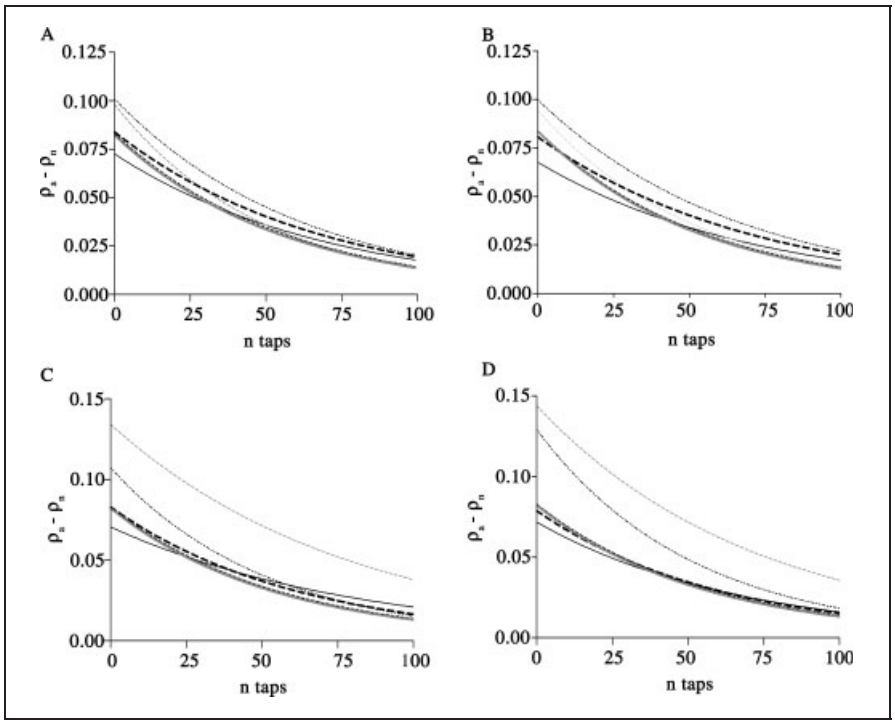

Fig. 3:
Asymptotic density, ρ_a, and tapped density at n-taps, ρ_n, differences with respect to the number of taps (see text for further explanation). A) method a, r.c.; B) method b, r.c.; C) method a, RH = 35%; D) method b, RH = 35%. —— S1, – – – PS1, ▬ ▬ PS2, —— PS3, ··–·· PS4, ----- PS5

the apparent volume differences as obtained by the official (method c) and step-by-step tap modalities (methods a and b) were observed when comparing the behaviour of each sample. In detail, method c) vs. method a) led to $P < 0.001$ for both PS2 and PS4 under room conditions, while RH = 35% led to significant differences for S1 and PS2, with $P < 0.05$ and $P < 0.001$, respectively. As for a comparsion of method c) vs. method b) under room conditions was concerned, $P < 0.05$ was obtained for both PS2 and PS5, while at RH = 35%, $P < 0.001$ was obtained in the cases of S1, PS2 and PS5, and $P < 0.05$ for the remaining samples vs. both PS2 and PS4, as well as for PS4 vs. PS5. By comparing the pattern for the different commercial starches, an interesting result was obtained. In fact, all the samples gave similar differences ($P < 0.049$ only for S1 vs. PS5) under room conditions, while at RH = 35% some statistical differences were unexpectedly obtained between the samples, as shown in Fig. 2, emphasising the importance of consolidation behaviour during the initial stages of powder processing. The influence of tapping was, therefore, investigated by the difference between the asymptotic density, ρ_a, and the tapped density ρ_n, after an initial 100 taps (Berg and Mehta 2001; Brey and Prados 2001) as reported in Fig. 3. The asymptotic density was calculated with respect to the volume obtained after 500 taps. In fact, even if minimal differences (<2 ml) were obtained when 1250 taps were given, the selected 500 tap condition appeared more appropriate to investigate the densification pattern under mild stress, the primary aim of this work. A typical exponential decay in relation to the number of taps was obtained, as expected. While the trend of the data could be fitted by numerous mathematical functions, the monoexponential model (1) was chosen (see Experimental section for details).

$$\rho_a - \rho_n = A[e^{-n/k}] \quad (1)$$

Equation (1) provides good results in terms of fitting a mathematical description of most of the density variation profiles under different tapping procedures. They are reported in Table 3 together with both the numerical coefficient values A and k obtained, as well as the correlation coefficient, r^2. In particular, the parameter A may be considered as a proportionality constant linked to the system characteristics, while the k values represent, for a same material, a useful estimation of the powder's ability to pack with respect to both stress and environmental conditions. Evaluation of the data always gave acceptable r^2 values where the experiments were conducted with 100 g of powder ($r^2 \geq 0.939$). On the other hand, for different sizes of sample the mathematical description often did not appear to be entirely adequate. In detail, if 50 g were used, substantially different behaviour between methods a) and b) was evident for S1, PS2 and PS4, where either $r^2 \leq 0.853$, or non-convergence of the fitting analysis (see S1, method b, under room conditions) were obtained. Analogous results were found for both PS4 and PS5 with a sample sizes of 150 g ($r^2 \leq 0.917$, data not shown). These outcomes were partly explained by the use of a non-standard mass of powder with respect to the official monographs. Attempts to investigate different functions to improve the best-fit (Ludewig et al. 2006; Arsenović et al. 2007) were considered beyond the aim of the present study. It was not possible to study the behaviour of 150 g of the remaining products because of exceeding the cylinder volume limit.

In conclusion, among the various possible considerations, the following ones could be considered very important:

Table 3: Numerical and correlation coefficients of Eq. (1) describing variations in powder densification by tapping as obtained by the various powders at the different conditions adopted (see text for details)

Sample amount	Method a, r.c.			Method a, RH = 35%			Method b, r.c.			Method b, RH = 35%		
	A	k	r^2	A	k	r^2	A	k	r^2	A	k	r^2
100 g												
S1	0.07 ± 1.7E-3	71.0 ± 4.8	0.967	0.07 ± 1.3E-3	66.9 ± 4.8	0.939	0.07 ± 8.6E-4	72.7 ± 3.7	0.970	0.07 ± 1.4E-3	82.4 ± 5.1	0.984
PS1	0.08 ± 2.4E-3	52.2 ± 3.8	0.998	0.08 ± 2.3E-3	50.0 ± 3.7	0.987	0.08 ± 1.5E-3	54.4 ± 2.3	0.990	0.08 ± 2.0E-3	51.2 ± 3.7	0.985
PS2	0.08 ± 1.1E-3	68.2 ± 2.5	0.990	0.08 ± 7.2E-4	62.0 ± 1.4	0.990	0.08 ± 8.6E-4	70.5 ± 3.1	0.967	0.08 ± 1.1E-3	60.6 ± 3.2	0.967
PS3	0.08 ± 2.3E-3	53.8 ± 3.8	0.982	0.09 ± 2.2E-3	51.2 ± 3.6	0.976	0.08 ± 1.5E-3	56.8 ± 2.3	0.978	0.08 ± 2.2E-3	52.7 ± 3.6	0.988
PS4	0.10 ± 2.7E-3	62.1 ± 4.2	0.966	0.11 ± 3.8E-3	50.2 ± 4.2	0.961	0.10 ± 1.7E-3	66.3 ± 4.3	0.954	0.13 ± 2.3E-3	51.2 ± 3.1	0.967
PS5	0.10 ± 3.5E-3	49.7 ± 4.0	0.954	0.13 ± 1.8E-3	79.2 ± 3.2	0.990	0.10 ± 1.6E-3	52.6 ± 3.1	0.963	0.14 ± 1.5E-3	71.8 ± 3.0	0.985
50 g												
S1	0.08 ± 1.3E-3	55.9 ± 2.1	0.990	0.10 ± 1.7E-3	71.5 ± 3.6	0.983	no fit	no fit	no fit	0.07 ± 2.3E-3	96.6 ± 14	0.853
PS1	0.09 ± 1.5E-3	48.4 ± 3.4	0.986	0.10 ± 1.3E-3	88.7 ± 2.9	0.989	0.09 ± 2.4E-3	71.4 ± 5.9	0.991	0.11 ± 5.1E-3	63.1 ± 6.2	0.989
PS2	0.10 ± 2.7E-3	76.9 ± 5.9	0.957	0.09 ± 1.7E-3	65.5 ± 3.4	0.981	0.10 ± 3.8E-3	94.3 ± 16	0.739	0.09 ± 3.3E-3	84.7 ± 13	0.788
PS3	0.09 ± 1.1E-3	49.1 ± 2.7	0.987	0.10 ± 3.9E-3	88.3 ± 4.2	0.981	0.09 ± 1.5E-3	70.9 ± 3.1	0.981	0.11 ± 1.3E-3	62.2 ± 3.3	0.983
PS4	0.17 ± 5.7E-3	61.7 ± 5.1	0.949	0.11 ± 2.8E-3	233 ± 40	0.781	0.18 ± 7.1E-3	62.7 ± 8.5	0.836	0.11 ± 2.3E-3	163 ± 24	0.749
PS5	0.16 ± 3.5E-3	74.2 ± 4.7	0.970	0.09 ± 1.5E-3	61.1 ± 2.7	0.986	0.15 ± 2.2E-3	67.5 ± 3.6	0.970	0.10 ± 7.8E-3	135 ± 6.4	0.970

S1, PS1, PS2, PS3 and PS4 are not influenced by RH conditions in respect of $V_{10}-V_{500}$ or V_0-V_{10} values while with PS5 there is a big difference between room conditions and RH 35%.

The investigation aimed to verify the settling behaviour of various commercial samples of nominally the same material in the presence of both physical modifications and excipients. Data fitting with the function adopted was helpful to obtain information relevant to dosage-form formulation and, in-process control as well as "QbD". The selection of three different sample sizes of the products allowed us to confirm that the "quantity" parameter influenced the packing properties of the preparations analyzed. In addition the relative humidity conditions should also be accurately evaluated to ensure reproducibility in powder densification (Coelho and Harnby 1979), together with dimensional classification by particle size.

3. Experimental

3.1. Starch samples

Six commercially available samples were tested. They represent pregranulated and free-flowing powders of a grade suitable for direct compression and capsule filling. In detail: i) Amylum Tritici Ph. Eur. Ntr. 1998, hereinafter referred to as S1; ii) Starch 1500, subsequently referred to as PS1, batch number IN504527, generously donated by Colorcon Limited, Kent, England; iii) C☆Pharm DC93000, subsequently referred to as PS2, batch numbers AW3824 and HP3891, generously donated by Cerestar France S.A; iv) Sepistab ST200 subsequently referred to as PS3, batch number 24510, generously donated by Seppic Italia S.p.A.; v) Excipient A, subsequently referred to as PS4, Comifar Distribuzione S.p.A (Italy), batch number 803869; vi) Excipient B, subsequently referred to as PS5, Comifar Distribuzione S.p.A. (Italy), batch number 803949.

3.2. Relative humidity conditioning

The samples were conditioned as follows: a weighed amount of the various starches (100.0 g, unless otherwise stated) was exposed for at least 24 h under normal conditions ($22 \pm 0.5\,^{\circ}C$) or at constant relative humidity (RH%) in closed vessels. In particular, to obtain the desired RH%, saturated aqueous solutions containing large amounts of calcium chloride hexahydrate (about 35% RH) were used (Moyers and Baldwin 1997). Samples were poured into glass Petri dishes of appropriate diameter (8 cm, 16 cm and 24 cm for 50 g, 100 g and 150 g, respectively) with a resulting powder depth between 10.2 and 12.5 mm.

3.3. Apparent volume determination

Apparatus for testing apparent volume according to official monographs was used (Tap Denser IG/4, Giuliani Tecnologie, Torino, Italy). 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 aid 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 using a spatula, without compacting. The opening was secured with parafilm and the unsettled volume (V_0) was noted. The graduated cylinder was secured in its holder and progressively subjected to the number of taps, n. These taps were given in different ways: a) in terms of a modification to the pharmacopoeial method, tapping by increments of one (n ranging from 1 to 50, increment of one, then 100 and 500 taps); b) the same as method a), but giving taps by increments of one up to 10 taps all the volume values were evaluated: in the range 15–50 taps, the volume values were recorded at intervals of 5, then 100 and 500 taps); c) complying with the pharmacopoeial method for the first three steps ($n = 10, 100, 500$). The changes in methods a) and b), compared with that of the European Pharmacopoeia, was chosen to simulate the behaviour of the samples under the solicitations to which they are subjected during normal processing operations. In all cases, the corresponding settled volumes were recorded (V_n). At least three determinations were conducted for each trial with the same excipient sample. At least three independent trials were run for each material and for each experimental condition adopted.

3.4. Particle size analysis

Particle size of all samples except than PS2 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 0.5 bar. For sample PS2 a Helos KA/LA laser diffraction analyzer (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 feeder and the Vibri feeder was used, as reported in a previous paper (Travagli and Zanardi 2007). Results are expressed in D10, D50 and D90, that is the particle diameter for which the fraction of the particles with a 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).

3.5. Mathematical fitting

To describe the results, we have proposed Eq. (1), see above, to describe the packing of the powder material dependent on the physical and dimensional characteristics of the samples.

In the equation, ρ_a is the asymptotic density ($n = 500$), ρ_n is the density after n taps ($n \leq 100$) and A and k are the packing coefficients, which take into account, among other factors, the system characteristics, the tapping modalities, and the densification pattern, as well as the amount of powder (Ludewig et al. 2006; Ortega-Rivas 2008).

An iterative non-linear least-squares fitting method (NLLSQ) was applied to the data (GraphPad Prism 4.0 software).

3.6. Statistical evaluation

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

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