Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 257 (2003) 301–304
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Note

Note on the measurement of flowability according to the European Pharmacopoeia

Andrea Schüssele, Annette Bauer-Brandl*

Department of Pharmaceutcis and Biopharmaceutics, Institute of Pharmacy, University of Tromsø, Universitetsveien 57, N-9037 Tromsø, Norway

Received 22 November 2002; accepted 10 January 2003

Abstract

Flowabilities of six commercially available, direct compression excipients, Emcompress™, Fujicalin™, Starch 1500™, Avicel™ PH-102, Tablettose™ 80, and Tablettose™ 100 were examined according to the technical procedure described in the current European Pharmacopoeia, and with a Sotax Flow Tester.

Results revealed unfavourable properties for Fujicalin compared to other substances. Fujicalin, however, appeared macroscopically to be of extremely pronounced free-flowing properties. This contradiction was studied in more detail, proposing to express powder flow in terms of volume per time unit rather than mass per time unit (volume-flowability).

Keywords: Flowability; Bulk powder properties; Volume-flowability; Carr index; Hausner ratio; Direct compression excipients; Uniformity of mass of tablets

Optimum flowability of powders is crucial in the manufacturing process of solid single dose preparations. The European Pharmacopoeia (Ph. Eur.) therefore contains a test on "Flowability" (Ph. Eur., 2002a) which examines the ability of a powder to flow vertically out of a funnel. The results are expressed in units time per mass. In the manufacturing processes both for tablets and capsules, dosing for single dosage forms takes place after the volume rather than the mass. However, bulk densities of commonly used materials differ widely, considering that both organic substances like cellulose derivatives and inorganic substances like calcium phosphates are typical tableting excipients. The aim of the present experiment was to study flowability with respect to usefulness for practical applications.

Six commonly used tableting excipients were used as delivered:

- Tablettose™ 80, batch number 900719, and
- Tablettose™ 100, batch number 901250, both generous gifts of Meggle GmbH, 83512 Wasserburg, Germany
- Fujicalin™, Lot. No. CP711026, generous gift from Fuij Chemical Ind. Co. Ltd., Tokyo, Japan
- Emcompress™ Dihydrat, Penwest GmbH, 55294 Bodenheim, Germany
- Avicel™ PH-102, FMC International, Little Island, Cork
- Starch 1500™, batch number IN 502797, generous gift from Colorcon Ltd., Dartford, Kent, England.

* Corresponding author. Tel.: +47-77-64-61-60; fax: +47-77-64-61-51.
E-mail address: annetteb@farmasi.uit.no (A. Bauer-Brandl).

0378-5173/03/$ – see front matter
doi:10.1016/S0378-5173(03)00142-X

Densities of bulk and settled product were examined as suggested by the European Pharmacopoeia's Technical Procedure "Apparent Volume" (Ph. Eur., 2002b) using an Erweka SVM volumeter (Erweka, Heusenstamm, Germany). Deviating from the instructions, a 100 ml graduated cylinder was used for better accuracy of reading volumes, which is in accordance to the respective USP procedure (US Pharmacopoeia, 2000). The cylinder was filled with a certain mass of deagglomerated powder (Sartorius LP62OS balance, accuracy ± 1 mg). The initial volume was measured in three parallels and poured densities calculated. After 10, 250, 500, and 1250 taps the corresponding volume was read to the nearest millilitre (according to Ph. Eur.). As the difference in all cases between V_{500} and V_{1250} was smaller than 2 ml (Ph. Eur., 2002b) and 2% (US Pharmacopoeia, 2000), respectively V_{1250} was used to calculate tapped density.

From the poured and tapped densities, Hausner ratio (HR, Eq. (1)) (Hausner, 1967) and Carr's compressibility index (I_c; Eq. (2)) (Carr, 1965) were calculated for the respective powders:

$$\mathrm{HR} = \frac{\mathrm{density}_{\mathrm{tapped}}}{\mathrm{density}_{\mathrm{poured}}} \quad (1)$$

$$I_c\,(\%) = \frac{\rho_{\mathrm{tapped}} - \rho_{\mathrm{poured}}}{\rho_{\mathrm{tapped}}} \times 100 \quad (2)$$

Poured densities of the substances (Table 1) range from 0.93 g/ml (Emcompress™) to 0.34 g/ml (Avicel™ PH-102), and tapped densities from 1.1 g/ml (Emcompress™) to 0.43 g/ml (Avicel™ PH-102). Hausner ratios (Table 1) differ from 1.16 (Fujicalin™) to 1.3 (Starch 1500), with a variability of ±0.2 between repetitions. According to commonly accepted criteria of Hausner factors (Ritschel and Bauer-Brandl, 2002), Fujicalin and Emcompress have excellent flowability, both Tablettose types are regarded good, Avicel and Starch are fair. The same ranking is yielded with the Carr index because it is derived from the very same data.

A glass funnel as described in the European Pharmacopoeia's flowability test (Ph. Eur., 2002a) was fixed in a strictly vertical position. The bottom opening was blocked impermeably. Test samples were weighed (Sartorius LP62OS balance) and introduced carefully into the dry funnel in order to avoid dusting and compaction. The funnel was unblocked and the time the entire powder needed to flow out of the funnel measured ($n = 6$). Flowability was expressed in seconds per 100 g of sample (Ph. Eur., 2002a). The values show that the flowability can be measured reproducibly.

Avicel™ PH-102 and Starch 1500 did not flow freely out of the funnel. These two substances have a Hausner value above 1.25, which in the literature is regarded to represent the threshold between free flow and no flow (Ritschel and Bauer-Brandl, 2002; Podzeck, 1998). Tablettose™ 80 and Tablettose™ 100 need almost the same time to flow out of the funnel, whereas Emcompress™ appears to be the best flowing of the substances, while Fujicalin™ is worst. The latter is in contrast to the poured/tapped density measurements (Table 1), and to the macroscopic observation that Fujicalin appears extremely free-flowing, which is expected due to its round-shaped particles (Schlack et al., 2001).

The powder bed density of Fujicalin is much smaller compared to the other flowing substances (Table 1), which is due to the porous structure of the particles (Schlack et al., 2001). In contrast to this, Emcompress, consisting of compact agglomerates of inorganic crystals, has a particularly high density. This would mean that flowability expressed in terms of mass per time

Table 1
Results of density measurements, averages of three measurements each, total range: volumes ± 0.5 ml, masses ± 0.1 g

Substance	Sample mass (g)	Poured volume (ml)	Tapped volume (ml)	Poured density (g/ml)	Tapped density (g/ml)	Hausner ratio	Carr index (%)
Fujicalin™	40	93	80	0.43	0.50	1.16	14.0
Emcompress™	90	97	82	0.93	1.10	1.18	15.4
Tablettose™80	55	93	79	0.59	0.70	1.19	15.7
Tablettose™100	50	91	76	0.55	0.66	1.20	16.7
Starch 1500™	50	75	58	0.66	0.86	1.29	23.3
Avicel™ PH-102	30	88	69	0.34	0.43	1.26	21.0

Table 2
Flowability measurements, $n = 7$

Substance	Mass of sample (g) ± S.D.	Flow time (s) ± S.D.	Flow time per mass (s/100 g) ± range	Poured density (g/ml) ± range	Flow time per volume (s/100 ml) ± range	Sotax value original	Sotax time per 100 ml
Fujicalin™	181.3 ± 0.1	4.8 ± 0.1	2.6 ± 0.1	0.43 ± 0.1	1.14 ± 0.1	0.86	5.4
Emcompress™	379.8 ± 0.2	5.3 ± 0.1	1.4 ± 0.1	0.93 ± 0.1	1.30 ± 0.1	0.99	5.2
Tablettose™ 80	251.3 ± 0.4	5.6 ± 0.1	2.3 ± 0.1	0.59 ± 0.1	1.31	0.95	4.6
Tablettose™ 100	227.2 ± 0.3	5.3 ± 0.1	2.3 ± 0.1	0.55 ± 0.1	1.28	0.72	12.0 (6.4 without #5)
Starch 1500™	260 ± 0.4	No flow	–	0.66 ± 0.1	–	0.56	17.9
Avicel™ PH-102	100 ± 0.4	No flow	–	0.34 ± 0.1	–	0.43	24.5

necessarily is much higher in the case of Emcompress compared to Fujicalin, even if the speed of flow of individual particles is equal. Therefore, alternatively, the time consumed for flow of a certain volume of the bulk powder was calculated using poured density (Table 2). The "volume-flowability" reveals that all the free-flowing materials (Emcompress, Fujicalin, Tablettose 80 and Tablettose 100) are almost equal (no significant difference at $\alpha = 0.05$); Fujicalin™, however, may have a tendency to even perform a little better. These values are in good agreement with the macroscopically observed flowability.

In contrast to the Ph. Eur.-method, the commercially available Sotax Powder Flow Tester FT 300 (Sotax, Allschwil, Switzerland) introduces vibrations before and/or during the flow test in order to simulate manufacturing processes. According to the instructions, flowability was measured as the average time consumption for 300 g of substance in six different experiments (different vibration schemes) and normalized by a reference value (300 g quartz sand, generous gift from Quarzwerke GmbH, 50207 Frechen, Germany), expressed as the angle of a line in a standardized graph plotting percent sample mass versus time (=100 s). SOTAFISH software (Sotax) was used to evaluate the results. As can be seen from Table 2, vibrations induce flow of the non-freely-flowing materials. Accordingly a value of >0.9 is regarded very good flowability (Emkompress and Tablettose 80), 0.8–0.9 is good (Fujicalin), satisfactory (Tablettose 100), Starch unsatisfactory, and Avicel poor. Furthermore, as the "Sotax-flowability" values are expressed as the time consumed by 100 ml of sample to flow out of the Sotax-funnel (Table 2) with no respect to a reference. Sensitivity to vibrations is the main effect in this experiment.

One may expect a relationship between flowability and uniformity of mass of tablets. Small tablets (6 mm diameter) were compressed on a Korsch EK0-1 single punch tablet press (Korsch GmbH, Berlin). No systematic differences nor trends were found and all batches passed the test on uniformity of mass (Ph. Eur., 2002c) (data not shown). Tablet mass appears to be widely independent of flow properties because of the filling mechanisms of tablet presses being particularly designed for low mass variation even with material of bad flow properties.

It can be concluded that the flowability test is reproducible, quick and cheap. However, due to widely different bulk densities of powders, the expression of flowability in terms of time per mass may in some cases not match the macroscopic flow qualities. It is proposed that "volume-flowability" is a better description.

Neither the United States Pharmacopoeia 24 nor the Japanese Pharmacopoeia (13th Edition) contain any method for measuring flow properties of powders. The usefulness of the flowability test in the European Pharmacopoeia—with respect to manufacture of solid dosage forms—may be up to discussion.

Acknowledgements

We would like to express our thanks to Drs. S. Hirsch and D. Becker, Novartis Inc., Basle, Switzerland, for measurements with the Sotax Flow Tester, and for useful discussions, respectively.

References

Carr, R.L., 1965. Evaluating flow properties of solids. Chem. Eng. 18.

Hausner, H., 1967. Friction conditions in a mass of metal powder. Int. J. Powder Metall. 3.

Podzeck, F., 1998. Particle–Particle Adhesion in Pharmaceutical Powder Handling. Imperial College Press, London, pp. 95–114.

Ritschel, W.A., Bauer-Brandl, A., 2002. Die Tablette. 2nd. ed. Edito Cantor Verlag, Aulendorf, Germany.

Schlack, H., Bauer-Brandl, A., Schubert, R., Becker, D., 2001. Properties of Fujicalin, a new modified anhydrous dibasic calcium phosphate for direct compression. Drug Dev. Ind. Pharm. 27, 789–801.

The European Pharmacopoeia 4 (2002a). Pharmaceutical Technical Procedures, 2.9.16 Flowability, p. 208.

The European Pharmacopoeia 4 (2002b). Pharmaceutical Technical Procedures, 2.9.15 Apparent Volume, p. 207.

The European Pharmacopoeia 4 (2002c). Pharmaceutical Technical Procedures, 2.9.5 Uniformity of mass of single-dose preparations, p. 199.

US Pharmacopoeia XXIV (2000). In: Proceedings of the US Pharmacopoeial Convention, Rockville, MD, p. 1913.