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The bulk volume changes of powders by granulation and compression with respect to capsule filling

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Abstract

Experiments were performed to study the possibility of predicting the bulk volume changes of a powder bed due to granulation and/or low compression, to aid the development of powder filled hard gelatin capsules. Granulation techniques used were a high speed mixer/granulator and an oscillating granulator. For each of a series of typical filler powders and the granules produced from them, the tapped volume and the Kawakita constant *a* were determined on the basis of tap density volumetry. The Kawakita constant was also obtained from low compression experiments using a Höfliger and Karg powder plug simulator. Only the granules produced in the high speed mixer/granulator partly provided a reduced tap volume, whereas the processing by an oscillating granulator resulted generally in an increased tap volume. For the decrease in volume, a limiting value of the tap volume of the original powders of 1.4 cm^3/g appears to exist. Powders with a tap volume below this threshold cannot be densified by granulation, whereas the degree of possible volume reduction increases with an increase in tap volume above the limiting value. After application of a sufficient number of taps, Carr's compressibility index and the Kawakita constant *a* are similar in value. However, the Kawakita constant *a* is increased by on average 5% if determined using low compression. Thus, the application of the Kawakita equation has no advantage over the use of Carr's compressibility index as an indicator of possible volume reduction. Therefore, an estimate of the volume reduction due to low compression can be found by adding 5% to Carr's compressibility index. A combination of granulation and compression to further densify a powder failed in providing smaller plug volumes. Hence, if a reduction in capsule size is the only reason to use a densification method, low compression is preferable to granulation.

Keywords: Bulk volume; Capsule filling; Carr's compressibility index; Kawakita constant; Wet granulation

1. Introduction

Capsules are often regarded as intermittent formulation step in early clinical trials for tablet

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formulation (Iskandarani et al., 1993). However, the formulation of drugs into powder filled hard gelatin capsules as a dosage form of its own right is increasingly popular (Pfeifer, 1991). Often, capsules are filled with granules rather than with powder mixtures. In this respect, granulation can have several functions. Granules usually provide better flow properties than powders. Segregation of fine particles can be inhibited, and especially for low dose formulations the homogeneity of the powder mixtures can be improved. Of particular interest is also the enhancement of the permeability of the powder bed due to granulation, which provides an elegant tool to increase the drug release of hydrophobic drugs (Newton and Rowley, 1970). In the process of capsule formulation development, the problem of powder volume reduction with the aim to reduce the necessary capsule size can also occur, especially for drugs of higher dose. In this respect, the two main strategies applied are granulation and compression.

The calculation of the suitable capsule size, which will allow the incorporation of drug substance and the necessary qualities and quantities of excipient, for powder mixtures if filled at maximum bulk density is possible from the bulk densities of the single powder components (Newton and Bader, 1981). However, to date no reports exist about the prediction of the fill volume of granules. Furthermore, the volume reduction achievable by compression is usually assessed experimentally using the Höfliger and Karg powder plug simulator (Jones, 1988).

The aim of the present paper is to study the possibility of predicting the volume changes of a powder due to granulation and/or low compression to aid the development of powder filled hard gelatin capsules.

2. Materials and methods

The following powders have been used: microcrystalline cellulose (Avicel PH105®, FMC Corporation, Delaware, USA; Emcocel®, Edward Mendel, New York, USA), maize starch B.P. (Roquette freres, Lestrem, France), pregelatinized starch (Starch 1500®, Colorcon, Orpington, UK), mannitol (BDH, Poole, UK), lactose monohydrate B.P. (Lactochem, Saltney, UK). PVP (BDH, Poole, UK) and gelatin (BDH, Poole, UK) were used as binders.

Granules were prepared using a Collette high speed mixer/granulator (type GRAL 10, Antwerp, Belgium). Depending on the bulk volume of the powder, 500–1000 g powder were mixed with an appropriate amount of binder solution (2% PVP or 5% gelatin), until a homogeneous wet mass was produced. Thereafter, the chopper was switched on for 6 min. The granules were dried at room temperature, and large agglomerates were removed by sieving. A second set of granules was prepared using an oscillating granulator (Erweka AR 400, Heusenstamm, Germany) fitted with a 1 mm sieve. In this case, the wet mass was produced in a planetary mixer (Kenwood Chef KM 201, Havant, UK).

The bulk and tapped volume of the powders and granules was measured using a tap density volumeter (JTV 1, Copley, Nottingham, UK). After measuring the initial volume of an accurately weighed amount of powder or granule, the decrease in volume after a fixed number of taps was determined, initially in steps of ten taps until the change in volume was less than 2 cm^3. The number of taps per measurement was then successively increased to 20, 50, 100, 200 and 500. If the volume did not change during the application of 500 taps, the assessment of the dynamic change of the bulk volume due to tapping was terminated, but a further 5000 taps were applied before reading the tapped volume of the powder or granule. Subsequently, about 30 000 taps were applied to each powder or granule. The dynamic change of the bulk volume was quantified using the Kawakita equation in its version for tapping experiments (Lüdde and Kawakita, 1966; Yamashiro et al., 1983). Carr's compressibility index (Carr, 1965) was calculated from the initial and the tapped volume.

The change in powder or granule volume due to applied pressure was assessed using the Höfliger and Karg powder plug simulator (Bosch, Stuttgart, Germany). The plug length was measured after application of compaction pressures between 0.7 and 7.3 kPa. At least ten different pressures were used, and all experiments were replicated three times. The dynamic change of the

Table 1
Tapped volume V_t presented as specific volume per gram powder before and after granulation

Material	V_t (powder) (cm^3/g)	High-speed mixer/granulator		oscillating granulator	
		Change (%) (PVP)	Change (%) (gelatin)	Change (%) (PVP)	Change (%) (gelatin)
Avicel PH105	2.56	−53.8	−51.8	−13.5	+2.3
Emcocel	2.38	−52.8	−52.2	+4.8	+6.4
Mannitol	1.52	−10.0	−13.8	+30.5	+31.6
Lactose	1.47	−12.4	−8.0	+0.2	+6.8
Maize starch	1.39	+31.9	+37.6	+32.0	+27.6
Starch 1500	1.20	+20.1	+50.9	+86.0	+46.7

−, volume decreased; +, volume increased.

plug volume due to applied pressure was again estimated using the Kawakita equation in its version for compression (Kawakita and Lüdde, 1970/71).

The geometric mean particle size and geometric standard deviation (Martin et al., 1983) of the powders and granules was determined by sieve analysis (Endecotts, London, UK) using sieves in a size range between 36 μm and 4 mm. The amount of 100 g powder or granules was placed on the top sieve of the sieve set and subjected to vibration for 10 min. The cumulative percentage of powder/granule undersize was plotted as a linear function of sieve size on a probability scale, and the characteristic parameters (see above) were read.

3. Results and discussion

Particle size analysis was used to check the success of the granulation procedure in terms of particle agglomeration only. The increase in median particle size due to granulation with either method and binder was between six and ten times the particle size of the original powder. Granules produced by the oscillating granulator were found to be generally larger than those produced by the high speed mixer/granulator.

With respect to capsule filling, the important property of the powders and granules is the tapped volume, thus the maximum decrease in volume without application of compressive force. Table 1 summarises the changes in tapped volume achieved by granulation. The oscillating granulator produced granules, which are more bulky than the original powders. This implies, that this technique cannot be used, if granulation is undertaken to decrease the bulk volume with the aim to fit the formulation into a smaller capsule size than necessary for the ungranulated powder. Also, the increase in bulk volume due to oscillating granulation appears to be more pronounced for powders with a smaller tapped volume, i.e. the two properties are indirectly proportional. On the other hand, the high speed mixer/granulator in some cases produced granules providing a significant reduction in tapped volume of the original powder. A tapped volume of 1.4 cm^3/g appears to be a limiting value. Below this threshold, no volume reduction could be achieved. However, above this limiting value, the relative volume reduction achieved increased with the increase in tapped volume of the original powder. The choice of the binder apparently did not influence the level of volume reduction. The decrease in tapped volume of a powder due to granulation depends therefore mainly on the packing properties of the original powder. A prediction of the degree of volume changes appears impossible, because too many variables are involved in the granulation method, e.g. granulator type, granulation speed, target granule particle size, can be changed. Hence, granulation is not a safe method to be applied if the use of a smaller capsule size is the objective of granulation.

To investigate the predictability of the possible volume reduction induced by low compression, Kawakita's equation has been used. Theoretically, the Kawakita constant *a*, which quantifies the maximum possible volume reduction, e.g. due to tapping, vibration or applied load, should equal Carr's compressibility index (Lüdde and Kawakita, 1966). However, the Kawakita constant *a* was often found to be larger than Carr's compressibility index (Tan and Newton, 1990), and therefore the volume under low compression should be predictable from the Kawakita constant *a*. However, by using automatic tap density volumeters, the true tap volume cannot always be reached (Podczeck and Sharma, 1996). Thus, the deviations between *a* and Carr's compressibility index reported might be an artefact, because the Kawakita equation is a linear equation and hence should successfully achieve an extrapolation to the correct tapped volume of a powder. Fig. 1 shows *a* as a function of Carr's compressibility index, considering all values obtained from the original powders and granules produced. The slope of the function obtained is 1.0, and the straight line passes the origin. Hence, in this study the values of the Kawakita constant *a* and Carr's compressibility index were found to be similar, and therefore the use of *a* will not allow the prediction of the possible volume reduction by applying low compression during capsule filling.

Low compression during capsule filling was simulated using the Höfliger and Karg powder plug simulator. Again, the Kawakita constant *a*

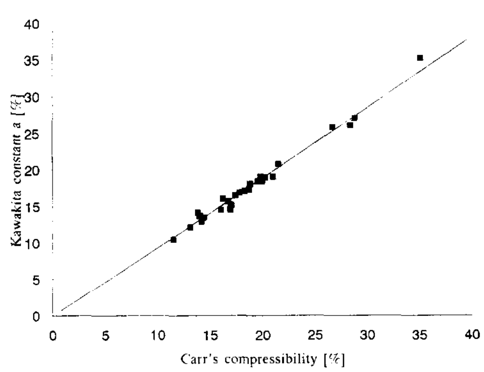

Fig. 1. Kawakita constant *a* as a function of Carr's compressibility index, determined on the basis of tap density volumetry.

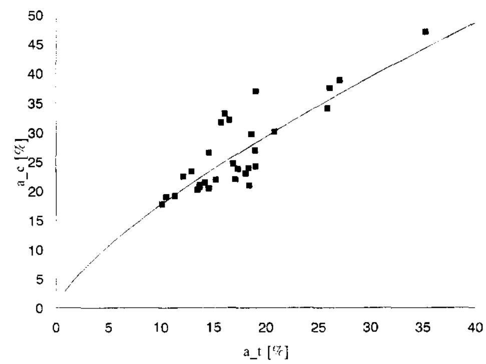

Fig. 2. Kawakita constant $\underline{a}$–$\underline{c}$ obtained from low compression experiments in the Höfliger and Karg powder plug simulator as a function of the Kawakita constant $\underline{a}$–$\underline{t}$ obtained on the basis of tap density volumetry.

was determined. Fig. 2 shows the relationship between the Kawakita constants obtained from tapping and compression experiments. On average, the Kawakita constant obtained by low compression was 5% higher than that obtained using tap density volumetry. Therefore, a prediction of the decrease in powder or granule volume due to low compression could be undertaken on the basis of the simpler Carr's compressibility index, adding 5%. However, this will only provide true estimates, if the measurements are performed so that the true tapped volume has been reached. In this study, about 30 000 taps were necessary to reach the final tapped volume of the powders and granules studied. However, often only 200–300 taps are used to determine the tap volume of a powder. An alternative way would be the assessment of Kawakita's constant *a* from the commonly used smaller number of taps. Under the assumption of linearity beyond the measuring range, *a* would be a true estimate of Carr's compressibility index, and thus by again adding 5% the possible volume reduction due to low compression could be estimated.

Finally, it could be assumed that the combination of granulation and compression should provide a further possible way to reduce the fill volume of capsules and thus offer the possibility of using a smaller capsule size. Table 2 compares the final powder and granule volume

Table 2
Final tapped volume V_t presented as specific volume per gram powder of powders and granules after low compression in a Höfliger and Karg powder plug simulator

Material	V_t (cm^3/g) (powder)	High-speed mixer/granulator		Oscillating granulator	
		V_t (cm^3/g) (PVP)	V_t (cm^3/g) (gelatin)	V_t (cm^3/g) (PVP)	V_t (cm^3/g) (gelatin)
Avicel PH105	2.23	1.11	1.18	2.10	2.40
Emcocel	2.05	1.00	1.01	2.22	2.22
Mannitol	1.19	1.25	1.04	1.63	1.75
Lactose	1.20	1.20	1.23	1.35	1.44
Maize starch	1.25	1.78	1.75	1.72	1.73
Starch 1500	1.15	1.41	1.71	2.13	1.62

achieved after low compression in the Höfliger and Karg powder plug simulator. With few exceptions, the final plug volume using granules is larger than that using the original powders. This is due to a steric hindrance of the larger, mostly irregular shaped granule particles. It can therefore be concluded, that the use of low compression during the filling of powders into hard gelatin capsules is more effective than a granulation procedure. If a reduction in capsule size is the only reason for the application of a densification procedure, compression should be used instead of granulation.

The experiments undertaken have shown, that granulation is able to change the bulk volume of a powder both by increasing or decreasing its original volume. The choice of the granulation method appears to be the key factor in this respect, but the bulk properties of the original powder are also important. The type of granulation liquid does not appear to be of importance. If granulation has been thought to improve, e.g. flow or mixing homogeneity, the changes might be of less interest, as long as the formulator is aware of the fact that a change in required capsule size either to a larger or to a smaller number could occur. If granulation is applied to enhance powder bed permeability, only methods that increase the bulk volume are appropriate, and from this study it follows that a high speed mixer/granulator should not be used. However, if granulation has been chosen as a densification procedure, the technique must be able to reduce the bulk volume by application of a force during mixing and/or granulation. The high speed mixer/granulator was found to provide such facilities. However, the amount of volume reduction in such a system depends on the original powder bulk volume. The lower this value is, the less successful is the granulation process.

References

Carr, R.L., Evaluating flow properties of solids. *Chem. Eng.*, 18 (1965) 163–168.

Iskandarani, B., Clair, J.H., Patel, P., Shiromani, P.K. and Dempski, R.E., Simultaneous optimization of capsule and tablet formulation using response surface methodology. *Drug Dev. Ind. Pharm.*, 19 (1993) 2089–2101.

Jones, B., Powder formulations for capsule filling. *Manuf. Chem.*, 2(7) (1988) 28–33.

Kawakita, K. and Lüdde, K.-H., Some considerations on powder compression equations. *Powder Technol.*, 4 (1970/71) 61–68.

Lüdde, K.-H. and K. Kawakita, Die Pulverkompression. *Pharmazie*, 21 (1966) 393–403.

Martin, A., Swarbrick, J. and Cammarata, A. (eds.), *Physical Pharmacy*. Lea and Febiger, Philadelphia, 1983, pp. 495–503.

Newton, J.M. and Bader, F., The prediction of the bulk densities of powder mixtures, and its relationship to the filling of hard gelatin capsules. *J. Pharm. Pharmacol.*, 33 (1981) 621–626.

Newton, J.M. and Rowley, G., On the release of drug from hard gelatin capsules. *J. Pharm. Pharmacol.*, 22 (Suppl.) (1970) 163S–168S.

Pfeifer, W., Entwicklung von Hartgelatinekapseln. in Sucker, H., Fuchs, P. and Speiser, P., *Pharmazeutische*

Technologie. Georg Thieme, Stuttgart, 1991, pp. 320-324.

Podczeck, F. and M. Sharma, The influence of particle size and shape of components of binary powder mixtures on the maximum volume reduction due to tapping. *Int. J. Pharm.*, 137 (1996) 41-47.

Tan, S.B. and Newton, J.M., Powder flowability as an indication of capsule filling performance. *Int. J. Pharm.*, 61 (1990) 145-155.

Yamashiro, M., Yuasa, Y. and K. Kawakita, An experimental study on the relationships between compressibility, fluidity and cohesion of powder solids at small tapping numbers. *Powder Technol.*, 34 (1983) 225-231.