ELSEVIER

International Journal of Pharmaceutics 188 (1999) 59–69

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

The filling of granules into hard gelatine capsules

Fridrun Podczeck *, Simon Blackwell, Matthew Gold, J. Michael Newton

Department of Pharmaceutics, The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, UK

Received 8 December 1998; accepted 9 June 1999

Abstract

Four different granule size fractions of Sorbitol instant® were filled into hard gelatine capsules on a tamp filling (Bosch) and a dosator nozzle machine (Zanasi) to allow comparison of the filling principles. An acceptable filling performance was always achieved and was independent of the machine type employed. Tamp filling was found to be slightly better for the coarser granule size fractions, because it does not seem to rely on a firm plug formation. A direct relationship between the angle of internal flow (Varthalis and Pilpel, 1976) and the coefficient of fill weight variation was found for both systems. Using the dosator nozzle machine, the plug formed was always denser than the maximum bulk density, whereas on the tamp filling machine for smallest granule size the maximum plug density could not be achieved with the settings employed. The results suggest that in situations where a low plug density is an essential prerequisite for drug dissolution and bioavailability the tamp filling machine appears the more suitable filling principle. However, if a greater extent of compression is required in order to fill large dose drugs or to use a smaller capsule size, the dosator nozzle principle might work more successfully for granules. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Angle of internal flow; Capsule filling; Compaction constant; Dosator nozzle machine; Granulation; Tamp filling machine

---

1. Introduction

The use of powder filled hard gelatine capsules as solid oral dosage form has become increasingly popular (Pfeifer, 1991). However, high speed capsule filling machines put a high standard of powder flow and packing properties onto the powder bulk (Jones, 1988; van Ooteghem et al., 1988). To avoid large variations in fill weight due to impaired powder flow or stickiness, capsules are often filled with granules rather than with powders (Lai et al., 1996). Granules are also known to prevent fine powder segregation, which is especially important if the particle size of the drug cannot be matched to any compatible and suitable excipient. Furthermore, granulation can enhance the homogeneity of the powder mixtures, which is important for low dose drugs. Finally, hydrophobic drugs show enhanced drug release from granule filled hard gelatine capsules due to an increased permeability of the powder plug (Newton and Rowley, 1981).

---

* Corresponding author.

E-mail address: podczeck@cua.ulsop.ac.uk (F. Podczeck)

PII: S0378-5173(99)00208-2

Only a few direct comparisons of the filling of powders/granules on different machine types have been performed. Pfeifer and Marquardt (1984) compared the filling of a powder mixture and granulation on a tamp filling and a dosator nozzle machine of unidentified origins. They found that filling was overall better (i.e. no over- or underfilling) on the tamp filling machine than on the dosator nozzle machine. Also, granules filled better than powders. However, their experiments lacked a description of the granule properties such as granule size, flow and packing properties. Also, there is no indication as to the critical granule size to be identified.

The aim of this work was to compare different size fractions of a granulation in terms of granule bulk properties and their relation to capsule filling on a tamp filling and a dosator nozzle machine.

2. Materials and methods

Sorbitol instant® (Merck, Darmstadt, Germany; batch M768140) was used as commercially available model granulation.

The granulation was size classified using a vibration sieve shaker (Endecotts, London, UK). From an initial determination of the granule size distribution, it appeared reasonable to split the granulation into the following four sieve size fractions: +710–1400 μm (fraction 1), +500–710 μm (fraction 2), +355–500 μm (fraction 3) and +150–355 μm (fraction 4). In this way, material loss could be minimised.

The flow and packing properties of the granule size fractions were determined using an automatic tap volumeter (Jencons Scientific Equipment, Radon Ind. Electronics, Worthing, UK) with a lift height of 30 mm and a tapping frequency of 30 taps/min. About 200 ml granulation were carefully filled into the tared, mounted measuring cylinder, and the maximum granule volume (i.e. minimum bulk density) was read. A single tap was employed, and the volume was read again. This procedure was repeated, whereby gradually increasing the number of taps between individual readings, until three consecutive replicates of 100 taps did not reduce the granule volume further. Hence, the minimum granule volume (i.e. maximum bulk density) had been reached. The measuring cylinder was then weighed to determine the granule weight. The granule density was evaluated as a function of the number of taps using the model described by Mohammadi and Harnby (1997). The dynamic packing profile was also used to derive the angle of internal flow (Varthalis and Pilpel, 1976). Carr's compressibility index (Carr, 1965) was calculated from the minimum and maximum bulk densities for each granule size fraction.

The granules were filled into hard gelatine capsules size 1 (Capsugel, Colmare, France) on a Bosch GKF–400S tamp filling machine (Robert Bosch GmbH, Waiblingen, Germany) with a 19.6-mm dosing disk. Filling into size 0 capsules was undertaken using a Zanasi AZ 5 dosator nozzle machine (Industria Macchine Automatiche, Bologna, Italy).

Sorbitol instant is a fairly sticky material. Hence, magnesium stearate was added as a lubricant. Preliminary tests were performed on unsieved material to identify the suitable lubricant concentration. The stickiness was judged by visual inspection of the pins of the tamp filling machine after 5 min of filling at moderate tamping pressure. A lubricant amount of 1% was found to be a suitable concentration. Below that concentration the granule mass stuck more and more firmly to the tamping fingers. For comparison, the same magnesium stearate concentration was used for filling on the dosator nozzle machine. The lubricant and granule fractions were mixed in portions of 500 g in a Turbula mixer (type Schatz T2C, Willy A. Bachofen, Basle, Switzerland). Four portions were mixed for each granule fraction to give a total of 2 kg. The portions were merged in a large plastic bag prior to use.

To determine the capsule fill weight and the coefficient of fill weight variation, 50 capsules were weighed on an analytical balance to ±0.1 mg (Sartorius, Göttingen, Germany). The average weight and variance of weight were corrected for the influence of the weight and variation in weight of the empty capsule shells exploiting the additivity of these parameters (Snedecor and Cochran, 1980).

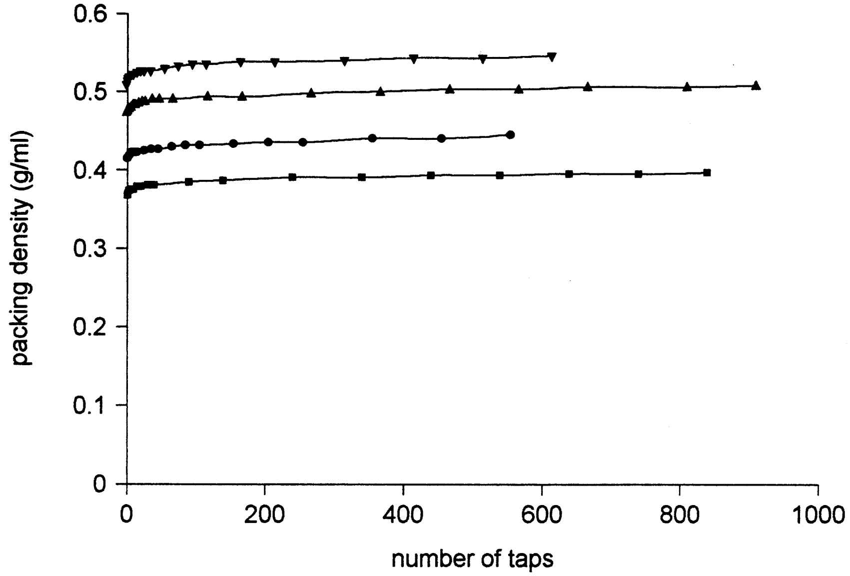

Fig. 1. Change in packing density as a function of the number of taps applied. ■, granule size fraction 1; ●, granule size fraction 2; ▲, granule size fraction 3; ▼, granule size fraction 4.

All mathematical and statistical analyses were undertaken using SPSS 8.0 (SPSS, Woking, UK).

3. Results and discussion

3.1. Granule bulk properties

The main difference in the granulation bulk properties of the four size fractions lies in their bulk densities. Fig. 1 compares the change in bulk density with the number of taps applied. The smaller the particle size, the denser the granules are packed. The complete packing profiles presented in Fig. 1 do not imply gross differences in powder flow, because the slopes of the packing functions above about 200 taps appear similar. This is confirmed by comparatively similar Carr's compressibility indices (Table 1). The small differences observed are statistically not significant at $P = 0.05$ (Analysis of Variance). The magnitude of the values of Carr's compressibility index is indicative of very good flow properties (Carr, 1965) for all four granule size fractions.

When analysing the complete dynamic packing profiles by deriving the angle of internal flow (Table 1), major differences between the four granule size fractions are found. These represent statistically significant differences (Analysis of Variance, $P < 0.001$). The angle of internal flow is related to interparticulate friction in a powder/granule bulk during flow. Larger values imply the

Table 1
Bulk properties of the four granule size fractions[a]

Fraction (μm)	Granule size	Θ (°)	T	Carr's index (%)
1	+710–1400	64.0 ± 0.5	83.8	5.3 ± 0.4
2	+500–710	58.0 ± 1.0	101.9	5.6 ± 0.6
3	+355–500	51.8 ± 0.3	136.7	4.8 ± 0.1
4	+150–355	47.4 ± 0.7	75.7	5.3 ± 0.5

[a] Θ, angle of internal flow (arithmetic mean and standard deviation of three replicates); T, compaction constant.

presence of increased interparticulate forces (Varthalis and Pilpel, 1976). Here, this suggests that during capsule filling firmer plugs could be formed from granule size fraction 1, and the ability of plug formation would decrease with smaller granule size. However, all four granule size fractions have very good flow properties. This could result in overall poor densification and larger variation in fill weight (Hauer et al., 1993), regardless of the ability to form firm plugs. To investigate this apparent discrepancy between the angle of internal flow and Carr's compressibility index, the compaction constant (Mohammadi and Harnby, 1997) was determined (Table 1), which should provide further information. Values larger than 35 are related to a rapid densification due to the initial presence of large primary or aggregated particles. Rapid densification of the filling material is favourable in capsule filling, because it guarantees a quick settlement of the bed structure into an equilibrium state. Hence, the large values of the compaction constant found here imply that capsule filling should be possible without major filling problems, and that the coefficient of fill weight variation will be very small in most cases.

3.2. Capsule filling

3.2.1. General considerations

Capsule filling was undertaken on a tamp filling system into capsules size 1, and on a dosator nozzle system into capsules size 0. The discrepancy in capsule size by 1 unit could not be avoided due to the high costs of a purchase of either size 1 dosators or a size 0 dosing disc and the necessary opening and closing segments for either machine. The difference in the inner capsule body diameter between size 0 and size 1 capsules is about 700 μm. Hence, plug retention in the dosator nozzles or flowability of the granules into the bores of the dosing disc could be at a disadvantage comparing the experiments.

Flemming and Mielck (1995) found that powders with a Carr's compressibility index of less than 25% flow through any orifice ≥ 2 mm. This implies that filling of the four granule size fractions, which have a Carr's compressibility index below 10% (Table 1) will not be impaired by the dosing bore diameter down to capsule size 5. Filling problems, if any, should be contributed to 'flooding' or weak plugs only. Plug retention, on the other hand, depends on the radius of the dosator nozzle or dosing bore (Jolliffe et al., 1980). The minimum stress to be applied to a powder bed to form a stable arch, i.e. to retain the powder in a dosator nozzle can be calculated from Jolliffe et al. (1980):

$$\sigma_{\mathrm{ret}} = \frac{FF \cdot r \cdot \rho_{\min} \cdot g}{\sin 2\phi} \quad (1)$$

where FF is the flow factor (Jenike, 1961), r is the powder bed radius [m], $\rho_{\min}$ is the minimum bulk density (kg/m^3), ϕ is the angle of wall friction (Jolliffe and Newton, 1982), and g is the gravity constant (9.81 m/s^2). For a given powder and dosator nozzle material, Eq. (1) reduces to:

$$\sigma_{\mathrm{ret}} = c \cdot r \quad (2)$$

where c is a constant. The ratio of the powder bed radii for capsule sizes 0 and 1 is 1.11. Hence, a slightly higher consolidation pressure is required when filling into capsules of size 0. To remove the disadvantage thus presented for the filling on the dosator nozzle machine, only machine settings, which produced a stable arch at the nozzle orifice were used (see Section 3.2.3). This guarantees transfer of the powder plug, thus removing any disadvantage for the dosator nozzle principle produced by the slightly larger capsule size. However, it does not alter plug formation and plug strength properties as such, which become obvious during plug ejection, either from a dosator nozzle or from a dosing bore of the tamping ring.

After consideration of the above points, the experiments carried out therefore allow comparison of the two machines to be made.

3.2.2. Tamp filling

On the tamp filling machine, three different bed heights were used when possible, and six different tamping pin settings were tested for each bed height. The pin settings ranged from no compression to firm compression. This is illustrated in Fig. 2. The cumulative tamping distance is here

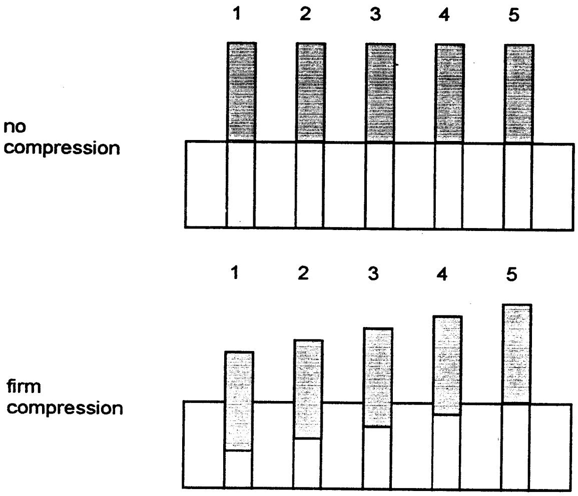

Fig. 2. Schematic diagram of the pin setting in the tamp filling machine. Top: no compression, i.e. no tamping pin penetrates the dosing disk at its lowest position during tamping, but all pins are at dosing disk level. Bottom: firm compression, i.e. tamping pins 1–4 penetrate the dosing disk during tamping.

defined as the sum of the depths (mm), which the tamping pins penetrate into the dosing disk at their lowest position during tamping. The filling results are summarised in Table 2.

A disadvantage of a small-scale machine such as the GKF-400S is that the hopper design used is similar in size to the production scale machines of this type. During operation, materials with very good flow properties can run through the feeding mechanism comparatively unhindered due to machine vibration. On a production scale machine this effect remains unnoticed because of the large volume of the powder bowl. However, on the small-scale machine this causes the powder/granulation to overflow the bowl. Special hopper accessories can be purchased in such a situation, which avoid these problems, but for this work they were not available. Hence, for granule size fraction 1 only two bed heights, and for granule size fraction 4 only one bed height could be used without the bowl overflowing. Thus the flow properties are best for granule fractions 4 and 1, although not reflected in Carr's compressibility index. For granule size fractions 2 and 3, the three bed settings used refer to a bed height at tamping station 5 of 5 cm ('20'), 5.5 cm ('25') and 6 cm ('30'). For granule size fractions 4 and 1, the bed height was always 1 (fraction 4) or 0.5 cm (fraction 1) higher. In all cases the granule size fractions provided a smooth bed structure inside the powder bowl, which was only slightly tilted.

Different regulations exist in the various Pharmacopoeias for an upper limit of the coefficient of fill weight, depending, for example, on capsule weight and drug content. For low dose drugs, the test of content uniformity of fill weight is usually replaced by a test of content uniformity of dose. However, industrial standards always apply a determination of the coefficient of fill weight variation, and usually a value of 3% is accepted as the upper limiting value (Newton et al., 1998). Employing this limit, the filling performance of the granule size fractions improves with a decrease in granule size, and at larger cumulative tamping distances. However, for any granule size fraction, a coefficient of fill weight variation below even 2% could be achieved for some bed height/tamping pin setting combinations (Table 2). Hence, it appears that granulation would be a safe means of guaranteeing adequate capsule filling.

To study the influence of all significant powder properties (angle of internal flow, compaction constant, see Table 1) and the machine settings (bed height, cumulative tamping distance) on the coefficient of fill weight variation more systematically, multiple regression analysis was performed. Only significant factors (Analysis of Variance, $P < 0.05$) were used in the final model. The relationship that was found is plotted in Fig. 3 ($R^2 = 0.835$, root mean square deviation 18.2%, $F = 134.79$, $P < 0.001$). The relative importance of the two remaining factors is similar (angle of internal flow: $\beta = 0.614$, cumulative tamping distance: $\beta = -0.681$). The filling performance of granulations of similar type will, presumably, be improved by increasing the cumulative tamping distance and/or reducing the angle of internal flow via an adjustment of the granule size to smaller values.

Capsule filling does not only rely, however, on an accurate filling process reflected in a low coefficient of fill weight variation, but also on the ability to reduce the powder/granule volume to achieve an appropriate capsule size. Granulation

Table 2
Filling results obtained on the tamp filling machine[a]

F	B	Setting	CTD (mm)	Weight (mg)	CV (%)
1	20	0–0–0–0–0	0	231.1 ± 7.8	3.38
		1–0–0–0–0	1	232.6 ± 8.2	3.54
		2–1–0–0–0	3	253.2 ± 10.3	4.06
		3–2–1–0–0	6	285.8 ± 9.5	3.34
		4–3–2–1–0	10	304.0 ± 7.2	2.38
		5–4–3–2–0	14	313.7 ± 4.7	1.54
	25	0–0–0–0–0	0	251.8 ± 8.1	3.23
		1–0–0–0–0	1	263.8 ± 9.8	3.72
		2–1–0–0–0	3	279.7 ± 9.2	3.30
		3–2–1–0–0	6	282.2 ± 7.6	2.70
		4–3–2–1–0	10	308.7 ± 4.3	1.39
		5–4–3–2–0	14	320.3 ± 3.4	1.06
2	20	0–0–0–0–0	0	251.5 ± 7.8	3.11
		1–0–0–0–0	1	271.8 ± 8.4	3.10
		2–1–0–0–0	3	295.7 ± 7.0	2.36
		3–2–1–0–0	6	290.7 ± 5.6	1.91
		4–3–2–1–0	10	307.2 ± 4.1	1.34
		5–4–3–2–0	14	320.3 ± 3.2	1.01
	25	0–0–0–0–0	0	265.5 ± 7.8	2.92
		1–0–0–0–0	1	266.2 ± 6.8	2.56
		2–1–0–0–0	3	270.3 ± 7.3	2.71
		3–2–1–0–0	6	279.4 ± 5.3	1.88
		4–3–2–1–0	10	307.0 ± 6.3	2.06
		5–4–3–2–0	14	319.8 ± 2.8	0.88
	30	0–0–0–0–0	0	266.4 ± 6.8	2.54
		1–0–0–0–0	1	266.9 ± 7.6	2.85
		2–1–0–0–0	3	271.2 ± 6.3	2.32
		3–2–1–0–0	6	281.9 ± 5.6	1.98
		4–3–2–1–0	10	307.6 ± 4.9	1.60
		5–4–3–2–0	14	320.8 ± 3.1	0.96
3	20	0–0–0–0–0	0	268.6 ± 6.0	2.22
		1–0–0–0–0	1	264.7 ± 6.7	2.54
		2–1–0–0–0	3	279.2 ± 4.4	1.59
		3–2–1–0–0	6	299.1 ± 3.1	1.02
		4–3–2–1–0	10	314.5 ± 2.8	0.91
		5–4–3–2–0	14	326.5 ± 2.9	0.88
	25	0–0–0–0–0	0	268.7 ± 5.7	2.14
		1–0–0–0–0	1	266.4 ± 5.7	2.14
		2–1–0–0–0	3	282.0 ± 5.0	1.76
		3–2–1–0–0	6	302.7 ± 4.1	1.34
		4–3–2–1–0	10	316.7 ± 3.1	0.98
		5–4–3–2–0	14	328.5 ± 3.0	0.91
	30	0–0–0–0–0	0	271.8 ± 5.7	2.09
		1–0–0–0–0	1	268.6 ± 7.0	2.60
		2–1–0–0–0	3	280.0 ± 5.7	2.04
		3–2–1–0–0	6	306.2 ± 3.0	0.97
		4–3–2–1–0	10	318.1 ± 3.3	1.05
		5–4–3–2–0	14	329.1 ± 3.1	0.93
4	20	0–0–0–0–0	0	285.6 ± 3.7	1.31
		1–0–0–0–0	1	292.2 ± 3.6	1.24
		2–1–0–0–0	3	302.7 ± 3.0	1.00
		3–2–1–0–0	6	306.1 ± 3.6	1.17
		4–3–2–1–0	10	308.8 ± 2.9	0.93
		5–4–3–2–0	14	314.2 ± 2.9	0.93

[a] Results are the mean and standard deviation of 50 capsules, size 1; F, granule size fraction; B, bed height (arbitrary machine unit); Setting, penetration depths of the tamping fingers (mm) in the order 1 to 5; CTD, cumulative tamping distance; CV, coefficient of fill weight variation.

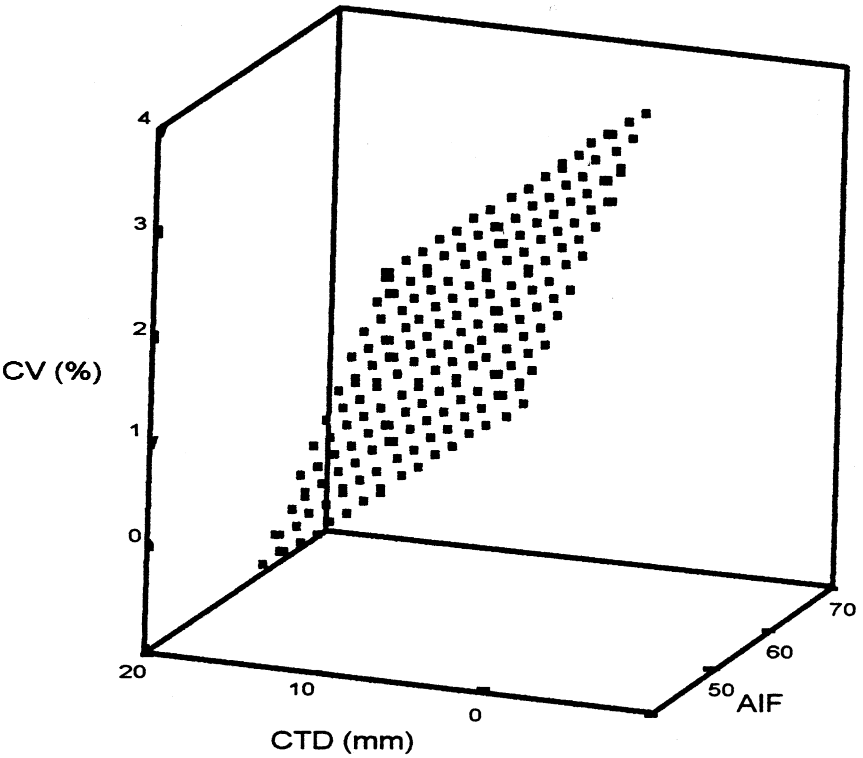

Fig. 3. Relationship between coefficient of fill weight variation (CV), cumulative tamping distance (CTD) and angle of internal flow (AIF), based on tamp filling results.

is often sought to reduce the powder volume even further in order to be able to fill larger doses or to use smaller capsule sizes. It has been shown previously, that the method of granulation is a main influence factor in this respect (Podczeck and Lee-Amies, 1996). However, there should be a balance between densification and plug porosity achieved, otherwise, problems with drug dissolution and bioavailability might arise. Hence, Newton (1987) advised that capsules should not be filled beyond the level of the maximum bulk density of the powder or granulation. In Fig. 4, the plug densities achieved during tamp filling are compared. For granule fractions 1–3 at least some of the machine settings produced plugs, which are densified above the maximum bulk density. Using granule fraction 4, however, the maximum bulk density cannot be fully achieved under the set filling conditions. The ability to reach the maximum bulk density as the plug density is directly related to the angle of internal flow. The lower the value for the angle of internal flow, the less dense the plugs become. This indicates the involvement of adhesion forces dominating over the friction between the particles during densification. Also, smaller agglomerates resist the pressure of the tamping pins more strongly. Presumably, less fragmentation will occur and consequently the plug formation is less firm. The less dense plug structure is, however, not reflected in a larger coefficient of fill weight variation. It should be pointed out that all capsules were overfilled intentionally (plug length 19.6 mm compared with the length of the capsule body of 16.6 mm) to highlight filling problems due to weak plugs. Thus, the tamp filling process is less vulnerable to poor plug formation properties.

3.2.3. Dosator nozzle filling

Filling with the dosator nozzle machine employed three different bed heights. Three compression settings of the plunger were always chosen so that a plug was formed in all cases. For all granule size fractions it was found that a compression setting above 1.8 (arbitrary machine unit) did not form firm plugs. This suggests that all settings that could be used involved a pre-compression of the granules before the plunger was depressed. For the lowest bed height (30 mm), compression settings below 1.6 caused machine overload. With increasing bed height it was not even possible to use a compression setting of 1.6, and hence the compression setting had to be adjusted. The possible range of settings was reduced to 1.65–1.8 and 1.7–1.8 for bed heights of 35 and 40 mm, respectively. The filling results are summarised in Table 3.

The coefficients of fill weight variation were highest for granule size fraction 1 and decreased with the decrease in granule size, i.e. were on average smallest for the granule size fractions 3 and 4. A less firm plug formation using the large granule size fraction (fraction 1) is certainly the main reason for this behaviour. The break-up of only a few agglomerates from the plug edges during plug ejection has a bigger influence on the final plug weight, if the agglomerates are larger in size, which can be assumed for the larger granule size fractions.

Statistical analysis indicated that the compression setting and the angle of internal flow are the only important variables to consider here with respect to the coefficient of fill weight variation. The angle of internal flow is about twice as important as the compression setting for this filling property ($\beta = 0.325$ and 0.614 for compression setting and angle of internal flow, respectively). In contrast to the tamp filling results, here the coefficient of fill weight variation increases with increasing value for the angle of internal flow. Hence, a formulation that fills well on a tamp filling machine

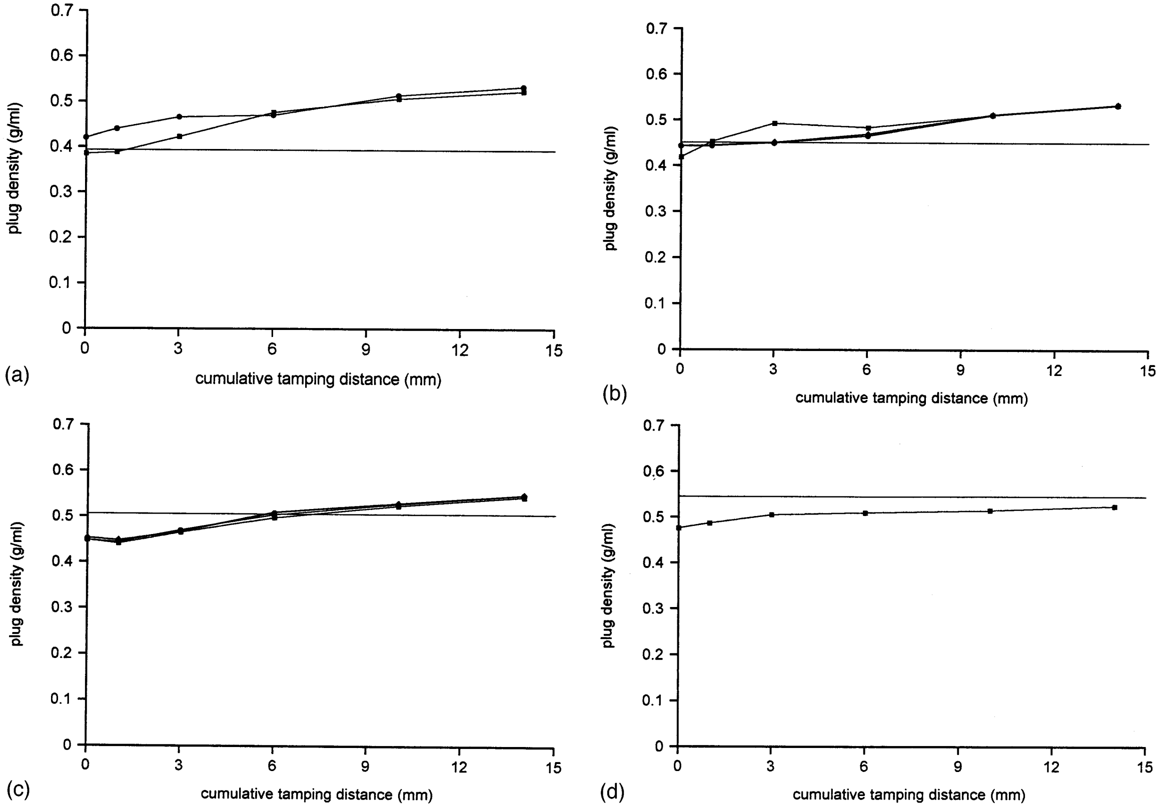

Fig. 4. Plug density as a function of the cumulative tamping distance; (a) granule size fraction 1; (b) granule size fraction 2; (c) granule size fraction 3; (d) granule size fraction 4; ■, low powder bed; ●, medium powder bed; ◆, high powder bed.

Table 3
Filling results obtained on the dosator nozzle machine[a]

F	B (mm)	CS	Weight (mg)	CV (%)
1	30	1.8	362.1 ± 11.6	3.20
		1.7	363.8 ± 6.4	1.75
		1.6	351.4 ± 5.7	1.63
	35	1.8	366.5 ± 25.1	6.85
		1.7	398.4 ± 8.5	2.14
		1.65	383.0 ± 6.2	1.61
	40	1.8	389.2 ± 11.4	2.93
		1.75	404.4 ± 6.9	1.70
		1.7	399.8 ± 7.0	1.74
2	30	1.8	342.8 ± 4.3	1.25
		1.7	340.9 ± 3.1	0.92
		1.6	339.0 ± 3.5	1.04
	35	1.8	360.1 ± 4.6	1.28
		1.7	361.5 ± 4.9	1.37
		1.65	362.2 ± 3.9	1.09
	40	1.8	386.0 ± 7.5	1.95
		1.75	393.9 ± 6.6	1.68
		1.7	394.7 ± 10.4	2.64
3	30	1.8	369.5 ± 2.6	0.71
		1.7	373.8 ± 1.9	0.50
		1.6	371.5 ± 1.1	0.30
	35	1.8	376.0 ± 4.6	1.23
		1.7	378.8 ± 3.4	0.90
		1.65	379.7 ± 3.0	0.78
	40	1.8	390.0 ± 5.6	1.44
		1.75	398.0 ± 3.4	0.84
		1.7	400.6 ± 3.8	0.95
4	30	1.8	422.1 ± 4.6	1.10
		1.7	411.0 ± 4.6	0.97
		1.6	405.2 ± 2.6	0.64
	35	1.8	409.5 ± 3.7	0.90
		1.7	413.9 ± 3.6	0.86
		1.65	415.2 ± 2.9	0.70
	40	1.8	429.7 ± 4.3	1.00
		1.75	432.2 ± 2.8	0.65
		1.7	433.9 ± 1.8	0.41

[a] Results are the mean and standard deviation of 50 capsules, size 0. F, granule size fraction; B, bed height; CS, compression setting (arbitrary machine units); CV, coefficient of fill weight variation.

might not fill on a dosator nozzle machine and vice versa. The relationship consisted, however, of a larger variability reflected in a large value of root mean square in the residual analysis (57.4%). Hence no graphical presentation was attempted.

If the smallest coefficients of fill weight variation achieved for a defined bed height are compared to those achieved on the tamp filling machine (Table 4), it appears that the tamp filling process fills larger granule sizes better than the dosator nozzle principle, whereas for smaller granule sizes the dosator nozzle filling is slightly advantageous. However, in practical terms, both machine types provided filling results far better than sought as limiting (coefficient of fill weight variation below 3%). However, the results confirm that the dosator nozzle principle relies on a firm plug formation in order to achieve appropriate filling results, whereas the tamp filling principle is less influenced by this feature. It can be assumed, therefore, that the applicability of the tamp filling principle covers a wider range of materials.

A comparison of the plug densities achieved using the dosator nozzle machine is presented in Fig. 5. In the possible range of machine settings, all plugs had a greater density than the maximum bulk density of the granule size fractions. The trend that the plug density in relation to the maximum bulk density decreases with decreasing granule size, as was obtained for the tamp filling process, is also visible. The plug density being always greater than the maximum bulk density of the granule size fractions implies that filling of formulations with expected low bioavailability has to be carefully reconsidered when using the dosator nozzle principle. To overcome the influence of the higher plug density on the disintegration and

Table 4
Comparison of the smallest coefficients of fill weight variation (%) for a given bed height obtained on the tamp filling or dosator nozzle machine

Fraction	Bed height	Tamp filling	Dosator nozzle
1	Low	1.54	1.63
	Medium	1.06	1.61
	High	–	1.70
2	Low	1.01	0.92
	Medium	0.88	1.09
	High	0.96	1.68
3	Low	0.88	0.30
	Medium	0.91	0.78
	High	0.93	0.84
4	Low	0.93	0.64
	Medium	–	0.70
	High	–	0.41

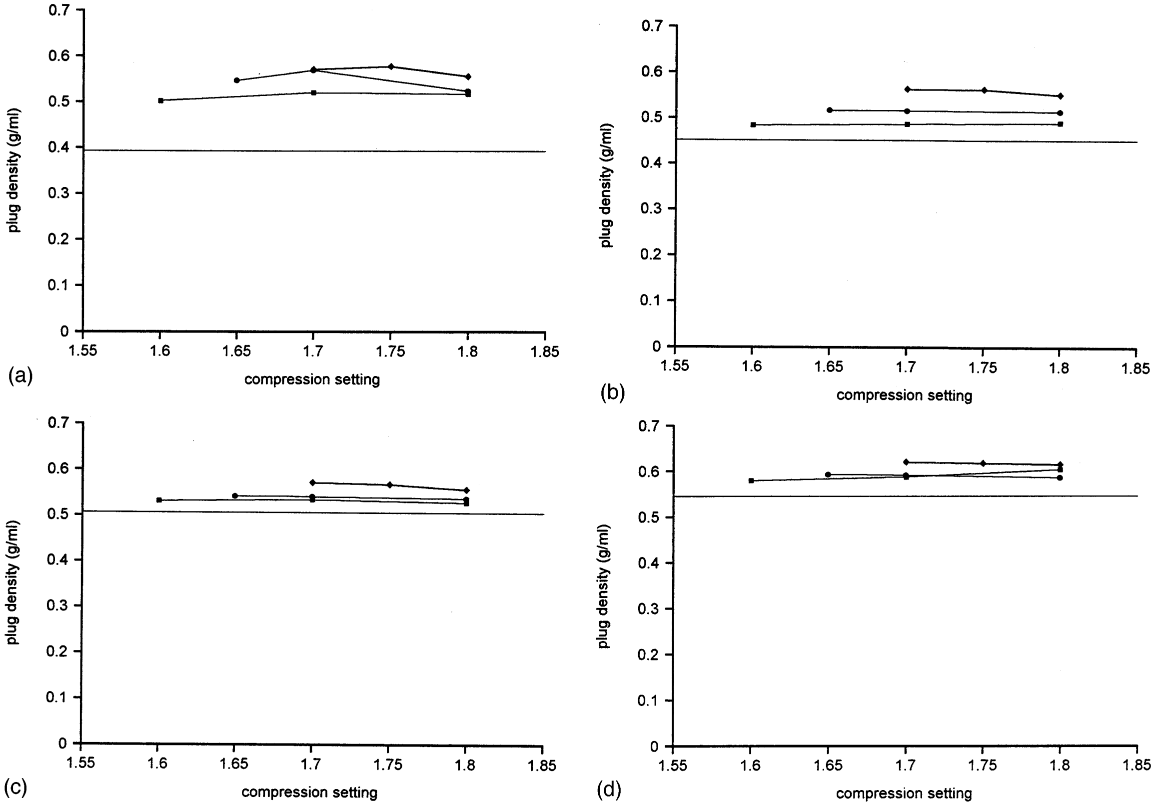

Fig. 5. Plug density as a function of the compression setting; (a) granule size fraction 1; (b) granule size fraction 2; (c) granule size fraction 3; (d) granule size fraction 4; ■, low powder bed; ●, medium powder bed; ◆, high powder bed.

drug dissolution process, highly effective disintegrants might be required. The lower plug densities, which can be produced on a tamp filling machine, appear advantageous in this respect. On the other hand, the maximum fill weight that can be achieved is larger on the dosator nozzle machine, which is advantageous for filling of high dose drugs such as antibiotics or non-steroidal anti-inflammatory drugs.

4. Conclusions

When filling a granulated powder formulation into hard gelatine capsules, an acceptable filling performance can always be achieved and is independent of the type of machine used. However, tamp filling is slightly better for coarser granules, and in particular, when no solid plug can be formed. The formation of the plug appears to be closely related to the magnitude of interparticulate forces in the bulk. Here a direct relationship between the angle of internal flow and the coefficient of fill weight variation was found. Using the dosator nozzle filling machine, the plug formed is always denser than the maximum bulk density of the granulation, whereas on the tamp filling machine for smaller granule sizes the maximum bulk density apparently cannot be reached easily. Thus, in those situations where a low plug density is essential, for example, for low bioavailability drugs, the tamp filling machine appears favourable. However, if a greater extent of compression is required, for example, for high dose drugs, the dosator nozzle principle can be employed more successfully.

Acknowledgements

F. Podczeck was supported financially by the Deutsche Forschungsgemeinschaft via a Heisenberg fellowship. The GKF–400S tamp filling machine was provided by Robert Bosch GmbH. The hard gelatine capsules were a gift from Capsugel.

References

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

Flemming, J., Mielck, J.B., 1995. Requirements for the production of microtablets: Suitability of direct-compression excipients estimated from powder characteristics and flow rates. Drug Dev. Ind. Pharm. 21, 2239–2251.

Hauer, B., Remmele, T., Züger, O., Sucker, H., 1993. Gezieltes Entwickeln und Optimieren von Kapselformulierungen mit einer instrumentierten Dosierröhrchen–Kapselabfüllmaschine. 1. Mitt.: Instrumentierung und Einfluß der Füllgut–und Maschinenparameter. Pharm. Ind. 55, 509–515.

Jenike, A.W., 1961. Gravity flow of bulk solids. Utah Eng. Exp. Stu. Bull. 108, 1–294.

Jolliffe, I.G., Newton, J.M., 1982. Practical implications of theoretical consideration of capsule filling by the dosator nozzle system. J. Pharm. Pharmacol. 34, 293–298.

Jolliffe, I.G., Newton, J.M., Walters, J.K., 1980. Theoretical considerations of the filling of pharmaceutical hard gelatine capsules. Powder Technol. 27, 189–195.

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

Lai, S., Podczeck, F., Newton, J.M., Daumesnil, R., 1996. An Expert System to aid the development of capsule formulations. Pharm. Technol. Eur. 8 (9), 60–68.

Mohammadi, M.S., Harnby, N., 1997. Bulk density modelling as a means of typifying the microstructure and flow characteristics of cohesive powders. Powder Technol. 92, 1–8.

Newton, J.M., 1987. Drug release from capsules. In: Ridgway, K. (Ed.), Hard Capsules. Development and Technology. The Pharmaceutical Press, London, pp. 195–204.

Newton, J.M., Rowley, G., 1981. On the release of drug from hard gelatin capsules. J. Pharm. Pharmacol. 33, 621–626.

Newton, J.M., Podczeck, F., Lai, S., Daumesnil, R., 1998. The design of an expert system to aid the development of capsule formulations (in Japanese). In: Hashida, M. (Ed.), Formulation Design of Oral Dosage Forms. Yakugyo Jiho, Tokyo, pp. 236–244.

Pfeifer, W., 1991. Entwicklung von Hartgelatinekapseln. In: Sucker, H., Fuchs, P., Speiser, P. (Eds.), Pharmazeutische Technologie. Thieme, Stuttgart, pp. 320–324.

Pfeifer, W., Marquardt, G., 1984. Untersuchungen zur Häufigkeit und Ursachen von Fehldosierungen bei der Abfüllung von Hartgelatinekapseln. 1. Mitt.: Fehldosierungen während der Abfüllung von Pulvern bzw. Granulaten in Hartgelatinekapseln. Pharm. Ind. 46, 860–863.

Podczeck, F., Lee-Amies, G., 1996. The bulk volume changes of powders by granulation and compression with respect to capsule filling. Int. J. Pharm. 142, 97–102.

Snedecor, G.W., Cochran, W.G., 1980. Statistical Methods, 7th edn. Iowa State University Press, IA, pp. 34–35.

van Ooteghem, M., de Winter, B., Ludwig, A., 1988. Influence of the mixing conditions on the flow properties of powders to be filled into hard gelatin capsules. Acta Pharm. Jugosl. 38, 287–295.

Varthalis, S., Pilpel, N., 1976. Anomalies in some properties of powder mixtures. J. Pharm. Pharmacol. 28, 415–419.