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International Journal of Pharmaceutics 185 (1999) 237–254

international journal of pharmaceutics

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Powder filling into hard gelatine capsules on a tamp filling machine

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Received 3 February 1999; received in revised form 7 April 1999; accepted 5 May 1999

Abstract

A series of pharmaceutical excipient powders used in capsule formulations as fillers have been filled into hard gelatine capsules on a Bosch GKF–400S tamp filling machine. These machines depend on pushing pins through a powder bed so that a unit dose is transferred into a dosing disc. This dose is then ejected into the capsule body. The results indicate that the range of powders that can be filled on this type of machine exceeds that applicable to a dosator nozzle system. Filling problems due to powder flooding could be solved by increasing the powder bed height in the powder bowl. The fact that such powders usually do not form a firm plug was not reflected in the coefficient of fill weight variation, and uniform filling could hence be achieved without problems. The influence of the powder bed height on the capsule fill weight increased with decreasing powder flow. The influence of the setting of the tamping pins on the capsule fill weight was comparatively small and further decreased with a decrease in powder flow. However, when a granulated product (Elcema G250®) was filled, the tamping pin setting was more important than the influence of the powder bed height on the capsule fill weight. For moderate flowing powders the coefficient of fill weight variation appeared to be nearly independent of powder bed height or tamping pin setting. However, the filling performance of powders with poor flow properties could be adjusted by optimising both machine settings. Very complex relationships were found between the powder properties such as angle of internal flow, dynamic densification profile, Carr's compressibility index and particle size and shape, and the filling behaviour.

Keywords: Angle of internal flow; Capsule filling; Carr's compressibility index; Dynamic powder densification; Powder filled hard gelatine capsules; Tamp filling machine

1. Introduction

The use of hard gelatine capsules as solid oral dosage forms has several advantages over the more commonly used tablets such as taste masking, unlimited possibilities of identification markings, or reduced levels of excipients, in particular

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0378-5173/99/$ - see front matter
PII: S0378-5173(99)00169-6

fillers, which is especially important for high dose drugs. However, while the food and health market acknowledges these advantages and is providing a growing number of capsule products, in the pharmaceutical industry tablets are still preferred. This is associated with the perceived contribution to increased manufacturing costs, associated with lower output rates and the need to invest in new machinery. However, another reason appears to be a limited knowledge about capsule formulation. Often it is assumed that tablet and capsule formulations are interchangeable. However, capsule formulations represent a different dosage form with different needs, and significant differences can exist in the composition when compared to tablet formulations.

Over the years, a body of information has been built up with respect to capsule filling on dosator nozzle machines. This is mainly due to the availability of instrumented machines (Cole and May, 1972, 1975; Small and Augsburger, 1977) and simulators (Jolliffe et al., 1982). The latter can provide adequate information on the filling properties of powders using small quantities. The amount of literature reports on tamp filling, however, is sparse. There is, therefore, a need to investigate the filling of powders into capsules on tamp filling machines.

The aim of this work was to study the filling properties of excipients commonly used in powder filled capsules (Jones, 1995) as fillers. The influence of various machine settings and the relationships between the powder properties and the filling performance were sought.

2. Materials and methods

The following excipients were studied as received: microfine cellulose (Elcema G250®, Degussa, Frankfurt, Germany, batch 816208), lactose monohydrate (Pharmatose 110M®, De Melkindustrie, Veghel, Netherlands, batch 025512), dicalciumphosphate dihydate (Emcompress®, Edward Mendell, Carmel, NY, USA, batch 3G–12), microcrystalline cellulose (Emcocel 50M®, Emcocel 90M®, Forum Chemicals, Redhill, Surrey, UK, batches 8068 and 6137), microcrystalline cellulose (Unimac MG–200®, Unitika Rayon, Osaka, Japan, batch 5125–107), microcrystalline cellulose (Avicel PH103®, FMC, Philadelphia, PA, USA, batch 3505–49), pregelatinised starch (Starch 1500®, Colorcon, Dartford, Kent, UK, batch 710048), corn starch (Zetmeelbedrijven De Bijenkorf, Amsterdam, Netherlands, batch 306034) and magnesium carbonate (East Anglia Chemicals, Hadleigh, Ipswich, Suffolk, UK, batch 004139).

The flow and packing properties of the powders were determined using an automatic tap volumeter (Jencons Scientific Equipment, Radon Industrial Electronics, Worthing, UK) with a lift height of 30 mm and a tapping frequency of 30 taps/min. About 200 ml powder was carefully filled into the tared, mounted measuring cylinder. The powder bed was levelled with a spatula, and the maximum bulk volume (to give the minimum bulk density) was read. A single tap was employed, and the volume was read again. This procedure was repeated, thereby gradually increasing the number of taps between individual readings, until three consecutive replicates of 200 taps did not reduce the powder volume further. Hence, the minimum powder volume (to give the maximum bulk density) had been reached. The measuring cylinder was then weighed to determine the powder mass. The powder 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), a packing kinetics model (Hauer et al., 1993a), and the Kawakita constants a and b (Yamashiro et al., 1983). The Carr's compressibility index (Carr, 1965; BS 2955, 1993) was calculated from the minimum and maximum bulk densities for each powder.

The particle size and shape of the powders were determined using light microscopy (BH–2, Olympus, Tokyo, Japan) in combination with image analysis (Solitaire 512, Seescan, Cambridge, UK). A tiny amount of powder was suspended in an appropriate immersion liquid (Refractive index liquids, series RF, McCrone Scientific, London, UK) to give maximum contrast. The samples were covered with a glass cover slip. Initially, the Feret diameter and particle shape (Podczeck, 1997) of

1500 particles were measured. The distribution of Feret diameters was then used to calculate the surface–weighed mean particle size according to Edmundson (1967).

The powders were filled into hard gelatine capsules size 1 (Capsugel, Colmar, France) on a Bosch GKF–400S tamp filling machine (Robert Bosch, Waiblingen, Germany) with a 19.6 mm dosing disk. The powders were filled without addition of lubricants or anti-adhesives. The machine was taken apart after each run and carefully cleaned to remove adhering powder particles from the tamping pins, the dosing disk and the tamping ring. All capsule body transporting segments were also cleaned after each run.

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 (AE 160, Mettler Instruments, Greifensee/Zürich, Switzerland). Each capsule weight was corrected for the average weight of the capsule shells (74.9 ± 0.6 mg). The arithmetic mean and S.D. as well as the coefficient of fill weight variation were calculated from the corrected capsule weights.

3. Results and discussion

3.1. Powder characterisation

Particle size analysis was performed by microscopy, because in addition to a particle size descriptor particle shape can be assessed. To characterise the particle size, the surface–weighed mean (d_{vs}) was obtained, because this value is inversely proportional to the specific surface area of the powder (Edmundson, 1967). The powders tested can be divided into three groups (Table 1): fine powders ($d_{vs} < 50$ μm), i.e. corn starch, pregelatinised starch and magnesium carbonate and medium size powders ($d_{vs} + 50–100$ μm), i.e. microcrystalline cellulose products Avicel PH103® ('MCC PH103'), Emcocel 50M® ('MCC 50M') and Unimac MG200® ('MCC MG200'), and coarse powders ($d_{vs} > 100$ μm), i.e. Emcocel 90M® ('MCC 90M'), lactose and dicalciumphosphate dihydrate ('DCP'). The microfine cellulose product Elcema G250® ('MFC G250') is a granulation and hence forms a separate group.

With respect to the particle shape of the powders, corn starch and MFC G250 consist of roundish particles (shape factor SF < 4, Table 1). All MCC products are rod-shaped (particle aspect ratio AR > 1.5 and SF 7–7.5). Lactose consists of angular particles, as does DCP and magnesium carbonate. However, the values of the shape factor SF (Table 1) for magnesium carbonate and DCP indicate increasing irregularity in particle shape.

All powders with a minimum bulk density below 0.4 g/cm^3 can be characterised as bulky (all MCC products and MFC G250, Table 1). The other extreme form powders with a large value of the

Table 1
Static powder bulk characteristics[a]

Powder	d_{vs} (μm)	SF	AR	ρ_{min} (g/cm^3)	ρ_{max} (g/cm^3)	CI (%)
Corn starch	16.7	3.52	1.29	0.517 ± 0.001	0.803 ± 0.003	35.6 ± 0.3
Starch (pre-gelatinised)	26.7	7.49	1.39	0.620 ± 0.006	0.848 ± 0.002	26.9 ± 0.5
Mg-carbonate	31.3	7.52	1.31	0.438 ± 0.006	0.636 ± 0.001	31.2 ± 1.0
MCC PH103	64.2	7.35	1.65	0.315 ± 0.008	0.448 ± 0.002	29.6 ± 1.6
MCC 50M	71.8	7.17	1.79	0.291 ± 0.001	0.416 ± 0.001	29.9 ± 0.2
MCC MG200	87.3	7.16	1.85	0.362 ± 0.001	0.530 ± 0.000	31.6 ± 0.2
MCC 90M	120.1	7.15	1.75	0.292 ± 0.001	0.386 ± 0.003	24.5 ± 0.6
Lactose	156.6	6.90	1.45	0.740 ± 0.004	0.864 ± 0.005	14.4 ± 0.0
DCP	199.7	8.20	1.48	0.796 ± 0.011	0.916 ± 0.012	13.1 ± 2.2
MFC G250	312.4	3.20	1.62	0.371 ± 0.004	0.492 ± 0.007	24.5 ± 0.8

[a] The results are the arithmetic mean and S.D. of three investigations. d_{vs}, Surface-weighed mean particle size (Edmundson, 1967); SF, shape factor (Podczeck, 1997); AR, particle aspect ratio; ρ_{min}, minimum bulk density; ρ_{max}, maximum bulk density; CI, Carr's compressibility index.

Table 2
Dynamic powder bulk characteristics[a]

Powder	Kawakita		Kinetics model		θ (°)	T
	a (%)	b	k_1	$k_2 \times 1000$		
Corn starch	36.2 ± 0.3	0.070 ± 0.004	4.171 ± 0.077	23.3 ± 2.5	37.74 ± 3.74	41.3 ± 4.0
Starch (pre-gelatinised)	27.0 ± 0.5	0.109 ± 0.045	4.209 ± 0.003	46.0 ± 3.6	37.74 ± 0.18	20.4 ± 1.6
Mg-carbonate	31.5 ± 1.0	0.121 ± 0.006	3.866 ± 0.001	45.0 ± 1.7	3.19 ± 0.03	20.5 ± 0.7
MCC PH103	30.1 ± 1.6	0.083 ± 0.004	3.576 ± 0.003	37.7 ± 3.1	6.82 ± 0.09	25.5 ± 1.9
MCC 50M	30.2 ± 0.2	0.098 ± 0.006	3.576 ± 0.009	41.3 ± 2.5	5.71 ± 0.00	22.5 ± 1.2
MCC MG200	31.9 ± 0.1	0.095 ± 0.004	3.715 ± 0.002	39.0 ± 1.7	10.26 ± 0.00	24.0 ± 0.5
MCC 90M	24.8 ± 0.8	0.120 ± 0.022	3.575 ± 0.007	52.0 ± 3.6	4.82 ± 0.12	17.6 ± 1.1
Lactose	14.5 ± 0.0	0.208 ± 0.031	4.161 ± 0.005	159.0 ± 12.8	35.68 ± 0.46	5.2 ± 0.7
DCP	14.0 ± 1.5	0.155 ± 0.034	4.275 ± 0.170	79.3 ± 14.5	14.00 ± 0.45	6.7 ± 0.7
MFC G250	24.5 ± 0.7	0.051 ± 0.004	3.725 ± 0.001	24.0 ± 1.7	9.09 ± 0.30	35.4 ± 3.0

[a] The results are the arithmetic mean and S.D. of three investigations). a, b, Constants of the Kawakita model; k_1, k_2, constants of the kinetics model (Hauer et al., 1993a); θ, angle of internal flow; T, compaction constant.

minimum bulk density (> 0.7 g/cm^3). These are lactose and DCP. It can be assumed that the average fill weight of capsules increases with the minimum bulk density (Cole, 1991), although powder plug formation requires densification of the powder towards or even above the maximum bulk density. The maximum bulk density of powder mixtures depends on the values of the single components (Newton and Bader, 1981; Podczeck and Sharma, 1996), whereby the addition of a bulky component is reflected in a decreased maximum bulk density of the powder mixture. Hence, as excipients in powder filling, bulky powders such as MCC products are less suitable if the dose of the active ingredients is already high and a restriction on the capsule size is made.

Excellent flow properties may also be detrimental to capsule formulations, because often the powders that flow well cannot be densified, the plug formation is impaired, and the variability in fill weight increases (Hauer et al., 1993a). In the decision tree of a previously described expert system (Lai et al., 1996), for dosator nozzle machines the lower limit has been set to a Carr's compressibility index of 15%. For tamp filling machines, such a limiting value has not yet been defined. From the Carr's compressibility indices obtained (Table 1), and assuming a validity of threshold levels observed using the dosator nozzle principle (Jolliffe and Newton, 1982; Tan and Newton, 1990), for the two extremes, i.e. excellent flow (lactose, DCP) and no powder flow (corn starch), filling problems might be anticipated.

A variety of dynamic packing models have been introduced into powder technology aiming at a wider understanding of the packing and flow mechanisms involved in powder handling. The Kawakita model (Kawakita, 1956) describes the compressibility and flow properties of a powder bulk under small loads, i.e. employing free fall conditions (force of gravity) in a tapping device. The correct choice of the tapping device is crucial for the success of this and other dynamic packing models (Podczeck, 1998). The Kawakita method appears more sensitive for smaller particle size ranges (Yamashiro et al., 1983). Under the correct tapping conditions, the constant a, i.e. the value of the slope of the Kawakita equation and Carr's compressibility index are identical (Lüdde and Kawakita, 1966). However, small deviations between the two values are often found (Podczeck and Lee-Amies, 1996). This is due to the difficulties in determining the minimum bulk density with reasonable accuracy. In this study, again the values for Carr's compressibility index (Table 1) and the Kawakita constant a (Table 2) are similar, and hence no additional information can be gained from this Kawakita constant. However, the constant b, i.e. the intercept of the Kawakita equation is related to the shear strength of the powder particles (Adams and McKeown, 1996). Particles of MFC G250 are granules and hence

vulnerable to shear forces. This is reflected in a very low value of b (Table 2) for this material. Also corn starch appears to have a low shear strength. At the other end of the spectrum are the hard, crystalline powders such as lactose and DCP. These materials resist shearing. During tamping this would result in less dense plugs.

The angle of internal flow θ (Varthalis and Pilpel, 1976) is related to the angle of internal friction obtained from shear cell measurements. Larger values of θ imply an impaired powder flow due to increased interparticulate forces. Newton and Bader (1987) found indirect proportionality between the weight of capsules filled by a tamp filling process and the angle of internal flow. However, Tan and Newton (1990) found no significant relationship between the coefficient of fill weight variation and the angle of internal flow for dosator nozzle filling. The values for the angle of internal flow for the powders tested in this study are listed in Table 2. Larger interparticulate forces appear to operate in the powder bulk of corn starch, lactose and pregelatinised starch. However, in the case of lactose, these forces apparently do not hinder powder flow. Interparticulate forces are also related to plug formation. Hence, while in the case of corn starch the large angle of internal flow is mainly an expression of poor powder flow, in the case of pregelatinised starch and lactose it might be an indication of good plug forming properties.

The compaction constant T (Mohammadi and Harnby, 1997) evaluates the ease and velocity of densification in a powder bed. Ideally, a powder bed should densify rapidly in order to give a similar powder bed density during the whole filling process (Hauer et al., 1993a) while reforming quickly and uniformly after each single dosing step (Jones, 1988). So far, values of T significantly larger than 35 have been interpreted as a sign of slow densification in combination with a small particle size and/or firm individual particles such as crystals (Mohammadi and Harnby, 1997). This is certainly true for corn starch (Table 2). Also the kinetics model by Hauer et al. (1993a) aims to quantify the velocity of densification. Here, the process is regarded as a two-phase process, split into an initial phase and a secondary phase. Hauer et al. (1993a) found large differences between powders with respect to the two kinetic constants derived. For the powders here, however, the differences between individual powders are very small (Table 2). Also, following the interpretation of Hauer et al. (1993a), the values found would imply that corn starch flows as well as DCP or lactose, which is clearly not the case. Presumably, direct comparisons between powders are only possible, if these are composed of similar material, i.e. identical particle shape but different particle size, as was the case in the study of Hauer et al. (1993a).

3.2. Capsule filling

One disadvantage of filling of capsules on a tamp filling machine is the large variety of possible machine settings which makes process validation very difficult (Hauer et al., 1993b). First of all, different tamping forces can be achieved, which could influence the plug strength and the fill weight of the capsules. Shah et al. (1986) tested different maximum tamping forces between 50 and 250 N on a H&K GKF tamp filling machine. Heda et al. (1998) also used large tamping forces (100 and 200 N). In a simulation procedure (Davar et al., 1997) even higher forces were considered. In this work, a Bosch GKF tamp filling machine was used. All Bosch GKF machines are supplied with two sets of springs, used to control the force exerted on the powder via the tamping pins. The normal or 'standard spring' for powder filling can be used for forces between 20 and 60 N, whereby a load of 40 N appears optimal. The alternative spring, which is used for overfilling due to compression beyond the maximum bulk density, works in the range between 40 and 120 N, but not more than 90 N can be applied for a long time without damage to the dosing disk drive. Hence, in any case on modern tamp filling machines the force exerted on the powder is much smaller than on the old H&K GKF machines. The higher the tamping force, the firmer the powder plug will be, and filling problems due to loose plugs will vanish (Pfeifer and Marquardt, 1984). Tamp filling machines are also less sensitive to flow problems than dosator nozzle machines

(Hauer et al., 1993a; Podczeck et al., 1999a,b). Hence, to enhance the differences in the filling behaviour of the powders selected for this study, first of all a low tamping force (≤ 50 N) was employed. Under these conditions, the plug density will normally not exceed the maximum bulk density of the powder, and problems of filling due to impaired plug formation should be clearly seen. Also, all capsules were overfilled by using a 19.9 mm dosing disk, i.e. the plug will protrude from the capsule body by about 3 mm before it is closed. Also, all powders were filled without the addition of lubricant or anti-adhesive to allow a study of a wider range of powder flow properties and the influence of stickiness on the capsule filling performance. The stickiness was rated by visual inspection of the tamping pins and the dosing disk bores after the powder had been filled. Non-sticky powders (rating 0) were MFC G250, all MCC products and pregelatinised starch. On the other hand, lactose and DCP were found to be extremely sticky (rating 1), causing seizure of the machine after longer running times. In these cases, the pins became covered by a fused powder layer preventing any movement upwards or downwards during tamping. Magnesium carbonate and corn starch particles adhered to the pin surfaces but did not form a fused film or hinder machine operation (rating 0.5).

In Table 3 the filling results are listed as fill weights and the coefficient of fill weight variation. During tamping, the pins penetrate the dosing disk to a certain degree thereby densifying the powder positioned between the pin surface and the tamping ring. The formation of a plug segment in a previous tamping step will reduce the space in the dosing bore so that the column of additional uncompressed powder becomes smaller each time. The maximum column height is limited, therefore, by the distance between the tamping ring and the pin face, when the tamping pins are at their highest position. A greater influence of the powder bed height on the capsule fill weight can only be expected if the pins are redrawn from the powder bed during tamping. The gap between the powder bed level and the pin surfaces when these are at their highest position is largest at tamping stations 1 and 2. If, however, all pins are fully immersed in the powder bed during a complete cycle of the up and down movement of the pins, no or only limited change in fill weight will occur if the powder bed level is raised further. In Fig. 1, the influence of the powder bed height and the pin settings on the capsule fill weight is presented. The pin setting is expressed as cumulative tamping distance, i.e. the cumulative penetration depth of the tamping pins into the dosing disk after five tamping events.

Fig. 1a shows lactose as an example for powders with excellent flow properties. The powder bed structure within the bowl was smooth and only slightly angled, so that the difference between the bed height at tamping stations 5 and 1 was negligible. At the lowest powder bed height, the tamping pins were above the powder bed when at their highest position. It is, therefore, not surprising that the capsule fill weights were the lowest in this case. An increase in the powder bed height increased the capsule fill weight at low cumulative tamping distances, i.e. at only small tamping forces. At higher tamping forces, however, the capsule fill weights were similar for all powder bed heights. In all cases the increase in cumulative tamping distance increased the capsule fill weight only slightly. In total, the capsule fill weight could only be varied by about 20 mg. An appreciable change in fill weight cannot, therefore, be achieved without adjustment of the dosing disk height.

Fig. 1b compares the capsule fill weights of pregelatinised starch as an example of the powders showing moderate flow properties. The powder bed structure was smooth but clearly angled. At the lowest powder bed height (pins above the powder bed at their highest position) the capsule fill weight is markedly decreased, whereas the difference in powder bed height does not influence the capsule fill weight when all pins are fully immersed in the powder (medium and high powder bed). The tamping pin setting has only a slight influence on the capsule fill weight at higher powder bed levels. In a low powder bed, however, increased compression can compensate for the reduced powder column length, so that capsule fill weights similar to those at high powder bed levels could be achieved. As the operational life time of

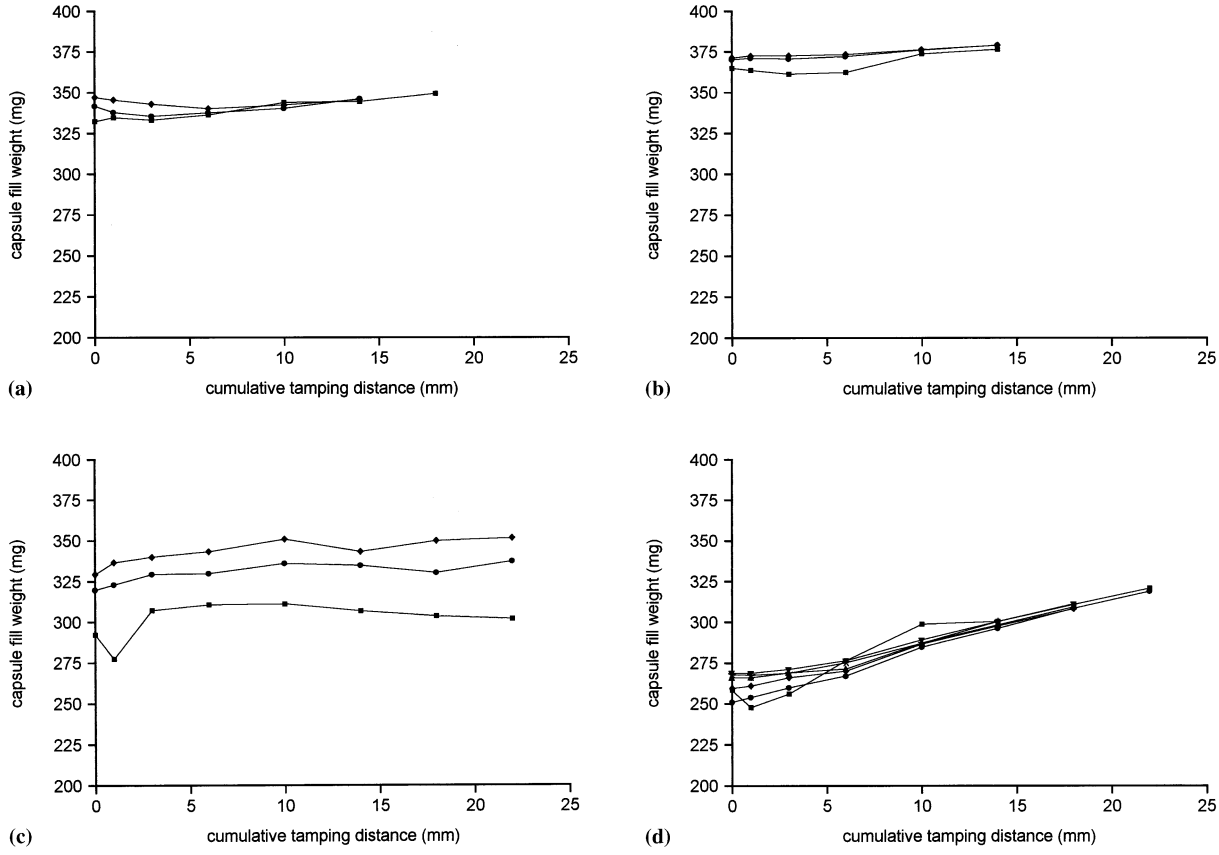

Fig. 1. Capsule fill weight as a function of the powder bed height and the pin setting, expressed as 'cumulative tamping distance'. (a) Lactose, powder bed height: ■, 2.5 cm; ●, 5.0 cm; and◆, 6.5 cm. (b) Pregelatinised starch, powder bed height: ■, 2.5 cm; ●, 4.0 cm; and◆, 5.5 cm. (c) Corn starch, powder bed height: ■, 2.5 cm; ●, 4.0 cm; and ◆, 5.5 cm. (d) MFC G250, powder bed height: ■, 3.5 cm; ●, 4.0 cm; ◆, 4.5 cm; ▲, 5.0 cm; ▼, 5.5 cm; and *, 6.0 cm.

the machine is longer the lower the compression used, the capsule fill weight should be controlled via the powder bed height rather than by the compression setting.

Fig. 1c depicts the influence of the powder bed height and the cumulative tamping distance for a non-flowing powder (corn starch). The influence of the powder bed height is here very strong. The powder bed structure was inhomogeneous, and the powder piled up around the 4th and 5th tamping station. Even at the highest powder bed setting the tamping pins at tamping stations 1 and 2 were not immersed in the powder at their highest position. This is in contrast to the two other powders examined in Fig. 1a and b, and highlights the importance of the first two tamping stations. If the first two tamping stations are not filled by the powder due to impaired flow, the capsule fill weight will drop. This effect cannot be compensated for by an increased compression setting on the consecutive tamping stations, as there is apparently no real influence of the cumulative tamping distance on the capsule fill weight. Shah et al. (1986) suggested that tamping machines could presumably work sufficiently with only three tamping stations. However, the results presented here contradict this opinion. The advantage of a tamp filling machine is its ability to also fill powders with poor flow properties into capsules. This advantage would be lost, if the number of tamping stations were reduced.

Table 3
Capsule filling results[a]

Powder	Bed height (cm)	Pin setting (mm)					Weight (mg)	CV (%)
		1	2	3	4	5		
Corn starch	2.5	0	0	0	0	0	292.2 ± 27.7	9.49
		1	0	0	0	0	277.3 ± 34.6	12.47
		2	1	0	0	0	307.2 ± 12.6	4.09
		3	2	1	0	0	310.6 ± 13.7	4.41
		4	3	2	1	0	311.1 ± 11.4	3.68
		5	4	3	2	0	306.8 ± 16.5	5.38
		6	5	4	3	0	303.6 ± 18.6	6.13
		7	6	5	4	0	301.8 ± 21.7	7.19
	4.0	0	0	0	0	0	319.8 ± 21.6	6.77
		1	0	0	0	0	323.0 ± 18.1	5.62
		2	1	0	0	0	329.4 ± 14.9	4.52
		3	2	1	0	0	329.8 ± 10.8	3.27
		4	3	2	1	0	336.0 ± 12.0	3.58
		5	4	3	2	0	334.7 ± 15.8	4.71
		6	5	4	3	0	330.3 ± 16.0	4.85
		7	6	5	4	0	337.3 ± 12.9	3.83
	5.5	0	0	0	0	0	329.4 ± 20.7	6.29
		1	0	0	0	0	336.6 ± 12.0	3.58
		2	1	0	0	0	339.9 ± 13.6	3.99
		3	2	1	0	0	343.2 ± 17.4	5.08
		4	3	2	1	0	350.8 ± 8.3	2.35
		5	4	3	2	0	343.2 ± 12.7	3.71
		6	5	4	3	0	349.8 ± 9.9	2.83
		7	6	5	4	0	351.4 ± 17.1	4.87
Pregelatinised starch	2.5	0	0	0	0	0	365.0 ± 3.9	1.06
		1	0	0	0	0	363.7 ± 3.5	0.96
		2	1	0	0	0	361.3 ± 3.4	0.94
		3	2	1	0	0	362.3 ± 2.8	0.79
		4	3	2	1	0	373.9 ± 2.5	0.66
		5	4	3	2	0	376.7 ± 2.1	0.56
	4.0	0	0	0	0	0	370.3 ± 2.5	0.69
		1	0	0	0	0	371.2 ± 3.3	0.89
		2	1	0	0	0	370.7 ± 3.3	0.88
		3	2	1	0	0	372.1 ± 2.9	0.79
		4	3	2	1	0	376.2 ± 2.9	0.76
		5	4	3	2	0	379.3 ± 2.3	0.61
	5.5	0	0	0	0	0	371.3 ± 2.5	0.67
		1	0	0	0	0	372.5 ± 2.6	0.70
		2	1	0	0	0	372.7 ± 2.8	0.75
		3	2	1	0	0	373.4 ± 3.1	0.84
		4	3	2	1	0	376.5 ± 3.0	0.80
		5	4	3	2	0	379.2 ± 2.3	0.60
Magnesium carbonate	3.0	0	0	0	0	0	298.3 ± 4.4	1.48
		1	0	0	0	0	299.9 ± 3.5	1.16
		2	1	0	0	0	301.8 ± 3.7	1.24
		3	2	1	0	0	300.8 ± 4.7	1.56
		4	3	2	1	0	309.5 ± 4.2	1.35
		5	4	3	2	0	319.2 ± 4.8	1.51
		6	5	4	3	0	337.3 ± 6.9	2.05

Table 3 (*Continued*)

Powder	Bed height (cm)	Pin setting (mm)					Weight (mg)	CV (%)
		1	2	3	4	5		
	6.5	0	0	0	0	0	305.2 ± 6.3	2.06
		1	0	0	0	0	308.7 ± 5.7	1.83
		2	1	0	0	0	307.7 ± 5.8	1.90
		3	2	1	0	0	308.4 ± 6.7	2.17
		4	3	2	1	0	319.8 ± 5.5	1.73
		5	4	3	2	0	331.2 ± 5.1	1.54
		6	5	4	3	0	346.1 ± 3.6	1.04
MCC PH103	4.0	0	0	0	0	0	213.1 ± 5.9	2.75
		1	0	0	0	0	213.2 ± 5.9	2.77
		2	1	0	0	0	211.9 ± 4.9	2.30
		3	2	1	0	0	215.3 ± 5.7	2.62
		4	3	2	1	0	225.3 ± 3.0	1.32
		5	4	3	2	0	232.0 ± 3.1	1.34
	6.0	0	0	0	0	0	216.8 ± 4.7	2.18
		1	0	0	0	0	217.9 ± 3.7	1.70
		2	1	0	0	0	219.1 ± 4.0	1.81
		3	2	1	0	0	222.5 ± 3.7	1.68
		4	3	2	1	0	228.1 ± 3.4	1.48
		5	4	3	2	0	235.0 ± 3.1	1.30
		6	5	4	3	0	244.6 ± 3.1	1.27
MCC 50M	3.5	0	0	0	0	0	197.7 ± 4.8	2.41
		1	0	0	0	0	199.3 ± 4.2	2.09
		2	1	0	0	0	201.5 ± 4.3	2.15
		3	2	1	0	0	207.1 ± 3.7	1.78
		4	3	2	1	0	218.7 ± 2.2	0.99
		5	4	3	2	0	225.4 ± 2.3	1.03
		6	5	4	3	0	233.5 ± 2.3	1.00
	6.0	0	0	0	0	0	206.9 ± 3.5	1.68
		1	0	0	0	0	207.7 ± 3.1	1.50
		2	1	0	0	0	209.0 ± 3.4	1.60
		3	2	1	0	0	211.1 ± 4.1	1.96
		4	3	2	1	0	219.2 ± 2.3	1.04
		5	4	3	2	0	227.8 ± 2.8	1.22
MCC MG200	3.5	0	0	0	0	0	257.4 ± 3.7	1.45
		1	0	0	0	0	258.5 ± 2.9	1.12
		2	1	0	0	0	259.0 ± 2.2	0.85
		3	2	1	0	0	261.9 ± 3.2	1.22
		4	3	2	1	0	272.3 ± 1.7	0.63
		5	4	3	2	0	280.0 ± 2.0	0.72
	6.0	0	0	0	0	0	261.8 ± 3.3	1.27
		1	0	0	0	0	262.5 ± 3.4	1.29
		2	1	0	0	0	260.9 ± 3.8	1.45
		3	2	1	0	0	264.9 ± 2.6	1.00
		4	3	2	1	0	272.4 ± 2.0	0.74
		5	4	3	2	0	280.3 ± 1.9	0.69
MCC 90M	5.0	0	0	0	0	0	152.8 ± 2.0	1.32
		1	0	0	0	0	156.2 ± 2.2	1.43
		2	1	0	0	0	158.4 ± 2.6	1.66
		3	2	1	0	0	160.3 ± 3.1	1.94

Table 3 (*Continued*)

Powder	Bed height (cm)	Pin setting (mm)					Weight (mg)	CV (%)
		1	2	3	4	5		
		4	3	2	1	0	170.5 ± 3.4	1.99
		5	4	3	2	0	177.1 ± 3.1	1.76
	6.5	0	0	0	0	0	161.9 ± 6.1	3.79
		1	0	0	0	0	158.1 ± 2.5	1.56
		2	1	0	0	0	165.6 ± 2.3	1.38
		3	2	1	0	0	168.2 ± 2.9	1.71
		4	3	2	1	0	175.8 ± 4.0	2.29
		5	4	3	2	0	184.0 ± 4.2	2.30
Lactose	2.5	0	0	0	0	0	332.3 ± 9.6	2.90
		1	0	0	0	0	334.8 ± 11.0	3.29
		2	1	0	0	0	333.2 ± 9.5	2.86
		3	2	1	0	0	336.4 ± 10.6	3.15
		4	3	2	1	0	344.0 ± 9.7	2.81
		5	4	3	2	0	344.7 ± 10.0	2.90
		6	5	4	3	0	349.6 ± 8.0	2.29
	5.0	0	0	0	0	0	341.7 ± 9.0	2.63
		1	0	0	0	0	337.9 ± 11.7	3.46
		2	1	0	0	0	335.6 ± 12.1	3.61
		3	2	1	0	0	337.6 ± 11.2	3.33
		4	3	2	1	0	340.4 ± 9.8	2.88
		5	4	3	2	0	346.4 ± 9.3	2.69
	6.5	0	0	0	0	0	347.1 ± 12.2	3.50
		1	0	0	0	0	345.6 ± 7.8	2.26
		2	1	0	0	0	343.0 ± 8.7	2.55
		3	2	1	0	0	340.2 ± 8.6	2.52
		4	3	2	1	0	342.5 ± 8.5	2.48
		5	4	3	2	0	345.7 ± 8.0	2.32
DCP	2.0	0	0	0	0	0	397.0 ± 9.6	2.41
		1	0	0	0	0	396.9 ± 10.3	2.59
		2	1	0	0	0	401.8 ± 10.9	2.71
		3	2	1	0	0	410.1 ± 12.2	2.99
		4	3	2	1	0	409.8 ± 9.1	2.21
		5	4	3	2	0	417.3 ± 8.4	2.00
		6	5	4	3	0	422.6 ± 7.0	1.67
	5.5	0	0	0	0	0	407.8 ± 8.3	2.03
		1	0	0	0	0	405.5 ± 8.6	2.12
		2	1	0	0	0	410.5 ± 10.8	2.63
		3	2	1	0	0	413.2 ± 14.0	3.39
		4	3	2	1	0	421.9 ± 12.1	2.88
		5	4	3	2	0	427.0 ± 12.3	2.88
MFC G250	3.5	0	0	0	0	0	258.5 ± 11.8	4.55
		1	0	0	0	0	247.7 ± 8.4	3.39
		2	1	0	0	0	256.2 ± 8.4	3.29
		3	2	1	0	0	276.5 ± 8.6	3.13
		4	3	2	1	0	298.9 ± 6.0	2.02
		5	4	3	2	0	300.7 ± 3.7	1.24
		6	5	4	3	0	311.0 ± 3.3	1.07
		7	6	5	4	0	321.1 ± 2.4	0.75
	4.0	0	0	0	0	0	251.0 ± 5.5	2.18
		1	0	0	0	0	253.8 ± 5.8	2.27

Table 3 (*Continued*)

Powder	Bed height (cm)	Pin setting (mm)					Weight (mg)	CV (%)
		1	2	3	4	5		
		2	1	0	0	0	260.0 ± 4.8	1.83
		3	2	1	0	0	267.0 ± 3.8	1.43
		4	3	2	1	0	284.9 ± 2.0	0.70
		5	4	3	2	0	296.4 ± 1.7	0.58
		6	5	4	3	0	308.7 ± 1.5	0.50
		7	6	5	4	0	319.2 ± 1.7	0.54
	4.5	0	0	0	0	0	259.4 ± 5.4	2.09
		1	0	0	0	0	261.0 ± 5.4	2.09
		2	1	0	0	0	266.2 ± 4.1	1.56
		3	2	1	0	0	270.2 ± 3.6	1.34
		4	3	2	1	0	286.8 ± 2.1	0.73
		5	4	3	2	0	297.9 ± 1.8	0.59
		6	5	4	3	0	308.5 ± 1.9	0.62
	5.0	0	0	0	0	0	266.2 ± 4.1	1.53
		1	0	0	0	0	266.1 ± 4.1	1.54
		2	1	0	0	0	269.2 ± 3.7	1.39
		3	2	1	0	0	271.4 ± 4.0	1.49
		4	3	2	1	0	287.4 ± 2.1	0.73
		5	4	3	2	0	298.5 ± 2.2	0.74
		6	5	4	3	0	309.5 ± 1.5	0.50
	5.5	0	0	0	0	0	269.2 ± 4.7	1.74
		1	0	0	0	0	268.9 ± 4.5	1.68
		2	1	0	0	0	271.1 ± 3.8	1.42
		3	2	1	0	0	276.5 ± 4.2	1.50
		4	3	2	1	0	289.3 ± 2.0	0.69
		5	4	3	2	0	300.5 ± 1.9	0.63
		6	5	4	3	0	311.5 ± 1.7	0.54
	6.0	0	0	0	0	0	268.0 ± 4.1	1.55
		1	0	0	0	0	267.5 ± 4.2	1.57
		2	1	0	0	0	268.8 ± 3.7	1.36
		3	2	1	0	0	275.2 ± 3.8	1.39
		4	3	2	1	0	287.2 ± 2.3	0.82
		5	4	3	2	0	300.5 ± 2.1	0.70

[a] The values are the arithmetic mean and S.D. of 50 observations.

In Fig. 1d the filling properties of the granulated product MFC G250 are illustrated. The granulation behaves very differently to the other powders. Here, a major increase in capsule fill weight up to about 75 mg can be achieved by changing the tamping pin settings. The powder bed structure was flat and smooth, so that six different powder bed heights could be tested. A change in bed height is here less effective than a change in the cumulative tamping distance. Granules are usually highly porous materials. The particle density of MFC G250 is 1.5 g/cm^3 (Podczeck and Révész, 1993), and the minimum bulk density is 0.37 g/cm^3 (Table 1). Hence, the granule porosity is about 75%. Granules are also brittle at low external loads applied. The brittleness and the high porosity are the reasons for the apparent collapse of the granules during tamping, which results in increased densification and consequently in the strong influence of the cumulative tamping distance on capsule fill weight.

Capsule fill weight is not the only property to monitor during capsule filling. The coefficient of fill weight variation is also important. Pharmaco-

poeias regulate the maximum variation in fill weight allowed with respect to the capsule weight and dose. For a capsule weight up to 300 mg, two out of 20 inspected units may deviate by 10%, and for larger fill weights, two out of 20 inspected units may deviate by 7.5% from the mean capsule fill weight. No unit should deviate by more than 20% or 15% for weights up to 300 mg or larger, respectively (British Pharmacopoeia, 1998; European Pharmacopoeia, 1997). These requirements translate into a maximum coefficient of fill weight variation of 5% for a capsule fill weight of up to 300 mg, and about 4% for larger capsule fill weights. However, in industry the major target is a coefficient of fill weight variation below 3% in all cases (Newton et al., 1998). In Fig. 2 the influence of powder bed height and cumulative tamping distance on the coefficient of fill weight variation are explored in four examples.

The coefficient of fill weight variation decreased considerably for the excellent flowing lactose at the highest powder bed (Fig. 2a). At this bed height, the cumulative tamping distance had no influence on the coefficient of fill weight variation. Apparently a higher powder bed can suppress 'flooding' of the powder during the act of tamping, presumably due to a slightly denser powder bed caused by the own weight of the powder mass. The coefficient of fill weight variation of the moderate flowing pregelatinised starch, which represents the majority of capsule formulations, is neither influenced by the powder bed height, nor the cumulative tamping distance (Fig. 2b). However, when the powder flow is grossly impaired (corn starch, Fig.

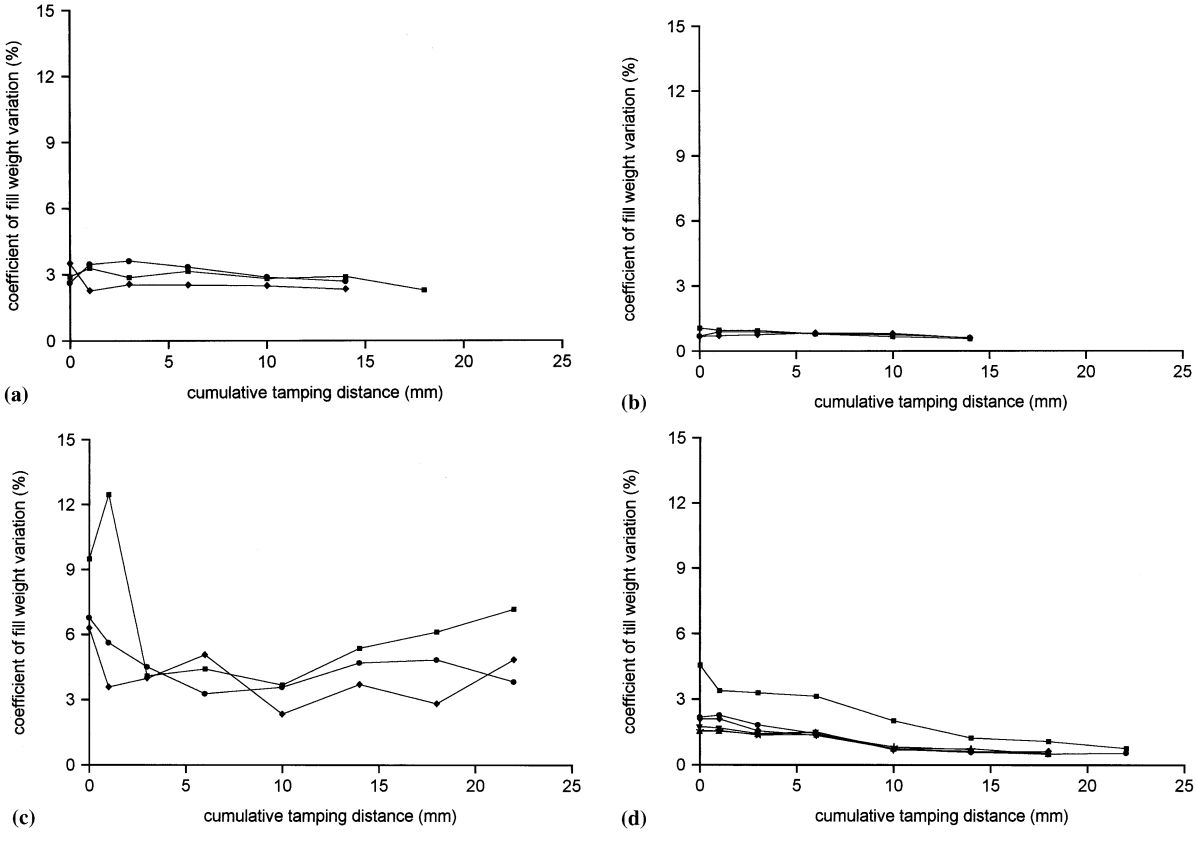

Fig. 2. Coefficient of fill weight variation as a function of the powder bed height and the pin setting, expressed as 'cumulative tamping distance'.(a) Lactose, powder bed height: ■, 2.5 cm; ●, 5.0 cm; and ◆, 6.5 cm. (b) pregelatinised starch, powder bed height: ■, 2.5 cm; ●, 4.0 cm; and ◆, 5.5 cm. (c) Corn starch, powder bed height: ■, 2.5 cm; ●, 4.0 cm; and ◆, 5.5 cm. (d) MFC G250, powder bed height: ■, 3.5 cm; ●, 4.0 cm; ◆, 4.5 cm; ▲, 5.0 cm; ▼, 5.5 cm; and *, 6.0 cm.

2c) both the powder bed height and the cumulative tamping distance are important variables to monitor. Even here some settings were found to satisfy the requirements on the coefficient of fill weight variation, mainly for the highest powder bed and a moderate compression setting. A stronger compression, i.e. larger cumulative tamping distance, however, proved negative in this respect, because the coefficient of fill weight variation increased. A different effect can be seen for the granulation (Fig. 2d). Here, the increase in cumulative tamping distance also initially decreased the coefficient of fill weight variation, but at larger compression settings the coefficient of fill weight variation became independent of this machine parameter. The less satisfactory filling results for the lowest powder bed height could again be attributed to 'flooding' during tamping.

3.3. Relationships between powder properties and capsule filling

In order to identify global relationships between the powder properties (Table 1) and the capsule filling results, the latter were summarised to give a few explicit numbers that can be used in a mathematical analysis (Table 4). These numbers consider the possibility of varying the capsule fill weight using different powder bed heights as absolute figures, and as a relative increase in capsule fill weight considering all machine settings together. To obtain a comparable figure for the degree of capsule filling, the maximum relative plug density achieved was calculated. Further descriptors of the filling properties are the maximum and minimum coefficient of fill weight variation produced considering all the machine settings employed.

To get a general impression of the relationships present in the data material, a perceptual map was drawn using non-linear canonical correlation analysis (Tenenhaus and Young, 1985). The perceptual map (Fig. 3) can be read as follows:

Relationships between variables exist if these are positioned along a correlation axis or along the co-ordinate axes. Here, two correlation axes can be defined, which are marked as dashed lines in Fig. 3. A close relationship exists between the minimum coefficient of fill weight variation achieved and the angle of internal flow, the stickiness of the powder and the dynamic packing behaviour represented by the kinetics constant k_1. The maximum relative plug density and the maximum coefficient of fill weight are related to the same set of powder properties. The differences in capsule fill weight found in the lowest and highest powder bed by variation of the tamping setting and the overall relative increase in capsule fill weight appear not to be closely related to any measured powder property. However, the mini-

Table 4
Summary of the capsule filling results: parameters used in the mathematical analysis[a]

Powder	Mg_{high} (mg)	Mg_{low} (mg)	$Mg_{variation}$ (%)	CV_{max} (%)	CV_{min} (%)	Plug density (%)
Corn starch	22.0	33.8	26.7	12.47	2.35	71.6
Pregelatinised starch	7.9	15.4	5.0	1.06	0.56	73.1
Magnesium carbonate	40.9	39.0	16.0	2.17	1.04	89.0
MCC PH103	27.8	20.1	15.4	2.77	1.27	89.3
MCC 50M	20.9	35.8	18.1	2.41	0.99	91.8
MCC MG200	19.4	22.6	8.9	1.45	0.63	86.4
MCC 90M	25.9	24.3	20.4	3.79	1.32	89.1
Lactose	6.9	17.3	5.2	3.50	2.26	83.7
DCP	21.5	25.7	7.6	3.39	1.67	93.1
MFC G250	32.5	62.6	29.6	4.55	0.50	106.7

[a] Mg_{high}, Mg_{low}, weight variation achieved by different pin settings in the highest and lowest powder bed; $Mg_{variation}$, relative increase in capsule fill weight achieved considering all machine settings; CV_{min}, CV_{max}, largest and smallest coefficient of fill weight variation produced considering all machine settings; plug density, maximum plug density achieved considering all machine settings.

mum coefficient of fill weight can also be related to a completely different set of powder properties positioned along the second correlation axis. These are: particle shape, Carr's compressibility index, Kawakita constant b and the compaction constant T.

Some powder properties (minimum and maximum bulk density) were not included in the construction of the perceptual map, because they were linearly correlated to Carr's compressibility index.

The relationships found by perceptual mapping are complex, and there is not enough data to build a numerical model for each relationship. In Fig. 4, the minimum coefficient of fill weight variation shows a tendency to increase with an increase in the angle of internal flow, except for pregelatinised starch. It can also be seen that the sticky powders such as lactose, DCP and corn starch are less good fillers. The stickiness might have influenced both the values of the angle of internal flow and the filling performance, hence giving rise to a complex and entangled relationship. The dynamic packing properties represented by the kinetic constant k_1 (Table 1) appear to play a different role. Here, an optimum value around 3.5–3.7 appears to exist. Powders, which densify more (larger values of k_1) or less quickly (smaller values of k_1) are characterised by less satisfactorily filling properties. The same pattern is detectable for the maximum coefficient of fill weight variation. The packing velocity is related to the flow properties of a powder. Hence, the relationships found indicate that a good filling performance, i.e. a low coefficient of fill weight variation can be achieved for non-sticky, moderately flowing powders. While the range of 'moderate flow' can be defined slightly wider, the prevention of stickiness is the main goal when formulating a powder filled capsule preparation for tamp filling machines.

The plug density that can be achieved decreases for most powders with an increase in the angle of internal flow. The most likely reason for this is that friction hinders slippage and particle rearrangement, so that the tamping force applied will densify these powders less. Exceptions are the MCC products. These have comparatively low values for the angle of internal flow. Here the pronounced elastic properties appear to play a role. Presumably the

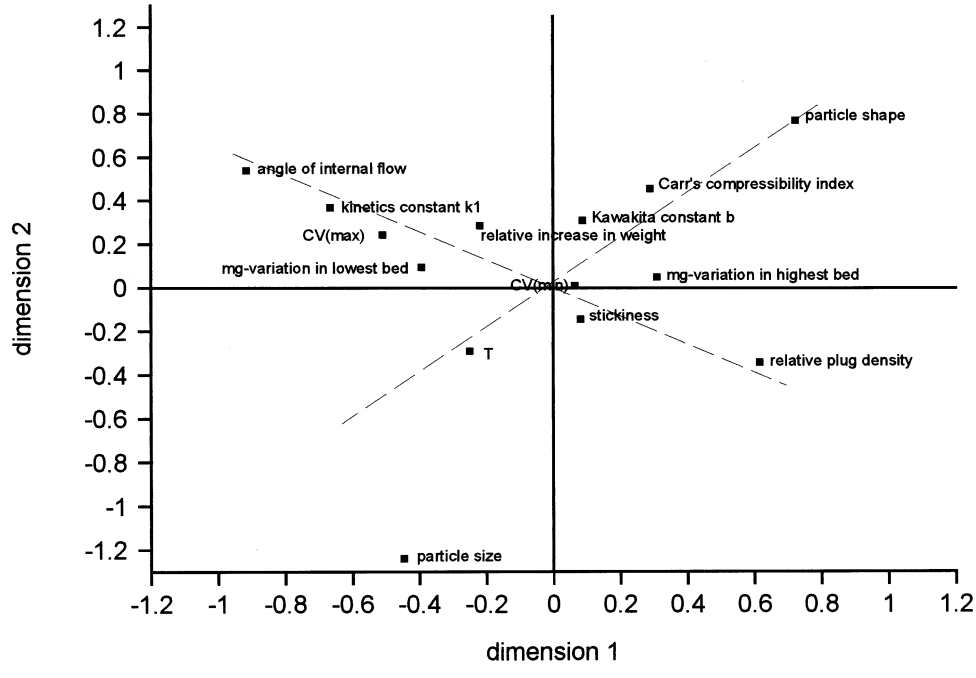

Fig. 3. Perceptual map to illustrate the relationships between the powder properties and the capsule filling behaviour (the dimensions 1 and 2 are the 1st and 2nd component loadings of the non-linear canonical correlation analysis).

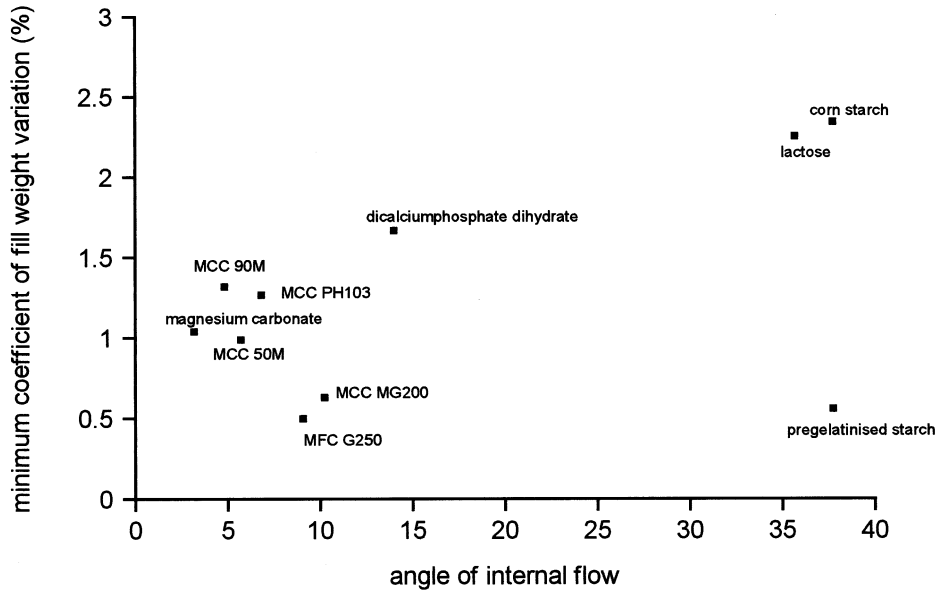

Fig. 4. Minimum coefficient of fill weight variation achieved considering all machine settings as a function of the angle of internal flow.

plug segments formed at the earlier tamping stations relax thereby loosening the plug structure. Later segments are denser, but the tamping force is too small to be transmitted through the whole plug column to re-densify the earlier formed plug segments. Evidence for this mechanism was found when opening these capsules. The top of the plug was solid, tablet like, but only about 2 mm long. Below this segment, i.e. at the bottom of the capsule body loose powder, which was not compressed into any plug structure, was identified. Again, an interrelationship between stickiness, angle of internal flow and plug density was found. With increasing stickiness, the plug density became lower. Also here, an optimum dynamic packing range appears to exist for moderate flowing powders.

The possibility of explaining the minimum coefficient of fill weight variation by two different sets of variables (two correlation axes in Fig. 3) indicates that the information included in the single variables overlaps, and that none of the variables measured represents a true, fundamental powder characteristic. Other properties measured provide only a different way of expressing the same basic property. For example, the compaction constant T and the kinetics constant k_1 both describe the dynamic packing properties of a powder. Also for T an optimum value appears to exist with respect to the minimum coefficient of fill weight variation. This is depicted in Fig. 5. The advantage of using T is first founded on the more simple mathematical expression, although the evaluation of both constants requires a non-linear regression. Secondly, the scale of values is wide, and hence T-values can

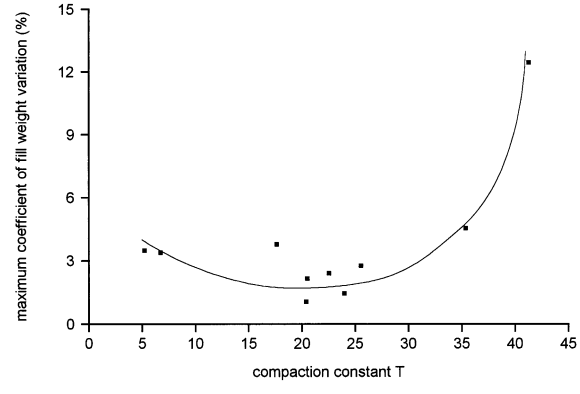

Fig. 5. Maximum coefficient of fill weight variation achieved considering all machine settings as a function of the compaction constant T.

provide a better distinction between powders. The optimum value for T appears to lie between 20 and 25. Below the optimum, i.e. for rapid densification and good powder flow, larger variability in capsule fill weight can be expected, presumably caused by "powder flooding" in the powder bowl when the tamping pins hit the powder bed and/or reach the level of the dosing disc. A value for this constant above 30 indicates here major filling problems. However, the upper threshold value does not apply to granules (Podczeck et al., 1999b). The influence of the flow properties on the filling performance is also reflected in a broad relationship to Carr's compressibility index. Also here, an optimum range exists, apparently for values between 15 and 30. However, this does not exclude satisfactory filling of powders outside this range at optimum machine settings. The influence of the particle shape on the minimum coefficient of fill weight variation is clearly present up to a value of the shape factor (Table 1) of about 7, i.e. for roundish and angular particles. Here, the change from a roundish to an angular particle shape on the whole decreases the coefficient of fill weight variation. This might again be linked to a parallel change from good to rather moderate flow properties. However, for more irregular particles (shape factor > 7, Table 1), an influence of particle shape on the minimum coefficient of fill weight variation cannot be seen. As discussed above, the values of the Kawakita constant b indicate resistance to shearing for lactose and DCP, whereas corn starch appears to be vulnerable to the occurrence of shear forces. Coincidentally, these are the powders which have higher values for the minimum coefficient of fill weight variation. Presumably this is an indication of impaired plug formation. Opening of these capsules confirmed that no plug had formed during tamping. In contrast to the capsules filled with corn starch, however, the lactose and DCP filled capsules were completely filled.

4. Conclusions

The range of powders that can be filled into hard gelatine capsules using a tamp filling machine appears somewhat wider than would be expected by applying the knowledge of capsule filling based on experiences with dosator nozzle machines. Hence, although Jones (1988) suggested, that a good capsule formulation should fill on both types of machine equally well, there might be some formulations which cannot be improved to satisfy this high standard. However, these can still be filled successfully into hard gelatine capsules on one or the other type of machine. Filling problems due to powder flooding on a tamp filling machine can be solved by increasing the powder bed height in the powder bowl. Such powders usually do not form sufficiently firm plugs to allow the use of a dosator nozzle machine, but they can be filled without major problems on the tamp filling machine. The influence of the powder bed height on the capsule fill weight increases with decreasing flow properties. The influence of the tamping pin setting on the capsule fill weight is comparatively small and further decreases with an increasing impairment of powder flow. However, when granules are filled, the tamping setting dominates over the influence of the powder bed height on the capsule fill weight. While, for moderate flowing powders, the coefficient of fill weight variation appears to be nearly independent of powder bed height or tamping pin setting, the filling performance of powders with poor flow properties can be varied by adjustment of the powder bed height and/or the tamping pin setting. In this work, even a non-flowing powder could be filled to a satisfactorily low coefficient of fill weight variation at an optimum machine setting. The filling properties are related to various powder characteristics such as dynamic densification propensity, angle of internal flow, Carr's compressibility index, and particle size and shape. However, the relationships are very complex, and none of them can fully explain the whole range of filling properties observed. Hence, more work is needed to gain a deeper understanding of the capsule filling process on a tamp filling system.

Acknowledgements

FP was supported financially by the Deutsche Forschungsgemeinschaft via a Heisenberg fellow

ship. The tamp filling machine was provided by Robert Bosch GmbH (Waiblingen, Germany). Starch 1500 was a gift from Colorcon (Dartford, UK), and the hard gelatine capsules were a gift from Capsugel (Colmar, France).

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