J. Pharm. Pharmacol. 1998, 50: 713–721
Received January 13, 1998
Accepted March 2, 1998

Resistance to Densification, Tensile Strength and Capsule-filling Performance of some Pharmaceutical Diluents

I. NIKOLAKAKIS, O. BALLESTEROS ARAGON AND S. MALAMATARIS

Laboratory of Pharmaceutical Technology, Pharmacy Department, University of Thessaloniki, Thessaloniki 54006, Greece

Abstract

The purpose of this study was to compare some indicators of capsule-filling performance, as measured by tapped density under different conditions, and elucidate possible quantitative relationships between variation of capsule fill-weight (%CV) and gravitational and inter-particle forces (attractive or frictional) derived from measurements of particle size, true density, low compression and tensile strength. Five common pharmaceutical diluents (lactose, maize starch, talc, Emcocel and Avicel) were investigated and two capsule-filling methods (pouring powder and dosator nozzle) were employed.

It was found that for the pouring-type method the appropriateness of Hausner's ratio (HR), Carr's compressibility index (CC%) and Kawakita's constant (α) as indicators of capsule fill-weight variation decreases in the order $\alpha > CC\% > HR$; the appropriateness of these indicators also decreases with increasing cylinder size and with impact velocity during tapping. For the dosator-type method the appropriateness of the indicators decreases in the order $HR > CC\% > \alpha$, the opposite of that for the pouring-type method; the appropriateness of the indicators increases with decreasing cylinder size and impact velocity. The relationship between %CV and the ratio of inter-particle attractive to gravitational forces calculated from measurements of particle size and true density (F_{vdw}/W_p) was more significant for the pouring-type capsule-filling method. For the dosator-type method a significant relationship (1% level) was found between %CV and the product of F_{vdw}/W_p and a function expressing the increase, with packing density (p_f), in the ratio of frictional to attractive inter-particle forces derived from compression (P) and tensile-strength (T) testing, $d(\log(P/T))/d(p_f)$.

The value of tapped density in predictions of capsule-filling performance is affected by the testing conditions in a manner depending on the filling method applied. For the pouring-type method predictions can be based on the ratio of attractive (inter-particle) to gravitational forces, whereas for the dosator-type method the contribution of frictional and attractive forces should, because of packing density change, also be taken into account.

Optimum powder packing and flow properties are essential for successful capsule filling or the achievement of acceptable fill-weight-variation. Moreover, vibration and tapping is often applied in bench-scale equipment and low compression in industrial-scale machines to optimize the filling of hard-gelatin capsules. Several workers have correlated the fill-weight-variation of capsules filled in different machines with numerous powder-flow and packing or densification parameters, for example angle of repose, angle of internal flow, angle of effective friction, Carr's compressibility index, consolidation ratio, Jenike's flow factor, flow through orifice, Hausner's ratio and Kawakita's constants α and $1/b$ (Irwin et al 1970; Kurihara & Ichikawa 1978; Chowan & Chow 1980; Chowan & Young 1981; Tan & Newton 1990; Patel & Podczeck 1996).

For bench-scale equipment in which capsules are filled by pouring powder into the capsule bodies and applying only vibration or tapping, without any additional compression, the packing behaviour of powders during capsule filling can be predicted from tapped density results. For industrial-scale capsule-filling machines, prediction of behaviour is more difficult, because it is based on the formation of a powder plug or on the extent to which a powder can be readily densified as a result of the

Correspondence: S. Malamataris, Laboratory of Pharmaceutical Technology, Pharmacy Department, University of Thessaloniki, Thessaloniki 54006, Greece.

low compression applied. A relationship has been proposed between the coefficient of capsule fill-weight variation and the compression of the powder in the dosator nozzle, as well as with the ease of powder ejection (Jollife et al 1980). Therefore, the densification or the packing characteristics of a powder, under the action of a low compression pressure, and its tensile strength, considered in combination with gravitational forces, might provide better information about the densification of the powder possibly needed during filling into capsules with the dosator nozzle. Also, the differences noticed in capsule-filling performance between different powders and between different types of capsule-filling machine (Kurihara & Ichikawa 1978) might arise from the range and magnitude of the inter-particle attractive physical (van der Waals) and mechanical-frictional forces that act between the particle surfaces and their ratio to gravitational forces. Gravitational forces depend on the volume and density of the powder particles, whereas inter-particle attractive forces can be quantified as tensile strength or can be calculated from the particle size, and the frictional forces can be represented by indices of resistance to densification derived from volume-reduction of powder beds under compression or tapping.

In this work hard-gelatin capsules were filled with five common capsule diluents, either by pouring into capsule bodies followed by tapping and leveling on a bench-scale equipment, or by using an industrial-scale machine of the dosator nozzle-type. Tensile strength and resistance to densification were measured as representative of inter-particle attractive and frictional forces, respectively. Resistance to densification was expressed as indices derived from volume reduction under different tapping conditions (Hausner's ratio, Carr's compressibility index and angle of internal flow), as the pressure required to compress the powder to a particular packing density, and as Kawakita's constants (α and $1/b$) derived from both tapping and low compression. Gravitational and inter-particle van der Waals attractive forces were calculated from measured values of particle size and density.

The aim of this work was to compare the various indices of resistance to densification measured with tapping or compression, and to elucidate any possible relationships between them, the tensile strength, the ratio of inter-particle attractive to gravitational forces and variation of capsule fill-weight for the two capsule-filling methods used.

Materials and Methods

Materials

The powdered materials used in this study were: lactose monohydrate (DMV, Veghel, The Netherlands), maize starch (Cerestar, Milano, Italy), talc (Lusenac, Torino, Italy) and two brands of microcrystalline cellulose, Emcocel (E. Mendell, Kuopio, Finland) and Avicel PH102 (FMC Corporation, PA).

Characterization of the powders

Mean particle size and weight, roundness, and mean inter-particle van der Waals force. Particle-size analysis of each diluent was undertaken with a Leica (Cambridge, UK) Quantimet 500 image-processing and analysis system. The powders were dispersed in paraffin oil and the projected area-equivalent diameter and the particle shape were determined for at least 1000 particles. Particle size was expressed as the mean volume-number diameter and particle shape as the mean particle roundness which is equal to the square of the perimeter divided by 12·56 times the projected area, so that for a circle it has a minimum value of unity.

The mean weight of the particles (W_p) and the mean inter-particle attractive van der Waals force (F_{vdw}) were calculated from the mean volume-number particle diameter (d) and the true density (D). $W_p = \pi d^3 D/6$ and $F_{vdw} = Ad/24x^2$, where A is the Hammaker constant ($\approx 10^{-19}$ J) and x is the distance between two interacting particles with an average value of 10^{-9} m (Krupp 1967).

Density and densification under tapping. The true density of the powders was measured on an air-comparison pycnometer (Beckman, Model 930). The bulk and tapped densities were measured in a J. Engelsmann (Ludvwigshafen, Germany) Model JEL ST2 volumeter, using 5- and 100-mL measuring cylinders, and in a 5-mL cylinder attached to bench-scale (Tevopharm) capsule-filling equipment. Before determination each powder was passed through a 0·4-mm sieve to deaggregate any macro-agglomerates. Initially, powder was poured into the cylinder and the bulk density was determined from the weight and volume after inverting it 10 times. The cylinder was then tapped and changes of the volume were closely monitored after every 2 taps up to 50, then every 5 taps up to 100, then every 10 taps up to 200, every 20 taps up to 300, and every 50 taps thereafter. When the powder was tapped in the capsule bodies there was no measurable volume change after 150 taps. Tapped density was determined from the weight and volume of the powder when the plot of volume against number of taps became asymptotic (see Results and Discussion). Each experiment was repeated five times to obtain mean values for the bulk (D_b) and tapped density (D_t), and for

maximum packing reproducibility the same weight of powder was used every time. Kawakita's equation constants (α and $1/b$) (Kawakita & Ludde 1970/71), the Carr compressibility index $CC\% = [(D_t - D_b)/D_t] \times 100$ (Carr 1965), the Hausner ratio $HR = D_t/D_b$ (Hausner 1967) and the angle of internal flow (θ) (Varthalis & Pilpel 1976) were determined from these volume readings.

Tensile strength and densification tests under compression

The tensile strength of the diluents was measured at packing densities produced by compressing them at different pressure levels with loads ranging from approximately 10 to 60 N. The apparatus for performing the tensile strength measurements was a modified version of the horizontal split cell. It was equipped with a plunger attached to a load platform for consolidation of the powders at different interparticle porosity values or packing densities. More details on the theory and design of the equipment have been published elsewhere (Ashton et al 1964; Eaves & Jones 1972).

Samples were prepared for testing by filling the cell with powder, after passing it through a 0·4-mm sieve to deaggregate any macro-agglomerates. The powder bed was then consolidated by means of the plunger and the force required to split it at the packing density achieved was determined. The tensile strength (T) was obtained from the force required to cause failure divided by its cross-sectional area. The packing density, p_f, was calculated from the dimensions (volume) and the weight of the powder bed ($p_f = D_c/D$, where D_c is the bulk density of the consolidated powder bed and D the true density).

For each powder the resistance to densification was calculated from the compression pressure (P) required to achieve a packing density corresponding to tapped density $p_{ft} = D_t/D$. Both T and P at a certain packing density were calculated from logarithmic equations relating them to p_f (Malamataris & Pilpel 1980):

$$\log T = A_1 p_f + B_1 \quad (1)$$

$$\log P = A_2 p_f + B_2 \quad (2)$$

where A_1, B_1, A_2 and B_2 are constants for each experimental powder.

Capsule filling

Hard-gelatin capsules were filled on bench-scale capsule-filling equipment (Tevopharm-Schiedam N.V., Holland), and on an automatic intermittent-motion capsule-filling machine of the dosator-nozzle type (Zanasi LZ-64, Industria Machine Automatische, Bologna, Italy), using size 0 capsule shells (Elanco Qualicaps, Basingstoke, UK).

In the first method filling was performed by pouring powder into the capsule bodies and leveling with a spatula after applying three taps to the plate holding the capsule bodies. In the dosator-type machine, filling was always performed at maximum fill volume and capsules were collected for evaluation after running the machine for about 2 min, to ensure that a constant powder coating was formed on the nozzle surface. For lactose, only, capsules were collected immediately after starting the machine, because this diluent could only be filled with a clean dosator nozzle (Tan & Newton 1990). No lubricant was used in the capsule-filling trials and 20 capsules were randomly obtained for the determination of the coefficient of variation of fill-weight.

The capsule fill-weight was determined from the total weight of the filled capsule by subtracting the mean weight of empty capsule shells (93 mg). Capsules were weighed (±0·1 mg) on an analytical balance (ADA 180, ADAM Equipment, Milton Keynes, UK), which was linked to a computer for transfer and statistical analysis of the data. For each sample, the coefficient of fill-weight variation (%CV) was computed by use of the equation:

$$\%CV = ((\sum \chi i^2 - n\chi^2)/(n-1))^{1/2} \times 100/\chi \quad (3)$$

where, χi is the individual fill-weight, and χ is the mean capsule fill-weight.

Results

Table 1 summarizes the particle properties of the different diluents employed, namely the mean volume-number diameter, the mean particle weight, the true density, the particle roundness and the mean inter-particle van der Waals attractive force (F_{vdw}), together with the coefficient of variation of capsule fill-weight for both the capsule-filling methods employed.

Figure 1 shows the densification capacity, or how the packing density of the different diluents increases with the number of taps applied under different conditions. Figure 1A shows plots for all the diluents tested (except Avicel) on the Engelsman volumeter by use of 100- and 5-mL cylinders. Figure 1B includes plots obtained by tapping on the Tevopharm capsule filler, in a 5-mL cylinder and in capsule bodies, for smaller numbers of taps (up to 150) realizable in capsule filling. Plots for Avicel are not included in Figure 1 because they coincide with those of Emcocel.

Table 2 lists the flow and packing or densification parameters of the diluents, namely Hausner's ratio,

Table 1. Particle properties of diluents and the coefficient of variation of fill-weight (%CV) for capsules filled on pouring-powder and dosator-nozzle-type machines.

Diluent	Mean volume-number-diameter (μm)	Mean particle weight ($N \times 10^{12}$)	True density (g cm^{-3})	Particle roundness	Mean inter-particle van der Waals attractive force ($N \times 10^{9}$)	Coefficient of variation for:	
						Dosator	Pouring
Lactose	18	46	1·52	1·62	75	5·0	2·2
Starch	14	21	1·48	1·48	58	5·3	1·9
Talc	16	59	2·75	1·68	67	10·9	2·1
Emcocel	49	942	1·54	1·88	200	3·1	1·5
Avicel	62	1910	1·54	2·16	260	2·0	1·2

Carr's compressibility index, the constants in Kawakita's equation (α and 1/b) and the angle of internal flow (θ), derived from tapping under different conditions. Constants α and 1/b derived from compression during the tensile testing are also included in Table 2. Table 2 also includes (in parentheses) the percentage change in the values of the aforementioned parameters as a result of tapping in a smaller cylinder (5- instead of 100-mL), in a different machine (Tevopharm capsule filler instead of Engelsman volumeter) and under real capsule-filling conditions (capsule bodies instead of cylinder).

Figure 2 shows logarithmic plots of the tensile strength and of the pressure applied to consolidate the powder beds against their packing density. The numerical terms in equations 1 and 2 describing the straight lines in Figure 2 were obtained by regression analysis of the experimental data. These are listed in Table 3 together with the corresponding correlation coefficients. Table 3 also includes numerical terms of the equation:

$$\log(P/T) = A_3 p_f + B_3 \qquad (4)$$

which is a combination of equations 1 and 2. P/T is a parameter which can be thought of as representing the ratio of mechanical (frictional) forces to van der Waals attractive (physical) forces between particles, because the tensile strength of powders arises primarily from the operation of van der Waals forces between particles and the resistance to densification under low compression arises primarily from the operation of mechanical (frictional) forces between particles (Malamataris & Pilpel 1980). Logarithmic plots of the experimental values of the ratio P/T against p_f are shown in Figure 3 for all the diluents under investigation; allowing for the errors involved in measuring tensile strengths (Cheng 1968) it is apparent that the points fall on reasonably straight lines.

Discussion

From plots of packing density change due to tapping ($\Delta p_f/\Delta N$) against number of taps, N, it was estimated that the curves in Figure 1 become asymptotic, i.e. $\Delta p_f/\Delta N$ approaches zero, after approximately 280 to 320 taps for all the powders examined. Therefore, it was considered reasonable to use the density of the powders after 300 taps as the tapped density. Also, from the plots in Figure 1 it is apparent that, in general, when the powders are tapped in the larger (100-mL) cylinder they rearrange and pack more closely; this results in higher packing-density values. By using the same cylinder (5-mL) but different tapping equipment, it was found that the p_f achieved is always lower when tapping is applied in the Tevopharm capsule filler than in the Engelsman volumeter.

The better packing achieved in the 100-mL cylinder can be attributed to the smaller adhesion area per gram of powder particles with the wall of the cylinder and to the larger momentum exerted on the powder particles because of the greater total weight of the powder column inside the cylinder. Similarly, the lower extent of packing when tapping is applied on the Tevopharm capsule filler compared with that on the Engelsman volumeter can be attributed to the smaller amount of kinetic energy transmitted to the particles, because the impact velocity is smaller for the Tevopharm capsule filler.

When the volume reductions of diluents in the capsule bodies tapped on the Tevopharm equipment are compared with those in the cylinders tapped on both tapping machines (Figure 1), it is apparent that densification is closer to that obtained in the 5-mL cylinder attached to the Tevopharm capsule-filling equipment. Therefore, from a practical point of view it can be said that measuring tapped density in a cylinder as small as possible is advantageous for the prediction of capsule fill-weight.

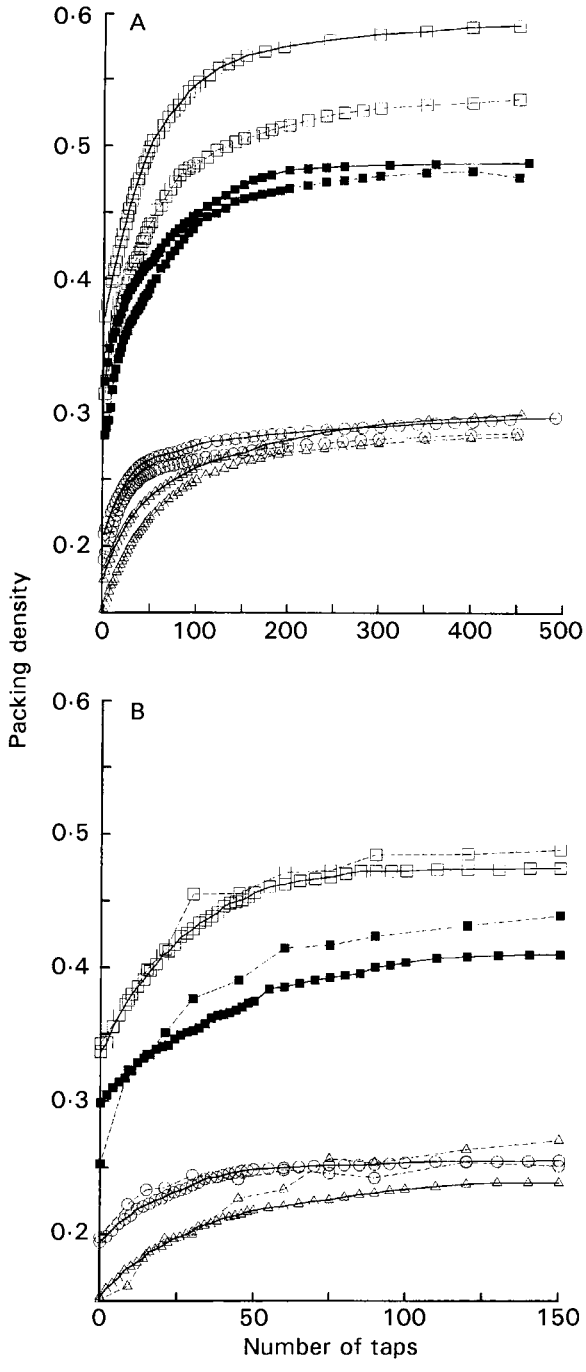

Figure 1. Plots of packing density of diluents against number of taps applied under different conditions. □ Lactose; ■ maize starch; △ talc; ○ Emcocel. Tapping was applied with (A) an Engelsman volumeter in a 100-mL (–) or 5-mL (- - -) cylinder, and (B) a Tevopharm capsule-filler in a 5-mL cylinder (—) or in capsule bodies (– – –).

On the basis of volume reduction (densification) or change in packing density during tapping and compression (Figure 1 and Figure 2B), and the angle of internal flow values (θ, in Table 2), the diluents examined fell into two groups. One group comprised talc and both the brands of microcrystalline cellulose (Emcocel and Avicel), which have higher θ values ($\approx$60) and lower p_f values. The other group contained lactose and maize starch, which have low θ values (15–35) and higher p_f values. Furthermore, when changes in the p_f of the diluents are compared with particle properties (Table 1) no simple and general relationship is apparent. Also, no simple and general relationship can be found between p_f changes and the flow and packing or densification parameters of the diluents given in Table 2.

The flow and packing or densification parameters, which are derived from tapping experiments, show some unexpected differences for the diluents examined and particularly for talc. For talc the value of angle of internal flow (θ) is similar to that of microcrystalline cellulose (Emcocel and Avicel) whereas the other parameters (HR, CC%, α and 1/b) are similar to those of lactose and starch. However, talc, which has a particle size similar to that of lactose and starch gives low p_f values or small volume reduction during tapping and compression (Figure 1A, Figure 2B) like microcrystalline cellulose (Emcocel and Avicel). Also, lactose and starch, although they have smaller and lighter particles than Emcocel and Avicel (Table 1) and give higher HR, CC% and α values (Table 2), indicative of worse flow and packing ability during tapping, unexpectedly have higher p_f or closer packing during tapping and compression (Figure 1, Figure 2B). These discrepancies can be attributed to the roundness and surface smoothness of particles or to the higher ratio of gravitational forces to attractive and frictional inter-particle forces resisting powder densification. During tapping and compression, talc has a volume reduction similar to that of microcrystalline cellulose (Emcocel and Avicel), even though it has particle properties and flow and densification parameters (except θ) similar to those of lactose and starch; this can be attributed to the angular and generally asymmetrical (flaky or platelet) shape of its particles. They probably inhibit closer packing because of a large increase of inter-particle frictional forces for a small packing-density increase.

From Table 1, which presents a quantitative evaluation of capsule-filling performance, we can say that filling, in general, is more uniform on the pouring-type (Tevopharm) equipment and that it deteriorates as a result of the nature of the diluent in the order lactose > talc > starch > Emcocel > Avicel. On the dosator-type capsule filler the order of deterioration is talc > starch > lactose > Emcocel >Avicel.

Linear regression analysis was used to correlate %CV of capsule fill-weight with the flow and packing or densification parameters (Table 2).

Table 2. Flow and packing or densification parameters of diluents derived from tapping under different conditions and from compression.

Parameter	Tapping equipment and cylinder size				Compression
	Engelsman volumeter		Tevopharm capsule filler		
	100 mL	5 mL	5 mL	Capsule body	
Lactose					
Hausner's ratio	1·57	1·68 (+7)	1·43 (−9)	1·43 (−9)	–
Carr's compressibility index	36·3	40·6 (+11)	30·0 (−17)	29·8 (−18)	–
Kawakita equation constant α	0·41	0·44 (+8)	0·33 (−21)	0·34 (−17)	0·39
Kawakita equation constant 1/b	32·5	26·7 (−18)	20·9 (−36)	19·6 (−40)	0·25
Angle of internal flow (θ)	15·3	21·8 (+43)	28·3 (+85)	26·3 (+72)	–
Starch					
Hausner's ratio	1·52	1·69 (+11)	1·41 (−7)	1·74 (+15)	–
Carr's compressibility index	34·0	40·8 (+20)	28·8 (−15)	42·5 (+25)	–
Kawakita equation constant α	0·38	0·45 (+17)	0·36 (−6)	0·46 (+19)	0·34
Kawakita equation constant 1/b	40·6	26·7 (−34)	38·7 (−5)	12·1 (−70)	0·57
Angle of internal flow (θ)	27·3	28·3 (+4)	40·5 (+48)	33·3 (+22)	–
Talc					
Hausner's ratio	1·66	1·82 (+9)	1·57 (−5)	1·79 (+8)	–
Carr's compressibility index	39·9	45·1 (+13)	36·5 (−9)	44·3 (+11)	–
Kawakita equation constant α	0·43	0·50 (+17)	0·43 (−2)	0·59 (+38)	0·40
Kawakita equation constant 1/b	32·1	31·2 (−3)	22·4 (−30)	43·4 (+35)	0·15
Angle of internal flow (θ)	60·1	61·2 (+2)	67·6 (12)	60·6 (+1)	–
Emcocel					
Hausner's ratio	1·39	1·48 (+ 7)	1·34 (−4)	1·27 (−8)	–
Carr's compressibility index	28·0	32·4 (+16)	25·2 (−10)	21·4 (−24)	–
Kawakita equation constant α	0·30	0·34 (+13)	0·29 (−3)	0·23 (−24)	0·32
Kawakita equation constant 1/b	21·9	17·1 (−22)	18·8 (−14)	9·02 (−59)	0·73
Angle of internal flow (θ)	60·0	61·5 (+3)	64·8 (+8)	65·4 (+9)	–
Avicel					
Hausner's ratio	1·34	1·46 (+9)	1·29 (−4)	1·23 (−8)	–
Carr's compressibility index	25·3	31·6 (+25)	22·5 (−11)	18·7 (−26)	–
Kawakita equation constant α	0·26	0·33 (+23)	0·23 (−14)	0·20 (−61)	0·30
Kawakita equation constant 1/b	20·8	14·1 (−32)	8·27 (−60)	8·06 (−61)	0·97
Angle of internal flow (θ)	59·9	60·1 (+1)	66·0 (+10)	64·9 (+8)	–

Values in parentheses are the percentage change of the parameters as a result of tapping in a smaller cylinder (5 mL), with different tapping equipment (Tevopharm capsule filler instead of Engelsman volumeter) and under real capsule-filling conditions (capsule bodies instead of cylinder).

The results, listed in Table 4, show that the correlation coefficients are high (approx. 0·9) for the parameters HR, CC% and α, for both capsule-filling methods used, whereas those for the angle of internal flow (θ) are small (0·057–0·681) and for the Kawakita's parameter 1/b are intermediate and variable (0·571–0·888). These findings agree, in general, with previous reports (Tan & Newton 1990) and show that the parameters HR, CC%, and α can be used as indices of capsule-filling performance. Also, the correlation coefficients in Table 4 show that, for the pouring-type (Tevopharm) capsule filler, the appropriateness of the aforementioned parameters as indicators of capsule-filling performance decreases in the order: $\alpha > CC\% > HR$, and furthermore decreases with the cylinder size and impact velocity during-tapping. For the dosator-type capsule filler the correlation coefficients change in the reverse order of that for the pouring type filler ($HR > CC\% > \alpha$) and increase with a decrease in cylinder size and in the impact velocity.

Therefore we can conclude that the value of Hausner's ratio, Carr's compressibility index and Kawakita's constant α as indicators of capsule-filling performance is greatly affected by the tapping conditions used during determination, for both of the filling methods employed; they are, however, affected differently, depending on the type of capsule filler employed.

Kawakita's constant 1/b does not seem to follow a trend similar to those followed by any of the other flow and packing or densification parameters for

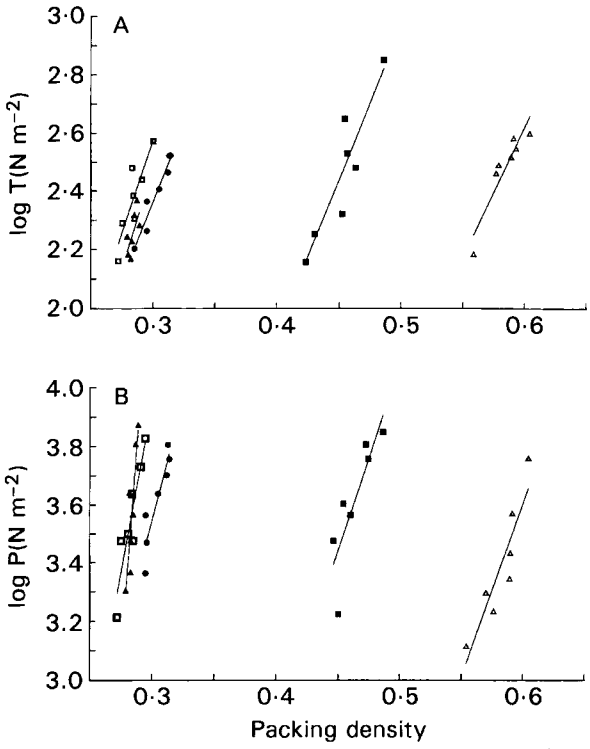

Figure 2. Plots of (A) log tensile strength (T) (N m^{-2}) and (B) log consolidation pressure (P) (N m^{-2}) against packing density for different diluents. △ Lactose; ■ maize starch; ▲ talc; □ Emcocel; ● Avicel.

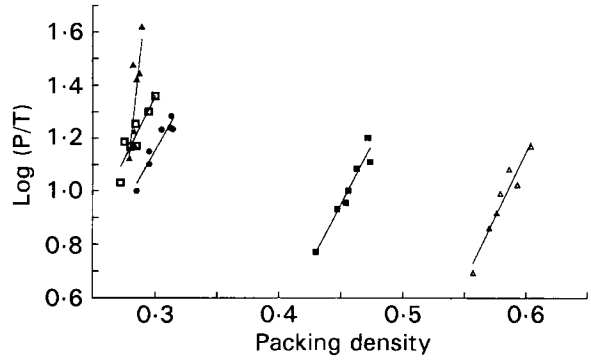

Figure 3. Plots of log (P/T) against packing density for different diluents. △ Lactose; ■ maize starch; ▲ talc; □ Emcocel; ● Avicel.

the diluents examined (Table 2), or similar to those of the particle properties (Table 1). The expression 1/b can be considered as representative of inter-particle forces resisting volume reduction (attractive and frictional), although a clear relationship was not established (Kawakita & Ludde 1970/71; Yamashiro et al 1983). In this work the relationships between the parameter 1/b derived from tapping and the representative measurements of attractive and frictional inter-particle forces, at packing densities corresponding to tapped density (p_{ft}), Tp_{ft}, Pp_{ft}, and Pp_{ft}/Tp_{ft}, were examined. Correlation coefficients calculated from regression analysis were low (< 0·8) and variable, although, most of the Tp_{ft}, Pp_{ft}, and Pp_{ft}/Tp_{ft} values increase as 1/b increases. This might be attributable to the different p_f range to which the data refer (below tapped density for 1/b and above it for Tp_{ft}, Pp_{ft}, and Pp_{ft}/Tp_{ft}).

The lower uniformity of capsule filling, observed as higher and more variable %CV, for the dosator-type (2–11%) than for the pouring-type capsule filler (1·5–2·2%), might be attributed to more extensive alteration in flowability, packing and cohesiveness of the powders during plug formation. It might be because of changes in the proportion of attractive and frictional to gravitational forces as p_f increases. Also, in the dosator-type machine, besides the flow and packing of the powder during the plug formation, uniformity of capsule filling might be affected by the lubricating action of the powder or the friction on the dosator wall, as well as by the retention of the powder in the dosator nozzle (Joliffe et al 1980). Because it has been established that the initial or the final value of the powder volume, bulk or tapped density, do not have a large influence on capsule fill-weight-variation, which is more affected by the rate of packing down (Tan 1987), the influence of the proportion of attractive, frictional and gravitational forces or their ratios should be considered.

Capsules filled in the Tevopharm equipment with lactose, maize starch or talc, which have small particle size, resulted in higher percentage variation of fill-weight, between 1·9 and 2·3. In contrast, Emcocel and Avicel with bigger particles and better flow and packing during tapping resulted in lower percentage variation of fill-weight, between 1·0 and 1·5. This is probably because with pouring-type capsule-filling machines the changes in the

Table 3. Numerical terms in the relationships: $\log T = A_1 p_f + B_1$, $\log P = A_2 p_f + B_2$ and $\log(P/T) = A_3 + B_3$ (n = 7).

Diluent	A_1	B_1	r_1	A_2	B_2	r_2	A_3	B_3	r_3
Lactose	8·02	2·20	0·936	11·62	3·38	0·925	7·59	3·43	0·970
Starch	8·80	1·47	0·846	14·39	3·05	0·882	5·59	1·58	0·833
Talc	15·85	2·29	0·839	57·42	12·74	0·857	41·57	10·45	0·880
Emcocel	13·49	1·47	0·931	23·05	2·98	0·903	9·56	1·45	0·938
Avicel	10·67	0·84	0·941	16·16	1·30	0·898	5·49	0·46	0·888

Table 4. Correlation coefficients (r) between capsule fill-weight variation (%CV) and the flow and packing or densification parameters derived from tapping* under different conditions and from compression.

Parameter		Tapping equipment and cylinder size				Compression
		Engelsman volumeter		Tevopharm capsule filler		
		100 mL	5 mL	5 mL	Capsule body	
Hausner's ratio	Pouring	0·977	0·895	0·810	0·708	–
	Dosator	0·826	0·906	0·925	0·935	–
Carr's compressibility index	Pouring	0·984	0·908	0·844	0·756	–
	Dosator	0·820	0·886	0·957	0·948	–
Kawakita equation constant α	Pouring	0·992	0·915	0·796	0·763	0·692
	Dosator	0·741	0·886	0·958	0·949	0·683
Kawakita equation constant 1/b	Pouring	0·888	0·729	0·571	0·662	−0·961
	Dosator	0·447	0·738	0·409	0·765	−0·844
Angle of internal flow (θ)	Pouring	−0·606	−0·586	−0·607	−0·681	–
	Dosator	0·063	0·057	0·058	−0·070	–

*In the tap number range $n < 150$.

gravitational and inter-particle attractive forces with particle size are predominant factors in successful filling. Because particle-size increase means greater gravitational force and greater van der Waals attractive force (F_{vdw}) between two interacting particles but smaller total inter-particle binding force (tensile strength) in a powder bed, it might be expected that F_{vdw} is related inversely to the flow and packing ability, and therefore directly related to the capsule fill-weight variation expressed as %CV. The dependence of the fill-weight variation on the ratio of inter-particle attractive (F_{vdw}) to gravitational forces (W_p) when capsules are filled in the powder-pouring capsule-filler, is demonstrated in Figure 4A. The correlation coefficients of linear regression analysis between %CV and the logarithm of F_{vdw}/W_p are 0·886 and 0·586 for pouring and dosator capsule-filling, respectively. This means that the relationship between %CV and the ratio F_{vdw}/W_p for all of the five diluents examined, irrespective of their nature, is more significant for the pouring-type capsule-filling method.

Correlating the variation in the fill-weight results (%CV, in Table 1) with the parameters describing the behaviour of the powders during compression, α and 1/b (Table 2), or plots of T, P, and P/T against p_f (Figure 2, Figure 3), it can be seen that: the correlation coefficient between %CV and Kawakita's parameter 1/b is greater than that between %CV and parameter α (Table 4) for both capsule-filling methods employed, although the parameter α from compression is close to that derived from tapping (10% deviation, in Table 2), as is expected (Podczeck & Lee-Amies 1996); and, for talc, the diluent with the worst variation of fill-weight in the dosator-type capsule filler, the slope of plots of log(P/T) against p_f (Figure 3) or the A_3 value in Table 3 is the highest, whereas for Avicel, with best filling properties, it is the smallest. It seems, therefore, that there is a relationship between %CV for capsules filled in the dosator-type machine and the parameter 1/b or $d(P/T)/d(p_f)$. Thus, capsule filling is improved (i.e. %CV is lower) for powders for which changes of log(P/T) with p_f are relatively small, i.e. those with high 1/b values. This is true either when densification of the powder is affected by small consolidation pressures (P) or when the inter-particle attractive forces (T) enable low-pressure formation of a powder plug able to withstand losses during transfer from the dosator nozzle to the capsule body. Furthermore, because powder flowability promotes packing uniformity and constant depth of powder bed (after every piston plunging for dose removal), the fill-weight variation, %CV, for the dosator-type capsule-filling machines should decrease with increasing flowability, i.e. should be directly related to the ratio F_{vdw}/W_p. Combination of the two factors influencing capsule filling, leads to the conclusion that %CV is related to the function $(d(\log(P/T))/d(p_f))(F_{vdw}/W_p)$. This relationship is tested in Figure 4B, where it can be seen that it is linear and highly significant ($r = 0.995$) for the dosator-type filling method.

In conclusion, the values of Hausner's ratio, Carr's compressibility index and Kawakita's constant α as predictors of the capsule-filling performance of powders is greatly affected by the tapping conditions used during their determination; the effect is, however, different, depending on the filling method employed. For capsule filling by pouring and then tapping the powder into capsule bodies, the variation in fill-weight is related significantly (1% level) to the ratio of inter-particle attractive to gravitational forces $[F_{vdw}/W_p]$ calcu-

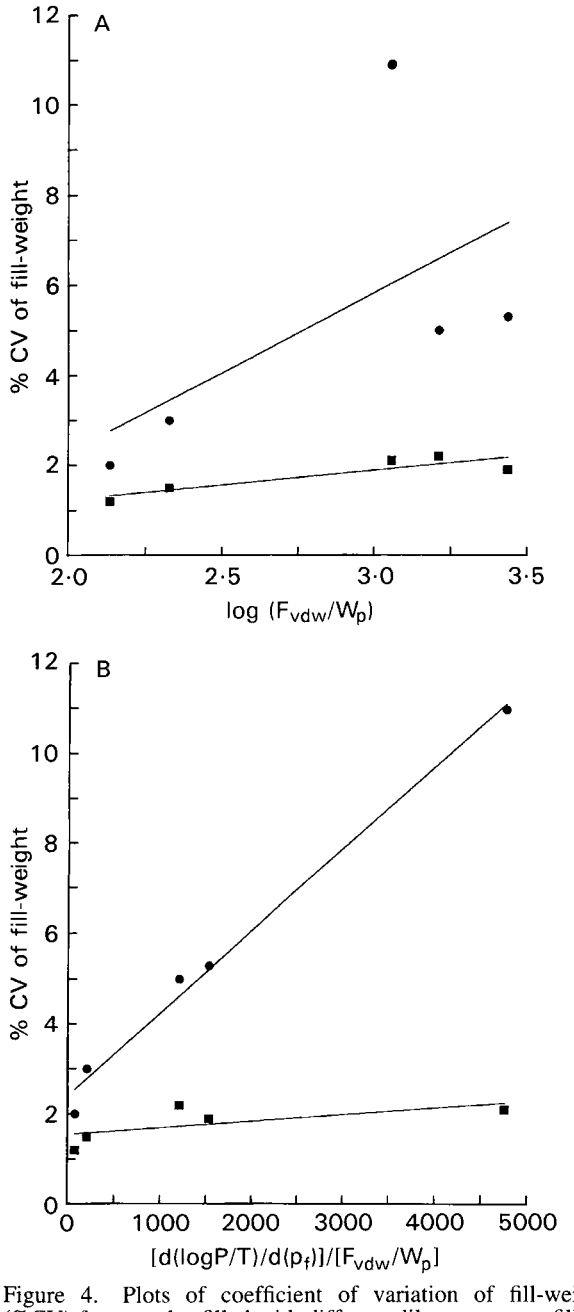

Figure 4. Plots of coefficient of variation of fill-weight (%CV) for capsules filled with different diluents on two filling machines (■ pouring type and ● dosator nozzle-type) against (A) the ratio of inter-particle attractive to gravitational forces, F_{vdw}/W_p, and (B) the product of F_{vdw}/W_p and a function expressing the increase, with packing density d(p_f), in the ratio of frictional to attractive interpacticle forces derived from compression (P) and tensile strength (T) testing, d(log(P/T))/d(p_f).

lated from particle size and density data. For capsule filling by the dosator nozzle method, the fill-weight variation is significantly related (1% level) to the product of the ratio F_{vdw}/W_p and the increase in the proportion of frictional to attractive interparticle forces with packing density, $[d(\log(P/T))/d(p_f)][F_{vdw}/W_p]$.

Acknowledgements

The authors would like to thank Mr K. Theophanopoulos and Remedina Pharmaceutical Laboratories, Greece, for use of the dosator-nozzle machine.

References

Ashton, M. D., Farlley, R. F., Valentin, F. H. H. (1964) An improved apparatus for measuring the tensile strength of powders. J. Sci. Instr. 41: 763–765

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

Cheng, D. C.-H. (1968) The tensile strength of powders. Chem. Eng. Sci. 23: 1405–1420

Chowan, Z. T., Chow, Y. P. (1980) Powder flow studies I. Powder consolidation ratio and its relationship to capsule filling-weight variation. Int. J. Pharm. 4: 317–326

Chowan, Z. T., Young, I. C. (1981) Powder flow studies. III: Tensile strength, consolidation ratio, flow rate and capsule-filling-weight variation relationships. J. Pharm. Sci. 70: 927–930

Eaves, T., Jones, T. M. (1972) Effect of moisture on tensile strength of bulk solids I: sodium chloride and effect of particle size. J. Pharm. Sci. 61: 256–261

Hausner, H. H. (1967) Friction conditions in a mass of metal powder. Int. J. Powder Metall. 3: 7–13

Irwin, G. M., Dodsom, G. J., Ravin, L. J. (1970) Encapsulation of clomacran phosphate. I: Effect of flowability of powder blends, lot-to-lot variability, and concentration of active ingredients on weight variation of capsules filled on an automatic capsule-filling machine. J. Pharm. Sci. 59: 547–550

Jollife, I. G., Newton, J. M., Walters, J. K. (1980) Theoretical considerations of the filling of pharmaceutical hard-gelatin capsules. Powder Technol. 27: 189–195

Kawakita, K., Ludde, K. H. (1970/71) Some consideration on powder compression equations. Powder Technol. 4: 57–60

Krupp, H. (1967) Particle adhesion theory and experiment. Adv. Colloid Interface Sci. 1: 111–239

Kurihara, K., Ichikawa, I. (1978) Effect of powder flowability on capsule-filling-weight-variation. Chem. Pharm. Bull. 26: 1250–1256

Malamataris, S., Pilpel, N. (1980) The effect of temperature on the tensile strength and densification of lactose powders coated with fatty acids. Powder Technol. 26: 205–211

Patel, R., Podczeck, F. (1996) Investigation of the effect of type and source of microcrystalline cellulose on capsule filling. Int. J. Pharm. 128: 123–127

Podczeck, F., Lee-Amies, G. (1996) The bulk volume change of powders by granulation and compression with respect to capsule filling. Int. J. Pharm. 42: 97–102

Tan, S. B. (1987) Filling of Hard-gelatin Capsules with Powders of Different Flow Properties. PhD Thesis, University of London

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

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

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