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Invited review

# The filling of powders into two-piece hard capsules

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**Abstract**

The factors that influence the filling of powders into hard capsules are reviewed. Powder properties that affect machine performance and influence plug formation are highlighted. The use of instrumented machines and machine simulators in formulation development are described. The properties of excipients that are required for uniform filling are identified. The use of optimisation techniques to produce rational formulations is discussed. © 2001 Elsevier Science B.V. All rights reserved.

*Keywords:* Hard capsules; Powder; Filling properties; Powder plug formation; Instrumented machines; Machine simulators; Excipient properties; Formulation optimisation

## 1. Introduction

The hard two-piece capsule was first patented in 1846 and has been manufactured on an industrial scale since the 1870s (Jones, 1987a). The first country in which there was widespread usage was the USA and at the beginning of the 20th century hundreds of millions of capsules were being filled by hand in pharmacies. The first industrial-scale filling machines were developed at this time to cope with the demand and the most notable example was the semi-automatic Model No. 8 machine invented by Arthur Colton, the American doyen of pharmaceutical engineering. Encapsulated products became very popular and by the 1950s were in use in most regions of the world. This large increase in demand lead to the development of automatic filling machines and companies based in Germany and Italy were at the forefront of this work. However, the pharmaceutics of powder filling into capsules has been studied by relatively few workers despite this long history of usage. This being due in part to the fact that the capsules are only used in the pharmaceutical and nutraceutical fields unlike tablets which are widely used in other industries, e.g. ceramics and powder metallurgy, and thus there has been more stimulus for tablet research activities. Another factor that has a bearing on this, often mentioned in the literature, is that powder filled capsules are a very simple product that do not need much skill to prepare. In the 1960s one of the standard ways of preparing clinical trial materials was to fill the

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active 'as-is' into a shell without any excipients. Since that time a much better understanding has been developed about the release of materials from capsules (Jones, 1987b). A similar position occurs with the filling process where there is little published information on the interactions between formulations, filling machines and capsule shells. The study of filling machines is further complicated by the number of dosing systems that are used, again unlike tabletting where all machines use sets of punches and dies. The dosing mechanisms for capsules can be divided up into two groups; the dependent-type machines that use the capsule body directly to measure the dose, which is filled as a loose mass, and the independent-type machines that measure the dose in a separate system, which is filled as a plug of material (Hofer, 1983). There are two main types of dosing mechanisms on independent-type machines, the dosator and the tamping. The former is the most widely used system and this is reflected in the number of publications. The properties of the powders in relation to filling machines must be taken into account in the formulation products. This paper will review the literature that is available to the formulator to help them produce rational formulations that fill well on the industrial scale and will take into account the work done on measuring powder properties that help in understanding the mechanics of the capsule filling process.

The papers published on filling reflect the history of the development of filling machines. Taking the 1960s as a starting point, several review papers were published that described the filling machines in use, both semi- and fully automatic, and discussed their various methods for dosing powders (Anon, 1966; Clement and Marquardt, 1970; Gallet, 1971; Ridgway and Callow, 1973). This was the period when a lot of mechanical design work went into improving the quality and speed of output of filling machines. Most of the companies active in the area were primarily packaging machine manufacturers and used their skills acquired from handling small articles. However, at that time the knowledge of powder behaviour on filling machines was limited and as a result the methods of powder handling were not as good as they are today.

## 2. Powder properties and filling machines

The first papers to investigate the effect of powder properties and machine settings on filling performance were from studies using dependent machines with an auger, a model no. 8 type, because these were the most widespread in use at that time (see Fig. 1). Reier et al. (1968) published a paper on the derivation of a mathematical model that could relate machine settings to the properties of a powder formulation. They used two machine operating variables, capsule size and turntable speed, each at three levels and multiple powder blends with variations in particle size, flow and density and with the addition of a lubricant and a glidant. A model was constructed that related weight variation to machine speed, capsule size and powder specific volume and it was successfully used to predict the fill weights of some experimental formulations. In the following year Ito et al. (1969) carried out a study to relate the flow properties of powders to the uniformity of capsule fill weight. They studied the effect of using a glidant, colloidal silicon dioxide, on the filling of lactose and corn (maize) starch. They demonstrated that when using a screw auger that there was a level of glidant that gave the best fill weight uniformity and below and above this value it was worse. The effect was most noticeable for lactose. Standard powder packing equations were applied to the results and they found a relationship between, auger design, ring velocity and fill weight.

Takagi et al. (1969) were the first group to publish a paper on an independent type automatic machine with a dosator dosing system, a Pedini XXXI. A series of commonly used diluents were

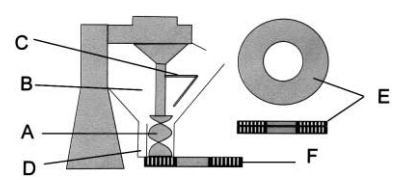


Fig. 1. Schematic diagram of auger filling system (Model No. 8): (A) auger; (B) powder hopper; (C) stirrer arm; (D) pressure relief hole; (E) capsule carrying rings; (F) body ring holder (Jones 2001, reproduced with permission from the author and publishers).

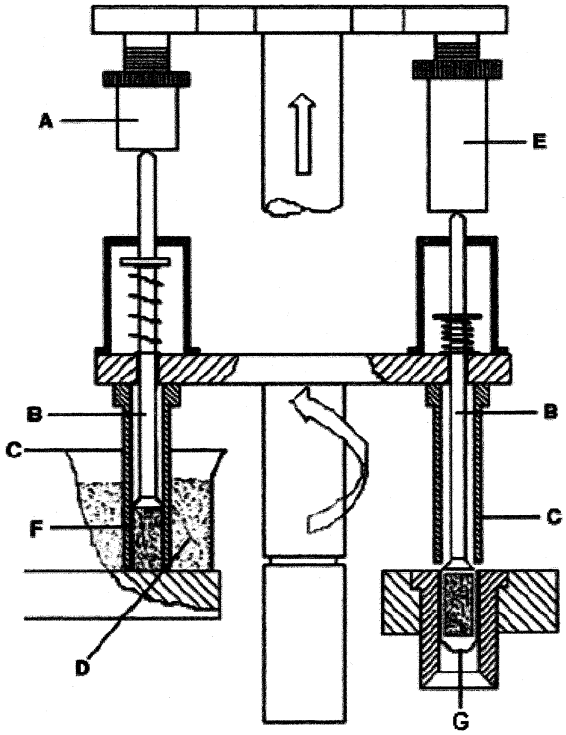


Fig. 2. Diagram of a dosator or dosing tube system (Zanasi RM63): (A) compression force platen; (B) piston; (C) dosing tube; (D) powder hopper; (E) plug ejection platen; (F) powder plug; (G) capsule body in bush (Jones 2001, reproduced with permission from the author and publishers).

used that were characterised by their particle size, absolute density and angle of repose. They expressed the force applied to the powder bed as a compression ratio, $C_r$, which was calculated from the powder bed height minus the height of the bed after compression by the piston divided by the original height expressed as a percentage. They related the uniformity of fill weight to the compression and showed the effect of adding magnesium stearate and silicon dioxide to the diluents. Irwin et al. (1970) investigated the relationship of powder blends with different rates of flow, which were prepared by mixing an active ingredient with different diluents with the addition of a glidant, a lubricant and a wetting agent. They used a Zanasi LZ64 machine, see Fig. 2. There was a significant correlation between flow rate and fill weight uniformity. They related this to the fact that the powder bed in the dosing hopper with the free flowing powders reformed better after the dosator had removed its plug ensuring that when the dosator returned it would enter a well packed bed. Miyake et al. (1974) extended this work by examining the packing behaviour of powders in dosators on a Zanasi Z-25R. Three common diluents were used, microcrystalline cellulose, lactose and corn (maize) starch, which were characterised by measuring their particle size, angle of repose and apparent, tapped and true densities. Capsules were filled at a range of machine settings, different powder bed heights and positions of the piston inside the dosator nozzle. The formation of the plug was shown to be a compaction phenomenon, with the plug density being related to the compression ratio of Takagi et al. (1969). The most uniform fill weights were obtained when the piston setting in the dosator was half the depth of the powder bed. Kurihara and Ichikawa (1978) characterised a range of commonly used diluents by their flow properties as measured by angle of repose, minimum orifice diameter and discharge rate. These were filled into capsules on a tamping machine, an H&K GKF 1000, and on an automatic specialist dependent-type machine with a vibratory filling mechanism, an Osaka OCF-120. On the vibratory machine they found that weight uniformity correlated well with the minimum orifice diameter for the diluents and on the tamping machine with their angle of repose. They expressed the opinion that the angle of repose represents the mobility of particles on the surface of a powder bed and that the minimum orifice diameter represents the mobility in a bed under dynamic conditions. On the tamping machine there was a range of values for the angle of repose, 38–44° that gave the best fill weight uniformity. This was thought to be due to the powder becoming too fluid at lower values being displaced from the holes of the dosing disc during its indexing movement.

## 3. Powder plug formation

Newton and his group of co-workers started an exercise during the latter part of the 1970s to understand more completely the behaviour of powders during plug formation and the mechanics of the process on a dosator machine. They first

considered the theoretical aspects of forming an arch of powder at the open end of the dosator (Jolliffe et al., 1978; Jolliffe and Newton, 1978). The theory of arching conditions in mass flow hoppers was used to identify the principle factor involved, which was shown to be the angle of powder-wall friction. They showed that the ability of a dosator nozzle to pick up a dose of lactose powder was related to bulk density and the volumetric diameter. There was a size above which it was not possible to pick up any material. This work indicated that there was a need to be able to measure the porosity variations in a powder bed on a filling machine. Woodhead et al. (1982) developed a gamma-ray attenuation technique to do this. The prediction of the bulk densities of mixtures of acetylsalicylic acid and lactose from their individual values was found to be possible (Newton and Bader, 1981). This was found to correlate with capsule fill weight for non-compressive dosing systems. The practical implications of this work on the use of dosator systems were studied (Jolliffe and Newton, 1982a). The failure properties for a number of lactose fractions with a range of particle sizes, from 15.6 to 155.2 μm, were measured in a Jenike shear cell. The angle of internal friction was found to be the same for all fractions. The angle of wall friction was determined on ground and turned stainless steel surfaces. Powder retention tests in a dosator nozzle showed that it was not possible for particles larger than 40 μm to form a plug. The values of wall friction were applied to the derived theoretical equation, which enabled the minimum compressive stresses that would need to be applied to retain the plug to be calculated, see Fig. 3. This indicated that the freer flowing the powder the greater the compressive stress required and that the angle of wall friction needed to be lower to permit the stresses to be transmitted through the plug (Jolliffe and Newton, 1983b). A further paper explored the theoretical method to improve the design of a dosator nozzle to obtain better filling performance (Jolliffe and Newton, 1983a). They proposed a dosator nozzle with two areas of different angles of wall friction. The area nearest the outlet should have highest value to assist in arch formation and the area furthest from the outlet to have a low value to enable efficient transfer of stress through the powder plug. In a latter paper, the usefulness of the angle of internal flow (Varthalis and Pilpel, 1976) as an indicator of filling properties was studied (Newton and Bader, 1987). Mixtures were made of different size fractions of acetylsalicylic acid and lactose and their change in volume after tapping was measured. From this the angle of internal flow ($\varphi$) was estimated. For acetylsalicylic acid the value of $\varphi$ was found to decrease with the particle size but not for lactose and $\varphi$ was found to be dependent upon the particle size and ratio of acetylsalicylic acid in the blend. Capsules were filled by tamping and compression, and there was a general relationship that the lower the value of $\varphi$ the higher the fill weights achieved.

Chowhan and his co-workers were studying this problem at the same time from another aspect (Chowhan and Chow, 1980a,b; Chowhan and Yang, 1981). They considered the theoretical implications of the consolidation of loosely packed powders in cylindrical containers. A series of powder mixtures, an active plus diluent and lubricant, were placed in a series of cylinders of in-creasing diameter and a load applied to the surface (Chowhan and Chow, 1980a). The changes in volume were measured and the logarithm of the change in volume plotted against the logarithm of the applied pressure. Examination of these graphs

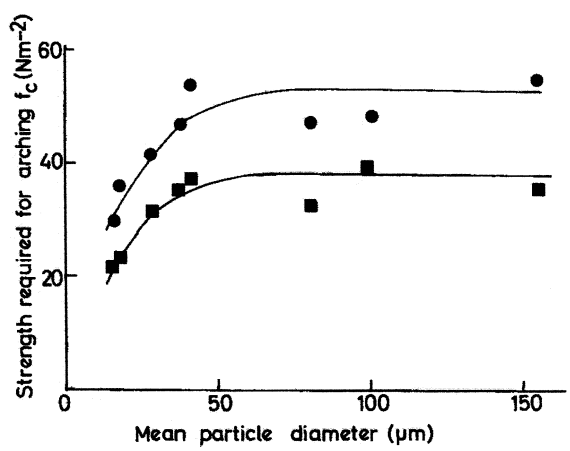


Fig. 3. The strength required in the powder for arching to occur ($f_c$) as a function of mean particle size of lactose: (●) face ground surface; (■) turned surface (Jolliffe and Newton, 1982a, reproduced with permission from the authors and publishers).

suggested that these values were related to powder flow. The powder blends were filled on a dosator machine, a Zanasi, and the uniformity of fill weight had a linear relationship to the powder consolidation ratio. This work was extended by using mixtures of the same active ingredient with lactose, starch and magnesium stearate (Chowhan and Chow, 1980b). The same data and calculations were made. The powder compactibility increased as the bulk density decreased and at lower values of bulk density they were linearly related. The plots of the logarithms of flow rate and weight variation on a filling machine were found to be linearly related to the compactibility factor. In the final paper in the series, the tensile strength of the consolidated beds was measured in an apparatus consisting of split cylinder, one half attached to the main frame and the other moveable, into which the powder was packed (Chowhan and Yang, 1981). A constant speed motor pulled a spring through the powder bed and a strain gauge measured the force to break the bed and a linear displacement transducer (LVDT) measured the powder bed displacement. This showed that there was a direct relationship between tensile strength and consolidation pressure. Empirical equations were derived which indicated that the consolidation ratio is probably a function of the ratio of the initial volume to the net volume, and to the coefficient of Rankine, which is related to the angle of internal friction.

## 4. Instrumented dosator machines

The second main thrust in investigating the pharmaceutics of capsule filling was the development of instrumented filling machines and machine simulators. Augsburger (1982) likened the task to that of instrumenting tablet machines because they both rely on a compression process. He pointed out that it was not possible to make precise measurements in studies associated with dissolution without being able to control precisely the compression cycle on the filling machine. He made the comment also that without such devices it would be more difficult to understand the interplay between the formulation components (Augsburger, 1988). The first machine type to be instrumented was the dosator. The major problem to overcome on the machines in use in the 1970s was the fact that they had an intermittent motion and the dosators oscillated through 180° and therefore if strain gauges were applied to them there would be a problem with routing of the electrical leads.

The first papers published that solved this problem came from workers in Merck Sharp & Dohme who used a Zanasi filling machine, LZ64 (Cole and May, 1972, 1975). They attached a pair of strain gauges to the shank of the piston, and modified the dosator holding mechanism. The compression platen was removed and a mechanism attached to the dosators so that they rotated in their holder to maintain the same direction during the turning cycle of the dosator holder. This enabled simple electrical leads to be used to carry the electrical signal from the strain gauges to the capture device. The usefulness of the machine was demonstrated by filling several commonly used diluents with and without magnesium stearate. The amount of compression to form the plugs was changed by altering the powder bed depth in the dosing hopper. Unlubricated microcrystalline cellulose and a modified corn (maize) starch were run without problems but with lactose powder binding in the dosator caused the machine to stop. The force of ejection for the lactose plugs increased from about 25 N at the beginning of the run up to 130 N. Lactose with magnesium stearate 0.5% ran without problems and the ejection force was less than 5 N. They noted that there was a residual force recorded between the compression and ejection events, which they ascribed to an expansion of the powder plug. They observed a negative force as the piston was being raised in the case where powder binding was occurring due to frictional resistance on the piston. Shortly afterwards, Small and Augsburger (1977) published their solution which involved less modification to the same model of Zanasi machine. They used a mercury contact swivel to pick up the signals from the strain gauges and because of this they were able to use the platen on the machine to apply a compressive force to the piston during plug formation. The compression trace from this machine was different to that obtained by Cole and May (1975). They were able to distinguish the force

generated by simply lowering the dosator into the powder bed from that generated by the contact between the platen and the piston. They likened the first force to pre-compression on a tabletting machine. In a further paper, Mehta and Augsburger (1980) developed the machine by adding LVDTs to enable them to measure the movement of the dosing parts during the compression and ejection cycle. This enabled them to detect that the maximum compressive force was reached slightly before the maximum piston displacement, which was due to movement of the overload spring. This machine was used in further studies on formulations filled as plugs with known physical properties and used to examine the relationship of dissolution rates to plug strength (Mehta and Augsburger, 1980) and to investigate the mechanism of disintegrant action (Mehta and Augsburger, 1981; Botzolakis et al., 1982; Botzolakis and Augsburger, 1984).

A different method of measuring the stress was used by Mony et al. (1977) who used quartz load washers mounted on the ends of the dosator pistons of a Zanasi RV59. Different grades of lactose, cellulose and starch were filled in to size 1 capsules, either 'as-is' or with the addition of magnesium stearate and talc. The addition of a lubricant and or an anti-adhesive reduced both the forces of compression and ejection and the magnitude of the force was sometimes related to fill weight uniformity. An example was given of a development product where the forces of compression and ejection were significantly reduced by a change in formulation. A similar system was used by Maury et al. (1986) on another Zanasi machine, an LZ64. Their quartz load washers were mounted on the compression and ejection platens and not on the dosator pistons. The traces obtained from these devices included several stray peaks, caused each time the platen came into contact with the piston. They were able to measure the force of adhesion of the powder plugs that stuck to the piston during ejection.

The use of instrumented machines in formulation development work is now well established. Hauer et al. (1993a,b) reported on the use of an instrumented Zanasi LZ64 to examine the formulation variables in a model formulation composed of a mixture of microcrystalline cellulose (Avicel® PH101) and anhydrous lactose. The former material was chosen as an example of a visco-elastic material and the latter as an example of a brittle material. They related compressibility to the change of the tapped bulk density which they linearised by using the Kawakita equation (Kawakita and Lüdde, 1970/71). Very free flowing powders were found to be difficult to control because the devices in the dosing hopper could not maintain a uniform level bed because of powder flooding. The better the powder flow the more difficult it was to densify and the fill weight variations were greater. The addition of magnesium stearate to the powders reduced the ejection force, which was related to uniformity of fill weight (Hauer et al. 1993b). The level of lubricant was shown to be critical and increasing concentrations interfered with plug formation and increased weight variation. Magnesium stearate and Precirol™ were shown to be better lubricants than stearic acid. They confirmed the earlier work of Newton and Rowley (1975), who showed that corn (maize) starch did not function as a disintegrant in capsules and that better results were obtained with lactose or microcrystalline cellulose. El-Shaboury et al. (1993) used an instrumented machine in a formulation exercise to study the effect of effervescent mixtures on the release of fenoprofen and ketoprofen from capsule formulations. They used three compression forces to control capsule filling and showed an increase in the effectiveness of disintegrants at the higher compression force. In a recent abstract Guo and Augsburger (2000) reported a study with a new excipient, silicified microcrystalline cellulose, using a fully instrumented dosator machine, a Zanasi LZ64. Standard fillers/diluents were used as comparators and all materials were lubricated with 0.3% Pruv®. Filling was assessed from the coeffi-cient of fill weight uniformity and measurements of plug strength. They showed that microcrystalline-based excipients were more compactible at lower compression forces than lactose and starch 1500®.

## 5. Filling machine simulators

There were concurrent developments in the production of machine simulators to overcome the mechanical problems of using electrical leads on moving parts and to able to work with smaller quantities of material. Jolliffe and Newton, 1980 were the first to report a simulator of an indexing dosator-type machine. Powder samples were packed in aluminium tubes that enabled beds of known density to be prepared. A dosator, which was instrumented with a load cell and LVDTs, was operated pneumatically. This enabled plugs to be formed under controlled conditions. The influence of the nozzle/piston clearance on capsule fill weights was studied and shown to have a significant effect (Woodhead and Newton, 1981). If the clearance was too small, it was difficult to fill the dosator chamber with powder because air was unable to escape from the nozzle and if too large powder was lost behind the piston. During the 1970s rotary dosator machines were developed that further complicated the problem of wiring because of revolving turrets. Jolliffe et al. (1982) overcame this by constructing a simulator using a rotary dosator turret from an mG2 G36 machine held in a fixed position, see Fig. 4. Attached to this was a mechanism that rotated the powder hopper around a single fixed dosator in exactly the same manner as if the roles were reversed. A strain gauge was mounted about half way along the piston barrel and two LVDTs measured the movement of the piston and the dosator nozzle. The output from the instrumentation is shown in Fig. 5. The simulator was used to carry out studies on the relationship between particle size and compression (Jolliffe and Newton, 1982b). Four different particle size fractions of lactose were studied at different compression ratios to find out the conditions under which uniform filling could be obtained, see Fig. 6. Particle size was the most significant factor. Fine particle sizes gave the most uniform fill weights over a wide range of compression ratios and as the particle size increases the range decreases. The filling ability was also linked to powder compaction and fine cohesive powders gave the best results because they are able to undergo greater volume reduction

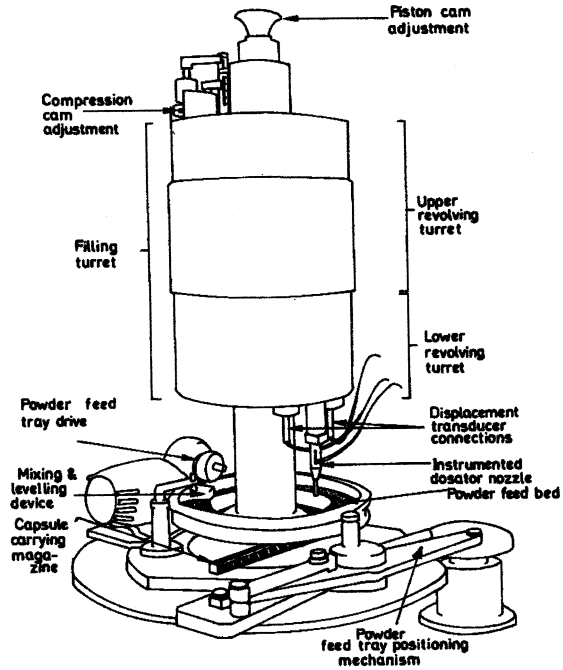


Fig. 4. Diagrammatic representation of an mG2 capsule filling simulator (Jolliffe et al., 1982, reproduced with permission from the authors and publishers).

than coarse free flowing powders. Jolliffe and Newton had in a theoretical study proposed that the nozzle wall texture would have an effect on fill weight uniformity (Jolliffe and Newton, 1983c). This was tested using the simulator (Jolliffe and Newton, 1983a). It is not possible to measure the angle of wall friction inside a dosator and thus this was determined by using flat metal plates in an annular shear cell. Plates and dosators with different surface textures were prepared by using a variety of techniques and their surface roughness, Ra, measured (British Standard, 1972). The nozzles with altered surface textures gave more uniform fill weights and less compression and ejection stresses compared with untreated nozzles. This confirmed that there is an optimum angle for wall friction to obtain good powder retention in the dosator. In a final study, Jolliffe and Newton (1983b) used an mG2 production machine, a model G36, and confirmed their findings from the simulator. There was an optimum surface finish that gave slightly more uniform weights and the

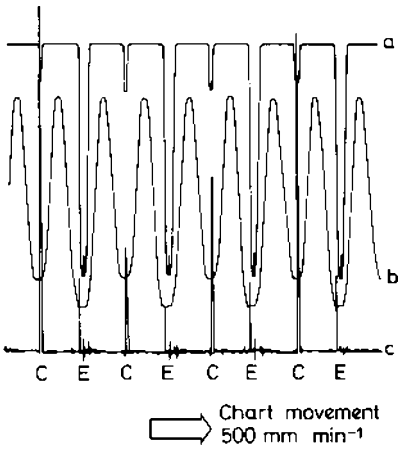


Fig. 5. An example of the u.v. recording obtained from the simulator instrumentation: (a) vertical displacement of the piston relative to the nozzle; (b) vertical displacement of the dosator nozzle; (c) stress exerted by piston. C = compression, E = ejection. Operating conditions: $C_m = 1.5$, compression ratio = 0.22. Preliminary running time 15 min (Jolliffe et al., 1982, reproduced with permission from the authors and publishers).

nozzle was unaffected by powder coating inside. Fine cohesive powders gave uniform fill weights over a wide range of compression settings. For free flowing powders, this range was reduced and a minimum compression force was required to retain them in the nozzle.

Britten and Barnett (1991) constructed a simulator based on the dosator principle and which extended the stresses that could be measured to the radial as well as the axial. A dosator from a Macophar MT13-2 machine was used and the machine was operated pneumatically. LVDTs

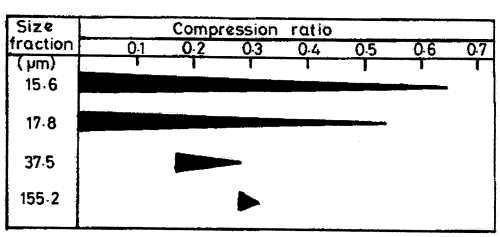


Fig. 6. Range of compression ratios over which fill weight uniformity is satisfactory for the size fractions of lactose studied. ▶ denotes the zone over which satisfactory capsule filling is feasible. Widest part of bar indicates the best conditions (Jolliffe and Newton, 1982b, reproduced with permission from the authors and publishers).

were used to monitor movement of the powder bowl and the dosator piston. Strain gauges were applied to the piston and in addition to the outside surface of the nozzle. The speed of operation of the machine was comparable to medium velocities on a production machine. The effect of changing machine parameters on plug weight and density were studied (Britten et al., 1996). It was found that the speed of plug ejection had no effect on plug properties that were effected more by the speed of compression. Higher speeds led to a less consolidated plug and lower weights. The axial and radial pressures generated by filling pregelatinised starch (Starch 1500™) and a lubricated lactose mixture were compared. The differences were attributable to the different consolidation and elastic properties of the two materials. Starch was more elastic and there was evidence that it also exhibited some plastic deformation. In a further paper, Tattawasart and Armstrong (1997) studied the effect of lubricant concentration, dosator pressure and piston height setting on the properties of lactose plugs using a Box-Behnken 3 factor, 3 level experimental design. The derived factors measured were, plug porosity under compression and after ejection, ejection pressure, uniformity of plug weight and length of plug after ejection. The analysis showed that plug porosity was dependent upon piston pressure and that plug weight and length were dependent upon piston height. The ejection pressure was dependent upon both piston pressure and height. The lubricant concentration played little part in the analysis and it was concluded that 0.5% magnesium stearate provide adequate lubrication for lactose plugs. They thought that the lack of interaction between variables would permit simpler experimental designs to be used in future work.

A tablet compaction simulator has been proposed as a means of simulating plug formation on a tamping machine (Heda et al., 1999). One of the main differences between capsules and tablets is the length of the powder plug compared with the thickness of a tablet. A special holder was made to hold the plug. A single ended saw tooth waveform was used to produce plugs at constant punch speeds, similar to those on an H&K GKF-330 machine. The dies were lubricated manually

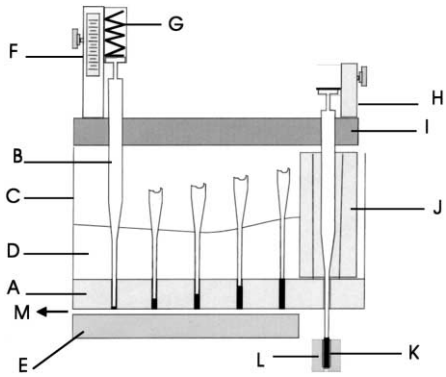


Fig. 7. Schematic diagram of a dosing disc and tamping finger system (Bosch GKF machine): (A) dosing disc; (B) tamping finger; (C) powder hopper; (D) powder bed; (E) support plate; (F) tamp depth adjuster; (G) overload relief spring; (H) ejection adjuster; (I) guide block; (J) transfer block; (K) powder plug; (L) capsule body in bush; (M) suction (Jones 2001, reproduced with permission from the author and publishers).

with magnesium stearate solutions. Three commonly used fillers/diluents were used in the study. The maximum forces at which the plugs were compressed were about 300 N. The compression data obtained was fitted to the standard equations used to describe tablet compression and found to be applicable with the appropriate interpretation. Plugs of different lengths were made and there was a significant change in the coefficient of lubrication as the plugs got longer, which was attributed to poor axial load transmission.

## 6. Instrumented tamping machines

The more complex dosing mechanism to instrument is the tamping system, see Fig. 7. On this machine the plug is formed in more than one operation unlike the single action on a dosator machine. The first reported instrumentation of a machine was by Shah et al. (1983). Strain gauges were attached to the neck of a tamping finger, which could be placed in one of any of the six holders on a Höfliger & Karg GKF 330 machine. Two fingers were instrumented, one was left in the ejection station and other was swapped between the first through to the fifth tamping station. The penetration of the tamping fingers into the disc was changed from station to station in a step-wise fashion. It was observed that the fourth tamping position had the greatest influence on compression force and fill weight whereas the second station had the least. The work was extended by comparing the filling behaviour of three common diluents, anhydrous lactose, dicalcium phosphate and microcrystalline cellulose lubricated with magnesium stearate (Shah et al., 1986). It was reported that all stations except station no. 1 made an equal contribution to plug formation. It was shown that the effective available volume was greater than the nominal volume of the disc holes. This was due to powder above station no. 5 being pushed into the hole during the descent of the tamping finger and this was confirmed by the use of a scraper bar at this position. A device was reported that was able to measure the strength of the powder plugs by determining the maximum resistance to bending in a three-point flexure test. This was used to show the effect of magnesium stearate on plug strength and for microcrystalline cellulose the optimum level was found to be 0.1%. Calculations were presented that showed that the fill weights could be achieved by using only three tamping stations. The machine was then used to examine the effects of machine variables on the dissolution rate of hydrochlorthiazide mixtures (Shah et al., 1987). The effect of increasing the compression force was dependent upon the filler/diluent used and for anhydrous lactose mixtures increased force improved the rate whereas for dicalcium phosphate it decreased it. The inclusion of super disintegrant, 4% croscarmellose, in the formulation nullified the effects of the number and force of tamps. Further development of the machine by the addition of LVDTs was reported (Cropp et al., 1991). The effect of the overload spring on the compaction process was measured. The use of a spring made from a thicker gauge wire resulted in an increase in the compression force. It was possible to measure the penetration of the tamping finger into the disc and estimate the resulting plug length, which enabled calculations to be made on the energy of plug compaction and to determine the pressure–density relationship. The instrumentation on this machine was increased further, each tamping station was instrumented with commercially available instrumented tamping fingers and additional LVDTs

added to measure tamping pin penetration, pin displacement at peak pressure, the movement of the brass guide block with one spare (Davar et al., 1997). A series of formulations were filled at a range of compression forces. Equations and a spreadsheet were proposed to calculate the size of the plugs produced based on powder density. Profiles were constructed of plug length, strength and target density related to compression force.

The company manufacturing Höfliger and Karg machines are now part of the Bosch Gruppe and with continuing design changes to improve machine performance certain aspects of the machine have changed from the original design. The most noticeable feature is that the overload springs no longer allow such high compression forces to be used in order to reduce wear and tear on the machine. Podczeck (2000) has recently reported on the instrumentation of a Bosch GKF 400S machine. The spring set used gave a maximum compression force of 90–100 N. The tamping block, which holds the metal fingers, was removed and replaced with dash pots and a chamber filled with compressed air. A single chamber contained all three fingers at a tamping station and in the upper part of which was fitted a piezoelectric force transducer. The air pressure in the chamber was monitored via a manometer with a feedback pressure valve, which was controlled manually in this work. Microcrystalline cellulose (Avicel® PH103), pregelatinised starch (Starch 1500®) and microfine cellulose (Elcema® G25) were used 'as-is' in a series of filling trials. These were characterised by measuring their size, shape, flow, compressibility and other physical properties. The machine was run with tamping finger insertions that were gradually increased following a set pattern. At each setting samples of filled capsules were collected and weighed. It was shown that the pneumatic head could control fill weight during running but only by small increments and that greater changes would require alteration of the tamping finger settings and changing the powder bed depth. It was shown that the majority of powder enters the holes in the dosing disc during its rotation rather than being pushed in by the tamping fingers. In an extension to this work, Podczeck (2001) further explored the use of this pneumatic device to control capsule fill weight. Two soft ductile powders, microcrystalline cellulose (Avicel® PH103) and pregelatinised starch (Starch 1500®), were used for the machine trials. Capsules were filled at a range of tamping finger insertions and samples collected. The mean compression forces and weights were calculated. This indicated that the best way to control fill weight would be to place the instrumented head at the fourth station where the plug was formed to its final length and density. It was suggested that another non-instrumented pneumatic head be placed at the third tamping station and its internal air chamber pressure regulated according to the signals from the other head. The pins settings would have to be pre-set to achieve control and then if more weight required the capsule to be overfilled this would be detected as an increase in the variability of the tamping force at the fourth station. The development of the plug after each tamping station was determined. This showed that at each succeeding station there was further compression of the existing part plug, which was contrary to the findings of Shah et al. (1983). This was explained by the fact that they had used brittle materials, anhydrous lactose and dicalcium phosphate for their work as opposed to the soft ductile ones used in this study.

## 7. Assessing filling properties

Another need of the capsule formulator is to be able to assess powder-filling properties using only small samples of material. Several workers have tried to translate the findings from instrumented machines and simulators in to practical devices. Lerk et al. (1979) simulated a dosator machine by using a special die and plunger assembly mounted in a drill stand and connected to a load cell. For this experiment plugs were compressed at 120 N. These were filled manually into capsules and used in a dissolution study. A similar set-up was used in a paper by Ludwig and Van Ootegheim (1980) to produce plugs compressed at 950 N for a dissolution study. Jolliffe and Newton used a dosator with a piston to measure the ability of powder to be retained within the nozzle (Jolliffe and Newton, 1982a). A dosator barrel and nozzle was mounted in a rig, which was lowered pneumatically into a

powder bed to form a powder plug. The dosator was then carefully raised and nozzle jolted. The powder retention in the nozzle was assessed by the number of tapping strokes required to dislodge the plug. Veski and Marvola (1991) constructed a rig using parts of the dosator mechanism from an mG2 machine. A dosator nozzle was connected to a plastic plate placed on a digital balance. The piston from the dosator was fixed to a lever system, which enabled it to be raised and lowered into the dosator nozzle. Plugs were compressed in the dosator at 100, 200 and 300 N of force and then hand filled into capsules for use in dissolution tests. Jones (1988, 1998) reported on the use of a powder plug tester originally developed by Höfliger & Karg to determine the correct thickness of dosing disc to be used for a specific powder formulation. This consists of two parts, a die and a rod. The die has a central hole that corresponds to the diameter of the holes in the dosing disc for each size of capsule shell. The top half of the die is dished to form a funnel to aid powder transfer into the hole. The other part is a metal rod, corresponding to the diameter of the tamping finger for the same size of capsule. The die is placed on a platform, which is part of a rig. The finger attached to a lever can be lowered into the die. The force generated on the rod can be measured either by an air pressure gauge or by a load cell. A mechanical finger attached to a dial gauge measures the movement of the platform, which gives the plug length (Jones, 1988). A weighed amount of powder is transferred to the die that is then placed on the platform. The rod is lowered into the die and the length of the plug formed read from the gauge at regular intervals of force, e.g. 10, 20, 50, 100 and 150 N. For most powders, the dosing disc thickness is chosen as the mean of the plug lengths obtained at 20 and 50 N (Jones, 1998). The plug is ejected from the die manually. The higher compression forces are used because if the plug is difficult to eject then the formulation is insufficiently lubricated. Davar et al. (1997) suggested the use of an Instron tester to select the correct dosing disc. Six formulations containing microcrystalline cellulose and anhydrous lactose lubricated with 0.5% magnesium stearate were prepared, which had a wide range of tapped density. The plug height and strength was measured for each of the formulations. The optimum dosing disk thickness for each formulation was predicted and tested by running on an instrumented machine. The target fill weights were successfully achieved.

## 8. Powder properties and machine performance

The 1990s saw another resurgence in interest in relating powder properties to machine performance. In this work, Professor Newton and his co-workers were again to the fore. Tan and Newton (1990a,b,c,d,e,f) in a series of papers extended the work of previous workers in this group. The filling properties of five commonly used excipients were studied: microcrystalline cellulose (Avicel® PH101), heavy precipitated magnesium carbonate, fine lactose (B170), maize (corn) starch and pregelatinised starch (starch 1500®) (Tan and Newton, 1990a). The materials were size graded into fractions of less than 45 μm. Particle shapes were assessed using an image analyser and the particle density and moisture content were determined. The angle of repose ($\alpha$) and poured and tapped density were determined for each powder fraction. From the latter data various flow values were calculated, Carr's compressibility index (CC, Carr, 1965), Hausner's ratio (HR, Hausner, 1967), Kawakita's constants ($a$ and $b$, Kawakita and Lüdde, 1970/71) and the angle of internal flow ($\Theta$) (Varthalis and Pilpel, 1976). In addition Jenike's flow factor (FF, Jenike, 1961) and the angle of effective friction ($\delta$) were measured using an annular shear cell (Carr and Walker, 1967). The powders were filled into capsules using the mG2 simulator reported previously (Jolliffe et al., 1982) only now fitted with a computer to capture and handle the data. The initial piston setting was to the same height as the powder bed to give no compression of the plug. Filling was carried out over range of compression ratios, $C_r$. After each filling cycle the change in weight of the dosator was measured, which corresponds to the powder coating on the inside surface. The lactose samples tended to bind more to the dosator wall than the other materials. Samples of filled capsules were

weighed and means and coefficients of variation calculated. There was a significant correlation between the values of CC, HR, $\alpha$, Kawakita's $a$ and FF and the uniformity of fill weight. The coefficient of variation was related to the powder bed density and the variation in compression stress. There was no correlation between fill weight variation and the angles of internal flow and effective friction. The effect of filling powder using a coated dosator instead of a clean one was investigated. The bulk density per se did not influence the weight uniformity, which appeared to be dependent upon the rate of packing down and the extent of bulk density changes during consolidation. In the next study the same powder samples were used (Tan and Newton, 1990b). The angle of wall friction, ($\psi$), for the dosator nozzle was estimated by extrapolation from values obtained using an annular shear cell with a plate of material with a similar texture and Ra value. The theoretical minimum stress requirements for arching and powder plug retention were predicted for each of the powder samples by using the equations from the paper by Jolliffe et al. (1978). It was shown that higher compressive stress requirements for arching in the dosator required a greater compressive stress from the top of the powder plug. These stresses were too small to be measured on their simulator. However, their results correlated with the filling performance of the powders. The same powder samples were used to investigate the influence of the dosator wall texture and powder properties on filling (Tan and Newton, 1990c). The surface texture, Ra, of two different dosator nozzles was measured by profilimetry and visualised using scanning electron micrographs. Powder-wall friction was measured using an annular shear cell with specially prepared metal plate lids with a defined surface texture. The angles of wall friction, ($\psi$), and powder-wall adhesion were shown to be functions of the powder material, its particle size and the metal wall texture. The angle $\psi$ was reduced for larger particles on the smoother surface. These findings were used to set up experiments on the mG2 machine simulator to measure the effect of using dosator nozzles with different surface textures (Tan and Newton, 1990d). Size fractions of microcrystalline cellulose (Avicel® PH101) and pregelatinised starch (Starch 1500®) were used. Two nozzles were used, one with a 'smooth' surface and one with a 'rough' surface. Filling was carried out with clean and coated nozzles. For both powders there was no significant difference in fill weight uniformity between the nozzle states. For Starch 1500® there were no retention problems even for the coarsest size particles in the smooth wall nozzle, which reduced the angle of wall friction but still provided enough frictional support. Similar result were obtained with Avicel® PH102 except that the coarsest particles were not so well retained. This showed that wall texture exerted only a minor influence on powders with a low binding affinity. Next they turned their attention to measuring the influence of the compression ratio on capsule fill weight using the fractionated samples of the five powders used in the earlier studies (Tan and Newton, 1990e). Capsules were filled on the mG2 simulator with clean and coated nozzles. For calcium carbonate, Starch 1500®, maize starch and lactose powders the initial mean fill weights were direct functions of the particle size. The coarser particles having the higher bed densities and fill weights. The reverse was true for Avicel® PH101 because the finer particles gave the high bed densities. For all powders there was decrease in fill weight with an increase in the compression ratio, which was ascribed to coating of the nozzle wall and loss of powder behind the piston tip, see Fig. 8. The smallest particle size fractions of lactose and maize starch required some compression for them to be retained in the nozzle. For the larger particle size fractions higher values of the compression ratio caused the piston to jam in the nozzle. The amount of material adhering to the nozzle wall increased with both a decrease in particle size and an increase in compression ratio. Lactose showed the greatest tendency to adhere to the nozzle. The final paper in this series compared the densities of the powder plugs obtained to their projected values (Tan and Newton, 1990f). The same fractionated samples of the five powders were used. The predicted plug density was calculated by multiplying the powder bed density by the ratio of the distance of the piston from the nozzle tip to the length of the powder plug determined from the piston displace ment during filling. Capsules were filled at a range of compression ratios

and samples were weighed. The observed densities were calculated from weight and the plug dimensions. The correlation between the values was poor because of weight variation, which was most notable with the finer powders at the higher compression settings.

In an extension to this work Podczeck (1999a,b) used a centrifuge technique to measure adhesion of particles to metal surfaces. The surfaces of a series of small stainless steel plates and tamping fingers for a Bosch GKF 400 were modified by using various metal coatings. The characteristics of the surfaces were described in terms of surface roughness (non-contact laser profilometry) and surface free energy (using set of liquids of known surface tension and acid/base character). Three model powders were used, lactose monohydrate, pregelatinised starch (starch 1500®) and heavy precipitated calcium carbonate.

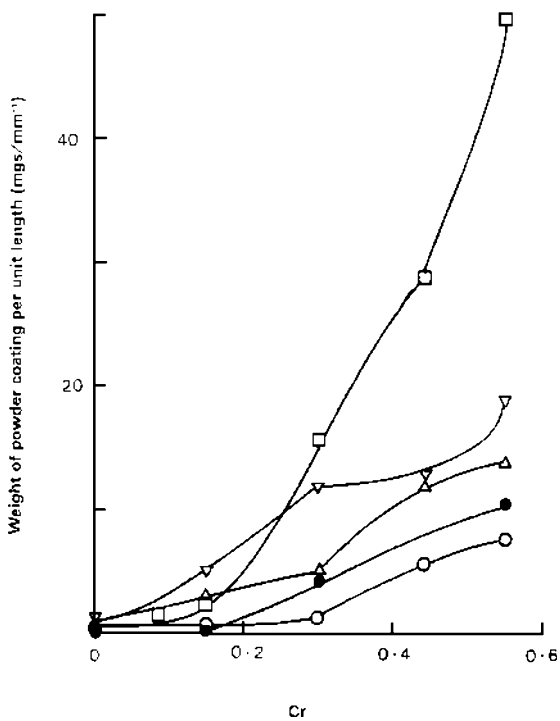


Fig. 8. Weight of powder coating per unit length of nozzle as a function of the compression ratio, $C_r$, for those powder systems showing greater coating than 2 mg/mm. Calcium carbonate C1 (□), lactose L1 (○), L2 (●), maize starch M1 (▽), Starch 1500 S1 (△) (Tan and Newton, 1990e, reproduced with permission from the authors and publishers).

Samples of particles in the range 32–45 μm were obtained by air jet sieving. A sessile drop technique was used to estimate the surface free energy of each of the metal and powder samples. The surfaces of the metal plates were about the same and thus the difference in powder adhesion was not caused by this. There was a significant difference in their surface free energy. Powder adhesion was related to base character of the surfaces. This was true for each powder except that in some cases the calcium carbonate adhesion was influenced more by particle and surface hardness. The powder samples were filled on the machine. Three treated tamping fingers were placed in station no. 5, the point of maximum compression force. The same ranking between powder adhesion on the machine and on the metal discs was obtained. Lactose and calcium carbonate were the most adhesive and the machine could only be run for a short period before powder build up on the tamping finger faces and shafts. The addition of 1% magnesium stearate improved the performance of these two materials to that obtained with unlubricated pregelatinised starch.

Podczeck and Newton (1999) published a seminal work on the filling of powders on a tamp fill machine. A series of commonly used excipients with a wide range of powder properties was studied: microfine cellulose (Elcema G250®), lactose monohydrate (Pharmatose 110M), dicalcium phosphate dihydrate, microcrystalline cellulose (Emcocel 90M®, Unimac MC-200® and Avicel® PH102), pregelatinised starch (starch 1500®), maize (corn) starch and magnesium carbonate. The powders were characterised by their particle size distribution and shape. Their flow and packing properties were measured on a tap volumeter and their angle of internal flow (Varthalis and Pilpel, 1976), Kawakita's constants $a$ and $b$ (Kawakita and Lüdde, 1970/71), Carr's compressibility index (Carr, 1965) and dynamic densification profile were calculated. The surface weighted mean diameter, $d_{vs}$, was used to divide the powders up into three groups: fine powders, $< 50$ μm, medium size powders, 50–100 μm and coarse powders $> 100$ μm. The microfine cellulose was a granulation and formed a separate group. A shape factor (Podczeck, 1997) was used to divide

the particles up into roundish, rod-shaped and angular. The minimum bulk density was used to divide the powders into bulky, $< 0.4$ g/cm$^3$, at one end and the dense powders, $> 0.7$ g/cm$^3$ at the other extreme. The filling machine was a Bosch GKF 400S fitted with 19.6 mm dosing disk. The powders were filled into size 1 capsules and samples of capsules were collected, weighed and the means and coefficients of variation of fill weight calculated. The powder bed height and the cumulative tamping distance varied for each run following a predetermined plan. The cumulative tamping distance is the sum of the distances that the tamping fingers penetrate into the dosing disk. The pattern of insertion was for the first station to be set at 1 mm and all the rest to zero and then increase the first by a further 1 mm and the second set to 1 mm and the rest to zero. This was increased until all the fingers penetrated into the plate except for the fifth station. The range of powders that can be filled on a tamp machine was shown to be wider than on a dosator machine. This was true for very free flowing powders that tend to flood on a dosator machine and have poor weight uniformity (Hauer et al., 1993a,b). On the tamp machine they showed that this could be overcome by increasing the powder bed height (Podczeck and Newton, 1999). The influence of the powder bed height increased with decreasing powder flow. The tamping finger settings had a comparatively small influence on capsule fill weight that decreased with a decrease in powder flow, see Fig. 9. The exception was the granulated microfine cellulose for which the tamping finger setting had a greater influence than the powder bed height because these particles are highly porous and brittle. For moderately flowing powders, the uniformity of fill weight was unaffected by the powder bed height and tamping finger settings. For the powders with poor flow properties, the weight uniformity could be optimised through the machine settings. The relationships between the measured powder properties and filling behaviour were shown to be very complex.

## 9. Excipient filling properties

All the materials used as excipients in capsule powder formulations were not specifically designed for this purpose (Jones, 1995). Most were developed for the food industry or sometimes for use in tabletting. Thus they are used under very different conditions to that which they were developed for. The need to investigate materials in the context of capsule filling was studied by Patel and Podczeck (1996). They examined different lots of microcrystalline cellulose with different particle sizes from a variety of sources. The samples were characterised by measuring their particle size, minimum and maximum bulk density and from the latter test data, the Lüdde–Kawakita constants, $a$ and $b$ (Lüdde and Kawakita, 1966), Carr's compressibility index (Carr, 1965) and Hausner's ratio (Hausner, 1967) were calculated. The angle of wall friction was measured using an annular shear cell (Richards, 1966). Capsules were filled on a dosator machine, a Zanasi AZ5, at their maximum bulk density with no further compression. Samples were weighed and the mean weight and coefficient of uniformity calculated. After each run the dosator nozzle was examined and rated for the amount of powder coating. Fine grades were found to be unsuitable for capsule filling because of their poor flow properties. The medium and coarse grades from most sources were considered to be good capsule filling excipients. The filling performance could be predicted from Lüdde–Kawakita's constant $a$ and from Hausner's ratio. There were different amounts of powder coating on the nozzles, which did not affect the results and was not related to particle size. In a further study Hogan et al. (1996) used a multivariate experiment to examine the effect of powder properties on both the filling and release of actives. Five active ingredients and five diluents with a range solubilities were chosen together with five disintegrants, magnesium stearate as a lubricant and colloidal silicon dioxide as a glidant. Thirty three powder mixtures were made according to a plan to permit statistical analysis of the results. The minimum and maximum bulk densities were determined for each mixture, and Carr's compressibility index and Hausner's ratio calculated. They were filled on a dosator machine, a Zanasi Z5. The machine was adjusted by trial and error to give a fill weight corresponding to the maximum density of the formulation. Non para metric canonical analysis was

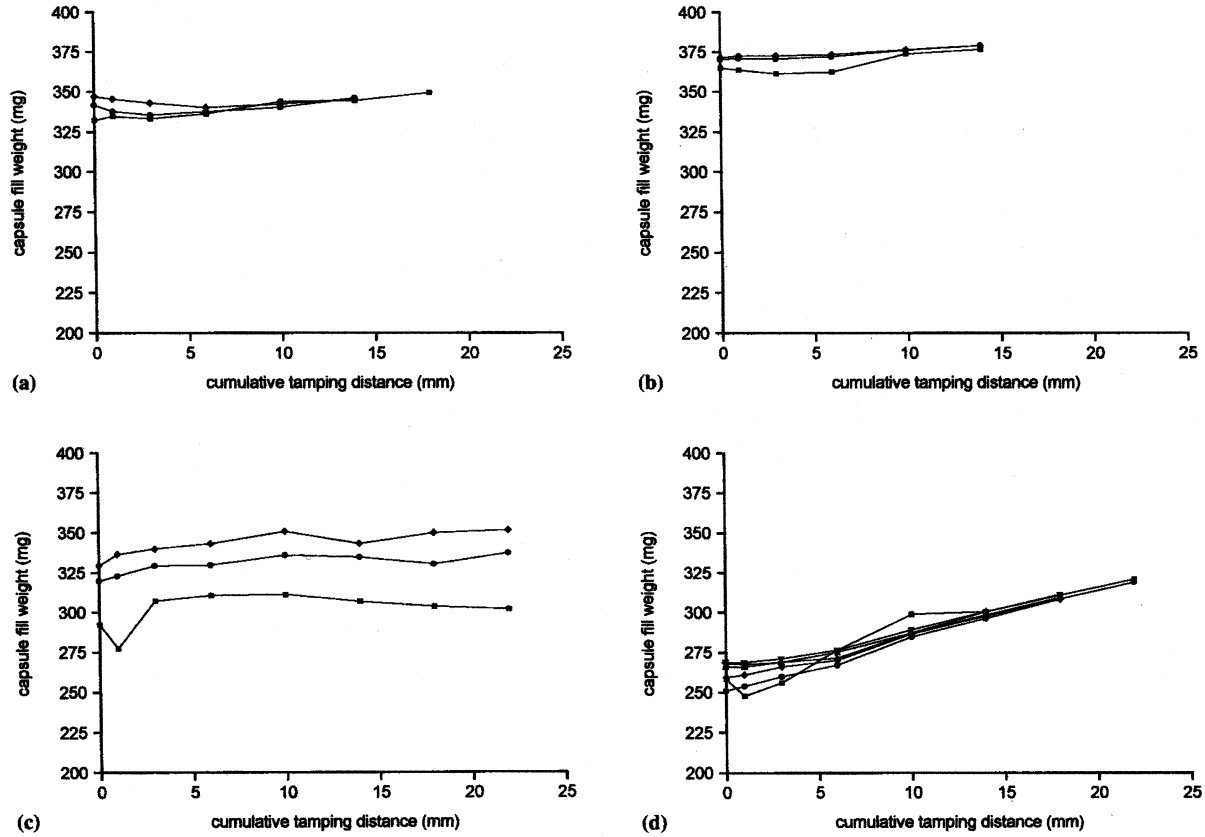


Fig. 9. Capsule fill weight as a function of the powder bed height and the tamping pin setting, expressed as 'cumulative tamping distance'. (a) Lactose powder bed height: ■, 2.5 cm; ●, 5.0 cm; and ◆, 6.5 cm. (b) Pregelatinised starch, powder bed height: ■, 2.5 cm; ●, 4.0 cm; and ◆, 5.5 cm. (c) Corn (maize) starch, powder bed height: ■, 2.5 cm; ●, 4.0 cm; and ◆, 5.5 cm. (d) Microfine cellulose G250, powder bed height: ■, 3.5 cm; ●, 4.0 cm; ◆, 4.5 cm; ▲, 5.0 cm; ▼, 5.5 cm; *, 6.0 cm (Podczeck and Newton, 1999, reproduced with permission from the authors and publishers).

shown to be the best way to identify the relationships between the variables. The filling performance of the powders was shown to be dependent upon the active ingredient particle size, the type of diluent and the concentration of the active ingredient and glidant. Another approach to this problem was suggested by Nikolakakis et al. (1998) who examined the resistance to densification and tensile strength of diluents in relationship to their filling property. Capsule filling was carried out manually on a hand-filling machine, a Tevopharm, by levellingand on a dosator machine, a Zanasi LZ64, to the maximum fill volume. The diluents that they used were lactose monohydrate, maize starch, talc and two brands of microcrystalline cellulose (Emcocel® and Avicel® PH102). The true density of the powders was measured by air pycnometry, and the poured and tapped densities measured in a standard laboratory apparatus and by using the Tevopharm to 'tap' the cylinder. Two cylinders were used—a 5 ml and a 100 ml. From the latter data the Kawakita's equation constants, $a$ and $1/b$ (Kawakita and Lüdde, 1970/71), Carr's compressibility index (CC, Carr, 1965), Hausner's ratio (HR, Hausner, 1967) and the angle of internal flow (Varthalis and Pilpel, 1976) were calculated. A modified shear cell was used to measure the tensile strength of the powders at a range of loads and packing densities. The resistance to densification was calculated from the compression pressure

to achieve packing density corresponding to the tapped value. Samples of filled capsules were collected and weighed and the mean fill weight and coefficient of variation were calculated. For the levelling method the rank order of factors to indicate for filling performance was $a > CC > HR$ and for the dosator method the order was $HR > CC > a$. The value of the indicators was influenced by diameter of the cylinder used to measure the tapped densities. For the levelling method better correlations were obtained by increasing the diameter of the cylinders and the impact velocity and the converse was true for the dosator system. They showed that in predicting capsule filling performance the tapped density predictions were influenced by the test conditions, which was related to the method of filling. In the levelling system the best predictions were obtained from a ratio of the inter-particle attractive forces to gravity whereas in the dosator system both frictional and attractive forces need to be taken into account.

Most of the papers that assess powder properties for capsule filling rely on measurements made in a tap density apparatus. Some workers have assessed flow by measuring the rheological properties of powder systems. Cole (1987) described a simple powder flow test using a Contraves viscometer. It was modified by replacing the cylinder with a propeller and stirrer arm. It was used as a comparative test to distinguish between the filling performance of different lots of active ingredients by comparing them with known 'good' and 'bad' samples. A more advanced powder rheometer has been manufactured that consists of a cylinder in to which a rotating blade can be lowered. The force and torque that a powder exerts on the blade can be measured. The direction and speed of the rotor can be changed and measurements can be made in a slicing, compaction or shear mode. Podczeck (1999a,b) used this device to compare different lots of microcrystalline cellulose, different grades and different manufacturers, and to assess their capsule filling potential. Carr's compressibility index (Carr, 1965) was determined for each lot from tapped density measurements. The rheometer results correlated with the physical properties and Carr's index of the samples. The device was able to measure small differences between samples that could not be detected by tapped density measurements.

## 10. Formulation scale-up

The behaviour of powder formulations when filled on a production scale is different from the results obtained during development trials. Several explanations have been put forward for this. The mixing operation in the manufacture of formulations had been shown to be a critical step in the process especially for the dispersion of the lubricant. The effect of using different types of mixer on the flow properties of powders for filling into capsules was shown by Van Ooteghem et al. (1988). Lactose and magnesium stearate (1%) were blended in a planetary and a tumbling mixer (Turbula) at different loads and for different times. The properties of the powder blends were assessed by measuring the rate and regularity of flow through a vibrating funnel apparatus. It took longer to produce powders with regular flow behaviour in the planetary than the tumbling mixer. The optimum loading for the Turbula mixer was 50% of the volume and for the planetary mixer the bowl needed to be filled so that the paddle arms were covered. During the filling of products on the industrial scale formulations are subjected to further mixing in the storage and dosing hoppers. Johansen et al. (1989) reported on a problem of powder segregation and over mixing during a production test. The formulation consisted of a blend of indomethacin, lactose, silicon dioxide and magnesium stearate. The problem was shown by a variation in active ingredient content and dissolution rate with time during the run. A small-scale test showed that once the magnesium stearate was added, the dissolution rate was reduced with mixing time. The production test lot had only been mixed for short time after the addition of the lubricant. The formulation was registered and so the problem was overcome by making changes to the dosator machine, an mG2 G36/4. The powder feed hopper was redesigned. The internal stirrer arm was removed and an insert fitted to convert it to a mass flow hopper,

thus reducing further mixing of the powder prior to dosing. Magnesium stearate has the effect of making the powder plug weaker (Mehta and Augsburger, 1981), and this can be seen as an increase in fill weight variability (Hauer et al. 1993b). The importance of stressing powders during the development stage was highlighted in a paper by Harding et al. (1989). At the initial stages of devising a formulation for a new chemical entity the amount of material available is often limited. They proposed a method to test the 'robustness' of a formulation that would ensure no problems during production. A tumbling mixer (Turbula) was used to simulate the mixing action in the hopper on a dosator machine. A number of commonly used diluents, lactose, maize starch, starch 1500®, microcrystalline cellulose and dibasic calcium phosphate were mixed with 1% magnesium stearate for varying lengths of time, up to 6 h, and at different mixer speeds. The tapped bulk density and fluid penetration of each blend was measured. The values of these parameters changed with time in a different way for each blend. The tapped bulk density changed most for blends of lactose/microcrystalline cellulose and maize starch/microcrystalline cellulose/dicalcium phosphate. The fluid penetration rate of each blend decreased with time, more for some blends than others. The authors thought this experiment replicated the conditions on a Zanasi LZ64 during running over a period of time. The differences were caused by the increased dispersion of the magnesium stearate and the extent of the effect was more influenced by shearing energy than the extent of mixing. Jones (1998) in a similar study mixed small lots of microcrystalline cellulose (Avicel® PH102) and starch 1500® with 1% of magnesium stearate. The blends were mixed in a rotating cube mixer and samples taken at intervals up to 2 h. Powder plugs from each sample were made using a Höfliger & Karg plug tester using the same compression forces. There was significant change in the lengths of plug formed with time. This could have a practical effect on a production scale filling machine where the force to produce a plug would need to be reduced with time to maintain the same length. This in turn could have an influence on plug porosity that might influence both fill weight uniformity and dissolution rate. In a survey of registered capsule formulations in Italy, it was found that the median levels of magnesium stearate were over 1% (Jones, 1995).

## 11. Filling of granulated powders

Some powders are processed by granulation before filling. The filling of such products on automatic machines is well known. The ability of filling machines to handle such products uniformly has been reported (Pfeifer and Marquardt, 1984). A series of powders and granules were filled on two different types of machines. Also 100 000 filled capsules from each sample were weighed on an automatic weight-sorting device, the Vericap™ 1800. The proportion of filled capsules that was outside $\pm 20\%$ from the mean values were greater for powders, 1.9–9.8/100 000, than for granules, 0.4–1.7/100 000. The reasons as to why capsules were both under-filled and over-filled were discussed in terms of machines, material properties and empty capsule faults. The reason given most often as to why powders are processed into granules for filling is that it is possible to obtain an increase in fill weight. Podczeck and Lee-Amies (1996) studied the effect of granulation on some commonly used diluents/fillers, microcrystalline cellulose, maize (corn) starch, and pregelatinised starch. Granules were prepared using gelatin and PVP as binders in both a high shear and an oscillating granulator. The particle size and the bulk and tapped volumes of both the powders and the granules were measured. The dynamic change in bulk volume and Carr's compressibility index (Carr, 1965) were calculated. Plugs of both powders and granules were made using a Höfliger & Karg powder plug test rig at a range on compression pressures. Granules prepared on the oscillating granulator were generally more bulky than from the powders from which they were made whereas the granules made on the high shear granulator were generally less bulky than the powders. It was found that powders with a tapped volume of less than 1.4 $cm^3/g$ could not be densified by this process. In a

further paper, the filling property of granules on different types of filling machine was studied (Podczeck et al., 1999a,b). Sorbitol instant® granules lubricated with magnesium stearate were filled into size 0 capsules on a dosator machine, Zanasi AZ5, and into size 1 capsules on a tamping machine, Bosch GKF 400S. The sorbitol granules were fractionated into four size ranges and their flow and packing properties measured on an automatic tap volumeter. From these results the angle of internal flow (Varthalis and Pilpel, 1976) and Carr's compressibility index (Carr, 1965) were calculated. Acceptable capsule fill weight uniformity was achieved on both machines. The coarser granules filled better on the tamping machine because it does not require the formation of a firm plug. For both systems there was a correlation between the angle of internal flow and the coefficient of weight uniformity. The plugs formed on the dosator machine were always denser than the maximum bulk density. This was true on the tamping machine for the three larger size fractions. The plugs formed from the finest fractions could not be densified to a value greater than the maximum bulk density. The authors concluded that if a less dense plug was required for dissolution purposes then the system of choice would be the tamping one whereas if a greater extent of compression was required to achieve a high fill weight then the dosator system would be better. Large particles are sometimes used in interactive mixing as carrier particles because of their large rough surfaces. Podczeck and Newton (2000) examined the capsule filling properties of a granulated cellulose powder, Vivacel® A300, on a tamp machine. Samples of granules lubricated with a range of magnesium stearate concentrations were prepared. The properties of each lot granule were determined: particle size, flow and density by using a tap volumeter, flow in a powder rheometer and the angle of wall friction determined in an annular shear cell. The blends were filled on a Bosch GKF 400S fitted with an instrumented pneumatic head. Samples of capsules were collected, weighed and the means and coefficients of weight uniformity calculated. There was a difference between the effect that magnesium stearate had on the bulk powder properties of the granules to that on the filling machine. From shear cell and powder rheometer measurements, the blend with magnesium stearate 0.2% gave the optimum values and when the concentration was increased above this the powder flow decreased and interparticulate friction increased. When capsule were filled with zero compression the fill weight could be predicted from Carr's compressibility index and the maximum bulk density. Increasing magnesium stearate concentrations caused the fill weight and plug density to reach maximum values at 0.4%. When compression was used in filling then the uniformity of fill weight decreased and the plug density remained constant. The optimum concentration of magnesium stearate in terms of machine running was found to be 0.8% from the tamp compression pressure measurements. The reason for the differences in behaviour was discussed and was thought to be due to the way that the magnesium stearate particles coated the granules.

Capsules are a popular dosage form not only for pharmaceuticals but also for nutraceuticals. In this later field there is much interest in the use of herbal medicines. These medicines are required to be filled into capsules with the minimum of formulation and to satisfy the demand they need to be filled on automatic machines. Herbs are the ground dried parts of plants that have many different anatomical features, which govern their properties. Podczeck et al. (1999a,b) studied the filling behaviour of a range of herbs obtained from different parts of plants, roots, leaves, bark and seeds. They characterised the powders by measuring their particle size distribution, angle of repose and their packing properties with a tap volumeter. The tap results were used to calculate Carr's compressibility index (Carr, 1965), the angle of internal flow (Varthalis and Pilpel, 1976) and the compaction constant, $T$ (Mohammadi and Harnby, 1997). The herbs were filled on a dosator machine, a Zanasi AZ5, and a tamp machine, Bosch GKF 400S. The herbs were filled either 'as-is' or with the addition of magnesium stearate 1%. The herb samples that they used had bimodal size distributions. All the samples had poor flow properties as assessed by Carr's compressibility index and the addition of magnesium

stearate did not improve the flow in all cases. All the lubricated samples of herbs could be filled on the tamp machine. Some powders filled better with no compression and others with high compression and this was specific for each herb. On the dosator machine some of the powders could not be filled successfully. A powder plug could not be formed, which is essential for correct dosing using a dosator, otherwise some of the dose is lost from the nozzle in its passage from the hopper to the capsule body. The authors thought that a tamp fill machine could handle a wider range of herbs than a dosator machine.

## 12. Formulation development

A formulator has to satisfy the two main requirements of filling and release when developing a powder blend for a product. Certain excipients have positive effects on one factor and negative effects on the other, for example magnesium stearate. A variety of mathematical tools have been proposed in order to be able to optimise the formulation to satisfy both goals (Fonner et al., 1970; Shek et al., 1980). These techniques were applied by Brugueria et al. (1989) to a pre-formulation exercise for a magnesium and vitamin $B_6$ capsule. The flow properties, angle of repose and tapped density, and particle size distribution of a range of magnesium salts were measured. They used three variables, lubricant and surfactant levels together with the compression force that was derived from the degree of packing of the powder in the filled capsule. A model equation was derived from an Analysis of Variation that enabled them to predict the optimum formulation. The use of computers has enabled more extensive analysis to be made. The so called 'Expert Systems' have been developed that have enabled all the mathematical filling models together with the pragmatic experiences of experts in the subject to be interrogated in an interactive system. The formulations produced by these systems are designed to optimise both filling and release properties. In addition, these systems are a means of storing in-house knowledge and in training personnel. Tadou et al. (1994) proposed a general computer system to aid in the development of the formulation of oral solid dosage forms including hard capsules. Bateman et al. (1996) described the development and validation of a capsule based formulation system. This was based on interviewing experienced formulators and entering this knowledge into decision support software. This contained in addition another database on the properties of excipients. The properties of the active ingredient are fed into the system and trials formulations were suggested. Lai et al. (1996) described the setting up of a system based on three sets of data: details of registered formulations in use in Western Europe and the USA, knowledge acquired from a group of industrial experts and mathematical models derived from statistically designed experiments. The input to the system was specified in an input form of material properties, dosage requirements and filling machines to be used. The output was in the form of several documents: a data summary, recommended qualitative and quantitative formulations, filling and processing conditions, capsule size, specifications for raw materials, an experimental design for testing the formulations, a test to validate the formulation and documentation of the decision process. Heda et al. (1998a) in a preliminary study attempted to quantify powder properties with filling machine performance and dissolution rates of a variety of formulations in order to provide information for an expert system. Formulations with a range of fluidity, lubricity and compactibility were filled on a tamp machine, H&K GKF 400, and a dosator machine, Zanasi LZ64. An optimal degree of fluidity was required for uniform filling. The tamping system required a lower level of lubricity and cohesiveness than the dosator system for uniformity filling. Heda et al. (1998b) in a further study used an artificial neural network as a pattern recognition tool to predict filling performance. Formulations were prepared with different levels of fluidity, lubricity and compactibility and filled on two different types of filling machine. They showed that this method had advantages over response surface methodology.

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