10

The instrumentation of capsule-filling machinery

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Introduction

The hard-shell capsule is a commonly used dosage form, and it has been estimated that approximately 60 billion capsule shells are used annually for pharmaceutical products (Podczeck, 2004). The product essentially consists of a hard shell, usually gelatin based, that is almost always filled with a particulate solid. Among the advantages claimed for the hard-shell capsule compared with tablets are enhanced bioavailability owing to the highly porous nature of the fill, less-demanding requirements for powder flow and the ability to fill formulations into a capsule shell that are not compressible to the extent needed for tablet manufacture. However, Jones (2001) has pointed out the fallacy of the belief that 'powder filled capsules are a very simple product that does not need much skill to prepare'. The requirements of formulations to be filled into hard shells can be quite complex, and understanding the filling process has been greatly facilitated by fitting appropriate instrumentation to the filling equipment.

There are several similarities between instrumentation for a tablet press and that of capsule-filling equipment. Tablet making and capsule shell filling involve compressing a particulate mass and so in both types of instrumentation, the parameters of most interest are force (pressure) and distance, both almost invariably recorded as a function of time. The transducers that have been used to measure these in tablet presses – various types of strain gauge and displacement transducer – have been used in capsule-filling equipment, and an instrumentation system for capsule-filling equipment requires the same components as for an instrumented tablet press, namely a power supply, suitably calibrated transducers, amplification circuitry and devices for recording and manipulating the amplified outputs of the transducers. Many of the approaches that have been used in the instrumentation of tablet presses have also been used to instrument capsule-filling equipment, and the use of simulators has been particularly successful.

However, there are important differences. The forces used in the compression of the contents of hard-shell capsules are much lower – of the order of tens of newtons – whereas in tablet manufacture, forces of tens of kilonewtons are needed. Hence a sensitive measuring system that is capable of distinguishing a signal of this magnitude from background noise is required to study capsule filling. Earlier chapters in this book have stressed the importance of the correct siting of transducers and this is just as important with capsule-filling machinery. Indeed there is a particular problem in this case. To give a stable and meaningful output, the transducer must be attached to a massive and secure component of the equipment. Suitable sites are readily available in a tablet press but are not so available in capsule-filling equipment.

The uses made of instrumented capsule-filling machines parallel those of instrumented tablet presses: the effect of compression force on plug properties such as physical strength, dispersion and dissolution have been studied, together with the lubricant requirements of the formulation.

Capsule-filling equipment

Though there are two types of tablet press – eccentric and rotary – the way in which they operate is essentially the same in that a particulate mass is constrained in a die and compressed between an upper and a lower punch. In contrast, there are several types of capsule-filling equipment, each with its own modus operandi. The fill material is treated in different ways in each case, and hence the challenges of fitting instrumentation also differ.

The two most popular types of capsule-filling equipment are those based on a tamping mechanism into a dosating disk and those that make use of a dosating tube. Both types have been fully described by Jones (2001) and Podzceck (2004), but a brief description of their operating principles is necessary here.

Dosating disk machines

The dosating disk machine, shown diagrammatically in Figure 10.1, in some ways resembles a tablet press. The dosating disk has a number of holes bored through it, all except one being closed off by a base plate. Powder flows into the first hole and is compressed by tamping pin 1. This hole is then moved to position two; further powder flows in and is compressed again, this time by tamping pin 2. This is repeated until the last hole is reached when, after excess powder has been scraped off, the dosating disk positions the plug of powder over a capsule body. The plug is then ejected by a piston, and the upper part of the shell is fitted. The overall arrangement is analogous to the die cavity of a tablet press that is progressively filled and the contents repeatedly consolidated. The several filling positions are usually arranged in a circle.

The tamping pins are spring loaded to avoid the application of an excessive force. The resultant plugs are fragile and of high porosity and hence dispersion and dissolution of the contents after ingestion are facilitated. This type of machine is exemplified by those made by Höfliger & Karg (now part of the Bosch Group) and Harro Höfliger.

Dosating nozzle machines

In dosating nozzle machines, the dosator consists of a tube, open at one end, within which is a moveable piston. The dosator is plunged into a bed of particulate solid contained in a hopper.

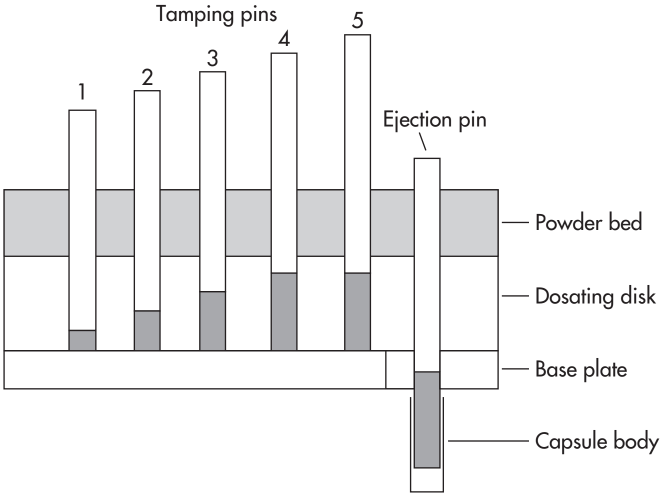

Figure 10.1 A dosating disk capsule-filling machine.

Powder enters the open end of the dosator and is then consolidated by a downward movement of the piston to form a plug. The dosator is then withdrawn from the hopper, taking the plug with it, and is positioned over the body of the capsule shell. The piston again moves downwards, ejects the plug into the capsule body and the upper part of the shell is then fitted. Since the plug must be retained inside the dosator tube while the latter is being moved into position over the capsule body, a free-flowing powder is not a prerequisite. However, the powder cannot be too cohesive since the powder bed must be maintained at a relatively uniform depth to facilitate reproducible filling. A lubricant such as magnesium stearate may be required. Examples of machines using this technique, shown diagrammatically in Figure 10.2, are the mG2, Zanasi and Macofar.

Instrumentation of dosating disk capsule-filling machines

The consolidation process on a dosating disk machine is more complex than that of a tablet press. In the latter, plugs are formed by a single compressive stroke, whereas in the former, the plugs are formed progressively by compression from a series of tamping pins, five in the case of Bosch equipment. The aim is to obtain a plug of powder of specific weight, and the increase in weight achieved at each tamping is dependent on the degree of volume reduction applied by the previous tamping pin. Each pin can be set to a different depth of penetration and so a large number of different combinations can be obtained. If two successive positions are adjusted to the same depth of penetration, then the fill weight gain at the second station depends on the volume of the void left after the preceding tamp.

The group headed by Professor Augsburger at the University of Maryland have been pioneers in instrumentation of capsule-filling equipment. In 1983, Shah *et al.* described the instrumentation of a Höfliger & Karg GKF330 machine, fitting strain gauges to the necks of two tamping pins. One instrumented pin was kept at the ejection station, and the other could be inserted at any of the five tamping positions. Data were stored on a data logger and viewed by oscilloscope. They observed that the fourth tamping position had the greatest influence on fill weight and compression force while the second position had the least.

The instrumentation was then developed so that each of the five tamping pins was equipped with strain gauges so that the whole compressive history of a single plug could be examined (Shah *et al.*, 1986). As the tamping pin penetrates the powder bed, it pushes particulate matter into the

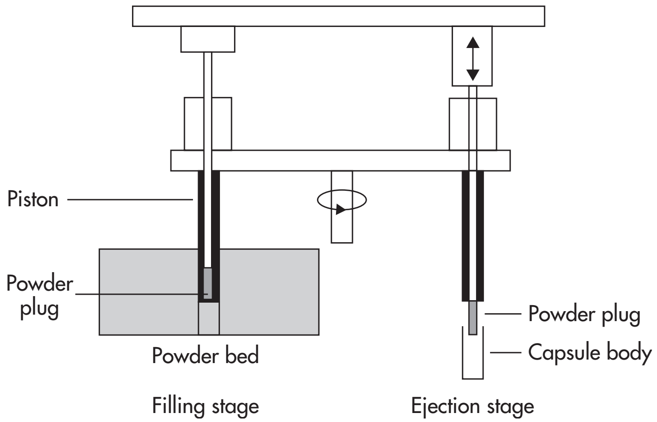

Figure 10.2 A dosating nozzle capsule-filling machine.

hole in the disk. Force rises smoothly to a maximum of approximately 200 N. Then the tamping pin begins to rise, and there is a consequent decrease in force until a plateau is reached. The height of the plateau is dependent on the maximum force, but its duration is constant at approximately 65 ms. The plateau is caused by a brief halt in the upward movement of the tamping pin, caused by the intermittent motion of a Höfliger & Karg machine, which brings on the next capsule shell to be filled. Thus the plateau is a feature introduced by the design of the machine and has nothing to do with the properties of the plug. Contact between the top surface of the plug and the end of the tamping pin is maintained by the partially relaxed relief spring, and hence a force continues to be detected. Once the plateau has been passed, decompression proceeds (Figure 10.3). The ejection force is approximately 50 N.

Shah *et al.* (1986) found that the target weight of the plug could be achieved after three tamps, but not after just two. They also found that effective compression began before the tamping pin enters the dosating disk, powder being pushed ahead of it. Therefore, the higher the tamping force, the heavier the plug. Shah *et al.* also measured the physical strength of the plugs using a three-point flexure test. As compression force was increased, not unexpectedly plug strength also increased. Because of repeated application of force during plug formation, it might be expected that the lowest part of the plug would show a progressive increase in strength as it was compressed for a second or third time. This was found not to be the case, provided that the subsequent compressions were at the same force. An increased force led to higher consolidation and hence greater plug strength.

Using this filling equipment, Shah *et al.* (1986) examined the plug-forming properties of anhydrous lactose, dicalcium phosphate dihydrate and microcrystalline cellulose. They found that, with the last named diluent, there was an optimum concentration of magnesium stearate of 0.1%, in that plugs with this level of lubricant were both stronger and heavier than unlubricated plugs for any combination of force and number of tamps. This they attributed to improved powder flow. Magnesium stearate concentrations in excess of 0.1% caused softening of the plugs, ultimately to a lower strength than those made with the unlubricated powder.

In a later paper (Shah *et al.*, 1987), the effects of multiple tamping on dissolution were studied, using the same instrumented equipment and hydrochlorothiazide as the active ingredient. In general, increasing the number of tamps resulted in slower dissolution. Higher compression forces accelerated drug release when anhydrous lactose was used as the filler, but the reverse was true with dicalcium phosphate dihydrate. They made the important observation that dissolution of the active ingredient was not changed by altering the tamping force or the number of tamps provided that sufficient disintegrating agent was present (4% croscarmellose was used).

The fitting of displacement transducers (LVDTs) to tablet presses in an attempt to quantify the compression process was pioneered by de

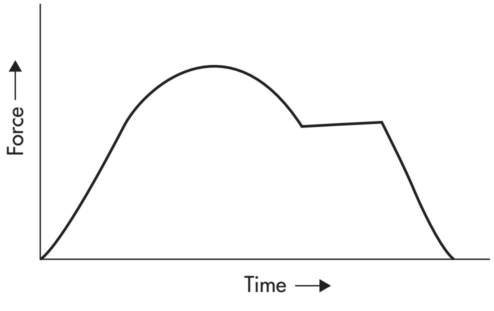

Figure 10.3 Force–time profile from instrumented Höfliger & Karg dosating disk capsule-filling equipment.

Blaey and Polderman at the University of Leiden (e.g. de Blaey and Polderman, 1970). By plotting force as a function of punch, the work expended in the compression event could be calculated since work is dimensionally equal to the area enclosed by the force–displacement curve.

Fitting displacement transducers in addition to strain gauges to capsule-filling equipment so that force and tamping pin position could be monitored simultaneously was reported by Cropp *et al.* in 1991. Two LVDTs were fitted to the instrumented Höfliger & Karg GLF330 equipment already described. The first of these monitored the movement of the brass ring to which the tamping pin holder assembly was anchored. The second was attached to a modified pin that rested on the head of the tamping pin and beneath the overload spring, and thus movement of the overload spring could be detected. This allowed measurement of the precise penetration of the dosating disk by the tamping pin using a combination of the output of the two LVDTs. Transducer outputs were stored and recorded by digital oscilloscope and computer.

Force–time relationships were obtained as described above (Shah et al, 1986), and both ring displacement and pin displacement showed a pause in upward movement shortly after maximum displacement had been achieved. This confirmed that the plateau in the force–time profile was caused by movement of the transport mechanism for the capsule shells. Peak maximum force occurred at the same time as maximum displacement. Some of the data obtained are shown in Table 10.1.

The authors pointed out that the choice of overload spring could affect the properties of the powder plug. An increase in the strength of the spring caused the applied force to rise with consequent changes in plug properties such as strength and dissolution, though a significant change in plug weight was not observed. Stronger springs are often used for reasons of durability but this approach may have negative consequences on product quality.

Plugs made from anhydrous lactose were subjected to a higher peak force during compression than microcrystalline cellulose plugs over a whole range of settings for the tamping pin. Microcrystalline cellulose has a lower bulk density than anhydrous lactose, and so pin displacement is greater for the former.

Cropp *et al.* (1991) combined force and displacement data to construct force–displacement curves for dosating disk capsule-filling equipment. A force was registered before any tamping displacement was detected. This was because the tamping pin detects a resistance to its movement while travelling through the powder prior to penetrating the dosating disk. After peak penetration is reached, displacement falls to a plateau and then the curve returns to the baseline. Calculation of the work of compaction after correction for elastic recovery gave much lower values (a fraction of a joule) than those needed to compress tablets. Though the displacement of the tamping pin of a few millimetres was similar to that of a punch in a tablet press, the applied force was only tens of newtons. The need for precise measuring systems in such circumstances is

Table 10.1 Data from Höfliger & Karg GKF330 capsule-filling equipment fitted with force and displacement transducers (Cropp *et al.*,1991)

Pin penetration setting (mm)	Peak force (N)	Force at plateau (N)	Peak pin displacement (mm)	Pin displacement at plateau (mm)	Plug length at peak (mm)	Contact time (ms)	Time to peak force (ms)
0	8.5	0.0	0.5	0.0	15.8	80	54
5	48.5	11.2	2.6	0.7	13.4	206	80
10	107.0	69.3	5.8	3.9	11.6	250	99
14	158.4	118.7	8.6	6.5	10.4	280	117

apparent. Owing to the greater pin displacement with microcrystalline cellulose, work expended in compressing this substance was about double that used for compressing anhydrous lactose.

Further development of the same machine was carried out by Davar *et al.* (1997), who fitted each station with instrumented tamping pins. LVDTs were added to measure tamping pin penetration, pin displacement at peak pressure and the movement of the brass guide block. Using six formulations containing either lactose or microcrystalline cellulose, the relationships between compressing force and plug properties such as physical strength and density were investigated.

A totally different approach to instrumentation of tamping disk capsule-filling equipment has been described by Podczeck (2000, 2001). In the first of these papers, Podczeck pointed out that advances in instrumentation in tablet manufacture have led to feedback mechanisms that can be used to control tablet weight automatically (Chapter 11), but such developments in capsule filling had yet to be achieved. One possibility of changing fill weight was by altering the tamping distance of one or more of the tamping pins, but Podczeck and Newton (1999) demonstrated that only modest changes of a few milligrams could be achieved in this way. Larger changes in fill weight could be brought about by exchanging the springs inside the tamping fingers. However, changing springs and adjustment of penetrative depth can only be carried out when the equipment is stationary and so neither method lends itself to a feedback mechanism. For weight adjustment to take place when the machine was running, some form of electrical or electronic control was required.

Podczeck used a Bosch GKF 400S machine. In this equipment, there are five tamping stations each fitted with three tamping pins. In the one tamping block that was instrumented, the springs were removed and replaced with dashpots and a chamber filled with compressed air. The latter was in contact with a piezoelectric force transducer. By this arrangement, the point at which the springs were deflected could be altered continuously, and hence the volume available in the hole of the dosating disk was also changed. Force rapidly rose to a maximum, was maintained virtually constant for a time and then fell to a plateau level. It then remained constant for a further period before returning to zero. The change of force between maximum and plateau was attributed to deflection of the spring in the tamping pin, which in this case was simulated by air pressure. The plateau was not detected at tamping forces of less than approximately 60 N.

In practice, it was found that the pneumatic head was able to control fill weight but could only change it in small increments. If larger changes were needed, then the tamping pins had to be adjusted or the powder bed depth had to be altered. A significant finding in this work was that most of the powder that ultimately formed the plug entered the holes of the dosating disk by flow under gravity as the disk rotated. Only a minor portion of the plug came from powder pushed in by the tamping pins. It follows, therefore, that the ultimate plug weight is largely dependent on the flow properties of the powders rather than the force exerted by the tamping pins.

In a further study using this apparatus (Podczeck, 2001), the station bearing the instrumented head was varied so that the contribution of each station to plug formation could be assessed. It was found that the plug achieved its final length and density at station four, and so the best way to control plug weight would be to position the instrumented head at this station. Podczeck suggested that a feedback device could be achieved with the instrumented head at station four and a non-instrumented pneumatic head at station three. The internal pressure of the latter would be controlled by electrical signals from the former.

An important finding in this work was that, for any given plug, each successive tamp caused further densification. It will be recalled that Shah *et al.* (1986) reported that the density of each segment of the plug did not increase despite multiple applications of tamping force. Podczeck explained these contradictory results with reference to the consolidation mechanisms of the solids involved. Shah and colleagues had used lactose and dicalcium phosphate dihydrate in their studies. Both of these undergo consolidation by particle fracture, and since the forces involved in plug formation are well below the yield points of such substances, it is unlikely that these particles would undergo fragmentation. However, Podczeck used microcrystalline cellulose and pregelatinised starch. Both of these are ductile materials and are readily deformed by low forces. Hence progressive consolidation can be anticipated.

The simulation of dosating disk capsule-filling machines

A disadvantage of conventional tablet presses and capsule-filling equipment is that several hundred grams or even kilograms of particulate material may be needed for them to operate efficiently or even at all. In some circumstances, this quantity may not be available, and even if it were, considerable wastage would be unavoidable. It was primarily for this reason that tablet press simulators were introduced in the 1970s. These are hydraulic presses fitted with a die and two punches, the movement of the punches being precisely controlled. The die is usually filled manually and individual tablets are made and examined. A further advantage of tablet press simulators is that by adjusting the rate of movement of the punches to conform to a predetermined pattern, the speed of compression as well as the applied force can be controlled. Hence one versatile simulator can, in theory at least, imitate the mode of operation of any tablet press.

Though the advantages of economy and versatility can apply equally to simulation of capsule-filling equipment, there are other considerations that require a different emphasis. As already discussed, there are fewer suitable points of attachment for transducers to capsule-filling machinery without major modifications of the equipment. Hence a simulator can be designed so that it has the sufficiency of robust fixing points for the transducers that would not be available on the equipment itself. A further feature is that they are usually somewhat cheaper to construct and operate than their tablet counterparts. As mentioned above, tablet press simulators are hydraulic presses, and much of their expense arises from the need to move large volumes of hydraulic fluid rapidly and precisely at high pressures. Since capsule-filling simulators apply much lower forces than tablet presses, their control systems are less demanding and, therefore, cheaper. For example, the simulator described by Britten *et al.* (1995) is operated pneumatically from a commercial compressed air cylinder.

Any simulator must be capable of exerting the forces and reproducing the patterns of component movement of the equipment that it is designed to imitate. Since equations have been derived to predict punch movement of both rotary and eccentric presses (Chapter 9), a 'universal' simulator for tablet presses is at least theoretically possible. Not so with capsule-filling equipment, since each manufacturer has a different mechanism for inducing component movement. Consequently, movement is simulated either by using isolated parts of the equipment (e.g. Jolliffe *et al.*, 1982) or by measuring component movement on an actual machine with a transducer and incorporating this knowledge into the design of the simulator (e.g. Britten *et al.*, 1995). The latter method, of course, depends on the measuring device being properly sited, and lack of such siting points is one of the reasons for using a simulator in the first place.

The earliest attempts to simulate plug formation by tamping were not intended to imitate capsule filling per se, but to produce plugs under controlled conditions for dissolution studies. For example, Lerk *et al.* (1979) used a hand-operated press fitted with a plunger and die to produce plugs at a known constant force. This force was measured by a load cell fitted to the top of the plunger.

A device designed by Höfliger and Karg to select the correct dosating disk for a given formulation was used by Jones (1988, 1998) as a simulator. The device had one tamping pin, the force exerted by which could be measured with a load cell. Movement could also be detected, from which plug length could be calculated. Davar *et al.* (1997) used an Instron testing machine for the same purpose and confirmed their results by using the instrumented capsule-filling apparatus described above.

As stated above, the production of powder plugs by dosating disk machines is somewhat analogous to the compression of tablets. In their paper describing pin displacement measurements on dosating disk machines, Cropp *et al.* (1991) pointed out that if tamping pin displacement was known it should be possible to make a compaction simulator that could mimic the component movement and the low forces involved in plug formation. This development was reported by Heda *et al.* in 1999, using a Mand tablet compaction simulator so that both force and tamping pin movement could be independently controlled.

Since powder plugs for capsule fills have a greater height-to-diameter ratio than tablets, it was necessary to use a die that was much deeper than normal. A diameter of 5.71 mm was chosen, this being the same diameter as the tamping pin used to prepare a plug for a number 1 size capsule. In this, plugs of heights up to 12 mm could be prepared. Anhydrous lactose, microcrystalline cellulose and pregelatinised starch were used, and the die was lubricated by hand with a saturated solution of magnesium stearate in acetone. Forces up to around 400 N were used.

A feature of tablet press simulators is that they can be operated at a range of punch speeds, and Heda *et al.* (1999) studied plug formation at constant punch speeds of 1, 10 and 100 mm s^{-1}, using a saw-tooth waveform. The last speed is slightly greater than that of the tamping pins in a Bosch GKF 330 capsule-filling machine, and considerably higher than speeds encountered in a dosating piston machine such as the Zanasi LZ64.

These authors discovered that force transmission through the length of the plug was very dependent on plug length, as measured by the ratio of force detected at the lower punch to that applied by the upper punch. This they attributed to the large difference in packing densities between the two ends of the plug, which, in turn, leads to poor axial force transmission. Nevertheless, they found that their data could be fitted to the Shaxby–Evans equation (Shaxby and Evans, 1923), which predicts that force applied by the upper punch decays exponentially towards the lower punch at a rate dependent on plug dimensions and a constant that is substance specific. They also found that the Heckel (1961) and Kawakita (Kawakita and Ludde, 1970/71) equations, which have been applied to the study of tablet compression, apply equally well to the low-force environments of plug formation. Punch speed had no effect on the properties of plugs made from lactose, but with microcrystalline cellulose and pregelatinised starch, peak forces were at a maximum at a punch speed of 10 mm s^{-1}, again confirming findings in tablet preparation. As plug length was decreased, the forces that were generated also decreased through diminution of the total resistance to compression.

The authors pointed out that, though the information gained in this study is more obviously applicable to dosating disk machines, consolidation also occurs in dosating tube equipment and the same low-force powder physics could well apply to those machines too.

Instrumentation of dosating nozzle capsule-filling machines

The first published reports of instrumented capsule-filling equipment of the dosating nozzle type were made by Cole and May (1972, 1975), using a Zanasi LZ64 machine. Foil strain gauges (120 Ω) were mounted on flat surfaces ground on to opposing sides of the dosator piston shank, and the wiring from the strain gauges was led out through a hole drilled along the length of the piston to an amplifier and a recording oscillograph. Compression forces were thus measured along the axis of the dosator piston. Since the dosator on this type of machine constantly rotates during operation, Cole and May were faced with a problem similar to that encountered by users of instrumented rotary tablet presses, namely how to prevent twisting and rupture of the electrical cables leading to and from the transducers. They overcame this by fitting a planetary gear to the dosator head, which caused the dosator to make a complete clockwise rotation for each anticlockwise revolution of the dosator support arm.

Using this device, Cole and May were for the first time able to record the compression and ejection forces generated during plug formation and transfer for plugs made from lactose, microcrystalline cellulose and pregelatinised starch.

These powders were used either unlubricated or after the addition of 0.5% magnesium stearate. Cole and May noted that the low magnitude of the forces (typically 20–30 N) made measurement difficult, since a high degree of signal amplification was needed, with attendant problems caused by the signal-to-noise ratio. They reported that up to four regions could be distinguished on the oscillograph trace:

1. A force, tens of newtons in magnitude, represented the compression force generated as the dosator was pushed into the powder bed. It is worth noting that the compressive force in a tablet press would be of the order of tens of kilonewtons.
2. A force of a few newtons, termed the retention force, was detected while the dosator was being raised from the powder bed and positioned over the empty capsule shell. The presence of a retention force proved that the plug remained in contact with the face of the piston during transfer.
3. An ejection force occurred when the plug was pushed out of the dosator into the capsule shell. This force was very dependent on lubrication. For example, with unlubricated lactose, it could progressively rise to several hundred newtons, but the addition of 0.5% magnesium stearate virtually abolished it.
4. A 'drag force' resisted the full retraction of the dosator piston after ejection of the plug was complete, indicating that the dostor rod was in tension. The drag force, the magnitude of which was also dependent on the degree of lubrication, was attributed to particles lodging between the sides of the dosator rod and the inner surface of the nozzle. It was most marked with pregelatinised starch, which had the smallest particle size of the powders studied, and thus would be expected to show greatest penetration beyond the tip of the dosator piston.

Shortly after the full publication of the pioneering work of Cole and May, further work describing the instrumentation of a Zanasi LZ64 machine was published by Small and Augsburger (1977). This was the first part of a major body of work in the field of instrumented capsule-filling machines to come from a group led by Professor Augsburger at the University of Maryland.

One of the aims of Small and Augsburger was to modify the original equipment as little as possible. Four foil strain gauges (120 Ω) were bonded to flattened areas of the middle piston shank to give a complete Wheatstone bridge. They faced the same problem as Cole and May in getting the electrical supply to the transducer and the signals out while the dosator heads was rotating. They solved this by using a mercury contact swivel between the instrumentation and the amplifier. Signals were then fed into an oscilloscope or a recorder.

Small and Augsburger (1977) detected the compression, retention, ejection and drag forces reported by Cole and May. Additionally, they showed that the compression event itself could be divided into two stages. The first stage occurred as the dosator plunged into the powder bed. No force was detected until the dosator had penetrated to a depth equal to the height of the piston in the dosator. Then, a force built up as the dosator continued downwards, the maximum force coinciding with maximum penetration. This they termed pre-compression. Then the main compression event took place, caused by downward movement of the piston inside the dosator, the body of the dosator remaining stationary. The adjustable movement of the piston is a feature of the Zanasi design but was not commented upon by Cole and May in their work.

Retention forces were not observed with lubricated powders, and the authors surmised that this was because the lubricant had allowed the plug to slip inside the dosator, contact between the plug and the piston tip thereby being lost. The negative force after ejection that been reported by Cole and May was also noted by Small and Augsburger, and attributed to the same cause.

Thus from the work of Cole and May (1975) and Small and Augsburger (1977), the sequence of changes in force that occur when a plug is formed in a dosating nozzle machine can be envisaged (Figure 10.4). The instrumentation consisted of force transducers mounted on the piston shank. It must be borne in mind that Figure 10.4 shows all the events that can occur. The magnitude of these events will depend on the formulation, especially the degree of lubrication, and some events might not be detectable at all.

Point A. The dosating nozzle descends into the powder bed. Powder enters the tube and comes into contact with the piston tip, where a force is detected.

Point B. The dosating nozzle continues to descend, and hence an increasing force is detected at the piston tip. There is no *relative* movement between the piston tip and the end of the dosating nozzle. At B, the nozzle descends no further, and a constant force – the pre-compression force – is detected.

Points C–E. The piston now moves down the dosating nozzle, compressing the powder in it. Force increases to a maximum at D, after which it decreases rapidly as the dosator is drawn out of the powder bed. However, force does not drop to zero if the plug remains in contact with the piston tip (point E).

Between points E and F. The dosator assembly is rotated so that the nozzle containing the plug is positioned over the body of an empty capsule shell.

Points F and G. The piston moves downwards, thereby ejecting the plug from the dosator nozzle. The magnitude of the ejection force (point G) is very dependent on the concentration of lubricant in the formulation.

Point H. After the plug has been ejected, there is now no contact between it and the piston tip. Hence force should fall to zero, but in fact it may fall below zero. This means that an extensive stress rather than a compressive stress is detected by the transducers. This has been termed the 'drag force' and is attributed to powder on the inside of the dosator tube preventing full retraction of the piston.

In a subsequent study, Small and Augsburger (1978) examined the effects of powder bed height, piston height, lubricant type, lubricant concentration and compression force on the force needed to eject the plug from the dosator, using three fillers (microcrystalline cellulose, pregelatinised starch and anhydrous lactose). As might be expected, ejection force increased with compression force. However, ejection force was also directly proportional to powder bed height and piston height. As these two factors are increased, the plug length is also increased and hence there is a greater area of contact between the sides of the plug and the inside of the dosator tube. It follows from this work that con-

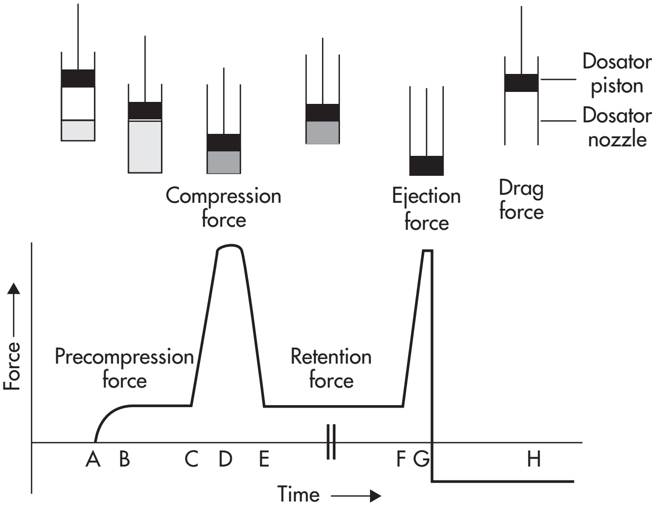

Figure 10.4 Force–time profile from instrumented dosating nozzle capsule-filling equipment. See text for details.

sistency in both powder bed height and piston settings is necessary for reproducible plug properties.

Ejection force minima were achieved with 1% magnesium stearate for anhydrous lactose, 0.5% for microcrystalline cellulose and 0.1% for pregelatinised starch. It is interesting to note that, despite the much lower forces used for compression, the ejection forces were comparable to those encountered in tablet presses and the required levels of lubricant were very similar to those needed for tablet formulations containing these three diluents.

Properties of the powder plug such as physical strength and release characteristics that are dependent on the compression force were investigated by Mehta and Augsburger (1981a), using the instrumented machine described above. They studied the effect of magnesium stearate concentration on plug strength and dissolution of active ingredient (hydrochlorothiazide) at a constant compressing force of 15 kg (approximately 150 N). They measured the physical strength of plugs by a three-point bending test and found that this could be correlated with dissolution rate. With microcrystalline cellulose, the strength of the plugs decreased markedly as the magnesium stearate concentration was increased. A similar reduction has been noted with microcrystalline cellulose tablets lubricated with magnesium stearate (Bolhuis and Hölzer, 1996).

The effect on release characteristics was more complex. At low lubricant concentrations, the reduction in physical strength of the plugs permitted easier water penetration, but as the level of lubricant was raised, increased hydrophobicity inhibited drug release. With lactose, strength was not significantly reduced, and only the retarding effect on dissolution was noted. This too has parallels in tablet formulation.

The instrumented Zanasi LZ64 filling apparatus was modified by Botzolakis *et al.* (1982), who replaced the potentially hazardous mercury swivel contact with slip-rings, an approach that had been used with rotary tablet presses by Ridgway Watt and Rue (1979). They studied the effect of disintegrating agents on capsule fills containing hydrochlorothiazide and paracetamol (acetaminophen) and pointed out that the capsules had been hand-filled in many previous studies on the release of active ingredient from hard-shell capsules, with a resulting high porosity. It was therefore, not surprising that disintegrating agents appeared to have little effect, since there was no structure for them to press against, and hence wettability and water penetration would be the more important factors. Botzolakis *et al.* (1982) were able to keep piston height, powder bed height and compression force constant while they examined the effects of a range of disintegrating agents on capsule fills made from dicalcium phosphate dihydrate lubricated with magnesium stearate. All disintegrating agents improved the release of active ingredient, with cross-linked sodium carboxymethyl cellulose being the most effective and cross-linked polyvinylpyrollidone being the least effective.

In a more elaborate study, Botzolakis and Augsburger (1984) used hydrochlorothiazide mixed with either dicalcium phosphate dihydrate or anhydrous lactose in a three-factor, two-level factorial design, the three factors being disintegrant concentration, lubricant concentration and compression force. The responses were physical strength, disintegration time and dissolution rate. They found that disintegration times did not always have the same rank order as dissolution rates, but that all three factors and their interactions had significant effects, the magnitude of which differed according to the solubility of the filler in water.

Fitting LVDTs to dosating nozzle capsule-filling equipment was first reported by Mehta and Augsburger (1980). They monitored movement of the instrumented piston described by Small and Augsburger (1977), a task complicated by the rotation of the piston during operation. This was overcome by threading a spring-loaded rod on to the core of the LVDT, which, in turn, was kept in contact with a bracket fixed to the dosator housing. Cables for all transducers were connected to the mercury swivel assembly described above.

The force and displacement traces obtained by Mehta and Augsburger (1980) confirmed suggestions made earlier. When the dosator enters the powder bed, pre-compression force develops without piston movement. After the dosator has descended fully, the piston moves downwards, exerting the compression force. Mehta and Augsburger reported that the maximum compression force preceded the point of maximum piston displacement by approximately 40 ms and attributed this to the action of the overload spring. However, a similar non-coincidence of force and displacement maxima has been noted in the force–displacement curve for tablets and this has been linked to viscoelastic behaviour of the powder particles (Ho and Jones, 1988). At the ejection stage, downward movement of the piston results in a rise in the force detected at the piston tip, and this rapidly falls away as the frictional forces holding the plug in the nozzle are overcome. Though the authors signified their intention to calculate work expenditure during plug formation by calculating areas under the force–displacement curves (Mehta and Augsburger, 1981b), few results seem to have been published. Since forces are so low, the work expended will consequently also be low. The accuracy of the results would be highly dependent on accurate measurement of displacement and this would undoubtedly be complicated by the presence of the return spring in the dosator.

Teams of workers other than Augsburger's group have fitted instrumentation to dosating nozzle capsule-filling equipment. For example, Mony *et al.* (1977) fitted piezoelectric load washers to the ends of the pistons of a Zanasi RV59 machine. With this arrangement, a force can only be detected during the compression and ejection events when the piston is being depressed and so pre-compression, retention and residual forces cannot be studied. These workers investigated the effect of magnesium stearate and talc on compression and ejection forces. A similar study was carried out by Maury *et al.* (1986), using load washers mounted not on the pistons but on the compression and ejection platens. Again only compression and ejection can be studied. Rowley *et al.* (1983) attached a load washer to the ejection knob of a Zanasi LZ64, and this arrangement can only be used to study the ejection event.

An instrumented Zanasi LZ64 was used by Hauer *et al.* (1993) to examine the formulation variables of a mixture of microcrystalline cellulose – a viscoelastic material – and anhydrous lactose – a brittle material. They found that the better the powder flow the more variable the fill weight, as the mixture was more difficult to densify. Magnesium stearate proved to be a superior lubricant to stearic acid, but the concentration was shown to be critical in each case.

The simulation of dosating nozzle capsule-filling equipment

An important development in capsule machine instrumentation came with the publication by Jolliffe *et al.* in 1982 of details of the construction of a dosating tube simulator based on an mG2 model G36 machine. The problems of connecting electrical wiring to a rotating component have been discussed above. In conventional mG2 machines, the filling turret rotates and the powder hopper beneath it is stationary. In this simulator, these roles were reversed so that the turret to which the transducers were connected was stationary and the powder hopper rotated around the dosator. There was no relative movement between the feed tray and the nozzle at the moment when the dosator entered the powder bed. Four semiconductor strain gauges were mounted on the dosator piston in a Wheatstone bridge configuration to measure stress, and displacement transducers monitored the vertical movements of the piston and the dosator nozzle. In this way, the movement of the whole dosator and the relative movement of dosator and piston could be followed. A force could be applied in two ways. A pre-compression force was exerted by adjusting the height of the piston in the nozzle, and this was found to be particularly useful to consolidate beds of low bulk density. Compression force was exerted by movement of the piston when the nozzle was in the powder bed and was altered by raising or lowering the compression cam, the precise position of which was recorded by the piston movement transducer.

A considerable body of work carried out on this simulator has been published. Newton and his colleagues were particularly interested in elucidating those factors that contributed to uniformity of plug weight. They found that fine lactose particles gave acceptable uniformity over a wide range of compression settings, whereas the larger the particles, the smaller the range over which satisfactory filling was achieved (Jolliffe and Newton, 1982). Fine cohesive powders gave the best results because they underwent greater volume reduction on compression than coarser particles.

Jolliffe and Newton (1978, 1980) had shown theoretically that a stable arch had to be formed at the outlet of the nozzle in order for a powder to be retained within the dosator nozzle during transfer from powder bed to capsule shell. This was related to the flow properties of the powder, in that cohesive powders would require a lower degree of compression for the arch to form. They also surmised that arch formation would depend on the nature of the surface of the inside of the nozzle, which would, in turn, govern the frictional forces between the nozzle and powder. The surface could be affected either by roughness of the metal or by a coating of powder. They prepared nozzles with a range of surface textures and confirmed that there is an optimum degree of surface roughness needed to ensure powder retention in the nozzle (Jolliffe and Newton, 1983a). These findings were confirmed when they used an mG2 G36 production machine, thereby validating their original approach of using a simulator (Jolliffe and Newton, 1983b). They found that fine cohesive powders gave acceptable fill weight uniformity over a wide range of compression settings, but this range was reduced with more free-flowing powders.

A series of papers by Tan and Newton (1990a–d) extended this work using the same simulator, which was now connected to a computer to capture and manipulate data. Using five common capsule diluents, the relationship between uniformity of fill weight and a range of parameters related to powder flow were investigated. Particle size, morphology, bulk density and compressive force were found to be important. They found that there was no correlation between uniformity of weight and measures of friction such as angle of internal flow and angle of effective friction (Tan and Newton 1990a). After each filling cycle, the dosator was weighed, and hence information was gained on the build-up of powder on the inner surface. It was found that lactose was particularly prone to binding. They found that the texture of the inner wall of the dosator had no significant influence with powders with low binding affinity such as microcrystalline cellulose and pregelatinised starch (Tan and Newton, 1990b).

A later paper (Tan and Newton, 1990c) showed that fill weight variability also depended on powder bed density. The most uniform weights were achieved when no compressing force was applied during the filling process. As compression was increased, fill weight decreased. This was attributed to coating of the wall of the nozzle and loss of powder as particles were forced behind the tip of the piston, which in extreme cases led to the piston jamming in the nozzle. Tan and Newton (1990d) then compared the observed plug densities calculated from plug dimensions with predicted values based on knowledge of powder bed density and piston position. Correlation was poor because of weight variation, which was greatest with fine powders at high compression settings.

Another simulator based on the dosating nozzle principle was constructed by Britten and colleagues (Britton and Barnett, 1991; Britton *et al.*, 1995). In this pneumatically driven apparatus that simulated the Macofar MT13-2 machine, there were no rotating components at all. In a conventional Macofar machine, the dosator nozzles are plunged into the powder bed, a plug is withdrawn and then ejected. In this simulator, the dosator mechanism was stationary and the powder brought to it by upward vertical movement of the powder bowl. A pre-compression force could be exerted, followed by a compression force that was applied by a downward movement of the piston. Once the plug was formed, the dosator nozzle ascended out of the powder bed, and the plug was ejected by means of further downward motion of the piston. No attempt was made to eject the plug into an empty capsule shell.

Compression force was measured by semiconductor strain gauges fitted to the dosator piston and arranged in a Wheatstone bridge conformation. An additional development on this apparatus was to fit strain gauges to the outer surface of the dosating nozzle in order to measure axial stresses brought about by the presence of the plug in the dosator. These strain gauges were positioned 6 mm from the tip of the dosator. Since direct contact between the piston and the LVDT was not feasible, a small arm, fitted to the piston shank and in contact with the LVDT was used to determine the position of the piston within the dosator. Vertical movement of the powder bowl was also determined by LVDT. The output of all transducers was fed into a computer and manipulated with a spreadsheet program.

This simulator could be set to operate in a variety of modes, all at a range of bowl and piston speeds:

- pre-compression simulation, when the powder plug was formed solely by the dosator plunging into the powder bed
- constant displacement simulation, when an additional tamp was applied to each plug by the dosator piston moving a predetermined distance
- constant pressure simulation, when the piston was allowed to travel as far as possible until the resistance of the powder to undergo further consolidation equalled the applied compression pressure.

Two-factor, two-level factorial designs were used to study variation in plug weight and density in relation to compression pressure, pre-compression velocity, compression velocity and ejection velocity using plugs made from pregelatinised starch and lactose (Britten *et al.*, 1996). It was possible to form plugs of starch without lubrication, but addition of 1% magnesium stearate was necessary for lactose. The rate of ejection had no effect on plug weight or density. However, an increase in the pre-compression speed caused a fall in plug weight. At higher speeds, powder was pushed ahead of the nozzle rather than entering it, and there was also less consolidation. A similar observation of reduced consolidation was made during tablet compression, especially with pregelatinised starch (Armstrong and Palfrey, 1989).

When the simulator was run in constant pressure mode, the effect of pre-compression velocity disappeared, and there was no evidence that higher pressures had a significant effect on plug density. Consequently, a relatively high tamping pressure is indicated if reproducible and predictable plug weights are required. However, this may cause an increase in the physical strength of the plugs, which may, in turn, delay drug release (Mehta and Augsburger, 1981a). Hence for any given formulation, an optimum pressure must be sought. Britten *et al.* (1996) noted that no plugs fell out of the dosating tube before active ejection by the piston despite the radial pressures being as low as 0.01 MPa. It followed that, from the point of view of plug retention, high compression pressures are not required, a view also expressed by Tan and Newton (1990d).

A more elaborate study on lactose using the same simulator was carried out by Tattawasart and Armstrong (1997), who studied the effects of lubricant concentration, dosator pressure and dosator piston height on plug properties by means of a three-factor, three-level Box Behnken design followed by stepwise multiple regression. While pressure and piston height had significant effects on plug properties, lubricant concentration did not, and it was concluded that the lowest concentration of magnesium stearate examined (0.5%) was more than adequate.

References

Armstrong NA, Palfrey LP (1989). The effect of machine speed on the consolidation of four directly compressible tablet diluents. *J Pharm Pharmacol* 41: 149–151.

Bolhuis GK, Hölzer AW (1996). Lubricant sensitivity. In Alderborn G, Nystrom C (eds), *Pharmaceutical Powder Compaction Technology*. New York: Marcel Dekker, pp 517–560.

Botzolakis JE, Augsburger LL (1984). The role of disintegrants in hard-gelatin capsules. *J Pharm Pharmacol* 36: 77–84.

Botzolakis JE, Small LE, Augsburger LL (1982). Effect of disintegrants on drug dissolution from capsules filled on a dosator-type automatic capsule filling machine. *Int J Pharm* 12: 341–349.

Britten JR, Barnett MI (1991). Development and validation of a capsule filling machine simulator. *Int J Pharm* 71: R5–R8.

Britten JR, Barnett MI, Armstrong NA (1995). Construction of an intermittent-motion capsule filling machine simulator. *Pharm Res* 12: 196–200.

Britten JR, Barnett MI, Armstrong NA (1996). Studies on powder plug formation using a simulated capsule filling machine. *J Pharm Pharmacol* 48: 249–254.

Cole GC, May G (1972). Instrumentation of a hard shell encapsulation machine. *J Pharm Pharmacol* 24: 122P.

Cole GC, May G (1975). The instrumentation of a Zanasi LZ/64 capsule filling machine. *J Pharm Pharmacol* 27: 353–358.

Cropp JW, Augsburger LL, Marshall K (1991). Simultaneous monitoring of tamping force and pin displacement (F–D) on an Höfliger-Karg capsule filling machine. *Int. J. Pharm* 71: 127–136.

Davar N, Shah R, Pope DG, Augsburger LL (1997). The selection of a dosing disk on a Höfliger-Karg capsule-filling machine. *Pharm Technol* 21: 32–48.

de Blaey CJ, Polderman J (1970). Compression of pharmaceuticals. 1: The quantitative interpretation of force–displacement curves. *Pharm Weekblad* 105: 241–250.

Hauer B, Remmele T, Züger O, Sucker H (1993). Rational development and optimisation of capsule formulations with an instrumented dosator capsule filling machine. 1: Instrumentation and influence of the filling material and the machine parameters. *Pharm Ind* 55: 509–515.

Heckel RW (1961). Density-pressure relationships in powder compression. *Trans Metal Soc AIME* 221: 671–675.

Heda PK, Muller FX, Augsburger LL (1999). Capsule filling machine simulation. 1: Low force powder compaction physics relevant to plug formation. *Pharm Dev Tech* 4: 209–219.

Ho AYK, Jones TM (1988). Punch travel beyond peak force during tablet compression. *J Pharm Pharmacol* 40: 75P.

Jolliffe IG, Newton JM (1978). Powder retention within a capsule dosator nozzle. *J Pharm Pharmacol* 30: 41P.

Jolliffe IG, Newton JM (1980). The effect of powder coating on capsule filling with a dosator nozzle. *Acta Pharm Technol* 26: 324–326.

Jolliffe IG, Newton JM (1982). An investigation of the relationship between particle size and compression during capsule filling in an mG2 simulator. *J Pharm Pharmacol* 34: 415–419.

Jolliffe IG, Newton JM (1983a). The effect of dosator wall texture on capsule filling with the mG2 simulator. *J Pharm Pharmacol* 35: 7–11.

Jolliffe IG, Newton JM (1983b). Capsule filling studies using an mG2 production machine. *J Pharm Pharmacol* 35: 74–78.

Jolliffe IG, Newton JM, Cooper D (1982). The design and use of an instrumented mG2 capsule filling machine simulator. *J Pharm Pharmacol* 34: 230–235.

Jones BE (1988). Powder formulations for capsule filling. *Mfg Chem* 59: 28–30, 33.

Jones BE (1998). New thoughts on capsule filling. *STP Pharmacol* 3: 777–783.

Jones BE (2001). The filling of powders into two-piece hard capsules. *Int J Pharm* 227: 5–26.

Kawakita K, Ludde KH (1970/71). Some considerations on powder compression equations. *Powder Technol* 4: 61–68.

Lerk CF, Lagas M, Lie-A-Huen L *et al.* (1979). *In vitro* and *in vivo* availability of hydrophilised phenytoin from capsules. *J Pharm Sci* 68: 634–638.

Maury M, Heraud P, Etienne A *et al.* (1986). Measurement of compression during the filling of capsules. In *Proceedings of the 4th International Conference on Pharmaceutical Technology*, Paris, pp 384–388.

Mehta AM, Augsburger LL (1980). Simultaneous measurement of force and displacement in an automatic capsule filling machine. *Int J Pharm* 4: 347–351.

Mehta AM, Augsburger LL (1981a). A preliminary study of the effect of slug hardness on drug dissolution from hard gelatin capsules filled on an automatic capsule-filling machine. *Int J Pharm* 7: 327–334.

Mehta AM, Augsburger LL (1981b). Quantitative evaluation of force–displacement curves in an automatic capsule-filling operation. In *30th National Meeting of the American Association of Pharmaceutical Scientists*, St Louis.

Mony C, Sambeat C, Cousins C (1977). The measurement of compression during the formulation and filling of capsules. In *Proceedings of the 1st International Conference on Pharmaceutical Technology*, Paris, pp 98–108.

Podczeck F (2000). The development of an instrumented tamp-filling capsule machine. 1: Instrumentation of a Bosch GKF 400S machine and feasibility study. *Eur J Pharm Sci* 10: 267–274.

Podczeck F (2001). The development of an instrumented tamp-filling capsule machine. 2: Investigations of plug development and tamping pressure at different filling stations. *Eur J Pharm Sci* 12: 515–521.

Podczeck F (2004). Dry filling of hard capsules. In Podczeck F, Jones BE (eds), *Pharmaceutical Capsules* 2nd edn. London: Pharmaceutical Press, 119–138.

Podczeck F, Newton JM (1999). Powder filling into hard gelatine capsules on a tamp filling machine. *Int J Pharm* 185: 237–254.

Ridgway Watt P, Rue PJ (1979). The design and construction of a fully instrumented tablet machine. In *Proceedings of the International Conference of Pharmacy Technology and Product Manufacture*, Copenhagen.

Rowley D, Hendry R, Ward MD, Timmins P (1983). The instrumentation of an automatic capsule filling machine for formulation design studies. In *Proceedings of the 3rd International Conference on Pharmaceutical Technology*, Paris, pp 287–291.

Shah KB, Augsburger LL, Small LE, Polli GP (1983). Instrumentation of a dosing disk automatic capsule filling machine. *Pharm Tech* 7: 42–54.

Shah KB, Augsburger LL, Marshall K (1986). An investigation of some factors influencing plug formation and fill weight in a disk-type automatic capsule filling machine. *J Pharm Sci* 75: 291–296.

Shah KB, Augsburger LL, Marshall K (1987). Multiple tamping effects on drug dissolution from capsules filled on a dosing disk type automatic capsule filling machine. *J Pharm Sci* 76: 639–645.

Shaxby JH, Evans JC (1923). The variation of pressure with depth in columns of powders. *Trans Faraday Soc* 19: 60–72.

Small LE, Augsburger LL (1977). Instrumentation of an automatic capsule-filling machine. *J Pharm Sci* 66: 504–509.

Small LE, Augsburger LL (1978). Aspects of the lubrication requirements for an automatic capsule filling machine. *Drug Dev Ind Pharm* 4: 345–372.

Tan SB, Newton JM (1990a). Powder flowability as an indicator of capsule filling performance. *Int J Pharm* 61: 145–155.

Tan SB, Newton JM (1990b). Capsule filling performance of powders with dosator nozzles of different wall texture. *Int J Pharm* 66: 207–211.

Tan SB, Newton JM (1990c). Influence of compression setting ratio on capsule fill weight and weight variability. *Int J Pharm* 66: 273–282.

Tan SB, Newton JM (1990d). Observed and expected powder plug densities obtained by a capsule dosator nozzle system. *Int J Pharm* 66: 283–288.

Tattawasart A, Armstrong NA (1997). The formation of lactose plugs for hard shell capsule fills. *Pharm Dev Technol* 2: 335–343.

Further reading

Augsburger LL (1988). Instrumented capsule filling machines. Methodology and application to product development. *STP Pharma* 4: 116–122.

Hardy IJ, Fitzpatrick S, Booth SW (2003). Rational design of powder formulations for tamp filling processes. *J Pharm Pharmacol* 55: 1593–1599.