JPP Journal of Pharmacy and Pharmacology

JPP 2003, 55: 1593–1599

Received September 24, 2003
Accepted October 14, 2003
DOI 10.1211/0022357022610
ISSN 0022-3573

Review Article

Rational design of powder formulations for tamp filling processes

Ian J. Hardy, Shaun Fitzpatrick and Steven W. Booth

Abstract

Tamp filling processes are widely used for the filling of powders into hard gelatin capsules, whereby capsule fill weight is controlled by the formation of a loosely packed plug of material that is dispensed into the capsule shell. To rationally design formulations for tamp filling processes the formulator must have an intimate knowledge of the synergy between machine parameters and powder properties and the corresponding effect on product quality. However, despite ubiquitous use throughout the pharmaceutical industry, relatively little is understood about the design of powders for tamp filling processes. The aim of the following review is to summarize the published literature to date from a formulation design perspective and to provide a framework for future scientific research.

Introduction

Filling processes for hard gelatin capsules are termed either dependent, whereby the dose is measured using the capsule body, or independent, in which the dose is measured by forming a plug of material that is dispensed into the capsule shell (Jones 2001). Independent filling machinery may be further categorised as either dosator or tamp filling equipment.

Tamp filling machinery typically consists of a powder bowl situated over a dosing disk and a series of tamping stations, the number of which normally depends on the manufacturer (Bosch with 5 stations, Höfliger & Karg with 3 stations and Shinogi Qualicaps with 2 stations). Powder flows into the holes of the dosing disk during indexing between tamping stations and a powder plug is formed by successively compressing the powder at each tamping station. The penetration depth of the tamping pin into the dosing disk controls the compression pressure, which is typically in the range of 50–150 N (Mok 2000; Podczeck 2000). At the sixth station, the plug is ejected into the body, the cap replaced and the capsule closed to form the final dosage form.

In contrast to the wealth of publications related to tablet technology, the literature on capsule technology is relatively sparse, with those pertaining to tamp filling processes at a premium. The following report summarizes the literature available with the aim of providing a logical framework for designing formulations for tamp filling processes.

Formulation Design for Tamp Filling Processes

To systematically design formulations for tamp filling processes, the formulator must have an intimate knowledge of the synergy between machine parameters and powder properties and the corresponding effect on product quality.

The formulator is mainly restricted to using materials common to tablet formulation, but should not assume that a single formulation will be suitable for both capsule and tablet applications (Podczeck & Newton 1999). Tablet processes operate at high compression forces (10–15 kN) and the compaction event occurs over a short timescale (in the order milliseconds), therefore the viscoelastic properties of the formulation are of paramount importance. In contrast, tamp processes operate at relatively low forces (50–150 N) – in this case the low pressure densification and packing behaviour

Pharmaceutical Research & Development, Merck Sharp & Dohme Ltd., Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU, UK

Ian J. Hardy, Shaun Fitzpatrick, Steven W. Booth

Correspondence: I. J. Hardy, Pharmaceutical Research & Development, Merck, Sharp & Dohme Ltd, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU, UK.
E-mail: ian_hardy@merck.com

of the material is more important. In addition, the plug is formed by a series of tamps and consequently over an extended period; the time-dependent viscoelastic deformation of the material is less important.

The following sections will in turn deal with the key process parameters involved during tamp filling, the powder properties of importance and small-scale experiments that may be used during formulation design.

Process parameters of importance

Knowledge of the impact of various process parameters on filling performance and the quality of the final product has been obtained, in part, through attempts at instrumenting tamp filling processes (Shah et al 1983; Cropp et al 1991; Mok 2000; Podczeck 2000, 2001). To control a tamp filling process, the operator has control over a number of variables including the dosing disk thickness, powder bed height, encapsulator speed, powder bed depth, tamping force and the number of tamping stations.

Dosing disk

Selection of an appropriate dosing disk for a particular formulation is a key step in obtaining reproducible weight and dose uniformity. A relationship exists between the required fill weight, the volume of the dosing disk cavity and the tamping force. If the volume of the dosing disk cavity is too low for a given fill weight, it will be difficult to acquire the necessary force to compact the powder during tamping. If the volume is too high the applied compression may be insufficient to produce a coherent plug for efficient ejection and transfer to the capsule body (Davar et al 1997).

The thickness of the dosing disk will also influence the maximum achievable dose and the minimum capsule size that may be used for a given formulation, with defined density and compression characteristics. For a range of lactose-microcrystalline cellulose mixtures, Davar et al (1997) used two approaches to predict the dosing disk thickness required for uniform fill weights, the first being based on the compactibility of the formulation and second on the required fill weight and the tapped density of the formulation.

Powder bed depth

Powder bed depth can affect two characteristics of the final product: the maximum achievable fill weight and fill weight uniformity. Powder bed depth has a minimal effect on the maximum achievable fill weight when each tamping pin is fully immersed in the powder bed throughout the tamping cycle. The powder bed depth assumes more importance for poorly flowing powders. It has been suggested that for free-flowing powders, a uniform bed height is readily achieved and the tamping pins at each station remain fully immersed in the powder. In contrast, for poor-flowing cohesive powders, the bed depth often exhibits a substantial slant with powder building up against the ejection block increasing the bed depth over the 4th and 5th tamping stations, while the tamping pins at the earlier stations are positioned above the powder bed. Consequently, less powder is filled at the earlier tamping stations reducing the maximum achievable fill weight (Podczeck & Newton 1999).

The effect of powder bed depth on fill weight uniformity is more complex; for free flowing and cohesive powders, fill weight uniformity improves at higher bed depths. It has been suggested that the improved fill weight is a result of reduced flooding of the dosing disk, caused by the increased mass and density of the powder bed above each tamping station. For moderately flowing powders, which describes the majority of formulations used in tamp filling, the powder bed height has little effect on fill weight uniformity (Podczeck & Newton 1999). It has been suggested that an increase in powder bed height can result in greater ejection forces (Small & Augsburger 1978).

Encapsulation speed

At slow encapsulation speeds, fill weights and compression forces are typically higher, as more powder is able to flow into the dosing disk cavity before indexing between tamping stations (Mok 2000). One would suspect that slow encapsulation speeds would allow a higher maximum achievable fill weight and improved fill weight uniformity for poor flowing powders.

Tamping pressure

Increasing the tamping pressure can reduce fill weight variation, resulting drop from powder loss during the ejection of loose plugs. However, high compression pressures can limit the length of time a machine can be run without damaging the dosing disk drive. Most modern machines limit the maximum achievable tamping force to < 90 N to circumvent this problem (Podczeck & Newton 1999).

A high tamping pressure can also have an effect on the dissolution of active drug from a capsule formulation. Shah et al (1987) studied the effect of tamping pressure on the release of hydrochlorothiazide from lactose and dicalcium phosphate plugs using an instrumented tamp filling machine. At higher tamping pressures, hydrochlorothiazide release was increased from lactose plugs but reduced from dicalcium phosphate plugs. It was suggested that this may have resulted from increased fracture of the lower-strength lactose particles revealing fresh surfaces which were not coated with hydrophobic magnesium stearate. The addition of croscarmellose sodium decreased the magnitude of these effects.

Powder properties of importance

Formulations for hard gelatin capsules are as diverse as the products they support. For immediate-release powder fill capsules the formulation will typically contain a filler (lactose, microcrystalline cellulose, starch, calcium phosphate), a disintegrant (croscarmellose sodium, starch, sodium starch glycolate), a lubricant (magnesium stearate, talc) and a glidant (colloidal silica, magnesium stearate, talc). Powders are commonly presented as a dry powder blend, a granulation or, in some cases, as controlled-release pellets. It has been suggested that the range of powders that can be filled on a tamp filling machine, exceed those capable of being filled on a dosator machine (Podczeck & Newton 1999; Podczeck et al

1999). However, complex multivariate non-linear interactions typically determine the processing behaviour and properties of the powder, representing a significant challenge in formulation design.

The critical quality parameter when designing an encapsulated product is to ensure that the correct quantity of stable active ingredient is reproducibly dosed into, and released from, the capsule shell within the desired time frame. The effect of formulation design on product stability will not be addressed here. Therefore, three factors are of interest when designing powders for tamp filling processes: the maximum achievable fill weight; fill weight uniformity; and drug release behaviour.

Maximum achievable fill weight

The maximum achievable fill weight of a powder is related to the capsule size, the packing properties, density and compressibility of the powder. Each size of capsule has a finite volume, therefore the mass of powder in the capsule can be increased by increasing powder density through compression or by granulation, or by engineering particles to form a closer packing structure. Bulky powders such as microcrystalline cellulose are unsuitable if the dose of an active ingredient is high and there is a restriction on capsule size (Newton & Bader 1981; Podczeck & Sharma 1996; Podczeck & Newton 1999).

Podczeck & Lee-Amies (1996) studied the effect of compression and granulation on the bulk density of materials filled into capsules and concluded that compression was more successful at increasing density than granulation. In part, this is the result of coarse granular material resisting further densification on compression due to steric hindrance (Podczeck & Lee-Amies 1996).

Increasing the maximum achievable fill weight through compression is reliant on a highly compressible powder, which correspondingly is dependent on a number of powder properties. Firstly, the particle size of the material is important, with a powder column of finer particles typically being more compressible (Podczeck & Sharma 1996). Varthalis & Pilpel (1976) defined the angle of internal flow, which is discussed in greater detail below. The angle of internal flow describes the ratio of cohesion to frictional forces within a powder bed undergoing compression. Evidence has been provided to suggest that plug density, and consequently capsule fill weight, increases for powder with a lower angle of internal flow (Newton & Bader 1987; Podczeck & Newton 1999; Podczeck et al 1999), possibly resulting from reduced inter-particle friction enhancing densification on compression.

The viscoelastic properties of the material can also influence the maximum achievable fill weight, which is reduced for more elastic materials (Podczeck & Newton 1999). As highlighted in the Introduction, a capsule plug is formed by tamping at five separate tamping stations. Once compressed, an elastic material will attempt to return to its original density when the tamping force is removed between tamping stations, reducing the available volume for further powder filling. In contrast, a plastic material will not only retain its compressed density, but will undergo further permanent compression at each successive tamping station, leaving a greater free volume for increasing the fill weight. Podczeck (2001) studied the effect of increasing the number of tamping stations from 1 to 5 on capsule fill weight for a plastic material (microcrystalline cellulose) and an elastic material (pre-gelatinised starch). Pre-gelatinised starch showed no increase in fill weight with an increasing number of active tamping stations. The constant fill weight results from the dosing disk becoming full at the first tamping station and further compression does not increase the available dosing volume within the dosing disk bore. For microcrystalline cellulose, increasing the number of active tamping stations increased the fill weight as a result of previous powder becoming increasingly densified at further tamping stations (Podczeck 2001).

Particle size and shape can also influence the compression and packing properties of a powder column, offering the opportunity to design powders to achieve an optimum packing density and fill weight (Podczeck & Lee-Amies 1996; Podczeck & Sharma 1996). An optimum packing density can be achieved by using a mixture of fine and coarse particles. In a perfectly bi-modal system, the fine particles are believed to occupy the voids between coarse particle (Podczeck & Sharma 1996). Primary particle shape exerts its influence over the packing structure of capsule plugs, as the forces that operate in tamp filling are less than those required to modify particle size and shape. Podczeck & Sharma (1996) studied the effect of microcrystalline cellulose particle size and the shape of a second component on the densification of a binary mixture. For fine grades of microcrystalline cellulose, the addition of spherical (Elcema) and needle-shaped (acetylsalicylic acid) particles results in a steady decrease in volume reduction ability. For medium and coarse grades, volume reduction increases and then decreases on addition of needle-shaped and spherical particles (Podczeck & Sharma 1996). The addition of angular particles (lactose) improved the densification behaviour, irrespective of microcrystalline cellulose particle size.

Fill weight uniformity

Three processes are believed to operate during tamp filling, which can influence the weight uniformity of the filled capsules: flow of powder into the dosing disk bore during indexing; reproducible densification of the powder bed during tamping; and efficient and reproducible ejection of the plug into the capsule body.

Powder flow To produce capsules with a consistent fill weight it is necessary to ensure the powder has appropriate flow properties. For poor-flowing powders, minimal and inconsistent quantities of powder will enter the dosing disk during indexing and, consequently, fill weight reproducibility will be poor (e.g. dicalcium phosphate (Hogan et al 1996)). However, fill weight uniformity can also be poor for free-flowing powders, as a result of powder flooding, leading to inconsistent filling of the dosing disk. In addition, powders with excellent flow properties may be difficult to compress, leading to weak plugs that

break on ejection (Heda et al 2002). Therefore, an optimum range of powder flow exists, above and below which fill weight uniformity will be poor. Heda et al (2002) suggested a Carr's index in the range 20–30%, whereas Podczeck & Newton (1999) suggested a range of 15–30%.

The effect of even minor formulation changes on the flow properties of a material should be considered. For example, the level of glidant in a formulation often exhibits an optimal value (Hogan et al 1996), which is influenced by the surface area of the components in the formulation. The weight uniformity above and below the optimum value often deteriorates. Similarly, increasing the drug loading in the formulation is commonly detrimental to its flow properties and consequently weight uniformity (Hogan et al 1996). Changes in the particle size and shape of the formulation constituents can also influence the quantities of lubricant required to produce desirable weight uniformity characteristics. In capsule formulations, magnesium stearate can act as both a lubricant (reduce angle of internal friction) and a glidant (increase flow). Podczeck & Miah (1996) provided evidence to suggest that magnesium stearate requirements are less for needle-shaped or round particles compared with angular, cubic or rod-shaped particles, which have a larger aspect ratio and consequently higher inter-particle friction. Flow properties were primarily dependent on particle shape, whereas the optimal magnesium stearate concentration was dependent on particle size.

Reproducible densification To improve capsule weight uniformity, the powder should densify within the dosing disk on tamping, to a constant and reproducible amount. This will ensure a consistent void volume for further powder filling between tamping stations. Mohammadi & Harnby (1997) used the compaction constant to define the rate of powder bed densification, which will be discussed in greater detail below. Podczeck et al (1999) suggested that rapid densification, as defined by the compaction constant, was favourable for capsule formulations due to quick settlement of the bed structure into an equilibrium state. A correlation has also been established between the angle of internal flow and capsule weight uniformity, with fill weight uniformity reaching an optimum level for powders with an angle of internal flow of 20–30° (Podczeck et al 1999). Above and below this level, the powder will not densify consistently as a result of excessive friction or cohesion.

Plug ejection Once a reproducible plug has been formed, the plug must be strong enough to retain mass when ejected into the capsule body. A balance must be maintained between plug strength and ejection force, to maintain the integrity of the plug. Ejection forces have been found to increase for fine powders and at higher tamping forces (Small & Augsburger 1978; Heda et al 2002). Fine powders will have a greater surface area and thus an increase in the number of contact points with the wall of the dosing disk, resulting in higher ejection forces. The level of lubricant in the formulation has a profound effect on the ejection force–plug strength relationship. Low levels of lubricant can increase the strength of the plug as a result of increased densification during tamping. However, above an optimum level related to the surface area of the formulation, the plug strength will decrease from a reduction in inter-particle bonding (Shah et al 1986). To complicate matters further the ejection force will also decrease at higher lubricant levels, which is beneficial to plug integrity. Therefore, the effect of lubricant level on plug strength, ejection force and capsule fill weight uniformity must be studied carefully.

Properties of pellets influencing fill weight uniformity
Capsules are occasionally filled with film-coated controlled-release pellets, which offer additional technical challenges during tamp filling. Chopra et al (2002) studied the influence of pellet shape, roughness and coating on capsule fill weight uniformity. For uncoated pellets, pellet shape was found to have the greatest effect on fill weight uniformity with a limited contribution from surface roughness. Pellets with an aspect ratio of greater than 1.2 were found to yield inconsistent fill weights. High levels of surface roughness increased the inconsistency in fill weight data as a result of raised inter-pellet friction and a greater propensity to electrostatic charging. Coated pellets were characterized by poor and inconsistent fill weights; it was postulated this was a result of increased surface roughness leading to friction and charging by magnifying surface asperities through successive layers of coating. These effects were removed by lubricating the pellets with 1% talc when pellet shape was the only limiting factor and the surface roughness had little effect due to lubricant filling the asperities.

Drug release kinetics
The primary factor influencing drug release rates from a capsule are the particle size and aqueous solubility of the drug (Hogan et al 1996). However, interactions between the various components within a formulation can either accelerate or inhibit the release of drug from the capsule. For example, competition for available water between a highly soluble drug and a disintegrant with a high swelling capacity may exist, which can result in retarded drug dissolution (Hogan et al 1996). The type of filler can also have an impact on this relationship.

It has been suggested that the interaction between the type of filler and the magnesium stearate level may also influence drug dissolution rates. For insoluble fillers, higher lubricant levels reduced drug release rates, whereas for soluble fillers, the effect is more unpredictable, where an optimum level exists above and below which drug release is retarded (Stewart et al 1979; Mehta & Augsburger 1981). Mehta & Augsburger (1981) provided evidence to suggest that drug dissolution from microcrystalline cellulose plugs was related to the effect of magnesium stearate on plug strength. At low magnesium stearate levels, the capsule plug strength is highest and therefore drug release rate was slower; as the magnesium stearate level increases the plug strength decreases, enhancing plug disintegration and drug release. Above an optimum mag-

nesium stearate level, the effect of plug hydrophobicity suppresses the influence of decreasing plug strength and drug release is retarded.

Small-scale predictive experiments during formulation design

The formulator is often faced with the task of producing a robust formulation that may be manufactured over a range of process scales, using minimal drug substance and time (Hardy & Cook 2003). A number of techniques exist, which enable the formulator to characterize formulations on a small-scale, offering a degree of prediction for larger-scale behaviour.

Compressibility

The compressibility of a formulation is a key determinant of processability, both in terms of material flow and plug formation. Traditionally, for tamp filling processes this has been assessed using the Höfliger & Karg powder plug simulator, which measures the length of a plug compressed at a defined tamp setting (Jones 1988; Podczeck & Lee-Amies 1996). However, this provides little information on the kinetics of densification and comparison with other formulations may prove difficult.

Carr's index measurements are a reliable method for measuring flow and compression properties. This technique involves calculating the percentage change in density on tapping, with poorly compressible free-flowing powders exhibiting the lowest percentage change in density. A disadvantage of Carr's index measurements is the quantity of material required (in excess of 50 g, depending on density). Podczeck & Lee-Amies (1996) compared Carr's index measurements with the Kawakita constant. The Kawakita equation measures the low-pressure compression behaviour of materials to derive two constants, which relate to the ability of a material to densify and the shear strength of the particles (Adams & McKeown 1996; Podczeck & Newton 1999). Podczeck & Lee-Amies (1996) demonstrated that the Kawakita equation exhibited a clear linear correlation with Carr's index for a series of powders, but suggested that Kawakita represented no advantage over Carr's index measurements. However, with the aid of a compaction simulator, Kawakita measurements may be determined under pressure rather than purely tapping the sample and are therefore more representative of a tamping process. In addition, Kawakita measurements can be determined on quantities < 1 g, which may be critical in early phase formulation development.

A knowledge of the forces resisting and promoting compression in tamp filling is also of interest to the formulation scientist. Varthalis & Pilpel (1976) defined the angle of internal flow, which can be measured by manipulating the data from tapped density experiments. The angle of internal flow is the ratio between inter-particle frictional and cohesional forces, with powders susceptible to increased inter-particle friction exhibiting a higher angle of internal flow. Newton & Bader (1987) stated that measuring the angle of internal flow was a worthwhile predictor of capsule filling performance, with lower angle of internal flows giving a higher maximum achievable fill weight. Subsequent studies have shown that an optimum range for angle of internal flow exists (20–30°) to give improved capsule fill weight uniformity (Podczeck & Newton 1999).

As suggested above, the rate of powder densification is also important to ensure that a reproducible plug and powder bed is achieved. Two descriptors have been used for the rate of densification – the compaction constant (Mohammadi & Harnby 1997) and the kinetic constant (Hauer et al 1993). Podczeck & Newton (1999) suggested that the compaction constant was the most suitable technique as a result of its easier mathematical treatment and a wider scale providing greater distinction between samples. Compaction constants can be determined through a simple mathematical manipulation of tapped density data and offers a reliable means of measuring the dynamic packing properties of materials.

Bulk density

The capsule fill weight can be predicted based on the available volume within the capsule body and the theoretical tapped density of the powder. Newton & Bader (1981) demonstrated that the theoretical tapped density for a powder mixture could be calculated from the bulk density of the individual components. This methodology loses some predictive accuracy during tamping operations as it does not account for differences in tamping pressure, which may operate above or below the tapped density of the formulation.

Capsule plug strength

The strength of a capsule plug is also important for the maintenance of capsule fill weight uniformity (see above). Little attention has been given in the published literature to the measurement of capsule plug compactiblity (ability to attain strength on compression). It is possible to measure the flexure strength of capsule plugs using a three-point beam-bending apparatus, to give a rank order of compactibility for investigational formulations (internal unpublished data).

It is clear from the previous sections that the quality of the final dosage form is related to a host of interacting factors, where a modification of one property will undoubtedly lead to a change in another property. Table 1 provides a trouble-shooting guide based on published literature, which may be used in the design of formulations, along with the counter effects that these formulation changes may bring.

Summary

Tamp filling processes, despite being ubiquitous throughout the industry, are still relatively poorly understood. To design an effective formulation, the formulation scientist must have an understanding of the effect of both machine

Table 1 Formulation trouble-shooting guide (tamp filling).

Problem	Potential corrective actions	Potential counter-effects
High ejection forces	Increase particle size	Reduce compressibility/increase flow
	Increase lubricant level	Increase compressibility/reduce flow/slower dissolution rate
	Reduce tamping force	Weak plugs leading to less uniform weights
Slow drug dissolution	Reduce tamping force	Weak plugs leading to less uniform weights
	Reduce lubricant level	Higher ejection forces. Depending on level, weaker or stronger plugs
Variable fill weights	Increase powder flow	Excessive flow may increase variation/reduce compressibility
	Increase plug strength	Slower drug release rate
	Modify angle of internal flow	Above or below optimum, variation may increase
Poor pellet filling performance	Decrease coat thickness	Modify release kinetics
	Lubricate to reduce surface roughness	Modify release kinetics
Low achievable fill weight/large capsule size	Enhance formulation compressibility	Reduced flow may lead to weight variation
	Increase bulk density (granulate)	Reduce compressiblity
	Increase packing efficiency	Modified flow properties

parameters and powder properties on the quality of the final product during tamp filling. As a result of the complex multivariate nature of powder formulations, one must consider the impact of a change in formulation or process parameters on a whole host of product characteristics. For example, if one wants to increase the proportion of fine material in a formulation to improve compressibility, the impact on flow properties and fill weight uniformity must be considered. If one wants to increase the tamping force to increase the fill weight in a capsule, the effect on drug dissolution must be considered. To design increasingly effective formulations, a greater understanding of these interactions is required, in combination with the development of more reliable predictive techniques. The limited quantity of publications in this field represents a fertile environment for future scientific investigation.

References

Adams, M. J., McKeown, R. (1996) Micromechanical analyses of the pressure-volume relationships for powders under confined uniaxial compression. *Powder Technol*. **88**: 155–163

Chopra, R., Podczeck, F., Newton, J. M., Alderborn, G. (2002) The influence of pellet shape and film coating on the filling of pellets into hard shell capsules. *Eur. J. Pharm. Biopharm*. **53**: 327–333

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

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

Hauer, B., Remmele, T., Zuger, O., Sucker, H. (1993) Gezieltes Endtwikeln und Optimieren von Kapsulformulierungen mit einer instrumentierten Dosierröhrchen-Kapselabfüllmaschine. 1. Mitt: Instrumentierung und Einfluß der Füllgut und Maschinenparameter. *Pharm. Ind*. **55**: 509–515

Hardy, I. J., Cook, W. G. (2003) Predictive and correlative techniques for the design, optimisation and manufacture of solid dosage forms. *J. Pharm. Pharmacol*. **55**: 3–18

Heda, P. K., Muteba, K. Augsburger, L. L. (2002) Comparison of the formulation requirements of dosator and dosing disk automatic capsule filling machines. *AAPS Pharm. Sci*. **4**: article 17

Hogan, J., Shue, P. I., Podczeck. F., Newton, J. M. (1996) Investigations into the relationship between drug properties, filling, and the release of drugs from hard gelatin capsules using multivariate statistical analysis. *Pharm. Res*. **13**: 944–949

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

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

Mehta, A. M., Augsburger, L. L. (1981) 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

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

Mok, W. (2000) *Effect of process parameters on capsule plug formation using instrumented encapsulator tamping blocks*. Internal memorandum, Merck Research Laboratories, December 12th 2000

Newton, J. M., Bader, F. (1981) The prediction of the bulk densities of powder mixtures and its relationship to the filling of hard gelatin capsules. *J. Pharm. Pharmacol*. **33**: 621–626

Newton, J. M., Bader, F. (1987) The angle of internal flow as an indicator of filling and drug release properties of capsule formulations. *J. Pharm. Pharmacol*. **39**: 164–168

Podczeck, F. (2000) The development of an instrumented tamp filling machine. I. 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 machine. II. Investigations of plug development and tamping pressure at different filling stations. *Eur. J. Pharm Sci.* **12**: 515–521

Podczeck, F., Lee-Amies, G. (1996) The bulk volume changes of powders by granulation and compression with respect to capsule filling. *Int. J. Pharm.* **142**: 97–192

Podczeck, F., Miah, Y. (1996) The influence of particle size and shape on the angle of internal friction and the flow factor of unlubricated and lubricated powders. *Int. J. Pharm.* **144**: 187–194

Podczeck, F., Sharma, M. (1996) The influence of particle size and shape of components of binary powder mixtures on the maximum volume reduction due to packing. *Int. J. Pharm.* **137**: 41–47

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

Podczeck, F., Blackwell, S., Gold, M., Newton, J. M. (1999) The filling of granules into hard gelatin capsules. *Int. J. Pharm.* **188**: 59–69

Shah, K., Augsburger, L. L., Small, L. E., G. P. (1983) Instrumentation of a dosing disk automatic capsule filling machine. *Pharm. Technol.* **7**: 42–54

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

Shah, K. B., Augsburger, L. L., 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

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

Stewart, A. G., Grant, D. J. W., Newton, J. M. (1979) The release of a model low dose drug (riboflavin) from hard gelatin capsule formulations. *J. Pharm. Pharmacol.* **31**: 1–6

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