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Modeling powder encapsulation in dosator-based machines: I. Theory

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ABSTRACT

Automatic encapsulation machines have two dosing principles: dosing disc and dosator. Dosator-based machines compress the powder to plugs that are transferred into capsules. The encapsulation process in dosator-based capsule machines was modeled in this work. A model was proposed to predict the weight and length of produced plugs. According to the model, the plug weight is a function of piston dimensions, powder-bed height, bulk powder density and precompression densification inside dosator while plug length is a function of piston height, set piston displacement, spring stiffness and powder compressibility. Powder densification within the dosator can be achieved by precompression, compression or both. Precompression densification depends on the powder to piston height ratio while compression densification depends on piston displacement against powder. This article provides the theoretical basis of the encapsulation model, including applications and limitations. The model will be applied to experimental data separately.

1. Introduction

Capsules are one of the most common dosage forms in the pharmaceutical industry. Compared to tablets, capsules have a simpler formulation and manufacturing process, which usually translates into a faster development time. There are several methods of encapsulation which can be generally classified to manual, semiautomatic and automatic (Augsburger, 2002; Podczeck, 2004). Automatic machines have two dosing principles: dosing disc and dosator with the later being the most common amongst automatic methods (Jones, 2001).

Much work was done to study encapsulation including: machine instrumentation (Mehta and Augsburger, 1980; Podczeck, 2000, 2001; Shah et al., 1983; Small and Augsburger, 1977), compression analysis (Britten et al., 1996; Chowhan and Chow, 1980; Guo et al., 2002b; Heda et al., 1999), formulation requirements (Guo and Augsburger, 2003; Heda et al., 2002; Irwin et al., 1970; Podczeck and Newton, 2000; Small and Augsburger, 1978), powder densification predictions (Miyake et al., 1974; Newton and Bader, 1981) and recently; the combined use of artificial neural networks (ANN) with model expert systems (MES) for formulation development of BCS class II drugs (Guo et al., 2002a; Wilson et al., 2005a,b).

More knowledge is needed to further reduce empiricism in unit operation, formulation and process development. For example; it is often necessary to estimate the encapsulation fill weight in different capsule sizes, which requires further encapsulation experiments. Scarcity of the active pharmaceutical ingredient (API), especially at early development stages, limits such experiments. This work provides the solution through modeling the encapsulation process to give these estimates in a material sparing approach in accordance to quality by design (QbD) principles.

This manuscript presents the theoretical basis of the powder encapsulation model. The model will be applied to experimental data separately.

2. The mathematical model

A model is a theoretical expression that mathematically predicts an experimental process. In this work, several equations were proposed to predict the encapsulation process. Traditionally, encapsulation fill weight is estimated according to Eq. (1):

$$W = \rho V \qquad (1)$$

where W is the fill weight (g); ρ is the powder density (g/ml); V is the capsule body volume (ml).

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Fig. 1. Capsules produced from different encapsulation methods: (a) loose powder (manual filling); (b) plug (dosator-based machine).

Table 1
Comparison between capsule and plug dimensions for a size "0" capsule.

Dimensions for a size "0" capsule	Capsule body	Plug
Diameter	7.34 mm	6.35 mm
Length	18.44 mm	15.19 mm[a]
Volume	0.68 ml	0.48 ml

[a] Represents the length of cylinder portion of the capsule body (plugs with higher lengths extend outside the capsule body).

Capsule volumes and dimensions are provided by capsule vendors for different capsule sizes. The density term in Eq. (1) could be either the bulk or tapped density; therefore, weights predicted by Eq. (1) have a wide range. For example, if a powder has a bulk and tapped density of 0.3 and 0.5 g/ml; respectively, the weight that can be filled in a size "0" capsule (body volume = 0.68 ml) ranges from 204 to 340 mg.

Eq. (1) is helpful in predicting fill weights of manually filled capsules where actual fill weights fall within the predicted range (depending on the extent of tapping applied). However, the predicted range is wide, and the equation does not make any densification predictions; therefore, it is not representative of capsules attainable by automatic encapsulation machines. Automatic machines produce plugs (i.e., compacts) rather than loose fills (Fig. 1). Plugs are smaller in size compared to capsule bodies (Table 1) but can pack more powder than loose fills. Therefore, another model is needed for automatic machines. To predict encapsulation in dosator-based machines, a model needs to be developed based on the dosator operation principle. The model can then be generalized to any dosator-based machine since they share the same operational principle.

2.1. Dosator operation principle

A dosator is a hollow cylinder (i.e., dosing tube) containing a spring-controlled moving piston as shown in Fig. 2. There are three sequential stages of encapsulation in dosator-based machines: powder insertion, piston compression and ejection into capsules. In the insertion step, the dosator is inserted into a bowl containing a uniform powder bed (i.e., the dosing station). After dosator insertion, it is necessary to compress the powder within the dosator to form a plug. Compression inside the dosator is achieved by piston movement (i.e., displacement) against the powder which is known as compression densification (Fig. 3). Powder densification is needed to achieve a powder arch strong enough to support the powder's weight and keep it in the dosator during transfer. Powder densification could occur during the insertion step which is known as precompression densification (Fig. 3) (Small and Augsburger, 1977).

After the dosator is lifted from the powder bed and transferred to the ejection station, the piston is fully displaced to eject the plug outside the dosator and into the capsule. During capsule ejection, significant powder sticking to piston and dosator walls could occur, such sticking could contribute to fill weight variation and production of empty capsules; therefore, a lubricant is usually added to the formulation.

2.2. Dosator machine settings

Three settings control encapsulation in dosator-based machines:

1. *Powder height* (H_{Powder}): Represents the height of the powder bed formed in the powder bowl.
2. *Piston height* (H_{Piston}): Represents the depth of the piston within a dosator, the higher the piston height, the more powder can be filled in a dosator (Fig. 2).

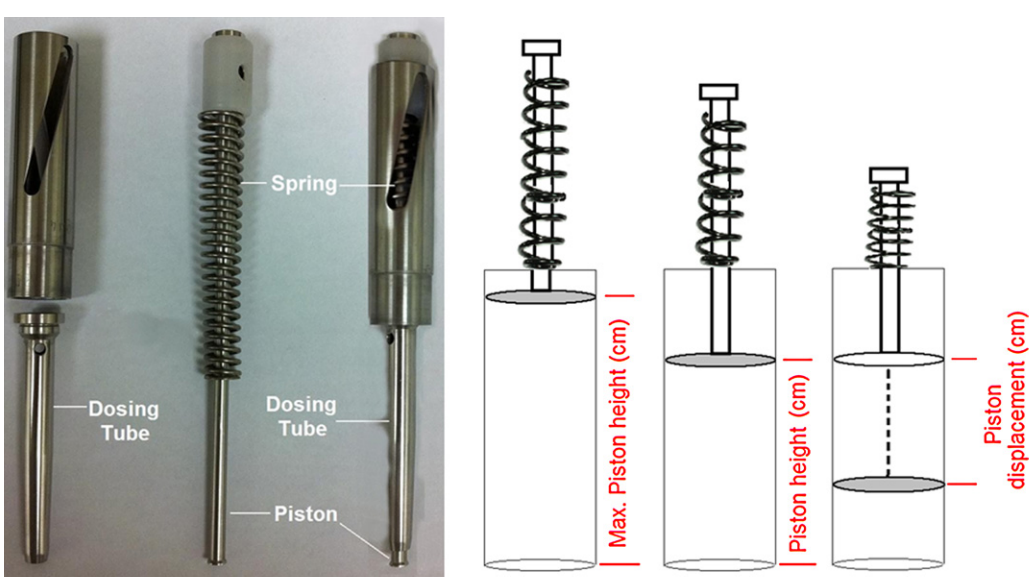

Fig. 2. Schematic presentation of the dosator.

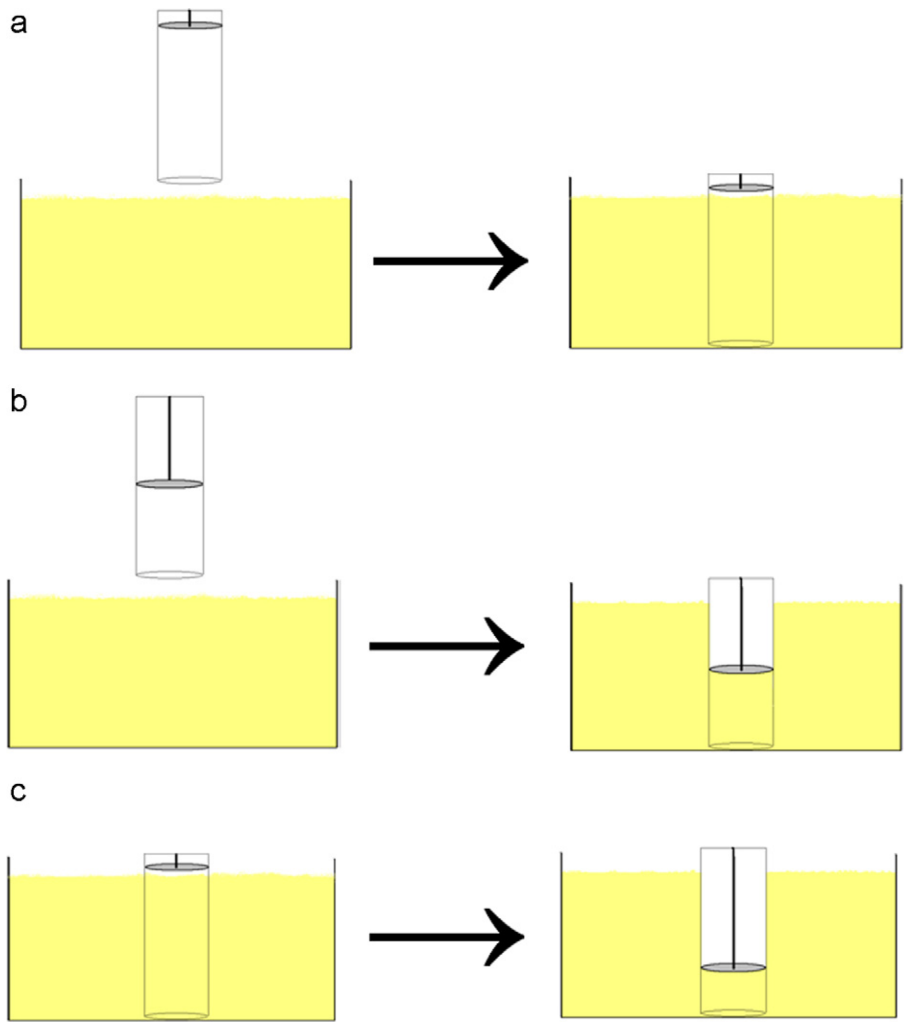

Fig. 3. Schematic presentation of densification during dosator insertion into the powder bed: (a) no densification; (b) powder densification due to precompression; (c) powder densification due to compression (piston displacement).

3. *Compression* (*i.e., set piston displacement* – H_{com}): represents the distance a piston travels within a dosator to compress the powder (Fig. 2).

Combinations of these settings determine the fill weight and plug length in a dosator-based machine. The piston height and compression settings are settings that are controlled by a spring within the dosator, actual values will deviate from set values based on the dosator's spring and powder compressibility properties.

2.2.1. Dosator's spring factor

Within a dosator, the piston height and its displacement are determined by a single spring movement (Fig. 2), this movement depends on the spring's constant defined by Hooke's law of elasticity (Serway and Jewett, 2006) as shown in Eq. (2):

$$F_s = -k_s x_s \tag{2}$$

where F_s is the force applied on a spring (N); k_s is the spring stiffness constant (N/m); x_s is the spring displacement (m).

To accurately predict piston movement in a dosator, it is necessary to relate set displacement values to those actually achieved regardless of spring's stiffness. This can be experimentally done in an empty powder bowl by applying Eq. (3):

$$k = \frac{\Delta H_0}{H_{com}} \tag{3}$$

where k is the spring factor; H_{com} is the set piston displacement (cm); ΔH_0 is the achieved piston displacement in an empty bowl (cm).

The spring factor (k) is a unitless factor different from that in Hooke's law; it relates set piston displacement values (H_{com}) to those actually achieved in an empty powder bowl (ΔH_0). The spring factor is an important factor because it determines the piston height in a dosator prior to compression (i.e., initial piston height). Initial piston heights can be calculated from set heights using Eq. (4):

$$H_{Piston} = H_{Piston}^{Max} - (k(H_{Piston}^{Max} - H_{Piston}^{Set})) \tag{4}$$

where H_{Piston} is the initial piston height (cm); H_{Piston}^{Set} is the set piston height (cm); H_{Piston}^{Max} is the maximum piston height (Fig. 2; k is the spring factor.

The maximum piston height value (H_{Piston}^{Max}) is needed to calculate initial piston height values (H_{Piston}), because the piston height is set from the highest setting (H_{Piston}^{Max}) to lower settings. At maximum piston height, the spring controlling piston position is fully relaxed and its compression produces piston movement. Initial piston heights

(H_{Piston}) deviate from set values (H^{Set}_{Piston}) when the spring factor (k) deviates from unity; especially at lower H^{Set}_{Piston} values that require higher spring compression as shown in Eq. (4). If the spring factor was equal to unity, the set and initial piston heights would be equal ($H_{Piston} = H^{Set}_{Piston}$).

2.2.2. The powder compression factor

Heda et al. (1999) previously studied powder plug formation using a tablet compaction simulator, their work showed that tabletting compression models can be generally applied to powder plug formation if appropriately interpreted.

In non-instrumented capsule machines, force profiles cannot be directly measured, but powder compression can be studied by measuring the piston displacement against the powder within the dosator.

The piston displacement is determined by a spring's movement as previously discussed. In an empty bowl, this movement is controlled by the spring factor (k). However, in the presence of powder, the actual displacement achieved for a set displacement value will depend on the compression resistance exhibited by the powder being compressed. Different powders have different compression properties, thus, achieved piston displacements will differ accordingly. When the piston and powder heights are set to the maximum piston height value ($H_{Powder} = H_{Piston} = H^{Max}_{Piston}$), the achieved piston displacement in a powder can be calculated from the set displacement using Eq. (5):

$$X = \frac{\Delta H}{H_{com}} \tag{5}$$

where X is the powder compression factor; H_{com} is the set piston displacement (cm); ΔH is the achieved piston displacement against powder (cm).

The powder compression factor is a unitless factor that relates the set piston displacement (H_{com}) to that actually achieved against a powder (ΔH). It is similar to the spring factor derived in Eq. (3), except that it is measured in the presence of powder not in an empty bowl. The powder compression factor ≤ spring factor because resistance to compression is higher in a powder compared to air. The more compressible the powder, the higher the powder compressibility factor will be.

2.3. Dosator-based model

A dosator-specific model is one that predicts the encapsulation outcome in a dosator-based encapsulation process. There are two aspects to this prediction, powder fill weight and plug length.

2.3.1. Powder fill weights

The volume of a dosator is defined by that of a cylinder (Gieck and Gieck, 1997):

$$V = r^2\pi \times H \tag{6}$$

where V is the cylinder volume (ml); r is the cylinder radius (cm); H is the cylinder length (cm).

The powder weight that can be packed within a dosator is given by Eq. (7):

$$W = \left(\left(\frac{D_{piston}}{2}\right)^2 \pi \times H_{dosator}\right) \times (\rho_{bulk} \times f_1(p)) \tag{7}$$

where W is the dosator fill weight (g); D_{piston} is the piston diameter (cm); $H_{dosator}$ is the powder height in dosator (cm); ρ_{bulk} is the bulk powder density (g/ml); $f_1(p)$ is the precompression densification factor.

Piston widths vary based on the desired capsule size and they are provided by machine vendors or can be directly measured. Powder height in a dosator is the minimum value of either the powder bed height (H_{Powder}) or the piston height (H_{Piston}) as described by Eq. (8):

$$H_{dosator} = \mathrm{Min}(H_{Piston},\ H_{Powder}) \tag{8}$$

where H_{Powder} is the powder bed height (cm); H_{Piston} is the initial piston height (cm) – according to Eq. (4).

The precompression densification factor ($f_1(p)$) is a factor ≥1 that defines the extent of densification occurring solely due to precompression as discussed below. In the absence of precompression, the density term in Eq. (7) reduces to the bulk powder density.

2.3.2. Plug length and powder densification inside dosator

Powder densification inside the dosator is needed to form arches strong enough to support the powder's weight and keep it in the dosator with greater compression being required to retain freer flowing powders (Jolliffe and Newton, 1982; Jolliffe et al., 1980). If weak bridges are formed with dosator walls, powder will partially or completely drop outside the dosator after it is lifted from the powder bed or during transfer between dosing and ejection stations. Densification is also needed to fit a plug in the capsule body, where, plugs longer than capsule bodies will protrude above the body and can cause some powder loss during encapsulation if the formed plug is soft. The density of the powder within a dosator ($\rho_{dosator}$) is a cumulative density from precompression and compression densification as shown in Eq. (9):

$$\rho_{dosator} = \rho_{bulk} \times f_1(p) \times f_2(p) \tag{9}$$

where $\rho_{dosator}$ is the powder density within the dosator (g/ml); ρ_{bulk} is the bulk powder density (g/ml); $f_1(p)$ is the precompression densification factor; $f_2(p)$ is the compression densification factor.

The precompression and compression densification factors have values ≥1, where unity represents no densification. If both factors equal unity; the density within a dosator would equal the bulk powder density.

2.3.2.1. Precompression densification factor ($f_1(p)$).

The precompression densification factor reflects densification achieved due to precompression which occurs during dosator insertion in the powder bed when the powder height is more than the piston height ($H_{Powder} > H_{Piston}$). The extent of precompression densification is determined by the powder to piston height ratio and powder flow where the more fluid the powder, the less the precompression densification. The precompression densification factor is calculated according to Eq. (10):

$$f_1(p) = ((1 - F)\ln f_1(p)_{set}) + 1 \tag{10}$$

where $f_1(p)$ is the actual precompression densification factor; F is the powder flow factor; $f_1(p)_{set}$ is the set precompression densification factor.

$f_1(p)_{set}$ is be defined by Eq. (11):

$$f(p)_{set} = \frac{H_{Powder}}{H_{Piston}} \tag{11}$$

where H_{Powder} is the powder height in the powder bowl (cm); H_{Piston} is the initial piston height (cm) – according to Eq. (4).

Eq. (10) is similar to that previously reported by Miyake et al. (Miyake et al., 1974):

$$\rho_r = -a_{(i)} \ln P_r + b_{(i)} \tag{12}$$

where ρ_r is the density ratio (similar to $f_1(p)$ in Eq. (10)); P_r is the compression ratio, $P_r = (H_{Powder} - H_{Piston})/H_{Piston}$; $a_{(i)}$ and $b_{(i)}$ are constants.

The powder flow factor (F) in Eq. (10) has an upper boundary limit of unity because values higher than unity produce a negative slope. Negative slopes indicate that powder de-densification

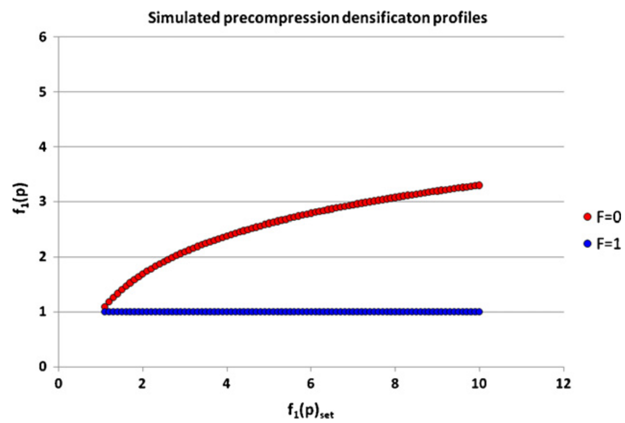

Fig. 4. Simulated precompression densification profiles of two theoretical powders that are freely flowing ($F = 1$) and poorly flowing ($F = 0$).

($f_1(p) < 1$)) is occurring in the dosator as the precompression densification is increased ($f_1(p)_{set} > 1$) which is realistically not possible. Therefore, the −ve sign reported by Miyake et al. ($-a_{(i)}$ in Eq. (12)) cannot be practically justified. Table 2 compares between the two equations.

A freely flowing (e.g., fluid) powder will have an F and $f_1(p)$ value of unity, indicating no precompression is possible for such a powder (Fig. 4). The powder flow factor (F) is not directly related to Carr index; for example, a powder with $F = 1$ will not necessarily have a Carr index = 0%.

2.3.2.2. Compression densification factor ($f_2(p)$). Compression densification occurs from piston displacement against the powder within a dosator. The compression densification factor is defined by Eq. (13):

$$f_2(p) = \frac{H_{dosator}}{H_{plug}} \quad (13)$$

where $f_2(p)$ is the compression densification factor; $H_{dosator}$ is the powder height (cm) in dosator (Eq. (8)); H_{plug} is the plug height (i.e., length) (cm).

The plug height represents the powder height reached within the dosator as a result of piston displacement (ΔH) according to Eq. (14):

$$H_{plug} = H_{dosator} - \Delta H \quad (14)$$

where $H_{dosator}$ is the powder height (cm) in dosator (Eq. (8)); ΔH is the piston displacement against powder (cm).

The piston displacement is calculated according to Eq. (15):

$$\Delta H = [H_{com} - (d_0 + d_1)]X \quad (15)$$

where H_{com} is the set piston displacement (cm); d_0 is the starting point of displacement (cm); d_1 is the piston displacement against air (cm); X is the powder compression factor.

The starting point of displacement (d_0) represents the value below which no piston displacement occurs because, in a dosator, the piston height and piston displacement settings are opposite settings controlled by the same spring (Fig. 2). The value of d_0 depends on the difference between the maximum achievable piston height and set piston height according to Eq. (16):

$$d_0 = (H_{Piston}^{Max} - H_{Piston}) \quad (16)$$

where H_{Piston}^{Max} is the maximum piston height (cm); H_{Piston} is the initial piston height (cm).

Substituting H_{Piston} from Eq. (4) in Eq. (16) gives:

$$d_0 = k(H_{Piston}^{Max} - H_{Piston}^{Set}) \quad (17)$$

where H_{Piston}^{Set} is the set piston height (cm) and k is the spring factor.

Piston displacement against air (d_1) represents the distance the piston moves within the dosator before touching the powder, this occurs when the piston height is more than the powder height as shown in Eq. (18):

$$d_1 = \frac{H_{Piston} - H_{Powder}}{k} \quad (18)$$

where H_{Piston} is the initial piston height (cm) – according to Eq. (4); H_{Powder} is the powder height in the powder bowl (cm); k is the spring factor.

For any densification to occur from piston displacement, the set piston displacement setting (H_{com}) should be higher than ($d_0 + d_1$).

The plug height (H_{plug}) is an important parameter to control during encapsulation, as it should ideally be equal or less than the capsule body length. Plugs with lengths more than the capsule body will protrude which can cause weight variation and/or dusty machine operation if the plug was too soft.

3. Model applications

The suggested model is a useful tool for predicting encapsulation using various machine and powder variables listed in Table 3. The model can be applied during unit operation or formulation and process development.

3.1. Formulation and process development

It is often necessary during early development stages to estimate the maximum fill weight that can be encapsulated in different sized capsules. Such estimation usually requires encapsulation runs that are API consuming. Alternatively, the maximum fill weight (W_{Max}) in a dosator-based machine can be estimated using Eq. (7).

Eq. (7) contains a precompression factor term ($f_1(p)$) which depends on powder flow properties (i.e., powder flow factor) that are usually not available at early development stages. Estimation of such properties requires significant powder amounts. Therefore, for material sparing, it is usually prudent not to consider precompression densification in these early-stage estimates. This can be achieved when $H_{Piston} \geq H_{Powder}$ and Eq. (7) reduces to:

$$W_{Max} = \left(\left(\frac{D_{piston}}{2}\right)^2 \pi \times H_{Piston}^{Max} \times \rho_{bulk}\right) \times \left(\frac{C}{100}\right) \quad (19)$$

where W_{Max} is the maximum dosator fill weight (g); D_{piston} is the piston diameter (cm); H_{Piston}^{Max} is the maximum piston height (cm); C is the fill capacity (%) and ρ_{bulk} is the bulk powder density (g/ml).

Eq. (19) predicts the maximum powder weight that can be packed into a dosator and eventually transferred into capsules. To provide a safety margin for batch to batch variations, a factor (C) was included in Eq. (19) that represents the percent fill capacity of the dosator. The fill capacity factor (C) can have any value up to 100%.

Similarly, at early development stages, it is usually necessary to estimate the minimum bulk powder density required to achieve a desired fill weight. This density can be estimated from Eq. (7) which transforms (after ignoring precompression densification) to:

$$\rho_{Min} = \frac{W}{(D_{piston}/2)^2 \pi \times H_{Piston}^{Max} \times (C/100)} \quad (20)$$

where ρ_{min} is the minimum density required to achieve a W fill weight (g); D_{piston} (cm); H_{Piston}^{Max} is the maximum piston height (cm); C is the fill capacity (%).

A formulation with a density above the ρ_{min} can be encapsulated in that capsule size (some compression densification in the dosator might be required to form arches), if the formulation's

Table 2
Comparison of precompression densification calculated according to Eqs. (10) and (12).

Parameter	Eq. (10)			Eq. (12) (Miyake et al., 1974)		
H_{Powder} (mm)	11	20	30	11	20	30
H_{Piston} (mm)	10	10	10	10	10	10
$f_1(p)_{set}$ [a]	1.1	2.0	3.0	0.10	1.0	2.0
Ln $f_1(p)_{set}$	0.1	0.69	1.10	-2.30	0.00	0.69
$f_1(p)$[b]	1.05	1.35	1.55	2.15	1.00	0.65

[a] Calculated as H_{Powder}/H_{Piston} (Eq. (10)), or $(H_{Powder} - H_{Piston})/H_{Piston}$ (Eq. (10)).
[b] Assumptions: $F = 0.5$; $a_{(i)} = 0.5$; $b_{(i)} = 1$.

Table 3
Parameters needed to model the encapsulation process in a dosator-based machine.

	Parameter	Symbol	Eq.	Utility in prediction
Powder	Bulk density	ρ_{bulk}	(7), (9)	Fill weight
	Compression factor	X	(5), (15)	Compression densification
	Flow factor	F	(10)	Precompression densification
Machine	Spring factor	k	(3), (4), (18)	Fill weight and densification.
	Maximum piston height	H_{Piston}^{Max}	(4), (16)	Fill weight and densification
	Piston width	D_{piston}	(7)	Fill weight
	Powder height[a]	H_{Powder}	(8), (18)	Fill weight and precompression densification
	Set piston height[a]	H_{Piston}^{Set}	(4)	Fill weight and precompression densification
	Set piston displacement[a]	H_{com}	(3), (5), (15)	Compression densification

[a] Programmable parameters.

bulk density is below the ρ_{min}, then further powder densification is needed, which can be achieved by formulation or process changes (Podczeck and Lee-Amies, 1996).

3.2. Unit operation

Eq. (7) is a useful predictor of the powder weight that can be packed within a dosator, which often cannot be transferred into the capsule without further densification. Densification is achieved by compression through piston displacement as depicted in Eq. (14).

Eqs. (7) and (14) can be used as a tool for setting machine parameters during machine operation instead of the empirical approach of parameter selection. Knowing the target machine parameters can help the machine operator shorten the encapsulation set-up time and costs, and fit the process to the formulation needs. For example, a formulation that shows increased sticking as a function of compression can be encapsulated to achieve longer plugs that require less compression. Additionally, excessive powder densification within the dosator can cause dosator walls to crack, this can be prevented by careful selection of less stressful machine parameters which satisfy encapsulation requirements but do not cause excessive stress on dosator walls.

4. Model limitations

The model described in this work provides a tool for predicting the encapsulation process, like any model, it is based on assumptions and has its limitations. One of the main assumptions is that powder arching will always occur at any machine setting and thus, the powder will always be held within the dosator. In reality, absence of powder arches will produce empty capsules, weak arches can cause actual fill weights to deviate from predictions, but deviations disappear as more densification is applied to the powder.

The model does not account for compaction properties of different powders. For example, some powders will form strong plugs at certain densification, others will form weaker or no plugs at the same densification, the model does not discriminate between the two powders and the plug height term (H_{plug}) in Eq. (14) represents the final piston height after displacement which is not necessarily a physical plug.

Fill weight predictions using Eq. (7) are based on the bulk powder density, if the powder density changes during operation, deviations from the predicted weight could be observed. The model does not predict fill weight variation (i.e., CV) caused by flow or lubricity effects. It only predicts a single theoretical fill weight value rather than a range of values. For example, if a formulation is not adequately lubricated, weight deviations can occur from powder sticking to piston or dosator walls. In excessive cases, empty capsules can be produced from improper plug ejection which cannot be predicted by the model.

Finally, one of the complications of the model is that powder flow (F) and compression (X) factors need to be experimentally measured for each powder and are not directly linked to material properties of that powder (e.g., Carr index, flow function or Heckel compressibility parameters). Analysis of several powder formulations is needed to find if such a correlation actually exists.

5. Summary

Dosator-based encapsulation methods are the most common automatic encapsulation methods. Encapsulation in dosator-based machines was modeled in this work. Two equations were proposed to model the encapsulation process, one for the encapsulation fill weight and the other for powder densification in its two forms: precompression and compression densification.

The proposed model can be applied during early stages of formulation and process development to estimate encapsulation fill weights or at later development stages involving operations. Like any model, there are limitations that need to be understood for maximum benefit from this model.

The model presents an *in silico* analysis tool that can be used for capsule dosage form development. It can steer capsule dosage form development from a trial and error based development to a quality by design (QbD) based development that reduces development time and resources.

References

Augsburger, L.L., 2002. Hard and soft shell capsules. In: Banker, G.S., Rohdes, C.T. (Eds.), Modern Pharmaceutics. , 4th ed. Marcel Dekker, New York, pp. 335–380.

Britten, J.R., Barnett, M.I., Armstrong, N.A., 1996. Studies on powder plug formation using a simulated capsule filling machine. J. Pharm. Pharmacol. 48, 249–254.

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

Gieck, K., Gieck, R., 1997. Engineering Formulas, 7th ed. McGraw-Hill Inc.

Guo, M., Augsburger, L.L., 2003. Potential application of silicified microcrystalline cellulose in direct-fill formulations for automatic capsule-filling machines. Pharm. Dev. Technol. 8, 47–59.

Guo, M., Karla, G., Wilson, W., Peng, Y., Augsburger, L.L., 2002a. A Prototype intelligent hybrid system for hard gelatin capsule formulation development. Pharm. Technol. 26, 44–60.

Guo, M., Muller, F.X., Augsburger, L.L., 2002b. Evaluation of the plug formation process of silicified microcrystalline cellulose. Int. J. Pharm. 233, 99–109.

Heda, P.K., Muller, F.X., Augsburger, L.L., 1999. Capsule filling machine simulation. I. Low-force powder compression physics relevant to plug formation. Pharm. Dev. Technol. 4, 209–219.

Heda, P.K., Muteba, K., Augsburger, L.L., 2002. Comparison of the formulation requirements of dosator and dosing disc automatic capsule filling machines. AAPS PharmSci 4, E17.

Irwin, G.M., Dodson, G.J., Ravin, L.J., 1970. Encapsulation of clomacran phosphate [2-chloro-9[3-(dimethylamino) propyl]acridan phosphate]. I. Effect of flowability of powder blends, lot-to-lot variability, and concentration of active ingredient on weight variation of capsules filled on an automatic capsule-filling machine. J. Pharm. Sci. 59, 547–550.

Jolliffe, I.G., Newton, J.M., 1982. Practical implications of theoretical consideration of capsule filling by dosator nozzle system. J. Pharm. Pharmacol. 34, 293–298.

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

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., 1980. Simultaneous measurement of force and displacement in an automatic capsule filling machine. Int. J. Pharm. 4, 347–351.

Miyake, Y., Shimoda, A., Jasu, T., Furukawa, M., Nesuji, K., Hoshi, K., 1974. Packing properties of pharmaceutical powders into hard gelatin capsules. Yakuzaigaku 34, 32–37.

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.

Podczeck, F., 2000. The development of an instrumented tamp-filling capsule 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 capsule machine II. 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, B.E. (Eds.), Pharmaceutical Capsules. , 2nd ed. Pharmaceutical Press, pp. 119–138.

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, 97–102.

Podczeck, F., Newton, J.M., 2000. Powder and capsule filling properties of lubricated granulated cellulose powder. Eur. J. Pharm. Biopharm. 50, 373–377.

Serway, R.A., Jewett, J.W.J., 2006. Principles of Physics: A Calculus-Based Text, 4th ed. Brooks/Cole—Thomson Learning, p. 163.

Shah, K., Augsburger, L.L., Small, L.E., Polli, G.P., 1983. Instrumentation of a dosing disc automatic capsule filling machine. Pharm. Technol. 7, 42–54.

Small, L.E., Augsburger, L.L., 1977. Instrumentation of an automatic capsule-filling machine. J. Pharm. Sci. 66, 504–509.

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.

Wilson, W.I., Peng, Y., Augsburger, L.L., 2005a. Comparison of statistical analysis and Bayesian Networks in the evaluation of dissolution performance of BCS Class II model drugs. J. Pharm. Sci. 94, 2764–2776.

Wilson, W.I., Peng, Y., Augsburger, L.L., 2005b. Generalization of a prototype intelligent hybrid system for hard gelatin capsule formulation development. AAPS PharmSciTech 6, E449–E457.