International Journal of Pharmaceutics 421 (2011) 210–219

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

# Modeling powder encapsulation in dosator-based machines: II. Experimental evaluation

Ammar Khawam*, Leon Schultz

*Department of Pharmaceutics, Boehringer Ingelheim Pharmaceuticals, 900 Ridgebury Road, Ridgefield, CT 06877, USA*

ARTICLE INFO

*Article history:*
Received 11 June 2011
Received in revised form 28 August 2011
Accepted 15 September 2011
Available online 24 September 2011

*Keywords:*
Encapsulation
Filling
Powder technology
*In silico* modeling
Compression
Excipients
Formulation
Mathematical model
Solid dosage form
Capsules

ABSTRACT

A theoretical model was previously derived to predict powder encapsulation in dosator-based machines. The theoretical basis of the model was discussed earlier. In this part; the model was evaluated experimentally using two powder formulations with substantially different flow behavior. Encapsulation experiments were performed using a Zanasi encapsulation machine under two sets of experimental conditions. Model predicted outcomes such as encapsulation fill weight and plug height were compared to those experimentally obtained. Results showed a high correlation between predicted and actual outcomes demonstrating the model's success in predicting the encapsulation of both formulations. The model is a potentially useful *in silico* analysis tool that can be used for capsule dosage form development in accordance to quality by design (QbD) principles.



## 1. Introduction

A theoretical model was previously derived to predict powder encapsulation in dosator-based machines (Khawam, 2011). The model can estimate powder fill weights and plug heights in different sized capsules. This work applies the derived model to the encapsulation of two powder formulations with significantly different flow behavior. The model's accuracy was determined by comparing model predicted parameters to those experimentally achieved using a dosator-based machine.

### *The mathematical model*

A mathematical model was derived based on the dosator operation principle which consists of a hollow cylinder open at the bottom that is immersed into a powder bed, a piston within the dosator compresses the powder to form plugs, which are ejected into capsules. According to the model, encapsulation outcomes such as fill weight and plug height can be predicted from machine adjustable settings like powder height ($H_{powder}$), piston height ($H_{piston}$), and compression (i.e., set piston displacement – $H_{com}$) (Khawam, 2011). The powder weight that can be packed into a dosator is given by:

$$W = \left(\left(\frac{D_{piston}}{2}\right)^2 \pi \times \min(H_{piston}, H_{powder})\right) \times (\rho_{bulk} \times f_1(p)) \tag{1}$$

where $W$ is the dosator fill weight (g), $D_{piston}$ is the piston diameter (cm), $H_{powder}$ is the powder bed height (cm), $H_{piston}$ is the initial piston height (cm), $\rho_{bulk}$ is the bulk powder density (g/ml) and $f_1(p)$ is the precompression densification factor.

The initial piston height ($H_{piston}$) is calculated from the set height using Eq. (2):

$$H_{piston} = H_{piston}^{max} - (k(H_{piston}^{max} - H_{piston}^{set})) \tag{2}$$

where $H_{piston}^{max}$ is the maximum piston height (cm), $H_{piston}^{set}$ is the set piston height (cm) and $k$ is the spring factor.

The spring factor ($k$) is a unitless factor that relates set piston displacement values ($H_{com}$) to those actually achieved in an empty powder bowl ($\Delta H_0$) according to:

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

where $H_{com}$ is the set piston displacement and $\Delta H_0$ is the measured piston displacement in air.

* Corresponding author. Tel.: +1 203 798 5013; fax: +1 203 791 6197.
*E-mail address:* ammar.khawam@boehringer-ingelheim.com (A. Khawam).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.09.027

The precompression densification factor ($f_1(p)$) is a factor $\geq 1$ that describes the extent of powder densification when $H_{powder} > H_{piston}$. This factor is given by:

$$f_1(p) = (1 - F) \ln f_1(p)_{set} + 1 \quad (4)$$

where $F$ is the powder flow factor and $f_1(p)_{set}$ is the set precompression densification factor which is the ratio of powder to piston heights ($H_{powder}/H_{piston}$).

The compression densification factor ($f_2(p)$) is a factor $\geq 1$ that describes the extent of powder densification by piston displacement when the compression setting is set to values greater than zero (i.e., $H_{com} > 0$). This factor is given by:

$$f_2(p) = \frac{\min(H_{piston}, H_{powder})}{H_{plug}} \quad (5)$$

where $H_{plug}$ is the plug height (cm) and $H_{piston}$ is the initial piston height (cm).

The plug (i.e., compact) height in Eq. (5) represents the final piston height reached inside the dosator after piston displacement. This height represents the in-die plug height inside the dosator and can be calculated using Eq. (6):

$$H_{plug} = \min(H_{piston}, H_{powder}) - \left[ H_{com} - \left( (H_{piston}^{max} - H_{piston}) + \left( \frac{H_{piston} - H_{powder}}{k} \right) \right) \right] X \quad (6)$$

where $H_{plug}$ is the plug length (cm), $H_{piston}$ is the initial piston height (cm), $H_{powder}$ is the powder bed height (cm), $H_{com}$ is the set piston displacement (cm), $H_{piston}^{max}$ is the maximum piston height (cm), $k$ is the spring factor and $X$ is the powder compression factor.

The powder compression factor ($X$) is a unitless factor that relates set piston displacement values ($H_{com}$) to those actually achieved against a powder ($\Delta H$) according to:

$$X = \frac{\Delta H}{H_{com}} \quad (7)$$

where $X$ is the powder compression factor, $H_{com}$ is the set piston displacement and $\Delta H$ is the achieved piston displacement against powder.

Two terms can be defined from Eq. (6): $d_0 = (H_{piston}^{max} - H_{piston})$ and $d_1 = \left((H_{piston} - H_{powder})/k\right)$, where $d_0$ represents the starting point of displacement while, $d_1$ represents piston displacement against air. For any compression densification to occur, $H_{com}$ should exceed $d_0 + d_1$, otherwise, Eq. (6) reduces to $H_{plug} = \min(H_{piston}, H_{powder})$ and $f_2(p) = 1$.

## 2. Experimental

The objective of the experimental work was to validate the model by evaluating its ability to predict the experimental outcome of two substantially different powder formulations. Work was done in two parts: first, machine-specific (i.e., spring factor) and powder-specific (i.e., powder flow and compression factors) parameters were determined. These parameters were then used in the model to make predictions for each powder where the correlation between measured and predicted values was assessed.

### 2.1. Materials and equipment

Excipients used in this work included: microcrystalline cellulose (Vivapur® 102 SCG; JRS Pharma; Lot#: 5612281044 and Avicel® PH-105; FMC biopolymer; Lot#: 50901C), lactose monohydrate (Tabletose® 80; Meggle; Lot#: L0915), polyvinylpyrrolidone (Kollidon® 25; BASF; Lot#:15116716K0) and magnesium stearate (Ligamed® MF-2-V-BI; Peter Greven; Lot#: C917002). All capsules used were size 0 CS white opaque capsules (Lot: 90018201; Capsugel®). The machine used for encapsulation was a Zanasi 6F (IMA S.p.A.; Italy) with a maximum dosator piston height ($H_{piston}^{max}$) of 26 mm and a piston diameter ($D_{piston}$) of 6.4 mm. A Hanson Research Flodex® powder flowability tester (Model 21-101-050) was used for testing powder flowability. Tapped density was determined using a VanKel Model 50-1200 machine. Sieve analysis was done using a Model L3P ATM Arrow Sonic Sifter, with 18, 35, 60, 120, 230 mesh screens and a fines collection pan. Moisture content was determined using a Mettler Toledo HR73 moisture analyzer. Data analysis was performed using Microsoft Excel®.

### 2.2. Powder formulations and physical testing

Two powder formulas were prepared for encapsulation (Table 1), the first, a directly compressible lubricated placebo formulation. The second formula consisted of a fine grade of microcrystalline cellulose (Avicel® PH-105) that was used as received without lubrication. None of the formulations were processed by granulation.

Several tests were done to determine the physical properties of formulations such as particle size, moisture content, density and flow. All tests were done in duplicate.

Particle size distribution of each formula was determined by passing a 3 g sample through 18–230 mesh screens in a sonic sifter programmed to sift the powder with pulsation for 3 min. Moisture content was determined by isothermally heating a 4 g sample at 100 °C and following its weight loss, the final sample weight was determined when weight loss stabilized. The bulk powder density was determined by filling the powder in a 100 ml graduated cylinder and measuring its weight and volume. The powder volume in the cylinder was also measured after 1000 taps. The Carr compressibility index (CI%) was calculated from the bulk and tapped densities using the following equation:

$$\text{CI\%} = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \times 100$$

where $\rho_{bulk}$ is the bulk density (g/ml) and $\rho_{tapped}$ is the tapped density (g/ml).

The Carr index was used to determine powder flowability according to USP criteria (Table 2) (USP34-NF29, 2011). Powder flowability was also assessed using the FLODEX® tester according to the procedure described by Gioia (Gioia, 1981). This test determines a flowability index over an arbitrary scale of 4–34, this scale represents the diameter of the smallest circular orifice through which a powder freely flows from a flat-bottom cylindrical hopper. Smaller Flowdex values are indicative of better flow.

### 2.3. Machine-specific parameters

Machine validation was performed to verify that machine adjustable settings ($H_{powder}$, $H_{piston}$, $H_{com}$) were accurately

**Table 1**
Composition of powder formulations.

| Component | % W/W | |
|---|---|---|
| | Formulation A | Formulation B |
| Microcrystalline cellulose (Avicel® PH105) | – | 100 |
| Microcrystalline cellulose (Vivapur® 102 SCG) | 38.6 | – |
| Lactose monohydrate (Tabletose® 80) | 58 | – |
| PVP (K-25) | 2.4 | – |
| Magnesium stearate | 1 | – |
| Total (%) | 100 | 100 |

**Table 2**
Powder flowability scale according to the Carr index.

| Carr index (%) | Flow character[a] |
|---|---|
| ≤10 | Excellent |
| 11–15 | Good |
| 16–20 | Fair |
| 21–25 | Passable |
| 26–31 | Poor |
| 32–37 | Very poor |
| >38 | Very, very poor |

[a] Determined according to USP criteria (USP34-NF29, 2011).

achieved experimentally. This was done by direct measurement of outcomes from these settings such as powder bed height, piston height and piston displacement using a caliper. The powder height ($H_{powder}$) was verified by immersing the "depth probe" of a caliper into the leveled powder bed and measuring the powder bed depth within the bowl. The depth probe was also used to measure the initial piston height ($H_{piston}$) within a dosator. The piston displacement was determined by marking the starting and ending piston positions within a dosator for a set displacement value ($H_{com}$) and physically measuring the distance between the two positions (Fig. 1). In the absence of powder (i.e., in an empty bowl), the measured piston displacement is used to determine the spring factor ($k$) according to Eq. (3).

### 2.4. Powder-specific parameters

The model requires the determination of formulation specific parameters such as flow ($F$) and powder compression ($X$) factors. These properties were determined for each powder formulation.

#### 2.4.1. Powder flow factor (F)

The powder flow factor ($F$) was estimated for both formulations by running the encapsulation machine at several settings (Table 3) selected to achieve precompression densification only ($H_{piston} < H_{powder}$ and $H_{com} = 0$). The encapsulation fill weight was measured at each setting and used to calculate the actual precompression densification factor ($f_1(p)$) according to Eq. (1) which can be rearranged to:

**Table 3**
Machine settings used to estimate the powder flow factor (F).

| Setting | $H_{powder}$ (mm) | $H_{piston}^{set}$ (mm) | $H_{com}$ (mm) | $H_{piston}$ (mm) |
|---|---|---|---|---|
| | | Formulation A | | |
| S1 | 20 | 16 | 0 | 17 |
| S2 | 20 | 15 | 0 | 16.1 |
| S3 | 20 | 14 | 0 | 15.2 |
| S4 | 20 | 13 | 0 | 14.3 |
| S5 | 20 | 12 | 0 | 13.4 |
| S6 | 20 | 11 | 0 | 12.5 |
| S7 | 20 | 10 | 0 | 11.6 |
| S8 | 20 | 8 | 0 | 9.8 |
| S9 | 20 | 5 | 0 | 7.1 |
| S10 | 20 | 2 | 0 | 4.4 |
| | | Formulation B | | |
| S11 | 20 | 14 | 0 | 15.2 |
| S12 | 20 | 12 | 0 | 13.4 |
| S13 | 20 | 10 | 0 | 11.6 |
| S14 | 20 | 5 | 0 | 7.1 |
| S15 | 23.5 | 17.5 | 0 | 18.35 |
| S16 | 23.5 | 12.5 | 0 | 13.85 |
| S17 | 23.5 | 7.5 | 0 | 9.35 |
| S18 | 30 | 17 | 0 | 17.9 |
| S19 | 30 | 15 | 0 | 16.1 |
| S20 | 30 | 10 | 0 | 11.6 |
| S21 | 30 | 6 | 0 | 8 |
| S22 | 38.5 | 16 | 0 | 17 |
| S23 | 40 | 24 | 0 | 24.2 |
| S24 | 40 | 22 | 0 | 22.4 |
| S25 | 40 | 20 | 0 | 20.6 |
| S26 | 40 | 10 | 0 | 11.6 |
| S27 | 40 | 5 | 0 | 7.1 |

$$f_1(p) = \frac{W}{((D_{piston}/2)^2\pi \times H_{dosator} \times \rho_{bulk})} \quad (8)$$

The set precompression densification factor was calculated from the ratio of powder to piston heights (i.e., $f_1(p)_{set} = H_{powder}/H_{piston}$). The actual and set precompression densification factors were plotted and the powder flow factor ($F$) was determined from the fitted logarithmic function according to Eq. (4).

**Fig. 1.** Piston displacement measurement within a dosator.

#### 2.4.2. Powder compression factor (X)

Eq. (6) can be rearranged to:

$$X = \frac{\min(H_{piston}, H_{powder}) - H_{plug}}{[H_{com} - ((H_{piston}^{max} - H_{piston}) + ((H_{piston} - H_{powder})/k))]} \quad (6')$$

The numerator of the above equation represents the achieved piston displacement against powder ($\Delta H$) (Khawam, 2011):

$$\Delta H = \min(H_{piston}, H_{powder}) - H_{plug} \quad (9)$$

Eq. (6′) is the general equation for determining the powder densification factor at any machine setting. When the piston and powder heights are set to the maximum piston height value ($H_{powder} = H_{piston} = H_{piston}^{max}$), Eq. (6′) reduces to Eq. (7).

Eq. (6′) was used to calculate the powder compression factor ($X$), the numerator of that equation ($\Delta H$ term) was determined by two means:

I. *Direct measurement*: Piston displacement can be directly measured by measuring the distance between the starting and ending piston positions (Fig. 1). If $H_{powder} \geq H_{piston}$; the experimentally measured displacement represents $\Delta H$ (piston displacement against powder); otherwise, the measured displacement represents $d_1 + \Delta H$ (i.e., piston displacement against both air and powder).

II. Indirectly from the measured plug height ($H_{plug}$) which is used to calculate $\Delta H$ values according to Eq. (9).

Values from the first approach can be used to calculate in-die plug heights because of the direct measurement of piston displacement. On the other hand, values from the second approach give out-of-die plug heights because they account for plug expansion. Results from the second approach generally give lower powder compression factors, especially for highly viscoelastic materials. In this work, the second approach was used to calculate the powder densification factor, while, the first was only used for comparison.

### 2.5. Model predictions

For a successful encapsulation process, powder densification is needed to form strong arches. Densification could be achieved by precompression only ($f_1(p) > 1$; $f_2(p) = 1$), compression only ($f_1(p) = 1$; $f_2(p) > 1$) or both ($f_1(p) > 1$; $f_2(p) > 1$). For simplification, this work only assessed densification by either precompression or compression but not both. Therefore, encapsulation occurred under two sets of experimental settings each producing a measurable outcome (i.e., fill weight and plug height). The outcome from each setting was measured for both powders and compared to that predicted by the model. The correlation between measured and predicted values was assessed.

#### 2.5.1. Precompression densification settings

Precompression densification was achieved for each powder by setting piston heights below powder height values ($H_{piston} < H_{powder}$) and disabling piston displacement ($H_{com} = 0$), as shown in Table 4 for formulation A (settings A1–A9) and Table 5 for formulation B (setting B1–B20). For these settings; Eqs. (1) and (6) transform to:

$$W = \left( \left( \frac{D_{piston}}{2} \right)^2 \pi \times H_{Piston} \right) \times (\rho_{bulk} \times f_1(p)) \quad (10)$$

and

$$H_{plug} = H_{piston} \quad (11)$$

Eqs. (10) and (11) were used to predict powder fill weight and plug height; respectively. The experimentally determined powder flow factor ($F$) was used to calculate the value of $f_1(p)$. Experimental sets used to evaluate encapsulation after precompression densification (Tables 4–5) were different from those used to calculate the powder flow factor (Table 3).

#### 2.5.2. Compression densification settings

Compression densification was achieved for each powder by setting piston heights equal to or above powder height values ($H_{piston} \geq H_{powder}$) and selecting piston displacement values above zero ($H_{com} > 0$), as shown in Table 4 for formulation A (settings A10–A25) and Table 5 for formulation B (setting B21–B40). For these settings; Eqs. (1) and (6) transform to:

$$W = \left( \left( \frac{D_{piston}}{2} \right)^2 \pi \times H_{powder} \right) \times \rho_{bulk} \quad (12)$$

**Table 4**
Machine settings used for evaluating formulation A encapsulation.

| Setting | $H_{powder}$ (mm) | $H^{set}_{piston}$ (mm) | $H_{com}$ (mm) | $H_{piston}$ (mm) |
|---|---|---|---|---|
| Precompression densification | | | | |
| A1 | 30 | 22 | 0 | 22.4 |
| A2 | 30 | 20 | 0 | 20.6 |
| A3 | 30 | 18 | 0 | 18.8 |
| A4 | 30 | 16 | 0 | 17.0 |
| A5 | 30 | 14 | 0 | 15.2 |
| A6 | 30 | 10 | 0 | 11.6 |
| A7 | 30 | 8 | 0 | 9.8 |
| A8 | 30 | 6 | 0 | 8.0 |
| A9 | 30 | 4 | 0 | 6.2 |
| Compression densification | | | | |
| A10 | 15.5 | 17 | 19.5 | 17.9 |
| A11 | 15.5 | 17 | 23 | 17.9 |
| A12 | 18 | 18 | 18 | 18.8 |
| A13 | 20 | 20 | 18 | 20.6 |
| A14 | 20 | 21.5 | 15 | 21.95 |
| A15 | 20 | 21.5 | 20 | 21.95 |
| A16 | 20 | 21.5 | 24 | 21.95 |
| A17 | 20 | 25 | 15 | 25.1 |
| A18 | 20 | 25 | 24 | 25.1 |
| A19 | 20 | 25 | 25 | 25.1 |
| A20 | 21.5 | 22 | 18 | 22.4 |
| A21 | 23.5 | 25 | 12 | 25.1 |
| A22 | 23.5 | 25 | 17.5 | 25.1 |
| A23 | 23.5 | 25 | 19.5 | 25.1 |
| A24 | 23.5 | 25 | 22 | 25.1 |
| A25 | 26 | 26 | 18 | 26.0 |

**Table 5**
Machine settings used for evaluating formulation B encapsulation.

| Setting | $H_{powder}$ (mm) | $H^{set}_{piston}$ (mm) | $H_{com}$ (mm) | $H_{piston}$ (mm) |
|---|---|---|---|---|
| Precompression densification | | | | |
| B1 | 20 | 2 | 0 | 4.4 |
| B2 | 20 | 5 | 0 | 7.1 |
| B3 | 20 | 8 | 0 | 9.8 |
| B4 | 20 | 11 | 0 | 12.5 |
| B5 | 20 | 13 | 0 | 14.3 |
| B6 | 23.5 | 5 | 0 | 7.1 |
| B7 | 23.5 | 7.5 | 0 | 9.35 |
| B8 | 23.5 | 10 | 0 | 11.6 |
| B9 | 23.5 | 12.5 | 0 | 13.85 |
| B10 | 23.5 | 15 | 0 | 16.1 |
| B11 | 30 | 6 | 0 | 8.0 |
| B12 | 30 | 8 | 0 | 9.8 |
| B13 | 30 | 12 | 0 | 13.4 |
| B14 | 30 | 16 | 0 | 17.0 |
| B15 | 38.5 | 16 | 0 | 17.0 |
| B16 | 38.5 | 24 | 0 | 24.2 |
| B17 | 40 | 16 | 0 | 17.0 |
| B18 | 40 | 21 | 0 | 21.5 |
| B19 | 40 | 23 | 0 | 23.3 |
| B20 | 40 | 25 | 0 | 25.1 |
| Compression densification | | | | |
| B21 | 9.5 | 11 | 19 | 12.5 |
| B22 | 9.5 | 11 | 20 | 12.5 |
| B23 | 9.5 | 11 | 21 | 12.5 |
| B24 | 9.5 | 11 | 22 | 12.5 |
| B25 | 9.5 | 11 | 23 | 12.5 |
| B26 | 9.5 | 25 | 25 | 25.1 |
| B27 | 12 | 12 | 20 | 13.4 |
| B28 | 15 | 15 | 20 | 16.1 |
| B29 | 17 | 17 | 15 | 17.9 |
| B30 | 17 | 17 | 18 | 17.9 |
| B31 | 20 | 20 | 15 | 20.6 |
| B32 | 20.5 | 22 | 11 | 22.4 |
| B33 | 20.5 | 22 | 13 | 22.4 |
| B34 | 20.5 | 22 | 19 | 22.4 |
| B35 | 20.5 | 22 | 21 | 22.4 |
| B36 | 23.5 | 25 | 12 | 25.1 |
| B37 | 23.5 | 25 | 16 | 25.1 |
| B38 | 23.5 | 25 | 18 | 25.1 |
| B39 | 23.5 | 25 | 20 | 25.1 |
| B40 | 23.5 | 25 | 22 | 25.1 |

**Table 6**
Physical characteristics of powder formulations.

| Property | Formulation A | Formulation B |
|---|---|---|
| Bulk density (g/ml) | 0.570 | 0.346 |
| Tap density (g/ml) | 0.671 | 0.545 |
| Carr index (%) | 15 | 37 |
| Moisture content (%) | 2.46 | 4.65 |
| Flow (based on Carr index) | Good | Very poor |
| FLODEX® flowability index | 4 mm | 34 mm |

and

$$H_{plug} = H_{powder} - \left[\left(H_{com} - (H_{piston}^{max} - H_{piston}) + \left(\frac{H_{piston} - H_{powder}}{k}\right)\right)\right] X \quad (13)$$

Eqs. (12) and (13) were used to predict powder fill weight and plug height; respectively.

The plug height in Eq. (13) was calculated using the experimentally determined powder compression factor ($X$).

## 3. Results and discussion

### 3.1. Physical testing of powder blends

Physical test results are summarized in Table 6 for the two formulations. Flowability results (Carr and FLODEX® indices) show that the two powder formulations represent opposite examples of powder flow (Table 2), with, formulation A having good flow properties (CI = 15%, FLODEX® = 4 mm), and, formulation B having poor flow properties (CI = 37%, FLODEX® = 34 mm). These flow patterns agree with the particle size distribution results of the two blends (Fig. 2) which show that formulation B mainly consists of fine particles.

### 3.2. Machine-specific parameters

Direct measurements using a caliper have verified that the set parameters such as powder ($H_{powder}$) and piston ($H_{piston}$) heights were experimentally achieved. Piston displacement measured in an empty bowl (Table 7) showed that the spring factor ($k$) was 0.9. Therefore, for each 1 mm set piston displacement, a 0.9 mm displacement was actually achieved in an empty bowl.

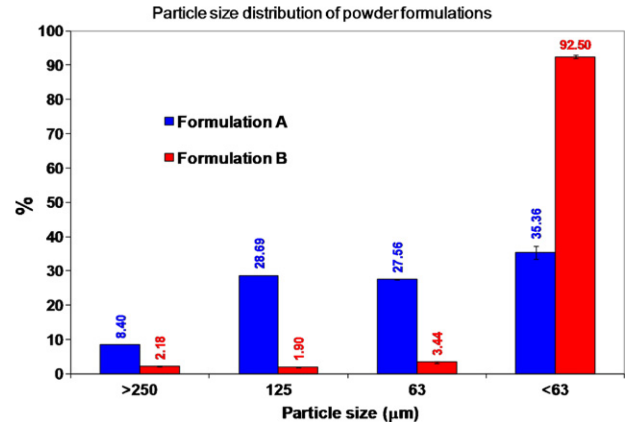


**Fig. 2.** Particle size distribution of the two powder formulations.

**Table 7**
Set and measured piston displacement in an empty bowl.

| Set piston displacement (mm) ($H_{com}$) | Measured displacement (mm) ($\Delta H_0$) | Spring factor ($k$) $\Delta H_0/H_{com}$ (Eq. (3)) |
|---|---|---|
| 10 | 9 | 0.90 |
| 15 | 13.5 | 0.90 |
| 20 | 18 | 0.90 |
| 22 | 19.8 | 0.90 |
| 25 | 22.5 | 0.90 |
| | Average | 0.90 |

### 3.3. Powder-specific parameters

Measured piston displacements in powder formulations (Table 8) show that the powder compression factor ($X$) was 0.70 and 0.80 for formulations A and B; respectively. The higher factor indicates that formulation B is more compressible than formulation A (i.e., less resistance to compression).

Precompression densification factors ($f_1(p)$) were calculated for both powders at several machine settings (Table 9) using Eq. (8). Plots of set and actual precompression densification factors ($f_1(p)_{set}$

**Table 8**
Compression factor ($X$) determination of powder formulations.

| $H_{powder}$ (mm) | $H_{piston}^{set}$ (mm) | $H_{com}$ (mm) | $H_{piston}$ (mm) | $d_0$ (mm) | $d_1$ (mm) | Measured $\Delta H + d_1$ (mm) | Measured $H_{plug}$ (mm) | $X_{(I)}$[b] | $X_{(II)}$[c] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Formulation A | | | | | |
| 23.5 | 25 | 10 | 25.10 | 0.90 | 1.78 | 7.53 | N/A[a] | 0.79 | – |
| 23.5 | 25 | 20 | 25.10 | 0.90 | 1.78 | 16.00 | 11.00 | 0.82 | 0.72 |
| 23.5 | 25 | 22 | 25.10 | 0.90 | 1.78 | 17.60 | 9.50 | 0.82 | 0.72 |
| 20 | 21.5 | 15 | 21.95 | 4.05 | 2.17 | 7.68 | 14.30 | 0.63 | 0.65 |
| | | | | | | | Average | 0.76 | 0.70 |
| | | | | | | | s.d. | 0.09 | 0.04 |
| | | | | | | | RSD (%) | 12.03 | 6.13 |
| | | | | Formulation B | | | | | |
| 23.5 | 25 | 20 | 25.10 | 0.90 | 1.78 | 15.60 | 9.48 | 0.82 | 0.81 |
| 23.5 | 25 | 20 | 25.10 | 0.90 | 1.78 | – | 9.50 | – | 0.81 |
| 23.5 | 25 | 22 | 25.10 | 0.90 | 1.78 | 17.80 | 8.35 | 0.83 | 0.78 |
| 23.5 | 25 | 22 | 25.10 | 0.90 | 1.78 | – | 8.36 | – | 0.78 |
| | | | | | | | Average | 0.81 | 0.80 |
| | | | | | | | s.d. | 0.02 | 0.01 |
| | | | | | | | RSD (%) | 2.72 | 1.81 |

[a] N/A: plugs were not formed or were too soft to measure at this setting.
[b] Calculated from measured piston displacement ($\Delta H + d_1$).
[c] Calculated from measured plug height.

**Table 9**
Determination of precompression densification factor from capsule fill weights.

| Setting[a] | $f_1(p)_{set}$ | Fill weight (mg)[b] | $f_1(p)$ |
|---|---|---|---|
| | | Formulation A | |
| S1 | 1.18 | 280 ± 14.17 | 0.91 |
| S2 | 1.24 | 306 ± 13.48 | 1.05 |
| S3 | 1.32 | 294 ± 10.41 | 1.07 |
| S4 | 1.40 | 274 ± 6.66 | 1.06 |
| S5 | 1.49 | 249 ± 8 | 1.03 |
| S6 | 1.60 | 236 ± 11.55 | 1.05 |
| S7 | 1.72 | 210 ± 14.04 | 1.00 |
| S8 | 2.04 | 181 ± 9.36 | 1.02 |
| S9 | 2.82 | 130 ± 2.21 | 1.02 |
| S10 | 4.55 | 69 ± 8.37 | 0.87 |
| | | Formulation B | |
| S11 | 1.32 | 204 ± 31.92 | 1.22 |
| S12 | 1.49 | 194 ± 17.37 | 1.32 |
| S13 | 1.72 | 199 ± 17.98 | 1.57 |
| S14 | 2.82 | 142 ± 2.45 | 1.83 |
| S15 | 1.28 | 231 ± 5.19 | 1.15 |
| S16 | 1.70 | 218 ± 8.18 | 1.43 |
| S17 | 2.51 | 174 ± 4.33 | 1.69 |
| S18 | 1.68 | 242 ± 21.06 | 1.23 |
| S19 | 1.86 | 248 ± 21.4 | 1.41 |
| S20 | 2.59 | 213 ± 7.87 | 1.68 |
| S21 | 3.75 | 152 ± 4.68 | 1.74 |
| S22 | 2.26 | 314 ± 11.41 | 1.68 |
| S23 | 1.65 | 351 ± 25.08 | 1.33 |
| S24 | 1.79 | 337 ± 34.97 | 1.37 |
| S25 | 1.94 | 308 ± 48.94 | 1.36 |
| S26 | 3.45 | 235 ± 13.02 | 1.85 |
| S27 | 5.63 | 154 ± 3.58 | 1.98 |

[a] Instrument settings detailed in Table 3.
[b] Weights were averaged from at least 7 capsules.

vs. $f_1(p)$) were generated for both powders and a logarithmic function (Eq. (4)) was fit to this data as shown in Fig. 3. Regression results showed that slopes were 0 and 0.58 for formulation A and B; respectively, therefore powder flow factors ($F$) were 1.0 and 0.42; respectively as shown in Eq. (4). Fig. 3 shows the two formulations had significantly different precompression densification profiles corresponding to their different flow behavior. Profiles agree with those previously simulated in earlier work (Khawam, 2011).

The slope in Fig. 3a (formulation A) was slightly negative (−0.09) which is theoretically impossible because a negative slope indicates that powder de-densification is occurring as the set precompression densification is increased. Negative slopes can be attributed to experimental errors that arise from weak arch formation with dosator walls, causing powder portions to drop from dosator during its movement (Fig. 4), this loss produces capsules with lower weight and $f_1(p)$ than theoretically predicted by Eq. (8) which is evident in S1 and S10 settings (Table 9).

Statistical analysis of regression results (Table 10) shows a good correlation between $f_1(p)_{set}$ and $f_1(p)$ for formulation B ($r^2 = 0.85$) but not for formulation A ($r^2 = 0.31$). Additionally, both the slope and intercept were statistically significant ($p < 0.05$) for formulation B, but only the intercept was significant for formulation A. Analysis results agree with the model that suggests that the relationship between $f_1(p)_{set}$ and $f_1(p)$ is a logarithmic relationship according to Eq. (4) which is the case for formulation B, however, this relationship reduces to a linear relationship (slope = 0 and intercept = 1) for a good flowing powder such as formulation A ($F$ = 1) and that explains why $f_1(p)$ shows little correlation with $f_1(p)_{set}$ in that case.

### 3.4. Model predictions

Encapsulation results at different machine settings are summarized in Tables 11 (formulation A) and 12 (formulation B). For each densification type, predicted encapsulation outcomes (fill weight and plug height) were compared to those actually achieved during encapsulation (Figs. 5–8). A correlation between the parameters was established by regression analysis where the $y$-intercept was forced to zero. For precompression densification settings, results showed a high correlation ($r^2 > 0.98$) between predicted and actual values of fill weights (Fig. 5) and plug heights (Fig. 7). For compression densification settings, results also showed a high correlation ($r^2 > 0.96$) between predicted and actual values of fill weights (Fig. 6) and plug heights (Fig. 8). High correlation between predicted and actual results shows that the model was successful in predicting encapsulation outcome for both powders. Statistical

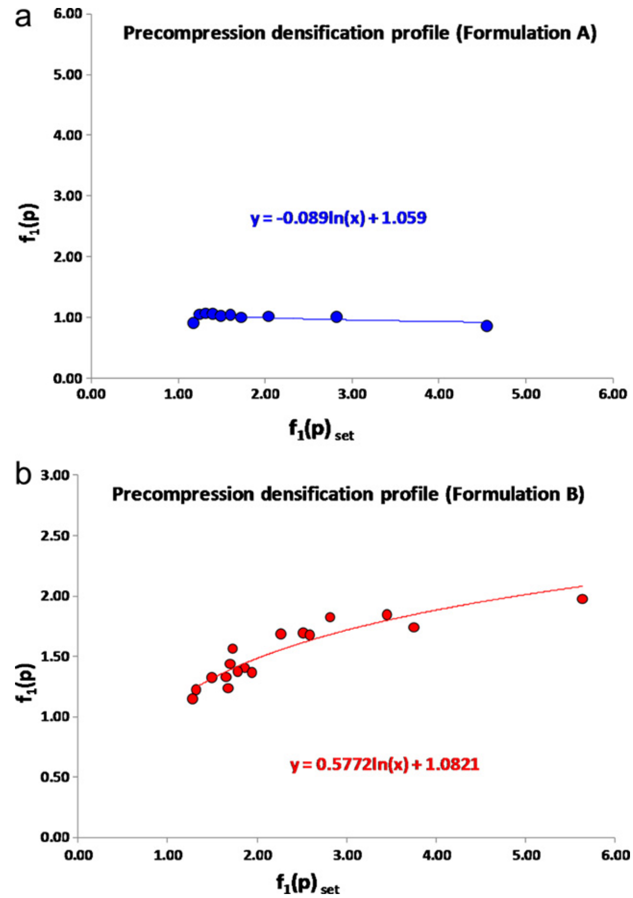


**Fig. 3.** Precompression densification profiles for the two powder formulations.

**Fig. 4.** Powder collapse during dosator movement due to formation of weak arches.

**Table 10**
Statistical analysis of precompression densification regression results (Fig. 3).

| Regression statistics | Formulation A | | Formulation B | |
|---|---|---|---|---|
| $R^2$ | 0.31 | | 0.85 | |
| Adj. $R^2$ | 0.23 | | 0.84 | |
| Standard err. | 0.06 | | 0.1 | |
| Observations | 10 | | 17 | |
| **Parameter estimation** | **Formulation A** | | **Formulation B** | |
| | Intercept | Slope | Intercept | Slope |
| Coefficients | 1.06 | −0.09 | 1.08 | 0.58 |
| Standard err. | 0.03 | 0.05 | 0.05 | 0.06 |
| $t$ stat | 32.80 | −1.90 | 20.58 | 9.35 |
| $p$-Value | $8.14 \times 10^{-10}$ | 0.0935 | $2.08 \times 10^{-12}$ | $1.21 \times 10^{-7}$ |

analysis of regression results (Table 13) shows that regression slopes in Figs. 5–8 were statistically significant ($p < 0.05$), analysis also showed a high correlation between predicted and actual results.

Results showed that formulation B had higher weight variation compared to formulation A, this variation was attributed to poor flow which can cause significant non-homogeneity within the powder bed. For formulation A; a higher weight variation was observed when precompression densification was applied compared to compression densification, this is likely due to formation of weaker powder arches resulting in portions of the powder falling outside the dosator during its movement (Fig. 4).

Precompression densification results showed that plugs were formed for formulation B but not A, which can be explained by Eq. (4) showing that precompression densification is dependent on powder flow. A freely flowing powder (i.e., formulation A; $F \approx 1$) will have limited densification from precompression ($f_1(p) \approx 1$), however, the achieved densification was sufficient to form an arch within the dosator but not a plug. On the other hand, a poorly flowing powder (i.e., formulation B; $F = 0.42$) will have significant precompression densification ($f_1(p) > 1$) that is sufficient to form a plug dense enough to be measured. This generally shows that precompression densification is not an effective means of densification for good flowing powders, and compression densification is more effective for such powders.

Overall, the model showed excellent prediction capabilities for the formulations tested, which represent two extreme cases that can be encountered during formulation development. The model's

**Table 11**
Formulation A encapsulation settings and outcomes.

| Setting[a] | $f_1(p)_{set}$ | $f_1(p)$ | $f_2(p)$ | $d_0$ (mm) | $d_1$ (mm) | Fill weight (mg) | | $H_{plug}$ (mm) | |
|---|---|---|---|---|---|---|---|---|---|
| **Precompression densification** | | | | | | | | | |
| | | | | | | Predicted | Measured[b] | Predicted | Measured[b] |
| A1 | 1.34 | 1.00 | 1.00 | 3.6 | 0.0 | 404 | 396 ± 18 | 22.4 | N/A[c] |
| A2 | 1.46 | 1.00 | 1.00 | 5.4 | 0.0 | 372 | 382 ± 16 | 20.6 | N/A[c] |
| A3 | 1.60 | 1.00 | 1.00 | 7.2 | 0.0 | 339 | 362 ± 26 | 18.8 | N/A[c] |
| A4 | 1.76 | 1.00 | 1.00 | 9.0 | 0.0 | 307 | 332 ± 14 | 17.0 | N/A[c] |
| A5 | 1.97 | 1.00 | 1.00 | 10.8 | 0.0 | 274 | 300 ± 14 | 15.2 | N/A[c] |
| A6 | 2.59 | 1.00 | 1.00 | 14.4 | 0.0 | 209 | 232 ± 3 | 11.6 | N/A[c] |
| A7 | 3.06 | 1.00 | 1.00 | 16.2 | 0.0 | 177 | 193 ± 2 | 9.8 | N/A[c] |
| A8 | 3.75 | 1.00 | 1.00 | 18 | 0.0 | 144 | 150 ± 2 | 8.0 | N/A[c] |
| A9 | 4.84 | 1.00 | 1.00 | 19.8 | 0.0 | 112 | 113 ± 2 | 6.2 | N/A[c] |
| **Compression densification** | | | | | | | | | |
| Setting[a] | $f_1(p)_{set}$ | $f_1(p)$ | $f_2(p)$ | $d_0$ (mm) | $d_1$ (mm) | Fill weight (mg) | | $H_{plug}$ (mm) | |
| | | | | | | Predicted | Actual[b] | Predicted | Actual[b] |
| A10 | 1.00 | 1.00 | 1.65 | 8.1 | 2.7 | 280 | 292 ± 2.9 | 9.39 | 10.23 ± 0.04 |
| A11 | 1.00 | 1.00 | 2.23 | 8.1 | 2.7 | | | 6.94 | 7.85 ± 0.05 |
| A12 | 1.00 | 1.00 | 1.63 | 7.2 | 0.9 | 325 | 321 ± 4.6 | 11.06 | N/A[c] |
| A13 | 1.00 | 1.00 | 1.72 | 5.4 | 0.7 | | 363 ± 5.0 | 11.65 | N/A[c] |
| A14 | 1.00 | 1.00 | 1.44 | 4.1 | 2.2 | | | 13.85 | 14.3 ± 0.05 |
| A15 | 1.00 | 1.00 | 1.93 | 4.1 | 2.2 | | | 10.35 | 10.88 ± 0.11 |
| A16 | 1.00 | 1.00 | 2.65 | 4.1 | 2.2 | 361 | | 7.55 | 8.28 ± 0.07 |
| A17 | 1.00 | 1.00 | 1.42 | 0.9 | 5.7 | | N/A[c] | 14.10 | 14.42 ± 0.02 |
| A18 | 1.00 | 1.00 | 2.57 | 0.9 | 5.7 | | N/A[c] | 7.80 | 8.25 ± 0.05 |
| A19 | 1.00 | 1.00 | 2.82 | 0.9 | 5.7 | | N/A[c] | 7.10 | 7.3 ± 0.1 |
| A20 | 1.00 | 1.00 | 1.77 | 3.6 | 1.0 | 388 | 381 ± 4.8 | 12.12 | N/A[c] |
| A21 | 1.00 | 1.00 | 1.38 | 0.9 | 1.8 | | | 16.97 | N/A[c] |
| A22 | 1.00 | 1.00 | 1.79 | 0.9 | 1.8 | 424 | 425 ± 7.6 | 13.12 | 13.65 ± 0.06 |
| A23 | 1.00 | 1.00 | 2.00 | 0.9 | 1.8 | | | 11.72 | 11.19 ± 0.04 |
| A24 | 1.00 | 1.00 | 2.36 | 0.9 | 1.8 | | | 9.97 | 9.97 ± 0.07 |
| A25 | 1.00 | 1.00 | 1.94 | 0.0 | 0.0 | 469 | 445 ± 6.1 | 13.40 | 13.03 ± 0.02 |

[a] Instrument settings detailed in Table 4.
[b] Weight was averaged from at least 7 capsules and plug height from at least 2 capsules.
[c] N/A: fill weight or plug height not measured at this setting or plugs were too soft to measure.

**Table 12**
Formulation B encapsulation settings and outcomes.

| Precompression densification | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Setting[a] | $f_1(p)_{set}$ | $f_1(p)$ | $f_2(p)$ | $d_0$ (mm) | $d_1$ (mm) | Fill weight (mg) | | $H_{plug}$ (mm) | |
| | | | | | | Predicted | Measured[b] | Predicted | Measured[b] |
| B1 | 4.55 | 1.87 | 1.00 | 21.6 | 0.0 | 90 | 94 ± 1.7 | 4.40 | 3.69 ± 0.02 |
| B2 | 2.82 | 1.60 | 1.00 | 18.9 | 0.0 | 124 | N/A[c] | 7.10 | 6.03 ± 0.03 |
| B3 | 2.04 | 1.41 | 1.00 | 16.2 | 0.0 | 152 | 181 ± 7.9 | 9.80 | 8.84 ± 0.05 |
| B4 | 1.60 | 1.27 | 1.00 | 13.5 | 0.0 | 174 | 199 ± 14.1 | 12.50 | N/A[c] |
| B5 | 1.40 | 1.19 | 1.00 | 11.7 | 0.0 | 187 | 199 ± 17 | 14.30 | N/A[c] |
| B6 | 3.31 | 1.69 | 1.00 | 18.9 | 0.0 | 132 | 133 ± 7.2 | 7.10 | 5.68 ± 0.01 |
| B7 | 2.51 | 1.53 | 1.00 | 16.7 | 0.0 | 157 | N/A[c] | 9.35 | 8.05 ± 0.01 |
| B8 | 2.03 | 1.41 | 1.00 | 14.4 | 0.0 | 179 | 208 ± 4.4 | 11.60 | 10.5 ± 0.07 |
| B9 | 1.70 | 1.31 | 1.00 | 12.2 | 0.0 | 198 | N/A[c] | 13.85 | 12.5 ± 0.01 |
| B10 | 1.46 | 1.22 | 1.00 | 9.9 | 0.0 | 215 | 222 ± 6.4 | 16.10 | N/A[c] |
| B11 | 3.75 | 1.76 | 1.00 | 18.0 | 0.0 | 155 | N/A[c] | 8.00 | 7.05 ± 0.07 |
| B12 | 3.06 | 1.65 | 1.00 | 16.2 | 0.0 | 177 | 185 ± 5.3 | 9.80 | 8.84 ± 0.12 |
| B13 | 2.24 | 1.47 | 1.00 | 12.6 | 0.0 | 215 | 211 ± 20.4 | 13.4 | N/A[c] |
| B14 | 1.76 | 1.33 | 1.00 | 9.0 | 0.0 | 247 | 239 ± 17.9 | 17.0 | N/A[c] |
| B15 | 2.26 | 1.47 | 1.00 | 9.0 | 0.0 | 274 | N/A[c] | 17.00 | 16 ± 0 |
| B16 | 1.59 | 1.27 | 1.00 | 1.8 | 0.0 | 336 | 336 ± 20 | 24.2 | N/A[c] |
| B17 | 2.35 | 1.49 | 1.00 | 9.0 | 0.0 | 278 | 284 ± 32.2 | 17.0 | N/A[c] |
| B18 | 1.86 | 1.36 | 1.00 | 4.5 | 0.0 | 320 | 328 ± 44.4 | 21.5 | N/A[c] |
| B19 | 1.72 | 1.31 | 1.00 | 2.7 | 0.0 | 335 | 327 ± 36.3 | 23.3 | N/A[c] |
| B20 | 1.59 | 1.27 | 1.00 | 0.9 | 0.0 | 349 | 360 ± 25.7 | 25.1 | N/A[c] |
| Compression densification | | | | | | | | | |
| Setting[a] | $f_1(p)_{set}$ | $f_1(p)$ | $f_2(p)$ | $d_0$ mm | $d_1$ mm | Fill weight (mg) | | $H_{plug}$ (mm) | |
| | | | | | | Predicted | Actual[b] | Predicted | Actual[b] |
| B21 | 1.00 | 1.00 | 1.22 | 13.5 | 3.3 | | | 7.77 | N/A[c] |
| B22 | 1.00 | 1.00 | 1.36 | 13.5 | 3.3 | | | 6.97 | N/A[c] |
| B23 | 1.00 | 1.00 | 1.54 | 13.5 | 3.3 | | | 6.17 | N/A[c] |
| B24 | 1.00 | 1.00 | 1.77 | 13.5 | 3.3 | 104 | 102 ± 12.3 | 5.37 | 5.48 ± 0.04 |
| B25 | 1.00 | 1.00 | 2.08 | 13.5 | 3.3 | | | 4.57 | 4.72 ± 0.02 |
| B26 | 1.00 | 1.00 | 2.32 | 0.9 | 17.3 | | | 4.09 | 4.18 ± 0.07 |
| B27 | 1.00 | 1.00 | 1.64 | 12.6 | 1.6 | 131 | 138 ± 6.0 | 7.32 | 7.61 ± 0.16 |
| B28 | 1.00 | 1.00 | 1.90 | 9.9 | 1.2 | 164 | 167 ± 9.8 | 7.90 | 8 ± 0.01 |
| B29 | 1.00 | 1.00 | 1.38 | 8.1 | 1.0 | 186 | 187 ± 12.8 | 12.28 | N/A[c] |
| B30 | 1.00 | 1.00 | 1.72 | 8.1 | 1.0 | 219 | 211 ± 13.4 | 9.88 | 9.83 ± 0.03 |
| B31 | 1.00 | 1.00 | 1.56 | 5.4 | 0.7 | | | 12.85 | N/A[c] |
| B32 | 1.00 | 1.00 | 1.26 | 3.6 | 2.1 | | | 16.27 | N/A[c] |
| B33 | 1.00 | 1.00 | 1.40 | 3.6 | 2.1 | 225 | 224 ± 15.2 | 14.67 | N/A[c] |
| B34 | 1.00 | 1.00 | 2.08 | 3.6 | 2.1 | | | 9.87 | 9.54 ± 0.09 |
| B35 | 1.00 | 1.00 | 2.48 | 3.6 | 2.1 | | | 8.27 | 8.83 ± 0.33 |
| B36 | 1.00 | 1.00 | 1.46 | 0.9 | 1.8 | | | 16.04 | N/A[c] |
| B37 | 1.00 | 1.00 | 1.83 | 0.9 | 1.8 | | | 12.84 | 12.29 ± 0.2 |
| B38 | 1.00 | 1.00 | 2.09 | 0.9 | 1.8 | 258 | 235 ± 18.8 | 11.24 | 10.72 ± 0.4 |
| B39 | 1.00 | 1.00 | 2.44 | 0.9 | 1.8 | | | 9.64 | 9.49 ± 0.01 |
| B40 | 1.00 | 1.00 | 2.92 | 0.9 | 1.8 | | | 8.04 | 8.36 ± 0.01 |

[a] Instrument settings detailed in Table 5.
[b] Weight was averaged from at least 7 capsules and plug height from at least 2 capsules.
[c] N/A: Fill weight or plug height not measured at this setting or plugs were too soft to measure.

**Table 13**
Statistical analysis of model prediction regression results (Figs. 5–8).

| | Formulation A | | | | Formulation B | | | |
|---|---|---|---|---|---|---|---|---|
| | Precompression | | Compression | | Precompression | | Compression | |
| | Weight | $H_{plug}$ | Weight | $H_{plug}$ | Weight | $H_{plug}$ | Weight | $H_{plug}$ |
| Regression statistics | | | | | | | | |
| $R^2$ | 0.9848 | N/A | 0.9632 | 0.9643 | 0.9723 | 0.9882 | 0.9743 | 0.9816 |
| Adj. $R^2$ | 0.8732 | N/A | 0.7992 | 0.9073 | 0.9260 | 0.8873 | 0.8314 | 0.9077 |
| Standard err. | 12.95 | N/A | 11.28 | 0.49 | 12.99 | 0.39 | 8.92 | 0.33 |
| Observations | 9 | N/A | 6 | 12 | 15 | 10 | 7 | 12 |
| Parameter estimation | | | | | | | | |
| Coefficients | 1.05 | N/A | 0.99 | 1.03 | 1.03 | 0.90 | 0.97 | 0.99 |
| Standard err. | 0.02 | N/A | 0.01 | 0.01 | 0.01 | 0.01 | 0.02 | 0.01 |
| $t$ stat | 67.27 | N/A | 81.38 | 78.38 | 73.10 | 76.02 | 55.10 | 89.55 |
| $p$-Value | $2.7 \times 10^{-12}$ | N/A | $5.3 \times 10^{-9}$ | $1.8 \times 10^{-16}$ | $1.7 \times 10^{-19}$ | $6.0 \times 10^{-14}$ | $2.4 \times 10^{-9}$ | $4.2 \times 10^{-17}$ |

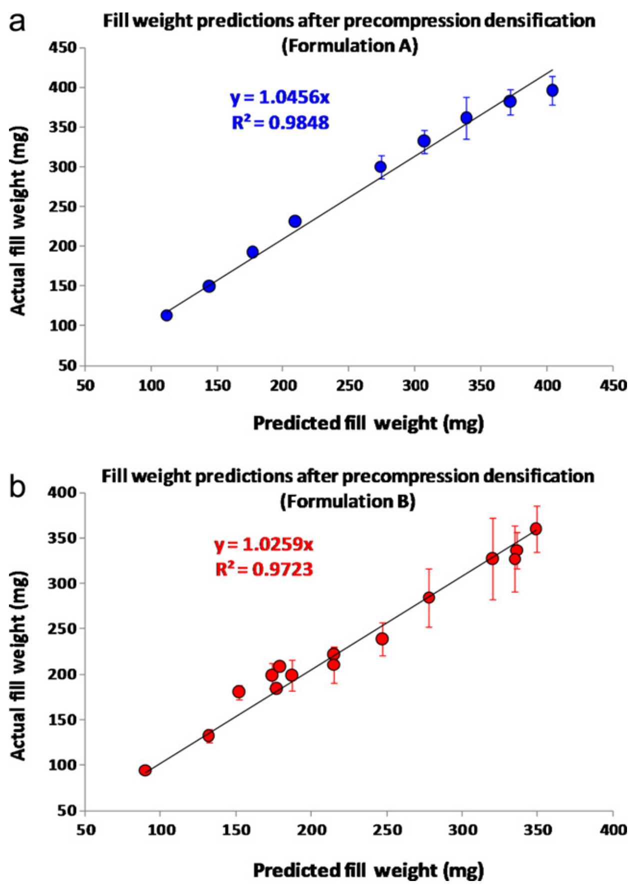


**Fig. 5.** Fill weight predictions after precompression densification.

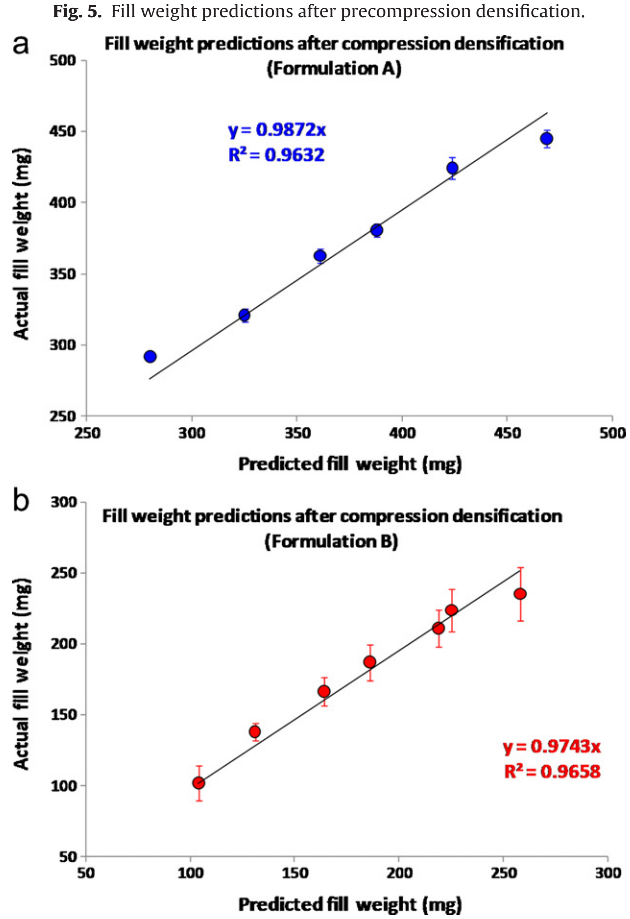


**Fig. 6.** Fill weight predictions after compression densification.

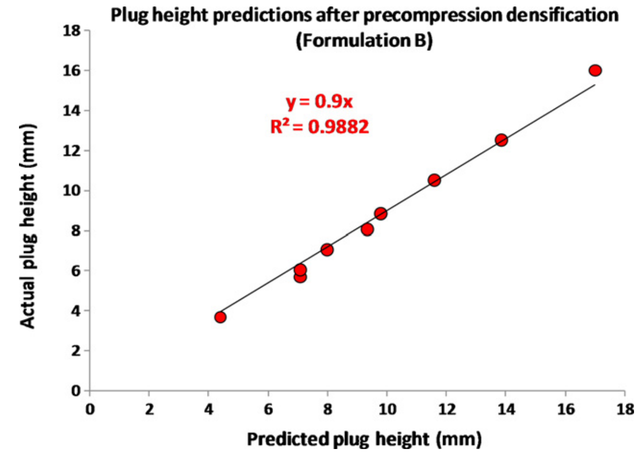


**Fig. 7.** Plug height predictions after precompression densification.

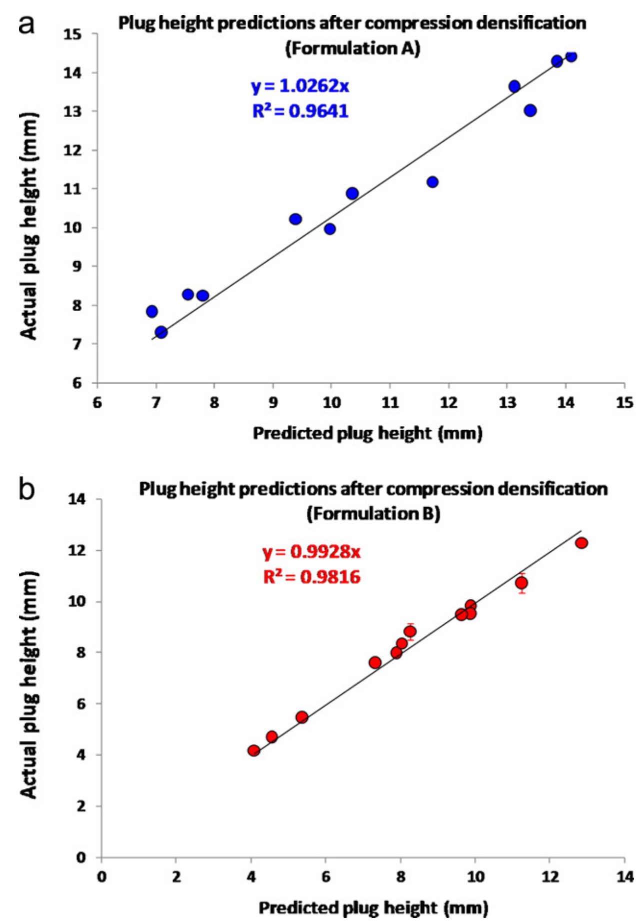


**Fig. 8.** Plug height predictions after compression densification.

true potential, sensitivity and limitations can be fully revealed after testing several other powder formulations.

## 4. Conclusions

A theoretical model was utilized to model dosator-based encapsulation which requires powder densification within a dosator for successful encapsulation. According to the model, powder densification within a dosator could be achieved by precompression, compression or both. Precompression densification occurs when powder bed heights are higher than piston heights ($H_{powder} > H_{piston}$) while compression densification occurs from piston displacement against the powder ($\Delta H$).

Model predictions were compared to encapsulation results obtained using a Zanasi automatic encapsulation machine. The model successfully predicted the encapsulation outcome of two substantially different powder formulations having significantly different flow properties. For each powder, the model correctly predicted the encapsulation fill weight and plug height achieved under both precompression and compression densification settings. The extent of precompression densification was inversely related to powder flow as predicted by the model.

The model offers a promising *in silico* analysis tool that can be used for capsule dosage form development.


## Acknowledgements

The authors would like to thank Dr. Jaromir Mikl for his input on statistical analysis of data, Dr. Manami Tsutsumi for her help during the literature review and Dr. Sumaya Hamadmad for the encouragement and fruitful discussions during the preparation of this manuscript.


## References


Gioia, A., 1981. Powder Flowability Test Equipment, United States Patent. Gruppo Lepitit S.p.A.

Khawam, A., 2011. Modeling powder encapsulation in dosator-based machines. I. Theory. Int. J. Pharm. 421, 203–209.

USP34-NF29, 2011. United States Pharmacopeia, General Chapters: <1174> Powder flow, U.S. Pharmacopeia, Rockville, Maryland, USA, p. 723.