

## **The Influence of Pellet Shape, Size and Distribution on Capsule Filling – Three Dimensional Computer Simulation using a Monte-Carlo Technique**

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### **Abstract**

A computer simulation based on a Monte Carlo technique has been developed and used to investigate the influence of pellet size, dispersity, shape and aggregation on the filling of hard shell capsules. The results are in agreement with experimental observations previously reported. The results also confirm recent findings that filling is a function of pellet shape and that a threshold aspect ratio value of 1.2 is important for reproducible filling. The methodology is simple and rapid in execution allowing many computer-based experiments to be performed with minimum effort.

### **1 Introduction.**

Hard shell capsules coating pellets are now a recognised formulation for controlled or modified release oral dosage forms and there are an increasing number of products on the market. They offer advantages over monolithic single dosage forms such as tablets in that the risk of dose dumping is significantly reduced. Accuracy of filling is essential for dosage control but literature data on this aspect is (are? Data being plural?) sparse. Marquardt and Clement (1970) investigated the effect of pellet size concluding that any variation in dose was a consequence of fluctuations in particle size. In a later paper Pfeifer and Marquardt (1986) reported that errors in filling were a consequence either of aggregation or of the build up of electrostatic charge. Recently Chopra et al (2002) concluded that the pellets did not need to be perfectly spherical in shape but that there was a threshold value for the aspect ratio of 1.2. In addition both the surface roughness and the build up of electrostatic charge were important variables.

A problem with conclusions drawn from laboratory experiments is that they inherently depend on the experimental conditions and filling machine settings and it is difficult to decouple the interactions between variables. A simple way of factoring out these variables and to investigate individual variables independent of others is to use computer simulation. The aim of this work is to investigate the applicability of a Monte-Carlo technique to study the effects of pellet shape, size and size (otherwise the implication might be spatial distribution) distribution on filling accuracy for different capsule sizes.

### **2 Materials and methods**

#### **2.1 Capsule definition.**

Filling simulations were performed on standard capsule sizes 0-4. The capsules were simulated as cylindrical tubes with rounded bottoms, with dimensions chosen to give

the correct size of the capsule bodies as given by Cole (1987). The sides and bottom of capsules were treated as hard walls, so that no part of any particle could cross them. The top of the capsule was treated as a 'soft' boundary, as introduced by Evans and Ferrar (1989). A particle that crosses this boundary is permitted in the packing, provided the centre of gravity of that particle lies within the capsule.

## 2.2 Pellet shape definition

Pellets varied in shape and included spheres of diameter 1 mm, ellipses (with diameter 1.0 and aspect ratios 1.2 and 1.5) and cylinders (with diameter 1 and an aspect ratio of 2). The elliptical and cylindrical pellet shapes, as shown in Figure 1(a) – 1(c), were each made of three overlapping spheres using the MacroPac ShapeBuilder as published by Intelligensys (2001). The concept of using overlapping spheres to build up complex shapes was introduced by Evans and Ferrar (1989) and is a particularly efficient way of studying the packing of non-spherical particles, since checking whether two particles collide reduces to a simple sphere-checking calculation that is quick to perform.

Where pellets of different size were used, the size distributions were taken by selecting from a uniform distribution ranging from the minimum to the maximum values. The MacroPac ShapeBuilder incorporates a volume calculation for the non-spherical pellets, and hence packing volumes and fill weights (if a density is assumed) can be calculated.

Aggregates of pellets were also investigated, by building up two different structures of spheres with diameter 1 mm. These are shown in Figure 1(d) and 1(e). The first of these is a very loose aggregate made of 7 spheres. The second is a more dense aggregate of 5 spheres, three in a triangular array, with single spheres above and below the 3-fold hollow.

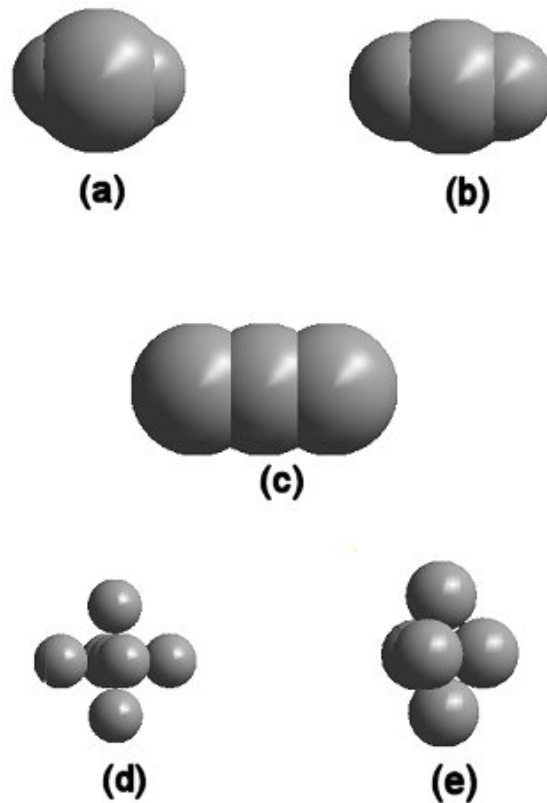


Figure 1

Shapes of pellets and aggregates used in simulations (not to scale)

### 2.3 Filling simulation

A Monte Carlo algorithm implemented in the MacroPac program from Intelligensys (2001) was used to fill the capsules. This follows ideas introduced by Soppe (1990) and Rosato et al (1987) but has been extended to encompass random numbers of non-spherical particles. Soppe's algorithm is a two-step process: in stage 1, a defined number of particles is packed using a ballistic algorithm, and in stage 2, these particles are moved randomly using a Monte Carlo algorithm, to simulate more densely packed systems. For the simulations reported here, because the number of particles to be packed is not known at the outset, Soppe's first step (ballistic packing of the particles) is inappropriate. In our algorithm, as each particle is packed, the whole system is subjected to a "settling" process; this is similar in concept to the second stage of Soppe's algorithm. In each Monte Carlo step, a random particle is chosen, and is given a random displacement of magnitude between 0 and an upper limit  $R_{\max}$ . Non-spherical particles are also rotated randomly by a small amount. If the new position of the particle overlaps with any other particle, the move is rejected. If there is no overlap, the move is accepted, provided the displacement of the particle's centre of mass along the long axis of the capsule is negative (so that the particle moves towards the bottom of the capsule). Particles are not allowed to move outside the box. Within this procedure,  $R_{\max}$  starts at a user-specified value, and

decreases inversely with the number of unsuccessful attempts to move an object. Although in principle this algorithm might lead to size segregation, in practice the studies used here had sufficiently small polydispersity that this effect was not significant.

#### 2.4 Analysis of results

For each case, 10 different simulations were performed, using a different random seed in each case to start the Monte Carlo calculation. Both the number of particles and the total volume and weights (assuming a constant density) of these particles were calculated. In all the simulations a density of 1.0 was assumed. The mean weight  $\pm$  standard deviation were recorded.

### 3 Results

#### 3.1 The effect of pellet size

Pellets manufactured by the process of extrusion and spheronisation generally have a mean size of between 0.8mm and 1.2mm depending on the diameter of the hole in the extruder die plate. Computer simulations of the packing of No 0 capsules with unimodal spherical pellets of mean sizes of 0.8 and 1.0mm are shown in Figure 2. Both simulations were completed within minutes despite the fact that the capsule filled with 0.8 mm pellets contained in excess of 1420 pellets. Fill weight data (Table 1) for all sizes of capsules showed a gradual decrease in fill weight and increasing variability with increasing pellet size confirming experimental observations (Marquardt and Clement, 1970).

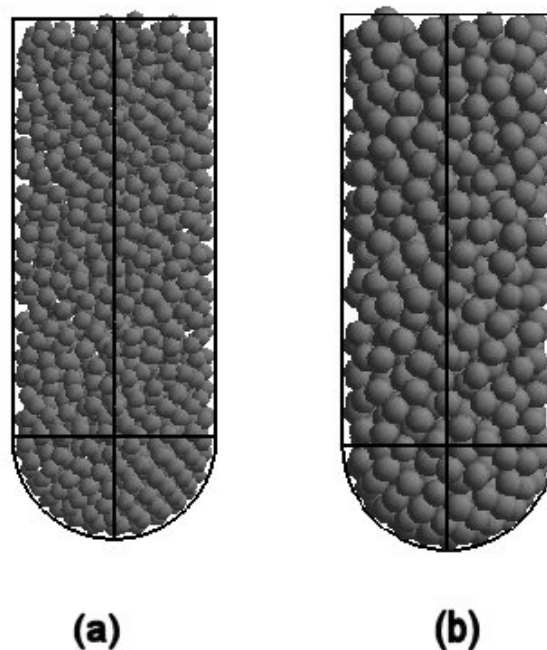


Figure 2 Computer simulations of a No 0 capsules containing (a) 0.8mm uniform pellets and (b) 1.0mm uniform pellets

Capsule size	0.8mm pellets	1.0mm pellets	1.2mm pellets
0	381.9±1.5	377.3±1.0	369.9±3.2
1	273.1±1.2	269.2±2.2	267.4±1.7
2	210.2±1.0	207.5±1.4	205.8±2.2
3	152.4±0.8	150.7±1.2	149.4±2.4
4	135.8±0.9	134.8±1.2	133.9±1.3

Table 1 The effect of pellet size on fill weight (all pellets uniform size, weights in mg)

### 3.2 The effect of pellet size distribution

Size polydispersity of pellets is an important factor to be considered if the pellets are to be film coated for controlled release (Husson et al., 1992). A computer simulation of a No. 0 capsule containing 1.0mm pellets with a width of distribution of 0.8-1.2 mm is shown in Figure 3. Fill weight data (Table 2) indicate that, for all sizes of capsules, increasing polydispersity within the set range normally seen with pellets produced by extrusion and spheronisation has no effect on fill weight or weight variation.

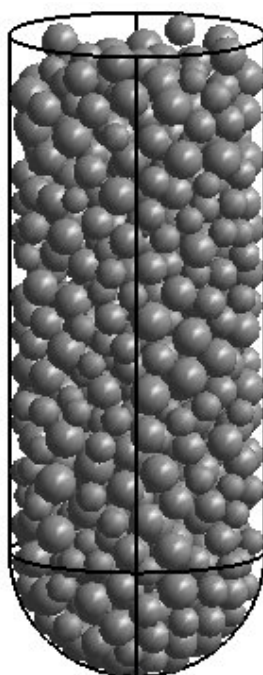


Figure 3 Computer simulation of a No 0 capsules containing 1.0 mm pellets with increasing width of distribution

Capsule size	Uniform	0.9-1.1mm	0.8-1.2mm	0.7-1.3mm
0	377.3 ± 1.0	378.9±2.2	377.8±1.8	378.1±2.9
1	269.2±2.2	269.3±2.4	268.9±1.4	271.6±2.0
2	207.5±1.4	208.4±1.4	207.6±2.0	209.2±1.6
3	150.7±1.2	151.8±1.3	151.2±1.3	151.1±1.6
4	134.8±1.2	135.4±1.0	135.2±1.1	136.2±0.9

Table 2 The effect of increasing width of distribution of pellets of mean size 1.0mm on fill weight in mg

### 3.3 The effect of pellet shape

A whole range of pellet shapes ranging from rounded cylinders to dumbbells and ellipsoids can be obtained if the process of extrusion and spheronisation is not optimised (Rowe 1985). Recently Chopra et al (2002) have investigated the influence of pellet shape on capsule filling. Shapes in this case were defined in terms of their aspect ratio and it was these shapes that have been simulated in this study. A computer simulation of a No. 0 capsule filled with pellets with an aspect ratio of 1.5 is shown in Figure 4. Fill weight data for all sizes of capsule with pellets of increasing aspect ratio and pellet size both unimodal and with a distribution of between 0.8-1.2 mm are shown in Table 3. For aspect ratios of 1.2 and below, there is no difference in fill weight or weight variation. However above this value fill weight decreases, with a corresponding increase in variability. This threshold value of 1.2 confirms the experimental observations (Chopra et al 2002).

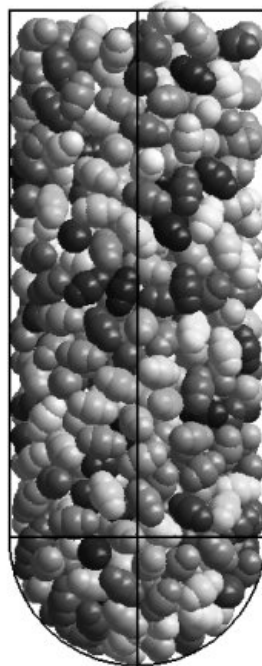


Figure 4 Computer simulation of a No 0 capsule containing pellets with an aspect ratio of 1.5

#### A. Uniform Size

Capsule size	AR 1.0	AR 1.2	AR 1.5	AR 2.0
0	377.3±1.0	380.2±2.4	370.7±3.6	354.0±5.6
1	269.2±2.2	271.2±1.5	265.4±2.9	250.5±5.6
2	207.5±1.4	208.0±2.0	205.1±2.8	194.4±3.7
3	150.7±1.2	152.4±2.0	149.2±2.1	141.6±1.8
4	134.8±1.2	136.0±1.2	132.5±2.4	128.0±2.9

#### B. Size distribution 0.9-1.1

Capsule size	AR 1.0	AR 1.2	AR 1.5	AR 2.0
0	378.9±2.2	376.9±2.8	367.6±4.5	344.8±5.8
1	269.3±2.4	271.4±1.9	262.7±3.2	248.9±3.0
2	208.4±1.4	209.0±1.3	204.5±3.5	192.7±2.5
3	151.8±1.3	150.8±1.7	148.1±2.4	141.6±3.8
4	135.4±1.0	135.8±1.4	134.4±2.2	126.3±3.9

Table 3 The effect of pellet shape as defined by aspect ratio (AR) on fill weight (in mg)

#### 3.4 The effect of the addition of aggregates

Pellet aggregation either due to electrostatic charging or as a consequence of a non optimised drying process is a problem well-known in the filling of pellets into hard shell capsules (Pfeifer and Marquardt, 1986). Unfortunately there are no details of the shape of aggregated pellets in the literature and it is not possible to simulate the aggregation process per se. However it is possible to pre-define an aggregate shape and then simulate the effect of the inclusion of a fixed concentration of the aggregates in non aggregated pellets of a defined shape and size and predict fill weight. A computer simulation of a No 0 capsule containing 10% of an aggregate of 5 spherical pellets (Figure 1e) in unimodal pellets of 1.0 mm diameter is shown in Figure 5a. Removal of the non-aggregated pellets shows the distribution of the aggregates in the capsule shell (Figure 5b). Inclusion of this aggregate at this concentration did not have any effect on fill weight or variability for all capsule sizes (Table 4). However if this aggregate was replaced by a larger looser type consisting of seven spherical pellets (Figure 1d), under-filling occurred.

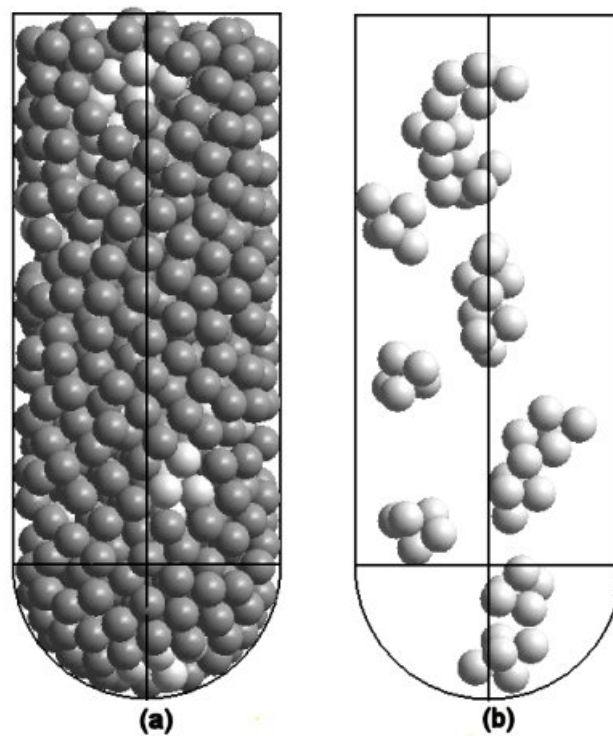


Figure 5 Computer simulations of a No 0 capsule coating 1.0 mm uniform pellets with 10% aggregate 2 complete (5a) and showing just the spatial distribution of the aggregates(5b)

Capsule size	Aggregate 1	Aggregate 2
0	357.1 $\pm$ 2.0	374.4 $\pm$ 2.5
1	255.3 $\pm$ 1.7	267.1 $\pm$ 2.2
2	198.0 $\pm$ 1.6	205.6 $\pm$ 2.0
3	144.0 $\pm$ 1.6	150.1 $\pm$ 1.0
4	126.4 $\pm$ 1.5	134.8 $\pm$ 1.5

Table 4 The effect of aggregate shape on fill weight (aggregate concentration 10%)

#### 4 Conclusion

The results seen with the computer simulations are in agreement with the experimental observations previously reported for filling real capsules with real pellets on automatic capsule filling machines. Although it is not yet possible to simulate the specific process of a filling machine within practicable computer resources, computer simulation can decouple the variables and allow the investigation of those pellet variables (size, shape, polydispersity) that are known to affect capsule filling. An area not previously studied is that of aggregate shape, size, polydispersity and concentration. Preliminary studies indicate that computer simulation will be appropriate in this case where it will be difficult to reproduce the experiments in the laboratory. The calculations are rapid and easy to perform allowing a large number of variables to be studied within realistic timescales. It is envisaged that this technique

will be invaluable to formulators developing pelleted products where drug cost and availability is an issue (are important issues?).

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