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Research paper

The influence of pellet shape and film coating on the filling of pellets into hard shell capsules

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Abstract

Pellets of different shape, varying from spherical to cylindrical, were filled into hard shell capsules. When no film coat was applied, the pellets had not to be perfectly spherical in order to be filled reproducibly. An aspect ratio of 1.2 or less appeared to be the threshold value. However, pronounced surface roughness hindered the filling process, and hence it appears necessary to monitor this parameter. After coating of the pellets with an ethylcellulose film, none of the batches could be filled to an acceptable standard, because electrostatic loading led to a blockage of the filling mechanism. However, the addition of 1% talcum powder was sufficient to remove all charges, and again filling became a function of the pellet shape, confirming the threshold aspect ratio value of 1.2.

Keywords: Capsule filling; Electrostatic charging; Pellet shape; Pellet surface roughness

1. Introduction

The use of pellets in controlled-release oral solid dosage forms provides advantages over monolithic single-dose units such as tablets. For example, the risk of dose dumping is reduced, and mixtures of pellets of different release patterns can be used to control drug delivery with time. However, pellets need to be transformed into suitable single doses, which can be achieved by filling them into hard shell capsules.

The main problems when filling pellets into capsules are their propensity to acquire electrostatic loading and to show flow problems. Literature reports on the filling of pellets into capsules are sparse, although there is an increasing number of pellet-filled hard shell capsule products on the market, for example, Inderal®, Surgam®, and Losec MUPS®. Marquardt and Clement [1] investigated the dosing accuracy of pellets during automatic capsule filling. The pellets used by these authors produced capsule fill weights spreading over a narrow range and showing little fill weight variation. Unfortunately, the authors described their pellets only with respect to size, and the shape was not mentioned. The conclusion that any fluctuation in dose was a result of variations in pellet size is hence questionable. Pfeifer and Marquardt [2] reported that dosage errors when filling pellets resulted mainly in underfilled, but occasionally also in overfilled capsules. Underfilling was contributed to the presence of agglomerates and a build-up of electrostatic charges. Also dust could hinder pellet flow and thus lead to lower fill weights than expected. Overfilling was mainly a result of a faulty or a non-cut capsule being unable to accept any pellets. This subsequently led to the following capsules being overfilled. While the authors suggested the prevention of underfilling by deagglomeration and addition of an external lubricant, they concluded that the placing of the capsule body bushing was important to prevent overfilling in terms of a prevention of capsules jamming or being sheared.

The aim of this work was to identify factors related to the filling performance of uncoated and coated pellets, which varied in their shape and surface roughness.

2. Materials and methods

2.1. Materials

The materials used were all of British Pharmacopoeia (BP) grade and were used as supplied. The model drug included was paracetamol, fine powder (Bechpharm, Harlow, UK, batch 3D169). The basic material used to ensure successful extrusion/spheronization was micro-

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Table 1
Pellet shape, surface roughness and flow characteristics of uncoated pellets[a]

Batch	AR	EL	e_R	CL(s)	CI (%)	R_a (μm)	R_q (μm)	R_{tm} (μm)	CL(r)
SP	1.06 ± 0.04	0.53 ± 0.10	0.38 ± 0.09	1	2.22	1.99 ± 0.25	2.54 ± 0.29	11.5 ± 1.1	2
AL	1.08 ± 0.03	0.49 ± 0.08	0.42 ± 0.08	1	4.53	2.69 ± 0.61	3.54 ± 0.84	13.1 ± 2.0	3
GR	1.11 ± 0.06	0.54 ± 0.10	0.36 ± 0.10	1	4.85	2.79 ± 0.79	3.59 ± 0.97	13.6 ± 3.0	3
DS	1.10 ± 0.03	0.43 ± 0.09	0.47 ± 0.09	1	4.93	2.94 ± 0.25	3.98 ± 0.59	15.4 ± 2.0	4
OV	1.22 ± 0.06	0.74 ± 0.08	0.19 ± 0.08	2	3.24	2.19 ± 1.01	2.78 ± 1.26	10.2 ± 2.6	2
DU	1.44 ± 0.10	0.99 ± 0.08	−0.06 ± 0.07	2	4.14	1.48 ± 0.13	1.88 ± 0.16	8.3 ± 0.3	1
LD	1.59 ± 0.17	1.10 ± 0.04	−0.16 ± 0.04	3	4.20	1.60 ± 0.21	2.00 ± 0.25	7.9 ± 0.6	1
CY	1.80 ± 0.26	1.19 ± 0.05	−0.26 ± 0.06	3	7.64	2.41 ± 0.56	3.11 ± 0.57	12.3 ± 1.8	2

[a] AR, aspect ratio; EL, elipticity as defined in Ref. [4]; e_R, 3D-shape factor as defined in Ref. [4]; CL(s), cluster number for shape factors; CI, Carr's compressibility index; R_a, rugosity; R_q, root-mean-square deviation of the roughness profile from the mean line; R_{tm}, mean peak-to-valley ratio; CL(r), cluster number for surface roughness parameters.

crystalline cellulose (Avicel PH101®, FMC Corp., Cork, Ireland, batch 6015 and 6240). A further aid to extrusion was the inclusion of glyceryl monostearate supplied as Imwitor 940 (Hüls, Milton Keynes, UK, batch 209215). The filler included as a water insoluble material was barium sulphate (Chemische Werke GmbH, Sachtleben, Germany, batch 7727-43-7). The water used as an essential fluid for processing was purified by reverse osmosis. For one set of pellets this was replaced with a 70 v/v-% solution of ethanol (Merck, Poole, UK) in water. The basic formulation was paracetamol 10%, glyceryl monostearate 16%, microcrystalline cellulose 50%, barium sulphate 24% and liquid q.s.

2.2. Manufacture of pellets

Pellets were produced by a standardized process of extrusion and spheronization, but differences were incorporated so that the pellets had a range of shapes. The variables, which were employed to achieve this, were: (a) the solid to water ratio; (b) the length of time on the spheronizer plate; (c) passing the wet mass through an oscillating granulator (ERWEKA type FGS, Heusenstamm, Germany) fitted with a 1 mm square aperture mesh, set at an oscillation speed of 4 instead of extruding it; and (d) spheronizing the wet mass directly from the planetary mixer.

The wet mass was produced by dry mixing the powders for 5 min in a planetary mixer (Hobart, London, UK). The necessary quantity of fluid was gradually added and mixing was continued for 10 min, scraping the sides of the bowl at regular intervals. Samples to be extruded were processed with a capillary extrusion rheometer (ACER 2000, Rheometric Scientific, Loughborough, UK), fitted with a die of 1 mm diameter and 4 mm length with a 60° entry angle. The ram speed employed was 200 mm/min. The extrusion process was repeated until there was sufficient extrudate, at least 500 g, to process for 10 min unless otherwise stated on a 22.5 cm diameter radial geometry plate fitted to a spheronizer (GB Caleva, Stourminster Newton, UK) rotating at 1000 rev./min. The wet mass from both the granulation and planetary mixing were subjected to the same spheronization conditions. To prepare elongated pellets, one batch of extrudate was spheronized for 10 s only (see Table 1). The pellets were dried for 24 h at 45 °C in an oven (Hotbox size 1, Gallenkamp, London, UK). Each batch of pellets was sieved (Endecotts, London, UK) to obtain a 1–1.4 mm size fraction. In total, eight batches of pellets were produced, which can be described as follows:

- batch SP (extrusion/spheronization employing standard conditions), spherical;
- batch AL (extrusion/spheronization using 70% ethanol as binder liquid), spherical;
- batch GR (granulation/spheronization), spherical;
- batch DS (direct spheronization), spherical;
- batch OV (extrusion/spheronization, reduced liquid binder concentration), oval;
- batch DU (extrusion/spheronization, reduced liquid binder concentration), dumbbells;
- batch LD (extrusion/spheronization, reduced liquid binder concentration), long dumbbells;
- batch CY (extrusion/spheronization, spheronization time 10 s), cylindrical.

2.3. Film coating

A desirable film coating thickness of about 25 μm was chosen. The amount of coating material required per gram of pellets was estimated taking into account the mean diameter and surface area of the pellets and the calculated volume of the coating layer and its density. Preliminary experiments established that a 3% solution of ethylcellulose (Ethocel®, Dow Chemical Company, Midland, MI) in ethanol (Finsprit® 95 v/v-%, Kemetyl, Stockholm, Sweden) containing 17.5% of povidone (PVP; Kollidon® K90, BASF, Ludwigshafen, Germany) provided a film coat with pores which would allow controlled release of a model drug (paracetamol).

The film coating was carried out using the 'Gandalf 0' fluidized bed coater (Astra Hässle, Mölndal, Sweden), which had a 10 cm diameter perforated bottom plate and a 5 cm diameter Wurster cylinder and was fitted with a bottom

spray pneumatic nozzle (Schlich 970, Germany). Preliminary studies established that the optimum conditions, i.e. even coating with no pellet agglomeration, were batch size 400 g, inlet temperature 50 °C, outlet temperature 31 °C, atomizing air flow 1.33 m^3h^{-1}, fluidizing air flow 34 m^3h^{-1}, atomizing air pressure 169 kPa, pump speed 46 rev./min and coating solution 1202 g. Under these conditions of operation without spraying fluid less than 5 g of weight loss of pellets was observed in any of the formulations. Thus, pellets were not subjected to gross size changes caused by their friable nature.

The equipment was set up and the pellets placed into the coating chamber. After the optimum conditions were achieved the coating cycle lasted 115 min.

2.4. Pellet size and shape

Pellet size and shape were simultaneously analyzed using an image analyzer (Solitaire 512, Seescan, Cambridge, UK) connected to a b/w CCD-4 camera (Rengo Co., Toyohashi, Japan) and a zoom lens (18–108/2.5, Olympus Europe, Hamburg, Germany). Breadth and length were determined as the shortest and the shortest-perpendicular Feret-diameter of 36 diameters measured around the pellets. The aspect ratio as defined by Schneiderhöhn [3] and a three-dimensional shape factor as described by Podczeck and Newton [4] were obtained. The degree of ellipticity [4] was also recorded. All values are the mean and standard deviation of 30 pellets.

2.5. Surface roughness

The surface roughness was evaluated by laser profilometry (UBM Microfocus Measuring System, UBM Meßtechnik GmbH, Ettlingen, Germany). The laser spot size was 1 μm, and the aperture angle was 53°. The measured area was 200×200 μm with a resolution of 1000 points/mm in X-direction and 500 points/mm in Y-direction. The scanning speed was 100 points/s. The results are the mean and standard deviation of five pellets. The parameters recorded were the rugosity R_a, which is the arithmetic average distance value of all points of the profile from the centre line, the root-mean-square deviation R_q of all points of the profile from the centre line, which characterizes the variability of the profile, and the mean-peak-to-valley height R_{tm}, which represents the difference between the maximum and minimum point of the entire profile (average of 25 equal square sections of the profile).

2.6. Minimum and maximum bulk density

A mechanical tapping device, the jolting volumeter (J. Engelsmann, Ludwigshafen, Germany) was used to determine the minimum and maximum bulk density of the pellet batches. Eighty grams were placed into a 100 ml measuring cylinder. The starting volume and the volume after 1000 taps were recorded. All values are the mean and standard deviation of three replicates.

2.7. Capsule filling

The uncoated pellets were filled into hard gelatin capsule shells size 0 (red/beige, Capsugel, Colmare, France) on an intermittent three-head capsule filling machine (KFM III, Harro Höfliger, Allmersbach, Germany). The filling speed was 300/min. The capsules were weighed automatically on a capsule weighing machine (KWS 12-S, Harro Höfliger, Allmersbach, Germany). The acceptable weight range was set to 400–500 mg. Capsules outside this range were counted as over- or underfilled. Between 800 and 1500 capsules were filled in an attempt to achieve 800 capsules in the target range of fill weight. The coated pellets were also filled into hard gelatin capsules size 0, but using pale blue/dark blue shells (Capsugel, Bornem, Belgium). Here, a GKF 700 S (Robert Bosch GmbH, Waiblingen, Germany) with pellet filling station (330 capsules/min) was employed, because the previously used machine was no longer available. The fill weight was assessed using a Bosch KKE 2000S automatic check weight system (Robert Bosch GmbH, Waiblingen, Germany), whereby the target fill weight after correction for the empty shells (94 ± 1 mg) was set to 393 mg ± 10%, i.e. an accepted range of 354–432 mg. To lubricate the pellets, these were mixed with 1% talcum powder (EP-grade, Merck, Darmstadt, Germany) for 5 min in a drum hoop mixer (type Mini 80, J. Engelsmann AG, Ludwigshafen, Germany) at a mixing speed of 28 rev./min. The change from one to the other machine is not expected to have an influence on the filling performance of the pellets. Both machines fill via the classical slide mechanism [5] and hence the amount of electrostatic charging acquired due to the opening and closing of the dosing slide and the extent of pellet damage will be similar.

2.8. Statistical data evaluation

All statistical evaluation was undertaken using SPSS 10.0 (SPSS Inc., Woking, UK).

3. Results and discussion

3.1. Filling of uncoated pellets without the addition of a lubricant

Particle shape and surface roughness parameters are not available as absolute values. Several parameters have to be evaluated simultaneously to be able to characterize and classify particles [6]. Hence, several shape and roughness parameters were obtained. These are summarized in Table 1. To separate the influence of the degree of ellipticity from the total values of the three-dimensional shape factor, the ellipticity component [4] is also included in Table 1. The table also provides an indication of the pellet flow properties

expressed as Carr's compressibility index. In order to assess the influence of the pellet properties on the filling performance, it is of vital importance to avoid the introduction of additional factors such as lubrication, as these can alter the surface properties of the pellets. Hence, the pellets were filled without pre-treatment with a lubricant. In Table 2 the filling performance of the uncoated pellets into hard shell capsules is illustrated. The filling results are here described as the number of capsules required to be filled to obtain 800 capsules in the target weight range, the percentage of capsules underfilled, and the mean weight of the capsules in the target weight range. In general, no overfilled capsules were found. Hence, a poor filling performance is here demonstrated by a larger amount of capsules being underfilled, and to some degree by a decrease in the mean fill weight of capsules in the target weight range.

Due to the limited number of pellet batches tested, a numerical analysis of the influence of pellet shape and surface roughness on the filling properties of the pellets into hard shell capsules would not be possible. However, the utilization of non-parametric test procedures on the basis of parameter clusters had been found useful previously [6]. Hence, cluster analysis as described by Podczeck [7] was employed to group the data available (Tables 1 and 2).

An optimal scaling procedure (SPSS software package, advanced statistics module) was employed to relate the cluster numbers for the percentage of underfilled capsules to the groups of pellets as ascertained by cluster analysis on the basis of pellet shape and surface roughness. The correlation between the optimally scaled variables (r_o) showed that the amount of underfilled capsules (%) is mainly a function of the pellet shape ($r_o = 0.929$). The surface roughness of the pellets ($r_o = 0.553$) and the pellet flow properties ($r_o = 0.581$) are not as strongly related as the pellet shape, but the values indicate some degree of relationship. In addition, the component loadings of the scaled values identified a close relationship between pellet flow and pellet surface roughness, so that in fact the pellet flow appears to be a function of the surface roughness and hence is only a secondary factor influencing the filling performance. If an amount of underfilled capsules of 1% was regarded as acceptable, it appears as though pellets need not be ideally spherical to provide good filling results. Under this assumption it follows that a simple shape factor such as the aspect ratio is sufficient to identify filling and non-filling batches, and the limiting value appears to lie just above 1.2. However, the results also suggest that an increased surface roughness (value for rugosity R_a significantly larger than 2 μm) can lead to disturbances of the filling process, presumably due to increased friction and thus a more pronounced sensitivity to electrostatic charging. This is illustrated in Fig. 1 comparing the capsule fill weight distributions for pellet batches SP ($R_a = 1.99$ μm; no underfilled capsules) and DS (1% of underfilled capsules and $R_a = 2.94$ μm, i.e. being significantly larger than 2 μm) as an example. The R_a values are different by about 1 μm, and the fill weight distribution has shifted for batch DS to smaller weights and has a more pronounced tail of underfilled capsules.

3.2. Filling of coated pellets without the addition of a lubricant

The key values of pellet shape and surface roughness are summarized in Table 3. Undertaking the same filling procedure, none of the pellet batches could be filled satisfactorily into the hard shell capsules. This is demonstrated in the tabulated values (Table 4). A large amount of underfilled capsules was produced, and for batches DU, LD and CY the target of 800 correctly filled capsules could not be achieved. The influence of pellet shape on the filling performance can still be seen, but the influence of gross differences in surface roughness is no longer detectable. This is not surprising as the surface roughness of the coated pellets is in all cases a multiple of that obtained on uncoated pellets and clearly significantly larger than the threshold value of 2 μm identified above. Visual observation of the filling process indicated pronounced agglomeration and bridge formation, both causing blockage of the filling mechanism. The most likely reason for this phenomenon is electrostatic charging due to friction [8] as a result of the overall increased surface roughness of the pellet surfaces or the electrostatic properties of the film coating material itself. This would also explain why Carr's compressibility index was found to be zero or close to zero in all cases. The zero values do not indicate improved

Table 2
Filling properties of uncoated, unlubricated pellets into hard gelatin capsules on a KFM III filling machine[a]

Batch	Total number filled	Target weight achieved	Underweight number	%	Mean fill weight (mg)*	CL(c)
SP	816	816	0	0.0	464.1 ± 1.2	1
AL	816	812	4	0.5	450.7 ± 1.4	2
GR	816	816	0	0.0	458.6 ± 1.3	1
DS	822	814	8	1.0	460.9 ± 1.4	3
OV	816	812	4	0.5	456.5 ± 1.3	2
DU	876	815	61	7.0	446.9 ± 2.3	4
LD	936	811	125	13.4	444.7 ± 3.2	5
CY	1790	75	1715	95.8	405.2 ± 1.1	6

[a] *, calculated for capsules in the target weight range; CL(c), cluster number for capsule filling results.

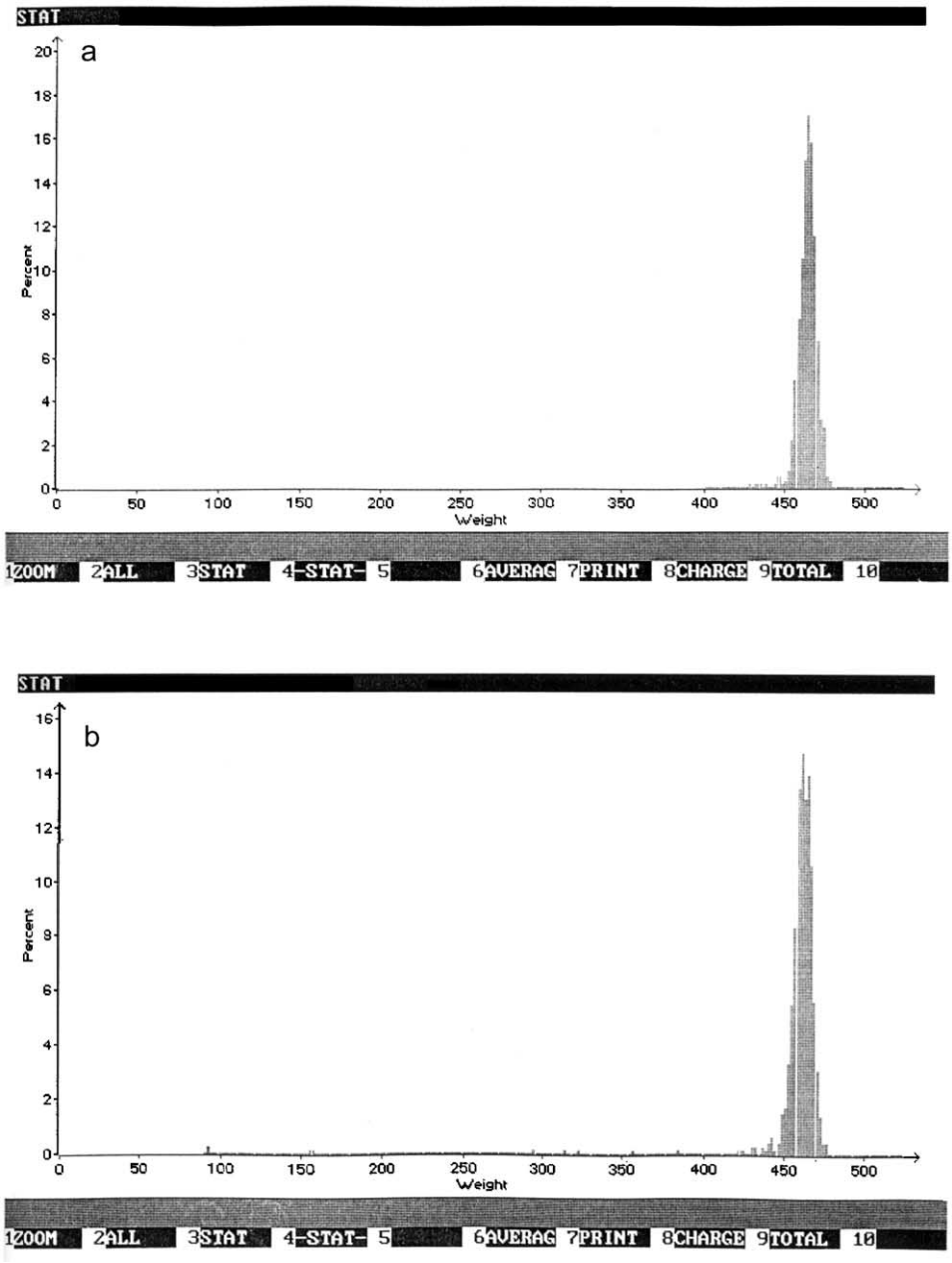

Fig. 1. Capsule fill weight distributions of uncoated pellets obtained with an automatic check weight system for batches SP (a) and DS (b).

Table 3
Pellet shape, surface roughness and flow characteristics of coated pellets[a]

Batch	AR	EL	e_R	CI (%)	R_a (μm)	R_q (μm)	R_{tm} (μm)
SP	1.09 ± 0.05	0.61 ± 0.09	0.31 ± 0.08	0.57	4.95 ± 2.38	7.40 ± 3.13	25.3 ± 10.9
AL	1.09 ± 0.04	0.58 ± 0.11	0.35 ± 0.11	0.35	3.72 ± 1.47	5.47 ± 2.70	20.2 ± 8.7
GR	1.12 ± 0.06	0.58 ± 0.12	0.36 ± 0.10	0.00	6.01 ± 3.03	9.04 ± 5.71	31.6 ± 18.1
DS	1.09 ± 0.05	0.63 ± 0.08	0.30 ± 0.08	0.23	6.52 ± 2.62	9.27 ± 3.14	34.3 ± 12.2
OV	1.20 ± 0.05	0.64 ± 0.08	0.29 ± 0.08	0.00	5.15 ± 2.77	7.66 ± 4.11	28.6 ± 16.3
DU	1.33 ± 0.07	0.91 ± 0.06	0.04 ± 0.06	0.00	6.57 ± 3.07	11.08 ± 5.93	33.0 ± 11.4
LD	1.59 ± 0.09	1.06 ± 0.05	− 0.12 ± 0.05	0.59	6.79 ± 1.92	10.89 ± 3.04	31.4 ± 9.1
CY	1.78 ± 0.23	1.07 ± 0.07	− 0.13 ± 0.06	0.00	6.59 ± 1.25	9.92 ± 2.05	30.4 ± 4.4

[a] AR, aspect ratio; EL, elipticity as defined in Ref. [4]; e_R, 3D-shape factor as defined in Ref. [4]; CI, Carr's compressibility index; R_a, rugosity; R_q, root-mean-square deviation of the roughness profile from the mean line; R_{tm}, mean peak-to-valley ratio.

Table 4
Filling properties of coated, unlubricated (filled on KFM III) and lubricated pellets (filled on GKF 700 S) into hard gelatin capsules

Batch	Unlubricated pellets					Lubricated pellets				
	Total number filled	Target weight achieved	Underweight number	%	Mean fill weight (mg)[a]	Total number filled	Target weight achieved	Underweight number	%	Mean fill weight (mg)[a]
SP	1038	811	227	21.9	450.7 ± 3.0	855	849	6	0.7	395.1 ± 5.1
AL	1176	818	358	30.4	442.2 ± 3.0	824	822	2	0.2	383.2 ± 6.2
GR	844	808	36	4.3	457.7 ± 1.9	731	731	0	0.0	391.8 ± 4.7
DS	1080	801	279	25.8	454.2 ± 2.8	880	879	1	0.1	393.3 ± 4.6
OV	1044	777	267	25.6	446.9 ± 2.7	783	779	4	0.5	385.7 ± 5.1
DU	1635	449	1186	72.5	433.0 ± 3.4	873	750	123	14.1	380.2 ± 8.4
LD	1531	428	1103	72.0	431.5 ± 3.7	891	721	170	19.1	385.3 ± 8.4
CY	1618	110	1508	93.2	412.3 ± 2.0	1074	444	630	58.7	364.1 ± 6.2

[a] Calculated for capsules in the target weight range.

powder flow, but the inability to pack due to electrostatic charging [9].

3.3. Filling of coated pellets after addition of lubricant

To remove the potential of electrostatic charging the coated pellets were mixed with 1% talcum powder [2] in a tumbler mixer. As can be seen from Table 4, filling again became possible for all pellets with an aspect ratio of or below 1.2. The number of underfilled capsules increased rapidly with an increase in aspect ratio for batches DU, LD and CY. The frequency distributions of the capsule fill weights are compared in Fig. 2. The small differences in the percentage of underfilled capsules for batches SP, AL, GR, DS and OV are not correlated to the surface roughness of the pellets. This is not surprising as the lubricant will have covered the asperity tips responsible for the tribo-electric charging process, and hence the gross magnitude of the surface texture is no longer of importance [10].

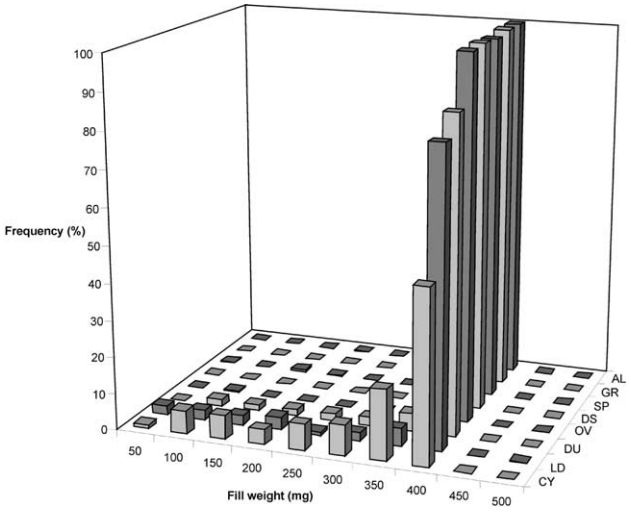

Fig. 2. Frequency distributions of the capsule fill weight obtained after addition of 1% talcum powder to coated pellets using a tumbler mixer.

As capsules are filled by volume, the bulk density of the pellets contributes to the capsule fill weight. If the differences in packing would have influenced the total fill weight of the capsules, the above results could be questioned. However, the ratios between capsule fill weight and bulk density are similar for all batches (see Table 5) and confirm a filling by volume.

4. Conclusions

Pellets need not be ideally spherical to be filled reproducibly into hard shell capsules. An aspect ratio of 1.2 or less appears to be the threshold value. However, pronounced surface roughness of pellets hinders filling, and therefore the surface roughness of pellets needs to be monitored. Film coating can result in pronounced electrostatic charges and thus in agglomeration, bridge formation and blockage of the filling mechanism. However, an addition of an adequate amount of lubricant such as 1% of talcum powder can prevent this effect. For film coated pellets, the surface roughness is generally large and hence responsible for the tribo-electrification, whereas the pellet shape dominates the filling performance.

Table 5
Ratios between capsule fill weight and minimum or maximum bulk density for coated pellets

Batch	Fill weight/minimum bulk density	Fill weight/maximum bulk density
SP	454.5	451.9
AL	452.2	453.8
GR	452.1	452.1
DS	455.9	454.9
OV	454.6	454.6
DU	449.2	449.2
LD	457.2	454.5
CY	459.6	459.6

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