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New insights into segregation during tabletting

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ABSTRACT

The aim of this study was to evaluate how different granule size distributions affect the tablet compression process. The emphasis was on developing new analytic methods for compression data for entire batch. In all, 18 batches of granules containing theophylline and lactose were tabletted, using an instrumented eccentric tabletting machine. During tablet compression, upper and lower punch forces were recorded. Mathematical methods were developed for analysing the compression data during tabletting. The results suggested two types of undulation in the tabletting data: (1) short-time scale variation or tablet-to-tablet changes in force data and (2) long-time scale undulation describing the changes occurring throughout the tabletting process, such as segregation. These undulation phenomena were analysed, using various mathematical methods. In addition the results suggest that smaller particles have better tabletting properties, to a certain limit. However particle size alone cannot explain the tabletability of granules.

1. Introduction

The importance of initial particle size in compaction processes has been known since the 1950s (Hersey et al., 1967). Particle size and size distribution influence flowability (Fan et al., 2005; Li, 2008; Deanne and Etzler, 2007), tabletability (Sun and Himmelspach, 2006), content uniformity (Yalkowsky and Bolton, 1990; Rohrs et al., 2006), tensile strength of tablets (Olsson and Nyström, 2001) and tablet dissolution properties (Carless and Sheak, 1975; Jillavenkatesa et al., 2002; Deanne and Etzler, 2007).

Factors that influence the bulk density of the mass can affect the weight of the tablet, because the weight is dependent on the particle packing in the die (Ridgway and Williams, 1977). Particle rearrangement during compaction is affected by the particle size and size distribution (Patel et al., 2006). Smaller particles can enter the voids between the larger particles, thereby inducing a closer packing arrangement during the tabletting process. The particle surface area capable of forming interparticulate bonding is increased when particle size is decreased (Nyström et al., 1993; Fichtner et al., 2008). For most pharmaceutical powders, compaction of smaller particles results in stronger tablets, because they have larger surface areas available for bond formation (Hersey et al., 1967; Yajima et al., 1996; Sun and Grant, 2001a,b; Fichtner et al., 2005; Patel et al., 2006; Lee and Kuo, 2006). The initial particle size can affect both the number and bonding force of the interparticulate bonds (Eriksson and Alderborn, 1995). However, fragmentation of larger particles can equalize the particle size and reduce the influence of size difference (Sun and Grant, 2001a).

The variability in tablet weights decreases with decreasing granule size (Marks and Sciarra, 1968; Spring, 1977). Spring (1977) noted that the variation was greatest at the beginning and end of the tabletting process. The particle size distribution of the compressed mass can also change during the tabletting process, due to the segregation phenomenon (Virtanen et al., 2009). Powder segregation can occur as a result of variation in the physical and mechanical properties of the particles. Segregation can eventually cause weight variation in tablets and therefore quality problems for the final dosage form. A distinct trend was found between the segregation tendency and weight variation of the tablets (Antikainen et al., 2006; Virtanen et al., 2009). In general, segregation tendency increases as the particle size increases (Xie et al., 2008). Segregation is also more likely to occur for wide size distributions than for narrow size distributions (Virtanen et al., 2009).

Compression data have usually been evaluated by studying the compression force profile for single tablets (Marshall, 1989; Hoblitzell and Rhodes, 1990; Schmidt and Vogel, 1994; Yliruusi et al., 1997; Nicklasson and Alderborn, 2000; Palmieri et al., 2005; Patel et al., 2007). Force, time and displacement curves have usually been studied to acquire information on the compaction properties of pharmaceutical materials. Equations, such as those of Heckel (1961), Cooper and Eaton (1962) and Kawakita and Lüdde (1970/1971), have been generated to describe force profiles. Few studies are available in which all the compression data of the entire batch have been evaluated. Virtanen et al. (2009) studied the gran-

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ule size distribution of tablets during tabletting. In addition, they evaluated the segregation phenomenon, using compression data of the entire batch.

The aim of the study was to evaluate how different granule size distributions affect tablet compression processes. The emphasis was on developing new analytic methods for compression data for entire batch.

2. Materials and methods

2.1. Materials

Theophylline anhydrate (TP, 200 M, BASF Corporation, Ludwigshafen, Germany) and α-lactose monohydrate (LMH, 200 M, DMV International GmbH, Veghel, The Netherlands) were granulated, using a 7.5% aqueous binder solution of polyvinylpyrrolidone (PVP, Kollidon K-30; BASF Corporation, Ludwigshafen, Germany). Microcrystalline spheres (cellets, Syntapharm, Mülheim an der Ruhr, Germany) with particle size fractions of 200 μm (cel200) and 700 μm (cel700), were used as model granules. Magnesium stearate (MS, Orion Pharma, Espoo, Finland) with a concentration of 1% (w/w) was used as a lubricant in the subsequent tablet compression studies.

2.2. Methods

TP (2 kg) and LMH (2 kg) were granulated with PVP solution (2 kg), using an instrumented fluid bed granulator (Glatt WSG 5, Glatt GmbH, Binzen, Germany). The design of experiments and the variables for the granulation process were specified by Närvänen et al. (2008). In the model by Närvänen et al., the granulation liquid feed rate was altered as a function of the relative humidity of the inlet air. The inlet air temperature was fixed at 40 °C for the granulation and 60 °C for the drying phase. The atomization pressure of the granulation liquid and nozzle height was constant. The granulated mass was put through a 3.15-mm sieve to remove possible clumps. A total of 18 batches were granulated, including three centre point triplicates. The batches were labelled from 1 to 18.

The particle size was measured after granulation, using Parsum® equipment (IPP 70, Gesellschaft für Partikel-, Strömungs-und Umweltmesstechnik GmbH, Chemnitz, Germany). The granules were distributed, using a sample divider (Fritsch Sample Divider Laborette 27, Fritsch GmbH, Idar-Oberstein, Germany). The particle size was also measured, using sieves as a comparison for the Parsum method. For sieve analysis, a 50 g sample was vibrated, using an automatic sieve shaker (Fritsch analysette, Idar-Oberstein, Germany) for 5 min. The sieve analysis (range 71–2000 μm with $\sqrt{2}$ increment) was performed in triplicate and the mean value for the median granule size was determined. The morphology of the final granules and cellets was measured, using a scanning electron microscope (SEM, Zeiss DSM 962, Oberkochen, Germany). In addition, the total porosity and pore size distribution were measured from five batches (batches 2, 5, 9, 13 and 17) using mercury intrusion porosimetry (Autopore IV9505, Micromeritics, Norcross, USA). The samples were dried at 45 °C 20 h prior to the analysis and stored in a desiccator. All the measurements were conducted as two replicate measurements.

The granules were mixed with MS, using a Turbula blender (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland). The mixing speed was 46 rpm and mixing time 3 min. The batch size was 250 g and the materials were loaded into a glass jar in a systematic fashion, with MS in the middle of the jar (49.5% granules – 1% MS – 49.5% granules).

After mixing the granules were tabletted, using an instrumented eccentric tabletting machine (Korsch EK0, Erweka Apparatebau GmbH, Heusenstamm, Germany) with strain gauges. The rotating speed was 60 rpm and flat-faced 9 mm punches were used in the study. The weight of the tablets was adjusted to 250 mg and the crushing strength to 60 N. During tablet compression, the upper punch force (F_{up}), lower punch force (F_{lp}) and ejection force (F_e) were recorded. The effective compression force (F_{eff}) was also calculated as an additional tabletting parameter (Eq. (1)).

$$F_{eff} = \sqrt{F_{up} \cdot F_{lp}} \quad (1)$$

From each batch, 400 tablets were collected into plastic tubing during the tabletting. The relative humidity of the air was 50–55% during distribution, mixing and tabletting.

2.3. Tablet analysis

Before analysis the tablets were collected in the plastic tubes in the same order in which they were compressed. This procedure ensured that each tablet was analysed individually. Hence, the results were not averaged as the prevailing method normally does. A novel feeding apparatus was used for weighing of the tablets. The machine dropped the tablets from the plastic tube one at a time and the dropping time interval was kept the same. The tablets were dropped in the multitester apparatus (Erweka GmbH, Heusenstamm, Germany). The multitester measured the weight, diameters and crushing strength of the tablet. Only the weights of the tablets are further analysed in this study. The relative standard deviation (Rsd) was calculated for the weights of the tablets, using Eq. (2),

$$\mathrm{Rsd} = \frac{\sum_{i=1}^{N} \sqrt{((w_i - w_{ave})^2)/N} \cdot 100}{w_{ave}} \quad (2)$$

where w_i is the individual tablet weight, w_{ave} is the average tablet weight and N is the number of tablets.

2.4. Principal component analysis

The granule size distributions of the batches were analysed, using principal component analysis (PCA). PCA categorized data so that similar distributions were plotted at the same area in the scatter plot. The granule size distributions were divided into four categories: <90, 90–250, 250–710 and >710 μm. Analysis was performed using SIMCA-P (v. 10.5, Umetrics, Umeå, Sweden) software.

2.5. Analysis of the compression data

Various methods were used to analyse the tabletting data to define both short- and long-time scale undulation. All of the following analyses were made, using Matlab software (v. 7.0, The MathWorks Inc., Natick, MA, USA). The analyses were based on F_{eff} values if nothing else was indicated.

2.5.1. Reference value

The tabletting machine was adjusted with the same setting for each batch. We assumed that granules with different properties need different amounts of force to compact. Consequently, different forces were applied to compress the batches. This suggests that forces that have different magnitudes cannot be directly compared. For example s noise level of 10 units would be on a different scale if the average of the data were 100 instead of 1000. Another way to compare the batches would be related to the compression data (Virtanen et al., 2009). However, the tablet weights are not always available. In such cases the F_{eff} values can be used instead if the reference values are calculated. Thus, to keep batches comparable the results were scaled. This was done by dividing every y value

with the averages of the compression forces (y_{ave}) of the batch in question. Batch 11 was chosen as the reference batch, because its y_{ave} was nearest to the y_{ave} for all of the batches. The reference value for this batch was set at 1. The other batches were compared with this reference batch.

The compression data for every batch have 400 measurement points. These are called y_i, where i is the index of the measurement ranging from 1 to 400. To analyse the long-time scale undulation, the data were smoothed. Smoothed data points are called Y_i, so that

$$Y_i = \sum_{j=i-20}^{i+20} \frac{y_j}{41} \quad (3)$$

2.5.2. Amount of noise, A_n

The amount of noise was calculated, using Eq. (4).

$$A_n = \frac{\sum_{i=1}^{N-1} |y_i - y_{i+1}|}{N} \quad (4)$$

where y_i is the measuring point for the compression force and N is the total number of compression forces. A_n describes the short-time scale variation in the compression data.

2.5.3. Linearity, L

Linearity (L) describes how much the data points of the smoothed data differ from the first-order polynomial that was fitted into the compression data (Eq. (5)).

$$L = \frac{\sum_{i=1}^{N} |Y_i - (\alpha + \beta \cdot i)|}{N} \quad (5)$$

where α and β are parameters for the polynomial and N is the total number of compression forces. L describes the linearity of the changes in the compression data.

2.5.4. Quality of fit, Q

Quality of fit (Q) is the standard deviation of the polynomial function that was fitted to the compression force (Eq. (6)).

$$Q = \sum_{i=1}^{N} \sqrt{\frac{(p_i - p_{ave})^2}{N}} \quad (6)$$

where each p_i is the value of the polynomial function corresponding to the y_i, p_{ave} is the average of all p_i and N is the total number of compression forces. A small value for Q indicates a good fit.

2.5.5. Relative quality of fit, Q_r

Relative quality of fit (Q_r) is the relative standard deviation of the polynomial function that was fitted to the compression force data (Eq. (7)).

$$Q_r = \frac{Q}{y_{ave}} \quad (7)$$

where y_{ave} is the average of the compression data. A small value for Q_r indicates a good fit.

3. Results and discussion

3.1. The effect of median particle size

The median granule size measured using the Parsum method, and sieve analysis are presented in Fig. 1. Regarding median particle size, five batches were chosen for closer inspection. These five batches were chosen so that the batch with the smallest median granule size (batch 2), largest granule size (batch 13) and midsized granule size (batch 9) were included. In addition, one batch in which the median granule size was between the smallest and midsized (batch 5) was included as well as one batch in which the median granule size was between the midsized and largest (batch 17). The granule size distributions for these five batches are presented in Fig. 2.

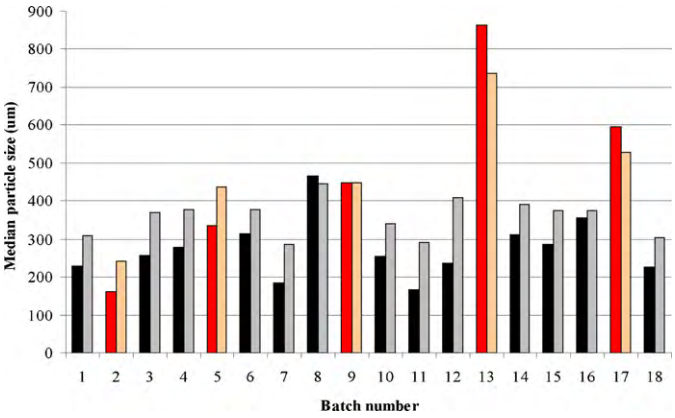

Fig. 1. Median values for granule size, determined by Parsum method (black) and with a sieve analysis (grey). Five batches which were examined more carefully are marked with red (Parsum) and yellowish (sieve). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Changes in compression data

The changes present in the tabletting data can be divided into two different kinds of phenomenon: short-time scale and large-time scale undulations.

3.2.1. Short-time scale undulation

Tablet-to-tablet changes in force data during the tabletting process are called short-time scale variations in this study. Homogenous and sufficiently small material has no undulation of this kind, although it is possible only in theory. However, when spherical pellets whose particle size was 200 μm were compressed, the undulation was small (Fig. 3). The undulation increased when the particle size of the pellets was increased–when the pellet size was 700 μm, the undulation was considerably larger (Fig. 3). In this case the undulation was derived from the fact that the larger pellets could not fill the tabletting mould evenly, in which case there were various amounts of pellets in the mould each time. If the size of the pellets was small enough, the mass filled the mould evenly each time (Fig. 3). If the mass included several sizes of particles, as tabletted masses usually do, the smaller particles could fit into the gaps between the larger particles, leading to smaller undulations in the tabletting data. The increase in particle size distribution could also increase the undulation, compared with the compression of only small particles. Variations in the mass in the mould increased and the mould was filled differently each time. In practice, each mass induces some short-time scale variation in the compression data.

3.2.2. Long-time scale undulation

Long-time scale undulation is defined as a waving kind of undulation that occurs during tabletting. Long-time scale undulation could reveal segregation or compaction of the mass in the hopper. If there were broad particle size distributions in the mass, the possibility of segregation would be clear. In the present study segregation was established in as simple a way as possible, using variously sized cellets. A 50/50 mixture of cellets (200

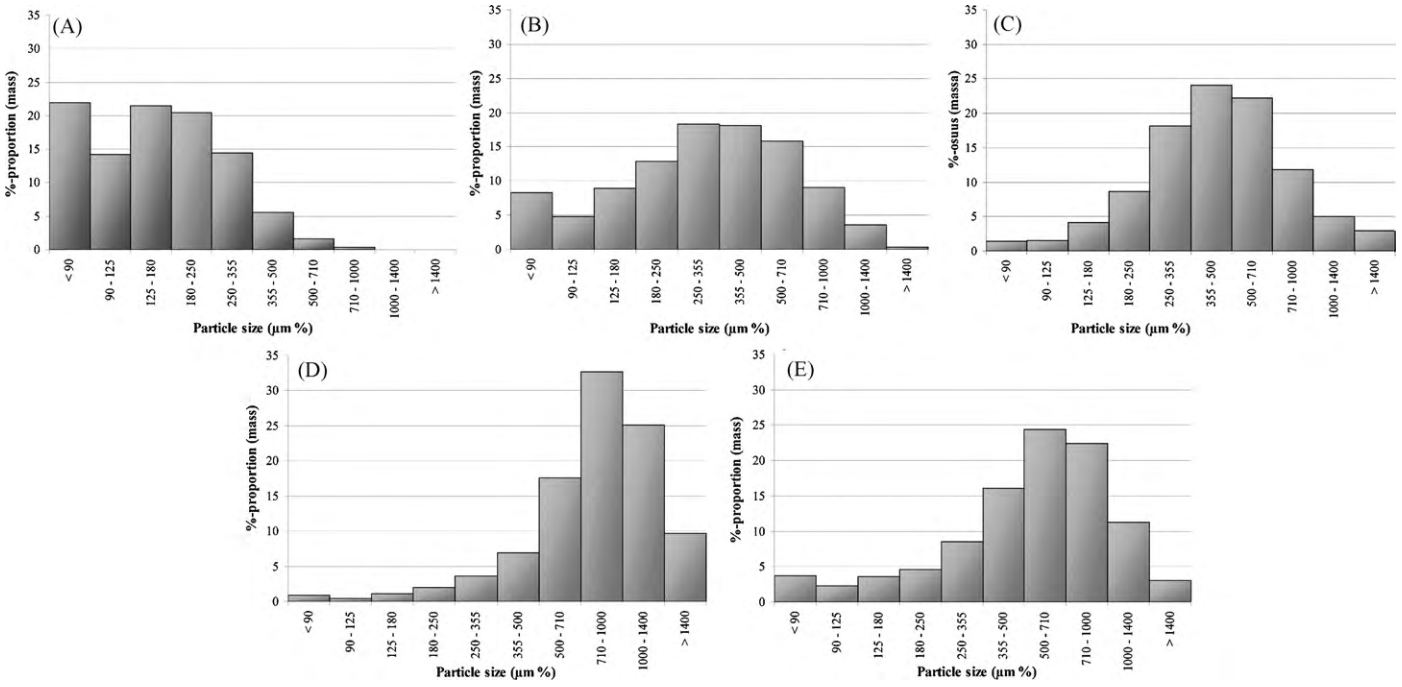

Fig. 2. Particle size distributions of the granules. (A) Batch 2, (B) batch 5, (C) batch 9, (D) batch 13, and (E) batch 17. The pictures have the same scaling to ease the comparison.

and 700 μm) was compressed. Fluctuation that was typical for segregation can be seen in Fig. 3. Fluctuation in the F_{up} during tabletting was clearly smaller with cellets having a smaller particle size than that observed with cellets of a larger particle size.

3.3. Analysis of the compression data

3.3.1. Undulation

Various methods were used to analyse the tabletting data. Short-time scale variation was evaluated, using Eq. (4), which gave A_n values describing the amount of noise. Long-time scale undulation was studied using L, Q and Q_r values. All of the equations gave a single value as a result; these values were gathered into Table 1. The Rsd of the tablet weights was included in the table. The minimum and maximum values were determined for each analysis. The batches were divided into good, mediocre and bad batches. Values under (max–min) 0.1 + min were described as good and values over max–(max–min) 0.5 as bad; the other values were mediocre. The values are marked in Table 1 as follows: bold text describes the best, underlined text the poorest and the normal text as mediocre values. The constants 0.1 and 0.5 were chosen so that a reasonable amount of good, bad and mediocre values were obtained.

The results showed that some of the batches were good in all of the analyses (batches 1, 2 and 3), while batches 7, 8, 11 and 17 were mediocre in all of the analyses. Four of the remaining 11 batches (4, 6, 9 and 10) gave either favourable or mediocre results depending on the analysis method and six (5, 13, 14, 15, 16 and 18) gave either

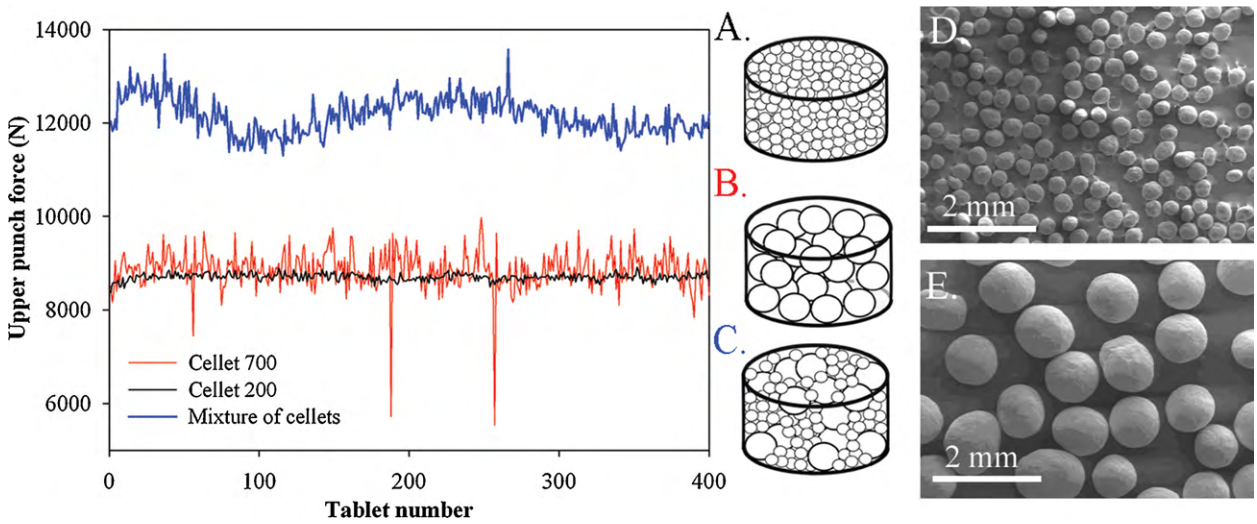

Fig. 3. Effects of particle size of cellets on upper punch force during tabletting. Red line represents the tabletting behaviour of cellets with a larger particle size of 700 μm and black line represents the cellets with a smaller particle size of 200 μm. Blue line represents upper punch force during cellet mixture tabletting. Mixture contains cel200 and cel700 (50/50). (A) Schematic diagram of the die filling of smaller cellets, (B) larger cellets and (C) cellet mixture, (D) SEM micrograph of cel200, and (E) SEM micrograph of cel700. Magnification is 20× in the SEM micrographs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Results from compression data analysis. Functions have been fitted to F_{eff} data. Batches have been divided in relation to the goodness of the tabletability, according to mathematical analysis. Bold text indicates good, normal mediocre and underlined bad.

Batch	Rsd[a]	A_n	L	Q	Q_r	Reference value[b]
1	**0.82**	**52.5**	**16.9**	**71.3**	**1.3**	1
2	**0.56**	**41.3**	**17.8**	**83.0**	**1.8**	0.87
3	**0.45**	**34.1**	**15.6**	**68.2**	**1.9**	0.68
4	1.71	**42.0**	**17.9**	195.1	4.5	0.82
5	5.27	92.1	141.0	522.3	11.7	0.84
6	**0.81**	111.1	**30.8**	**123.8**	**1.9**	1.22
7	2.45	90.8	45.8	510.7	8.7	1.12
8	1.74	123.3	50.7	399.8	6.3	1.21
9	**1.22**	81.4	**40.0**	**136.0**	**2.5**	1.10
10	0.79	173.1	66.0	219.7	**2.6**	1.61
11	0.63	188.9	64.2	367.0	5.6	1.25
12	**1.21**	317.8	101.7	715.4	8.6	1.58
13	2.21	500.7	182.1	989.8	13.9	1.37
14	3.56	244.4	108.1	1042.0	14.2	1.40
15	10.96	153.9	58.4	996.3	21.1	0.93
16	4.93	169.4	302.3	953.8	15.3	1.19
17	4.68	91.1	61.0	417.9	9.6	0.82
18	1.94	129.4	271.8	514.5	8.8	1.11

[a] Calculated using the weights of the tablets.
[b] Reference value calculated to ease comparison of the results.

mediocre or poor results. Batch 12 gave favourable results in tablet weight analysis, mediocre in L and Q_r and poor in A_n and Q. When these results were compared with the median particle size, smaller particles usually gave better results i.e. their tabletability was better. Tabletability in this study is defined as the general ability to form tablets with low variation in the compression data (or low weight variation of tablets). However, some of the batches with smaller median particle size, such as batches 7, 11 and 18 gave mediocre results. The poorest batch according to the analysis was 13, it also had the largest particle size. On the other hand, batch 16 had quite poor tabletability, even though its particle size was medium. In conclusion, tabletability was also affected by factors other than just the particle size. In addition, the values Q and Q_r take the quality of the fit into account; if the fitting of the polynomial was poor these values were large, as was the case batch 15.

The simplest way to draw conclusions regarding the values obtained from the analysis was to focus on A_n, if A_n was small the compression data were smooth. Usually, if the data are smooth regarding tablet-to-tablet analysis, there is likewise no significant segregation.

3.3.2. Compaction and segregation

When only the five chosen batches were examined, batch 2 differed from the other four. The shape of its compression force data plot was different from those of the others (Fig. 4). We concluded that the punch behaviour of batch 2 was dictated by phenomena different from those of the other batches. When the compression data were examined more carefully, we noted no clear maximum values or peaks. Instead, the compression force curve approached the maximum value asymptotically. The other batches had clear maximum values at the early phase of the tabletting process.

The weights of the tablets correlated the compression force in batch 2. This indicated that ever time, the density of the mass increased, because the volume of the mould was kept constant. We reasoned that the mass of batch 2 became compacted in the hopper during tabletting or that the particle size increased. The particle size of batch 2 was small and the size distribution narrow. This indicated that there was no significant segregation during tabletting and the particle size of the granules did not increase in the hopper at the end of tabletting. In addition, the granules did not break in the hopper during tabletting. In conclusion the main

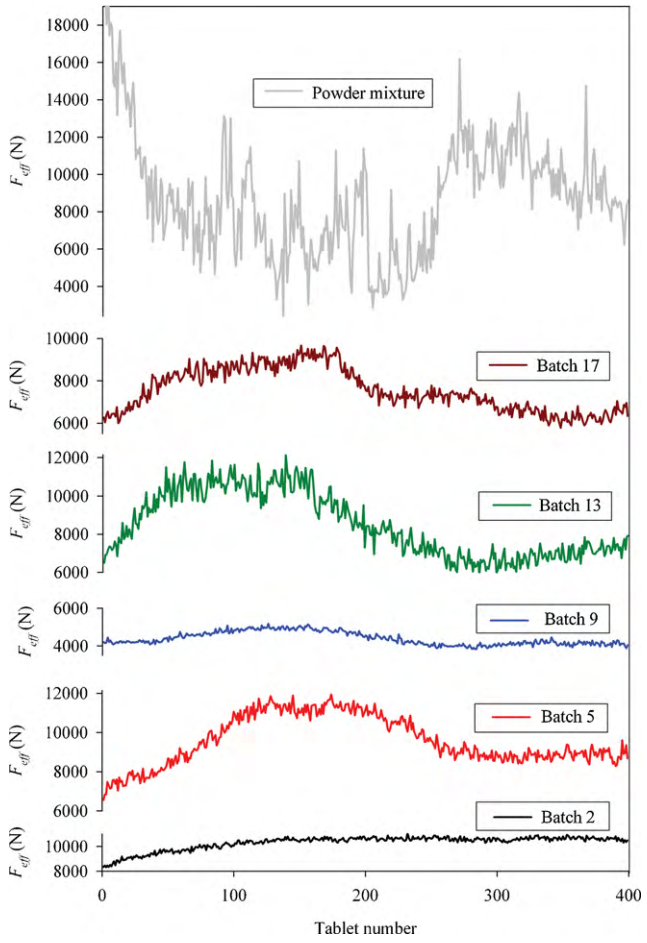

Fig. 4. F_{eff} for powder mixture (grey), batch 17 (brown), batch 13 (green), batch 9 (blue), batch 5 (red) and batch 2 (black). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reason for the compression force data to approach maximum value was apparently compaction of the mass in the hopper due to hopper movement.

The particle size distributions of the other batches were broader and the particles were larger than in batch 2. We assumed that segregation occurred in these batches during tabletting. The segregation could be detected from the compression force data plot: at first the plots rose strongly and when the peak values were achieved they decreased almost to the original level (Fig. 4).

Segregation was also examined by compressing cellets, whose particle size was homogenous. Two size fractions were used: cel200 and cel700. There was no segregation, because the particle size was standardized. The force curve for cel200 was steady and there was little difference between consecutive forces (Fig. 3). The force curve for cel700 was steady for long-time scale examination, but there were substantially larger differences between consecutive forces than with cel200. This could be explained with the larger particle size of cel700. When the particles were larger the packing in the mould varied more then when smaller particles were used. In addition a 50/50 mixture of cel200 and cel700 was compressed. There was segregation in the compression force data for the cellet mixture. Segregation occurred in many phases during compression (Fig. 3).

3.4. Principal component analysis based on particle size distributions

PCA was established, based on the particle size distributions measured with Parsum equipment (Fig. 5). Similar size distribu-

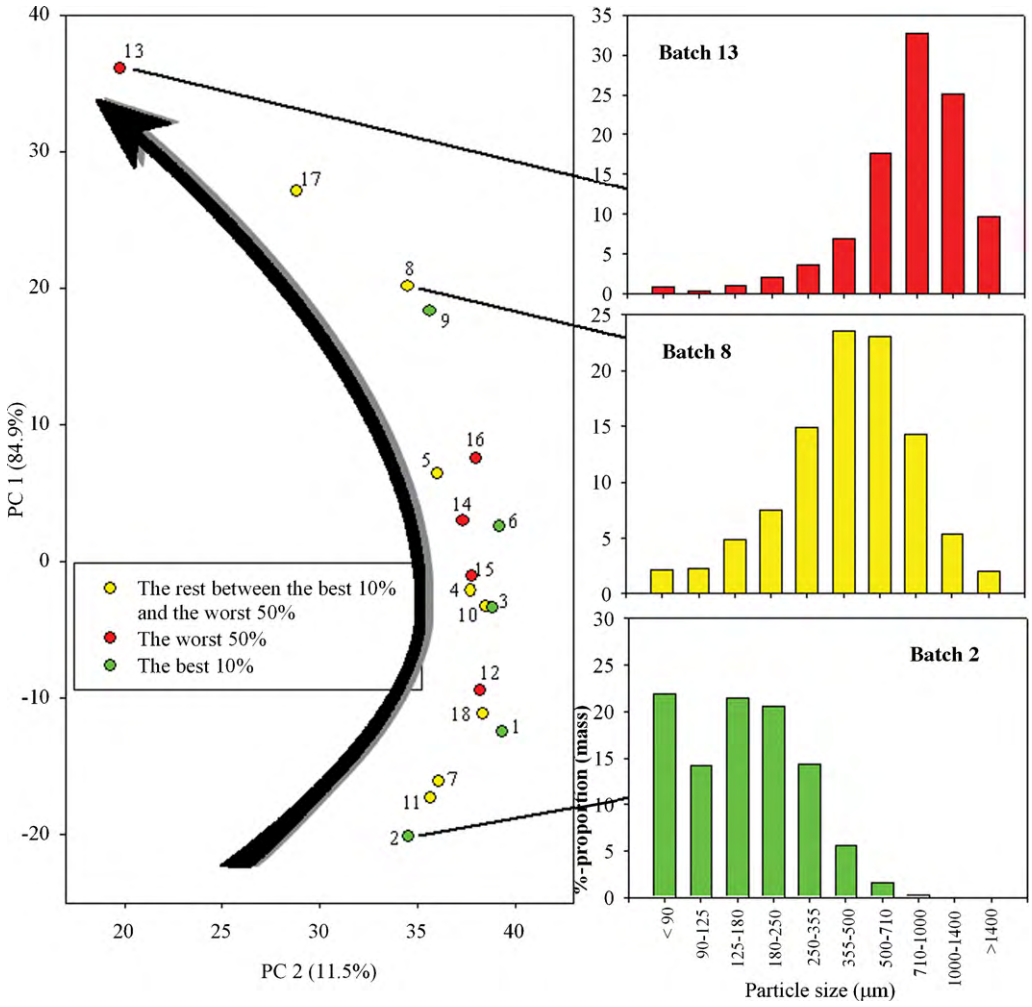

Fig. 5. Particle size distributions measured, using Parsum equipment as PCA scatter plot. Colours describe Q values. Sample corresponding granule size distributions on the right. The arrow represents increasing particle size. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tions were plotted in the same area in the scatter plot, so the data can be divided according to the particle size distribution. The R^2 value (correlation coefficient) was 96.4% and Q^2 value (test set validation coefficient) was 64.2%. The loading plot showed that all of the particle size groups were almost equally important (results not shown). In addition, even if the particle size groups were slightly altered within the four groups, the results remained similar. The points could be marked to outline eligible characteristics. In Fig. 5 the points were coloured, using Q values.

The results suggest that the behaviour of the batches could not alone be explained by particle size information, because the above-mentioned groups were not consistent in certain sectors in the PCA scatter plot. This was because things other than particle size distribution could also have affected the results. As already mentioned, median particle size also affects tabletability. PCA also considered median particle size in some aspect, but it was not the main focus of investigation. Some generalizations could still be made, however. The tabletability of the smaller granules (<0.3 mm) was generally better than that of the larger granules (>0.5 mm). However, these size limits were only indicative; e.g. batch 17 had better tabletability characteristics in many analyses than batch 5, even though the granule size of batch 17 was much larger than in batch 5.

The results suggested that the smaller the particle size, the better the tabletability. However, there has assumed to be a minimum particle size for adequate flowability. To determine the smallest acceptable particle size, an additional study was preformed. The starting materials (TP, LMH and PVP) were mixed in a Turbula mixer (60 min, 22 rpm) with no granulation. This mixture showed difficulties in compression i.e. it did not flow from the hopper onto the tabletting table. The mixture also showed the poorest tabletting properties: the compression data showed significant undulation and the weight variation of the tablets was wide (Fig. 4). For example, the Rsd of F_{eff} was 33.1 for the powder mixture, but 5.4 for batch 2. In conclusion, the smallest granules (d_{50} < 200 μm) had good tabletability, but the mixture of starting materials (d_{50} ~ 75 μm) had very poor tabletability. d_{50} is the particle diameter at which 50% of the particles have diameters that are greater or smaller than the d_{50} value. For these materials, the adequate particle size for tabletting was approximately 200 μm.

3.5. Porosity, granule shape and surface

As mentioned above, the particle size and particle size distribution cannot alone explain the tabletting ability of the granules. Porosity, flowability, density, moisture and surface texture and particle shape also affect tabletting attributes.

The porosity of the granules was measured in five batches (2, 5, 9, 13 and 17) (data not shown). In the pore size distribution, a growing population at pore diameter of approximately 10 μm was seen with increasing batch numbering from 5 to 17. In batch 2 this population was not apparent, indicating that batch 2 did not have inter particulate porosity. It had one local maximum in the pore distribution at pore diameter below 100 μm describing intra particulate porosity. The other batches had two local maxima, the

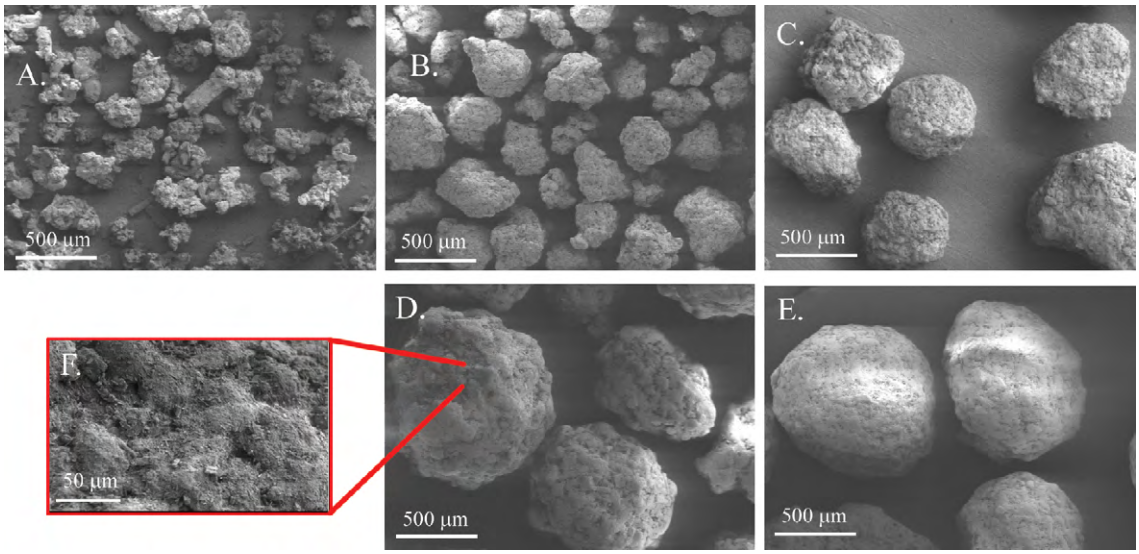

Fig. 6. SEM micrographs of granules. (A) Batch 2, (B) batch 5, (C) batch 9, (D) batch 13, (E) batch 17, and (F) batch 13 close-up. Magnification is 50× for (A) to (E) and 500× for (F).

first describing inter particulate porosity and the second describing intra particulate porosity. The total intrusion volume decreased with increasing batch number from 2 to 13. The results from batch 17 fell between those of 9 and 13.

The shape and surface characteristics of the granules could influence tabletability through flowability. Good flowability of the powder mixture aids in achieving favourable content uniformity and low weight variation of the tablets (Fan et al., 2005). Particle shape also influences filling of the tabletting mould (Ridgway and Scotton, 1970) and packing density of the particles (Pitkin and Carstensen, 1990). The appearances of the granules differed significantly; e.g. the granules in batch 2 were irregularly shaped and their surface was rough (Fig. 6), whereas the granules in batch 17 were smooth and almost round. The SEM images could explain why the tabletability of batch 9 was better than in batch 5: the granules of batch 9 were much rounder than those of batch 5. Round granules flowed better than irregular granules. The surfaces of the granules in batches 2 and 5 were rougher than in the other batches. The granule surfaces of batch 17 were very smooth. There were loose particles (size under 10 μm) on the surfaces of the batch 13 granules. Granulation was performed under very moist conditions that led to large granules. The single particles on the surface were assumed to be recrystallised theophylline monohydrate, due to the moist granulation conditions (Fig. 6F).

4. Discussion

The results suggested that the smaller the particle size the better the tabletability. However, the present study focused mainly on the effect of the particle size and particle size distribution of the granules and these factors cannot alone explain how the granules behave when compressed. Other factors influencing tabletability included flowability and surface texture of the granules, while porosity, density and particle shape could also have an effect. In addition, the better tabletability of the smaller granules can be partly attributed to the behaviour of MS and humidity of the air. The humidity decreased triboelectricity clearly, leading to substantially better flowability (Pingali et al., 2009). MS, on the other hand, lubricated the granule mass and the flowability increased.

The results showed that short-time scale variation with small granules (<300 μm) is affected by flowability. If the granules have poor flowability, they do not have time to flow into the mould, which will induce short-time-scale variation in the compression data. With larger granules, short-time scale variation is due to uneven filling of the mould. As previously mentioned, large granules fill the mould variously each time and establish different densities for the mass in the mould. Large-time scale undulation can be introduced if large granules have a broad size distribution. If the granule size distribution is narrow, there is no large-time scale undulation.

Although smaller particles show the most favourable properties for tabletting, the situation is not always this clear. When the eccentric tabletting machine is used, the mass is tabletted more easily than with rotational tabletting machines, which have higher tabletting speed, larger masses, longer dwell time and movement of both punches (Palmieri et al., 2005).

According to the Food and Drug Administration (FDA) draft guidance, product and process specifications are based on understanding of how formulation and process factors affect product performance (FDA, 2004). In addition, quality assurance is in real-time and there is the capability for process control related to product quality and performance. The previously mentioned mathematical methods for analysing the compression data could be used for real-time monitoring. This would enable detection of segregation during tabletting and the required means could be used to prevent variations in the content uniformity of tablets. This prevents rejection of product and waste and enables real-time product release, which are primary goals for process analytical technologies (PAT).

5. Conclusions

There were two types of undulation in the tabletting data and these changes could be divided into two different phenomena: short-time scale and large-time scale undulation. Short-time scale variation was due to tablet-to-tablet changes in the force data during the tabletting process. Long-time scale undulation described changes occurring throughout the tabletting process. Long-time scale undulation could reveal segregation or compaction of the mass in the hopper. The undulation phenomena could be analysed, using mathematical methods.

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References

Antikainen, O., Tervakangas, H., Pietiläinen, J., Yliruusi, J., Sandler, N., 2006. Screening of particle size related segregation behavior of granules with surface image analysis. AAPS J. 8.

Carless, J.E., Sheak, S., 1975. Changes in the particle size distribution during tableting of sulphathiazole powder. J. Pharm. Pharmacol. 28, 17–22.

Cooper, A.R., Eaton, L.R., 1962. Compaction behavior of some ceramic powders. J. Am. Ceram. Soc. 45, 97–103.

Deanne, R., Etzler, F.M., 2007. Particle size analysis and powder sampling. Am. Pharm. Rev. 10, 132–136.

Eriksson, M., Alderborn, G., 1995. The effect of particle fragmentation and deformation on the interparticulate bond formation process during powder compaction. Pharm. Res. 12, 1031–1039.

Fan, A., Parlerla, S., Carlson, G., Ladipo, D., Dukich, J., Capella, R., Leung, S., 2005. Effect of particle size distribution and flow property of powder blend on tablet weight variation. Am. Pharm. Rev. 8, 73–78.

Food and Drug Administration, 2004. Guidance for Industry; PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance. Food and Drug Administration.

Fichtner, F., Rasmuson, A., Alderborn, G., 2005. Particle size distribution and evolution in tablet structure during and after compaction. Int. J. Pharm. 292, 211–225.

Fichtner, F., Mahlin, D., Welch, K., Gaisford, S., Alderborn, G., 2008. Effect of surface energy on powder compactibility. Pharm. Res. 25, 2750–2759.

Heckel, R.W., 1961. Density–pressure relationship in powder compaction. Trans. Metal. Soc. AIME 221, 671–675.

Hersey, J.A., Bayraktar, G., Shotton, E., 1967. The effect of particle size on the strength of sodium chloride tablets. J. Pharm. Pharmacol. 19, 24S–30S.

Hoblitzell, J.R., Rhodes, C.T., 1990. Instrumented tablet press studies on the effect of some formulation and processing variables on the compaction process. Drug Dev. Ind. Pharm. 16, 469–507.

Jillavenkatesa, A., Kelly, J., Dapkunas, S.J., 2002. Some issues in particle size and size distribution characterization of powders. Am. Pharm. Rev. 5, 98–105.

Kawakita, K., Lüdde, K.H., 1970/1971. Some considerations on powder compression equations. Powder Technol. 4, 61–67.

Lee, T., Kuo, C.S., 2006. Effects of initial average particle size on tableting: Evaluating predictive tools for crystal engineers and formulators. Pharm. Technol. March.

Li, T., 2008. Materials engineering of solid-state dosage forms. Pharm. Res. 25, 949–952.

Marks, A.M., Sciarra, J.J., 1968. Effect of size on other physical properties of granules and their corresponding tablets. J. Pharm. Sci. 57, 497–504.

Marshall, K., 1989. Monitoring punch forces and punch movements as an aid to developing robust tablet formulations. Drug Dev. Ind. Pharm. 15, 2153–2176.

Närvänen, T., Lipsanen, T., Antikainen, O., Räikkönen, H., Yliruusi, J., 2008. Controlling granule size of granulation liquid feed pulsing. Int. J. Pharm. 357, 132–138.

Nicklasson, F., Alderborn, G., 2000. Analysis of the compression mechanics of pharmaceutical agglomerates of different porosity and composition using the Adams and Kawakita equations. Pharm. Res. 17, 949–954.

Nyström, C., Alderborn, G., Duberg, M., 1993. Bonding surface area and bonding mechanism – two important factors for the understanding of powder compactibility. Drug Dev. Ind. Pharm. 19, 2143–2196.

Olsson, H., Nyström, C., 2001. Assessing tablet bond types from structural features that affect tablet tensile strength. Pharm. Res. 18, 203–210.

Palmieri, G.F., Joiris, E., Bonacucina, G., Cespi, M., Mercuri, A., 2005. Differences between eccentric and rotary tablet machines in the evaluation of powder densification behaviour. Int. J. Pharm. 298, 164–175.

Patel, S., Kaushal, A.D., Bansal, A.K., 2006. Compression physics in the formulation development of tablets. Crit. Rev. Ther. Drug Carrier Syst. 23, 1–65.

Patel, S., Kaushal, A.M., Bansal, A.K., 2007. Effect of particle size and compression force on compaction behavior and derived mathematical parameters of compressibility. Pharm. Res. 24, 111–124.

Pingali, K.C., Hammond, S.V., Muzzio, F.J., Shinbrot, T., 2009. Use of a static eliminator to improve powder flow. Int. J. Pharm. 269, 2–4.

Pitkin, C., Carstensen, J.T., 1990. Effect of particle shape on some bulk solids properties. Drug Dev. Ind. Pharm. 16, 1–12.

Ridgway, K., Scotton, J.B., 1970. The effect of particle shape on the variation of fill of a tabletting die. J. Pharm. Pharmacol. 22, 24S–28S.

Ridgway, K., Williams, I.E., 1977. The effect of particle shape and size distribution on granulation bulk density and tablet weight variation. J. Pharm. Pharmacol. 29, 57P.

Rohrs, B.R., Amidon, G.E., Meury, R.H., Secreast, P.J., King, H.M., Skoug, C.J., 2006. Particle size limits to meet USP content uniformity criteria for tablets and capsules. J. Pharm. Sci. 95, 1049–1059.

Schmidt, C., Vogel, P.J., 1994. Force-time-curves of a modern rotary tablet machine I. Evaluation techniques and behaviour of pharmaceutical substances characterization of deformation. Drug Dev. Ind. Pharm. 20, 921–934.

Spring, M.S., 1977. The segregation of granules during tableting. J. Pharm. Pharmacol. Commun. 29, 513–514.

Sun, C., Grant, D.J.W., 2001a. Effects of initial particle size on the tableting properties of L-lysine monohydrochloride dehydrate powder. Int. J. Pharm. 215, 221–228.

Sun, C., Grant, D.J.W., 2001b. Influence of crystal structure on the tableting properties of Sulfamerazine polymorphs. Pharm. Res. 18, 274–280.

Sun, C.C., Himmelspach, M.W., 2006. Reduced tabletability of roller compacted granules as a result of granule size enlargement. J. Pharm. Sci. 95, 200–206.

Virtanen, S., Antikainen, O., Räikkönen, H., Yliruusi, J., 2009. Granule size distribution of tablets. J. Pharm. Sci. 99, 2061–2069.

Xie, L., Wu, H., Shen, M., Augsburger, L.L., Lyon, R.C., Khan, M.A., Hussain, A.S., Hoag, S.W., 2008. Quality-by-Design (QbD): effects of testing parameters and formulation variables on the segregation tendency of pharmaceutical powders measured by the ASTM D 6940-04 segregation tester. J. Pharm. Sci. 97, 4485–4497.

Yajima, T., Itai, S., Hayashi, H., Takayama, K., Nagai, T., 1996. Optimization of size distribution of granules for tablet compression. Chem. Pharm. Bull. 44, 1056–1060.

Yalkowsky, S.H., Bolton, S., 1990. Particle size and content uniformity. Pharm. Res. 7, 962–966.

Yliruusi, J., Merkku, P., Hellen, L., Antikainen, O., 1997. A new method to evaluate the elastic behavior of tablets during compression. Drug Dev. Ind. Pharm. 23, 63–68.