Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 67 (2007) 458–463
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Abrasion of tablets during scale-up: The influence of different crushing forces in laboratory and production perforated pan coaters

Ronny Mueller, Peter Kleinebudde *

Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany

Received 23 November 2006; accepted in revised form 5 March 2007
Available online 12 March 2007

Abstract

The purpose of this study was to investigate the influence of batch size during scale-up on the abrasion of biconvex tablets. Labelled tracer tablets of six different crushing forces (23–116 N) were mixed at different times and peripheral speeds in a laboratory (4 kg) and production (360 kg) perforated pan coater. The weight loss of these tracer tablets was determined.

The main factor affecting the abrasion in both scales is the tablet crushing force as a nonlinear decrease in the abrasion was observed with increasing crushing force of the tablets. An increase in mixing time results in an increase in abrasion for the laboratory scale. In contrast to the production scale an influence of the peripheral speed on the abrasion could not be observed in laboratory scale. There is no difference in total abrasion for the laboratory scale and production scale for low peripheral speed. At higher peripheral speeds the abrasion in the production scale is slightly higher than in the laboratory scale.

Keywords: Scale-up; Abrasion; Pan speed; Bohle Film Coater

1. Introduction

The scale-up of the film coating process in perforated pan coaters is a critical step in the pharmaceutical industry. Different process parameters had to be carefully converted in order to achieve the same product properties as in the laboratory scale. However, a change in the acting forces on the tablets with increasing batch size is difficult to predict.

Various terms can be used to describe the unwanted breakdown of particles within a process. The terms abrasion and friability are used in this paper and are defined in the British Standard (BS 2955) [1]. Abrasion is the removal of material from a particle (tablet) such that the material removed is very much smaller than the particle. Friability is the tendency of particles to break down in size during storage and handling under the influence of small forces. The influence of small forces on uncoated tablets is determined in a conventional friability tester according to the European Pharmacopoeia 5. The tablets are mixed in a baffled drum at 25 rpm for 4 min and the weight loss of the tablets is determined.

The magnitude of breakdown of tablets caused by higher forces in perforated pan coaters in the scale-up process is the focus of this study. The weight loss caused by the mechanical mixing in perforated pan coaters is termed as abrasion. An increase in friction and, consequently, in abrasion of tablets with increasing batch size in scale-up was reported [2,3].

Furthermore there is a lack of experimental data to assess the acting strains on the tablets in the scale-up process.

In a previous work the abrasion of flat faced tablets depending on pan speed and mixing time in a laboratory and pilot scale perforated pan coater was investigated [4]. The abrasion of these tablets decreased from the laboratory scale to the pilot scale due to the lower number of impacts at the pan wall.

* Corresponding author. Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitaetsstr. 1, 40225 Duesseldorf, Germany. Tel.: +49 211 8114220; fax: +49 211 8114251.
E-mail address: Kleinebudde@uni-duesseldorf.de (P. Kleinebudde).

0939-6411/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2007.03.004

Besides the impact at the pan wall the friction between the tablets caused by the mutual rubbing is another reason for the abrasion of tablets. The surface roughness of tablets increases with increasing friability of the tablets [5] and this extends the magnitude of friction.

The motion of tablets in rotating cylinders is described in the literature [6–10]. The abrasion of the tablets will be affected by the movement of the tablets. There are three types of contact areas for tablets: tablet-pan wall, tablet-baffle and tablet–tablet. The abrasion is supposed to be influenced by:

- the velocity differences at the contact areas
- the surface roughness of the tablets and
- the pressure on the tablets caused by the tablets lying above.

Since all these effects are difficult to predict in scale-up, a statistical design of experiment was used in the current study to evaluate the abrasion of biconvex tablets in a laboratory (4 kg) and production (360 kg) perforated pan coater. The influence of the crushing force of tablets, mixing time and peripheral speed on the abrasion was examined.

2. Materials and methods

2.1. Tablets and tracer tablets

The abrasion of biconvex tablets was investigated in laboratory and production perforated pan coaters as a function of the pan speed, mixing time and crushing force of the tablets. Numerically labelled and exactly weighted tracer tablets (see Fig. 1) of different crushing forces were used. The composition of the tablets is lactose monohydrate 42% (Granulac 70, Meggle, Germany), corn starch 5% (Meritena 141, Tate & Lyle, United Kingdom), polyvinylpyrrolldone K30 2.5% (Kollidon 30, BASF, Germany), microcrystalline cellulose 50% (Avicel PH 101, FMC Bio Polymers, USA), and magnesium stearate 0.5% (MF-2-V, Peter Greven Fett-Chemie GmbH & Co., KG, Germany). Tracer tablets were compressed at 6 different force levels in order to determine the abrasion of tablets with different crushing forces. The geometric dimensions of the tablets were measured with a micrometer screw (Mitutoyo, Neuss) and were constant for all used tablets, different crushing forces. However this resulted in tablets of different weights. The tablet diameter is 8.07 mm (±0.02 mm) and the tablet height 4.07 mm (±0.04 mm). The friability was tested in a conventional friability tester according to European Pharmacopoeia 5. The mechanical strength of the tablets was measured with a diametral strength tester (HT-1, Sotax, Germany) at a constant speed of 1 mm/s. The mean of 30 tablets was used. The properties of the used tracer tablets are listed in Table 1. Tablets with a crushing force of 116 N were used as filling tablets. The bulk density of these tablets was 0.7712 kg/L. The tracer tablets were labelled with a number and conditioned at 21 °C, 45% relative humidity (%R.H.) for 24 h. The tracer tablets were exactly weighted (balance Satorius MC210P, Germany).

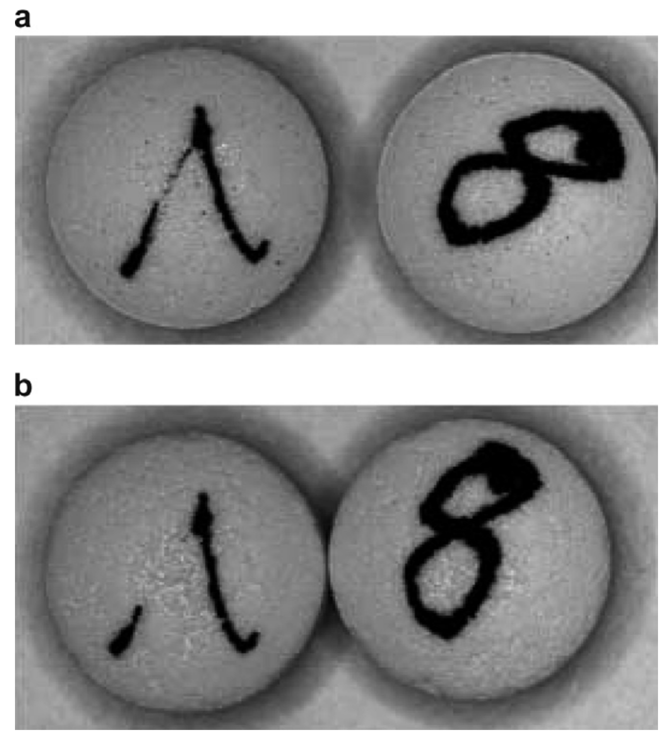

Fig. 1. Picture of tracer tablets (23 kN) (a) before mixing and (b) after mixing (13 min) in BFC 5.

Each 60 reference tablets (10 tablets per crushing force) were used to determine any weight change caused by the humidity. The reference tablets were treated as the tracer tablets, i.e. weighted at the same time, stored under the same condition and when the trial was running the reference tablets were open deposited.

2.2. Determination of the abrasion in laboratory scale and production scale

The tablets' abrasion was investigated in two different coater sizes. For the laboratory scale a Bohle Film Coater (BFC) 5 (L.B. Bohle Maschinen + Verfahren GmbH, Ennigerloh, Germany) with a pan diameter d_{pan} of 316 mm and pan length l_{pan} of 356 mm and for the production scale a BFC 400 with a pan diameter of 1430 mm and

Table 1
Properties of used tablets (SD – standard deviation in parentheses)

Average crushing strength [N] (SD) $n = 30$	Average weight [mg] (SD) $n = 40$	Friability [%] (SD) $n = 3$
23 (1.6)	172.27 (1.60)	0.217 (0.010)
31 (1.5)	177.93 (1.32)	0.144 (0.009)
44 (3.1)	186.17 (1.16)	0.061 (0.006)
66 (3.9)	195.63 (1.24)	0.037 (0.003)
88 (5.4)	204.30 (1.39)	0.035 (0.004)
116 (8.0)	210.93 (2.20)	0.025 (0.003)

pan length of 1609 mm were used. Fig. 2 shows a schematic depiction of a BFC. The BFCs are equipped with integrated transport ribbons on the bottom of the pan and reverse running mixing ribbons.

Tracer tablets were labelled with a number according to Table 2 for trials in laboratory scale as well as in production scale. The tracer tablets were exactly weighted w_b. The pan was charged with the tablets of a crushing force of 116 N (filling tablets) with the calculated batch size (see Section 2.3). Afterwards for each of the six used crushing forces ten tracer tablets of the same crushing forces were added (tablets with numbers 1–60). Then the pan was started with the lowest pan speed. After 4 min mixing the pan was stopped and additional new 60 tracer tablets (tablets with numbers 61–120) were added. The same was done after 8 min (tablets with numbers 121–180). All tracer tablets (180 tablets) were carefully removed after 13 min mixing, dusted off and weighed back w_a. The same procedure was repeated for the other investigated pan speeds with new tracer tablets. For all trials the same filling tablets were used. The abrasion was calculated according to Eq. (1).

Manual removal of all tracer tablets in BFC 400 was not possible because the drum was too large. Therefore the drum was run reversed for a few seconds for discharging. The abrasion A is calculated according to Eq. (1). For every trial new tracer tablets were used.

$$A(\%) = \left(1 - \frac{w_a}{w_b}\right) \cdot 100 \tag{1}$$

where w_b is weight of the tracer tablet before mixing and w_a is weight of the tracer tablet after mixing.

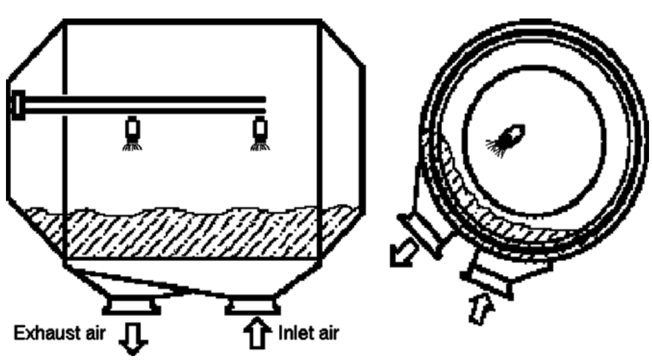

Fig. 2. Schematic diagram of Bohle Film Coater.

The average abrasion and 95% confidence interval was calculated from the ten tracer tablets.

2.3. Scale-up of the pan speed and batch size

The tablets' abrasion in the BFC 5 was investigated with three different pan speeds n_{pan} (10, 18 and 25 rpm). The use of the same peripheral speeds in the laboratory coater and the production coater is a common approach for scaling up the pan speed [11–13]. The peripheral speed v is calculated as follows:

$$v = \pi \cdot d_{pan} \cdot n_{pan} \tag{2}$$

The calculated pan speeds based on constant peripheral speeds are shown in Table 3.

The batch size for the trials in BFC 5 was 3.856 kg. The measured tablet bed depth in the BFC 5 was approximately 7.4 cm. The batch size for the BFC 400 was calculated based on a constant filling degree φ (Eq. (3)) of the pan. The volume of the cylindrical part of the pan is calculated from the diameter and the length of the pan.

$$\varphi = \frac{m_{batch}}{\frac{\pi}{4} \cdot d_{pan}^2 \cdot l_{pan} \cdot \rho_{tablets}} \tag{3}$$

The value of the filling degree in the BFC 5 was calculated to be 0.179. The batch size of the BFC 400 for the same filling degree is calculated to be 356.9 kg. The tablet bed depth in BFC 400 is approximately 33.5 cm.

2.4. Experimental design

The influence of mixing time (T), crushing force (CF) and peripheral speed (S) on the abrasion of tablets was investigated in laboratory scale and production scale. Two designs of experiments (DoE) with a full mixed design with 54 trials for the laboratory and production scale were used for the evaluation. The levels for the designs of experiments are shown in Table 4. The results were evaluated with Excel program and Modde 7 (Umetrics). The response

Table 3
Calculated pan speeds based on constant peripheral speed

BFC 5, rpm	BFC 400, rpm	Peripheral speed, cm/s
10	2.2	16.5
18	4.0	29.8
25	5.5	41.4

Table 2
Labelling of tracer tablets (e.g. tablet number 105 had a crushing force of 88 N and was mixed in the pan for 9 min)

Tablet number	Mixing time	Tablet number	Mixing time	Tablet number	Mixing time	Crushing force [N]
1–10	13 min	61–70	9 min	121–130	5 min	23
11–20		71–80		131–140		31
21–30		81–90		141–150		44
31–40		91–100		151–160		64
41–50		101–110		161–170		88
51–60		111–120		171–180		116

Table 4
Levels for the DoEs

Level	−1	−0.8	−0.5	0	0.4	1
Crushing force [N]	23	31	44	64	88	116
Peripheral speed [cm/s]	16.5	–	–	29.8	–	41.4
Mixing time [min]	5	–	–	9	–	13

variable is the abrasion A (%). The regression model for the three variables can be presented in a general formula (Eq. (4)):

$$Y = \beta_0 + \beta_1\mathrm{CF} + \beta_2 T + \beta_3 S + \beta_4\mathrm{CF}\cdot T + \beta_5\mathrm{CF}\cdot S + \beta_6 T\cdot S + \beta_7\mathrm{CF}^2 + \beta_8 T^2 + \beta_9 S^2 \quad (4)$$

where $\beta_1, \ldots, \beta_9$ are the regression coefficients and β_0 is the regression constant. When the equation is presented with coded values the magnitude of the coefficient specifies the change in the response variable if the variable is altered from the lower level to zero or from zero to the upper level and the sign indicates the direction of the change. The model was simplified with a backward regression which means that some terms were removed stepwise from the model if their p-values were higher than 0.05. First, the term with the highest p-value was removed. Coefficient plots and a surface plot are used for the graphical illustration of the results. The scaled and centred coefficients for the response variables are depicted in a coefficient plot. The adjusted coefficient of determination ($R^2_{\mathrm{adj.}}$) is given in the plots.

3. Results and discussion

3.1. Evaluation of the amount of water absorption for the reference tablets

The trials in BFC 400 were carried out at the machine supplier L.B.Bohle (Ennigerloh, Germany) without air supply thus the conditions in the pan can be assumed as the same as in the room (18 °C and 40–45% R.H.). The reference tablets for the BFC 400 were weighted back after completing the trials. Due to the water sorption from the environment humidity, the weight of the reference tablets increased and, consequently the abrasion could be determined as too low based on this weight. Therefore, the reference tablets and tracer tablets from the trials in BFC 400 were conditioned at 21 °C, 45% R.H. to achieve a constant weight. After 7 days the tablets reached a constant weight. The reference tablets were weighted back and the amount of water sorption was determined. The average weight of the reference tablets increased by 0.856% (±0.0162%, $\alpha = 0.05$). Thus, the weights of the tracer tablets were corrected by the weight increase of the reference tablets due to the humidity. The BFC 5 trials were performed at the University of Duesseldorf. The reference tablets (in BFC 5) did not show any weight change, since the trials were carried out under defined conditions (21 °C, 45% R.H.).

3.2. Evaluation of the abrasion of the tablets in laboratory scale and production scale

The aim of this study was to investigate the influence of scale-up, starting from laboratory scale to production scale, on the abrasion of uncoated biconvex tablets. The maximal mixing time was 13 min in order to mimic the initial phase of a coating cycle until the first film protected the core. The friability of the used tablets (according to Ph. Eur. 5) decreased with increasing crushing force of the tablets (Table 1). Riipi et al. [5] showed a correlation between the friability and the surface roughness of tablets, thus the surface roughness of the used tablets should increase with increasing friability of the tablets. Fig. 1 shows a picture of the used tablets before (a) and after (b) mixing in the pan of the laboratory scale. The abrasion of the tablets in the laboratory scale and production scale for different mixing times and crushing forces for a peripheral speed of 29.8 cm/s is shown in Fig. 3. The total abrasion of the tablets was lower as expected. Even the highest abrasion of the tablets with the lowest crushing force for the highest pan speed and a mixing time of 13 min was less than 1%. The tablet abrasion increased with decreasing the crushing force for both the laboratory scale and production scale. The results of the designs of experiment expressed as the scaled and centred coefficients for the abrasion of the tablets are shown in Fig. 4. The crushing force of the tablets was the major factor influencing the tablet abrasions in both scales. The influence of the crushing force on the abrasion was not linear. There was a quadratic effect. With increasing crushing force of the tablets the decrease in tablet abrasion was lower as indicated by the positive sign of the quadratic effects of the crushing force (CF^2) (Figs. 4 and 5). An interaction between the crushing force of tablets and the mixing time could be observed for both scales. The higher the crushing force of the tablets the lower was the influence of the mixing time on the abrasion. Furthermore a slight increase in abrasion was observed at higher mixing time (T). An increase in mixing time of 4 min resulted only in an increase in abrasion of 0.05%. Furthermore

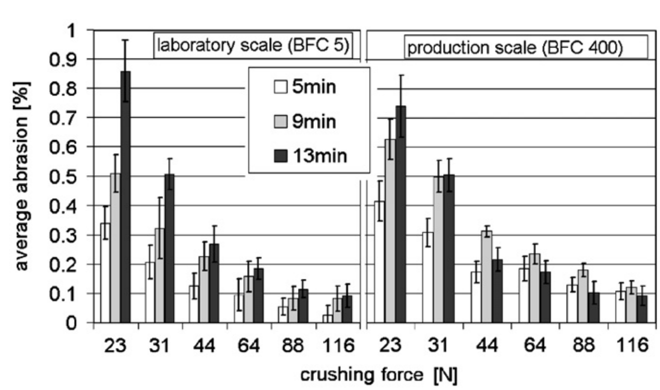

Fig. 3. Average abrasion of tablets in laboratory scale and production scale at a peripheral speed of 29.8 cm/s (bars: 95% confidence interval; $n = 10$).

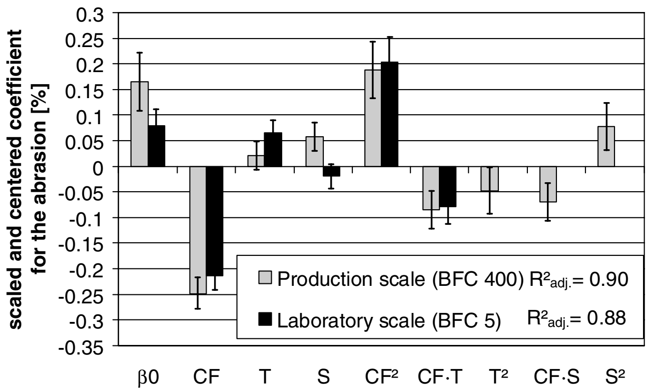

Fig. 4. Coefficient plot for the abrasion of the biconvex tablets in laboratory scale and production scale (bars 95% confidence interval). (β_0, regression constant; CF, crushing force; T, mixing time; S, pan speed.)

an increase in peripheral speed led to a slight increase in abrasion for the production scale. In contrast to a previous work [4] a significant influence of the peripheral speed on the abrasion in laboratory scale could not be observed ($p > 0.05$).

The main abrasion of the used biconvex tablets was at the surface. In contrast, the flat faced tablets used in the previous study [4] showed mainly edge damaging caused by impact at the pan wall. However, the main reason for the abrasion of the biconvex tablets was the mutual rubbing of the tablets. The velocity of tablets increased with increasing pan speed, which should result in a higher friction. However the tablet bed has a lower density with increasing pan speed. Thus the rubbing was reduced by the decreased pressure of the tablets. In the laboratory scale the tablet bed depth was 7.4 cm in contrast to the production scale of 33.5 cm. The higher tablet bed depth in the production scale resulted in an increased pressure on the tracer tablets caused by the tablets lying above. The tablet bed in the production scale has a higher density than the tablet bed in the laboratory scale for higher pan speeds. Therefore, in contrast to the production scale no influence of the pan speed on the abrasion was observed for the laboratory scale.

In order to compare the laboratory scale and production scale, the two designs were evaluated in one design of experiment. The pan loading was used as the fourth factor,

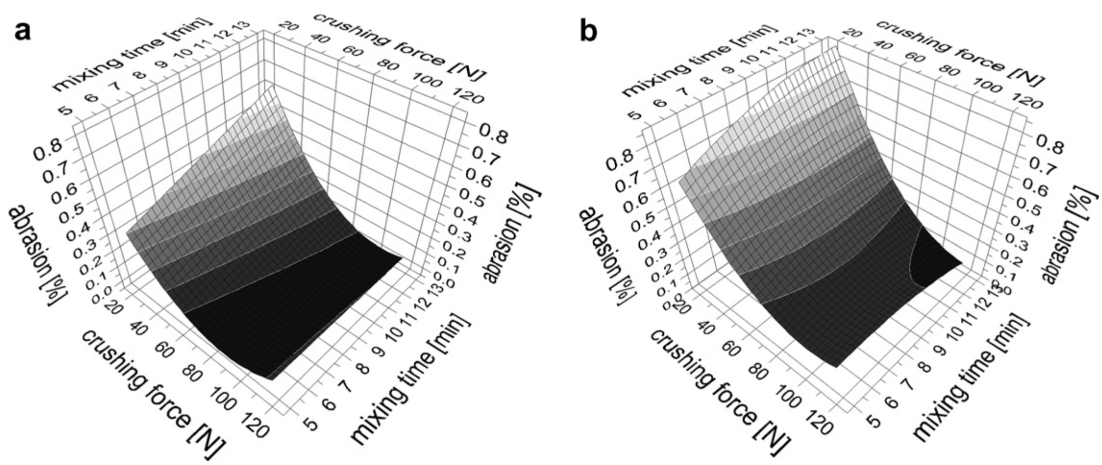

Fig. 5. Response surface plots for the abrasion for (a) laboratory scale, (b) production scale depending on mixing time and crushing force of the tablets for a peripheral speed of 41.4 cm/s.

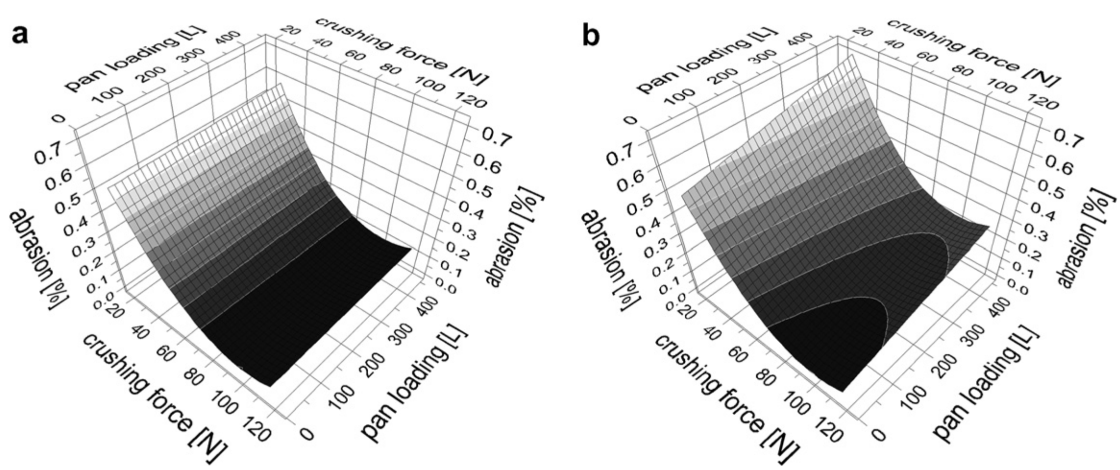

Fig. 6. Response surface plot for the abrasion depending on pan loading and crushing force (mixing time 9 min; peripheral speed $a = 16.5$ cm/s; $b = 41.4$ cm/s).

for the laboratory scale 5 L and for the production scale 463 L. Fig. 6 shows the response surface plots for the abrasion as a function of the pan loading and the crushing force of the tablets.

For all levels of crushing forces only negligible differences in the abrasion between the laboratory scale and the production scale were observed for low peripheral speeds (Fig. 6a). This fact is important for the warming up of the tablet cores, as the cores are mixed gently at low pan speeds. At higher peripheral speed (41.4 cm/s), a slight increase in abrasion in the production scale compared to the laboratory scale was observed (Fig. 6b). This can be related to the tablets with low crushing force. Hence, soft cores should be warmed up at a low pan speed in the production scale if a successful scale-up should be accomplished. After a thin film is applied the pan speed can be successively increased for further coating.

In a previous work [4] the abrasion of flat faced tablets sensitive to impact decreased with increasing pan size. The suggested reason for this phenomenon was the higher number of impacts at the pan wall in the laboratory scale compared to the pilot scale. The biconvex tablets used in the current study did not show this phenomenon. The total abrasion of the biconvex tablet is mainly caused by abrasion on tablet surface.

4. Conclusion

The main factor influencing the abrasion in laboratory scale as well as production scale was the crushing force of the tablets.

For low peripheral speeds only marginal differences in the abrasion were observed between the laboratory scale and the production scale. For tablets with a very low crushing force the warming up step in the production scale should be carried out at a low pan speed (<16 cm/s) in order to avoid an increase in abrasion compared to the warming up step in laboratory scale. After applying a thin protective film the pan speed can be successively increased to the final pan speed in the production scale. Thus, a comparable abrasion can be achieved in the laboratory scale and production scale.

Acknowledgement

The authors greatly acknowledge the support from L.B. Bohle.

References

[1] C.R. Bemrose, J. Bridgwater, A review of attrition and attrition test methods, Powder Technol. 49 (1987) 97–126.
[2] W. Bueb, G. Warnke, K.H. Bauer, Tablet coating methods for very small batches and their suitability for scaling-up, Drug Dev. Ind. Pharm. 20 (1994) 1555–1569.
[3] E. Mentrup, Handling of process changes during scale-up, Pharm. Tech. Eur. 9 (1997) 62–72.
[4] R. Mueller, P. Kleinebudde, Influence of scale-up on the abrasion of tablets in a pan coater, Eur. J. Pharm. Biopharm. (2006) 388–392.
[5] M. Riippi, O. Antikainen, T. Niskanen, J. Yliruusi, The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets, Eur. J. Pharm. Biopharm. 46 (1998) 339–345.
[6] M. Kwapinska, G. Saage, E. Tsotsas, Mixing of particles in rotary drums: a comparison of discrete element simulations with experimental results and penetration models for thermal processes, Powder Technol. 161 (2006) 69–79.
[7] J. Mellmann, The transverse motion of solids in rotating cylinders – forms of motion and transition behavior, Powder Technol. 118 (2001) 251–270.
[8] K.H. Bauer, Über einige grundlegende Gutbewegungs- und Mischvogänge beim Umhüllen von festen Arzneiformen, Pharm. Ind. 39 (1977) 149–156.
[9] P. Pandey, R. Turton, Movement of different-shaped particles in a pan-coating device using novel video-imaging techniques, AAPS PharmSciTech 6 (2005) 237–244.
[10] P. Pandey, Y. Song, F. Kayihan, R. Turton, Simulation of particle movement in a pan coating device using discrete element modeling and its comparison with video-imaging experiments, Powder Technol. 161 (2006) 79–88.
[11] R. Müller, P. Kleinebudde, Scale-down experiments in a new type of pan coaters, Pharm. Ind. 67 (2005) 950–957.
[12] R. Turton, X.X. Cheng, The scale-up of spray coating processes for granular solids and tablets, Powder Technol. 150 (2005) 78–85.
[13] S.C. Porter, Scale-up of film coating, in: M. Levin (Ed.), Pharmaceutical Process Scale-up, Marcel Dekker; Inc., New York, Basel, 2001, pp. 259–310.