Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 56 (2003) 3–9
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Coating uniformity and coating efficiency in a Bohle Lab-Coater using oval tablets

Susanne Tobiska[a], Peter Kleinebudde[b,*]

[a]Martin-Luther-University, Halle-Wittenberg, Halle, Germany
[b]Institute of Pharmaceutical Technology, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany

Received 7 November 2002; accepted in revised form 6 February 2003

Dedicated to Prof. Dr. Dr.h.c. Bernd W. Müller on the occasion of his 60th birthday.

Abstract

The aim of this study was the examination of the influence of tablet size (two different sized oval tablets), batch size, pan speed and inclination of the rotation axis on the coating uniformity and efficiency in a Bohle Lab-Coater BLC 5. The coating uniformity was appraised using the mass variance, the dissolved amount of acetaminophen after 2 h in hydrochloric acid pH 1.0 at a polymer loading of 3 mg/cm^2 and the minimum amount of polymer for an enteric coating. The mass variance of the final tablets decreased with increasing pan speed. There was a linear and quadratic effect in the case of small oval tablets and a linear effect for the large tablets. The minimum amount of polymer required for gastric resistance depends on the pan speed for both tablet sizes. The dissolved amount of acetaminophen after 2 h in simulated gastric fluid was influenced linearly by the batch size for both kind of tablets. In the case of the large oval tablets it was also influenced by the pan speed, the batch size and the inclination of the rotation axis. The dissolved amount of acetaminophen increased with increasing pan speed and batch size. A relation between the coating process efficiency and the investigated influence variables could not be established.

Keywords: Film coating; Oval tablets; Coating uniformity; Mass variance; Dissolution of acetaminophen; Coating process efficiency

Nomenclature

σ^2_{m1}	variance of weight increase per tablet during one cycle
$\sigma_{m,\mathrm{tot}}$	standard deviation of the weight increase
σ^2_{t1}	variance of time per cycle
A_O	surface area of one tablet
CPE	coating process efficiency
k	slope in the $m_p/A_\mathrm{O}(m_t/A_\mathrm{O})$-diagram
m_1	mean weight increase per tablet during one cycle
m_tot	mean weight increase per tablet
$m_{p(0)}$	mean mass of the cores
$m_{p(i)}$	mean mass of the tablet at time i
m_p/A_O	practical mass increase
m_SS	content of the solid substances in the suspension
m_t/A_O	theoretical mass increase
n	number of cycles
$n_{(i)}$	number of tablets at each time i

1. Introduction

Mixing is one of the unit operations in aqueous film coating. Adequate mixing is necessary to obtain uniform tablets. There are two different kinds of coating uniformity – the intra-tablet and the inter-tablet coating uniformity. The first describes the homogeneity of the film on a single tablet and the second describes the uniformity of the applied coating between different tablets within one batch. The inter-tablet coating uniformity is generally defined as the variation in weight gain of coated tablets [1].

For the calculation of the relative standard deviation of the mass of particles ($\sigma_{m,\mathrm{tot}}/m_\mathrm{tot}$) which were coated in a fluidized bed using a Wurster column the following equation [2] or modified equations can be found [3–5]:

$$\frac{\sigma_{m,\mathrm{tot}}}{m_\mathrm{tot}} = \sqrt{\frac{\left(\frac{\sigma_{m1}}{m_1}\right)^2 + \left(\frac{\sigma_{t1}}{t_1}\right)^2}{n}} \quad (1)$$

Therefore the coating uniformity depends on the variance of

* Corresponding author. Institute of Pharmaceutical Technology, Heinrich-Heine-University Duesseldorf, Universitaetsstr. 1, D-40225 Duesseldorf, Germany. Tel.: +49-221-811-4220; fax: +49-211-811-4251.
E-mail address: kleinebudde@uni-duesseldorf.de (P. Kleinebudde).

0939-6411/03/$ - see front matter © 2003 Published by Elsevier Science B.V.
doi:10.1016/S0939-6411(03)00026-2

the applied film coating per tablet in one cycle σ^2_{m1}, the mean amount of film coating applied per tablet in one cycle m_1, the variance of time per cycle σ^2_{t1}, the mean time of one cycle t_1 and the total number of cycles. Using the equation from the fluidized bed for the coating in drum coaters the standard deviation should decrease with increasing process time (increasing number of cycles n), with decreasing circulation time of the tablets t_1 and with decreasing amount of polymer applied during one cycle m_1. The circulation time of the tablets in a drum coater was investigated for round biconvex tablets in dependence of the batch size, the tablet size and the pan speed by Leaver et al. [6]. Increasing pan speed lead, in their study, to a decrease in the circulation time. That increasing pan speeds lead to a decrease of the mass variance has been shown for the film coating of round, biconvex tablets in a Bohle Lab-Coater [7].

The intra-tablet uniformity of different shaped tablets was examined by Wilson and Crossman [8]. Investigations of the film thickness at different points on the tablet surface showed that the intra-tablet homogeneity decreased from round tablets over oval tablets to large oval tablets.

In addition to the coating uniformity a good process should also achieve a high coating process efficiency (CPE), but unfortunately the statements regarding the influence of the pan speed on the efficiency are contradictory [1,9–11].

The aim of this study was the investigation of process parameters that will have an influence on the coating uniformity and efficiency when oval tablets were used. For the examination the parameters batch size, pan speed and inclination of the rotation axis were selected. Using design of experiments the influence of these parameters on the variance of the tablet mass, the minimum amount of polymer, the dissolved amount of acetaminophen and the CPE was studied.

2. Materials and methods

2.1. Statistical design

For the study two $3^{(3-1)}$ factorial design with two additional repetitions on the zero level were used. The variables (batch size, pan speed and inclination of the rotation axis) were investigated on the levels that are listed in Table 1. The coating trials were performed in a randomized order. The results were evaluated with the program Statistica® (Statsoft®) using analysis of variance (ANOVA). For the graphical illustration of these results pareto-diagrams were used. In these diagrams the vertical line shows the level of significance (here $P = 0.05$). If the bar of one parameter crosses this vertical line, it has a statistical significant influence on the investigated parameter. The L in brackets behind the name of the parameter means that the effect of this parameter is linear, and in the case of Q quadratic. Another feature of a pareto-diagram is the fact that the effects are put in descending order according to their size.

Table 1
Variables of the $3^{(3-1)}$-design

Variable	−1	0	+1
BS: batch size (l)	4	5	6
PS: pan speed (rpm)	10	15	20
IA: inclination of the rotation axis (degrees)	0	2	4

2.2. Coating of the tablets

Two different sized oval tablets containing acetaminophen (12 × 5.862 mm: lot. # 090300B and 18.7 × 8 mm: lot. # 090300A, both from Boehringer Ingelheim Pharma KG, Biberach, Germany) were used in this study. The composition of the tablets is shown in Table 2 and their properties are listed in Table 3. These tablets were coated with a coating suspension containing the methacrylic acid copolymer, type C USP/NF (Kollicoat MAE 30 DP, BASF, Germany). The final composition of the suspension is based on the total surface of the tablet bed and can be calculated from the information shown in Tables 3 and 4. For the preparation of the coating dispersion one part of the water was heated to over 70°C. Polysorbate 80 (Tween 80, lot. # 9906B036, Synopharm GmbH, Barsbüttel, Germany) and Glyceryl monostearate (Myvaplex 600P NF, lot. # 1997/003531, Eastman Chemicals, Kingsport, USA) were added. Then the suspension was dispersed using a rotor–stator–homogeniser Diax 600 (Heidolph Instruments, Schwabach, Germany). After adding triethyl citrate (lot. # 280664, Boehringer Ingelheim Pharma KG, Ingelheim; Germany) and Sicovit azorubine 85 E 122 (lot. # 28802, BASF Pigment GmbH, Besigheim, Germany) the suspension was dispersed again. This preparation was cooled down to 25°C before it was added to the polymer dispersion of methacrylic acid copolymer type C (Kollicoat MAE 30 DP, lot. 99-9482, BASF, Ludwigshafen, Germany). The lacking water was added to the coating dispersion. The preparation was stirred during the whole coating run with a blade stirrer (Rührwerk PW 20 DZM, IKA-Werk, Staufen, Germany). The tablets were coated in the Bohle Lab-Coater BLC 5 (L.B. Bohle Maschinen und Verfahren GmbH, Ennigerloh, Germany) using the process parameters shown in Table 5. During the coating process samples of 130 tablets were taken at each increase of 1 mg/cm^2 polymer up to 10 mg/cm^2 polymer.

Table 2
Composition of the acetaminophen-tablets

Substance	%(w/w)
Acetaminophen, powdered	5.0
Lactose	62.8
Microcrystalline cellulose	31.4
Magnesium stearate	0.8

Table 3
Properties of the oval tablets

Tablets	12 mm × 5.862 mm	18.7 mm × 8 mm
Mass of the tablets ($n = 1000$)		
Mean (mg)	253.42	682.56
Variance (mg^2)	3.52	16.31
Content of acetaminophen ($n = 30$)		
Mean (%)	4.90	5.38
Variance (%^{2})	0.06	0.14
Surface (cm^2)	1.98	4.12
Bulk density (g/l)	829.6	762.5
Crushing strength (N)	145.5	118.4
Friability (%)	<0.1	<0.1
Disintegration time (s)	<12	<18

2.3. Evaluation of the density and viscosity of the coating suspension

For the determination of the density and viscosity of the coating dispersion 100 g of different coating preparations were prepared using the method described above. The density was measured using a pycnometer (type B, Vagra, GDR). For the determination of the dynamic viscosity an Ubbelohde viscometer with capillary I (Schott-Geräte GmbH, Hofheim a. Ts., Germany) was used. The measurements of the viscosity were performed at 20°C and were done in quintuplicate.

2.4. Evaluation of the mass distribution and the CPE

The mass of the cores ($n = 1000$) and the final tablets ($n = 50$) was evaluated using a Checkweigher UCW 4 (CGS, Hamburg, Germany). Then the mass variance of the final tablets was calculated for each run. For the calculation of the CPE the cores ($n = 1000$) and tablets of each sample were dried for 24 h at a temperature of 110°C in a drying oven. Then the masses of 50 tablets of each sample were evaluated using the Checkweigher UCW 4. From the content of the solid substances in the suspension m_{SS}, the surface area of one tablet A_O, the number of samples N and the number of tablets at each time $n_{(i)}$ the theoretical mass increase m_t/A_O could be calculated according to Eq. (2). The practical mass increase m_t/A_O could be calculated from Eq. (3) using the mean mass of the cores $m_{p(0)}$, the mean mass of the tablet $m_{p(i)}$ at the time i. The CPE could then be calculated from the slope k in the $m_p/A_O(m_t/A_O)$ diagram (see Fig. 1 and Eq. (4)).

$$m_t/A_O = \sum_{i=1}^{N} \frac{m_{SS}}{Nn_{(i)}A_O} \quad (2)$$

$$m_p/A_O = \frac{m_{p(i)} - m_{p(0)}}{A_O} \quad (3)$$

$$CPE = k100\% \quad (4)$$

Table 4
Composition of the spray suspension

Component	Proportion by area (mg/cm^2)
Methacrylic acid copolymer type C	10.00
Triethyl citrate	1.00
Glyceryl monostearate	0.20
Polysorbate 80	0.08
Sicovit Azorubine 85 E 122	0.20
Water	To 2200 g
Total	11.48 mg/cm^2

2.5. Evaluation of the dissolved amount of acetaminophen and the minimum amount of polymer

The dissolution test were performed according to method A in the USP 24 [12]. A paddle-apparatus was used. The pan speed was set to 50 rpm. As dissolution medium 750 ml hydrochloric acid at pH 1.0 were used. The temperature of the medium was kept constant at 37.0 ± 0.5°C during the test. After 2 h in hydrochloric acid a sample of 10 ml was taken from each vessel. The absorption of the sample was measured against hydrochloric acid at pH 1.0 at 240 nm (acetaminophen and azorubine) and 516 nm (azorubine) using a HP 8451 A diode array spectrometer (Hewlett Packard Company, Palo Alto, USA). The dissolved amount of acetaminophen was calculated using the calibration equations for acetaminophen and azorubine at 240 and 516 nm and taking in to consideration the content of acetaminophen in one tablet.

The dissolution of acetaminophen was determined for six tablets from all samples with equal to or more than 3 mg/cm^2 polymer content. Only for the determination of the dissolved amount of acetaminophen 12 tablets with a theoretical polymer content of 3 mg/cm^2 in the film were investigated. The minimum amount of polymer is defined as the polymer content in the film when the dissolved amount of acetaminophen of all six tablets of this sample and of the tablets of the following samples is less than 10%.

3. Results and discussion

In this study two different sized oval tablets were coated

Table 5
Process parameters of the coating trials

Parameter	
Inlet air temperature (°C)	50
Air flow rate (Nm^3/h)	120
Spray rate (g/min)	12
Spray nozzle	Walther Pilot WA 50
Atomizing air pressure (bar)	1.5

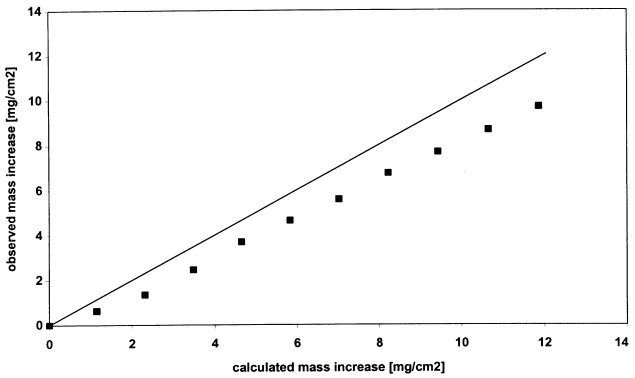

Fig. 1. Practical versus theoretical mass increase (line: without spray loss, squares: sample batch).

in the Bohle Lab-Coater using batch sizes between 4 and 6 l. These circumstances demand different amounts of polymer and other auxiliary substances. Due to the fact that the process time itself influenced the relative standard deviation of the tablet mass [13], the process time was kept constant during the study. This was accomplished by adding different amounts of water to the dispersion, so that the total amount of the preparation was held constant.

Changing the amount of water in the preparation implicated a change in the density and dynamic viscosity of the coating dispersion. The results of the density and viscosity measurements in dependence of tablet size and batch size (Table 6) showed that there are only small differences between the values of the smallest and largest batch size. The density increased by 1.011 and the viscosity by 1.326 for one tablet size. Therefore no serious changes in the droplet size distribution are to be expected.

Beside density and viscosity the surface tension and contact angle are two important properties in influencing the wetting of the tablet surface. Twitchell et al. [14] described the connection between the concentration of an aqueous HPMC E5 solution and the observed contact angle on uncoated and coated tablet cores. The results of this study showed that changing the concentration of the solution between 6 and 12% (w/w) (which corresponds to a change in the viscosity from 45 up to 520 mPa s) led to an increase of the contact angle on the uncoated surface (from 39 to 73°), whereas the contact angle on the coated surface remained relatively constant.

Table 6
Density and viscosity of the coating preparations

Batch size	4l	5l	6l
Tablet size 12 mm × 5.862 mm			
Dynamic viscosity (mPa s)	1.57	1.81	2.09
Density (g/cm^3)	1.024	1.031	1.035
Tablet size 18.7 mm × 8 mm			
Dynamic viscosity (mPa s)	1.32	1.50	1.67
Density (g/cm^3)	1.016	1.020	1.025

Due to the comparable small viscosity increase (see Table 6) no greater influence of the contact angle is expected and therefore the surface effects of the film coating suspension (wetting, spreading and penetration) should not be influenced by the amount of water in the suspension.

Table 7 shows the minimum and maximum values of the investigated parameters (mass variance, minimum amount of polymer, dissolved amount of acetaminophen at a polymer loading of 3 mg/cm^2, coating efficiency) in dependence of the tablet size.

Due to the difference of the mass variance of the cores ($P < 0.01$, Table 3) a comparison of both film tablets with regard to the variance of their mass was not possible. Therefore, the influence of the parameters on the mass variance was analysed for each tablet size separately. For both tablets there is an influence between the pan speed and the mass variance of the final tablets ($P > 0.05$). The pareto-diagram for the large oval tablets (Fig. 2a) shows only a slight linear effect of the pan speed on the mass variance. As Fig. 2b shows in the case of small oval tablets, the effect of the pan speed is linear and quadratic, meaning that an optimum for the pan speed with regard to the variance exists. Using the regression equations the optimum pan speed within the investigated area could be calculated. For a medium batch size (5 l) the pan speed should be 20 rpm for the large oval tablets and 17 rpm for the small oval tablets.

Another parameter for the assessment of the coating uniformity was the minimum amount of polymer needed for an enteric coating. This parameter was determined from the dissolution test. The pareto-diagram (Fig. 3a) showed that there is a relationship between tablet size and minimum amount of polymer. The small oval tablets need less polymer to get enterically coated in comparison with the large ones. The same results could be shown for round, biconvex tablets in a recently published paper [7]. For the small oval tablets there was no correlation between the minimum amount of polymer and the investigated parameters, whereas for the large oval tablets a linear effect of the pan speed, a linear effect of the inclination of the rotation axis and a linear and quadratic effect of the batch size could be observed (Fig. 3b). The linear and quadratic effects of the batch size indicate that with regard to the minimum amount of polymer an optimum exists. With increasing pan speed and inclination of the rotation axis less polymer have to be applied to get enterically coated tablets.

A higher inclination of the rotation axis seemed to be advantageous with regard to the CPE of the large oval tablets, because the efficiency increased with increasing inclination angle, as shown in Fig. 4a. Due to this connection it could be assumed that the decrease of the minimum amount of polymer with increasing inclination angles traced back to the slower spray loss rather than to an improved homogeneity of the film coat. In contrast to the

Table 7
Results of the study, range of yield values

Tablet size	12 mm × 5.862 mm	18.7 mm × 8 mm
Mass variance (mg^2)	5.4–21.9	23.2–55.9
Minimum amount of polymer (mg/cm^2)	4.1–10.5	9.8–11.6
Dissolved amount acetaminophen after 2 h at pH1 at a polymer loading of 3 mg/cm^2 (%)	6.3–71.6	1.7–54.3
CPE (%)	67.9–81.2	60.4–69.4

large oval tablets the CPE of the small oval tablets is not influenced by any of the investigated parameters (Fig. 4b).

The homogeneity of a film coat could not only be evaluated on the basis of the mass variance and the minimum amount of polymer but also by means of the dissolved amount of an active substance at low polymer loadings. For the determination of the uniformity of the film coat tablets with a theoretical polymer increase of 3 mg/cm^2 were used. For the statistical analysis the arithmetic mean of the dissolved amount of acetaminophen of 12 tablets after 2 h in hydrochloric acid pH 1.0 was calculated. As the pareto-diagram (Fig. 5a) shows a lot of different parameters have an influence on the dissolved amount of acetaminophen. Concerning the batch size (linear and quadratic effect) and the pan speed (linear and quadratic effect) there seemed to be an optimum. Another, but slight influence of the tablet size could be also seen in the diagram. According to this, the dissolved amount of acetaminophen is greater for the smaller tablets. From the surface plot (Fig. 5b) the optimum

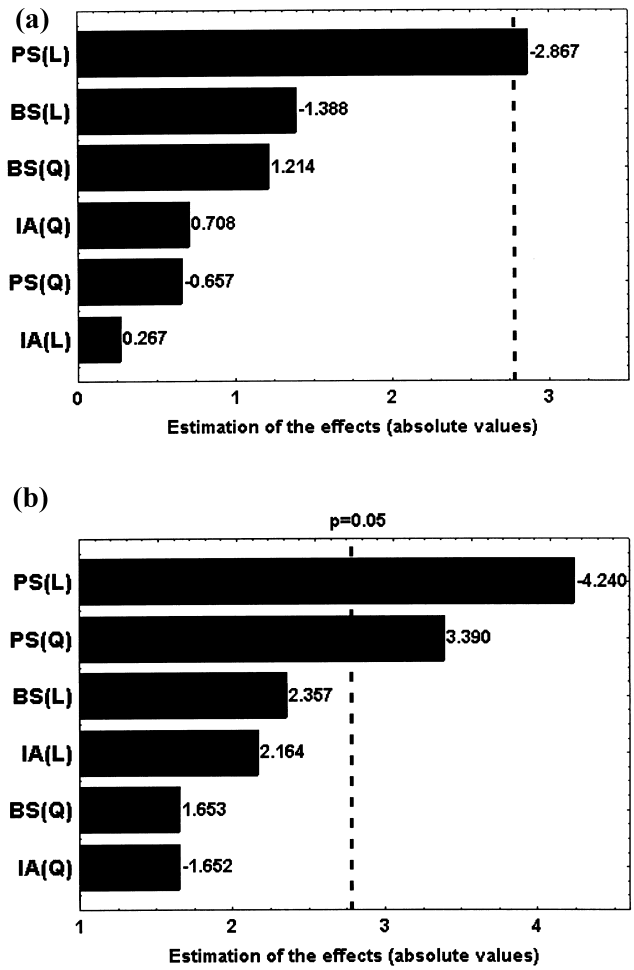

Fig. 2. (a) Pareto-diagram for the mass variance of the large oval tablets ($R^2_{adj.} = 0.40$) : linear (L) and quadratic (Q) effects of BS – batch size, IA – Inclination angle and PS – pan speed. (b) Pareto-diagram for the mass variance of the small oval tablets ($R^2_{adj.} = 0.80$) : linear (L) and quadratic (Q) effects of BS – batch size, IA – Inclination angle and PS – pan speed.

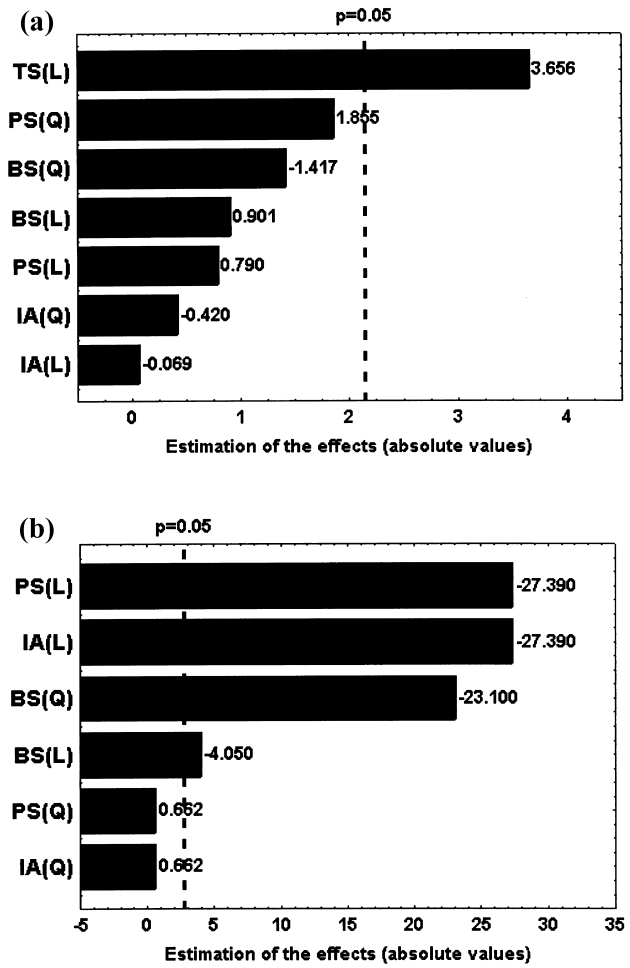

Fig. 3. (a) Pareto-diagram for the minimum amount of polymer of both oval tablets ($R^2_{adj.} = 0.37$) : linear (L) and quadratic (Q) effects of BS – batch size, IA – Inclination angle, PS – pan speed and TS – tablet size. (b) Pareto-diagram for the minimum amount of polymer of the large oval tablets ($R^2_{adj.} = 1.00$) : linear (L) and quadratic (Q) effects of BS, batch size; IA, inclination angle; and PS, pan speed.

for the pan speed and batch size could be determined. Thus the best results were obtained for pan speeds of about 15 rpm and small up to medium batch sizes.

4. Conclusion

The results of the coating trials with the round, biconvex tablets [7] and with the oval tablets showed clearly that the pan speed has a big influence on the quality of the film tablets produced in a Bohle Lab-Coater. The pan speed had an influence on the mass variance of the tablets as well as on the disintegration and dissolution behaviour, so that it determined decisively the amount of polymer needed for an enteric coating. In the case of the oval tablets beside the influence of the pan speed on the minimum amount of polymer also an effect of the batch size and inclination of the rotation axis could be detected. Independent of the size and shape of the tablet, the quality of the film improved with increasing pan speed. But there is an upper limit for the pan speed because with increasing pan speed the attrition will rise and also the incidence of damaged edges will increase.

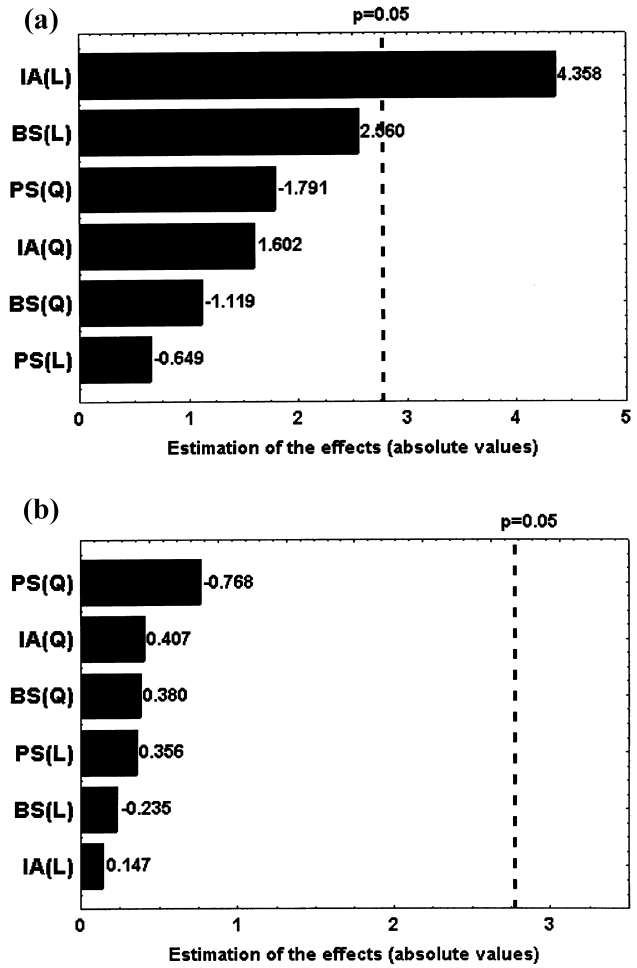

Fig. 4. (a) Pareto-diagram for the CPE of the large oval tablets ($R^2_{adj.} = 0.72$) : linear (L) and quadratic (Q) effects of BS, batch size; IA, inclination angle; and PS, pan speed. (b) Pareto-diagram for the CPE of the small oval tablets ($R^2_{adj.} = 0$) : linear (L) and quadratic (Q) effects of BS, batch size, IA, inclination angle; and PS, pan speed.

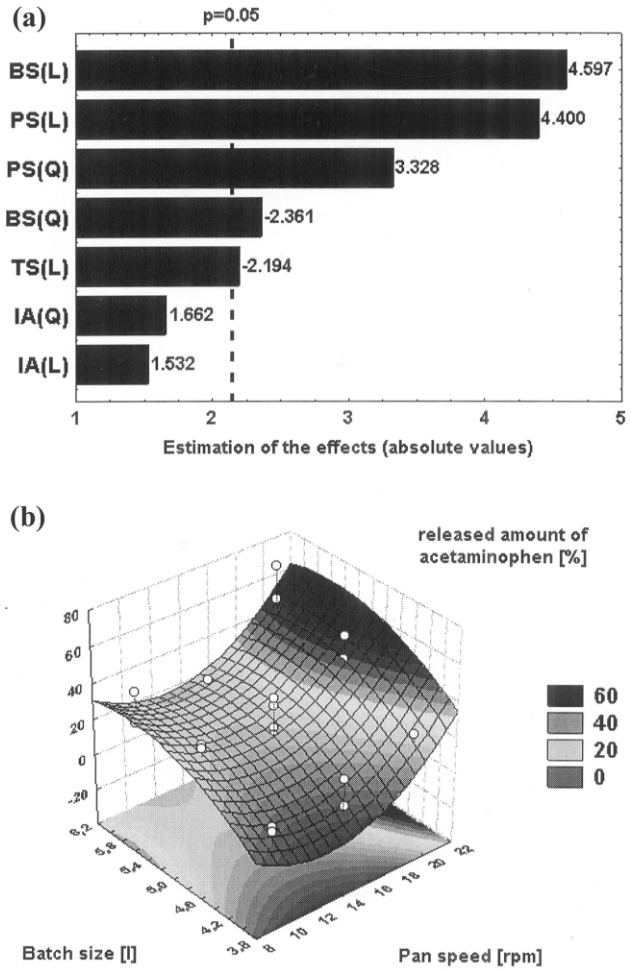

Fig. 5. (a) Pareto-diagram for the dissolved amount of acetaminophen of both oval tablets ($R^2_{adj.} = 0.74$) : linear (L) and quadratic (Q) effects of BS, batch size; IA, inclination angle; PS, pan speed; and TS, tablet size. (b) Surface plot for the dissolved amount of acetaminophen of both oval tablets.

Acknowledgements

The authors would like to thank the company L.B. Bohle (Ennigerloh, Germany) for the opportunity to work with the Bohle coaters. We also thank the companies BASF and Boehringer Ingelheim for the material.

References

[1] S.C. Porter, R.P. Verseput, C.R. Cunningham, Process optimization using design of experiments, Pharm. Tech. Eur. (1998) 44–52.
[2] V.U. Blank, Coating of tablets in fluidized bed processes, PhD thesis (German), University of Cologne, 1999.
[3] U. Mann, Analysis of spouted-bed coating and granulation. 1. Batch operation, industrial and engineering chemistry, Proc. Des. Dev. 22 (1983) 288–292.

[4] X.X. Cheng, R. Turton, The uniformity of particle coating occurring in fluidized beds, AIChE Symp. Ser. 301 (1994) 142–151.
[5] S. Shelukar, J. Ho, J. Zega, E. Roland, N. Yeh, D. Quiram, A. Nole, A. Katdare, S. Reynolds, Identification and characterization of factors controlling tablet coating uniformity in a Wurster coating process, Powder Technol. 110 (2000) 29–36.
[6] T.M. Leaver, H.D. Shannon, R.C. Rowe, A photometric analysis of tablet movement in a side-vented perforated drum (Accela-Cota), J. Pharm. Pharmacol. 37 (1985) 17–21.
[7] S. Tobiska, G. Reich, P. Kleinebudde, Influence of process parameters on the coating uniformity and efficiency in a Bohle Lab Coater, PharmSci., submitted for publication.
[8] K.E. Wilson, E. Crossman, The influence of tablet shape and pan speed on intra-tablet film coating uniformity, Drug Dev. Ind. Pharm. 23 (1997) 1239–1243.
[9] M.A.K. Kara, T.M. Leaver, R.C. Rowe, Material carryover and process efficiency during tablet film coating in a side-vented perforated drum (Accela-Cota), J. Pharm. Pharmacol. 34 (1982) 469–470.
[10] R. Chittamuru, G. Reyes, J. Pollock, T. Farrell, Optimal coating process parameters for a new, fully formulated, acrylicbased, enteric, film-coating system. Proceedings of the AAPS Annual Meeting, Indianapolis (2000).
[11] B.D. Rege, J. Gawel, J.H. Kou, Identification of critical process variables for coating actives onto tablets via statistically designed experiments, Int. J. Pharm. 237 (2002) 87–94.
[12] United States Pharmacopeial Inc, The United States Pharmacopeia, The National Formulary, Rockville, MD, 2000.
[13] R.-K. Chang, M. Leonzio, The effect of run time on the inter-unit uniformity of aqueous film coating applied to glass beads in a Hi-Coater, Drug Dev. Ind. Pharm. 21 (1995) 1895–1899.
[14] A.M. Twitchell, J.E. Hogan, M.E. Aulton, Proceedings of the 12th Pharmacological and Technical Conference, Solid Dosage Research Unit, Helsingor, Denmark, 1 (1993) 246–257. Cited In: G.C. Cole, J.E. Hogan, M.E. Aulton, Pharmaceutical coating technology. Taylor & Francis, London (1995) 130.