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Research paper

Effects of roller compaction settings on the preparation of bioadhesive granules and ocular minitablets

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Abstract

An experimental factorial design was employed to evaluate bioadhesive granules and bioerodible ocular minitablets (6 mg and Ø 2 mm). The purpose of this study was to compare minitablets prepared using roller compacted granules with an optimised minitablet formulation, manufactured on laboratory scale by direct compression. The formulation consisted of drum dried waxy maize starch, Carbopol® 974P, and ciprofloxacin in a ratio of 90.5/5/3 (w/w/w). Three roller compactor parameters were varied, i.e. the roller speed, the horizontal screw speed and the compaction force, while the vertical screw speed was kept constant. Afterwards, the ribbons were milled to obtain granules suitable for compression. The friability, the flow properties, the bulk material characteristics (apparent and tap density and porosity) and the particle size distributions of two granule sieve fractions (90–125 and 125–355 μm) were investigated. The roller speed and the compaction force have the largest influence on the granule characteristics, followed by the horizontal screw speed. The physical properties of non- and gamma-irradiated minitablets were determined. From the tablet strength, friability and dissolution results, a low compaction force and a high roller speed were shown to be preferable to prepare granules which can be further tabletted into adequate ocular minitablets.

Keywords: Ocular minitablet; Roller compaction/dry granulation; Bioadhesive formulation; Experimental design; Ciprofloxacin

1. Introduction

The bioavailability of drugs applied as aqueous eye drops is low due to rapid drainage, reflex blinking, lacrimation and low corneal permeability. When applying conventional eye drops, frequent instillations are necessary to obtain a therapeutic drug level in the tear film or at the site of action. A high administration frequency is associated with patient non-compliance. Furthermore, the frequent use of concentrated solutions can lead to toxic side-effects and cellular damage at the ocular surface [1,2]. Therefore, numerous strategies were developed to increase the drug bioavailability by prolonging the contact time between drug and corneal/conjunctival epithelium. One of the approaches to optimise the dosage form was the implementation of the use of films or inserts, proposed to allow a slow drug release over a long period of time after their application in the fornix [3–5].

In previous studies, ocular bioadhesive minitablets were developed and optimised which showed sustained drug release properties [6,7]. The bioadhesive polymers employed were drum dried waxy maize starch and Carbopol® 974P. The minitablets are bioerodible, show no mucosal irritation and are well-accepted by volunteers. The gelling of the minitablet in the cul-de-sac is an advantage since its rheological properties result in an extended residence at the absorption site. Ciprofloxacin, a frequently used antimicrobial agent in ophthalmology, was selected in these ocular preparations, because it is a powerful single agent for treating mild and moderate bacterial keratitis and conjunctivitis [8]. The in vitro evaluation and clinical studies proved the usefulness of this formulation, however, there are some difficulties in manufacturing these minitablets, as the bioadhesive blend, used to prepare the ocular minitablets has poor flow properties [9]. In order to

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manufacture the minitablets at a larger scale, it was necessary to improve the flow properties of the powders by dry granulation with a roller compactor.

The goal of the present study is to investigate and optimise the roller compactor settings in order to obtain granules which can be compressed into ocular minitablets with similar properties as the minitablets prepared with direct compression. An expanded 2^3 full factorial experimental design with centerpoint was set-up in order to evaluate the influence of three roller compaction parameters (compaction force, horizontal screw speed and roller speed) on the granulation. The various granules were characterised by the determination of friability, flow properties, particle size distribution, porosity, apparent and tap density. Furthermore in this study, the influences of the settings of the roller compactor parameters, gamma-irradiation and the compression force on the features of the ocular minitablets were examined. The ocular minitablets prepared were characterised by their crushing strength, friability, hydration grade and drug release pattern.

2. Materials and methods

2.1. Materials

Drum dried waxy maize starch (DDWM, containing 99.9% amylopectin) was supplied by Eridania Béghin-Say Cerestar (Vilvoorde, Belgium) and Carbopol® 974P by Noveon (Cleveland, Ohio, USA). Sodium stearyl fumarate was a gift of Edward Mendell Co., Inc. (New York, USA). Ciprofloxacin hydrochloride hydrate was purchased from Roig Farma (Barcelona, Spain). Simulated Lacrimal Fluid (SLF) was prepared with 8.3 g/L NaCl, 1.4 g/L KCl and 84 mg/L $CaCl_2$ in MilliQ water [10]. A NaOH 1 N solution was used to adjust the pH to a value of 7.4 ± 0.1 (Benchtop 420A pH meter, Orion, MA, USA).

2.2. Production of granules and minitablets

2.2.1. Blending and roller compaction—dry granulation

The bioadhesive powder mixture was prepared in a planetary mixer (Kenwood Chef, Hampshire, UK) by blending drum dried waxy maize starch, Carbopol® 974P and ciprofloxacin hydrochloride hydrate in a ratio of 90.5/5/3.5 (w/w/w).

Dry granulation was performed on a Fitzpatrick IR220 roller compactor (The Fitzpatrick Company Europe, Sint-Niklaas, Belgium). A hydraulic system is used to maintain the bearing blocks of the smooth movable rollers. Three compactor parameters were varied, i.e. roller speed (3, 5 and 7 rpm), horizontal screw speed (25, 30 and 35 rpm) and compaction force (10, 17 and 24 kN/cm), while the vertical screw speed was kept constant at 200 rpm (Table 1). The gap between the rolls and the resulting thickness of the compacts depended on the settings of these parameters. The run (RC 9) with a roller speed of 3 rpm, compaction force of 24 kN/cm and horizontal screw speed of 35 rpm, did not allow roller compaction. As deviation from the 2^3-experimental design, two extra runs (RC 1 and RC 11) were performed in order to obtain more information about the influence of the roller compactor parameters on the features of the granules.

Table 1
Variables set in each run

Run	RS (rpm)	F (kN/cm)	HS (rpm)
RC 1	3	10	30
RC 2	7	10	25
RC 3	7	24	35
RC 4	3	24	25
RC 5	7	10	35
RC 6	7	24	25
RC 7	3	10	25
RC 8	3	10	35
RC 9[a]	3	24	35
RC 10	5	17	30
RC 11	7	24	30

[a] Dry granulation could not be performed.

After roller compaction, ribbons were milled using a FitzMill Type M5A (The Fitzpatrick Company Europe, Sint-Niklaas, Belgium) to obtain granules. The granules from each run (1.2 kg) were sieved on a Retsch VE 1000 shaker (Retsch, Haan, Germany), employing sieves with the following opening sizes: 45, 90, 125, 355 and 500 μm. The two sieve fractions 90–125 and 125–355 μm were used for further evaluation.

2.2.2. Blending and tableting

The 90–125 and 125–355 μm granules of three differently performed runs were carefully mixed in a mortar with the lubricant sodium stearyl fumarate (1%, w/w), and blended afterwards in a laboratory mixer for 10 min (Turbula T2A, Willy A. Bachoffen-WAB, Maschinenfabrik, Basel, Switzerland).

The six different granule fractions obtained and the physical powder mixture were then compressed into minitablets using an eccentric compression machine (Korsch, Type EKO, Berlin, Germany) with a standard filling shoe. Punch holders were equipped with four concave punches of 2 mm in diameter. Based on preliminary experiments with minitablets containing ciprofloxacin, three different compression forces were used: 0.500 (range 0.475–0.525), 1.000 (range 0.900–1.100) and 1.500 (1.400–1.600) kN. As ocular dosage forms must be sterile, half of each of the 21 different batches of minitablets were taken for gamma-irradiation at 25 kGy (Sterigenics, IBA-Mediris, Fleurus, Belgium), since autoclaving and the moisture level with EtO sterilisation would cause gelling of the dry minitablet [9].

2.3. Characterisation of granules and minitablets

2.3.1. Granules

2.3.1.1. SEM. The structure, shape and surface of the granules were evaluated using scanning electron microscopy (JSM 5600 LV-SEM, JEOL, Tokyo, Japan). The granules were coated with platinum, employing a sputter coater (Auto Fine Coater, JFC-1300, JEOL, Tokyo, Japan).

2.3.1.2. Flowability, densities and porosity. The flow time was determined with a dry glass funnel with stem, and the time needed for the entire sample (50 g) to flow out of the funnel was measured. The granules with size fraction of 90–125 and 125–355 μm were selected for further analysis and compression tests. As the narrow diameter of the compression die (2 mm) required granules with excellent flow properties, the flow time through a funnel, the Carr Index (compressibility index) and the Hausner ratio were determined. Apparent density was calculated from the amount of granules poured into a 100 mL graduated cylinder up to a total volume of 50 mL, while for the tap density determination the cylinder was tapped until no measurable change in the volume was observed (J. Englesman, Ludwigshafen, Germany). Based on apparent and tap density, both the Carr Index (%) ((tapped − apparent) × 100/tapped) and Hausner ratio (tapped/apparent) were calculated. According to literature data, excellent and good flow properties are seen for powders with a Carr Index in a range from 5 to 15 and 12 to 16%, respectively. Hausner ratios below 1.25 indicate good flow properties of powders or granules [11]. The total granular porosity was obtained by measuring the true density of the powder mixture with a helium pycnometer (AccuPyc 1330, Micrometric, Norcross, GA, USA) and the apparent density of the granules prepared, was determined as mentioned previously.

2.3.1.3. Granule friability. The quality of the granules obtained was evaluated by determining their friability (F_g). Herewith 10 g of the 90–125 or 125–355 μm granule fractions together with 200 glass beads (mean diameter: 4 mm) were subjected to mechanical shocks in a Pharma Test-type friabilator (Pharma Test, Hainburg, Germany) for 10 min at a rotational speed of 25 rev/min. After 250 rotations, the glass beads were removed, and the granules were sieved over a 90 or 125 μm screen on a sieve-shaker (Retsch, Haan, Germany) for 2 min at an amplitude of 2 mm. The material remaining on the screen was weighed and the friability value, expressed as percentage was calculated using the following equation

$$F_g(\%) = 100 \times (P - P')/P \quad (1)$$

where P is the initial weight of granules (10 g) and P' is the final weight after sieving over a 90 or 125 μm screen.

2.3.1.4. Particle size distribution. The mean particle size distributions of the different granule fractions were determined with a laser diffraction analyzer (Master Sizer, Malvern Instruments,Worcestershire, UK) by suspending the particles in air. The volume median diameter $D(v,0.5)$ was employed to calculate the average particle size of the 90–125 and 125–355 μm granule fractions.

2.3.2. Minitablets

2.3.2.1. Crushing strength. The behaviour of ocular minitablets under force was analysed using an instrumented uniaxial press Lloyd (type L1000R, Lloyd Instruments, Segenworth, Fareham, UK), equipped with a 20 N load cell. The data of the test were obtained from 10 tablets, prepared at the same compression force. Herewith, minitablets prepared at three different compression forces were evaluated.

2.3.2.2. Friability. The friability of the matrix minitablets (F_m) was determined by subjecting 10 tablets weighed together with 100 glass beads (average diameter of 4 mm) to falling shocks for 10 min in a Pharma Test friabilator (Hainburg, Germany), set at a speed of 25 rev/min. After 10 min, the glass beads were removed, the tablets were then weighed and the percentage friability was calculated, using the following equation

$$F_m(\%) = 100 \times (P - P')/P \quad (2)$$

where P is the initial weight of 10 minitablets and P' is the final weight after the friability test [7].

2.3.2.3. Water uptake. The water uptake or hydration grade at room temperature was studied gravimetrically. The weighed minitablets (m_d) were placed on the upper side of a sintered glass-filter (Robu Glasfilter, Hattert, Germany) which was connected on the lower side to a reservoir filled with Simulated Lacrimal Fluid. The weight of the wet, swollen matrix (m_w) was determined after 8 h in order to calculate the water uptake of the minitablets (W) [7]

$$W = \frac{m_w - m_d}{m_d} \quad (3)$$

2.3.2.4. In vitro drug release. The release of ciprofloxacin from the various series of minitablets ($n = 3$) was examined using glass vials in an oscillating water bath. This dissolution method is the most appropriate to obtain a suitable in vivo simulation [9]. A minitablet was accurately weighed, and transferred to a glass vial containing 1.00 mL Simulated Lacrimal Fluid or SLF (pH 7.4). To avoid water evaporation, the vials were covered with rubber caps and placed in an oscillating (25 rpm) water bath at 32 ± 1 °C. Throughout the experiment, aliquots of 80 μL were withdrawn after 0, 20, 40, 60, 90, 120, 180, 240, 300 and 1440 min, and replaced by an equal volume of SLF. The samples were diluted and centrifuged at 3000 rpm for

10 min. The concentration of ciprofloxacin was determined spectrophotometrically at 275 nm (U-1500, Merck-Hitachi, Darmstadt, Germany). The percentage released at each time point was expressed as a fraction of the total amount of drug in the minitablet.

To compare the dissolution profiles, the difference (f_1) and the similarity (f_2) factors were calculated. The difference factor (f_1) measures the percent error between two curves over all time points

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \quad (4)$$

where n is the sampling number, R_j and T_j are the percent dissolved of the reference and test products at each time point j. The percent error is zero when the test and drug reference profiles are identical and increases proportionally with the dissimilarity between the two dissolution profiles.

In another approach, similarity between two drug products can be defined by an f_2 between 50 and 100, f_2 equals 100 for identical dissolution profiles. The similarity factor f_2 is defined as a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and the reference products. An average difference of 10% at all measured time points results in an f_2 value of 50. The f_2 value can be calculated as follows

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{j=1}^{n} w_j |R_j - T_j|^2\right]^{-0.5} \times 100\right\} \quad (5)$$

R_j and T_j represent the average percentage of drug dissolved from the minitablets measured at the jth time point of the reference and test preparations, respectively, n is the number of time points tested (n is considered in the calculations as not more than one measurement after 85% of drug released in the test preparation) and w_j is an optional weigth factor [12].

2.4. Statistical analysis

The designs were developed and analysed by the statistical software Statistica® (Statsoft, Tulsa, OK, USA).

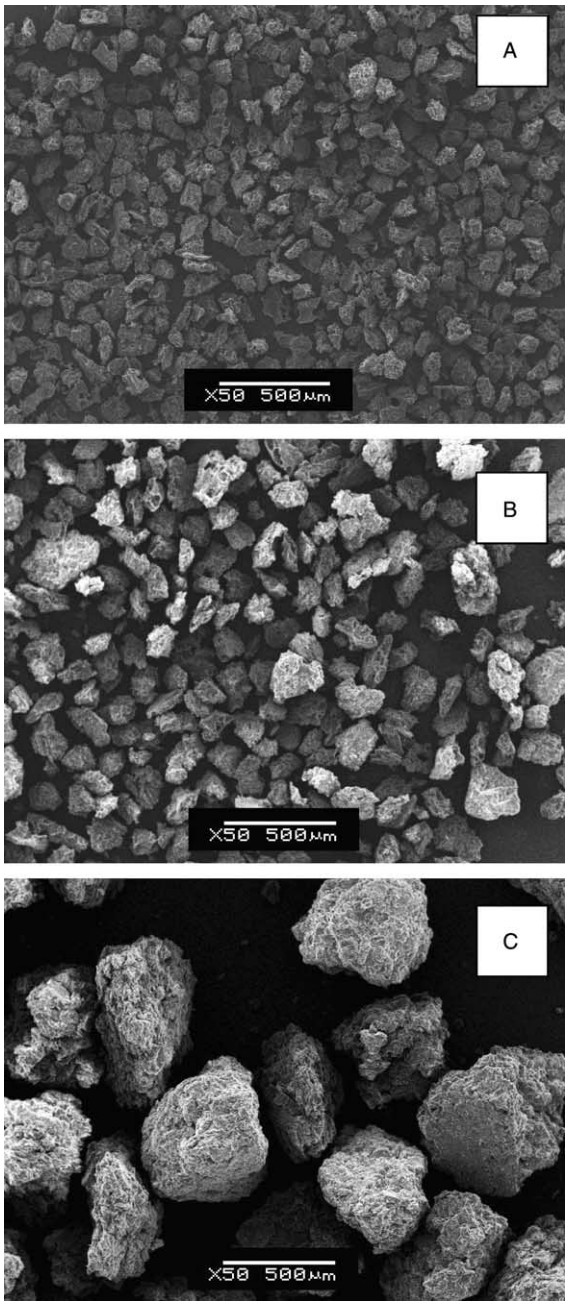

Fig. 1. Scanning electron micrographs of differently prepared granules: (A) 90–125 μm, (B) 125–355 μm and (C) >500 μm.

3. Results and discussion

3.1. Properties of granules

Micro-photographs of three granule fractions: 90–125, 125–355 and >500 μm are shown in Fig. 1.

The flow times measured, the Carr Indices and Hausner ratios calculated are summarised in Table 2. The flow time of the powder mixture could not be determined due to strong cohesion, while for the 90–125 and 125–355 μm fractions these were in the range of 9.8–11.3 and 5.0–7.0 s, respectively. All the formulations tested had Carr indices ranging between 11.19 and 16.31%, while their Hausner ratios were below 1.20. These results demonstrate the adequate flowing properties of the granules prepared. From Fig. 2, one can deduce that the roller speed (RS) and the compaction force influence the flow times of the various granule fractions. For both granule fractions, the flow time increases when the roller speed is increased. The flow time is the lowest, when a low roller speed and a high compaction force are combined. The Pareto-diagrams in Fig. 3 show that

Table 2
Flow properties of the granule fractions 90–125 and 125–355 μm

	Flow time (s)	Carr index (%)	Hausner ratio
90–125 μm			
RC 1	10.28 (0.30)	13.19	1.15
RC 2	11.27 (0.29)	13.78	1.15
RC 3	10.39 (0.31)	16.01	1.19
RC 4	9.83 (0.20)	15.34	1.18
RC 5	11.17 (0.33)	15.36	1.18
RC 6	11.07 (0.17)	16.31	1.19
RC 7	10.69 (0.14)	15.16	1.18
RC 8	10.07 (0.11)	14.53	1.17
RC 10	9.91 (0.25)	15.76	1.19
RC 11	10.19 (0.27)	16.02	1.19
125–355 μm			
RC 1	6.00 (0.03)	12.96	1.15
RC 2	6.94 (0.02)	14.90	1.18
RC 3	5.67 (0.06)	14.79	1.17
RC 4	5.01 (0.05)	12.89	1.15
RC 5	6.17 (0.03)	11.19	1.13
RC 6	6.44 (0.04)	14.03	1.16
RC 7	5.86 (0.04)	13.45	1.16
RC 8	6.06 (0.07)	14.76	1.17
RC 10	5.42 (0.07)	13.72	1.16
RC 11	5.92 (0.04)	12.43	1.14

mainly the roller speed (R), then the compaction force (F) and finally the horizontal screw speed (H) of the roller compactor influence significantly the flow times of all different granules (P-value <0.05). The absolute values of the estimated effects are larger for the flow time of the 125–355 μm granule fraction than in the case of the 90–125 μm fraction. The estimation of the interactions or interaction effects between the parameters indicated that only the interaction between the compaction force (F) and the horizontal screw speed (H) had no significant effect on the flow time of the 125–355 μm granule fraction.

The apparent and tap densities of the granules of the 125–355 μm fraction were significantly influenced by the three roller compactor settings, as can be derived from Table 3. The apparent density, tap density and porosity of the 90–125 μm granule fraction were significantly affected by the roller speed (R) and the compaction force (F).

The friability of the granules is reported in Fig. 4. In Fig. 4B, it can be clearly seen that the friability of the 125–355 μm granule fraction was increased when the compactor settings were set at the highest roller speed and the lowest compaction force. The response surfaces of the friability of the 10 differently prepared granules from each fraction indicated that increasing the compaction force resulted in granules with a lower friability. In the data plots of both fractions, the interaction effect between the roller speed and the compaction force of the roller compactor can be observed. This positive interaction results in a skewness of the response surface. As can be noted in Table 3, the interaction value (i.e. 5.094) between the roller speed and the compaction force is significant for

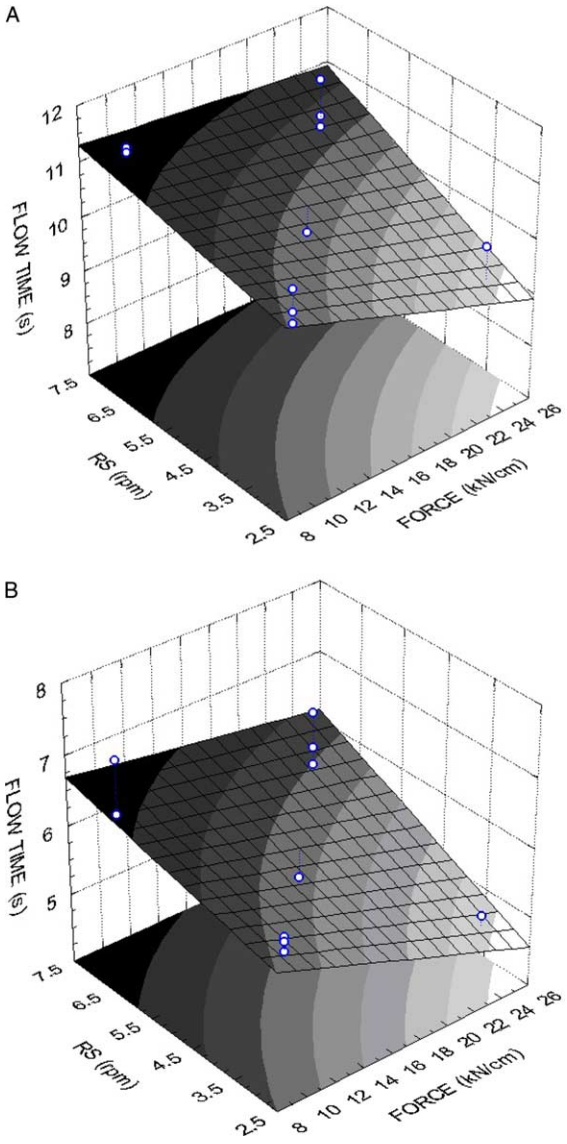

Fig. 2. Effect of the compaction force and the roller speed on the flow time of the prepared granules (A) 90–125 μm and (B) 125–355 μm.

the friability of the 125–355 μm fraction. The two other interactions of the roller compactor settings ($R\times H$ and $F\times H$) are also significant for the friability of this granule fraction.

The settings used to prepare the roller compaction ribbons affect also the average diameter of the 10 batches of the 125–355 μm fraction. As can be derived from Table 3, the compaction force (13.443) is the most important parameter, influencing the sizes of the granules from 125 to 355 μm fraction, followed by the roller speed (−11.832) and the horizontal screw speed (4.183). However, these three roller compaction parameters did not influence significantly the average diameters of the granules from the 90–125 μm fraction.

Generally, one can conclude from the estimations of effects that the roller speed and compaction force have

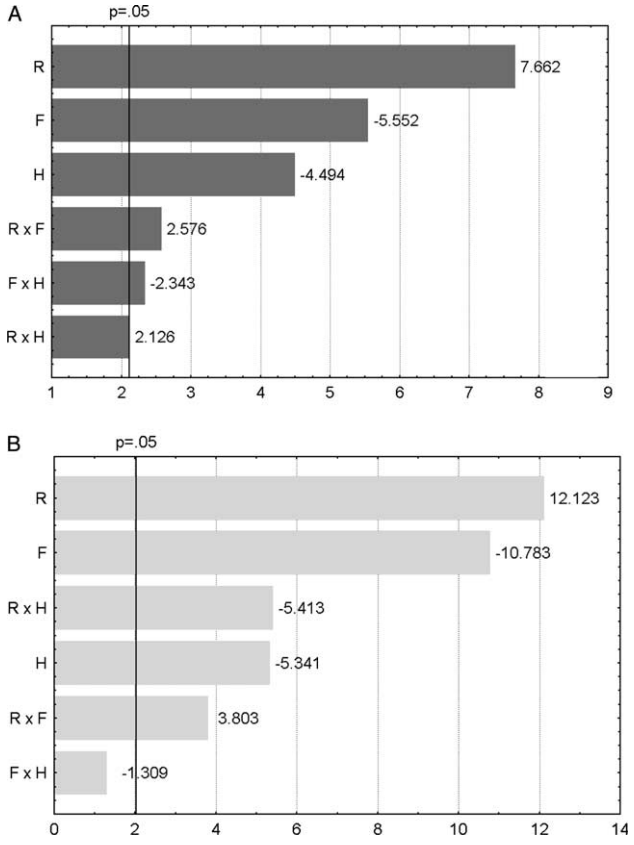

Fig. 3. Pareto-diagrams for the flow properties (s) of granule fraction 90–125 μm (A) and 125–355 μm (B).

the largest influences on the granule characteristics, followed by the horizontal screw speed. Significant effects can be mainly seen for the 125–355 μm granule fraction. The effects calculated are small for the 90–125 μm fraction, mainly due to the smaller size range compared to the 125–355 μm fraction. The 125–355 μm granule fraction with the lowest flow time, the lowest friability and the highest apparent density was obtained using the highest compaction force (24 kN/cm), the lowest roll speed (3 rpm) and the lowest horizontal screw speed (25 rpm). These granules also have the largest average diameter. These characteristics are the result of the high compaction force, and the longer dwell time between the rolls under these conditions. This dwell time is already known to have a significant influence on type and extent of binding of plastic deforming materials, such as DDWM, the major component of the powder mixture employed [13]. Inghelbrecht et al. [14] also reported that the friability of DDWM granules is decreased, when they are mainly prepared at higher compaction forces.

The correlations between the friability and the average size of the various granules are shown in Fig. 5A and B, in which the particle size and the corresponding friability of the granules prepared are presented. The correlation line in Fig. 5B suggests less friability values for larger granules ($R=0.9487$). Sheskey et al. [15] also reported this trend, which can be mainly explained by the fact that ribbons compacted at low roller speeds and high compaction forces, are the most robust. Milling these robust ribbons results in larger agglomerates, which are also stronger than the granules obtained from ribbons compacted at a high roller speed and a low compaction force.

3.2. Properties of minitablets

Different granules were prepared in order to produce minitablets on a larger scale. The bioadhesive physical powder mixture and six granule batches obtained after sieving the milled ribbons, prepared at three different roller compactor settings (RC4, RC5, and RC10) were used to prepare ocular minitablets. These three compactor runs were chosen for the evaluation of the influence of roller compactor settings on the properties of the minitablets.

The physical properties of the minitablets are summarised in Table 4. The crushing strength of the minitablets increased with increasing compression forces, while it was not influenced by gamma-irradiation. The minitablets prepared with the 125–355 μm granule fraction did not comply with the Ph. Eur. and USP requirements for friability. The friability of the minitablets is not influenced by gamma-irradiation, used as a sterilisation method; this can also be deduced from the crushing strength measurements. This was also confirmed in one of our previous studies [9]. The minitablets prepared with the granules from the largest granule fraction (125–355 μm) had a lower

Table 3
Estimation of the absolute effects and interactions for the 90–125 μm (>90) and 125–355 μm (>125) granule fractions

	Bulk density (g/ml)		Tap density (g/ml)		Porosity (%)		Friability (%)		Average diameter (μm)	
	> 90	> 125	>90	>125	>90	>125	>90	>125	>90	>125
Roller Speed (R)	−5.880*	−10.253*	−4.320*	−5.203*	5.880*	3.595*	−1.441	5.840*	−0.426	−11.832*
Force (F)	3.583*	9.415*	3.914*	5.237*	−3.583*	−3.422*	−2.101	−7.806*	0.637	13.443*
Horizontal Screw speed (H)	1.244	4.472*	0.733	2.153*	−1.245	−0.994	0.7962	−1.611	1.357	4.183*
($R\times F$)	0.085	−5.569*	1.107	−2.562*	−0.084	1.878	1.079	5.094*	−0.133	−7.033*
($R\times H$)	3.349*	2.942*	4.039*	1.256	−3.349*	−2.770*	−2.576*	−2.329*	0.709	0.744
($F\times H$)	−0.802	0.751	−1.575	0.841	0.802	0.793	1.559	− 3.071*	−0.223	4.037*

The significant influence of the roller compactor settings are marked with *($P=0.05$). The larger the number, the larger the influence of the roller compactor settings on the properties of the granule fractions.

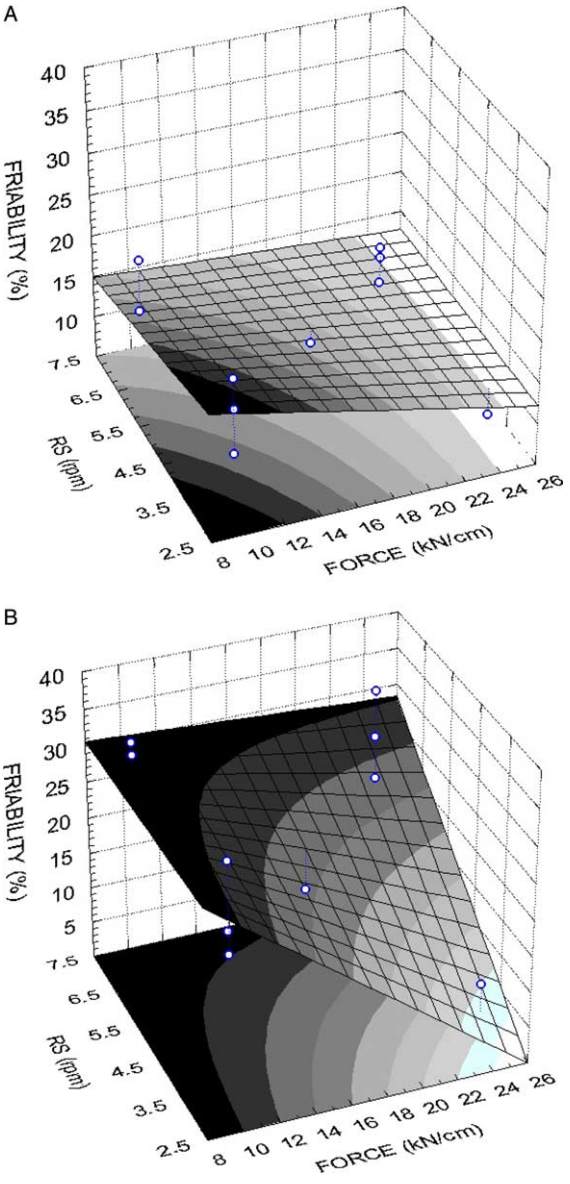

Fig. 4. Effect of the compaction force and the roller speed on the friability properties of the prepared granules (A) 90–125 μm and (B) 125–355 μm.

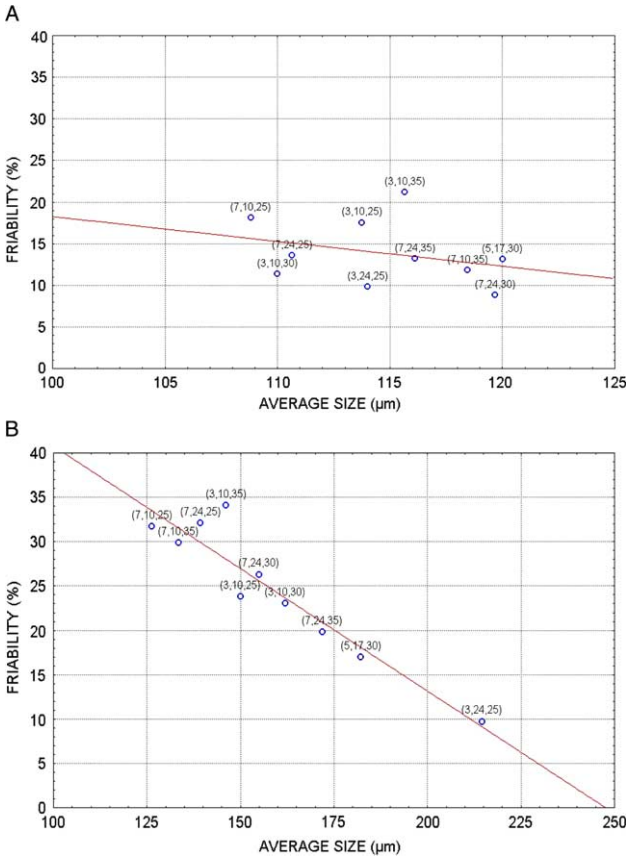

Fig. 5. Relation between the friability and average size for granule fraction 90–125 μm (A) and granule fraction 125–355 μm (B), (RS,F,HS).

crushing strength and a higher friability than the tablets prepared with smaller granules (90–125 μm) obtained from the same roller compactor runs. The improved granule quality obtained with a decreasing particle size was in agreement with the results of De Boer et al., McKenna and McCafferty and Inghelbrecht and Remon [16–18] who also observed an increase in the compactibility with a decreasing particle size. This phenomenon was explained by the higher surface area available for bonding if a finer particle size was employed. The tablet strength was significantly higher, at lower roller compaction forces, employed for the preparation of the granules. The effect of this compaction force on the tablet strength was also confirmed by Sheskey and Cabelka [19]. An increasing resistance to fragmentation at tablet compression, was exhibited by the robust granules prepared at high compaction forces. This phenomenon is also known as the working hardening principle [20–22]. Brittle granules are necessary to form new surfaces for bonding and influence, therefore, the tablet strength, as mentioned previously [23,24]. This might explain the increased strength of the tablets, prepared with granules manufactured at low roller compaction forces and thus exhibiting a higher friability.

Increasing the compression force from 0.500 to 1.500 kN resulted in a decreased water uptake by the minitablets. This was also reported in the evaluation of the compression force on the physical properties of directly compressed ocular minitablets [7]. The uptake of Simulated Lacrimal Fluid by the ocular gelling minitablets, prepared by direct compression was decreased, after gamma-irradiation. The hydration rate of the directly compressed minitablets prepared at three different compression forces was higher and was more influenced by gamma-sterilisation than the minitablets manufactured with the granules.

Based on all the results obtained, one can conclude that the sterilised minitablets prepared at 1.500 kN with the 90–125 μm granule fraction from roller compactor setting RC 5, RC 10 and the RC 4, have the most adequate physical

Table 4
Properties of minitablets, prepared with the physical powder mixture and granules from RC4 (RS = 3 rpm, F = 24 kN/cm, HS = 25 rpm), RC5 (RS = 7 rpm, F = 10 kN/cm, HS = 35 rpm) and RC10 (RS = 5 rpm, F = 17 kN/cm, HS = 30 rpm), compressed at 0.500, 1.000 and 1.500 kN

			Crushing strength (N) ±SD (n = 10)		Friability (%) ±SD (n = 3)		Water uptake ±SD (n = 3)	
			0 kGy	25 kGy	0 kGy	25 kGy	0 kGy	25 kGy
Physical powder Mixture (PM)		0.500 kN	8.17 ± 0.72	8.37 ± 0.82	1.02 ± 0.11	1.12 ± 0.01	2.02 ± 0.25	1.82 ± 0.30
		1.000 kN	13.21 ± 1.33	14.03 ± 1.26	0.32 ± 0.01	0.39 ± 0.10	1.84 ± 0.27	1.71 ± 0.21
		1.500 kN	15.70 ± 0.49	15.37 ± 0.55	0.16 ± 0.01	0.40 ± 0.12	1.74 ± 0.24	1.64 ± 0.12
Granules								
RC 4	90–125 μm	0.500 kN	2.60 ± 0.71	2.23 ± 0.29	10.37 ± 2.41	7.98 ± 0.56	1.79 ± 0.24	1.76 ± 0.34
		1.000 kN	4.60 ± 0.63	4.37 ± 0.23	2.12 ± 0.60	2.46 ± 0.83	1.74 ± 0.23	1.74 ± 0.31
		1.500 kN	6.03 ± 0.40	6.48 ± 1.20	0.75 ± 0.12	0.92 ± 0.11	1.58 ± 0.39	1.57 ± 0.11
	125–355 μm	0.500 kN	0.87 ± 0.21	0.67 ± 0.34	100.00 ± 0.00	100.00 ± 0.00	1.85 ± 0.15	1.76 ± 0.14
		1.000 kN	1.01 ± 0.12	0.89 ± 0.15	100.00 ± 0.00	100.00 ± 0.00	1.56 ± 0.20	1.55 ± 0.29
		1.500 kN	1.33 ± 0.29	1.02 ± 0.15	84.46 ± 1.10	100.00 ± 0.00	1.56 ± 0.13	1.52 ± 0.60
RC 5	90–125 μm	0.500 kN	7.15 ± 0.99	7.05 ± 0.30	0.93 ± 0.06	1.05 ± 0.17	1.72 ± 0.28	1.65 ± 0.31
		1.000 kN	11.53 ± 0.59	12.01 ± 0.47	0.50 ± 0.02	0.35 ± 0.27	1.53 ± 0.27	1.62 ± 0.26
		1.500 kN	13.04 ± 1.17	13.77 ± 1.17	0.38 ± 0.08	0.54 ± 0.31	1.60 ± 0.30	1.61 ± 0.28
	125–355 μm	0.500 kN	3.67 ± 0.28	3.50 ± 0.39	18.22 ± 5.59	18.24 ± 12.14	1.84 ± 0.15	1.72 ± 0.11
		1.000 kN	4.57 ± 0.25	4.02 ± 0.25	1.43 ± 0.09	1.63 ± 0.10	1.57 ± 0.09	1.49 ± 0.03
		1.500 kN	4.98 ± 0.25	5.07 ± 0.39	1.34 ± 0.89	1.12 ± 0.31	1.42 ± 0.16	1.42 ± 0.13
RC 10	90–125 μm	0.500 kN	4.12 ± 0.55	4.27 ± 0.53	2.71 ± 1.65	2.04 ± 1.41	1.69 ± 0.25	1.73 ± 0.25
		1.000 kN	6.93 ± 0.31	6.72 ± 0.65	0.89 ± 0.05	0.70 ± 0.28	1.65 ± 0.22	1.69 ± 0.24
		1.500 kN	8.17 ± 0.52	8.47 ± 0.46	0.81 ± 0.06	0.54 ± 0.28	1.64 ± 0.22	1.67 ± 0.27
	125–355 μm	0.500 kN	2.93 ± 0.45	3.17 ± 0.34	11.55 ± 2.95	11.85 ± 2.31	1.70 ± 0.14	1.80 ± 0.14
		1.000 kN	4.23 ± 0.49	3.83 ± 0.87	4.13 ± 0.78	4.13 ± 0.78	1.53 ± 0.13	1.50 ± 0.03
		1.500 kN	4.75 ± 0.34	4.32 ± 0.58	1.79 ± 0.69	1.79 ± 0.69	1.55 ± 0.02	1.37 ± 0.04

properties and were most similar to the directly compressed minitablets.

In the present study, the effects of the roller compactor parameters and gamma-irradiation on the dissolution profiles were also evaluated. The non- and sterilised minitablets compressed at 1.500 kN, were selected in order to study the release behaviour. The release profiles of ciprofloxacin during 5 h for directly compressed minitablets and the granules from different roller compactor runs are given in Fig. 6A and B. The graphs show that dissolution profiles are not equal for all runs. Table 5 lists the dissimilarity (f_1) and similarity (f_2) factors for the runs, compared with the optimised non-sterilised reference minitablet R_1 and the reference sterilised minitablet R_2, both prepared by direct compression. The f_2-value from the sterilised minitablets prepared with the 125–355 μm granule fraction is not listed, because of the fast disintegration and release of ciprofloxacin from the minitablets, resulting in a complete release over 60 min (Fig. 6A). The largest f_2 and the lowest f_1 values were obtained for the minitablets manufactured with the 90–125 μm granule fraction from roller compactor run 5 (RC5), in comparison to our optimised and sterilised ocular minitablet prepared by direct compression and evaluated in vivo [9]. Comparing the dissolution profiles of the tablets prepared with the two granule fractions of roller compactor run 5 (RC5), it can be concluded that gamma-sterilisation had a larger influence on the release properties than the use of different granule fractions.

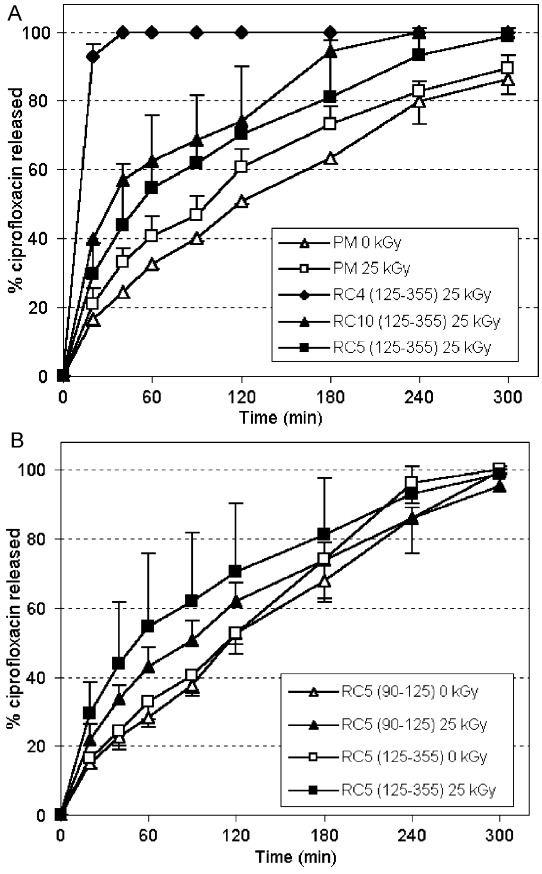

Fig. 6. Dissolution profiles of minitablets prepared with powder mixture and granules made from different roller compactor settings (RC).

Table 5
Difference factor f_1 and similarity factor f_2 for 85% drug release from the ocular minitablets compressed at 1.500 kN ($n=3$)

	f_1	f_2
R_1-R_2	12.75	58.46
R_1-RC4 (90–125) 0 kGy	6.54	67.14
R_1-RC4 (90–125) 25 kGy	20.20	49.27
R_1-RC10 (90–125) 0 kGy	4.70	77.91
R_1-RC10 (90–125) 25 kGy	17.08	50.84
R_1-RC5 (90–125) 0 kGy	4.13	79.06
R_1-RC5 (90–125) 25 kGy	15.94	54.27
R_1-RC4 (125–355) 0 kGy	4.23	72.65
R_1-RC4 (125–355) 25 kGy	38.55	22.29
R_1-RC10 (125–355) 0 kGy	5.43	64.58
R_1-RC10 (125–355) 25 kGy	34.90	34.19
R_1-RC5 (125–355) 0 kGy	3.36	71.07
R_1-RC5 (125–355) 25 kGy	28.75	40.28
R_2-RC4 (90–125) 25 kGy	6.56	70.08
R_2-RC10 (90–125) 25 kGy	4.42	72.43
R_2-RC5 (90–125) 25 kGy	2.80	83.09
R_2-RC4 (125–355) 25 kGy	31.01	–
R_2-RC10 (125–355) 25 kGy	22.31	40.96
R_2--RC5 (125–355) 25 kGy	14.70	51.53

R_1, REF PM 1.500 kN, 0 kGy and R_2, REF PM 1.500 kN, 25 kGy.

4. Conclusions

The physical properties of the bioadhesive granules can be mainly optimised by adjusting the roller speed and the compaction force. The granules with the lowest flow time and the lowest friability properties were obtained by milling the ribbons, prepared at the highest compaction force and at the lowest roller speed. The horizontal screw speed did not affect the characteristics of the granules to a large extent. Based on the tablet strength, friability and dissolution results, a low compaction force and a high roller speed were shown to be preferable for the preparation of granules suitable for large-scale tableting into minitablets with similar release properties as the previously optimised and in vivo tested minitablet, manufactured by direct compression.

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References

[1] C. Baudouin, Side effects of antiglaucomatous drugs on the ocular surface, Curr. Opin. Ophthalmol. 7 (1996) 80–86.
[2] A. Topalkara, C. Güler, D.S. Arici, M.K. Arici, Adverse effects of topical antiglaucoma drugs on the ocular surface, Clin. Exp. Ophthalmol. 28 (2000) 113–117.
[3] M.F. Saettone, L. Salminen, Ocular inserts for topical delivery, Adv. Drug. Deliv. Rev. 16 (1995) 94–106.
[4] G. Di Colo, S. Burgalassi, P. Chetoni, M.P. Fiaschi, Y. Zambito, M.F. Saettone, Gel-forming erodible inserts for ocular controlled delivery of ofloxacin, Int. J. Pharm. 215 (2001) 101–111.
[5] F. Gurtler, R. Gurny, Patent literature review of ophthalmic inserts, Drug. Dev. Ind. Pharm. 21 (1995) 1–18.
[6] J. Ceulemans, A. Vermeire, E. Adriaens, J.P. Remon, A. Ludwig, Evaluation of a mucoadhesive tablet for ocular use, J. Controlled Release 77 (2001) 333–344.
[7] W. Weyenberg, A. Vermeire, J.P. Remon, A. Ludwig, Characterization and evaluation of ocular bioadhesive minitablets compressed at different forces, J. Controlled Release 89 (2003) 329–340.
[8] A. Smith, P.M. Pennefather, S.B. Kaye, C.A. Hart, Fluoroquinolones—place in ocular therapy, Drugs 61 (2001) 747–761.
[9] W. Weyenberg, A. Vermeire, E. D'Haese, G. Vanhaelewyn, P. Kestelyn, F. Callens, H.J. Nelis, J.P. Remon, A. Ludwig, Effect of different sterilisation methods on the properties of bioadhesive powders and ocular minitablets, and clinical evaluation, Eur. J. Pharm. Sci. 23 (2004) 77–87.
[10] M. Paulsson, K. Edsman, Controlled drug release from gels using surfactant aggregates: I. Effect of lipophilic interactions for a series of uncharged substances, J. Pharm. Sci. 90 (2001) 1216–1225.
[11] J.L. Wells, Tablet testing in: J. Swarbrick, J.C. Boylan (Eds.), Encyclopedia of Pharmaceutical Technology, vol. 14, Marcel Dekker, New York, NY, 1997, pp. 401–418.
[12] V.P. Shah, Y. Tsong, P. Sathe, J.P. Liu, In vitro dissolution profile comparison—statistics and analysis of the similarity factor f_2, Pharm. Res. 15 (1998) 889–896.
[13] B. Rambali, L. Baert, E. Jans, D.L. Massart, Influence of the roll compactor parameter settings and the compression pressure on the buccal bio-adhesive tablet properties, Int. J. Pharm. 220 (2001) 129–140.
[14] S. Inghelbrecht, J.P. Remon, P. Fernandes de Aguiar, B. Walczak, D.L. Massart, F. Van de Velde, P. De Baets, H. Vermeersch, P. De Backer, Instrumentation of a roll compactor and the evaluation of the parameter settings by neural networks, Int. J. Pharm. 148 (1997) 103–115.
[15] P.J. Sheskey, T.D. Cabelka, R.T. Robb, B.M. Boyce, Use of roller compaction in the preparation of controlled-release hydrophilic matrix tablets containing methylcellulose and hydroxypropylmethylcellulose polymers, Pharm. Technol. 9 (1994) 133–150.
[16] A.H. De Boer, H. Vromans, C.F. Lerk, G.K. Bolhuis, K.D. Kussendrager, H. Bosch, Studies on tableting properties of lactose. III. The consolidation behaviour of sieve fractions of crystalline α-lactose monohydrate, Pharm. Weekbl. Sci. Ed. 8 (1986) 145–150.
[17] A. McKenna, D.F. McCafferty, Effect of particle size on the compaction mechanism and tensile strength of tablets, J. Pharm. Pharmacol. 34 (1982) 347–351.
[18] S. Inghelbrecht, J.P. Remon, The roller compaction of different types of lactose, Int. J. Pharm. 166 (1998) 135–144.
[19] P.J. Sheskey, T.D. Cabelka, Reworkability of sustained-release tablet formulations containing HPMC polymers, Pharm. Technol. 7 (1992) 60–74.
[20] S. Malkowska, K.A. Khan, Effect of recompression on the properties of tablets prepared by dry granulation, Drug Dev. Ind. Pharm. 9 (1983) 331–347.

[21] S.K. Kochlar, M.H. Rubinstein, D. Barnes, The effects of slugging and recompression on pharmaceutical excipients, Int. J. Pharm. 115 (1995) 35–43.
[22] P. Kleinebudde, Review article: roll compaction/dry granulation: pharmaceutical applications, Eur. J. Pharm. Biopharm. 58 (2004) 317–326.
[23] C. Nystöm, P.G. Karehill, The importance of intermolecular bonding forces and the concept of bonding surface area in: G. Alderborn, C. Nyström (Eds.), Pharmaceutical Powder Compaction Technology, Marcel Dekker, New York, NY, 1996, pp. 17–54.
[24] E.N. Hiestand, Mechanical properties of compacts and particles that control tableting success, J. Pharm. Sci. 86 (1997) 985–990.