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RESEARCH PAPER

Extrusion Granulation and High Shear Granulation of Different Grades of Lactose and Highly Dosed Drugs: A Comparative Study

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ABSTRACT

Formulations containing different lactose grades, paracetamol, and cimetidine were granulated by extrusion granulation and high shear granulation. Granules were evaluated for yield, friability, and compressibility. Tablets were prepared from those granules and evaluated for tensile strength, friability, disintegration time, and dissolution. The different lactose grades had an important effect on the extrusion granulation process. Particle size and morphology affected powder feeding and power consumption, but had only a minor influence on the granule and tablet properties obtained by extrusion granulation. In contrast, the lactose grades had a major influence on the granule properties obtained by high shear granulation. Addition of polyvinylpyrrolidone (PVP) was required to process pure paracetamol and cimetidine by high shear granulation, whereas it was feasible to granulate these drugs without PVP by extrusion granulation. Granules prepared by extrusion granulation exhibited a higher yield and a lower friability than those produced by high shear granulation. Paracetamol and cimetidine tablets compressed from granules prepared by extrusion granulation showed a higher tensile strength, lower friability, and lower disintegration time than those prepared from granules produced by high shear granulation. Paracetamol tablets obtained via extrusion granulation exhibited faster dissolution than those obtained via high shear granulation. For all lactose grades studied, extrusion granulation resulted in superior granule and tablet properties in comparison with those obtained by high shear granulation. These results indicate that extrusion granulation is more efficient than high shear granulation.

Key Words: Extrusion granulation; High shear granulation; α-Lactose monohydrate; Anhydrous β-lactose; Particle size; Particle morphology; Paracetamol; Cimetidine.

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INTRODUCTION

In the pharmaceutical industry, the choice of a suitable granulation process depends, to some extent, on the physical properties of the powders to be granulated and on the requirements of the final granules. The physical characteristics of granules, such as particle size distribution, friability, and porosity, are of interest as they will affect the downstream processes. The granulation technique, as well as the processing parameters employed during granulation, have a significant effect on granule characteristics and hence, the properties of the tablets prepared from the granules. In addition, the physical properties of the raw materials will also affect the granulation process as well as granule properties. A granulation technique that eliminates any differences between the starting materials would therefore be of interest.

Extrusion granulation is a semicontinuous wet granulation technique, which was shown to be more efficient for the granulation of α-lactose monohydrate 200M than conventional high shear granulation.[1] The aim of this study was to evaluate the robustness of the extrusion granulation process using different lactose grades by examining the influence of lactose particle size and morphology on the granulation process and on the granule and tablet properties (in comparison with high shear granulation). In addition, the feasibility of processing formulations containing a high drug concentration and having poor compaction properties (paracetamol) or poor flow and disintegration properties (cimetidine) was evaluated.

MATERIALS

The different grades of lactose used were: crystalline α-lactose monohydrate (Pharmatose® 450M, 200M, 100M, 90M) and anhydrous β-lactose (Pharmatose DCL 21) (DMV, Veghel, The Netherlands). The physical properties of lactose grades are listed in Table 1. Paracetamol was received from Mallinckrodt (Capitol Boulevard, Raleigh, NC, USA) and cimetidine was purchased from Roig Farma (Barcelona, Spain). Polyvinylpyrrolidone (PVP, Kollidon® K30) and crospovidone (Kollidon CL) were received from BASF (Ludwigshafen, Germany).

METHODS

Preparation of Granules

Extrusion Granulation

Granulation was performed on a MP 19 TC 25 laboratory scale corotating twin screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length-to-diameter ratio of 25/1 and equipped with a standard screw profile with two mixing sections and a die block (having one opening of 2.2×1.0 cm). The granulation liquid (pure water or an aqueous 2.5% PVP solution) was pumped into the first zone of the extruder barrel using a peristaltic pump (Watson Marlow, Cornwall, UK). Granulation was carried out at 25°C barrel temperature, 250 rpm screw speed, 5.6 $kg.h^{-1}$ total input rate, and 7.5% (w/w) water content during extrusion. If required, paracetamol, cimetidine, or crospovidone were blended before granulation with α-lactose monohydrate for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK). Extrudates were collected 10 min after the granulation was started in order to allow the system to equilibrate, then the extrudates (400 g) were immediately wet sized using a 1-mm oscillating sieve (Frewitt, Fribourg, Switzerland), operated at a minimal distance between rotor and sieve.[1] The granules obtained were oven-dried at 25°C for 20 h. All water concentrations were based on the wet extruded mass, whereas PVP, cimetidine, and paracetamol concentrations were based on dry weight.

The extrusion granulation process was evaluated by monitoring power consumption and barrel temperature. If the power consumption exceeded 80% of the maximum capacity, the process was stopped in order to avoid machine damage.

Table 1. The physical properties of different grades of lactose.

Grade	Particle size[a] (μm)	Morphology	Bulk density (g/cm^3)	Solubility
α-Lactose monohydrate 90 M	135	Non-granular	0.76	1 in 5
α-Lactose monohydrate 100 M	130	Non-granular	0.75	1 in 5
α-Lactose monohydrate 200 M	40	Non-granular	0.55	1 in 5
α-Lactose monohydrate 450 M	20	Non-granular	0.47	1 in 5
Anhydrous β-lactose	150	Granular	0.67	1 in 2.2

[a]Average particle size by sieving (certificate of analysis, DMV).

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High Shear Granulation

The granulation was performed in a high shear granulator (Gral 10, Machines Collette, Wommelgem, Belgium) at 500 rpm impeller speed, 3000 rpm chopper speed, and 10% (w/w) water concentration. If required, paracetamol, cimetidine, or crospovidone were blended before granulation with α-lactose monohydrate for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK). The granulation liquid (pure water or an aqueous 2.5% PVP solution) was added using a peristaltic pump (Watson Marlow, Cornwall, UK). After a 2-min mixing period of the powder, the required amount of granulation liquid was continuously added over a period of 10 min. Wet massing was continued for 2 min following complete liquid addition. The granules obtained were oven-dried at 25°C for 20 h. All water concentrations were based on the wet extruded mass, while PVP and drug concentrations were based on dry weight.

Compression of Tablets

The granules (fraction 250–710 μm) were blended with 0.5% (w/w) magnesium stearate (< 90 μm) (BUFA, Brussels, Belgium) in a Turbula mixer (W.A. Bachofen, Basel, Switzerland) for 1 min. Tablets (250 mg) were prepared using an eccentric compression machine (Korsch EKO, Berlin, Germany) equipped with a flat faced double punch of 9 mm at a compression force of 10 kN per tablet.

Evaluation of Granules

Particle Size Analysis

The particle size distribution of the granules ($F_{<1400\ \mu m}$) was determined using laser diffraction (Master Sizer, Malvern, UK) after suspending the particles in air. The volume diameter (d_v) was used to calculate the fractions as follows: ($F_{<250\ \mu m}$, $F_{250\ \mu m-1000\ \mu m}$, and $F_{>1000\ \mu m}$). The analysis was performed at minimal air pressure (0.4 bar) to avoid desagglomeration and/or disintegration of the granules during the test.

Yield

$F_{250-1000\ \mu m}$ was used as a measure for the yield of the process and was calculated as

$$F_{<1400\ \mu m}(\%) * F_{250-1000\ \mu m}(\%)/100$$

where $F_{<1400\ \mu m}$=the fraction of dried granules smaller than 1400 μm and $F_{250-1000\ \mu m}$=the granule fraction between 250–1000 μm as determined by particle size analysis.

Friability of Granules

Granule friability was determined in a friabilator (Pharma Test, Hainburg, Germany) at a speed of 25 rpm for 10 min, by subjecting 10 g (I_{wt}) of granules ($F_{250-1000\ \mu m}$) together with 200 glass beads (mean diameter 4 mm) to falling shocks. Afterwards, the glass beads were removed and the weight of the granules retained on a 250-μm sieve (F_{wt}) was determined after vibrating for 5 min (Retsch VE 1000, Haan, Germany) at an amplitude of 2 mm. The friability was calculated as $[(I_{wt}-F_{wt})/I_{wt}]^*100$.

Bulk and Tapped Density

The bulk volume (V_0) of 50 g granules ($F_{250-1000\ \mu m}$) was recorded in a 100-mL measuring cylinder as well as the volume after 1500 taps (V_{1500}) in a tapping machine (J. Englesman, Ludwigshafen, Germany). Bulk and tapped densities were calculated as 50 g/V_0 and 50 g/V_{1500}, respectively. The compressibility index (C%) was calculated from the bulk and tapped density using the following equation

$$C\% = \{(\rho_f - \rho_i)/\rho_f\}^*100$$

where ρ_i=the bulk density and ρ_f=the tapped density.

Tablet Evaluation

Immediately after compression, tablets were stored for 24 h at 25°C and 60% relative humidity (RH) prior to evaluation. For the stability study, tablets were immediately stored at the specified conditions.

Tablet Friability

The tablet friability was determined using a friabilator (Pharma Test, Hainburg, Germany) at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

Tablet Tensile Strength

The hardness, thickness, and diameter of the tablets (n=6) was determined (Pharma Test, Hainburg, Germany). The tablet tensile strength T was calculated using the equation described by Fell and Newton:[2]

$$T = 2F/\pi \cdot d \cdot t$$

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where F, d, and t=the diametral crushing force, the tablet diameter, and the tablet thickness, respectively.

Tablet Porosity

The tablet porosity ε was determined (n=3) using He-pycnometry (Micromeritics, Norcross, GA) by the following equation;

$$\varepsilon = (\text{bulk volume} - \text{skeletal volume}) / \text{bulk volume}^{*}100$$

Disintegration Time

The disintegration time was determined (n=6) using the apparatus described in Eur. Ph. IV (Pharma-Test, Hainburg, Germany). Tests were performed in distilled water at 37°C using disks.

Dissolution Test

Dissolution tests on paracetamol tablets were performed in 900-mL phosphate buffer (pH 5.8) using the paddle method (Vankel, Cary, NC). The dissolution medium was maintained at 37±0.5°C, while the rotation speed was set at 50 rpm (USP XXIV). Samples (5 mL) were withdrawn after 5, 10, 15, 20, 25, and 30 min and concentrations were spectrophotometrically determined at 243 nm (Lambda 12 Perkin Elmer, Norwalk, CT). Similarly, dissolution tests were performed on cimetidine tablets in 900 mL of water using the basket method (Vankel, Cary, NC). The dissolution medium was maintained at 37±0.5°C, while the rotation speed was set at 100 rpm (USP XXIV). Samples (5 mL) were withdrawn after 3, 6, 9, 12, and 15 min, and concentrations were spectrophotometrically determined at 218 nm (Lambda 12 Perkin Elmer, Norwalk, CT).

Statistical Analysis

Statistical analysis was performed using the computer program SPSS version 11.0. The influence of lactose particle size, particle morphology, composition, storage conditions, and granulation technique on granule friability, tablet tensile strength, and disintegration time was analysed using one-way analysis of variance (ANOVA). For further comparison, a multiple comparison among pairs of means was performed using the Scheffé test with $P<0.05$ as a significance level. The data were tested for normal distribution with a Kolmogorov-Smirnov test and the homogeneity of variances was tested with the Levene's test.

RESULTS AND DISCUSSION

Granulation of Different Grades of Lactose

Extrusion granulation of all different grades of α-lactose monohydrate resulted in a similar barrel temperature and power consumption (especially for formulation without PVP) as shown in Table 2. For formulations with PVP, the barrel temperature was decreased, as lactose particle size increased due to the decrease in particle surface area resulting in improved particle lubrication. All particle sizes were processed smoothly except for α-lactose monohydrate 90 M, as its larger particle size resulted in high frictional forces. Extrusion granulation of anhydrous β-lactose was associated with a remarkable increase in barrel temperature and in power consumption, mainly due to its granular particles having a hard, irregular structure.

In addition, it should be reported that although α-lactose monohydrate 200 M was fed smoothly using a double screw feeder during extrusion granulation,[1] other lactose grades having a larger or smaller particle size exhibited some problems during feeding. A gradual decrease in feed rate and difficulties with the screw rotation (or even blocking of the screw movement) were observed for α-lactose monohydrate 100 M, 90 M, and

Table 2. Process parameters during extrusion granulation of different grades of lactose.

PVP (%)	Temperature (°C)	Power consumption (%)
α-Lactose monohydrate 450 M		
0	44	27
2.5	40	29
α-Lactose monohydrate 200 M		
0	42	26
2.5	35	24
α-Lactose monohydrate 100 M		
0	36	28
2.5	29	21
α-Lactose monohydrate 90 M		
0	39	20
2.5	29	17
Anhydrous β-lactose		
0	58	72
2.5	50	65

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Table 3. Granule properties of different grades of lactose prepared by extrusion granulation and high shear granulation.

Parameters	Granule properties							
					Particle size distribution			
Lactose type	PVP (%)	Water (%)	Friability (%)	Yield (%)	<250 μm	250–1000 μm	>1000 μm	Compressibility (%)
Extrusion granulation								
α-Lactose monohydrate 90 M	0	7.5	32	34	46	49	5	9
α-Lactose monohydrate 100 M	0	7.5	22	54	24	65	11	12
α-Lactose monohydrate 200 M	0	7.5	17	60	26	63	11	11
α-Lactose monohydrate 450 M	0	7.5	20	58	17	61	22	14
Anhydrous β-lactose	0	7.5	23	59	26	61	14	13
α-Lactose monohydrate 90 M	2.5	7.5	15	17	13	75	12	15
α-Lactose monohydrate 90 M	2.5	6.5	23	33	14	76	10	15
α-Lactose monohydrate 100 M	2.5	7.5	13	41	19	78	2	13
α-Lactose monohydrate 100 M	2.5	6.5	16	51	29	65	5	15
α-Lactose monohydrate 200 M	2.5	7.5	20	41	15	73	12	14
α-Lactose monohydrate 200 M	2.5	6.5	16	52	29	65	5	15
α-Lactose monohydrate 450 M	2.5	7.5	19	33	22	59	19	14
Anhydrous β-lactose	2.5	7.5	8	61	23	63	14	13
High shear granulation								
α-Lactose monohydrate 90 M	0	10	84	32	34	52	14	16
α-Lactose monohydrate 100 M	0	10	91	33	33	56	10	16
α-Lactose monohydrate 200 M	0	10	72	17	56	32	12	10
α-Lactose monohydrate 450 M	0	10	52	24	44	47	12	15
Anhydrous β-lactose	0	10	81	38	55	42	4	15
α-Lactose monohydrate 90 M	2.5	10	15	20	10	64	27	14
α-Lactose monohydrate 100 M	2.5	10	17	25	7	72	20	14
α-Lactose monohydrate 200 M	2.5	10	22	48	19	69	12	14
α-Lactose monohydrate 450 M	2.5	10	28	30	38	53	9	15
Anhydrous β-lactose	2.5	10	27	51	37	58	5	13

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anhydrous β-lactose. α-Lactose monohydrate 450 M tended to adhere to the hopper surface, mainly due to the cohesiveness of its particles.

These feeding problems did not hamper obtaining accurate feeding rates during short-term experiments, but could cause inaccurate feeding rates during longer processing times. There is a need for the selection of adequate feeding systems in order to allow a broad range of materials with different flow properties to be easily processed.

For extrusion granulation, optimization of the water concentration was essential for processing, as well as for obtaining good granule properties. The water concentration was optimized in a previous study for α-lactose monohydrate 200 M[1] and this water concentration was used for granulation of all different grades of lactose. The particle size of lactose did influence the optimal water concentration. The influence of particle size on the optimal water concentration can be explained by different viscoelastic properties of the wet mass, which affect extrudability, agglomeration, as well as the performance of wet sieving.[1,3]

During extrusion granulation of anhydrous β-lactose and α-lactose monohydrate 90 M at reference water concentration, a lower yield was obtained for the latter and required a further reduction of the water concentration. Anhydrous β-lactose has a higher solubility, and according to Lustig-Gustafsson,[4] a lower water concentration will be required for successful granulation. However, α-lactose monohydrate 90 M required less water than anhydrous β-lactose. This difference is probably due to the differences in the surface area and powder bed porosity.

Comparison of the optimal water concentration for the two different granulation techniques showed that extrusion granulation required a lower water concentration than high shear granulation. The properties of α-lactose monohydrate and anhydrous β-lactose granules produced by extrusion granulation and high shear granulation are shown in Table 3. For extrusion

Table 4. Tablet properties of different grades of lactose prepared by compression after extrusion granulation and high shear granulation.

Parameters	Tablet properties				
Lactose grade	PVP (%)	Water (%)	Tensile strength (MPa)	Friability (%)	Disintegration (s)
Extrusion granulation					
α-Lactose monohydrate 90 M	0	7.5	0.75	1.7	164
α-Lactose monohydrate 100 M	0	7.5	0.47	1.9	192
α-Lactose monohydrate 200 M	0	7.5	0.50	1.9	123
α-Lactose monohydrate 450 M	0	7.5	0.32	2.2	189
Anhydrous β-lactose	0	7.5	0.88	1.1	348
α-Lactose monohydrate 90 M	2.5	7.5	1.11	0.7	648
α-Lactose monohydrate 90 M	2.5	6.5	0.99	0.8	589
α-Lactose monohydrate 100 M	2.5	7.5	0.75	0.9	697
α-Lactose monohydrate 100 M	2.5	6.5	1.00	0.7	577
α-Lactose monohydrate 200 M	2.5	7.5	0.97	0.7	615
α-Lactose monohydrate 200 M	2.5	6.5	1.04	0.7	577
α-Lactose monohydrate 450 M	2.5	7.5	1.12	0.6	594
Anhydrous β-lactose	2.5	7.5	1.26	0.7	299
High shear granulation					
α-Lactose monohydrate 90 M	0	10	0.13	2.9	66
α-Lactose monohydrate 100 M	0	10	0.15	2.7	116
α-Lactose monohydrate 200 M	0	10	0.67	1.7	83
α-Lactose monohydrate 450 M	0	10	0.28	1.7	112
Anhydrous β-lactose	0	10	0.59	1.2	163
α-Lactose monohydrate 90 M	2.5	10	0.32	0.9	417
α-Lactose monohydrate 100 M	2.5	10	0.31	1.2	360
α-Lactose monohydrate 200 M	2.5	10	0.91	0.8	266
α-Lactose monohydrate 450 M	2.5	10	0.51	0.6	373
Anhydrous β-lactose	2.5	10	0.73	0.7	286

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granulation and high shear granulation, the particle size affected the granule properties. For formulations without PVP, a significantly higher friability was obtained for α-lactose monohydrate grades having a larger particle size. The lower yield for α-lactose monohydrate grades with larger particle size is in agreement with the data of Mackaplow et al.,[5] who found that granulation of α-lactose monohydrate with a large particle size resulted in weak granules. This was explained by the fact that water did not provide the necessary strength to the agglomerates formed and breakage would often dominate due to low agglomerate strength.

Comparison of extrusion granulation with high shear granulation showed that the former resulted in a significantly lower granule friability and a higher yield. Table 4 shows the properties of tablets produced from granules prepared by extrusion granulation and high shear granulation. The particle size of α-lactose monohydrate did affect tablet properties after extrusion granulation. The properties of tablets obtained after high shear granulation were more affected by particle size where an influence on tensile strength as well as disintegration time was observed.

In contrast to the lactose particle size, the lactose grade has a similar effect on the tablet properties obtained by both techniques. Tablets prepared from anhydrous β-lactose exhibited a significantly higher tensile strength and lower friability than those prepared from α-lactose monohydrate 90 M, irrespective of the granulation technique used. This is probably due to higher compactability of anhydrous β-lactose.

The tablet properties obtained from granules compressed after extrusion granulation showed a significantly higher tensile strength compared to the high shear prepared granules for all lactose grades evaluated, indicating that extrusion granulation resulted in improved granule properties.

Granulation of Paracetamol

During extrusion granulation of all formulations containing paracetamol, a similar barrel temperature and power consumption was recorded. The barrel temperature and power consumption ranged between 31° and 39°C and between 21% and 29%, respectively. All paracetamol formulations without PVP showed no problems during wet sizing, while at a 7.5% water concentration, the extrudates (containing 2.5% PVP) stuck to the sieve during wet sizing and the water concentration had to be lowered in order to solve the problem.[1] High shear granulation of pure paracetamol without PVP was not possible, even at higher water concentrations.

Table 5 shows the properties of paracetamol granules prepared by extrusion granulation and high shear granulation. Extrusion granulation without PVP at all paracetamol concentrations resulted in a yield of about 40%. At 20% paracetamol, a granule friability of 27% was obtained. However, the friability significantly increased as the paracetamol concentration increased, reaching 76% for pure paracetamol granules. This trend in the friability data was directly correlated with the gradual decrease of α-lactose monohydrate present in the granules. All granules without PVP obtained by high shear granulation showed a significantly higher granule friability and a lower yield than those prepared by extrusion granulation. Although extrusion granulation showed a higher efficiency than high shear granulation, it failed to produce good quality paracetamol granules without PVP.

The addition of 2.5% PVP at reference water concentration only significantly improved the friability at a paracetamol concentration of 80% and above, but resulted in a markedly lower yield. For high shear granulation, addition of PVP always resulted in a significant decrease of the friability, while the effect on the yield depended on the formulation. The yield gradually decreased as the paracetamol concentration increased, due to an increasing amount of lumps formed at higher paracetamol concentration.

The compressibility of all formulations ranged between 8% and 14%, indicating good flow properties of the granules, irrespective of the granulation technique.

From these results it is obvious that extrusion granulation is more efficient than high shear granulation for the granulation of paracetamol.

Table 5 also shows the properties of tablets containing different concentrations of paracetamol prepared by extrusion granulation and high shear granulation. For tablets compressed from granules prepared by extrusion granulation, a tendency for capping and lamination was observed at paracetamol concentration above 80%. Tablets without PVP containing up to 60% paracetamol showed a tensile strength below 0.59 MPa.

For tablets prepared from granules without PVP produced by high shear granulation, the tendency for capping and lamination was observed from 60% paracetamol onwards, while tablets without PVP containing up to 40% paracetamol had a tensile strength below 0.38 MPa. These results are in agreement with Becker et al.[6] who reported that paracetamol tablets produced without binder possess poor strength. The addition of PVP allowed the preparation of tablets containing a higher paracetamol concentration and yielded stronger tablets.

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Table 5. Influence of granulation technique on the granule and tablet properties of paracetamol formulations.

Processing variables			Granule properties						Tablet properties		
					Particle size analysis						
Paracetamol (%)	Water (%)	PVP (%)	Friability (%)	Yield (%)	<250 μm	250–1000 μm	>1000 μm	Compressibility (%)	Tensile strength MPa	Friability (%)	Disintegration (s)
Extrusion granulation											
20	7.5	0	27	34	27	37	36	13	0.53	2.5	115
40			34	42	38	47	15	12	0.56	3.0	422
60			39	40	38	43	19	12	0.60	3.3	1157
80			50	39	41	41	18	13		Poor compactibility	
100			76	36	41	39	20	11		Poor compactibility	
20	7.5	2.5	30	19	26	69	5	14	1.06	1.2	636
40			32	20	11	66	26	14	0.96	1.4	906
60			33	20	21	58	21	14	0.96	1.7	1023
80			30	20	31	48	21	10	0.95	1.9	1712
97.5			42	20	28	40	32	11	1.12	1.9	3299
92.5[a]											
High shear granulation											
20	10	0	66	30	27	52	21	14	0.38	2.8	93
40			61	34	20	65	15	12	0.36	15.0	476
60			61	30	16	67	17	13		Poor compactibility	
80			61	32	18	66	16	12		Poor compactibility	
100					Granulation not possible						
20	10	2.5	21	42	7	70	25	13	0.95	1.1	359
40			18	24	5	66	29	8	0.82	1.6	1071
60			32	18	3	63	34	10	0.71	2	1489
80			22	16	8	65	27	14	0.75	2.2	2799
97.5			33	16	6	65	29	11		Poor compactibility	

[a]Formulation containing 5% crospovidone.

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It is obvious that a PVP concentration of 2.5% allowed the preparation of pure paracetamol tablets with an acceptable tensile strength when extrusion granulation was used, whereas no tablets were obtained using high shear granulation. Although the addition of PVP resulted in considerable reduction of tablet friability, it remained above 1%.

Similar disintegration times for tablets prepared by extrusion granulation and by high shear granulation were obtained. Increasing the paracetamol concentration resulted in a significant increase in the disintegration time. For paracetamol tablets (without PVP) prepared by both techniques, only those containing 20% paracetamol complied with the requirements of the U.S. pharmacopoeia (80% paracetamol released within 30 min) (data not shown). The results of the dissolution experiments on paracetamol tablets with PVP are shown in Figs. 1a and b. The addition of PVP dramatically enhanced the dissolution rate of paracetamol tablets. This effect can be attributed to the interaction of PVP with paracetamol.[7]

Comparison of the dissolution of paracetamol tablets obtained by both processes clearly showed that tablets prepared from granules obtained by extrusion granulation showed faster dissolution than those obtained by high shear granulation.

For tablets containing 97.5% paracetamol produced via extrusion granulation, the dissolution profiles did not comply with U.S. pharmacopoeia requirements. However, on addition of 5% crospovidone, a fast dissolution rate was obtained. These results indicated that extrusion granulation resulted in tablets with a higher paracetamol concentration and in improved tablet properties in comparison with high shear granulation.

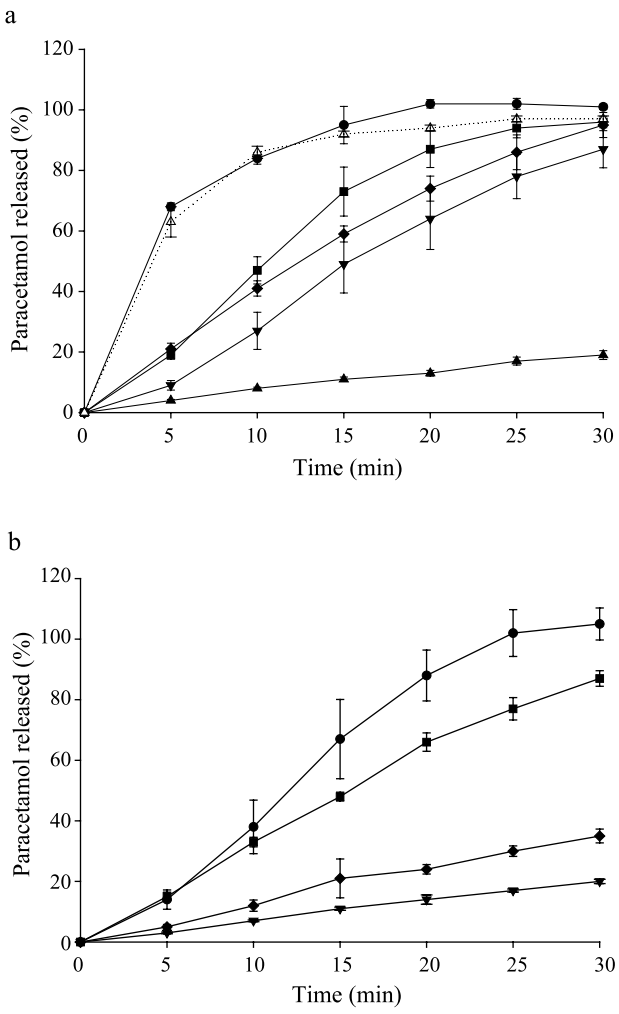

Figure 1. (a) Dissolution profiles of tablets (with 2.5% PVP) containing 20% (●), 40% (■), 60% (◆), 80% (▼), and 97.5% (▲) paracetamol and containing 92.5% paracetamol and 5% crospovidone (△). The tablets were prepared from granules produced by compression after extrusion granulation. (b) Dissolution profiles of tablets (with 2.5% PVP) containing 20% (●), 40% (■), 60% (◆), and 80% (▼) paracetamol. Tablets were prepared from granules produced by high shear granulation.

Granulation of Cimetidine

Granulation of cimetidine by extrusion granulation at reference conditions was associated with a high barrel temperature (52–54°C) and high power consumption (54–58%). The extrudates obtained had a rough surface and were difficult to wet size due to the hardness of the extrudates. The low water concentration in combination with the pressure exerted on the extrudates at the die block, as well as the elevated barrel temperature, could be responsible for the extrudate hardness. Increasing the water concentration to 17.5% and 14.5% for the formulation without and with PVP, respectively, reduced the barrel temperature to below 39°C and the power consumption to below 23%. Moreover, cimetidine extrudates produced at those water concentrations were easily wet sized.

High shear granulation of cimetidine without PVP was not feasible even at a water concentration up to 17.5%, whereas the addition of PVP was required to process cimetidine.

Table 6 compares the properties of cimetidine granules prepared by extrusion granulation and high shear granulation. For extrusion granulation of cimetidine (without PVP) at reference conditions, a friability of 11% and a yield of 32% were obtained. This low yield was mainly due to the hardness of the extrudates, which made them difficult to break down into granules

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Table 6. Influence of granulation technique on the granule and tablet properties of cimetidine formulations.

Parameters			Granule properties						Tablet properties		
					Particle size distribution						
PVP (%)	PVP-CL (%)	Water (%)	Friability (%)	Yield (%)	<250 μm	250–1000 μm	>1000 μm	Compressibility (%)	Tensile strength (MPa)	Friability (%)	Disintegration (s)
Extrusion granulation											
0	0	7.5	11	32	30	64	7	13	1.76	0.78	>3600
2.5	0	7.5	12	46	27	67	6	14	1.86	0.71	>3600
0	5	17.5	43	54	40	57	3	14	1.23	0.71	52
2.5	5	14.5	30	40	48	50	2	18	1.70	0.74	154
0*	0	17.5	87	13	50	41	9	15	1.85	0.70	2751
2.5*	0	14.5	35	30	41	51	15	15	2.26	0.76	3000
High shear granulation											
0	0	10.0					No granules obtained				
0	0	17.5					No granules obtained				
2.5	0	10.0	64	22	58	40	2	16	1.83	0.49	>3600
2.5	5	14.5	89	9	87	13	0	18	0.93	1.29	124
2.5[a]	0	14.5	45	12	81	15	3	16	1.91	0.48	2518

[a]Formulation containing 17.5% α-lactose monohydrate 200 M.

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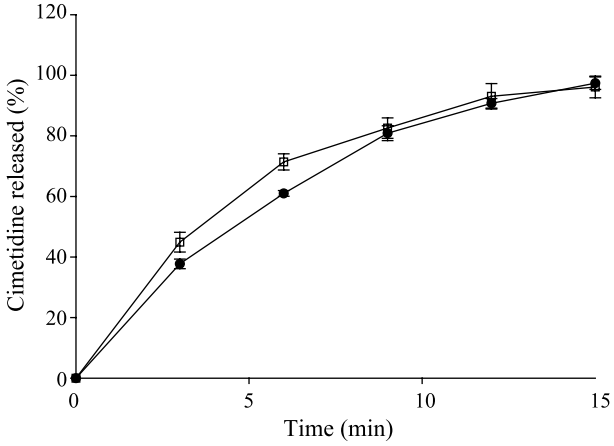

Figure 2. Dissolution profiles of tablets containing 92.5% cimetidine, 2.5% PVP, and 5% crospovidone prepared by compression after extrusion granulation (●) and after high shear granulation (□).

during wet sizing. Increasing the water concentration to 17.5% made the extrudates suitable for wet sizing and increased the yield to 62% (data not shown). The addition of 2.5% PVP to cimetidine resulted in a yield of 46% and 22% and a friability of 12% and 64% for extrusion granulation and high shear granulation, respectively. The compressibility ranged between 13% and 18% for all granules produced by both techniques, indicating good flow properties. These results show that extrusion granulation is far more efficient for the wet granulation of cimetidine compared to high shear granulation.

Table 6 also shows the properties of cimetidine tablets produced by extrusion granulation and by high shear granulation. Similar tablet properties were obtained for both granulation techniques. For all tablets, a friability below 1% and a tensile strength above 0.79 MPa was obtained. However, the disintegration time was above 60 min and the dissolution failed to meet U.S. pharmacopoeia requirements. The addition of 5% crospovidone significantly reduced the disintegration time to below 154 s. The dissolution profiles of cimetidine formulations containing crospovidone complied with U.S. pharmacopoeia requirements (60% cimetidine released within 15 min) as shown in Fig. 2.

The fact that cimetidine tablet properties are not affected by the granulation method is in contrast to paracetamol tablets, where the granulation method was shown to be the predominant factor for tablet production. This different behavior of both drugs can be explained by their differences in compactability. Paracetamol has poor compactability, and therefore the tablet properties are determined by the granule properties, which mainly depend on the granulation method. On the contrary, cimetidine has good compaction properties, and thus granulation had a less predominant role.

Stability of Paracetamol Tablets Produced After Extrusion Granulation

Tablets without PVP containing 20% paracetamol and with 2.5% PVP containing 80% paracetamol were stored during one year at 60% RH and 25°C and at 75% RH and 40°C (Table 7 and Fig. 3). For tablets

Table 7. The influence of long term and accelerated stability conditions on the properties of tablets containing 20% paracetamol (without PVP) and 80% paracetamol (with 2.5% PVP).

			60% RH–25°C			75% RH–40°C		
Paracetamol (%)	PVP (%)	Time (days)	Tensile strength (MPa)	Friability (%)	Disintegration (s)	Tensile strength (MPa)	Friability (%)	Disintegration (s)
20	0	1	0.61 (0.06)[a]	2.10	95 (44)[a]	0.75 (0.09)[a]	2.25	216 (43)[a]
		90	0.48 (0.06)[a]	2.29	130 (15)[a]	0.82 (0.12)[a]	1.74	226 (23)[a]
		180	0.55 (0.07)[a]	2.18	83 (16)[a]	0.94 (0.21)[a]	1.71	247 (21)[a]
		360	0.49 (0.02)[a]	2.02	1.29 (12)[a]	0.75 (0.14)[a]	1.72	279 (23)[a]
80	2.5	1	1.01 (0.06)[a]	1.42	1091 (84)[a]	1.36 (0.11)[a]	1.41	1679 (142)[a]
		90	1.21 (0.16)[a]	1.52	1003 (50)[a]	1.70 (0.17)[b]	1.04	1658 (59)[a]
		180	1.09 (0.14)[a]	1.26	1254 (70)[b]	1.56 (0.05)[a,b]	0.95	1738 (126)[a]
		360	1.27 (0.18)[a]	1.20	1550 (82)[c]	1.62 (0.17)[b]	0.89	2021 (90)[b]

Note: Standard deviations are given between parentheses.
The tablets were prepared from granules produced by extrusion granulation.
[a,b,c]Values within the same group having the same superscript are not significantly different from each other (Scheffé test, $P<0.05$).

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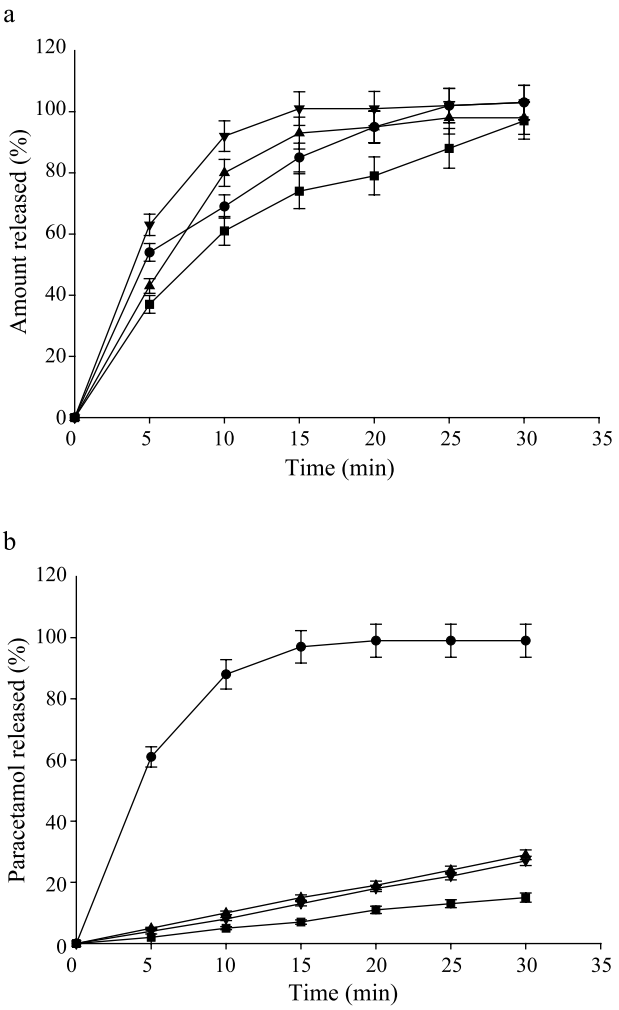

Figure 3. Dissolution profiles of (a) tablets without PVP containing 20% paracetamol and (b) tablets with 2.5% PVP containing 80% paracetamol. Tablets were prepared by compression of granules produced by extrusion granulation. Storage time: 1 (●), 90 (■), 270 (▲), and 360 days (▼) at 60% RH and 25°C.

containing 20% paracetamol, storage did not significantly influence the tensile strength and disintegration time. The porosity of the tablets significantly decreased from 16.1% to 10.2% and 8.9% for tablets stored for 1 year at 60% RH and 25°C and at 75% RH and 40°C, respectively.

The storage at 75% RH and 40°C resulted in a significantly higher tensile strength and disintegration time than the storage at 60% RH and 25°C. The dissolution profiles obtained for formulations containing 20% paracetamol without PVP complied with the U.S. pharmacopoeia requirement as shown in Fig. 3a. This is probably due to the presence of a high concentration of water-soluble α-lactose monohydrate.

For tablets containing 80% paracetamol, storage under both conditions resulted in a significant increase in tensile strength and disintegration time. The tensile strength and disintegration time obtained for tablets stored at 75% RH and 40°C was always significantly higher than for those stored at 60% RH and 25°C. Only after 1 day of storage, the dissolution profile of tablets containing 80% paracetamol and 2.5% PVP complied with the U.S. pharmacopoeia requirement, while all tablets failed to meet these requirements after storage for 90 days or more at both conditions (Fig. 3b). These results correspond with data reported by Khattab et al.[8] and Sarisuta and Parrott[9] for paracetamol tablets stored at ambient conditions. Again, this could be explained by a decrease in the porosity. A significant decrease in the porosity from an initial value of 19.4% to 13.1% and 13.9% was seen after 1 year of storage at 60% RH/25°C and 75% RH/40°C, respectively. The decrease in porosity can be attributed to the continuous swelling of PVP under the influence of humidity.[10] Exposure of tablets containing PVP to elevated humidity and temperature will cause a transition of PVP from the glassy to the rubbery state, which produces changes in the dissolution profile.[11] The similar decrease observed for both storage conditions indicated that other factors such as pore size were probably involved.

CONCLUSION

This study showed that during granulation of different grades of lactose, particle size and morphology had only a minor influence on the extrusion granulation, whereas significant differences were observed after high shear granulation.

On comparing granules and tablets produced by both granulation processes, granules and tablets produced by extrusion granulation showed better properties than those produced by high shear granulation.

Granulation of highly dosed drugs (paracetamol or cimetidine) using extrusion granulation was more efficient than high shear granulation, resulting in a higher yield and lower friability for a lower water concentration.

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