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Validation of a continuous granulation process using a twin-screw extruder

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Abstract

Using twin-screw granulation as particle size enlargement technique, the effect of modifying the screw configuration (number of mixing zones, configuration of kneading block) on granule quality, tablet properties and mixing efficiency was investigated. The amount of oversized agglomerates and yield was significantly influenced by the presence of an extra conveying element at the screw end. Changing the staggering angle of the kneading block significantly affected yield and granule friability. The 90° configuration resulted in a lower yield and granule friability. Disintegration time was the only tablet property significantly influenced by the screw configuration as disintegration was significantly faster when an extra conveying element was placed at the screw end. The influence of tracer addition method (wet vs. dry) on mixing efficiency inside the extruder barrel was investigated by means of different tracers: riboflavin (0.05%) suspended in the granulation liquid and hydrochlorothiazide (2.5%) added separately as powder. Mixing efficiency in function of time and granule size (above and below 1400 μm) was tested using riboflavine sodium phosphate (0.05%) dissolved in the granulation liquid. Since a good mixing efficiency was obtained independent of tracer addition method, tracer solubility, granulation time and granule size, continuous granulation using a twin-screw extruder was identified as a robust process.

Keywords: Continuous process; Wet granulation; Twin-screw extruder; Screw configuration; Mixing efficiency

1. Introduction

With the increasing demand for solid dosage forms the pharmaceutical industry is becoming more and more interested in continuous processes as they enable a larger production capacity, reduce cost, save on space and labour and avoid scale-up problems. Tablets are the most popular solid dosage form, due to ease of manufacture and ease of intake for the patient. Wet granulation is used for the manufacturing of tablets, as it improves flow properties, reduces dust and segregation of particles and improves compressibility of the powder mix. The tablet production process consists of a series of steps, whereby a powder mixture is transformed into a compact mass, i.e. the tablet: weighing of the individual powders, granulation, compression of the granules into a tablet and the packaging of the tablets. The two last steps can be considered as continuous processes, but the first steps of the process are mainly batchwise. In recent years the development of continuous granulation processes gained some interest in the pharmaceutical world. A semi-continuous fluidised bed granulator has been developed by Leuenberger (2001). In the pharmaceutical industry the use of a twin-screw extruder for wet granulation was introduced by Gamlen and Eardley (1986). Lindberg et al. (1987, 1988) used a twin-screw extruder to make an effervescent paracetamol granulate. Milling of these paracetamol granules was necessary to remove the oversized fraction. A modified twin-screw extruder which eliminated the need of (dry or wet) milling was developed by changing the screw configuration and removing the die plate, producing granules of the correct size (Keleb et al., 2004). This paper further investigates the effect of screw configuration (number and position of kneading blocks, position of liquid addition point) on granule quality and tablet properties.

During the production of tablets, the authorities not only demand that the tablets meet the content uniformity specifications, but also the intermediate products must meet the content uniformity specifications (FDA, 1996, 2003). Already in 1964 the problem of granule inhomogeneity using a high-shear mixer was addressed by Lachman and Sylwestrowicz, where the larger granules contained a higher concentration of a poorly water-soluble drug. Dingwall and Ismail (1977) observed differences

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in binder distribution during high-shear granulation, where the binder up-take depended on the primary particle size of the glass spheres used for granulation. The solubility of the drug substance also played a role in granule inhomogeneity as the drug concentration found in different granule sizes depended on the drug solubility (Ojile et al., 1982). The link between granule inhomogeneity and granule growth mechanism was made by Egermann and Reiss (1988) and Vromans et al. (1999). They found that larger granules contained more drug when the drug particles were smaller than the diluent particles and less drug when the drug particles were larger than the diluent particles. A hypothesis was that the strength of the granules depended, amongst others, on the primary particle size of the powders: the strongthest granules were formed by the smallest particles, whereas high-shear forces may induce breakage of the larger and weaker granules. In this paper the content uniformity of the granules formed via twin-screw extrusion is determined and the mixing efficiency of the twin-screw extruder is investigated.

2. Materials

α-Lactose monohydrate (Pharmatose® 200 M, DMV, Veghel, The Netherlands) was used as filler for granulation. Polyvinylpyrrolidone (PVP) (Kollidon® 30, BASF, Ludwigshafen, Germany) was used as binder. Riboflavin sodium phosphate (Certa, Braine-l'Alleud, Belgium), riboflavin (ABC chemicals, Wauthier-Braine, Belgium) and hydrochlorothiazide (BUFA, Uitgeest, The Netherlands) were used as tracers. Hydroxypropylmethylcellulose (Metolose® 60 SH, Shin-Etsu Chemicals, Tokyo, Japan) served as viscosity enhancing agent for the preparation of a riboflavin suspension. Distilled water was used as granulation liquid. Magnesium stearate (BUFA, Uitgeest, The Netherlands) was used as lubricant during tabletting.

3. Methods

Granulation experiments were performed on a laboratory-scale co-rotating twin-screw extruder (MP 19 TC 25, APV Baker, Newcastle-under-Lyme, United Kingdom) having a length-to-diameter ratio of 25:1. All experiments were performed in triplicate at a total feed rate of 5.6 kg/h, a screw speed of 250 rpm and a barrel temperature of 25 °C. Powder and liquid feed rates were determined prior to each experiment by repeatedly ($n = 3$) weighing the powder and liquid amount delivered over a period of 5 min. During granulation the powder volume in the feed hopper was maintained at a constant level (85–100% of the total feeder capacity). The granulation liquid was pumped into the extruder barrel using a peristaltic pump (Watson Marlow, Cornwall, UK). When the influence of screw configuration on granule and tablet properties was tested, PVP was used as a binder, 2.5% (w/w) in granules, based on dry mass. PVP was dissolved in the granulation liquid prior to the granulation experiments. Water concentrations were 7.5% (w/w) and 8.5% (w/w), measured on dry mass, for experiments concerning screw configuration and mixing efficiency, respectively. After granulation the samples were oven-dried at 25 °C during 24 h.

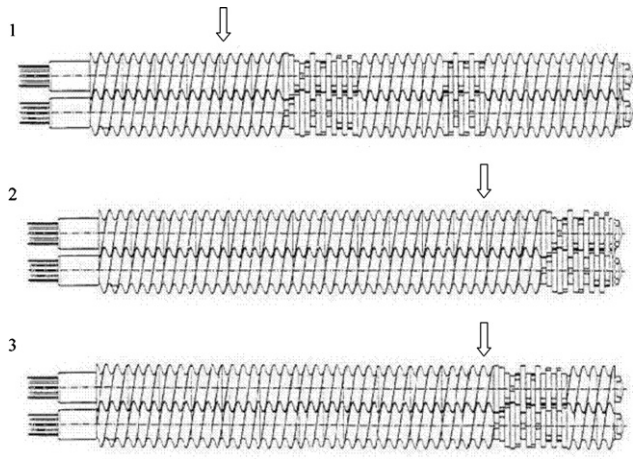

Fig. 1. Screw configurations used for twin-screw granulation: (1) screw configuration used by Keleb et al. (2004); (2) screw configuration A with standard design of kneading block; (3) screw configuration B with standard design of kneading block. Arrow indicates point for liquid addition.

3.1. Investigation of screw configuration

To investigate the influence of screw configuration on granule and tablet properties, the standard screw configuration with two kneading blocks used by Keleb et al. (2004) (Fig. 1) was modified into a screw profile with only one kneading block (Fig. 1). The screw consisted of two zones (configuration A): a transport zone and a kneading block. The transport zone is built from several conveying elements which serve as drivers to transport the dry powder towards the kneading block. The kneading block (which ensures powder blending and mixing of powders and granulation liquid) has 10 disks (each 4.7 mm thick), having a configuration with a staggering angle increasing from 30° (4 disks), 60° (5 disks) to 90° (1 disk). Liquid addition takes place in front of the kneading block, shortening the length of the granulation zone (the distance where powder and granulation liquid are mixed) to 8 cm (the standard screw configuration of Keleb et al. (2004) has a granulation length of 38.5 cm).

In a second modification of the screw configuration (Fig. 1, configuration B), an additional conveying element was placed behind the kneading block (Fig. 1) and four configurations of the kneading block (10 disks of 4.7 mm) were tested: the same kneading block configuration as described for screw profile A and three configurations where all disks had the same staggering angle throughout the kneading block in an orientation of 30°, 60° and 90°. Kneading blocks can be classified as forwarding, neutral and reversing: forwarding kneading blocks are capable of transporting material (in this case the 30°, 60° and 90° combination (configuration A) kneading block), reversing kneading blocks tend to push the material backwards and neutral kneading blocks such as the 90° kneading block do neither (Thiele, 2003). The staggering angle and the width of the disks in the kneading block have an influence on the type of mixing which occurs in the extruder barrel: distributive or dispersive mixing. A wider disk and smaller staggering angle result in more dispersive mixing, whereby droplets and agglomerates are broken down into morphological units. Distributive mixers spread out the morpho-

logical units without changing them. To investigate whether the disk thickness had an influence on the mixing behaviour in the modified screw profile, a kneading block of 8 thin disks (each 2.4 mm thick) with a staggering angle of 60° was used in an additional experiment.

After a start-up period of 5 min, granules were collected during 10 min and dried during 24 h at 25 °C. Yield, granule friability and granule compressibility were determined using the granule size fraction of 250–1000 μm. Tablets were made using the size fraction 250–710 μm. The granules were blended with 0.5% (w/w) magnesium stearate in a tumbling mixer (W.A. Bachofen, Basel, Switzerland). Tablets (250 mg) were prepared using an eccentric compression machine (Korsch EK0, Berlin, Germany) equipped with a flat faced double punch of 9 mm at a compression force of 10 kN per tablet. Friability, tensile strength and disintegration time of the tablets were tested.

To investigate the mixing efficiency of the modified screw configurations riboflavin sodium phosphate was used as a tracer. Riboflavin sodium phosphate was dissolved in the granulation liquid (8.5% (w/w), measured on wet mass) and no binder was used. Granule samples (100 mg) were collected during 15 min at 1 min intervals, after a start-up period of 5 min. The samples were dried and the tracer concentration in the granules was determined spectrophotometrically (λ = 267 nm).

3.2. Investigation of mixing efficiency

The influence of the tracer addition method (wet vs. dry) on the mixing efficiency inside the extruder barrel (using screw configuration A) was investigated by means of different tracers: (a) riboflavin (0.05%, w/w) suspended in the granulation liquid (2% HPMC dispersion in water) and (b) hydrochlorothiazide (2.5%, w/w) added separately to the extruder barrel as a powder using a second powder feeding unit (Mini Twin feeder, Brabender Technology, Duisburg, Germany). A higher concentration of hydrochlorothiazide was necessary since a reproducible flow at concentrations below 2.5% could not be obtained using this feeding unit. After a start-up period of 5 min granule samples (100 mg) were collected every minute during 15 min. After drying the tracer concentrations were determined spectrophotometrically (riboflavin: 267 nm; hydrochlorothiazide: 272 nm).

Mixing efficiency of the twin-screw extruder in function of time was tested using riboflavin sodium phosphate (0.05%, w/w), which was dissolved in the granulation liquid prior to granulation. Granule samples (100 mg) were collected at regular time intervals (1–5 min) during a 1-h granulation trial without a start-up period. In addition, the water content of the granules was determined by Karl Fisher titration.

The tracer concentrations in function of granule size was examined using riboflavin sodium phosphate (0.05%, w/w) dissolved in the granulation liquid. After a start-up period of 5 min, granule samples (100 mg) were collected during 15 min at 1 min intervals. The samples were divided in fractions above and below 1400 μm. Tracer concentrations were spectrophotometrically determined (267 nm) after drying. All tracer concentrations are expressed as the percentage found compared to the target strength.

3.3. Characterisation of granules and tablets

3.3.1. Amount of oversized agglomerates and yield

The total granule fraction was placed on a sieve shaker (Retsch VE 1000, Haan, Germany) during 5 min at an amplitude of 2 mm using a sieve of 3.15 mm, all particles retained were considered oversized agglomerates. The percentage of oversized agglomerates was calculated from the weight of agglomerates >3.15 mm and the total granule weight. The particle size distribution of the $F_{<3.15\,\mathrm{mm}}$ was determined using a series of sieves (125, 250, 500, 710, 1000, 1400 and 2000 μm). The sieves were shaken (Retsch VE 1000, Haan, Germany) during 10 min at an amplitude of 2 mm. The amount of granules retained on each sieve was determined and the yield of the granulation process was defined as the fraction below 1400 μm.

3.3.2. Friability of granules

The granule friability was determined using a friabilator (PTFE 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 retained on a 250 μm sieve (F_{wt}) was determined after vibrating for 5 min at an amplitude of 2 mm. The friability was calculated as $((I_{wt} - F_{wt})/I_{wt}) \times 100$.

3.3.3. 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:

$$C\% = \left(\frac{\rho_f - \rho_i}{\rho_f}\right) \times 100$$

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

3.3.4. Granule porosity

The granule porosity and median pore diameter (μm) of the granules (500–1000 μm) were determined ($n = 3$) using mercury porosimetry (Autopore III, Micromeritics, Norcross, Georgia, USA). The limits for intragranular porosity were determined using the cumulative intrusion curve.

3.3.5. Tablet friability

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

3.3.6. Tablet tensile strength

The hardness, thickness and diameter of the tablets ($n = 6$) was determined (PTB 311 Pharma Test, Hainburg, Germany) after a 24 h storage period at 25 °C and 60% RH. The tablet tensile strength T was calculated using the equation described

by Fell and Newton (1970):

$$T = \frac{2F}{\pi dt}$$

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

3.3.7. Disintegration time

The disintegration time was determined ($n = 6$) using the apparatus described in Eur. Ph. (PTZ-E Pharma Test, Hainburg, Germany). Tests were performed in distilled water at 37 ± 0.5 °C using disks.

3.3.8. Statistical analysis

Statistical analysis was carried out using the software package Design-Expert® Version 6.0.10. The influence of screw configuration on the granule and tablet properties was determined using one-way ANOVA ($p < 0.05$).

4. Results and discussion

4.1. Influence of screw configuration

Removing the die plate from the end of the extrusion barrel and the discharge element from the end of the screw allowed to produce granules of the correct particle size distribution required for subsequent tabletting (Keleb et al., 2004). Due to the limited material densification during this twin-screw granulation technique, no additional (wet or dry) milling steps were required, resulting in an efficient continuous granulation technique. Further preliminary experiments showed that only the kneading blocks in the screw configuration were responsible for granule formation and that a single kneading block was sufficient to obtain granules. Based on these results the length of granulation zone (zone where powder and liquid interact to form granules) was reduced in this study by modifying the design of the screws: the kneading block and the liquid addition point were moved towards the end of the screws, reducing the length of the granulation zone from 38.5 cm (Keleb et al., 2004) to 8 cm. Using a shorter granulation length the drug(s) that are granulated, are less subjected to possible degradation, such as mechanical stress or higher temperature. Lindberg et al. (1987, 1988) showed that the screw configuration used during granulation had a significant influence on output, temperature of the extrudates, dwell time in the extruder, the coarse and fine fraction of unmilled granules, the mean diameter of the milled granulation and granule porosity. Several other publications also showed that changing the screw configuration has an important influence on the extrudate properties (Lee and McCarthy, 1996; Gautan and Choudhury, 1999; Koksel et al., 2004).

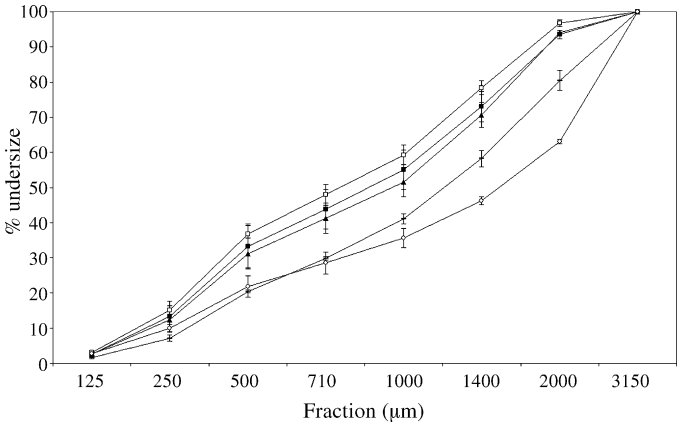

Fig. 2. Cumulative particle size distribution with different screw configurations: screw configurations A (◯) and B (■) with standard design of kneading block; screw configurations with kneading block having disks with a staggering angle of 30° (▲), 60° (□) and 90° (—).

The effect of modifying the screw configuration on granule and tablet properties is shown in Table 1, the presence of an extra conveying element after the kneading block (configuration B) having a significant influence on the amount of oversized agglomerates and yield. The amount of oversized agglomerates found for screw configuration A was significantly higher (11.9%) than with the other screw configurations. Granulation yield (granule fraction <1400 μm) increased from 46% for screw configuration A to 73% for screw configuration B, a similar yield as obtained by Keleb et al. (2004) using a screw profile with a longer granulation zone. From the particle size distributions (Fig. 2) it is clear that the percentage of granules smaller than 1400 μm increased when using an extra conveying element. These results showed that the extra conveying element placed after the kneading block breaks up the majority of oversized granules formed during transfer through the kneading block.

The additional conveying element (screw configuration B) did not influence the other granule properties (Table 1). Chang-

Table 1
Granule quality and tablet properties in function of screw profile ($n = 3$)

Screw profile	Granule properties						Tablet properties		
	Agglomerates (%)	Yield (%)	Friability (%)	Compressibility index (%)	Porosity (%)	Median pore diameter (μm)	Friability (%)	Tensile strength (MPa)	Disintegration time (s)
A	11.9 ± 0.4*	46 ± 2*	18 ± 3	15 ± 0	5.5 ± 0.1	0.58 ± 0.02	0.93 ± 0.13	1.10 ± 0.21	796 ± 31
B	1.1 ± 0.3	73 ± 5*	17 ± 2	15 ± 1	5.3 ± 0.3	0.60 ± 0.01	1.01 ± 0.17	1.17 ± 0.15	562 ± 24*
30°	1.2 ± 0.3	71 ± 4	23 ± 3	15 ± 1	5.2 ± 0.2	0.71 ± 0.01	0.97 ± 0.09	1.04 ± 0.12	775 ± 33
60°	1.9 ± 0.6	78 ± 4	21 ± 3	15 ± 1	4.9 ± 0.2	0.83 ± 0.01	1.03 ± 0.03	1.00 ± 0.06	792 ± 24
90°	1.8 ± 0.5	58 ± 2*	11 ± 3*	15 ± 1	5.6 ± 0.4	0.28 ± 0.02*	1.10 ± 0.06	0.90 ± 0.08	791 ± 65
60° (thin)	2.8 ± 1.0	76 ± 1	28 ± 1*	16 ± 1	5.0 ± 0.2	0.96 ± 0.05	1.11 ± 0.11	1.30 ± 0.07*	474 ± 12*

* Significantly different.

ing the staggering angle of the kneading block had a significant influence on yield and granule friability. The 90° configuration resulted in a significantly lower yield and granule friability (Table 1). Although the porosities of the granules were comparable, the median pore diameter of the granules from the 90° configuration was significantly smaller (Table 1). This neutral configuration of the kneading block increased the pressure on the material since the material is less transported through the kneading block, thus densifying material, improving the distribution of granulation liquid inside the granules and yielding stronger granules. Although the 90° configuration yielded the strongest granules, all granule friabilities were below 30% (Table 1), indicating an acceptable granule strength. The compressibility of the granules was not significantly influenced by the staggering angle of the kneading block used during granulation. Disintegration time was the only tablet property significantly influenced by the screw configuration. Although all tablets disintegrated within 15 min, the disintegration time with screw configuration B was significantly shorter (Table 1).

Next to the influence of screw configuration on granule quality and tablet properties, the influence of the screw configuration on the mixing efficiency was investigated. Another formulation without PVP was used as a binder and the water concentration in the granules was increased to 8.5%. The mixing efficiency for all screw configurations was good: the average tracer concentration ranged from 100.3% and 102.7%, the R.S.D. values ranged from 0.5 to 1.1% and all individual tracer concentrations were within the 75–125% range of the target strength with a minimum of 99% and a maximum of 105%. These values comply with the FDA requirements for drug distribution in granules (mean within 90 and 110% of the target strength, R.S.D. $\leq 4\%$, and all individual values should be within a 25% range of the target strength) (FDA, 2003).

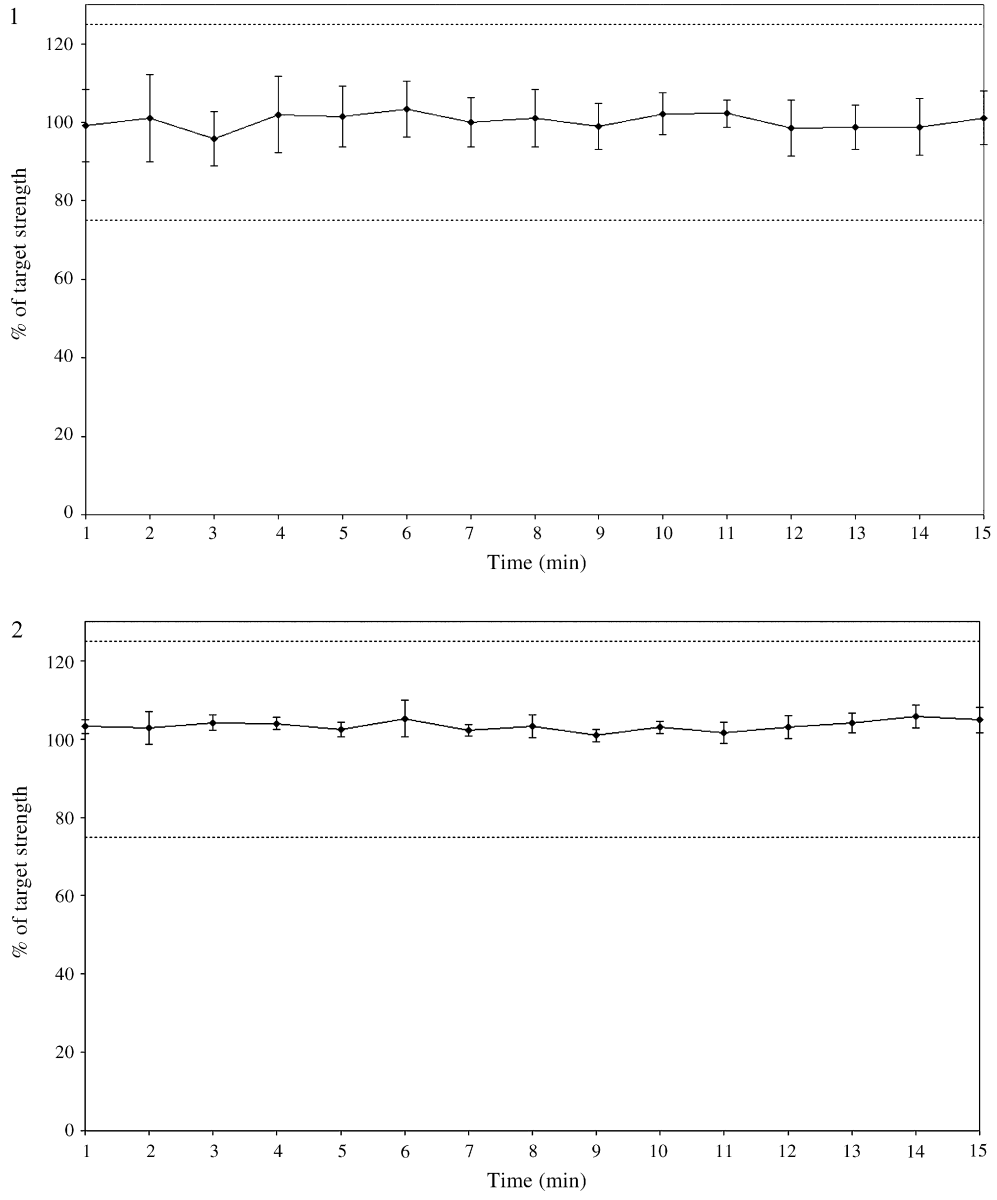

Fig. 3. (1) Mixing efficiency using hydrochlorothiazide (2.5%, w/w) as tracer; (2) Mixing efficiency using riboflavin (0.05%, w/w) as tracer.

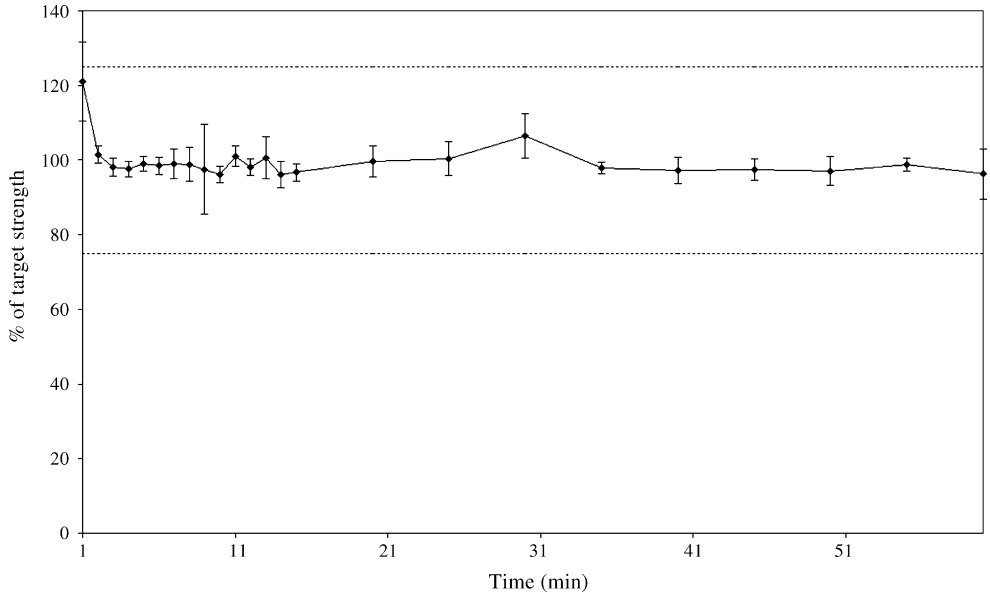

Fig. 4. Mixing efficiency in function of time.

In an additional experiment the granule and tablet properties and mixing efficiency of a screw configuration with a kneading block of 10 disks at a staggering angle of 60° was compared with a screw configuration having a kneading block of 8 small disks at a staggering angle of 60°. Using the smaller disks shortened the kneading block from 47 mm to 19 mm, but these thinner disks provided a more distributive character to the kneading block. The granule friability was significantly influenced by the disk thickness (Table 1): a higher friability was obtained when the thinner disks were used, although both friabilities are acceptable (<30%). The other granule characteristics were not influenced by the disk thickness. The use of thinner disks in the kneading block resulted in a significantly higher tensile strength and a significantly lower disintegration time, but the tablet friability was not influenced. Mixing efficiency was good using a kneading block with the thinner disks: an average tracer concentration of 103.0 ± 1.3%, a R.S.D. value of 1.2%, and all individual tracer concentrations within the 25% limit of the target concentration, ranging from 101% to 106%.

4.2. Investigation of mixing efficiency

Since it is not possible to preblend powders when running a continuous granulation process, it is of high importance that homogenous powder mixing occurs inside the extruder barrel during the granulation process.

Fig. 3 shows the mixing efficiency in the extruder barrel when hydrochlorothiazide was added as a powder to the granulation process using a separate feeder system: the average hydrochlorothiazide concentration was 100.2% with a R.S.D. value of 1.9% and all individual results were within the 25% range of the target strength. Since hydrochlorothiazide and lactose were adequately blended during transport through the extruder barrel, even for low dosed drugs no preblending was necessary. Adding the tracer riboflavin as a suspension to the granulation process led to an average riboflavin concentration of 103.4% and a R.S.D. value of 1.3%. All the individual results where within the 25% range (Fig. 3). These results showed that a good content uniformity and homogeneity was obtained during continuous granulation using a twin-screw extruder when a water-insoluble tracer was added as a powder or as a suspension.

Fig. 4 shows the evolution of riboflavin sodium phosphate concentration in function of time. The average tracer concentration during a 1-h granulation trial was 99.6% of the target strength and the R.S.D. value was 2.7%. The average water content was 99.1 ± 3.0%. The riboflavin sodium phosphate concentration found in the granules immediately after start-up (1 min) was 121 ± 11% in combination with a water content in the granules of 114 ± 2%. Since riboflavine sodium phosphate was dissolved in the granulation liquid, the imbalance between powder and liquid feed during the initial stages of the granulation process explained the higher tracer concentration immediately after start-up. However, as the balance between powder and liquid feed was already obtained after 1 min, only a small amount of granules needs to be discarded at start-up of this continuous granulation process. Although all individual results were within the 75–125% range, Fig. 4 shows that the standard deviation after 9 and 30 min was higher compared to the rest of the values. This is probable due to a bias of the detection method of the tracer: riboflavin sodium phosphate as a water-soluble drug will migrate to the surface of the granules during drying. During sampling of the dried granules, abrasion of the granules can result in a higher variability of the riboflavin sodium phosphate in the samples.

Fig. 5 shows the tracer concentrations in function of granule size. Riboflavin sodium phosphate was homogeneously distributed over granules independent of granule size as the average tracer concentration in the granules fraction above 1400 μm was 100.4% with a R.S.D. value of 1.5% and the average tracer concentration in the fraction <1400 μm was 101.2% with a R.S.D.

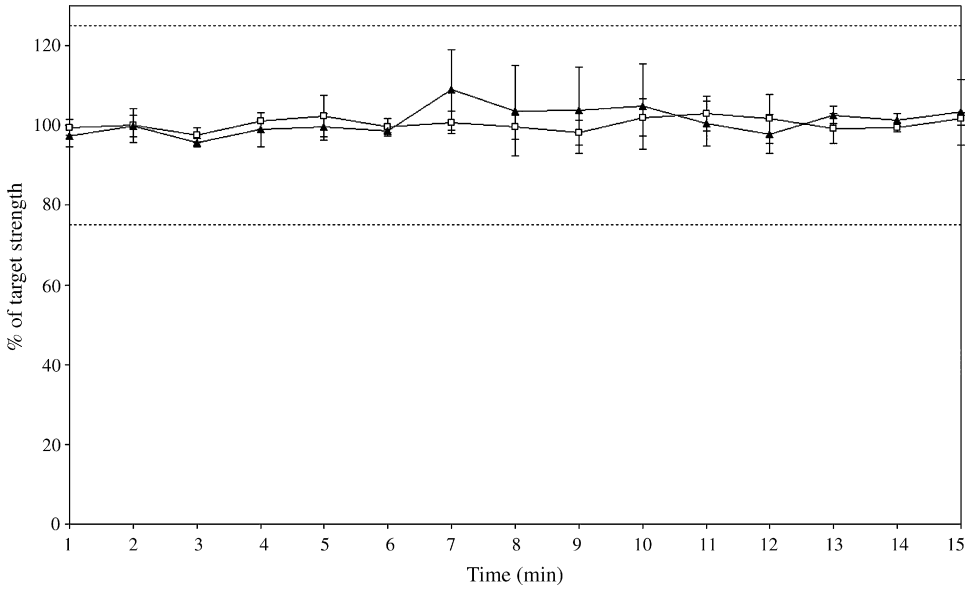

Fig. 5. Mixing efficiency in function of granule size $F_{>1400\,\mu m}$ (□) and $F_{<1400\,\mu m}$ (▲).

value of 3.8%. All individual tracer concentrations fell within the 75–125% range of the target concentration. In contrast to some reports about drug inhomogeneity in high-shear granulation (Egermann and Reiss, 1988; Vromans et al., 1999; van den Dries and Vromans, 2002), the mixing and granulation action of the kneading block ensured a homogeneous drug distribution within the different size fractions of granules produced via twin-screw granulation.

5. Conclusion

From these results it became evident that reducing the length of the granulation zone did not have a negative effect on granule and tablet properties of formulations processed via twin-screw granulation. However, an extra conveying element after the kneading block was essential to improve the granulation yield based on a reduction of the oversized agglomerates. Twin-screw granulation was identified as a robust process, since a good mixing efficiency was obtained independent of screw configuration, tracer addition method, tracer solubility, granulation time and granule size.

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