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RESEARCH PAPER

Effect of the Granulation Process on Nitrofurantoin Granule Characteristics

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ABSTRACT

We studied four granulation methods on the same quantitative and qualitative formula: wet massing by forced agglomeration (Lödige) and free agglomeration (Glatt); and dry massing by slugging and roller compaction technique.

Three different particle sizes of nitrofurantoin (bioinequivalent drug) were used.

The nitrofurantoin particle size has a very low influence on the physical characteristics of the granules.

The granulating process influenced the binding of the particles. Granules processed using the wet granulating method were harder than those made by dry process. Lödige granules were more bonded than Glatt granules. Granules prepared by dry massing presented broken particles. The surface area and the porosity of Glatt granules were the most important parameters. Dissolution studies must be effected to make a correlation between the physical results and the dissolution rates. It is necessary to effect a new validation and a comparison of the results when a new granulating apparatus is used.

INTRODUCTION

The many advantages of tablets as oral pharmaceutical dosage forms have resulted in their widespread use. Tablets can be compacted by direct compression or after the granulation process. Granulation is designed to improve the tabletting properties, including fluidity, compressibility, and compactibility of the blend of ingredients. The various steps involved in the process of granulation have a significant effect on the particulate characteristics of the resulting granulation (1).

The powder preliminary agglomeration designed for producing tablets has a key role. The behavior of bulk solids is strongly influenced by the shape of particles. Powders and granules with identical size and size distribution, density, and chemical composition may behave

quite differently as a result of particle or granule morphology. According to the granulating method chosen, either through wet or dry massing, granules will have some determined physical and mechanical features (2–5). However, relatively few studies, as compared to the great number of studies on direct compression, have been performed concerning the relation between the primary properties of ingredients, the characteristics of the granulation, and the properties of the final granule.

Next to the primary properties of the ingredients (drugs and excipients such as filler-binders and disintegrants), the incorporation of a wet-binder is an important factor for increasing the compactibility of a granulate. This effect is largely determined by the type of wet binder used, the concentration within the granulate, and the method of incorporation (6,7).

Seager et al. (8) have suggested that the structure depended on the binder distribution (Table 1). By a fluidized bed process (9,10) some binder fragments are frequently present on the tablet surface; they are then the proof of some difficulties with the mixing process. With the dry massing process and roller compaction, granules consist of crushed particles with cracked surfaces.

The physical characteristics of granules, such as porosity, diameter, and strength, are of interest as they can affect the compactibility of the particulate mass. The behavior of bulk solids is strongly influenced by the shape of particles. Powders with identical size and size distribution, density, and chemical composition may behave quite differently as a result of particle morphology (11).

The aim of this paper was to study four granulation methods with the same quantitative and qualitative formula: wet massing by forced agglomeration (Lödige) and free agglomeration (Glatt); and dry massing by slugging and the roller compaction process.

Nitrofurantoin has a broad spectrum of activity and is widely used in the treatment of urinary tract infection. Three different granulometries of nitrofurantoin (bioinequivalent drug) were used.

MATERIALS AND METHODS

Materials

Nitrofurantoin (M. Quarre, France) was supplied as a crystalline yellow powder with 10–300 μm particles sieved into three groups of 50–80 μm, 80–125 μm, 125–200 μm. This is a poorly soluble drug (283 mg/ml at 37°C).

Anhydrous lactose (Cooper, France) and direct-compressed lactose (Fast Flo™, Seppic, France) were supplied according to the European Pharmacopoeia.

Corn starch (Cooper) and pregelatinized starch (Starch 1500™, Colorcon, France) were supplied according to the European Pharmacopoeia.

Sodium carboxymethylamidon, Explotab™, was supplied by SPCI, France.

Talc was supplied by Cooper, according to the European Pharmacopoeia.

Magnesium stearate was supplied by Cooper, according to the European Pharmacopoeia.

The formulae are summarized in Table 2.

Methods

Granulation

Four processes were selected: wet massing–forced agglomeration (Lödige, ATR, Fe 234 hr., Paris, France); free agglomeration (Glatt, WSG5, Germany); dry massing–slugging (Frogerais OA, Vitry sur Seine,

Table 1

Granule Structure (8)

Granulating Method	Binder	Binding Mechanism	Binder Concentration	Tabletting Properties
Wet massing	Sponge-like matrice	Drug–drug Drug–binder Binder–binder	Medium	Good
Nebulization	Surface shell	Binder–binder	High	Very good
Roller compaction	Particle crushed and broken	Drug–drug little plastic deformation	Low	Low

Table 2

Composition of the Formulae

Granulation	Percent (w/w)
Nitrofurantoin	20.00
Lactose	38.90
Corn starch	33.00
Corn starch (10% paste)	4.00

France) with 20 mm punches, tablet mass was 1 g and hardness 60 N; and roller compaction (Hutt 7105). The batches were 5000 g. Cylinders were stripped 0.3 mm and speed was 90 rpm. The operating conditions were standardized (Table 3).

In the dry massing process powdered corn starch (4%) was added and each granule was mixed with magnesium stearate (0.3%) and talc (0.5%). The granule with >1000 μm granulometry was sieved through a 1000-μm sieve oscillating granulator (Erweka FGS, Euraf, Courbevoie, France).

Mixture

Each granule was mixed for 5 min with sodium carboxymethylamidon, talc, and magnesium stearate in a mixing apparatus (Turbula W.A., Bachofen, Switzerland).

Structure

The granule and tablet structure was studied with a scanning electron microscope (JSMCF35, Jeol, Rueil-Malmaison, France) after a 24-hr vacuum degassing and metallizing with gold produced by cathodic evaporation. About 50 granules were used in each analysis.

Granulometric Size Distribution

These measurements were carried out with samples of 500 g of each granule during 10 min with an automatic siever (Tamisor, Paris, France) with a range of 125, 315, 630, and 1000 μm sieves. The results were expressed in percentage of amounts on each sieve.

Flow Properties

Flow rate was estimated by assessing the time required for a given volume of granules (100 ml) to flow through a vibrating funnel (Erweka GDTA).

Packing Characteristics (Bulk Volume)

Packing characteristics were evaluated in a standard graduated cylinder (Engelsman, Regamay, Paris, France) with 50-g samples of granules. The volume measurements were carried out before tapping (V_0 = bulk volume) and after 500 taps (V_t = tap volume), and then the tapping rate ($\%T$) was estimated.

Porosity

The granule porosity was measured with a mercury porosimeter (Coultronics 9300 Auto, Margency, France).

Surface Area

Surface area was measured with a manometric process device (Coultronics 2100 Auto), to study the total surface area, and the 9300 Auto device (Coultronics).

Friability

The granule friability tests were made with specially designed equipment consisting of a friabilimeter adap-

Table 3

Wet Massing Operating Conditions

Operating Conditions	Lödige	Glatt
Batch	1000 g	4500 g
Mixing time	5 min	5 min (80°C)
Wetting	400 g 10% paste starch at 60°C (200 g during 5 min then 200 g during 5 min)	1800 g 10% starch paste at 60°C Air pressure 4.5 kg/cm^2 Pulverization speed 80 rpm (10 min)
Drying (Glatt WSG5)	20 min Inlet air temperature: 65°C Outlet air temperature: 55°C	20 min Inlet air temperature: 65°C Outlet air temperature: 55°C

tive plastic disk (Erweka) with four 67-ml glass vials. Five grams of the 630–1000 μm granulometric size was added to a vial with ten 10-mm diameter steel balls. After a 10-min rotation, the granule quantities remaining on a 630-μm sieve were weighed. The hardness was expressed as the opposite of the friability.

Dissolution Rate

The nitrofurantoin powder and the granule dissolution tests were made according to the European Pharmacopoeia and USP XXIII (method 2) using the rotating paddle at 50 rpm in 1 liter of enzyme-free gastric medium in each vessel. The amount of nitrofurantoin was measured continuously at 367 nm during 90 min with spectrophotometric equipment (Turner 330, OSI, Paris, France). Powder and granule samples were 250 mg, containing 50 mg of nitrofurantoin. Dissolution rates were expressed as efficiency of dissolution at 90 min. The statistical analysis was made using the Newman and Keuls test (Univac, Orsay, France).

RESULTS

The symbols used were L = Lödige process, G = Glatt process, S = slugging process, and R = roller compaction process.

Macroscopic and Microscopic Aspects

Only data on the 630–100 μm granule granulometry are given. The Lödige processed granules were sharp-angled with a tightly linked 2–10 μm particle internal structure (Fig. 1). The Glatt processed granules were hemispherical with irregular pellets: their internal structure consisted of 2–10 μm particles without any tight links; the particles seemed to be suspended (Fig. 2). The slugging processed granules were sharp-angled with irregular flat surfaces. The roller compaction processed granules were sharp-angled with smooth surfaces and split particles.

Granulometric Size Distribution

The results were calculated by the percentage of each granulometric group according to the processing method and the nitrofurantoin granulometry.

In the wet massing process, the granulometric size distribution seemed the same among the three groups (125–315 μm; 315–630 μm; 630–1000 μm). Only data on the 630–100 μm granule granulometry are given

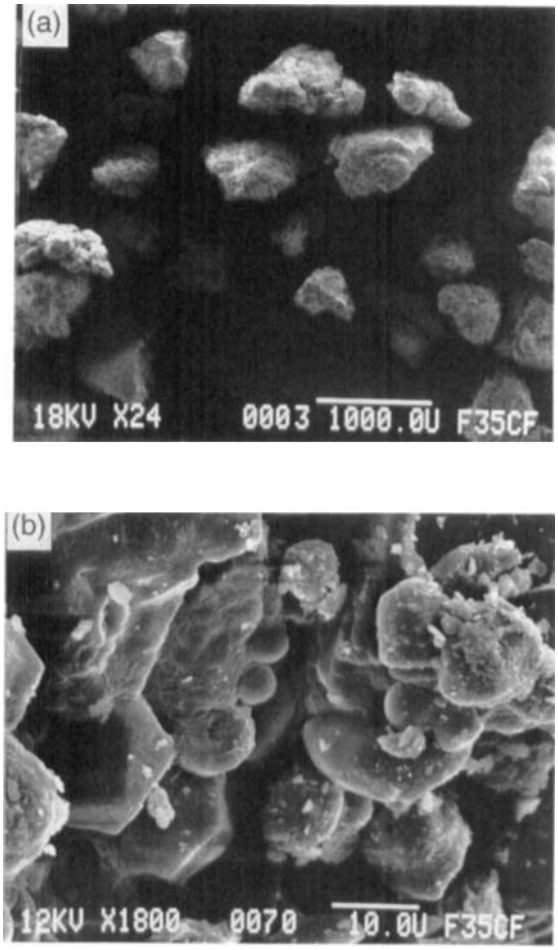

Figure 1. Structure of Lödige processed granules (scanning electronic microscope). (a) 24×; (b) 1800×.

(Table 4). In the Lödige process an increase in the nitrofurantoin particle size resulted in an increase in the small particle amount. This result seemed opposite in the Glatt process.

In the dry massing process, the slugging generated about 50% of granules with a 630- to 1000-μm granulometry, while the roller compaction produced 20% particles. Bricks and compacted ribbons, however, did not have the same hardness. The nitrofurantoin particle size did not have any influence.

Flow Properties (Flowability)

The processing method had a limited impact on the flowability of this granule granulometry. Only data on the 630–1000 μm granule granulometry are given (Table 5).

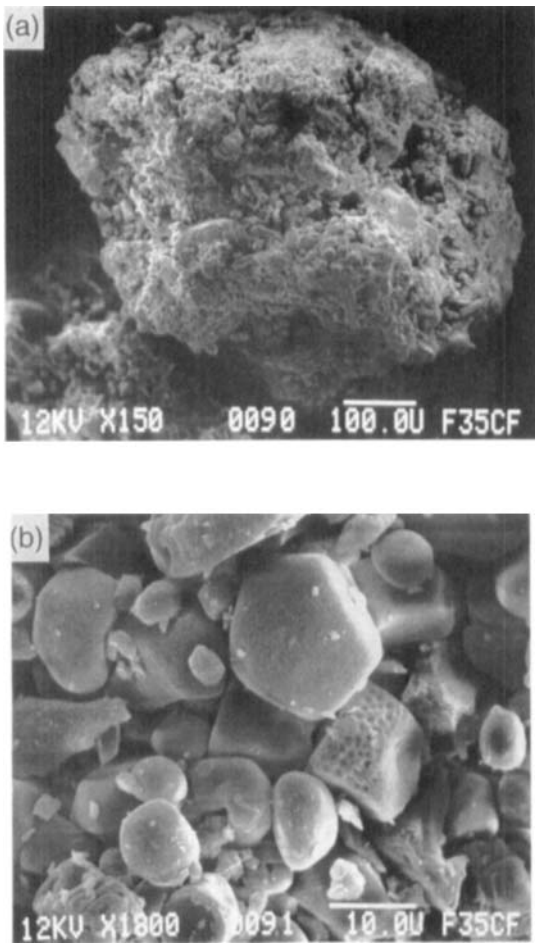

Figure 2. Structure of Glatt processed granules (scanning electronic microscope). (a) 150×; (b) 1800×.

The wet granules have a good flowability, which decreased as the the granule size increased. Granules produced by a dry granulation method have a poor flowability probably due to the presence of smaller granules and to their irregular shape. It seems that there is an optimum for granule size: 315–630 μm. The flowability was L = G > R = S.

Packing Characteristics (Bulk Volume)

A statistical study could not be carried out due to the limited number of experiments. Nevertheless, the following factors were observed. Only data on the 630–1000 μm granule granulometry are given (Table 6). Whatever the selected processing method, the nitrofurantoin particle size did not have any impact on the bulk and tap volumes or on the tapped percentage.

In the wet massing methods, the bulk volume (V_0) and tap volume (V_t) were high and the tapped percentage ($\%T$) low, while in the dry massing process, the bulk and tap volumes were low and the tapped percentage high. Glatt granules gave the higher volume due to the free agglomeration of particles.

V_0: G > L > R = S

V_t: G > L > R = S

$\%T$: S = R > G > L

There was an accurate parallel between V_0 and V_t. and $\%T$.

Porosity

The total porosity volumes resulted in the following sequence (Table 7): G > R > L > S.
When analyzing the porosity volume versus pore size curves, we showed that they were two basic pore populations (data not shown): (*a*) macropore, which took up a large volume. Their average radius was about 100 μm; the sequence was G > L > S > R. (*b*) Micropore, which took up a lesser volume. Their radius was between 0.3 and 0.8 μm; the sequence was G > R > L > S.

Table 4

Influence of the Granulating Method on the Particle Size Distribution (Percent): Granule Granulometry 630–1000 μm

Granulating Method	Nitrofurantoin Granulometry		
	50–80 μm	80–125 μm	125–200 μm
Lödige	22.7	28.6	37.8
Glatt	54.4	25.0	28.6
Slugging	54.4	53.9	52.7
Roller compaction	18.8	21.7	21.0

Table 5

Influence of the Granulating Method on the Flowability (s): Granule Granulometry 630–1000 μm

Granulating Method	Nitrofurantoin Granulometry		
	50–80 μm	80–125 μm	125–200 μm
Lödige	10.3 ± 1.2	10.4 ± 0.05	10.7 ± 0.1
Glatt	10.6 ± 1.4	10.6 ± 0.3	11.9 ± 0.7
Slugging	10.9 ± 1.9	10.5 ± 1.7	9.9 ± 0.9
Roller compaction	10.5 ± 1.5	10.6 ± 1.4	10.3 ± 1.4

Table 6

Influence of the Granulating Method on the Bulk Volume and the Tapped Volume: Granule Granulometry 630–1000 μm

Granulating Method	Nitrofurantoin Granulometry								
	50–80 μm			80–125 μm			125–200 μm		
	V_0 ml	V_t ml	*T%*	V_0 ml	V_t ml	*T%*	V_0 ml	V_t ml	*T%*
Lödige	106	91	14.2	108	94	13.0	113	97	14.2
Glatt	124	107	13.7	119	99	16.8	128	106	17.2
Slugging	74	65	12.2	76	64	15.8	73	64	12.3
Roller compaction	76	64	15.8	75	63	13.7	80	68	15.0

Table 7

Influence of the Granulating Method on the Granule Porosity (cm^3/g)

Lödige	0.681
Glatt	0.868
Slugging	0.449
Roller compaction	0.688

Table 8

Influence of the Granulating Method on the Granule Surface Area (m^2/g)

	9300 Auto	2100 Auto
Lödige	1.241	17.380
Glatt	0.771	24.612
Slugging	0.748	14.641
Roller compaction	0.953	18.915

Surface Area

Resulting sequences are listed according to the equipment used (Table 8): the 9300 Auto device, L > R > G > S; with the 2100 Auto device, G > R > L > S. The latter was according to the porosity volume micropore sequence which was quite consistent with the type of equipment used.

The surface area versus pore size curves showed the presence of two populations (data not shown): (*a*) a pore with 0.03–0.07 μm diameter taking up a limited space, and (*b*) a pore with a diameter less than 0.01 μm taking up a large amount of space.

Friability

Apparently the nitrofurantoin particle size did not have any influence on the granule friability (Table 9). Two method groups could be distinguished: the wet massing method, resulting in granules with low weight loss percentages, hence with high abrasion resistance abilities; and the dry massing method, resulting in granules with high weight loss percentages and thus limited abrasion resistance abilities. This method produced granules with the lower friability since the highest hardness

Table 9

Influence of the Granulating Method on the Granule Friability (Percent)

Granulating Method	Nitrofurantoin Granulometry		
	50–80 μm	80–125 μm	125–200 μm
Lödige	18.08	17.53	16.56
Glatt	28.62	22.56	24.84
Slugging	53.86	36.26	44.08
Roller compaction	30.14	31.96	45.04

granules were processed by the Lödige method. These results of the hardness in the sequence allowed the conclusion: L > G > CP > S.

Dissolution Rate

The dissolution rate over 90 min (DE 90) of nitrofurantoin powder was 85.00 ± 5.91 for 50–80 μm 56.90 ± 3.52 for 80–125 μm and 43.53 ± 2.50 for 125–200 μm.

The dissolution curves of granules 630–100 μm and nitrofurantoin particle size 80–125 μm (Fig. 3) and the DE 90 values shown in Table 10 illustrate that the wet massing methods resulted in low dissolution rate granules. The Lödige processed granules had the slowest dissolution. Those processed by roller compaction had the fasted release. Thus the result was R > S > G > L. The nitrofurantoin granulometry had impact for wet massing methods only. When it increased, the dissolution efficiency decreased.

DISCUSSION

Macroscopic and Microscopic Aspects

The Glatt processed granules were hemispherical, with irregular shapes according to their fabrication by fluidization (12). Active substance crystals were intact: they were linked by crystalline connections and a fiber binder spongy network (9,10). Either many granules included large internal crystals or electrostatic attraction generated aggregates and created a nucleus before granule growth. The binder fragments on the surface were the signs of some difficulties with the fluidized mixture process. Through water evaporation, there was a coat or sets of gluey binder left. Other particles came into

Table 10

Influence of the Granulating Method on the DE 90

Granulating Method	Granule Granulometry (μm)	Nitrofurantoin Granulometry (μm)		
		50–80	80–125	125–200
Lödige	630–1000	40.09 ± 4.25	34.30 ± 1.58	23.12 ± 1.11
	315–630	55.04 ± 5.46	47.81 ± 1.89	29.00 ± 0.90
	125–315	66.31 ± 7.14	65.11 ± 2.68	65.84 ± 6.36
Glatt	630–1000	65.10 ± 2.41	45.00 ± 3.43	40.92 ± 1.22
	315–630	62.85 ± 2.56	57.79 ± 0.99	58.29 ± 3.17
	125–315	74.92 ± 2.61	74.59 ± 2.59	74.32 ± 4.62
Slugging	630–1000	93.47 ± 5.20	95.40 ± 0.40	90.99 ± 2.87
	315–630	92.55 ± 6.95	85.98 ± 3.69	88.37 ± 5.26
	125–315	87.62 ± 4.01	84.50 ± 3.36	83.43 ± 1.34
Roller compaction	630–1000	96.26 ± 0.59	96.44 ± 0.50	92.52 ± 2.18
	315–630	96.11 ± 0.65	94.80 ± 0.51	92.67 ± 1.61
	125–315	94.73 ± 0.57	93.18 ± 0.31	90.37 ± 2.71

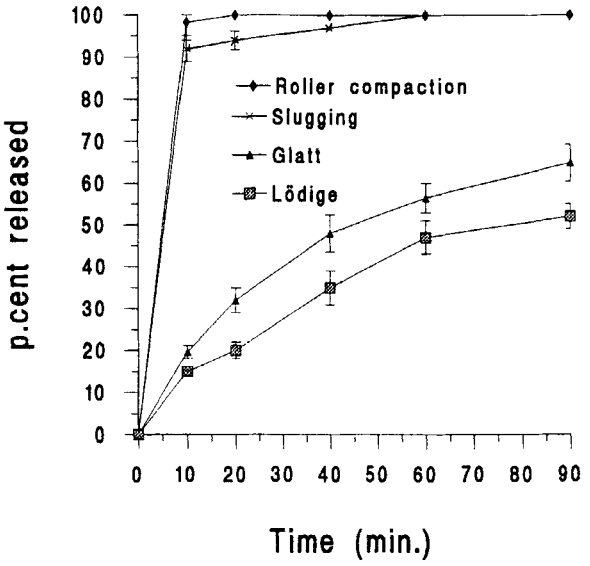

Figure 3. Dissolution rate of granules (630–1000 μm), nitrofurantoin (80–125 μm).

contact with these gluey crystals and generated aggregates by adhering to the binder fragments. The aggregates got covered with binder solution and the process was repeated until the aggregate transformed into granules. During the drying operation, some of the active substance dissolved by the binder solution generated crystalline connections, promoting the granule's growth. Spray-dried lactose presented the highest degree of roundness, the lowest degree of elongation, and the lowest boundary variation. The roughness of spray-dried lactose results from multiple invaginations created by α-monohydrate crystals held together by a glue of amorphous lactose. Furthermore, fine particles of spray-dried lactose from large agglomerates also contributed to irregularity of the surface geometry (13).

The Lödige processed granules showed intact active substance particles within a binder that looked like a sponge. During the drying process, a small part of the active substance was dissolved and the connections were strengthened by its crystallization (8).

During the roller compaction process, granules made of crushed particles, with flat irregular surfaces, showed some cracking. The cracks resulted from the connection between the active substance crystals from the roller compaction process. During size reduction the particles tend to loose their corners and edges. Grinding processes may explain the high surface rugosity (13).

Friability

The Lödige processed granules were stronger because mechanical mixtures were more important. The Lödige method apparently favored a better distribution of binder and perhaps lactose, too. The Glatt processed granules were more friable since they resulted from original particle contacts (14).

The roller compaction processed granules were stronger than the slugging processed granules. This was possibly due to heating during agglomeration, which might generate supplementary connections (15).

Flow Properties (Flowability)

The dry processed granules had a shorter flowability time than the wet massing granules because of the lubricant used. The Lödige and Glatt processed granules had the same flowability in spite of the higher density of the former ones. The hemispherical shape of the Glatt granules and the sharp-angled shape of the Lödige granules could account for this flowability property. Granules that are the most irregular in shape and surface geometry present the lowest flow properties (13).

Packing Characteristics (Bulk Volume)

The wet massing processed granule tapping percentage was lower when the granule granulometry decreased. This was due to their more spherical shapes and tendency to pile up (16).

The highest bulk volume was seen in the the Glatt processed granules because of free particle agglomeration.

These results suggest (13) that there is a relationship between surface micromorphology and packing properties: particles with irregular surfaces have the lowest bulk density. Increases in surface irregularity contribute significantly to increased porosity and changes in the packing arrangement of particles.

Porosity and Surface Area

The porosity of Lödige granules was limited (16,17). Apparently there was a bimodal pore size distribution. First, micropores were generated and then the consolidation process resulted in macropores. The smallest micropores were in a limited number for lactose, creating a structure homogenization through dissolution and recrystallization (solid connections).

The highest porosity was shown by the fluidized bed processed granules. Their surface area was limited: pores were larger and were generally extra-granular, since there was a free agglomeration without any mechanical process.

The slugging processed granules' porosity was less than that of the roller compaction processed granules.

Dissolution Rate

The DE 90 of nitrofurantoin powder increased as the particle size decreased according to an increase in surface area of the particles.

The nitrofurantoin granulometry (NFG) influenced wet processing methods only. Where it got higher the dissolution efficiency decreased. There was a linear relationship for the Lödige processed granules: DE 90 = 61.93 - 0.119 NFG; $r = 0.996$.

For the Glatt processed granules: DE 90 = 67.25 - 0.06 NFG; $r = 0.890$. The nitrofurantoin particle size had a limited impact on the dissolution efficiency of dry granules. This might be due to the mechanical crushing of active substance particles during the dry process. The wet process was less disturbing for the initial granulometry with a poorly soluble drug; thus the initial properties could be identified more easily (18).

In the case of the wet process, the dissolution efficiency increased when the granule granulometry (Ggr) decreased.

For the Lödige processed granules, there was a log-type relationship: DE 90 = 20.60 - 25.85 ln Ggr; $r = 0.999$.

For the Glatt processed granules, there was a log-type relationship DE 90 = 187.92 - 20.96 ln Ggr; $r = 0.998$.

There was a log relationship between dissolution efficiency and friability (F) ln DE 90 = 1.22 + 1.44 ln F; $r = 0.999$. There was no relationship between dissolution efficiency and total porosity or surface area.

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