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Comparison of the effects of different drying techniques on properties of granules and tablets made on a production scale

Ágota Hegedűs [a], Klára Pintye-Hódi [b,*]

[a] *Gedeon Richter Ltd., H-1475 Budapest 10, PO Box 27, Hungary*
[b] *Department of Pharmaceutical Technology, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*

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Abstract

The aims of this study were to compare the properties of granules prepared in a high-shear granulator and dried by using different methods (fluid-bed and microwave-vacuum drying) and to compare the properties of tablets pressed from such granules. Experiments on a production scale were performed with Collette Ultima Pro 600 single-pot processing equipment and a Glatt WSG 200 fluid-bed granulator and drier. The particles granulated in the traditional high-shear granulator and dried in a vacuum chamber had a higher porosity and higher bulk and tapped densities, as a consequence of the special characteristics of the drying process. They retained their spherical form, in contrast with the particles dried via the fluid-bed technology. The two types of granules required different compressing forces for tabletting.

Keywords: Single-pot processing equipment; Fluid-bed drier; Production scale; Particle size distribution; Bulk and tapped densities; Porosity; SEM

1. Introduction

Granulation is a size-enlargement process in the course of which small particles are formed into larger, physically strong agglomerates in which the original particles can still be identified. The agglomeration of solid particles renders them more suitable for further processing, such as tablet formation. It improves the flowability, ensures optimal particle size distribution and better homogenization of the active ingredient, and allows control of the granules, making them suitable for compression. In the wet-granulating process, a granulating liquid is used to facilitate the agglomeration process, and the moist granules are then dried (Parikh, 1997).

Drying involves the removal of liquid from solid material that contains moisture, through a process of evaporation resulting from the application of heat. Thermal energy can be applied to the granules by convection, conduction or vacuum drying (Fox, 2005).

1.1. Convection is achieved by means of a flowing gaseous medium, in which the gaseous particles transmit heat while changing place. Fluid-bed drying is an example of a convective drying method. In the process of fluid-bed drying, the granules to be dried are placed in a device fitted with a perforated screen or sieve, and air is circulated through this layer at a rate sufficient to lift and separate the granules, which are set in motion and take on what is termed a fluidized state. The drying occurs as a result of the consequent intensive contact between the granules and the gaseous drying medium.

1.2. Conduction can be attained by heat exchange between adjacent particles of matter, heat transfer through a jacked bowl wall and vacuum drying.

1.3. In the process of vacuum drying, the material is placed in a vacuum chamber, and the heat necessary to remove the moisture is applied directly to the solid material.

The process of pure vacuum drying requires a longer drying time, but its undisputed advantage over other methods is that the drying takes place at a lower temperature, which could be important when heat-sensitive materials are to be dried (Fox, 2005; Stahl, 2004). Gas-assisted vacuum drying, and more commonly microwave-vacuum drying, allow quicker drying in a single-pot processor, used consecutively or simultaneously (Fox and Bohle, 2001; McMinn et al., 2005).

In production-scale pharmaceutical manufacturing, the methods most commonly used to produce granules are fluid-bed

* Corresponding author. Tel.: +36 62 545 576; fax: +36 62 545 571.
E-mail address: klara.hodi@pharm.u-szeged.hu (K. Pintye-Hódi).

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granulation and drying, or a combination of high-shear granulation and fluid-bed drying. In recent years, however, single-pot technology has grown in popularity, partly because the transfer of the moist granules from the high-shear granulator to the fluid-bed drier is critical. The single-pot equipment has taken the form of a mixer/granulator retrofitted with a drying unit (Stahl, 2000). The drying unit is capable of pure vacuum drying, microwave-vacuum drying, gas-assisted vacuum drying, or a combination of microwave and gas-assisted vacuum drying. Microwaves are waves of electromagnetic radiation, generated by magnetrons under the combined action of electric and magnetic forces. Microwave drying is based on the absorption of electromagnetic radiation by dielectric materials. The dielectric material is placed in an electromagnetic field, when the material becomes polarized and stores electrical energy through polarization. The level of polarization depends on the state and composition of the material and the frequency of the applied electric field. For pharmaceutical-industry drying, microwaves with a frequency of 2450 MHz (wavelength 12.2 cm) are used. The microwaves are not forms of heat, but rather forms of energy that are manifested as heat through their interaction with materials. The permittivity (ε) of materials sensitive to microwaves is complex and comprises two parts, the first corresponding to the real part or relative dielectric constant, and the second representing the imaginary part or loss factor. The dielectric loss factor of a material is a measure of how much heat is generated inside a material per unit time when an electric field is applied, when subjected to microwave heating (McLoughlin et al., 2003). Most of the materials commonly used in the pharmaceutical industry have a relatively low loss factor and absorb microwave power only at high field strengths. By comparison, granulation liquids (water or organic solvents) have high loss factors relative to the dry materials used (Fox and Bohle, 2001; Péré and Rodier, 2002).

The purpose of this study was to compare the properties of granules produced in the same manner, through high-shear granulation, but dried by using two different techniques (fluid-bed and microwave-vacuum drying).

2. Materials and equipment

2.1. Materials

The given tablets contained 50% (w/w) active ingredient. The binding solution was an aqueous solution of PVP K-30 (4.5%, w/w). The other excipients were corn starch (30%, w/w) as diluent; colloidal anhydrous silica (4%, w/w) and glycerine (1.5%, w/w) as moisture regulators; and microcrystalline cellulose (7.9%, w/w), talc (1.6%, w/w) and magnesium stearate (0.5%, w/w) to improve tablet formation. We used the same composition and batch size (150 kg) in both sets of equipment.

2.2. Equipment

In both cases, we performed the granulation in a Collette Ultima Pro 600 single-pot processor (Fig. 1). The drying was carried out in a Glatt WSG 200 fluid-bed granulator and drier (Fig. 2) and in Collette Ultima Pro 600 single-pot processing equipment.

Fig. 1. Photograph of Collette Ultima Pro 600 single-pot equipment.

2.2.1. Collette Ultima Pro 600

This is a closed, single-pot system, which means that the entire granulation process can be performed in the one device. The bowl has a jacket wall to allow the circulation of hot or cold water, in order to regulate the temperature of the product. Both the impeller and the chopper are positioned vertically, and protrude into the machine from above. The speeds of the impeller and the chopper are adjustable within a given range. The liquid binder addition is regulated, and the machine is suitable for the spraying of binder solution with high or low viscosity. A number of parameters can be used to set up the end-point of granulation: the processing time, the torque, the product temperature, etc., or a combination of these. The granules can be dried by vacuum and microwave energy, which can be combined with side-wall heating. The drying cycle of this machine is therefore more energy-efficient than other drying processes. There are three possible drying methods: vacuum, vacuum-trans flow and vacuum-microwave. The machine is suitable for computer-controlled, automated manufacturing.

2.2.2. Glatt WSG 200

This is also a single-pot system which is suitable for granulation and drying process in the one device. There is an inlet air handling unit fit for air filtering, air heating, and air cooling. The air must be introduced at the bottom of the product container through the perforated air distributor plate (screen type) which is important to fluidize and mix material in the container.

Fig. 2. Photograph of Glatt WSG 200 fluid-bed granulator and drier.

The spraying head with three or six nozzles can be set in three different positions over the distribution plate. Within the expansion chamber, granules are formed. There are bag filters within the machine which retain the particles. The filter bag is made of polyester-lined material which is of a certain mesh size. Safety air filters are built in the outlet air product. Main processes such as air flow and spraying rate are controlled. The machine is equipped with a data acquisition system.

3. Methods

3.1. Preparation of granules and tablets

We performed the granulation in the Collette Ultima Pro 600 processing equipment. The active ingredient, the corn starch and the colloidal anhydrous silica were homogenized (impeller speed: 65 rpm, process time: 6 min). The liquid binder was added to the powder mixture (impeller speed: 95 rpm, chopper speed: 600 rpm, liquid binder flow rate: 7 kg/min, process time: approximately 4 min). After addition of the liquid binder, mixing was continued to the torque value (wet massing—impeller speed: 95 rpm, chopper speed: 2700 rpm, torque value: 6.5 kW).

The granules were dried to the prescribed value of the loss on drying by using two different methods.

In one case, we removed the wet granules from the Collette Ultima Pro 600 equipment, loaded them into the Glatt WSG 200 fluid-bed drier and performed the drying at 60 °C (process time: 35 min, maximum product temperature: 35.5 °C).

In the other case, drying was carried out in the Collette Ultima Pro 600 equipment by microwave-vacuum drying. The aim was to achieve the shortest possible drying time, and we therefore used the maximum forward energy (vacuum: 50 mbar, microwave forward energy: 22 kW, continuous mixing: 20 rpm, process time: 58 min, maximum product temperature: 43 °C).

After drying, the granules were sized in a 1.5 mm sieve (rotation speed: 500 rpm), and next homogenized for 2 min with the tabletting excipients (microcrystalline cellulose, talc) and then 5 min (magnesium stearate) in a container blender.

Fig. 3 shows the detailed flowcharts of the manufacturing processes.

We determined the size distribution of the granules, their tapped and bulk densities, porosity and moisture content, and took SEM photographs. The individual and average masses, heights and hardnesses of the tablets were examined.

3.2. Testing of granules and tablets

3.2.1. Particle size analysis

We determined the particle size distribution of an approximately 25 g sample of the final granules, using a Hosokawa Alpine 200 LS air jet sieve with an array of five sieves.

3.2.2. Bulk and tapped densities

Hundred millilitres of granules was poured into a 250 ml graduated tared measuring cylinder, and the granules were then weighed and their bulk density, ρ_T, was determined in g/100 ml.

The density of 100 ml of granules of known weight was measured with a Stampfvolumeter 2003 (J. Engelsmann Apparatebau, Ludwigshafen, Germany). After 200–300 taps (when a constant value had been achieved), the volume of the tapped column of granules was read off, and the density, ρ_T, was determined in g/100 ml.

3.2.3. Porosity

The properties of granules and tablets are influenced by the porosity of the granules. Porosity can be defined through the relationship between the particle (ρ_{part}) and tapped (ρ_T) densities, using the following equation (Kumar et al., 2002):

$$\varepsilon = \left(1 - \frac{\rho_T}{\rho_{part}}\right) \times 100$$

The particle density (ρ_{part}) was determined with a Stereopycnometer SPY-5 (Quantachrome Corp.). The pycnometric particle density was determined by measuring the volume occupied by a known mass of powder, which is equivalent to the volume of helium gas displaced. The particle density was calculated via the following equation:

$$\rho_{part} = \frac{w}{v}$$

where w is the weight of sample and v is the volume of samples.

3.2.4. Moisture determination

The loss on drying of 2 g of granules (homogenized with the external phase) to mass constancy at 70 °C was determined, with a Mettler Toledo HR 73 halogen moisture analyser. The loss on

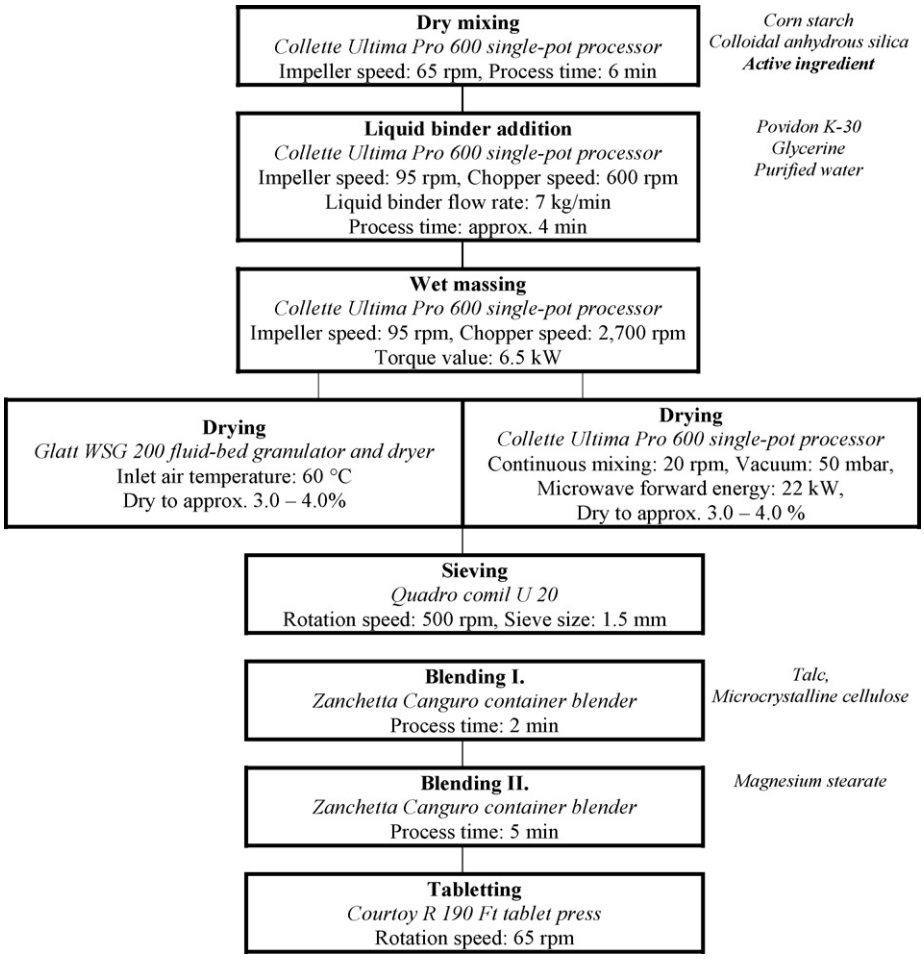

Fig. 3. Flow sheet of granulation in two types of dryer and tabletting.

drying of the granules must be within the range 2.5–4.5%, this range being suitable for the tabletting of this product.

3.2.5. Scanning electron microscopy (SEM)

The morphological properties of the granules prepared in both sets of equipment were examined with a JEOL JSM-5600LV scanning electron microscope fitted with an energy dispersive X-ray spectrometer. A Polaron sputter coating apparatus was applied to induce electric conductivity on the surface of the sample. The air pressure was 1.3–13 mPa.

3.2.6. Tablet evaluation

The granules were pressed into 500 mg tablets by using a Courtoy R190 Ft tablet press with 36 punches. The rotational speed of the press was 65 rpm. We measured the average and individual masses, the thickness, the hardness (Pharma Test WHT-2ME) and the disintegration (Pharma Test PTZ-E) five times in the course of the tablet-formation process. The relative standard deviation (R.S.D.) of the mass of the individual tablets was determined by measuring 20 tablets.

4. Results and discussion

Depending on the composition of the material system and the solvents used (organic or water), and their quantities, preference is given to different drying techniques (e.g. fluid-bed or vacuum) in the pharmaceutical industry. However, for certain material systems, the differences between the drying technologies are not marked enough to make one or the other unambiguously preferable. The products under study do not contain organic solvents or materials that are sensitive to heat or oxygen, or which contain toxic or potent compounds, in which cases the single-pot technology would be clearly preferable. On the other hand, we are not using a liquid binder with a high water content, and it is therefore not necessary to ensure a low loss on drying when the granules are dried (Table 1), in which case fluid-bed drying would be preferable. For this reason, with these products we had the opportunity to perform a comparative granulometric analysis

Table 1
Granule properties of batches dried in the Collette Ultima Pro 600 and in the Glatt WSG 200

	Glatt WSG 200	Collette Ultima Pro 600
Bulk density (g/100 ml)	68.49–71.43	79.37–83.30
Tapped density (g/100 ml)	80.55–84.29	94.53–104.17
Loss on drying (%)	2.70–3.45	3.07–4.08
Fine particles (%)	<21	<23
D_{50} (μm)	310–370	360–420
Porosity, ε (%)	73.9	63.1

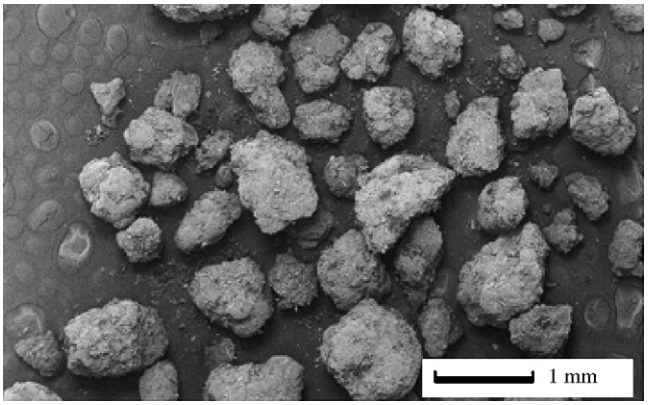

Fig. 4. SEM photographs of granules dried in Glatt WSG 200.

of different techniques used for drying wet granules prepared by using the same method. The advantage of fluid-bed drying is the short drying time, in contrast with pure vacuum drying, which entails a long processing time. Accordingly, we combined vacuum drying with microwave drying, since the duration of processing is an important consideration in the pharmaceutical industry. In the drying process, the primary goal was to shorten the processing time. In the experiments, the difference between the maximum product temperatures attained with the two drying techniques (35.5 °C and 43 °C) had no impact on the product quality.

Granule size increase is influenced by the impeller speed, the wet massing time and the amount of liquid in the case of high-shear granulation. In this study, the granules were granulated by means of the same technology, but dried with different methods. The powder fraction was relatively high for both vacuum and fluid-bed drying, at <21% and <23%, respectively, as shown in Table 1, but a significant difference in the powder fraction was not detected (Vromans et al., 1999). As conserns the composition under study, the mean particle size (D_{50}) was larger for the granules dried by using microwaves than for the fluid-bed dried sample. This is because the granules collide with each other and the wall of the equipment during the fluid-bed drying process. Particles therefore constantly break off and are eroded.

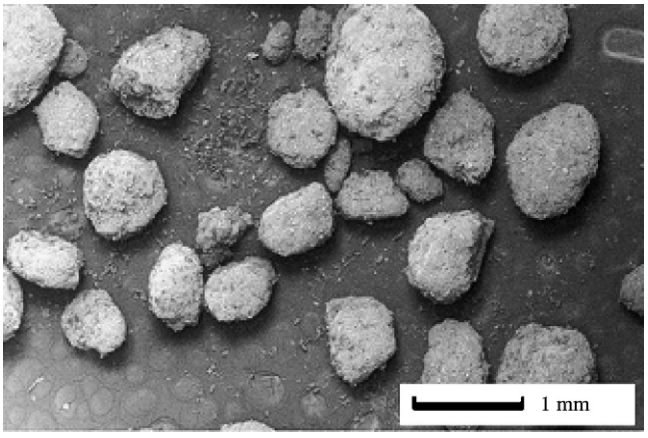

Fig. 5. SEM photographs of granules dried in Collette Ultima Pro 600.

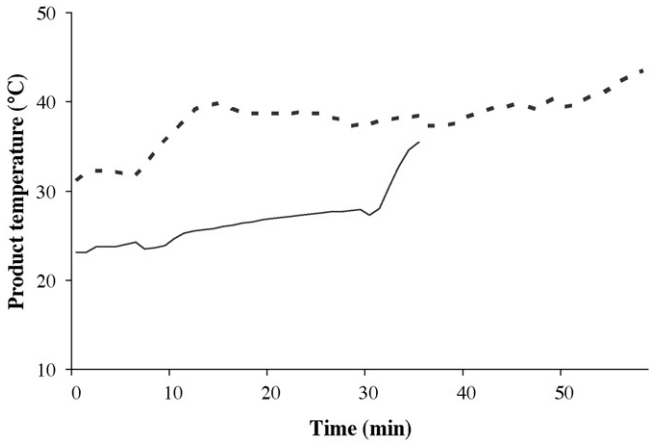

Fig. 6. Drying curves of the vacuum-microwave (- - -) and fluid-bed (—) drying technology.

Besides D_{50}, our findings were also corroborated by the SEM images shown in Figs. 4 and 5. The granules dried in the vacuum chamber were more geometrically regular and spherical, and thus had a different external physical structure from that of the granules dried with the fluid-bed technology.

The physical differences between the granules could result partly from the drying time, and partly from the nature of the drying curves (Fig. 6). In order for a material system with the same moisture content to develop by the end of the drying process, approximately 1.5 times the drying time is necessary in the case of vacuum drying than in the case of fluid-bed drying. In other words, the expulsion of moisture is slower, gentler and more even, with the result that the primary physical structure of the granules remains more intact. In the case of fluid-bed drying, the raggedness and erosion of the granules arise not only from the impact, but also as a result of the sudden temperature change, owing to the rapid expulsion of moisture. This rapid evaporation inflicts more intensive damage on the granules.

It is known from the literature that the porosity of granules is affected considerably by the impeller speed and the wet massing time (Badawy et al., 2000). However, less research has been conducted into the extent to which the porosity of granules prepared by using the same granulation technology is influenced by the subsequent use of different drying methods.

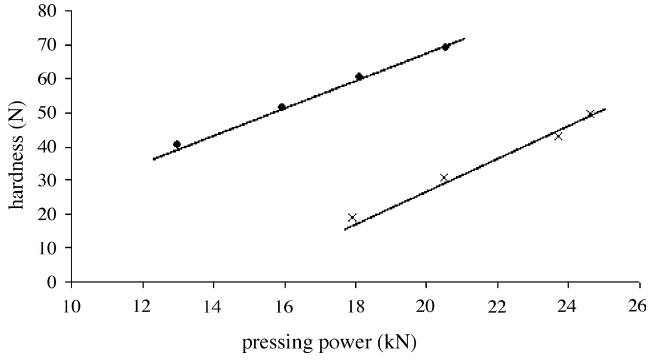

Fig. 7. Correlation between hardness and pressing power. Vacuum-microwave technology (×), fluid-bed dried granules (♦).

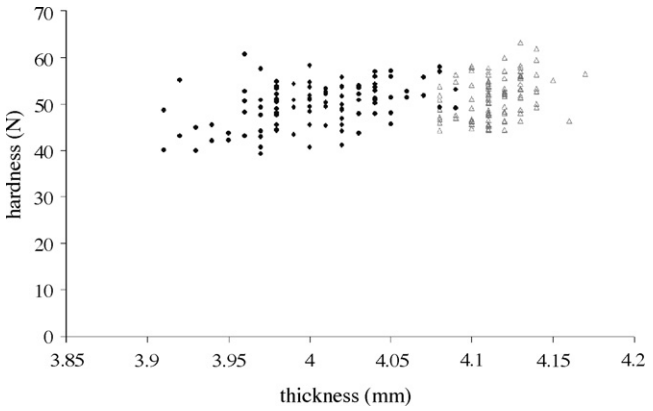

Fig. 8. Correlation between hardness and thickness. (●) Tablets pressed from granules dried in Collette Ultima Pro 600. (△) Tablets pressed from granules dried in Glatt WSG 200.

The data in Table 1 show that the granules dried in the vacuum chamber had a lower level of porosity than those dried by using the fluid-bed process, although the drying process was slower. This is due to the mechanism by which the moisture is forced out of the capillaries in the granules under sub-atmospheric pressure, which results in the formation of "channels" in the interior of the granules as the moisture leaves the granules. In the course of fluid-bed drying, which takes place at atmospheric pressure, the granules dry from their surface inwards, which results in a higher level of porosity.

The lower porosity values entail higher bulk and tapped density values, as shown in Table 1.

A reduction in porosity generally leads to a deterioration in compressibility. In the systems we examined, this took the form of a shift in the range of compressing force required to produce a tablet of the same hardness.

The correlation between compressing force and hardness is shown in Fig. 7. The granules prepared by using microwave-vacuum drying are denser, with the result that the tablets are lower and easily compressible, but a higher pressure force must be applied than in the case of the granules dried with the fluid-bed technology. The correlation between hardness and height is shown in Fig. 8. The height of the compressed tablets from the granules dried with the microwave-vacuum technology was lower than that of the tablets compressed from granules of the same hardness, dried with the fluid-bed technology. The differences in compressibility can be attributed to the differences between the structures of the granules, caused by the differing drying technologies. As can be seen in Table 2, the use of the different drying techniques had no effect on the individual mass distribution or disintegration time of the tablets; they had a relatively low mass distribution and short disintegration time (<1 min) in both cases.

Table 2
Properties of tablets pressed from granules dried in the Collette Ultima Pro 600 and the Glatt WSG 200

	Glatt WSG 200	Collette Ultima Pro 600
Relative standard deviation (R.S.D.) of individual mass from average mass (%)	<1.00	<1.07
Thickness (mm)	4.01–4.17	3.91–4.09
Disintegration (min)	<1	<1

5. Conclusions

Following the wet massing process, the drying technologies applied in the pharmaceutical industry were selected on the basis of a number of criteria, such as the properties of the active ingredient, the type of solvent, the processing time, etc. The choice of the most suitable technology for the given purpose requires careful consideration and testing. Two drying techniques, based on differing principles (fluid-bed and microwave-vacuum) were selected for the purposes of the present research, and the properties of the granules produced by using these methods were compared.

The granules produced in the traditional high-shear granulator and dried in a vacuum chamber had a lower level of porosity, and higher bulk and tapped densities, owing to the special characteristics of the drying process. They retained their spherical form, in contrast with the granules dried by using the fluid-bed technology. These characteristics of the granules also determined the properties of the tablets pressed from them, and made it necessary to apply a greater compressing force in the case of the granules prepared by using the microwave-vacuum drying process. At the same time, the mass distribution and disintegration time were not affected.

Despite the measurable physical differences arising from the differing principles of the two drying methods, both drying technologies proved highly suitable for production-scale manufacturing of the compositions under study.

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