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and

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Ph.D. Thesis

COMPARISON OF THE EFFECT OF GRANULATION AND DRYING TECHNIQUES ON THE QUALITY OF A PHARMACEUTICAL PRODUCT WITH A HIGH ACTIVE INGREDIENT CONTENT

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Introduction

Granulation of powder to produce a pharmaceutical solid-dosage form is an essential unit operation. Granulation in the pharmaceutical industry poses unique challenges, as it has the additional requirements of content uniformity and consistent physical properties, such as particle size, moisture, bulk density, porosity, hardness and compressibility.

In the past 20 years, the pharmaceutical industry has been introduced to a number of different methods for producing pharmaceutical granulation. These methods have offered a number of advantages, such as process efficiency, while addressing product quality and regulatory compliance. Potent compounds can now be granulated in so-called “one-pot” systems, which offer a greater measure of safety to operators by providing a single ”pot,” or bowl, to granulate and dry product.

Aim

My objective was to adapt the production-scale granulation process, previously performed with a traditional high-shear granulator (Diosna P400) and a fluid-bed drier (Glatt WSG-200), so that it could be carried out in a single-pot high-shear granulator (Collette Ultima Pro 600). Because of the considerable differences between the two machines, the fact that my experiments were not preceded by laboratory and pilot tests, and the fact that I was working on a production scale, I decided to adapt the processes in two stages: first the granulation step, and then the overall process, including the drying step.

The first aim of this experiment was to compare the granulation results that can be achieved in different production-scale high-shear granulator models in the case of a product with a high active ingredient content, and the characteristics and tablet-forming properties of the granules produced. I studied granules prepared in the Diosna P400 and the Collette Ultima Pro 600 industrial high-shear granulators. The macroscopic and microscopic textures of the granules prepared in these machine (which have identical manufacturing capacity) were examined. The aim was to create, optimize and reproduce a robust technology that furnishes granules (and the tablets formed from them) with similar physical properties in both sets of equipment.

The second aim of this study was to compare the properties of granules prepared in the same manner, in a high-shear granulator (Collette Ultima Pro 600 single-pot processing equipment) 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 the Collette Ultima Pro 600 single-pot processing equipment and a Glatt WSG 200 fluid-bed granulator and drier.

Materials

The given tablets contained 50% w/w metronidazole. The binding solution was an aqueous solution of Povidone 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 regulator; and microcrystalline cellulose (7.9% w/w), talc (1.6% w/w) and magnesium stearate (0.5% w/w) to improve tablet formation. I used the same composition and batch size (150 kg).

Equipment

-Diosna P400 conventional high shear mixer-granulator
-Glatt WSG 200 fluid-bed granulator and drier
-Collette Ultima Pro 600 single-pot equipment

Test of granules and tablets

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

-*Bulk and tapped densities:* 100 ml 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.

-*Carr compressibility index:* The flow properties of the granules can be determined through compaction, and the extent of the compaction can be defined through the relationship between the bulk and tapped densities, which can be expressed with the Carr compressibility index, using the following equation:

$$\textbf{Carr compressibility index (\%)} = \frac{\rho_T - \rho_t}{\rho_T} \bullet 100$$

where ρ_T = tapped density

ρt = bulk density

-*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:

$$\varepsilon = (1 - \frac{\rho_T}{\rho_{part}}) \bullet 100$$

The particle density (ρ_{part}) was determined with a Stereopycnometer SPY-5 (Quantachrome Corp.).

-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 *morphological properties* of the granules prepared were examined with a JEOL JSM-5600LV scanning electron microscope fitted with an energy dispersive X-ray spectrometer.

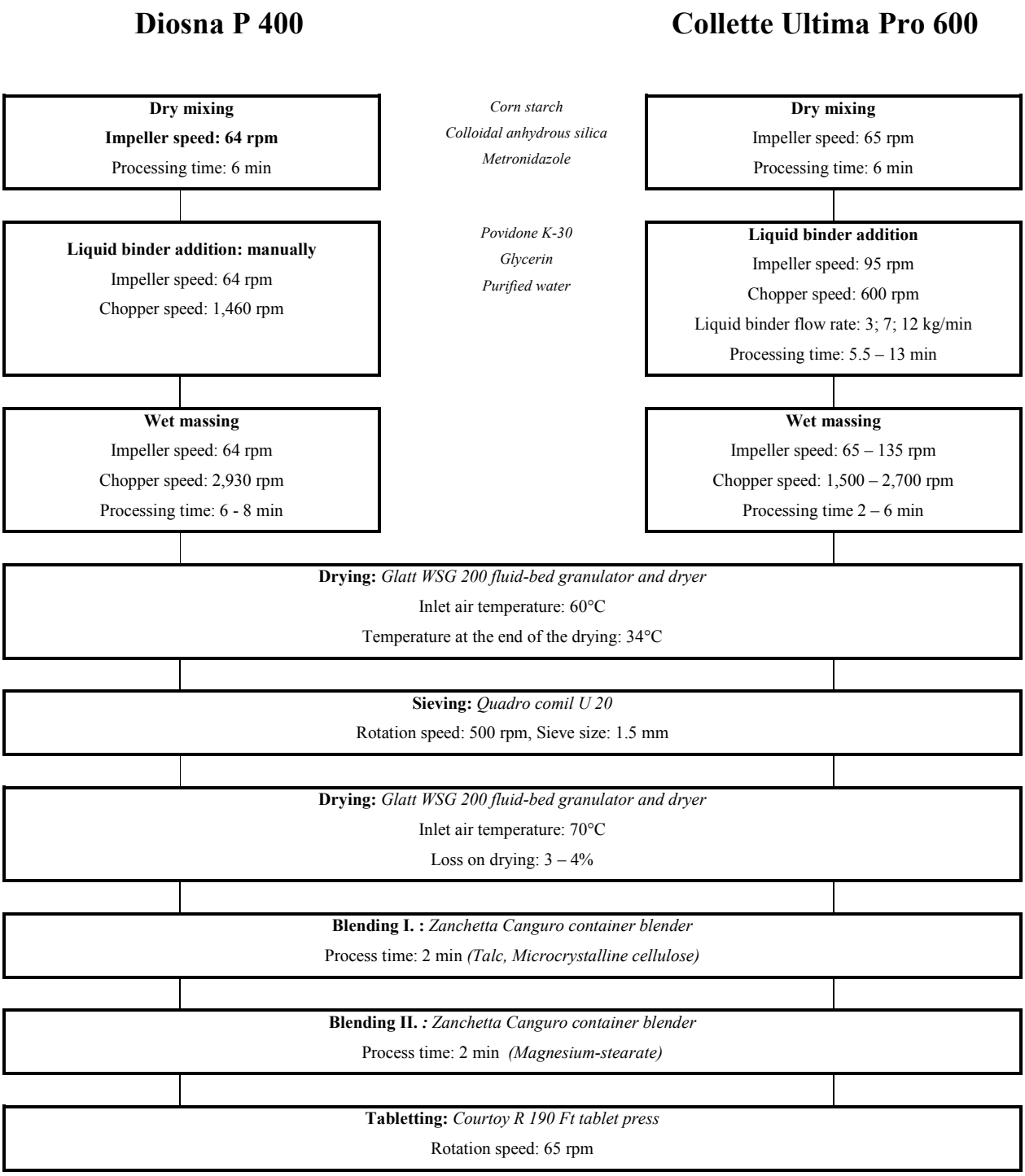
-*Tablet evaluation:* The granules were pressed into 500 mg tablets by using a Courtoy R190 Ft tablet press with 36 punches. The rotational speed of the press was 65 rpm. The average and individual masses, the thickness, the hardness (Pharma Test WHT-2ME), the friability (Pharmatest PT-TD) and the disintegration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

-The *assay, Blend Uniformity Analysis* (BUA) and *dissolution* determination are carried out by spectrophotometric method (UV-VIS). The test for *purity* (related substance) determination is carried out by TLC method.

Results

-Influence of the type of the high-shear granulator on the physico-chemical properties of granules

Figure 1. shows the flowcharts of the manufacturing processes in the Diosna P400 and the Collette Ultima Pro 600.



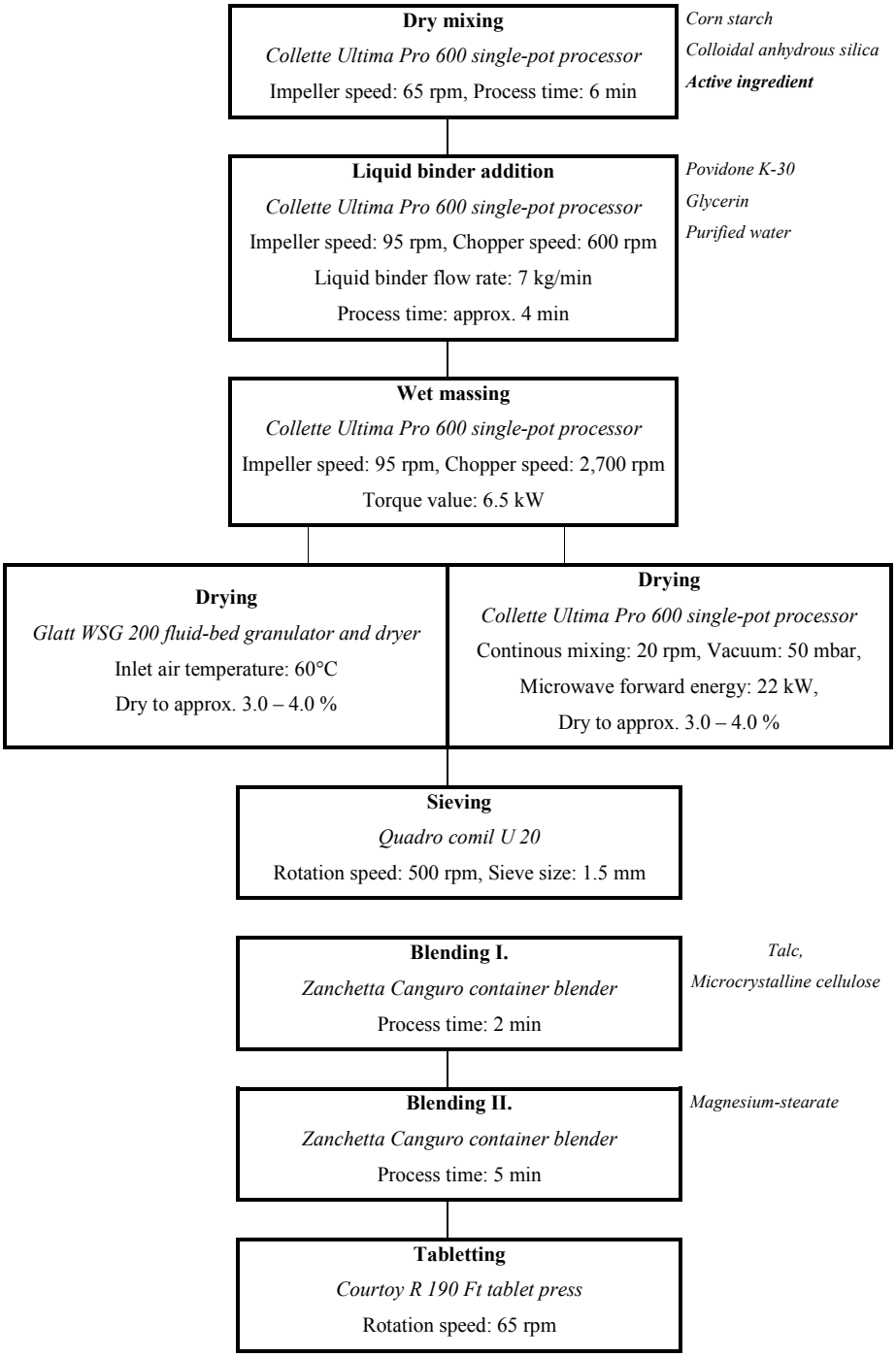
For two high-shear granulators with different constructions, I established the ranges of parameter settings which ensure the safe transference of the technologies for a preparation with a high content of active ingredient.

I determined the optimal setting ranges for mass production (impeller speed: 80-135 rpm; ideal torque associated with the impeller speed: 560-800 Nm; chopper speed: 600-2,700 rpm; ideal water content of the binder solution: 26 kg; liquid binder flow rate: 3-12 kg/min; massing time: 2-6 min), within which parameter ranges a satisfactory product could be manufactured in a manner such that the drying stage took place within the same fluid-bed drying equipment. The experiment demonstrated that, although the two technological devices perform granulation according to similar principles of operation, their different geometric properties require different technical settings in order for the end-products to have the same physical characteristics.

The textures of the granules prepared in the two types of machine differed considerably, but the differences between the measured physical parameters were not as great. The granulation process was highly controllable, the product was suitably robust and the results were easy to reproduce in the Collette Ultima 600 granulator, which allowed elimination of the inconsistencies resulting from the use of the Diosna P 400.

-Investigation of fluid-bed and vacuum microwave drying

Figure 2. shows the flowchart of the manufacturing processes in the same high-shear granulator and in two types of dryers.



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 to 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. (Fig. 3.) 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.

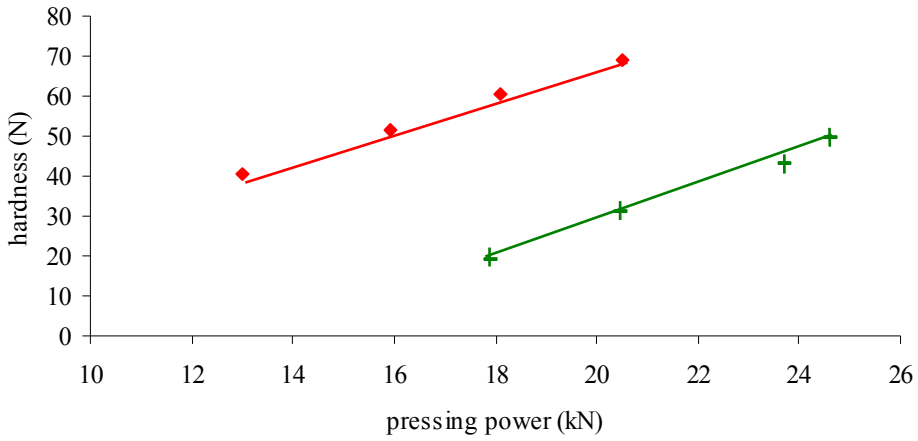


Figure 3. The correlation between hardness and pressing power
vacuum-microwave dried granules (+); fluid-bed dried granules (◆)

Summary

The objective of my research was to facilitate the technology transfer of a product prepared in a production-scale traditional high-shear granulator and dried using fluid-bed technology, into a "single-pot" type machine, without any change to its composition. In "single-pot" or "one-pot" equipment, the entire manufacturing process, the granulation process, as well as the drying stage that follows, takes place in the one device. With respect to the granulation process, I performed my experiments in traditional high-shear and single-pot machines with differing geometrical attributes. The drying process did not follow the fluid-bed principle, but was carried out using vacuum and microwave technology. This study aims to shed light on the similarities and differences between the two procedures, through a study of the – primarily physical – attributes of the granules and tablets produced.

I have reached the following conclusions:

The aggregation process of the granules is influenced considerably by the geometrical properties of the equipment, as well as the location and shape of the impeller and chopper.

The quality characteristics of the particles can only be objectively analysed by performing several physical examinations.

In the case of granules containing metronidazole, the fluid-bed (moving layer) drying method results in a smaller average granule size (D_{50}) than the vacuum-microwave drying method.

However, in the case of aqueous systems, the process time for vacuum-microwave drying is considerably longer than that of fluid-bed drying. Vacuum-microwave technology is unable to match the speed of fluid-bed drying.

In the case of vacuum-microwave drying the dry granules are more spherical and geometrically regular, as a result of abrasion between the granules.

In the course of fluid-bed drying, the erosion caused by the particles colliding is what causes greater reduction in granule size. In the case of the vacuum-microwave drying method, less erosion results from a combination of the longer process time and the constant agitation necessary to ensure even heat dissipation.

The texture of the aggregates is mainly influenced by the drying method, rather than by the granulation process.

The porosity value of granules prepared using vacuum-microwave drying is lower that those prepared using fluid-bed drying, owing to the means by which the moisture exits the system.

In the case of lower-porosity products, a higher pressure must be applied when pressing tablets.

In the course of pressing, the differences in porosity result in changes to the hardness and thickness of the tablets.

In the case of robust technologies, when selecting the drying method, its effect on the quality and stability of the material systems must also be taken into consideration.

Practical usefulness:

Pharmaceutical companies often find that they have to present scientific evidence to justify the replacement or modernization of equipment that could be up to one or two decades old. Pharmaceutical companies endeavour to achieve more cost-effective and better-regulated processes, in line with the standards of Good Manufacturing Practice (GMP). The advantages of single-pot high-shear granulators include the facts that the entire process takes place in one set of equipment, GMP requirements are met, the processing time is reduced, cleaning is simplified through the use of integrated, programmed cleaning systems, and the granulators are equipped with the appropriate safety systems. [39-40]

The purpose of my experiments was to search for the correlations that can be identified in the course of technology transfers, and which influence the quality of the products. In an industrial environment technology transfers are very common. Pharmaceutical technology should not only focus on the behaviour of material systems, but should also take into consideration the attributes of the equipment used, and the affect they have on the end product.

In the course of the technology transfer I compared the processes that take place during granulation and drying in the case of industrial equipment operating under identical and differing principles, while optimising the technological parameters of a product that is currently in use. At the same time, an opportunity was created to learn about the operating mechanisms of a relatively new technological culture. The experience thus gained could also be of practical use in the course of future technology transfers.

Publications

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