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Scale-up in the 4th dimension in the field of granulation and drying or how to avoid classical scale-up

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Abstract

In the pharmaceutical industry, the production of granules is based on a batch concept. This concept offers many advantages, as a batch can be accepted or rejected. However, the scale-up of the batch size may lead to problems. The variety of the equipment involved does not facilitate the scale-up process and the capital invested in space and equipment is high. An alternative approach is the use of a continuous process. However, continuous processes have the disadvantage among others that the batch size is not well defined. Thus, a special quasi-continuous production concept was developed, taking into account the advantages of a batch type and a continuous process. This concept was developed in cooperation with the Institute of Pharmaceutical Technology of the University of Basel, Glatt CH-4133 Pratteln and F. Hoffmann-La Roche, CH-4070 Basel. The equipment allows to implement a "Just in Time Production Concept" as a large batch B consists of n subunit (SU) batches b, i.e. $B = nb$. The subunit batch b corresponds to, e.g. 7-kg material for the production of pharmaceutical granules for further processing such as tabletting. At the Roche production site, this novel process equipment was used to manufacture batch sizes B with $n = 10$, $n = 100$ and so far up to $n = 600$ subunits. This leads to an optimal use of capital invested in GMP space and equipment. The difference to the classical scale-up is the following: with classical scale-up, the dimensions of the equipment x, y, z is enlarged and the process time is more or less kept constant. With this novel concept, the dimension x, y, z of the equipment is kept constant and the process is repeated in the 4th dimension "n times". Thus, for the scale-up in the 4th dimension, i.e. in the time, the equipment needs to show a "self-cleaning" property and appropriate formulations. The novel concept is of special interest, as the quality of the product is not changed during scale-up.

Keywords: Scale-up; Batch versus continuous process; Glatt Multicell®—a quasi-continuous production line of granules; Reduction of time to market; Just-in-time production; Lights-out operation

1. Introduction

Today, the production of pharmaceutical granules is still based on the batch concept. In the early stage of the development of a solid dosage form, the batch size is small, e.g. for first clinical trials. In a later stage, the size of the batch produced in the pharmaceutical production department may be up to a 100 times larger. Thus, the scale-up process is an extremely important one. Unfortunately, in many cases, the variety of the equipment involved does not facilitate the task of scale-up. During the scale-up process, the quality of the granules may change. A change in the granule size distribution, final moisture content, friability, compressibility and compactibility of the granules may strongly influence the properties of the final tablet, such as tablet hardness, tablet friability, disintegration time, dissolution rate of the active substance, aging of the tablet, etc. In order to avoid such scale-up problems, a new concept concerning a quasi-continuous production line of granules is presented [1–8]. This concept permits the production of small-scale batches for clinical trials and of production batches using the same equipment. Thus, scale-up problems can be avoided in an elegant and cost-efficient way.

2. Experimental: The development of a quasi-continuous granulation and drying process to avoid scale-up problems

2.1. Continuous processes and the batch concept

In the food and chemical industry, continuous production lines play an important role, whereas the pharmaceutical industry production is mainly based on a batch type proce-

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dure. Concerning the safety of a dosage form and quality assurance, the batch concept is very convenient. Thus, a well-defined batch can be accepted or rejected.

In the case of a continuous process, a batch has to be defined somehow artificially, i.e. the amount of product, e.g. amount of granules produced within 6–8 h. On the other hand, continuous processes offer two important advantages:

(a) there is no difficult scale-up exercise necessary for larger "batches";
(b) a 24-h automatic production line ("lights-out" operation) should be possible.

2.2. Concept of the quasi-continuous production line for granules

In order to combine the advantages of a batch type and continuous production, a prototype for a quasi-continuous production line was developed [1–5,7,8]. The principle of this quasi-continuous production line is based on a semi-continuous production of mini-batches in a specially designed high-shear mixer/granulator that is connected to a continuous multicell-fluidized (Glatt Multicell®) bed dryer (see Fig. 1).

In order to study the feasibility of such a quasi-continuous production line, different formulations were tested and compared with a conventional batch process.

The weighing system (see No. 1, Fig. 1: Transport and dosage system for mixer/granulator filling), which is available on the market, was not involved in the first experiments. Thus, a prefixed amount of powder of the placebo formulation was added to the specially designed high-shear mixer (No. 2, Fig. 1: Horizontal high-speed ploughshare mixer) and thoroughly mixed. Subsequently, this amount of powder is granulated by continuously adding granulating liquid (prepared in advance, i.e. granulating liquid: in general deionized water with or without a binder dissolved) using an airless spray nozzle up to a fixed amount. The ideal amount of granulating can be defined according to the results of a power consumption measurement [5,6]. Afterwards, the moist granules are discharged from the high-shear mixer (No. 2, Fig. 1) through a screen (No. 3, Fig. 1: Rotary sieving machines for wet and final sieving) into the first cell of the multicell-fluidized (No. 4., Fig. 1: Three-chambered fluid-bed dryer) bed dryer unit to avoid any formation of lumps. Thus, the quasi-continuous production of granules can be described as a train of mini-batches passing like parcels the compartments of dry mixing, granulation and drying. The multicell dryer consists, in general, of three cells (No. 4, Fig. 1), which are designed for different air temperatures, i.e. in the first cell, the granules are dried at a high temperature, e.g. 60 °C, and in the last cell, ambient air temperature and humidity can be used to achieve equilibrium conditions. If appropriate, more cells can be added. As an example, it may be of interest to add an additional chamber for coating the granules with a water-based nanosuspension to control the release of the drug substance. As the amount of material to be coated is relatively small per unit time, it is also possible to add a chamber with a solvent recovery system and to use an organic-solvent-based coating! Each subunit is collected with the pneumatic transport system (No. 5, Fig. 1) into the final container for further processing (preparing the final blend for the tabletting machine of for capsule filling purposes, etc.).

Due to this principle, a batch B defined for quality control purposes consists of a fixed number of n mini-batches (subunits), i.e. $B = nb$. Thus, a tight in-process control of the mixing/granulation and drying step provides an excellent "batch" record of the quasi-continuous production of granules and an excellent opportunity for a continuous validation of the process and the equipment.

Thus, based on the positive results obtained with the thesis work of Schade [1] and Dörr [3], a new plant for quasi-continuous wet granulation and multiple-chambered

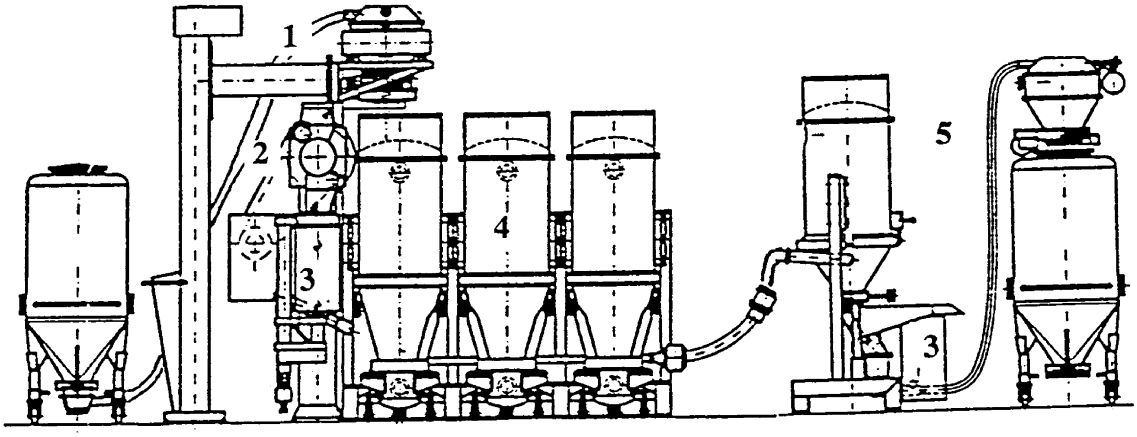

Fig. 1. Glatt Multicell® production line for granules with three drying cells (Glatt®, CH-4133 Pratteln).

fluid-bed drying was developed by Glatt CH-Pratteln in cooperation with F. Hoffmann-La Roche Basel and the Institute of Pharmaceutical Technology of the University of Basel. For this achievement, the Institute of Pharmaceutical Technology received the Innovation Award of the Cantons Basel-City and Basel Country in 1994.

The system gives a new possibility for industrial manufacturing and galenical development of pharmaceutical solids specialties and has following purposes.

Automatized unattended production (i.e. ''light-out'' operation), withdrawing from scale-up experiments and, thus a shorter development time for new specialties, with the aim of a shorter time to market. Manufacturing procedures can be simplified, validated faster, and the quality of granules, tablets and kernels compared to common production is equal to better. Different solids specialties have been tested and validated.

2.3. Goals of the quasi-continuous granulation and drying line

2.3.1. Unattended production

One of the general aims of quasi-continuous granulation and fluid-bed drying is unattended production. The production of small subunits of 6–9 kg instead of a whole batch allows an automatized, iterative granulation and drying procedure. The amount of 6–9 kg depends on the poured volume, i.e. of the relative densities of the components of the formulation. It is, in general, advantageous that the volume of the mixer/granulator (in this case 27 l) is not filled more than 2/3.

The division of the production process into different compartments (mixing, sieving and drying compartments) with a tight in-process control guarantees the reproducibility of the galenical properties of each subunit.

2.3.2. No necessity for scale-up experiments

The granulation and drying of subunits of 7–9 kg instead of a whole batch gives the possibility to use the plant for laboratory and production scale, because the batch size is no more characterized by the machine size, but by the number of produced subunits. Using the same plant in galenical research, development and production may shorten the time to market for new solids specialties.

2.3.3. Simplification of manufacturing procedures

Existing manufacturing procedures can be taken over from common equipment without changing components. In certain cases, it is possible to simplify the procedure: the small mixer size and the geometry of the mixing elements allow to add the binders into the premixture and just to granulate with water.

2.3.4. Identical or better quality of granules and tablets

The quality of the produced granules and tablets has to be equal or better and needs to fulfill the product specifications.

2.3.4. Procedure

For the development of the quasi-continuous production equipment, placebo formulations were used in the beginning (see Materials and methods with two examples of placebo formulations). Subsequently existing marketed formulations were used to check whether these formulations can be used without any changement. These formulations tested were produced within the Roche group with a classical high-shear mixer and a separate subsequent fluid bed drying equipment, i.e. identical or similar to a Diosna® P-600 high-shear mixer/granulator with a subsequent dryer identical or similar to a Glatt large-scale fluid-bed drying equipment. It is evident that the marketed formulations cannot be published here. In the following, the materials and methods are described to check the performance of the Glatt Multicell® Equipment and for the comparison with the classical production process using large-scale equipment.

2.4. Materials and methods

2.4.1. Materials

Formulation 1	
Lactose 350 M	65.5%
Maize starch	25.5%
Povidone K-30	6.5%
Primojel	2.5%
Granulation liquid: Aqua purificata Ph. Eur. II	
Formulation 2	
Lactose 350 M	68.7% (w/w)
Maize starch	27.0% (w/w)
HPMC 2910/3 cP	4.3% (w/w)
Granulation liquid: Aqua purificata Ph. Eur. II	

2.4.2. Production parameters

Subunit size	7.0 kg	
Rotational speed of mixer/granulator	206 rpm	
Granulation liquid per subunit	1.0 kg (Formulation 1)	1.3 kg (Formulation 2)
Spray rate	800 g/min (Formulation 1)	900 g/min (Formulation 2)
Mixing time	85 s (Formulation 1)	90 s (Formulation 2)
Sieve diameter	5 mm wet sieving, 1.5/1.0 mm dry sieving	
Drying temperature	60 °C	
Inlet air quantity	600 m^3/h	

2.4.3. Test methods

The relative humidity of the granule batch sample was measured with a Rotronic® hygroscope. Loss on drying was obtained with a Mettler® LP 16/PM 480 Deltarange infrared

balance. Sieve analysis was performed with a Fritsch® Analysette laboratory sieving machine. Bulk volume/tapped volume was measured using a Jel STAV® 2003 volumeter. Compression force/hardness profile was obtained with a Manesty® Deltapress tabletting machine and a Tegimenta® Pharmatest PTB 301 hardness tester. Disintegration time was measured with a Tegimenta® Pharmatest PT 21 and a Kramer® DES-2A disintegration tester. Friability/abrasion was tested using a Roche® friabilator.

3. Results

3.1. General comments

Constant values and reproducibility of the process are important facts of quasi-continuous granulation. The tests performed at the Roche Production Plant showed equal to better quality of granules and tablets compared to common large-size granulation equipment such as a Diosna P-600 high-speed granulator separately used before drying the wet mass in a large fluidized bed dryer.

3.2. Results obtained during the development of the equipment

During the development of the equipment, the performance of each subunit was tested. For this purpose, the high-shear mixer/granulator was operated separately from the subsequent drying system. The following properties were tested:

(1) Yield (percent mass): tested for each subunit in order to check qualitatively the "self-cleaning" property of the mixer/granulator (see Fig. 2). In this context, it is important to realize that the formulation has no "sticking" problem. If a formulation has a "sticking tendency" the mixer/granulator can be blocked by the wet, sticking mass. A total of 30 existing (marketed) formulations at Roche Basel were tested and only 2 out of 30 showed such a "sticking tendency". This sticking tendency could in one case be traced back to the use of a high viscous binder (high viscous starch paste) and in another case to the property of the drug substance. As a binder, it is recommended to use a low viscous binder dissolved in the aqueous granulating liquid or to use preferentially an appropriate well water-soluble binder in a dry state in the powder mixture added to the mixer/granulator and to granulate with pure water. The yield (percent mass) of the subunit typically varied between 95% and 105% (w/w) or better. The results show that a negative deviation from 100% was usually followed by a positive deviation indicating that hat "surplus" mass remained in the precedent subunit is discharged in the following one. It has to be kept in mind that a fixed small amount of material always remains in the system. The important point is that the remaining material is continuously exchanged and that there is no chance that the same material can remain for a longer

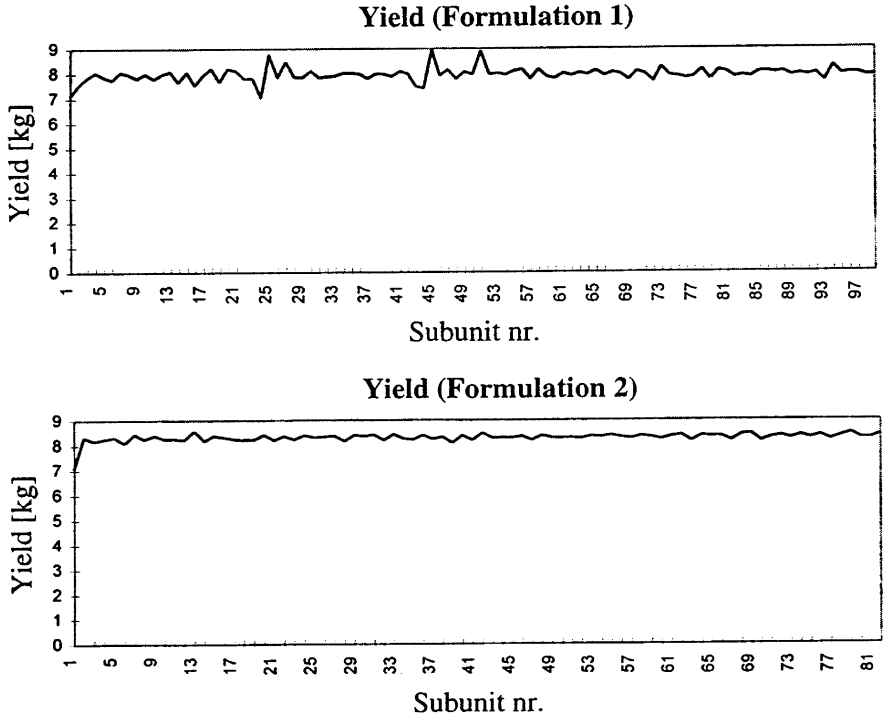

Fig. 2. Yield (kg mass) after emptying of each subunit from the high-shear mixer as a function of the subunit number.

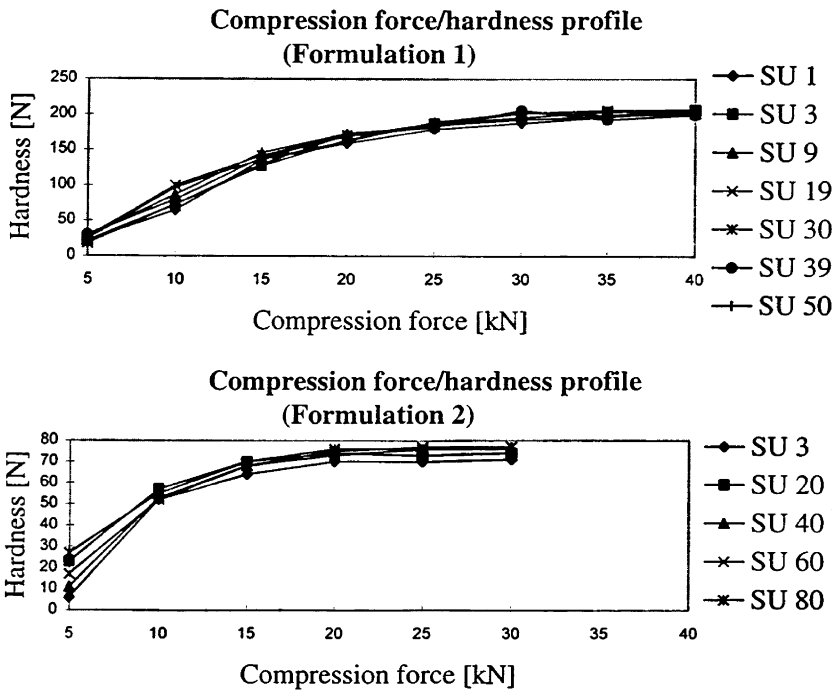

Fig. 3. Compression force/hardness profile (Formulations 1 and 2) as a function of the subunit number.

time in one of the compartments. The high yield of the subunit batches and the concept to accumulate the total number of subunit batches in a final large container to add the outer phase of the granule formulation leads to high final yields of large batches.

(2) Bulk/tapped volume: The bulk and the tapped volume of each subunit was tested during the thesis of Dörr in order to check a possible variation between initial, intermediate and final subunits. Dörr used selected subunits for a subsequent drying in a fluidized bed dryer and tested these subunits of granules for bulk/tapped volume and relative humidity. He also tested selected subunits in a series of up to 100 subunits produced. It has to be kept in mind that this procedure was appropriate during the first development phase for the equipment. In an industrial environment, it is advantageous to test the integral system. The scale-up in

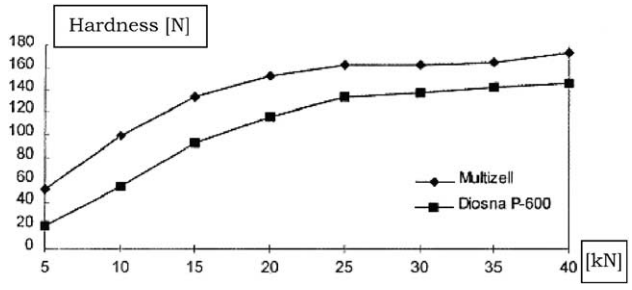

Fig. 4. Compression/hardness profile of a formulation produced with the Glatt Multicell® Equipment compared to a classical production (Diosna® P-600 mixer/granulator with subsequent separate drying). In case of this formulation, the classical scale-up leads to a reduction of the tablet hardness.

Fig. 5. Glatt Multicell® Production Plant at Pfizer Goedecke, Freiburg, Germany.

the 4th dimension, i.e. in the time–dimension, means to check the performance of producing a small number of n subunits and a large number of n subunits showing an identical quality without cleaning the equipment in between. It has been reported [9] that the upper limit in case of a marketed Roche formulation is not known, but that it was possible to produce a large batch $B = nb$, with $n = 600$ and $b = 7$ kg.

(3) Compression/hardness profile: The compression/hardness profile of a granule batch is an important property. Dörr and Leuenberger [4] selected different subunits (SU) and compressed the subunits using different compression forces in order to obtain tablets. The tablets were subsequently tested for hardness as a function of different subunit numbers (see Fig. 3). From experience, it is well known that certain formulations show small batches as an excellent compression property but can fail as large batches (see Fig. 4). This is another advantage of the quasi-continuous production concept, as in principle the quality of the small batch does not change by the repetitive procedure. Thus, it is important to compare the compression/hardness profile of the Glatt Multicell® Equipment with a batch obtained with the classical large-size pharmaceutical production (see Fig. 4).

(4) Disintegration time: Dörr and Leuenberger [4] also analyzed, as a function of the subunit numbers, the variation of the disintegration time of the tablets obtained according to the standard operation procedure. The results show that all the disintegration times measured were well within the limits and that the variation was negligible.

4. Conclusions: Advantages of the quasi-continuous granulation and drying line

Such a production line has been successfully tested in operation at the Roche pharma production plant in Basel. A further developed version (with 10 bar shock-proof drying cells) has been installed at the technology center at Goedecke (Pfizer Group) in Freiburg, Germany (see Fig. 5). From the experience obtained so far, the following conclusions can be derived.

The production line can be fully automated and equipped with a cleaning in place (CIP) system. The moist agglomeration process can be monitored for each subunit by a power consumption in-process control device. Due to the three different cells of the Glatt Multicell® drying equipment, a gentle drying of temperature-sensitive drug substances are possible. According to the needs, a ‘‘Just-in-Time Production’’ of the desired batch size B can be implemented. Early small-sized batches can be already considered as production batches of identical quality. Thus, these early batches can be put on a long-term stability test already at the beginning of the development of the dosage form. As the early clinical batches are produced on exactly the same equipment as the large production batches, no bioequivalence test between early clinical batches and later production batches is needed. Due to these facts, no scale-up development is necessary. Thus, the development time and the time needed to market can be reduced. For globally active large pharmaceutical companies, time to market is an important issue. It is believed that for a ‘‘blockbuster’’ product, 1 day earlier on the market can mean US$1 million more sales. Due to the better knowledge of the human genome, it is moreover believed that in future, the novel drug substances and solid dosage forms will be specially adjusted to the needs of the different groups of patients according to the differences in their genome. Thus, more flexibility in the production of drug substances and dosage forms will be needed! For such purposes, the high flexibility of the Glatt Multicell® quasi-continuous production line will be very beneficial for the pharmaproduction.

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