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Review article

New trends in the production of pharmaceutical granules: batch versus continuous processing

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Abstract

In the pharmaceutical industry, the production of granules is based on a batch concept. This concept offers many advantages with respect to quality assurance 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 often does not facilitate the scale-up process. In order to avoid scale-up problems, continuous or semi-continuous processes have to be evaluated as alternatives to a batch production. Thus, a quasi-continuous production line is presented, which permits the production of small-scale batches, e.g. for clinical trials and for large-scale batches using the same equipment. © 2001 Published by Elsevier Science B.V.

Keywords: Production of pharmaceutical granules; Scale-up; Batch versus continuous process; Quasi-continuous process

1. Introduction

In the pharmaceutical industry, the production of granules is still based on a batch concept. This concept offers many advantages in respect of quality assurance as a batch can be accepted or rejected. What are the reasons for the new trend to evaluate the feasibility of alternative concepts such as a continuous process? The registration authorities have become more and more interested in whether the quality of the production batch is the same as the quality of the batches used for clinical trials. Thus, the scale-up problem is an important issue. Unfortunately, the variety of the equipment involved often does not facilitate the scale-up process and the capital invested in space and equipment is high. The theory of scale-up is often not taken into account for the design of larger equipment by the manufacturers. In general, it is not enough to design larger equipment in the x, y, z dimensions just based on geometrical similarity [1]. An alternative approach is the use of a continuous process.

Continuous processes are well established in food processing and food technology with high production volumes, i.e. a production rate of tons per hour is not unusual. As pharmaceutical and food technology are neighboring disciplines it is evident that it may be of interest to take advantage of the existing experience in the food industry with respect to a continuous production line. However, it has to be noticed that a technology and knowledge transfer, which worked well in the area of cleaning in place (CIP) and sterilization in place (SIP) [2], has so far been less than successful in the case of continuous processing of pharmaceutical granules. There are numbers of reasons.

Continuous processes have the disadvantage that the batch size is not well defined and that the system is in general not in the equilibrium condition from the beginning.

In addition, drug substances can be very sensitive to degradation by temperature and humidity. Thus, it is a prerequisite that there is no risk of a drug particle remaining for a longer period of time than necessary in the process unit and so being less exposed to degradation and later contaminating the batch. The other point is that in the pharmaceutical industry, the production rate is much less than in the food industry. In the case of a relatively high production rate of a pharmaceutical product (>1 ton/day) dedicated solutions have been developed, e.g. for paracetamol, etc. Thus, product change and time consuming cleaning processes can be avoided. As an alternative to the batch-type wet granulation process, which cannot be so easily transformed into a continuous process, there is a clear trend to study the dry roll compactor process [3–5]. The dry roll compactor (such as Alexanderwerk®, Bepex®, and Gerteis®) permits the agglomeration of fine powder between two rolls, e.g. into ribbons with a certain porosity. It has to be noticed that the

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fine powder premix needs to contain an appropriate amount of lubricant before compaction. The ribbon is subsequently sieved through a mill. If the resulting dry granule size distribution contains too many fines, the surplus of fines can be reworked using an appropriate feed-back device. In fact, the dry compaction system clearly represents a continuous process. The resulting dry granules can substitute a more expensive drug-direct compression excipient mixture or, as already mentioned, granules obtained by wet granulation. The amount of dry granules produced represents a certain batch size, which is, in general, used for tabletting. In such a case, no further lubrication needs to be added in the outer phase. However, depending on the wettability of the drug substance, and on the necessity of reworking fines, the dry compaction process is not always the method of choice. In the case of wet granulation, extruders can be used for continuous processing. A lot of research has been invested in this extrusion process for the production of pellets [6–8]. Due to the fact that the material extruded needs to be spheronized in a special device such as a marumerizer with a fixed capacity, the manufacture of pellets ends up as a batch-type process. Thus, the final option is to develop a quasi-continuous production line for pharmaceutical granules based on the moist agglomeration process. The development of such equipment will be described in this paper.

A quasi-continuous production concept can take into account the advantages of a batch-type and a continuous process. Such a concept [9–13] was developed in co-operation with the Institute of Pharmaceutical Technology of the University of Basel, Glatt Ltd., CH-4133 Pratteln and F. Hoffmann-La Roche Ltd., CH-4070 Basel. This quasi-continuous production line permits the production of small-scale batches, e.g. for clinical trials and for large-scale batches using the same equipment. A 'lights-out' operation is possible due to a well designed automation. The result of this concept is the Glatt Multicell® equipment, which has been installed at the Roche production site and is now fully operating. The equipment allows the implementation of a 'just in time production concept' as a large batch B consists of n subunit batches b, i.e. $B = nb$. The subunit batch b corresponds to, for example, 7 kg of 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 up to $n = 600$ subunits (B. Dörr, pers. commun.). If the formulation is fine the Glatt Multicell® equipment can run for $n = 100$ up to $n = X$ hundred subunits without interrupting the process for cleaning, etc. This leads to an optimal use of capital invested, in GMP space and equipment (i.e. designed according to GMP = Good Manufacturing Principles). It is important to notice that the Glatt Multicell® equipment is the same for small and large batches. The difference from the classical scale-up is the following: with classical scale-up the dimensions of the equipment x, y, z are enlarged and the process time is more or less kept constant. With this novel concept the dimensions x, y, z of the equipment are kept constant and the process is repeated in the fourth dimension 'n times'. Thus, for the scale-up in the fourth dimension, i.e. in the time, the equipment needs to show special properties such as the 'self-cleaning' ability of the high-shear mixer involved. The novel concept is of special interest, as the quality of the product is not changed during scale-up. An optimization of the formulation can be done with small batch sizes. It has to be emphasized that a process and formulation optimization of large-scale batches using large-scale equipment is practically no more possible in a later development phase, when production size batches are needed! If the formulation is shown to be critical, the company needs to live with a weak point in the formulation or process using larger equipment, which is often difficult to resolve. Thus, if the formulation and process are optimized with the quasi-continuous production line no further optimization or testing on large-scale equipment is needed. In fact, these batches are then already suitable as 'production batches' for a long-term stability test!

As no classical scale-up is necessary, 'time to market' can be reduced. This is an important issue for pharmaceutical products. A second generation of Glatt Multicell® equipment has been actually installed at the Pfizer Goedecke plant in Freiburg, Germany.

It is important to keep in mind that the concept of a quasi-continuous production line is a repetition of a small batch production process. Thus, problems related to variations in the residence time of particles in a real continuous process can be avoided. For the same reason, there is no need to develop complicated theoretical population balance models for the quasi-continuous process. In fact, the same in-process control devices such as the power consumption profile measurement can be used for the batch-type and the quasi-continuous process. Thus, this in-process can be used for the 'subunit batch' record for validation purposes of the full batch size B of the quasi-continuous process.

2. 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 procedure. 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.

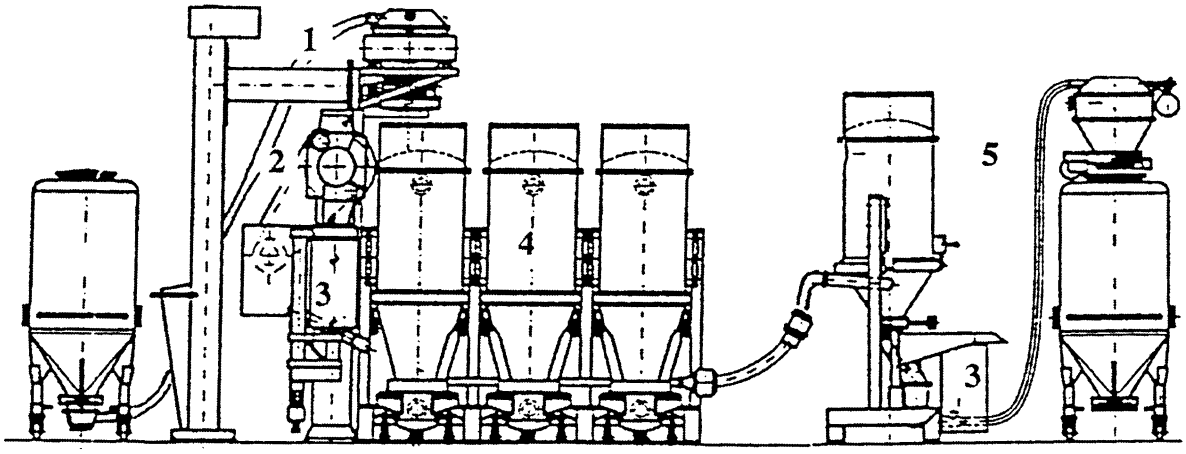

Fig. 1. Glatt Multicell® production line for granules with three drying cells (Glatt AG, CH-4133 Pratteln).

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

In order to combine the advantages of batch-type and continuous production a prototype for a quasi-continuous production line was developed [9–13]. The principle of this quasi-continuous production line is based on a semi-continuous production of mini-batches (subunits) in a specially designed high-shear mixer/granulator, which 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 Fig. 1, no. 1: transport and dosage system for mixer/granulator filling), which is available on the market, was not involved in the first experiments of the PhD thesis work of A. Schade and later B. Dörr [9,11]. Thus, a prefixed amount of powder of the placebo formulation was added to the specially designed high-shear mixer (Fig. 1, no. 2: horizontal high-speed plough-share mixer) and thoroughly mixed. Subsequently this amount of powder is granulated by continuously adding granulating liquid (prepared in advance, i.e. 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 liquid can be defined according to the results of a power consumption measurement [14]. Afterwards the moist granules are discharged from the high-shear mixer (Fig. 1, no. 2) through a screen (Fig. 1, no. 3: rotary sieving machines for wet and final sieving) into the first cell of the multicell-fluidized (Fig. 1, no. 4: 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 series of mini-batches passing like parcels through the compartments of dry mixing, granulation and drying. The multicell dryer consists in general of three cells (Fig. 1, no. 4) 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 (Fig. 1, no. 5) into the final container for further processing (preparing the final blend for the tabletting machine or 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 A. Schade [9,10] and B. Dörr [11] a new plant for quasi-continuous wet granulation and multiple-chambered fluid-bed drying was developed by Glatt AG, CH-Pratteln in cooperation with F. Hoffmann-La Roche Ltd., 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-County in 1994.

The system gives a new possibility for industrial manufacturing and galenical development of pharmaceutical solid specialties and has the following purposes: automatized unattended production (i.e. 'lights-out' operation) and withdrawing from scale-up experiments resulting in a shorter development time for new specialties, with the aim of a shorter time to market. Manufacturing procedures can be simplified and validated faster, and the quality of gran-

ules, tablets and kernels compared to common production is equal if not better. Different solid 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. 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 two-thirds.

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 makes it possible to use the plant for laboratory and production scales, because the batch size is no longer characterized by the machine size but by the number of subunits produced. The use of the same plant in galenical research, development and production allows for shortening of the time to market for new solid 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 the water-soluble binder to be added 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 is equal to or better than the results obtained using the classical processes (B. Dörr, pers. commun.).

2.3.5. Procedure

For the development of the quasi-continuous production equipment placebo formulations were used in the beginning (see Section 2.4) of this study. Later in the study, marketed formulations of Roche Ltd. were used to check whether these formulations can be used without any adjustment. The formulations tested were produced within the Roche group with a classical high-shear mixer and 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 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 to compare the novel process with the classical process using large-scale equipment.

Table 1
Composition of formulations 1 and 2

Formulation	%
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. Typical materials

The composition of formulations 1 and 2 for typical materials is given in Table 1.

2.5. Process parameters

The process parameters for formulations 1 and 2 are given in Table 2.

2.6. Test methods

The relative humidity of the granule batch sample was measured with a Rotronic® hygroscope. Loss on drying was determined 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 were measured using a Jel STAV® 2003 volumeter. Compression force/hardness profiles were obtained with a Manesty® Deltapress tabletting machine and a Tegimenta® Pharmatest PTB 301 hardness tester. Disintegration time

Table 2
Process parameters for formulations 1 and 2

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

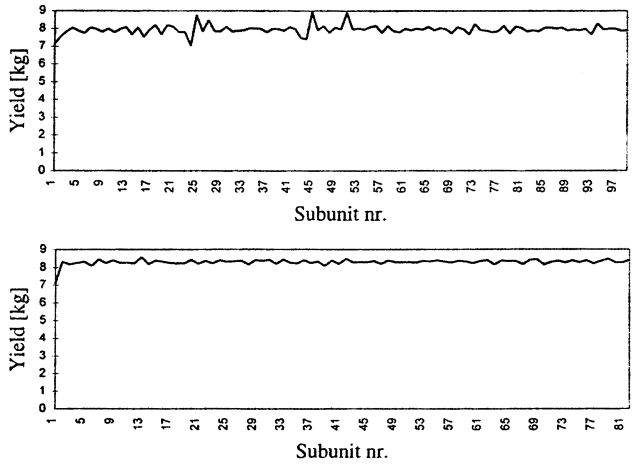

Fig. 2. Yield (kg mass) after emptying of each subunit from the high-shear mixer as a function of the subunit number (see text).

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 and discussion

3.1. 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 system was dismantled and the high-shear mixer/granulator was operated separately from the subsequent drying system. The following properties were tested [12].

3.1.1. Yield (kg mass)

The yield (kg mass) of each subunit was checked in order to check qualitatively the 'self-cleaning' property of the mixer/granulator. 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. In total, 30 existing (marketed) formulations at Roche Basel were tested and only two 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 (low melting point). It is recommended to use a low viscosity 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 (kg 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 the 'surplus' mass remaining 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 time in one of the compartments. The concept of accumulating 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. The yield per subunit of two different formulations is shown in Fig. 2.

3.1.2. Bulk/tapped volume

The bulk and the tapped volume of each subunit was tested during the thesis of B. Dörr in order to check a possible variation between initial, intermediate and final subunits. For this purpose, B. Dörr selected a number of subunits for subsequent drying in a fluidized bed dryer and tested these subunits of granules for bulk/tapped volume and relative humidity.

3.1.3. Compression/hardness profile

The compression/hardness profile of a granule batch is an important property. B. Dörr 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 an excellent compression profile as small batches but do not keep this property on increasing batch size. This is another advantage of the quasi-continuous production concept as, in principle, the quality of the small batch is not changed 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 unit (see Fig. 4).

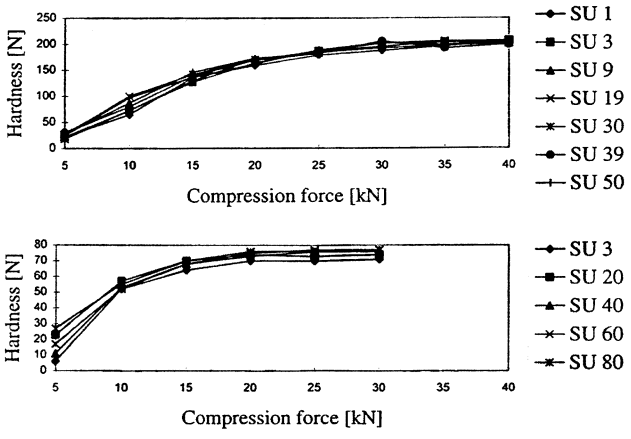

Fig. 3. Compression/hardness profile as a function of the subunit number for two formulations (see text).

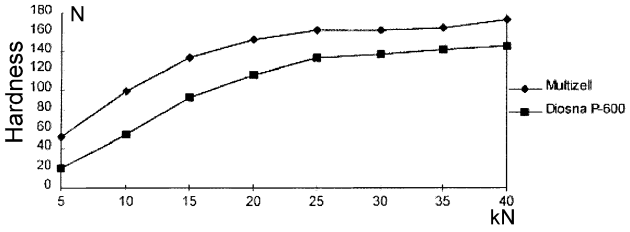

Fig. 4. Compression/hardness profile of a formulation produced with the Glatt Multicell® equipment compared to a classical production (Diosna® P-600 mixer/granulator with subsequent separate drying) demonstrating a 'Scale-up' Effect [12].

3.1.4. Disintegration time

B. Dörr 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 showed that all the disintegration times measured were well within the limits and that the variation was negligible [11,12].

It is important to realize that these tests with the dismantled system were 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 the fourth dimension, i.e. in the time dimension, involves monitoring the production of a small and a large number of n subunits to see if identical quality is obtained without cleaning the equipment in between. It has been reported (B. Dörr, pers. commun.) that the upper limit in the 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.

3.2. 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 if not 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 (B. Dörr, pers. commun.).

It has to be kept in mind that the approach of checking the performance of each subunit has been necessary during the development of the equipment. In the industrial application, the Multicell® equipment does not need to be dismantled into the principal components of high-shear mixer and dryers. Thus, the new process can be validated in the same way as the classical equipment suitable for the production of a fixed batch size. Thus, as an example, for the development of a 30 kg batch size, i.e. for the scale-up in the fourth dimension (i.e. in the time dimension), five subunits of 6 kg mass are collected in the final bin. This bin can be used directly for further processing, which consists, for example, of adding the outer phase or just the lubricant in a gravity mixer. Afterwards the bin is transported and fixed to the tabletting machine for manufacturing the desired batch size. It has to be noted as well that for the production of the 30 kg batch, a premix of the inner phase is prepared in the starting bin, which is used as a reservoir for a pneumatic transfer of material with a subsequent dosing of 6 kg into the specially designed high-shear mixer.

Taking into account that the processed material of the initial prepared batch size (premix of 30 kg) is collected at the outlet of the Glatt Multicell® in the transport bin, it becomes evident that the process can be treated in the same way as a batch-type process. The scale-up exercise consists of the evaluation of the number X of subunit batches, which can be produced without intermediate cleaning. This number depends on the formulation. As mentioned Roche was able to produce a batch size $B = 600b$ for a recently introduced pharmaceutical product. As the Glatt Multicell® equipment can be viewed conceptually as a chain of existing unit processes, i.e. granulation in a high-shear mixer with subsequent drying in a fluidized bed system, it is not surprising that the change of a commercial product from a conventional (high-shear mixer, fluidized bed dryer) to the Glatt Multicell® production line can be considered as a minor change.

3.3. Advantages of the quasi-continuous granulation and drying line

Such a production line is successfully in operation at the Roche pharma production plant in Basel. A further developed version (ten 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 to date, the following conclusions can be derived.

4. Conclusions

The production line can be fully automated and equipped with a 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 is possible. According to 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 at the beginning of the development of the dosage form. As the early clinical batches are produced using 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 the time to market is an important issue. It is

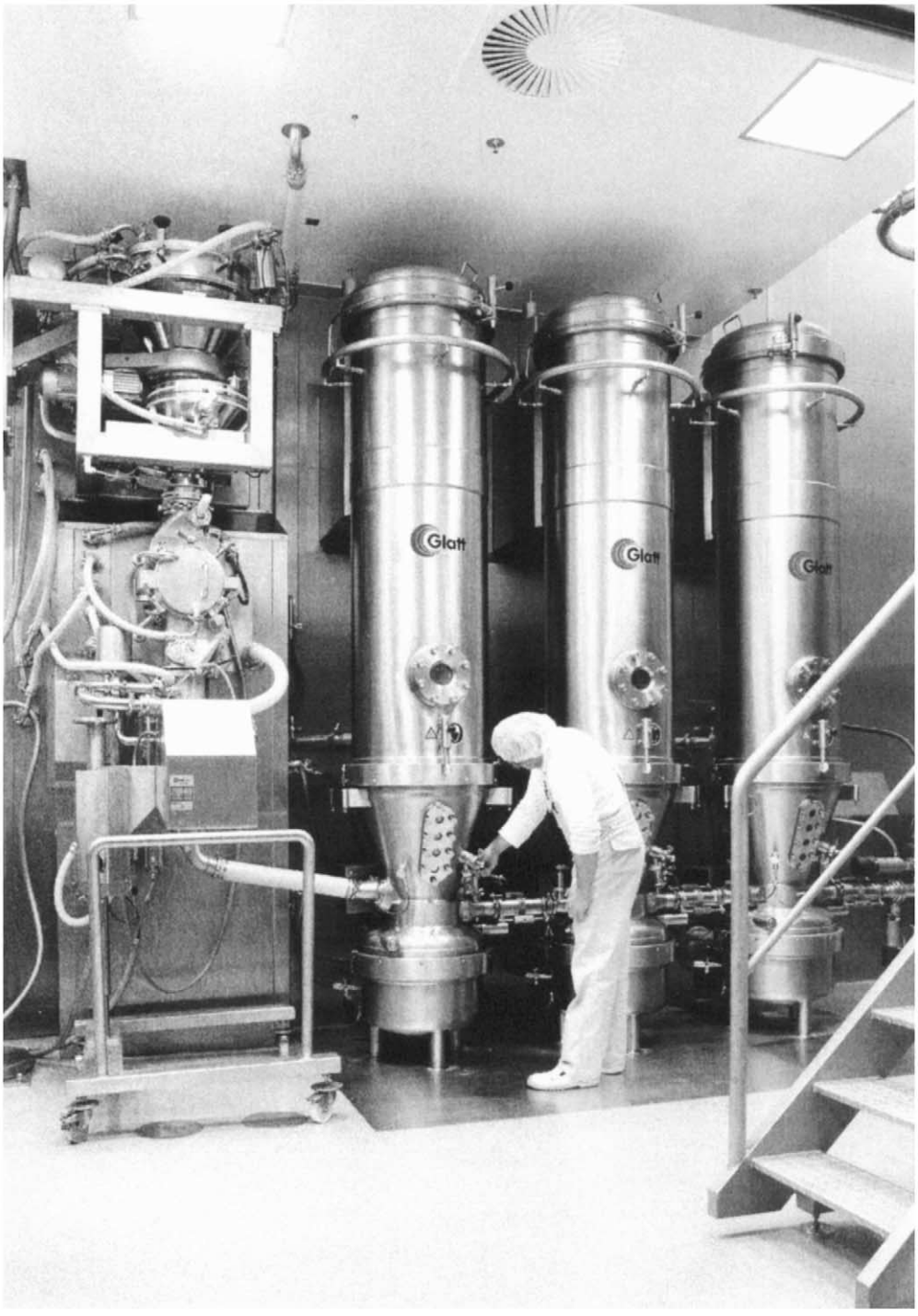

Fig. 5. Glatt Multicell® production plant at Pfizer Goedecke (Freiburg, Germany).

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 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 genomes. 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 pharmaproduction.

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