Pharmaceutical Process Scale-Up

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Scale-Up in the Field of Granulation and Drying

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I. 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 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, and aging of the tablet. In the following sections, the scale-up process is analyzed, taking into account mathematical considerations of scale-up theory [1], the search for scale-up invariants [2–5], the establishment of in-process control methods [6–9], as well as the design of a robust dosage form [10–13]. In this respect new concepts such as percolation theory [13] play an important role. Finally, a new concept concerning a quasi-continuous production line of granules is presented [14–20]. 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.

II. THEORETICAL CONSIDERATIONS

A. Principle of Similarity

1. Definition of Similarity and Dimensionless Groups

The important concept for scale-up is the principle of similarity [1–6]. When scaling up any mixer/granulator (e.g., planetary mixer, high-speed mixer, pelletizing dish) the following three types of similarity need to be considered: geometric, kinematic, and dynamic. Two systems are *geometrically* similar when the ratio of the linear dimensions of the small-scale and scaled-up system are constant. Two systems of different size are *kinematically* similar when, in addition to the systems' being geometrically similar, the ratio of velocities between corresponding points in the two systems are equal. Two systems of different size are *dynamically* similar when *in addition* to their being geometrically and kinematically similar, the ratio of forces between corresponding points in the two systems are equal.

a. Similarity Criteria. There are two general methods of arriving at similarity criteria:

1. When the differential equations, or in general the equations, that govern the behavior of the system are known, they can be transformed into dimensionless forms.
2. When the differential equations, or in general the equations, that govern the behavior of a system are not known, such similarity criteria can be derived by means of dimensional analysis.

Both methods yield dimensionless groups, which correspond to dimensionless numbers [1], e.g.:

Reynolds number Re
Froude number Fr
Nusselt number Nu
Sherwood number Sh
Schmidt number Sc etc. [2]

The classical principle of similarity can then be expressed by an equation of the form

$$\pi_1 = F(\pi_2, \pi_3, \ldots) \tag{1}$$

This equation may be a mechanistic one (case A) or an empirical one (case B).

Case A: $\pi_1 = e^{-\pi_2}$, with the dimensionless groups:

$$\pi_1 = \frac{P(x)}{P(0)}$$

where

$P(x)$ = pressure at level x

$P(0)$ = pressure above sea level ($x = 0$)

$$\pi_2 = \frac{E(x)}{RT} \tag{2}$$

with

$$E(x) = Mgx$$

where

$E(x)$ = molar potential energy
M = molecular weight
g = gravitational accelaration
x = height above sea level
RT = molar kinetic energy

Case B:

$$\pi_1 = a(\pi_2)^b \cdot (\pi_3)^c \tag{3}$$

The unknown parameters a, b, c are usually determined by nonlinear regression calculus.

2. Buckingham's Theorem

For a correct dimensional analysis it is necessary to consider Buckingham's theorem, which may be stated as follows [3,4]:

1. The solution to every dimensionally homogeneous physical equation has the form

$$F(\pi_1, \pi_2, \pi_3 \ldots) = 0$$

in which π_1, π_2, π_3 . . . represent a complete set of dimensionless groups of the variables and the dimensional constants of the equation.

2. If an equation contains n separate variables and dimensional constants and these are given dimensional formulas in terms of m primary quantities (dimensions), the number of dimensionless groups in a complete set is $(n - m)$.

III. SCALE-UP AND MONITORING OF THE WET GRANULATION PROCESS

A. Dimensionless Groups

Because the behavior of the wet granulation process cannot yet be described adequately by mathematical equations, the dimensionless groups have to be deter-

mined by a dimensional analysis. For this reason the following idealized behavior of the granulation process in the high-speed mixer is assumed:

The particles are fluidized.
The interacting particles have similar physical properties.
There is only a short-range particle–particle interaction.
There is no system property equivalent to viscosity, i.e., (1) there are no long-range particle–particle interactions and (2) the viscosity of the dispersion medium air is negligible.

According to Buckingham's theorem, the following dimensionless groups can be identified:

$$\pi_1 = \frac{P}{r^5\omega^3\rho}$$ Power number

$$\pi_2 = \frac{qt}{V\rho}$$ Specific amount of granulation liquid

$$\pi_3 = \frac{V}{V^*}$$ Fraction of volume loaded with particles

$$\pi_4 = \frac{r\omega^2}{g}$$ Froude number (centrifugal/gravitational energy)

$$\pi_5 = \frac{r}{d}$$ Geometric number (ratio of characteristic lengths)

where

P = Power consumption
r = Radius of the rotating blade (first characteristic length of the mixer)
ω = Angular velocity
ρ = Specific density of the particles
q = Mass (kg) of granulating liquid added per unit time
t = Process time
V = Volume loaded with particles
V^* = Total volume of the vessel (mixer unit)
g = Gravitational acceleration
d = Diameter of the vessel (second characteristic length of the mixer)

In principle the following scale-up equation can be established:

$$\pi_1 = a(\pi_2)^b \cdot (\pi_3)^c \cdot (\pi_4)^d \cdot (\pi_5)^e \quad (4)$$

In general, however, it may not be the primary goal to know exactly the empirical parameters *a, b, c, d, e* of the process under investigation, but to check or monitor pragmatically the behavior of the dimensionless groups (process variables, dimensionless constant) in the small- and large-scale equipment. The ultimate goal would be to identify scale-up invariants.

B. Experimental Evidence for Scale-Up Invariables

In the case of the wet granulation process in a mixer/kneader, the granulation process can easily be monitored by the determination of the power consumption [6–9] (Fig. 1).

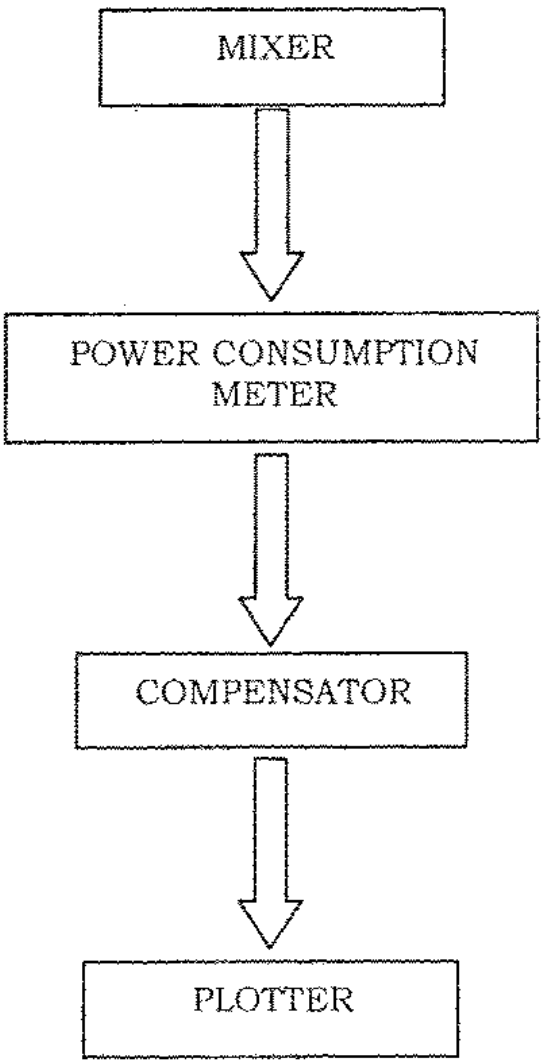


Figure 1 Block diagram of measuring equipment.

The typical power profile consists of five different phases (Fig. 2). Usable granulates can be produced in a conventional way only within the plateau region S_3–S_4 according to the nomenclature in Figure 2. As Figure 3 indicates, changing the type of mixer has only a slight effect on the *phases* of the kneading process. However, the actual power consumption of mixers of different type differs greatly for a given granulate composition.

The important point now is that the power consumption profile as defined by the parameters S_3, S_4, S_5 is independent of the batch size. For this investigation, mixers of the planetary type (Dominici, Glen, Molteni) were used. The batch size ranged from 3.75 kg up to 60 kg. To obtain precise scale-up measurements, the excipients used belonged to identical lots of primary material (10% (W/W) corn starch, 4% (W/W) polyvinylpyrrolidone as binder, and 86% (W/W) lactose). As can be seen from Figure 4, the amount of granulating liquid is linearly dependent on the batch size. During the scale-up exercise the rate of addition of the granulation liquid was enhanced in proportion to the larger batch size. Thus the power profile, which was plotted on the chart recorder, showed the characteristic S_3, S_4, S_5—values independent of batch size within the same amount of time since the start of the addition of granulation liquid. This fact is not surprising because in terms of scale-up theory, the functional dependencies of the dimensionless group numbers π_1 and π_2— were measured:

$$\pi_1 = F(\pi_2) \tag{5}$$

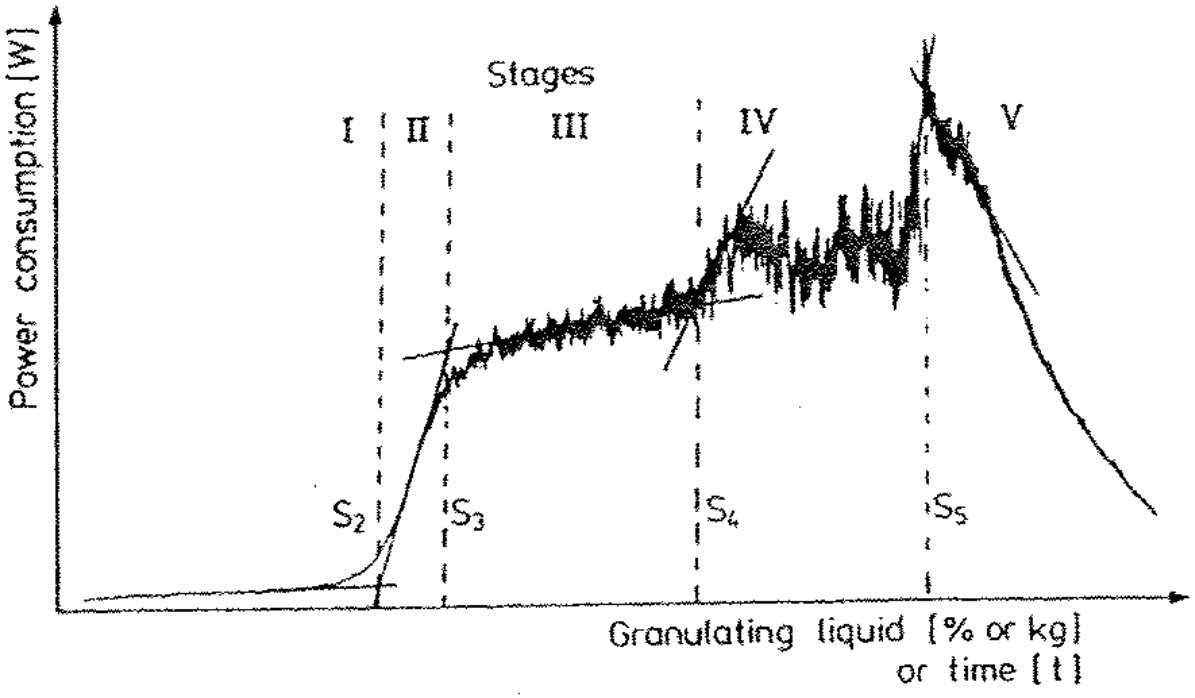


Figure 2 Division of a power consumption curve. (From Ref. 8.)

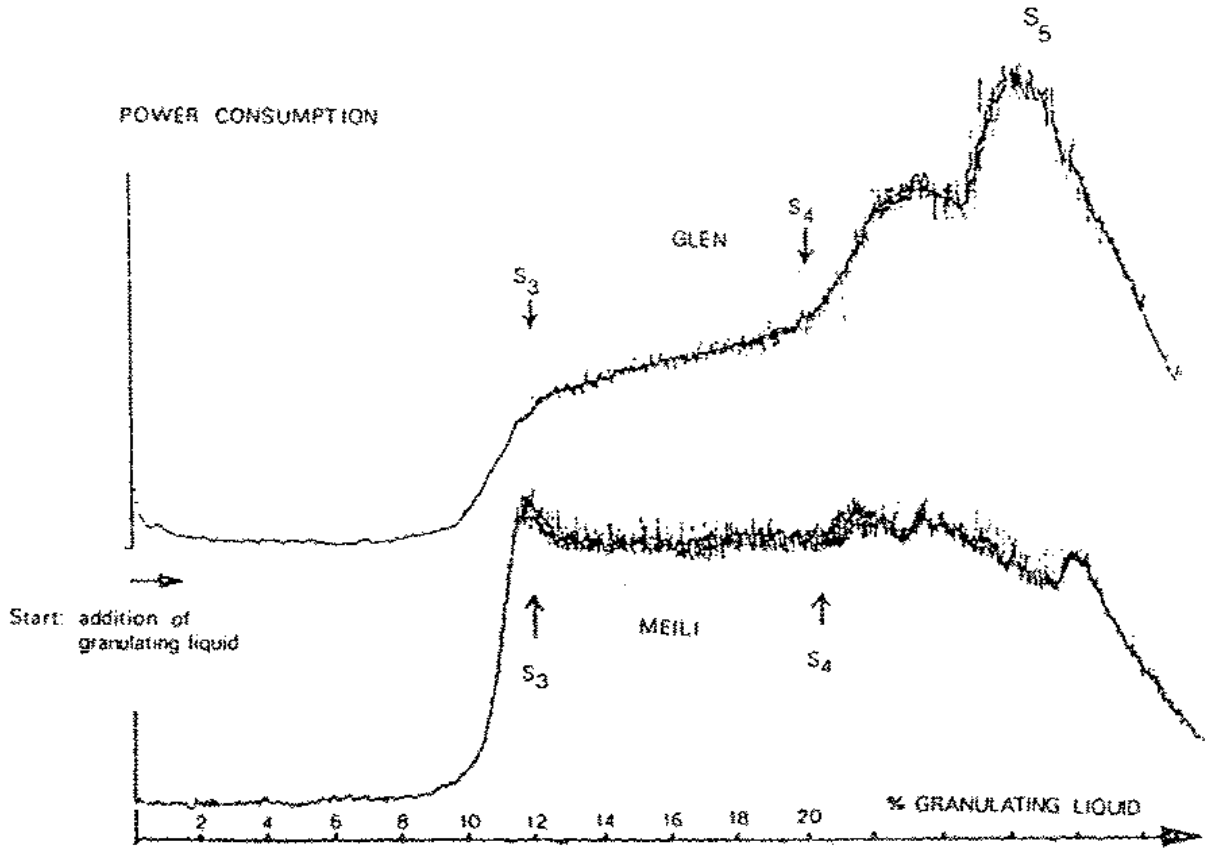


Figure 3 Power consumption profiles of two types of a mixer/kneader.

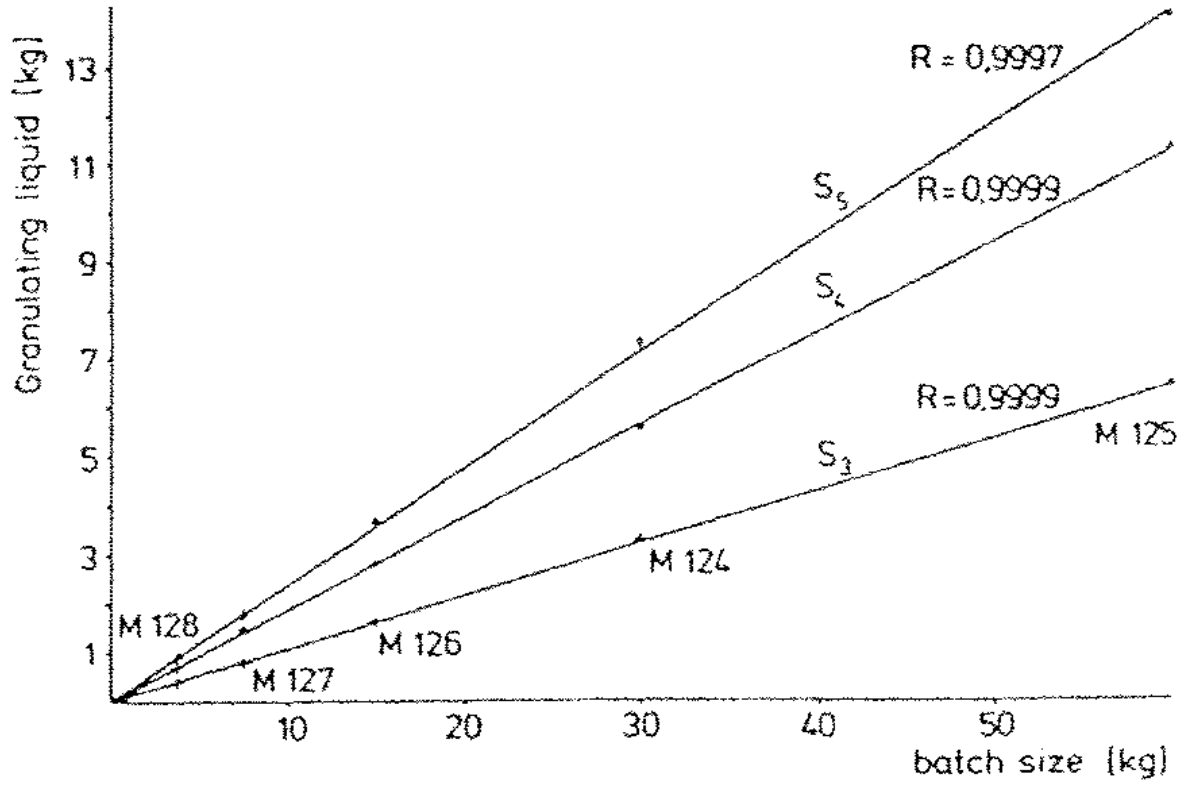


Figure 4 Scale-up precision measurements with identical charges. (From Ref. 6.)

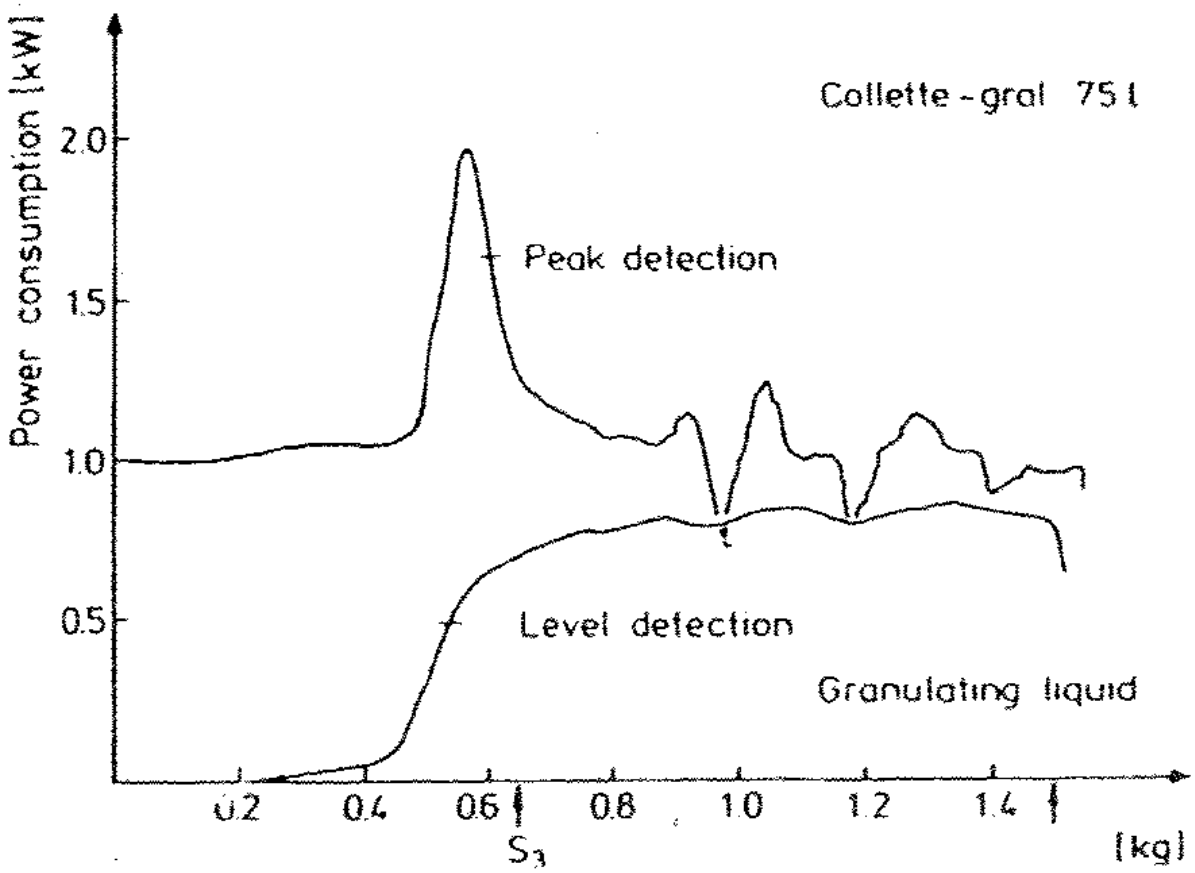


Figure 5 Power consumption profile of a high-speed-mixer (Collette–Gral 75 l) with peak and level detection. (From Ref. 8.)

The other numbers π_3, π_4, π_5, were kept essentially constant. From these findings one can conclude that the correct amount of granulating liquid per amount of particles to be granulated is a scale-up invariable [6–9]. It is necessary, however, to mention that during this scale-up exercise only a low-viscous granulating liquid was used. The exact behavior of a granulation process using high-viscous binders and different batch sizes is unknown. It is evident that the first derivative of the power consumption curve is a scale-up invariant and can be used as an in-process control and for a fine-tuning of the correct amount of granulating liquid (see Fig. 5).

C. Use of the Power Consumption Method in Dosage Form Design

Robust formulations are today an absolute prerequisite. Concerning the production of granules, the granule size distribution should not vary from batch to batch. The key factors are the correct amount and the type of granulating liquid. The interpretation of the power consumption method can be very important for an optimal selection of the type of granulating liquid. The possible variation of the initial particle size distribution of the active substance and/or excipients can be compen-

sated in case of an intelligent in-process control method, e.g., based on the power consumption profile (see Table 1). However, the formulation may not be very robust if the volume-to-volume ratio of certain excipients, such as maize starch and lactose, correspond to a critical ratio or percolation threshold.

With dosage form design it is often necessary to compare the performance of two different granule formulations. These two formulations differ in composition and as a consequence vary also in the amount of granulating liquid required. Thus the following question arises: How can the quantity of granulating liquid be adjusted to achieve a correct comparison? The answer is not too difficult, because it is based on identified physical principles. A correct comparison between two formulations is often a prerequisite because the dissolution process of the active substance in the final granulate or tablet can be affected by both the amount of granulating liquid and the qualitative change (excipients) in the formulation. In order to calculate corresponding, i.e., similar amounts of, granulating liquid in different compositions, it is necessary to introduce a dimensionless amount of granulating liquid π. This amount π can be defined as degree of saturation of the interparticulate void space between the solid material:

$$\pi = \frac{S - S_2}{S_5 - S_2}$$

where

S = Amount of granulating liquid (in liters)

S_2 = Amount of granulating liquid (in liters) necessary, which corresponds to a moisture equilibrium at approx. 100% relative humidity

S_5 = Complete saturation of interparticulate void space before a slurry is formed (amount in liters)

Power consumption is used as an analytical tool to define S values for different compositions. Thus the granule formation and granule size distribution of a

Table 1 Comparison Between the Manual and the Automatic Mode of Controlling the Moist Agglomeration Process

Type of mode	Yield (% w/w) 90–710 μm	% Undersize <710 μm	% Undersize <90 μm
Manual mode, $n = 20$ batches	82.03 ± 2.42	88.30 ± 2.05	6.80 ± 0.51
Automatic mode, $n = 18$ batches	91.45 ± 0.36	96.80 ± 0.31	5.40 ± 0.35

Source: Ref. 9.

Table 2 Physical Properties of Lactose and Corn Starch

Property	Lactose	Corn starch
Bulk density (g/cm^3)	0.58	0.49
Tapped density (g/cm^3)	0.84	0.65
True density (g/cm^3)	1.54	1.50
S_m (mass specific surface) (cm^2/g)	3055	
Mean diameter (μm)	40	25

binary mixture of excipients are analyzed as a function of the dimensionless amount of granulating liquid π. This strategy allows an unbiased study of the growth kinetics of granules consisting of a single substance or of a binary mixture of excipients. Thus it is important to realize that the properties of the granule batches are analyzed as a function of the dimensionless amount of granulating liquid [6–9].

1. Materials

The physical characteristics of the starting materials are compiled in Table 2. Polyvinylpyrrolidone was added in a dry state to the powder mix of lactose and corn starch at a level of 3% (w/w). As a granulating liquid, demineralized water was used and pumped to the powder mix at constant rate of 15 g $min^{-1}kg^{-1}$.

2. Methods

The principle of power consumption method was described in detail in Refs. 6–9 and 14. As a high-shear mixer, a Diosna V 10 was used, keeping constant impeller speed (270 rpm) and chopper speed (3000 rpm) during the experiments.

In order to reduce the possible effects of friability or second agglomeration during a drying process in dish dryers on the granule size distribution as a function of the amount π of granulating liquid added, the granules are dried for 3–5 min in a fluidized bed (Glatt Uniglatt) and subsequently for 15–25 min in a dish dryer to obtain moisture equilibrium corresponding to 50% relative humidity of the air at ambient temperature (20°C). The particle size distributions were determined according to DIN 4188 using ISO-norm sieve sizes [9].

IV. ROBUST FORMULATIONS AND DOSAGE FORM DESIGN

In the case of binary mixtures consisting of different substances, which, individually, may have a considerable effect on the physical properties (e.g., electrical con-

ductivity) of the final product (granules, tablets, etc.), the ratio of components is essential. Thus with a mixture between Al_2O_3 (an electrically insulating material) and copper powder, electrical conductivity of the Al_2O_3/copper tablet is observed only if the copper powder forms an electrical pathway between the electrodes attached to the surface of the tablet produced. The critical ratio where conductivity is measured corresponds to the so-called percolation threshold p_c [10]. In the case of a fixed normalized amount π of granulating liquid, it is interesting to note that the granules obtained from a lactose/corn starch powder mixture lead to granule size distributions equivalent to the granule size distribution of either lactose or corn starch. This result can be interpreted on the basis of percolation theory (Fig. 6), i.e., that the properties differ for compositions below or above a critical ratio p_c of components between lactose and corn starch (Table 2).

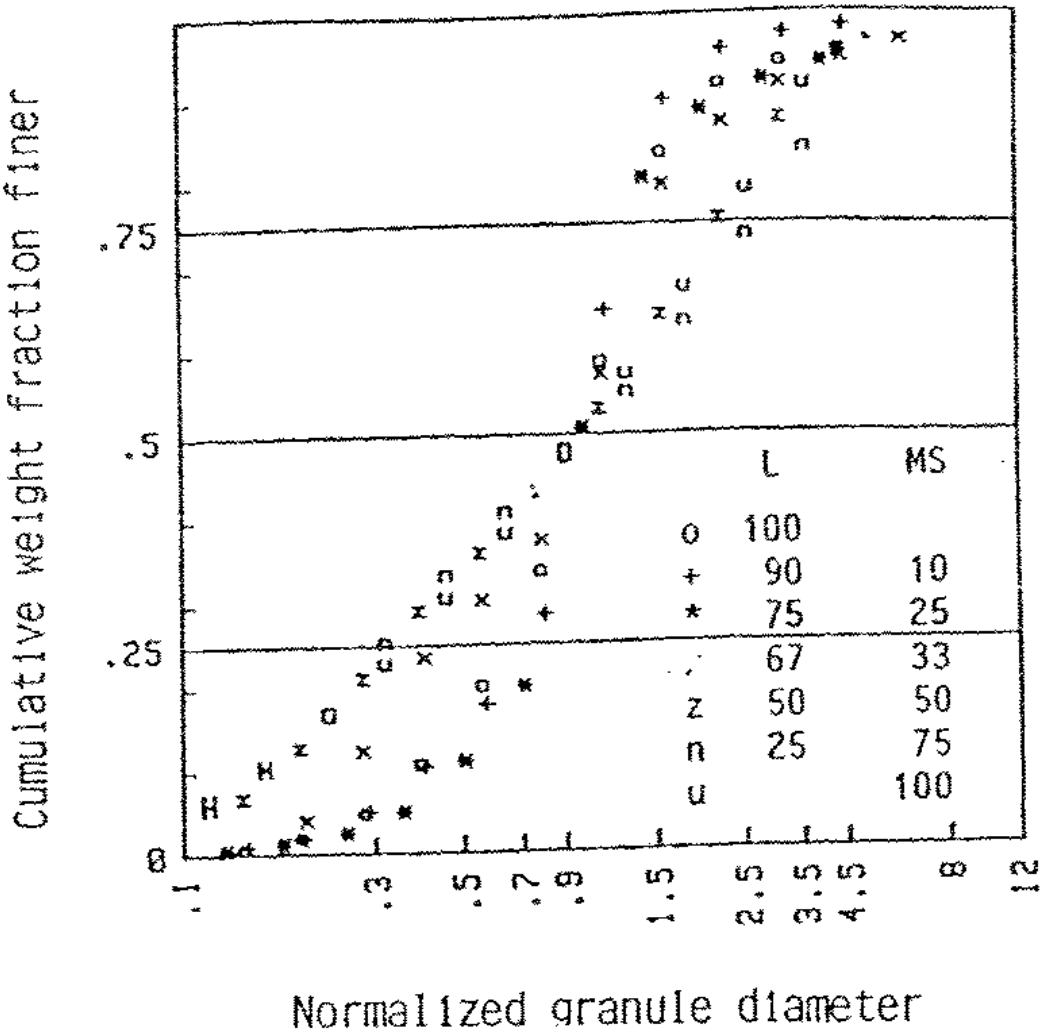


Figure 6 Cumulative particle size distribution of the agglomerates at a fixed normalized amount π (= 0.62) of granulating liquid for different ratios of the binary powder mixture lactose/corn starch.

V. A QUASI-CONTINUOUS GRANULATION AND DRYING PROCESS (QCGDP) TO AVOID SCALE-UP PROBLEMS

A. Continuous Processes and the Batch Concept

In the food and chemical industries, continuous production lines play an important role, whereas pharmaceutical industry production is based mainly 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 hours. On the other hand, continuous processes offer two important advantages: (1) there is no difficult scale-up exercise necessary for larger "batches"; (2) a 24-hour automatic production line should be possible.

B. Development 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 [15–18]. The principle of this quasi-continuous production line is based on a semicontinuous production of minibatches in a specially designed high-shear mixer/granulator connected to a continuous multicell-fluidized-(Glatt Multicell®) bed dryer (see Fig. 7).

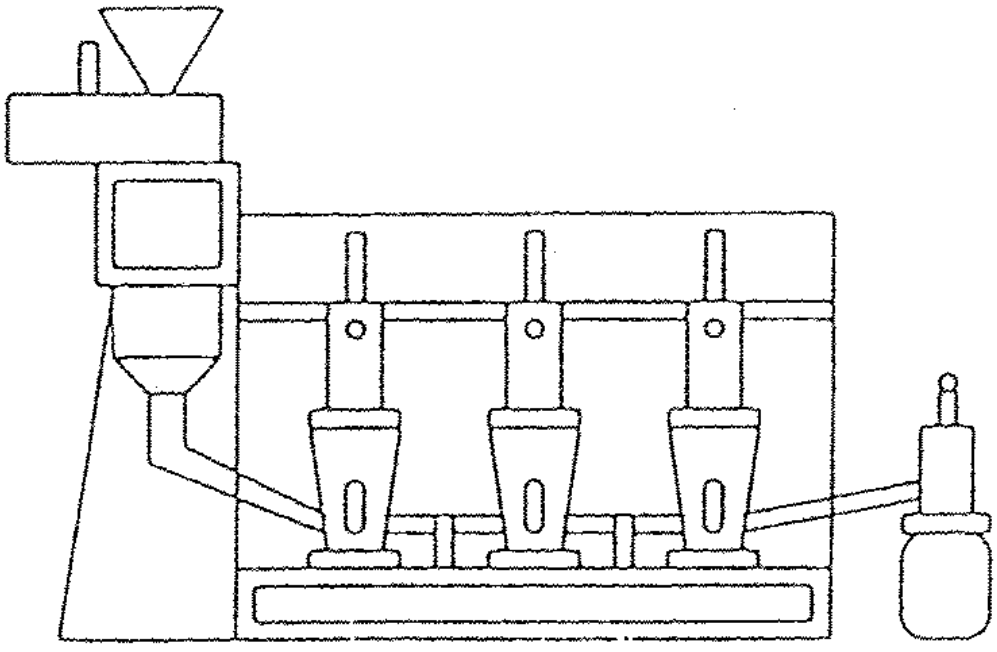


Figure 7 A quasi-continuous production line for granules with three drying cells (Glatt AG, CH-4133 Pratteln).

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 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 and thoroughly mixed. Subsequently this amount of powder is granulated by continuously adding granulating liquid up to a fixed amount. The ideal amount of granulating can be defined according to the results of a power consumption measurement [6–9]. Afterwards the moist granules are discharged through a screen into the first cell of the multicell-fluidized-bed dryer unit to avoid any formation of lumps. Thus the quasi-continuous production of granules can be described as a train of minibatches passing like parcels through the compartments of dry mixing, granulation, and drying. The multicell dryer consists in general of three cells 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.

Due to this principle, a batch defined for quality control purposes consists of a fixed number of n minibatches. Thus a tight in-process control of the mixing/granulation [6–9] and drying step [14] 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 [14–20].

Thus, based on the positive results obtained with the thesis work of Schade and Leuen berger [15] and B. Dörr [17] 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–Country in 1994.

The system provides a new possibility for industrial manufacturing and galenical development of pharmaceutical solids specialties and has following purposes: to make possible automated, unattended production, 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 and validated faster, and the quality of granules, tablets, and kernels compared to common production is equal or better. Different solids specialties have been tested and validated.

1. Goals of the Quasi-Continuous Granulation and Drying Line

a. Unattended Production. One of the general aims of quasi-continuous granulation and fluid-bed drying is unattended production. The production of

small subunits of 7–9 kg instead of a whole batch allows an automated, iterative granulation and drying procedure. The division of the process into different compartments (mixing, sieving, and drying compartments) guarantees the reproducibility of the galenical properties of each subunit.

b. No Necessity for Scale-Up Experiments. The granulation and drying of subunits of 7–9 kg instead of a whole batch leads to the possibility of using the plant for laboratory and production scale, because the batch size is no longer characterized by 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.

c. Simplification of Manufacturing Procedures. Existing manufacturing procedures can be taken over from common equipment without changing components. In certain cases it's possible to simplify the procedures. The small mixer size and the geometry of the mixing elements allow the binders to be added to the premixture and granulation just with water.

d. Identical or Better Quality of Granules and Tablets. The quality of the produced granules and tablets has to be equal or better and fulfill product specifications.

2. Results

Constant values and the reproducibility of the process are important benefits of quasi-continuous granulation. The tests could also show equal or better quality of granules and tablets compared to common granulation equipment (Diosna P-600 high-speed granulator). Figures 8–13 show the results obtained during the devel-

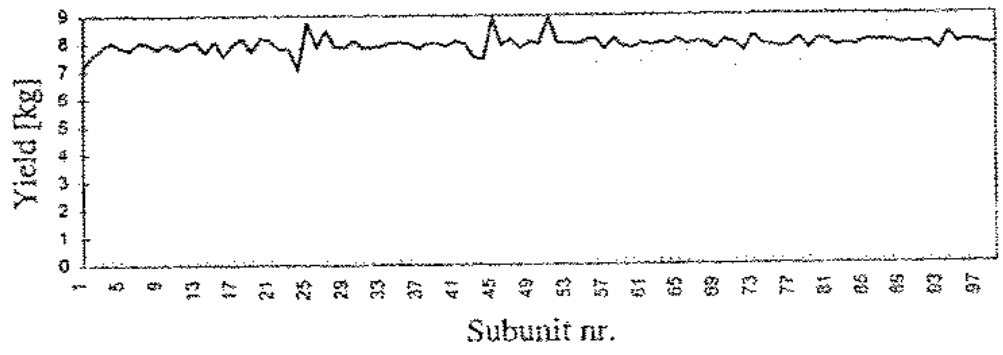


Figure 8 Yield (Formulation 1).

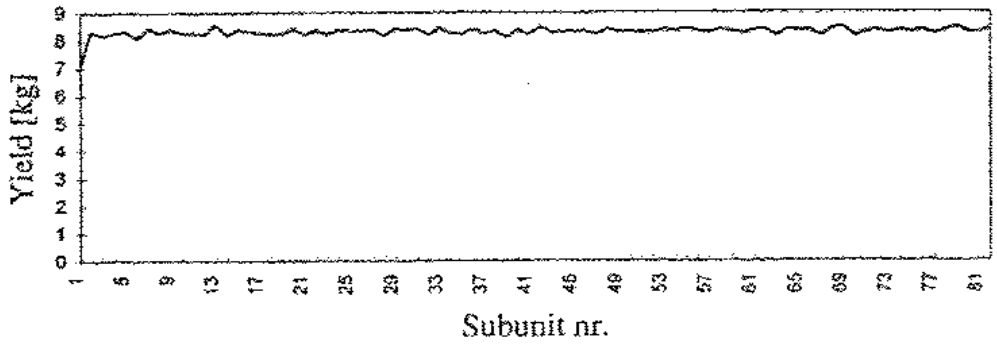


Figure 9 Yield (Formulation 2).

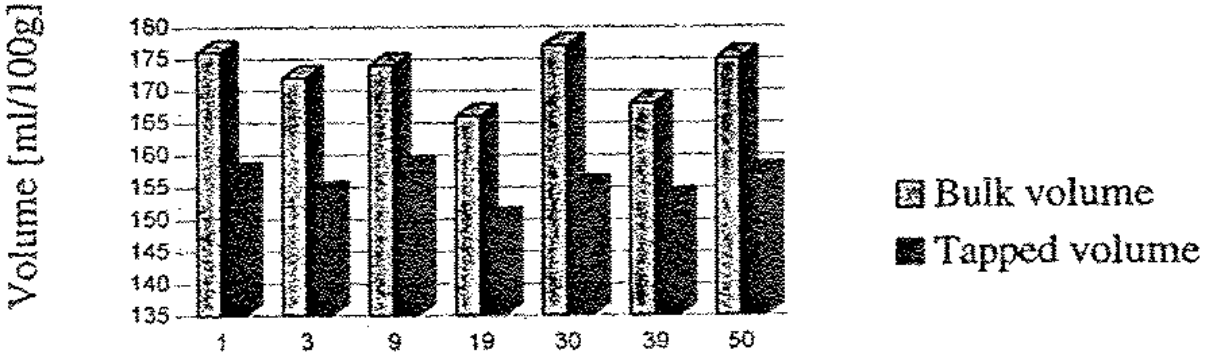


Figure 10 Bulk volume/tapped volume (Formulation 1).

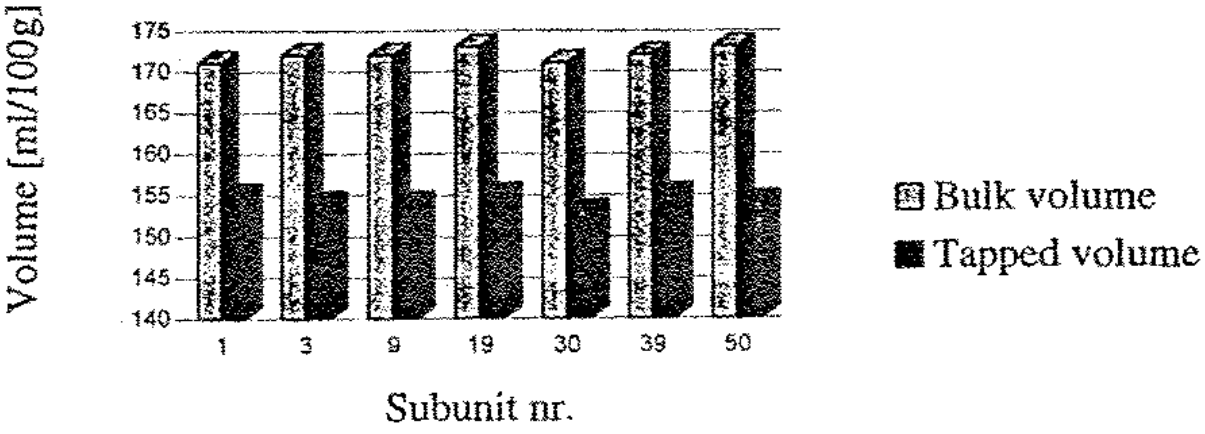


Figure 11 Bulk volume/tapped volume (Formulation 2).

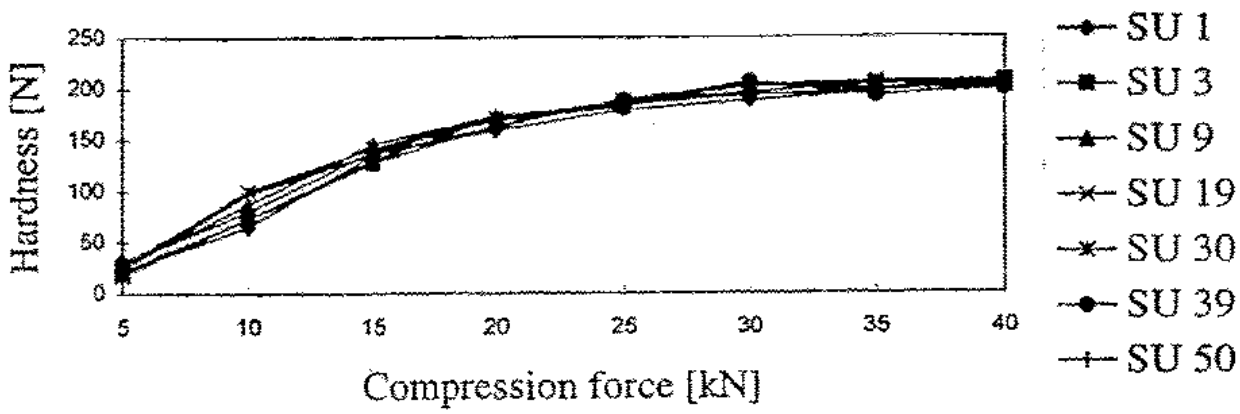


Figure 12 Compression force/hardness profile (Formulation 1).

opment of the equipment, where the high-shear mixer/granulator was operated separately from the subsequent drying system. The tests show the performance of the individual minibatches as a function of the subunit number. Because the subunits are collected in the container (see Layout 1) for the preparation of the final tablet blend, these tests are not necessary with the fully equipped quasi-continuous system.

In case of the yield (e.g., mass) per subunit, a negative deviation from the mean was followed by a positive deviation, showing the "self-cleaning" property of the mixer (Figs. 8–9). This test is not needed if the system is

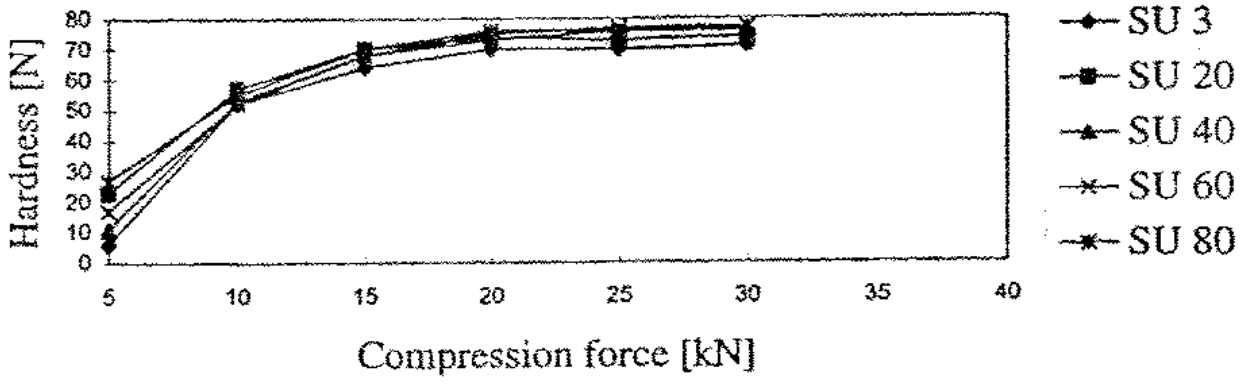


Figure 13 Compression force/hardness profile (Formulation 2).

equipped with an in-process control based on power consumption measurement [6–9].

3. Materials and Methods

a. Materials.

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

b. Production Parameters.

Subunit size: 7.0 kg
Rotational speed of mixer: 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 sec (Formulation 1); 90 sec (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/hr

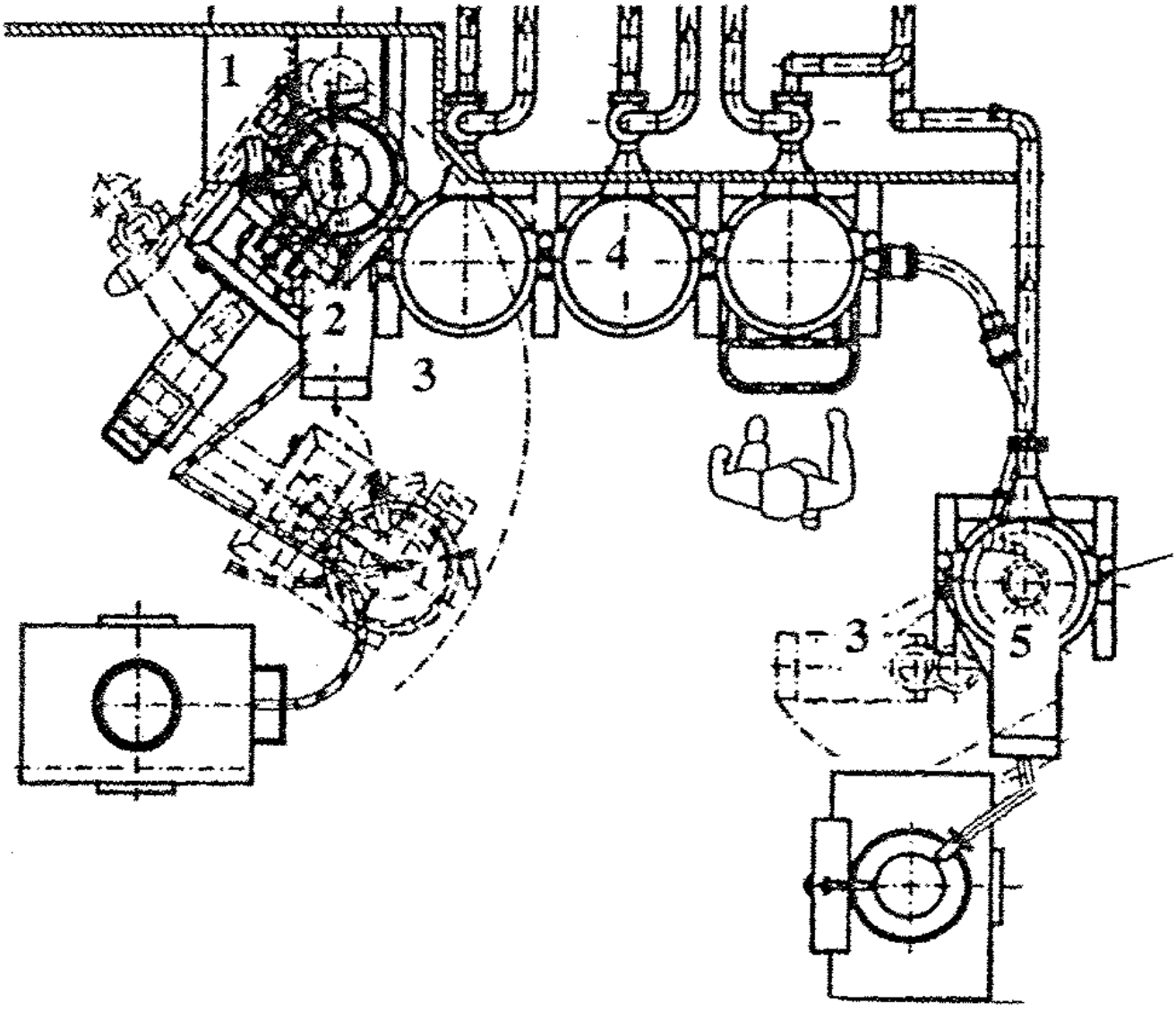
c. Test Methods.

Relative humidity (Rotronic® hygroscope)
Loss on drying (Mettler® LP 16/PM 480 Deltarange infrared balance)
Sieve analysis (Fritsch® Analysette laboratory sieving machine)
Bulk volume/tapped volume (Jel STAV® 2003 volumeter)
Compression force/hardness profile (Manesty® Deltapress tableting machine with Tegimenta® Pharmatest PTB 301 hardness tester)
Hardness (Tegimenta® Pharmatest PTB 301 and Kramer® Computest hardness tester)
Disintegration time (Tegimenta® Pharmatest PT 21 and Kramer® DES-2A disintegration tester)
Friability/abrasion (Roche® friabilator)

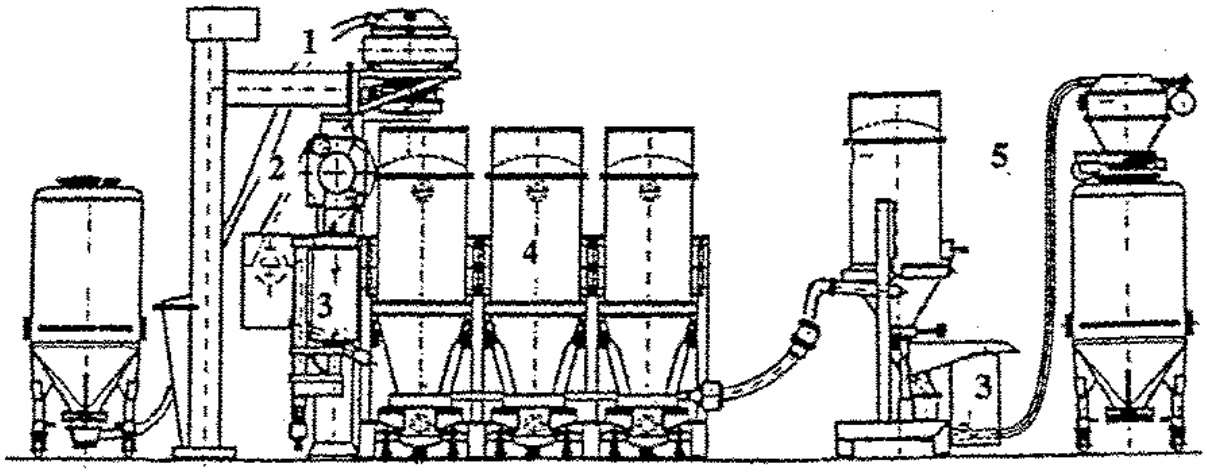
VI. DESCRIPTION OF THE PRODUCTION PLANT

The Glatt Multicell® unit for quasi-continuous granulation and fluid-bed drying (see Layouts 1 and 2) consists of the following elements: a transport and dosage system for mixer filling (1), a horizontal high-speed plough-share mixer (subunits of 4–9 kg of premixture can be granulated) with an airless spray pump for the granulation liquid (2), rotary sieving machines for wet and final sieving (3), a three-chambered fluid-bed dryer for predrying, final drying, and cooling down to room temperature (4), a transport system to collect the granulated subunits in a container (5), and an integrated washing-in-place or cleaning-in-place (CIP) system.

A. Layout



Layout 1 Top view of the Glatt Multicell®.



Layout 2 Front view of the Glatt Multicell®.

1. Transport and dosage system for mixer filling
2. Horizontal high-speed plough-share mixer
3. Rotary sieving machines for wet and final sieving
4. Three-chambered fluid-bed dryer
5. Transport system

B. Advantages of the Quasi-Continuous Granulation and Drying Line (Glatt Multicell®)

Such a production line is now successfully in operation at the Roche pharma production plant in Basel. A further-developed version has been installed at the technology center at Goedecke (Pfizer Group) in Freiburg, Germany. From the experience obtained so far the following conclusions can be drawn: The production line can be fully automated and equipped with a a CIP (cleaning-in-place) 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 need, 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 even at the beginning of the development of the dosage form. Because 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 get to market can be reduced.

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