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Invited review paper

Pharmaceutical powder technology — from art to science: the challenge of the FDA's Process Analytical Technology initiative

H. LEUENBERGER* and M. LANZ

Institute of Pharmaceutical Technology, Pharmacenter of the University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland

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Abstract—This paper describes with typical examples the state of art. The list of examples includes the problems of non-robust formulations and critical processes. The paper demonstrates the necessity and the challenge of the FDA's Process Analytical Technology initiative, which is an important stimulus to develop a rigorous scientific framework in the area of pharmaceutical powder technology. The paper suggests a kind of 'road map' to achieve as fast as possible the top of the 'knowledge pyramid'. The road map includes the extensive use of a multivariate design of experiments, the use of artificial neural networks (ANN), the use of the laws of physical pharmacy and percolation theory, and, last but not least, tries to 'translate' the existing laws of physical chemistry into the area of pharmaceutical powder technology, where we have the problem that the number of particles involved is much lower than the Avogadro number N_A. For this reason it will be of interest to monitor closely the progress in nanoscience, especially in the area of mathematical modeling of the fascinating special physical properties of nanoparticles, which again consist of a finite number N of atoms, respectively molecules, with $N \ll N_A$.

Keywords: PAT initiative; robust formulations; design of experiments; artificial neural networks; percolation theory; granulation end-point; freeze-drying; scale-up; first principles.

1. INTRODUCTION

Powder technology is as old as mankind and has been used in a broad field of industrial activities, including as food preparation, ceramics, glass and building technology [1]. Some people consider powder technology as the second oldest profession of mankind (see Fig. 1). In many areas powder technology is still considered as

Dedicated to Drs Ajaz Hussain and Janet Woodcock, FDA, initiators of the PAT initiative and the new concept of quality assurance in the 21st century.

*To whom correspondence should be addressed. E-mail: Hans.Leuenberger@unibas.ch

an art and not a science. However, there is no rule without an exception: some industrialized food production processes are high-tech exercises leaving far behind the process performance in pharmaceutical industry (see L. Abboud and S. Hensley, New prescription for drug makers, *The Wall Street Journal*, 3 September 2003; J. Carey and M. Arndt, Making pills the smart way, *Businessweek*, 3 May 2004). The problem is that pharmaceutical formulations are in fact complex systems consisting not only of the active drug substance, but also of a number of excipients in order to fulfill the goals of such a dosage form. Thus, for example, a tablet needs to have a convenient size, to be easily swallowable, to have adequate hardness, to be (if necessary) easily dividable into two parts, to have an adequate physical, chemical and microbiological stability leading to an adequate shelf life (3–5 years), to contain the correct amount of drug substance, to show minimal friability, to have the correct disintegration time in the gastro-intestinal fluid, and to show a reproducible and appropriate dissolution profile of the drug substance. We omit in the following discussion the necessary tests for the *in vivo* performance (pharmacokinetics, pharmocodynamics, minimizing side-effects, etc.). The development of such a medication is complex and can be compared to the development of an aircraft with the goal to transport all passengers (i.e. exact amount of drug) to the right destination at the right time. In practice pharmaceutical powder technology, e.g. the formulation of solid dosage forms with powder (active drug substance, excipients) as starting material, is still considered as an art. The transformation from art to science began only in the middle of the last century and, in central Europe, is related to the scientific work of Hans Rumpf [2]. Thanks to the Process Analytical Technology (PAT) initiative of the American Food and Drug Administration (FDA) it can be expected that the change of pharmaceutical powder technology from an 'art to a science' [3] will be accelerated. FDA pushes forward the PAT initiative (http://www.fda.gov/cder/OPS/PAT.htm) for very good reasons: the variability of most pharmaceutical processes needs to be reduced. The performance

Figure 1. 'Powder technology' in ancient Egypt illustrating the 'threshing process'. Picture from a wall painting in the tomb of Menna, Thebes: from L. Casson, *Ancient Egypt*. Time-Life Books, New York (1975).

of a manufacturing process can be described by its Sigma Value. The champion is the chip industry with a Six Sigma Value, i.e. with an amount of defective samples $\leqslant 2$ p.p.b. which is a prerequisite to guarantee the functioning of our computer hardware. It is surprising, that the pharmaceutical manufacturing performance is only about Two Sigma, which corresponds to around 4.6% defectives, creating high costs. The White Paper 'Innovation or Stagnation' published by the FDA in March 2004 (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html) goes beyond the original PAT initiative, identifying three areas of research and development which need to be improved: 'Assessing Safety', 'Demonstrating Medical Utility' and, last but not least, 'Industrialization'. The paper focuses on the fact that the actual drug discovery activities are today a high-tech business, but that the above-mentioned three areas to bring the drug successfully to the market are still low tech and need improvements. The FDA describes these three areas as the three dimensions in the critical path from the discovery of the drug substance to the market place. Solid dosage forms such as tablets are the most desired types of medication and represent the majority in the market place. Thus, pharmaceutical powder technology plays a major role in this 'industrialization process'. In fact, research promotion in this area should be a rewarding investment. What are the reasons for the relative low Sigma Value of pharmaceutical manufacturing processes? What are the sources of the relatively high variability of processes and of the product quality? As already mentioned, one of the major problems consists of the fact that pharmaceutical formulations are complex systems and that they are often developed empirically under a high time-pressure on the basis of 'trial and error' experiments (see Fig. 2). This procedure can easily lead to a non-robust formulation. The situation is complicated by the fact that in addition many pharmaceutical processes are only poorly understood. Thus, the predictability of the manufacturing performance is suffering or completely absent. The goal of the FDA's PAT initiative is to achieve scientifically based decisions, i.e. to design the quality of the product and not to 'test-in' the quality by eliminating the bad items at the end of the production, cre-

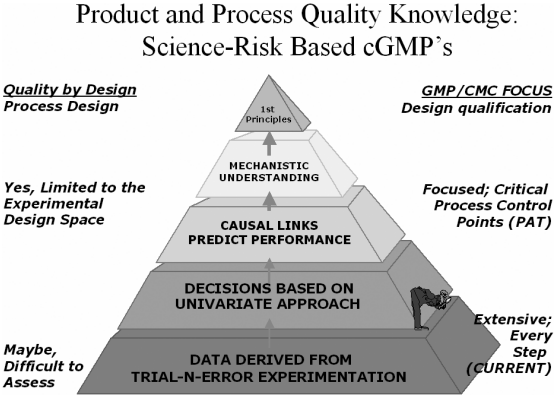

Figure 2. Product and process quality knowledge (courtesy Dr. A. Hussain, FDA).

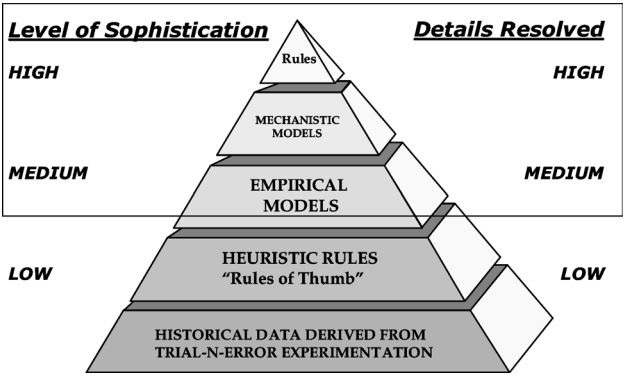

Figure 3. Knowledge pyramid (courtesy Dr. A. Hussain, FDA).

ating waste of time and money. The best solutions could be obtained if mechanistic models or even first principles in the knowledge pyramid (see Fig. 3) are known. The following sections describe typical examples in pharmaceutical powder technology to illustrate different levels of knowledge as steps of the knowledge pyramid (see Fig. 3).

2. EXAMPLES ILLUSTRATING THE KNOWLEDGE PYRAMID

2.1. Capsule formulation in early clinical trials — a case study [4]

It is evident that only a low amount of active substance is used in the first clinical trials. Subsequently, the dose will be increased to find the optimal therapeutic effect with a minimum of side-effects. For this purpose the amount of drug substance is increased and the amount of filler, usually lactose, is decreased in the powder mixture which is filled into the hard gelatin capsule as a standard formulation. Figure 4 shows the dissolution profile for the drug substance for three different drug contents of a specific capsule formulation as an example. In the case of the first low dose, a rapid dissolution is observed. The dissolution profile is obtained as a result of a 'trial and error' formulation. As the dissolution profile for the lowest dose was excellent, leading to excellent bioavailability, there was no immediate incentive to develop a more complicated dosage form such as a tablet. At a later stage the amount of drug in the capsule formulation had to be increased with the result that the dissolution slowed down. Thus, only a fraction of this drug content was absorbed *in vivo* and the bioavailability suffered. Consequently, it was necessary to develop a robust tablet formulation with a dissolution profile of the drug that was independent of the drug load (see Fig. 5). Such effects are not uncommon and often are the results of simple 'trial and error' experiments. Due to lack of time it is often not possible to explore the reasons for the behavior of the capsule versus the tablet formulation [4].

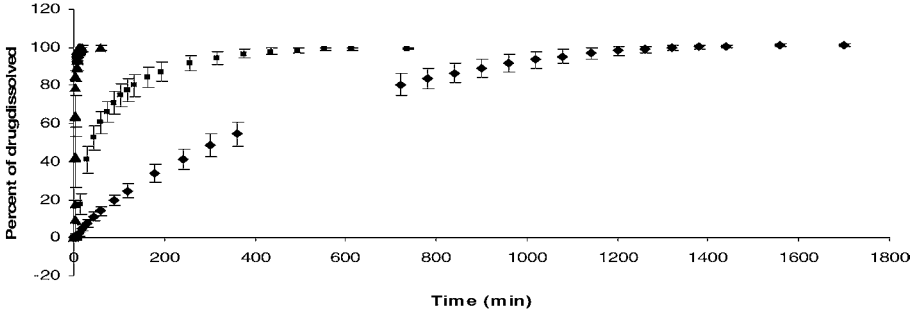

Figure 4. Dissolution profile for the drug substance for three different drug contents [▲: 10; ■: 50 and ◆: 70% (w/w)] in a capsule formulation.

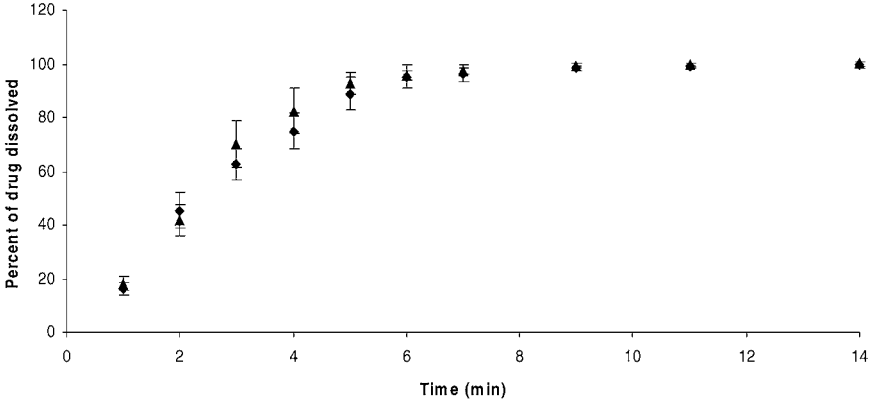

Figure 5. Dissolution profile for the drug substance for two different drug contents [▲: 50 and ◆: 70% (w/w)] in a tablet formulation.

2.2. Response surface methodology (RSM)

A tablet formulation is a complex system, which contains the drug substance, usually a hydrophilic filler such as lactose, a disintegrant such as cornstarch, a lubricant such as magnesium stearate and maybe a flow-regulating excipient such as silicium dioxide (Aerosil®). Unfortunately, the quality of the ingredients may vary slightly, leading to a variability of the properties of the tablet such as hardness, disintegration time, dissolution profile, etc. Thus, in a first approximation a qualitative change of a component may have the same result as a quantitative change of the amount of the original component in the formulation. In such a case it is of interest to vary the composition of the formulation and to explore the sensitivity of the properties of the dosage form as a result of the quantitative change of the components. Figure 6 shows the results obtained with a central composite design [5] in case of a tablet formulation. If the results are plotted in three dimensions, the meaning of the RSM becomes evident. In the case of a robust formulation, the response surface has to be flat. It has to be kept in mind that the use of statistical experimental design leads to a descriptive mathematical model,

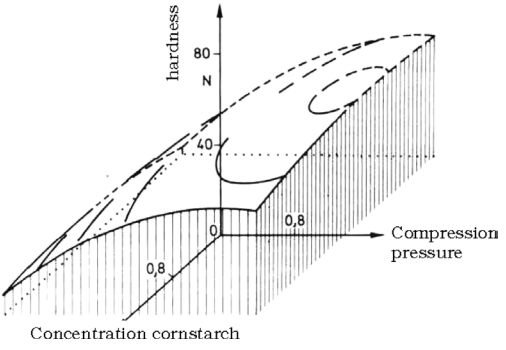

Figure 6. Response surface with a local maximum [5].

which is an approximation within a limited space of the variables (factors). The approximation may contain only linear or also quadratic (etc.) terms depending on the specific design of experiments.

2.3. The use of ANN [6]

As already mentioned, the choice of the statistical design of experiments (DoE) leads in general to a linear (factorial design) or quadratic (central composite design) regression model, which permits the prediction of system properties (RSM) within the variable space. The use of ANN goes beyond the application of the statistical DoE as historical data can be included in the analysis. The proper use of ANN can lead to additional conclusions due to its classification power based on Kohonen networks, such as self-organizing feature maps: SOFM-MLP (Multiplayer Perceptron) [7].

However, it makes sense to use both techniques, i.e. RSM and ANN. Thus historical data and the data of RSM (for validation of ANN) can be analyzed by ANN. The following example concerns the simultaneous use of RSM and ANN (SOFM-MLP and GFF-MLP) in the case of tablet formulation [7, 8]. The values of the mechanical stability of the tablet, i.e. the hardness Generalized Feed Forward-Multilayer Perceptron (GFF-MLP), can be easily predicted by the GFF-MLP. However, in the case of the important biopharmaceutical tablet property of '*in vitro* dissolution of the drug' the classification power of SOFM-MLP becomes evident: modelling is only possible by taking into account the batch number (see Table 1). Unfortunately, the batch number is useless for the prediction of the properties of future batches to be manufactured. The results show that there is an effect of the batch number, i.e. there is batch-to-batch variability, which needs to be studied in detail to find the reason for this.

As an ultimate goal, the use of DoE and ANN leads to the creation of expert systems including general rules as a valuable tool in the development of robust formulations (see Fig. 7).

Table 1.
R^2 results for the tablet compression study for the modeling of the 'dissolution of a drug' with two networks (GFF-MLP and SOFM-MLP) and the RSM [8]

	GFF-MLP	SOFM-MLP	RSM
Percentage of drug dissolved after 15 min (%)			
R^2 without factor 'batch'	0.2589	0.1040	0.1366
R^2 with factor 'batch'	0.8809	0.8775	0.8679
Time to 50% drug dissolution (min)			
R^2 without factor 'batch'	0.3411	0.2942	0.2739
R^2 with factor 'batch'	0.8709	0.8536	0.8449

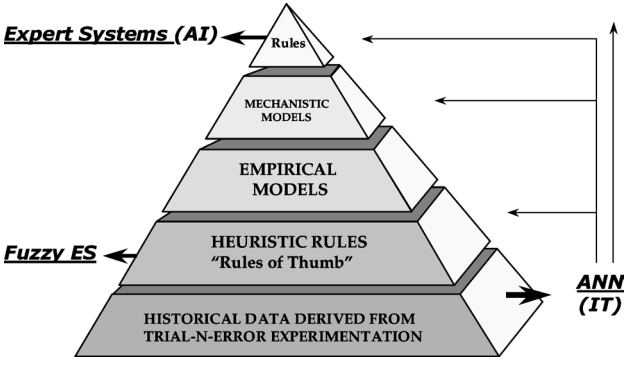

Figure 7. Artificial intelligence and information technology can improve the utility of historical data (courtesy Dr. A. Hussain, FDA).

2.4. Robust formulations and the application of percolation theory [9]

It is generally accepted that an oil-in-water (O/W) emulsion has totally different properties to a water-in-oil emulsion (W/O), as we have either water or oil as a continuous phase. It is astonishing that many people do not make a distinction between a drug-in-excipient (D/E) and an excipient-in-drug (E/D) powder system. In the case of a poorly wettable drug and a hydrophilic filler such as lactose the formulation becomes non-robust close to the critical concentration, where the component starts to percolate (percolation threshold [10]). In case of a corn starch/lactose granule formulation the shape of the normalized granule size distribution depends on the dominating outer phase of the two components (see Fig. 8). The size distribution assumes a linear or an S-shaped behavior close to the critical concentration.

2.5. The problem of an intrinsic process variability: the heat transfer process in classical lyophilization

Classical lyophilization is an important process, and is often used for the formulation of first-class temperature- and structure-sensitive drugs of biological origin (biopharmaceuticals, biologicals). Unfortunately, the classical lyophilization proce-

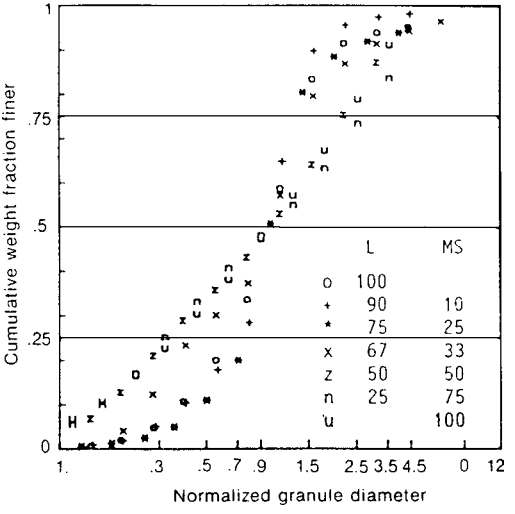

Figure 8. Cumulative particle size distribution at $p = 0.62$ for different ratios of the binary mixture lactose (L)/corn starch (MS). The granule diameter is critically linked to the concentration ratio (percolation effect!) [10].

dure has two critical steps: (i) the correct freezing of the solution in the vial, which depends mainly on the temperature profile and its rate to achieve the temperature endpoint, and (ii) the time-consuming lyophilization process with the vials standing on a plate, often having a non-uniform temperature distribution. Both problems are related to the intrinsic poor heat transfer process between the plate and the solution in the vials. The variability of the quality of the end-product may need a final non-destructive 100% inspection of the moisture content. Such a procedure was developed using chemometric methods and near IR spectroscopy [11]. Thus defective samples can be eliminated and an excellent quality can be produced. However, it has to be kept in mind that such a final 100% inspection does not correspond to the idea of the PAT initiative to 'build-in' and not to 'test-in' the quality. It seems to be that the problem of the poor heat transfer can only be resolved by applying a novel technology: the atmospheric spray freeze-drying process [12]. In such a case, the droplets of a solution are frozen immediately in a cold air stream of $-60°C$ and subsequently lyophilized in a fluidized air dryer at $-20°C$, for example. Due to the much better heat transfer than in classical lyophlization, the process time is shorter and as a result a free-flowing powder consisting of spherical particles (see Fig. 9) is obtained. It is a surprising fact that atmospheric spray freeze-drying equipment is not yet commercially available. Thus, the development of the formulation will be mainly based on the 'trial and error' approach and the validation of the classical lyophilization procedure will remain difficult.

2.6. The myth of the granulation end-point

The manufacture of granules (granulation) is still poorly understood, especially in cases where the necessary boundary conditions for optimal granulation are

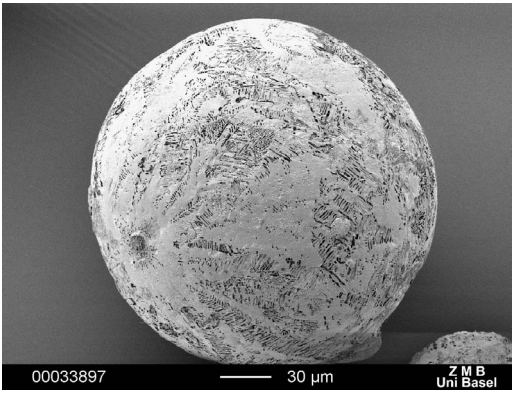

Figure 9. A particle out of dextran as a product of an atmospheric spray freeze-drying process.

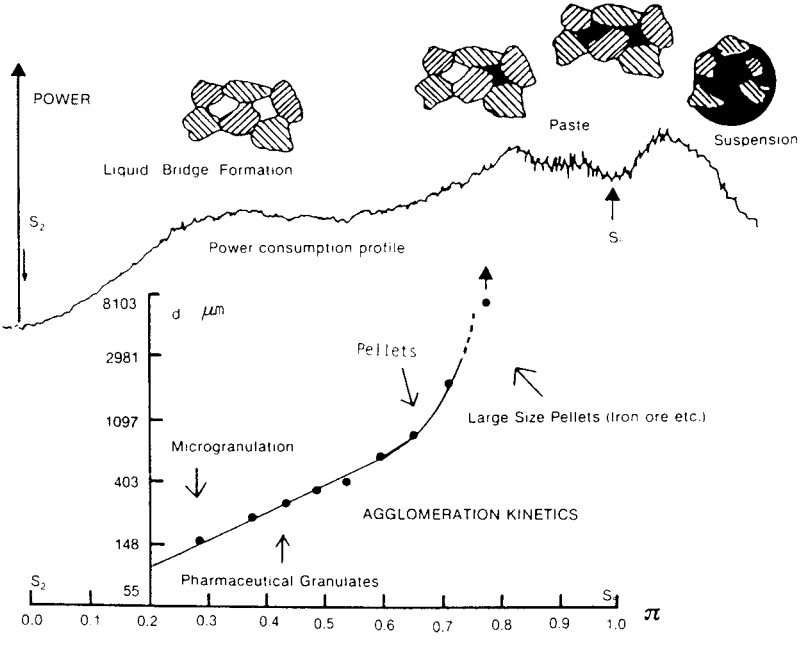

Figure 10. Formation of liquid bridges as a function of the granulating liquid [10].

not fulfilled. Problems can arise if the granulating liquid (i) is non-Newtonian, (ii) dissolves an important amount of the powder formulation, (iii) if it causes a hydration process or (iv) if it causes gelation at higher temperatures. In an ideal case, the only function of the granulating liquid is to form liquid bridges between the particles (see Fig. 10) creating liquid bridge forces for the granulation process. Thus, if the cohesivity of the moist powder mass is monitored, e.g. by torque or power consumption measurement, a typical profile (see Fig. 11) is obtained [13, 14]. Figure 11 shows the power consumption profile for a composition with 86% (w/w) lactose 200 mesh, 4% (w/w) polyvinylpyrrolidon (as a binder in a dry state in

the powder mixture, the only component which will be completely dissolved) and 10% (w/w) corn starch. The granulating liquid is demineralized water, which is added by a pump at constant speed. The different phases can be easily interpreted: (i) water uptake by corn starch, (ii) start of formation of liquid bridges and (iii) filling-up of the interparticular void space by the granulating liquid (see also Fig. 10). Granules with a reproducible granule size distribution can be manufactured

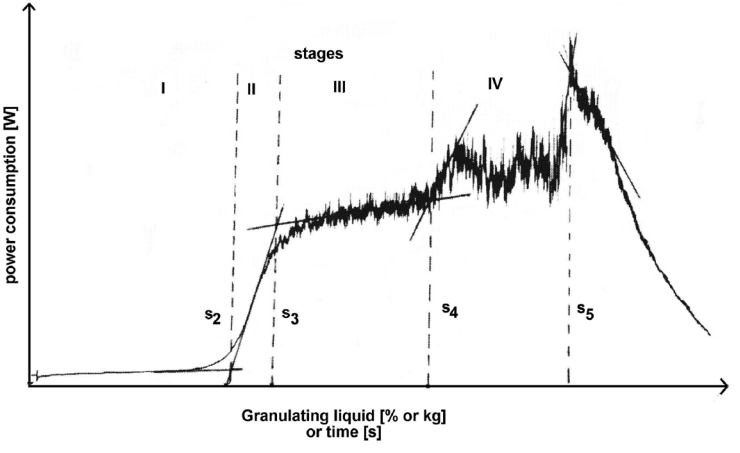

Figure 11. Power consumption profile [13].

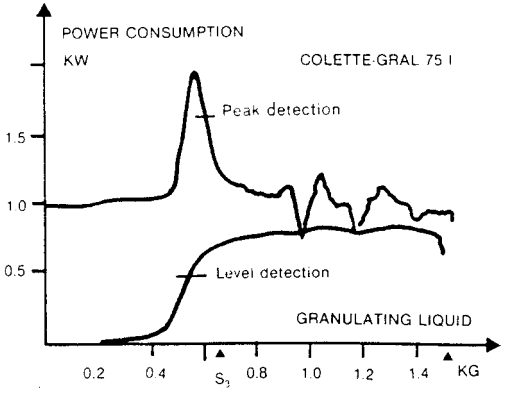

Figure 12. The peak or level detection method can help to find the right amount of granulating liquid [13].

Table 2.
Yield and size distribution of granules after manual and automatic granulation [9]

Type of mode	Yield (% w/w) 90–710 μm	Undersize (%) <710 μm	<90 μm
Manual mode ($n = 20$ batches)	81.03 ± 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

for amounts of granulating liquid which correspond to a well-defined point of the plateau (see also the semi-logarithmic plot of the mean granule size in Fig. 10 as a function of granulating liquid added). There is no granulation end-point; however, there is the possibility to control the granulation process by the detection of the steepest ascent in the power consumption profile (level or peak detection method, see Fig. 12) and adding a constant amount of liquid. As an alternative, the inflexion point of the S-shaped curve of the power consumption profile can be determined for this 'fine-tuning' process [15]. The peak in Fig. 12 describes a certain cohesiveness of the moistened powder bed at the beginning of the plateau phase. The peak (which equals the first derivative of the power consumption curve) is a signal provided by the powder mass and has a self-correcting property, as the signal appears at an earlier time for a slightly coarser starting material, later for a slightly finer material and taking into account the initial moisture content of the primary material, which depends on seasonal effects.

In this respect, the automated controlled mode leads to a higher homogeneity of the granule size distribution (see Table 2) than in the case of manually adding a predetermined constant amount of granulating liquid. Thus, the variability of the yield could be reduced by understanding the process.

2.7. Scale-up exercises [3, 16]

The major problem consists of the fact that the formulation is optimized on small-scale equipment, but is for obvious reasons no longer optimal for large-scale equipment. A possible solution is the introduction of a semi-continuous process using small-scale equipment for optimization and for small- and large-scale production (see Fig. 13) [17, 18]. To take advantage of such a concept, it is important that such equipment is available in the R&D and manufacturing departments.

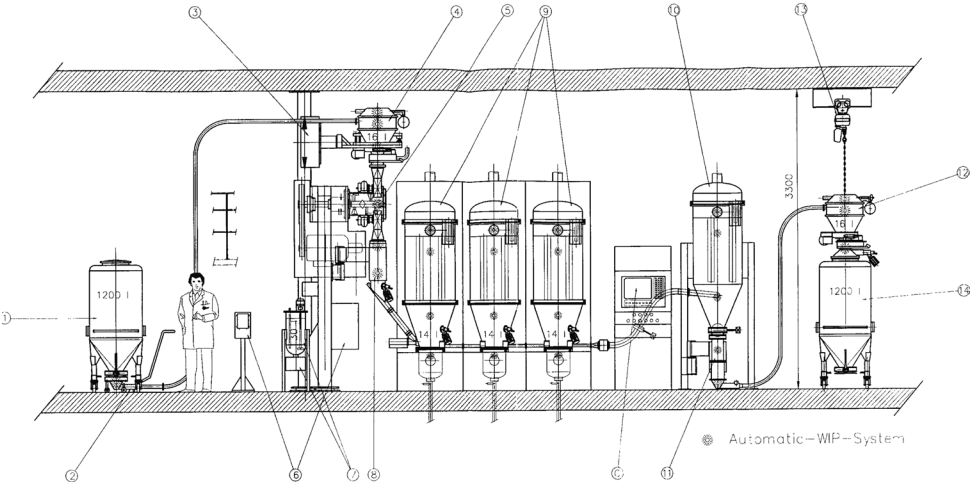

Figure 13. Glatt® Multicell™ equipment for the production of granules (courtesy Glatt AG, Pratteln).

In the case of the scale-up concerning the subsequent tabletting process novel test methods may be needed, such as the Presster™ (http://www.mcc-online.com) equipment, simulating high-speed tabletting machines [19].

3. FIRST PRINCIPLES

3.1. Introduction

Last, but not least, it is essential that the 'art of formulation', which is complex in the area of pharmaceutical powder technology, is converted into a science taking into account percolation theory [9] and the laws of physical pharmacy [20]. In fact, the existing laws in powder technology may be compared to the laws known in chemistry in the 18th/19th century. Thus, thanks to the tremendous research effort in the 19th/20th century the chemistry laws could be brought into a rigorous scientific framework of physical chemistry parallel to the success of the emerging chemical industry. The following sections represent an attempt to find a rigorous scientific framework in the area of pharmaceutical powder technology. The approach is based on the hypothesis that the laws which govern atoms and molecules in physical chemistry can be 'translated' into laws for particles and particulate matter, respectively. Two points are important in this context: (i) to what extent can particles be considered as 'atomistic', elementary units and (ii) to what extent the statistical laws of thermodynamics, which are based on the high number N_A of 'particles' in a molar volume V_m, can be applied for much lower number of particles.

Thus, the 'translated' results have to be checked with caution. It may be that deviations can be related to the fact that the number N of 'atomistic' particles is much lower than N_A. In this context it will be of interest to monitor the progress in nanoscience, i.e. the analogous mathematical modeling of the special properties of nanoparticles consisting of a finite number N of atoms or molecules with $N \ll N_A$.

Interestingly, powder systems can behave like a gas, like a liquid and/or like a solid. Due to the differences of the number and of the size of particles involved in powder technology compared to the particles (atoms, molecules, ions) in physical chemistry, the question arises whether the particulate material should be conceived as a fourth state of matter which does not obey the normal physical laws. An analogous view has been adopted for very small particles in the submicrometer range, i.e. for nanoparticulate material. Actually, in the area of nanotechnology and nanoscience an enormous amount of money is invested to boost the activities with the goal to create a new industrial revolution. The transformation of ordinary powder technology from an art to a science will also lead to important advances in industry and society. The following sections represent ideas about how some concepts applied in physical chemistry can be translated into the science of powder. In China, the science taking care of powder is called 'particuology' [21]. In fact the word 'particuology' is coined to correspond to the Chinese terminology 颗粒学 (ke-li-xue), which denotes both the science and technology of particles [22]. The

following contribution is an extension and modification of the Award Lecture 'Powder — The 4th State of Matter?', presented on 24 October 2001, in Toyohashi, Japan [23].

3.2. Classical thermodynamics and the three states of matter

3.2.1. The 'atomistic' view for a later discussion of the 'particulate state of matter'. Thermodynamics is based on the 'atomistic' view, i.e. the matter consists of 'elementary' particles such as atoms and molecules, which cannot be divided into smaller units. The three different states of matter are the result of the simultaneous interaction of a very large number, usually $N = N_A = 6.02 \times 10^{23}$, of 'elementary' particles. Thus, the macroscopic behavior of an ensemble of particles can be mathematically described as a 'state' function, which can be related to the individual behavior on a molecular scale leading to the scientifically rigorous framework of statistical thermodynamics [24].

The classical three states of matter and the transition from one state to another state of matter will be critically discussed first. In addition, case studies have been selected for a later comparison with similar phenomena in the field of powder technology.

3.2.2. The transition from the first to the second state of matter (gas–liquid). In the case of an ideal gas the interaction between the 'elementary' particles, i.e. the atoms or molecules, can be neglected. For this purpose the distance between the individual atoms or molecules needs to be large. Thus, if b represents the volume of the individual atom or molecule and N is the Avogadro number N_A, i.e. the number of molecules per mole, no interaction between the particles can be expected for

$$\frac{Nb}{V} \ll 1, \tag{1}$$

where V is the molar volume of the gas.

The following equation is closely related to the van der Waals model of a gas [24]:

$$p = -\frac{N^2 a}{V^2} + \frac{NkT}{V}\left(1 + \frac{Nb}{V} - \left(\frac{Nb}{V}\right)^2 + \cdots\right), \tag{2}$$

with k is the Boltzmann constant, T is the temperature (K), and a and b are van der Waals parameters (material specific value), representing a Taylor expansion for $(Nb)/V \ll 1$. If the terms $N^2a/(V^2)$, $(Nb)/V$ and higher power terms in $(Nb)/V$ are neglected, (2) becomes the ideal gas equation:

$$p = \frac{NkT}{V} \text{ respectively } pV = RT, \tag{3}$$

with $Nk = R$ is the ideal gas constant. In (2), the first term, i.e. $-N^2a/(V^2)$ can be interpreted as an attractive 'volume' specific energy. In this context it has to be

kept in mind that 'pressure' does not only mean 'force per surface' (N/m^2) but also 'energy per volume' (Nm/m^3).

Thus, the first term is equivalent to the volume specific cohesion energy E_{coh}.

$$E_{coh} = P_{attr} = \frac{-N^2 a}{V^2}. \tag{4}$$

The second part of (2) corresponds to the volume specific kinetic energy ε_{kin} with $E_{kin} = NkT$:

$$\varepsilon_{kin} = P_{kin} = \frac{NkT}{V}. \tag{5}$$

Equation (5) describes exactly the ideal gas equation, where the individual particles do not interact, i.e. do not show any attractive and repulsive forces. At low distances between the particles the attractive and repulsive forces start to become visible. Thus, the third and the higher terms in (Nb/V) take into account the 'hardness', respectively 'softness', of the individual particles. In a first approximation, the atom or molecule is considered as a sphere with a hard core of volume b. The behavior can be better approximated by also taking into account higher terms of the Taylor expansion. It is impressive that the van der Waals equation allows us to calculate the critical parameters p_c, T_c and V_c, where the gas condensates and becomes a liquid:

$$p_c = \frac{a}{27b^2}, \quad T_c = \frac{8a}{27Nkb}, \quad \text{and} \quad V_c = 3b. \tag{6}$$

Figure 14 shows the van der Waals isotherms for CO_2 with $a = 3.69$ l^2 bar/mol^2 and $b = 4.267 \times 10^{-2}$ l/mol which lead to the following critical values.

$$p_c = 75.1\ (73.8)\ \text{bar}$$
$$V_c = 128.0\ (94.0)\ \text{cm}^3/\text{mol}$$
$$T_c = 308.2\ (304.2)\ \text{K}$$

For comparison, the experimental values are given in parentheses. Equation (2) is equivalent to the so-called virial equation:

$$p = \frac{RT}{V}\left(1 + \frac{B(T)}{V} + \frac{C(T)}{V^2} + \cdots\right). \tag{7}$$

This equation will be used in the case study on the compression of a powder.

3.2.3. The liquid state of matter. In the preceding discussion CO_2 was treated as a uniform substance undergoing a phase transition $\alpha \rightarrow \beta$ from the gas (α) to the liquid (β) state with Fig. 15 showing the phase diagram. The critical point is defined by p_c and T_c, above the critical point, i.e. for $p > p_c$ and for $T > T_c$ there is no distinction between the gas and liquid state of CO_2. Supercritical CO_2 can be used as a solvent for drugs and during the rapid expansion to atmospheric pressure fine particles can precipitate. Nowadays this process has become popular for the production of very fine powder [27].

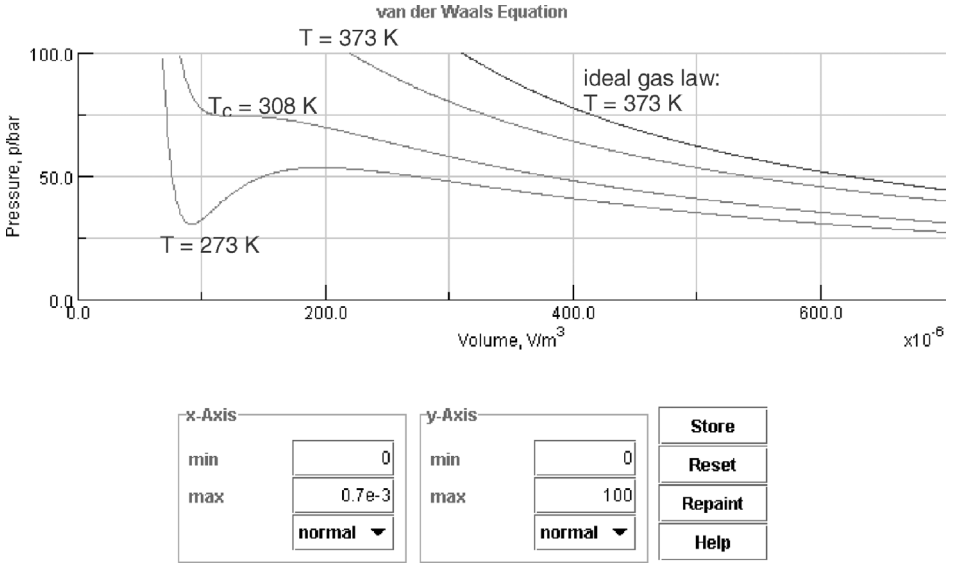

Figure 14. Van der Waals isotherms for CO_2 with $a = 3.69\ \mathrm{l}^2\ \mathrm{bar/mol}^2$ and $b = 4.267 \times 10^{-2}$ l/mol which lead to the following critical values [25].

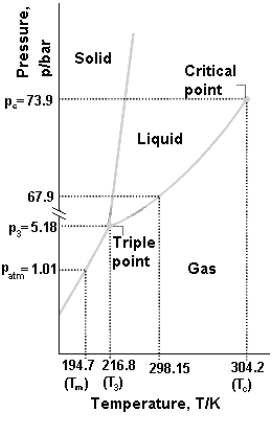

Figure 15. The phase diagram of CO_2 according to [26].

3.2.4. The solid state of matter. Figure 15 shows the experimental phase diagram of CO_2. At the triple point (T_3) the three states of matter of CO_2 are present simultaneously: gas, liquid and solid. Below the temperature T_3 and below the pressure $p_3 = 5.18$ bar, e.g. at atmospheric pressure (1.01 bar), CO_2 forms a solid, i.e. 'dry ice', with a 'melting point' of $T_\mathrm{m} = 194.7$ K. Thus, at normal pressure and at temperatures below T_m, CO_2 is present as a gas and as a solid only. Thus, at the boundary solid–gas/gas–solid a dynamic equilibrium exists, i.e. gas molecules condensate, directly becoming a solid, and molecules can leave the solid into the gaseous phase.

3.2.5. The difference between the liquid and solid state. Solid glass (at ambient temperature) is considered as a liquid with very high viscosity, which leads to the question what is the real nature of a solid? Is a solid in the solid state if the solid exhibits a crystalline structure, i.e. if the solid corresponds to a highly ordered system, which can be described by a lattice? How perfect does the lattice need to be? In fact, the high order of a perfect crystalline lattice facilitates the mathematical modeling of a solid material. Thus, a crystal can be described by the oscillations of the lattice i.e. by the phonon spectrum (wave–particle dualism). What about defects? What about polycrystalline solid material? What about an amorphous material? Is amorphous material a solid or a liquid? Does a liquid have a structure? A liquid can be considered as a gas of high density. In fact, above the critical point the gas and the liquid state cannot be distinguished. In the case of a gas with high density the molecule–molecule distance is small and the molecule–molecule interaction is large. Thus, in a microscopic view (molecular scale) the radial pair correlation function $g(r)$ can be introduced. This function $g(r)$ describes the localization of a molecule or particle at the position $r > 0$, which corresponds to the relative probability to find at a distance r/a_0 a second or third molecule (particle) (see Fig. 16).

Figure 16 shows the pair correlation function for a one-dimensioned perfect crystal with molecules at a regular distance $r = 0, r = na_0, n = 1, 2, 3, \ldots$.

Figure 17 shows the case of a liquid, of glass and of an amorphous solid.

Thus, in such a case no distinction can be made between an amorphous solid and a liquid. On the other hand, it can be concluded that liquids and amorphous solids exhibit a kind of order, which is given by the local arrangement of the molecules, i.e. by the local order of the neighborhood of a molecule.

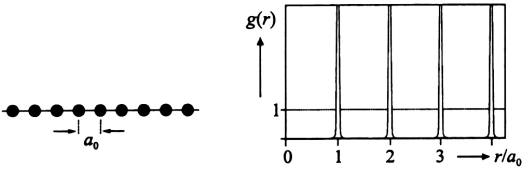

Figure 16. The pair correlation function for a one-dimensional perfect crystal [24].

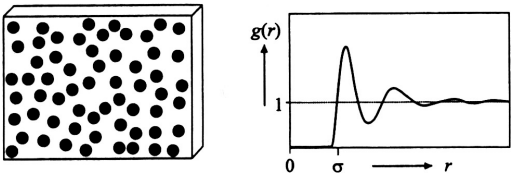

Figure 17. Pair correlation function for the case of a liquid, glass and/or amorphous solid [24].

3.3. The particulate state of matter

What is the particulate state of matter? It has to be kept in mind that particulate materials are dispersions. In fact, the classical powder is a concentrated dispersion of solid particles in air. At a very low concentration very fine particles (micron and submicron size) can form an aerosol. In such a case — due to the large interparticulate distance — the particle–particle interactions can be neglected. In general, a particle can exhibit a substructure, i.e. a particle may have external and internal pores. An external pore can be related to the roughness of the surface of a particle. Porous particles can also absorb liquids. In an ideal case, the surface is smooth and the shape of a particle can be spherical. A number of smaller sized particles can form a cluster or a large size particle.

The milling of particles leads to the conclusion of a lower limit of the size of a particle, i.e. putting forward an 'atomistic' view. Thus, analogies between classical thermodynamics of molecules and the behavior of powder particles should be expected. The following case studies are discussed for this purpose.

3.4. Case studies

3.4.1. The compression of a powder. In the pharmaceutical industry free-flowing powders consisting of the active substance and excipients are compressed to tablets. Due to the relative large size of the particles, the powder is free flowing. Thus, there is no strong interaction between the particles. Large particles such as the grains of granules can be considered as clusters of smaller particles. Thus, during the compaction process larger particles can disintegrate into smaller, i.e. 'elementary', particles before forming a dense tablet. It is evident that the strength of the interaction depends on the distance between the 'elementary' particles. This model is equivalent to the compression of a real gas (of molecules or atoms), i.e. 'elementary' particles that exhibit an intense interaction as a function of the interparticulate distance. This process can be well simulated with the help of the virial equation (7), which corresponds to the van der Waals equation (see Fig. 14). For appropriate values of the volume, pressure and temperature, the gas becomes a liquid. According to the phase diagram of CO_2 (see Fig. 15) a transition from the gaseous to the solid state is possible, too. As discussed before (see Figs 16 and 17) a distinction between an amorphous solid and a liquid is difficult. Figure 18 shows the pressure–punch displacement (p–s) relationship for lactose anhydrous. The virial equation with the constants A, B and C is applied [see Fig. 18, cf. (7) and (8)]. A similar approach, based on a hyperbel equation, goes back to Parmentier [28].

$$p = -\frac{A}{s}\left(1 + \frac{B}{s} + \frac{C}{s^2} + \cdots\right). \tag{8}$$

3.4.2. The pressure susceptibility χ_p of a powder. The so-called Heckel equation (9) [29] is one of the most popular models to describe the reduction of the relative

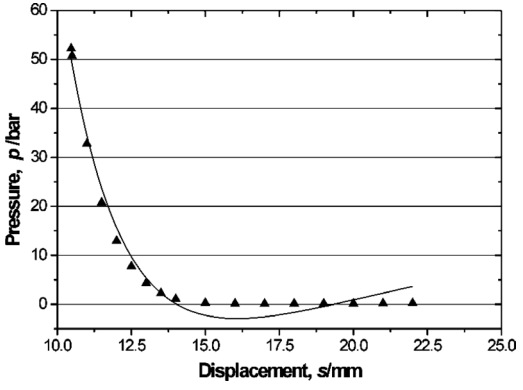

Figure 18. Experimental values for the pressure–punch displacement curve and theoretical model according to (8) with the following values: $A = -1793$ bar mm, $B = -33$ mm and $C = 272$ mm^2 (*cf.* Fig. 14), [28].

density ρ as a function of the pressure (compressional stress) σ:

$$\ln\left(\frac{1}{1-\rho}\right) = K\sigma + A, \tag{9}$$

where K and A are constants, ρ is $1 - \varepsilon$ and ε is the porosity. In a differential form the following equation is equivalent to (9):

$$-\frac{1}{\varepsilon}\frac{\mathrm{d}\varepsilon}{\mathrm{d}\sigma} = K \equiv \chi_{\mathrm{p}}. \tag{10}$$

In the case of a gas, the cubic compressibility χ can be defined as follows

$$-\frac{1}{V}\left(\frac{\mathrm{d}V}{\mathrm{d}p}\right)_{\mathrm{T}} \equiv \chi, \tag{11}$$

where p is the pressure and V is the volume at a constant temperature T.

It has to be kept in mind, however, that the Heckel equation (9) is only valid for medium pressures, but fails at low pressures. This is due to the fact that there is a critical porosity ε_{c}, where a reaction force on the punch exerting the pressure σ can be measured. This point leads to the following modified Heckel equation [30]:

$$-\frac{1}{\varepsilon}\frac{\mathrm{d}\varepsilon}{\mathrm{d}\sigma} = \frac{C}{\varepsilon_{\mathrm{c}} - \varepsilon}. \tag{12}$$

In an integral form of (12) reads as:

$$\sigma = \frac{1}{C}\left(\varepsilon - \varepsilon_{\mathrm{c}} - \varepsilon_{\mathrm{c}} \ln\frac{\varepsilon}{\varepsilon_{\mathrm{c}}}\right). \tag{13}$$

As a first approximation, a comparison of (10) and (11) leads to the conclusion that, in this case, the powder behaves like a gas.

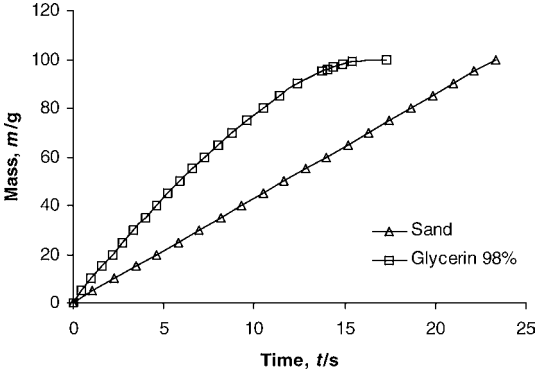

Figure 19. Flow of liquid (glycerin) versus the flow of a powder (sea sand).

3.4.3. Flow of a liquid versus the flow of a powder from a hopper. Figure 19 shows the flow of a liquid (glycerin 98%, viscosity $\eta = 0.939$ Pa s at room temperature) and of sea sand (mean particle diameter $= 222$ μm, based on laser diffractometry), i.e. the amount of mass discharged per unit time till the hopper is completely empty. The hopper has a conical shape (half center angle $= 17°$) and an outlet orifice with a diameter of 5 mm. It is evident that the flow rate of the 'powder' (sea sand) is constant and reflects the use of a 'sand clock'. The amount of liquid discharged per unit time $\mathrm{d}m/\mathrm{d}t$ depends on the hydrostatic pressure, resulting in a non-linear relationship, i.e. a decrease of the flow rate as a function of time until the hopper is completely emptied. In the following, the flow of the powder is tentatively described by Fick's law.

3.5. Considerations about the flow of spherical particles out of a hopper

In order to describe the flowability of powders we followed the concept of applying a model that has proved to be very successful in physical chemistry at a molecular level. During the flow of a powder out of a hopper the particles move from a region with a high to one with a low package density. We could therefore assume a similarity to the diffusion process, which can be described by Fick's first law (14). In the field of blending we can also observe a similar process, where the blend is achieved by changing positions between particles. The blenders that take advantage of this principle are therefore also called diffusion blenders (e.g. Turbula, T2A; Bachofen AG, Basel, Switzerland).

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{D \cdot A \cdot \mathrm{d}c}{\mathrm{d}h} \approx \frac{D \cdot A \cdot (c_1 - c_2)}{\Delta h}, \tag{14}$$

where $\mathrm{d}m/\mathrm{d}t$ is the transported mass per time, A is the area, D is the diffusion coefficient (diffusivity) and $(c_1 - c_2)/\Delta h$ is the gradient of the concentration. The experiment we refer to consists of the measurement of the mass discharge of the particulate material out of a conical shaped hopper with an orifice of 5 mm and a half center angle of 17° (see Fig. 20).

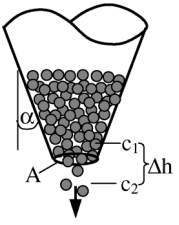

Figure 20. Flow of particles out of a hopper (A: area of the orifice; α: half center angle; c_1: concentration in the hopper; c_2: concentration out of the hopper).

In order to apply Fick's first law to the flow of particulate material, we have to consider some modifications.

- For each powder material there is a critical area A_{crit} of the orifice below which flow is impossible. The effective area must therefore be corrected by this critical area.
- We assume the bulk density ρ_{bulk} in the hopper experiment to be the analogous term to the concentration c_1 in Fick's first law. In addition, we suppose the density out of the hopper to be negligible in comparison to the bulk density ρ_{bulk} ('sink conditions').
- Because Δh is hard to determine, D and Δh are summarized in a new constant Π^* (mass permeability coefficient) analogous to the permeability coefficient P in physical chemistry. Π^* has the dimension of volume flux or of linear velocity.

Taking into account these assumptions, we can suppose for the flow of a particulate material out of a hopper:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \Pi^* \cdot \rho_{\text{bulk}} \cdot (A - A_{\text{crit}}), \tag{15}$$

where

$$\Pi^* = \frac{D}{\Delta h}, \tag{16}$$

$\mathrm{d}m/\mathrm{d}t$ is the discharged mass per time (flow rate), Π^* is the mass permeability coefficient, ρ_{bulk} is the bulk density, A is the area of the orifice and A_{crit} is the critical Area of the orifice. To verify this approach we carried out some experiments measuring the discharged mass per time of glass ballotini, pellets made out of microcrystalline cellulose (Cellets®; Pharmatrans Sanaq AG, Basel, Switzerland) and pellets made out of sugar (Sugar spheres®; Pharmatrans Sanaq AG, Basel, Switzerland) of different sizes. A balance that was connected to a computer recorded the mass. Typical flow diagrams are depicted in Fig. 21. The flow rate (slope of the curve) is constant and is fully in agreement with (15).

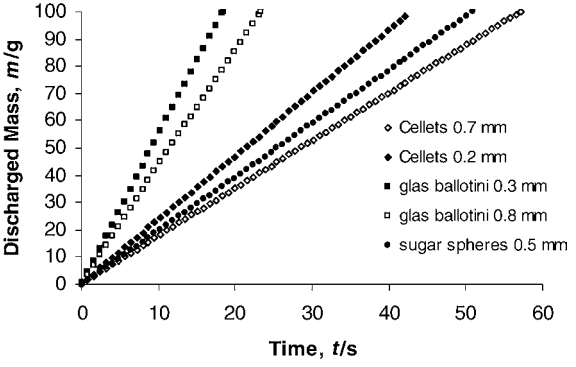

Figure 21. Flow of cellets (pellets made of microcrystalline cellulose), glass ballotini and sugar spheres with different diameters out of a hopper with an orifice of 5 mm diameter.

4. CONCLUSIONS

FDA's PAT initiative and its new concept for quality assurance of the 21st century will positively affect the Sigma Value of the pharmaceutical manufacturing performance, and will optimally lead to cost savings due to more robust formulations and processes. From the academic point of view the challenge of FDA's PAT initiative is very fruitful and an important stimulus for the development of a rigorous scientific framework in powder technology, i.e. to achieve the status of 'physical particuology'. The different examples of the problems related to non-robust formulations and critical processes support the use of the 'knowledge pyramid' to describe the actual situation in pharmaceutical powder technology. To achieve the top of the 'knowledge pyramid' as fast as possible we suggest as a kind of 'road map' to use DoE, i.e. a multivariate approach in the case of complex formulations and processes, to use the benefits of ANN, to apply the laws of physical pharmacy and percolation theory, and, finally, to try to 'translate' the existing laws of physical chemistry into corresponding laws of pharmaceutical powder technology. In addition, progress in nanoscience should be monitored very closely, especially mathematical modeling of the very special properties of nanoparticles consisting of a finite number N of atoms and, respectively, molecules with $N \ll$ the Avogadro number N_A. It may be possible that the methodology to obtain these results can be 'translated' to be used to explain the behavior of powder aggregates with a finite number N of powder particles.

To achieve this ambitious goal, a close transdisciplinary cooperation between scientists with different background, will be imperative: industrial pharmacists, chemical and pharmaceutical engineers, physicists and IT specialists in mechanistic mathematical modeling as well as in ANN, and, last but not least, experts in Nanoscience.

In this context it would be an exciting idea to copy the Nanoinitiative of the US National Science Foundation, which actually has successfully boosted research in nanoscience. Thus, we propose to launch a similar research program providing the

necessary resources to develop innovative pharmaceutical manufacturing processes leading to the desired excellent quality of pharmaceutical products for the benefit of the society.

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