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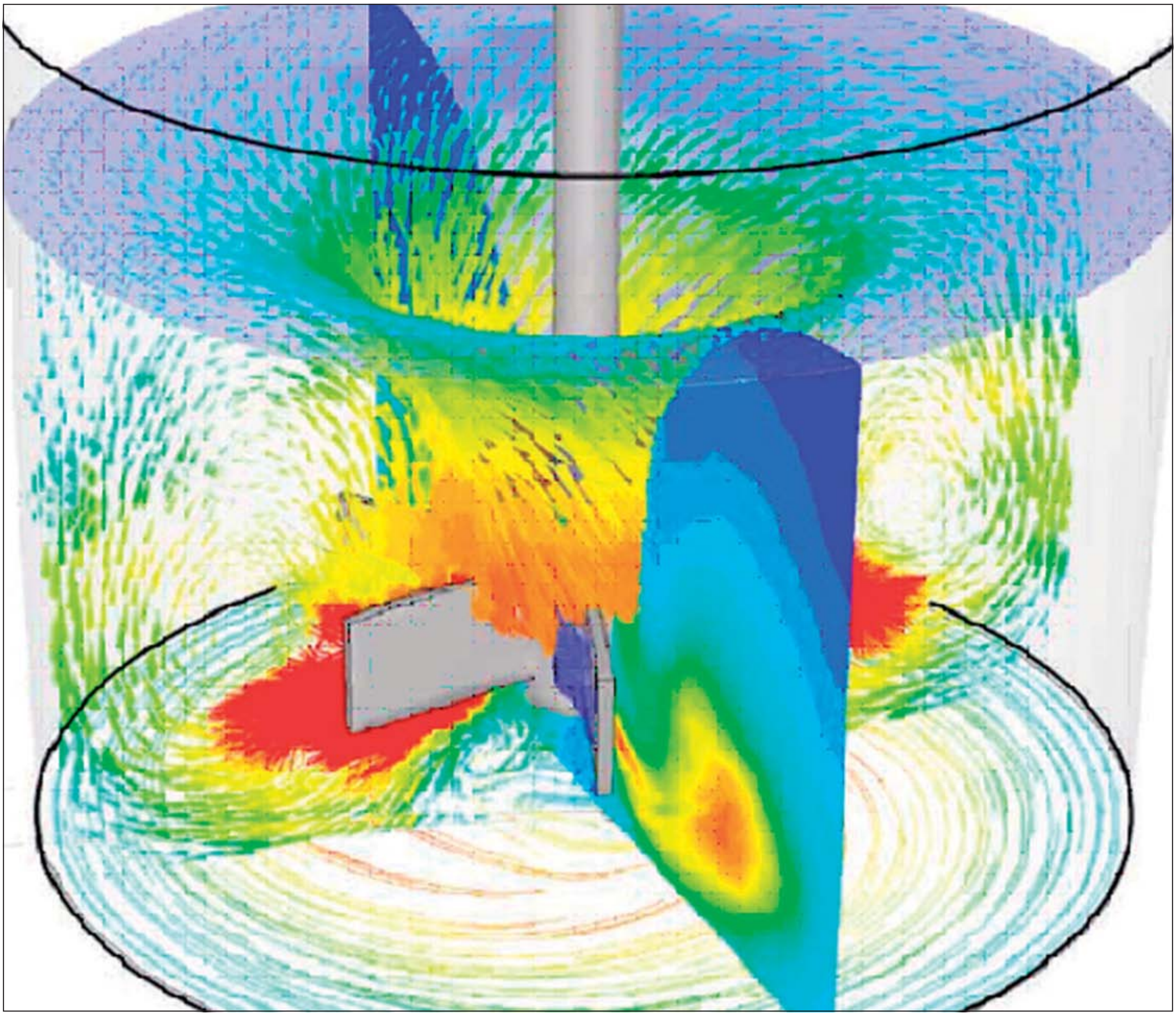

Process Modelling

Use of computational fluid dynamics for analysis of pharmaceutical equipment

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Abstract: Computational fluid dynamics (CFD) uses numerical methods and physical models to analyze and solve various problems involving fluid flow, heat transfer, mass transfer, and chemical reactions. CFD modeling is used to optimize various process parameters, increase understanding of the processes, and obtain information regarding various process values that could not otherwise be measured or are difficult to measure.

Keywords: Computational fluid dynamics, CFD, technological processes, pharmaceutical equipment

1 Introduction

Improving computing power has made computer simulations faster and more accurate, and therefore very useful for equipment and process development. Computer simulations are used in various fields, particularly the pharmaceutical industry. Moore's Law describes the improvements in computing power, stating that the number of transistors per integrated circuit is doubling every 18 months [1]. This increase in performance is also true for the fastest supercomputers on the top500.org list [2].

One of the most commonly used computer simulation tools is computational fluid dynamics (CFD), which is mainly used for fluid flow analysis. It is used to analyze and solve various fluid flow problems in aerodynamics, hydrodynamics, electronics, the chemical industry, the food industry, the pharmaceutical industry, and many others [3]. Much of the published CFD research was done for the food industry, using very similar equipment to that used in pharmaceutical research. This means that many of the rules and models developed for CFD simulations of food industry equipment can be also applied to pharmaceutical research and development [4] and industrial scale production as well. In the last few years, CFD simulations have become more and more popular, but there have been few articles reviewing the use of CFD in pharmaceutical research. One of these, published by Kremer and Hancock, analyzed process simulations in the pharmaceutical industry and noted CFD as being a very promising modeling approach [5].

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2 Computational fluid dynamics

2.1 History

It is known that even the ancient Greeks were fascinated by various flow dynamics, particularly water and air flow. Their flow studies, however, were more oriented towards philosophy than science. In that time, Heraclitus made one of the best-known postulates about water flow (ca. 450 BCE): *Ta Panta rhei* (Everything flows). Around 200 years later, Archimedes developed the basic principles of static mechanics and hydrostatics and developed methods for the measurement of density and volume. This science was further developed by the Romans in terms of the development of aqueducts, canals, harbors, and bathhouses. After the Romans, fluid flow was not taken up again until the time of Leonardo da Vinci, who was one of the first to study fluid flow. He made accurate qualitative descriptions of many different water phenomena. Newton followed da Vinci in the analysis of fluid flow and other phenomena. His contributions to the field were his well-known second law ($F = ma$), the concept of Newtonian viscosity, and the principle of reciprocity, which states that the force exerted by a fluid on an object equals the change of momentum of this fluid.

Daniel Bernoulli and Leonhard Euler made significant contributions to the field of fluid dynamics in the 18th and 19th centuries. Euler suggested equations for the conservation of mass and momentum for inviscid fluid. Claude Louis Marie Henry Navier and George Gabriel Stokes made another very significant contribution to the science of fluid flow. In the 19th century, they added the effect of viscous transport to the Euler equations and established the famous Navier-Stokes equation. This equation is a basis for all computational fluid dynamics. These equations are difficult to adapt to real-life problems but gained greater practical usefulness with the advent of modern computer technology between 1960 and 1970 [6].

In 1910, Luis Fry Richardson was the first to numerically solve the Navier-Stokes equations. He was trying to predict weather behavior, but his predictions were not useful due to their inaccuracy. The calculations took a long time to work out, as they were performed by hand. The first successful calculations of low velocity fluid flow past circular cylinders were performed by Thom [7]. The Japanese scientist Mitutosi Kawaguti was occupied 20 hours per week for 18 months calculating flow around a cylinder using only a mechanical calculator. After 1960, a theoretical division of NASA in Los Alamos made a significant contribution by creating the commonly used k-epsilon turbulence model. CFD codes were further developed at the Imperial College in London with the creation of the SIMPLE algorithm, which is now used in modern CFD codes. Another important milestone in CFD development came with the publication of

Patankar's book *Numerical Heat Transfer and Fluid Flow*. In the early 1980s, many commercial codes became available and were first used by the aerospace industry, later the automobile industry, and then others [6].

2.2 What is computational fluid dynamics?

The physics of any fluid flow can be described by three fundamental principles: conservation of mass, conservation of energy, and F=ma (Newton's second law). These principles can be expressed with mathematical equations- in the case of fluid flows they are usually in the form of differential equations. Computational fluid dynamics uses numerical algorithms to solve these equations in order to obtain numerical rather than analytical descriptions of the fluid flow. CFD calculations are computationally intensive because they perform millions of number operations and have therefore gained practical use only with the advent of modern computers. With increasing computer speed one can perform faster and more accurate CFD simulations. The use of supercomputers in CFD is therefore quite common [8].

Differential equations that are used in computational fluid dynamics are:

1. The continuity equation

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{v}) = 0$$

where ρ is the density of the fluid and $\vec{v}$ is the velocity of the fluid.

This equation is based upon the law of conservation of mass and states that the change of mass in a volume over time is equal to the mass flow through the surface of this volume [8, 9].

2. Momentum equation (Navier-Stokes equation)

$$\frac{\partial}{\partial t}(\rho \vec{v}) + \nabla \cdot (\rho \vec{v}\vec{v}) = -\nabla p + \nabla \cdot (\bar{\bar{\tau}}) + \rho \vec{g} + \vec{F}$$

where ρ is static pressure, $\vec{g}$ is gravitational force and $\vec{F}$ is other forces, for example forces in porous zones. The stress tensor $\bar{\bar{\tau}}$ is defined as $\bar{\bar{\tau}} = \mu[(\nabla \vec{v} + \nabla \vec{v}^T) - \frac{2}{3}(\nabla \cdot \vec{v})\bar{\bar{I}}]$, where μ is viscosity and $\bar{\bar{I}}$ is unit tensor.

The momentum equation is derived from Newton's second law ($\vec{F} = m\vec{a}$). The equation describes two types of forces that act on a volume: the first are long acting, such as gravitational force, and the second are those that act on the surface of the volume. These forces are due to viscosity and pressure differences in the surrounding fluid [8, 9].

3. Energy equation

$$\frac{\partial}{\partial t}(\rho E) + \nabla \cdot (\vec{v}(\rho E + p)) = \nabla \cdot (k_{eff} \nabla T - \sum_j h_j \vec{J}_j + (\bar{\bar{\tau}}_{eff} \cdot \vec{v})) + S_h$$

where k_{eff} is effective heat conductivity and $\vec{J}_j$ is the diffusion flux of component j. The first three terms on the right side of equation describe energy transfer due to conduction, diffusion, and loss of energy due to viscosity. S_h represents heat that is released or consumed during the chemical reactions.

The equation is derived from the first law of thermodynamics and describes the energy change due to heat flux and work done by the various acting forces [8, 9].

Numerical methods are used because, in general, analytical solutions to these equations are not known. In this case, the two main methods used are the finite difference and finite volume method. The finite volume method is used in most commercial and open-source CFD packages. The main principle of both methods is that the derivatives in differential equations are expressed as differences. Using the finite volume method, the domain is discretized into computational cells for which a system of equations is written and iteratively solved [8, 9].

CFD simulations are used in single-phase flows (e.g., flow of gas) as well as in the analysis of multiphase flows (e.g., flow of particles in gas or fluid), which are common in many pharmaceutical processes. Multiphase simulations use additional equations for additional phases and consume more computational resources compared to the single-phase simulations. Common models used in multiphase flow modeling are Volume of Fluid (VOF), Mixture and Eulerian (Euler-Euler), and the coupled Eulerian Langrangian model.

There are few commercial CFD packages available and the most commonly used are Fluent (Ansys), CFX (Ansys), and Fire (AVL). There are also many open-source CFD packages, the most popular being OpenFOAM, a package supported by OpenCFD [10, 11].

2.3 Basic procedure for CFD simulation

Before each CFD simulation, one must define the modeling goals, decide what physical models will be used, determine the domain of simulation, and consider the boundary conditions for the studied domain. The CFD simulation procedure is divided into three separate steps: i) creation of the computational model and grid, ii) model selection, and iii) calculation and post-processing of the results [9].

2.3.1 Creation of the computational model and mesh

For creation of the computational model (Figure 1) and computational mesh it is important to determine possible model simplifications because they can greatly reduce the calculation time. The computational mesh (Figure 2) is the base for numerically solving transport equations. When designing the computational mesh, the complexity of the flow and the total number of computational cells must be considered. More cells mean a more accurate solution, but also more memory and more computational power and time required for the calculation [9].

2.3.2 Physical model selection and calculation

When choosing physical models we are limited by these models' complexity and speed of calculation on the one hand and the accuracy and appropriate selection of these models on the other. For example, when modeling laminar fluid flow, turbulent models are

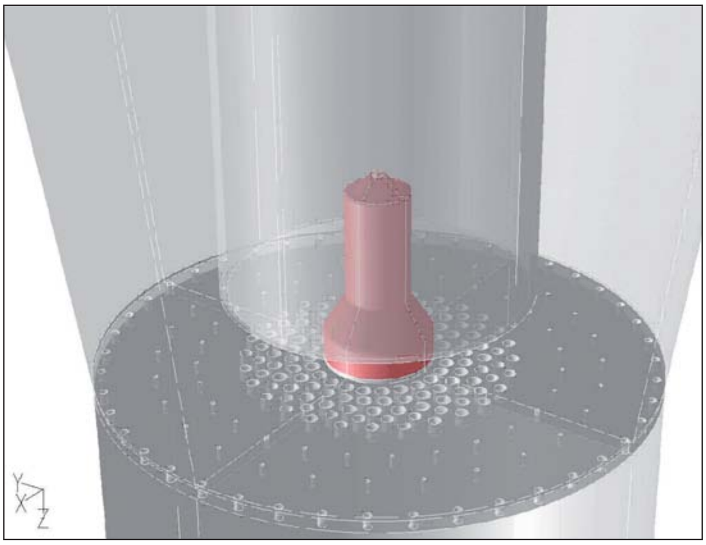

Figure 1: 3D model of Wurster chamber nozzle

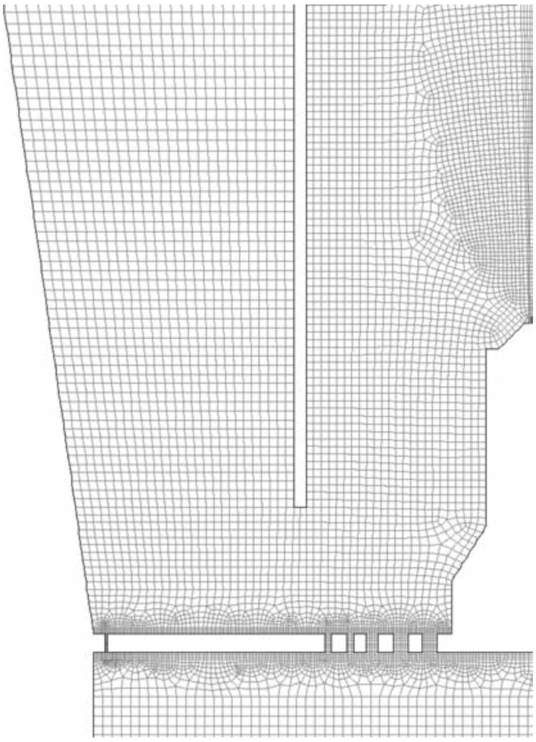

Figure 2: 2D computational mesh of Wurster chamber

unnecessary and would only increase the calculation time. The properties of the simulated fluid, such as temperature and viscosity, all boundary conditions (e.g., fluidizing air mass flow), and all initial conditions (e.g., volume fraction of pellets) must be set prior to the calculations. Numerical algorithms can solve all equations using iteration until convergence criteria are met. Calculations can take anywhere from a few minutes for simple geometries with basic models up to a few months for complex systems. Calculations that take longer than one month are generally impractical and rarely used [9].

2.3.3 Post-processing of simulation results

Numerical simulation results can be represented in numerical or graphical form. The graphical form (Figure 3) can be, for example, a vector field of a variable such as air velocity at a certain plane, colored pressure contours, or others [12]. The value of a variable is represented in color, most commonly using a blue-green-red color scale, where blue represents the lowest value of a particular variable and red the highest value. Data can be exported for any variable along a certain line of interest and then represented in the form of an XY plot (Figure 4). Average, minimum, and/or maximum values can be reported for selected domains. Mass and volume flow through the selected surfaces can be calculated as well. Fluid flow is often represented using pathways colored according to certain variables (e.g., components of velocity, pressure, temperature). An important part of post-processing is validation of the solution to check its correctness and to check the validity of selected models. In order to obtain more accurate simulation results, we can refine the computational mesh, use more complex models, and redo the calculations. Using a validated model, we are able to check how the system behaves using different boundary conditions and different fluid properties [9].

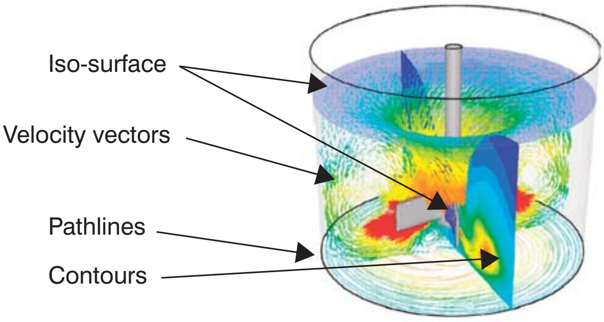

Figure 3: Example of the graphical presentation of simulation results [12].

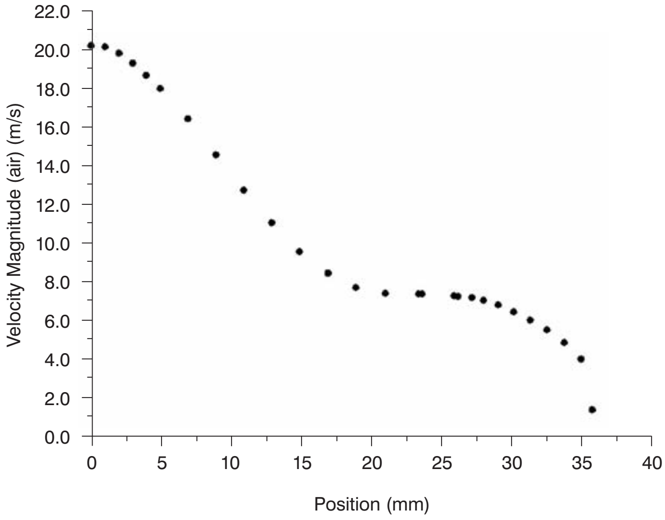

Figure 4: Example of an XY plot showing the air velocity profile inside the Wurster draft tube, where 0 represents the center of the draft tube.

3 Some examples of CFD process simulations using pharmaceutical equipment

Ansys (producer of the two largest commercial CFD packages) states that their software can be widely applied in the pharmaceutical industry. In their promotional material, they promote the use of CFD in drug production, analysis of pharmaceutical processes, and in studies of drug delivery systems, packaging, and transport. They also point out that CFD process simulations are in accordance with the FDA's QbD guidelines that promote process understanding. Studies of chemical reactions in reactors, crystallization, nozzle sprays, particle movement in a Wurster fluid-bed, mixing, segregation, and others have been performed using Ansys software. Many studies were conducted in the areas of delivery systems and medical devices such as coronary stents, ophthalmic drug delivery systems, and inhalers. An important aspect of CFD research in the pharmaceutical and medical fields is the studies of various pathophysiological states. Ansys states that half of the leading pharmaceutical companies use CFD software [13–15].

3.1 Mixers

Kay et al. have been studying new equipment for powder milling and mixing using CFD. Experimental validation for milling was performed using lactose particles and blending experiments were conducted using lactose and NaCl. An important parameter of the milling device was the amount of airflow used for particle acceleration, collision power, and consequent milling (jet-mill). The simulations detected dead zones in the chamber, which were later confirmed by the experiments [16].

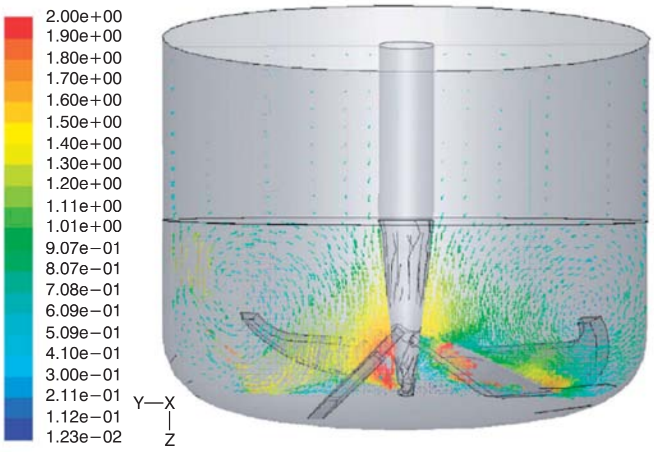

Figure 5: Particle velocity (scale on the left, m/s) in a high-shear mixer [17].

Another CFD simulation conducted by Darelius et al. studied particle movement in a high-shear mixer (Figure 5). The authors argued that using this type of simulation improves understanding of the granulation process and supports the development of process models. The simulation was validated using a particle velocity profile obtained using a high-speed camera on the wall of the mixer. The experimental data were not in complete accordance with the simulation. It was concluded that the two-phase models that describe particle interactions must be developed further [17].

3.2 Fluid-bed equipment

CFD simulation coupled with a population balance model was used to examine granule growth during granulation in a fluid-bed chamber. From experimental data, the authors concluded that the principal parameter that affects granule formation is the roughness of the starting material; in other words, the active pharmaceutical ingredients (APIs) and excipients. They constructed a population balance model with one parameter and used it to measure the granule growth rate [18].

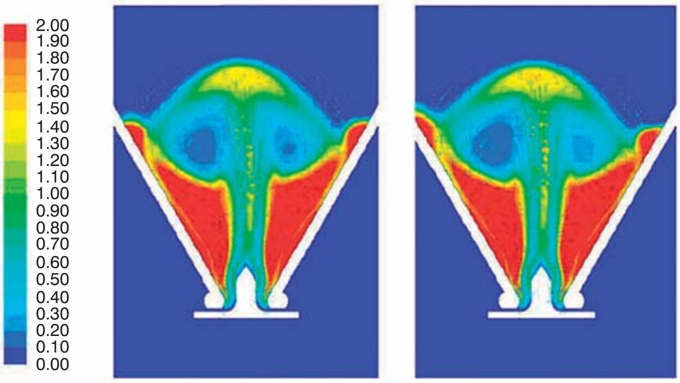

Figure 6: Velocity vectors and volume fraction contours of pellets at two different time intervals (difference of 0.2 seconds) in a novel fluid-bed device [20]

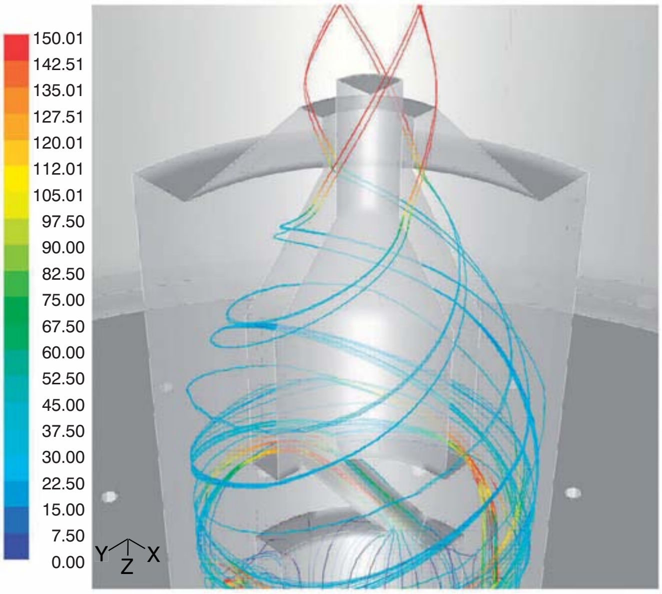

Figure 7: Air pathways in a spray nozzle colored according to velocity (m/s)

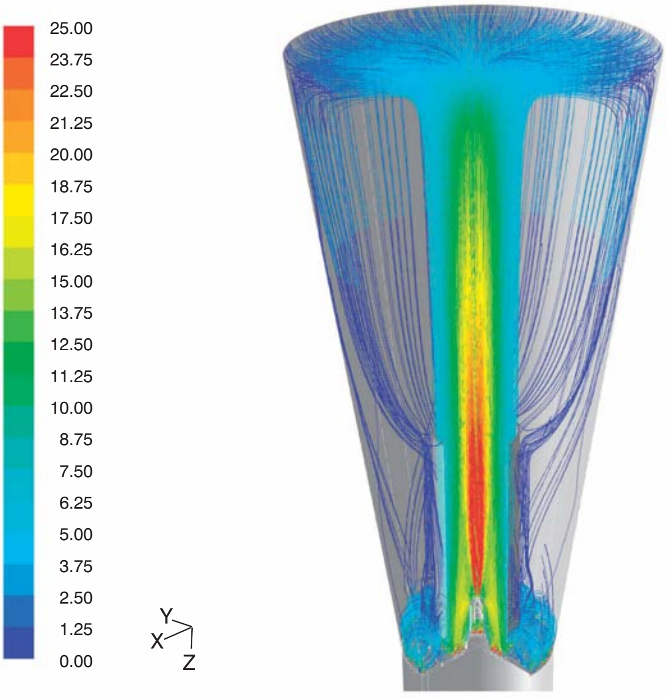

Figure 8: Air pathways and their velocities (m/s) in a fluid-bed coater

Studies of fluidizing air distribution in a Wurster chamber have also been performed. Experimental data was used to determine the coefficients of permeability of the distribution plate and that parameter was used in simulations analyzing the homogeneity of air flow. Simulation results were confirmed using chamber wall temperature measurements and comparing those to the simulation predictions. The authors concluded that this type of simulation can be used to test construction changes in order to improve the performance of the chamber [19].

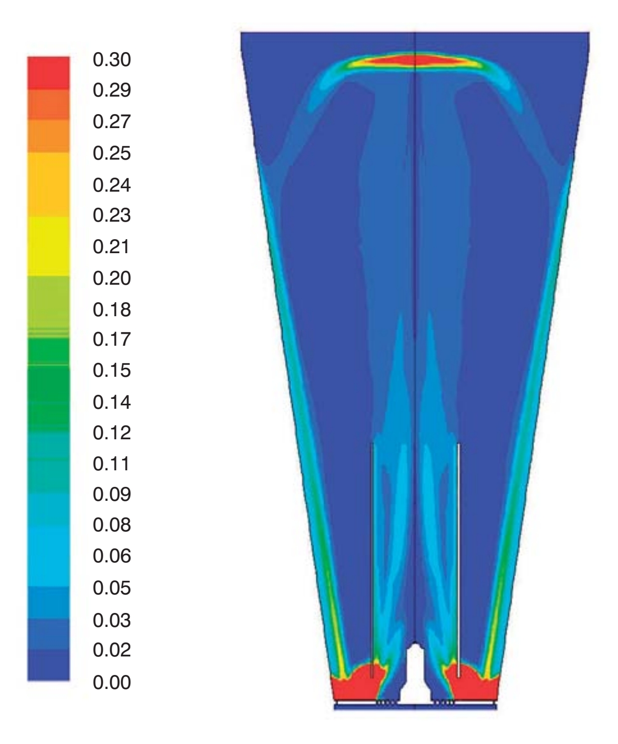

Figure 9: Particle distribution in a fluid-bed coater

CFD simulations are becoming increasingly important because they are more and more commonly used in the development of new equipment. Glatt used CFD simulation to analyze their new ProCell technology, which is used for granulation and particle coating. They used the two-phase Euler approach to observe particle movement within the chamber (Figure 6). The simulation was validated by pressure drop measurements and by visual analysis of a model device. CFD simulations are useful for determination of the device's process parameters [20].

The main purpose of CFD simulations for our research group is to analyze the fluid-bed coating process. Our 2D axisymmetric and 3D computer meshes were based upon the real geometry of GPCG-1. The 2D mesh had far fewer computational cells compared to the 3D (about 50,000 compared to 1 million) and was used for two-phase simulations. The common method for performing the simulations is to start with single-phase simulations; in our case a simulation of fluidizing and atomizing air flow only. We conducted a simulation of atomizing air flow through a spray nozzle (Figure 7) and observed its effect on the hydrodynamics in the chamber by analyzing the pressure field and air velocity values (Figure 8).

The next step was two-phase flow modeling for example of the particles (pellets) in the air. Figure 9 gives a snapshot of the simulation data at a certain point and shows the particle distribution inside the chamber. The color scale represents the particle volume fraction, where dark blue represents the presence of air only and the red represents a particle concentration of 30% or higher. These simulations have been validated and used for the study of Wurster gaps, air velocities, the effect of a spray nozzle, amounts of materials in a chamber, and other process parameters that affect the uniformity of particle coating and process efficiency.

3.3 Spray drying

Spray drying is a common process in the pharmaceutical industry, but it is even more common in the food industry. This is why there are many publications on the topic. The basic principles of spray drying are the same for both industries. Ansys argues that their CFD software can be used to analyze spray nozzles and cyclone performance [13].

CFD can be used to analyze various spray-dryer designs such as the performance of wide or elongated drying chambers. Simulations can search for optimization in regard to material loss on the chamber walls during operation. It has been shown and confirmed that one of the main parameters in spray drying is droplet size. Droplets of sizes below 5 μm completely follow the air pathways while droplets of sizes between 5 and 30 μm decrease in size during the drying procedure and then start to follow the air flow. Droplets of over 30 μm, however, have the tendency to hit and stick to the walls due to the geometry of the chamber studied in this case. Simulations can predict the area where the highest amount of material will be deposited and this information can be used for simulation validation. The validation of spray-drying simulation has been performed with experiments using an NaCl water solution. Using simulations, the effect of inlet drying air angle was found to be an important factor for flow pattern changes and consequently for drying changes. Research done to analyze the effect of the spray nozzle on drying performance was given much attention [21].

Fletcher et al. [22] found that 3D transient simulation should be used for spray-dry modeling. They found that it is able to predict the formation of unstable flows, flows which result in a significant wall deposition. The authors argued that spray-drying simulation should be performed using more complex turbulence models such as Reynolds Averaged Navier-Stokes (RANS) or Large Eddy Simulation (LES). In cases where the k-epsilon turbulence model is used it should be in combination with a finer computational mesh and shorter time intervals.

Langrish [23] describes various levels of spray-dryer modeling. The robust approach considers only mass and heat balance and CFD is considered to be the most detailed method of modeling. The study considers CFD as an appropriate tool for analysis of material deposition and new spray-dryer designs.

3.4 Reactors

Reactors are commonly used in the first stages of medicine production, for example in the production of APIs. They are used in chemical reactions, crystallizations, and in the production of biotech APIs. Mixers and reactors are similar from a construction point of view and are used in the preparation of solutions, emulsions, and suspensions that represent either final dosage form preparation or a step in their preparation [13, 14].

Crystallization of APIs is an important phase in the pharmaceutical development process because crystal size and shape might have a significant effect on various processes. The behavior of variously sized particles in a crystallization chamber has been studied. Particles with sizes between 50 and 900 μm were divided into six size fractions and spread homogenously in the chamber at the beginning of the simulation. The speed of the impeller and the particle size were found to significantly affect particle distribution in the device. Simulations showed that additional construction elements could diminish the sedimentation of the largest particles [24]. Crystallization simulations can be used to study shear stress and its effect upon particle growth and damage. Additional models in CFD simulations can be used to study the crystal growth and assess their final size [13].

CFD simulations represent a valuable tool in the analysis of biotechnological production. The distribution of air bubbles, dissolved gases, and other components in solutions can be predicted and controlled. CFD seems to be applicable for optimizing a reactor's operation and in making scale-up processing more efficient [13, 25].

4 Conclusion

In this article, some examples are given of CFD use in the pharmaceutical industry. There are, however, many other potential areas of CFD usage: HVAC (Heating, Ventilating, and Air Conditioning), the design of pilot space clean rooms [26], safety dynamics such as preventing dust explosions [27], in environmental sciences, and for water quality control. CFD simulations can also support the understanding of basic human physiology (e.g., gastrointestinal tract, heart, blood vessels), something that is necessary for designing medicinal products [13]. Drug delivery and drug release studies have also been supported by CFD simulation by improving the understanding of the process and the hydrodynamics of the environment [28, 29]. In vivo experimentation studies have also been conducted using CFD. These results can help in choosing the appropriate tests for the in vitro/in vivo correlation [30].

CFD simulations alone have a limited ability to model real systems. This is the reason that they are coupled with other simulation methods. Some of the models that are coupled with CFD are the discrete element method (DEM) and finite element method (FEM). These couplings require even more processing power, so they have only been used in the last ten years. Application of such a simulation approach is useful for pneumatic transport systems and fluid-bed systems [31] or for the study of air-particle interactions in tableting machines [32]. Further development of computer hardware and simulation models will enable the extensive simulation of drug delivery and drug release applications [33] and the simulation of industrial processes with millions of particles in the air flow [34], something that is still not possible today.

It is important to note that simulations are never to be used alone; that is, without any experiment or model development. All three aspects of research – modeling, simulation, and experimental validation – should be used in conjunction and only this can provide better process understanding and contribute to process efficiency and the development of products of increased quality. Better understanding of pharmaceutical processes is part of the FDA's paradigm and is expressed in the QbD guidelines [35].

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Enteric coating of pharmaceutical products

By Krisanin Chansanroj

Enteric coating formulations

Enteric coating is aimed to prevent the formulations from gastric fluid in the stomach and release the drug component in the intestinal region. Based on this approach, enteric coating is suitably applied for drugs which cause gastric irritation or are deteriorated by the gastric fluid or gastric enzyme.

Enteric coating polymer

With an acid-resistant property, enteric coating polymers generally possess free carboxylic acid groups on the polymer backbone. They are insoluble in acidic media but become deprotonated and dissolved in basic media at nearly neutral pH values (pH>5). Enteric coating polymers can be classified into 3 groups based on chemical compositions as listed below:

- Polymethacrylates
  - Methacrylic acid/ethyl acrylate
- Cellulose esters
  - Cellulose acetate phthalate (CAP)
  - Cellulose acetate trimellitate (CAT)
  - Hydroxypropylmethylcellulose acetate succinate (HPMCAS)
- Polyvinyl derivatives
  - Polyvinyl acetate phthalate (PVAP)

Solubility of the polymers depends on the number of carboxylic acid groups varied in the composition. Commercial enteric coating polymers are available as powder, aqueous dispersion and organic solution.

Enteric coating formulations need special care of coating operation due to the constrain of drug release specified in the regulatory requirements. Enteric formulations should have less than 10% drug release after 2 hours in the acid stage. The completion of the drug release in the continuation testing in the buffer stage should take place within 45 min.

Organic solution and aqueous dispersion

Generally, enteric coating polymers dissolve well in organic solvents, giving a stable coating solution that facilitates faster coating processes due to easy evaporation of organic solvents. However, the practical use of organic solvents in pharmaceutical formulations has decreased since organic solvent residues in final products are restricted by the authorities. Flammability of organic solvents and their toxicity to operators, as well as their harmfulness to the environment are further reasons. These concerns encourage the use of aqueous dispersion systems with 30-40% wt. dry polymer dispersed in water systems, assisted by surfactants. The last years efforts have been made to develop ready to use dispersions which include all auxiliary components such as plasticizers, opacifiers, and antifoaming agents.

However, the film formation process based on organic solvents and aqueous dispersions is basically different. The polymer in the organic solutions undergoes sol to gel transitions during solvent evaporation whereas polymer particles in aqueous dispersions deposit layer by layer on the surfaces of the coating substrates. Whilst water evaporates, polymer particles approach each other, due to capillary force, and gradually fuse to a uniform layer [1]. Therefore the size of polymer particles in the dispersion could influence film formation. The smaller the particles are, the larger the contact area between the polymer particles becomes. This accelerates polymer coalescence [2]. By consequence a lower amount of dry polymer is required for the enteric protection [3].

Enteric coating based on aqueous dispersion systems has also some limitations. Coating processes take longer than with organic solvent systems as there is more energy required to evaporate water than for solvents. This could increase the deterioration of heat- and/or moisture-sensitive drugs during coating processes [3]. Furthermore, the aqueous dispersion systems are generally susceptible to coagulation because of a number of factors, such as additions of fine powder pigments or wetting agents, high shear gradients during mixing and pH change. Therefore, the preparation of coating dispersion needs careful operations following the directions for use suggested by the producer.

Plasticizer

Success of enteric coating efficiency mostly relies on the addition of plasticizers. Plasticizers are a group of auxiliary components that improve elasticity of the polymeric film which is generally rigid and breakable. Plasticizers reduce the minimum film forming temperature (MFFT) of the polymers, softening the polymeric film at lower temperature. This improves the spreadability of the polymer on the surface of the coating substrates and generates a smoother surface texture of the coating layer [3].

The type of plasticizer should be selected carefully as it influences the film brittleness [4], compatibility with the coating substrates [5] and product stability [3, 5]. Hydrophilic plasticizer, triethyl citrate, is reported to improve the property of Eudragit L 30 D-55 film in the soft gelatin capsule formulations regardless of the type of filled liquid whereas hydrophobic plasticizer, tributyl citrate, gives satisfactory enteric protection only with hydrophobic filled liquid [5]. The latter plasticizer could migrate to the hydrophobic filled liquid upon storage, resulting in the reduction of the enteric protection.

Besides the plasticizer type, the amount of plasticizer is important for film flexibility. Insufficient amount of plasticizer causes the film blistering which could lead to a premature drug release in acidic media, as shown in Figure 1. However, high amount of plasticizer reduces the strength of the film and may accelerate the water uptake into the cores upon storage.

Fig. 1: Enteric coated tablets with insufficient plasticizer; (A) before dissolution test, (B) and (C) after dissolution test in the acid stage for 1 and 2 h, respectively.

Subcoating

The major concern in enteric coating formulations is a risk of premature drug release through the enteric coating film in acid media. This problem could be solved by an application of a subcoating layer where the coating substrates are subject to coating with a small amount of a soluble material, i.e., HPMC, amylopectin, prior to enteric coating. This thin film layer impedes water penetration through the cores and thus prevents the premature drug release.

Subcoating is supportive in formulations which contain highly water-soluble drugs [6-8]. This is where premature drug release mostly occurres. On the contrary, subcoating could also enhance the release of acidic drugs in basic media. This causes a problem of acidic microenvironment at the interface between the core and the enteric film. The migration of diffused drug through the interface results in the delay of drug release in basic media [9].

Due to the restriction in the regulatory requirements, not only the prevention of premature drug release in acidic media should be taken into account, but also the accomplishment of rapid drug release in basic media. To cope with the latter constrain, a new concept of organic acids addition in coating substrates or subcoating layer is initiated in order to promote the basic microenvironment (pH 5-6) at the interface between the enteric film and the cores which could accelerate the polymer dissolution [6, 8, 10-11].

Furthermore, the subcoating layer reduces surface roughness of the coating substrate and improves adhesion of the enteric film on the substrate surface. This generates a robust film formation where a lower amount of enteric coating polymer may be required for enteric protection [3].

Coating operation

Minimum film forming temperature (MFFT)

Besides the knowledge of enteric coating liquids, the coating condition are important for coating efficiency. Since film formation requires the coalescence of the polymer particles on the coating substrates' surface, product temperature should be set to about the polymer's MFFT. This temperature characterizes each polymer. It can be influenced by the type and amount of plasticizers. For enteric coating processes based on aqueous dispersion systems, product temperature is usually set to a range of 30-40°C, in practical operations.

The effect of product temperature becomes troublesome in enteric coating due to the hydrophilicity of enteric coating polymers. They tend to become sticky under humid conditions. The agglomeration of coated particles most likely occurs when the temperature is set too low. This problem becomes crucial in the case of pellet formulations as the growth of sticky pellets takes place in a very short time which could ruin the whole batch if the coating conditions cannot be adjusted in time, see Figure 2.

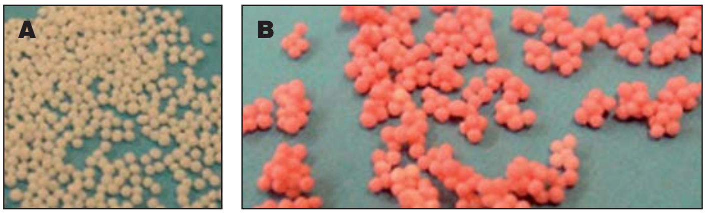

Fig. 2: Effect of low product temperature during coating process; (A) uncoated pellets, (B) coated pellets with agglomeration.

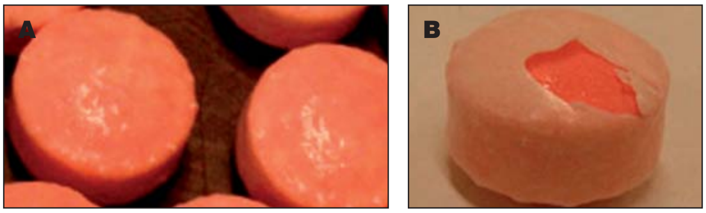

Fig. 3: Effect of high product temperature during coating process; (A) orange peel surface, (B) air trapped under coating layer.

On the other hand, if the product temperature is set too high, this accelerates the solvent/ aqueous evaporation, generating more viscous sprayed-liquid droplets which barely spread on the surface of the coating substrates. This leads to one kind of coating failure which is called 'orange peel appearance'. It results in an inconsistency of the coating layer. Furthermore, high temperature condition could accelerate the volume expansion of the air trapped under the coating layer, shown as the blow out of the film layer, see Figure 3. High temperature and long time processing also accelerate the evaporation of some plasticizers, for example triethylcitrate, thus changing the enteric film property [3].

Coating film distribution

Coating uniformity is attributed to the distribution of sprayed liquid on the surface of the coating substrates. This correlates with the design of the equipment used. For example, in pan coating systems, pan speed has a significant influence on the quality of the film distribution through the mass variance of the moving tablets which determines the optimal amount of polymer for the enteric protection [12]. In Wurster-type fluid bed systems, the coating uniformity depends on the mass of coating substrates passing through the spray zone. it is influenced by inlet air volume, spray shape, flow pattern of the substrates and the gap between the Wurster partition and the air distributing plate [13-15]. The condition of low inlet air volume and low level of the partition tends to generate a dead zone, where the coating substrates cannot be uniformly coated [15].

Curing process and storage condition

Some types of enteric coating polymers, such as HPMCAS, require a special curing process at an elevated temperature and high relative humidity to induce the polymer coalescence [3, 16]. CAP and CAT coatings present instability of the film upon storage especially at high temperatures. This is due to the hydrolysis of ester groups followed by the formation of insoluble cellulose acetate. Furthermore, final products coated with aqueous dispersion systems tend to be sintered upon storage if hydrophilic plasticizers are incorporated [3].

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Fluidised bed granule coating: Case studies of top and bottom spray coating

By Abdullah Alrashidi and Ei Leen Chan

Granule coating, an essential technique used predominantly in the pharmaceutical, food and fertilizer industries, involves the application of a film or coating to solid particles [1]. Granules are coated for a number of reasons: to provide a barrier to oxidation, humidity, light or any other potential sources of degradation of the active principal, to improve the appearance, mask the taste or odours of products, to functionalise powder and to avoid caking phenomena during storage and transport [2]. A number of coating technologies are commercially available and could be generally divided into two categories: systems using mechanical agitation such as rotating drum and pan and those that use pneumatic mixing; for example fluidised beds and spouted beds. The fluidised bed is a widely used process in the production of coated granules, having been successfully used for coating solid particles such as pellets, granules and powder. During this process, granules are fluidised by hot air in which the coating solution is applied using a spraying nozzle. The nozzle could be positioned at either the top or bottom of the fluidised bed [1].

The quality and functionality of the coated granule could be evaluated using various tests, one of which is the dissolution test. It is performed to determine the effect of coating on the rate of release of the active ingredient in a suitable (and usually physiologically relevant) media. Scanning electron microscopy (SEM) is another invaluable technique in this area of study and has improved the general understanding of the physical properties of coated granules [3]. Moreover, a few studies have made use of SEM to determine the thickness of deposited materials on coated granules [3, 4].

A number of studies have focused on the effect of different variables on the coating process by conducting coating experiments at bench scale using bottom spray or top spray methods [5, 6]. The present study uses dissolution tests, coating content tests and SEM to evaluate the film coating applied to granules for different coating methods in a fluidised bed coater (ie: bottom and top spray methods).

1. Top and bottom spray coated granules

The granules were firstly prepared in a high-shear granulator (Romaco Roto Junior) using microcrystalline cellulose (MCC) and lactose M200 powders. The experiments were performed as follow: 850g of MCC and 150g of lactose were added into the high-shear granulator for each batch, the granulation powder was premixed for 2 minutes by running the impeller at 250 rpm. A binding solution of 1kg of water with 10g of sodium chloride (NaCl) was then poured into the mixer with the binder addition time kept constant at 1 minute for all batches. NaCl was added for the dissolution tests carried out subsequently (Section 2.1). The mixture was then allowed to granulate for 10 minutes. The granules were dried in the vacuum oven for 4 hours at a temperature of 40 °C and subsequently sieved into different size ranges (180, 360, 655 and 1090 microns).

A fluidised bed coater (Glatt WSG/GPCG-3), with both top-spray and bottom-spray (Figure 1) configurations was used to spray the coating solution onto the surface of the granules. Hydroxypropyl methylcellulose, HPMC (Pharmacoat 603W, Shin-Etsu Chemical Co. Ltd) solution was used as the coating agent which was mixed with red dye for analysis purposes (Section 2.2). For the top-spray configuration, coating liquid was sprayed from above through a nozzle against the fluidising air flow while a draft tube (Wurster tube) was used to assist an upwards spray of the coating agent for the bottom-spray method. 250g batches of granules were allowed to fluidise until the inlet air had reached the required temperature. The coating liquid was sprayed into the fluidised bed using a pump and nozzle arrangement. Table 1 shows the operating conditions for both spray methods.

2. Assessment of coating properties

Following the production of the coated granules, the properties of the coating had to be analysed to ascertain its functionality. General attributes of the coating are as such: dissolution behavior of coated granules, coating content, thickness of coating, coated

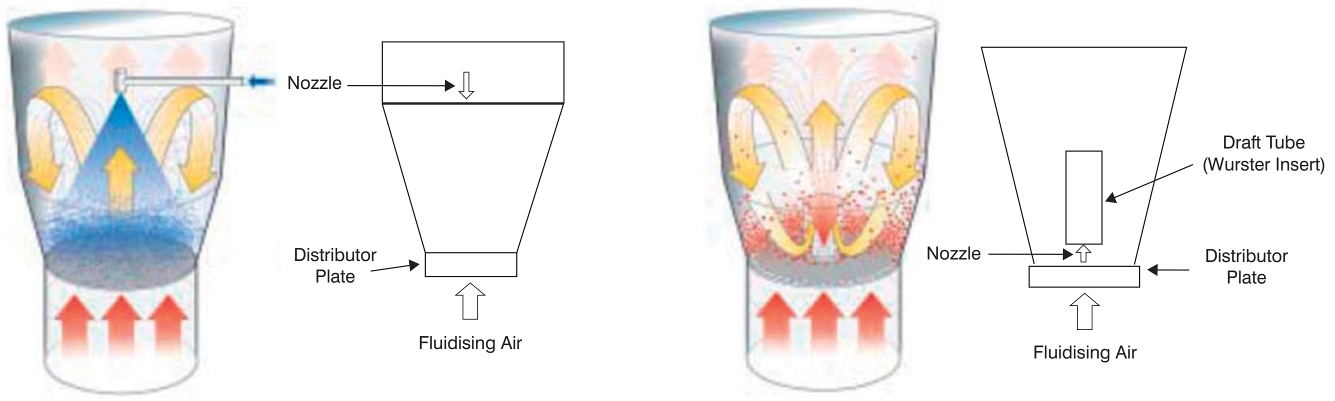


Figure 1: Top spray (left) and bottom spray (right) configurations for the fluidised bed coater [adapted from 7].

Table 1: Standard operating conditions for the fluidised bed coater.

Parameter	Top spray	Bottom spray
Fluidising air flow rate (m³/h)	400	300
Mass of bed (g)	250	
Initial granule size (µm)	780	
Atomising pressure (bar)	2	
Bed temperature (°C)	50	
Spray flow rate (g/min)	12	
Mass of coating solution (g)	60	
Coating concentration (%)	5	
Droplet size (µm)	18	

* Concentration % = mass of coating powder (mass of distilled water + mass of coating powder)

granule flowability, strength etc. The attributes of particular interest would ultimately depend on the application of the coating. The dissolution time, coating content and coated granule morphology were analysed for the produced granules.

2.1 Dissolution time

Dissolution time and coating content are linked, since granules of less coating will dissolve quicker than those with more coating. Dissolution test is often used as an indirect measure of the coated granule quality and functionality and could serve as a better indication of the products actual performance.

Dissolution tests or the release of NaCl were carried out using a Hanna Instruments HI9932 conductivity meter with real time data logging by a PC. The release of NaCl was evaluated by measuring the conductivity of the solution with a probe. The method involved measuring the rate of NaCl release of 1g of coated granules in 600ml of distilled water stirred at a constant rotating speed of 600rpm and kept at a constant temperature of 20°C.

Using the optimal, pre-determined operating conditions for each of the spray methods (Table 1), Figures 2a-b show a comparison of the dissolution test results. The release of NaCl using the bottom spray method is slower than the top spray method; an indirect indication that the amount of coating for bottom spray coated granules is larger than top sprayed ones. The greater distance between the spray nozzle and granules for the top spray method leads to quicker spray drying of the coating droplets, thus reducing the amount of coating agent available when it reaches the granule bed.

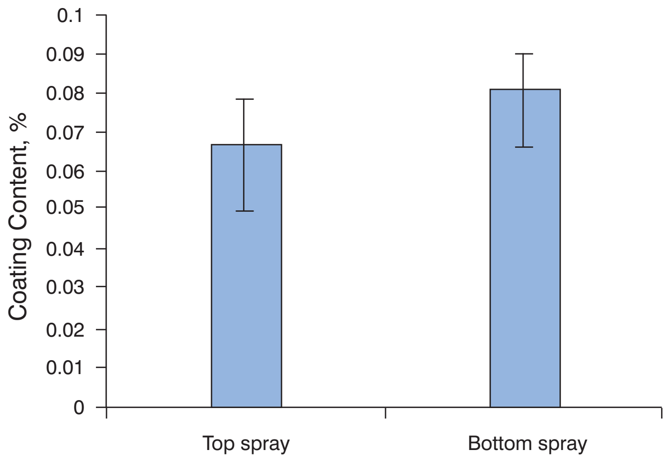
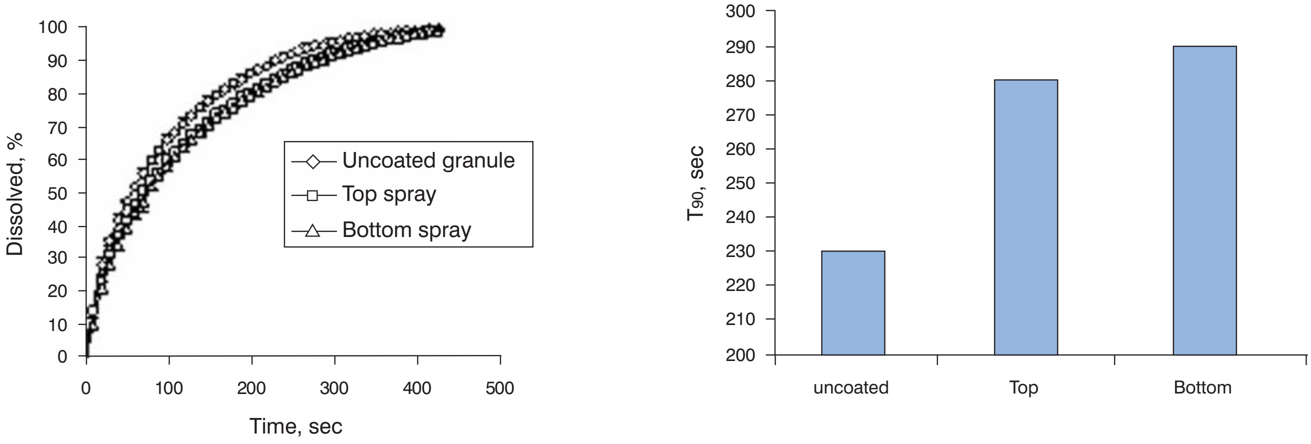


Figure 3: Coating content of coated granules for different spray methods.

2.2 Coating content

The coating content was determined by dissolving 1g of coated granules of different sieved sizes into 100ml of distilled water. Absorbance (of the red dye from the coating) was determined spectrophotometrically at 525nm using a Shimadzu UV-160A spectrophotometer. Prior to that, the spectrophotometer was calibrated using red dye dissolved in the coating agent (HPMC) solution. A calibration curve was obtained by plotting the absorbance versus concentration and applying a regression fit to the data.

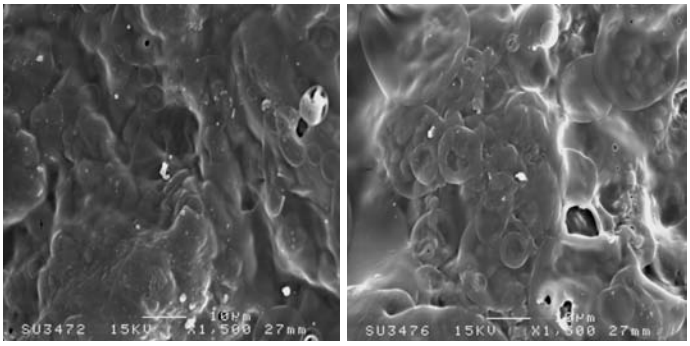
In Figure 3, the results show that the coating content is higher for the bottom sprayed coated granules. The higher amount of deposited mass on granules for the bottom spray coating agrees with the result of the dissolution test method.



(a)

(b)

Figure 2: Dissolution test results (a) Dissolved percentage% with test time (b) Dissolution time for a 90% dissolved amount (T90, sec).



(a) (b)

Figure 4: SEM images of the coated granules for the (a) bottom spray method (b) top spray method.

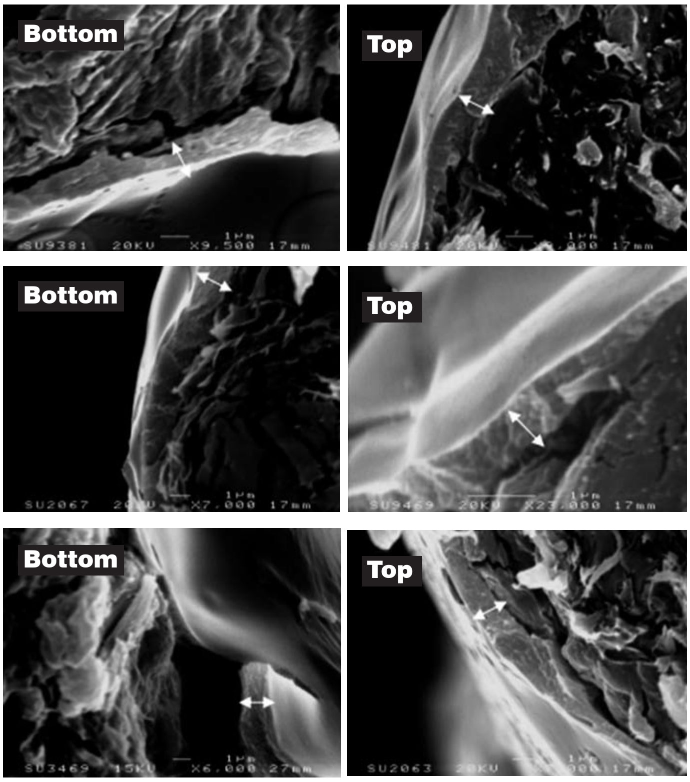


Figure 5: SEM images of coated granules' cross sections for the bottom and top spray methods.

2.3 Granule morphology

Scanning electron microscopy (SEM) provides information on the quality of surface coating, such as uniformity of coated granules and the shape of the granule as well as coating thickness. After being coated, each granule was cut manually by pushing a sharp blade through the granule. The cut section was then coated with gold in order to be conductive. The cross section of coated granules and uniformity of coating were observed using the scanning electron microscope.

2.3.1 Uniformity of coating

For this work, the same processing parameters were applied for both top and bottom spray methods except for the fluidising air flow (400 m^3/h for top spray and 300 m^3/h for bottom spray). In previous works, Yang et al [8] have noticed a rough and flaky appearance of top spray coated pellets, as compared to a smooth and even surface of the bottom spray coated pellets using the same processing parameters for both methods.

The scanning electron microscope (SEM) images of the coated granules, however clearly show smooth and even granule surfaces for both the top and bottom spray methods as shown in Figures 4a-b. There is no real discernable difference in the granule coating quality.

2.3.2 Coating thickness

It is not simple to use direct methods to measure the thickness of coating on granules of irregular shapes. In this work, evaluation of the thickness of the coating using SEM was attempted.

Figure 5 shows the cross section of coated granules of the different spray methods. The images show that very thin coatings (arrows in the figure) could be observed and determined from the SEM images.

3. Conclusion

Analysis of the coating properties (dissolution testing, coating content and SEM) have shown that the amount of coating is higher for the bottom spray method as compared to the top spray. The bottom spray approach ensures a higher degree of interaction between coating binder and granules. Also, spray droplet evaporation is reduced as the Wurster coater setup enables granules to be closer to the spray nozzle. Furthermore, this method allows each layer of coating to dry more completely before granules are recycled to receive further coating. In a top spray arrangement, the droplet travels random distances before impinging on the granules and also, the coating solution is sprayed against the heated air stream causing evaporation of the solution to be more rapid. In previous literature, it is reported that bottom-spray coated pellets released the drug at a slower rate than the top-spray coated pellets [8] which supports the current results. On the other hand, this study noted the similar surface morphology of the coated granules for both top and bottom spray methods while Yang et al [8] observed that top-spray coated pellets had rough and flaky surface as opposed to the smooth and even surface of bottom-coated pellets. This may be due to the physical properties of the coating solution.

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Modern Pharmaceutical Process

By Ralf Kretzschmar, Glatt Systemtechnik GmbH, Dresden

The modern pharmaceutical product handling processes are characterized by their increasing complexity and variability, whilst at the same time containment requirements are rising.

The common strategies are therefore no longer valid and general solutions are needed to deal with the pharmaceutical process.

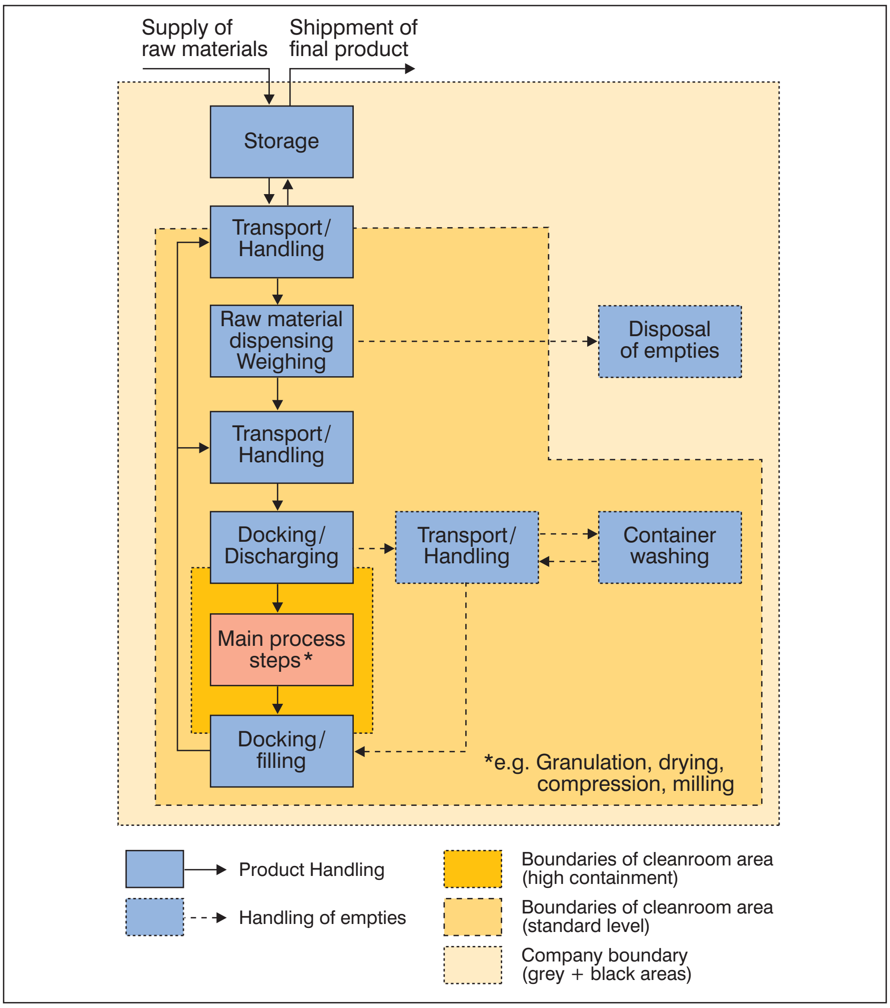
Modern product handling is the integration of different processes and adjustment of the process interfaces to provide a total solution.

Therefore we have to take in to consideration the general need to proceed with new individual solutions for product handling, coupled with process integration for the modern pharmaceutical plant.

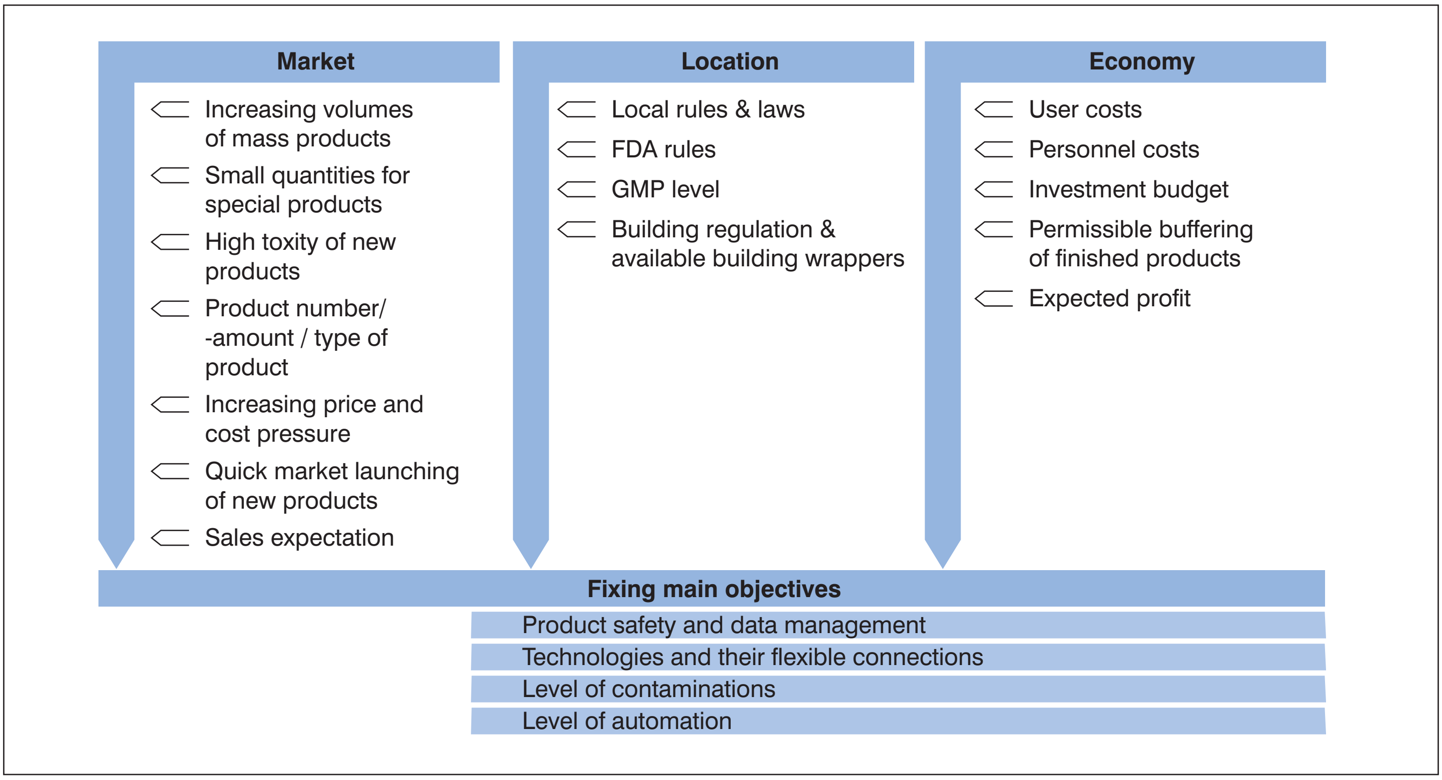
An integrated solution for all processes is only possible with the appropriate knowledge of the process itself. The pharmaceutical process starts with dispensing. Care in developing an engineering solution at this stage, will ensure the overall process can be controlled.

The knowledge of all process relevant data can reduce the running costs of the pharmaceutical plant, by using intelligent handling solutions. The specified level of automation has a major impact on the solution, as does the containment level and cleaning philosophy.

Flexibility in relation to containment levels is the main challenge for modern pharmaceutical projects.



Influencing Factors for the Type of Product Handling



Market

- Increasing volumes of mass products
- Small quantities for special products
- High toxity of new products
- Product number/ -amount / type of product
- Increasing price and cost pressure
- Quick market launching of new products
- Sales expectation

Location

- Local rules & laws
- FDA rules
- GMP level
- Building regulation & available building wrappers

Economy

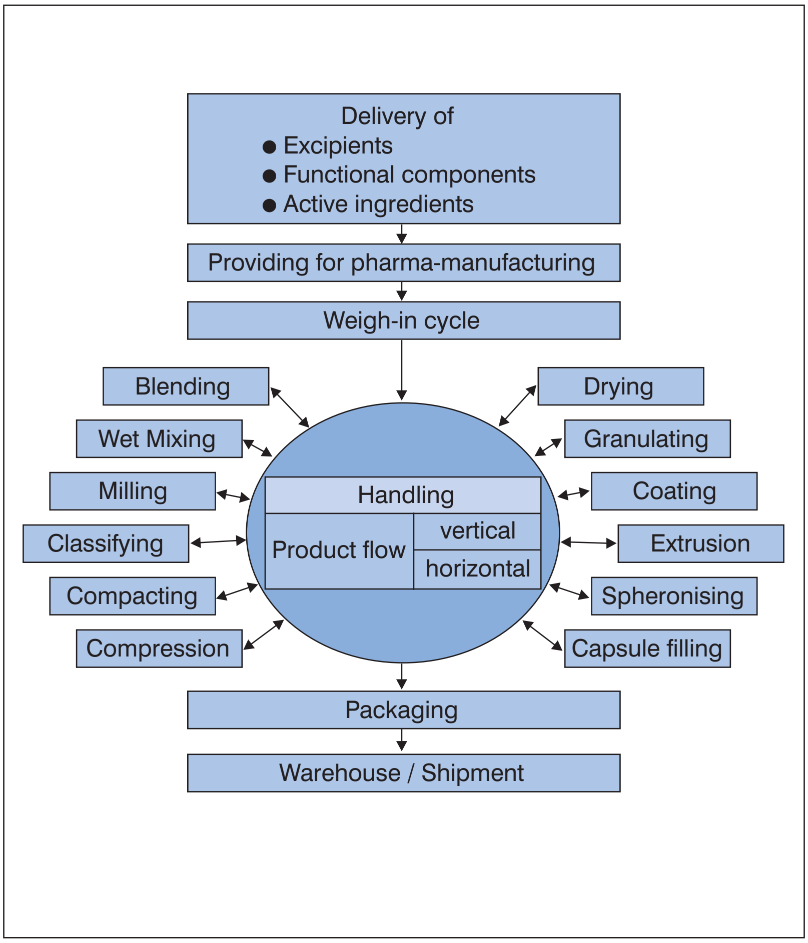
- User costs
- Personnel costs
- Investment budget
- Permissible buffering of finished products
- Expected profit

Fixing main objectives

- Product safety and data management
- Technologies and their flexible connections
- Level of contaminations
- Level of automation

The identification of the main processes, together with a simulation of the complete process flow, is a good basis for a successful project realization.

Technologies and their flexible interfaces



Weighing Systems:
Key Factor in Solid Dosage Fabrication

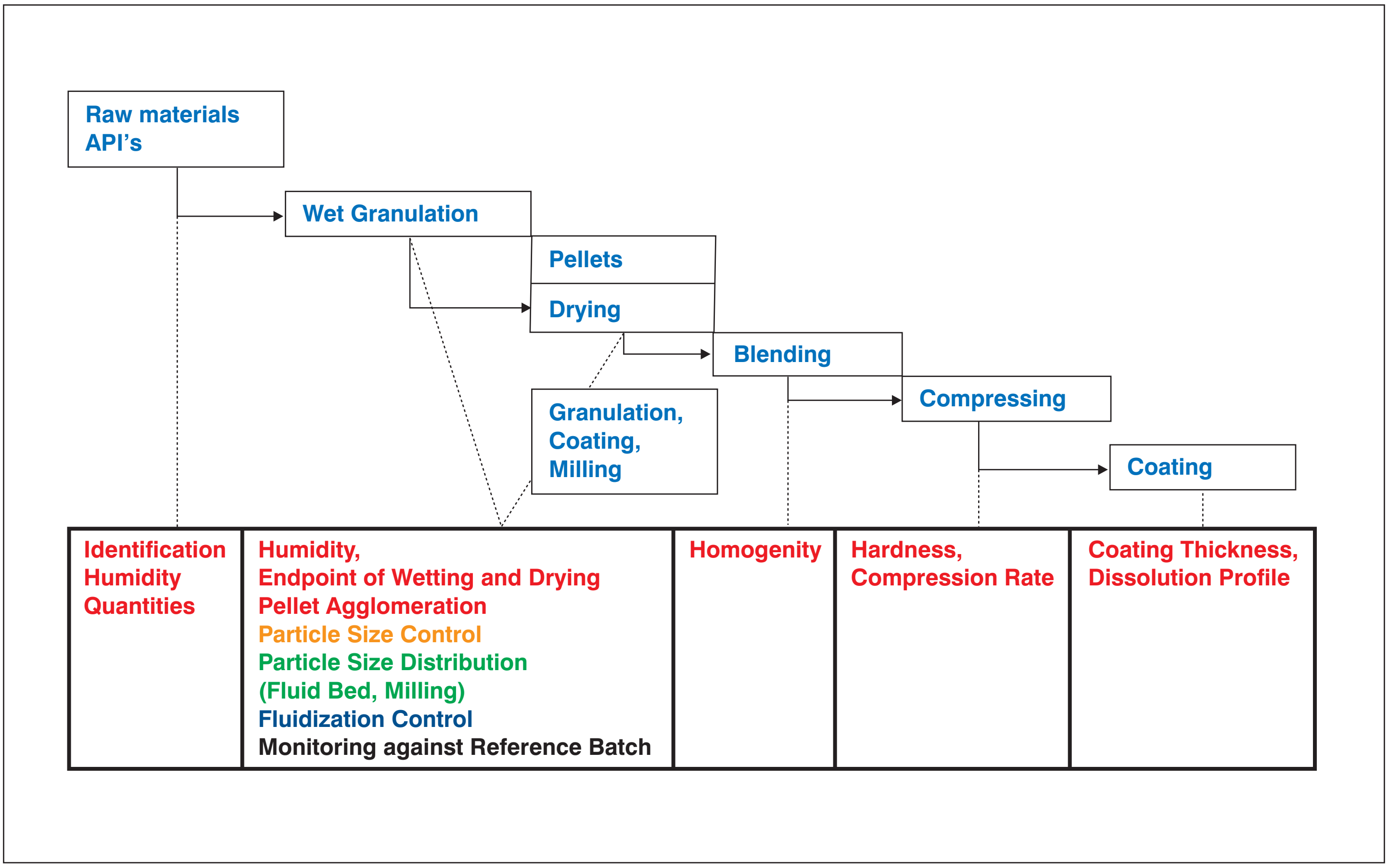
The weigh-in procedure as the first unit operation of the fabrication process has a substantial influence on . . .

- Product quality
- Productivity
- Process validation
- Operator protection measures

Characteristics

- 1 . . . 10 discharge stations / dosage lines
- 1 dispensing station for active ingredients
- Dispensing inc. documentation generally automated
- Recipe management possible
- high productivity (2 . . . 4 bins per hour)
- low cleaning efforts, because of product-dedicated stations
  (regular cleaning only for dispensing of active ingredients)
- high investment costs
- Containment within all levels possible

The new pharmaceutical products will be more complex and difficult to produce under higher containment requirements and increased product quality control. The need to control the quality at all the process steps is essential for a successful manufacturing. The process equipment, as well as the material handling equipment must be designed for the new technologies.



The main design parameters are related to the building restrictions and the possible process flow options:

Product Handling - General criteria for layout of the dispensing process

1. Predominant direction of product flow	● horizontal ● vertical ● rotating
2. Building Layout	● number of usable floors ● room heights (e.g. max. IBC sizes, working platform sizes)
3. Flexibility of system	● multi purpose stations ● modular composition of equipment
4. Degree of automation	● safety interlocks ● control interlinks to higher ranked equipment ● batch tractability ● ergonomy
5. GMP conformity / cleaning philosophy	● CIP / manual cleaning
6. Type of control	● higher ranked system ● island control

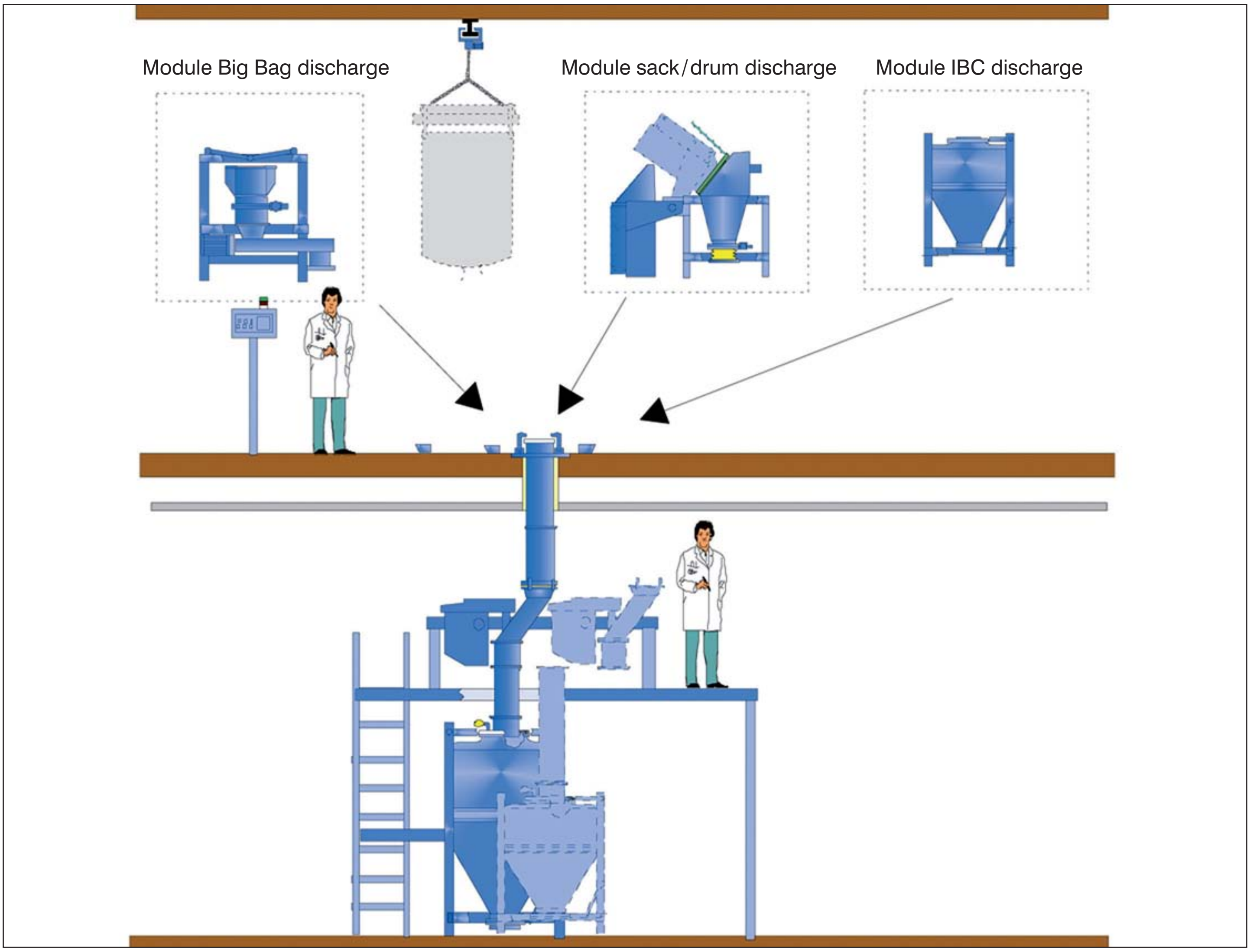
Product Handling - Product relevant criteria for dispensing system design

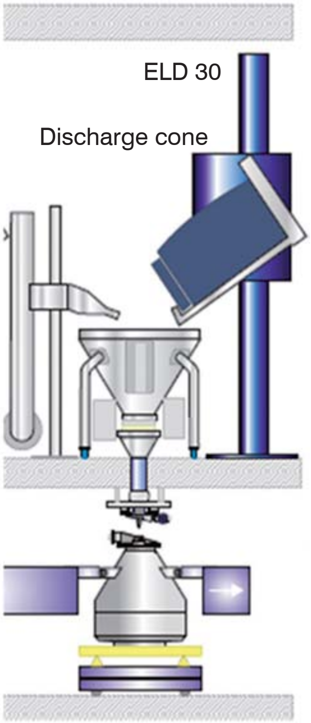
1. Raw material receptacles	● supersacks ● sacks ● drums ● cardboard boxes
2. Types of intra-process containers	● drums ● IBCs (one or more sizes)
3. Properties of handled product	● composition ● flow ability ● effects for operator and environment
4. Quantity of dispensed product	● bulk quantity dispensary ● dispensary for actives / small quantities
5. Dispensing accuracy	● choice of dosing and weighing equipment
6. Necessary intermediate process steps	● separation of foreign material ● de-agglomeration ● milling ● metal detection ● flow measurement ● moisture measurement ● monitoring of discharge ● discharge support

Layout criteria

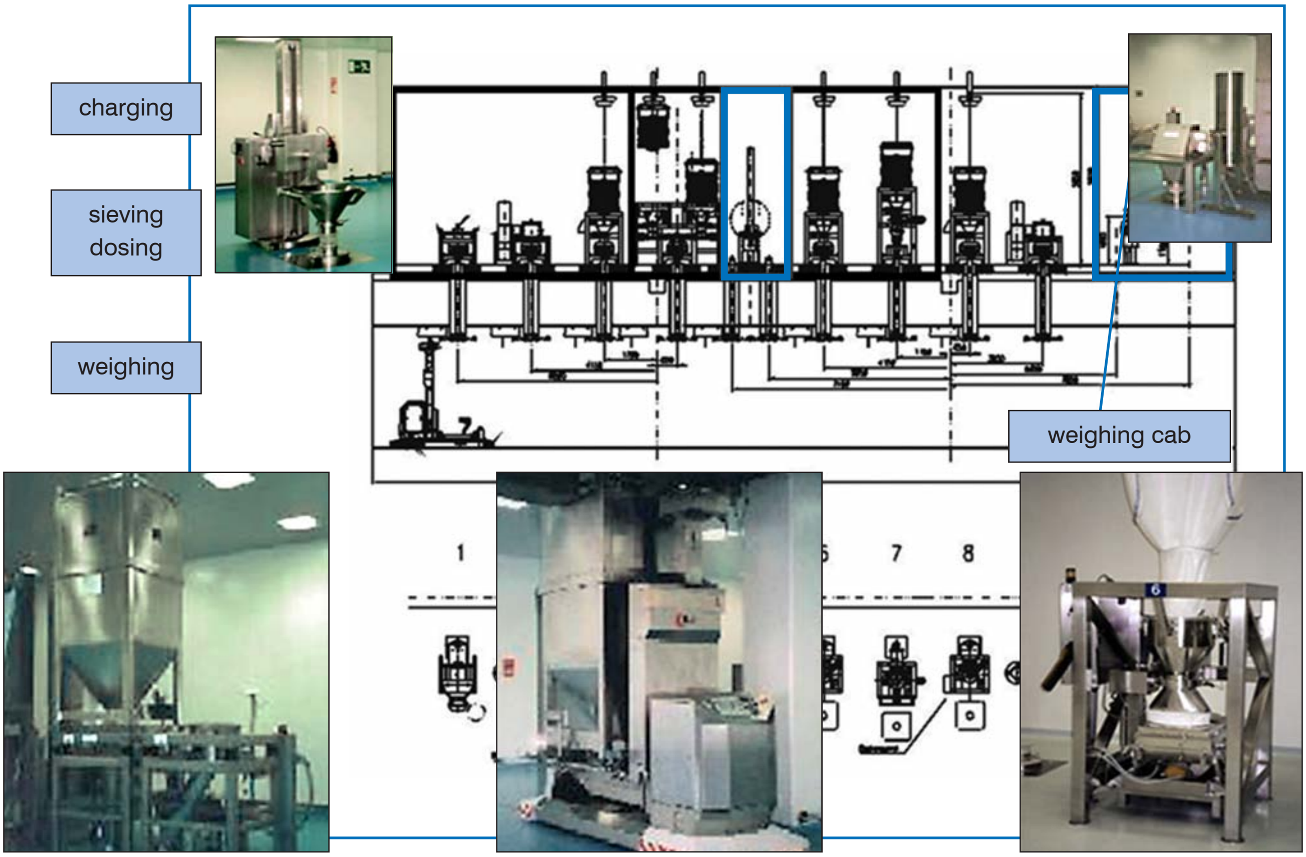
1. Level of containment	● total containment ● normal dust containment
2. Building Layout	● usage of storey to storey drop station or working platforms ● room heights (e.g. max. IBC sizes) ● vacuum conveying / gravity flow
3. Mode of operation	● automatic / semi-automatic / manual (e.g. flap actuation) ● batch traceability
4. Discharging aids	● external / internal beaters ● agitators ● IBC discharge angle
5. Type of IBC	● design, trolley / caster mounted / feet ● type of charging ● type of discharge flap
6. Type of IBC handling devices	● fork truck / AGV / pallet jack / castermounted container
7. Weighing systems	● loss in weight / gain in weight system ● control of dosing equipment

One of the key factors for a modern pharmaceutical design solution is the level of flexibility. The process design should have the capability to accommodate future development and possible new applications.



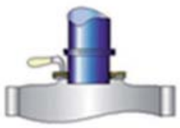


Dispensing of drums



The number of projects with high containment requirements is constantly growing.
The future trend suggests that total containment applications will increase at a higher ratio than standard applications.

Charging



Silicone collar with adapter pipe

Static sealing with lifting unit

Contact free docking system

Inflatable radial seal

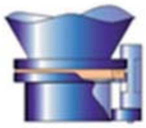
Valve system KS / SKS / TKS

CONTAINMENT LEVEL

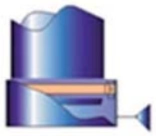
Discharging

Silicone collar

Tulip shaped docking collar



Inflatable axial seal



Inflatable radial seal

Valve system KS / SKS / TKS

Contact free docking system

Tulip shaped docking collar

Inflatable axial seal

Inflatable radial seal

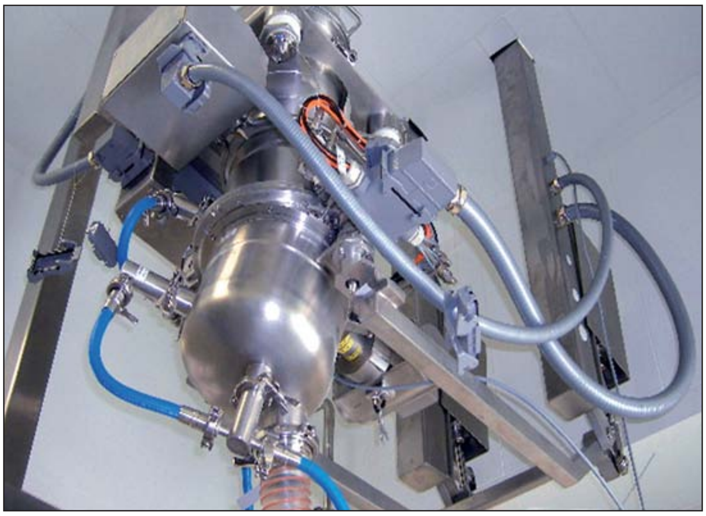
Valve system KS / SKS / TKS

The level of automation will in the majority of cases have the benefit to the customer of reducing the number of operators. The product handling system should therefore be designed with this in mind. The use of automated transport and handling systems can lead to a fully automated pharmaceutical facility vastly reducing the number of operators required.

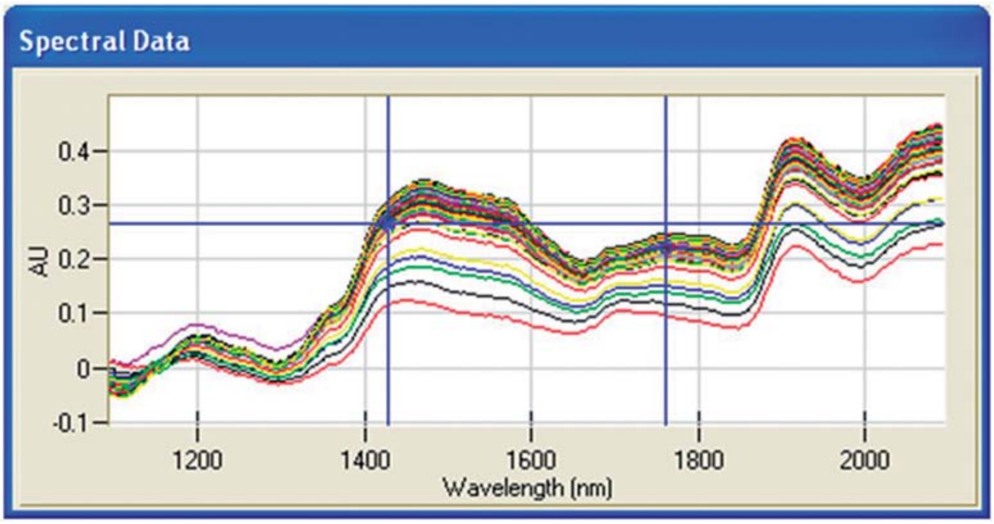
Blender solution with automatic charging ability:

WIP-connections directly docked

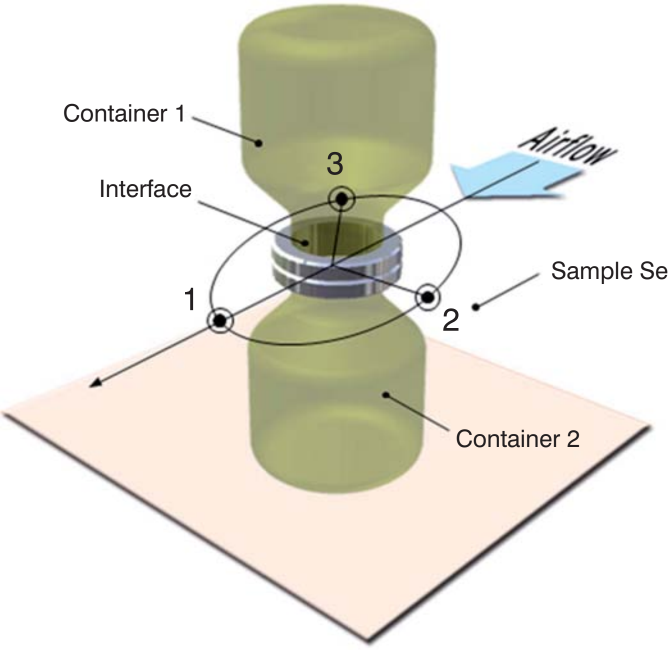
WIP-Rack with drainage for automated docking systems



New measurement technology based on PAT will be the basis for the various quality control steps, e.g. NIR technology for measuring blend uniformity and the granulation process.



With containment solution measurements according to the SMEPAC guideline:



Even in the electronic age the level of documentation will be increased with automatic documentation systems. The equipment supplier must be prepared to fulfill the advanced requirements associated with new documentation systems.

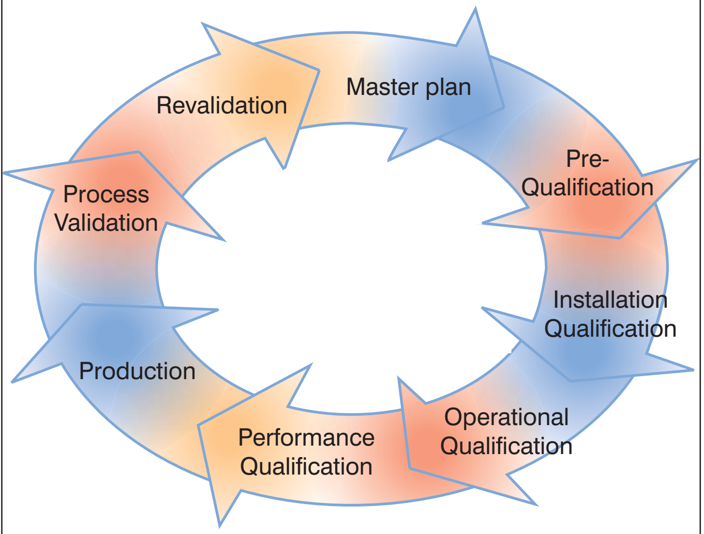
DQ – **D**esign **Q**ualification

IQ –**I**nstallation **Q**ualification

OQ – **O**perational **Q**ualification

The documentation package may cover the following equipment:

Mechanical parts of the plant
Electronic installations
Measuring and control devices
Software PLC and PC
Operational qualification of complete machine functions



Conclusion:

New projects will provide new challenges in relation to the containment levels and the overall project solutions. The material handling will act as the interface component between the different process steps. Successful project solutions will only be possible with interdisciplinary cooperation between the different departments and / or suppliers.

Ralf Kretzschmar is a graduated engineer in cybernetics from the University of Ilmenau, Germany. After ten years of sound experience in light engineering he joined Glatt Systemtechnik Dresden as Vice President and Sales Director.
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SPOTLIGHT

PHARMATRONIC AG at the ILMAC exhibition September 2010 in Basel

Division of Glatt® Group

The ILMAC exhibition is the industry exhibition for Research and Development, Environmental and Process Technology for the pharmaceutical, chemical and biotechnology industries and took place this year from 21st to 24th September in Basel, Switzerland.

This exhibition takes place every 3 years in Basel and, after a successful first-time exhibition in 2007, Pharmatronic AG decided to participate again with a booth at this year's ILMAC.

This highly specialized exhibition mainly attracted visitors from the chemical and pharmaceutical industry from the greater Basel area.

Visitors to the ILMAC are highly qualified and such leading to sophisticated discussions and great interest in the products and services of Pharmatronic

PHARMATRONIC AG

Division of Glatt® Group

25th anniversary celebration "we love to entertain you"

After 25 successful years, Pharmatronic AG celebrated their anniversary on 14th October 2010 this year, with some 90 guests and business partners.

The venue was the historical "Klingental" which was founded in 1274 as a convent and was converted into a museum with historical rooms in 1938/39.

The evening started with a tram ride around Basel, not only to get an impression of the city and to welcome guests but also to show people who already know Basel some new aspects and sights of the city.

For those who did not have time for the tram ride, there was the option of visiting the historical Klingental museum, to learn more about the history of the convent which is closely linked with the history of the city of Basel.

The official proceedings started with a cocktail reception, where all guests had the opportunity to meet and were warmly welcomed by Harald Freudig, the managing director of Pharmatronic AG, and his assistant Isabella Späne.

A delightful dinner was served in the evening, which was playfully interspersed with light comedy provided by some waiters.

The highlights of the evening were not only the speeches given by Prof. Dr. Hans Leuenberger and Mr. Max Hippenmeyer, the deputy mayor of Pratteln, where Pharmatronic AG is located, but also the well-chosen entertainment, which included a hands-on demonstration on how to bake the famous Basel “Leckerli” cookie, the fascinating magician “Collin”, the official Swiss drumming champion Mr. Ivan Kim and last but not least an exotic dancer.

After an evening packed with entertainment, pleasant conversation, excellent food and good wines, Pharmatronic AG has not only shown their experience in being a successful part of the Glatt Group, but also has fully lived up to the motto of the evening: “we love to entertain you”.

Forthcoming Events

interpack
PROCESSES AND PACKAGING

Please visit us
Hall 4, Booth C06

Düsseldorf, Germany
12 - 18 May 2011

LOUNGES 2011

Glatt Ingenieurtechnik GmbH, Weimar
Booth A 3.3

Messe Karlsruhe, Germany
15 - 17 FEBRUARY 2011

POWTECH

Nürnberg, Germany
11 - 15 October 2011

38th Annual Meeting & Exposition of the Controlled Release Society

Innovative and Low-cost Technologies for Healthcare and Consumer Products

July 30 - August 3, 2011 ● Gaylord National Hotel & Convention Center ● National Harbor, Maryland, U.S.A.

TTC
TECHNOLOGY
TRAINING
CENTER

Workshop Nr. 162

Pan Coating

German language

Stichworte zum Inhalt

Mit ständig wachsendem globalen Wettbewerb wächst auch die Notwendigkeit für viele Betriebe, ihre Struktur so anzupassen, dass eine deutlich verbesserte Produktausbeute, Effizienz und Marktposition erzielt wird, möglichst auch mit deutlich verbessertem Gewinn.

Auf der anderen Seite sind Universitäten und Fachhochschulen nicht genügend ausgerüstet und vorbereitet, parallel zur theoretischen Ausbildung auch industrieorientierte und praxisnahe Ausbildung anzubieten, um der Industrie bei der Erreichung der neuen Ziele zu helfen.

Auf direkten Wunsch der Industrie möchten wir helfen, diese Lücke zu schließen. Unsere Qualifikation für diese Aufgabe liegt sicherlich nicht nur in unserer jahrzehntelangen Erfahrung im pharmazeutischen Apparatebau, sondern vor allem im gleichfalls jahrzehntelangen Betrieb dieser Anlagen. Dadurch erhalten unsere Seminare den gewünschten

HANDS-ON-APPROACH

Referenten

Jochen Berger
Ecolab (Schweiz) GmbH, Schweiz

Jörg Crönlein
Colorcon GmbH, Deutschland

Wolfgang Dejan
Glatt AG, Schweiz

Timo Helms
SEPPIC GmbH, Deutschland

Werner Hurst
Glatt GmbH, Deutschland

Philip Parmentier
Glatt AG, Schweiz

Christopher Scheer
Glatt AG, Schweiz

Wolfgang Weisbrod
Evonik AG, Deutschland

Themen

- **Technisches Konzept eines perforierten Trommelcoaters**
- **Optimierung von Filmcoatingprozessen**
- **Wahl der Hilfsstoffe zum Filmcoaten**
- **Praktische Demonstrationen:**
  Suspensionsaufbereitung
  Pellet- oder Tablettencoating
  Düsenwartung
  Scale-up
  Trouble Shooting
  Factory Tour
- **Wichtige Einflussparameter bei der Verarbeitung von Eudragit-Polymeren**
- **Einfluss von Weichmachern und Füllstoffen in HPMC Filmüberzügen**
- **Coatingtechnologien für perforierte Coater**
- **GMP-gerechte Reinigung**

25. - 27. Januar 2011

Anmeldung ▶ **www.ttc-binzen.de**

TECHNOLOGY
TRAINING
CENTER

Technology Workshops in 2011

Workshop No. 162

Pan Coating

GERMAN LANGUAGE

Tue/Wed/Thu 25-27 January 2011

Workshop No. 168

Optimized Plant Engineering

Tue/Wed 13-14 September 2011 · Weimar

Workshop No. 163

Explosionsschutz in der Feststofffertigung

Tue/Wed 15-16 February 2011

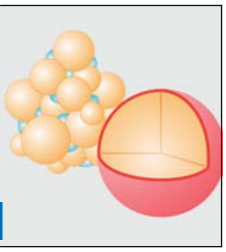
Workshop No. 169

Functional Filmcoating

Tue/Wed/Thu 27-29 September 2011

Workshop No. 164

Fluid Bed Processing



Tue/Wed/Thu 8-10 March 2011

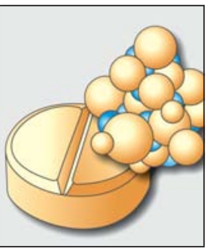
Workshop No. 170

Pan Coating

Tue/Wed/Thu 18-20 October 2011

Workshop No. 165

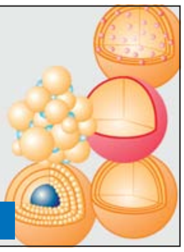
Granulation & Tabletting



Tue/Wed/Thu 5-7 April 2011

Workshop No. 171

Verfahrensoptionen der Wirbelschicht



Tue/Wed/Thu 8-10 November 2011

Workshop No. 166

Continuous Particle Processing

Tue/Wed/Thu 7-9 June 2011 · Weimar

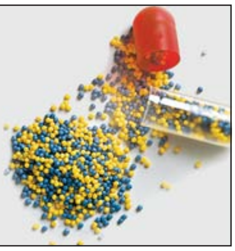
Workshop No. 172

Cellets

Tue/Wed 22-23 November 2011

Workshop No. 167

Multiparticle Dosage Forms



Tue/Wed/Thu 5-7 July 2011

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