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Review article

Mechanistic modelling of fluidized bed drying processes of wet porous granules: A review

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ABSTRACT

Fluidized bed dryers are frequently used in industrial applications and also in the pharmaceutical industry. The general incentives to develop mechanistic models for pharmaceutical processes are listed, and our vision on how this can particularly be done for fluidized bed drying processes of wet granules is given. This review provides a basis for future mechanistic model development for the drying process of wet granules in pharmaceutical processes. It is intended for a broad audience with a varying level of knowledge on pharmaceutical processes and mathematical modelling. Mathematical models are powerful tools to gain process insight and eventually develop well-controlled processes. The level of detail embedded in such a model depends on the goal of the model. Several models have therefore been proposed in the literature and are reviewed here. The drying behaviour of one single granule, a porous particle, can be described using the continuum approach, the pore network modelling method and the shrinkage of the diameter of the wet core approach. As several granules dry at a drying rate dependent on the gas temperature, gas velocity, porosity, etc., the moisture content of a batch of granules will reside in a certain interval. Population Balance Model (ling) (PBM) offers a tool to describe the distribution of particle properties which can be of interest for the application. PBM formulation and solution methods are therefore reviewed. In a fluidized bed, the granules show a fluidization pattern depending on the geometry of the gas inlet, the gas velocity, characteristics of the particles, the dryer design, etc. Computational Fluid Dynamics (CFD) allows to model this behaviour. Moreover, turbulence can be modelled using several approaches: Reynolds-averaged Navier–Stokes Equations (RANS) or Large Eddy Simulation (LES). Another important aspect of CFD is the choice between the Eulerian–Lagrangian and the Eulerian–Eulerian approach. Finally, the PBM and CFD frameworks can be integrated, to describe the evolution of the moisture content of granules during fluidized bed drying.

1. Introduction

This review focuses on the mechanistic modelling of fluidized bed drying processes of wet granules. The main incentive to undertake this review is the current general trend towards development of mechanistic models of unit operations in pharmaceutical production, often as part of ongoing efforts in defining the Design Space of a process. Fluidized bed drying is an important unit operation in the production process of solid dosage forms. Whereas modelling of reactive systems with homogeneous catalysis is relatively straightforward, the development of a mechanistic model of multi-phase systems such as a fluidized bed drying process is still a scientific challenge. In a first part of this review, the focus is given to the pharmaceutical industry and the importance of mechanistic modelling for traditionally applied and new (continuous) pharmaceutical production processes. The incentives to model pharmaceutical production processes are listed, hereby considering regulatory aspects and challenges.

In a second part, the different steps during the production of pharmaceutical tablets are briefly discussed, including the available equipment for the continuous production of tablets.

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A third part focuses on fluidized bed drying systems. Information is given about fluidization, the fluidized bed drying system and the current difficulties to optimize the operation of these dryers. The basic concepts and advantages of mechanistic modelling of a process are discussed. The section ends by presenting the conceptual structure of a model of a fluidized bed drying process.

In a next part, the different steps in the modelling approach are discussed. The available models describing the drying of porous materials are reviewed: the continuum approach, pore network modelling and variants of these models using a crust formation approach. A subsequent section deals with the modelling of processes for a population of particulate entities, namely Population Balance Modelling (PBM). The resulting Population Balance Equation (PBE) is not straightforward to solve; hence, several solution methods are discussed briefly. Also, the use of either a one or a higher dimensional PBM model is discussed. As fluidization is important for the local ambient conditions, a tool to describe the flow of fluid, namely Computational Fluid Dynamics (CFD), is introduced. Here, a section about turbulence modelling is included as well as two approaches to calculate the flow: the Eulerian–Lagrangian and the Eulerian–Eulerian approach. Obviously, the focus lies on the flow of particles in gas. Furthermore, the coupling of PBM and CFD models is highlighted. Where relevant, a short overview about validation methods is included in the different sections of the paper.

As an intentional shift from traditional batch processing towards continuous production exists within the pharmaceutical industry, the authors' view on the advantages and opportunities of this new approach (w.r.t. the shift from batch to continuous and hence the necessity for modelling) to pharmaceutical production is provided as well.

It is noteworthy that the authors want to address a broad audience with this review paper. It should be accessible and useful for researchers and practitioners with a broad range of skills and knowledge in pharmaceutical processes and mathematical modelling. It is not our intention to address all topics in detail, but rather to provide an overview on the state-of-the-art in modelling and how it can be used in the current paradigm shift taking place in the pharmaceutical industry. We suggest the reader to select the sections of interest based on the table of contents and to consult the references that are cited in each section in case more detail is needed.

2. Incentives for developing mechanistic models for pharmaceutical production processes

2.1. Advantages of mechanistic process modelling

Mechanistic process models can be used in two ways:

1. to increase the fundamental scientific understanding of a process
2. to optimize a process that is understood up to a certain level (process control).

An advantage of using models is their solution speed, allowing to compute many different scenarios as opposed to performing expensive experiments. This usually allows process development and optimization with a significantly reduced number of experiments to be performed. Indeed, a range of values can be selected for different input variables and adopted in the model. Of course, it should be clear that a limited number of experiments will always be required for checking the model performance with respect to the real process. The usefulness of the model will depend on the reliability of the model, i.e., reliable mathematical models are necessary to allow for trustworthy conclusions or decisions based on them.

An important aspect in this respect, often overlooked in practice, is the thorough validation of the model, i.e., an evaluation of the performance of the model to ensure that the model is a sufficiently accurate representation of the real process. Without validation, it is impossible and dangerous to use the model for improving, understanding and explaining a process and its performance. A model should include all process elements that are considered to be important for the purpose of the model (model objective) (Section 4.2.1). Furthermore, it needs to be able to describe experimental data of the real system. Lack of these characteristics provides a lack of confidence in the model [1].

2.2. Quality regulation and its impact on the pharmaceutical industry

The pharmaceutical industry is strictly regulated. Good Manufacturing Practices (GMP) are defined to ensure that pharmaceutical products are consistently produced according to the quality standards appropriate to their intended use. The main purpose of the GMP rules is to ensure that each product is produced consistently, safely, reliably and with high quality [2]. Before pharmaceuticals can be released on the market, a product licence from the relevant regulatory body is obligatory. The latter is time-consuming and expensive to obtain, but is required for distribution of the product [3].

Traditionally, regulations had a serious impact on the way pharmaceuticals are produced. Indeed, once a process was licensed, it was considered to be nearly impossible to change something in the way of processing [3]. The intention of the Food and Drug Administration (FDA) with its publication of the Process Analytical Technology (PAT) guidance is to overcome this situation of unchangeable, unflexible traditional 'frozen' production processes. Indeed, despite the fact that it is known that many processes could operate in a better way (e.g. more cost-effective), changes to the production process have not been implemented due to the considerable amount of work that was related to obtaining an updated manufacturing licence. The scope of PAT is to support innovation and efficiency in Pharmaceutical Development, manufacturing and quality assurance. As mentioned in PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance: *quality cannot be tested into products; it should be built-in or should be by design* [4].

A risk and science-based approach has to be applied to pharmaceuticals in a quality system. The guidelines on Pharmaceutical Development (Q8), Quality Risk management (Q9) and Pharmaceutical Quality System (Q10) were drafted. The ICH Quality vision statement is 'Develop a harmonized Pharmaceutical Quality System applicable across the life cycle of the product emphasizing an integrated approach to Quality Risk management and science'. Quality By Design (QbD) is an important concept and has been defined as 'a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and Quality Risk management' [5].

A central PAT-concept is the Design Space. The process design space is defined as: 'The multidimensional combination and interaction of input variables, i.e., material attributes and process parameters that have been demonstrated to provide assurance of quality. Working within the Design Space is not considered as a change. Movement out of the Design Space is considered to be a change and would normally initiate a regulatory post-approval change process. The Design Space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8).' The pharmaceutical industry now has to demonstrate that the product is safe within the Design Space. Once such a Design Space

has been approved, it is allowed to further optimize the process as long as one guarantees that the production process stays within the Design Space. However, process and product knowledge form the basis for the definition of the Design Space. Advanced mechanistic models as the ones that will be reviewed in this paper (Sections 3–6) are by far the most powerful means to gain this missing process knowledge and to actively optimize processes. Therefore, a thorough overview of models and how they can assist in achieving the above are crucial and are part of the intent of this contribution.

A final aim of the PAT and QbD concepts is Real Time Release Testing, meaning 'the ability to evaluate and ensure the quality of in-process and/or final product specifications based on process data, which typically includes a valid combination of measured material attributes and process controls' [5,6].

Also, here, models can be used to support the development of a Design Space for the process. In other words, process model development is completely in line with the PAT guidance. The model summarizes available process knowledge which would help to understand the influence of input variables on the process and hence on the quality of the product.

2.3. Towards continuous production in pharmaceutical industry

2.3.1. Batch versus continuous production

In several industries (e.g. bulk chemical industry and food industry) continuous manufacturing is already well established. In contrast, the pharmaceutical industry still heavily relies on batch processing.

Batch processes have certain advantages [7]:

- In terms of quality assurance, i.e., a batch is well defined and can simply be accepted or rejected based on a quality assessment. In the continuous approach, the quality of the product can be monitored during the process. Hence, once process knowledge is developed, the continuous approach will be equally able to guarantee product quality and on the long run be more effective due to its higher flexibility and, hence, reduced losses.
- The flexibility in the equipment. Indeed, in batch processing, a set of different operations can be performed in almost any sequence of the available equipment in order to produce the pharmaceutical product. For instance, after the drying of wet granules, a milling or a post-blending step can be performed (Fig. 1). Establishing a suitable sequence of unit process operations is considerably more complicated in a continuous process. However, improved process knowledge and process control will help to overcome such drawbacks and, hence, eliminate this advantage.
- The expertise that has been compiled, as batch processes have been optimized for decades. A similar learning curve is needed for continuous operation. It is expected that the batch expertise will be of value for this and, hence, will most likely result in a much shorter learning curve.

Some of the disadvantages of batch production processes can be tackled by switching to continuous production processes. Advantages of continuous processing are [3,7]:

- Easier to understand. The problems are three-dimensional instead of four-dimensional, at least at steady state, because the time-variable can be eliminated.
- Increasing the production rate can be achieved by numbering up (scaling out) instead of scaling up, which would reduce the time-to-market. During the development of a pharmaceutical product, clinical trials are set up at a small scale. Afterwards, scale-up is of major importance in order to design equipment with larger volume and will affect the operational conditions to achieve a similar system behaviour and performance. This step is no longer required when operating in continuous mode.
- Connection with naturally (semi-) continuous processes such as spray-drying or tabletting is more straightforward. To date, these process steps need to be started up when a batch of for instance dried granules arrives and shut down when awaiting the next product batch, making this very inefficient and introducing variability in the product properties.
- Improving the quality. In a batch, the transfer of mass, heat and momentum is not homogeneous, which leads to a lower product quality [8]. A lot of process properties will be locally varying, leading to a wide distribution in the properties of the output. Continuous processes can minimize these effects (i.e. less variance), because mass and heat transfer is more efficient as the surface to volume ratio is higher. Last but not least, continuous processes are typically easier to control compared with batch processes, as a consequence of the smaller scale.

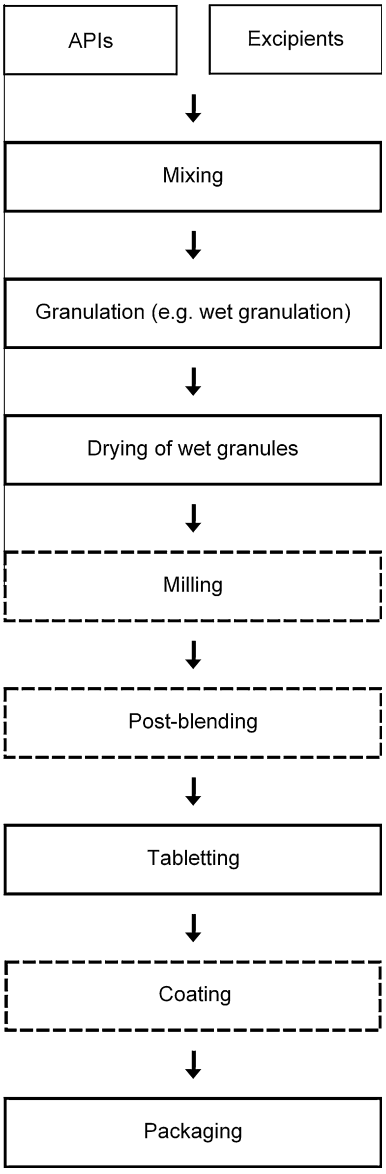


Fig. 1. Scheme of typical processing of pharmaceutical products during the formulation of tablets.

- Reduced problems due to increased market share. A need for a higher capacity in batch processes gives rise to a large capital investment, whereas in a continuous operation, this is only necessary if no spare capacity is available. If spare capacity exists, the output can simply be expanded by means of a longer production time. The ability to vary production rates reduces startup and shutdown of process chains.
- Reduced generation of waste through inline measurements.
- Increased safety due to the fact that a continuous process will operate at a much smaller scale compared with a batch process (less material is processed at the same time in the continuous process) and less start-up and shut down time is needed.

Evaluating the advantages and the disadvantages of both ways of operating pharmaceutical processes, and given the fact that continuous processes still have a large marginal improvement potential, it can be concluded that the continuous way of operation is the way to go for the industry. However, as stated before, the shift towards continuous processes largely depends on improved process knowledge. This emphasizes the necessity for the development of mechanistic models. A validated model will be essential to develop a trustworthy system to control quality based on online measurements and real-time adjustment of process parameters. A model can help to better understand the process and can be used to develop and test algorithms to control the process. Next to the fact that a model is necessary to take full advantage of a continuous process, the development of a model can be easier for a continuous process. As mentioned earlier, a batch process is four-dimensional. Also, the ambient conditions are often more homogeneous for a continuous process compared with batch processes, often allowing reduction of the full model to a model without spatial heterogeneity.

2.3.2. State of the art and required needs for the pharmaceutical industry

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with off-line time-consuming and less efficient laboratory testing conducted on randomly collected samples to evaluate quality. Hence, limited relevant information is mainly obtained after the process, making process control difficult and provoking unnecessary batch losses. Furthermore, the batch processes themselves are often poorly understood inefficient black-boxes. In this respect, availability of a mechanistic model would increase the understanding of the fundamental scientific phenomena and processes. The advantages of continuous production increase when a model is available to support the development of real-time process control.

The pharmaceutical industry has a continuous focus on Research and Development of new drugs. It is in the interest of the pharmaceutical industry to reduce the development time for new drug products as much as possible. In this way, the product can be brought quickly to the market and the profit is maximized. Indeed, patent-life is finite and rather short, and the market share in most cases decreases significantly when a patent expires due to competition from generic drug product manufacturers [3]. This is a strong driver for investigating new systems. However, the belief that continuous production systems are only feasible for large volume productions and production sites that systematically produce the same product hamper the development of continuous production processes. Further reasons for not moving towards continuous operation are the difficulties to meet the high product quality standards (Section 2.2). Finally, also regulatory authorities have delayed the introduction through their conservatism and negativism towards continuous processes [6]. The 'real-time release' concept is an important driver for the increased interest of the pharmaceutical industry in continuous production processes, since the benefits of 'real-time release' are highest when applied to a continuous process. However, in our opinion, such continuous production methods need to be implemented already in the development phase of the drug production process [5,6].

From the above, it is clear that improved process understanding is really the key to launch continuous production in pharmacy and convince those who are still hesitant. The switch to continuous production processes with on-line control requires, next to a validated model, reliable sensors and adapted equipment. The eventual goal should be to build a set of validated models for the whole continuous line.

3. Production of pharmaceutical tablets

Industrial-scale pharmaceutical production can be subdivided in a number of stages. A pharmaceutical product typically consists of both Active Pharmaceutical Ingredient (APIs) and excipients. An APIs is produced through either chemical synthesis, through biological processing, or a combination of both. The excipients are produced separately, often at a different production site or by a different company. Examples of excipients are water, lactose, starch, sugar, colouring agents. Excipients have no therapeutic effect, but are necessary for the manufacturing of the drug product.

Subsequently, the API and the excipients are formulated into drug products, which are in many cases tablets, but could also be capsules, aerosols, injectables, etc. The last step in the production sequence is the packaging, which can be bottles, blister packs, etc. [3].

In this contribution, the focus will be on tablets as pharmaceutical solid dosage end product form (Fig. 1). Their classical manufacturing process consists of several consecutive steps (Fig. 1). The starting point is the blending of the individual components, i.e., the APIs and the excipients. After blending, granulation is performed to agglomerate particles into granules. The purpose of this step is to improve the powder flow properties, to reduce demixing, to reduce dust formation and to promote the compressibility of the powder mix. Several granulation procedures exist (e.g. wet granulation, dry granulation) [9].

The choice of the technique for drying wet granules might influence the properties of the granules and, hence, the further downstream processing. Convection, conduction or vacuum drying are the means to supply thermal energy needed for the drying process. Fluidized bed drying, an example of a convective drying method, is the most commonly used method in production-scale pharmaceutical manufacturing [10]. Fluidized bed drying is compared with microwave-vacuum drying processes. Using a vacuum chamber, the resulting dried granules had a lower level of porosity and higher bulk and tapped densities. Another aspect is the spherical form that is more retained when using a vacuum chamber. Furthermore, the mean particle size was larger for granules dried in the vacuum chamber. The powder fraction after drying was comparable for both vacuum and fluidized bed drying. An advantage of fluidized bed drying is the shorter drying time [10].

This review focuses on a first isolated unit process, the fluidized bed dryer and more specifically on the available tools for the development of a detailed mechanistic model. To date, the equipment to produce tablets in continuous mode is limited. The ConsiGmA Continuous Tableting Line of GEA Pharma Systems enables the production of tablets from powders in 20 min. It consists of the ConsiGma high-shear granulator and dryer, combined with the GEA Courtoy MODUL P rotary tablet press [11]. The CWG line of Lödige Process Technology is a continuous wet granulation line and is also a complete system from raw material dosing till tabletting [12].

4. Fluidized bed drying process

4.1. Introduction and related problems

Fluidized bed dryers are widely used in industrial applications for the drying of wet solid particles. Products such as maize [13], coconut [14], baker's yeast [15], beans [16], black tea [17] are successfully dried in a fluidized bed. In industrial processes, a high drying rate is desirable, in other words a high rate of heat and mass transfer. Fluidized beds have the advantage of achieving a large contact area between the solids and the gas, a high mixing degree of the solids and high transfer coefficients of heat and moisture between solids and gas. All these factors shorten the drying time without the disadvantage of damaging the materials (e.g. heat sensitive products). However, the process also has some downsides: scale-up problems, poor fluidization, non-uniform product quality. These are in fact mainly caused by poor understanding of the process. Due to the lack of reliable mathematical models for fluidized bed drying processes, process optimization and scale-up are typically performed empirically based on pilot-plant data. Prediction of the performance of industrial fluidized bed dryers is impossible without such data [18].

Several materials are nowadays mostly produced in batch mode. However, drying is a very energy and time-consuming process. Significant benefits could be achieved by improving the drying process, for example through the implementation of a continuous drying process [3].

The fluidization process, the process whereby the granular material behaves in a fluid-like state, in itself is not so trivial. Solid particles can be divided into several fluidization classes, the so-called Geldart classes [19]. Particles are classified based on (1) the density difference with the gas phase and (2) their mean particle size (Fig. 2). Each group has distinguishable characteristics and displays a certain fluidization pattern (Fig. 3) [20,19]. Powders belonging to group A will display a dense phase expansion after minimum fluidization, before bubbling starts, whereas particles of group B start bubbling at minimum fluidization. Group C particles are even more difficult to fluidize. Finally, particles in group D, characterized by large size and/or density, can show a spouted bed behaviour. A spouted bed is a fluidized bed where the air forms a single channel trough which some particles flow, whereas particles fall down again once they are outside this channel. In practice, it is more difficult to distinguish between these different groups. Next to the criteria of Geldart, there are additional criteria to classify fluidized beds. Some are based on interparticle forces in the vicinity of bubbles, leading to a dimensionless Froude number, or combinations of this number with the Reynolds number. Others consider the stability or growth of disturbances, the maximum size of the bubble to be stable or the occurrence of shock waves for defining criteria [19].

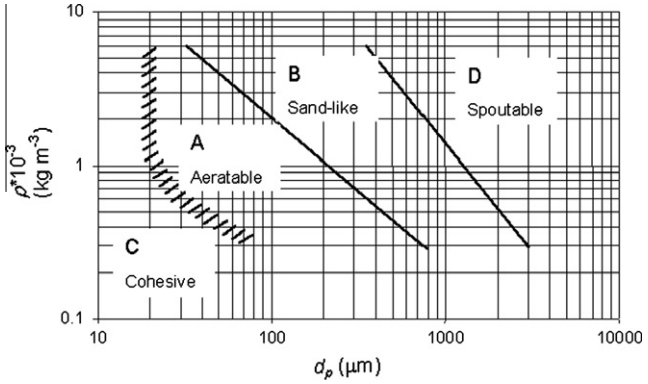


Fig. 2. Geldarts fluidization classification of powders [19].

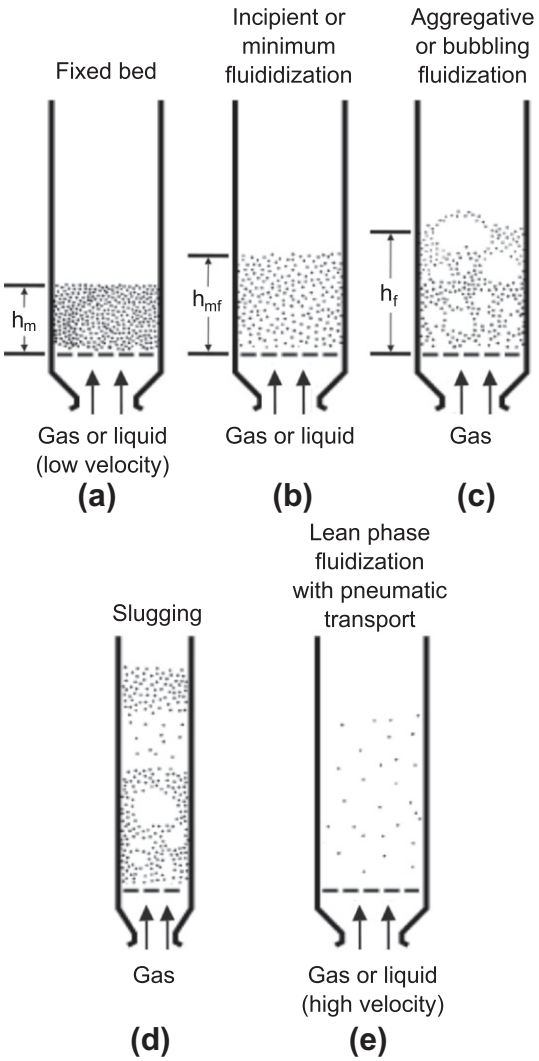


Fig. 3. Different regimes of fluidization after Kunii [20].

Drying of particles makes it even more difficult to characterize the fluidization behaviour of powders since the drying itself will influence the fluidization behaviour. During drying, the moisture content drops, which improves the fluidization. Using the classification of Geldart, it is known that particles can shift from a Geldart C type of powder to Geldart B powders during drying. Parameters such as the full support velocity, full support bed voidage and Hausner ratio have been used to determine the powder behaviour [21].

Granulation is the process whereby smaller particles are converted into larger agglomerates. This size enlargement process occurs often in the pharmaceutical industry to agglomerate powders to granules. During this process, granules of different sizes are produced. A certain Particle Size Distribution (PSD) of the granules is desired for the subsequent tabletting step. The influence of the PSD on the fluidization pattern is discussed in the literature, and it is concluded that granules with a wider PSD are more inclined to show a spouted bed behaviour [22].

4.2. Modelling of fluidized bed drying processes

4.2.1. Objective of mechanistic fluidized bed drying models

Every model development exercise should start with formulating the goal or objective of the model (Fig. 4). One should list the

requirements and questions one wants to answer. In the case of a drying process, the model will typically help to understand the process in more detail. Changing input variables and parameters, for example in the frame of a sensitivity analysis (to study how the variation in the simulated output can be apportioned to different sources of variation in the input/parameters of the model), helps to gain information about the dynamics of the process. Moreover, such simulations can also be helpful to find out which input variables are important to control in order to produce granules with the required quality. Furthermore, a model can also be helpful to develop and tune control systems. Using the knowledge about the process incorporated in the model will indeed be important for the selection of input variables that can be used to adapt the process in real-time, resulting in enhanced product quality and/or an optimized energy consumption.

The collection of experimental data is important in order to build a mathematical model (step 1 in Fig. 4), relying on physical mechanisms. After the model has been built, experimental data have to be used to calibrate the model (step 2 in Fig. 4). Model predictions have to be compared with experimental data to validate the parameters of the model. If a good agreement is found, the model can be used to run predictive simulations. Otherwise, the described physical mechanisms should be reconsidered and altered where needed.

4.2.2. Structure of fluidized bed drying models

When modelling the fluidized bed drying process of wet granules, two distinct processes need to be accounted for. First, granules are dried, a process which is significantly influenced by the local conditions of the gas (velocity, vapour pressure). Secondly, the granules are fluidized in the dryer, thereby exhibiting a certain fluidization pattern which depends on the gas flow rate and the particle density. Depending on the fluidization pattern, particles will follow a certain trajectory in the dryer. The gas that is flowing through the body of the dryer will exhibit dynamic varying properties when moving from inlet to outlet. This is caused by water evaporating from the granules inducing the temperature of the gas to drop and the moisture content to increase. Hence, the drying behaviour of particles in different locations of the dryer will be different. Both processes, the drying processes and the fluidization, are strongly interrelated.

A thermodynamic model for a fluidized bed drying process has been developed in order to optimize the input and output conditions. For this, study energy and exergy models were used [23]. Operating conditions, such as gas velocity, inlet gas temperature, outlet gas temperature, feed temperature, influence the quality of the dried product. Drying processes require significant amounts of energy, and optimizing process operation, for example on the basis of model simulations, can reduce the process operating costs significantly. An exergy and enery analysis can help to determine the influence of thermodynamic and hydrodynamic parameters on process effectiveness in order to improve the drying process [23].

A batch fluidized bed dryer for fine powders has been modelled in order to predict the bed temperature, the humidity of the outlet gas, the moisture content of the solid particles and heat and mass transfer in an inert medium fluidized bed. Model predictions agreed well with the experimental data [24].

5. Modelling the drying of porous material

The drying behaviour of porous material can be described with a model. In this section, an overview of such models is given.

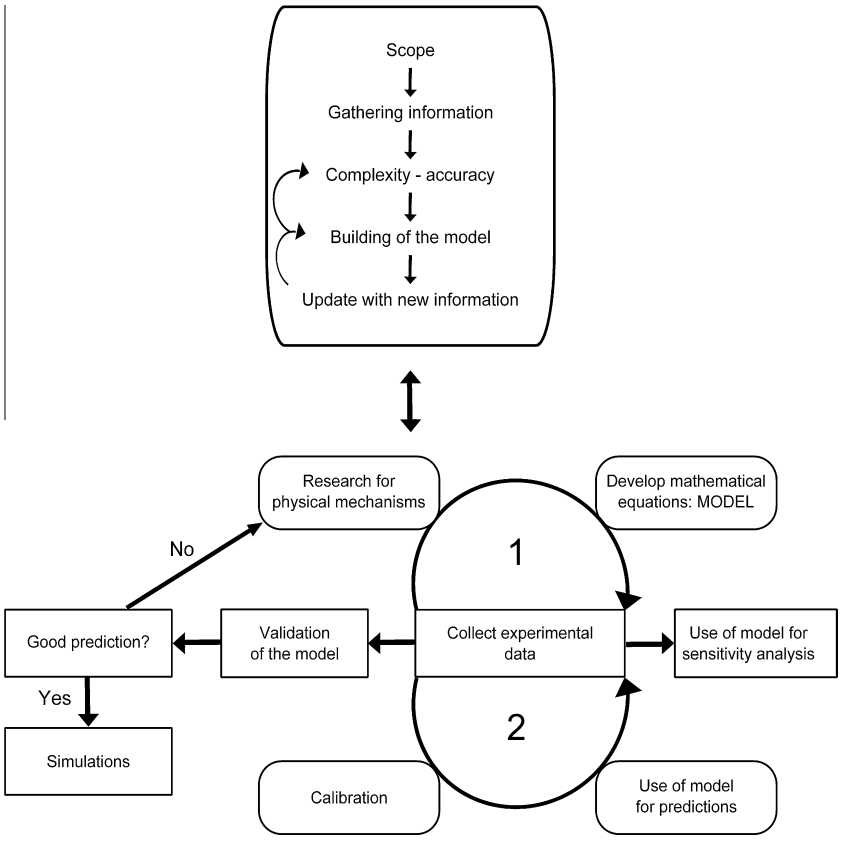


Fig. 4. Scheme of the steps needed to build a model.

5.1. Introduction

The development of models for the description of drying kinetics of porous material has received a lot of attention in the literature. Drying of porous media is commonly used in several industries, for example the food industry [25], the pharmaceutical industry [26], the paper industry [27], and the chemical industry [28]. The process is studied at different scales, ranging from the pore scale to the dryer scale. Modelling at the scale of the pore can be the starting point for a detailed model. Performing a sensitivity analysis on a detailed model can give insight into the most influential parameters. This information can then be used in a subsequent model reduction step, where the behaviour is approximated by a simpler model, leading to a model that can be implemented to describe the process on a larger scale with an acceptable computational cost.

Hence, the development of a model at the dryer scale could be seen as a scale-up problem, meaning that the application field of the model is extended [29]. In this case, the interesting scale is the product scale, being one single granule. When the dried product is an intermediate, the ultimate goal is optimizing the quality of the end product.

Several aspects have been taken into account when describing drying processes at the pore scale. There is a difference in the way water is fixed in the product, in the porosity of the product, in the size of the pore, etc. [30]. Hygroscopic materials will fix a large amount of water by adsorption, whereas non-hygroscopic porous media will fix water only by capillarity. Next to capillarity, gravity and viscous forces are also responsible for liquid transport, whereas diffusion is the important mechanism in the gas phase [29].

During drying, both heat and mass transfer have to be taken into account. Some studies do not account for temperature gradients, which is a valid assumption in the case of slow drying. However, a more detailed model, which incorporates the transport of energy and thus also temperature gradients, will be more accurate [31]. Distinct approaches for the modelling of the drying of porous media can be found in literature: the continuum approach, pore network models and variants of crust formation. These will be briefly discussed in the next sections.

5.2. The continuum approach

This first approach was proposed by Whitaker and considers the porous medium as a fictitious macroscopic continuum [32]. The effects of the different physical phenomena (e.g. capillary effects) are lumped into phenomenological coefficients, implying that the detailed effects of the pore microstructure are ignored. The state variables (pressure, volume, temperature of the solid media) are spatially averaged and are dynamic with respect to time and position. Gradients in quantities and effective parameters are responsible for transport. These effective parameters have to be determined by experiments [32,33,29].

By means of volume averaging techniques or homogenization methods, the continuum model is derived from the drying process at the pore level. This means that the macroscopic properties are predicted based on the microscopic description of the porous, heterogeneous medium. Since the medium is taken as a continuum, the system should be large compared with the pores. In many situations (due to the lack of length-scale separation), this is not the case, and it is assumed that the approach is valid. However, in these situations, the discrete approach should in fact give better results [34]. The homogenization method is frequently described in the literature [35–37].

Most work has been carried out in the area of volume averaging. In each individual macroscopic averaging volume, a solid, free liquid and gas exists. In this averaging volume, model parameters are measurable [38]. Variables (e.g. temperature) are averaged over the volume, the Representative Elementary Volume (REV). This REV should be large enough to define averaged quantities. On the other hand, variations should be avoided, in order to limit the size due to macroscopic gradients and non-equilibrium equations at the microscopic level [39].

Equations for the conservation of liquid, air and energy are supplemented with boundary and initial conditions [40]. The resulting non-linear Partial Differential Equation (PDEs) has no analytical solutions and requires a numerical solution technique. The equations can be solved using the control volume finite element technique (Fig. 5), otherwise known as the vertex centred control volume method, which is a combination of the finite element method and the cell-centred control volume method [38].

The volume averaging method has been developed in two and three dimensions. Several models are available for the study of the drying process and have been applied to materials such as wood [39,41] and brick [42]. The two-dimensional models provide a good understanding of the drying process, but certain physical phenomena (e.g. drying stresses) have to be investigated in three dimensions. The TransPore code is extended to a three-dimensional version [40]. The development of a three-dimensional version is motivated by two reasons. Firstly, drying stresses that develop in wood during drying depend strongly on the board width, while the longitudinal direction is important to represent transport phenomena. Secondly, the three-dimensional model is necessary to simulate comprehensive radio frequency or microwave drying behaviour. When moving from two to three dimensions, the computational burden to solve the equations increases significantly [40].

The continuum approach can be solved by efficient numerical techniques at a large scale in comparison with the pore scale, which is a great advantage. When the micro- and macroscales cannot be separated, this is a problem where a discrete approach can provide a solution [39].

Another difficulty is the determination of the effective parameters, such as vapour diffusivity, permeability, thermal conductivity and capillary pressure. These need to be obtained through dedicated, time-consuming experiments. The continuum approach is not able to easily take structural features of the medium into account. To study the influence of the size of pores, pore network modelling will give more satisfactory results [39,43].

5.3. Pore network modelling

Pore network models represent the porous structure as a network of pores and throats. The different pores are connected by the

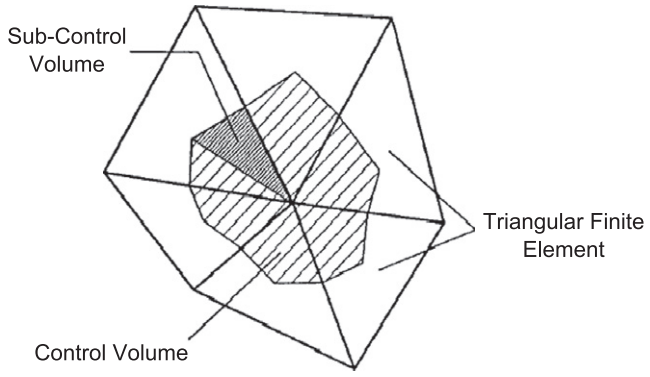


Fig. 5. Construction of a control volume from the triangular finite element mesh after Ferguson et al. [38].

throats, forming an irregular network, in which each pore receives a coordination, i.e., the number of neighbouring connected pores (Fig. 6). In most cases, the irregular network is substituted by a regular one with a mean coordination in order to simplify the model. In the network, the width of the throats is not taken uniformly, but varies according to a distribution function. A bottleneck is the strong assumption about the geometry of the pores [44].

These models can be used to simulate the drying process at the pore level. The continuum approach fails when the pores are large compared with the system. Moreover, an appealing approach for the computation of the effective properties at the scale of a REV is necessary in the continuum approach. Furthermore, it is useful to investigate the influence of the microstructure on these effective transport parameters [45]. Pore network models can offer the advantage of taking the features of the microstructure into account [29]. Drying of porous material takes place at pore scale: motion of the gas–liquid menisci in the pores, diffusion, viscous flow, capillarity, liquid flow. The role of large pores and their distribution can be examined.

The development of these models in drying processes is fairly recent [46][47]. A pore network model was used to study the patterns that are formed during drying and their influence on the drying rate [29].

Pore network models have been described in two [49] and three dimensions [50]. Gravity can be included by defining an appropriate invasion throat potential, which depends on the width of the throat, the relative position in the gravity field and the Bond number (the ratio between gravity and capillary forces) [44]. The pore network model needs to be coupled with mass transfer at the open surfaces. Traditionally, isothermal conditions are assumed when doing this, but one might want to include thermal effects. Indeed, temperature has an effect on several aspects of the liquid, e.g., viscosity, surface tension and vapour diffusion coefficient, among others. Moreover, the temperature gradient influences the drying process and distribution of water during drying. The combination of heat and mass flow has been examined [51,52].

This approach is very detailed and provides more rigour and accuracy. However, the downside is the CPU time required to solve the drying problem. It is therefore only used if this level of accuracy is needed to meet the objective of the modelling exercise. It is also useful for verifying a continuum approach model. The parameters of the continuum model can be assessed for a certain pore structure using a pore network model.

5.4. Modelling of drying processes for single particles

In this approach, the internal structure of the particle is ignored and the porous medium is treated as a whole. The continuum approach and pore network modelling (Sections 5.2 and 5.3) are described in the literature for the drying of structures with a large volume compared with pharmaceutical granules (e.g. pieces of 1 m × 3 cm × 3 cm [40] versus particles of 0.272 μm as diameter for a pharmaceutical product [53]). During drying, the evaporation of liquid occurs and a diffusion equation can be used to describe the diffusion of water from the entire particle.

In literature, the description of theoretical models for the drying of single droplets is subdivided in droplets containing dissolved and/or insoluble solids. Both approaches are of interest for pharmaceutical applications since pharmaceutical granules can both contain soluble and insoluble solids.

5.4.1. Models for soluble solids

A drying model for a single droplet with dissolved solids was developed by several researchers [54–57]. The temperature gradients in the wet particle were either ignored or only taken into account for the crust (the region of the particle that is already dry). In the latter case, a linear temperature distribution in the crust is mostly assumed. The drying rate of the particles was calculated assuming a constant change of total particle mass [54]. In contrast, an energy conservation equation was used to describe the temperature variations. For the boundary condition of the PDE, the assumption was made that the temperature of the wet core-crust

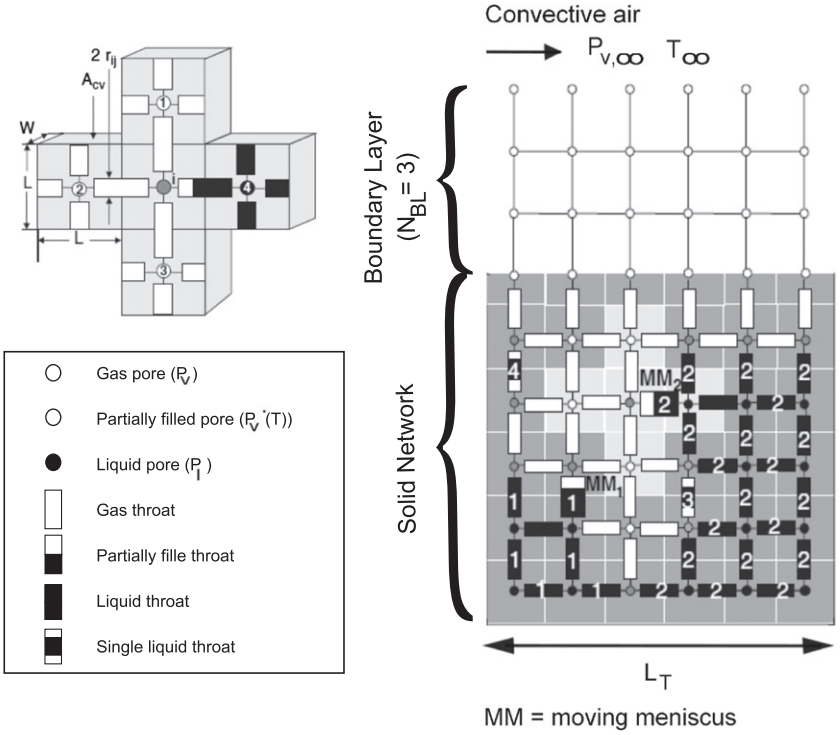


Fig. 6. Pore network with boundary layer and control volume after Surasani et al. [48].

interface equals the wet-bulb temperature of the drying air. In this model, the change of the moisture content was either linear or exponential in time [55]. Equations for the evaporation from a single spherical droplet that contains colloidal material were also derived. The authors assumed a uniform droplet temperature and that water is diffusing through the solid and evaporates at the surface. A diffusion equation with an effective diffusivity was used to describe the water diffusion. The latter is different from the molecular diffusivity and is difficult to measure. The effective and the molecular diffusivity are related through the tortuosity and the particle porosity [58]. In this model, no explicit crust formation is considered. Due to crust formation, a resistance for mass transport builds up, reducing the effective diffusion. Experimental data of droplets containing skimmed milk were compared with the computed results. A good agreement was found. However, comparisons between their model predictions and experimental data, provided by other scientists, showed a distinct discrepancy [59,56]. The drying behaviour was described by two different models. They first modelled the drying behaviour as a competition between evaporation and condensation (Reaction Engineering Approach (REA)-model). In the other approach, the Characteristic Drying Rate Curve (CDRC) model, the process was divided into different drying stages. Both models displayed a good agreement with the experimental data, but the REA-model performed globally better [57].

5.4.2. Models for insoluble solids

The kinetics of models for particles with insoluble solids are in several cases based on average moisture content and the temperature distribution in the wet core is ignored. The temperature distribution in the crust region was assumed to be linear [60]. In this model, the core temperature is not linked to the wet-bulb air temperature. Ignoring the sensible heating of the crust significantly simplified the model. Simulations compared well with experimental data. These data were collected using single drops of slurry, which were suspended on the tip of a flexible glass cantilever inserted in a vertical wind tunnel. A thermocouple was formed with a nickel wire to measure the temperature at the core of the drop, where the deflection of the beam gave the loss in weight during drying [60]. The evaporation rate was determined by multiplying the vapour diffusion mass flow rate through one crust pore with the void fraction of the crust [61]. This evaporation rate is also used by Elperin and Krasovitov [62]. A more simple equation of the evaporation rate of Abuaf and Staub was derived, which can be used for relatively low temperatures of the drying air under atmospheric pressure [63].

5.4.3. Models for insoluble and soluble solids

Models were developed for droplets containing dissolved and insoluble solids [64,65]. Nesic's approach is based on the formation of a crust. The distribution of the temperature for the whole droplet is neglected in both models. A diffusion equation was used to describe the diffusion of water vapour through the crust, using a diffusivity which depends on the water concentration. Several experiments were executed with droplets of water, colloidal silica, sodium sulphate and skimmed milk. The weight and temperature of the individual droplets was measured during the evaporation. Comparison with simulations showed good agreement for droplets containing colloidal silica and sodium sulphate. However, for skimmed milk, a great discrepancy was found [64,65].

A model based on average moisture content was developed [66]. A PDE of energy conservation for the crust and the wet core region was solved (Fig. 7). It was assumed that the temperature over the wet core-crust interface is constant and equal to that of the wet bulb, similar to Kuts [55]. The model neglected, however, the resistance of mass transfer through the crust. The porosity of the crust has to be accounted for in order to obtain accurate calculation of the particle drying rate. A model was developed taking into account the permeability of the crust. The evaporation of liquid from the wet core is due to heat transfer from the drying air. The vapour then moves through the pores towards the particle surface [59]. The vapour mass transfer rate is calculated with the equation of Abuaf and Staub [61]. Simulations showed good agreement with experimental data. Under different conditions, the temperature and the mass were evaluated for the drying of colloidal silica. In the case of skimmed milk droplets, the discrepancy did not exceed 5% for temperature prediction. The mass predictions had a relative difference below 4% [59]. A modified equation was utilized for the calculation of the vapour mass transfer rate [67] for occasions exhibiting a pressure difference between the crust and the ambient environment. In this case, the mass transfer rate through the pores is the sum of the diffusion and the forced flow rate due to the pressure gradient. In a further development of the drying model, full unsteady heat and mass transfer were considered. The pores were considered as cylindrical bodies, where conservation laws for mass, energy and momentum were applied [53].

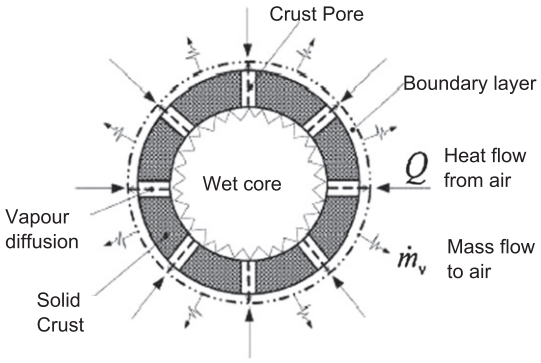


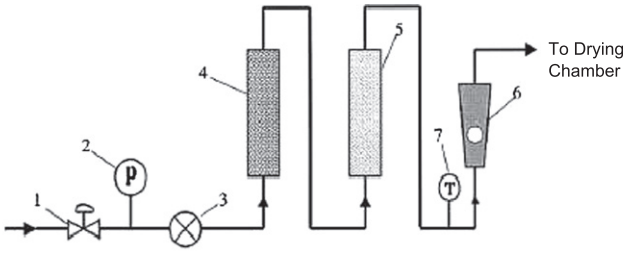
Fig. 7. Drying of a wet particle – crust formation after Mezhericher et al. [59].

5.5. Validation of the drying model

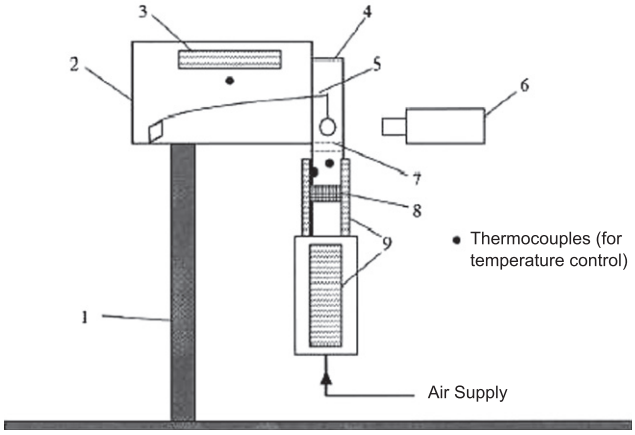
The developed drying model for one single particle has to be validated by experimental data. In other words, key variables (moisture content, gas temperature, temperature of particles, etc.) need to be measured and compared with model predictions. If the model does a good job (using, e.g., evaluation of the Mean Bias Error (MBE) or Root Mean Squared Error (RMSE)), it can be regarded as validated. If not, one has to re-iterate the model structure and figure out why the predictions are poor. Dependent on the model structure, it can be neccessary to measure the temperature or the moisture content of the particles and/or the gasflow at different locations. In this section, some methods to measure these key variables during drying are summarized.

The drying behaviour of single apricots, hanging in the flow direction of hot air in a drying chamber, was described. Drying data were collected through measuring the mass and inner temperature of the apricots. Apricots were hanging in an air stream. With an Fe–constantan thermocouple of 1.2 mm diameter, inserted in the apricot, the inner temperature was continuously monitored. The mass of the apricots was measured using a balance with an accuracy of ±0.001 g. The initial and final moisture content were determined with a Mettler infrared moisture analyzer at 80 °C [68].

A steam drying process of a single porous ceramic sphere (10 mm diameter) was modelled. The drying process was investigated with a thermobalance in order to accurately register the sample weight and the surrounding temperature. The temperature of the inlet steam and the weight of the sample were monitored



(a) Air supply system: 1. precision pressure regulator; 2. pressure gauge; 3. flow regulator; 4. silicate gel column; 5. molecule sieve column; 6. rotameter; 7. thermocouple



(b) Droplet drying system: 1. main support; 2. glass filament box; 3. heater for temperature control of the box; 4. drying chamber; 5. glass filament (200-350 mm long); 6. videa camera; 7. by-pass switch; 8. mesh block; 9. heaters

Fig. 8. Schematic diagram of the experimental set-up after Lin and Chen [70].

every 10 s. A gravimetric method was used to determine the final moisture content. In some experiments, the temperature at the centre of the sample was measured using a thermocouple. In these cases, it was impossible to register the weight of the samples [69].

The glass-filament method (Fig. 8) is described as an accurate measurement of drying kinetics of liquid droplets. It is a cost-effective system that generates high-quality results. With the help of a TV monitor and video camera, the droplet diameter and the glass filament deflections were monitored, which allows to determine the droplet weight loss, droplet size an droplet morphology at any time. The droplet diameter, the feret diameter, is measured from the perpendicular direction of the flow of the drying air. In drying modelling, the drying surface area is an important parameter, and an estimated accuracy of 10% is mentioned for the drying area. Using the deflection of the glass filament, the change of weight of the particle/droplet can be determined. Several experiments were executed; considering all uncertainties, an accuracy of 0.05 mg can be mentioned for the weight measurement. The droplet temperature was measured separately with two thermocouple wires [70].

Comparing the different possibilities, the glass-filament method seems to be a good compromise between accuracy and cost. Using this system, several variables of the drying process can be measured simultaneously.

6. Population Balance Modelling

6.1. General introduction

The sections above focused on the drying behaviour of individual particles. As a multitude of particles are dried together, the interest can also be focused on the drying behaviour of a batch of particles. A tool to describe this behaviour is PBM. It is indeed often assumed that the system behaviour can be described by the 'averaged' behaviour of single particles. However, in a real system, this is a coarse assumption as both spatial and population heterogeneity occur and will impact the system behaviour. Indeed, particles can both interact with the continuous phase and with each other. Hence, the behaviour of individual particles in a population depends on different (distributed) properties of the individuals and the local environment. For thorough analysis of this type of systems, PBMs can be applied. In the PBM framework, a distinction is made between external and internal coordinates, which represents, respectively, the physical position and the distributed properties of the particles.

A basic Population Balance Equation (Eq. (1)), which describes the change of the number density distribution $f_1(x, r, t)$ in time is given by:

$$\frac{\partial}{\partial t} f_1(x,r,t) + \nabla \dot{X}(x,r,Y,t) f_1(x,r,t) + \nabla \dot{R}(x,r,Y,t) f_1(x,r,t) = h(X,r,Y,t) \quad (1)$$

where x, r, t, Y and h are the internal coordinate, the external (spatial) coordinate, the time, the continuous phase vector and the net birth rate. $\dot{X}$ and $\dot{R}$ are the partial derivatives of the internal and external coordinates, respectively. The continuous phase vector should cover all continuous phase quantities that affect the behaviour of single particles. The two divergence terms represent the convective transport, one along the internal coordinate and one along the external coordinate. These terms are continuous in time, and describe the evolution of x and r. The net birth rate term is responsible for the change in number of particles due to discrete birth and death processes, like aggregation, nucleation or breakage. This last term is discontinuous, as particles appear and disappear at discrete timesteps. This equation has to be supplemented by initial and boundary conditions to be solved [71].

A PBM model for simultaneous agglomeration and drying in fluidized beds has been described [72]. The interesting internal properties were the particle size, the moisture content and the temperature of the particles. In terms of PBM, the agglomeration gives rise to a discrete term or the birth term, whereas the drying process is a continuous process, leading to a growth term.

When considering a fluidized bed with drying particles, each particle has a drying rate dependent on the local ambient conditions. During drying, the moisture content of particles drops. In terms of a PBM, this could be described by an internal coordinate. In this case, the interesting output is the temporal change of the number distribution with respect to the moisture content [72].

Evaporation of water from a granule means that the total mass of the granules is not conserved, and in this sense, it becomes a variable [73].

The granules have an input size distribution, and thus, a second internal coordinate could be defined. The disadvantage of increasing the number of internal coordinates of the PBM is the increasing mathematical complexity and computational power required to solve the resulting set of equations for a specific problem. An interesting approach could be reducing the resulting two-dimensional PBE to a set of one-dimensional PBEs. The resulting two-dimensional PBM would have $n(t, c, d)$ as general form, where t represents time and c and d are two other properties, in this case particle size and moisture content. The particle size can either be the entire volume, i.e., including the water content or a representation of the volume, such as the diameter. Another approach is using a one-dimensional PBE for a selection of size classes. In this case, only the moisture content is adopted as internal coordinate.

6.2. Studies using a PBM with a growth term for drying

Limited work is done in the area of drying of a batch of granules using PBM. However, in a PBM context, other processes like spray-drying [74] or wet granulation in combination with drying [75] are discussed more frequently in literature. In these cases, less attention is paid to the drying kinetics. In spray-drying, the crystallization receives most attention, whereas for the wet granulation process, aggregation of solids is regarded as most important.

Studies about the modelling of the drying of one single particle using a PBM approach are more frequently reported. In these studies, the particles are described as a number of discrete solid particles. These models are interesting for simulating the dried particle morphology. Droplets containing dissolved or suspended solids will develop different morphologies during drying [76]. Depending on the temperature, droplet size and temperature of the microstructure that is formed will vary [77]. Specifically for a pharmaceutical production line, the morphology of the dried granule is important for the subsequent tabletting step. However, including this detail into drying models would result in a significant increase of the computational burden. This is not desired when the goal is to describe the dynamic behaviour of the moisture content of the entire batch of granules using a PBM. In this case, a PBM with only a growth term seems sufficient.

Population balances with a growth term are most often found for crystallization processes, where the size of the crystals is the internal coordinate of interest. In this case, the growth term is a positive term. In industrial applications, the crystallizer is often assumed as being well mixed, meaning that the number density does not depend on the spatial coordinates, and the PBM can be simplified to a PBM without spatial coordinates. In the secondary step of the crystallization, nucleation can also be neglected, as the secondary nucleation most likely only produces infinitesimally small crystals, further simplifying the PBM [78].

Fluidized bed coating and agglomeration of solid particles has been studied. The developed model assumed also independency of spatial coordinates for the batch fluidized bed. With this model, the PSD could be simulated and the duration of the stable operation could also be predicted successfully [79].

6.3. Solution techniques for PBM with a growth term

Population Balance Models which have to take growth into account are more difficult to solve. At first sight, it seems simpler to include growth compared with breakage or aggregation. However, the difficulty of including growth terms is that they lead to hyperbolicity in the resulting equations. For solving of PBEs, several numerical methods exist such as: methods of moments, Monte Carlo simulation, discretization methods such as finite difference method, finite volume method, finite element method, and method of lines.

The main requirement for the model is the accurate prediction of the desired properties. Sectional methods are the best choice for this type of problem [80]. Dividing the entire domain in a number of bins leads to a set of Ordinary Differential Equations (ODEs) which have to be solved simultaneously in order to calculate the number of particles in each bin. The number of bins, or in other words the coarseness of the grid, influences the accuracy of the method. Certain sectional methods utilize a linear grid, and several examples can be found in literature [81]. The disadvantage of linear grid discretization is the necessary computational power as a lot of size classes are required to cover large ranges. In this respect, geometric grids can offer a solution. A geometric grid with a factor of two in progression in size was used [82]; in this way, the total number and total volume of particles could be predicted correctly. It is an extended discretization technique for aggregation to size-dependent particle growth. Coefficients are estimated using expressions conserving three moments. The method can lead, however, to a negative value for the number of particles, which is corrected by replacing it by zero [82].

The method of lines is used for a PBE with only growth and nucleation in order to transform a PDE in a set of ODEs. In a first paper, the growth term was rewritten using central differences, leading to negative density function values [83]. In a second paper, this was solved by adopting a first-order upwind differentiation [84]. Another problem in the homogeneous model of the first paper is the sensitivity to size spacing, which was solved by adopting a small fixed size spacing of 1 nm [83,84].

The method of Hounslow was adjusted for adjustable geometric discretizations with a factor of $2^{1/q}$ [85], and a further development was made [86]. The fixed pivot technique is consistent with the first two moments [87]. The formulation generalizes the method proposed by Hounslow. It calculates some selected moments accurately, but becomes less accurate for the calculation of the whole particle property distribution. However, this method can only be applied for aggregation and breakage problems [87]. An alternative scheme is proposed for combined processes of aggregation or breakage with growth and nucleation. It is a combination of the discretization technique and a method of characteristics. The technique can be used for pure growth problems or combinations. Particle growth and nucleation have the feature of being continuous, and in this way, they are more difficult to implement in the discrete version of the PBEs [88]. A general scheme was developed to solve all processes simultaneously [80]. It is an extension of the cell average technique [89], but could only be used for aggregation problems. The idea is that growth of a particle can be seen as the adherence of small nuclei on the particle surface. In such a way, the model concept is similar to aggregation, namely the aggregation of particles with imaginary particles. These models can be solved with the extended cell average technique. The numerical discretization is consistent with the first two moments.

Another solution method used for growth problems is the method of moments [90]. Using the method of moments, the distribution is approximated by its moments. Under certain conditions, the moment equations are closed, and the differential equations for the lower order moments do not depend on values for the higher-order moments, resulting in a set of ODEs, which can be solved efficiently and accurately. However, for complex problems, the moment closure conditions are violated [91]. A solution for this problem is the use of the Quadrature Method of Moments (QMOM) or the Discrete Quadrature Method of Moments (DQMOM) [92]. The growth of crystals without aggregation is described [90]. The PBEs are solved with the moments method in order to have detailed information about the crystal size distribution [90].

High-resolution finite volume algorithms were proposed for solving highly non-linear multidimensional PBEs as the growth of crystals is associated with the change of multiple internal coordinates. These algorithms are developed for solving hyperbolic partial differential equations, and are state-of-the-art methods in engineering areas such as aerodynamics, astrophysics, and detonation waves. The high-resolution finite volume methods for compressible gas dynamics were adapted for PBEs. This method provides an accurate solution without large computational effort [93]. The growth problem is compared with the advection problem, which has been thoroughly studied in fluid dynamics. One-dimensional and multidimensional PBEs were simulated using high-resolution finite volume methods. The simulated results are consistent and accurate for batch and continuous PBM using several initial conditions [94].

Several population balance solution methods are compared for a crystallization process, namely the method of characteristics,

the finite volume methods and the finite element methods, in terms of the performance requirements essential for on-line control applications. The method of characteristics gives the most accurate predictions; the needed computational effort is, however, a disadvantage. High-order finite volume methods in combination with flux limiting functions give satisfactory results with a reduced computational demand, whereas finite element methods fail due to the complex implementation and high computational demand [78].

6.4. Two-dimensional PBMs to model drying processes

Two-dimensional PBMs were investigated [95]. As internal coordinates the particle size, and the particle tracer mass was chosen. The two-dimensional PBE was reduced to a set of two one-dimensional PBE using the marginal distribution approach, which is based on the assumption that particles of the same size contain the same amount of tracer.

A two-dimensional PBM was used for the simultaneous agglomeration and drying in fluidized beds [72]. The energy and mass balances for the solid and the gas phase were derived by means of a heterogeneous fluidized bed with an active bypass. The solid phase was described with a set of one-dimensional PBEs, using the reduction proposed by Hounslow et al. [95]. A PBM with only the particle size as internal coordinate is not sufficient, as the kinetics for heat and mass transfer require the temperature and moisture content of the particles. As a consequence, a vector of internal coordinates is used. The PBE cannot be applied to the temperature and the moisture content of the solid phase. These properties are therefore related to the corresponding extensive properties. The resulting set of equations was solved using a new discrete formulation of the PBE and simple backward differences.

6.5. Validation of stand-alone PBM models

Focussing on the validation of a stand-alone PBM model, it will be necessary to register variables for an entire bed of granules. On the other hand, methods to determine the moisture content or the temperature can be the same as for the drying model described in Section 5.5.

Experiments for the validation of the mathematical model describing the fluidized bed spray agglomeration and drying were conducted. Microcrystalline cellulose was used as material. For each sample (with a time interval of 2 min), the moisture content and the PSD were measured several times during the experiment using a Halogen Moisture Content Analyzer and a camera. In addition, the inlet gas temperature, the inlet flow rate and the humidity of the gas were measured [72].

For the validation of a steam drying process of a bed of porous spheres, it was necessary to register the weight of the entire bed, the inlet and outlet steam temperature and the steam mass flux accurately. At the inlet, the steam was kept at a constant temperature with a temperature controller, which assured a maximum temperature deviation of ±0.3 °C. The mass flux was controlled with a flow-regulating valve. A high-resolution load cell continuously monitored the weight of the entire bed. The steam inlet and outlet and the temperature of a varying number of spheres were measured [96].

7. Computational Fluid Dynamics

7.1. Introduction

In order to capture detailed spatial behaviour of the system, the flow of the particles can be analysed using CFD. As mentioned in Section 4.1, several fluidization patterns can be distinguished, i.e., particles can be classified in several Geldart classes [19]. Considering the configuration of the gas inlet, the fluidized bed dryer used in our case produces a normal fluidized bed and not a spouted bed behaviour.

CFD consists of mathematical expressions that describe the conservation laws for momentum, mass and energy (contains thermal energy, contributions from radiation or other heat sources). The resulting PDEs are simplified using a discretization technique, which translates the continuous equations into discrete ones. The result is a set of algebraic equations. Numerical solution techniques yield the flow field at discrete points in the domain. CFD models are thoroughly explored for single-phase flow, however multi-phase flow – i.e. more than one phase is considered in the model – or complex geometries are more difficult to handle. In multi-phase flow CFD applications each phase is described in terms of a separate set of conservation equations, while appropriate interaction terms are necessary to describe the coupling between the phases [97].

In industry, gas/particle flow and fluidization applications are widespread, and hence, as a consequence, there is a need for fundamentally based and realistic simulations, accurate and detailed experiments, and also a proper set of design tools for these systems. Recently, significant progress has been achieved in the area of gas/particle flows [98]. Several multi-fluid models can be found in the literature describing the dynamics in fluidized beds. Basically, two approaches can be distinguished: the Eulerian–Eulerian and the Eulerian–Lagrangian approach. Both will be discussed in detail (Sections 7.3 and 7.4, respectively).

In a fluidized bed, several regions are apparent: (1) dense regions where particles are in long-term contact with each other and the solid volume fraction is high and frictional stresses dominate and (2) dilute regions where particles are in collisional contact and the kinetic stresses are most important. In the intermediate region, both kinetic and frictional stresses are important [99].

7.2. Turbulence modelling

7.2.1. Introduction

An important aspect in CFD is turbulence modelling which is necessary when the Reynolds number (Re) exceeds the value of 3000. The mathematical modelling of turbulence is very complicated due to the three-dimensional behaviour and the time dependence. Different models have been developed to describe turbulence [100]. Traditionally, the time-averaged Navier–Stokes equations (RANS) have received most attention. In the latter, several options exist to describe turbulent stresses, including zero-equation models (or algebraic models), one-equation models, two-equation models and the second-order closure models (or Reynolds Stress Model (RSM)-models). In general, the k–ϵ-model, a two-equation model, is most frequently used. Alternative to the RANS approach, turbulence can also be modelled using LES. Here, the time-dependent flow equations for the mean flow and for the largest eddies are solved, and the effect of the smaller eddies is modelled using representative equations. Models based on LES have recently received more attention, despite their large computational power requirement. Finally, direct numerical simulation takes all scales relevant to turbulent motion into account, further increasing the computational burden [100–102].

7.2.2. Turbulence modelling in fluidized beds

A k–ϵ turbulence model on two-dimensional and three-dimensional grids was used for the simulation of a bubble plume in a rectangular, flat bubble column. A low Reynolds k–ϵ-model has also been tested, and no significant changes were observed from the standard k–ϵ-model [103]. The influence of the turbulence

Table 1
Parameters used by Tabib et al. [102].

Geometry details	Number of nodes used for simulations and timestep		
	k–ϵ	RSM	LES
D = 0.15 m	36,000	36,000	150,000
H = 1 m	0.05 s	0.05 s	0.005 s

modelling was investigated in a rectangular bubble column with different types of spargers. Experimental results were obtained using Laser Doppler Anemometry (LDA) and Particle Image Velocimetry (PIV). PIV is an optical method for the visualization of fluid motion. The particle concentration is limited in order to identify individual particles in an image. Three-dimensional simulations are necessary to show the periodic bubble hose movement. Simulations were performed using a laminar and a standard k–ϵ turbulence model with and without dispersion. The laminar model was insufficient to describe the turbulence in the continuous fluid. The turbulence model without dispersion gave good agreement with the experimental results, while the model with dispersion did not seem to be necessary for the test cast [104]. The concept of LES turbulence modelling was applied to describe turbulence for vertical bubble-driven flows. According to these authors, this gives the best physical representation of the actual flow. If the detailed bubble flow has to be described, the unaveraged equations should be used, and in practice the LES model is a suitable alternative [105]. The performance of LES and k–ϵ turbulence models for gas–liquid flow were compared for a bubble column reactor. The equations of the motion of the gas–liquid flow were studied by the Eulerian–Eulerian approach. It was found that the LES results were in better quantitative agreement with the experiments compared with those of the k–ϵ-model [106].

Three different turbulence models were compared, i.e., two RANS-based models, the k–ϵ-model and the RSM, and the LES-model [102]. Simulation results were compared with experimental data of Bhole et al. [107]. The experiments were conducted with laboratory scale cylindrical bubble columns with three different spargers [107]. The Reynolds stress model was expected to perform better than the k–ϵ-model in predicting average axial velocity profiles. However, results were found to be comparable. For the prediction of the turbulent kinetic energy, the Reynolds stress model performed better than the k–ϵ-model. The LES-model was able to predict the average flow behaviour. However, the required computational resources are much higher for the LES-model compared to the Reynolds stress model and the k–ϵ-model (Table 1). Moreover, the gain in information is limited (comparing results of the radial profile of axial velocity, the radial profile of gas hold-up, the radial profile of turbulent kinetic energy and the radial profile of Reynolds stress), which leads to the conclusion that the k–ϵ-model is sufficient for the simulation of a three-dimensional bubble column [102].

7.3. Eulerian–Lagrangian approach

7.3.1. Introduction

In the Eulerian–Lagrangian approach, or the discrete approach, the behaviour of each single particle is calculated, taking into account interactions with other particles and with the continuous phase. The limitation is, however, the number of particles which can be tracked, as the computational effort increases significantly with the number of particles. The numerical simulation performed with the Eulerian–Lagrangian approach needed a CPU time which is four orders of magnitude higher than the time required to perform an Eulerian–Eulerian simulation [97]. The insight gained in the fluid dynamics and the straightforward inclusion of PSDs are on the other hand great advantages of the Euler–Lagrangian approach [97]. For complex physics, the Eulerian–Lagrangian approach is the easiest way to describe the motion of the particles. Two methods prevail depending on the size of the particles compared to the grid points: when particles are much smaller, particle methods are used; when particles are larger, the immersed boundary method is used. The particles in a gas-fluidized bed are relatively small, so a point particle method needs to be used. In the Discrete Particle Model (DPM), a grid point particle method, one numerical particle represents one physical particle and in this case the interparticle forces can be modelled directly. This means that only a limited number of particles can be tracked in order not to blow up the computational load. Using the Particle Cloud Model (PCM), another grid point particle method, one numerical particle represents many real physical particles with the same physical properties [108]. In fluidized bed drying, the DPM method is mostly applied.

7.3.2. DPM and fluidized bed modelling

In DPMs a hard or a soft sphere, approach for the collision model can be used. In a hard-sphere collision model, the trajectory of particles is determined by momentum-conserving binary collisions. Collisions are assumed to be additive and instantaneous. This collision model was used [109,110] to study gas–solid two-phase flows in gas-fluidized beds. Bubble formation due to particle–particle interaction and the particle segregation due to differences in particle size and density were investigated [109,110].

In the soft sphere collision model, trajectories are determined by integrating the Newtonian equations of motion. Particles can overlap slightly [111]. Tsuji et al. [112] were the first who used the soft sphere model for gas-fluidized beds. The contact forces were modelled by Cundall's Distinct Element Method. The flow of the gas was solved simultaneously with the motion of the particles, taking into account the interaction between both. Experimental results and calculated pressure fluctuations compared well [112].

In studies about spouted bed systems, the hard sphere DPM is mostly used, whereas the soft sphere approach is most suited for cases in which defluidized zones can prevail [113].

The equations for the gas phase and the solids are coupled using the porosity and the inter-phase momentum exchange. Quantities should be averaged over a relevant volume, which has to be large as compared to the particles. The method of Hoomans et al. [109] can be used for the calculation of the porosity. It gives good results for small particles in large grid cells. However, detailed information of the gas flow is achieved using smaller grid cells [109]. The porosity was calculated in a grid-independent manner, and a similar method was used for the calculation of the drag force acting on the particle [113].

The flow of particles in bubbling fluidized beds was studied using LES and DPM. The gas-phase model was based on locally averaged two-dimensional Navier–Stokes equations for two-phase flow whereby the turbulence is calculated by LES. The latter accounted for particle effects on subgrid-scale gas flow. Particles were assumed to interact through binary, instantaneous and non-elastic collisions [114].

7.4. Eulerian–Eulerian approach

7.4.1. Introduction

The Eulerian–Eulerian approach, also referred to as the continuum approach, is used most frequently for studying the behaviour of gas–particle flows in fluidized beds [115,116]. In this approach, both phases, i.e. the gas phase and the solids phase, are considered as being continuous and fully interpenetrating. For both phases, the conservation equations are solved, which has to be

supplemented by interaction terms for the coupling between both phases. The disadvantage of this approach is the difficulty with the incorporation of complex particle physics. Indeed, the continuum balances contain terms which require a constitutive relation. Eulerian–Eulerian models which include the effects of cohesion are very limited, and in this case, the Eulerian–Lagrangian approach can offer a way out. The averaging technique used to derive the continuum balances gives rise to terms which require a constitutive relation. The incorporation of cohesion into constitutive quantities is less straightforward than its incorporation into an Eulerian–Lagrangian model [117].

The Eulerian–Eulerian approach requires closure laws for particle interactions. Several options for the stress terms in the particulate momentum equations can be found in literature. The theory for frictional stresses is derived from soil mechanics. The frictional contribution of the momentum transfer is predicted using empirical correlations [99,118]. Also, several semi-empirical models can be found in the literature, described by among others [119–121]. In the past, the constant viscosity model was used whereby the solid phase pressure was assumed to be only a function of the local solid porosity, and the solid phase viscosity was assumed to be constant [122]. More recently, the kinetic theory of granular flow was accepted for modelling of kinetic stresses. Here, the solid phase properties are described in more detail, which yields a better insight into the particle–particle interactions [123]. The influence of frictional stresses on bubble dynamics was studied. Solid frictional stresses have a significant influence on the bubble size distribution, bubble rise velocity and visible bubble flow rate, and the predictions are significantly improved by the incorporation of these stresses in the kinetic theory of the granular flow model [124,125]. Different frictional stress models were compared for the simulation of dense gas–particle flows in bubbling fluidized beds. Experimental data were collected with a bubbling fluidized bed with central jet and a freely bubbling fluidized bed in order to investigate the effects of the frictional stress models on the numerical predictions. The general conclusion was that the sensitivity of the frictional stress models to the values of their parameters makes them inadequate. A more fundamental research effort is necessary to understand the dynamics of particles in ensuring contact in order to develop general expressions for the particulate phase stresses that are more reliable [126].

7.4.2. Eulerian–Eulerian approach and fluidized bed

A Two-Fluid Model (TFM) was used for gas-fluidized beds. The mass, momentum and thermal energy conservation equations, and the constitutive equations were solved by a finite difference method [127]. The disadvantage of this approach is the continuous character of the solid phase: physical characteristics such as shape and size are included through empirical relations for the interfacial friction, but the discreteness of the solids is not fully recognized [97].

The TFM was further extended to a multi-fluid model, i.e., instead of one solid phase a higher number of solid phases were considered, yielding a more realistic description of the PSD in gas–solids flow systems. The different solid phases were given respective diameters, densities and restitution coefficients. The presence of each phase was described by a volume fraction, varying from zero to unity. For each phase individually, the conservation laws for momentum, mass and energy are satisfied. The volume fraction and the momentum equations were solved for each phase. The gas phase turbulence was modelled by a LES-model [128].

7.5. Validation of CFD models

The bubbles in a fluidized bed can be monitored using several methods: X-ray imaging techniques [129], laser [130], optical fibre probes [131] coupled to spectrometers (e.g., Near Infrared Spectroscopy (NIRS) and Raman), pressure probes [132], high-speed three-dimensional capacitance imaging technique [133]. Bokkers et al. [134] took images of the fluidized bed by means of a high-speed digital camera. The PIV technique was used to determine the particle velocity fields [134]. The PIV technique was also used by Cheng et al. [135] to investigate the bubble velocity field in a bidimensional gas–liquid column at high bubble density. A CCD camera was used to record the bubble images, whereas the post-processing was done using several PIV and Particle Tracking Velocimetry (PTV) cross correlation methods. It was found that the PIV algorithm based on recursive cross correlation gave a fine structure of the bubble flow in a relatively short computational time [135].

A high-speed video camera was used to observe the motion of the bubbles. The bubble velocity was determined with an image analysis technique. First, a binarization processing was applied to distinguish a bubble from the background. Subsequently, the position of the centre of gravity of the binarized bubble image in a cylindrical coordinate system was determined for each bubble individually. Based on the displacement of the centre of gravity over time, the instantaneous radial and angular bubble velocities were calculated [136].

A Digital Image Analysis Technique (DIAT) was developed to study the hydrodynamics of a lab-scale two-dimensional bubbling fluidized bed. With the help of an in-house developed software, simultaneous measurements of the most significant bubble properties (position, shape and dimension) were possible. In order to self-validate velocity measurements, two kinds of velocimetry techniques were developed: (1) an Eulerian Velocimetry Technique (EVT) and (2) a Lagrangian Velocimetry Technique (LVT) [137].

Electrical Capacitance Tomography (ECT)-systems can give both quantitative and qualitative data for solid–gas flow. Several numerical methods are used to solve the inverse problem to render permittivity images from raw voltage data. The use of a back-projection algorithm was described [138]. The ECT method was used to investigate the influence of pressure on the average bed voidage and bubble size [139]. The multiple light scattering technique or Diffusing Wave Spectroscopy (DWS) was applied for a variety of dense fluidized bed systems. With DWS, the motion of particles and the mean of the square of the particle velocity fluctuations about the mean flow velocity can be studied [140].

8. The combination of CFD and PBM for fluidized bed drying of granules

8.1. Introduction

As mentioned in previous sections of this review, the fluidized particles in a fluidized bed dryer are subjected to a drying process. Hence, depending on the local ambient conditions, the drying process will go faster or slower, leading to a distribution of the granules' moisture content and, hence, also their behaviour in the fluidized bed. For a thorough description of the dynamic system behaviour, a combined PBM–CFD model will be necessary.

Recently, the integration of PBM- and CFD frameworks has received considerable attention. Examples can be found in distinct areas: oxygen transfer in bioreactors [141], production of solar grade silicon in fluidized beds [142], emulsification processes for food products [143], production of cellulase [144], turbulent gas–liquid systems [145], soot prediction models [146], aerosol modelling [146], etc.

8.2. Added value of the combination PBM–CFD

Traditionally, the PBE was solved in a spatially homogeneous system, where the fluid was assumed to be well mixed or to

behave in sequences of well-mixed flows. In reality, however, polydispersed particles, in this context indicating particles, with one or more distributed characteristics, which move in a flow field, will lead to an inhomogeneous spatial distribution of the particles in the gas flow. This is particulary true when the influence of the flow field on the process under study cannot be neglected, and vice versa, i.e., the presence of particles influences the flow field. A detailed review of the potential and limits of the PBE approach to flow problems, the link with Lagrangian and multi-fluid approaches and numerical solution methods was recently given. The described applications are reactive precipitation, soot formation and nanoparticle synthesis and sprays and bubbles. The turbulent flows receive the most attention, whereas the extension with PBE is still considered to be a great challenge [147].

8.3. PBM–CFD with growth term

Similar problems/systems can be found in other application domains. For the development of detailed models for a fluidized bed drying process, these other domains can offer knowledge; in particular, the models for crystallization are quite similar to the drying case. Batch crystallization processes are difficult to understand well. Indeed, due to the combination of fluid mixing, particle aggregation and particle breakage, the process becomes highly complex. The heterogeneity in the ambient conditions will lead to different local crystallization rates. For a correct prediction of the PSD, a coupling has to be made of a PBM with turbulent CFD. The Standard Method of Moments (SMOM) and the QMOM are both methods able to solve the PSD for industrial problems, such as batch crystallization and batch precipitation. SMOM and QMOM were compared for a batch crystallization process [148]. In SMOM and QMOM, the PBE is simplified into a series of a few discrete moment equations; typically, only six moments are calculated. Instead of solving the PBE directly, the SMOM approach converts the PBM in several moment equations which are solved separately. It is necessary to convert the growth term via a moment transformation. The reduction in dimensionality is an advantage with respect to computational requirements. However, the exact closure is complex. The closure problem is solved with the QMOM method [149]. This method requires a relatively small amount of scalar equations to compute the moments of populations with small errors. The QMOM method is preferred in the case of size-dependent growth. A quadrature approximation is the basis of the technique and calculates a number of weights and abscissas, which is achieved using the product-difference algorithm. The moment-based population balance results in a number of transport equations for the first moments. Comparing the simulation results showed that the QMOM method was able to predict the analytical solution of a PBE more accurately [148].

The problem of the computational expense of coupling a standard discretized population balance with a CFD model was addressed. This involves the solution of enormous amounts of transport equations. Indeed, instead of having 1 transport equation for a solid phase, now a transport equation for every size class of this solid phase is required in every bin of the CFD model. A higher number of discrete classes results in a more accurate prediction of the population balance dynamics, but also in a high number of scalars, making it computationally expensive to couple with CFD. The QMOM was tested for size-dependent growth and aggregation, and validated by comparison with Monte Carlo simulations and analytical solutions. For the size-independent and dependent growth rate, the QMOM showed a good agreement with the analytical solution. The authors concluded that the QMOM offers a great potential for the coupling of a PBE with CFD. The advantage over direct methods is the low number of scalars, the lower computational burden and the fact that there is no lower and upper limit on the number of involved classes [92].

The QMOM approach was also applied for the simulation of nano-particle formation by reactive precipitation. A new algorithm, namely In Situ Adaptive Tabulation (ISAT), was implemented for the simulation of micromixing, mostly applied together with CFD [150]. The ISAT algorithm was proposed by Pope [151] to incorporate detailed chemistry in reactive flow calculations. In this algorithm, results are stored in a table as these are computed. Combined with information concerning the accuracy of local linear interpolation, this linear interpolation replaces the direct integration. Combined with CFD, it has been demonstrated that a detailed kinetic mechanism can be used in calculations of turbulent combustion [151]. The PBE for turbulent aggregation of the growing particles was solved by the QMOM. The combined model with ISAT predicted the results accurately and needed considerably less computational time compared to direct integration [150].

Starting from a three-dimensional PBM, several reductions were made to a simplified PBM, which was implemented in the CFD code. The reduced model has been validated using available experimental results for the homogeneous situation. A qualitatively good agreement was observed for stoichiometric conditions, whereas in the case of higher concentration, excess of one reactant larger deviations were found. With the implementation in the CFD code several three-dimensional inhomogeneous hydrodynamic conditions could be investigated with acceptable computational time [152].

CFD and PBM were combined for the modelling of ice crystallization. For the solution of the four-dimensional PBM, the internal coordinate and the three external coordinates, the PBE was discretized into several ice crystal size ranges. The resulting diffusion-like PDEs could be implemented into conventional CFD models. Experimental data were compared with the predicted ice crystal distribution. In general, a good agreement was found, although an over-estimation of small and an under-estimation of large ice-crystals was predicted. This deviation could be the consequence of undetected small ice crystals or the over-simplified fluid flow and crystallization kinetics models. Through the combination, a generic tool was developed for testing of various hypotheses and kinetic models of ice crystallization under relatively simple experimental conditions [153].

The growth term in CFD–PBM models is not able to represent particle–particle interactions, since this term is merely convective. Incorporating particle–particle interactions in a CFD–PBM framework necessitates the use of agglomeration/aggregation kernels. In these kernels, the interaction can be modelled as a source term, and in this way, multiple properties can be introduced in the models, such as impact velocity, wetting, roughness of particles,

8.4. Validation of coupled CFD–PBM models

In-line NIRS can be applied to obtain the granule moisture content and particle size change during fluid bed granulation [154]. NIRS is described as a fast non-destructive and low-cost technique, which is frequently used in the pharmaceutical industry for quality and process control [155]. Real-time monitoring allows modifying the process conditions, if required, during granulation and can be used as well to identify the end-point of the granulation. This can lead to increased process reliability [154].

Continuous on-line measurement of solid moisture content during fluidization is possible using triboelectric probes. Triboelectric probes were validated with a Karl Fischer titration in gas–solid fluidized beds. The obtained sensitivity ranged from 0.01 to 0.2 wt.%. These inexpensive probes make it possible to perform real-time measurements of the moisture content at low cost [156].

The ECT-method, earlier discussed in the section about the validation of CFD-models, was used in a fluidized bed drying process of pharmaceutical granules. With the help of the S-statistic, it was possible to analyse both the reconstructed and the non-reconstructed ECT images to determine radial variations in hydrodynamic behaviour [157].

9. Towards mechanistic models for fluidized bed drying of porous granules in pharmaceutical production processes

In the area of pharmaceutical applications, limited work has been performed thus far in order to improve the description of multi-phase systems. Nevertheless, more research on multi-phase systems would be desirable, since several phases typically interact with each other during the production of pharmaceutical tablets: gas, liquid and solid phases. A development of a mechanistic description of the behaviour of multi-phase systems would be an advantage for the pharmaceutical industry in general, as it would form a good starting point for the development of improved process understanding and, as a consequence, better control of such processes (Section 2). The mechanistic description is already well established in some other industries, for example in the chemical industry. A design improvement of the modelled process can also be the consequence of the development and use of a detailed mechanistic model. For example, the model can predict the evolution of the process when changing process parameters, laying outside the boundary conditions of the available equipment.

The use of a mathematical model is strongly influenced by the modelling objective. Before developing a model, the scope and the intended use of the model have to be clear indeed. Specifically, for a fluidized bed dryer, to allow a detailed description of the drying kinetics and the distributed properties of the outgoing granules, both the fluidized bed behaviour and local drying behaviour need to be described. This can be established using a PBM model integrated in a CFD code as described in Section 8. The evaporation is the process that couples both modelling frameworks together. However, the coupled PBM–CFD-model is challenging to formulate, solve and validate (Fig. 9).

In the case of a dryer which is to be integrated and used within a continuous process, the model objective is to obtain a good prediction of several quality aspects (for example the compressibility or the moisture content) of the granules (that are required to be in specified ranges). The fluidized bed dryer embedded in the continuous process implies that a continuous supply of dried product to the tabletting machine is required. On the other hand, the continuous input of the dryer, originating from the granulator (Fig. 1), has distributed properties over the population of granules. Hence, the model needs to be able to predict process states depending on the input state properties. Moreover, the drying process model should be able to predict the impact of changing operating conditions on the output states. Hence, the model structure should include those parameters and state variables that influence the properties of the granules leaving the system if one wants to optimize or control the system.

Table 2 provides a concise overview of the different types of models described in this review.

In Section 5 an overview of existing drying models was given (see also Fig. 10). The first two approaches, namely the continuum and the pore network approach, are computationally expensive in order to calculate the detailed moisture content of the particles. These models calculate how the moisture content is evolving in the porous material. The question that has to be asked is whether it is necessary to describe the local moisture content in each particle in detail, considering that the global moisture content of the whole particle can give enough information. In this sense, the choice of one of these models will depend on the scope of the research that forms the basis for supporting a modelling project.

The choice of the drying model is also influenced by the global scope of the fluidized bed drying. Bearing in mind that the goal is to implement a drying model in a PBM- and coupled PBM–CFD-model limits the required computational demand for the drying model. The drying model has to be applied to a population of particles with different sizes, which are fluidized and will exhibit a distribution in the moisture content. However, the computational demand of the drying model needs to be

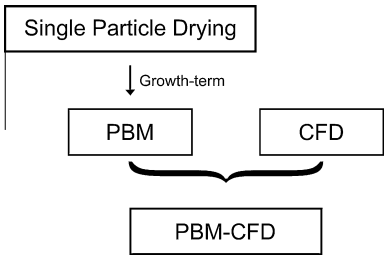


Fig. 9. Structure of fluidized bed drying process model.

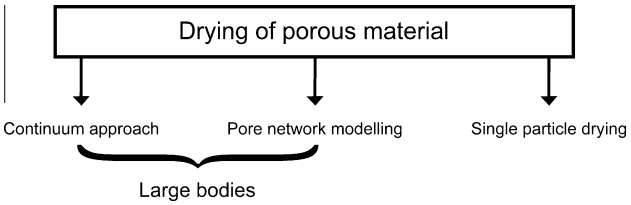


Fig. 10. Different options for the modelling of the drying behaviour of porous material.

Table 2
Overview of the different model concepts discussed.

Type	Goal	Limitation	Section
Drying of porous material	Allows describing the dynamic moisture content of porous media	Single paricle	5
PBM	Allows describing the behaviour of a population of particles. Starting from an initial distribution of the internal coordinates, the distribution after a certain timestep can be calculated. Dependent on the dimensionality of the PBM, one or more internal properties can be evaluated	Spatial coordinate not accounted for	6
CFD	Allows describing the fluid dynamics. The flow of particles, fluidum, gas, etc. can be studied with CFD	Does not include drying process	7
PBM–CFD	For spatially heterogeneous systems, the distribution of internal properties will be influenced by the environmental conditions. Through the use of a coupled CFD–PBM model the distribution can be calculated taking into account the location of the medium	n.a.	8

limited in a first modelling attempt of the system. More complex models are useful to highlight possible major shortcomings of the simplified models.

An extension of the drying model for one single particle towards a population of particles is made through the adoption of the PBM-concept (Table 2). PBM is a tool to describe the behaviour of a population of particles. In a PBE, the amount of internal coordinates can vary. The one-dimensional PBM, with one internal coordinate, is mostly used. However, in some cases, the results from a one-dimensional PBM are insufficient to describe the experimental data. An extension to a two-dimensional PBM can be done; however, the necessary computational power will increase. Moreover, when a coupling to a spatial CFD-model is pursued, the computational burden will become very large. Hence, the choice for a specific modelling approach strongly depends on the objective. It is our belief that a stepwise approach in tackling such a complex problem is the best one. Once a one-dimensional-PBM has been formulated, solved and validated, more complexity can be added, e.g., based on a sensitivity analysis that can point towards the weak parts of the model.

A CFD-model is used to describe the flow of the particles during fluidization (Table 2). Two options are available, the Eulerian–Lagrangian and the Eulerian–Eulerian approach. The first approach is very time-consuming, as the force balance for every particle in the system needs to be solved. For systems of industrial size, the Eulerian–Eulerian approach is computationally more efficient. As a rule of thumb, the Eulerian–Lagrangian approach is currently limited to systems containing less than 100,000 particles. When the modelling objective requires taking into account some instantaneous interactions, this approach is, however, preferable [117]. Moreover, general numerical diffusion errors are less apparent with this approach, and another advantage is the greater stability for flows with large particle velocity gradients. The application to poly-dispersed systems can be easily achieved. Disadvantages disappear in concentrated systems with plenty of interactions between particles and fluid and particles. In these cases, computational limitations like storage capacity and calculation time surface. Moreover, these models are characterized by a lack of fundamental understanding of the interactions. For high particle concentrations, the Eulerian–Eulerian approach is preferred. Using well-designed averaging methods, it can account for direct and indirect particle interactions and fluid turbulence. However, the constitutive equations for stresses are not yet fully understood and developed.

Chiesa et al. compared the Eulerian–Lagrangian and the Eulerian–Eulerian approach qualitatively by performing numerical simulations of the flow behaviour of a laboratory scale fluidized bed and also comparing simulation output with experimental results. The multi-fluid model of Mathiesen [158] was used as Eulerian–Eulerian model. The DPM – an Eulerian–Lagrangian model – results were in better agreement with the experimental data, but the computational time was four orders of magnitude higher [97].

The combination of a CFD- and PBM model can be necessary to include the heterogeneity of the ambient conditions in the PBM. When the local ambient conditions vary along the reactor, this can have an influence on the distribution of the internal coordinates of the PBM. In literature, the coupling of CFD with PBM including a growth term is rarely found. Mostly, the QMOM approach is described as solution method and seems to offer a great potential for coupling with CFD. The acceptable computational effort of this method is a great advantage, while the validation of the QMOM-method gives good results. However, the integrated CFD–PBM has to our knowledge never been used to describe a pharmaceutical drying process. Hence, this opens perspectives, especially since it has been applied successfully in many other applications.

Currently, Discrete Element Method (DEM)–PBM models gain popularity in cases where knowledge on the particle level is needed. Such models are indeed useful to study phenomena on the particle level because an explicit calculation of the particle contact mechanics in the particle-scale reference frame is done by means of a Lagrangian approach. The computational time needed for these type of calculations is, however, a major drawback. Limiting the number of particles, the needed computational time can be reduced, and in this way, it can be possible to study agglomerate growth and kinetics.

Although much effort is taken in the area of fluidized beds and drying, a complete descriptive model of a fluidized bed drying process is still lacking. Mostly both processes, i.e., the fluidized bed and the drying process, are studied separately. However, a coupled model is essential to better understand the process and in a later instance to optimize and control the process. Without a more complete description of the process, it is indeed impossible to predict the future process behaviour, given a set of inputs.

Model validation is crucially important in order to give credibility to a model. The complexity of the model is not only influenced by the process itself, but depends also on the data that can be obtained by experiments. As such, before the development of a model, one has to think about the capability to measure the variables that are modelled. A detailed mathematical model does not provide conclusive information about a process without validation using experimental data. The gathering of experimental data is an important step, as the data contain the most important dynamics of the process. Data collection for this type of models is often not straightforward.

10. General conclusion

This review provides an overview of the existing models and tools for the description of the drying behaviour in a fluidized bed and the incentives for the development of mechanistic models for pharmaceutical production processes:

- The strict regulation in the pharmaceutical industry has for a long time made it nearly impossible to change something in the way of processing. Mechanistic modelling could be helpful for the development of a Design Space. The necessary modelling frameworks to achieve this are now available.
- The quality control of continuous production processes based on on-line measurements and real-time adjustment of process parameters necessitate a detailed validated model. A proposal of the requirements of such a model was discussed.
- Models to describe the drying of porous media/particles are reviewed. Three models are described, two models for the detailed drying behaviour in porous media and one that studies the drying evolution of one single particle. The latter is in our opinion sufficient for modelling the drying process of pharmaceutical granules.
- The PBM-concept allows to extend the behaviour of particles to a population of particles with distributed properties. In this review, the focus lies on the PBE with a growth-term. Since the solution of a PBM model is not trivial, also a short overview of existing solution methods is given, again focusing on the PBE with a growth-term.
- The use of CFD to simulate and study the flow of particles in a fluidized bed is reviewed. This is necessary to study the local ambient conditions of single particles in the dryer.
- The use of a coupled PBM–CFD-model to describe the evolution of processes under inhomogeneous conditions, and in this case, the drying behaviour in a fluidized bed is reviewed.

As a general conclusion, it is suggested to use a stepwise approach to model the drying behaviour of granules for pharmaceutical application.

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