European Journal of Pharmaceutical Sciences 90 (2016) 14–24

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Analysis of large-scale tablet coating: Modeling, simulation and experiments

P. Boehling [a,*], G. Toschkoff [a], K. Knop [b], P. Kleinebudde [b], S. Just [d], A. Funke [d], H. Rehbaum [e], J.G. Khinast [a,c]

[a] Research Center Pharmaceutical Engineering GmbH, Graz, Austria
[b] Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Düsseldorf, Germany
[c] Institute for Process and Particle Engineering, Graz University of Technology, Graz, Austria
[d] Global Chemical and Pharmaceutical Development, Bayer Pharma AG Berlin, Germany
[e] L.B. Bohle Maschinen + Verfahren GmbH, Ennigerloh, Germany

ARTICLE INFO

Article history:
Received 4 November 2015
Accepted 14 December 2015
Available online 18 December 2015

Keywords:
DEM
Tablet coating
Industrial scale simulation
GPU simulation

ABSTRACT

This work concerns a tablet coating process in an industrial-scale drum coater. We set up a full-scale Design of Simulation Experiment (DoSE) using the Discrete Element Method (DEM) to investigate the influence of various process parameters (the spray rate, the number of nozzles, the rotation rate and the drum load) on the coefficient of inter-tablet coating variation ($c_{v,inter}$). The coater was filled with up to 290 kg of material, which is equivalent to 1,028,369 tablets. To mimic the tablet shape, the glued sphere approach was followed, and each modeled tablet consisted of eight spheres. We simulated the process via the eXtended Particle System (XPS), proving that it is possible to accurately simulate the tablet coating process on the industrial scale. The process time required to reach a uniform tablet coating was extrapolated based on the simulated data and was in good agreement with experimental results.

The results are provided at various levels of details, from thorough investigation of the influence that the process parameters have on the $c_{v,inter}$ and the amount of tablets that visit the spray zone during the simulated 90 s to the velocity in the spray zone and the spray and bed cycle time. It was found that increasing the number of nozzles and decreasing the spray rate had the highest influence on the $c_{v,inter}$. Although increasing the drum load and the rotation rate increased the tablet velocity, it did not have a relevant influence on the $c_{v,inter}$ and the process time.

1. Introduction

Tablets are the most common form of drug products and they are often coated to mask the API's taste, to add protection functionality, to provide a modified release of an active pharmaceutical ingredient (API) or to add a second API (active coating). Especially, with respect to active coating, ensuring content uniformity – and thus coating uniformity – is a challenging task. Consequently, intra-tablet and inter-tablet coating variability are critical quality attributes (CQAs). Intra-tablet coating variability is the variability in the coating mass on a single tablet, with the edges and the bands being especially critical. In contrast, inter-tablet coating variability refers to the variance between all tablets in one batch. For the case of active coating, inter-tablet variability is even more critical and is regulated by the corresponding guidelines and pharmacopoeias.

One of the main goals of designing a coating process is to ensure that it reliably delivers a low inter-tablet coating variability. Thus, mixing of the tablet bed and the spraying process are often studied experimentally, typically in a small-scale drum coater (Rege et al., 2002; Suzzi et al., 2010; Tobiska & Kleinebudde, 2003). Since extensive experimentation on the pilot or, even more demanding, on the production scale typically is prohibitively expensive, experimental studies are mainly performed on the laboratory scale. Scale-up rules and the experience of the process engineer are used to calculate/estimate the correct loads and rotation rates on larger scales (Mueller & Kleinebudde, 2007; Turton & Cheng, 2005; Just et al., 2013a; Koller et al., 2011). Verification of the process parameters is carried out via test runs on the industrial scale, which are also used for obtaining the approval of the regulatory agencies. Results of experiments on the industrial scale are rarely published (Chen et al., 2010).

One way to reduce the amount of experiments and the associated costs is to perform simulations in addition to experiments. In this context, the Discrete Element Method (DEM), developed by Cundall and Strack in 1979 (C. P. A. & Strack, 1979), has proven to be an effective simulation methodology. In this method, Newton's second law of motion and a momentum balance are solved for each particle in three dimensions. All forces, including normal and tangential contact forces are included and the detail of modeling distinguishes the different implementations of DEM. DEM has successfully been applied in the pharmaceutical industry (Yamane et al., 1995). Tablet coating is particularly suitable for DEM simulations as the number of particles (i.e., tablets) is relatively low compared to other processes involving granular material, where particle numbers easily reach many billions (Ketterhagen et al., 2009). In the past, simulations reported in the

* Corresponding author.

http://dx.doi.org/10.1016/j.ejps.2015.12.022
0928-0987/

literature focused mainly on small-scale systems, with the number of tablets being in the order of 10^4–10^5 (Toschkoff et al., 2015)–(Ketterhagen, 2011). Early simulations used spheres (Ketterhagen et al., 2010) to approximate the tablet's shape: the glued sphere approach was developed to model non-spherical particles (Favier et al., 1999) through multiple spheres (Suzzi et al., 2012; Ketterhagen, 2011; Toschkoff & Khinast, 2013; Toschkoff et al., 2012). However, due to an increasing computational power available and sophisticated parallelization efforts, it is now possible to simulate many millions of particles on a single graphical processing unit (GPU) (Glasser & Khinast, 2010; Jajcevic et al., 2013). In combination with the glued sphere approach, current models can simulate the tablet coating process on the pilot and even on production scales with up to 2 million tablets within a reasonable amount of time. Based upon these new approaches, it is possible to create a full factorial Design of Simulation Experiment (DoSE) with multiple factors on every scale.

In the current study, we modeled the coating process and simulated the flow of tablets in a production-scale drum tablet coater to determine the optimal process parameters. A full DoSE on the production scale was carried out, which so far was not possible due to the limited computational resources. The Coefficient of Variation in the coating drum was calculated for various process settings. Moreover, the influence of the drum load, the rotation rate, the spray rate and the number of nozzles on the $c_{v,inter}$ were studied. The end-point of the process (i.e., the time needed to complete the process with the desired coating thickness and quality) could be predicted based on the simulation data. The predicted end point was then compared to experimental results. The spray residence time, the bed cycle time and the tablet velocity in the spray zone and their effect on the $c_{v,inter}$ were investigated.

2. Material and Methods

2.1. Tablet Coating Process, Tablet and Drum Design

In this study an active coating process was considered for the production of tablets that contain two APIs: one in the coating and the other in the core. Gastrointestinal therapeutic systems (GITS, see Fig. 1) were used as a starting material (Bayer Pharma AG, Leverkusen, Germany). These are biconvex round tablets with a diameter of 9 mm and a height of 5 mm. During the coating process, a coating solution containing the API candesartan (Cilexetil) was sprayed on the tablets.

During the coating process, the tablet bed is flowing in the drum coater due to the drum rotation (Yang et al., 2008). Integrated baffles in the coater enhance axial and radial mixing and ensure that no dead zones are formed. Individual tablets are transported upwards in the bed. After reaching the top of the tablet bed, the tablets slide down and pass through the spray zone where the coating mass is applied. The spray droplets impact on the tablet surface, spread and the solvent is removed (dried) by the drying air. The remaining polymer particles of the coating suspension form first a tightly packed bed and then a film. This occurs only above the minimum film forming temperature (MFFT). Thus, a minimum temperature in the bed needs to be maintained.

The coating mass applied to an individual tablet mostly depends on the time a tablet stays in the spray zones. The results of a DEM simulation of the tablet bed during the coating process and the spray zone position are shown in Fig. 2. The tablet velocities are represented by color variations: the fastest tablets are on the top of the tablet bed.

2.2. Experimental Investigation

Experimental investigations were performed at the Bayer site to investigate the necessary process time for achieving a desired coating quality. The tablets were coated in a production-size coater (BFC 400, L.B Bohle Maschinen + Verfahren GmbH, Ennigerloh, Germany). The geometry of the coating apparatus was provided by the manufacturer (Fig. 3). During the experiments, the drum load was varied between 240 and 260 kg. The rotation rate was set to 9 rpm and the spray rate was varied between 160 g/min to 360 g/min. The tablets were coated between 172 up to 522 min. The set of experiments can be seen in Table 1.

2.3. Simulation Model

XPS is a DEM algorithm written in CUDA, which is a C-extension developed by Nvidia and is designed for GPU computing. While a modern CPU typically has about 24 cores, CUDA allows for parallel computing with over 2000 CUDA cores. Parallelization of the DEM algorithm allows the simulation of up to 130 million spheres in a single GPU, applying a linear spring dashpot model to calculate the forces acting on the particles upon collision (see Glasser & Khinast, 2010, Eqs. 1–11).

To compute the interaction between non-spherical particles (e.g., tablets), a glued sphere approach was applied. Each simulated particle was represented via several primitive shapes. XPS currently uses overlapping spheres to mimic the real shape of a complex-shaped particle. The material properties (Table 2) were taken from Just et al. (2013b) and adapted accordingly. The modeled tablets were represented via eight spheres (Fig. 4), which had the same volume as

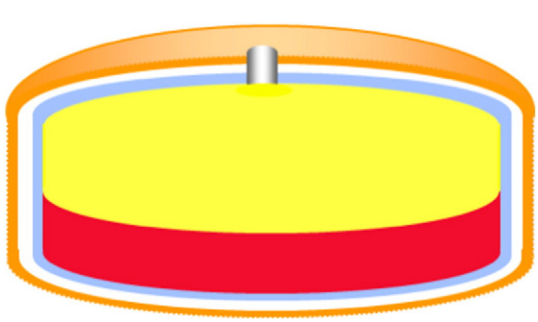

Fig. 1. GITS tablet schema, orange is an outer tablet color coating, white the active coating layer discussed in this paper, blue a semipermeable membrane with an orifice surrounding the inner drug layer (yellow) and the polymeric push compartment (red).

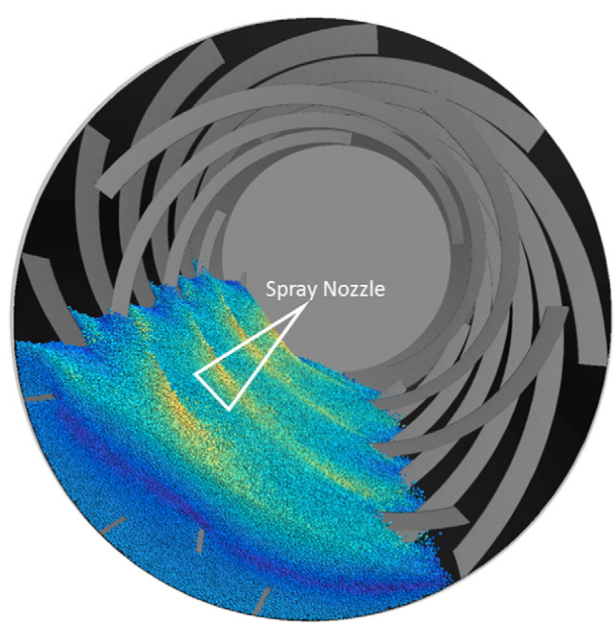

Fig. 2. Filled drum coater and the position of the spray nozzles. The drum is filled with 290 kg (1,028,369 tablets) of material and is rotating with 8 rpm. The tablets are colored according to their velocity.