Modeling of an Active Tablet Coating Process

GREGOR TOSCHKOFF,[1] SARAH JUST,[2] KLAUS KNOP,[2] PETER KLEINEBUDDE,[2] ADRIAN FUNKE,[4] DEJAN DJURIC,[5] GEORG SCHARRER,[1,6] JOHANNES G. KHINAST[1,3]

[1]Research Center Pharmaceutical Engineering GmbH, Graz, Austria
[2]Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Düsseldorf, Germany
[3]Institute for Process and Particle Engineering, Graz University of Technology, Graz, Austria
[4]Global Chemical and Pharmaceutical Development, Bayer Pharma AG Berlin, Berlin, Germany
[5]L.B. Bohle Maschinen + Verfahren GmbH, Ennigerloh, Germany
[6]Catra GmbH, Catra GmbH, Graz, Austria

Received 8 March 2015; revised 19 July 2015; accepted 4 August 2015

Published online 7 September 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24621

ABSTRACT: Tablet coating is a common unit operation in the pharmaceutical industry, during which a coating layer is applied to tablet cores. The coating uniformity of tablets in a batch is especially critical for active coating, that is, coating that contains an active pharmaceutical ingredient. In recent years, discrete element method (DEM) simulations became increasingly common for investigating tablet coating. In this work, DEM was applied to model an active coating process as closely as possible, using measured model parameters and non-spherical particles. We studied how operational conditions (rotation speed, fill level, number of nozzles, and spray rate) influence the coating uniformity. To this end, simulation runs were planned and interpreted according to a statistical design of (simulation) experiments. Our general goal was to achieve a deeper understanding of the process in terms of residence times and dimensionless scaling laws. With that regard, the results were interpreted in light of analytical models. The results were presented at various detail levels, ranging from an overview of all variations to in-depth considerations. It was determined that the biggest uniformity improvement in a realistic setting was achieved by increasing the number of spray nozzles, followed by increasing the rotation speed and decreasing the fill level. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:4082–4092, 2015

Keywords: factorial design; coating; *in silico* modeling; mathematical model; simulations; tablet

INTRODUCTION

Tablet coating is a common unit operation in the pharmaceutical industry. Its aim is to enclose the tablet core by one or more thin, solid layers. Most commonly, coating is applied by constantly moving tablets in a rotating drum and spraying them with a coating liquid containing a solvent and film-forming solutes. Heated air that flows through the system enhances the evaporation of the solvent.

A coating layer has various functions, such as protection from environmental influences, taste masking, and release control, and has to meet strict quality standards, including the coating uniformity. A special case is active coating that—in addition to excipients—contains an active pharmaceutical ingredient (API). Uniformity of coating is typically quantified by the coefficient of variation (c_v), also termed relative SD (RSD). Note that a high uniformity will give a low value for c_v. Here, two categories can be defined: intra- and inter-tablet uniformity. Intra-tablet uniformity ($c_{v,intra}$) is the uniformity of the coating layer's thickness on each tablet and inter-tablet uniformity ($c_{v,inter}$) is the uniformity of the coating mass of different tablets. During an active coating process, the latter is more critical than the former: the tablets have to pass the test for the uniformity of dosage units according to the regulations.[1–3] As this applies to the amount of API, it directly relates to the amount of the coating mass. The actual regulatory threshold value for the uniformity depends on a number of factors. For the purposes of this work, $c_{v,inter}$ must not exceed 6.25%.

In light of the above, the challenge is to design a coating process that will reliably yield tablets with high uniformity. To achieve this goal, a good understanding of the process is required, especially, of how the process parameters affect its outcome. To this end, various experimental studies have been performed (e.g., Refs. 4–10). In recent years, research efforts in that field have been complemented by computer simulations. Although simulations have certain drawbacks (e.g., the quality of a simulation depends on the input parameters and models applied), they can provide valuable data and allow extracting quantities that are difficult or impossible to measure. Depending on which part of the coating process was examined, various simulation approaches have been applied,[11] ranging from detailed methods like computational fluid dynamics[12] to quick analytic models such as renewal theory.[13] For particulate processes, which are common in the pharmaceutical industry, the discrete element method (DEM) has increasingly been used[14] as it is particularly suitable for studying tablet coating. A number of studies were performed, many of which investigate the inter-tablet coating uniformity. In an early application, Pandey et al.[15] applied a self-written DEM code implemented in MATLAB. The simulation comprised up to 7500 spherical particles in a flat unbaffled cylindrical drum, and showed agreement compared with similar experiments in terms of dynamic angle of repose. A scaling law for the tablet velocity was derived.

Correspondence to: Johannes G. Khinast (Telephone: +43 (316) 873 - 30400; Fax: +43 (316) 873 - 1030400; E-mail: khinast@tugraz.at)

Journal of Pharmaceutical Sciences, Vol. 104, 4082–4092 (2015)

Later, Dubey et al.[16] examined the influence of the drum rotation speed, fill level on tablet mixing, and coating uniformity. Different spray patterns were implemented during a post-processing step to record the residence time of tablets in the spray zone. The result of a DEM simulation was compared with the laser-induced breakdown spectroscopy measurements, showing good agreement. A significant effect of spray pattern was observed. The coating uniformity was higher (the c_v was lower) at higher rotation speeds and higher fill levels.

Kalbag et al.[17] performed experiments and DEM simulations with spherical particles. Particles in the spray zone were detected based on their solid fraction. For comparison purposes, a ray-tracing-based algorithm was used. The results were in agreement, and it was concluded that an increase in the pan speed led to a lower, narrower single-visit residence time distribution (RTD). Thus, a higher pan speed resulted in a better coating uniformity, as suggested by other research.[8,18,19] The results for different loads did not follow a simple trend: on the one hand, smaller loads with a higher sprayed-to-total tablets ratio yielded a better uniformity and, on the other hand, as Dubey et al.[20] also indicated, larger loads result in better mixing that in turn promotes uniformity. Suzzi et al.[21] investigated a cycled continuous coating process with a cylindrical spray zone defined in post-processing and found that for round and oval tablets an increased fill ratio resulted in a decreased uniformity (increased RSD of the fractional residence time). Kalbag and Wassgren[22] compared the DEM results with experiments and analytical models based on periodic random selection of tablets. An increase in the uniformity (decrease in c_v) was observed when decreasing the spray rate, increasing the number of tablets in the spray zone, increasing the mixing efficiency, and decreasing the total number of tablets. In addition to DEM simulations, a number of mathematical models exist.[11] Those necessarily are not as close to the physical process and make stronger assumptions (such as random mixing of tablets[23]), but allow for direct connection of process parameters and coating variation. A study for active coating was performed by Wang et al.,[4] developing a two-zone model (spray zone and drying zone) based on RTD theory as commonly applied in chemical reaction engineering. Model parameters are tablet velocity (itself based on empirical correlations), tablet number density (a measure for tablet passes in the spray zone area), and spray zone width. The model shows good correlation to experimental assays.

In this work, an active coating process was investigated, for which strict regulations apply with regards to the coating uniformity. To produce reliable results, an effort was made to model the process as close to the reality as possible, incorporating previous achievements and including new developments. DEM simulations were performed following a statistical Design of (Simulation) Experiments (DoSE), with the same process parameters as a real-life coating process. Most material parameters in the simulations were obtained by measuring the actual tablets, and the coater's geometry was provided by the manufacturer.

The main purpose of the study was to investigate how inter-tablet coating mass uniformity (and the API uniformity in particular) was affected by the process parameters. Furthermore, we aimed at achieving a deeper understanding of the underlying principles of the coating process. Based on this, guidelines were provided on how to consistently achieve a high coating uniformity that complies with the regulations.

METHODS

Coating Process

This work focuses on an active coating process for the production of tablets that contain two APIs: one with a delayed release in the core and the other with an immediate release in the coating. Gastrointestinal therapeutic systems (GITS) were used as a starting material (Bayer Pharma AG, Leverkusen, Germany). GITS are round biconvex two-layer tablets of approximately 9 mm in diameter and approximately 5 mm in height that contain the API nifedipine. They were already coated with a layer of cellulose acetate and polyethylene glycol. The investigated process adds an extra coating layer containing the API candesartan cilexetil.

Coating was performed in a lab coater (BFC 5; L.B. Bohle Maschinen + Verfahren GmbH, Ennigerloh, Germany). The geometry of the coating apparatus was provided by the manufacturer and directly uploaded into the DEM software (Fig. 1). The operation settings used for the simulation runs are described in sections *Investigated Parameter Space and Quality Criteria* and *Design of Simulation Experiments*.

The central quality attribute of the coating quality is the variation of coating mass of the tablets (inter-tablet uniformity). It was quantified as the coefficient of variation $c_{v,inter}$, which is defined as the SD of coating mass divided by the mean mass:

$$c_{v,inter} = \frac{\sigma_{m_c}}{\mu_{m_c}} = \frac{\sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(m_{c,i} - \overline{m_c}\right)^2}}{\overline{m_c}} \text{ with } \overline{m_c} = \frac{1}{N}\sum_{i=1}^{N} m_{c,i}, \quad (1)$$

where N is the number of tablets and $m_{c,i}$ is the coating mass of tablet i. The aim is to obtain consistently low values of $c_{v,inter}$. Note that although in an experimental investigation, the total variation was estimated based on the variation in a sample, in the DEM simulation, the coating of all tablets (i.e., the entire statistical population) was used in the calculation.

For active tablet coating, regulations define the maximum acceptable variation in the coating mass depending on the application.[1–3] For the application described in this work, the upper limit of $c_{v,\,inter}$ was 0.0625 (or 6.25%).

Simulation Setup

For the simulations, EDEM 2.4.4 (DEM Solutions Ltd., Edinburgh, UK) was used. The round biconvex tablet shape was approximated via the "glued sphere" approach. Each particle was made up of eight intersecting spheres fixed relative to each other such that the enclosed volume was equal to that of the bi-convex tablet (Fig. 2). Each tablet weighed 282 mg. Depending on the fill level, the total number of tablets ranged from 10,638 (3 kg) to 14,177 (4 kg).

For the DEM simulation, the material properties of the tablets are required. The values were taken from measurements reported in Ref. 24. It is known that the friction parameter (particle–particle and particle–wall) has a significant influence on the outcome.[17] At first, a direct measurement of the friction coefficients using "pin-on-disk" tribometry setup was attempted. As this approach did not yield reliable results, we followed another approach reported in the literature and obtained the friction values from indirect calibration. In this