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Laser based thermo-conductometry as an approach to determine ribbon solid fraction off-line and in-line

Raphael Wiedey, Rok Šibanc, Peter Kleinebudde*

Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Universitaetsstrasse 1, 40225 Duesseldorf, Germany

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ABSTRACT

Ribbon solid fraction is one of the most important quality attributes during roll compaction/dry granulation. Accurate and precise determination is challenging and no in-line measurement tool has been generally accepted, yet. In this study, a new analytical tool with potential off-line as well as in-line applicability is described. It is based on the thermo-conductivity of the compacted material, which is known to depend on the solid fraction. A laser diode was used to punctually heat the ribbon and the heat propagation monitored by infrared thermography. After performing a Gaussian fit of the transverse ribbon profile, the scale parameter σ showed correlation to ribbon solid fraction in *off-line* as well as *in-line* studies. Accurate predictions of the solid fraction were possible for a relevant range of process settings. Drug stability was not affected, as could be demonstrated for the model drug nifedipine. The application of this technique was limited when using certain fillers and working at higher roll speeds. This study showed the potentials of this new technique and is a starting point for additional work that has to be done to overcome these challenges.

1. Introduction

The relevance of ribbon solid fraction during roll compaction/dry granulation has been described elaborately in literature (Jaminet and Hess, 1966; Malkowska and Khan, 1983; Kleinebudde, 2004). It critically affects the granule size distribution and granule solid fraction and by that predominantly influences flowability and tabletability during subsequent processing (Jaminet and Hess, 1966; Malkowska and Khan, 1983; Mosig and Kleinebudde, 2015). However, the currently available methods to determine ribbon solid fraction are not fully satisfying. Regularly used pycnometric techniques, i.e. powder pycnometry (Acevedo et al., 2012; Samanta et al., 2013) and mercury pycnometry (Michrafy et al., 2011) are relatively time consuming, and show limited precision and accuracy, especially when ribbons laminate and have cracks and voids within them. The same is the case for a laser-based scanning of the outer geometry that has been used increasingly over the last years (Allesø et al., 2016; Iyer et al., 2014).

Near-infrared spectroscopy and terahertz spectroscopy are more complex techniques that derive the information not from a determination of the outer geometry, but from the interaction of the densified material with electromagnetic radiation (Acevedo et al., 2012; Khorasani et al., 2015; Souihi et al., 2015; Zhang et al., 2016). Thus, these techniques should not be limited by laminating or irregularly shaped ribbons, though no work has been published that systematically investigated this issue. Furthermore, as these techniques do not require additional weighing of the sample and need only short measurement times, these techniques can also be used for in-line measurements of ribbon solid fraction during the roll compaction step. Such an implementation as Process Analytical Technology (PAT) would be desirable, especially when aiming at continuous manufacturing and a parameter based release of pharmaceutical products (Food and Drug Administration, 2004).

Near infrared (NIR) spectroscopy is the most common PAT tool in pharmaceutical manufacturing and also the measurement of ribbon solid fraction has mostly been approached this way (Fonteyne et al., 2015). It has first been applied on roll compaction by Gupta et al., who found a correlation of the NIR absorption with the solid fraction (Gupta et al., 2004, 2005). Using PLS models based on certain ranges of the NIR spectra it was possible to make real-time predictions of the ribbon solid fraction. The character of the study was however preliminary and the difference between predictions and off-line values too high, as was concluded by Fonteyne et al. (2015). A systematic comparison revealed that PCA models seem to be more suitable for monitoring of ribbon solid fraction, but the authors still concluded that the predictive

Abbreviations: RCDG, roll compaction/dry granulation; PAT, Process Analytical Technology; MCC, microcrystalline cellulose; DCPA, dibasic calcium phosphate anhydrate; rpm, rounds per minute; SCF, specific compaction force; API, active pharmaceutical ingredient

* Corresponding author.
E-mail address: Kleinebudde@hhu.de (P. Kleinebudde).

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potential is limited (Acevedo et al., 2012). Khorasani et al. used NIR chemical imaging to also allow visualization of solid fraction distribution within the produced ribbons (Khorasani et al., 2015). Furthermore, analysis of acoustic emissions of the compaction unit as well as microwave resonance sensing have been demonstrated to give information on the ribbon solid fraction (Austin et al., 2013; Hakanen and Laine, 1993).

Still, none of it has found its way into pharmaceutical industries. This might be due to limited robustness on manufacturing conditions, the high price of the equipment, or the limited space that is available in the production unit of commercially available roll compactors. Following this, there is still a need for new or optimized analytical tools, that allow accurate, precise, and robust solid fraction measurements – preferably with a short measurement time and a size that allows an easy in-line implementation.

A technique that combines short measurement times, small size, and a relatively low price is the determination of ribbon solid fraction by thermography (Wiedey and Kleinebudde, 2016). The heat that is developed during RCDG derives from the inner friction within the powder during densification (Wiedey and Kleinebudde, 2016; Zavaliangos et al., 2008) and can thus be used to obtain the degree of densification from it. Even though sufficient precision for a range of materials and robustness to changes in various process parameters was demonstrated, the signal is sensitive to a heating up of the machine over process time (Wiedey and Kleinebudde, 2018). It was furthermore described before that also the cooling rate of ribbons correlates with the solid fraction (Wiedey and Kleinebudde, 2016). When using rim rolls, it was found that the cooling rate positively correlates with the ribbon solid fraction. Since the main mode of cooling can be assumed to be heat transfer to the master roll, it seems to be the correlation between solid fraction and thermal conductivity that causes this phenomenon. This correlation has been described with models proposed by Maxwell (1954) and Zavaliangos et al. (2008) and further been investigated by Krok et al. (2017). However, the before mentioned cooling rate measurements of ribbons have been performed by stopping the compactor in mid process and observing the ribbon temperature for the following 50–100 s, which means this technique is in this form not applicable in-line.

$$\frac{dE}{dt} = h*A*(T-T_{env}) \quad (1)$$

Heat flow by conduction is described by Newton's law of cooling (Eq. (1)) (Newton, 1952). The observed changes in temperature depend on the heat transfer coefficient (h), the heat transfer surface area (A), and the difference between object temperature (T) and environmental temperature (T_{env}). The heat transfer coefficient depends among other things on the solid fraction. If changes of h are to be derived from the heat flow and A is constant, the precision depends on the temperature difference ($T - T_{env}$), because higher signal-to-noise ratios are achieved. Therefore, it was hypothesized that an additional input of thermal energy allows to precisely monitor the ribbon solid fraction. Furthermore, a higher robustness towards changes in environmental temperature seemed plausible. In this study, a first approach should be made to test these hypotheses and use an additional input of thermal energy into the ribbon to determine the thermal conductivity and by that the solid fraction. This energy input was given by laser light. Furthermore, a first estimation of the applicability for off-line as well as in-line use should be made.

2. Materials and methods

2.1. Set-up of laser unit

A 450 nm laser diode (Nichia NUBM44-81) was installed into an aluminum case (40 × 50 × 20 mm) to allow adequate heat dissipation. The current and by that the laser power was controlled by a SHS-2500 Laser Diode Driver. In this set-up the laser power could be controlled between about 0.2 and 3.5 W. An on/off-switch as well as a reed relay for emergency cutout were installed via transistor-transistor logic (TTL).

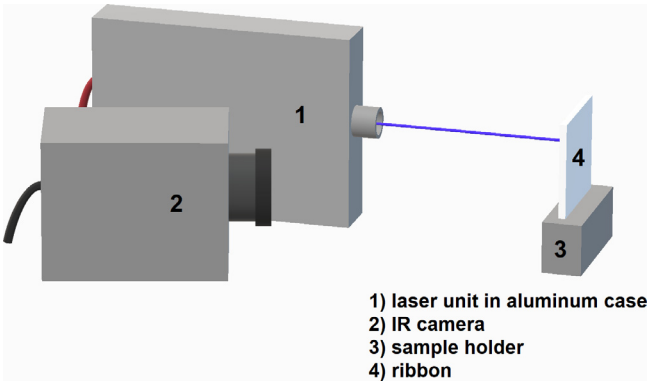

Fig. 1. Off-line experimental set-up containing laser unit, thermographic camera and sample holder.

2.2. Off-line experimental set-up

For off-line measurements, the unit was placed in a closed chamber with a ribbon positioned perpendicularly in a distance of 125 mm (Fig. 1). The laser was set to a power of 1.0 W and the beam focused on the center of the ribbon. A thermographic camera (optris PI 640, optris GmbH, D) was placed next to the laser unit to record the thermal events on the ribbon surface. The temperature data was evaluated using optris PI connect software (optris GmbH, D). Emissivity values (ε) used for determination of the sample temperature are given in Table 1. The experimental approach for determining the emissivity has already been described elsewhere (Wiedey and Kleinebudde, 2018). Ribbons produced at various specific compaction forces (see Table 2) were placed into the sample holder and the laser switched on for 1.0 s (± 0.1 s). To investigate the influence of laser exposure time on the measurement result, also experiments with 2, 3, and 4 s (± 0.1 s) were performed.

2.3. In-line experimental set-up

To implement the measurements into the roll compaction process, the single components were installed in the production chamber as displayed in Fig. 2. The laser beam was focused on the center of the ribbon a few centimeters below the gap and the camera placed in a way that allowed to observe the laser focus in the upper part of the image and follow the heated spot moving downward (see also Fig. 7). For safety reasons, the front window was sealed with a nontransparent shield. The reed relay was installed in a way that the laser could only operate with a shut roll compactor door.

2.4. Manufacturing of ribbons

The ribbons used for the off-line experiments were produced by roll compaction of microcrystalline cellulose (MCC, Vivapur 102, JRS Pharma, D) on a Gerteis Minipactor 250/25 (Gerteis, CH). For these experiments, the cheek plate sealing system was used. All following

Table 1
Emissivity values for the studied materials.

Material	ε
MCC	0.90
DCPA	0.85
lactose	0.88