Optimization of a film coating formulation for high solid content application suitable for continuous manufacturing

Sabrina Kreß, Hochschule Fresenius University of Applied Sciences, Idstein, Germany / **Dr. Raphael Janousek,** BIOGRUND GmbH / **Dr. Rainer Bastian, Bernd Grabherr, Dr. Matthias Kruse,** DRIAM Anlagenbau GmbH, Eriskirch, Germany

Introduction

With regard to continuous manufacturing (CM) of solid dosage forms, such as the tablet, the continuous film coating process plays an ever-growing role. Supported by actions of the US Food and Drug Administration (FDA) to introduce process analytical technology (PAT) and thus, generation of continuous process data, end-to-end monitoring of processes became possible [1] [2] [3]. At the same time, advances in the development of aqueous film coating systems led to significant improvements in process times and film tablet properties [4]. Due to the latter advances and the introduction of PAT, CM is expected to continue to grow in importance in the pharmaceutical industry.

At the end of the 20th century, pharmaceutical companies started to use Ready-to-Use (R2U) film coating formulations to exchange complex in-house formulations, which contain multiple raw materials like the film-forming polymer as well as auxiliaries, such as plasticizers, fillers, pigments or functional agents [5]. Due to the high degree of specialisation of companies producing such R2U formulations, new film coatings were developed that were specifically invented for continuous coating. Biogrund, as one of the leading companies in R2U premixes for the pharmaceutical industry specifically developed AquaPolish® PRO to meet those needs. AquaPolish® PRO is a film coating with immediate release and moisture protection, which protects the core of the solid dosage form and thus, the active ingredient from external environmental influences. Likewise, due to the low stickiness of the film, a very smooth surface can be achieved, which facilitates swallowing of the tablet [7] and ultimately increases patient compliance.

AquaPolish® PRO is based Kollicoat® Protect, which mainly consists of a polyvinyl alcohol (PVA)/polyethylene glycol (PEG) graft copolymer. The main feature of this formulation is that due to the low viscosity of the polymer, a high solid content (25-30%) of the coating suspension can be used [8]. Since a higher solid content at a constant spray rate shortens the process time, formulations with lower viscosities are a clearly advantage for continuous coating processes and hence, increased throughput [9]. In contrast, as a matter of the high viscosity, conventional film coating formulations – which often consist of PVA as the film-forming polymer – are most times applied with a solid content that should not exceed 15-20 [10].

The aim of this study was the optimization of an existing AquaPolish® PRO film coating formulation by means of an elaborated test plan – based on a Quality-by-Design (QbD) approach.

Materials and Methods

Kollicoat® protect was sourced from BASF SE and PVA from Japan Vam & Pocal Co. Ltd. Talc was purchased from Imerys Talc Italy S.p.A., titanium dioxide from Kronos International Inc., stearic acid from Peter Greven Nederland C.V. and PEG 6,000 from Clariant Produkte Deutschland GmbH. Placebo tablets were coated using AquaPolish® P white 619.03 PRO and AquaPolish® P white 610.26 PVA at 3% weight gain (wg). Optimal film coating parameters were determined using a Solidlab 1 (Hüttlin GmbH (Syntegon); Schopfheim, Germany) batch coater (see Table 1). The tablets were evaluated in terms of general surface texture and gloss. Furthermore, the AquaPolish® PRO and AquaPolish® PVA formulations were compared in terms of viscosity at different solid content levels. Afterwards, the optimized film coating parameters were transferred to a DRIACONTI-T pharma (Driam Anlagenbau GmbH; Eriskirch, Germany) in batch mode and later on scaled into continuous mode (see Table 1). This approach was possible due to the unique setup of the DRIACONTI-T pharma 450/3, which has three consecutive coating chambers that can be used individually (batch mode) or sequentially used as mini batches for continuous mode (see Figure 1). The tablet surface was again analyzed using stereomicroscope (S9i Leica Microsystems GmbH; Wetzlar, Germany) images and a PICOGLOSS 560 MC-X glossmeter (ERICHSEN GmbH & Co. KG; Hemer, Germany).

In addition, an optimized AquaPolish® PRO formulation (AquaPolish® P white 610.38 PRO) was developed and handled in a similar manner.

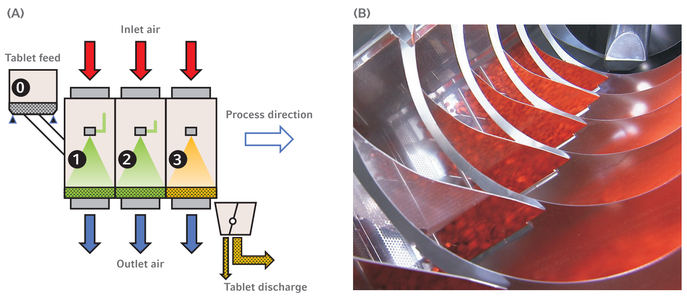

Figure 1: **A) schematic presentation of the axial DRN-T 450/3 and (B) view from the outlet through the open front door of DRN-T 1000/7 in transport phase (see flaps in separating walls)**

Table 1: **Coating parameters for film coating of oblong placebo tablets using the Solidlab 1 and the DRIACONTI-T pharma 450/3 Coater**

	Solidlab 1	DRIACONTI-T pharma 450/3
Mode	Batch	Continuous
Spray nozzle	1 x Schlick (Mod. 970/7-1-S75, Ø 1.2 mm)	3 x Schlick (Nano-ABC w82923, Ø 0.5 mm)
Spray angle	90°	90°
Spray nozzle distance (cm)	10-11	5-6
Atomizing air pressure (bar)	0.7	1.2
Formation air pressure (bar)	0.2	0.8
Inlet air volume (m³/h)	55	3 x 150 (150 per chamber)
Tablet bed temperature (°C)	40 or 46	45

Results and Discussion

Viscosity

Comparison of the viscosities of the tested formulations shows decreasing values from AquaPolish® P white 610.26 PVA to AquaPolish® P white 619.03 PRO and AquaPolish® P white 610.38 PRO (see Figure 1). Viscosities were evaluated in 5% increments of solid content. The highest viscosity that was determined for AquaPolish® P white 610.26 PVA is 30%, since the suspension could not be processed at a solid content level > 32%. Consideration of AquaPolish® P white 619.03 PRO at 30% solid content indicates a viscosity that is three magnitudes lower. Furthermore, AquaPolish® P white 619.03 PRO could still be processed at 35% solid content while still showing a slightly lower viscosity than AquaPolish® P white 610.26 PVA at 30% solid content. Comparison of AquaPolish® P white 610.38 PRO at 35% solid content with AquaPolish® P white 610.26 PVA at 30% solid content even showed a significantly lower viscosity, which eventually translates to good processability during film coating. Thus, fundamental differences in viscosity already suggest that AquaPolish® P white 610.38 PRO is significantly more suitable for application at higher solid content levels compared to available PVA formulations.

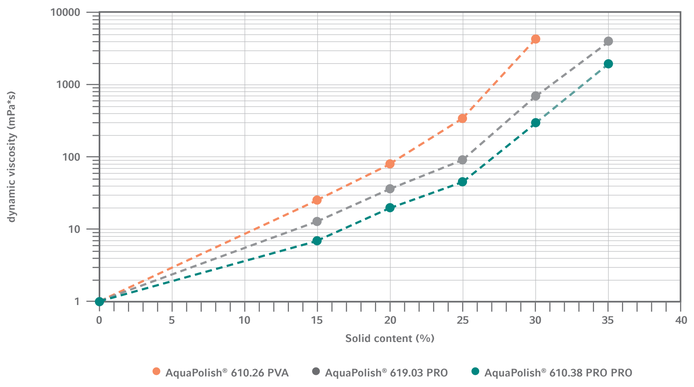

Figure 2: **Dynamic viscosity (mPa*s) of AquaPolish® P white 610.26 PVA (orange dots), AquaPolish® P white 619.03 PRO (gray dots) and AquaPolish® P white 610.38 PRO (green dots) plotted against the solid content level**

Surface texture and gloss values of produced film tablets

A series of film coating trials was performed in order to determine critical process parameters and define a suitable range for applicable solid content and applied spray rate for evaluated coating formulations. Figure 2 (A) shows the changing gloss value of tablets in relation to used solid content levels of the film coating suspension for AquaPolish® P white 619.03 PRO. Gloss units decreased with increasing solid content levels. A solid content of 25% showed the smallest deviation while still leading to good gloss values. Thus, AquaPolish® P white 619.03 PRO was further tested at 25% solid content with varying spray rates. The inlet air temperature was adjusted in order to maintain a tablet bed temperature according to Table 1. A spray rate of 1.3, 2.2 and 3.3 g/min did not affect the gloss value. Further increase of the spray rate led to lower absolute gloss values and higher deviation. Thus, a spray rate of 1.3-3.3 g/min was used as the optimal spray rate for further experiments.

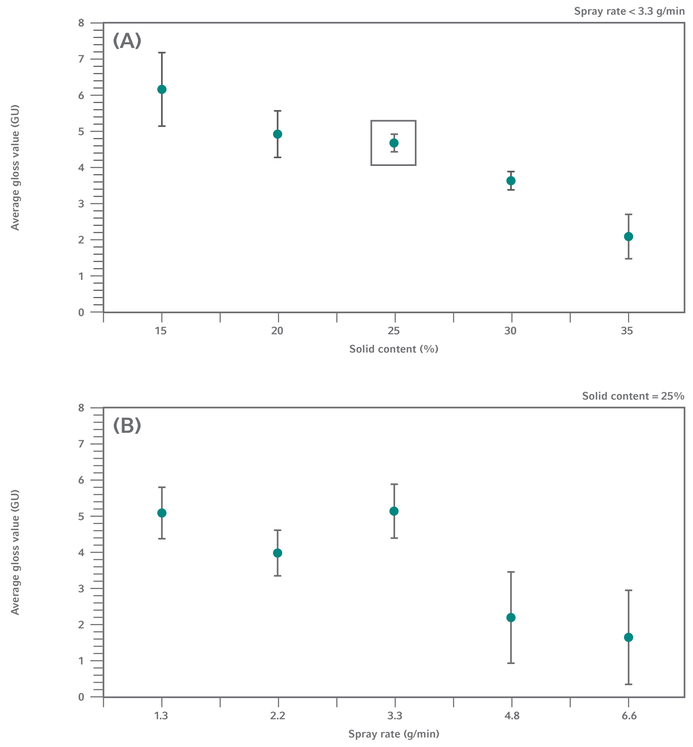

Figure 3: **Change of gloss value for AquaPolish® P white 619.03 PRO in dependence of (A) different solid content levels and steady spray rate (3.1 g/min) and (B) changing spray rates at 25% solid content in the Solidlab 1 batch coater**

Visual inspection of the film coated tablets confirmed results of the gloss measurements and revealed significant differences in surface texture. As indicated in Figure 3, film coating of placebo tablets at 25% solid content led to a smooth surface using AquaPolish® P white 619.03 PRO in the batch process.

Process transfer to the DRIACONTI-T pharma 450/3 was performed in batch mode (data not shown) and scaled to continuous mode. Film coating of placebo tablets with AquaPolish® P white 619.03 PRO using a continuous process was successful and led to equally good results as for tablets produced in a batch procedure (see Figure 4).

In comparison, AquaPolish® P white 610.26 PVA applied during batch process led to a good surface up to 20% solid content, but a rough surface at 25% solid content or higher. This is a so-called orange peel effect that is commonly observed when using film coating suspensions that show a high viscosity. The orange-peal effect was even more pronounced at 30% solid content of AquaPolish® P white 610.26 PVA, which can be attributed to the increased viscosity. Visual inspection of a modified AquaPolish® PRO formulation, namely AquaPolish® P white 610.38 PRO, showed no orange-peal effect at 30% solid content when applied in batch or continuous process (see Figure 4).

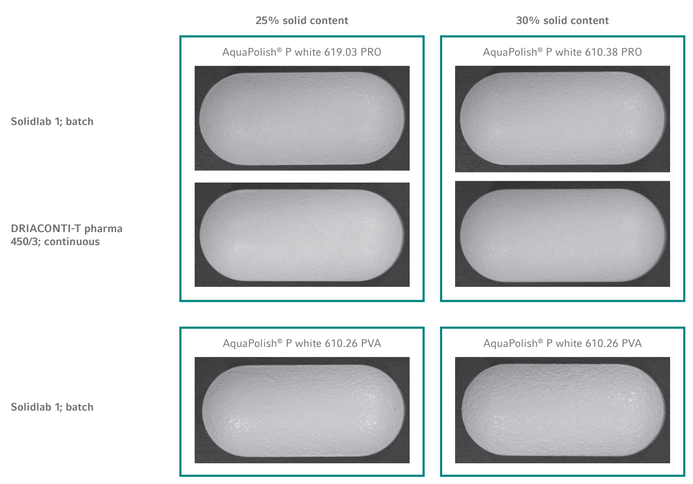

Figure 4: **Stereomicroscopy pictures of tablets coated with AquaPolish® P white 619.03 PRO (25% solid content) using the Solidlab 1 coater and the DRIACONTI-T coater, AquaPolish® P white 610.26 PVA (25% solid content) using the solidlab 1 coater, AquaPolish® P white 610.38 PRO (30% solid content) using the Solidlab 1 coater and the DRIACONTI-T 450/3 coater and AquaPolish® P white 610.26 PVA (30% solid content) using the solidlab 1 coater**

Additional variation of tablet bed temperatures was tested for further optimization of the results for AquaPolish® P white 619.03 PRO and AquaPolish® P white 610.38 PRO. As indicated in Figure 4 (A), an increased tablet bed temperature of 46 °C led to reduced gloss values for AquaPolish® P white 619.03 PRO with decreasing solid content levels compared to a lower temperature (see Figure 3 (A). However, an increased tablet bed temperature for AquaPolish® P white 610.38 PRO led to improved gloss values and a high stability of the gloss value with varying solid content levels while maintain low standard deviations (see Figure 4 (B). Thus, the surface texture could be drastically improved at solid content levels up to 30% and still led to good results at 35% solid content.

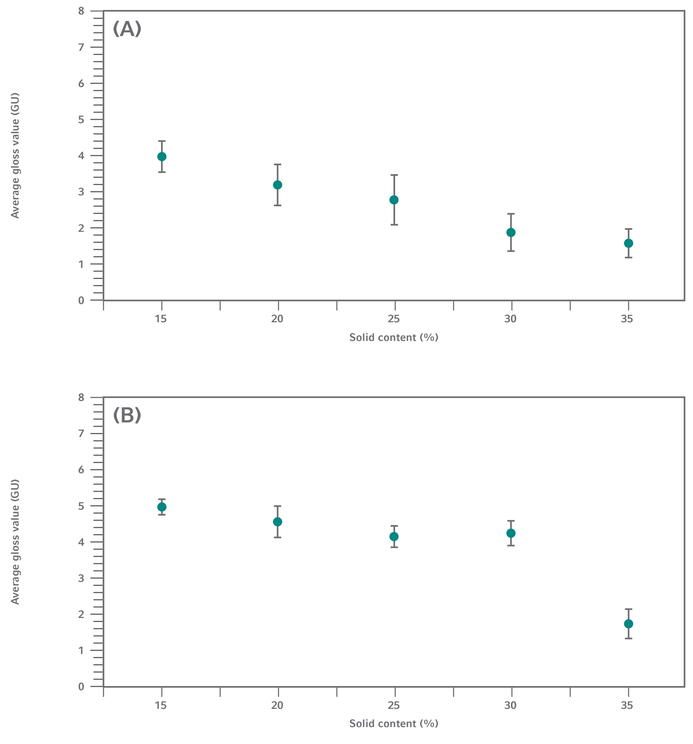

Figure 5: **Change of gloss value for (A) AquaPolish® P white 619.03 PRO and (B) AquaPolish® P white 610.38 PRO in dependence of solid content level at elevated tablet bed temperature in the Solidlab 1 batch coater**

Conclusion

The performed experiments demonstrate the importance of optimal coating parameters in order to obtain good surface properties of film coated tablets. Furthermore, optimized formulations (e.g. AquaPolish® P white 610.38 PRO) can lead to a higher range of suitable parameters without sacrificing surface properties. Also, reduced standard deviations of AquaPolish® P white 610.38 PRO indicate a better reproducibility of the results and hence, a more uniform coating result. This might also reflect on lower amounts of error-prone tablet rates and therefore, improved results for stability testing of tablets containing API (not tested in this study). Lastly, results indicated equally good surface properties when transferring the coating from a batch to a continuous process, which will be especially important for increasing demands of highly productive production processes and growing trends towards continuous manufacturing.

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AT A GLANCE

Continuous process for coating of tablets

In a continuous film coating system, the tablet cores are continuously introduced at one end of a rotating drum, coated by means of spray nozzles and transported to the opposite side. At the end, the coated tablets are continuously removed from the system. In contrast to a batch coating process, the coater in a continuous coating process consists of an elongated coating drum, which results in the need for a larger number of spray nozzles [5].

One advantage of the continuous coating process is an improved uniformity of the applied film coating on the tablets. This mainly results from the reduced tablet bed depth and the increased number of spray nozzles in relationship to the tablet bed surface. Likewise, the time required for handling of tablets (e.g. loading and unloading) is minimized. Thus, a larger number of tablets can be coated per time unit [11]. In addition, continuous coating offers advantages in the areas of control and automation of the process. Among other things, all stages of coated tablets are available simultaneously in the drum. This in turn facilitates inline measurement of process parameters and automated control. After a short time, the first coated tablets emerge at the drum exit and can be used for a quality inspection. If irregularities are already detected in these tablets, the necessary adjustments can be made immediately and – in contrast to the batch process – only a relatively small number of tablets needs to be discarded. In a batch process, the entire batch must be destroyed in the event of irregularities or defects [12].

The design of the Driaconti-T Continuous Coater is unique. The drum consists of distinguished by walls separated chambers (process rooms) where Mini-batches are treated. The process conditions are clearly defined with exact residence time of the tablets. Step by step (quasi-continuous) the Mini-batches are transported through the drum.

AquaPolish PRO® for continuous film coating

Despite the higher raw material price, a combination of film coating formulations that are applicable at high solid content levels (e.g. AquaPolish® P white 610.38 PRO) with continuous processes can lead to a significantly lower price per unit (see Figure 5). Thus, high throughput productions can increase the cost efficiency.

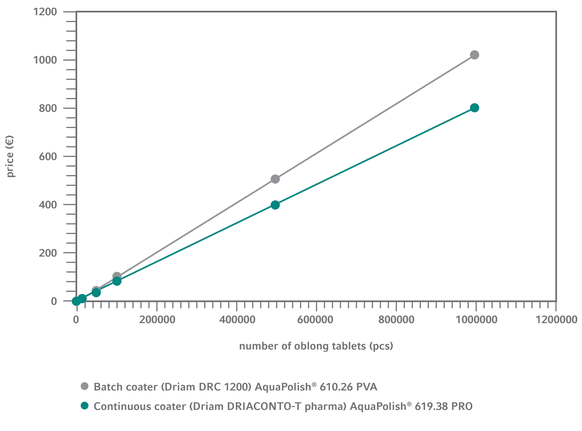

Figure 6: **Projected price evolution for application of a common batch process using AquaPolish® P white 610.26 PVA and a continous process using AquaPolish® P white 610.38 PRO. Calculations were carried out under the assumption of a linear relation between sourced raw material quantities and price per unit. Further aspects like absolute sources quantities, price dynamics or market related leverage (e.g. monopoly vs. oligopoly) were not taken into account.**

Did you know…

…that a reduced standard deviation of applied coating weight gain is highly influenced by an optimal mixing behavior of tablets in the coater? Thus, superior geometrics of the coating drum (e.g. barriers, strips, improved mixing elements, shallow bed) are essential for a good result. This was also tested in cooperation with Driam Anlagenbau GmbH and results indicated a drastically decreased mixing time for a homogenous distribution in the coating drum, which is one of the main factors influencing low RSD values of coating weight gain [13].

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