Comparing the performance of several Kollicoat® Smartseal based film-coating formulations, processed in a GEA ConsiGma® coater

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Introduction

Continuous manufacturing is a major trend in today's pharmaceutical industry. Short development times, technological flexibility, paired with cost-efficiency during development and production as well as the production of constantly high-quality dosage forms are some of the main reasons for this initiative [1].

One key element in continuous manufacturing is the interlink of various unit operations such as granulation, tableting, and film coating. Particularly, the coating process needs optimization, allowing for extremely short process cycles without compromising on coating quality.

From a Quality by Design (QbD) perspective, coating functionality and uniformity are potential Critical Material Attribute (pCMA). Consistently, these parameters require special attention, particularly with respect to polymers affecting drug release, since any variation of the coating uniformity might result in a deviation of the drug release pattern [2].

The aim of this work was the investigation of coating uniformity and its effect on drug release in the scope of continuous manufacturing. Several formulations, based on Kollicoat® Smartseal, applied in a GEA ConsiGma® coater were tested, altering the spray conditions (e.g. spray rate, inlet air temperature, inlet air volume).

Materials and Methods

Tablets, used for the coating trials, were composed of Ludipress® LCE (coprocessed lactose and povidone) 74.0%, Kollidon® CL-F (crospovidone, type B) 5.0%, Kollidon® VA 64 (copovidone) 5.0% (all BASF), caffeine anhydrous 0.2-0.5 15.5% (Siegfried), and magnesium stearate 0.5% (Baerlocher).

Taste masking functionality was to be delivered by two different grades of Kollicoat® Smartseal: Kollicoat® Smartseal 30 D is a low viscous aqueous dispersion of a methyl methacrylate (MMA) and diethylaminoethyl methacrylate (DEAEMA) copolymer, while Kollicoat® Smartseal 100 P represents a spray dried powder grade of the polymer. The cationic polymer is insoluble in water at neutral or basic pH values to ensure an effective taste masking in the saliva. At pH-values below 5.5 (e.g. in the patient's stomach) it dissolves readily, providing an immediate release of the active [3].

In the present case study, three main formulation concepts were applied to prepare the coating liquids:

a) The slightly alkaline, milky white dispersion of Kollicoat® Smartseal 30 D, was directly formulated with additional excipients [Table 1].

b) In comparison the powder grade, Kollicoat® Smartseal 100 P was redispersed in water under a required partial neutralization with succinic acid, before it was formulated.

c) Organic solutions of Kollicoat® Smartseal 100 P were prepared in an acetone-isopropanol mixture (1:1).

The solid matter content of all Kollicoat® Smartseal formulations was 20%.

Table 1. Composition of different coating formulations

Ingredient	Quantity [%]						
	F1	F2	F3	F4	F5	F6	F7
Kollicoat® Smartseal 30 D[*1]	57.8	42.0		57.8			
Kollicoat® Smartseal 100 P[*1]			12.4		10.0	6.3	14.3
Succinic acid[*2]			0.3				
Ponceau 4R HC 70% E124[*3]	0.4	0.4	0.4			0.2	
Buthylene hydroxy toluene (BHT)[*4]		0.3	0.3	0.3		0.2	
Tributyl O-acetylcitrate (ATBC)[*5]	2.3	1.6	1.6	2.3		0.8	2.1
Talc[*6]		5.0	5.0			2.5	
Aceton[*7]					45.0	45.0	41.8
Isopropanol					45.0	45.0	41.8
Water	39.5	50.7	80.0	39.6			

[*1] BASF SE, [*2] Bernd Kraft, [*3] Fiorio Colori, [*4] Lanxess, [*5] Jungbuzler, [*6] Sigma Aldrich, [*7] VWR Chemicals

Figure 1. Design of the ConsiGma® coater, used in the present case study.

The respective film coating formulations were applied onto the tablets in a ConsiGma® coater [Figure 1], which can be an integral part of a continuous manufacturing line or used as a standalone system as in the present case study.

Three kilograms of uncoated tablets were fed into the fully perforated coating chamber. Due to centrifugal forces at a wheel speed of 115 rpm, the tablets were moved towards the wall of the wheel. Two “air knifes”, situated outside the perforated wheel, caused a cascade in which the tablets were moved into a free fall state. Inside this cascade, the coating formulations were applied, using a spray nozzle positioned in the center of the wheel.

Several spray rates between 45 and 120 g/min were applied, at inlet air temperatures ranging between 45 and 70°C, and inlet air volumes of between 200 and 250 m³/h. Samples of tablets were taken at coating levels of 1, 2, 3, 4, 5, 6, 7 and 8 mg/cm².

The aqueous coating formulations (F1, F2, and F3) contained 0.4% of Ponceau 4R HC 70% E124, which was used as visual tracer to determine the amount of coating applied per tablet. This colorant has a high specific absorption rate in the UV/VIS spectra, while the other components in the formulation didn’t interfere with the determination of the colorant. Samples (n=5) of the respective tablets were dissolved individually in 200 ml 0.08 N HCl solution. As the Kollicoat® Smartseal coat is not soluble in water, but dissolves readily in acid media (< pH 5.5), 0.08 N HCl solution was chosen for the sample preparation. These samples were passed through a 0.45 µm syringe-filter (PVDF or PTFE) and then measured in an Agilent 8453 UV/VIS spectrometer assembled with a 1 cm cuvette. Signals of the Ponceau 4R HC (wavelength 509 nm) could be directly linked to the amount of coating applied.

Due to its insolubility in the solvent, Ponceau 4R HC could not be incorporated into the acetone/isopropanol – based formulations (F5 and F7). The amount of applied coating to these tablets, was determined by atomic absorption spectrometry (AAS) (ICP-OES Agilent 5100 SVDV) instead. Here the fact was considered, that Kollicoat® Smartseal 100 P contains a defined source of sodium, provided by the surfactant sodium lauryl sulfate (SLS), which is used to stabilize the dispersion. Knowing the quantity of detected sodium delivered by SLS (2.5% based on polymer), the coating level of the individual tablets could be easily calculated.

In addition to the quantification of the coating level on the tablets (content uniformity), the homogeneity of the applied coat (uniformity of thickness) was evaluated as well. This was done by visual inspection employing Scanning Electron Microscopy (SEM) micrographs.

A standard USP Dissolution Apparatus 2 (Paddle) from ERWEKA, equipped with continuous on-line UV measuring (Agilent 8453), was used for dissolution testing. Since taste-masking functionality is to be delivered in the oral cavity, phosphate buffer (pH 6.8) was used as dissolution media (700 mL ±1%, 37°C ±0.5°C, n=3). Hereby, a fully functional coat was indicated by no detectable drug release for 30 minutes. HCl buffer (pH 1.1) was used to test the immediate release character of the taste masked tablets (700 mL ±1%, 37°C ±0.5°C, n=3).

Results and Discussion

Both analytical methods (UV/VIS as well as AAS) were found to be suitable for the investigation of the coating level on individual tablets and thus the coating uniformity within a batch [Figure 2]. Differences of the actual determined coating level and the target coating level can be explained by a certain spray loss and by the sampling procedure itself: Samples were taken with a manual collector at defined times. Considering the exceptional high spray rates possible with the ConsiGma® coater, even smallest variabilities of the sampling time led to deviations of coating level applied in the meanwhile. However, the standard deviations of ±0.1 to 0.4 g/cm² within the tested samples (n=5) were acceptable.

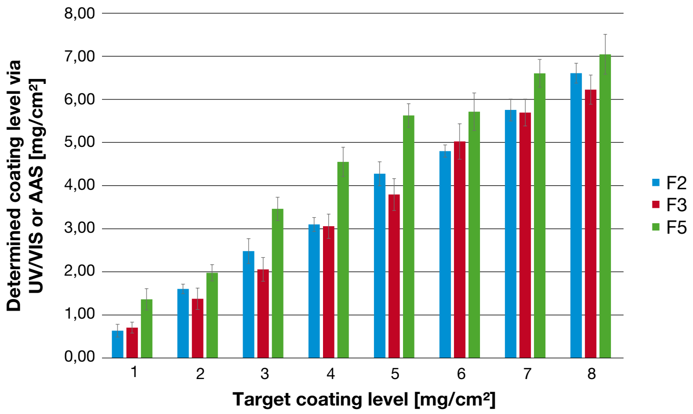

Figure 2. Comparison of the actual coating level of dispersed (F2), redispersed (F3) and organic (F5) Kollicoat® Smartseal formulations with the targeted value, determined via photometric (F2, F3) or spectroscopic (F5) measurement (mean value [n=5], ±abs. SD).

Applying Kollicoat® Smartseal based formulations in a ConsiGma® coater led to a uniform coating layer, independent of the tested formulations or parameters. As expected, higher weight gains showed the lowest relative standard deviations with respect to the applied amount of polymer within a batch [Figure 3]. At the maximum tested weight gain of 8 mg/cm², a relative standard deviation between 2 and 7% was found.

An inlet air temperature of 55°C led to lower standard deviations of the applied amount of polymer across all weight gains, when compared to higher temperatures such as 70°C. However, to guarantee the best performance of the applied polymer (especially at coating level of less than 3 mg/cm²), temperatures around 70°C should be preferred [Figure 4].

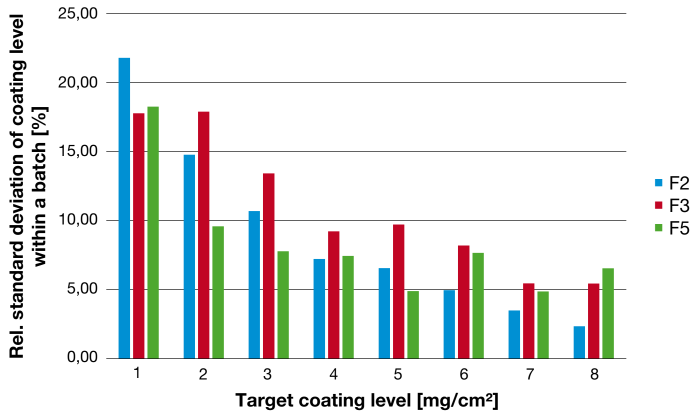

Figure 3. Comparison of the relative standard deviation (rel. SD) of applied amount of coating over the target coating level of dispersed (F2), redispersed (F3) and organic (F5) Kollicoat® Smartseal formulations.

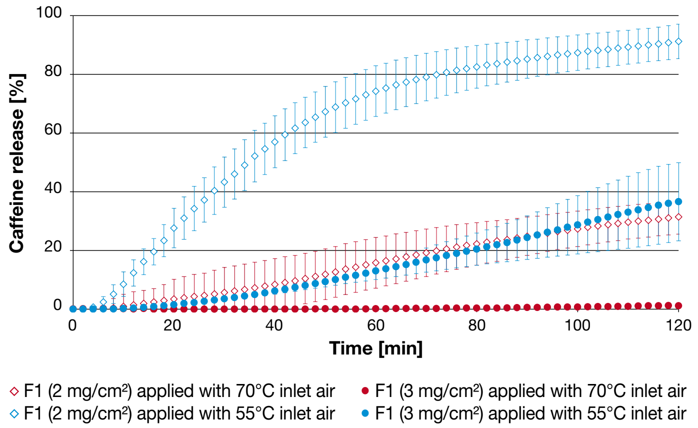

Figure 4. Dissolution profiles of tablets, coated with Kollicoat® Smartseal 30 D (F1), applied at different inlet air temperatures (mean value [n=3], ± abs. SD).

Increasing the inlet air volume hardly affected the uniformity of the film coat applied. Hence an inlet air volume of 200 m³/h can be recommended for the trials given. Less air consumed by the process, contributes to savings in energy and cost as well as a smaller environmental impact.

A reduction of the spray rate didn’t increase the uniformity of applied coating within a batch either. As short process cycles are essential in continuous coating processes, a higher spray rate can be applied, without compromising on the quality of the functional film coat.

Coating uniformity around the single tablets and even at the critical edges could be demonstrated with the help of the SEM pictures taken. Similar film thicknesses were found, on top of the curvature and around the edges [Figure 5]. Such uniform films were found, independent of the formulation applied, already at low coating levels. With the unique concept of the ConsiGma® Coater, the tablets were led into a free fall state (cascade), allowing the coating liquids to distribute evenly over the surface.

Conclusion

The application of all formulations, based on Kollicoat® Smartseal, in a ConsiGma® Coater led to robust processes in terms of coating uniformity and functionality.

Neither spray rate adoptions nor variations of the inlet air quantity indicated a relevant impact on the coating uniformity within the ranges tested.

A lower standard deviation was achieved at lower coating temperatures. However, to guarantee the best performance of the functional coating a sufficiently high temperature was required.

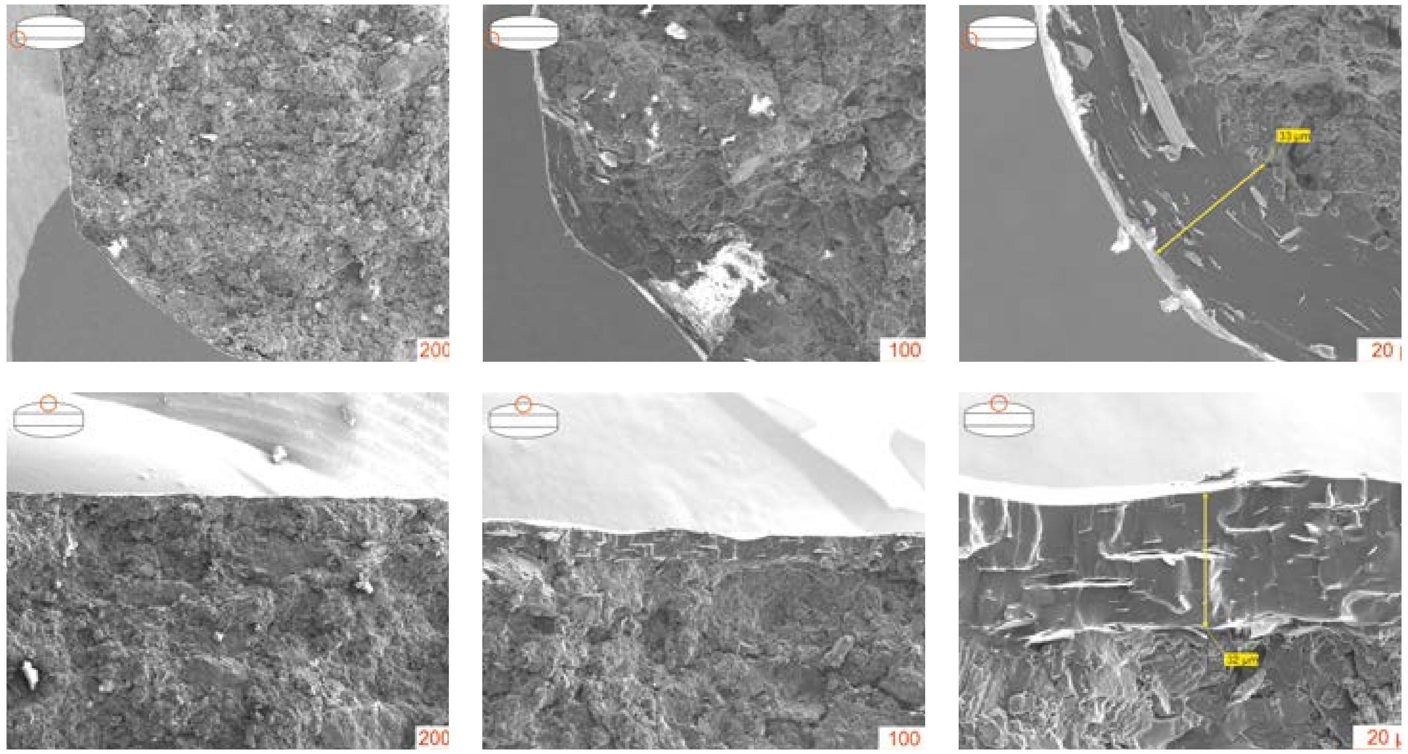

Figure 5. Cross section of tablets bearing a Kollicoat® Smartseal 30 D coat (F2) of 3 mg/cm², applied in a GEA ConsiGma® coater.

References

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