Investigation of the impact of Kollicoat® Smartseal formulation concepts on their taste masking functionality

Ivan Bogaerts[1]; Leslie van Eeckhout[1]; Frederik Detobel[1]; Andrea Beck[2]; Florian Bang[2]; Nils Rottmann[2]

[1] GEA Process Engineering nv, Keerbaan 70, 2160, Wommelgem, Belgium

[2] BASF SE, Carl-Bosch-Straße 38, 67056, Ludwigshafen am Rhein, Germany

Introduction

Taste-masking is typically considered to overcome the bitter or unpleasant taste of an active pharmaceutical ingredient, leading to a higher patient compliance and acceptability.

Different techniques are available to obtain such taste-masking functionality. An effective way is, to cover the surface of the individual oral solid dosage form (OSD) with a functional film coat. Components, having an unfavorable taste, are separated through this functional film from the patient's tongue and avoid thereby an unpleasant taste sensation.

Kollicoat® Smartseal is a product designed for such a taste masking application. 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, allowing for an immediate release of the active [1].

Three distinctly different formulation strategies, based on the same polymer were included in this study: Formulations, containing Kollicoat® Smartseal 30 D (aqueous dispersion), Kollicoat® Smartseal 100 P (spray dried powder grade, redispersed) and organic solutions of Kollicoat® Smartseal 100 P were coated in a GEA ConsiGma® coater.

The aim of this work was the investigation of the impact of the formulation concept for Kollicoat® Smartseal based film coatings on their taste masking functionality.

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).

A taste masking functionality was to be delivered by 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 [Figure 1], while Kollicoat® Smartseal 100 P represents a spray dried powder grade of the polymer.

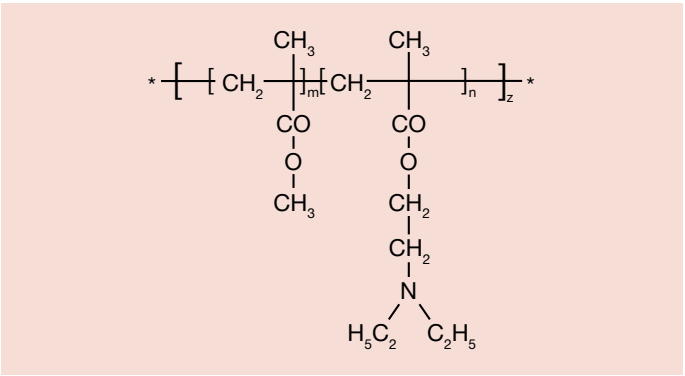

Figure 1. Structure of Kollicoat® Smartseal (methyl methacrylate (MMA) and diethylaminoethyl methacrylate (DEAEMA) copolymer).

The slightly alkaline, milky white dispersion of Kollicoat® Smartseal 30 D, was directly formulated with additional excipients [Table 1] and applied onto the caffeine tablets. In contrast, the powder grade Kollicoat® Smartseal 100 P had to be redispersed in water, by adding an organic acid (e.g. succinic acid) before being used.

All aqueous formulations required a plasticizer to reduce the minimum film forming temperature (MFFT) of the polymer (~57 °C) and to decrease the brittleness of the film formed. When selecting a plasticizer, it is important to consider that some plasticizers (e.g. citric acid esters) are prone to hydrolysis in alkaline aqueous environments and may cause the formation of free acid, counteracting the functionality of the cationic polymer [2]. In view of this and due to its wide acceptance in the pharmaceutical industry, tributyl O-acetylcitrate (ATBC) was selected as plasticizer for the present case study.

BASF
We create chemistry

The lipophilic antioxidant butylated hydroxytoluene (BHT) was used to stabilize the amino ester moiety of the polymer and thereby to avoid potential yellowing of the film on the tablets. Further excipients such as anti-tacking agents (talc) or colorants (Ponceau 4R HC) were used as listed in Table 1.

Organic solutions of Kollicoat® Smartseal 100 P were prepared with an acetone-isopropanol mixture (1:1). As the film forming mechanism of a polymer dispersed in water and the film forming mechanism of dissolved polymer is fundamentally different, the need for a plasticizer and other additives had to be tested. Organic Kollicoat® Smartseal solutions was tested with the respective formulations (F5-7).

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

All seven formulations were applied with a solid matter content (SMC) of 20%. The aqueous formulations were additionally coated with a SMC of 30%.

The respective film coating formulations were coated onto the tablets in a GEA ConsiGma® coater [Figure 2], which can be an integral part of a continuous manufacturing line or used as a standalone system as in the present case study.

Figure 2. Design of the ConsiGma® coater, used 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. With the unique concept of the ConsiGma® coater, the tablets were coated during the free fall phase, allowing the coating liquids to distribute evenly over the complete surface around the individual tablets. Remarkable uniform coatings around the tablets can be achieved, even at the critical edges of the tablet cores [3].

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 the caffeine tablets were taken at 1, 2, 3, 4, 5, 6, 7 and 8 mg/cm² coating level.

A standard USP Dissolution Apparatus 2 (Paddle) from ERWEKA, equipped with continuous on-line UV measuring (Agilent 8453), was used for the dissolution testing. Since taste-masking functionality is to be delivered in the saliva of the oral cavity, phosphate buffer (pH 6.8) was used as dissolution media (700 mL ±1%, 37°C ±0.5 K, n=3). Hereby, the criterion for a functional coat was that no drug release was detected for a period of >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 K, n=3).

Results and Discussion

Both, aqueous and organic based Kollicoat® Smartseal formulations could be processed without any problems in the ConsiGma® coater.

In a setup with just a single spray nozzle, process cycles of less than 10 minutes were achieved for the coating of a 3 kg batch with up to 8 mg/cm² coating level. Such exceptional short coating process cycles without compromising on coating quality are a prerequisite in continuous manufacturing installations.

All formulations tested were able to deliver taste masking functionality as per the pre-defined criterion of >30 minutes coating stability in phosphate buffer (pH 6.8). However, differences in performance of the three formulation concepts were seen, particularly with respect to the amount of coating required.

A Kollicoat® Smartseal 30 D based Formulation (e.g. F2) required a coating level of about 4 mg/cm² to deliver full taste masking functionality over more than 30 minutes [Figure 3].

In contrast, a redispersed Kollicoat® Smartseal 100 P formulation (e.g. F3) required a distinctively higher coating level to meet the same criterion. This effect was expected, as Kollicoat® Smartseal 100 P needs to be partially neutralized to be redispersed. Succinic acid used for the partial neutralization, increased the hydrophilicity respectively solubility of the cationic polymer slightly due to salt formation with the cationic polymer.

Organic solutions of Kollicoat® Smartseal 100 P provided taste masking functionality even below 3 mg/cm², outperforming both the other formulation concepts. This may be the preferred formulation concept for moisture sensitive APIs.

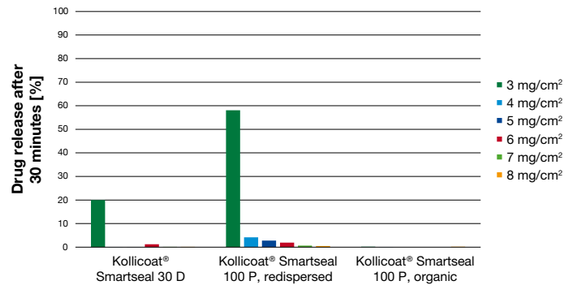

Figure 3. Amount of drug released after 30 minutes in phosphate buffer (pH 6.8), depending on formulation concept and coating level: Kollicoat® Smartseal 30 D (F2), redispersed aqueous Kollicoat® Smartseal 100 P (F3) and an organic Kollicoat® Smartseal formulation (F5) (mean value [n=3]).

Typically, tablets with an unfavorable taste are exposed to the tongue for just a few seconds, until swallowed. That leads to the conclusion that a taste masking functionality can practically exist although a certain release of active was detected after 30 minutes. Having a thin coating layer of just 3 mg/cm² all tested formulations were stable for at least 8 minutes (<1% active detected) [Figure 4].

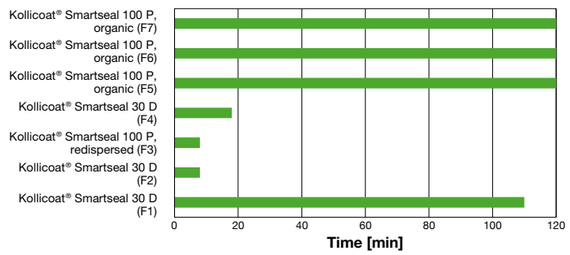

Figure 4. Delay in drug release as measure for the taste masking capability. Results provided by tablets coated with 3 mg/cm² tested in phosphate buffer (pH 6.8) (mean value [n=3]).

Both aqueous formulations were sprayed with 20% and 30% solid matter content (SMC), enabling the collation of the two formulation approaches at different SMCs. A difference in functionality between 20% and 30% SMC was hardly seen within each aqueous formulation concept [Figure 5 and 6]. Consistently, the process could be further optimized by selecting higher SMCs.

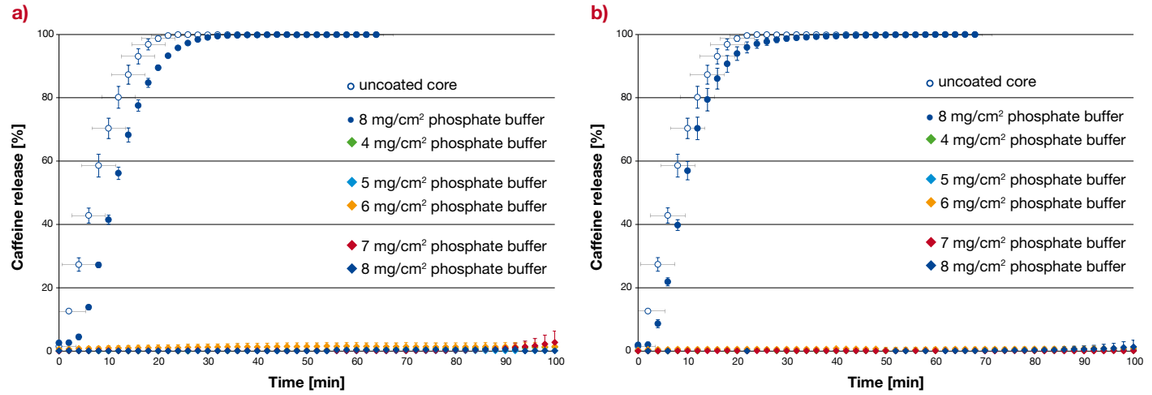

Figure 5. Dissolution profiles of tablets, bearing a Kollicoat® Smartseal 30 D (F2) film coat, applied with a) 20% SMC and b) 30% SMC (mean value [n=3], ± abs. SD).

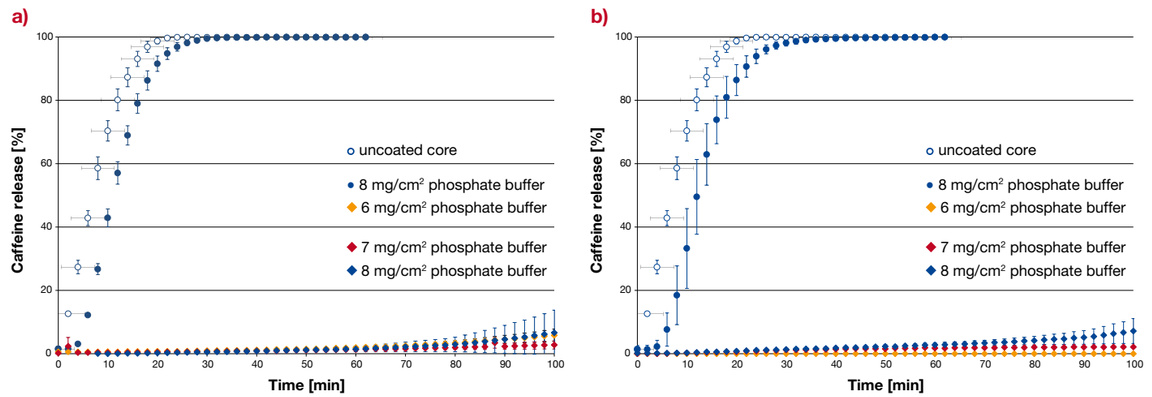

Figure 6. Dissolution profiles of tablets, bearing a Kollicoat® Smartseal 100 P (F3) film coat, applied with a) 20% SMC and b) 30% SMC (mean value [n=3], ± SD).

Comparing the dissolution profiles of organic formulations, coated with and without plasticizer, no differences can be seen [Figure 7]. Potential differences may occur during stability tests of the respective formulations, which were not included in this case study.

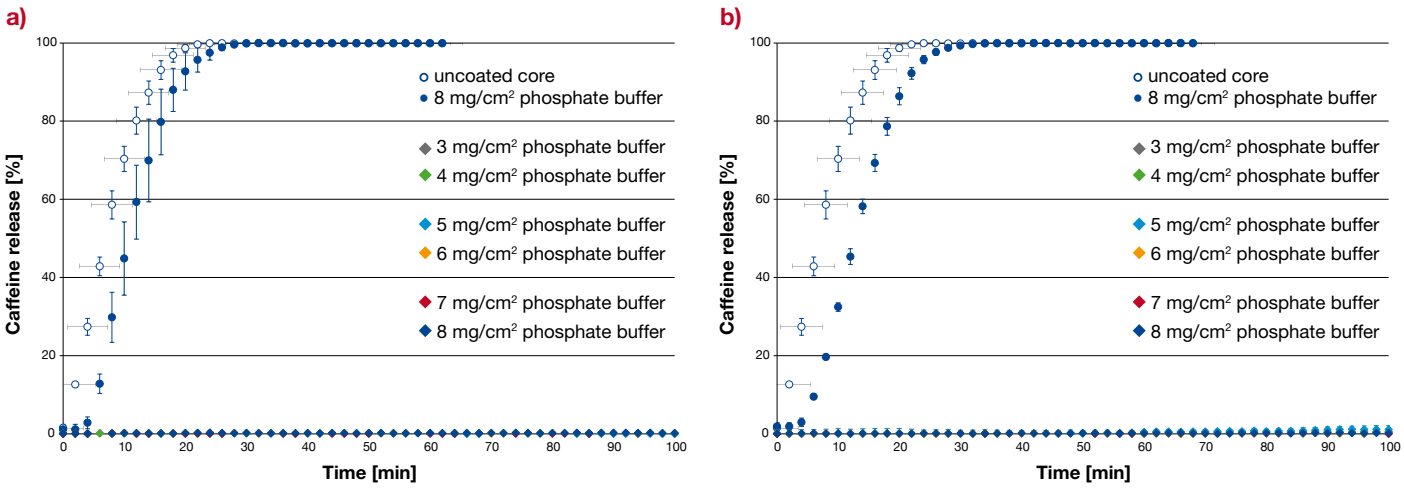

Figure 7. Dissolution profiles of tablets coated with an organic Kollicoat® Smartseal 100 P solution. a) without plasticizer (F5) b) with plasticizer (F7) (mean value [n=3], ± SD).

Conclusion

Organic solutions of Kollicoat® Smartseal 100 P showed the full taste masking performance at a coating level of less than 3 mg/cm². Hence organic coating formulations can be recommended if a minimum coating level is desired, without compromising on the taste masking performance. In case organic coating is not an option (e.g. due to safety or equipment constraints), the aqueous dispersion Kollicoat® Smartseal 30 D offers an appropriate alternative, delivering the same functionality at a slightly higher coating level. Partially neutralized, redispersed Kollicoat® Smartseal 100 P needs a markedly higher coating level to deliver the same taste masking performance, when compared with the dispersion or organic solution. Depending on the required delay of release in the saliva and on the amount of applied coating, the aqueous formulations of the powder grade may still be considered.

An influence of the SMC on the taste masking functionality was not seen. SMCs of 30% can be applied, to allow for a most economic processing.

References

[1] Kolter, K.; Guth, F.; Angel, M.; Physicochemical characteristics of a new aqueous polymer; AAPS Annual Meeting and Exposition, November 14 – 18, 2010, New Orleans, Louisiana, U.S.A.

[2] Bang, F.; Broicher, C.; Cech, T.; Haberecht, M.; Rillmann, T.; Evaluating the different characteristics of plasticisers used in cationic polymer based film-coating applications; 3rd Conference on Innovation in Drug Delivery, September 22 – 25, 2013, Pisa, Italy

[3] Bogaerts Iv.; Van Eeckhout L.; Detobel F.; Bang F.; Rottmann N.; Comparing the performance of several Kollicoat® Smartseal based film-coating formulations, processed in a GEA ConsiGma® coater; 8 – 11 February 2021 12th PBP World Meeting; Vienna, Austria

This document, or any information provided herein does not constitute a legally binding obligation of BASF and has been prepared in good faith and is believed to be accurate as of the date of issuance. Unless expressly agreed otherwise in writing in a supply contract or other written agreement between you and BASF:

(a) To the fullest extent not prohibited by the applicable laws, BASF EXPRESSLY DISCLAIMS ALL OTHER REPRESENTATIONS, WARRANTIES, CONDITIONS OR GUARANTEES OF ANY KIND, WHETHER EXPRESS OR IMPLIED, WRITTEN OR ORAL, BY FACT OR LAW, INCLUDING ANY IMPLIED WARRANTIES, REPRESENTATIONS OR CONDITIONS OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, SATISFACTORY QUALITY, NON-INFRINGEMENT, AND ANY REPRESENTATIONS, WARRANTIES, CONDITIONS OR GUARANTEES, ARISING FROM STATUTE, COURSE OF DEALING OR USAGE OF TRADE and BASF HEREBY EXPRESSLY EXCLUDES AND DISCLAIMS ANY LIABILITY RESULTING FROM OR IN CONNECTION WITH THIS DOCUMENT OR ANY INFORMATION PROVIDED HEREIN, including, without limitation, any liability for any direct, consequential, special, or punitive damages relating to or arising therefrom, except in cases of (i) death or personal injury to the extent caused by BASF's sole negligence, (ii) BASF's willful misconduct, fraud or fraudulent misrepresentation or (iii) any matter in respect of which it would be unlawful for BASF to exclude or restrict liability under the applicable laws;

(b) Any information provided herein can be changed at BASF's sole discretion anytime and neither this document nor the information provided herein may be relied upon to satisfy from any and all obligations you may have to undertake your own inspections and evaluations;

(c) BASF rejects any obligation to, and will not, automatically update this document and any information provided herein, unless required by applicable law; and

(d) The user is responsible for confirming that the user has retrieved the most current version of this document from BASF as appropriate

© 2023 BASF

BASF_Pharma BASF Pharma Solutions

www.pharma.basf.com

Inspiring Medicines for Better Lives

BASF

We create chemistry

MarComm-2021-00433