Development and Evaluation of Ready-to-Use Hot Melt Coating Formulations for Taste Masking

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Introduction

As bitterness is a basic taste modality of natural or anthropogenic organic chemicals [1], active pharmaceutical ingredients (APIs) can exhibit a bitter or unpleasant taste. Unfortunately, bitter taste can lead to poor patient compliance, which can directly influence the treatment outcome. Taste masking of solid oral dosage forms can be achieved by applying functional film coatings, sweeteners, flavorings or suitable excipients.

Coating of solid oral dosage forms is a common tool which formulators use for the modification of release profiles, to achieve aesthetic qualities such as color and texture or to increase physical and chemical protection [2]. Among others, common coating types for pharmaceutical or nutraceutical applications that are used today include sugar coating, polymer film coating and hot melt coating (HMC) [3].

HMC with materials such as thermoplastic resins, waxes, polyethylene glycols (PEG) began in the 1940s in the textile and paper industry [4]. In the 1980s the pharmaceutical industry used HMC as a simple and effective new coating technology [5]. The coating materials are melted fats or waxes and do not require the addition of solvents. Thus, HMC facilitates regulatory and manufacturing aspects, due to the absence of organic solvents [6,7]. HMC offers further advantages, such as: No drying steps are necessary or the possibility to achieve a higher batch throughput due to 100% solid content of melted waxes and hence, increased productivity [8,9]. HMC is an effective method to mask the unpleasant taste of APIs. Furthermore, HMC can be used to influence other factors such as prolonged stability, drug release and bioavailability. Finally, HMC also offers protection against chemical degradation [10].

The aim of this study was to develop and evaluate a reliable, ready-to-use HMC formulation that can be applicable via fluid bed technology and offers taste masking properties. In addition, we aimed not to influence the immediate release of the API by using an HMC formulation.

Materials and Methods

The model substance for taste masking and release was Ibuprofen, which is known for its bitter taste. A ready-to-use version of Ibuprofen (Ibuprofen DC 85 W) was provided by BASF. Different formulations were coated at 20% and 50% weight gain (wg) and the batch size was set to 500 g Ibuprofen DC 85 W. The coated Ibuprofen DC 85 W granulates were tested regarding taste masking, drug release, optical integrity and particle size. A total of eight different formulations were tested. Table 1 shows the materials tested in the HMC formulation.

Table 1: Materials used in HMC formulations, melting points and suppliers

Material	Chemical entity	Melting point [°C]	HLB value	Supplier
Kolliphor® P 188 micro	Poloxamer	43	29	BASF SE
Kolliphor® P 407 micro	Poloxamer	47	22	BASF SE
Kolliwax® GMS II	Glycerol Monostearate	58	3.8	BASF SE
Kolliwax® S Fine	Stearic acid + palmitic acid	55	15	BASF SE
Precirol® ATO 5	Glycerol distearate	55	2	Gattefossé SAS
Dynasan® P60	Hydrogenated Palm Oil	58-62	N/A	IOI Oleo GmbH
Dynasan® 118	Glycerol Tristearate	72	N/A	IOI Oleo GmbH
Softisan® 154	Hydrogenated Palm Oil	57	N/A	IOI Oleo GmbH
Witocan® 42/44	Hydrogenated Coco-Glyceride	42-44	2	IOI Oleo GmbH
Carnaubawachs	–	80-86	N/A	Multiceras S.A. de C.V.
Candelillawachs	–	68-73	14.5	Multiceras S.A. de C.V.
PEG 6000	–	58-63	19	Clariant

The coating process of Ibuprofen DC 85 W was performed in a fluidized bed coater (Ventilus V 2.5), using a hot melt system (IHD-2.5). The temperature of the pump and the entire hot melt unit was 120°C. Once 20% wg was reached approximately 100 g of the coated Ibuprofen was withdrawn as a sample. The process was continued until a total wg of 50% was achieved.

Test procedure

Volunteers (n=10) were selected to taste and assess the Ibuprofen granules that were coated with different HMC formulations. The quality of the coated granules was evaluated regarding texture and mouth feel and the inherent taste was documented by the volunteers. Furthermore, the time until a bitter taste of Ibuprofen could be perceived was timed and noted. The data was used to evaluate the overall taste masking properties of each formulation. Dissolution was evaluated using a photometer at a wavelength of 264 nm. The samples were placed in phosphate buffer (pH=7.2). A sample was automatically collected every 2 min and the API concentration was determined by photometry. The release profile of each sample was evaluated over 60 min.

HMC formulations were assessed regarding their release type (e.g. immediate vs. modified), dissolution profile and taste masking properties according to the following criteria:

- A minimum of 75% API should be released within 45 minutes according to Ph. Eur. (5.17.1) to fulfil the criteria for immediate release.
- Dissolution profile of coated granules should indicate a short lag phase compared to pure Ibuprofen DC 85 W and different weight gain levels should also produce distinct release profiles.
- Good subjective taste masking according to our taste panel.

Result and Discussion

Table 2 lists the average subjective assessments of the taste masking properties of the individual formulations and the average time until the bitter taste could be sensed. Each formulation with a wg of 50% scored better than the corresponding 20% wg version. This is also evident in the time to the perception of a bitter/unpleasant taste. The reason for this can be easily explained as the total amount of applied coating increases with an increasing wg. Thus, the protective, hydrophobic layer is thicker, which led to a prolonged taste masking.

However, the quality of a taste masking layer does not only depend on the amount of material applied by HMC but also on the composition of the formulation. For example, $F1_{20\%}$ had a better taste masking performance and a longer delay before the taste of Ibuprofen was detectable compared to $F4_{20\%}$ or $F5_{20\%}$. Hence, some formulations seemed more suitable to isolate the API during the first few seconds after contact with saliva. This – purely subjective – effect could also be confirmed after the comparison of observable differences in the individual release profiles. In order to fully understand the mode of action that leads to a certain release profile, it is mandatory to take a look at the individual formulations. All formulations that were tested in the course of the presented experiments consisted of 1-2 fats or waxes that formed the hydrophobic base of the HMC, which were then supplemented by 1-2 pore-forming compounds. Application of the hydrophobic base compounds led to a typically non-pH-dependent physical barrier that completely isolates the API and hinders dissolution, which can be attributed to high logP values of the compounds. A careful selection of appropriate pore-forming agents allows the fine tuning of the release profile. The overall goal for a taste masking formulation is to delay the release in the first few seconds after administration without sacrificing the later dissolution rate. The ability to fine tune HMC formulations in the first seconds after administration renders some formulations better suited for taste masking applications than others. Finally, the overall wetting behavior of the combination of base compounds and pore formers is responsible for the course of obtained release profiles. Although all formulations but F4 and F5 passed the criteria that were defined for the test procedure, only two of the best performing formulations will be briefly discussed in the following section.

Table 2: Evaluation of the coated granules, melting points of individual formulations and used excipients

Formulations	Melting point [°C]	Subjective evaluation of masking	Time until a bitter taste was sensed	Composed of
$F1_{20\%}$	60-64	2,6	40.0 s	Kolliphor® P 407 micro, Kolliwax® S Fine, Kolliwax® GMS II
$F1_{50\%}$	60-64	1,3	> 120 s	
$F2_{20\%}$	59-62	3,4	20.0 s	Precirol® ATO 5, Kolliphor® P 407 micro
$F2_{50\%}$	59-62	2,6	64.0 s	
$F3_{20\%}$	59-64	3,4	31.0 s	Kolliwax® GMS II, Dynasan® P60, Witocan® 42/44
$F3_{50\%}$	59-64	2,5	98.0 s	
$F4_{20\%}$	60-64	3,9	16.0 s	Kolliphor® P 188 micro, Kolliwax® GMS II, Softisan® 154
$F4_{50\%}$	60-64	3,6	29.0 s	
$F5_{20\%}$	74-79	4,4	11.0 s	Kolliwax® S Fine, Carnauba wax, Candellila wax
$F5_{50\%}$	74-79	4,1	31.0 s	
$F6_{20\%}$	77-81	3,2	15.0 s	Kolliwax® S Fine, Dynasan® 118, Carnaubawax
$F6_{50\%}$	77-81	2,2	85.0 s	
$F2.1_{35\%}$	58-61	2,8	30.0 s	Precirol® ATO 5, Kolliphor® P 407 micro, PEG 6000
$F2.1_{50\%}$	58-61	2,3	64.0 s	

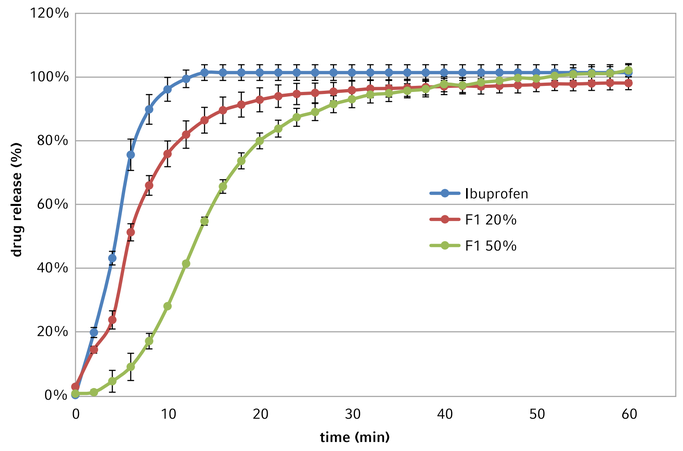

Figure 1: Ibuprofen release profile with coatings $F1_{20\%}$ (red) and $F1_{50\%}$ (green) compared to uncoated Ibuprofen (blue); n=3

Figure 1 shows the release profile of formulation $F1_{20\%}$ and $F1_{50\%}$ compared to uncoated Ibuprofen. The release profile of $F1_{20\%}$ is slightly different from that of Ibuprofen. Compared to uncoated Ibuprofen, the release rate of Ibuprofen from $F1_{20\%}$ is almost identical in the first few minutes and slightly delayed afterwards. Consideration of the release profile of $F1_{50\%}$ shows that a higher wg leads to a significant lag phase at the start. After approximately 8 min the release rate (described by the slope) is almost the same as the release rate of the uncoated Ibuprofen and $F1_{20\%}$. This delay of drug release can be sufficient to achieve taste masking properties. Furthermore, the release of 75% Ibuprofen within 45 minutes was achieved at both wg levels, thus, formulation F1 can be considered as an immediate release.

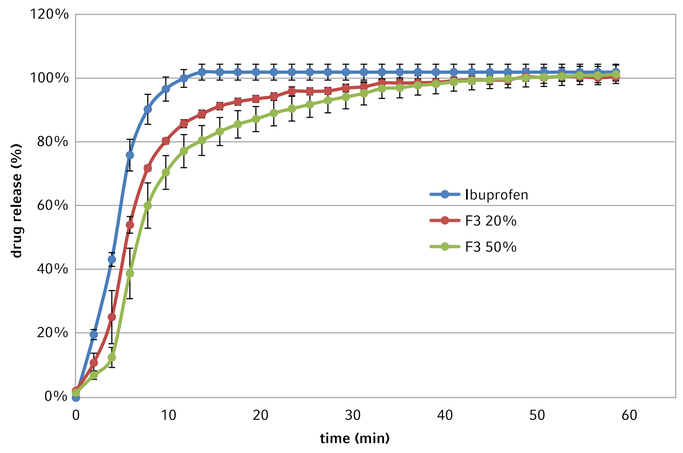

Figure 2: Ibuprofen release profile with coatings $F3_{20\%}$ (red) and $F3_{50\%}$ (green) compared to uncoated Ibuprofen (blue); n=3

Figure 2 shows the release profile of formulation $F3_{20\%}$, $F3_{50\%}$ and uncoated Ibuprofen. The application of 20% F3 already alters the release profile. Application of a higher wg level ($F3_{50\%}$) further leads to a slight delay, and still shows a comparable dissolution rate. A slight lag phase can be observed at 50% wg, however, this effect is not as pronounced as it was for formulation F1. Formulation F3 released more than 75% API at both wg levels within 45 minutes. In general, the release profile that can be obtained with formulation F3 looks promising. The higher the application rate of the formulation, the slower Ibuprofen is released and taste masking properties are observed. Furthermore, the release is not delayed too much even at high coating levels and can be considered to be immediate release. Hence, formulation F3 seems to be suitable to fine tune HMC for a taste masking application of unpleasant APIs. Both formulations (F1 and F3) fulfilled all three necessary criteria for a ready-to-use HMC formulation that offers taste masking, a short lag phase and immediate release.

Conclusion

The performed experiments showed that good taste masking properties can be achieved using novel HMC formulations. At the same time, they remain in the desired release category.

However, it must be ensured that the composition of the formulation is appropriate for the API used. Overall, this study demonstrated the broad bandwidth of HMC formulations that can be used to achieve the desired performance. Both formulations (F1 and F3) fulfilled all three necessary criteria for a ready-to-use HMC formulation that offers taste masking, a short lag phase and immediate release. Excellent results can be obtained through good R&D work combined with excellent technical support and the application of the right excipients.

Reference:

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AT A GLANCE

What is hot melt coating?
HMC is a process of applying melted fatty or waxy components onto solid particles and it is applied using fluid bed technology. Thus, it is mandatory to melt the waxes/fats and sustain the melting throughout the coating delivery into the reactor (see figure 3) [8,11]. This is achieved through a heated container and heated pipes and feeding pump. The applied temperatures of max 10-15°C above the melting temperature of the formulation, in order to avoid unnecessary heat stress to the API.

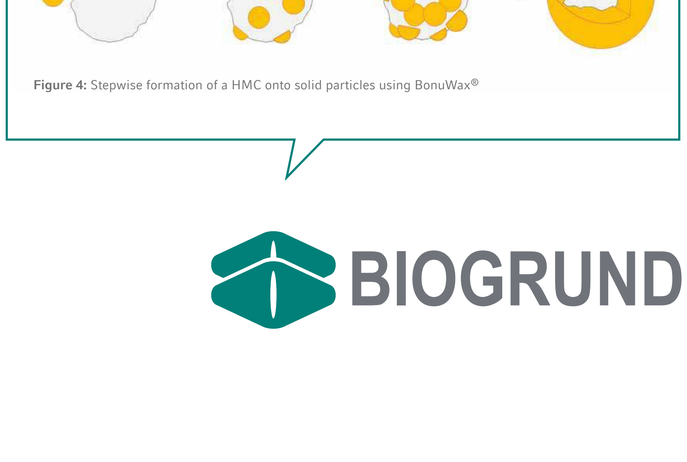

Figure 3: General Process of HMC using fluidized bed technology

Why BonuWax®?
The ready-to-use excipient premix BonuWax® is a combination of waxes and fats for HMC applications (see figure 4). BonuWax® is applied via fluid bed coating technology and can be sprayed at 100% solid content, yielding in high productivity. HMC using BonuWax® can be used for coating of mini tablets, granules or powders for pharmaceutical and nutraceutical products. Individual ingredients are carefully selected and combined for a tailor made solution that is designed to achieve the desired properties of the final coating. This allows the combination of multiple excipients and their individual advantages.

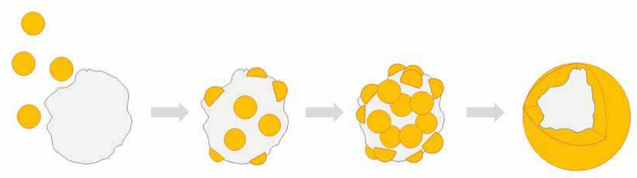

Figure 4: Stepwise formation of a HMC onto solid particles using BonuWax®

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