Hot Melt Coating for Controlling the Stability, Release Properties and Taste of Solid Oral Dosage Forms

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Summary

Traditional methods to coat solid oral dosage forms mostly use solvents, an approach that suffers from a range of drawbacks including cost, environmental concerns and lengthy processing times. Hot melt coating (HMC) is an innovative and effective alternative that is reliable, cheap and fast, while simultaneously offering an opportunity to better manipulate and control characteristics such as taste, stability and release rate. Here, we discuss the need for HMC, provide technical details of the process including the excipients involved, explore the relative merits and drawbacks of the technology and touch upon how the process can be scaled up ready for commercial production. In particular, we focus on using HMC to coat user-friendly dosage forms such as orally disintegrating granules (ODGs) and the constituents of traditional dosage forms such as hard gelatine capsules and tablets. In each case, HMC enables the development of medicines with fast or extended release profiles, improved stability and longer product shelf life. In the case of ODGs, palatability and ease of swallowing can be improved resulting in higher compliance.

1. Introduction

Pharmaceuticals and food supplements are often administered via the oral route, as it is the cheapest, simplest and safest approach available. However, many APIs must be effectively coated during the formulation process in order to successfully exert its functional effects after swallowing. There can be several reasons for this. For instance, many APIs are sensitive to environmental factors such as oxygen, light and humidity, the likes of which can lead to degradation. The internal microenvironment within the dosage form can also be important, with acidic, alkaline or functional excipients often causing API instability.

Solid oral dosage forms must also display other favorable characteristics in order to make them effective as medicines or supplements. Fast acting treatments such as analgesics must be dissolved very quickly in order to have the desired effect, while others require the API to be released over a prolonged period of time. By carefully choosing the coating agents of the dosage form or the API it is possible to control the dissolution profile, facilitating immediate, extended or even delayed release where appropriate. Coatings can also be used to manipulate particle size to facilitate easier downstream processing.

Coatings can also be used to make medicines more user-friendly. For example, the bitter taste of an API can be masked using a suitable coating, thereby providing the final product with an agreeable taste [1,2]. In addition, coatings can also be used to make medicines easier to swallow, give them a more pleasant appearance and improve mouth-feel, all of which can boost patient compliance and render treatments more effective.

2. The need for new coating methods

Traditionally, pharmaceutical coating involves dissolving the API and/or excipients in a solvent and using the mixture to coat a seed particle via a fluid-bed process. While well estab-

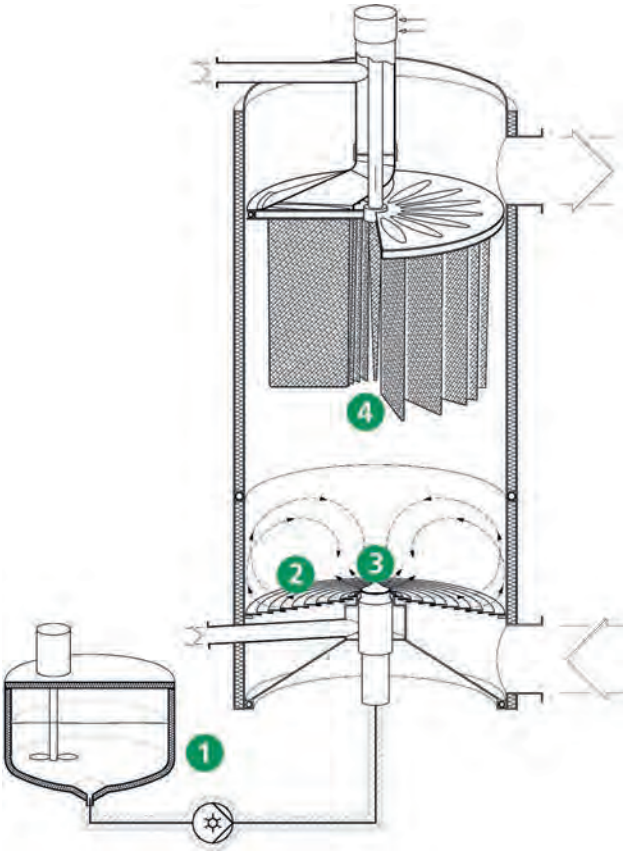

Figure 1: HMC takes place in a fluid bed coater under controlled environmental conditions. The melting device (1) contains a heated tank for the molten coating materials, a stirrer and a heated tubing system to avoid solidification during transport of the molten mass into the fluid bed. The air layer gliding process (2) moves the particles into the spraying zone, creating a homogeneous temperature distribution as well as a spiral air circulation. The liquid is sprayed through a heated nozzle (3) and is atomized by compressed air into fine droplets ensuring a precise coating. The dust filter system (4) works continuously during the process. The filter bags, of which there are several, are cleaned by blowing air through the filters, thus removing any dust stuck to them. This approach reduces downtime to a minimum (Image courtesy of INNOJET Herbert Hüttlin).

lished, solvent-based coating suffers from several important drawbacks. Firstly, the coated particles must be dried, which takes considerable time and heat energy, particularly when using water. Furthermore, the coating speed is relatively slow in order to avoid twin formation. In some cases, the constituents cannot be dissolved in water and organic solvents such as alcohols, ketones and ethers must be used instead. These substances are more volatile than water and dry faster. However, many are also more expensive, toxic and flammable than water so they must be used with care and then recycled following the coating process [3].

A range of solvent-free methods have subsequently been developed to overcome some of these drawbacks [3]. These include electrostatic, compression and super-critical fluid coating, although most alternatives have not yet been optimized for widespread industrial use. In addition, the increase in popularity of novel user-friendly dosage forms such as orally disintegrating granules (ODGs – see section 6.1) is putting further pressure on pharmaceutical manufacturers to adopt new coating techniques. When using such dosage forms, factors such as taste, stability and release profile become important issues that must be carefully considered and controlled.

3. The hot melt coating process

One technique that is fast becoming a go-to solution for companies looking to avoid the drawbacks of solvent-based coating, or to better control taste and release parameters, is hot melt coating (HMC) [4]. The seed API particles are suspended in a fluid bed coater, while the excipients are heated outside of the fluid bed in a suitable container until they are molten. The molten mix is then transported via a heated tubing system and sprayed onto the seed API particles using a heated nozzle (Figure 1).

In order to generate the desired effect, it is essential that the temperature of the air, apparatus and products are all carefully controlled throughout the process. The API particles are purposefully kept at a lower temperature than the melting point of the excipient mix, causing the molten droplets to attach to the API particles and solidify upon contact, forming a homogeneous coat around them (Figure 2). Once this process is complete, the newly coated particles can be further processed to create the final product. This often involves blending with further APIs, excipients and/or flavors to create the final formulation, which can be compacted to form tablets or used to fill hard gelatin capsules, sachets or 'stick packs', ready for use by patients.

3.1 HMC excipients

HMC involves melting the excipient mix to create a molten liquid, so the ideal excipients have low melting points around 60-80 °C. It is also preferable that the excipients have a precise melting point, rather than melting and softening over a significant temperature range, as this makes the process easier to control. Lastly, the API should have a fairly narrow particle size distribution (around 200-500 µm) so that coating takes place in a predictable and reproducible manner, leading to a consistent product with low batch-to-batch variability.

Lipids are often the excipients of choice for HMC, including animal and vegetable waxes such as bees wax and carnauba wax, hydrogenated vegetable oils and fats, polyoxylglycerides, fatty acids and partial glycerides. Many are naturally occurring compounds found in foodstuffs and tend to be better tolerated by the human body. In order to fine-tune the dissolution/release character-

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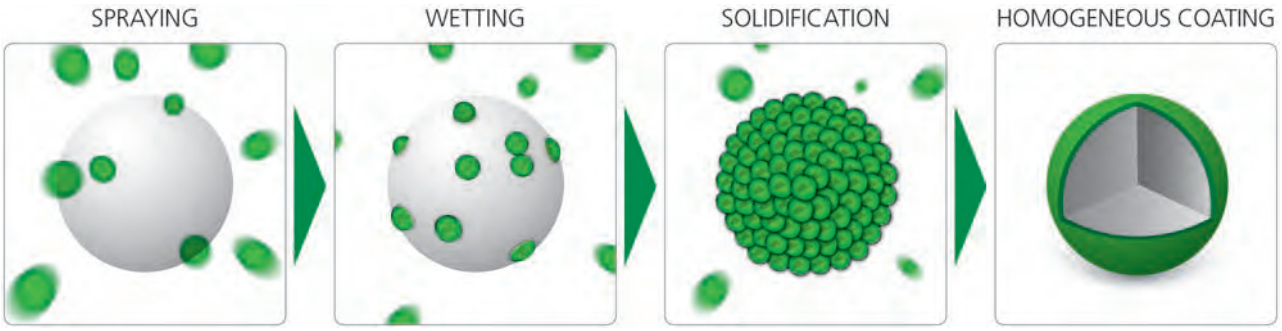

Figure 2: The HMC process, from spraying through to the finished coating. In the first step, the coating constituents are heated up and melted. Following this, the coating droplets are sprayed onto the seed particle (API) and wetting occurs on the surface. As the seed particle is colder than the melting temperature of the coating mixture, the droplets solidify and form a homogeneous layer.

istics of the API, emulsifiers are also typically added to the excipient mix [4].

3.2 The advantages and challenges of HMC

HMC offers many advantages over conventional solvent-based coating technologies. For a start, the elimination of water or organic-based solvents from the process effectively circumvents the drawbacks highlighted previously. The process is also faster than solvent-based methods, taking less than 2 hours for a full scale batch ranging from 50 kg up to 600 kg according to internal manufacturer data from INNOJET Herbert Hüttlin. Once the HMC parameters and excipient mix have been optimized there are no curing or sintering effects, while there is also very little risk of forming unwanted products such as agglomerates. The lipid coat also increases the overall hydrophobicity of the final product, inhibiting the uptake of moisture from the environment and further improving stability.

HMC is a rather new technology when it comes to the development of instant release formulations, and it requires specialized know-how and expertise to carry out effectively for this application. For example, the lipids commonly used as excipients can show unwanted polymorphism if the temperature and spray rate are not carefully monitored and controlled. The approach uses commonplace fluid-bed coaters. However, it also requires access to heated pumps, tubings and spray nozzles. While formulation and process development are not necessarily simple to carry out, the unique conditions required for each product can also prove advantageous, as they provide a means of protecting IP. Pharmaceutical companies can therefore employ HMC to revitalize ageing products, create new formulations that are more difficult for competitors to copy, and to create an opportunity for extending formulation patent protection.

4. Optimizing HMC during formulation

As is the case when starting any new formulation project, HMC parameters must be optimized early during the process to ensure the final product will perform as required. Many of the standard tests and procedures used to develop any new formulation also apply when using HMC. However, as the process is often used to manipulate taste and API release rate, there are several specific characterization steps that must be included.

4.1 Taste masking

HMC is especially powerful for creating pleasant tasting dosage forms, masking the unfavorable taste of APIs. As such, an important part of the development process is to test and check that the coating is working effectively. There are several ways in which this can be done. This includes

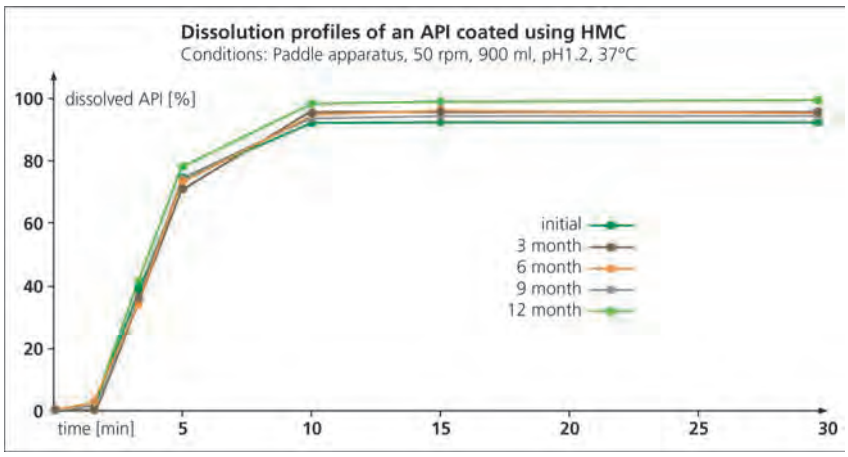

Figure 3: Dissolution profiles of a bitter tasting, fast acting API that has been coated with a lipid-based mixture using HMC. The profiles show that the coated API is stable over a period of at least twelve months. The intermediate was stored in bulk using polyethylene drums, in a warehouse under uncontrolled conditions.

modified dissolution testing, a common, compendial, cheap and rapid method used from early development through into routine production, which allows users to investigate the release of the API upon dosage form breakup in solution.

For user-friendly dosage forms designed to disintegrate in the mouth, the ideal profile is for API release to be inhibited for the first 30-60 seconds (i.e. while in the mouth and in contact with the taste buds). The second phase of release then depends on the medicine in question. For fast acting medicines, the API should be released as soon as possible after swallowing (see Figure 3), while for delayed or extended-release formulations, this should happen over several hours. Dissolution testing tends to be more insightful when using more physiologically relevant media, comparable media volumes and agitation to simulate the digestive tract.

In some cases, it is possible to have patients report directly on the taste of the formulation. However, this is usually only applicable when developing food supplements and is not generally considered an ethical way to test the flavor of active medicines. It is also important to note that carrying out such organoleptic panel tests can be expensive and time consuming, while underappreciated variables such as age, gender, race, smoking preferences, mood and time of day can all also influence the reliability and reproducibility of the data collected.

At the junction between dissolution and organoleptic panel testing sits a range of advanced technological solutions, most of which are based on mimicking the human tongue. These 'electronic tongues' tend to remain labor and cost intensive and are not currently used very often in formulation development [5].

4.2 Particle morphology

When carrying out HMC, it is important to monitor the size and shape of the particles, both before and after coating. If the seed particles are too small then they could clog the filter of the fluid bed, while the subsequent increase in overall surface area will lead to the coating on each particle

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being too thin. If the particles are too large then the opposite occurs, with the coating ending up too thick.

The size distribution of the particles must also be constrained to a tight but feasible range, so that each particle is coated in a reliable and reproducible way. Several options are available to monitor particle size distribution, including laser diffraction, optical analysis using a microscope and sieve analysis, with the latter being the simplest and most common. However, optical techniques are gaining popularity as they are fast to carry out and provide additional information of use to formulators. As well as ongoing testing during formulation development and later during manufacture, it is also important to conduct an initial analysis after receiving raw materials from suppliers, to be sure that they meet the expected specifications.

As well as being different sizes, particles can also have different shapes, from highly spherical through to needle shaped. An appreciation of these characteristics is important for maintaining processability in the fluid bed and also when moving to downstream production steps. In some cases, it is even necessary to use advanced techniques during development, such as scanning electron microscopy (SEM), dynamic scanning calorimetry and x-ray diffraction, as they allow users to more precisely characterize the coating surface and/or cross sections of the particles, and to analyze them for signs of polymorphisms or other structural defects (Figure 4). This is particularly relevant for dosage forms containing HMC particles, as the lipids commonly used as excipients can exist in several polymorphic forms [6]. It is also possible that changes in temperature may alter the polymorphism of the API, which could lead to unexpected stability and efficacy problems during later use. In both cases, process parameters can be adjusted so that polymorphism is controlled.

4.3 Stability and release profile

When developing coated medicines using HMC it is important to carry out stability studies, analyzing both production intermediates and the final formulation. The main concerns are that the API is not protected well enough and that the coating changes upon storage leading to poor taste and a drop in performance. This is particularly true of dosage forms such as ODGs, as they have been designed explicitly to break down rapidly in the gastro-intestinal tract after being swallowed. As such, an insufficiently thin coating can trigger an unwanted reaction and/or unpleasant taste and may render the medicine ineffective.

Inherently linked to stability testing is the analysis of API release. The biological effect of the API is highly dependent on where and when it is released during its passage through the digestive system, triggered either by environmental factors such as water or via biological agents such as enzymes, stomach acids and bile salts.

As such, API release is tightly monitored during all stages of formulation development and, at a reduced level, during manufacture, to ensure that the medicine will behave as expected. The most common method of analysis is dissolution testing. Data is collected at several time points, firstly to ensure the API is not inadvertently released too early (e.g. in the mouth), and secondly to be confident that the medicine will be released in the correct part of the digestive system (e.g. the stomach or intestine). In some cases, the formulation will also be analyzed to determine wettability in order to estimate dissolution/release characteristics, although this is usually only done on prototypes and is not a routine procedure.

5. Scale-up

Ease of scale-up is essential for any formulation process, in order to make the transition from development to bulk manufacture as fast, simple and cost-effective as possible. Fortunately, HMC is easy to scale up from pilot to production scale, with little to no increase in processing time when moving from small to large batches. This is also true when moving from batch to batch or when changing product type during manufacture. In fact, the geometry of fluid bed coating improves with increasing scale, as spraying is more effective in larger containers. HMC is also amenable to process analytical technology (PAT) solutions such as online near infrared (NIR) measurement, permitting effective ongoing monitoring of the coating process and the rapid identification of any deviations from initial specifications [7].

6. Hot melt coating of novel and traditional dosage forms

HMC offers many advantages for coating traditional and modern user-friendly dosage forms, as it enables formulators to develop both fast- and delayed-release medicines, each with optimal stability and taste characteristics. As discussed, it also avoids the need for costly organic solvents or lengthy drying steps.

6.1 Orally disintegrating granules (ODGs)

ODGs are a member of a new class of pharmaceutical dosage forms known

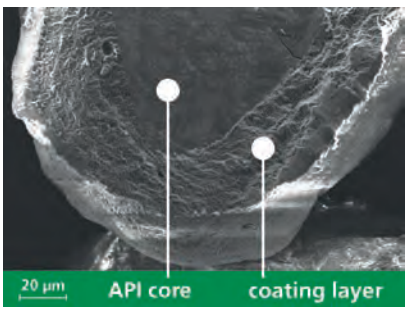

Figure 4: Scanning Electron Microscope (SEM) image of a bitter tasting, fast acting API coated with a lipid based mixture. The image shows a cross section of the crystalline structure of the API core covered with a very homogeneous coating layer.

as "user-friendly dosage forms". They start to dissolve in the mouth and are much easier for patients to swallow. In addition, as they are in powder form or are made up of small granules, they are not constrained by the physical limits inherent of solid tablets and can contain a greater amount of API (or even combinations of APIs). Furthermore, HMC parameters can be optimized to create both immediate and extended release forms, including both types within a single dose if required. This can be used to simplify complex dosage regimens, the likes of which have traditionally required multiple tablets taken throughout the day, down to one or two ODG doses per day, increasing patient compliance and treatment effectiveness. ODGs tend to spend more time in the mouth and are tasted more thoroughly than solid tablets or capsules. For these reasons, an effective coating is used to mask the potentially unpleasant taste of APIs, create a good mouth feel and protecting the API from being released too early. HMC provides an excellent opportunity to develop ODGs with all of these necessary characteristics.

6.2 Tablets

As for ODGs, HMC can be used to create new types of solid tablets, with altered API release profiles and better taste characteristics. Instead of being used to create a granulate, the coated particles are blended with further excipients and compressed to form a tablet called a multiple unit pellet system (MUPS) [8]. The main reason to select HMC for constituents of solid tablets is that tablets composed of uncoated constituent particles tend to absorb saliva and can feel unpleasant in the mouth. MUPS tablets created using HMC coated particles avoid these problems and are therefore easier for patients to swallow, while also offering the possibility to manipulate API release profile without risking stability.

6.3 Hard gelatin capsules (HGCs)

HGCs are a well-established dosage form used in medical treatment. As for tablets, HMC can be employed to create novel HGCs offering immediate or extended API release, or even a combination of the two, while ensuring the API is protected and stable until the medicine has been administered. Taste masking is less important in the case of HGCs, as the capsule shell carries out this function effectively. Instead, the real advantages offered by HGCs created using HMC-coated particles are twofold. Firstly, they offer the opportunity to easily develop medicines containing multiple APIs with different release parameters, simply by filling the capsule with different combinations of coated particles containing the different APIs. In addition, no further excipients are required during the formulation process, principally due to the benefits offered by using the capsule as both a protective shell and a mechanism for housing the particles.

7. Conclusion

HMC offers significant advantages in comparison to conventional solvent-based coating approaches and pharmaceutical products created using the technology are already being tested in clinical studies. HMC is frequently cheaper and faster than traditional methods, offers a shorter downtime between batch and product changes, and is a robust process compatible with current commercially available PAT systems. It can be used to coat constituents of "more traditional" solid medicines such as capsules and tablets, as well as user-friendly dosage forms, enabling formulators to produce fast or extended release dosage forms, or even a combination of the two (e. g. using ODGs). In cases where taste is crucial, the API can be effectively masked and stability ensured.

However, developing effective products using HMC requires specific expertise and modified equipment. Hermes Pharma has worked with a number of industry partners including INNOJET Herbert Hüttlin, CREMER OLEO GmbH & Co. KG, Research Center Pharmaceutical Engineering (RCPE) GmbH and the Karl Franzens University Graz to better understand the process through research, and to optimize it for formulation development and manufacture. The technique is now commercially available and ready for utilization by pharmaceutical companies interested in formulating new or existing medicines with specific API release, taste and user-friendly characteristics.

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Redaktion: Chefredakteur: Claudius Arndt, Redakteurin: Kerstin Jarosch. Verlag: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Germany), Tel.: +49 (0) 81 91-9 85 78 12, Fax: +49 (0) 81 91-9 85 78 19, e-mail: redaktion-tp@ecv.de, http://www.ecv.de. Herstellung: Rombach Druck- und Verlagshaus GmbH & Co. KG / Holzmann Druck GmbH & Co. KG.