dosage forms

Hot-melt coating: A method for creating user-friendly, extended-release formulations

Martin Koeberle and Detlev Haack
Hermes Pharma

In the treatment of many medical conditions and diseases, it is advantageous for the active pharmaceutical ingredient (API) to release gradually from the dosage form over a prolonged period. This article looks at how hot-melt coating was used to develop an effective and user-friendly extended-release formulation for vitamin C.

Vitamin C (also known as ascorbic acid) is essential for a healthy life, yet for many individuals, the amount supplied in food is insufficient to meet their needs. Smokers, pregnant and nursing mothers, and people with acute infectious diseases may all have an increased risk of vitamin C deficiency.

As a result, a large number of people take vitamin C supplements to boost levels in the body. But to be effective, dosing must be carefully regulated. Due to its water solubility, the body cannot build reservoirs of vitamin C. If administered in a large single dose, such as in an immediate-release formulation at the beginning of each day, the amount that cannot be absorbed by the body will simply be excreted. During the day, the need for vitamin C may increase, resulting in a deficiency of this essential nutrient.

One way to ensure the body receives a regular supply of vitamin C is by taking conventional immediate-release doses throughout the day. However, this can be inconvenient, leading to poor patient adherence to the treatment regimen. And with people increasingly used to enjoying convenience in all areas of their lives, this option simply doesn't meet consumer expectations.

So how do we develop a formulation that offers convenience for patients and consumers yet ensures effective delivery of the active ingredient?

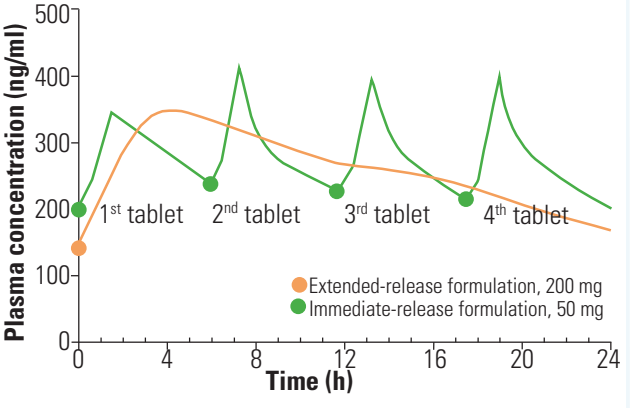
Extended release: A product development challenge

Time and again, pharmaceutical and nutraceutical companies are faced with a similar problem—the need to develop a single dosage form that produces a constant blood plasma concentration at an effective level over a prolonged period. Often, the solution is an extended-release formulation that delivers the API to the body slowly, overcoming the need for patients or consumers to take multiple doses throughout the day.

In many cases, including the example in Figure 1, a single dose of an extended-release formulation taken at the start of the day successfully achieves sustained blood plasma concentrations at levels that would otherwise require several immediate-release doses.

Figure 1

Plasma profiles of extended- and immediate-release formulations



Extended-release formulations exhibit a number of properties different from immediate-release dosage forms. See Table 1. While these different characteristics create new opportunities for manufacturers, they present a number of additional challenges. For example, all oral dosage forms, including extended-release formulations, should be easy to swallow and convenient to take. However, because extended-release dosage forms are often designed for once-daily dosing, the amount of active they need to carry can be double or triple what an immediate-release version requires.

To demonstrate the factors that must be considered, we share below the approach taken to formulate an extended-release vitamin C product. We recently developed the product for a market leader in the German food and dietary supplements industry.

Controlling release using coatings

Many extended-release formulations use coatings to control the rate of API dissolution and release. By carefully selecting the coating agents, it's possible to control the dissolution profile of the API, facilitating immediate, extended, and even delayed release depending on the product's requirements.

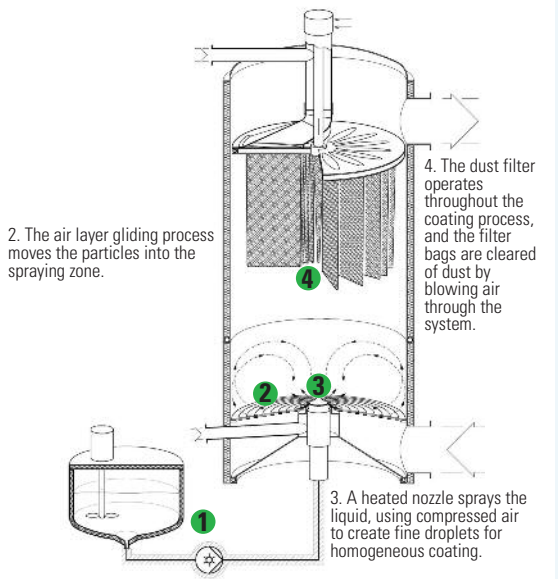
Traditional coating techniques apply a solution of the API and/or excipients to a seed particle using a fluid-bed process. While these are well-established methods, solvent-based coating techniques suffer from a number of drawbacks.

One challenge centers on the need to dry the coated particles, which requires large amounts of time and heat energy, particularly when water is the solvent. As many coating approaches require the application of several layers to achieve the desired extended-release effect, these steps can be time-consuming and resource-intensive.

Additionally, many coating excipients do not dissolve in water, so organic solvents such as alcohols, ketone, and ethers must be used. While these solvents are more volatile than water and therefore dry faster, they are also more expensive, toxic, and flammable and must be used with care.

FIGURE 2

Hot-melt fluid-bed coater



Hot-melt coating: A better approach

An increasingly popular coating technique that is well-suited to a range of extended-release dosage formulations is hot-melt coating (HMC) [1].

Originally developed for food manufacturing, HMC offers a number of advantages over conventional solvent-based coating techniques. Since no solvents are involved, the process is rapid, typically taking less than 2 hours for a batch of 50 to 600 kilograms. Additionally, once the process parameters and excipients have been optimized, there are no curing or sintering effects, and the risk of unwanted side-processes occurring, such as agglomeration, is minimal.

HMC works by coating API particles with a lipid excipient layer. The seed API particles are suspended in a fluid-bed coater (Figure 2), while the excipients are

TABLE 1

Characteristics of immediate- versus extended-release formulations

Immediate release	Extended release
Fast onset of action	Slow onset of action
Plasma concentration increases and decreases rapidly	Plasma concentration is sustained for extended period
Repeated dosing may be required (2 to 3 times daily)	Once-daily dosing
Frequent dosing may reduce compliance	Once-daily dosing may improve compliance
Less API per dosage unit	Larger amount of API per dosage unit; well-suited for formulation as ODGs
Potential for severe side effects because of high plasma concentration after ingestion	Attenuation of side effects by avoiding brief, high plasma concentrations
Crushing or chewing of dosage form unlikely to lead to high or toxic plasma concentrations	Crushing or chewing of dosage form could destroy extended-release mechanism, leading to high or toxic plasma concentrations

heated outside the fluid bed until they are molten. This molten mixture is then transported through a system of heated tubing and sprayed onto the seed API particles from a heated nozzle. As the API particles are kept at a lower temperature than the melting point of the excipient mixture, the molten droplets wet the API particles and solidify upon contact, forming a homogeneous layer. Once this process is complete, the newly coated particles can be further processed to create the final product. This often involves blending them with more APIs, excipients, and/or flavors.

Factors to consider when selecting excipients

HMC is particularly well suited to controlling the API release profile. Through the addition of emulsifiers to the excipient mixture, the rate of dissolution and/or release can be adjusted to suit the product's requirements.

Despite HMC's many advantages over conventional coating techniques, for many formulators it is a relatively new technology, and care must be taken to ensure that the process parameters and coating excipients are optimized to ensure success.

HMC requires excipients to be in molten (liquid) form when applied to the API, so the ideal excipients have low melting points, in the range of 60° to 80°C. Ideally, the excipients also have a precise melting point versus melting and softening over a wide temperature range. Any lipid excipients should have Generally Recognized As Safe, or GRAS, status and be well accepted by international authorities, as well as consumers.

Furthermore, the API should have a relatively narrow particle size distribution (200 to 500 microns) so that the coating process is predictable and reproducible, leading to a consistent product and low batch variability.

While process optimization—including specifying excipients and emulsifiers—adds an additional step to process development, the result is a unique formulation. Such formulations help protect product lines from competition and can strengthen intellectual property claims and patent applications.

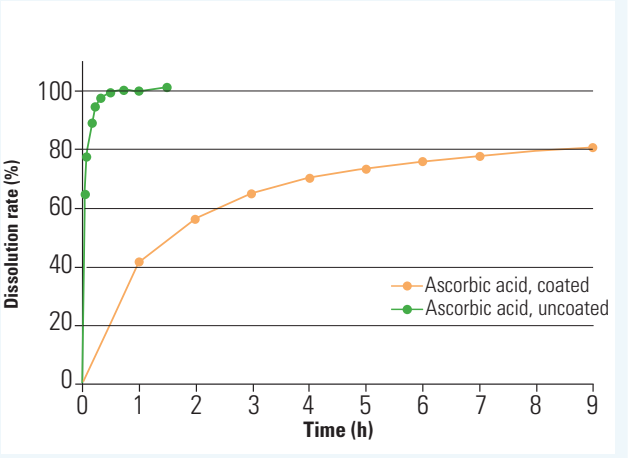
Suitable for a variety of dosage forms

One of the main advantages of HMC is its applicability to a range of oral formulations, including multi-layer tablets, multiple-unit pellet systems (MUPS), hard capsules, and alternative dosage forms such as orally disintegrating granules (ODGs).

While tablets are often the first choice for pharmaceutical and nutraceutical products, they may not be the best option—particularly when developing extended-release formulations. After all, many patients and consumers don't like swallowing tablets or capsules, as a recent study showed [2]. The study, based on a survey, found that 50 percent of the US population has difficulty swallowing tablets, with many describing them as too big or saying they become stuck in their throats. As a result, 10 percent of people admitted chewing the tablet before swallowing, 14 percent crushed it and dissolved it in water, and 23 percent broke it before swallowing. Such actions can destroy the extended-release mechanism, resulting in the immediate and complete release of the API. Such large doses are undesirable and, in some cases, can cause severe adverse effects.

FIGURE 3

Release profiles of uncoated and coated vitamin C formulations



Note: Hot-melt coating was used to create the extended-release characteristics. Dissolution testing was performed using the USP II (paddle) apparatus at 75 rpm, 37 °C, and in 900 milliliters of demineralized water.

It is also important to note that extended-release formulations must often contain much larger amounts of API within a single dose. Conventional tablets and capsules may not be able to contain such an amount without becoming overly large.

ODGs: A user-friendly formulation

ODGs are an increasingly attractive alternative to tablets for extended- and immediate-release formulations. This user-friendly dosage form consists of small granules sealed in a stick pack that is emptied directly into the mouth and swallowed without the need for water. ODGs eliminate many of the issues associated with poor patient compliance and even enhance the patient experience.

For extended-release applications, one of the main benefits of ODGs is their capacity to incorporate a much larger volume of API compared to tablets and capsules. They can also contain a combination of APIs. Because ODGs are much easier to swallow, they also reduce the likelihood that patients will crush or dissolve the product, ensuring that the extended-release mechanism works as intended.

ODGs also enable formulators to optimize HMC parameters, in both immediate- and extended-release forms. In fact, both types can be combined in a single dose, further simplifying dosage regimens.

HMC and ODGs: A perfect match

When developing our vitamin C formulation, the ability to carefully control the rate of API release and improve adherence to the dosage regimen were key considerations. Of all the available options, ODGs coated by HMC offered the best solution to these requirements and ensured sustained release while minimizing the potential for non-compliance thanks to ease of swallowing and

good taste and mouthfeel.

Figure 3 shows the extended-release profile of the coated vitamin C formulation compared to that of the uncoated raw material. While the raw material completely dissolved within 15 minutes, the coated product released just 40 percent after 1 hour. Furthermore, release was approximately 75 percent after 5 hours, demonstrating the formulation's ability to release vitamin C over a sustained period.

Vitamin C is a sour compound, so developing a pleasant oral experience was also an important consideration. HMC is particularly effective at masking the unfavorable taste of APIs. The technique also enhanced the product's mouthfeel compared to tablets because the formulation doesn't absorb saliva.

Scale-up is another important consideration for any formulation. Ideally, the transition from development to commercial manufacture is fast, simple, and cost-effective. HMC is a robust and relatively easy technology to scale up, and that is another reason why this technique was adopted. *T&C*

References

1. Jannin V, Cuppok Y. Hot-melt coating with lipid excipients, Int J Pharm, 2013, 457, 480-487.

2. Hermes Pharma, A Hard Truth to Swallow? www.swallowingtablets.com. Accessed 26 July 2017.

Martin Koeberle, PhD, is head of analytical development and stability testing, and Detlev Haack, PhD, is head of R&D at Hermes Pharma, a division of Hermes Arzneimittel, Georg-Kalb-Strasse 5-8, 82049 Pullach, Germany. Tel. +49 89 791 02 261. Website: www.hermes-pharma.com.