Working on a fluid bed granulator

Hot melt coating comes of age

There are many considerations when selecting a coating technology for user-friendly solid oral dosage forms. Dr Detlev Haack, Head of R&D, and Dr Martin Koeberle, Senior Manager Analytical Development, Hermes Pharma, consider the main issues

The simple and effective delivery of an active pharmaceutical ingredient (API) is an important factor influencing treatment efficacy, tolerability and patient compliance. For this reason, many APIs are administered orally, either in a solid or liquid form.

To further improve the user-friendliness and acceptance of solid oral dosage forms, orally disintegrating granules that start dissolving in the mouth are becoming more common. As they are extremely easy to ingest, they have proven especially popular with patients requiring regular doses or those that find it difficult to swallow solid tablets, such as children, the elderly or individuals suffering from esophagitis.

However, for this method to prove effective, most APIs must be effectively coated using one of a variety of methods, the choice of which affects formulation time and cost, while also influencing drug efficacy.

Pharmaceutical compounds are often prone to degradation if not stored in the right conditions, as prolonged exposure to light, air or moisture can significantly affect drug effectiveness. Fortunately, these factors can be mitigated by using the most suitable packaging as well as by applying a protective coating to the API. Such coatings also help to mask the bitter taste and unpleasant odour associated with many APIs, making medicines easier to chew or swallow, thereby boosting patient compliance. This is especially important for orally disintegrating granules (ODGs) as these tend to spend more time in the patient's mouth.

Traditionally, sugar coating was used to make medication more pleasant to ingest. However, this method can be difficult to perform in a standardised way and takes a long time – around five days – to complete.

Pros and cons of solvent use

The first major evolution in pharma coating technology involved dissolving the API in an organic or aqueous solvent together with other excipients, such as binding polymers, colourings, non-sugar sweeteners, sorbents or preservatives. The approach uses fluid-bed coating machinery to spray the mixture onto a seed particle, which is then dried.

The coating of APIs using liquid solvents is a well-understood process and is easily amenable to process optimisation. Robust, reliable and utilising well-characterised excipients, the method generates products with few ageing or sintering effects. In addition, the formulation of delayed- and sustained-release forms can be achieved using combinations of coatings that are sprayed on in sequential layers.

Although the mainstay of current pharmaceutical formulation, the solvent-based coating of solid oral dosage forms suffers from several important drawbacks. Many polymers used for coating must be dissolved in costly organic solvents, and while these offer some advantages (many are much more volatile than water, drying quickly at room temperature), they can be toxic to patients and workers, present a flammability risk and are potentially explosive. Many organic solvents are also environmental pollutants, meaning they must be effectively captured and recycled where possible. Unsurprisingly, organic solvent use is under strict control by regulatory bodies such as the US FDA and Environmental Protection Agency (EPA), emphasising how difficult it can be to work with them.

To circumvent these challenges, water has become the preferred solvent whenever possible. However, tablets, capsules, pellets, granules and APIs coated in this way must be dried using heat, adding substantial cost and time to the process. Perhaps even more importantly, high and prolonged thermal stress during drying may lead to API degradation or future instability, rendering the medicine ineffective during treatment.

Formulation using solvents also often involves several layers of coating, increasing process complexity, length and cost. Layering can also affect the crystalline form of the coating, leading to unwanted polymorphism. As well as affecting stability, activity and efficacy, structural variations can have important intellectual property implications. If such polymorphisms are ▶

not identified early in development of the formulation process, they can seriously threaten return on investment by providing possible grounds for patent disputes.

In the case of ODGs, the use of solvent-based coating can be even more troublesome, as the use of liquid sprays is associated with limited API stability, and further time and financial costs. In such cases, solvent-free approaches offer significant advantages.

Going solvent-free

Efforts have been underway to identify and develop solvent-free coating technologies to avoid using organic solvents or water. Several alternatives are now available, including compression, electrostatic spray powder, supercritical fluid and hot melt coating, although many are not yet ready to use at the scale necessary for efficient solid dose manufacture.

Compression coating involves encapsulating a core particle containing the API within a surrounding coating using pressure. All components of the final product start the process as powders, which are compressed to form a solid tablet. The method is well suited to producing multi-stage treatments combining two or more APIs that must be physically separated or administered to different parts of the digestive system.

The biggest drawback is that it can be difficult to position the active core accurately in the tablet's centre, which is important for reproducible formulation and reliable therapeutic action.

Electrostatic spray powder (ESP) coating uses electrostatically charged raw materials. These are then sprayed onto a seed pellet (which usually contains the API) such that the charged powder adheres to the pellet long enough to be fixed in place using heat. The process is fast and the final product can be easily modified by changing process parameters. Unfortunately, the coating and tablet core must possess certain conductive properties, or be modified via additional steps, to render them amenable to the process. ESP also requires heating the product up to 120°C or above, and therefore suffers from the stability issues associated with high temperature processes.

Supercritical fluid coating takes advantage of the properties of supercritical liquids, which fall between liquids and gases along a continuum that can be manipulated by changing the pressure and/or temperature. As a first step, the coating agent is solubilised in supercritical carbon dioxide and the API is applied to the solution. A reduction in pressure pushes the carbon dioxide towards the gaseous phase, causing the API/coating mixture to precipitate as a solid pellet ready for collection. The approach is good for producing very fine particles, but for it to work the core must be insoluble in the supercritical fluid. Perhaps the greatest adoption barriers for supercritical coating are the high cost and specialised equipment associated with the process, currently limiting its use to low dose, high price medicines.

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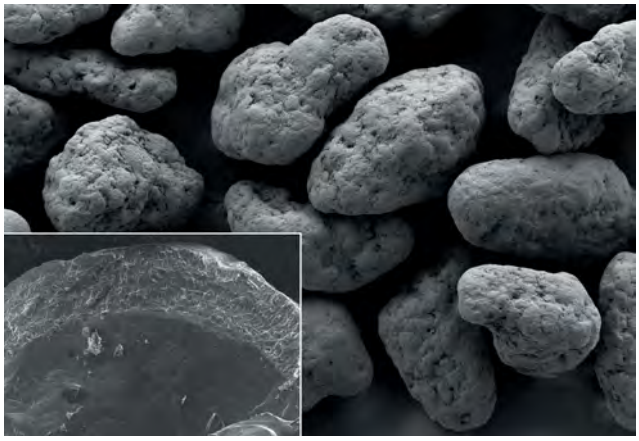
Figure 1
Scanning Electron Microscope image of taste-masked fast-acting API particles coated with a mixture containing lipids using HMC. (Insert: enlargement of a cross-sectioned particle)

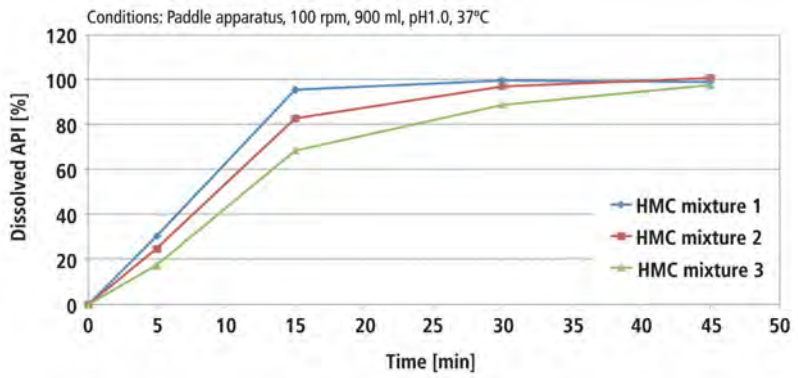


Rapid maturation

One of the most promising solvent-free approaches for use in pharmaceutical formulation is hot melt coating (HMC), as it offers a very short processing time (less than one hour depending on the API, coating thickness and scale) and significantly lowers costs. HMC involves covering the API solid core with a molten coating material at a carefully controlled temperature. This then solidifies to create a homogenous coating (Figure 1). Significant efforts have gone into developing the HMC process for widespread use, and many of the technical hurdles have now been overcome. This includes the accurate control over temperature during every stage of the process and the optimisation of PAT methods for determining the progress and endpoint of coating in real time.

Furthermore, specialised contract research and manufacturing organisations (CRMOs) such as Hermes Pharma have been exploring how the process parameters and excipients of the coating mixture can be optimised to provide the desired functionality. Until recently the formulation of user-friendly, immediate-release medicines using HMC had proved challenging. However, experts have now successfully optimised HMC parameters for formulating orally disintegrating granules, producing a pleasant-tasting product with immediate release properties, as is required for fast-acting medicines such as analgesics or mucolytics (Figure 2).

Figure 2
Dissolution profiles of a crystalline water soluble API coated with different mixtures using HMC



The new formulations illustrate that HMC is ready for more widespread adoption by pharmaceutical and nutraceutical companies. However, as the formulation and processing parameters must be optimised for each API individually, the process is best carried out by working with outsourced providers that have dedicated experience using the technique.

It is also important to note that, while this level of customisation might first appear to be a burden, it actually provides a useful means of creating a uniquely optimised coating protocol. This provides much tighter control over IP and patent protection.

In conclusion, the coating of APIs for solid oral dosage forms – especially user-friendly forms that do not require water for intake – is important for maintaining drug stability and activity, while reducing the effects of poor taste and odour on patient compliance. Many coating methods exist, with the traditional use of organic solvents now being replaced by aqueous approaches.

However, water-based coating takes longer and involves increased costs due to the necessary drying times and heat required, highlighting the need for a new generation of solvent-free approaches.

An attractive current alternative is HMC, which offers a robust process and a range of time and cost-benefits for API formulation. In addition, intensive R&D carried out by companies such as Hermes Pharma means the approach can now also be used to formulate user-friendly, solid oral dosage forms, such as orally dispersible granules (ODGs). These formulations exhibit the necessary taste and rapid-release properties required by fast-acting medicines, boosting patient compliance and efficacy.

HMC also makes it easier for pharmaceutical companies to safeguard their investments via stronger IP protection, as each API requires the individual optimisation of HMC process parameters and composition. In the future, solvent-free methods such as HMC are likely to become the go-to solutions for pharmaceutical and dietary supplement formulation, leading to lower processing costs, operating risks and turnaround times.

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