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From Bitter to Sweet: Developing a User-Friendly Painkiller

Hot-melt coating was used to develop taste-masked orally disintegrating granules of acetaminophen and caffeine.

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Caffeine is frequently added to common painkillers, such as acetaminophen, to increase their pain-relieving effect. Used primarily for mild to moderate pain, the acetaminophen plus caffeine combination is mostly produced in tablet form. Because of the extremely bitter taste of these APIs, formulation into other dosage forms that are not to be swallowed whole can be challenging. This case study shows how hot melt coating (HMC) was used to develop orally disintegrating granules (ODGs) of acetaminophen and caffeine; this dosage form has been specifically designed to be easier to swallow.

User-friendly dosage forms

User-friendly dosage forms, such as ODGs, effervescent tablets, chewable tablets, instant drinks, and lozenges, offer a wide range of benefits to both the pharmaceutical industry and the end user. In a recent consumer survey, more than half of the respondents reported difficulties swallowing tablets and capsules, with approximately a third reporting the issue as serious (1). The most frequent reasons cited were that the tablets/capsules were too big, got stuck in the throat, or had an unpleasant taste or odour. These people did not report similar problems with foodstuffs or fluids.

The same survey revealed that people who had experience with user-friendly dosage forms scored them more favourably than conventional tablets/capsules across almost all criteria (such as ease of intake, integration into daily routine, flavour, sensation in the mouth, and ease of swallowing). Such findings indicate that user-friendly dosage forms better meet consumer needs and can lead to improved compliance. In addition, pharmaceutical companies can expand their product lines and create new revenue opportunities with user-friendly dosage forms.

Orally disintegrating granules

To better meet the needs of patients and consumers, a demand was identified for an acetaminophen plus caffeine combination formulated as an ODG. Such granules are provided in stick packs that can be emptied directly into the mouth and swallowed without water. ODGs are a convenient dosage form and ideally suited to individuals who have difficulty swallowing conventional pills. A further benefit of ODGs is that, unlike tablets, they do not need to disintegrate in the stomach, which can lead to faster absorption, thereby achieving pain relief more quickly. While the benefits of an acetaminophen plus caffeine ODG were clear, a number of challenges were identified during the formulation development process.

The bitterness of both acetaminophen and caffeine makes effective taste-masking particularly challenging. Because ODGs tend to spend more time in the mouth and are tasted more thoroughly than conventional tablets and capsules, it is crucial that the final product is palatable.

HMC was identified as a suitable coating technology for the development of taste-masked acetaminophen and caffeine ODGs. Originally developed for food manufacturing, HMC offers a faster, more economical coating method than many traditional solvent-based approaches. The process involves covering a solid core particle with a molten coating material, which immediately solidifies to form a homogenous coating. The coatings, which comprise a lipid and an emulsifier, enable the production of coated immediate-release products with a neutral taste. Those coated intermediates are then blended with further excipients and flavours and filled into stick-packs to create a pleasant-tasting, user-friendly oral dosage form. HMC parameters often need to be optimized for each API due to their individual properties and morphology. Although optimization creates an extra step in the development process, it also makes the formulation unique and, therefore, can be used to protect product lines from competition. Some formulations can even be patented, further strengthening intellectual property protection.

Basic considerations

The first step in formulating the acetaminophen plus caffeine ODG was to define the quality target

Image is courtesy of Hermes Pharma.

Table I: Overview of the quality-by-design (QbD) elements used for the development of an orally disintegrating granule (ODG) formulation containing acetaminophen and caffeine.

Quality target product profile (QTPP)	
QTPP-Element	**Target**
Mode of administration	Oral administration
Dosage form	Coated granules
Dosage strength	500 mg acetaminophen, 65 mg caffeine
Pharmacokinetics	Immediate release
Container closure system	Sachet (laminated aluminum paper foil)
Stability	36-month shelf life for 25 °C, 60% relative humidity
Critical quality attributes (CQAs) of finished product	
Attribute	**Justification (impact on)**
Physical attributes (appearance, odour, particle size, flowability)	Compliance, safety, efficacy
API identity	Safety, efficacy
Assay	Safety, efficacy
Dissolution	Safety, efficacy
Taste masking	Compliance, safety, efficacy
Content uniformity	Safety, efficacy
Impurities	Safety
Moisture content	Safety
Microbial limits	Safety

Critical process parameters (CPPs)		
Production Step	**Process**	**Process parameter**
Manufacturing of intermediate product (coating process)	Coating	Product temperature Inlet air volume Inlet air temperature Spray pressure Spray rate Spray temperature
Manufacturing of final blend	Filling Blending	Blender filling level Blending time and speed
Filling of final blend	Filling	Filling amount Sealing temperature and duration Line speed

production profile (QTPP), which is a crucial element of a quality by design (QbD) approach. In this case, the main requirements of the QTPP were an ODG with 500 mg acetaminophen plus 65 mg caffeine, immediate release, pleasant taste, and storage stability of more than three years (see **Table I**).

Immediate-release ODGs should ideally have a two-phase dissolution profile. The first phase lasts 30–60 seconds and encompasses the swallowing of the granules. During this period, drug release should be minimal. In the second gastric phase, API release should be as fast as possible to enable drug absorption. Drug release is a critical quality attribute (CQA) and has to be analyzed during development, stability testing, and product release. For this analysis, a compendial dissolution instrument (paddle apparatus) was used in combination with ultra-high performance liquid chromatography (UHPLC) as it is both fast and simple to use.

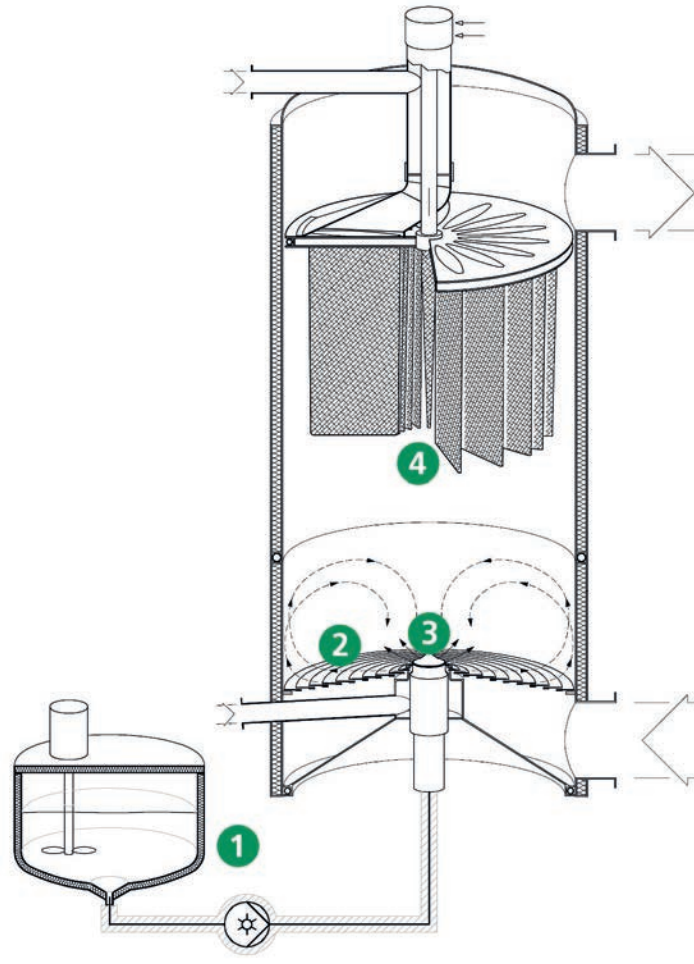
HMC was selected as the technology of choice to mask the bitter taste of acetaminophen and caffeine, followed by a blending step in which further excipients were added before filling into stick packs. For both manufacturing steps, a risk analysis identified the critical process parameters (CPPs), which were the key variables affecting the coating and blending process.

Process development

Much of the process development effort focused on coating acetaminophen and caffeine, which had to be performed separately. During the HMC process, the APIs were each suspended in the fluid bed coater and the molten coating mixture was sprayed onto the particles. The spray droplets first wet the API particle, before they solidified to form a homogenous layer. As no solvents were used, the process proved rapid and typically took less than 1.5 hours per batch. While developing the coating process, the intermediates were tested for successful taste masking, drug release, and content. Furthermore, the capability of the developed process was evaluated as to whether it could be scaled up for commercial production.

After the two APIs were coated, they were blended together with further excipients to create the final formulation. The selection of suitable excipients and flavours involved a focus on palatability and mouthfeel,

Figure 1: Hot melt coating using a fluid bed coater. The melting device (1) comprises a heated tank, stirrer, and heated tubing system that prevents the molten coating materials from solidifying en route to the fluid bed. The air layer gliding process (2) moves the particles into the spraying zone. The liquid is sprayed through a heated nozzle (3) and is atomized by compressed air into fine droplets for coating. The dust filter system (4) operates throughout the coating process and air is blown through the filters to keep them clear.



because these factors play a major role in the success of an ODG. A number of flavours were tested for their suitability including lemon, cassis, and cappuccino. Cappuccino was chosen for its association with caffeine and its pleasant taste. Then, the impact of these excipients on processing was assessed, including flowability and segregation (which were relevant when it comes to filling the granules into the small stick packs).

Finally, the blend homogeneity was evaluated and the required blending time determined using an near infrared (NIR) probe and a scaled-down laboratory blender. Both APIs were blended with the excipients. It was important that blending was performed long enough to achieve homogeneity, but it was also crucial not to overblend, as overblending can destroy the coating and negatively affect the taste and release of the formulation.

Scaling up and optimizing HMC

Ease of scale-up is essential for any formulation process to make the transition from development to bulk manufacture as fast, simple, and cost-effective as possible. An advantage of HMC is that it is relatively easy to scale up.

It was recognized that there would still be a number of challenges in scaling up the acetaminophen plus caffeine ODG. In moving from laboratory to production scale, it was necessary to upsize the HMC equipment from the Ventilus V2.5 (Romaco Innojet) to the Ventilus V100 (see **Figure 1**). The configurations of these instruments, particularly the spray geometry, are slightly different. To generate the desired HMC effect, it is essential that the spray rate and the temperature of the air, apparatus, and materials are all carefully controlled throughout the process. The equipment contains a number of sensors for temperature,

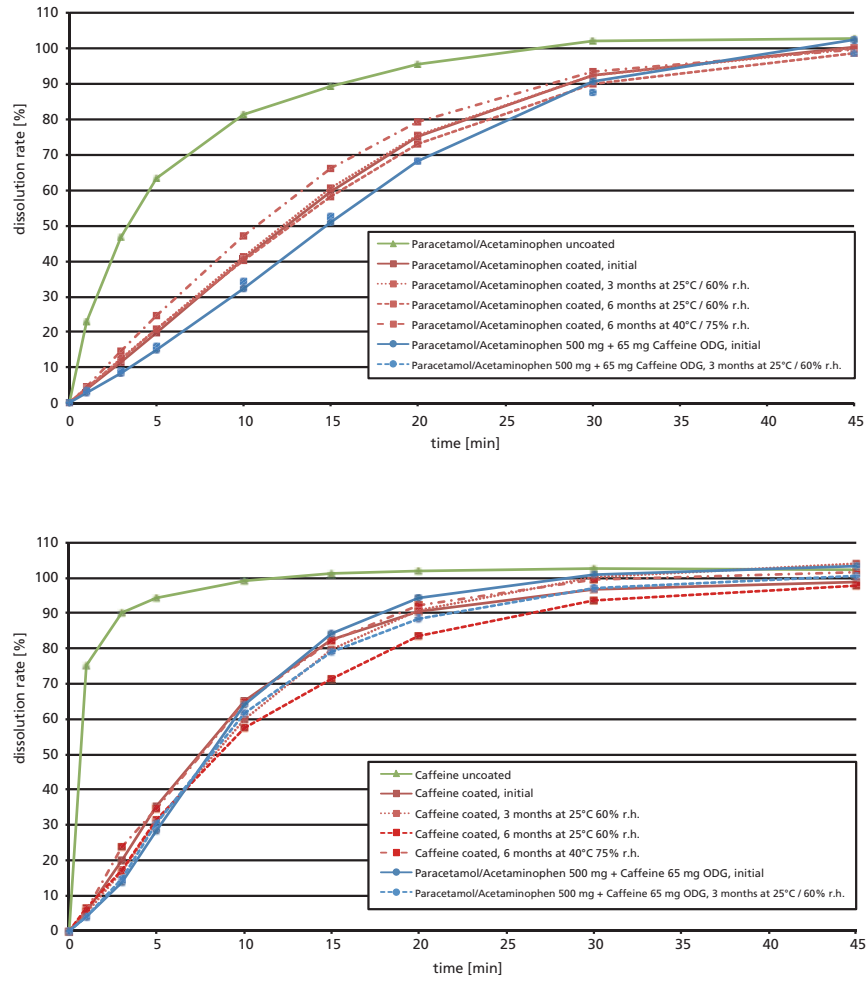
air-flow, and spray-rate, ensuring this process is not arduous and is reproducible. For the scale-up, the process times had to be extended from 50 to 70 minutes.

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, they could clog the filter of the fluid bed (see **Figure 1**), while the subsequent increase in overall surface area will lead to the coating on each particle being too thin. If the particles are too large, then the opposite occurs, with the coating ending up too thick. The frequency of filter changing becomes a more important factor for manufacturing campaigns. To optimize this parameter, a number of different filter materials and pore sizes were tested, and it was observed that the same filter can be used for a campaign of at least eight batches.

Another challenge faced during scale-up concerned the storage of the bulk intermediate. Even within just a few days, compression from the weight of the material could cause agglomeration. It was necessary to consider early on which coating excipients would be least susceptible to such agglomeration.

Also during scale-up, the final blend was optimized by making minute adjustments of excipients, sweeteners, and flavours to create a palatable and processable finished product. After this, the final step was to optimize the filling of the final blend into stick packs to achieve tight packaging and uniform fill weights at the highest possible speed. A stability study is now being performed both on a pilot batch and on each of the intermediates. In these studies, parameters such as content, related substances, taste masking, and dissolution are tested at long-term (25 °C/60% relative humidity [r.h.]), intermediate (30 °C/75% r.h.), and accelerated conditions (40 °C/75% r.h.) (see **Figure 2**).

Figure 2: Dissolution profiles of acetaminophen and caffeine over time.



Next steps

Having developed the acetaminophen plus caffeine ODG with proven processability, the next steps will be to manufacture three production scale batches to conduct process validation and to initiate stability studies for regulatory purposes. Depending on the regulatory strategy, it may be necessary to perform a bioequivalence study or to follow a biowaiver approach. Either way, the compilation of a dossier can begin because key elements have been successfully completed.

Conclusion

The HMC process was optimized at laboratory scale to mask the bitter taste inherent of both APIs. It was then successfully upscaled from laboratory to production scale. Appropriate excipients were selected to ensure a pleasant taste and mouthfeel—both of which are particularly important for ODGs. The excipients were also deliberately chosen to reduce agglomeration in the final product. Tests have shown that the goals of maintaining low API release while the ODGs are swallowed, followed by rapid release afterwards, were both achieved. Once the final stability tests have been completed, the intention is to bring the product quickly to market, offering consumers a convenient, fast-acting, and effective painkiller that overcomes many of the disadvantages of conventional tablets.

Reference

1. Hermes Pharma, "A Hard Truth to Swallow?" www.swallowingtablets.com, accessed 12 Oct. 2016. PTE

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