HOT-MELT COATED IMMEDIATE-RELEASE, TASTE-MASKED PARACETAMOL & CAFFEINE ORALLY DISINTEGRATING GRANULES

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INTRODUCTION

Paracetamol is a common non-opioid analgesic, which is especially used for the self-medication of minor to moderate pain. Caffeine is an analgesic adjuvant, which is often co-administered. There are various combination preparations on the market, which contain paracetamol and caffeine in addition to other drugs such as acetylsalicylic acid.

Orally disintegrating granules (ODG) are an innovative and user-friendly dosage form as the granules can be applied directly into the mouth and swallowed without water. While ODGs improve the swallowing experience for all people, they are especially well-suited for those with dysphagia, or those looking for a convenient dosage form that can be taken 'on the move'. Although ODGs offer a number of benefits, they also bring some technological challenges. For example, as ODGs remain in the mouth longer than a tablet, they are more thoroughly tasted and simple flavouring is not sufficient [1]. In the case of poor tasting drugs, such as the extremely bitter tasting paracetamol and caffeine, there is the need for taste-masking.

Hot-melt coating (HMC) is an effective technology to mask the poor taste of many APIs. HMC is a fast, cost-effective coating technology that avoids the use of any solvents. The coatings, which consist of a lipid and an emulsifier, enable the production of coated immediate-release products with a neutral taste [2, 3]. These 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.

The ideal dissolution profile of coated, immediate-release ODGs is characterized by two phases. The first phase lasts about 30 to 60 seconds and simulates the swallowing of the ODGs. At this time point, drug release should be kept to a minimum. Thereafter the gastric, second phase is simulated, at which point API release should be as fast as possible in order to enable drug absorption.

As such, drug release is a critical quality attribute (CQA) and has to be analyzed during development, stability testing and product release.

This is why there is the need for simple and fast techniques that can be used to analyze the dissolution samples. The method of choice is Ultra High Performance Liquid Chromatography (UHPLC).

In this work, we present data from immediate-release ODGs, that contain hot-melt coated, taste-masked paracetamol and caffeine. In addition, we demonstrate a newly developed UHPLC-method for the fast and simultaneous quantification of paracetamol and caffeine in dissolution samples.

METHODS

Instrumentation

Romaco Innojet Ventilus V2.5 (Laboratory Scale) and Ventilus V100 (Production Scale) fluid bed coater equipped with a hot-melt coating unit.
ERWEKA DT826 Dissolution tester (Apparatus II).

UHPLC set-up consisting of pump (LC-30AD; Shimadzu), Autosampler (SIL-30AC; Shimadzu), column oven (CTO20A; Shimadzu), diode array detector (SPD-M30A; Shimadzu), and software (Chromeleon V.6.80; Thermo Scientific).

Coating Process

The API (paracetamol and caffeine separately) is suspended in the fluid bed coater and the molten coating mixture is sprayed onto the particles. The temperature of the API particles is below the melting point of the coating mixture. The spray droplets first wet the API particle, and then solidify to form a homogenous coating layer (Figure 1). Since no solvents are involved the process is very rapid and typically takes less than 1.5 hours per batch.

The amount and composition of the coating mixture, as well as the process parameters, need to be adjusted for each product.

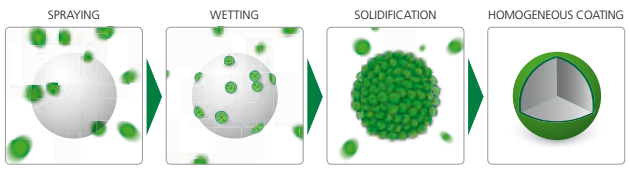

Figure 1: The hot-melt coating (HMC) process.

Dissolution Testing

Dissolution testing was performed according to Ph. Eur. 2.9.3 using apparatus II (paddle). Dissolution conditions were: dissolution medium 0.1 N HCl; temperature 37° C, volume 900 ml; stirring speed 75 rpm. Samples of 1 ml were filtered through a 1 µm filter and taken after 1, 3, 5, 10, 15, 20, 30 and 45 minutes without media replacement.

UHPLC method

For this approach, the dissolution samples were directly analyzed with a validated UHPLC-method using a Dionex Scientific Acclaim RSLC Polar Advantage II column (100 x 2.1 mm 2.2 µm) and an Acclaim Polar Advantage II guard column (2 x 10 mm 5 µm). The isocratic method employed a mobile phase of 20 % methanol and 80 % acetate-buffer pH 5.0 at a flow rate of 0.5 ml/min. In this case, the analytes can be detected at 245 nm (paracetamol) and 275 nm (caffeine). The column oven was set to 35° C and 1 µl sample was injected. The runtime was 3.0 minutes.

RESULTS AND DISCUSSION

The hot-melt coating process was successfully transferred from lab scale (Ventilus V2.5) to production scale (Ventilus V100). The goals of maintenance of low API release while the ODGs are 'swallowed' and subsequent fast release after they have been swallowed were both achieved. Once the coating parameters are defined in this way the process is robust and generates a reproducible product. As part of the method, the coated intermediates are blended with further excipients and flavours. It is during this blending step that individual customer requests, such as the amounts of API(s), flavor and sweetness, can all be easily considered. At the end of the process, ODGs are produced that can be filled in stick-packs and which form a palatable, user-friendly dosage form that may be taken without water.

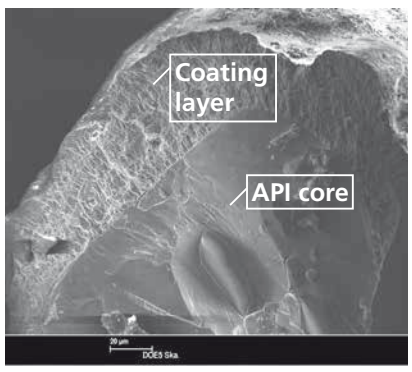

Figure 2: Exemplary scanning electron microscope image of a coated API particle.

A dissolution test for the evaluation of taste-masking efficiency and the release characteristics of the coated intermediates (paracetamol and caffeine individually, as well as of the finished product containing both) was established. For the analysis of the dissolution samples, a UHPLC method for the simultaneous quantification of paracetamol and caffeine was developed and validated according to ICH Q2 (R1). With a runtime of only 3 minutes, a complete dissolution profile can be analyzed in about 3 hours. Furthermore, less than 100 ml of mobile phase is required for this analysis sequence. As such, this represents a fast and cost-effective method.

Figures 3 and 4 illustrate the dissolution profiles of the uncoated raw material, the coated intermediates and of the finished product for paracetamol and caffeine, respectively.

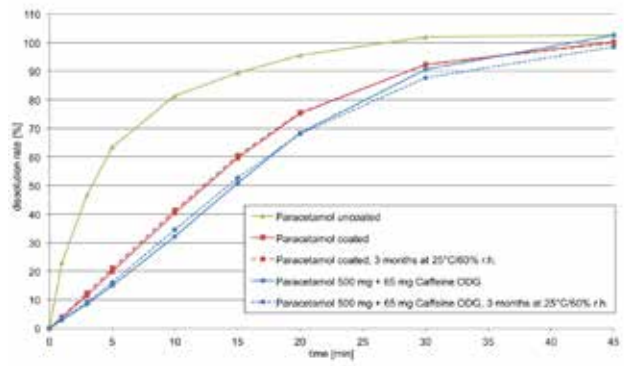

Figure 3: Dissolution profiles of paracetamol over time.

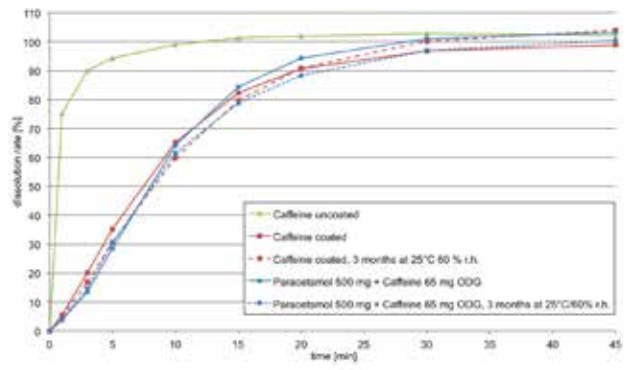

Figure 4: Dissolution profiles of caffeine over time.

After one minute only around 5 % of the APIs coated within the intermediates and finished product are released, indicating successful taste masking. In addition, after 30 minutes, more than 85 % of the APIs are released from the intermediates and finished product, which shows that they exhibit immediate release characteristics and remain stable over 3 months (stability study ongoing). Furthermore, there is no considerable difference in release between the coated intermediates and the finished product observable. This shows that the blending process and the filling into stick-packs do not impair product characteristics.

In summary, an ODG containing 500 mg paracetamol and 65 mg caffeine coated using HMC was successfully developed and up-scaled to create a stable, palatable and convenient dosage form.

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