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Enteric coating of micron-size drug particles through a Würster fluid-bed process

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ABSTRACT

Enteric coated active pharmaceutical ingredient (API) particles can provide advantages in clinical and pre-clinical formulation development targeting intestinal drug release over traditional tablet and capsule formulations. The challenge with this approach is developing a robust coating process to achieve sufficient gastric protection and efficient intestinal release on micron sized particles. A Würster coating fluid bed process to directly produce enteric coated API particles was developed at a 650 g scale and was scaled up to 20 kg. Generating API with low 3-dimensional aspect ratio structure was critical for this process and was achieved through a wet milling process. The starting particle size had D50 ~ 90 μm, and the D50 of the resulting coated particles could be as small as 180 μm. Scanning electron microscopy imaging and dissolution testing were used to characterize the properties of the enteric layer on the API particles as a function of coating thickness. Coated API particles achieved up to 8 h enteric protection in the gastric environment and rapid release in the intestinal environment.

1. Introduction

Enteric coated active pharmaceutical ingredient (API) particles can provide advantages over the conventional tablet and capsule formulations for targeting intestinal release. The coated API particles can spread widely throughout the small intestine during drug release to avoid localized dose dumping, which may help improve patient tolerability and reduce certain side effects [1–3]. In addition, enteric coated APIs can be combined with other formulation techniques such as gastro-retentive formulations or fixed-dose drug combinations. For gastro-retentive formulations, a matrix tablet with the API is typically formulated with swelling or floating polymers to prevent the tablet from entering into the small intestine [4–8]. If stomach dissolution is not preferred for the drug, matrix tablets containing the floating/expanding polymers can be formulated with enteric coated API. The floating/expanding polymer erodes in the stomach over time and the undissolved enteric coated API can be released to the upper intestine. The enteric coating is then dissolved in the upper intestine and the drug can be absorbed. A similar concept can be applied to fixed-dose drug combinations when one or more drug components require enteric protection [9,10]. The coated drug can be mixed with other drug components for direct compression or encapsulation. Additionally, these micron-size particles are optimal for pre-clinical studies in small animals such as rats or mice due to their ease of ingestion. Moreover, these particles have desirable properties such as improved flow and ease of encapsulation [11,12]. This can significantly minimize early phase formulation development activities and accelerate critical first in human clinical studies [13].

The primary challenge associated with enteric coating of API particles is to provide adequate surface area coverage and coating thickness to ensure sufficient gastric protection, while avoiding particle agglomeration during the coating process. Previous efforts have shown that a rotary coating process can be an effective technique to coat fine particles [14,15]. The rotary coating chambers can be purchased as an add-on to the fluid bed granulator. However, the process is not commonly used in industry and most contract manufacturing sites (CMO) rarely support this capability. Würster fluid bed coaters have been widely used in the pharmaceutical industry for drug layering and for coating particles that are a few hundred microns in size [16–18]. Previous Efforts have also been taken to evaluate the feasibility of using the process for enteric coating of API particles with D50 < 100 μm. Lactose was used as a soluble model drug for enteric coating. However, the enteric protection only lasts for around one hour even with a high enteric polymer weight gain [19,20].

In this paper we describe the successful coating of an internally developed API with enteric protection up to 8 h. A solvent-based spray solution was chosen over a water-based one to maintain the small droplet size necessary for coating micron sized API particles. Two types of particles with different morphologies were evaluated to illustrate the impact of API particle morphology on the coating process. Dissolution of the coated particles at different polymer weight gains was performed in

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simulated gastric fluid (SGF) to estimate the duration of gastric protection and in simulated intestinal fluid (SIF) to simulate release in the upper intestine. Scanning electron microscopy (SEM) was used to image the particles and correlate coated particle surface morphology with dissolution rates. The process was first developed at lab scale using a 6-in. Würster column and then scaled up to pilot scale with an 18-in. column.

2. Materials and methods

2.1. Materials

Methacrylic Acid - Methyl Methacrylate Copolymer (1:1) (Eudragit® L100) and silicon dioxide (Aerosol 200) were sourced from Evonik Industries (Essen, Germany). Triethyl citrate was sourced from Vertellus Performance Materials (Greensboro, NC, USA). The API was manufactured by one of Biogen's contract manufacturing sites.

2.2. Würster coating

Enteric coated API was developed in a Glatt GPCG-2 fluid bed granulator equipped with a 6-in. Würster column and a bottom spray system. The spray gun used was a Schlick Model 970 with a 1.2 mm nozzle. A bottom A plate was used with a 100 μm screen. Initially 647 g of API (99.5% w/w) and 3 g of silicon dioxide (0.5% w/w) were fluidized in the column for 5 min at 23 °C. The blend was sprayed with an organic solution containing Methacrylic Acid - Methyl Methacrylate Copolymer (1:1), triethyl citrate. All coating solutions were prepared by mixing the appropriate amount of excipient in water and 99% isopropyl alcohol (IPA) for 2 h. The coating solution formulation is shown in Table 1. The product temperature was kept between 22 and 25 °C throughout the process. Process air flow was 45 m^3/h, the maximum spray rate was 15 g/min and the atomization air pressure was 2.5 bar. Samples were taken in process until theoretical 100% weight gain of the enteric polymer was reached.

The process was scaled up to a Glatt GPCG-15 fluid bed granulator with an 18-in. Würster column. Spray gun model Schlick HS 04 with a 1.2 mm nozzle was used. A bottom A plate was used with a 100 μm screen. Initially 19.9 kg of API (99.5% w/w) and 0.1 kg of silicon dioxide (0.5% w/w) were fluidized in the column for 15 min at 23 °C. Formulation of the coating solution was kept the same. (Table 1) The product temperature was kept between 22 and 25 °C throughout the process. Process air flow was 540–600 m^3/h and the maximum spray rate was 130 g/min. Samples were taken in process until 80% weight gain of the enteric polymer was sprayed. The parameters of both processes are summarized in Table 2.

2.3. Scanning electron microscopy

The morphology of both uncoated and enteric coated API was studied using an SEM, JEOL JSM5610-LV (JEOL USA Inc. Peabody, MA). Uncoated API was prepared by lightly pressing carbon adhesive tabs into a powder bed of the sample and lightly spraying with compressed air to remove excess material. Samples were then mounted on a solid brass sample holder and cooled in liquid nitrogen before analysis. Images were obtained under low vacuum using a backscatter detector in composition mode at 15 kV and 100× magnification. Enteric coated API was prepared by lightly pressing carbon adhesive tabs into a powder bed of each sample and lightly spraying with compressed air to remove excess material. Samples were then mounted on 12 mm aluminum stubs and analyzed at 40×, 100× and 200× magnifications. Images were obtained under low vacuum using a backscatter detector in shadow mode. Voltage, spot size and chamber pressure were adjusted to achieve the best image for each specimen at a given magnification.

Table 1
Enteric coat formulation.

Ingredients	Weight %
Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)	6.5
IPA	90.7
Water	1.5
Triethyl citrate	1.3

Table 2
Parameters of the coating processes.

	GPCG-2	GPCG 15
Würster column diameter (inch)	6	18
Process air flow (m^3/h)	45	540–600
Coating product temperature (°C)	22–25	22–25
Spray gun model	Schlick 970	Schlick HS 04
Spray gun nozzle size (mm)	1.2	1.2
Maximum spray rate (g/min)	15	130
Atomization air pressure (bar)	2.5	1.8
Coating time for 80% polymer weight gain (hr)	9	31

2.4. Particle size analysis

The particle size distribution of the enteric coated API was determined using a dynamic imaging technique (Camsizer XT, Retsch, Germany). The coated API particles were spread out and transported from the back of a steel chute to the front by a vibrating mechanism and dropped through the sampling window by gravity. Area based volume distribution of particle size was obtained through image analysis software. The amount of sample was determined such that the number of particles captured by the basic camera was >1,000,000. The method repeatability was <0.4% RSD for D10, D50 and D90.

2.5. Dissolution

The in-vitro drug release testing of enteric coated API in SGF (pH = 1.2) and SIF (pH = 6.8) was performed using an Evolution 6100 dissolution unit (Distek Inc., North Brunswick, New Jersey) and is compliant with USP <37> for Apparatus II. The dissolution media (500 mL) was degassed by ezFill 4500 media dispensing unit (Distek, Inc., North Brunswick, New Jersey) before being transferred into 1-Liter dissolution vessels. The experiment was performed in triplicate and the medium temperature was maintained at 37 ± 0.5 °C with an agitation speed of 100 rpm for a predetermined period of time (2 h in SIF and 8 h in SGF). All experiments were performed in triplicate ($N = 3$) except the data reported in Table 4 due to limited samples.

The API release was measured in-situ and the result was verified by a validated HPLC methods. The real-time API release was measured in-situ by OPT-DISS-405 fiber optic probes (Distek Inc., North Brunswick, New Jersey) and collected UV absorbance data were analyzed at 223 nm using OPT-DISS software, version 1.18.2. The dissolution samples were also collected at 2 h (SGF and SIF) and 8 h (SGF), and then assayed for their API contents using a validated HPLC method. The percentage of API release was calculated by the following equation,

$$\%\text{Release} = \frac{A_t}{\text{Weight}_{\text{coated API}} \times \text{Assay}_{\text{coated API}}} \times 100$$

where A_t is the amount of released API at time t, $\text{Weight}_{\text{coated API}}$ is the amount of the enteric coated API samples, and $\text{Assay}_{\text{coated API}}$ is the assay value of the enteric coated API samples.

2.6. Assay

An appropriate amount of the enteric coated API sample (400–500 mg) was weighed based on the theoretical weight gain followed