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Continuous API-crystal coating via coacervation in a tubular reactor

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ABSTRACT

We present a proof-of-concept study of a continuous coating process of single API crystals in a tubular reactor using coacervation as a microencapsulation technique. Continuous API crystal coating can have several advantages, as in a single step (following crystallization) individual crystals can be prepared with a functional coating, either to change the release behavior, to protect the API from gastric juice or to modify the surface energetics of the API (i.e., to tailor the hydrophobic/hydrophilic characteristics, flowability or agglomeration tendency, etc.). The coating process was developed for the microencapsulation of a lipophilic core material (ibuprofen crystals of 20 μm- to 100 μm-size), with either hypromellose phthalate (HPMCP) or Eudragit L100-55. The core material was suspended in an aqueous solution containing one of these enteric polymers, fed into the tubing and mixed continuously with a sodium sulfate solution as an antisolvent to induce coacervation. A subsequent temperature treatment was applied to optimize the microencapsulation of crystals via the polymer-rich coacervate phase. Cross-linking of the coating shell was achieved by mixing the processed material with an acidic solution ($pH < 3$). Flow rates, temperature profiles and polymer-to-antisolvent ratios had to be tightly controlled to avoid excessive aggregation, leading to pipe plugging. This work demonstrates the potential of a tubular reactor design for continuous coating applications and is the basis for future work, combining continuous crystallization and coating.

1. Introduction

In pharmaceutical manufacturing, batch processing has significant advantages: single batches can be accepted or rejected as a part of a quality system and existing, (seemingly) well-understood equipment can be reused for a wide variety of different campaigns. Moreover, due to the inherent flexibility, batch processes with multi-purpose equipment are conceived to be more profitable for small-scale products than dedicated continuous plants (Plumb, 2005; Goršek and Glavič, 1997). However, batch manufacturing also has disadvantages: scale-up from small-sized laboratory equipment used in the early phase of development to the industrial scale is often highly complex and can pose serious problems, including regulatory issues due to the extensive validation required (Qiu et al., 2009; Närhi and Nordström, 2005). The design of large-scale equipment based solely on geometrical similarity is not sufficient (Montante et al., 2003; Leuenberger, 2001; Klinzing and Bell, 2005). For example, large-scale systems are more likely to create inhomogeneous process conditions with a noticeable impact on product quality. In addition to the scale-up problem, long throughput times, lower equipment usage and extensive equipment maintenance are daily reality in a batch-manufacturing environment. As a result, the development and implementation of innovative processing technologies, including continuous manufacturing has created significant interest. Moreover, this trend is supported by the regulatory authorities (FDA, 2014).

Together with crystallization, filtration (Lawton et al., 2009) and wet granulation (Vervaet and Remon, 2005), coating processes are still considered a bottleneck for an end-to-end continuous manufacturing process. Innovations in continuous functional coating (e.g., enteric coating) focus primarily on the improvement of pan coaters (Ferrero, 1993; O'Hara and Marjeram, 2006; Cunningham et al., 2010; Suzzi et al., 2012), fluidized bed (Liborius,

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1993; Rümpler et al., 2006; Teunou and Poncelet, 2002) and spouted bed reactors (Jacob et al., 2006; Innovations in Coating Technology, 2008). These technologies are most suitable for processing tablets and pellets. However, functional coatings can also be applied to the crystals themselves, obviating the need to coat pellets or tablets. Among the many microencapsulation techniques (Jyothi et al., 2010; Elkharraz et al., 2011; Im and Sah, 2009; Hirech et al., 2003; Dalmoro et al., 2012; Gouin, 2004; Ghosh, 2006; Kröber and Teipel, 2005), spray drying (Kondo et al., 2014) and solvent evaporation (Li et al., 2008; Lyons and Wright, 2001) are most frequently described. Another important microencapsulation technique relevant for the food and pharmaceutical industry is coacervation (Weiß et al., 1995a; Ganderton et al., 1995; Nakagawa and Nagao, 2012). The term was introduced by Bungenberg de Jong and Kruyt in 1926 (Bungenberg et al., 1929) to describe the formation of polymer-rich coacervate droplets. Coacervation can be induced by adding either an anti-solvent to the polymer (simple coacervation) or an oppositely charged polymer (complex coacervation). The concept of microencapsulation via coacervation involves the deposition of a newly-formed coacervate phase around core particles suspended or emulsified in the same reaction media. The formed shell can then be cross linked, i.e., hardened, for example, by adding an appropriate chemical cross linker or via temperature treatment (Gouin, 2004; Weiß et al., 1995b). Recently, coacervate microcapsules have also been used in the formulation of multilayer oral dosage forms (Feng et al., 2014; Salaün et al., 2009; Pommersheimer, 2005). However, coacervation has mainly done in a batch reactor, stirred-tank environment.

Tubular reactors (including micro-reactors) are increasingly used in research and industry (Roberge et al., 2005; Roberge et al., 2008; Mascia et al., 2013), e.g., for generating nano- and micro-particles (Kawase and Miura, 2007; Yadav et al., 2012; Petschacher et al., 2013; Alvarez and Myerson, 2010; Jiang et al., 2014; Kang et al., 2014) and for chemical synthesis (Kopetzki et al., 2013; Lévesque and Seeberger, 2011; Wahab et al., 2010; Michel and Greaney, 2014; Malet-Sanz and Susanne, 2012; He and Jamison, 2014; Wu et al., 2014). The high surface-to-volume ratio facilitates rapid heat exchange and therefore an accurate temperature control of the processed medium (Tabeling, 2005). These are the desirable conditions when dealing with temperature-dependent phase separation processes, such as coacervation.

The purpose of this work was to investigate the principle of continuous coating of single crystals in a long tubular reactor applying simple coacervation. Two enteric polymers of industrial relevance (HPMCP and Eudragit® L100-55) were used. The outline of the present study is as follows: first, the applied analytical methods are described and the proposed continuous coating process is illustrated. Next, in Section 3 the results of our study are presented. Finally, Section 4 provides a summary, together with a novel coacervation concept that may be highly practical for applications in a tubular reactor.

2. Materials and methods

The API used was ibuprofen (ibuprofen 25) – BASF, Germany. Its cumulative volume density distribution is shown in Fig. 1. Coatings used were hydroxy propyl methyl cellulose phthalate (HPMCP – hypromellose phrhalate, NF; HP-55, nominal phthalyl content: 31%) – Shin-Etsu Chemical Co. Ltd., Japan; Eudragit L100-55 (methacrylic acid–ethyl acrylate copolymer (1:1) Type A Ph. Eur.) – Carl Roth GmbH + Co. KG, Germany. (Anti-) solvents: Ethanol denaturized (≥99.8% with about 1% MEK) – Carl Roth GmbH + Co. KG, Germany; disodium hydrogen phosphate dihydrate (≥99.5%) – Carl Roth GmbH + Co. KG, Germany; sodium sulfate (≥99%) – Carl Roth GmbH + Co. KG, Karlsruhe. Acids: hydrochloric acid (1 N) – Carl Roth GmbH + KG Germany; acetic acid (100%) – Carl Roth GmbH + Co. KG, Germany.

2.2. Process equipment

Three peristaltic pumps (PI–III) were utilized in the coating experiments: PI: ISMATEK Type ISM 831C; PII: ISMATEK Reglo Model ISM 829 B and PIII: Heidolph Pumpdrive Type PD5106. Polysiloxane tubings with an inner diameter (d_{in}) of 2.0 mm and an outer diameter (d_{out}) of 4.0 mm and Y-fittings (PTFE, d_{in} = 2.0 mm) were used to assemble the tubular reactor. Temperature control was performed using two thermostatic bathes: BI (LAUSA Type E 111 Ecoline Staredition) and BII (LAUDA A 24). Agitation and temperature control of suspensions and solutions were carried out with two magnetic stirrers SI (VWR Advanced VMS-C4) and SII (IKAMAG RCT).

2.3. Dissolution studies

Dissolution studies were carried out in order to examine the coating quality according to a method described by Weiß (1991). The method is based on the different solubilities of ibuprofen and the coating polymers at pH = 4. Since ibuprofen crystals dissolve quickly if not coated, the dissolution profile reflects the coating quality. Powder dissolution was performed using an Erweka DT820 dissolution tester with a stirring paddle (Erweka GmbH, Germany). The stirring speed was 100 rpm and the vessels were filled with 900 mL of a dissolution medium that was kept at 37 °C ± 0.5 °C. The phosphate buffer, serving as the dissolution medium, was prepared by dissolving 6.8 g of potassium dihydrogen orthophosphate in deionized water and filled up to 1000 g. The pH value (determined using a FiveEasy from Mettler Toledo) was adjusted to pH 4 by less than 1 mL of phosphoric acid (85%). Adding 0.5 g of a wetting agent (Tween® 20) was sufficient to guarantee good wettability of the suspended particles. 1 g was used in the original method (Weiß, 1991). Since the maximum solubility of ibuprofen in the phosphate buffer medium is 71.4 mg/L at 37 °C (Weiß, 1991), 60 mg of uncoated ibuprofen crystals or the mass equivalent of coated material (see Section 2.4) were suspended in the dissolution vessel. Only sieved powder samples were measured (RETSCH vibratory sieve shake AS200 control, sieving time 5 min mesh size 50–100 μm) to ensure comparability of the dissolution profiles. The quantification of the dissolved ibuprofen concentration was carried out via UV/Vis-spectroscopy at 264 nm (Lambda 950 UV/Vis/NIR

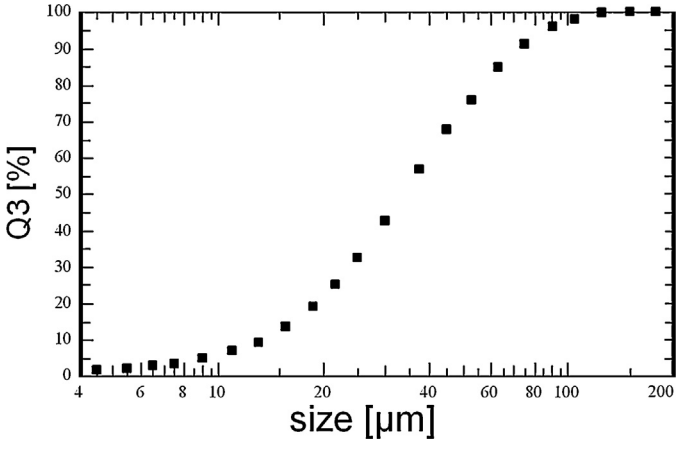

Fig. 1. Cumulative volume density distributions (Q3) of ibuprofen 25 determined by laser diffraction (HELOS/KR, Sympatec GmbH, Clausthal-Zellerfeld, Germany).