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Importance of air bubbles in the core of coated pellets: Synchrotron X-ray microtomography allows for new insights

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ABSTRACT

High-resolution X-ray microtomography was used to get deeper insight into the underlying mass transport mechanisms controlling drug release from coated pellets. Sugar starter cores were layered with propranolol HCl and subsequently coated with Kollicoat SR, plasticized with 10% TEC. Importantly, synchrotron X-ray computed microtomography (SR-μCT) allowed direct, non-invasive monitoring of crack formation in the film coatings upon exposure to the release medium. Propranolol HCl, as well as very small sugar particles from the pellets' core, were expulsed through these cracks into the surrounding bulk fluid. Interestingly, SR-μCT also revealed the existence of numerous tiny, air-filled pores (varying in size and shape) in the pellet cores before exposure to the release medium. Upon water penetration into the system, the contents of the pellet cores became semi-solid/liquid. Consequently, the air-pockets became mobile and fused together. They steadily increased in size (and decreased in number). Importantly, "big" air bubbles were often located in close vicinity of a crack within the film coating. Thus, they play a potentially crucial role for the control of drug release from coated pellets.

1. Introduction

Polymer coated pellets are well established as oral controlled drug delivery systems [1–4]. Numerous products are available on the market. The drug is generally layered onto a sugar or microcrystalline cellulose starter core, or is distributed throughout the pellet core. Different types of polymers can be used to surround these drug-loaded cores, forming thin films controlling drug release (e.g. [5–8]). The polymers can be applied using a variety of techniques, e.g. fluid bed coating using organic solutions or aqueous dispersions [9,10], or dry powder coating [11–13]. If aqueous polymer dispersions are used, care must be taken to assure complete film formation to provide long term stability [14–16]. In this study, Kollicoat SR 30D was used for film coating: an aqueous dispersion of poly(vinyl acetate), also containing small amounts of poly(vinyl pyrrolidone) and sodium lauryl sulfate [17]. The film coating was plasticized with triethyl citrate (TEC) and applied onto propranolol HCl layered sugar cores in a fluidized bed.

Despite the great practical importance of polymer coated pellets for advanced drug delivery, the underlying mass transport mechanisms controlling drug release from these systems are often yet not fully understood [18]. Consequently, product optimization generally requires highly time-consuming and cost-intensive series of trial-and-error experiments. This can be attributed to the fact that a variety of physicochemical phenomena can be involved in the control of drug release from polymer coated pellets, including water penetration into the system upon contact with aqueous body fluids, polymer swelling, drug dissolution, the dissolution of water-soluble excipients in the pellets' core and film coating, the diffusion of dissolved drug and excipients (e.g., plasticizers) out of the system into the bulk fluid, a significant increase in pellet size over time (due to substantial osmosis-driven water influx into the system, combined with a flexible film coating), potential crack formation in the polymeric film and convective mass transport through such cracks.

In order to elucidate which mass transport phenomena are decisive in a particular system (and which can be neglected or are not occurring), a variety of experimental and theoretical methods can be applied. For example, Terahertz pulsed imaging [19–21], NMR analysis [22], water permeability measurements through thin films [23] and Scanning Electron Microscopy [24] can be used. Also, specifically designed release cells, equipped with a manometer to measure the pressure built-up inside the cell, can be used [25]. Furthermore, X-ray micro-computed tomography is a highly promising analytical tool, which can offer interesting insight into the structure of advanced drug delivery systems [26,27]. Importantly, mechanistically realistic mathematical theories can also provide deeper insight into the underlying drug release mechanisms from polymer coated pellets [28,29]. For example, the group of

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Axelsson proposed very interesting advanced models considering for instance diffusional mass transport and osmotic pumping [30–32]. The comparison of theoretically calculated and experimentally measured drug release data can be very helpful in understanding how drug release is controlled [33].

The aim of this study was to elucidate the underlying drug release mechanisms in Kollicoat SR coated pellets, using a large spectrum of experimental and theoretical techniques. Particular emphasis was placed on the monitoring of potential crack formation, without the risk of artifact creation. For this reason high-resolution X-ray microtomography using synchrotron radiation was applied: In this case, the polymer coated pellets can be analyzed in the release medium during drug release (and no sample preparation procedure, e.g. involving a drying step, is required).

2. Materials and methods

2.1. Materials

Propranolol hydrochloride (Salfic-Alcan, Puteaux, France); sugar cores (sugar spheres, Suglets, 850–1000 μm) and hydroxypropyl methylcellulose (HPMC, Methocel E5) (Colorcon, Dartford, UK); an aqueous dispersion of poly(vinyl acetate) [Kollicoat SR 30D, also containing small amounts of poly(vinyl pyrrolidone) and sodium lauryl sulfate; BASF, Ludwigshafen, Germany]; triethyl citrate (TEC; Alfa Aesar, Karlsruhe, Germany); polyethylene glycol 4000 (PEG; Cooper, Melun, France); ethanol 95% (Charbonneaux-Brabant, Tressin, France).

2.2. Preparation of thin, drug-free films

TEC (10% w/w, based on the dry polymer mass) was added to aqueous Kollicoat SR dispersion (polymer content = 10% w/w, adjusted with demineralized water). The formulation was stirred for 24 h. Thin polymeric films were prepared by spraying the dispersion onto 20 × 20 cm Teflon plates using a spraying gun (LacAir SW gravity spray gun; Lacme, La Fleche, France), followed by drying at 60 °C for 24 h in an oven.

2.3. Characterization of free films

The thickness of the films was measured using a thickness gauge (Minitest 600; Erichsen, Hemer, Germany).

The mechanical properties (percent elongation and energy at break in the dry and wet state) of the films were measured using a texture analyzer (TA.XT Plus, Stable Micro Systems, Surrey, UK) before and after exposure to phosphate buffer pH 7.4 (USP 35). Film specimens of 8 × 8 cm were placed into 250 mL plastic flasks filled with 200 mL pre-heated medium and agitated in a horizontal shaker (80 rpm, 37 °C; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time points, samples were withdrawn and mounted on a film holder. The puncture probe (spherical end: 5 mm diameter) was fixed on the load cell (1 kg) and driven downward with a crosshead speed of 0.1 mm/s to the center of the film holder's hole (diameter: 10 mm). Load versus displacement curves were recorded until rupture of the film (n = 6) and used to determine the mechanical properties as follows:

$$\%\text{elongation at break} = \frac{\sqrt{R^2 + d^2} - R}{R} \cdot 100\% \quad (1)$$

Here, R denotes the radius of the film exposed in the cylindrical hole of the holder and d the displacement to puncture.

$$\text{energy at break} = \frac{AUC}{V} \quad (2)$$

where AUC is the area under the load versus displacement curve and V the volume of the film located in the die cavity of the film holder (the energy at break is normalized to the film's volume).

Water uptake and dry mass loss studies were performed by placing 5 × 5 cm film pieces into 100 mL plastic flaks filled with 100 mL pre-heated phosphate buffer pH 7.4 (USP 35), followed by horizontal shaking (37 °C, 80 rpm; GFL 3033; n = 3). At predetermined time points, film samples were withdrawn, excess surface water carefully removed, the films accurately weighed [wet mass (t)], and then dried to constant mass at 60 °C [dry mass (t)]. The water content (%) and dry film mass (%) at time t were calculated as follows:

$$\text{watercontent}(\%)(t) = \frac{\text{wet mass}(t) - \text{dry mass}(t)}{\text{wet mass}(t)} \cdot 100\% \quad (3)$$

$$\text{dry film mass}\ (\%)(t) = \frac{\text{dry mass}(t)}{\text{dry mass}\ (0)} \cdot 100\% \quad (4)$$

where *dry mass* (0) denotes the dry mass of the film before exposure to the release medium.

Drug transport through initially drug-free films was measured using side-by-side diffusion cells: drug-free films (thickness = 38 μm) were placed into horizontal side-by-side diffusion cells (2 × 100 mL, film surface area exposed to each medium: 28.3 cm^2; Permegear, Hellertown, PA, USA). The donor compartment was filled with a propranolol HCl solution (70 mg/mL) in phosphate buffer pH 7.4 (USP 35). The acceptor compartment was filled with phosphate buffer pH 7.4. The system was placed in a horizontal shaker at 37 °C (80 rpm, GFL 3033). At predetermined time points, 3 mL samples were withdrawn from the acceptor compartment and replaced with fresh medium. The propranolol HCl contents in the samples were determined by UV-spectrophotometry (λ = 289 nm, UV 1650 PC; Shimadzu, Champs-sur-Marne, France).

2.4. Preparation of coated pellets

2.4.1. Drug layered starter cores

Sugar cores were coated with a solution consisting of 21.7% (w/w) propranolol HCl, 1% (w/w) HPMC, 0.1% (w/w) PEG, 36.4% (w/w) demineralized water and 40.8% (w/w) ethanol in a fluidized bed equipped with a Wurster insert (Strea 1, Niro; Aeromatic-Fielder, Bubendorf, Switzerland). The process parameters were as follows: product temperature = 42 ± 2 °C, spray rate = 1–3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 0.8 mm. The final drug loading was 10%.

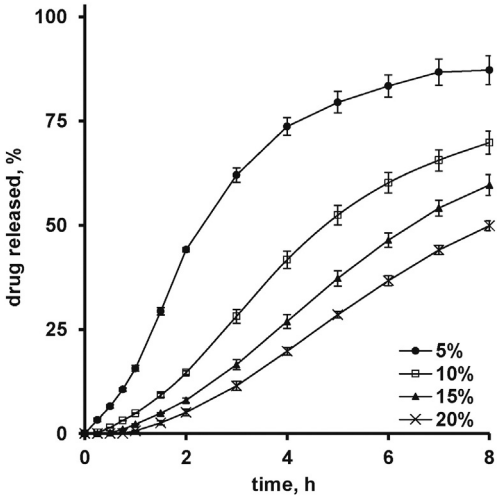

Fig. 1. Propranolol release from (ensembles of) pellets coated with 5–20% Kollicoat SR (as indicated in the diagram) in phosphate buffer pH 7.4 (initial drug loading: 10%; mean values ± SD).