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Determination of the release mechanism of Theophylline from pellets coated with Surelease®—A water dispersion of ethyl cellulose

Jurgita Kazlauske[a,b], Maria Margherita Cafaro[c], Diego Caccavo[c], Mariagrazia Marucci[b,d], Gaetano Lamberti[c], Anna Angela Barba[e], Anette Larsson[a,b,*]

[a] Pharmaceutical Technology, Applied Chemistry, Department of Chemistry and Chemical Engineering, Chalmers University of Technology, Gothenburg 412 96, Sweden
[b] SuMo BIOMATERIALS, A VINNOVA VINN Excellence Center at Chalmers University of Technology, Gothenburg 412 96, Sweden
[c] Department of Industrial Engineering, University of Salerno, Fisciano, SA 84084, Italy
[d] AstraZeneca R&D Gothenburg, 431 83 Mölndal, Sweden
[e] Department of Pharmacy, University of Salerno, Fisciano, SA 84084, Italy

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ABSTRACT

The aim of this study was to investigate the water transport over free standing films based on the aqueous ethyl cellulose (EC) coating Surelease® and the drug (Theophylline) release mechanism from coated pellets. It was found that the main drug release rate from pellets was controlled by a diffusion mechanism. However, the drug release rate was altered by addition of sodium chloride to the external release medium. A decrease in the drug release rate when sodium chloride is added to the release medium has traditionally been used to indicate an osmotic drug release mechanism. However, our findings that the release rate decreased by sodium chloride addition could be explained by sodium chloride diffusing through the coating layer into the inner parts of the pellets, decreasing the solubility of Theophylline. This gave a reduced drug concentration gradient over the coating layer and thus a slower release rate. Furthermore, this study shows, as expected, that the transport of water through Surelease® films into the pellets was faster than the transport out of Theophylline (approx. seven times), which was the reason why the pellets were swelling during the release. It was also shown that the drug release rate, determined for both whole dose release and for single pellets, decreased with increasing thickness (from 16 to 51 μm) of the coating layer controlling the drug release rate.

1. Introduction

Oral drug delivery systems are often used in clinical practice. One common dosage form is the modified release film coated pellets containing a drug. Pellets have several biopharmaceutical advantages over coated tablets as they completely avoid dose dumping and have less variation in the total adsorption due to spreading of the small units in the gastrointestinal tract (Abrahamsson et al., 1996; Aulton, 2013). Applications of polymeric films onto solid cores have advantages like possibilities to tune the drug release rate, mask undesirable tastes, improve stability, and protect the drug from a surrounding environment (Aulton, 2013; Maroni et al., 2013; Kucera et al., 2013).

Cellulose derivatives have attracted a considerable interest in pharmaceutical technologies due to their nontoxicity, biocompatibility, biodegradability and possibilities to vary the chemical structure of the substituents, the molecular weight and degree of substitution (Saleh and Guigon, 2007; Mazoniene et al., 2011). Water-based latex dispersions of cellulose derivatives like ethyl cellulose, EC, can be used as coating materials in various industrial applications e.g. pharmaceutical, cosmetics, packaging and food (Siepmann and Siepmann, 2013; Varum et al., 2013; Ebnesajjad, 2013). The development of aqueous-based latex coatings of pharmaceutically acceptable polymers reduced environmental issues such as solvent toxicity or flammability and the need for solvent collection systems in production. Aqueous polymer dispersions can also be sprayed in higher polymer concentrations while keeping low viscosities and higher spray rates can be achieved reducing the coating time (Siepmann and Siepmann, 2013). The use of aqueous-based coatings, however, presents its own challenges to scientists with drug release rates depending on

* Corresponding author.
E-mail address: anette.larsson@chalmers.se (A. Larsson).

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the time, temperature and choice and amount of plasticizers used (Linda and Felton, 2008; Lecomte et al., 2004; Frohoff-Hülsmann et al., 1999). Therefore, many factors and parameters must be considered and controlled when aqueous coated formulations are developed.

The drug release mechanism can be driven by either diffusion through the coherent film or pores/cracks depending on the drug concentration gradient over the film or the osmotic flow depending on the osmotic pressure difference over the barrier (Hjärtstam, 1998). For highly porous organic solvent-based ethyl (EC) and hydroxypropyl (HPC) cellulose films the release mechanism is diffusion controlled (Marucci et al., 2013a). Osmotic pumping could also be the release mechanism for pellets coated with EC: HPC blends when the osmotic pressure inside the coating is much higher compared to outside the coating (Marucci et al., 2007). The release mechanisms through aqueous-based coatings can be both diffusion and osmotic pressure controlled release (Muschert et al., 2009; Ozturk et al., 1990). In many cases an indication of osmotic pressure driven release mechanism can be achieved by studying the drug release rate in an external release medium with different osmotic pressures, achieved by addition of sodium chloride, for example (Muschert et al., 2009).

The microstructure of aqueous-based coatings is expected to determine the drug release rate and an important factor controlling the microstructure is how the films are formed. The film formation mechanism has been examined widely in the literature and dispersion's transition into a continuous polymer film divided into three major stages: close packing of particles due to water evaporation from dispersion (drying); deformation of the particles (honey-comb structure) and polymer's chains diffusion between the particles, which controls the degree of film's coalescence (Keddie and Joseph, 2010; König et al., 2008). So far, water transport in free standing aqueous-based EC films has been measured as the uptake of water (Lecomte et al., 2004) (but not as water permeability) and only a limited number of microstructures of free films have been determined. The aim of this study was to determine (i) the permeability of water and Theophylline (a model drug) through aqueous-based ethyl cellulose (Surelease®) free standing films, and (ii) the release rate and mechanism of Theophylline release from Surelease® coated pellets.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose pellets (Cellets® 500, Syntapharm GmbH, Germany) with a size distribution of 500–710 μm were used as inert cores. Surelease® E-7-19020, an aqueous ethyl cellulose dispersion with 28% ammonium hydroxide and plasticizers dibutylsebacate and oleic acid (24.7% w/w, kind gift from Colorcon, USA) were used to make the controlled release coating layer. Theophylline anhydrous (Sigma-Aldrich, USA), hydroxypropylmethyl cellulose 5 cP (Colorcon, USA), sodium phosphate monobasic monohydrate, disodium phosphate, sodium chloride (Sigma-Aldrich, USA) and paraffinum solidum (pharmaceutical grade, Fagron, Netherlands) were used without further purification. Tritium-labeled water (37 MBq/g) (PerkinElmer, USA) was used as the penetrant in the water permeability measurements and scintillation cocktail Ultima Gold® Hisafe 3 was also supplied by PerkinElmer, USA. Milli-Q water was used in all experiments.

2.2. Characterization of Surelease® dispersions and preparation of free standing films

The size and ζ-potential of the particles in the Surelease® dispersion were measured (n = 3) by using a ZetaPALS Zeta Potential Analyzer (Brookhaven Instruments Corporation, USA). The stabilities of the dispersions were studied in sealed glass vials containing 2.5 mL of the dispersion. The vials were kept at 50 °C to mimic the temperature during the film formation process. Sedimentation of the dispersions was detected by daily visual inspections of the vials and documented by taking photographs of the dispersions over 15 days.

Free standing films were sprayed in a modified fluid bed coater (Marucci et al., 2013b; Larsson et al., 2010a; Andersson et al., 2013), Gandalf 2, at AstraZeneca, Mölndal, Sweden. The equipment's chamber has a horizontally moving spraying nozzle and a rotating Teflon cylinder (Ø = 67 mm, length = 98 mm), covered by Nitro tape (Four Pillars Enterprise Co., Ltd.). The flow speed of the fluidizing air (40 m^3/h), inlet temperature in the bed (50 °C), air pressure in the atomizer (2 bar) and spraying rate (4.3 g/min) were accurately controlled. Hydrophobic tape (Nitro tape) was placed on the drum before spraying for easier removal of the films afterwards. About 30 g of Surelease® dispersion with a dry content of 15% was used to prepare the films, giving an average film thickness of 118 ± 9 μm. The thickness was determined by a micrometer IP 54, Mitutoyo (Japan). The films were sprayed using 4.3 g/min at 50 °C for 8 min. Curing of the films was done on the drum for 6 min and in the oven at 50 °C for 24 h, then peeled off from the Nitro tape. The films were stored at room temperature in a desiccator between measurements.

2.3. Characterization of free films

2.3.1. Films exposed to water

Films were exposed to water and water soluble substances leaked out for 24 h at 37 °C, 350 rpm in Grant-bio Thermoshaker PHMP-4 (Grant Instruments Ltd., UK) (Andersson et al., 2013). Pieces (1 × 1 cm) were put into a 12-well cell culturing plate containing 5 mL of deionized water per well. The water was replaced twice during the experiment. After water exposure the films were dried at 8 °C using a vacuum at 1.3 mbar for 6 h in the

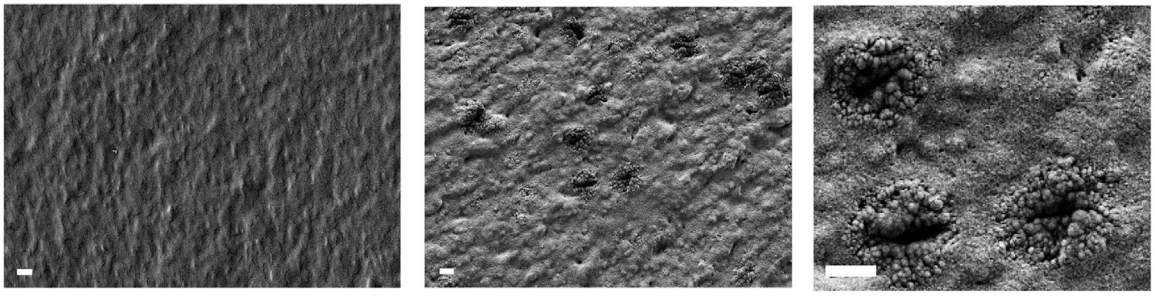

Fig. 1. SEM image of the cross-section of non-water exposed (left), water exposed (middle) and the view of individual latex particles around voids of water exposed (right) free standing ethyl cellulose films (scale bar is 1 μm).