Journal of Controlled Release 222 (2016) 151–158

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Characterization of pore structure of polymer blended films used for controlled drug release

Henrike Häbel [a,f,*], Helene Andersson [b,c,f], Anna Olsson [d,f], Eva Olsson [d,f], Anette Larsson [e,f], Aila Särkkä [a,f]

[a] Chalmers University of Technology and University of Gothenburg, Department of Mathematical Sciences, SE-412 96 Gothenburg, Sweden
[b] SP Food and Bioscience, Structure and Material Design, Box 5401, SE-402 29 Gothenburg, Sweden
[c] Chalmers University of Technology, Department of Materials and Manufacturing Technology, SE-412 96 Gothenburg, Sweden
[d] Chalmers University of Technology, Department of Applied Physics, SE-412 96 Gothenburg, Sweden
[e] Chalmers University of Technology, Department of Chemistry and Chemical Engineering, SE-412 96 Gothenburg, Sweden
[f] SuMo BIOMATERIALS, VINN Excellence Center, Chalmers University of Technology, SE-412 96 Gothenburg, Sweden

ARTICLE INFO

Article history:
Received 25 August 2015
Received in revised form 2 December 2015
Accepted 8 December 2015
Available online 11 December 2015

Keywords:
Pore shape
Permeability
Image processing
Porous material
Scanning electron microscopy

ABSTRACT

The characterization of the pore structure in pharmaceutical coatings is crucial for understanding and controlling mass transport properties and function in controlled drug release. Since the drug release rate can be associated with the film permeability, the effect of the pore structure on the permeability is important to study. In this paper, a new approach for characterizing the pore structure in polymer blended films was developed based on an image processing procedure for given two-dimensional scanning electron microscopy images of film cross-sections. The focus was on different measures for characterizing the complexity of the shape of a pore. The pore characterization developed was applied to ethyl cellulose (EC) and hydroxypropyl cellulose (HPC) blended films, often used as pharmaceutical coatings, where HPC acts as the pore former. It was studied how two different HPC viscosity grades influence the pore structure and, hence, mass transport through the respective films. The film with higher HPC viscosity grade had been observed to be more permeable than the other in a previous study; however, experiments had failed to show a difference between their pore structures. By instead characterizing the pore structures using tools from image analysis, statistically significant differences in pore area fraction and pore shape were identified. More specifically, it was found that the more permeable film with higher HPC viscosity grade seemed to have more extended and complex pore shapes than the film with lower HPC viscosity grade. This result indicates a greater degree of connectivity in the film with higher permeability and statistically confirms hypotheses on permeability from related experimental studies.

1. Introduction

Porous polymer blended films are often used as pharmaceutical coatings since they can provide a wide range of structures with different properties favorable for controlled drug release [1]. In order to understand and control mass transport properties like permeability, it is essential to characterize the pore structure within such films. While methods to experimentally study the porosity of a material have long been available [2], today's imaging techniques such as scanning electron microscopy (SEM) open up new opportunities to characterize the pore structure with more attention to details using tools from image analysis including, for instance, binarization and pore boundary detection [3,4]. These tools can be used to study porosity and pore shape. The pore shape, in turn, can be related to pore tortuousity and connectivity, which have previously been identified as important factors affecting mass transport and overall releasability of a drug [5]. Therefore, the development of appropriate image processing procedures to extract the pore structure and perform statistical image analysis of its detailed characteristics have become of large interest.

In this article, we statistically compare pore characteristics of blended films of two of the most common cellulosic polymers used in controlled release formulations, namely ethyl cellulose (EC) and hydroxypropyl cellulose (HPC). Such bio-based films are non-toxic, non-allergenic and have good film forming properties and stability [6]. Whereas EC is water insoluble, HPC is generally soluble in water or in the gastrointestinal tract at room temperature (0-solvent at about 41 °C) and can be used as a pore former [7]. The two polymers are dissolved in a common solvent, which evaporates during film spraying resulting in phase separation. In this way the film structure forms and the pores result from subsequent HPC leaching [8,9]. Hence, the HPC-rich domains serve as a template for pores and determine their size and shape. There are several factors influencing the formation of the pore structure of EC/HPC films such as film processing parameters [8], polymer blend composition [6] and polymer viscosity grade [10].

* Corresponding author.
E-mail address: henrike.habel@chalmers.se (H. Häbel).

http://dx.doi.org/10.1016/j.jconrel.2015.12.011
0168-3659/

In this study, a fixed polymer blend composition with 30% w/w HPC and two different HPC viscosity grades were used to produce two types of films. The polymer blend ratio was chosen to ensure that a percolating pore system forms, where the main release mechanism is diffusion through the pores. The choice was based on results from previously studied systems of EC and HPC [6] indicating that 30% w/w exceeds the critical HPC concentration for obtaining a connected, percolating pore network with channels going from one film side to the other. For films with HPC concentrations below the percolation threshold, micro-structural characteristics may be of less importance for drug release due to the possibility of a convective release process occurring through cracks in the film.

For the two films studied here, experiments on leakage of HPC indicated no prominent differences between the films, whereas a great differences in permeability was measured. The leaching experiments showed an expected high release of almost all HPC from both films confirming that the percolation threshold had been exceeded and that the porosities were similar. Hence, the results suggested that the pore shape is responsible for differences in permeability for the two films. However, mere visual inspection of microscopy images showed similar pore structures. That is why it was of great use to extract and quantify the pore structure and identify suitable pore characteristics in order to explain the difference in measured permeability.

The aim of this article is to present an image processing procedure to extract and analyze characteristics of porous materials. The pore characterization is used to draw general conclusions about the pore structure in EC/HPC films and its effect on permeability. Given two percolating pore systems with channels allowing for drug release by diffusion, we focus on the shape of a pore extending previous research on the pore size distribution [3]. As a result, our study has considerable potential to statistically prove what experiments failed to show, namely a difference between the pore structures of the two compared films.

2. Material and methods

2.1. Preparation of films

The two films investigated in this study were prepared by dissolving two cellulose derivatives in hydrous ethanol (95% v/v, Kemetyl AB, Sweden) at room temperature under stirring overnight. These polymer blended solutions contained 70% (w/w, dry basis) ethyl cellulose, EC, of viscosity grade 10 cps (29 10^3 g/mol, Dow Wolff Cellulosics GmbH, Germany) and 30% (w/w, dry basis) hydroxypropyl cellulose, HPC. HPC in two different viscosity grades, HPC-SL and HPC-L, were kindly provided by Nisso HPC, Nippon Soda Co. Ltd., Japan. The molecular weight M_w for the EC and HPC viscosity grades were determined by size exclusion chromatography as described by Andersson et al. [10]. Henceforth, the film with lower HPC molecular weight is referred to as SL film and the film with higher molecular weight as L film adopting the naming of pharmaceutical (viscosity) grades of Nisso's HPC. Details for both films are given in Table 1. The polymer concentrations of the solutions were chosen to be 6.5% w/w (EC/HPC-L) and 7.7% w/w (EC/HPC-SL) in order to have equal average viscosities of the solutions, which facilitates the use of similar processing parameters during spraying [10]. The blended polymer solutions were sprayed onto a rotating cylindrical Teflon drum with a moving atomizer nozzle in a modified fluidized-bed chamber at AstraZeneca R&D Mölndal, Sweden, following the procedures as described by Larsson et al. [11]. Before spraying, the center part of the Teflon drum was covered with a strip of plastic tape (Deer Brand, Four Pillars) to facilitate the film removal. After a drying time of about 50 min, the films were removed from the drum. As a consequence of the preparation, the films are relatively homogeneous in each sprayed layer, but inhomogeneous in the drum-to-air side direction showing periodic layers of different pore structures [8].

Table 1
Weight average HPC molecular weight M_w in 10^3 g/mol, average weight reduction in % w/w after HPC leaching and average water permeability in 10^{-10} m^2/s. Standard deviation is given within parenthesis. All averages are of three replicates, except the water permeability of the SL-film, which is of two replicates.

Film	HPC M_w	Weight reduction	Permeability
SL	55 (0.65)	28.12 (0.13)	0.42 (0.01)
L	83 (0.77)	28.92 (0.17)	1.30 (0.03)

2.2. Water permeability

In this study, the water permeability P of EC/HPC films was used as a measure of mass transport through their pore structure. In particular, the net transport of water from regions of relatively high concentrations c_1 to regions with relatively low concentration c_2 by random molecular motion in a thin film of thickness h was considered, such that

$$P = \frac{h}{A(c_1 - c_2)} \frac{\partial m}{\partial t}.$$

Here, A refers to the surface area of the film where mass transport occurs and $\frac{\partial m}{\partial t}$ denotes the mass transfer rate along the cross-section direction of the film [12]. Water permeability through the EC/HPC films was measured using radioactively labeled molecules, tritium-labeled water (Perkin Elmer Inc., USA) as the diffusant according to the procedure presented by Andersson et al. [10]. As Table 1 shows, the L film with higher molecular weight was about three times more permeable than the SL film even though the weight reduction after HPC leaching was almost the same for both films.

2.3. Data

The data analyzed in this study were two-dimensional field emission scanning electron microscopy (Leo Ultra 55 FEG SEM by LeoElectron Microscopy Ltd., Cambridge, UK) images of film cross-sections. Four about 2 mm wide and 1 cm long pieces from the central part of each film were extracted. The film pieces were embedded in epoxy-glue (Epoxy Rapid, Bostik) in 1.5 cm × 0.5 cm × 0.5 cm molds and the resulting stems of glue were cut in an ultramicrotome (Powertome XL, RMC products, Boeckeler Instruments Inc., Tucson, Arizona) to expose the film cross-sections. It should be noted that a smoothening effect of the exposed film surface morphology has been observed to occur as a result of the ultramicrotome cutting. The area fraction of the exposed surface corresponding to pores appeared to be reduced as a consequence of the cutting. However, the cutting was necessary to obtain flat surfaces suitable for the quantitative image analysis. The newly cut and smooth film cross-sections were exposed to water to allow HPC leaching and to reveal the pore structure in the films. The leaching procedure was done by mounting the glue stems, cross-sections side down, in a beaker with water (approximately 300 ml per film piece) under rigorous stirring for at least 24 h. The stems were attached to aluminum pin stubs using Pelco ® Colloidal Silver Liquid (TED PELLA INC.) with the exposed film cross-section surface facing up. Finally, the stub was coated with a thin layer of gold and examined in the SEM. From each of these cut film surfaces, three strips of the cross-section sufficiently far away from the edge of the film and at least 300 μm apart from each other were selected for microscopy and further analysis. All together 12 samples (image strips) from the SL and L films were taken. The pore structure from each of these $2 \cdot 4 \cdot 3 = 24$ strips was imaged by taking overlapping SEM gray-scale images of size 1024 by 691 pixels (ca. 37.9 × 25.6 μm) from where the film initially touched the Teflon drum (drum side) to the other side (air side). Fig. 1 gives an overview of the data setup.