Effects of Molecular Weight on Phase Separated Coatings for Controlled Release of Drugs

Helene Andersson[1,2,3], Mats Stading[1,2,3], Johan Hjärtstam[1,4], Christian von Corswant[1,4], and Anette Larsson[1,5]

[1] SuMo Biomaterials VINN Excellence Centre, Gothenburg, Sweden

[2] SIK – The Swedish Institute for Food and Biotechnology, Structure and Material Design BOX 5401, SE-402 29 Gothenburg, Sweden.

[3] Chalmers University of Technology, Dept. of Materials and Manufacturing Tehcnology, Gothenburg, Sweden.

[4] Astra Zeneca R&D Mölndal, Mölndal, Sweden

[3] Chalmers University of Technology, Dept. of Chemical and Biological Engineering, Gothenburg, Sweden.

ABSTRACT

Phase separated films with controlled porosity were made from ethyl cellulose (EC) and 30% w/w hydroxypropyl cellulose (HPC). The molecular weight of EC can be used to modify the mass transfer rate through coatings by effects on microstructure of the film. Processing conditions are, however, affected by the solution rheology, which could influence the film quality when using different molecular weights.

INTRODUCTION

Oral controlled release formulations often consist of drug pellets coated with insoluble membranes, which are intended to extend drug release in the gastrointestinal tract. Ethyl cellulose (EC) is a water-insoluble cellulose derivative commonly used for such coatings, but its permeability for most drugs is low[1]. In order to modify the release profile through EC coatings a water-soluble component, such as hydroxypropyl cellulose (HPC), can be added to the coating mixture. If the coating is exposed to aqueous liquids HPC could dissolve, leak out from the coating and cause pore formation in the coating through which the drug can be released[2].

The mechanical properties of the coating is important for drug release, i.e. for resistance of crack formation during the handling and tableting of pellets[3,4], as well as for withstanding stresses on the coating from water accumulation within the pellets[5]. However, the latter effect is more likely to affect drug release when the content of HPC in the EC-coating is low. Marucci et al.[6,7] found that above an HPC-content of 22% w/w drug release occurs predominantly though pores from HPC-leaching and this process reduces the pressure within the coating.

Another parameter that should be taken into account for films consisting of two polymers is the phase separation. During the coating of pellets a solution of EC, HPC and ethanol is sprayed onto drug cores in a fluidized bed[7]. Solvent evaporation during the coating process initiates phase

separation, which results in a structure of domains either enriched in EC or HPC[8,9]. If the HPC-rich domains are interconnected to both sides of the coating, they may serve as the template for the pores mediating drug release[9] (Fig. 1). The phase separated morphology of a coating could, thus, be crucial for the drug release rate as the shape of pores in porous systems is known to affect the diffusion rate[10].

The molecular weight of polymers is known to influence phase separation, through its effect on several parameters. For instance, an increasing chain length increases the free energy of mixing in polymer solutions and, thus, promotes phase separation[11]. However, greater complexities arise when dealing with polymer-polymer-solvent systems, such as EC-HPC-ethanol. Changing the molecular weight of one polymer can lead to substantial shifts and asymmetry of the two-phase area in the phase diagram[12]. On the other hand, phase diagrams only show equilibrium conditions. Thus, the slow dynamics of polymers in combination with rapid solvent evaporation would unlikely lead to equilibrium morphologies of the phase separated structures. Instead the phase separation process and domain coarsening proceeds until finally the coating microstructure is frozen by a high solution viscosity. It has been shown that if phase separation is allowed to progress to different stages in EC/HPC-films this will affect the film permeability[8].

We have studied the effects of EC molecular weight on the microstructure and mass transport properties through freestanding films in order to investigate its' potential use for the modification of drug release from pellets. The films used in this study contained 30% w/w HPC and are, thus, considered to be above the percolation threshold for substantial pore formation from polymer leaching.

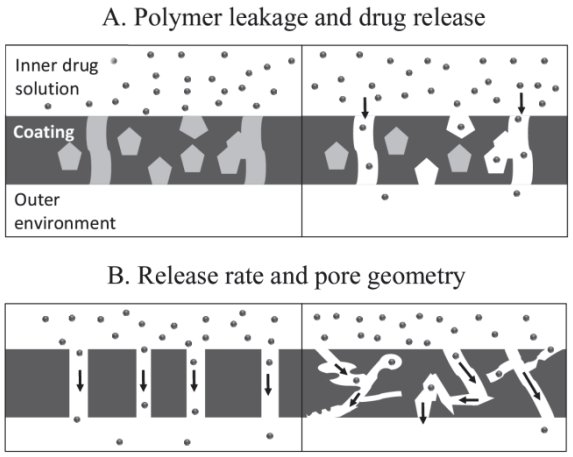

Figure 1. Schematic image illustrating pores formed from polymer leakage in a pellet coating (A) and how pore morphologies can affect the release rate (B).

MATERIALS AND METHODS

Different viscosity grades of EC (Ethocel™ Standard Premium, grades EC 4 cps, EC 20 cps, EC 100 cps) were kindly provided by DowWolff Cellulosics GmbH, Germany. HPC (Klucel® Pharm, grade LF, M_w=111·10^3) was from Aqualon, USA. The molecular weights of HPC-LF and the different EC grades used in films were determined with size exclusion chromatography with multi-angel light scattering and refractive index detectors (SEC-MALS/RI), described in detail elsewhere[13]. Results are presented with weight average molecular weights (M_w) of EC.

EC and HPC were co-dissolved in ethanol during stirring overnight. The polymer blend ratio was set to 70:30 w/w EC:HPC, but the total polymer content could differ depending on the type of film production process. Flow curves of the coating solutions were measured with a controlled strain rheometer ARES-G2 (TA Instruments, New Castle, USA) at shear rated of 0.1 s^{-1} to 1000 s^{-1} and back, using a concentric cylinder geometry (Cup: Ø=30 mm, Bob: Ø=27.7 mm).

Freestanding films were prepared by spray-coating a rotating Teflon drum in a

heated airflow of 72 °C. The outlet airflow was approximately 45 °C. Further processing parameters are found elsewhere[13]. Tritium-labelled mannitol was used to determine the permeability in a modified Ussing chamber. Experiments were performed in diluted mannitol solution (0.2 mM) at 37 °C and are described more thoroughly elsewhere[13].

Mechanical properties of sprayed films were measured with an Instron Universal Testing Machine model 5542 (Instron Coorporation, Canton, USA) at 23 °C and 50% RH. The films were conditioned in the same environment for 48 h prior to testing. The initial grip distance was set to 20-30 mm and the initial strain rate was 10%/min.

Cast films were prepared by adding 300µl polymer solution into a heated quartz cup with an inner diameter of 15 mm, followed by drying in an oven at 50 °C. The films were studied with a Leica TCS SP2 confocal laser scanning microscope (CLSM). Optical slices in the z-direction from the air-exposed surface and down the films were acquired every 4 µm. Staining was by Na-fluorescein (0.2 mM) added to the ethanol prior to polymer dissolution. Sprayed films were immersed in water during 24 h at 37 °C and dried for at least 72 h. The films were freeze fractured in liquid nitrogen, sputtered coated with gold and evaluated with a Leo Ultra 55 FEG scanning electron microscope (SEM) at 3 kV (LeoElectron Microscopy Ltd, Cambridge, UK).

RESULTS AND DISCUSSION

Microstructural effects from EC molecular weight and solution viscosity in cast films

Cast films were all prepared from 6% w/w polymer solutions and are shown in Fig. 2. The CLSM micrographs revealed phase separated structures with clear morphological differences between different molecular weights of EC used in the mixed EC/HPC-films[14]. The morphologies changed from bicontinous to HPC-discontinuous and the domain size decreased with increasing molecular weight. The domain size was also seen to increase with increasing depth of the film. This is an indication of later arrest of the phase separation process. Hence, larger domains are allowed to evolve at the bottom of the film where the viscosity is lower from higher solvent concentrations. It is possible that the trend in domain size with molecular weight stems from a similar mechanism.

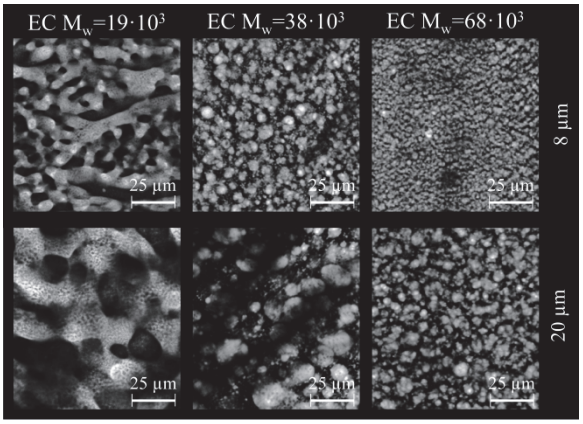

Figure 2. Phase separated structures of cast EC/HPC-films with different molecular weight grades of EC[14]. The HPC-rich phase is stained bright. The depth from the surface is indicated to the right. The total polymer content in the coating solutions used for films was 6% w/w. Mag.: 50X, scale bar: 25 µm.

Mechanical properties of EC/HPC-films

The mechanical properties of sprayed films are shown in Fig. 3. The elongation at break increased while the tensile strength reached a plateau with increasing molecular weights[13]. The mechanical properties of the mixed EC/HPC-films were, thus, improved with increasing molecular weight of EC. This indicates that high molecular weight EC/HPC-films could be better in resisting crack formation during handling and tableting of coated pellets. The importance of the mechanical properties during drug

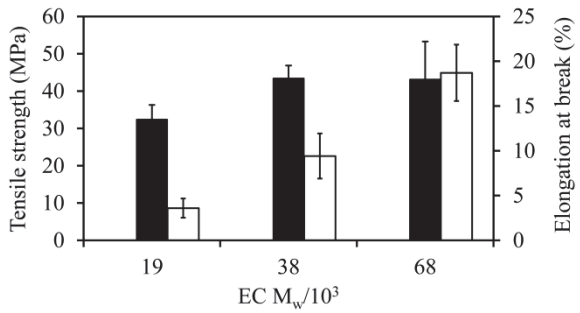

Figure 3. Tensile strength (black) and elongation at break (white) of sprayed EC/HPC-films with different molecular weight grades of EC. The total polymer content in the coating solutions was 6% w/w. n=5-7

release does, however, need further investigation. For instance, coatings with low molecular weight EC have been suggested to be more prone to form cracks and flaws during solvent evaporation in the coating process, which will affect drug release[15]. No such flaws were observed in the freestanding films.

Viscosity adjustment of spray solutions

Preparing films by spray-coating a rotating drum in a heated air-flow is a way to mimic the coating process of pellets. However, using different polymer molecular weights in the solutions give different rheological properties of the coating solutions. This can have profound effects on the processing conditions of the films. For instance, different solution viscosities can give different spray droplet sizes from the atomizer nozzle. In the coating of pellets, varying droplet size can either result in pellet agglomeration or excessive spray drying[16]. During spraying of freestanding films the result of too wet spraying conditions can sometimes cause drip from the drum, while too dry spraying conditions may result in a grainy, rough film from pre-dried spray droplets landing on the air-exposed film surface.

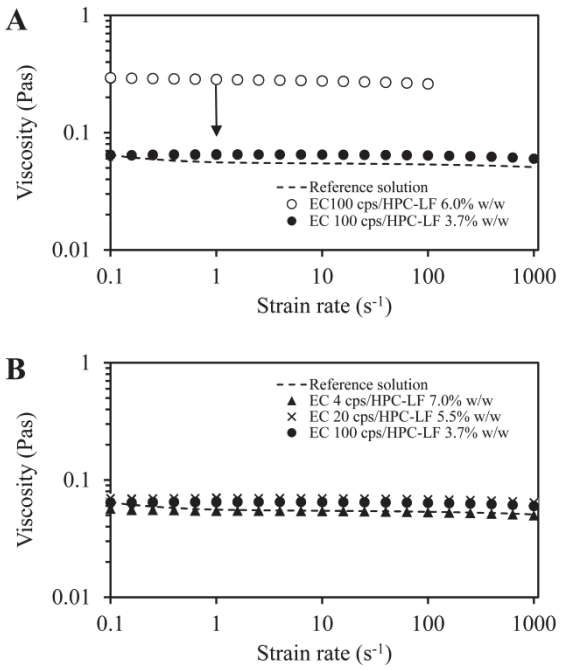

Figure 4. Flow curves of EC/HPC/ethanol-solutions. Example of a viscosity adjustment (A) by changing the polymer dry content from 6% w/w to 3.7% w/w for the solution containing EC 100 cps. Final flow curves (B) of solutions used for film spraying. In (A) the high polymer solution could only be measured accurately up to a strain rate of 100 s^{-1}. n=2

Since the same polymer content of high molecular weight solutions generally give greater viscosities than low molecular weight solutions, adjustment of processing parameters, such as inlet-temperature and pumping rate, could be needed to produce smooth films from different molecular weight polymers. The conditions for phase separation might then differ between the different manufacturing processes.

Adjusting processing parameters also complicates the pellet coating processes, as several test batches would be needed before a functional batch is produced. Thus, in order to be able to use similar processing parameters during film manufacturing the polymer dry content in the coating solutions were adjusted to give similar flow curves (see Fig. 4A). The resulting flow curves of

the solutions are shown in Fig. 4B. A total polymer dry content from 7.0% w/w to 3.7% w/w was, thus, chosen to prepare sprayed films. This allowed the same processing parameters to be used for the different films[13]. The resulting films all had a coherent smooth surface and were used for further investigations.

Microstructure-mass transport relation of sprayed films

The sprayed films were investigated in terms of the microstructure using SEM. Although the coating solutions were adjusted to give similar viscosities, the final film pore morphology differed for films of different EC viscosity grades (see Fig. 5A). In similarity with cast films, a trend of smaller pore structures was observed with increasing molecular weight of EC used in the coating[13].

The permeability (P) in the films of a model solute, i.e. mannitol, was determined with a diffusion cell using radioactive tracers[13]. The setup minimizes tensile stresses acting on the film. Any differences in permeability could, thus, be considered microstructural. Results showed that the permeability decreased with increasing molecular weight of EC (see Fig. 5B).

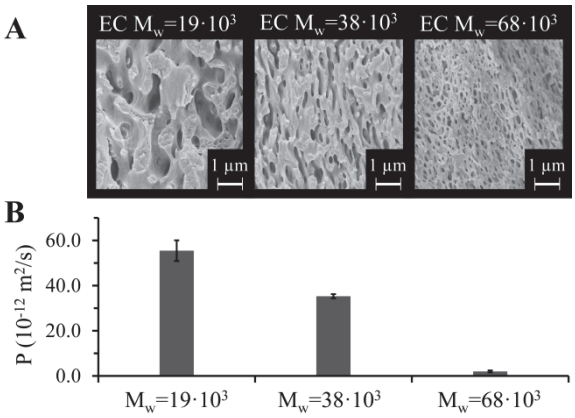

Figure 5. SEM-micrographs (mag.: 20 000X, scale bar 1 µm) of cross-sections of sprayed EC/HPC-films showing the internal pore structures (A). The permeability of mannitol (B) for the same films (n=2). The total polymer content in the coating solutions used for the films was 7.0%, 5.5% and 3.7% with increasing molecular weight, respectively[13].

CONCLUSIONS

The molecular weight in mixed cellulose derivative coatings can be used as a mean to modify the release rate from coated formulations. However, there exist at least three properties associated with deformation and rheology when creating mixed coatings from polymers of varying molecular weight. First, the coating solution viscosity and processing conditions are affected, secondly the molecular dynamics in the phase separation process is influenced and thirdly the mechanical properties of the final coating are affected. As a result, the mass transport through coatings of different molecular weights could be affected by the microstructure of the coating, as well as the film quality and resistance to crack formation.

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