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Structure evolution of phase-separated EC/HPC films for controlled drug release

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Structure evolution of phase-separated EC/HPC films for controlled drug release

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ABSTRACT

Porous phase-separated ethylcellulose/hydroxypropylcellulose (EC/HPC) films are used to control drug transport out of pharmaceutical pellets. The drug transport rate is determined by the structure of the porous films that are formed as the water-soluble HPC leaches out. In industry, the pellets are being coated using a fluidized bed spraying device, and layered films with varying porosity and structure are obtained. A detailed understanding of the formation mechanisms of the multilayered phase-separated structure during production is lacking. Here, we have investigated EC/HPC films produced by spin-coating, which mimics the industrial manufacturing process in a reproducible and well-controlled manner. This work is aimed to understand why the film structure is layered, and why it exhibits different porosities and structures by understanding the film formation mechanisms. The 2D and 3D structures of the EC/HPC films were characterized using confocal laser scanning microscopy (CLSM), scanning electron microscopy (SEM), focused ion beam SEM (FIB-SEM) and image analysis. The thickness of the films was measured by profilometry.

To be able to understand the multilayer formation, we first studied the structure evolution in EC/HPC monolayer films. The effect of the EC/HPC ratio (from 15 to 85 wt% HPC) on the in-plane and cross-sectional structure evolution was determined. Bicontinuous structures were found for 30 to 40 wt% HPC and discontinuous structures were found for the fractions 15 to 22 and 45 to 85 wt% HPC. The growth of the characteristic length scale followed a power law, $L(t) \sim t^n$, with $n \sim 1$ for bicontinuous structures, and $n \sim 0.45$ - 0.75 for discontinuous structures. An image analysis method to characterize the time-dependent 2D curvature evolution was developed. Two main coarsening mechanisms could be identified: interfacial tension-driven hydrodynamic growth for bicontinuous structures and diffusion-driven coalescence for discontinuous structures. The cross-sectional structure evolution shows that during shrinkage of the film, the phase-separated structure undergoes a transition from 3D to nearly 2D structure evolution along the surface. The shrinkage rate was found to be independent of the EC/HPC ratio. A new method to estimate part of the binodal curve in the ternary phase diagram for EC/HPC in ethanol has been developed. For multilayer films, the results showed that the inherent behaviour of the monolayer films have a strong impact on the formation of each new layer in multilayer films. A gradient in structure size with larger structures close to the substrate and smaller structures close to the air surface was found and explained by the redissolution of the layers already deposited during previous deposition cycles. By varying EC/HPC ratio during the multilayer film production, we showed *in situ* that the layers do not mix. By varying the spin speed every other layer, we produced a layered film exhibiting varying porosity, proposing a possible explanation for obtaining a layered coating in the industrial process. The findings of this work provide a good understanding of the mechanisms responsible for the morphology development and enable tailoring of multilayer EC/HPC films structure for controlled drug release.

Keywords: biopolymer, cellulose, coarsening, confocal laser scanning microscope, controlled drug release, drug delivery, electron microscopy, phase separation kinetics, phase separation mechanisms, porous film, spin-coating.