The importance of the molecular weight of ethyl cellulose on the properties of aqueous-based controlled release coatings

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A B S T R A C T

Previous investigations of aqueous based ethyl cellulose (EC) latex dispersions have mainly focused on the commercially available viscosity grade 20 cps. In this study, dispersions of EC with varying viscosity grades (which correspond to molecular weights), ranging from 4 to 100 cps, were produced and characterised. The dispersions showed particle sizes around 200 nm and highly negative ζ-potentials (approx. −100 mV), which indicated stable dispersions as confirmed by sedimentation studies. The different latexes were used to produce free-standing film coatings. We hypothesised that the different viscosity grades of EC would result in different properties of the films. We found that an increase in viscosity grade (and higher molecular weight) resulted in lower coalescence between the particles during film formation and thus to higher water permeability than in film coatings of lower molecular weight. After exposure to water the EC 4 cps and 20 cps film coatings had a more porous structure in the side facing the air during production and drying after immersion in water. Molecular weight is therefore a factor that should be considered when producing pharmaceutical coatings for controlled release.

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1. Introduction

Polymer film coatings for the controlled release of a pharmaceutical drug are traditionally done either by dissolving the polymers in organic solvents or by using aqueous-based polymer dispersions (also known as latex) (Wesseling and Bodmeier, 1999). The coating in both cases is formed as the organic solvent, or water in the case of a latex suspensions, evaporates. In recent years, the acceptability of organic solvents in pharmaceutical coating processes has decreased because of economic, environmental and health issues (Siepmann and Siepmann, 2013). Instead, interest in aqueous-based latex systems for pharmaceutical controlled-release applications increasing, because of direct advantages offered by the use of non-organic systems, which reduce the problems such as toxicity, flammability, residual solvents and solvent collection. Aqueous-based latex systems also allow higher solid drug loadings, lower spraying viscosities, and higher spray rates (Wesseling and Bodmeier, 1999; Siepmann and Siepmann, 2013). The major drawback using aqueous-based latex

system is the variation of drug release upon storage, which is closely connected to the film formation mechanism (Siepmann and Siepmann, 2013).

The film formation mechanism of a latex-based coating differs largely from that of polymers dissolved in organic solvents. In the case of the dissolved polymer, the solution undergoes a solid to gel transition, followed by a continuous film formation as the solvent evaporates (Porter, 1989; Siepmann et al., 2008). However, the film formation of latex particles is more complex (Steward et al., 2000; Siepmann et al., 2006) and there are several theories aiming to explain this (Keddie, 1997; Felton, 2013; Dillon et al., 1953). Dillon's theory (1953) includes two stages: evaporation followed by particle deformation (Dillon et al., 1953). Today, the most accepted theory involves three stages (Wesseling and Bodmeier, 1999; Siepmann and Siepmann, 2013; Keddie, 1997). In stage I, water droplets containing latex particles are sprayed onto a substrate on which the concentration of latex particles increases as the water evaporates. This stage is often the most time-consuming and lasts until the polymer has reached approximately 60% to 70% of the volume fraction (Steward et al., 2000). Stage II starts when the particles come into irreversible contact, which often results in a decreased evaporation rate, allowing for improved close-packing of the particles. In Stage II the particles also start to deform and

coalesce. Stage III is characterised by the final formation of a homogenous film as the last water molecules leave the film via diffusion. In this last stage, the polymer chains begin to interdiffuse (a process often referred to as maturation, autohesion, or further gradual coalescence), which gives the final film its mechanical strength (Steward et al., 2000; Keddie, 1997).

Routh and Russel have developed two dimensionless parameters to describe the mechanism of particle deformation (Routh and Russel, 1999). The first parameter, λ, is defined as the ratio between the time for deformation of the particles and the time for evaporation of the water. In this case, factors such as the film thickness, viscosity, particle radius, evaporation rate, and interfacial tension will affect λ. The second parameter that could describe the mechanism is the Peclet number, Pe, which is defined as the ratio between particle diffusion and time of drying, where parameters such as particle radius, evaporation rate, film thickness, temperature, and viscosity are important. It should be noted that the word *coalescence* is widely used with varying definitions (Keddie, 1997; Everett, 1988; Joanicot et al., 1990). In colloid science, the coalescence of the particles is often defined as the union of two particles through the reduction of their surface area by polymer interdiffusion between the latex particles driven by the reduction of the particles' surface (Everett, 1988). Joanicot et al. defined latex-based systems similarly, and stated that coalescence will not occur until the polymers within the particles are forced to come into contact as the solvent evaporates (Joanicot et al., 1990). The coalescence of the particles may be improved by adding plasticisers, which lower the glass transition temperature (T_g) and lead to increased mobility of the polymer chains during the coalescence (Bradford, 1952), but also contribute to more flexible films (Aulton and Taylor, 2013).

One of the most commonly used polymers for controlled release in aqueous-based coatings is ethyl cellulose (EC), a water-insoluble cellulose derivative (Rekhi and Jambhekar, 1995). Previous investigations of pharmaceutically approved aqueous-based EC dispersions have used an EC viscosity grade of 20 cps, commercially available as Surelease® and Aquacoat® (Wesseling and Bodmeier, 1999; Frohoff-Hülsmann et al., 1999; Parikh et al., 1993; Muschert et al., 2009; Hou et al., 2013). For example, Parikh and co-workers have shown that the drug release from a coating of Surelease® is affected by different process variables such as spray rate, inlet-air temperature in the fluid bed, and the solid content in the dispersion (Parikh et al., 1993). Due to the complexity of the film formation of water-based latex particles, there is a need for thorough investigations of parameters and factors that affect the characteristics of the final pharmaceutical coating. For example, it has been shown that the molecular weight of the polymer influences the controlled drug-release rate from pellets with a coating produced from an organic polymer solution (Marucci et al., 2013) and also decreases drug mobility due to increased polymer chain entanglements (Siepmann et al., 1999). In addition, previous work in our group has revealed that the molecular weights of EC are important for organic solvent- based coatings, where, for example, mixtures of hydroxypropyl cellulose and EC of different molecular weights gave different microstructures and permeabilities (Andersson et al., 2013). Molecular weight has also been shown to have an impact on polymer diffusion between latex particles (Wang and Winnik, 1993; Oh et al., 2003), but to our knowledge it is still unknown how molecular weight affects film formation from aqueous-based dispersions of EC for pharmaceutical applications.

The goal of this study was to investigate the film formation of dispersions of different molecular weights on a laboratory scale. One way to produce these aqueous-based dispersions of the water-insoluble EC is described in Fig. 1a–d. The first step involves the dissolution of EC (and a suitable plasticiser) in an appropriate solvent (such as acetone, which is mixable with water). When the acetone solution is added drop-by-drop to a beaker with water (as shown in Fig. 1a), the drops burst into several smaller drops because of the fast mixing (Jin et al., 2012) (see Fig. 1b). The acetone in these drop fragments is miscible and transported into the water, which increases the polymer concentration in the drops and causes the water-insoluble EC to precipitate (Fig. 1c), along with the plasticiser. The particle dispersion can be stabilised by addition of substances such as oleic acid, which can work both as stabilisers of the dispersion (when the dissociation occurs at high pH) and plasticisers.

The overall aim of this study was to evaluate the influence of the molecular weight of EC in a broad range of viscosities of EC (4 cps, 20 cps and 100 cps viscosity grades) on (i) the manufacturing process of the EC aqueous dispersions (ii) the characteristics of the EC dispersions (particle size, ζ-potential and sedimentation rate),
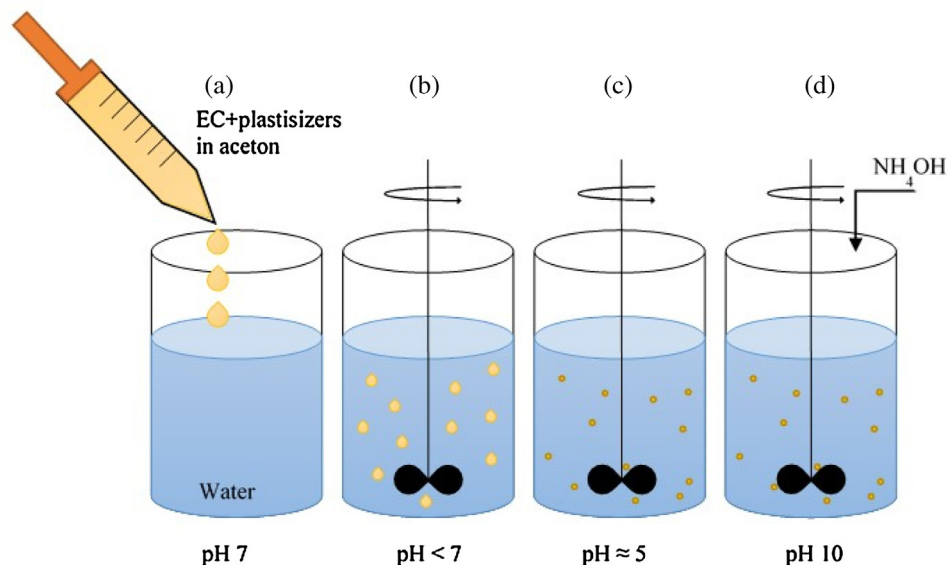

Fig. 1. EC latex dispersions where prepared by (a) the addition of dissolved EC to water at pH 7, followed by (b) implosion of droplets to smaller drops, whereby (c) the acetone dissolves in the water, which result in decreased EC particles and pH, and finally (d) the addition of NH₄OH to increase pH.