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A method for coating of hollow fiber membranes with calcium alginate

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ABSTRACT

We discuss how hydrophobic polyether sulfone hollow fiber membranes could be hydrophilized by surface coating them with natural hydrogel calcium alginate. The outer surface of the hollow fiber membrane was brought into contact with a solution of sodium alginate while calcium chloride solution was held within the lumen of the membrane. The divalent calcium ions diffused through the membrane pores and cross-linked the alginate, which formed a coating layer on the outer surface. The thickness of the calcium alginate layer could be controlled by changing the duration of cross-linking. The coated hollow fiber membrane samples were characterized by transmission electron microscopy (TEM). The increase in surface hydrophilicity was confirmed by water contact angle measurement. The hydraulic permeability of the coated membrane was higher than that of the uncoated membrane. The permeability of model solutes such as dimethyl sulfoxide (DMSO) and antipyrine was similar with both coated and uncoated membranes. Such hydrophilized hollow fiber membranes could potentially be used in membrane bioreactors and as scaffold for tissue engineering.

1. Introduction

Hollow fiber membranes have been widely used for biopharmaceutical purification and have significant potential for applications in the areas of mammalian cell culture and tissue engineering [1,2]. A typical hollow fiber membrane device consists of membranes arranged in the form of a bundle which is then housed within a shell-like module. This configuration provides a high surface area to volume ratio and therefore these devices could be used for continuous-perfusion based processes. Hollow fiber membrane bioreactors have been used for mammalian [3–7] and microbial cell culture [8], and for carrying out enzymatic reactions [9,10]. These devices have several advantages over static culture devices such as multi-well plates or T-flask in terms of better mass transport, and the potential to achieve high cell density through continuous nutrient addition and removal of toxic metabolites [11–13].

Despite these significant advantages, hollow fiber systems have not used to the extent to which the advantages discussed above would lead us to expect. In most hollow fiber devices, cells grow in the extra-capillary space, nutrients are provided from the lumen by diffusion through the membrane, while the metabolites diffuse from the extra-capillary into the lumen. Cells that are located at a large distance from the membrane have limited access to nutrients and oxygen, compared to those present close to the membrane pore. Therefore, there is a critical distance from the membrane surface, beyond which cells do not grow satisfactorily. If the hollow fiber spacing in devices exceeds that dictated by the above consideration, cells do not grow uniformly and there is poor utilization of reactor volume. Membrane fouling is another factor that poses a serious challenge in using hollow fiber devices for cell culture. Cells and biological macromolecules adhere very strongly to hydrophobic surfaces resulting in membrane fouling. However, such surfaces do not provide favorable conditions for cellular growth and consequently adhered cells synthesize structural polysaccharides to form an extracellular matrix which provides a better environment for cell growth and proliferation. The formation of extracellular matrix causes further membrane fouling which results in reduction in mass transport, and thereby a reduced supply of nutrients and simultaneous accumulation of toxic metabolites. This eventually results in necrosis of cells. Most hollow fibers made of synthetic polymers such as polysulfone (PS), polyvinylidene fluoride (PVDF), polypropylene (PP), polytetrafluoroethylene (PTFE), and polyethersulfone (PES) are hydrophobic. The use of hollow fiber devices is therefore largely restricted to applications involving cell culture for relatively short periods of time [14].

The surface of membranes can be made more hydrophilic by a variety of methods such as plasma treatment [15,16], hydrogel grafting, or coating [17–19], blend modification [20,21] and irradiation [22]. Some recent studies have focused on improving surface properties of hollow fiber membranes by coating hydrophilic biopolymers and biocompatible polymers. Ye et al. (2007) [14] used collagen for treatment of cellulose acetate hollow fibers for culturing fibroblast cells. Ellis and Chaudhuri (2007) [23] developed a poly(lactic-co-

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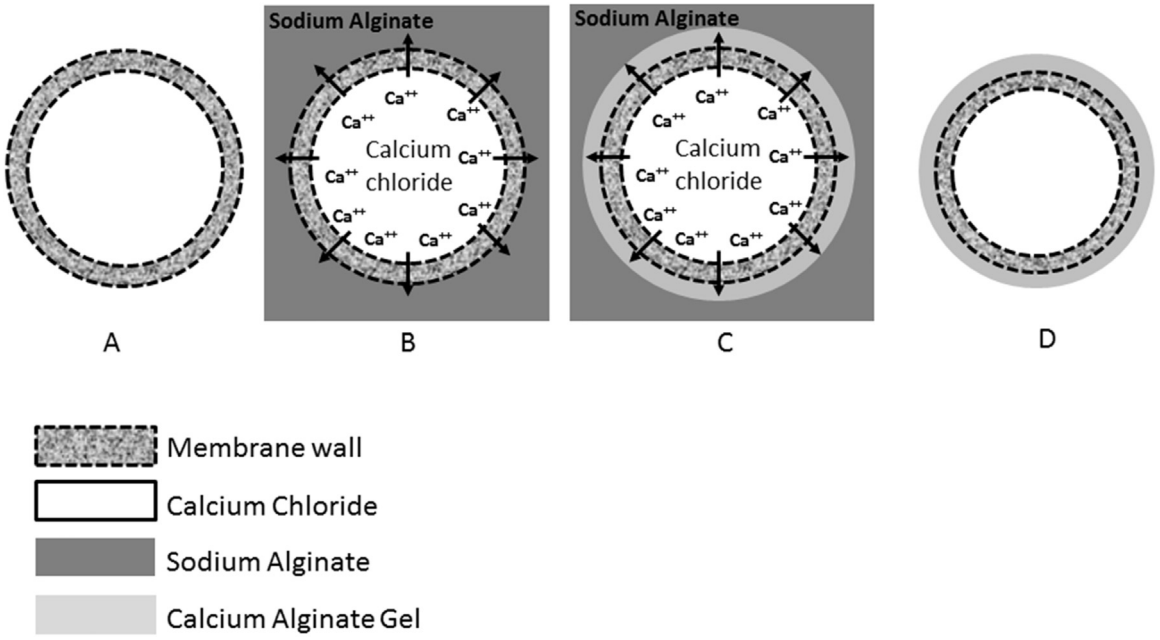

Fig. 1. Method for coating calcium alginate on ultrafiltration hollow fiber membrane (A: cross section of hollow fiber membrane; B: calcium chloride solution is introduced into the membrane lumen while the outer surface if exposed to sodium alginate solution; C: cross-linking of alginate due to the transmembrane diffusion of calcium ions; D: the cross section of coated hollow fiber membrane).

glycolic acid) (or PLGA) hollow fiber membrane that could be used in a bioreactor to enhances regeneration of bone tissues and provide an environment similar to the human circulatory system. Antwiler (2008) [24] demonstrated surface treatment of hollow fiber membrane with platelet lysate (PL), plasma, and fibronectin (FN) to make it more biocompatible. More recently Zhang et al. (2017) [25] modified PVDF hollow fiber membranes with carbon nanosphere sol to improve their anti-fouling properties. Dizon and Venault [26] have discussed *in-situ* modification of hydrophobic polyvinylidene fluoride (PVDF) membrane using a zwitterion copolymer to make it fouling resistant. Peyravi, et al. [27] have described how hydrophilic copolymers could be used to improve the surface properties of polyethersulfone (PES) ultrafiltration membranes. More recently, Shen, et al. [28] have discussed radiation grafting as surface modification method for PVDF membrane.

Sodium alginate is a natural polymer extracted from brown algae. It is a polysaccharide with (1 − 4)-linked β-D-mannuronate (M) and α-L-guluronic (G) residues, with the ratio and sequence of M and G depending on the extraction process [29,30]. The alginate can be cross-linked by divalent cations such as Ca^{2+}, Ba^{2+}, and Sr^{2+}, which link the G residues [31]. Calcium alginate is widely used for cell and drug encapsulation as it is hydrophilic, biocompatible, non-immunogenic and easy to cross-link [32,33]. Moreover, being a hydrogel, it is able to hold large volumes of water and is therefore used as extracellular matrix in wound healing and tissue engineering. In this paper, we discuss a simple method for coating calcium alginate on the outer surface of polyethersulfone (PES) hollow fiber membrane. By doing so, the hollow fiber membrane could be made more suitable to cell culture and tissue engineering applications. The change in surface properties of the membranes following alginate coating was evaluated based on water contact angle. The controllability of the coating process and the effects of process parameters on membrane coating were assessed. The main advantage of the proposed method is its simplicity. It involves no complicated chemical reactions such as polymer grafting or sophisticated physical techniques such as the use of radiation. The alginate layer is very easily coated on the membrane surface by immersing a calcium impregnated hollow fiber into a sodium alginate solution. This resulted in the crosslinking and deposition of the alginate layer on the outer surface of the hollow fiber membrane. The water permeability of the coated membrane was determined and compared with the uncoated membrane. The permeability of model solutes dimethyl sulfoxide (or DMSO), which is commonly used as a cryoprotectant to preserve living cells [34], and antipyrine, a model hydrophilic drug molecule [35] was compared. The coated membranes were also analyzed by light microscopy and transmission electron microscopy (TEM).

2. Materials and methods

2.1. Materials

Sodium alginate (W201502), antipyrine (A5882), and DMSO (D4540) were purchased from Sigma-Aldrich, St. Louis, MO, USA. Calcium chloride (C77–500) and ethanol (BP2818) were obtained from VWR, Mississauga, ON, Canada. Hydrophilic polyethersulfone (PES) hollow fiber membranes (Tetronic, 0.8 mm i.d., 1.2 mm o.d., 150 kDa MWCO) was kindly donated by Hydranautics Inc., Japan. All test solutions and reagents were prepared using ultra-pure water (18.2 MΩ-cm) obtained from a Diamond NANOpure water purification unit (Barnstead International, Dubuque, IA, USA), filtered just prior to use with Acrodisc® 25 mm syringe filter membranes (0.2 μm pore size, Pall Life Science, QC, Canada).

2.2. Methods

2.2.1. Alginate coating of hollow fiber membrane

Sodium alginate solution (1 wt%) was prepared in ultrapure water. Calcium chloride solution (0.1 M) which was used as the cross-linker was prepared in two solvents; water and 50% v/v ethanol in water. The alginate solution was allowed to stand for 24 h at 4 °C before use, in order to evenly disperse the sodium alginate and to remove entrapped air bubbles. Fig. 1 shows the steps involved in the coating process. The lumen of the hollow fiber membrane was first filled with the solvent (i.e. water or 50% v/v ethanol) for pre-wetting (Fig. 1A). The solvent was removed from the lumen and replaced with the corresponding calcium chloride solution (Fig. 1B). The external surface of the hollow fiber was patted-dry and the membrane was then placed in the sodium alginate solution (Fig. 1C). After cross-linking the alginate on the