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Does poly(vinyl alcohol) act as an amphiphilic polymer? An interaction study with simvastatin

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ABSTRACT

Simvastatin (SV) is a common drug, used for reducing LDL-C levels in blood. One of its drawbacks is poor solubility in water. This forces the use of large therapeutic doses, which enhances side effects. Poly(vinyl alcohol) (PVA) hydrogels have most of the desirable properties required as a matrix for dissolution and delivery of SV. The interaction between SV and PVA, in cryogel matrices, that leads to the enhancement of SV solubility was studied. From thermal analysis, it was found that upon increasing the amount of SV incorporated into PVA matrices, the degradation temperature of PVA decreases. This decrease is accompanied by a decrease in the melting temperature and in the corresponding melting enthalpy, as seen by differential scanning calorimetry (DSC), indicating that in the presence of SV, the PVA structure becomes more amorphous. Molecular dynamics (MD) studies show that the structure of PVA in water suffers changes in the presence of SV, such that the hydroxyl groups tend to move away from SV, allowing for a better interaction of the latter with the hydrocarbon chain, whilst hydroxyl groups interact with water molecules, suggesting an amphiphilic behavior of PVA. The interaction between SV and PVA is also confirmed by release kinetics to water-ethanol (1:1 v/v) and water. In conclusion, this brings new promising opportunities for using this polymer as a prolonged-release cryogel matrix suitable both for the entrapment and release of moderately or highly hydrophobic drugs into water.

1. Introduction

Simvastatin (SV), Fig. 1, is a long-established, although poorly water soluble, cholesterol-lowering agent, used in the treatment of hypercholesterolemia, dyslipidemia and coronary heart disease. It acts as an inhibitor of the 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, an enzyme which catalyzes the rate-limiting step in cholesterol biosynthesis [1,2]. In particular, when orally administered, SV, a lactone prodrug, is converted *in vivo*, in the liver and non-hepatic tissues, to the corresponding active β-hydroxy acid form (simvastatin acid, SVA), a potent competitive inhibitor of HMGCoA reductase [3]. This inhibition is mainly responsible for reducing low-density lipoprotein (LDL) cholesterol, but it has also been shown to reduce triglycerides and increase the high-density lipoprotein (HDL) cholesterol levels, although to a lesser extent. These are important properties that have been associated to the prevention of cardiovascular events in patients with high risk, and even low risk, of vascular disease [4,5].

Despite the numerous SV therapeutic actions [6–9], it exhibits low oral bioavailability due to its poor aqueous solubility and extensive metabolism by the cytochrome-3A (CYP3A) system in intestinal gut and liver, along with a short elimination half-life (1.9 h–3 h) [1,10]. This imposes the need of developing more effective delivery strategies.

Some hydrogels have been tested to overcome some of the drawbacks associated with the low simvastatin solubility. Kundu and Mati, were able to increase the solubility of SV by using cetyl gellan polymer taking advantage of its amphiphilic character and the ability to form micelles [11]. More recently, a SV solubility enhancement was reported by grafting of the drug to poly(methacrylic acid) followed by crosslinking with ethylene glycol [12]. Hydrogels are polymeric materials with a three dimensional network structure that can imbibe water, buffer or physiological solutions. They possess a high water content, have a soft and rubbery consistency and low interfacial tension towards water or biological fluids [13]. Among the polymers that show the ability to form hydrogels, poly(vinyl alcohol) (PVA) is of particular interest for various biomedical and pharmaceutical applications because of many desirable characteristics [14]. It is non-toxic, non-carcinogenic, shows bioadhesive characteristics and is easily processed [15]. PVA hydrogels exhibit a high degree of swelling in water, a rubbery and elastic nature and have demonstrated a great potential to act as a matrix for many

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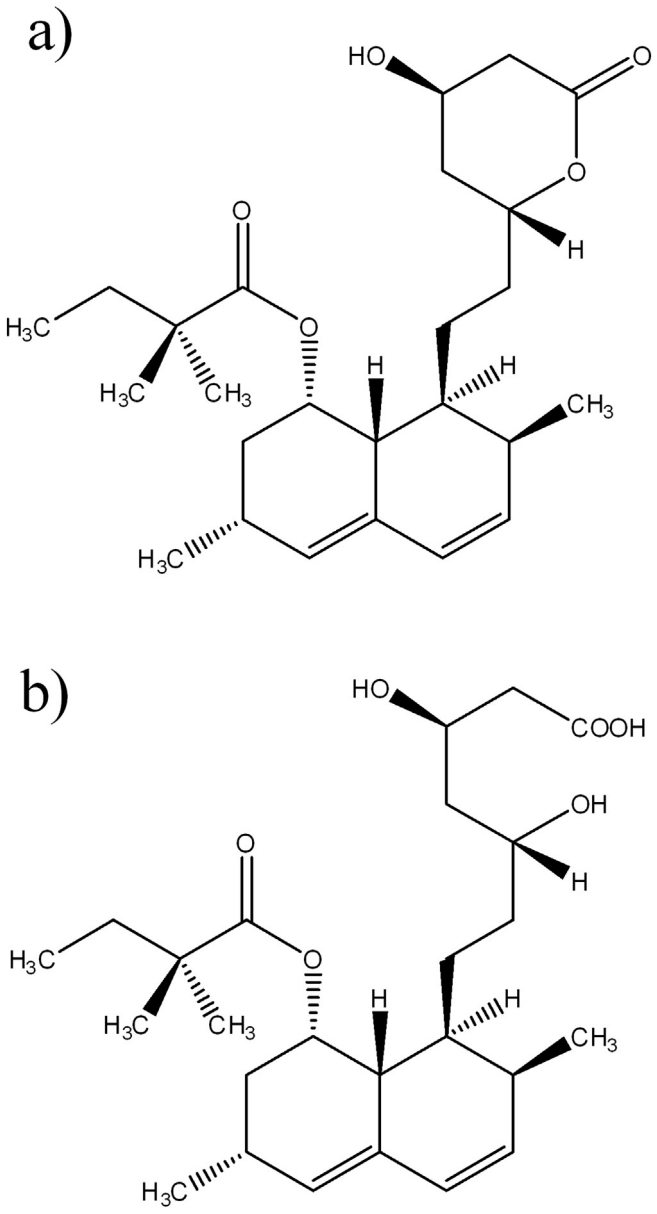

Fig. 1. Chemical structure of: a) simvastatin and b) its β-hydroxyl acid form.

applications, including drug delivery [16,17], wound dressing [18], sensors [19,20] and isomer differentiation [21,22].

In this paper, we report the synthesis and characterization of PVA-simvastatin cryogel matrices prepared using a freeze-thaw technique. This physical process addresses toxicity issues and leads to cross-linked gels with higher mechanical strength and elasticity than PVA hydrogels obtained by other methods [14,23]. Particular emphasis is given to understanding interactions, including the hydrophobic contribution and hydrogen bonding, between simvastatin and PVA, and the effect of these interactions and solvent polarity on the release kinetics.

2. Experimental

2.1. Materials

Simvastatin was kindly provided by Labesfal (Santiago de Besteiros, Portugal). Poly(vinyl alcohol), with an average molecular weight 72,000, a polymerization degree 1400 and a hydrolysis degree 98–98.8 mol%, was supplied by Fluka. Ethanol (99.8%) was supplied by Sigma-Aldrich. All reactants were used as received. All the solutions were prepared with Millipore-Q water.

2.2. Preparation of PVA – simvastatin cryogels

PVA solutions of 14% (w/v) were prepared by dissolving a known amount of the polymer into Millipore-Q water at 80 °C under continuous stirring for ca. three hours. After that, the PVA solution was allowed to cool naturally to room temperature. The entrapment of SV into PVA was achieved by dissolving a certain mass of the drug (10–40 mg) in 2 mL of PVA solution, under continuous stirring for 1 h. Simvastatin concentrations ranged between 5 and 20 mg mL^{-1}. The solutions obtained were cast in *Petri* boxes and submitted to a freezing process for 12 h at −20 °C and, subsequently, thawed for 12 h at 25 °C. The cycles of freezing and thawing were repeated three times. The resulting composite gel membranes show good mechanical resistance for handling and a white and opaque appearance caused by their heterogeneous structure [24].

2.3. Thermal, swelling and morphological studies

Membranes of PVA, previously loaded with SV, were weighed and immersed in solvent (water and water/ethanol). Samples were left immersed in the solvent for 1 week to attain equilibrium, and were then removed from the solvent and weighed, using an analytical balance (Scaltec SBC22, ±0.01 mg).

The swelling degree, *Q*, of the gel membranes in the solvents (water and water:ethanol (3:1 and 1:1 v/v)) was calculated from the weight of the membrane after the equilibrium has been achieved in a particular solvent (swollen gel, M_s) and the weight of the dried samples (xerogel, M_x) [25], using $Q = M_s / M_x$. Each swelling degree reported is an average of at least three independent measurements, with the standard deviation of the average swelling degree less than 8%.

Thermogravimetric analyses (TGA) of pure samples (PVA and SV) and composite gel membranes, prepared with different amounts of SV (10 and 20 mg mL^{-1}), were carried out on a thermo-microbalance thermogravimetric analyzer TG 209 F3 *Tarsus*®, from Netzsch Instruments. Samples (ca. 10 mg) were heated at 20 °C min^{-1} from 30 to 550 °C, under a nitrogen gas flow rate of 20 mL min^{-1}.

DSC measurements were performed using a Perkin Elmer power compensation calorimeter DSC7, with an intracooler cooling unit at −10 °C (ethyleneglycol-water, 1:1 (v/v) cooling mixture), 20 mL min^{-1} nitrogen purge and a scanning rate V = 10 °C min^{-1}. Temperature calibration [26,27] was performed with high grade standards, namely, biphenyl (CRM LGC 2610, T_{fus} = (68.93 ± 0.03) °C), benzoic acid (CRM LGC 2606, T_{fus} = (122.35 ± 0.02) °C), indium (Perkin-Elmer, *x* = 99.99%, T_{fus} = 156.60 °C), and caffeine (Mettler Toledo calibration substance, ME18 872, T_{fus} = (235.6 ± 0.2) °C). Enthalpy calibration was performed with indium ($\Delta_{fus}H$ = 3286 ± 13 J mol^{-1}).

The surface morphology of PVA-based composite membranes was analyzed using a ZEISS MERLIN Compact/VPCompact, Field emission scanning electron microscope (FDSEM). The membranes were submitted to a fast cryogenic treatment by diving gel samples into liquid nitrogen for 10 s, and left in a freeze dryer (Free Zone 4.5 – Labconco) for 12 h before coating with a gold film.

2.4. Molecular dynamics

Molecular dynamics simulations have been performed with the TINKER code (Version 6.2, February 2013) [28,29] using its internal OPLS-AA [30] force field implementation [31]. New atom types were not included and no changes in partial charges have been considered. For the fused ring of simvastatin, bending and torsion force constants were not available, and have been considered as zero. The choice of this force field is validated by comparing obtained geometries with X-ray and ab initio results. Using the present model force field, the geometries obtained of the most stable configurations are within 0.63 Å of the