International Journal of Pharmaceutics 466 (2014) 211–222

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Application of density functional theory in combination with FTIR and DSC to characterise polymer drug interactions for the preparation of sustained release formulations between fluvastatin and carrageenans

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ARTICLE INFO

Article history:
Received 28 February 2014
Received in revised form 28 February 2014
Accepted 28 February 2014
Available online 06 March 2014

Keywords:
Density functional theory
Fluvastatin
Carrageenans
Polymer–drug complex
Sustained release

ABSTRACT

In the present study, ι- and λ-carrageenans were used as appropriate carriers for sustained release formulations of fluvastatin drug. From viscosity measurements, it was found that both carrageenans can give miscible blends with fluvastatin due to the interactions between the sulfate groups of carrageenans and hydroxyl groups of fluvastatin. This was predicted by computational analysis using density functional theory and proved by FTIR spectroscopy. These interactions, which are in higher intensity using ι-carrageenan, lead to the formation of complexes between polymeric matrices and fluvastatin drug. DSC experiments also confirmed that miscible blends between carrageenans and fluvastatin can be formed since in all concentrations only one glass transition temperature was recorded. Fluvastatin release depends on the drug content and in all formulations of λ-carrageenans containing 10, 25 and 50 wt% drug, almost sustained release profiles were observed. Fluvastatin/carrageenan complexes have lower dissolution profiles compared with physical mixtures. Polymer swelling seems to be the dominant drug release mechanism. Besides to neat ι- and λ-carrageenans, their blends can be also used as effective matrices for sustained release.

1. Introduction

Hydrogels are a class of materials consisting of hydrophilic polymers that have the ability to hydrate, swell -presenting a three dimensional structure- and/or dissolve in aqueous environment. In addition to their good biocompatibility, hydrogels have many biomedical applications, especially as drug carriers (Yamada et al., 2012; Chen et al., 2012; Epstein-Barasha et al., 2012; Nuhn et al., 2012; Nanaki et al., 2012). There are two kinds of biodegradable polymers which have been used for preparation of hydrogels: synthetic polymers, like poly(acrylic acid), poly(*N*-isopropylacrylamide), methacrylates etc. and natural polymers, like chitosan, 2-hydroethyl strarch, dextran, gelatin, carrageenans, etc. Carrageenans are sulfated galactans extracted from red seaweed. They are composed of D-galactose residues linked alternately in 3-linked-β-D-galactopyranose and 4-linked-α-D-galactopyranose units and they are classified according to the degree of the substitution that occurs on their free hydroxyl groups to ι-, κ- and λ-carrageenans. The presence or absence of the anhydro bridges in their chemical structure leads to different rheological behaviors; ι-carrageenan has the ability to form gels, whereas λ-carrageenan acts as a thickener/viscosity agent (van de Velde and De Ruiter, 2005).

Carrageenans, alone or as mixtures with other polymers, were found to be effective carriers for drug applications especially for the preparation of controlled release formulations. For example, polymeric matrices based on ι-, κ- and λ-carrageenans or their blends, prepared either by simple mixing or by the solvent evaporation technique, have been tested for controlled release delivery of tolterodine l-tartrate (Nanaki et al., 2010). Grenha et al. reported the preparation and characterization of protein-loaded nanoparticles obtained by ionic complexation of chitosan and carrageenan as a valuable drug delivery system (Grenha et al., 2010). Pavli et al. investigated the interactions between doxazosinmesylate – a cationic drug- and carrageenans of different types (ι-, κ- and λ-) and found that drug release depends on the strength of interactions (Pavli et al., 2011). Fastest release was observed with the weakest binding. Dorozynski

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http://dx.doi.org/10.1016/j.ijpharm.2014.02.049
0378-5173/

et al. investigated the effects of carrageenans, and hydroxypropylmethylcellulose (HPMC) on the properties of hydrodynamically balanced systems using L-dopa as a model drug (Dorozynski et al., 2011). They found that the application of carrageenans in mixtures with HPMC, promotes water uptake by the formulations and that there is a linear increase in the releasing rate constant, *K*, with the carrageenan content in the matrix. Kulkarni et al. prepared interpenetrating polymer network (IPN) matrices of sodium alginate and carrageenan, loaded with propranolol-HCL by wet granulation leading to amorphization of the drug (Kulkarni et al., 2011). The pure drug propranolol-HCl showed rapid and complete dissolution within 60 min, while drug release from IPN tablets was prolonged over 18 h.

The aim of the present study was to use carrageenans and their blends in order to prepare sustained release formulations of fluvastatin drug. Fluvastatin is a statin; a drug used for the treatment of hypercholesterolemia, a disease related to an increased risk of heart diseases (Shitara and Sugiyama, 2006). Statins act as inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is a main enzyme in the regulation of cholesterol biosynthesis. In our previous studies, poly(propylene succinate), poly(vinyl pyrrolidone), eudragit RS100 and chitosan were used as drug carriers in order to evaluate their effect on fluvastatin release rate and stability during storage (Papageorgiou et al., 2009; Bikiaris et al., 2009). It was found that different polymer matrices produce completely different dissolution profiles. Chitosan/fluvastatin formulations led to controlled release profiles, while in the other cases immediately release formulations were prepared. In the present study, carrageenans have been chosen as effective carriers for fluvastatin, since it has already been reported that theoretically they can form hydrogen bond interactions with ι- and λ-carrageenan reactive groups (Papadopoulos and Sigalas, 2011). These interactions could lead to stabilization of fluvastatin drug during storage as well as to prepare sustained release formulations.

In the present investigation, physical mixtures of fluvastatin and ι-/λ-carrageenans as well as their formed complexes were studied aiming in preparing sustained release formulations. The physical properties, formed interactions and dissolution profiles of all formulations were evaluated.

2. Experimental

2.1. Materials

Carrageenans such as Gelcarin GP-379NF (ι-carrageenan) and Viscarin GP-209NF (λ-carrageenan) are naturally-occurring families of carbohydrates extracted from red seaweed and were kindly supplied by FMCBioPolymer (Netherlands). Fluvastatin sodium (Flu), [R*,S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt was supplied by Biocom. All other materials and solvents used for the analytical methods were of analytical grade.

2.2. Preparation of fluvastatin/carrageenans mixture solutions for intrinsic viscosity measurements

Fluvastatin/carrageenans mixtures at different concentrations were prepared by mixing the appropriate quantities of the solutions of neat compounds. Each carrageenan was initially dissolved in distilled water at 80 °C forming a solution of 0.5% w/v concentration. Fluvastatin was dissolved in water forming also a solution of 0.5% w/v. Proper amounts of each solution (carrageenan and fluvastatin) were mixed preparing solution mixtures of Flu/ι-Car and Flu/λ-Car at weight ratios 0/100, 10/90, 20/80, 30/70, 40/60, 50/50 and 100/0 w/w. Mixtures of fluvastatin and ι/λ-carrageenans blends [Flu/(ι,λ-Car)], instead of neat carrageenans were also prepared at the same weight ratios. In each mixture the weight ratios of ι-carrageenan/λ-carrageenan were 10/90, 20/80, 30/70, 40/60 and 50/50 w/w. All these solutions were used for intrinsic viscosity measurements as will be described in Section 2.4.

2.3. Preparation of fluvastatin–carrageenans complexes

Fluvastatin as well as neat ι- or λ-carrageenans were dissolved separately in distilled water forming solutions 0.5% w/v in concentration. The two solutions (fluvastatin solution and one carrageenan solution each time) were mixed under gently stirring at room temperature. The excessive water was removed by centrifuging the solutions at 8000 rpm for 20 min. The supernatant liquid was removed while the solid was frozen at −4 °C and then freeze dried. According to this procedure carrageenan-drug complexes contained 10, 25 and 50 wt% of fluvastatin were prepared and used for drug release studies. The same procedure was followed to prepare complexes of fluvastatin and carrageenan blends (ι/λ-Car) containing 25 wt% fluvastatin.

2.4. Characterization of fluvastatin/carrageenans mixtures

2.4.1. Viscosity measurements

Intrinsic viscosity [η] of Flu/ι-Car, Flu/λ-Car and Flu/ι, λ-Car solutions was measured using an Ubbelohde viscometer at 30 °C in distilled water solutions. For each one mixture several concentrations were prepared like 0.1, 0.2, 0.3, 0.4 and 0.5 w/v.

2.4.2. Fourier transformation-Infrared spectroscopy (FT-IR)

FTIR spectra of the prepared materials in KBr tablets were obtained using a PerkinElmer FTIR spectrometer (Waltham, MA USA), model Spectrum One. The IR absorbance spectra were obtained in absorbance mode and in the spectral region of 450–4000 cm^{-1} using a resolution of 4 cm^{-1} and 64 co-added scans. All spectra presented are baseline corrected and normalized.

2.4.3. Differential scanning calorimetry (DSC)

A PerkinElmer, Pyris Diamond differential scanning calorimeter (DSC) (Waltham, MA USA), calibrated with indium and zinc standards, was employed. A sample of about 10 mg was used for each test, placed in scaled aluminum pan and heated to 150 °C at a heating rate of 20 °C/min. The sample was held at that temperature for 5 min in order to remove the moisture traces. After that it was quenched to −30 °C under nitrogen atmosphere and immediately scanned again to 150 °C at a heating rate of 20 °C/min.

2.5. Computational study of carrageenan/fluvastatin interactions

Density functional theory (DFT) full geometry optimizations of the studied molecules and dimers have been carried out using the Gaussian 03W suite of programs (Frisch et al., 2003). The hybrid B3LYP method was applied with Becke's three-parameter functional (Becke, 1993) and the nonlocal correlation is provided by the LYP expression (Lee et al., 1988). The basis set used was 6–31G (Raghavachari et al., 1990; Frisch et al., 1984). In order to achieve a better description of the H-bond interactions, the basis set for the atoms of the groups potentially involved in H-bonds, that is hydroxyl group (OH) of fluvastatin, and the sulfate groups (—OSO_3) of ι- and λ-carrageenan model, has been augmented to 6–31G++ (d, p). Harmonic frequency calculations were performed for all of the optimized structures to verify that the stationary points found are real minima. In calculating the interaction energy in the hydrogen-bonded complexes, we accounted for the basis set superposition error (BSSE) by recalculating the monomer energies using the full dimer basis at the optimized geometry of the dimer using the counterpoise method (Rosenberg et al., 2000). Thus, the