J. of Supercritical Fluids 106 (2015) 16–22

Contents lists available at ScienceDirect

The Journal of Supercritical Fluids

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

Fast production of high-methoxyl pectin aerogels for enhancing the bioavailability of low-soluble drugs

Gabrijela Tkalec, Željko Knez, Zoran Novak*

University of Maribor, Faculty of Chemistry and Chemical Engineering, Smetanova 17, SI-2000 Maribor, Slovenia

ARTICLE INFO

Article history:
Received 5 February 2015
Received in revised form 6 June 2015
Accepted 8 June 2015
Available online 25 June 2015

Keywords:
Pectin
Aerogel
Ethanol gelation
Nifedipine
Supercritical adsorption
Drug loading

ABSTRACT

Aerogels are outstanding materials with high porosities, low densities and large surface areas. Moreover, polysaccharide aerogels e.g. pectin aerogels, are gaining interest due to their biodegradability and biocompatibility, which makes them interesting materials for medical, pharmaceutical or food applications. In this research we propose a new method for the gelation of high-methoxyl pectin. In later continuation those aerogels will be proposed as carriers to enhance the dissolution of poorly soluble drugs. Nifedipine was used as model drug. The aim of the research was to investigate two methods for the drug loading; first by adding the drug during the sol–gel process and second by supercritical adsorption. By the novel gelation method, the overall aerogel production time was shorter. In addition, prepared aerogels possessed highest yet reported surface area for high-methoxyl pectin monolithic aerogels, namely around 390 $m^2\ g^{-1}$. Drug loading during the sol–gel process was higher (22%), however also supercritical adsorption gave comparably good results (13%) according to the low solubility of nifedipine. Nifedipine release was controlled over 12 h and 100% (60 mg) drug release was achieved in this period.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Pectin is a polysaccharide found in abundance throughout nature. It makes up about one third of the cell walls of higher plants. Its highest concentrations can be found in the middle lamella of the cell wall [1]. Pectin attracts interest mostly because of its gelling and stabilising abilities. Therefore, it is mainly used in food applications [2–5] but lately also gaining interest regarding pharmaceuticals [6–8] and other applications [9,10].

The chemistry of pectin has been reported in several review papers and books [1,11,12]. Pectins are usually divided into two groups according to their degrees of esterification (DE). Low-methoxyl (LM) pectins have DEs of less than 50% and high-methoxyl (HM) pectins the opposite. LM pectins form gels in the presence of divalent ions. The mechanism of gelation is the egg-box model. HM pectins gel with sugar and acid, and the mechanism is the partial dehydrations of the pectin molecules.

The work reported here focused on high-methoxyl pectins. As reported in the literature, those pectins form gels at pHs lower than 3.6 and in the presence of cosolute. Cosolute is usually sucrose at concentrations greater than 55% by weight. As reported by Oakenfull and Scott [13], ethanol, dioxane or *t*-butanol may be used instead of sucrose. They proved that the addition of dioxane weakens the hydrophobic interactions but small concentrations of ethanol or *t*-butanol strengthen the hydrophobic interactions.

The drying step should be performed after obtaining the wet gel. Indeed, hydrogels or alcogels are unstable in dry air conditions and therefore their real-life applications are very limited. In order to retain most of the structure of the wet gel, the drying step should be performed under supercritical conditions [14]. The obtained materials are termed as aerogels and they usually possess large surface areas and high porosities.

In this paper aerogels were used for improving the technological characteristic of the poorly water-soluble calcium antagonist nifedipine. Nifedipine is a calcium-channel blocking agent. It is used for the treatment of angina pectoris and hypertension. According to the Biopharmaceutics Classification System (BCS), nifedipine is a typical Class II drug due to its low solubility and high permeability. As nifedipine has very low solubility in water, its oral bioavailability is very low. Improvement of this drug's solubility is of high interest as diseases such as angina, asthma and epilepsy require immediate drug responses. Enhancing the dissolution of nifedipine is therefore one of the main factors for obtaining the desired oral

* Corresponding author. Fax: +386 2 2527 774.
E-mail address: zoran.novak@um.si (Z. Novak).

http://dx.doi.org/10.1016/j.supflu.2015.06.009
0896-8446/© 2015 Elsevier B.V. All rights reserved.

bioavailability [15]. Moreover, controlling the release of this drug is highly desirable as it has been proved that long-term treatment results in decreasing blood pressure and achieving targeted blood pressures in patients with essential hypertensions [16].

This drug could be incorporated within the carrier during the sol–gel process or by supercritical adsorption, which is a relatively new method for incorporating drugs within aerogels under supercritical conditions. It is mainly used for poorly soluble drugs (such as nifedipine) that cannot be impregnated during the sol–gel process. In regard to those drugs supercritical adsorption has proved to be more effective than the traditional sol–gel method [17]. The drug should be soluble in supercritical fluid [18] and the carrier (aerogel) should have a high surface area designed for adsorption. Drug loading increases with increasing surface area and higher mesopore volume [19].

2. Chemicals

High-methoxyl pectin was kindly provided by Herbstraith&Fox, Germany. Ethanol (absolute) was obtained from Sigma–Aldrich. CO_2 (Messer) was used for supercritical drying. Nifedipine was obtained from Chemos GmbH. Hydrochloric acid and NaCl were obtained from Merck. KH_2PO_4 and NaOH was obtained from Sigma–Aldrich.

3. Aerogel synthesis

3.1. High-methoxyl pectin aerogel

High-methoxyl pectin monoliths were prepared by the sol–gel method. The pectin was weighted and then slowly poured into the mixing water in order to restrict the formations of clumps. The solution was further mixed until complete homogenisation. Then 10% v/v absolute ethanol was added to the solution. The solution was then transferred to an empty tablet mould, 1 mL in each. The mould was then sunk into absolute ethanol and the top layer of the solution gelled immediately. In order for complete gelation of the tablet-shaped monoliths (15 mm in diameter), these were left for 1 h in ethanol. Each step during the alcogel production was performed at room temperature.

Supercritical drying was performed within a 500 mL specially-designed autoclave. Its interior was divided into 3 volumetrically equal spaces; so three different batches could be dried at the same time under the same conditions. Supercritical drying was performed at 40 °C and 150 bar and additionally at 200 bar. After 7 h under these conditions, the reactor was slowly depressurized to ambient pressure and left to cool down. The materials obtained were of cylindrical/tablet shapes.

3.2. Drug loaded high-methoxyl pectin aerogel

3.2.1. Loading during the sol–gel process

The procedure was the same as described in 3.1. High-methoxyl pectin aerogel. 4% pectin solution was prepared and poured into a mould. Then the mould was sunk into ethanol, saturated with the model drug, nifedipine. Nifedipine is insoluble in water but slightly soluble in ethanol (1.7 g/100 mL). Therefore, the loading was performed over the same step as for gelation. After the mould had been sunk into the ethanol solution saturated with nifedipine, the pectin solution gelled and nifedipine diffused into the obtained monolith. First, the drug loading was performed for 1 h and additionally for 3 h in nifedipine–ethanol solution. The absorbance was measured after complete disintegration of the obtained alcogel in PBS. The absorbance and corresponding concentrations did not differ significantly with increasing times of drug loadings (49 mg L^{-1} and 51 mg L^{-1} for 1 h and 3 h, respectively). Henceforth the loadings of nifedipine onto polysaccharide monoliths were performed over 1 h. Then those drug-loaded alcogels were supercritically dried at 40 °C and 150 bar. The ethanol, used for supercritical drying was saturated with nifedipine to minimise the drug diffusion from the carrier. Each step in producing the drug-loaded HM pectin aerogel was performed either in complete darkness or under UV light due to the light-sensitivity of nifedipine.

3.2.2. Supercritical adsorption

Supercritical adsorption is a useful method for loading those drugs that are poorly water-soluble. The principle has been reviewed in the literature [20] and the method has been used for the adsorptions of different drugs such as ketoprofen [19,21–23], ibuprofen [19,24], miconazole [19,21] and others. Nifedipine is practically insoluble in water but slightly soluble in supercritical carbon dioxide. The solubility was measured at different pressures and temperatures [25].

The adsorption process was performed at 60 °C and 200 bar. Nifedipine was put into a filter bag and then placed at the bottom of the 500 mL autoclave and HM pectin aerogel above. (1:1 w/w). The autoclave was preheated to 60 °C and then slowly pressurized up to 200 bar. The materials were exposed to those conditions for 24 h. Then the system was slowly depressurized.

3.3. Analysis methodology

The surface areas, pore sizes and pore distributions of HM pectin aerogels were studied using low temperature nitrogen adsorption/desorption analysis. Prior to the measurements all the samples were degassed under reduced pressure (<1 mPa) at 70 °C for 10 h. Specific surface areas were then determined by the BET method. Pore volumes were determined by completely filling the pores with liquid nitrogen at $P/P_0 = 0.99$ and average pore size distribution was determined by the BJH desorption method.

Porosity was determined as the ratio between the volumes of the pores, as obtained from nitrogen adsorption measurements, and the total volume (solid + pores) calculated by Eq. (1).

$$\epsilon(\%) = \frac{V_{\text{pores}}}{V_{\text{total}}} \times 100 \quad (1)$$

Scanning electron micrographs of 4% pectin aerogel were obtained using a Sirion 400 NC scanning electron microscope (SEM). The samples were fractioned and then sputter-coated with gold particles and scanned at an accelerating voltage of 5 kV.

The thermal transitions were studied by a differential scanning calorimeter (DSC) within a N_2 atmosphere with 10 °C min^{-1} heating rate. DSC analysis was performed for studying the phase transitions, such as melting, glass transitions or exothermic decompositions. The analysis was performed on a HP DSC1 Mettler Toledo apparatus. The temperature range of the analysis was set at 20 °C–600 °C.

Additionally, XRD analysis was performed in order to determine the crystallinity of the loaded drug by both, ethanol diffusion and supercritical adsorption. XRD measurements were made on a D5005 diffractometer (Siemens–Bruker AXS).

3.4. Determination of the drug content

In order to determine the drug content in aerogels, the experiments were employed as already described [7]. Briefly, the drug-loaded aerogel samples were weighted and then placed in 100 mL of PBS. Then the solution was sonicated for 10 min and stirred for 6 h at 37 ± 0.5 °C until complete decomposition. Then 2 mL of solution was withdrawn and filtered through a Teflon

Download English Version:

https://daneshyari.com/en/article/230266

Download Persian Version:

https://daneshyari.com/article/230266

Daneshyari.com