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Characterisation of biodegradable pectin aerogels and their potential use as drug carriers

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ABSTRACT

The purpose of this work was to prepare stable citrus (CF) and apple (AF) pectin aerogels for potential pharmaceutical applications. Different shapes of low ester pectin aerogels were prepared by two fundamental methods of ionic cross-linking. Pectins' spherical and multi-membrane gels were first formed by the diffusion method using 0.2 M $CaCl_2$ solution as an ionic cross-linker. The highest specific surface area (593 m^2/g) that had so far been reported for pectin aerogels was achieved using this method. Monolithic pectin gels were formed by the internal setting method. Pectin gels were further converted into aerogels by supercritical drying using CO_2. As surface area/volume is one of the key parameters in controlling drug release, multi-membrane pectin aerogels were further used as drug delivery carriers. Theophylline and nicotinic acid were used as model drugs for the dissolution study. CF aerogels showed more controlled release behaviour than AF pectin aerogels. Moreover a higher release rate (100%) was observed with CF aerogels.

1. Introduction

The future of pharmacy is orienting towards a special category of therapeutics and diagnostics referred to as protein-based drugs. Currently most protein and polypeptide drugs are delivered into the body via a route other than the mouth, especially via infusion, injection or implantation, due to their high susceptibility to digestive enzymes in the gastrointestinal tract, and poor absorption. Formulations for other routes of administrations have to be developed in order to avoid constant injections. Namely, oral drug delivery is the more popular and convenient method for drug delivery. Therefore, new drug carriers for oral drug delivery could be synthesised for delivering drugs to the targeted locality (lower gastrointestinal tract). There is a wide-range of natural-origin polymeric biomaterials that can be used in oral drug delivery, such as proteins and polysaccharides. These natural biomaterials have been proved to be safe, stable, non-toxic and renewable, and have low costs because of their abundance in nature and ease of processing. Pectin as one of the naturally occurring polysaccharides that has become more and more important over recent years, as it is resistant to protease and amylase both of which are active within the upper GI tract, and is digested by micro-flora in the lower GI tract. Therefore, it could work as a drug vehicle from the mouth to the colon (Liu, Fishman, Kost, & Hicks, 2003).

Pectin by itself has applications throughout the pharmaceutical industry as it reduces cholesterol levels in blood (Sriamornsak, 2001). Pectin also acts against poisoning from toxic cations as it is namely capable of removing lead and mercury from the gastrointestinal tract and respiratory organs (Sriamornsak, 2001). When pectin is injected intravenously, it decreases the coagulation time of the blood and thus controls local bleeding. However, it also has the ability to naturally gel, thicken, and stabilise that has made pectin a very interesting carrier within the pharmaceutical and biotechnology industries.

The abilities of different pectins to form gel depend on their sources due to variations in parameters such as molecular sizes and degrees of esterification (DE) (Sriamornsak, 2003). Low ester pectins (LM) with DE of less than 50% require the presence of divalent cations for gelation by the well-known egg-box model. The obtained gel strength depends on the pectin's concentration, pH range, and the concentration of calcium ions. The resulting gels have brittle structures. LM amidated pectins, where ammonia instead of acids is used for de-esterification, require minor amounts of calcium ions for gelling. The degree of amidation is termed as DA.

Various pectin hydrogels and xerogels have already been prepared for drug delivery (Aydin & Akbuğa, 1996; Donato, Garnier, Novales, Durand, & Doublier, 2005; Itoh et al., 2007; Kubo, Konno, Miyazaki, & Attwood, 2004; Liu et al., 2003; Sriamornsak, 1998),

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but their instability under drying air conditions has led scientists to develop special coating materials for enhancing their lifetimes by several months or more instead of the current level of several hours. However, supercritical fluid technology using high-pressure and supercritical fluids is one of the more recent technologies that has been performed with the aim of preparing different biodegradable polysaccharide aerogels (Alnaief, Alzaitoun, García-González, & Smirnova, 2011; Boissière, Tourrette, Devoisselle, Di Renzo, & Quignard, 2006; Chang, Chen, & Jiao, 2008; García-González Carlos, Carenza, Zeng, Smirnova, & Roig, 2012; Mehling, Smirnova, Guenther, & Neubert, 2009; White, Budarin, & Clark, 2010). This technology is more advantageous in comparison with conventional processes. Firstly, it guarantees a better removal of organic solvents from products for medical or pharmaceutical applications without exposing drugs to high temperatures that may degrade them, especially when using protein drugs or enzymes. Dry and stable polysaccharide aerogels possess very high porosities and specific surface areas. As surface area/volume is one of the key variables in controlling drug release (Reynolds, Mitchell, & Balwinski, 2002), porous materials have attracted greater attention throughout the pharmaceutical industry. With the increasing surface areas of such nanoporous carriers, the drug could be absorbed and released in a more reproducible and predictable manner (Ahern, Crean, & Ryan, 2012; Andersson, Rosenholm, Areva, & Lindén, 2004; Charnay et al., 2004; Gren, Bjerre, Camber, & Ragnarsson, 1996; Li, Wen, Shao, & Chen, 2004; Streubel, Siepmann, & Bodmeier, 2002). Also the loading of a drug increases with increasing surface area.

Pectin aerogels by thermal and acidic gelation are already available in powder form (485 m^2/g) and as monoliths (200 m^2/g) (García-González, Alnaief, & Smirnova, 2011; White et al., 2010). In the presented research apple (AF) and citrus (CF) pectin aerogels as spheres and monoliths by cationic gelation were synthesised as a potential application for porous carriers in oral drug delivery. Amidations of galacturonic acids improves the gelation of LM-pectins, namely less calcium ions are needed and also a reduced possibility of precipitation is achieved at a high calcium concentration. Therefore, LM amidated pectins were used for the sol–gel synthesis.

2. Experimental

2.1. Materials

The pectin samples used were low-methoxyl citrus (DE = 23–28%, DA = 22–25%) and apple (DE = 27–32%, DA = 18–23%) pectins kindly provided by the Herbsteith & Fox KG company from Germany. The pectin solutions were prepared using distilled water. 0.2 M calcium chloride ($CaCl_2$) was used for ionic cross-linking by the diffusion method. Sodium hexa-metaphosphate $Na(PO_3)_6$ and dicalcium phosphate ($CaHPO_4$) were used when the internal setting method was applied for cross-linking. Glucono-δ-lactone was used for pH adjustment. Ethanol (100%) was used for solvent exchange prior to supercritical drying with CO_2. KH_2PO_4 aqueous solution was used for the phosphate buffer, 0.2 M NaOH was used for pH adjustment. HCl and NaCl were used for the preparation of simulated gastric fluid (SGF). The active substances, nicotinic acid and theophylline, were obtained from Sigma–Aldrich and Acros Organics, respectively.

2.2. Methodology

2.2.1. Preparation of pectin gel

Two methods of cationic cross-linking were used in the presented research, resulting in different gel shapes (Fig. 1). Ionically cross-linked hydrogel multi-membrane spheres were obtained by using the diffusion method. Solutions of 2% w/w pectin solutions were prepared by dispersing apple (AF) or citrus (CF) pectin into distilled water. Spheres were then produced by ionotropic gelation using a syringe pump and a needle of 0.80 mm inner diameter. The pectin solutions were dropped into a 0.2 M $CaCl_2$ solution under constant agitation. Gelled spheres were cured within the solution for 1 h, then separated by filtration and washed with distilled water. Further spheres were dropped one by one into 1% apple or citrus pectin solution filtered through a sieve and dropped into the cross-linking solution for 5 mins. Three-membranes' hydrogels were obtained by repeating the above process three times. After obtaining hydrogel, the alcogels were formed by solvent exchange. The hydrogel spheres were dehydrated by immersion within a series of successive ethanol–water baths of increasing alcohol concentrations (10, 30, 50, 70, 90 and 100%). If 100% ethanol were to be added immediately, the structure of the gel may be affected. Ethanol was later removed by supercritical drying with CO_2 (100 bar, 40 °C) which has been described elsewhere (Novak & Knez, 1997). Particle size distribution was determined by sieve analysis.

When the second ionic cross-linking by the internal setting method was applied, firstly 1% w/w or 2% w/w pectin was added to 15% EtOH solution. The prepared solutions were later mixed for 2 h at ambient temperature. Then $Na(PO_3)_6$ (1.5%w/w) was added, the mixture was stirred for 30 min and only heated up to 40 °C in the case of the used citrus pectin. Further $CaHPO_4$ was added followed by mixing for 60 min (Eq. (1)) following the addition of glucono-δ-lactone solution to reduce pH. The resulting mixture was quickly poured into cylinder moulds and left covered overnight to solidify in a refrigerator. The yielded monoliths were left in one piece or cut into smaller pieces and dehydrated by immersions in a series of successive ethanol–water baths of increasing alcohol concentrations (15, 30, 60, 90 and 100%) every hour until the equilibrium of gel shrinkage had been reached. The procedure for obtaining aerogels after gel synthesis was then the same as for spherical multi-membrane gels. By using the internal setting method the gel casting process was controlled by a chelator ($Na(PO_3)_6$) and an initiator ($C_6H_{10}O_6$). The chelator and Ca ions react with each other and form a three-dimensional network (Eq. (2)). The addition of glucono-δ-lactone slowly decomposes the complex, calcium ions are released (Eq. (3)), and the gelation process occurs (Akhondi, Taheri-Nassaj, Sarpoolaky, & Taavoni-Gilan, 2009).

$$\text{Pectin} + Ca^{+} \rightarrow \text{Ca-pectin} \quad (1)$$

$$6PO_3^{-} + 3Ca^{2+} \leftrightarrow Ca_3(PO_3)_6 \quad (2)$$

$$Ca_3(PO_3)_6 + 3C_6H_{10}O_6 \leftrightarrow 6HPO_3 + 3Ca^{2+} + 3C_6H_8O_6^{2-} \quad (3)$$

2.2.2. Preparation of drug loaded spherical aerogels

In order to test the release properties of pectin spheres, theophylline and nicotinic acid pectin hydrogels were prepared according to the same protocol as for pectin multi-membrane spheres. Model drugs, nicotinic acid and theophylline, were added to pectin solutions at the beginning of the preparation during the sol–gel process, respectively. Spheres were cross-linked with Ca^{2+} ions. The inner surfaces between the core and membrane or between two membranes were filled with the model drug. Both model drugs were chosen due to their solubility in H_2O, ethanol and supercritical CO_2. The solubility of nicotinic acid in water is 1.67 g/100 mL at 25 °C, in ethanol 0.73 g/100 mL at 25 °C and in supercritical CO_2 1.4×10^{-6} (mole fraction) at 100 bar and 40 °C. The solubility of theophylline in water is 0.76 g/100 mL at 25 °C, in ethanol 0.35 g/100 mL at 25 °C and in supercritical CO_2 0.5×10^{-6} (mole fraction) at 100 bar and 40 °C. The further process for obtaining aerogels was the same as described above, including immersion of hydrogels within a series of excessive ethanol baths and later supercritical drying.

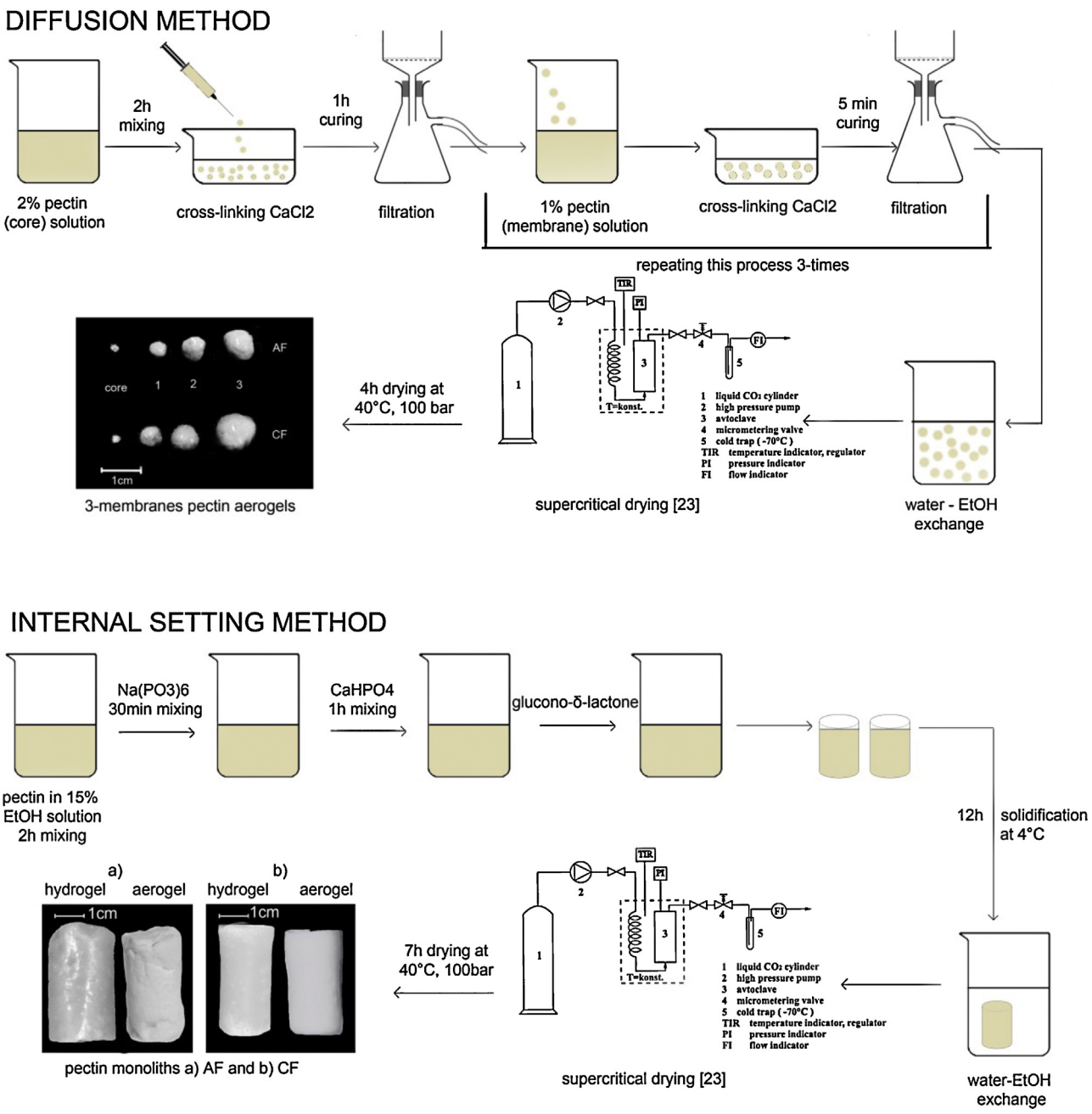

Fig. 1. Schematic presentation of gelation methods and obtained products.

2.2.3. Swelling studies

Swelling studies were performed by incubating the known amount of LM multi-membrane aerogel in 40 mL of either simulated gastric fluid (SGF) at pH 1.2 or phosphate buffer at pH 6.5, mimicking the conditions of the gastrointestinal tract. The experiment was performed for one sample each of AF and CF aerogels, cross-linked with 0.2 M $CaCl_2$. After the known period of time the gel samples were removed from the solution, blotted dry with tissue paper, and weighed. At least three measurements were carried out for each sample in each solution. The swelling ratio was calculated according to Eq. (4):

$$\text{Swelling ratio} = \frac{M_t}{M_0}, \tag{4}$$

where M_t is the mass of the swollen gel monolith after time t and M_0 is the initial mass of the dry aerogel monolith.

2.2.4. Drug loading

In order to determine the drug loading, the drug loaded aerogel sample was pounded and mixed with phosphate buffer solution. After 10 min of sonicating and 6 h of stirring at 250 rpm and $37 \pm 1\,^{\circ}C$, the solution was filtered through a TEFLON 0.45 μ filter and the amount of a drug was determined spectrophotochemically using a Varian, Cary 50 Probe UV spectrophotometer. Loading efficiency (LE) of theophylline and nicotinic acid was calculated by Eq. (5), assuming complete drug extraction:

$$\text{LE} = \frac{m_d}{m_s} \cdot 100\%, \tag{5}$$

where m_d is the mass of the drug (mg), obtained by UV analysis and m_s is the initial mass of the weighted aerogel sample. Each test was made in triplicate.

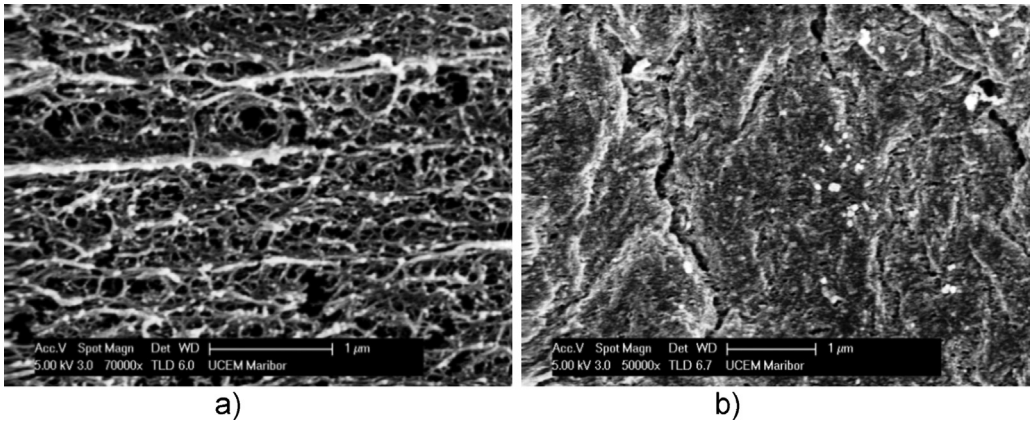

Fig. 2. SEM images of AF pectin (a) membrane and (b) spherical core.

2.2.5. Drug dissolution test

Dissolution studies of theophylline and nicotinic acid were performed in triplicate at 37 ± 0.5 °C by employing USP apparatus II (paddle) with a speed of 50 rpm (Model FARMATESTER-3, Dema-Ilirska Bistrica). The weighted amount of aerogel sample was placed in the cylindrical basket, immersed in a 900 mL buffer solution with pH 6.5 (simulating the conditions of the intestinal fluid), and left under stirring for 24 h. Aliquots (2 mL) of dissolution media were withdrawn manually using a 2 mL syringe at selected time intervals and passed through 0.45 μm membrane prior to analysis. The removed dissolution medium was replaced by the same amount of fresh buffer solution. All the samples were analysed using UV spectrophotometry (Model Varian, Cry 50 Probe spectrophotometer) at a wavelength of 262 nm and 272 nm for nicotinic acid and theophylline, respectively. Cumulated amounts released (in percentage of the initial amounts) were plotted vs. time.

2.3. Analysis

2.3.1. Scanning electron microscopy

The surface morphology of pectin aerogels was determined using a Sirion 400 NC scanning electron microscope. The samples were sputter-coated with gold particles and then scanned at an accelerating voltage of 5 kV.

2.3.2. Porosimetry

The total surface area and the porosities of the pectin aerogels were measured by nitrogen adsorption using a Micrometrics ASAP 2020MP porosimeter. Prior to analysis the weighed amounts of the samples were placed into the glass cells and outgassed at 70 °C for 660 min under a vacuum until obtaining stable 10 μm Hg pressure. Subsequently, the sample and the reference cells were immersed within the liquid nitrogen at −196 °C, and an absorption isotherm was obtained from the volume of nitrogen (cm^3/g) adsorbed onto the surface as a function of relative pressure. The total surface area was calculated by the BET method.

3. Results and discussion

3.1. Hydrogel synthesis and supercritical drying

The phenomena of the polymer gels were volume transitions as a function of their environment, induced by the temperature, pH or ionic strength (Osada & Gong, 1998). The principle of reversible volume contraction and dilatation was caused by reversible ionisation of suitable functional groups within the polymer networks. Shrinkage of the pectin hydrogel's structure after immersing in 100% EtOH did not appear, despite the presence of functional groups such as amide, carboxyl, and hydroxyl within the polymer network. The reason could be the higher mechanical strengths of pectin gels in comparison with some other organic gels such as alginate (Veronovski, Novak, & Knez, 2012). Fig. 1 displays both methods, used for preparing pectin aerogels. Spherical 3-membranes aerogels were obtained by the diffusion method. Fig. 1A shows the comparisons between the sizes of 3-membranes AF and CF aerogels, loaded with nicotinic acid. The sizes of the spherical aerogels were obtained by sieve analysis. The size of the AF 3-membrane aerogels was 8.0 ± 0.1 mm and CF 3-membrane aerogel 9.8 ± 0.2 mm. The difference in size could be due to differences in DE and DA between both pectins. The CF gels were mechanically more stable. The additional membranes were thicker, shrinkage of a gel was reduced and the final aerogel was bigger. When comparing the aerogel monoliths, prepared by the internal setting method (Fig. 1), the CF pectin aerogel looked lesser damaged and smoother. The sizes of the hydrogel monoliths in comparison with the aerogel monoliths were almost the same. Although the colours of the pectin hydrogels differed due to the origin of the pectin, in both cases the aerogel monoliths became white.

3.2. Characterizations of the spherical and monolithic aerogels

SEM imaging of the CF and AF pectin spherical and monolithic aerogels were performed for determine the influence of the cross-linking method and pectin type on the gel surface morphology. In the case of the spherical aerogels in Fig. 2, apparent differences could be observed between the membrane made of 1% and the spherical core made of 2% AF pectin solution. The surface of the sphere looked uniformly cross-linked and really dense in comparison with the surface of the membrane. The reason could be in the higher pectin concentration and also the longer period for cross-linking. Moreover, in the case of membranes, pectin also looked cross-linked in layer after layer.

Fig. 3 represents the SEM images of AF and CF pectin monolithic aerogel samples made from 2% pectin solution. It seems that by the internal setting method uniformly cross-linked aerogels were obtained irrespective of the pectin type. During the synthesis the Ca^{2+} ions had enough time to interact with the pectin chains and were cross-link slowly and in a controlled manner. If we compare Fig. 3A and B, it is difficult to observe any difference in the structures, only in the density. The explanation for the latter could be in the tiny difference between the DE and DA percentages.

We used a nitrogen adsorption/desorption assay to determine the structure of the obtained aerogels. Fig. 4A is the nitrogen

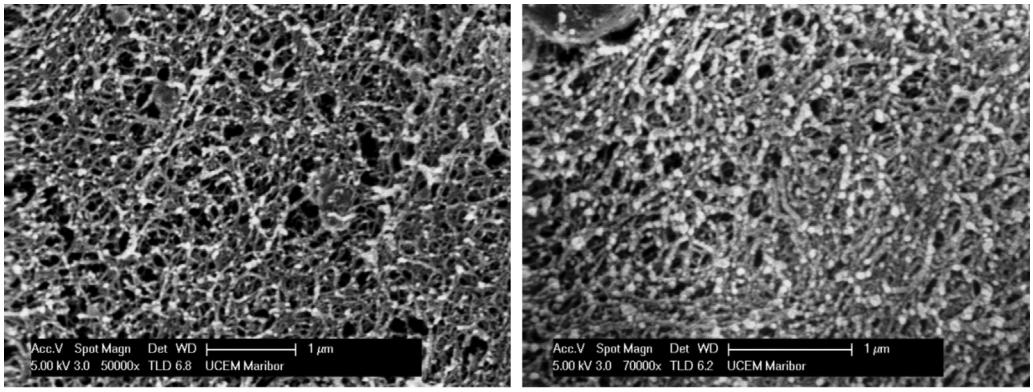

Fig. 3. SEM images of pectin (a) AF aerogel monolith and (b) CF aerogel monolith.

Table 1
Effect of the pectin type and concentration on the characteristics of the monolithic and spherical aerogel samples.

	Pectin (%)	S_{bet} of aerogel (m^2/g)	Overall pore volume of aerogel (cm^3/g)	Average pore diameter (nm)
Monoliths	2.0 (AF)	213.5 ± 2.0	0.339 ± 0.025	7.5 ± 1.5
	2.0 (CF)	248.9 ± 3.5	0.39 ± 0.02	7.4 ± 1.4
	1.0 (CF)	143.4 ± 0.5	0.214 ± 0.09	7.2 ± 1.3
Multi-membranes	Membrane 1.0 (AF)	515 ± 9	0.95 ± 0.07	8.7 ± 1.6
	Sphere 2.0 (AF)	469 ± 7	1.66 ± 0.02	15.2 ± 1.0
	Membrane 1.0 (CF)	593 ± 10	1.64 ± 0.03	12.0 ± 3.3
	Sphere 2.0 (CF)	544 ± 8	3.27 ± 0.03	26.3 ± 2.3

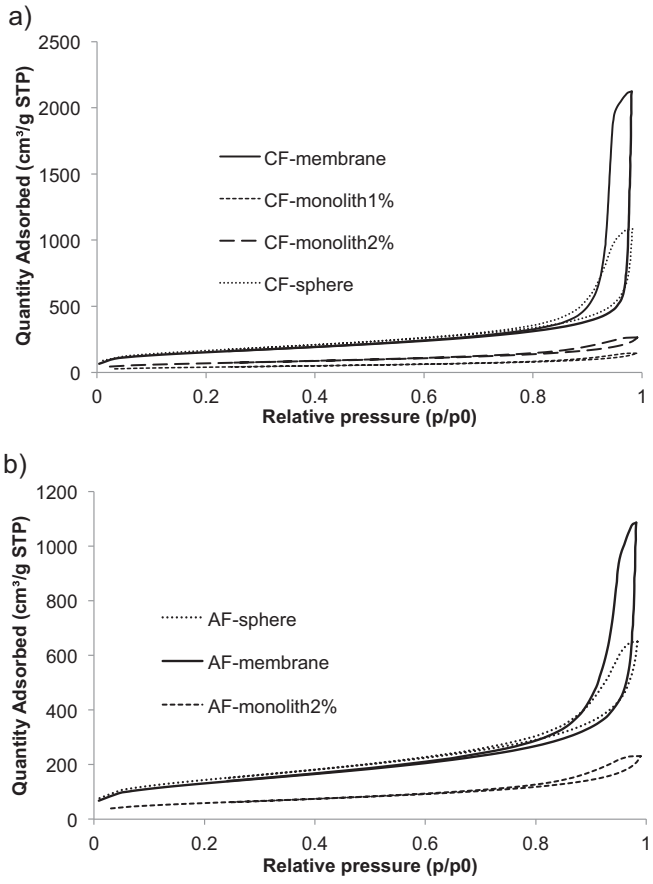

Fig. 4. N_2 adsorption/desorption isotherms for (a) AF and (b) CF pectin aerogels.

adsorption/desorption isotherm of the AF and Fig. 4B of CF spheres, membranes, and monoliths. The isotherms can be classified as type IV isotherms, characteristic of mesoporous materials. The porosimetric measurements in Table 1 present the effect of the pectin type with little difference between the DE and DA percentages and concentrations on the characteristics of the monolithic and spherical pectin aerogel samples. Pectin type CF showed higher specific surface areas and pore sizes in comparison with the AF pectin type. The reason could be in the differences between the DE and DA percentages. The CF pectin had lower DE and higher DA than the AF pectin which resulted in stronger and more uniform cross-linking. This affected the final structure of the gel and further provided more porous material. The results in this table also show that by increasing the pectin concentrations of the samples the CF specific surface area of the monolithic sample also increased. Specific surface areas and pore volumes were much higher in the cases of the spherical samples. Moreover, the obtained value for the specific surface area of the CF pectin membrane aerogel sample was the highest in comparison with all those previously reported from the other research groups (García-González et al., 2011; White et al., 2010). The reason could be in the method used for crosslinking. In previously reported work acidic and thermal gelations were proposed for obtaining porous pectin materials. The diffusion method thus seems to be the most promising method for obtaining high porous pectin aerogels. The average pore diameter for all the aerogel samples varied from 7.2 nm to 26.3 nm and was higher for the spherical samples. From the size of the pores as well as from type of isotherms, it could be concluded that all the pectin aerogel samples were mesoporous materials.

3.3. Swelling behaviour

Release of the drugs is influenced by the porosity of the aerogel and thus of the swelling (Betz, García-González, Subrahmanyam, Smirnova, & Kulozik, 2012). Swelling experiments were carried out at pH conditions mimicking those of the stomach (pH 1.2) and of

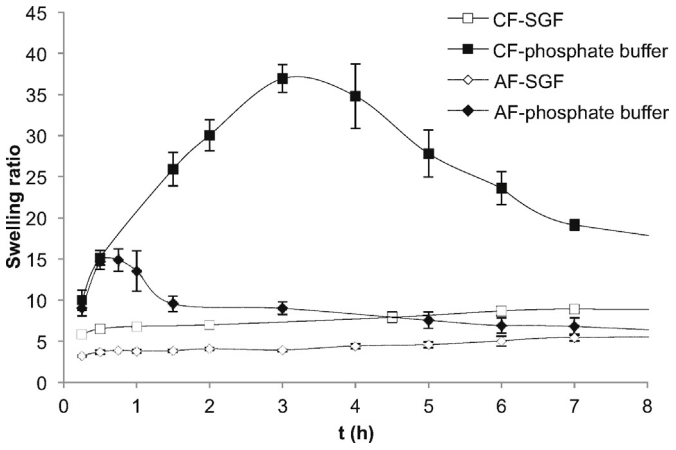

Fig. 5. Swelling ratio in aqueous buffers as a function of time of the aerogels prepared with 0.2 M $CaCl_2$ in SGF at pH 1.2 (open white symbols) and in buffer solution at pH 6.8 (closed black symbols).

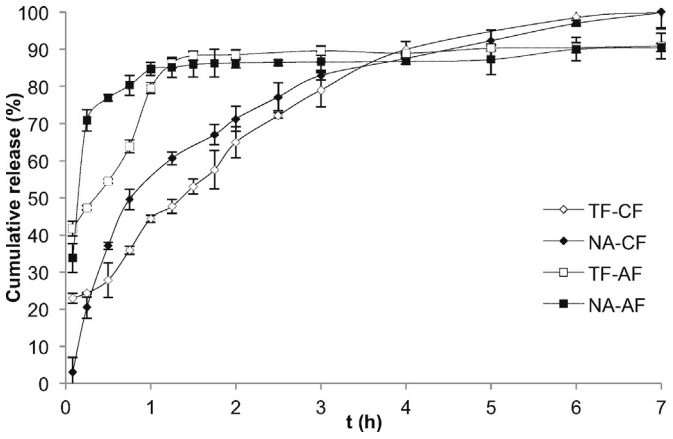

Fig. 6. Theophylline (TF) and nicotinic acid (NA) release kinetics for spherical multi-membrane aerogels using 0.2 M $CaCl_2$ for cross-linking (bars indicate SD, $n = 3$).

the colon (pH 6.5). Swelling ratio in SGF remained near constant over 8 h. In contrast the swelling of the pectin is strongly influenced by higher pH of the phosphate buffer leading to a degradation of the sample (Fig. 5). From these results it could be concluded, that CF aerogels are more stable materials as they stay resistant in a phosphate buffer for 4 h prior to degradation. AF pectin aerogels start to degrade after 30 min. This characteristic affect the release of active substances from the matrix, hence CF pectin aerogels are showing to be more promising carriers for active substances. Due to the resistances of both AF and CF pectin aerogels in SGF and their digestion in the phosphate buffer, those aerogels could be used as a drug vehicle from mouth to colon.

3.4. Drug loading

Aerogel samples were loaded with theophylline and nicotinic acid during the sol–gel process. The resulting loadings are shown in Table 2. The values reached for theophylline and nicotinic acid are slightly different within the same carrier. The reached drug fractions were within the same range for AF and CF aerogels, respectively. However, loadings for AF aerogels are slightly lower than those for CF aerogels, which could be a function of their slightly lower surface areas, as shown in Table 1. Higher loading of nicotinic acid in contrast to theophylline could be due to its higher solubility in water. During solvent exchange (water to ethanol and ethanol to $scCO_2$), the solutions were saturated with the drug to prevent diffusion from the carrier.

3.5. Dissolution of theophylline and nicotinic acid from multi-membrane pectin aerogels

During the dissolution test, nicotinic acid and theophylline were entrapped inside the multi-membrane aerogel, which strongly influenced the drug release due to the good solubility and high permeability of both model drugs at pH 6.5. Fig. 6 displays the dissolution profiles of theophylline (TF) and nicotinic acid (NA) from CF and AF pectin aerogels, cross-linked with 0.2 M $CaCl_2$. The addition of membranes affects the release of drugs. Burst release of the drugs occurs from single spherical aerogel. With the addition of membranes the drug is release in a more controlled manner. In addition higher drug loading is achieved (Veronovski, Knez, & Novak, 2013).

It is shown, that the CF pectin aerogels demonstrated better dissolution and more controlled release of both model drugs than AF pectin aerogels. Initial burst release of theophylline, non-ionic substance in initial 1 h, followed by slow and sustained drug release, was noted from both carriers. However, nicotinic acid as an ionic substance showed slower release. The obvious difference in release rate from both carriers can be seen from Fig. 6 as well as the impact of the type of model drug. When comparing the carriers, the release rate from CF pectin aerogel was 100% after 7 h and from AF pectin aerogel 90% for both model drugs. Moreover the initial burst release rate was noted from AF pectin aerogels. Furthermore the release rate was slowed down and remained near constant over the next 6 h until 90% of the release was reached after 7 h. The release rate from CF pectin aerogel was between 80–90% after more than 3 h. The same rate was reached by AF pectin aerogel after only 1 h, thus CF pectin aerogels provide more sustained drug release. Lower DE in CF pectin permits the enhancement of the pectin mass in the carrier which results in reduced drug release ability and longer degradation times of the spheres (Girod Fullana, Ternet, Freche, Lacout, & Rodriguez, 2010). These results can also be predicted by the swelling studies. AF pectin aerogel degraded in 1 h and CF pectin aerogel in 4 h. Degradation of the carrier leads to higher release rates. After the degradation the small amount of the substance which was left in the carrier, dissolved slowly until reaching 7 h. Both of the carriers showed prolonged drug release, most likely due to the presence of calcium ions in the buffer solution. This has been shown to enhance cross-linking and aggregation of the pectin chains (Sriamornsak, 1999) resulting in limited swelling and slower drug release from spheres. Choosing from amongst the structural properties of pectin as well amongst parameters in the sol–gel synthesis, such as concentrations of pectin and the cross-linker, carriers with varying properties can be made in order to achieve the desired dissolution profiles of the selected drugs.

Table 2
Loading of aerogels with drugs.

Type of aerogel	Theophylline (% w/w)	Nicotinic acid (% w/w)
AF	21 ± 0.6	25 ± 0.4
CF	33 ± 0.4	37 ± 0.8

4. Conclusion

In this research, biodegradable amidated low-methoxyl AF and CF pectin aerogels with different shapes and ionic cross-linking were produced and characterised. It could be concluded from the obtained results that those aerogels ionically cross-linked using the diffusion method exhibited higher specific surface areas in comparison with the monolithic ionically cross-linked aerogels obtained by the internal setting method. Moreover, the highest

specific surface area (593 m^2/g) of the spherical pectin aerogels was obtained, in comparison with the data reported by other research groups (García-González et al., 2011; White et al., 2010). As surface area/volume is one of the key variables in controlling drug release, different aerogel characteristics can be obtained by changing the types and degrees of DE and DA and the concentration of the pectin, thus influencing drug release. CF aerogels provided a better dissolution rate with 100% release after 7 h; AF pectin aerogels instead provided 90% release. The size of the spherical sample may also have affected the dissolution of the drug. With the addition of membranes, slower release can be expected due to a longer diffusion pathway. However, there has been no research to date on the difference in dissolution rates between multi-membrane aerogels and single spherical aerogel of the same size. Furthermore, research is thus needed to completely understand the impact of membranes and the size of the carrier. By performing swelling studies CF aerogels also show better characteristics by starting to degrade much later than AF aerogels in phosphate buffer. Both carriers stayed resistant in the SGF thus confirming that pectin aerogels could be used for targeted drug delivery without any degradation of the upper gastrointestinal tract, caused by digestive enzymes. Moreover pectin carriers can be used for orally administrated drugs that are soluble in basic medium and thus they dissolve at the lower GI. By combining pectin and aerogel characteristics, spherical and monolithic pectin aerogels show potential as highly porous drug carriers with highly specific surface areas, capable of controlling drug release.

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