4

Xylan, a Promising Hemicellulose for Pharmaceutical Use

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1. Introduction

Polymers are versatile materials with wide use in several industry fields, such as engineering, textile, automobile, packaging and biomedical. In the pharmaceutical industry, both natural and synthetic polymers have been largely used with different applications for the development and production of cosmetics and traditional dosage forms and novel drug delivery systems. For instance, a number of polymers are used as fillers, lubricants, disintegrants, binders, glidants, solubilizers, and stabilizers in tablets, capsules, creams, suspensions or solutions. Additionally, biodegradable and bioadhesive polymers may play an important role in the development of novel drug delivery systems, especially for controlled drug release.

Polymeric microparticles have been studied and developed for several years. Their contribution in the pharmacy field is of utmost importance in order to improve the efficiency of oral delivery of drugs. As drug carriers, polymer-based microparticles may avoid the early degradation of active molecules in undesirable sites of the gastrointestinal tract, mask unpleasant taste of drugs, reduce doses and side effects and improve bioavailability. Also, they allow the production of site-specific drug targeting, which consists of a suitable approach for the delivery of active molecules into desired tissues or cells in order to increase their efficiency.

Lately, the concern with environment and sustainability has been rising progressively and renewable sources of materials have been increasingly explored.

The aim of this chapter is to summarize some of the research findings on xylan, a natural polymer extracted from corn cobs, which presents a promising application in the development of colon-specific drug carriers. Physicochemical characterization of the polymer regarding particle size and morphology, composition, rheology, thermal behavior, and crystallinity will be provided. Additionally, research data on its extraction and the development of microparticles based on xylan and prepared by different methods will also be presented and discussed.

2. Xylan

For thousands of years, nature has provided humankind with a large variety of materials for the most diversified applications for its survival, such as food, energy, medicinal products, protection and defense tools, and others. The pharmaceutical industry has benefitted from such diversity of biomaterials and has exploited the use of natural products as sources of both drugs and excipients. One example of a promising biomaterial for pharmaceutical use is xylan, a hemicellulose largely found in nature, being considered the second most abundant polysaccharide after cellulose.

Xylan has drawn considerable interest due to its potential for packaging films and coating food, as well as for its use in biomedical products (Li et al., 2011). Because it is referred to as a corn fiber gum with a sticky behavior, xylan has been used as an adhesive, thickener, and additive to plastics. It increases their stretch and breaking resistance as well as their susceptibility to biodegradation (Ünlu et al., 2009). Xylan has also been studied because of its significant mitogenic and comitogenic properties, which enable it to be compared to the commercial immunomodulator Zymosan (Ebringerova et al., 1995). Another interesting application for xylan may be found in the food industry as an emulsifier and protein foam stabilizer during heating (Ebringerova et al., 1995). Previous papers have investigated the suitable use of xylan in papermaking (Ebringerova et al., 1994) and textile printing (Hromadkova et al., 1999). In the drug delivery field, xylan extracted from birch wood has been used for the production of nanoparticles after structural modification by the addition of different ester moieties, namely those with furoate and pyroglutamate functions (Heinze et al., 2007). On the other hand, the esterification of xylan from beech wood via activation of the carboxylic acid with *N,N*″-carbonyldiimidazole has been carried out in order to produce prodrugs for ibuprofen release (Daus & Heinze, 2010).

Egito and colleagues have been working for over a decade on the extraction of xylan from corn cobs and its use for the development of microparticles as drug carriers for colon-specific delivery of anti-inflammatory and toxic drugs, such as sodium diclofenac (SD), 5-aminosalycilic acid (5-ASA), and usnic acid (UA). Xylan-coated microparticles have also been developed by Egito and co-workers in order to deliver magnetite particles (Silva et al., 2007). Different microencapsulation techniques have been used for the production of xylan-based microparticles. Coacervation, interfacial cross-linking polymerization, and spray-drying have been shown to be the most successful methodologies for that purpose (Garcia et al., 2001; Nagashima et al., 2008).

Xylan degradation occurs by the action of hydrolytic enzymes named xylanases and β-xylosidases. Those enzymes are produced by a number of organisms, such as bacteria, algae, fungi, protozoa, gastropods, and arthropods (Kulkarni et al., 1999). The degradation of xylan in ruminants has been well reported, while some human intestinal bacteria have been investigated for their ability to produce xylan-polymer degrading enzymes. Among those intestinal species able to degrade complex carbohydrates, lactobacilli, bacteroides, and non-pathogenic clostridia have demonstrated that ability (Grootaert et al., 2007). Because of the presence of those bacteria in the human colon whether by induction of prebiotics or not, it is believed that xylan is a promising polymer for the composition of biodegradable drug carriers for colonic delivery. They would be able to undergo the upper gastrointestinal tract mostly intact, being degraded by xylanases when reaching the colon.

Additionally, corn cobs correspond to an abundant and low-cost renewable material in several countries worldwide and their recycling plays a very important role in the reduction of waste products. Consequently, such approach would lead to a relevant increase in the sustainability of agriculture around the world.

2.1 Sources, extraction, and structure

Hemicelluloses are the second most abundant polysaccharides in nature after cellulose. They occur in close association with cellulose and lignin and contribute to the rigidity of plant cell walls in lignified tissues. Hemicelluloses constitute about 20–30% of the total mass of annual and perennial plants and have a heterogeneous composition of various sugar units, depending on the type of plant and extraction process, being classified as xylans (β-1,4-linked D-xylose units), mannans (β-1,4-linked D-mannose units), arabinans (α-1,5-linked L-arabinose units), and galactans (β-1,3-linked D-galactose units) (Figure 1) (Belgacem & Gandini, 2008).

Xylans are the main hemicelluloses in hardwood and they also predominate in annual plants and cereals making up to 30% of the cell wall material and one of the major constituents (25–35%) of lignocellulosic materials. The most potential sources of xylans include many agricultural crops such as straw, sorghum, sugar cane, corn stalks and cobs, and hulls and husks from starch production, as well as forest and pulping waste products from hardwoods and softwoods (Ebringerova & Heinze, 2000; Kayserilioglu et al., 2003).

The structural diversity and complexity of xylans are shown to depend on the botanic source. Various suitable extraction procedures for the isolation of xylans from different plant sources are described and compared in the literature. It is suggested that certain structural types of xylans, such as glucuronoxylan, arabinoglucuronoxylan, and arabinoxylan, can be prepared from certain plant sources with similar chemical and physical properties. Its general structure has a linear backbone consisting of 1,4-linked D-xylopyranose residues, a reducing sugar with five carbon atoms. These may be substituted with branches containing acetyl, arabinosyl, and glucuronosyl residues, depending on the botanic source and method of extraction (Den Haan & Van Zyl, 2003; Habibi & Vignon, 2005).

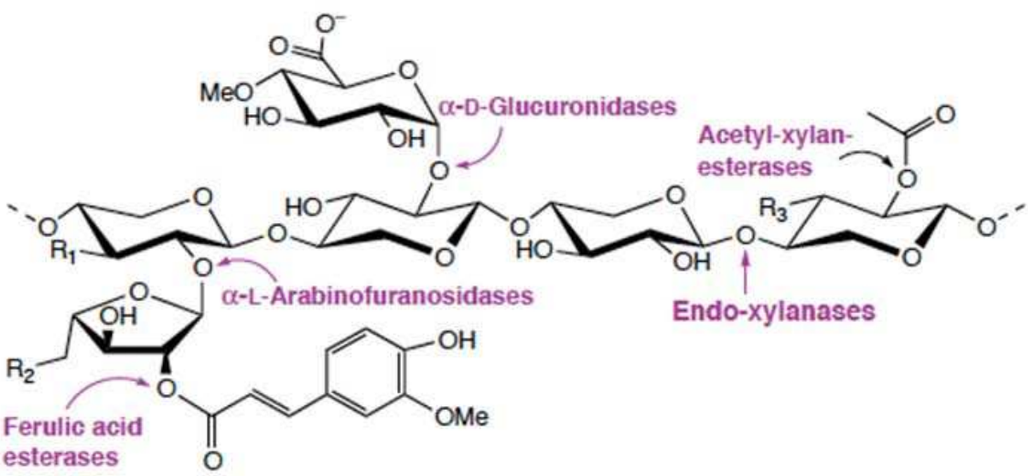


Fig. 1. Chemical structure of xylan (Shallom & Shoham, 2003).

A frequently used classification is based on the degree of substitution and types of side groups for characterization (Ebringerová, 2005; Sedlmeyer, 2011):

a. Homoxylans are linear polysaccharides common in some seaweeds.
b. Glucuronoxylans can be partly acetylated and have units substituted with α-(1→2)-4-O-methyl-D-glucopyranosyl uronic acid (MeGlcUA). They are found in hardwood, depending on the treatment.
c. (Arabino)glucuronoxylans have a substitution with α-(1→3)-L-arabinofuranosyl (ArbF) next to MeGlcUA. They are typical for softwoods.
d. Arabinoxylans with a substitution of the β-(1→4)-D-xylopyranose backbone at position 2 or 3 with ArbF can be esterified partly with phenolic acids. This type is frequently found in the starchy endosperm and the outer layers of cereal grains.
e. (Glucurono)arabinoxylans can be disubstituted with ArbF units, acetylated, and esterified with ferulic acid. This form is typical of lignified tissues of grasses and cereals.
f. Heteroxylans are heavily substituted with various mono- or oligosaccharides and are present in cereal bran, seed, and gum exudates.

Investigation of the xylan structure by various researchers is necessary. The use of xylan as a raw material is directly related to its structure. There is an interest in the application of the xylan polymer in the paper, pharmaceutical, cosmetic, biofuel and food industries. Several medical applications are cited in the literature. The films based on xylan show low oxygen permeability and thus have a potential application in the food packaging and pharmaceutical areas. Numerous studies use the xylan polymer as a specific substrate for xylanases. Besides that, xylan can be hydrolyzed into xylose and subsequently be converted into ethanol (Ebringerova & Heinze, 2000; Ebringerova & Hromadkova, 1999; Ebringerova et al., 1998; Garcia et al., 2000; Kayserilioglu et al., 2003; Oliveira et al., 2010; Sedlmeyer, 2011; Yang et al., 2005).

Previous studies on the corn cob xylan revealed the existence of at least two structurally different components. One is a low-branched arabinoglucuronoxylan, which is mostly water-insoluble (wis-X), and the second is a highly branched, water-soluble heteroxylan (ws-X), which possesses significant mitogenic and comitogenic activities (Ebringerova et al., 1995). The ws-X could be useful also as a food additive because of its emulsifying activity and ability to stabilize protein foam during heating. The wis-X has the ability to remain intact in the physiological stomach environment and small intestine. This property, together with the presence of xylanases (a group of enzymes which degrade the xylan) in the human colon, makes this polymer a suitable raw material for the medical field, especially as a constituent of colon-specific drug carriers (Oliveira et al., 2010; Rubinstein, 1995; Silva et al., 2007).

The most common method to extract xylan is the alkaline extraction. Several pretreatment methods can be used in association in order to break the covalent bonds that exist between xylan and other carbohydrates during the extraction (Wang & Zhang, 2006). A number of articles studied the use of ultrasound on the xylan extraction. Hromadkova and coworkers reported that 36.1% of xylan was extracted from corn cobs with 5% NaOH solution at 60˚C for 10 min of ultrasonication in comparison with 31.5% of xylan in the classical extraction. Both extractive methods yielded xylan with immunogenic properties (Hromadkova et al., 1999).

Wang and Zhang also investigated the effects on the xylan extracted from corn cobs enhanced by ultrasound at various lab-scale conditions. Results showed that the optimization conditions of xylan extraction should be carried out using (i) 1.8 M NaOH, (ii) corn cobs to NaOH solution ratio of 1:25 (w/w), (iii) sonication at 200 W ultrasound power for 30 min at 5 min intervals, and (iv) 60 °C (Wang & Zhang, 2006).

The process of the alkaline extraction of xylan from corn cobs was studied by Egito and colleagues (Unpublished data). The methodology applied in this work consisted of milling the corn cobs and separating the powder into different sizes. After that, the dried corn cobs were dispersed in water under stirring for 24h. The sample was treated with 1.3% (v/v) sodium hypochlorite solution in order to remove impurities. Then, an alkaline extraction was carried out by using NaOH solution. The bulk was neutralized with acetic acid, and xylan was extracted by settling down after methanol addition. Afterwards, several washing steps were performed by using methanol and isopropanol. Finally, the sample was filtered and dried at 50°C.

The efficiency of extraction was observed to be inversely proportional to the corn cob particle size. This was expected because the size reduction corresponds to an increase in total particle surface area. An increase in the time of the alkaline extraction and in the NaOH concentration also improves the efficiency of xylan extraction. This happened because when the NaOH concentration was lower, the xylan present in corn cobs could not be fully dissolved in the solution. Thus, it resulted in lower efficiency of xylan extraction. However, when the NaOH concentration was higher than 2 M, the yields decreased with continuously increasing of the NaOH concentration. This is probably due to the alkaline degradation of xylan chains, proceeding at the higher NaOH concentration, which indicated that the ideal NaOH concentration in the extraction was between 1.5 and 1.8 M (Unpublished data).

2.2 Characterization of corn cob xylan

Comprehensive physicochemical characterization of any raw material is a crucial and multi-phased requirement for the selection and validation of that matter as a constituent of a product or part of the product development process (Morris et al., 1998). Such demand is especially important in the pharmaceutical industry because of the presence of several compounds assembled in a formulation, such as active substances and excipients, which highlights the importance of compatibility among them. Besides, variations in raw materials due to different sources, periods of extraction and various environmental factors may lead to failures in production and/or in the dosage form performance (Morris et al., 1998). Additionally, economic issues are also related to the need for investigating the physicochemical characteristics of raw materials since those features may determine the most adequate and low-cost material for specific procedures and dosage forms.

After the extractive process described by Oliveira and colleagues, corn cob xylan appears to be an off-white fine powder with limited flowability. The xylan powder consists of a mixture of aggregated and non-aggregated particles with irregular morphology, a spherical shape, and a rough surface, as could be observed through the scanning electron microscopy (SEM) (Figure 2) (Oliveira et al., 2010).

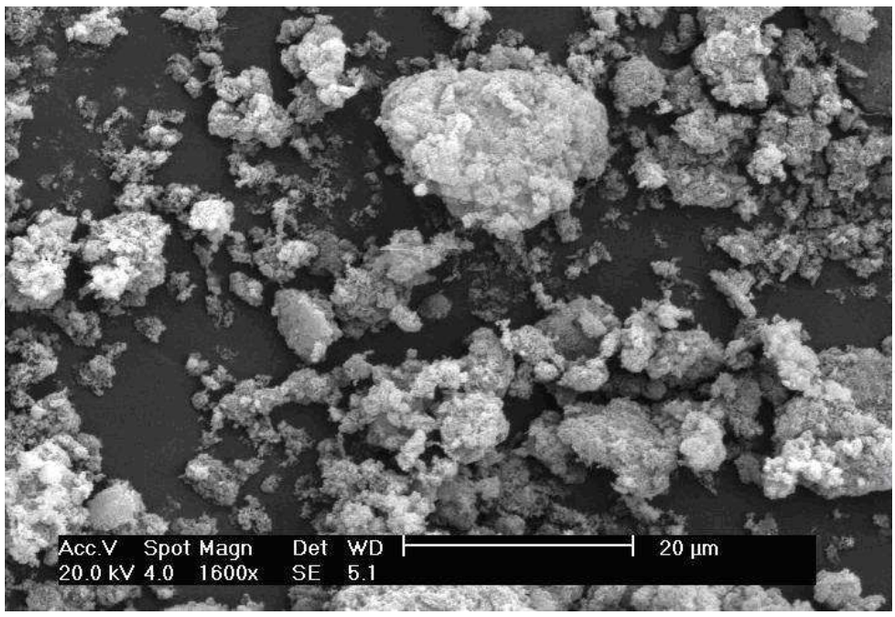


Fig. 2. SEM image of xylan powder after extraction from corn cobs (Oliveira et al., 2010).

The xylan particle size distribution was determined by laser diffraction. It was observed that approximately 90%, 50%, and 10% of the dry extract of xylan was smaller than 65.39 ± 1.76, 23.34 ± 1.2, and 7.68 ± 0.54 µm, respectively, while the mean particle size of xylan was found to be 30.53 ± 1.5 µm (Oliveira et al., 2010) (Figure 3).

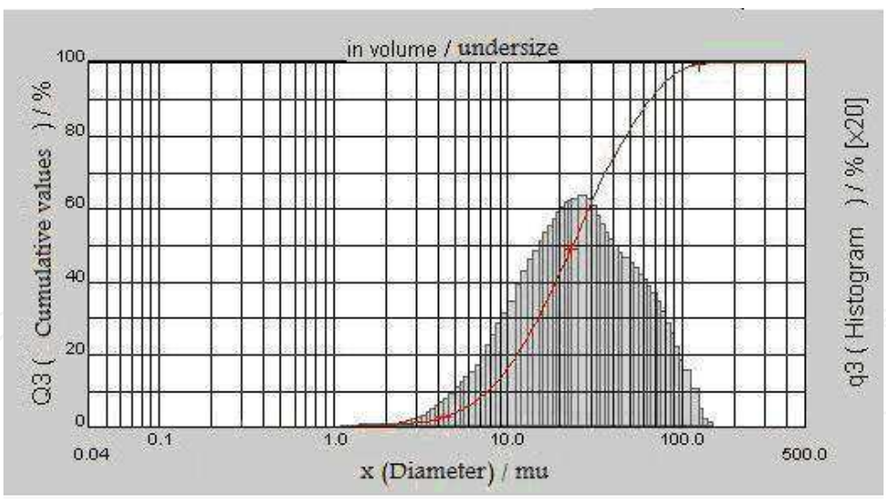


Fig. 3. Particle size distribution of xylan powder after extraction from corn cobs (Oliveira et al., 2010).

As a consequence of the irregular and rough structure of the xylan particles, entanglements between particles are promoted and this fact may explain the poor flow properties of this polymer (Kumar et al., 2002; Nunthanid et al., 2004). Additionally, rheological parameters of xylan powder have also been studied, such as bulk and tapped densities, Hausner ratio, Carr's index, and angle of repose values, and they are summarized in Table 1.

Property	Value (± standard deviation)
Bulk density	0.1336 (± 0.0029) g/ml
Tap density	0.2256 (± 0.0059) g/ml
Compressibility index	40.77 (± 0.0035) %
Hausner ratio	1.68 (± 0.01)
Compactability	32.6 (± 0.1) mL[a]
Angle of repose	40.70 (± 3.2318)^{o}

[a]extrapolating the values to 100 mL

Table 1. Rheological properties of xylan powder extracted from corn cobs

The bulk density of a powder is calculated by dividing its mass by the volume occupied by the powder (Abdullah & Geldart, 1999). Tapped bulk density, or simply tapped density, is the maximum packing density of a powder achieved under the influence of well-defined, externally applied forces (Oliveira et al., 2010). Because the volume includes the spaces between particles as well as the envelope volumes of the particles themselves, the bulk and tapped density of a powder are highly dependent on how the particles are packed. This fact is related to the morphology of its particles and such parameters are able to predict the powder flow properties and its compressibility.

Hausner ratio and the compressibility index measure the interparticle friction and the potential powder arch or bridge strength and stability, respectively (Carr, 1965; Hausner, 1967). They have been widely used to estimate the flow properties of powders. A Hausner ratio value of less than 1.20 is indicative of good flowability of the material, whereas a value of 1.5 or higher suggests a poor flow (Daggupati et al., 2011). The compressibility index is also called the Carr index. According to Carr, a value between 5 and 10, 12 and 16, 18 and 21, and 23 and 28 indicates excellent, good, fair, and poor flow properties of the material, respectively. The Hausner ratio and Carr's index values obtained for xylan are listed in Table 1 and suggest that xylan presents extremely poor flow properties. Although the Hausner ratio and the Carr index correspond to indirect measurements of flowability of materials during preliminary studies, the values obtained for xylan suggest the characterization of this biopolymer as a cohesive powder.

Another parameter of the flow behavior of a powder is the angle of repose, which evaluates the flowability of powders through an orifice onto a flat surface. It is considered a direct measurement. Angles of repose below 30^{o} indicate good flowability, 30^{o}-45^{o} some cohesiveness, 45^{o}-55^{o} true cohesiveness, and > 55^{o} sluggish or very high cohesiveness and very limited flowability (Geldart et al., 2006). The angle of repose for xylan is 40.70^{o}, which confirms its cohesive nature predicted by the aforementioned indirect measurements. This is due to the irregular shape of the xylan particles. Besides, the fine particles of xylan, having high surface-to-mass ratios, are more cohesive than coarser particles; hence, they are more influenced by gravitational force. In addition, it is generally believed that the flowability of powders decreases as the shapes of particles become more irregular (Oliveira et al., 2010).

Regarding the characterization of corn cob xylan by Fourier-transform infrared (FT-IR) spectroscopy, two main absorption bands at 3405 cm^{-1} and 1160 cm^{-1} are revealed. They can

be attributed to the OH stretching characteristic of glycosidic groups and to CC and COC stretching in hemicelluloses, respectively (Figure 4).

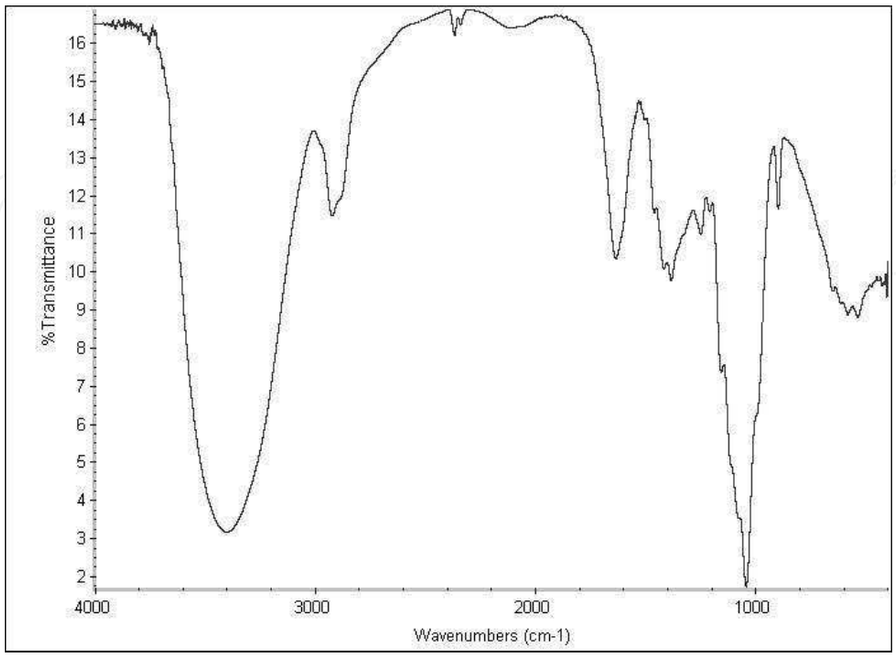


Fig. 4. FT-IR spectrum of xylan powder extracted from corn cobs.

Moreover, an absorption band near 1375 cm^{-1} is detected and it is assigned to the CH bending vibration present in cellulose and hemicellulose chemical structures (Sun et al., 1998). The prominent band at 1044 cm^{-1} is also associated with hemicelluloses and is attributed to the C–OH bending. Finally, a sharp band at 897 cm^{-1}, which is typical of b-glycosidic linkages between the sugar units in hemicelluloses, was detected in the anomeric region (Sun et al., 2005).

A solid-state ^{13}C nuclear magnetic resonance (NMR) experiment was carried out in 4 mm double bearing rotor made from ZrO_2 on a Bruker DSX 200 MHz spectrometer with resonance frequency at 75.468 MHz. The pulse length was 3.5 μs and the contact time of 1H–13C CP was 2–5 ms.

The NMR spectrum of the dry sample showed broad unresolved peaks that correspond to a typical mixture of 4-O-methyl-D-glucuronic acid, L-arabinose and D-xylose, and proteins (Oliveira et al., 2010) (Figure 5).

Concerning the analysis of crystallinity of xylan, the X-ray diffraction detects a few and small peaks, which indicate that xylan presents a low crystallinity (Figure 6).

On the other hand, thermal analysis of xylan by thermogravimetry demonstrates a first event of 8.9% weight loss detected in the range of 62 and 107ºC due to dehydration. The second and most relevant event of 49.8% weight loss appears in the range of 250 and 300ºC due to the polymer decomposition (Figure 7). The differential scanning calorimetry curve reveals an endothermic peak at 293.04ºC, which is attributed to the melting point of the polymer (Figure 7).

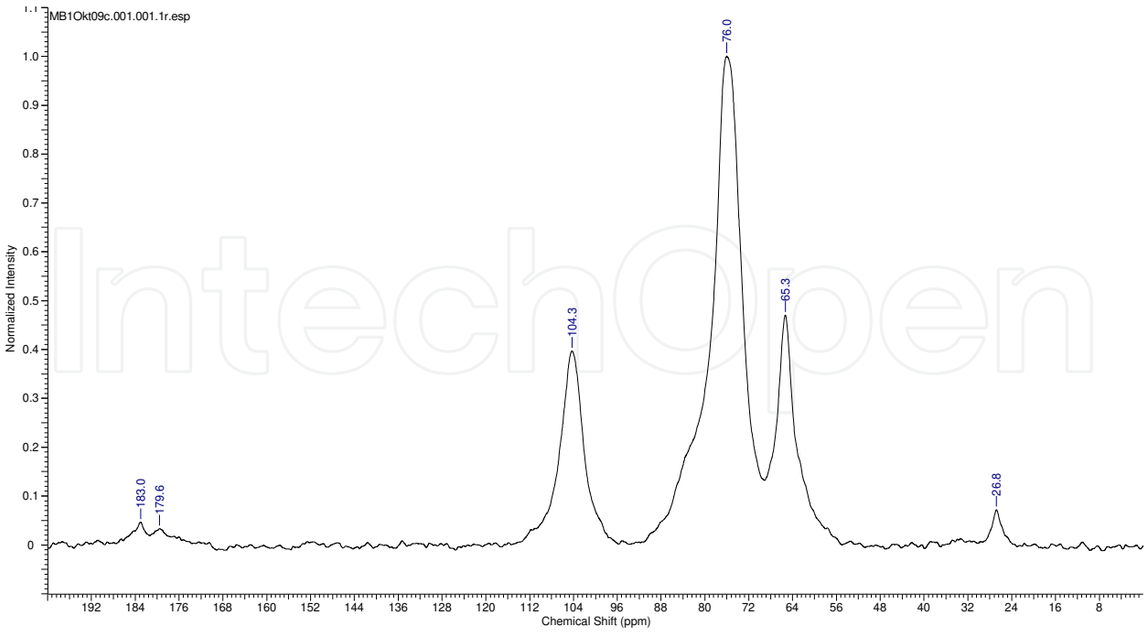


Fig. 5. Solid-state ^{13}C nuclear magnetic resonance spectrum of corn cob xylan.

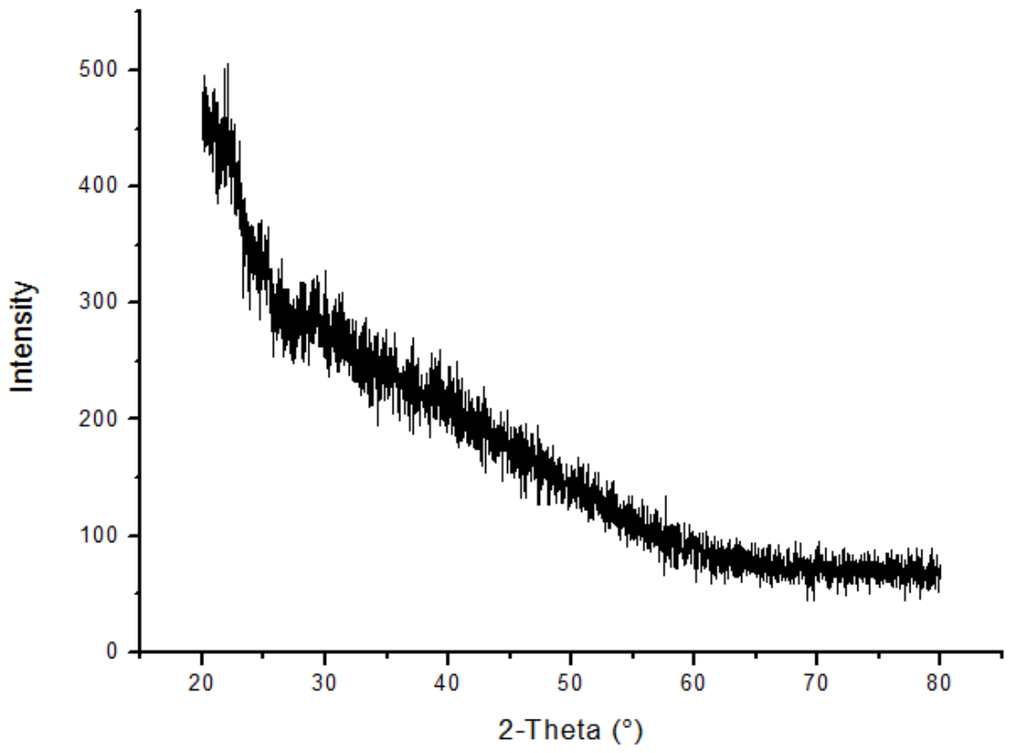


Fig. 6. X-ray diffraction pattern for corn cob xylan (Unpublished data).

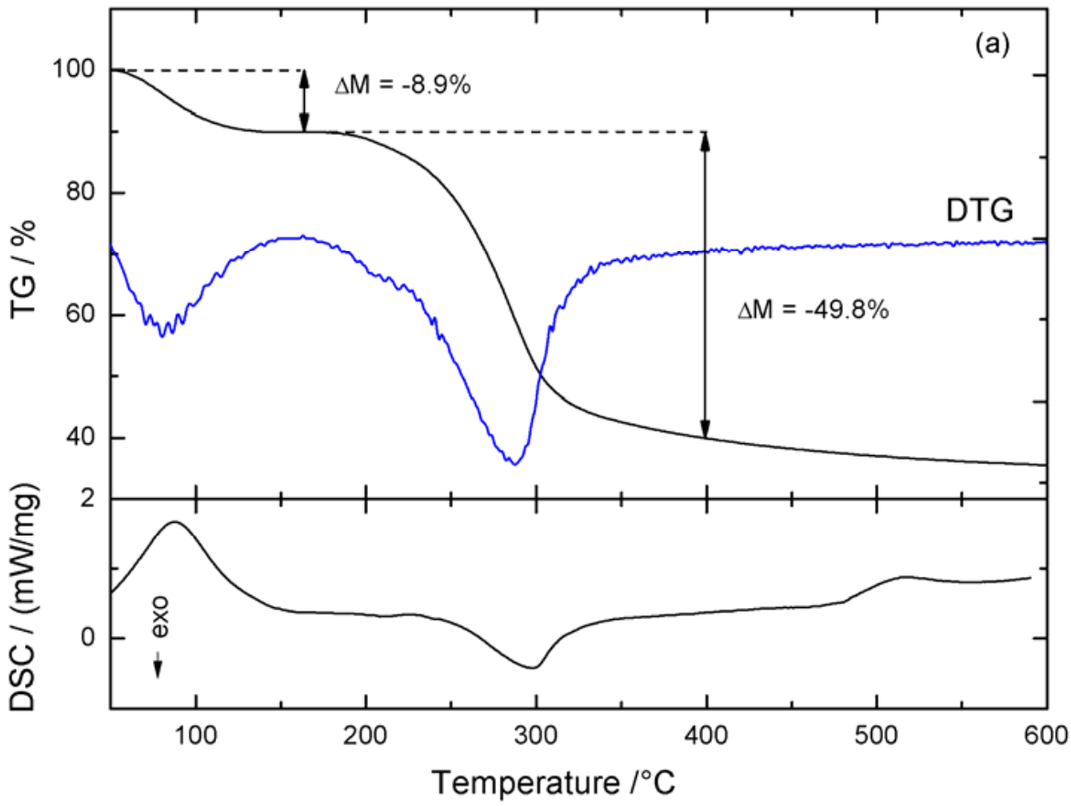


Fig. 7. Thermogravimetry and differential scanning calorimetry curves for corn cob xylan (Unpublished data).

3. Xylan microparticles

As previously described, xylan has been considered as a suitable raw material to produce colonic drug delivery systems due to the ability of enzymes produced by the colonic microflora to degrade the β-glycosidic bonds between the sugar units of the polymer backbone (Kacurakova et al., 2000; Oliveira et al., 2010; Saha, 2000). Regarding the colonic environment, it presents a neutral pH range of the colon and a local blood circulation that prevents the rapid distribution of the drug into the body before circulating into the intestinal blood vessels. As a result, the colonic absorption of drugs is an alternative approach to deliver molecules that are degraded in the stomach medium and are toxic in small quantities in the body (Luo et al., 2011).

A large variety of drug delivery systems are described in the literature, such as liposomes (Torchilin, 2006), micro and nanoparticles (Kumar, 2000), polymeric micelles (Torchilin, 2006), nanocrystals (Muller et al., 2011), among others. Microparticles are usually classified as microcapsules or microspheres (Figure 8). Microspheres are matrix spherical microparticles where the drug may be located on the surface or dissolved into the matrix. Microcapsules are characterized as spherical particles more than 1μm containing a core substance (aqueous or lipid), normally lipid, and are used to deliver poor soluble molecules

in hydrophilic medium (Couvreur et al., 2002; Kumar, 2000; Ribeiro et al., 1999). Furthermore, microcapsules may have one or more cores while the microspheres may show a homogenous or heterogeneous aspect with the drug distributed equally or aggregated into the particle.

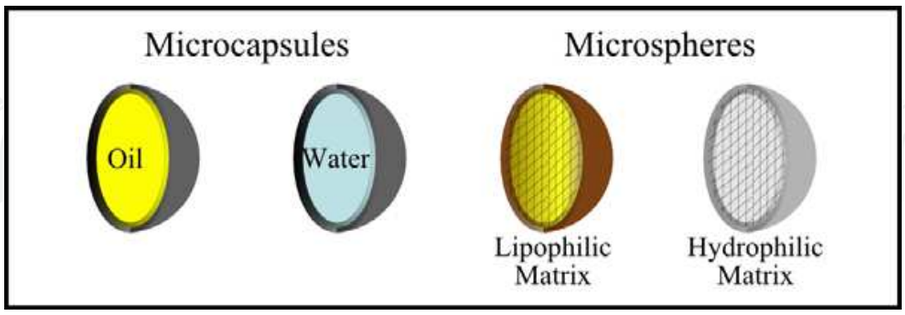


Fig. 8. Structural differences between microcapsules and microspheres.

In the past, microparticles were considered as mere carriers, usually micronized dry material without sophisticated attributes (Vehring, 2008). However, nowadays they have found a number of applications in the pharmaceutical field. For instance, microparticles have been used in order to achieve controlled release of drugs, deliver two or more agents in the same system, improve the bioavailability and the biodistribution of molecules, target drugs to specific cells or issues, or mask the unpleasant taste of some active molecules (Simó et al., 2003; Tran et al., 2011; Vehring, 2008). Xylan microparticles have been successfully produced by the following methods: coacervation (Garcia et al., 2001), interfacial cross-linking (Nagashima et al., 2008) and spray-drying (Unpublished data), all of which are described in the following subsection.

3.1 Methods of production

3.1.1 Coacervation

The coacervation technique is defined as a partial desolvation of a homogeneous polymer solution into a polymer-rich phase (coacervate) and the poor polymer phase (coacervation medium). It was the first process to be scaled-up to an industrial process (Jyothi et al., 2010). However, for the optimization of this method, some changes in the methodology were made and the technique was classified into two types: simple and complex. In simple coacervation the desolvation agent is added to form the coacervate, while the complex coacervation process is guided by the presence of two polymers with different charges, and divided into three steps: (i) formation of three immiscible phases, (ii) deposition of the coating, and (iii) strengthening of the coating (Gouin, 2004; Jyothi et al., 2010; Qv et al., 2011).

After the first step, which includes the formation of three immiscible phases (liquid manufacturing vehicle, core material, and coating material), the core material is dispersed in a solution of the coating polymer. The coating material phase, which corresponds to an immiscible polymer in liquid state, is formed by (i) changing the temperature of the polymer solution, (ii) adding a salt, (iii) adding a non-solvent, (iv) adding an incompatible polymer to the polymer solution, and (v) inducing polymer-polymer interaction. The second step includes deposition of the liquid polymer upon the core material. Finally, the prepared

microcapsules are stabilized by cross-linking, desolvation, or thermal treatment (Jyothi et al., 2010; Stuart, 2008).

Xylan-based micro- and nanoparticles have been produced by simple coacervation (Garcia et al., 2001). In the study, sodium hydroxide and chloride acid or acetic acid were used as solvent and non-solvent, respectively. Also, xylan and surfactant concentrations and the molar ratio between sodium hydroxide and chloride acid were observed as parameters for the formation of micro- and nanoparticles by the simple coacervation technique (Garcia et al., 2001). Different xylan concentrations allowed the formation of micro- and nanoparticles. More precisely, microparticles were found for higher concentrations of xylan while nanoparticles were produced for lower concentrations of the polymer solution. When the molar ratio between sodium hydroxide and chloride acid was greater than 1:1, the particles settled more rapidly at pH=7.0. Regarding the surfactant variations, an optimal concentration was found; however, at higher ones a supernatant layer was observed after 30 days (Garcia et al., 2001).

3.1.2 Interfacial cross-linking polymerization

The production of microparticles by this technique involves basically two experimental steps: (i) emulsification and (ii) cross-linking reaction (Figure 9). In fact, the emulsification is the major step of the process to determine the particle size distribution and the aggregation arrangement of the microparticles. Therefore, the chemical reactivity of the cross-linking agent is also important to determine the required time to complete the entire process (Chang, 1964; Jiang et al., 2006; Levy & Andry, 1990; Li et al., 2009).

In the first step of the interfacial cross-linking polymerization, the polymer is dissolved into the solvent, which is the internal phase of the emulsion, and another phase with a non-solvent to the polymer is produced; then the aqueous phase is poured to the organic phase to produce the emulsion. Afterwards, a solution containing the cross-linking agent is added to the emulsion to form a rigid structure of the microparticles (Couvreur et al., 2002; Rao & Geckeler, 2011).

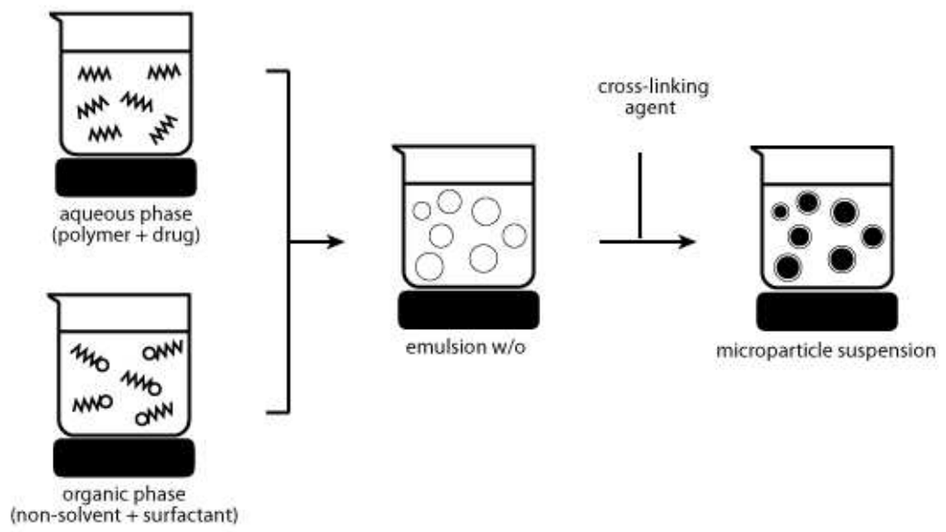
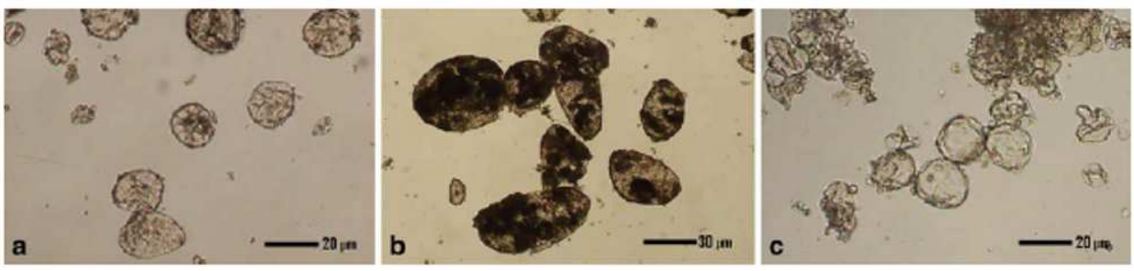


Fig. 9. Scheme for interfacial cross-linking polymerization.

The influence of the lipophilic external phase on the production of xylan-based microparticles by interfacial cross-linking polymerization has been investigated (Nagashima et al., 2008). Three different external phases were investigated: a 1:4 (v/v) chloroform:cyclohexane mixture, soybean oil, and a medium chain triglyceride, with viscosities below 1, 24, and 52 cP, respectively. It was observed that the use of these different lipid phases results in different macroscopic and microscopic aspects of the system (Figure 10).



a) 1:4 (v/v) Chloroform: cyclohexane mixture;
b) Soybean oil;
c) Medium chain triglycerides.

Fig. 10. Optical microscopy images of xylan microcapsules produced by interfacial cross-linking polymerization with different lipophilic external phases (Nagashima et al., 2008).

Because emulsions are susceptible to many destabilizing phenomena occurring since the formation of these systems, such as Ostwald ripping (Anton et al., 2008) and coalescence (Li et al., 2009), the formation of the microcapsules may be influenced by those phenomena, which can form aggregates and agglomerates, respectively. Also, the higher viscosity of the lipid phase may support the shaping of microcapsules with a bigger size than the oil phases with a lower viscosity (Nagashima et al., 2008).

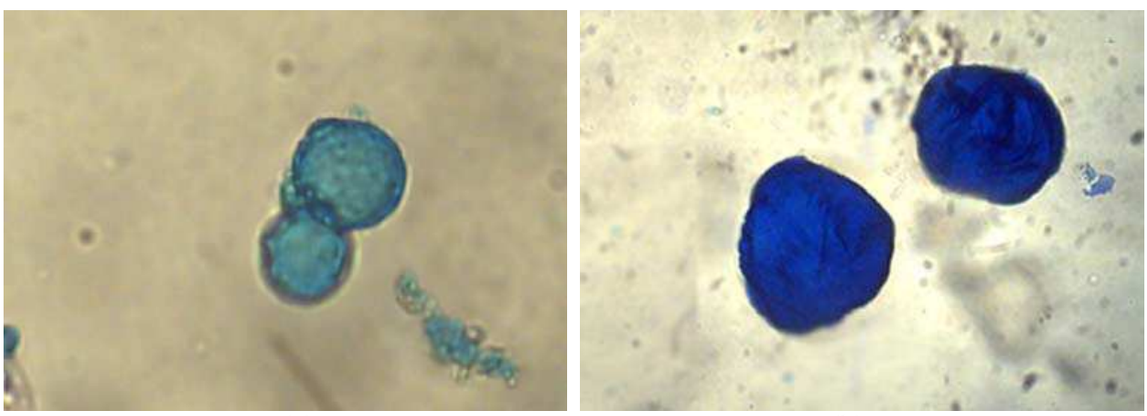
The cross-linking agent is present in the interfacial area, where the polymer should be adsorbed due to the poor solubility of the polymer at the external medium. It is known that the chemical reactivity of the cross-linking agent is a limiting parameter to determine the duration and the yield of the process (Li et al., 2009). Terephthaloyl chloride is a cross-linking agent used to produce microcapsules based on polysaccharides, and it was extensively studied by Levy to produce starch derivate microcapsules for pharmaceutical uses. According to Levy, the pH medium, the concentration of the polymer, the stirring speed, and the concentration of terephthaloyl chloride are significant parameters for the formation of the microparticles and their structure (Andry et al., 1996; Andry & Lévy, 1997; Edwards-Lévy et al., 1994; Levy & Andry, 1990).

Cross-linked xylan-based microparticles are produced by the emulsification of an alkaline solution of xylan with a lipophilic phase formed by a mixture of chloroform and cyclohexane by using 5% (w/v) sorbitan triesterate as the surfactant. Subsequently, the cross-linking reaction is carried out for 30 minutes with 5%(w/v) terephthaloyl chloride in order to yield a hard and rigid polymeric shell (Nagashima et al., 2008).

The interfacial cross-linking polymerization has been demonstrated to be a suitable method for the production of xylan microcapsules with high drug encapsulation efficiency. SD-

loaded cross-linked xylan microcapsules have been produced with three different amounts of the drug (3.1, 6.2, and 60mg). At the end of the process, yellowish suspensions of spherical polymeric microcapsules were produced. The mean particle size was found to be approximately 12.5 μm (Figure 11). Regarding the encapsulation efficiency, high and inversely concentration-dependent rates were achieved. While the SD concentration of 3.1 mg induced a load ability of 99 ± 2%, 6.2 mg of SD promoted 75.8 ± 1 %, and 60mg of SD yielded a 30.4 ± 6 % load efficiency. Accordingly, the results demonstrated the feasibility of producing xylan microcapsules with and without SD, presenting the same aspect and homogeneity, but concentration-dependent encapsulation rates (Unpublished data).

Regarding the stability of those formulations after storage, studies have been performed in order to evaluate the SD release. As a result of storage for 30 days, it was found that approximately 30 ± 5% of SD had been released to the external medium. This fact may be evidence that some adjustments in the methodology need to be made. One approach that has been shown as a promising strategy to avoid the drug release to the external medium is the spray-drying technique, which will produce a dried product instead of an aqueous suspension of microparticles. It may be used as a complement to the interfacial cross-linking polymerization and is described in the following subsection.



(a) (b)

a) SD-loaded cross-linked xylan microcapsules containing 60 mg of SD
b) SD-loaded cross-linked xylan microcapsules containing 3.1 mg of SD

Fig. 11. Optical microscopy of SD-loaded cross-linked xylan microcapsules at 40x magnification.

Cross-linked xylan microcapsules have also been successfully developed in order to protect superparamagnetic particles from gastric dissolution (Silva et al., 2007). First, magnetic particles were synthesized by coprecipitation using solutions of ferric chloride and ferrous sulphate as a source of iron. Subsequently, xylan was dissolved in 0.6 M NaOH solution and the magnetic suspension was added to the xylan solution after neutralization and sonication. Finally, the emulsification was carried out in chloroform:cyclohexane containing 5% (w/v) sorbitan tristerate followed by the cross-linking reaction with terephthaloyl chloride. As a result, polymeric microparticles with a mean diameter of 25.26 ± 0.42 μm and roughly spherical in shape were produced. They were suggested to involve more than one magnetic particle entity due to their five-fold

larger size. Additionally, dissolution studies revealed that only 2.3% of the magnetite content was dissolved in 0.1 M HCl solution at 37 ± 0.1 ºC after 120 min. This fact corroborates the feasibility of xylan as a material for colon delivery.

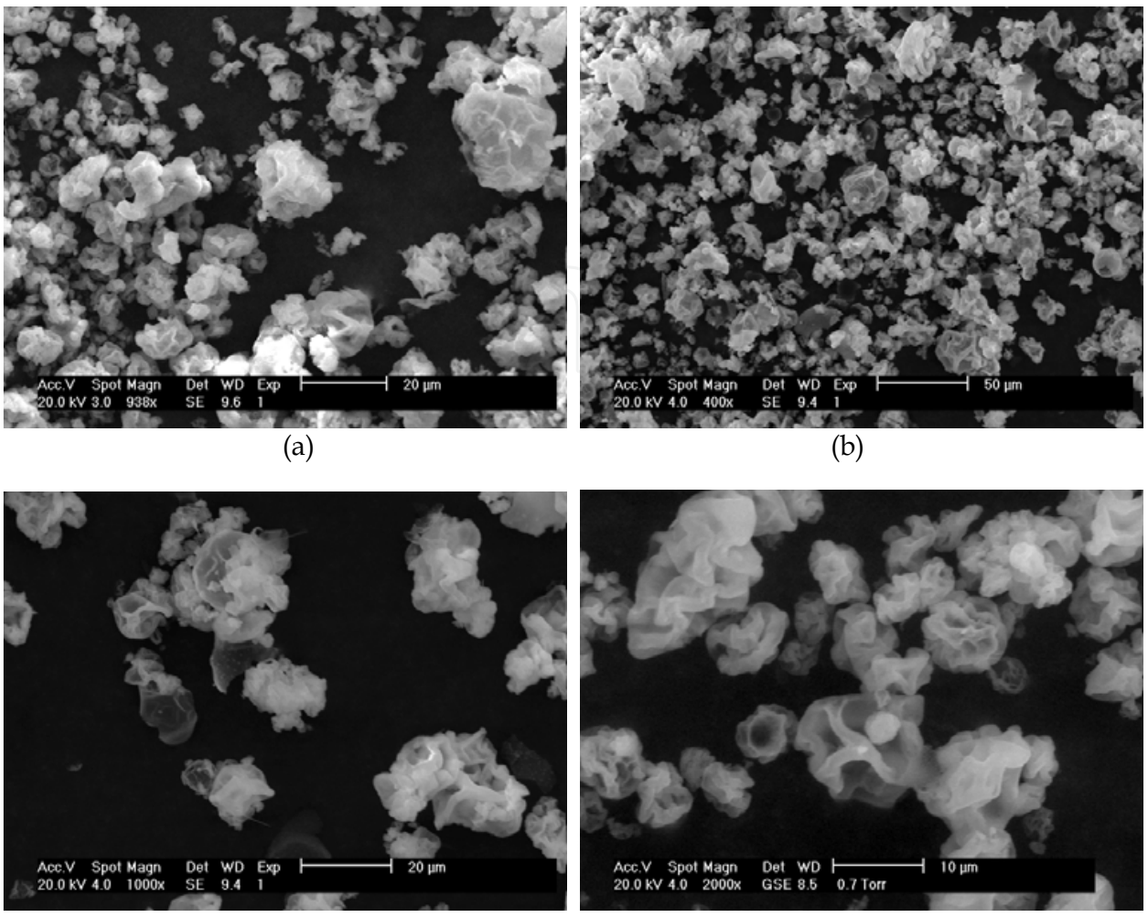
3.1.3 Spray-drying

The spray-drying technique is a one-step continuous operation characterized by the atomization of suspensions or solutions into fine droplets followed by a drying process that leads to the formation of solid particles (Tewa-Tagne et al., 2007). When compared to other approaches for producing and drying systems, this technique exhibits the advantages of low price, rapid process, and the possibility of modulating the physicochemical properties of particles, such as particle size, polydispersity, bulk and tapped densities, and cohesion (Raffin et al., 2006; Tewa-Tagne et al., 2006; Vehring, 2008). Briefly, the main steps of the process are (1) atomization of the feed into a spray, (2) spray-air contact, (3) drying of the spray, and (4) separation of the dried product from the drying gas (Tewa-Tagne et al., 2007; Tewa-Tagne et al., 2006). Because of the dry state of the final product obtained by the spray-drying technique, this method is highly appropriate to improve the stability of microparticulate systems due to the reduction of microbiological contamination, polymer hydrolysis, and physicochemical instability because of the elimination of the water content.

The production of xylan-based microparticles by spray drying has provided useful results. Although some limitation may be observed due to the sticky nature of xylan, which may lead to scarce amounts of final dry product, the use of other materials is very helpful. With that purpose, derivatives of methacrylic acid and methyl-methacrylate, also known as Eudragit®, have been used to prepare suitable xylan-based microparticles. In addition, Eudragit® S-100 (ES100) plays an additional role in the pharmacokinetic properties of the polymeric microparticles. ES100 is a synthetic gastroresistant polymer that has been largely used in the pharmaceutical industry due to its safety and degradation behavior. It is a pH-sensitive copolymer and, because of that, it is able to prevent drug release until the formulation passes through the stomach and reaches some distance down the small intestine (Friend, 2005).

Thus, spray-dried xylan/ES100 microparticles were produced at different polymer weight ratios dissolved in alkaline and neutral solutions, separately. More precisely, xylan and ES100 were dissolved in 1:1 and 1:3 weight ratios in 0.6 N NaOH and phosphate buffer (pH 7.4). Then, the suspensions were spray-dried at the feed rate of 1.2 mL/min (inlet temperature of 120ºC) using a Büchi Model 191 laboratory spray-dryer with a 0.7 mm nozzle, separately. Cross-linked xylan microcapsules were also coated by ES100 after spray-drying at the same conditions.

It was observed that this technique was able to produce microparticles with a mean diameter of approximately 10.17 ± 3.02 μm in a reasonable to satisfactory yield depending on the formulation. This value was observed to be higher for the polymer weight ratio of 1:3 (87.00 ± 4.25 %), which indicates that ES100 improves the final result of the spray-drying process. According to the SEM analysis, the polymeric microparticles were shown to be quite similar in shape. Regardless of the formulation, they appeared to be mostly concave and asymmetric (Figure 12).



(a) (b)

(c) (d)

a) 1:1 (w/w) xylan/ES100 microparticles (solvent: NaOH) at 938x magnification.
b) 1:3 (w/w) xylan/ES100 microparticles ((solvent: NaOH) at 400x magnification.
c) 1:3 (w/w) xylan/ES100 microparticles (solvent: phosphate buffer) at 1000x magnification.
d) 1:3 (w/w) xylan/ES100 microparticles (solvent: phosphate buffer) at 2000x magnification.

Fig. 12. SEM images of 5-ASA-loaded spray-dried xylan and ES100 microparticles in different polymer weight ratios (Unpublished data).

4. Biocompatibility of xylan and its products

Among other natural products, biopolymers have been largely studied, due to their numerous applications in which their contact to cells and tissues via their surface is of utmost importance. For instance, micro- and nanocapsules, film coatings, excipients for traditional dosage forms, and novel drug delivery systems have taken much advantage by using biopolymers, especially due to their biocompatibility and biodegradability properties (Drotleff et al., 2004; Villanova et al., 2010). Biopolymers are subject to degradation *in vivo* by hydrolysis or enzymatic attack. The use of these polymers may represent a lower cost compared to other conventional biodegradable polymers (Villanova et al., 2010).

During the development of pharmaceutical products, the toxic effect of biomaterials on cells is considered one of the most important issues to be evaluated. For instance, cell death, cell

proliferation, cell morphology, and cell adhesion are features directly correlated with the toxicity *in vitro.* Therefore, loss of viability could be a consequence of a toxic biomaterial (Marques, 2005). Although biopolymers are considered non-toxic and biocompatible, residues from their extraction methodology may cause toxicity issues.

In order to assess the effect of the corn cob xylan on the cell viability and proliferation rate, xylan solutions at concentrations of 0.1, 0.25, 0.50, 0.75, and 1 mg/ml were placed in contact with human cervical adenocarcinoma cells (HeLa cells) for 24 and 72 h. Finally, the cell viability was determined by the MTT assay. It was observed that regardless of the xylan concentration, the samples tested did not affect the viability of HeLa cells after incubation for 24 h (Figure 13) (Unpublished data).

Besides, the statistical analysis of the results obtained confirmed that the xylan samples did not present a significant effect on the cell viability and cell proliferation rate when in direct contact with HeLa cells at the concentrations used in this study and compared to the control.

Similarly, after a longer time of incubation, no significant changes in the cell proliferation rate was detected, as can be seen in the data for 72 h (Figure 13). In fact, this was expected due to the biocompatible nature of xylan. As a natural polyssacharide, this type of biomaterial is considered to be highly stable, non-toxic and hydrophilic (Liu et al., 2008). Accordingly, the alkaline extraction of xylan from corn has proved to be a safe approach for obtaining the polymer with no relevant toxicity (Unpublished data).

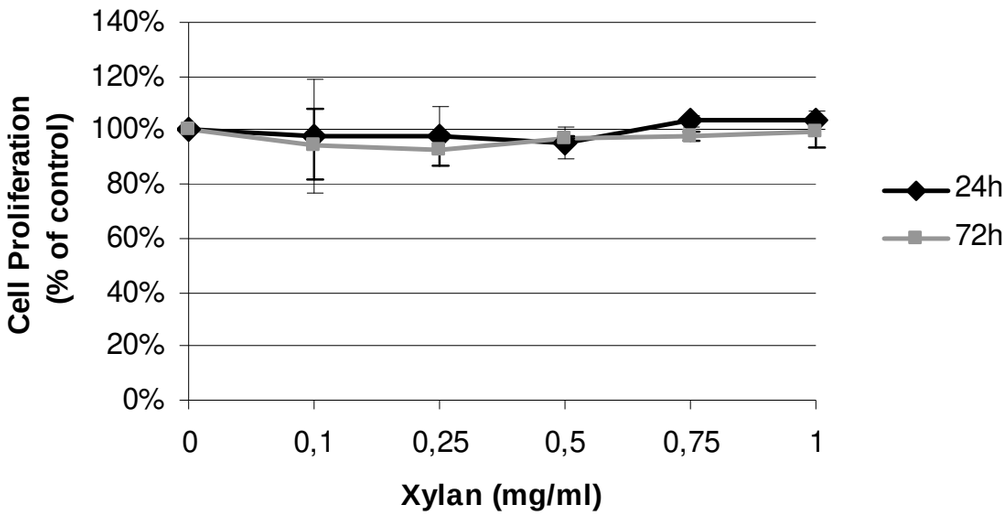


Fig. 13. Viability of HeLa cells after incubation for 24 and 72h with solutions of xylan at different concentrations.

Xylan-based microparticles were also evaluated regarding their *in vitro* toxicity. In fact, cross-liked (CLM) and spray-dried microparticles (SDM) based on xylan and ES100 were produced in order to carry UA and avoid its side effects, namely hepatotoxicity and nephrotoxicity. Additionally, CLM and SDM dispersions at concentrations of 50, 125, 250, and 500 μg/ml were placed in contact with human embryonic lung fibroblasts (MRC-5 cells)

for 24 h and the MTT assay was carried out to assess the cell viability. According to the MTT assay results, the cells treated with CLM presented an initial decrease in the cell viability of 56% at the lowest tested concentration (50 μg/mL) while the cell viability rate reached only 12.6% at the highest concentration (500 μg/mL) (Figure 14).

Nevertheless, SDM showed a maximum decrease in the cell survival rate of approximately 12% and 27% at the lowest and highest concentrations of microparticles, respectively (Figure 14). The massive cytotoxicity induced by CLM may be explained by the presence of remaining molecules of terephthaloyl chloride, which plays the role of cross-linking agent during the formation of CLM and is well known as a toxic substance.

In contrast, the MTT assay for SDM did not show high cytotoxicity. This fact confirms the advantage of using spray-drying in order to avoid toxic and hazardous reagents such as terephthaloyl chloride and other cross-linking agents. Additionally, such results indicate a relevant biocompatibility of spray-dried xylan/ES100 microparticles containing UA.

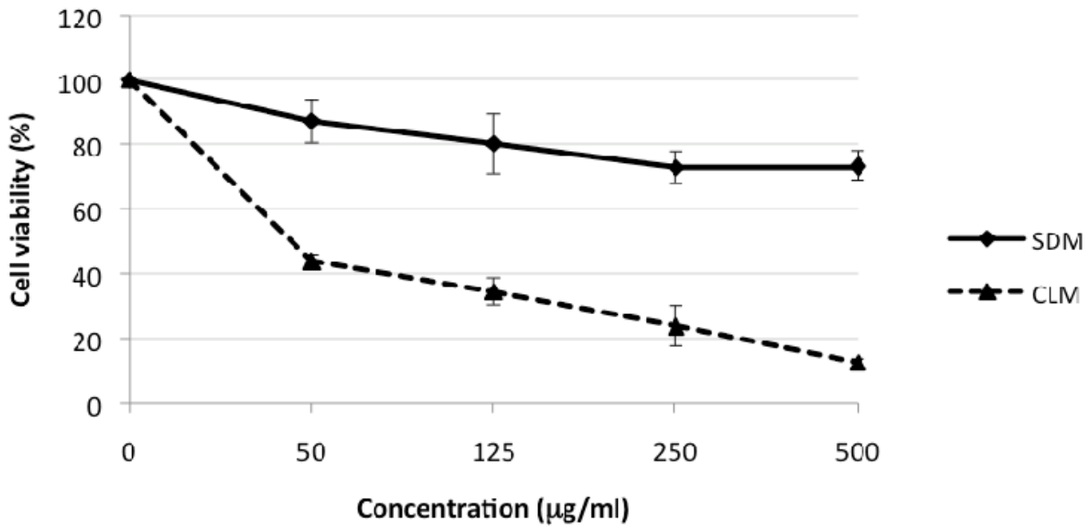


Fig. 14. Viability of MRC-5 cells after incubation for 24h with spray-dried (SDM) and cross-linked xylan microparticles (CLM) containing UA.

5. Conclusions

The need of modern science to achieve a sustainable future development has been shown in many circumstances in society. Finding strategies less harmful to the environment has been a quest for research in several areas, such as pharmaceuticals, biotechnology, and food industries. With that purpose, the increase in research and development of more applications of xylan and its derivatives has shown the versatility of this biopolymer, thus helping the search for sustainable alternatives.

Xylan may be extremely useful in the pharmaceutical field, especially for the production of colon-specific drug carriers, such as micro- and nanoparticles, and film coatings. In addition, because of its abundant sources in nature, its use would bring many benefits, including reducing costs to industry, optimizing the use of natural resources, and reducing environmental damage due to its biodegradability and biocompatibility.

Large amounts of agricultural waste products, such as corn cobs, are continuously provided in several developing countries. Xylan is considered to be a green polymer that may play an essential role in the renewability of waste products due to its biodegradable and biocompatible nature. Furthermore, as shown in this chapter, xylan presents particular properties that allow a wide range of applications.

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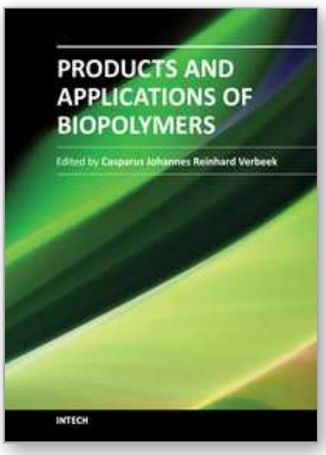

Products and Applications of Biopolymers

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It is interesting to consider that biopolymers are by no means new to this world. It is only because of our fascination with petrochemical products that these wonderful materials have been neglected for so long. Today we face a different challenge. Environmental pressure is pushing away from synthetic or petro-chemically derived products, while economic factors are pulling back from often more expensive "green" options. This book presents two aspects of biopolymers; potential products and some applications of biopolymers covering the current relevance of biopolymers.

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