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PECTIN MODIFICATION WITH A SOLVENT FREE PROCESS FOR THE FORMULATION OF DRUG DELIVERY SYSTEMS

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ABSTRACT

For the last decades, pectin has become one of the most studied material for drug targeting and biomedical applications. This biopolymer is an abundant polysaccharide extracted from plant cell walls which shows many interesting biological, economical and chemical properties. Due to its specific structure, pectin reveals a rapid hydration, swelling and dissolution in water. This fast dissolution appears as a major drawback for the formulation of drug delivery systems and dressings. Thus, the aim of this work is to increase the hydrophobicity of natural pectin by chemical modification. This work presents an esterification route using octenyl succinic anhydride for bringing hydrophobic segments onto pectin. The described process is achieved under solventless condition and the new materials are used to formulate a drug delivery system.

KEYWORDS

Pectin; Biopolymer; Solvent free; Esterification

1. INTRODUCTION

Pectin is a natural complex polysaccharide derived from plants cell walls. This biopolymer is mainly composed of D-Galacturonic acid repetition units with various grafted areas according to the plant origin. Pectin has interesting properties such as low cost, high stability, biocompatibility, non-toxicity and good gelling properties (Novosel'skaya et al., 2000). This last property depends on the degree of acetylation, degree of amidification and degree of esterification. Pectins are classified based on their degree of esterification. The low methoxy pectin grades are able to gelify by calcium complexation. This mechanism is described by the "egg box model" (Grant et al., 1973). The complexation of pectin backbones by ions is used to manufacture drug delivery systems such as films or beads (Mishra et al., 2012). However, low methoxy pectin applications are limited due to rapid hydration, swelling and dissolution in water (Novosel'skaya et al., 2000), rapid drug release of hydrophilic API, no release of hydrophobic API without surfactant. The purpose of this study is to overcome these limits by pectin chemical modification to reduce pectin affinity towards water**.** The chemical modification consists in grafting hydrophobic segments onto pectin backbone using mild conditions. This route described by Monfregola involves anhydrides grafting to functionalize hydroxyl functions of pectin (Monfregola et al., 2011). For this modification octenyl succinic anhydride was used because, this molecule is authorized by FDA and widely used in agrifood industry for starch modification.

2. MATERIALS & METHODES

2.1. Materials

Low methoxyl pectin (Cargill) (Unipectin® 300C, DE = 27-33%) was dried at 80°C, under vacuum, for 4h. Octenyl succinic anhydride (OSA), (Aldrich) and potassium carbonate (K_2CO_3), (Aldrich) were used as received.

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2.2. Synthesis of modified pectin

200 mg of pectin was manually milled with 1mL of OSA and 30, 60 and 90 mg of K_2CO_3. The heterogeneous mixture was heated in an oil bath at 160°C for 15min. After cooling at room temperature, the mixture was washed in acetone by successive centrifugations until take off of all the ungrafted OSA and dried one night at 30°C, under vacuum.

2.3. FT-IR

FT-IR experiments were conducted using a Thermo Scientific Nicolet IS10 spectrometer (Thermo Fisher Scientific, MA, USA) by a reflection technique (ATR). Each sample was subjected to 32 averaged scans over a wavenumber region of 600 to 4000 cm^{-1} at a resolution of 4 cm^{-1}.

2.4. ^{1}H NMR

^{1}H NMR analyses were carried out on a Bruker 500 UltrashieldTM apparatus. Pectin and modified pectin were dissolved in D_2O and ^{1}H NMR spectra were recorded at 500 MHz and 25°C.

2.5. TGA

Thermal analysis (TGA) was carried out in a nitrogen atmosphere with a TGA Q600 thermobalance from 25 to 1000°C, at a rate of 10 ◦ C min-1.

2.6. Gelation ability

500 mg of pectin (native or modified) was solubilized in 10 mL of water. The solution was dropped in a calcium chloride solution at 10% (m/m). After 5 min of complexation with Ca^{2+}, the beads were washed by water to take off free Ca^{2+} and dried over night at 30°C. The surface area of the beads was determined by optical microscopy.

3. RESULTS & DISCUSSION

3.1. Synthesis of modified pectin

The reaction involves OSA as reactant and potassium carbonate as initiator to activate hydroxyl functions on pectin. The aliphatic chains bring hydrophobic segments on pectin and anhydride functions react with pectin hydroxyl function by esterification (4) (Figure 1).

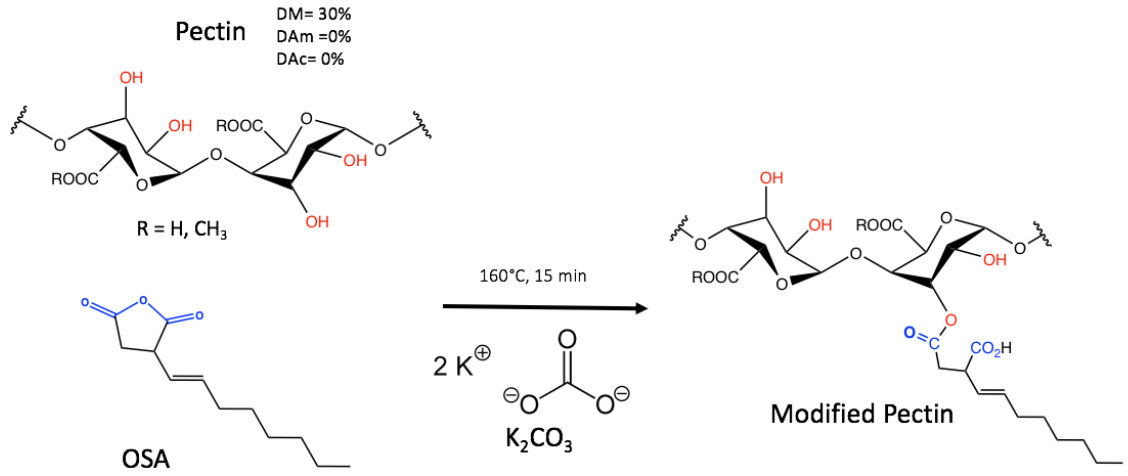

Figure 1. Chemical modification of pectin with OSA

3.2. FT-IR

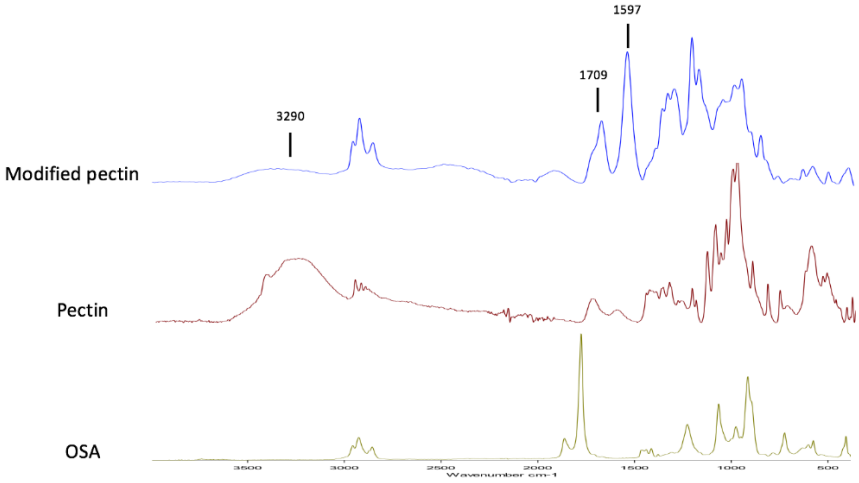

Figure 2. Spectra of modified pectin, pectin and OSA

The grafting was confirmed by FT-IR. The spectra showed a decrease of hydroxyl bands (3290 cm^{-1}), an increase of ester functions bands (1709 cm^{-1}) and appearance of double bond bands (1597 cm^{-1}) (Figure 2). The disappearance of anhydride functions (1785cm^{-1}) on the modified pectin confirmed a good elimination of unreacted OSA.

3.3. ^{1}H NMR

The proton NMR spectra of modified pectins are used to determine the percentage of substitution by comparing the integration of the peak accounting for the proton in position 3 in the galacturonic acid residue and the one accounting for the methyl of OSA (Figure 3). The percentage of substitution calculated is 2%, 13% and 29%.

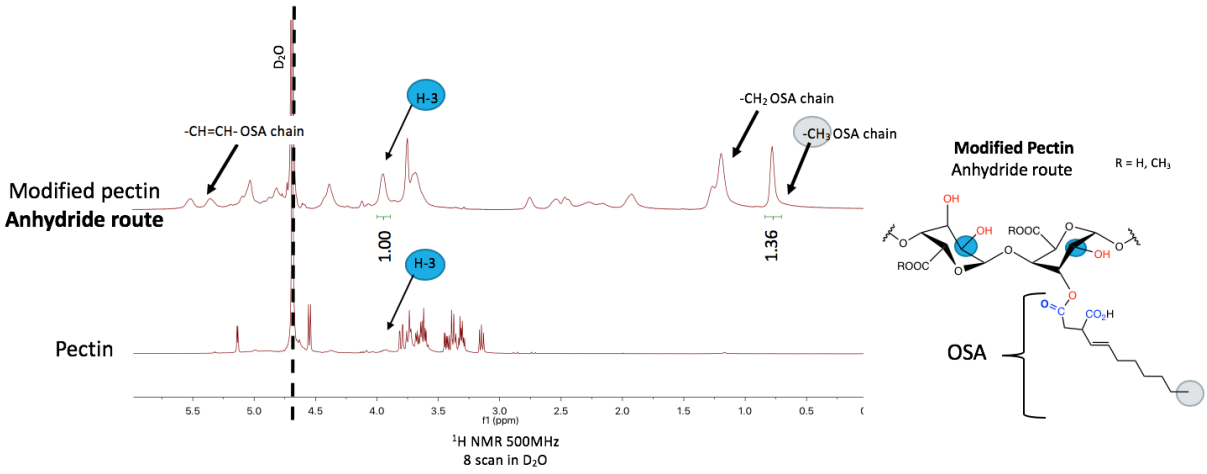

Figure 3. ^{1}H NMR spectra of pectin and modified pectin

3.4. TGA

Three significant loss weight are visible on the figure 3. The first one around 100 °C corresponds to water evaporation, the second and third ones around 200 and 420°C correspond to pyrolitic decomposition of both pectin and OSA fragments. Water evaporation is logically reduced when the grafting of hydrophobic OSA residues increase on pectin.

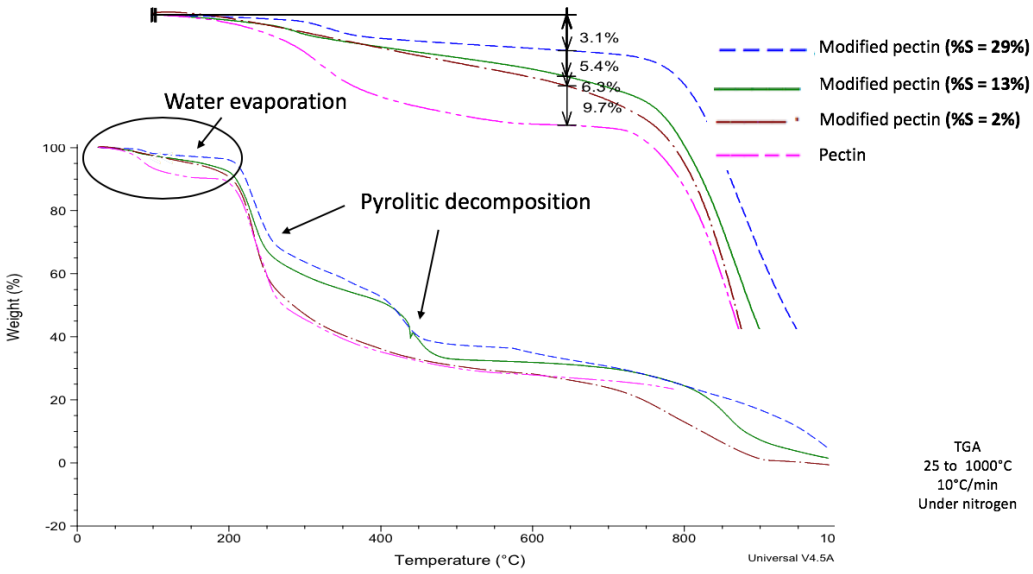

Figure 3. TGA spectra of pectin and modified pectin

3.5. Gelation ability

In order to evaluate the gelation ability of modified pectin with Ca^{2+}, beads are produced with modified pectin at 29% of substitution in comparison to LM pectin beads (Figure 4). The decrease of the surface area during drying is reduced by 37% for modified pectin and 79% for LM pectin. This result is directly related to the OSA content and confirmed the reduced affinity of modified materials towards water previously observed by TGA.

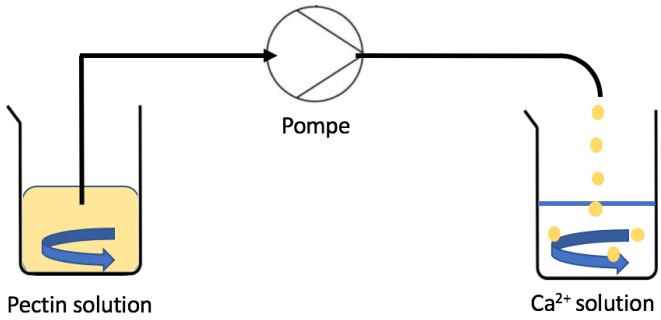

Figure 4. formulation of beads of modified pectin

4. CONCLUSION

To conclude, we used a free solvent process to obtain modified pectin ranging from 2 to 30% of substitution. The modified biopolymers show a reduced affinity towards water as shown by TGA. These modified pectins hold their gelation ability with calcium cations and allow the development of new drug delivery systems.

5. REFERENCES

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