



Polysaccharides and lignin based hydrogels with potential pharmaceutical use as a drug delivery system produced by a reactive extrusion process



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ABSTRACT

Currently, there is very strong interest to replace synthetic polymers with biological macromolecules of natural source for applications that interact with humans or the environment. This research describes the development of drug delivery hydrogels from natural polymers, starch, lignin and hemicelluloses by means of reactive extrusion. The hydrogels show a strong swelling ability dependent on pH which may be used to control diffusion rates of water and small molecules in and out of the gel. Also the hydrogels degradation rates were studied in a physiological solution (pH 7.4) for 15 days. The results indicated that for all three macromolecules, lower molecular weight and higher level of plasticizer both increase the rate of weight loss of the hydrogels. The degradation was extremely reduced when the polymers were extruded in the presence of a catalyst. Finally the dynamic mechanical analysis revealed that the degradation of the hydrogels induce a significant reduction in the compressive modulus. This study demonstrates the characteristics and potential of natural polymers as a drug release system.

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1. Introduction

Naturally occurring renewable and sustainable materials have become well known in the manufacturing of biobased products [1,2]. Biomass, which includes all plants and plant derivatives, has been widely used in many disciplines, and converted into a wide range of marketable products such as fuel, chemicals, paper, plastics, and pharmaceutical products [3,4]. Currently, there is very strong interest to replace synthetic polymers with natural polymers for applications that interact with humans or the environment [5]. This is based on human health, environmental impacts at end of life, the use of renewable resources, and for national security.

Biomass is divided into two categories, first and second generation. In the former, they are edible biomass based-products mostly composed of starch-rich plants [6]. Starch is a food based product and its wide industrial applications may lead to issues including food shortages and increased pressure on the current crops growth with possible food price increases. Societies increased demands on food systems has caused many to look for non food replacements

for starch, such as second-generation biomass, which consists of residual non-food parts of the current crops or other non-food sources such as forest resources. These materials include cellulose, hemicelluloses and lignin [6], available in massive quantities.

One application of natural polymers are as hydrogels which are crosslinked polymeric networks that are capable of absorbing large volumes of water or biological fluids in a short time and can retain the absorbed fluid even under heating or some pressure [7]. The presence of hydrophilic groups such as $-\text{OH}$, $-\text{CONH}-$, $-\text{COOH}$, $-\text{CONH}_2$, and $-\text{SO}_3\text{H}$ in polymers forming hydrogels stems from their affinity to absorb water [8]. In 1926, Dorothy Jordan Lloyd have defined hydrogels as “the colloidal condition, the gel, is one which is easier to recognize than to define” [9]. This definition was raised because hydrogels have certain solids and liquids properties. Indeed, as solids they don't flow and as liquids they allow the diffusion of small molecules. However, nowadays, hydrogels are viewed as smart and stimuli responsive materials that change their swelling property in response to environmental changes (pH, temperature and ionic strength) [10]. For instance, the presence of solutes depresses the thermodynamic activity of water which is linked to polymer swelling [11,12].

Hydrogels have been used in several applications that include; hygiene (disposable diapers and feminine care products), agricul-

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ture (water retention, and pesticide delivery), biomedical materials (drug carriers, wound dressings, and tissue engineering scaffolds), biosensors and others [13]. The hydrogels used in drug delivery systems are of great interest because they are able to alter their volume in response to environmental stimuli expeditiously [14,15]. Biopolymers, including starch, proteins, gelatin, hemicelluloses, lignin, cellulose, and their derivatives have been copolymerized or blended with other synthetic polymers to create composites that can be used to manufacture bio-polymer based hydrogels [16–18].

Reactive extrusion is a technique known to be exploited by the plastics industry to mix polymer formulations to obtain thermoplastic materials. It is known to be suitable for many reactions, including polymerization and grafting as a continuous and solvent-free process. This technique allows the material processing to be performed at a flexible scale without the need for solvents. Native bio-polymers typically cannot be processed by reactive extrusion due to the strong hydrogen bonds between the polymeric chains at the inter and intra molecular levels [19]. Several substances have been used as a plasticizer for biobased polymers including: citric acid, glycerol, sorbitol, urea and others [19,20]. The presence of plasticizer can facilitate the reactive extrusion processes and thus enables the biomass processing and modification with great advantages in scalability.

For instance, citric acid (CA) is a multi-carboxylic structure with three carboxyl and one hydroxyl groups. CA is produced mainly by the fermentation of some carbohydrates and is generated as a non-toxic metabolic product of the body in all living cells that use oxygen as part of cellular respiration. The carboxylic groups of CA can esterify the hydroxyl groups of biopolymers and at the same time crosslink polymers [21]. According to several studies, the structure of CA dictates its functions: as a plasticizer, crosslinking agent, and/or hydrolytic agent [21,22]. Although the crosslinking reaction of a biopolymer with CA can take place at high temperature, the presence of a catalyst, an example being sodium hypophosphite (SHP), is essential for the reaction to proceed rapidly to achieve a highly esterified crosslinked material [23,24].

In this research, we have developed biodegradable hydrogels based on the biological macromolecules, starch, lignin and hemicellulose, by reactive extrusion. To our knowledge, this is the first report of the development of drug delivery hydrogels by reactive extrusion from these macromolecules. The natural polymers were plasticized and crosslinked by CA in the presence and absence of SHP as a catalyst. The present investigation was aimed to focus on the basic differences between the first and second generation biomasses as a drug delivery system. The bio-based hydrogels were characterized for their feasible processing conditions. The influence of CA on the polymers forming hydrogels (processing, degree of esterification, and molecular weight) during the reaction was determined. The dynamic swelling of the resulting gels were studied at different pH in buffer solutions and the types of water-transport mechanisms were analyzed. Also the hydrogel degradation at physiological condition was determined over a period of 15 days and the effect of the degradation on the mechanical properties were examined. Interesting hydrogels were produced from all three biopolymers with good potential as drug delivery systems.

2. Materials and methods

2.1. Materials

Commercially available unmodified corn starch was provided from Cargill, USA (CAS: 9005-25-8). Kraft lignin was purchased (SWKL – Indulin ATTM, Westvaco). Bleached southern hardwood pulp was provided by International Paper. Citric acid monohydrate

granular was obtained from Mallinckrodt chemicals (CAS 5949-29-1) and sodium hypophosphite monohydrate (CAS 10039-56-2) was obtained from Sigma-Aldrich.

2.2. Isolation of hemicelluloses from bleached hardwood pulp

Hemicellulose was isolated from bleached hardwood pulp by an alkaline extraction method. Briefly, the pulp was transferred to a NaOH solution (10%) in a 1:20 solid to liquid ratio and stirred for 3 h at 50 °C to solubilize the hemicellulose. The suspension was then filtered with house vacuum on Whatman GF/A glass microfiber filter paper to remove the filtrate containing hemicellulose from the residual solids. The filtrate pH was adjusted to 5–6 by adding acetic acid and then transferred to 99.5% ethanol (3x ethanol volume relative to the filtrate). The mixture was left overnight to allow the hemicellulose to precipitate (no stirring) and settle to the bottom. The clear liquid above the precipitate layer was carefully removed by vacuum suction. The hemicellulose precipitate was washed 3 times by 70% ethanol. The product was freeze-dried to yield hemicellulose powder

2.3. Hydrogel preparation by reactive extrusion

Hydrogels were synthesized based on three different natural polymers, starch, lignin and hemicellulose. The hydrogels were prepared using a micro-extruder (Xplore, Micro 15cc Twin Screw Compounder). The extruder feed is open to atmosphere and the outlet pressure is not measured; there is a recirculation line in the extruder. Several formulations were prepared by varying the CA contents from 20 to 200% (wt CA:wt polymer). Also SHP was included in some formulations, when included it was 20% relative to CA content in the desired formulation (wt SHP:wt CA). The residence time in the extruder was either 2 or 5 min of recirculation, and a screw rotation speed of 120 rpm was used. The twin-screw extruder was maintained at a temperature of 120 °C. (Thermogravimetric analysis showed no degradation of the carbohydrates and lignin at 120 °C, data not shown.) The formulations are listed in Table 1 and the extrusion process is illustrated in Scheme 1.

2.4. Characterization

FTIR analysis was performed on the samples from 4000 to 650 cm⁻¹, with a spectral resolution of 4 cm⁻¹. The spectra were recorded on a single reflection attenuated total reflectance (ATR) FTIR technique performed by a Platinum ATR Alpha instrument with 40 scans. The samples were washed with copious amounts of water to remove unreacted citric acid and SHP prior to FTIR analysis.

The carboxyl content can be determined after excessive washing of the material with water to remove unreacted citric acid and SHP. Acid–base titrations were used to determine the carboxyl content of the absorbent materials; a known amount of synthesized product was dissolved in excess 0.1 N NaOH (pH 12.5) and was allowed to react with the sample for 1 h. The remaining excess amount of NaOH was determined by titration with 0.1 N HCl using phenolphthalein as an indicator. The carboxyl content in milliequivalents of acidity per 100 g is calculated as:

$$\text{Carboxyl Content} = \frac{(V_b - V_a) \times N}{W} \times 100$$

Where, N is the HCl normality (eq/L), V_b = Volume of HCl without sample (mL), V_a = Volume of HCl in the presence of sample (mL), W = Weight of sample (g)

The degree of esterification and degree of substitution were determined by first dissolving the product in DMSO in a conical flask for 12 h, and then adding an excess of 0.3 N NaOH to the solution to saponify the ester for 2 h. The excess NaOH was determined by

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