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Design, characterization and preliminary *in vitro* evaluation of a mucoadhesive polymer based on modified pectin and acrylic monomers with potential use as a pharmaceutical excipient

J.C.O. Villanova[a,*], E. Ayres[b], R.L. Oréfice[c]

[a] Departamento de Farmácia e Nutrição, Universidade Federal do Espírito Santo – UFES, Campus Alegre, Avenida Alto Universitário – sem número, CEP: 29.500-000 Guararema, Alegre, ES, Brazil
[b] Departamento de Materiais, Tecnologias e Processos, Escola de Design, Universidade Estadual de Minas Gerais – UEMG, Belo Horizonte, MG, Brazil
[c] Escola de Engenharia, Departamento de Engenharia de Materiais, Universidade Federal de Minas Gerais – UFMG, Belo Horizonte, MG, Brazil

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ABSTRACT

Bio-based polymers have been reported to have applications in biomedical and pharmaceutical areas. Polysaccharides, especially prepared from plant sources, have served a variety of uses. This work aims to prepare a polymer for use as a pharmaceutical excipient containing a functionalized carbohydrate (pectin) and acrylic monomers (methyl methacrylate, butyl methacrylate and ethyl acrylate) *via* an emulsion polymerization technique. Carbon double bonds were incorporated into the pectin by reacting this natural polymer with glycidyl methacrylate. The methacrylated pectin was then polymerized with acrylic monomers by emulsion polymerization. The mucoadhesive performance of the materials was investigated by *in vitro* preliminary assays based on viscometric studies, texture analysis and film wettability. The obtained results showed that the synergistic viscosity increase with greater concentrations of modified pectin. The contact angle decreased, suggesting an increase in the wettability for polymers with large amounts of methacrylated pectin. The addition of mucin in lattices caused an increase in the intermolecular forces and in the work of adhesion. This corroborates the use of pectin as a mucoadhesive excipient for mucoadhesive drug delivery systems.

1. Introduction

Advances in polymer science have led to the development of novel delivery systems. There is currently a growing interest regarding the use of carbohydrates that are individually modified and/or associated with synthetic polymers in the field of materials science for pharmaceutical, dental, biomedical and food applications. In recent years, there has also been increasing interest in the development of plant-derived composite materials, which are sometimes called "green composites" or "bio-based polymers". They combine the advantages of synthetic polymers, such as processability, stability and low hydrophilicity, with unique properties of natural materials, such as low toxicity, low cost, biodegradability and biocompatibility. Green composites are materials with ecofriendly properties primarily due to the renewability and sustainability of their sources (Abdul Khalil, Bhat, & IreanaYusra, 2012; Beneke, Viljoen, & Hamman, 2009; Carneiro-da-Cunha et al., 2012; Coviello, Matricardi, Marianecci, & Alhaique, 2007; Deshmukh, Setty, Badiger, & Muralikrishna, 2012; Kadajji & Betageri, 2011; Klein, 2009; Kumar et al., 2012; Rodrigues & Emeje, 2012; Sandolo, Coviello, Matricardi, & Alhaique, 2007; Sharma, Dhuldhoya, Merchant, & Merchant, 2006; Šimkovic, Gedeon, Uhliariková, Mendichi, & Kirschnerová, 2011). However, very high concentrations of carbohydrates in their putative form are required to successfully function as dose-dependent drug release modifiers due to their high swellability/solubility in gastric medium. Hence, such carbohydrates must be modified to alter their physicochemical properties (Rana et al., 2011).

Pectin is a cell wall structural carbohydrate present in all higher plants. Its heterogeneous and complex chemical structure has a linear backbone consisting of D-galacturonic acid units linked by α-(1-4) linkages that are randomly interrupted by L-rhamnose α-(1-2) linkages. Other neutral sugars such as D-galactose, L-arabinose, D-xylose, L-rhamnose, L-fucose and traces of 2-O-methyl fucose may be present in the side chains. Its molar mass is high, ranging between 50,000 and 180,000 g/mol. Galacturonic acid has carboxyl groups that can be naturally esterified by methyl groups (CH_3) or that can react with ammonia to produce

* Corresponding author. Tel.: +55 28 3552 8684.
E-mail address: pharmacotecnica@yahoo.com.br (J.C.O. Villanova).

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carboxyamide. The degree of esterification (DE) or amidation (DA) can be expressed as a percentage and provides a basis for the classification of the pectin. In general, pectins with a degree of esterification higher than 50% are considered high-ester pectins (HM), and those with a DE lower than 50% are considered low-ester pectins (LM) (Chen et al., 2014; Sharma et al., 2006; Sriamornsak, Wattanakorn, & Takeuchi, 2010; Sriamornsak, 2003).

This polysaccharide has been extensively studied due to its particular characteristics: its application in targeted drug delivery systems (DDS) for the colonic region and its adhesive properties. One of the main advantages associated with the use of pectin in drug delivery systems is its resistance to passage through the proximal portion of the gastrointestinal tract (GIT), as it is specifically biodegraded by the anaerobic bacteria resident in the colon. Thus, the use of pectin is associated with the development of delivery systems for colon-specific drugs used for local or systemic treatment of ulcerative colitis, irritable bowel syndrome, Crohn's disease, colon carcinoma and other pathologies (Jain, Gupta, & Jain, 2007; Raj, Rubila, Jayabalan, & Ranganathan, 2012; Shukla & Tiwari, 2012; Sinha & Kumria, 2001; Souto-Maior, Reis, Pedreiro, & Cavalcanti, 2009).

Pectin is rich in carboxylic groups and capable of interacting with functional groups in the mucus layer. Another advantage attributed to the use of pectin as a pharmaceutical excipient is its adhesive property, derived from the formation of hydrogen bonds between its polysaccharide carboxyl groups and mucus hydroxyl groups (Abruzzo et al., 2012; Charlton, Davis, & Illum, 2007; Hagesaether, Hiorth, & Sande, 2009; Hagesaether & Sande, 2008a, 2008b; Muzzarelli et al., 2012; Sharma & Ahuja, 2011; Srivastava & Malvyia, 2011; Thirawong, Kennedy, & Sriamornsak, 2008; Thirawong, Nunthanid, Puttipipatkhachorn, & Sriamornsak, 2007). Bioadhesion is a pharmaceutical strategy that has been explored to increase the residence time of DDS in the body. Another advantage is the possibility of greater contact between the drug and mucous membranes, reducing the required concentration of the drug administered and the number of doses per day (Dodou, Breedveld, & Wieringa, 2005; Hagesaether et al., 2009; Lai, Wang, & Hanes, 2009; Smart, 2005).

Bioadhesive polymers can be classified as mucoadhesives (those that adhere to the mucus layer) or cytoadhesives (those that adhere specifically to the cell membrane), most of which have a mucoadhesive property. Mucoadhesion can be achieved by the use of materials capable of interacting with mucin by forming non-covalent bonds, hydrogen bonds, ionic bonds or van der Waals interactions and, thus, promote polymer/mucus entanglement. Polymers that have bioadhesive properties are usually hydrogel-forming macromolecules with a large number of groups that form hydrogen bonds (carboxyls, hydroxyls, amides or sulfates) (Dodou et al., 2005; Streubel, Siepmann, & Bodmeier, 2006).

There are three sub-families of mucins: (a) gel-forming secreted mucin, (b) cell surface mucin, and (c) non-gel-forming secreted mucin. Gel-forming mucins are the major constituents of mucus, which are responsible for mucus viscoelasticity. They are rich in cysteines, an amino acid that has an N-terminal and a C-terminal, which have a role in intermolecular disulfide interactions. Mucin is an oligosaccharide composed of galactose, fucose, N-acetylglucosamine, N-acetylgalactosamine and sialic acid residues. At a pH above 3, the sialic acid and terminal sulfate groups are ionized, giving the molecule a negative charge. From the polymeric standpoint, mucin can be considered a polymer that has polyelectronic alternating domains and grafted sugars, connected by flexible regions showing a small tendency of glycosylation. The molecule has hydrophilic and hydrophobic regions, with the ability to form hydrogen bonds and electrostatic interactions (Bansil & Turner, 2006; Duchene, Touchard, & Peppas, 1988; Harding, Davis, Deacon, & Fiebrig, 1999; Linden, Sutton, Karlsson, Korolik, & Mcguckin, 2008; Svensson & Asnebrant, 2010).

It is believed that the following events are involved in bioadhesive phenomena: adsorption, spreading of the bioadhesive material on the mucosal membrane, an increase in contact area, and interpenetration between the mucosal membrane and polymer chains. The stages involved in the mucoadhesion and the possible interactions that may occur with mucin are shown in Fig. 1. Initially, an intimate contact between the layer and the mucoadhesive DDS occurs due to either a good wetting of the bioadhesive surface or swelling of the mucoadhesive polymer. Contact is then established, and the interpenetration of the mucoadhesive polymer chain on the mucus occurs. Weak chemical bonds are formed during the final stage. Numerous theories have been proposed to explain bio/mucoadhesion. The most prevalent theories are the same as those that describe adhesion events for metallic and polymeric materials. These include electronic, adsorption, wetting, diffusion and fracture theories (Bansil & Turner, 2006; Hagesaether et al., 2009; Huang, Leobandung, Foss, & Peppas, 2000; Sriamornsak et al., 2010).

During the development of adhesive materials and/or DDS, the determination of the bio/mucoadhesive capacity is necessary to quantify the adhesive strength, to compare different bioadhesive materials, and to allow for quality control tests. A simple procedure to assess the absolute force of bioadhesion *in vitro* is based on the viscous behavior of mucin-polymer blends. The flow of liquids and quasi-solids can be described by the shear viscosity, or simply viscosity, which is defined as the resistance of a material to flow. In other words, viscosity is a measurement of the internal friction of a fluid, which becomes apparent when a layer of the fluid moves over another layer. The amount of force required to cause this movement is called shear. Shear forces occur when a fluid is physically moved or distributed. Highly viscous fluids require a greater force to move a layer over another than less viscous materials. The reciprocal of viscosity is fluidity, an indicator of the "mobility" of a material. Stress and shear forces can be defined in terms of time, direction, and the extent of deformation. Because of their peculiar properties, polymers with high molar masses and entangled conformations show viscoelastic behavior, that is, they have elastic and viscous deformation components. In general, the higher the viscosity of a material, the greater is the resistance to flow (Chen, Wen, Janmey, Crocker, & Yodh, 2010; Macosko, 1994; Swarbrick, 2007). The results obtained by Awasthi (2011) suggested that dilute pectin solutions show Newtonian behavior, but at a moderate concentration, they exhibit non-Newtonian behavior, and this pseudoplastic nature was found to increase with concentration. As the pH of the polymer solution was lowered, an increase in the viscosity of the system has been observed, which may be due to the charges acquired by carboxyl acid groups.

Another important *in vitro* method used by various authors to measure the adhesion in materials, food and pharmaceutical products is texture analysis using texture analyzers. The test is performed by applying controlled forces to the sample and recording the resulting force, deformation and time. In a typical test, the probe touches the surface of the sample and progresses into the inside of the sample at a predetermined speed. For example, the maximum penetration resistance force and the performed work can be measured and associated with the work of cohesion of the sample or the work of adhesion to the probe (Jones, Lowlor, & Woolfson, 2002; Thirawong et al., 2007). Tamburic and Craig (1995) and other authors (Jones, Brown, & Woolfson, 2001; Jones et al., 2000) have described the relationship between the viscoelastic properties of pharmaceutical systems, in particular the elastic properties, and adhesion to mucin.

Another parameter that interferes with bioadhesion is the wettability of a material. The event occurring at the solid/liquid interface