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Evaluation of retrograded starch as excipient for controlled release matrix tablets

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ABSTRACT

High amylose starch (*HAS*) was retrograded by two different methods. The physicochemical properties of the retrograded materials were evaluated and structural changes were highlighted. Micromeritics properties were demonstrated as suitable for the compression process. Hydrophilic matrices were prepared by dry granulation of the retrograded starch. The *in vitro* release of diclofenac sodium (DS) in media with different pH values (1.2 and 7.4) was evaluated. The release profiles demonstrated the lowering of drug release rates in acid medium, mainly when pectin was associated to the matrix by physical mixture. In enteric medium, increased rates of drug release were observed, so that $t_{80\%}$ occurred at approximately 60 min, while for the tablets obtained with HAS, this time was of approximately 120 min. The matrix obtained with pectin (during retrogradation and by physical mixture) enabled a more effective control over the drug release rates, so that $t_{80\%}$ of DS was 150 min and 210 min, respectively.

1. Introduction

Despite the wide and successful research with alternative routes of drug administration, the oral route remains the preferable choice because of its inherent benefits, such as safety, easy administration, flexibility of formulation, greater patient adherence to the treatment and the possibility of releasing drugs both locally and systemically [1,2]. Among oral controlled release systems, matrix tablets were noteworthy by presenting efficient manufacturing technology and high reproducibility, which reflects in lower costs of production, mainly when the direct compression of the powders is their way of obtainment [3,4].

Swellable hydrophilic matrices are monolithic systems that do not degrade upon contact with the aqueous medium, undergoing hydration, which leads to the formation of a swollen diffusion layer, controlling the rates of release. The polymer swelling, the solute diffusion throughout the matrix, and erosion are also mechanisms involved in the control of drug release [5,6].

Natural polymers play an important role in the design of these systems, since they are materials from renewable and abundant sources, additionally, they are nontoxic and biodegradable. Besides, they can confer or enhance controlled release properties to the systems due to molecular properties of polymers, such as their monomer nature and type/degree of substitution [7–9]. Furthermore, *in situ* drug release can be reached because of the presence of glycoside bonds in the polymer structure that are hydrolytically cleaved by colonic enzymes [10].

Starch, a natural high molecular weight polysaccharide composed by glucose units, has received great attention as a carrier of matrix tablets, since it can be modified by a number of physical, chemical and enzymatic procedures, such as cross-linking [11], pregelatinization [12], retrogradation [13], complexation [14] and others, considering that native starch does not present suitable properties to reach desired drug release rates [12,13,15].

The retrogradation process of the starch, which occurs by hydrothermal treatments, converts the pregelatinized starch (amorphous) to a more resistant and compacted crystalline form [16,17], known as resistant starch (*RS*), which can exist in different

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subtypes. RS-I is physically inaccessible to digestion by its entrapment in the matrix of grains, seeds and legumes, whereas RS-II corresponds to the non-gelatinized starch (native granular starch). RS-III is the retrograded starch and finally RS-IV is the chemically modified starch. However, advantages such as high thermal stability and low water solubility are attributed to the RS-III [13,18].

RS has been considered a promising material for the development of systems intended for colonic drug delivery, since such starch fraction is not absorbed in the stomach and the small intestine, but is selectively degraded by the microbiota of the colon [19–21]. In this regard, the colon has been viewed as an important site for drug delivery due to reduced proteolytic activity, longer transit time, and pH values close to neutrality, being effective not only in the treatment of local pathologies, such as ulcerative colitis, Crohn's diseases, colon carcinomas and infections [22], but also in the treatment of systemic pathologies. Besides, the colon represents an important site for oral administration of proteins [23,24]. The brush-border present in the colonic membrane and the high responsiveness of the mucosa make the colon a site with increased chances of drug absorption [25].

Recently, a great number of studies have shown that high amylose starch (*HAS*) – a hybrid variety of starch composed of amylose and amylopectin (70:30) [26] - is the more suitable material to obtain high levels of *RS* because the crystallites formed remain embedded in the amylose matrix and thereby they are protected from rapid exposure to digestive enzymes [16,27].

Pectin (*P*) is a natural polysaccharide composed mainly by homogalacturonans and rhamnogalacturonans residues, which correspond to linear and smooth fractions, respectively [28]. It has been used as excipient for targeting drugs to the colon, because when in contact with acid medium, it remains as macromolecular aggregates and due to its digestibility by colonic microbiota [29]. In our research group, the impact of the pectin addition onto release properties has been studied in different drug delivery systems, such as cross-linked *HAS*/*P* matrices loaded with nimesulide [30], mucoadhesive beads of gellan gum/*P* intended to the controlled release of ketoprofen [31], blends of cross-linked *HAS*/*P* loaded with DS [11], free films of HAS/P mixtures cross-linked with sodium trimetaphosphate [32], colon-specific films coating based on *RS*/*P* [13], and more recently, *RS*/*P* free-standing films reinforced with nanocellulose to colon-specific release of methotrexate [33].

Based on promising results, the use of the *RS* and *RS*/*P* blend as an excipient to design hydrophilic matrix tablets was evaluated. Henceforth, *HAS* was retrograded by two different methods (through constant temperature and thermal cycles), in order to verify its impact on the *RS* yield and on the performance of tablets as a controlled release system. *DS*, a nonsteroidal anti-inflammatory drug (*NSAID*), was used as a model drug. The physicochemical (crystallinity, swelling and porosity) and thermal (*TG*/*DTG*) properties of such retrograded materials were evaluated, as well as micromeritic properties (size distribution, density and flow). The performance of the materials as tablet excipient intended to the control of drug release rates throughout gastrointestinal tract (*GIT*) was evaluated by *in vitro* tests in media with different pH values (1.2 and 7.4).

2. Materials and methods

2.1. Materials

High amylose corn starch (Hylon VII type – 70% amylose, lot:HA9140) was obtained from National Starch & Chemical (New Jersey, USA), sodium hydroxide (lot: 611648) was supplied by Grupo Química (Rio de Janeiro, Brazil), 37% hydrochloric acid (lot: 29957) was provided by Quimis (Diadema, Brazil), diclofenac sodium was purchased from Henrifarma (São Paulo, Brazil), pectin (type LM-5206CS – DE < 50%, lot: S74431) was provided by CP Kelco (Copenhagen, Denmark), pancreatin (lot: 0903372) was purchased from Vetec (Duque de Caxias, Brazil), 3,5-dinitrosalicylic acid (purity ≥ 98.0%, lot: 125k3664) was provided by Sigma–Aldrich Co. (St. Louis, USA), purified water (Milli Q, Millipore).

2.2. Methods

2.2.1. Retrogradation of high amylose starch (HAS)

Aqueous dispersions of *HAS* at different concentrations (20 or 40%) were autoclaved at 121 °C (15 min) for starch gelatinization. The gelatinized starch (*GS*) was retrograded according to two different methods in order to assess the impact of the storage time and temperature in the material properties. In *M1*, the temperature was kept constant (4 °C) for 8 days (isothermal cycle) and in *M2* it was employed alternating cycles of temperature (4 °C and 30 °C, 2 days at each temperature) for 16 days [34]. All samples were dried in a forced air circulation oven-drier at room temperature until constant weight.

Retrograded samples were labeled as *M120*, *M140*, *M220* and *M240* respective to the method of retrogradation (*M1* or *M2*) and concentration of polymers (20 or 40%). In this sense, the *M220* sample was those obtained from *M2* method and composed by 20% of polymer.

2.2.2. Enzymatic digestion and resistant starch content

In order to eliminate *RSI* and *RSII* fractions, a known mass (100 mg) of *HAS, M120, M140, M220* and *M240* samples were mixed with 2 mL of phosphate buffer (0.1 mol/L; pH 7.1) and kept in water bath (100 °C) by 30 min [35]. After that, cooled samples were incubated in 0.5 mL of a pancreatin enzymatic solution (0.15 g/mL), at 37 °C for different times (20, 60, 120, 150 and 180 min). Ethanol (80%) was added to the samples for stopping the enzymatic activity.

The glucose content provided by starch hydrolysis was quantified by the reaction with 3.5-dinitrosalicylic acid (*DNS*) [36] based on the standard glucose. Both *RDS* (rapid digestible starch – digested at 20 min) and *SDS* (slowly digestible starch – digested between 20 and 120 min) were used to calculate *RS* content, according to Equation (1) [37]:

$$RS = \frac{(Total\ Starch - RDS - SDS)}{Total\ Starch} \times 100 \quad (1)$$

2.2.3. Physicochemical characterization of samples

2.2.3.1. Moisture content. Moisture content of *HAS, M120, M140, M220* and *M240* samples was assessed gravimetrically on analytical infrared moisture balance (MettlerTM, PL 200/LP 11). A sufficient mass of samples (about 1 g) was uniformly disposed on the metallic pan of the balance and heated by infrared (105 °C) until constant weight was reached. The results were expressed as percentage of water loss in relation to the initial mass [38].

2.2.3.2. X-ray diffraction (XRD) analysis. Crystallinity patterns of the *GS*, *HAS*, *M120*, *M140*, *M220* and *M240* samples were evaluated from their diffractograms recorded on a X-ray diffractometer (Siemens® – Model D5000; Germany), using nickel-filtered Cu Kα radiation (λ = 1.5406 Å) (tube operating at 40 kV and 30 mA). The scanning regions were collected from 4 to 70° (2θ) in step size of 0.05° (2θ).