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Research Paper

Preparation, characterization and application in controlled release of Ibuprofen-loaded Guar Gum/Montmorillonite Bionanocomposites

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ABSTRACT

Neutral guar gum-montmorillonite and cationic guar gum-montmorillonite nanocomposites loaded with ibuprofen were prepared, and their ability to control *in vitro* release of the drug was presented. These materials exhibited a reduced initial burst release effect and sustained release of up to several hours in a pH 7.4 simulated intestinal fluid. Blank experiments suggested a nanocomposite-mediated action. Improved properties were demonstrated for two different clay minerals: Sodium Wyoming (SWy-2) montmorillonite from the Source Clay Repository and a Portuguese montmorillonite from the Benavila bentonite deposit. The prepared materials were based on abundant, low-cost, natural minerals and plant-extracted biopolymers, and were synthesized using a facile method, thus exhibiting a low environmental impact.

1. Introduction

Clay minerals are ubiquitous near the Earth's surface and offer remarkable potentials in material science (Bergaya and Lagaly, 2013). Among others, clay-polymer nanocomposites (CPN) are extensively investigated across disciplines (Bergaya et al., 2013). Currently, there is an urgent need to seek advanced functional materials with low environmental impact, which generates a strong interest in biopolymers. Clay-biopolymer nanocomposites are a novel class of versatile materials with an expanding range of possible applications involving drug delivery systems and tissue engineering (Dawson and Oreffo, 2013; Lambert and Bergaya, 2013; Ruiz-Hitzky et al., 2013; Mansa et al., 2015). Smectite is the most common clay mineral component of these materials (Lambert and Bergaya, 2013).

Montmorillonite (Mt) belongs to the smectite group, which comprises the 2:1 layer type, swelling clay minerals with relatively low layer charge (0.3 to 0.6 per half unit cell - $O_{10}[OH]_2$) (Velde and Meunier, 2008). In particular, Mt is a dioctahedral smectite with heterovalent substitutions in octahedral sheets ($Mg^{2+} \rightarrow Al^{3+}$) and the typical chemical formula - $(Na,Ca)_{0.3}(Al,Mg)_2Si_4O_{10}[OH]_2 \cdot n(H_2O)$.

Medicinal properties of clays have been recognized since ancient times (Young et al., 2011; Gomes et al., 2013), and up till now, raw clays and clay minerals have been used in pharmaceutical formulations as active agents and excipients. Due to their cation exchange capacity and adsorptive potential, they can interact with drug molecules, facilitating their liberation. Sustained release of drugs, controlled by desorption from clay mineral excipients, was found favorable in the case of antibiotics, amphetamines and anti-inflammatory drugs (Mcginity and Lach, 1977; Porubcan et al., 1978; Zheng et al., 2007; Gomes et al., 2013). Carretero and Pozo (2009) describe advantageous rheological, colloidal, thixotropic, mechanical and bioadhesive properties of clay mineral excipients. By making the gastric mucus more viscous and stable, clay minerals can act as gastrointestinal protectors against aggressive agents, such as pepsin and some anti-inflammatory drugs (More et al., 1987; Droy-Lefaix and Tateo, 2006). Smectite was demonstrated to be efficient in alleviating ailments caused by ingestion of non-steroidal anti-inflammatory drugs (Droy-Lefaix and Tateo, 2006).

Guar gum is a galactomannan biopolymer of high molecular weight, extracted from endosperm of guar plant's seeds (Mathur, 2011). It is a copolymer of mannose and galactose, comprised of a linear backbone of D-mannopyranose units, linked through β(1→4) glycosidic bonds. D-galactopyranose grafts are side-chained to mannose units at the C-6 position by α(1→6) glycosidic bonds. One derivative of guar gum is

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guar 2-hydroxy-3-(trimethylammonio)propyl ether chloride (cationic guar gum), modified with a quaternary ammonium cation. Guar gum and its derivatives are manufactured at an industrial scale and primarily serve as highly viscous food hydrocolloids. Cationic guar gum has extensive use in cosmetics, where it serves as a viscosity, volume and foam enhancer. Guar gum is used in pharmaceutical formulations and as an excipient with drug release controlling properties due to its non-toxicity, biodegradability, low cost and useful physicochemical properties (Mathur, 2011). Moreover, it is reported to be therapeutically active (Alam et al., 2000; Chaurasia et al., 2006; Gamal-Eldeen et al., 2006; Butt et al., 2007; Belo et al., 2008; Kuo et al., 2009; Takahashi et al., 2009). Native and chemically modified guar gum has been proposed to serve as a cost-effective matrix and a coating in colonic and retarded delivery of various drugs, as indicated by numerous in vitro and in vivo studies (Altaf et al., 1998; Prasad et al., 1998; Soppimath et al., 2001; Krishnaiah et al., 2002a, 2002b; Chourasia and Jain, 2004; Toti and Aminabhavi, 2004; Sen et al., 2010; Tiwari and Prabaharan, 2010; Prabaharan, 2011; Tripathy et al., 2013; Singh et al., 2014, Seeli and Prabaharan, 2016).

Biopolymers become adsorbed and intercalated in the interlayer space of smectite clay minerals, driven by electrostatic interactions or by a gain in the system's entropy (Henao and Mazeau, 2009; Theng, 2012). As a result, clay minerals may undergo delamination leading eventually to exfoliation giving rise to CPN. In such materials, clay mineral layers act as a nanometer-sized phase domain associated with a polymeric matrix (Theng, 2012; Bergaya and Lagaly, 2013). Such a unique structure may induce modulated release of the drug due to the interaction with both the polymer and the clay mineral. The potential use of the guar gum-Mt nanocomposites in drug delivery applications was suggested by Mansa and Detellier (2013).

Ibuprofen (IBU) is a non-steroidal, anti-inflammatory drug with analgesic and antipyretic properties. However, treatment with (IBU) frequently leads to side effects, due to the reported gastrointestinal toxicity of this drug (Lichtenstein et al., 1995). IBU contributes to topical injuries of the gastric mucus, what decreases mucus resistance to acidic environment, pepsin and some exogenous factors, such as the drug itself (Wolfe et al., 1999). Additionally, IBU has an adverse systemic effect on gastric, mucosal protective agents (Schoen and Vender, 1989). Another problematic issue is related to the fast absorption of the drug (maximum blood concentration levels of IBU are reached within 1-2 h) and its rapid elimination from the plasma (~2 h) (Wilson et al., 1989).

Due to its short half-life and adverse gastrointestinal side effects, modified drug delivery systems for IBU are desired. Such systems should exhibit sustained release of the drug so as to: decrease dosing frequency, prevent reaching toxic concentration of drug in the body, hinder unsteady release, and minimize occurrence of side effects (Wilson et al., 1989; Arida et al., 1999). Several authors report modified IBU delivery systems, based on polymers (Das et al., 2006; Pang et al., 2011; Abdeen and Salahuddin, 2013; Seeli et al., 2016), clay minerals (Zheng et al., 2007); halloysite nanotubes (Tan et al., 2013, 2014; Yuan et al., 2015); LDH (Rojas et al., 2012), zeolites (Horcajada et al., 2006), and CPN (Depan et al., 2009; Campbell et al., 2010). However, to the best of our knowledge, there are no such systems based on guar gum-Mt nanocomposites, which are attractive due to high adsorptive potential and cation exchange capacity of the clay mineral component, as well as intercalation of guar gum. The latter contributes to an increase of montmorillonite interlayer space, potentially contributing to further intercalation of drug molecules, which can also interact with guar gum's functional –OH groups. Mt in particular is advantageous for use in preparing nanocomposites with water-soluble polysaccharides due to its hydrophilicity and its dispersibility in water. Additionally, the use of Mt from a raw bentonite deposit can give substantial insight into clay mineral-polymer interactions, which are usually studied using commercial clay products and reference clay minerals.

2. Materials and Methods

2.1. Materials

Raw Portuguese Mt from the Benavila bentonite deposit (BV3) and the reference clay mineral, Sodium Wyoming Mt (SWy-2), were used to prepare the CPN. BV3 was collected from the Benavila bentonite deposit located in the central-east part of Portugal, close to Benavila town, which belongs to Portalegre district (-7.8522 W and 39.1275 N at the altitude of 158 m.a.s.l.). Typically, about 1kg of BV3 was purified using a wet sieving procedure. SWy-2 was supplied from the Source Clay Repository (the Clay Minerals Society, USA). Clay fraction (<2 μm) was achieved from both the BV3 and SWy-2 clays by a sedimentation procedure according to Stokes Law. The amount of clay fraction for the BV3 sample was determined by an X-ray beam particle size analyzer (Micromeritics® Sedigraph 5100). Subsequently, to enhance their swelling properties (Norrish and Quirk, 1954) Mt samples were saturated with Na^+ according to a procedure adapted from Carrado et al. (2006). Clay samples were then washed with distilled water and recovered by centrifugation (10 000 rpm). After washing, dialysis was performed to remove excess salts (using dialysis membranes from Spectrum Laboratories Inc., MCWO 12,000 – 14,000) until no Cl^- was detected by $AgNO_3$ test. The samples were dried at 60°C and ground with an agate mortar and a pestle. The sodium saturated samples were labelled Na^+-SWy and Na^+-BV3.

Neutral guar gum (NGG) was purchased from Sigma-Aldrich (USA). It has a total ash content <1% and loss on drying < 13%. Cationic guar gum (gum guar 2-hydroxy-3-(trimethylammonio)propyl ether chloride, CGG) with N content ranging from 0.8 – 1.8% was purchased from Spec-Chem Ind. (China). Both gums were used as received.

Ibuprofen (α-Methyl-4-(isobutyl)phenylacetic acid) sodium salt ≥98% with a molecular formula $C_{13}H_{17}O_2Na$ and a molecular weight of 228.3 g/mol, was supplied from Sigma-Aldrich and used as received (See Fig. 1).

2.2. Methods

2.2.1. Preparation of Ibuprofen-loaded Mt-NGG Nanocomposite

The IBU/SWy-NGG, having NGG : IBU sodium salt: Na^+-SWy mass ratio of 6 : 2 : 1 was prepared using the following procedure: 0.7 g of Na^+-SWy were dispersed in 600 mL of distilled water. Subsequently, 1.4 g of IBU sodium salt were added to the clay mineral dispersion, followed by the addition of 4.2 g of NGG. The mixture was stirred magnetically (1500 rpm) at room temperature for 2 weeks. Some part of the material was removed at that point, dried at 50°C and ground with an agate mortar (labeled as IBU/SWy-NGG-U). The remaining part was recovered by centrifugation at 5000 rpm for 5 min, the supernatant was discarded, and the sample was dried at 50°C and ground with an agate mortar, without further washing (labeled as IBU/SWy-NGG). The high NGG to Na^+-SWy ratio was chosen to enhance delamination of the clay mineral (Mansa and Detellier, 2013).

2.2.2. Preparation of Ibuprofen-loaded CGG-Mt Nanocomposites

The IBU/SWy-CGG and IBU/BV3-CGG nanocomposites, having CGG : IBU sodium salt: Mt mass ratio of 4 : 2: 1, were prepared using the following procedure. 0.5 g of Na^+-SWy or Na^+-BV3 were dispersed in 1L of distilled water prior to addition of 1.0 g of IBU sodium salt. After 30 min, 2.0 g of CGG were added to the dispersions and stirred 3 days at 500 rpm, at room temperature. The unwashed samples, labeled IBU/SWy-CGG-U and IBU/BV3-CGG-U were then dried at 50°C and ground with agate mortar. Subsequently, a portion of both materials was washed with water. Typically, ~1.5 g of the samples were dispersed in 200 mL of distilled water, shaken vigorously in a centrifuge bottle and centrifuged at 5000 rpm for 5 min. The samples were dried at 50°C and ground with an agate mortar. The resulting materials are referred to as IBU/SWy-CGG and IBU/BV3-CGG.

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