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Designing a biocompatible hydrogel for the delivery of mesalamine

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ABSTRACT

A new design for nanocomposite hydrogels based on cross-linked chitosan for the delivery of mesalamine is presented. To enhance drug loading in chitosan, the mineral montmorillonite was incorporated into the matrix. The exfoliated silica montmorillonite nanosheets form interactions with both chitosan and mesalamine, which affect the hydrogel's drug release mechanism and swelling properties.

The impact of montmorillonite and glutaraldehyde concentrations on the hydrogel properties was investigated. In vitro drug-release studies detected slower release over short times when montmorillonite was introduced into the matrix. This study is the first to evaluate the influence of pH during mixing and on mixing duration. It was shown that lowering the pH during mixing delayed the release since the positively charged drug was better introduced between the montmorillonite layers, as confirmed by differential scanning calorimetry (DSC) and fourier transform infrared spectroscopy (FTIR) analysis. All hydrogels showed prolonged sustained release of mesalamine over 24 h in simulated colonic fluid (pH 7.4). When modeled, the mesalamine release profile suggests a complex release mechanism, involving adsorption of the drug to the montmorillonite and its diffusion. The results imply that chitosan–montmorillonite hydrogels can serve as potential drug carriers for controlled-release applications.

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1. Introduction

Mesalamine (5-Aminosalicylic acid, 5-ASA) is a drug used extensively for long-term maintenance therapy in patients with mild to moderate inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis (Ritland et al., 1999). 5-ASA may additionally provide protection against the development of colorectal cancer. Numerous in vitro studies found that the beneficial effects of 5-ASA are related to its anti-inflammatory and anti-oxidant properties within the inflamed gut (Clemett and Markham, 2000). One major drawback of 5-ASA is its fast absorbance in the upper gastrointestinal tract, leading to a relatively small amount reaching the colon (Layer et al., 1995). Additionally, this treatment has gastrointestinal, hematological and general side effects. Agranulocytosis, toxic epidermal necrosis, paresthesia, hepatotoxicity, pancreatitis, pulmonary disease and male infertility have been reported (Omwancha et al., 2013).

In order to maximize the efficacy of the drug and avoid adverse effects associated with systemic absorption, targeted release of 5-ASA at the site of action, namely small bowel and/or colon, would be beneficial (Baumgart and Sandborn 2007). Many approaches aimed at the delivery of 5-ASA to the colon and circumventing the negative effects were suggested. Among these strategies, the use of bacterial degradable polymers that exploit metabolism by the colonic microflora to release the drug (Davaran et al., 1999) seems to be suitable as a site-specific approach for colonic drug delivery (Sinha and Kumria, 2001). An example of such a bacterial degradable polymer is chitosan, a polysaccharide derived from the *N*-deacetylation and de-polymerization of chitin. Chitosan has many useful characteristics including nontoxicity, good biocompatibility and non-antigenicity, that make them good candidates for clinical use (Ravi Kumar 2000). Furthermore, chitosan has the potential to be used as an absorption enhancer across intestinal epithelial cells due to its mucoadhesive property and its utility as a permeability enhancer (Borchard et al., 1996). The latter characteristic arises from chitosan's ability to open tight junctions between epithelial cells. The main limitation of chitosan as a carrier for 5-ASA is its short release times. As previously reported (Aguzzi et al., 2011), the release of 5-ASA from spray dried microspheres of chitosan was completed after one h in distilled water.

Researchers have proposed nanocomposites based on montmorillonite (MMT) and chitosan as a way to combine the benefits of both as drug carriers (Aguzzi et al., 2010; Banik et al., 2012; Cojocariu et al., 2012; Hua et al., 2010; Liu et al., 2008; Wang et al., 2008). MMT is a clay commonly used as both an excipient and an active substance in pharmaceutical products due to its adsorption and drug-carrying capabilities (Joshi et al., 2009). MMT has negatively charged layers that allow small positively charged

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molecules to intercalate between the exfoliated layers (Sinha Ray and Okamoto, 2003). There are several mechanisms that may be involved in the interaction between clay minerals and organic molecules such as hydrophobic interactions, Van der Waals forces, hydrogen bonding, ionic interactions and water bridging (Aguzzi et al., 2007). When chitosan and MMT are mixed, the exfoliated silica clay nanosheets act as a cross-linker for chitosan, which, as a result, forms a network structure (Liu et al., 2008). In addition, the interactions between the clay and the drug may improve the encapsulation efficiency and sustain its release (Wang et al., 2008). Chitosan/MMT nanocomposites were shown to provide slower 5-ASA release rates compared to chitosan alone. Yet, their ability to sustain the release of 5-ASA is still limited; drug release from compressed samples was completed within about 2 h in an acidic medium (Aguzzi et al., 2010).

In light of potential advantages of chitosan/MMT nanocomposites, the aim of this study was to develop an approach that produce longer release times. The underlying hypothesis was that none of the mechanisms described above, which are responsible for sustained release of 5-ASA, namely, physical cross-linking of the polymer and drug encapsulation within MMT, are efficient enough. It is further assumed that since 5-ASA is a hydrophilic molecule, regulating its release solely based on electrostatic interactions with MMT is difficult. Moreover, the efficacy of cross-linking chitosan with MMT alone could be limited. Therefore, this research explores another approach, where chitosan is cross-linked with glutaraldehyde (GA), the most common cross-linking agent for this polymer (Muzzarelli and Pariser 1978).

A systematic analysis of this new approach is presented. The effect of cross-linking density, MMT concentrations, pH of mixing and mixing duration before cross-linking on the potential of these hydrogels as a drug delivery system were investigated. It is demonstrated that sustained release over weeks can be obtained using these hydrogels.

The design of biomedical hydrogels that are both biodegradable and offer sustained release could open the door to a new generation of cross-linked functional hydrogels.

2. Materials and methods

2.1. Materials

5-Aminosalicylic acid (95% purity), montmorillonite K-10 and glutaraldehyde (GA) stock solution (50% (w/v)) were purchased from Sigma–Aldrich. Acetic acid (99.7% A.R.) was purchased from Gadot Biochemical Industries Ltd., Israel. Sodium hydroxide pearls and hydrochloric acid (32% A.R.) were purchased from Bio-Lab Ltd., Israel. $Na_2HPO_4 \cdot 12H_2O$ and $NaH_2PO_4 \cdot H_2O$ were purchased from Merck KGaA, NaCl was purchased from Frutarom Ltd., Israel. All chemicals were of analytical grade and were used as delivered, without further purification. Double-distilled water (DDW) was used in all aqueous solutions.

Low molecular weight chitosan was purchased from Sigma–Aldrich. The degree of deacetylation of the batch used in this study was determined in our previous work using FTIR and found to be 77%. The average molecular weight as determined by static light scattering was 207,000 g/mol (Keren Delmar 2015).

2.2. Hydrogel preparation

Chitosan hydrogels were prepared at a constant chitosan concentration and different MMT and GA concentrations. 0.5% (w/v) chitosan solution in 2% (v/v) acetic acid was mixed with 0.5% (w/v) 5-ASA solution. Different amounts of MMT powder were added to the mixture to obtain a concentration of 0.5% (w/v) or 1.5% (w/v) MMT. The acetic acid pH was adjusted to 5 with 5 M NaOH or to 1.4 with 1 M HCl. Next, 2.5 ml of acetic acid were poured into 8 ml glass vials and stirred at room temperature using a magnetic stirrer for 24 h or 2 h, depending on the experiment design. All solutions were freshly prepared, light-protected and nitrogen sealed to prevent the oxidative self-coupling of 5-ASA moieties (Jensen et al., 1992). Finally, the solution was mixed with 0.4% (v/v) or 0.2% (v/v) GA in order to achieve chemical cross-linking of chitosan. 300 μl of the final mixture were transferred into a PLA circular mold (diameter 14 mm, height 2 mm) to form hydrogels at room temperature.

2.3. Characterization of the hydrogels

2.3.1. Calibration curve of 5-ASA

Known concentrations of 5-ASA in PBS 130 mM pH 7.4 were scanned in the range 200–400 nm by a UV–vis spectrophotometer (aSynergy™ HTBioTek®) (Cui et al., 2008). A sharp peak was noticed at 330 nm; however, this peak was only observed at the concentration range of 0–0.2344 mg/ml. Therefore, the peak at 350 nm, where 5-ASA can be detected at the broader concentration range of 0–0.3125 mg/ml, was used. The linear calibration curve was $y = 5.8618 \times +0.0173$ ($R^2 = 0.9995$). Unknown concentrations of 5-ASA in drug release experiments were obtained by measuring the absorbance value at 350 nm.

2.3.2. Study of the drug-release rate from the hydrogels

2.3.2.1. Preparation of phosphate buffer saline (PBS). A phosphate buffer solution simulating intestinal fluids was prepared by dissolving 15.585 g $Na_2HPO_4 \cdot 12H_2O$ (di-sodium hydrogen phosphate dodeca-hydrate) and 1.166 g $NaH_2PO_4 \cdot H_2O$ (sodium di-hydrogen phosphate) in 100 ml double-distilled water (DDW). 20 ml of this solution were mixed with 8.9 g NaCl (sodium chloride), the volume was raised to 1 L using DDW, and the pH was adjusted to 7.4 using 5 M NaOH.

2.3.2.2. In vitro drug release. Unless otherwise stated, releases experiments were performed by submerging as-prepared wet hydrogels in 20 ml glass vials containing 4.8 ml PBS buffer with ionic strength of 130 mM and pH 7.4. This release medium was selected in order to simulate intestinal fluids and maintain the average pH of the colon (Fadda et al., 2010). Release studies were performed at physiological temperature of 37 °C in a bath shaken at 100 rpm.

A pinch of the release medium (200 μl) was withdrawn at scheduled time intervals in order to determine the 5-ASA concentration using the UV–vis spectrophotometer reading at 350 nm and a calibration curve. 200 μl of PBS were returned to the vial to maintain a constant volume. All drug release experiments were performed in triplets and the data is shown as the average ± standard deviation (SD).

The in vitro drug release data were analyzed by fitting it to the Peppas model (Ritger and Peppas 1987):

$$\frac{M_t}{M_\infty} = at^n \quad (1)$$

where M_t is the drug release at time t, M_∞ is the maximal drug release, a is the release rate constant correlated to the diffusion coefficient and n is the release exponent, indicative of the drug release mechanism.

2.3.3. Thermal analysis via differential scanning calorimetry (DSC)

DSC analysis was performed using a Q10, TA instrument. Physical mixtures of the compounds were mixed for 24 h in 2% acetic acid at pH 5, then dried overnight and ground to a powder. The samples (10–14 mg) were scanned in sealed aluminum pans.

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