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RESEARCH ARTICLE

Newly developed nano-biocomposite embedded hydrogel to enhance drug loading and modulated release of anti-inflammatory drug

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ABSTRACT

A newly developed iron-based nano-biocomposite (nano Fe-CNB) impregnated alginate formulation (CA) is proposed to improve drug loading and exhibit pH-responsive behavior of model anti-inflammatory drug-ibuprofen for controlled release applications. The proposed formulation is investigated with conventional β-CD addition in CA. The nano Fe-CNB-based formulations with and without β-CD, (Fe-CNB β-CD CA and Fe-CNB CA) are compared with only CA and β-CD incorporated CA formulations. The results indicate the incorporation of nano-biocomposite or β-CD into CA enhances the drug loading (>40%). However, pH-responsive controlled release behavior is observed for nano Fe-CNB based formulations only. The release studies from Fe-CNB β-CD CA indicate ∼ 45% release in stomach pH (1.2) within 2 h. In contrast, Fe-CNB CA shows ∼20% release only in stomach pH and improved release (∼49%) at colon pH (7.4). The rheology and swelling studies indicate Fe-CNB CA remains intact in stomach pH with a minimal drug release, but it disintegrates at colon pH due to charge reversal behavior of nano-biocomposite and ionization of polymeric chains. Thus, Fe-CNB CA formulation is found to be a potential candidate for targeting colon delivery, inflammatory bowel disease, and post-operative conditions.

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1. Introduction

The solubility of drugs play a crucial role in achieving therapeutic efficacy. Majority of the non-steroidal anti-inflammatory drugs (NSAID) are hydrophobic and belong to the bio-pharmaceutical classification system (BCS) class II, which are low soluble and high permeable. These drugs are commonly used for chronic conditions such as pain, rheumatoid, arthritis, inflammation, etc. Additionally, they are also used in post-operative dental implants, osteoporosis, inflammatory bowel disease (IBD), and colon targeting-based applications, which require administration for longer intervals, i.e. overnight controlled release. On frequent administration, they cause severe side effects such as gastric irritation due to poor aqueous solubility, stomach ulcers and bleeding, damage to the mucosal lining, and renal and cardiovascular damage (Luppi et al. 2003; Babazadeh 2006; Qu et al. 2006; Xing et al. 2012; Vieira et al. 2013). Moreover, the degradation of these drugs at gastric pH reduces their absorption (Vieira et al. 2013; Xing et al. 2012). Thus, most anti-inflammatory drugs such as ibuprofen (Arica et al. 2005; Woldum et al. 2008; Chen and Zhu 2012; Varghese and Ghoroi 2017), indomethacin, naproxen, ketoprofen, etc. are the potential candidates for controlled release.

The controlled release is generally achieved using the biopolymeric matrix (Chen and Zhu 2012), polymeric nano-encapsulation (Mokhtari et al. 2017), beads and film coating (Vieira et al. 2013), pro-drug approach (Peesa et al. 2016), and microencapsulation (Qiu et al. 2001) such as liposomes (Kaneda 2000), microgels (Qiu et al. 2001), micelles (Zhang et al. 2012), colloids (Xing et al. 2012), and hydrogels (Hoffman 2012), etc. The bio-polymers are used for controlled drug delivery due to their bioavailability, biocompatibility, and ease of availability. It offers certain advantages such as maintaining therapeutic concentration, targeted drug delivery, avoids frequent intake of medicine, and protects from damage to organs (Qu et al. 2006; Woldum et al. 2008; Chen and Zhu 2012). The biopolymers such as sodium alginate are widely used to form hydrogels for controlled drug delivery because of their ability to protect the mucosal lining in the GI tract (Hwang et al. 1995; Arica et al. 2005). However, hydrophilic hydrogels cause limitations in drug loading and release of hydrophobic drugs from the matrix due to a lack of interactions between the hydrophilic matrix and the hydrophobic drug. Also, it is challenging to attain therapeutic levels due to the aggregation tendency of the hydrophobic drugs in an aqueous environment, which increases the level of toxicity (Mateen and Hoare 2014; Li and Mooney 2016). To overcome this limitation, hydrophobic sites are introduced within the hydrophilic hydrogel matrix by the inclusion of hydrophobic macro-monomers such as cyclodextrins (CDs), which facilitate more binding sites to the hydrophobic drug (Mateen and Hoare 2014).

The CDs improve the solubility of the hydrophobic drug, bioavailability, oral absorption, stability, and reduce GI irritation (Bera et al. 2016). While the exterior hydrophilic groups of the CD form crosslinkers with the hydrophilic polymer, the hydrophobic cavity incorporates the hydrophobic drugs to improve their solubility and bioavailability (Salústio et al. 2011; Larrañeta et al. 2018). However, a specific application such as IBD and colon-targeted drug delivery demands pH responsiveness, controlled release with minimal drug release at stomach pH, and improved release at colon pH. Feeney et al. carried out the controlled release of ibuprofen for colon-specific delivery using dextran functionalized with methacrylic groups hydrogel, which retains the drug in the

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