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Controlled-release triple anti-inflammatory therapy based on novel gastroretentive sponges: Characterization and magnetic resonance imaging in healthy volunteers

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ABSTRACT

The current work aimed to develop novel composite sponges of chitosan (CH)–chondroitin sulfate (CS) as a low-density gastroretentive delivery system for lornoxicam (LOR). This triple anti-inflammatory therapy-loaded matrices are expected to expand and float upon contact with gastric fluids for prolonged times. CH and CS solutions (3%, w/w) were prepared, mixed in different ratios, lyophilized, coated with magnesium stearate and compressed. The CH:CS interpolymer complex (IPC) was evaluated *via* FT-IR, DSC, and XRD. The compressed-sponges were evaluated for appearance, structure, porosity, pore diameter, density, wetting-time, floating characteristics, adhesion-retention, and LOR-release. The gastroretentivity of the best achieved magnetite-loaded sponges was monitored in healthy volunteers *via* MRI. The interaction between CH (protonated amino groups) and CS (anionic carboxylate/sulfate groups) proved IPC formation. DSC and XRD studies confirmed loss of LOR crystallinity. The sponges possessed interconnecting porous-network structures. The porosity, mean pore diameter, and bulk density of CH:CS (10:3) IPC sponges were 11.779%, 25.4 nm, and 0.670 g/mL, respectively. They showed complete wetting within seconds, gradual size-expansion within minutes and prolonged adhesion for hours. Controlled LOR-release profiles were tailored over 12 h to satisfy individual patient needs. Monitoring of sponges *via* MRI proved their gastroretentivity for at least 5 h.

1. Introduction

Biomedical sponges are soft and flexible scaffolds with interconnected porous structures. The good fluid absorption capability and cell interaction make them suitable carriers for drug delivery (Jayakumar et al., 2011). According to Anisha et al. (2013), the ideal biomedical sponges should be biodegradable, non-toxic, non-allergic, and allow for proper nutrient and gas exchange as well. Like wafers, the sponges are able to maintain their swollen structure for a long period, and therefore, offer longer residence time that allows for effective drug absorption and enhanced bioavailability. The unique characteristics of sponges, attributed to their inter-connecting porous nature and higher surface area, qualify them for higher drug loading capacity compared to conventional equivalent dosage forms (Ayensu et al., 2012). On basis of the aforementioned, the sponges have been explored as promising drug delivery systems for buccal administration (Grimm et al., 2011), implantation (Foda et al., 2007), wound dressing (Chen et al., 2013), and gastroretention (Gröning et al., 2007). Simple drug-loaded sponges using natural polymers like chitosan (Foda et al., 2004), gelatin (Lee and Yalkowsky, 1999), carboxymethyl cellulose (Ryan and Sax, 1995), and collagen (Kim et al., 2014) were previously investigated. In addition, composite interpolymer complex (IPC) sponges based on the electrostatic interaction between polycationic polysaccharides like chitosan and polyanionic polysaccharides as chondroitin sulfate sodium (Park et al., 2000), collagen (Wang et al., 2013), and hyaluronic acid (Shang et al., 2014) were exploited to achieve tailored drug release characteristics.

Chitosan (CH) is the principle *N*-deacetylated derivative of the naturally occurring chitin, Fig. 1(a). CH has attracted great attention in the pharmaceutical and biomedical fields, especially for the controlled release drug delivery systems, due to its favorable biological properties transpired from being a non-toxic, biocompatible, biodegradable, and hydrophilic biopolymer. In fact, the 'tunable' aspect of CH *via* facile chemical modification enables optimization to give appropriate biomaterials for therapeutic applications (Hu et al., 2013). In acidic media, CH acquires a net

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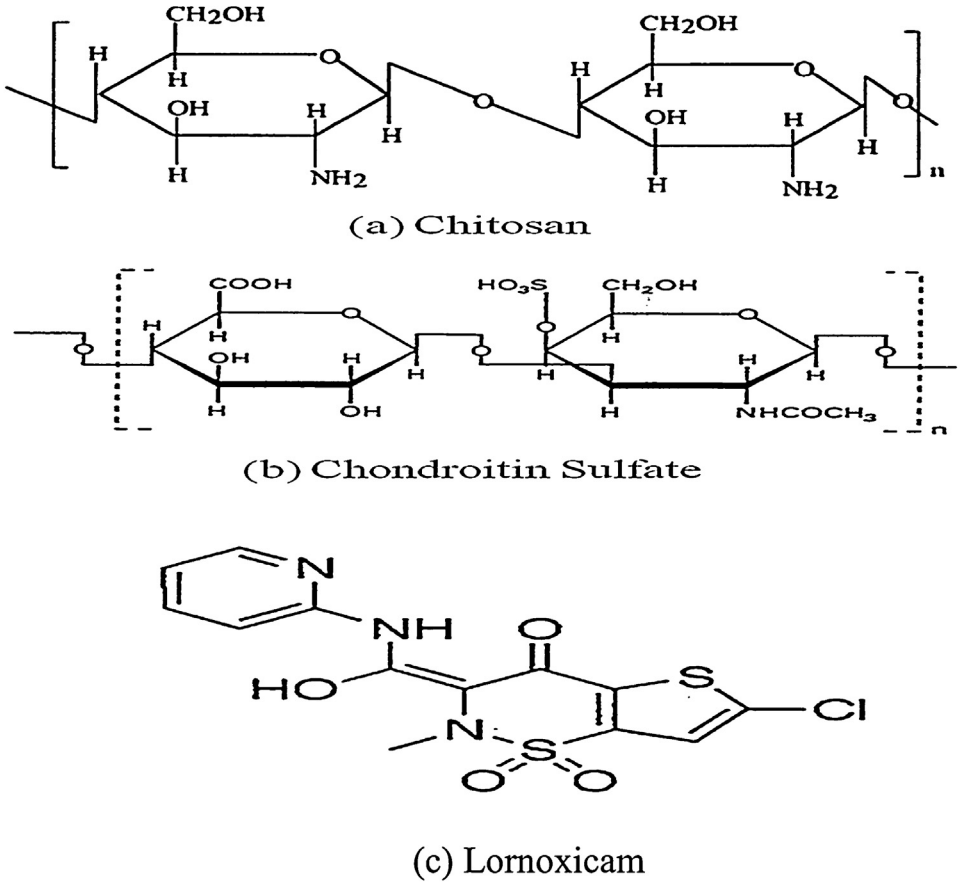

Fig. 1. Chemical structures of chitosan (a), chondroitin sulfate (b) and lornoxicam (c).

positive charge due to the protonation of amino groups allowing for facile cross-linking with negatively charged surfaces, drugs, and polymers (Sinha et al., 2004).

Chondroitin sulfate sodium (CS) is a natural sulfated glycosaminoglycan made up of alternating repeating units of *N*-acetylgalactosamine and D-glucuronic acid, Fig. 1(b). CS is a major component in the extracellular matrix of several human tissues such as humans' cartilage, bone, cornea, skin, and arterial walls (Vázquez et al., 2013). It acquires its polyanionic character from the existence of multiple carboxylate and sulfate groups in its molecular structure.

Lornoxicam (LOR) is a member of the oxicam group of NSAIDs, Fig. 1(c). It has more potent analgesic and anti-inflammatory activities than other NSAIDs like tenoxicam and dex-ketoprofen (Cevik et al., 2012). It is used for the symptomatic treatment of moderate to severe inflammatory pain in rheumatoid arthritis, osteoarthritis, perioperative, and postoperative pain associated with gynecological, orthopedic, abdominal, and dental surgeries (Sweetman, 2011). Unfortunately, the oral administration of LOR has some considerations including the limited solubility in the gastrointestinal tract especially in simulated gastric fluids (0.006 mg/mL) as well as the short elimination half-life; 3–4 h (Aburahma and Hamza, 2011). To maintain effective therapeutic drug concentrations for the treatment of osteoarthritis and rheumatoid arthritis, LOR is given by mouth in a daily dose of 12 mg in two or three divided doses (Sweetman, 2011). In fact, these large doses have been associated with severe local irritation and gastric ulcers due to the prolonged contact of insoluble drug crystals with the stomach wall.

To surmount LOR limitations, novel conceptual controlled-release gastroretentive LOR-loaded sponges were developed to (i) achieve more prolonged drug release rates taking the advantage of the controlled-release ability of CH–CS IPC matrix (Park et al., 2000), (ii) minimize the prolonged LOR contact with the stomach wall and benefit from the gastro-protective and ulcer-healing activities of CH (Anandan et al., 2004) and CS (Hori et al., 2001), (iii) maximize LOR absorption in the proximal part of the gastrointestinal tract (Sathiyaraj et al., 2011), and (iv) potentiate the chondrioprotective and anti-inflammatory activities of LOR with that of CH (Hu et al., 2013) and CS (Richette, 2012).

When designing a gastroretentive drug delivery system, the monitoring of its *in vivo* performance is of prime importance. To date, γ-scintigraphy and X-ray imaging are the most widely used imaging techniques for this purpose. On the other hand, few studies were conducted *via* magnetic resonance imaging (MRI). The latter technique has many advantages including high soft tissue contrast, high temporal and spatial resolution as well as lack of ionizing irradiation exposure; in contrary to the former imaging techniques (Knörgen et al., 2010; Kagan et al., 2006). Magnetite (ferric oxide) is used as additive (E 172) in food processing with an allowed daily intake of 0.5 mg/kg (Steingoetter et al., 2003). This low toxicity combined with low costs made magnetite the preferred MRI super-paramagnetic contrast marker for monitoring the best achieved gastroretentive sponges in healthy human volunteers.

In the current work, an attempt was investigated to develop, evaluate various composite sponges based on CH–CS interpolymer complexes (IPCs) and explore their potential as a gastroretentive delivery system for lornoxicam in healthy human volunteers.