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Coatless alginate pellets as sustained-release drug carrier for inflammatory bowel disease treatment

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ABSTRACT

Conventional alginate pellets underwent rapid drug dissolution and failed to exert colon targeting unless subjected to complex coating. This study designed coatless delayed-release oral colon-specific alginate pellets for ulcerative colitis treatment. Alginate pellets, formulated with water-insoluble ethylcellulose and various calcium salts, were prepared using solvent-free melt pelletization technique which prevented reaction between processing materials during agglomeration and allowed reaction to initiate only in dissolution. Combination of acid-soluble calcium carbonate and highly water-soluble calcium acetate did not impart colon-specific characteristics to pellets due to pore formation in fragmented matrices. Combination of moderately water-soluble calcium phosphate and calcium acetate delayed drug release due to rapid alginate crosslinking by soluble calcium from acetate salt followed by sustaining alginate crosslinking by calcium phosphate. The use of 1:3 ethylcellulose-to-alginate enhanced the sustained drug release attribute. The ethylcellulose was able to maintain the pellet integrity without calcium acetate. Using hydrophobic prednisolone as therapeutic, hydrophilic alginate pellets formulated with hydrophobic ethylcellulose and moderately polar calcium phosphate exhibited colon-specific *in vitro* drug release and *in vivo* anti-inflammatory action. Coatless oral colon-specific alginate pellets can be designed through optimal formulation with melt pelletization as the processing technology.

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1. Introduction

Inflammatory bowel disease such as ulcerative colitis is characterized by inflammation of intestinal mucosa (Amirshahrokhi, Bohlooli, & Chinifroush, 2011; Ha et al., 2012; Hassan and Soliman, 2010). It is considered as an autoimmune disease that affects mainly the colorectal region of the gastrointestinal tract (Ha et al., 2012; Hassan & Soliman, 2010). The main clinical symptoms of ulcerative colitis are diarrhea, mucilage or blood-pus stools and abdominal pain (Gong et al., 2012; Ramadass, Perumal, Jabaris, & Madhan, 2013). The ulcerative colitis is a long known medical condition that affects mainly the western population (Oosegi, Onishi, & Machida, 2008; Ramadass et al., 2013; Thippeswamy et al., 2011). Recent data indicates that significantly high rates of disease contraction occur among Asians with rising statistics over the years (Onishi, Oosegi, & Machida, 2008; Ramadass et al., 2013).

Alginate is a water-soluble polysaccharide commonly extracted from brown algae such as *Laminaria hyperborea*, *Ascophyllum nodosum* and *Macrocystis pyrifera* (Li et al., 2013; Pawar & Edgar, 2012; Schmid and Picker-Freyer, 2009). The alginate chain is made of homopolymeric zones of β-D-mannuronic acid blocks and α-L-guluronic acid blocks, interdispersed with alternating α-L-guluronic and β-D-mannuronic acid blocks. Alginate is non-toxic, non-immunogenic, biocompatible and biodegradable (González-Rodríguez, Holgado, Sánchez-Lafuente, Rabasco, & Fini, 2002; Lee & Mooney, 2012; Paques, van der Linden, van Rijn, & Sagis, 2014; Pawar & Edgar, 2012; Yang, Zhang, Wen, Liang, & Zhang, 2007; Yao, Ni, Xiong, Zhu, & Huang, 2010). It has been formulated as microspheres, microcapsules, gel beads, hydrogel, film, nanoparticles, pellets and tablets for drug delivery (Paques et al., 2014; Wong, 2011). With respect to lower intestinal tract- or colon-specific drug delivery, the multi-particulate drug delivery system such as pellets undergo a slower transit (Abrahamsson et al., 1996; Asghar & Chandran, 2006; Watts & Illum, 1997). The pellets can increase the mucosal exposure to drugs and the intended therapeutic effect

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(Bose, Elyagoby, & Wong, 2014; Kadunc, Šibanc, Dreu, Likar, & Tomaževič, 2014; Xu et al., 2012).

Melt pelletization is one of the latest technologies in pellet design and production. The pelletization process involves powder bed agitation with either a molten binding liquid or a solid binder which melts during the process. It is a one-pot, one-step technique which is simple to operate without aqueous or organic solvent (Wong & Heng, 2013). As a solvent-less method, the water-soluble additive such as calcium acetate can be loaded into the matrix without dissolving during the melt pelletization process and pre-crosslinking with alginate to form cakes and uncontrollable agglomeration (Nurulaini & Wong, 2011). Both sustained-release and fast-release melt pellets can be produced *via* judicious choice of binder. Over the years, sustained-release melt pellets can be prepared using hydrophobic meltable binders namely microcrystalline wax, stearic acid, glyceryl monostearate, glyceryl palmito-stearate and glyceryl behenate (Tan et al., 2014; Wong & Heng, 2013). Recently, hydrophilic melt pellets can be designed for intestinal-specific oral drug delivery using polyethylene glycol as meltable binder with sodium alginate and calcium acetate as non-meltable matrix polymer and water-soluble crosslinking agent respectively (Nurulaini & Wong, 2011). Different from alginate pellets processed using extrusion-spheronization technique (near 100% drug release within 180 min of dissolution in simulated gastric medium), substantially sustained-release alginate pellets can be produced using melt pelletization technique (<60% drug release at 360 min of dissolution in simulated gastric medium) in spite of hydrophilic excipients are employed (Nurulaini & Wong, 2011). A rapid dissolution of calcium acetate and polyethylene glycol of melt pellets induces fast pellet breakup and rigid calcium alginate crosslinkage formation. The drug release of hydrophilic melt pellets is retarded till their transit from medium of pH 1.2–6.8. The substitution of water-soluble calcium acetate with hydrophobic acid-soluble calcium carbonate gives rise to fast drug release. The calcium carbonate does not provide a fast release of soluble calcium to crosslink the alginate. In addition, the carbon dioxide gas produced from the reaction of carbonate salt with acidic medium can act as a porogen. The matrix becomes porous during dissolution and this ease the drug release.

With reference to ulcerative colitis, colon-specific drug delivery is imperative in order to reduce drug absorption in the upper gastrointestinal tract that can associate with systemic toxicity, and target drug accumulation and therapeutic effect in the colon. The sodium and calcium salts of alginate are known to undergo proton and sodium/potassium ion exchange in the gastric and intestinal milieu (Gao, Liu, Chen, Jin, & Chen, 2009; Lin, Zhou, Yingde, & Gunasekaran, 2010; Wang, Zhang, & Wang, 2009; Zhang, Wang, Xie, Li, & Wang, 2010). Using hydrophilic polyethylene glycol and sodium alginate as meltable binder and matrix material respectively, it is hypothesized that matrix hydrophobization with immediate availability of soluble calcium to crosslink the alginate can sustain drug release prior the matrix reaching the colon. The hydrophobic and crosslinked alginate matrix enables reduced levels of water ingress into the core, ion exchange between matrix and dissolution medium, and drug release. The mere crosslinked alginate matrix will not be able to survive the small intestinal transit under the influence of ion exchange. As such, this study investigates the drug release profiles of alginate melt pellets prepared using hydrophobic ethylcellulose, and calcium salts of varying water solubilities that confer different hydrophobicity and soluble calcium availability. In the development of colon-specific pellets, water-soluble chlorpheniramine maleate is used as the model drug in order to challenge the effectiveness of matrix in drug release retardation. The alginate melt pellets which exhibit colon-specific drug delivery are tested *in vivo* for their efficacy in ulcerative colitis treatment with prednisolone as the target therapeutic. These pellets are designed without the introduction of a barrier coat. Previous research studies largely focus on coated systems and enteric dosage forms using pH-dependent functional materials such as cellulose acetate phthalate (Bose et al., 2014; Chaturvedi, Kulkarni, & Aminabhavi, 2011; Ganguly, Aminabhavi, & Kulkarni, 2011). The present approach is presumed to incur less processes, time and cost in medicine development.

2. Materials and methods

2.1. Materials

Sodium alginate (mannuronate/guluronate ratio = 0.59, molecular weight = 4.765×10^6 Da; Manugel DMB, ISP, USA) was used as matrix polymer. Polyethylene glycol 3000 (Merck, Germany) was used as meltable binder. Chlorpheniramine maleate (Supriya Chemicals, India) was water-soluble model drug and prednisolone (Tianjin Tianyao Pharmaceuticals Co. Ltd, China) was drug for ulcerative colitis treatment used in the present study. Calcium carbonate as well as calcium phosphate and calcium acetate (Merck, Germany) were adopted as acid-soluble and water-soluble calcium salts respectively. Ethylcellulose 100 FP premium standard (ethoxyl content = 48.0–49.5%, viscosity = 90–110 mPa s, particle size = 30–60 μm), 100 premium standard (ethoxyl content = 48.0–49.5%, viscosity = 90–110 mPa s, particle size = 465 μm) and 45 premium standard (ethoxyl content = 48.0–49.5%, viscosity = 41–49 mPa s, particle size = 250–500 μm) were supplied by Colorcon Asia Pacific Pvt. Ltd., Singapore and were used as hydrophobic additive.

2.2. Preparation of melt pellets

The melt pellets were prepared using a high shear melt pelletizer (Laison Engineering Sdn Bhd, Malaysia). Each batch of processing powder load was 120 g, and consisted of drug, alginate, polyethylene glycol 3000 and calcium salt at 6, 46.3, 26.7 and 21%w/w respectively with reference to ethylcellulose-free melt pellets. The ethylcellulose loaded melt pellets were formulated with alginate content reduced in accordance to the mass of ethylcellulose incorporated.

The alginate, polyethylene glycol 3000, drug, calcium salt and ethylcellulose were placed in high shear melt pelletizer and preheated to 40 °C. The mixture was then agitated by impeller rotation at 250 rpm. The water-jacket temperature was kept at 60 °C throughout the pelletization process. At product temperatures of 50 °C, 52 °C and 53 °C, the impeller rotational speed was raised to 300 rpm, 450 rpm and 800 rpm respectively to prevent uncontrolled powder movement and wall deposition. At about 56 °C, the polyethylene glycol 3000 melted and bound the non-meltable powder mixture into agglomerates. The duration of post-melt phase was 11 min. The product temperature of 60 °C or below was kept to avoid product degradation. The formed pellets were collected. They were spread on an aluminum tray to cool to 25 ± 1 °C. Drug-free pellets were similarly prepared.

2.3. Physicochemical assessment

The melt pellets were classified into modal size fraction between 1.0 and 1.4 mm by mesh sieving at the vibration amplitude of 1.5 mm for 30 min (Retsch, Retsch GmbH, Germany). This fraction was characterized in term of size, shape, drug and calcium content, and drug release. Morphological changes of pellets were evaluated during the drug release. Solid state studies were performed with

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