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Optimization of magnetic retention in the gastrointestinal tract: Enhanced bioavailability of poorly permeable drug

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ABSTRACT

Oral administration of low permeable drugs remains a challenge as they do not cross biological membrane efficiently and therefore exhibit a poor bioavailability. Herein, the effect of magnetic retention on the circulation and bioavailability of magnetic beads in the gastrointestinal tract in the presence of an external magnetic field is evaluated. Retention efficiency is imaged using magnetic resonance and near infrared techniques. The effect on bioavailability is then evaluated in a pharmacokinetic study. Iron oxide nanoparticles, the drug (dipeptidyl peptidase-IV inhibitor) and a fluorophore (Alexa Fluor-750) are co-encapsulated in chitosan-alginate core-shell beads. Retention of these beads is induced by the presence of an external permanent magnet on the abdomen of rats. After single administration of magnetic beads containing 20 mg/kg of drug to fasted rats, a 2.5-fold increase in drug's bioavailability is observed in the presence of an external magnetic field, significantly higher than the same dose administered to rats without the field or for the drug in aqueous solution. Retention of the magnetic carriers in the presence of an external magnet proves to accumulate these carriers in a specific localization of the intestine leading to a significant improve in the drug's bioavailability.

1. Introduction

Bioavailability of oral drugs remains low because of the harsh gastrointestinal tract (GIT) environment. One of the major drawbacks of using the oral route to deliver drugs is that these molecules need to cross biological membranes in order to pass to the bloodstream and reach their physiological target. The large mucosal surface area of GIT presents opportunities as well as challenges, the former for retention of nanoparticles or microdevices and the latter as additional transport barriers (Chen and Langer, 1998; Gamboa and Leong, 2013; Reed and Wickham, 2009; You et al., 2015). A large number of drugs with high clinical potential have not yet been employed because of their limited bloodstream access. In this context, a growing attention has been focused over the past few decades on the design and manufacturing of advanced formulations intended for the release of bioactive compounds to selected regions of the GIT. By controlling the site of drug liberation throughout the gut, it would be possible to limit the tolerability issues associated with treatments that mainly affect specific GI districts, enhance the bioavailability of drugs that show regional differences in their stability and/or permeability profiles or, alternatively, improve the therapeutic outcome in the management of widespread local pathologies (*e.g.* phlogosis, ulcers, microbial infections, motility disorders). Gastroretentive pills have been investigated for decades because increasing the residence time of pills in the stomach would greatly benefit the numerous narrow absorption window therapeutics that are primarily absorbed in the proximal small intestines (Davis, 2005; Gröning et al., 1998; Nayak et al., 2010; Polyak and Friedman, 2009; Streubel et al., 2006). The most prevalent strategies for achieving gastric retention are density mismatching, geometry-based, and bioadhesive pills (Andrews et al., 2009; Bhardwaj et al., 2011; Chirra et al., 2014; Eiamtrakarn et al., 2002; Helliwell, 1993; Salamat-Miller et al., 2005; Whitehead et al., 2004; Wittaya-areekul et al., 2006). The use of magnetic force has also been described in order to increase the residence time of magnetic microparticulates. Previous studies have used static external magnets to improve the bioavailability of orally administered proteins including insulin for diabetics (Chen and Langer, 1998, 1997; Cheng et al., 2006; Häfeli, 2004), narrow absorption window (NAW) therapeutics such as acyclovir as an antiviral therapy (Chirra et al., 2014; Gamboa and Leong, 2013; Gröning et al., 1998) and therapeutics for site-specific pathologies including bleomycin for esophageal cancer (Ito et al., 1990; Nagano et al., 1997). However, the magnetic force required for pill immobilization has rarely been taken into account. Two studies bring considerably more insight in the field of magnetic pill retention as a safe method to target specific window and improve the

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bioavailability of drugs. E. Mathiowitz and coworkers reported a method, which enables tracking and localization of a magnetic pill (Laulicht et al., 2010). In a second publication the authors' study was focused on the forces experienced by an orally ingested magnetic pill, tracked by Hall array sensors. This paper presents a quantitative analysis of inertial net forces experienced by magnetic model pills during gastric residence in humans and two preclinical animal models both in fasted and fed states (Laulicht et al., 2011). They point out very important facts as the necessity to quantify the magnetic force involved, in order to have a feedback of the magnetic retention.

The orally active dipeptidyl peptidase-IV (DPP-4) inhibitor used in this study is currently developed for the treatment of type 2 diabetes mellitus (T2DM). *In vivo*, DPP4 rapidly inactivates incretins (GLP-1 and GIP) secreted by the intestinal cells, which stimulate glucose-induced insulin synthesis and secretion in response to food intake. However DPP4 inhibitors exhibit a very low oral bioavailability associated with a narrow absorption window in the upper part of the intestine as many highly hydrophilic molecules (acyclovir, amoxicillin, metformin) (Amidon et al., 1995; Lindenberg et al., 2004). Due to that, we propose to enhance the bioavailability of DPP4 inhibitors by using the magnetic retention technique.

We designed magnetic core-shell chitosan-alginate beads as theranostic carriers (Fig. 1a–c). The magnetic nanoparticles used to fabricate the magnetic beads are biocompatible iron oxide nanoparticles (M. Levy et al., 2011). These nanoparticles exhibit superparamagnetic behavior and are T_2 (negative) contrast agents in MRI (Magnetic Resonance Imaging) (Fig. 1d). According to a covalent coupling between the polymer and a fluorophore, dynamics of the beads along the intestine is visualized by near infra-red (NIR) microscopy during 6 h after beads administration (Fig. 1e). These magnetic beads were orally administrated to rats. A pharmacokinetic study was performed to quantify the amount of drug in plasma (Fig. 1f). The magnetic beads associated with an external magnet enabled investigation of the benefits of magnetic accumulation when compared to free drug and non-targeted beads. Finally, the safety of the magnetic beads was investigated using iron titration of the organ as well as histological examination of intestinal tissue.

2. Materials and methods

2.1. Materials

All chemical reagents were purchased from Sigma-Aldrich, France. Animals were provided from Charles River, France. Gelatin capsules (size 9: 2.65 mm × 8.6 mm) and cannulas (4 mm × 220 mm) used to force feed the rats were respectively provided from Torpac and Ecimed, France. The fluorescent probe, Alexa Fluor-750 Carboxylic Acid Succinimidyl Ester was purchased from Life Technologies, France.

2.2. Model drug

The drug used in this study was kindly provided by Technologie Servier (Fig. S1). This compound is a white powder soluble in water, highly hygroscopic which belongs to the chemical class of cyanopyrrolidines. This orally active dipeptidyl peptidase-IV (DPP-4) inhibitor is currently developed for the treatment of type 2 diabetes mellitus (T2DM). *In vivo*, DPP4 rapidly inactivates GLP-1 and GIP, incretins secreted by the intestinal cells, which stimulate glucose-induced insulin synthesis and secretion in response to food intake. The development of this active pharmaceutical ingredient has been delayed due to low oral bioavailability caused by its very poor intestinal permeability. This drug is classified as a Class III molecule (Biopharmaceutical Classification System and Formulation Development, 2011; Amidon et al., 1995; Blume and Schug, 1999). This means that the drug exhibits a very high solubility (12 mg/mL in phosphate buffer at pH 6) and a very low membrane permeability (Absorbed fraction on Caco-2 model is under 30%), (Sambuy et al., 2005; Artursson and Karlsson, 1991; Balimane and Chong, 2005). The physicochemical properties of the drug are: Mw = 769 g/mol; pKa = 7.4 and 3.5; Partition coefficient: Log $p = -1.11$, log D = −1.4 at pH 7.4.

2.3. Magnetic nanoparticles synthesis

The superparamagnetic particles were synthesized according to Massart's procedure (Massart, 1981; Canfarotta and Piletsky, 2014). Magnetite (Fe_3O_4) nanocrystals were prepared by alkaline coprecipitation of $FeCl_3$ (1.5 mol) and $FeCl_2.4H_2O$ (0.9 mol) salts in

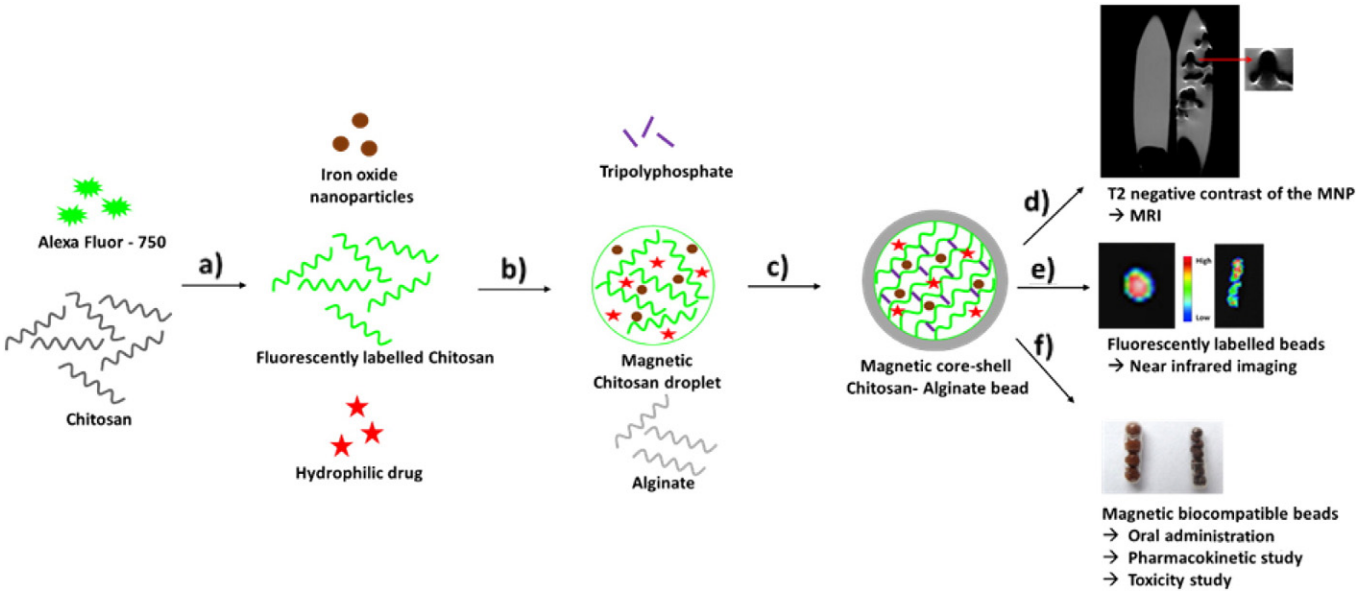

Fig. 1. Scheme of the synthesis of the magnetic and fluorescent core-shell chitosan-alginate beads. a) fluorescent labeling of the chitosan, b) formation of fluorescent chitosan beads containing MNPs and the drug, c) Crosslinking of the beads with tripolyphosphate and formation of the alginate shell, d) Imaging of the magnetic beads in MRI from left to right: tube containing agarose gel, tube containing magnetic beads embedded in agarose gel and zoom on one bead, e) Imaging of the magnetic beads in infrared fluorescence, from left to right: one magnetic beads and eight beads in a gelatin capsule, d) magnetic beads in a gelatin capsule for oral administration to the rats, four wet and eight dried beads.