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Characterization of a food-based enteric coating for capsules and its compatibility with an alternative sealing method

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ABSTRACT

Efficiency of a new protein-based enteric coating for capsules was studied. Coating physical–chemical properties were compared to those obtained from a well-known methacrylate-based enteric coating (Eudragit®). Swelling in simulated gastric fluid (SGF) was 20 times higher than for Eudragit® films. Mechanical properties (elastic modulus, elongation and puncture strength at break) were comparable to those measured from a standard Eudragit® formulation.

Pilot-scale coating trials were performed following three methods: using a standard spray-gun configuration, using a HPC-based seal-coat prior to enteric coating and using an "inverted" spray-gun configuration. The effect of these methods on capsules sealing and *in vitro* gastric performance was studied. *In vitro* tests were performed following the two USP official methods: disintegration and dissolution.

Inverted gun configuration and HPC-sealing showed the highest sealing efficiency and the best *in vitro* performance. Capsules with a weight gain of 14–16% generally passed all USP tests (no disintegration evidence after 60 min in SGF; release below 10% after 2 h of experiments in SGF). However, in some cases, slight differences between results obtained from dissolution and disintegration tests were pointed out.

This work demonstrates the potential of a protein-based enteric coating and underlines the importance of capsules sealing.

1. Introduction

Delayed-release dosage forms are commonly used for several pharmaceutical and nutraceutical applications. Delayed release is needed in order to (i) maintain the stability of active ingredients (AIs) that are unstable when exposed to the acidic conditions of the stomach, (ii) minimize the side-effects that can occur with certain AIs (*e.g.*, nausea, gastric irritation, burps).

Gastro-resistant forms are used for several AIs, including:

- Proton pump inhibitors such as lansoprazole, omeprazole or pantoprazole: these drugs undergo rapid acid degradation leading to a decrease of their efficiency (Brändström et al., 1989; Wahbi et al., 2002).
- Antibiotic such as erythromycin has poor stability in acidic environment and is degraded into intermediate metabolites after oral administration (Kim et al., 2004).
- Anti depressor such as duloxetine that is showed to be also acid labile (Kevin et al., 2008).
- Some non-steroidal anti-inflammatory drugs (NSAINs): even if gastric sides effects of NSAINs are mainly related to the inhibition of prostaglandin synthesis that results in mucosal erosion, delayed-release NSAINs are still used in order to reduce topical side effects (Hawkey, 2000; Boltin and Niv, 2014).
- Probiotics: most of the commercialized strains are rapidly degraded in the stomach and need a protection (Czarnocka and Alhnan, 2015).
- Enzymes (*e.g.*, pancreatin, lactase): like many peptidic drugs, enzymes are proteolyzed by pepsin. Their efficiency may be guaranteed using a delayed-release system (Czarnocka and Alhnan, 2015).

Delayed-release oral dosage forms are mainly achieved by applying an enteric coating onto tablets or capsules. Capsules coating generally needs a sealing step prior to enteric coating in order to close the gap between the body and the cap (Huyghebaert et al., 2004). This step can be achieved following several methods: LEMS™ (Liquid Encapsulation Microspray Sealing), band sealing or

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chemical sealing using a seal-coat. These methods are time-consuming and can be considered as expensive processes.

Enteric coatings are essentially polymers that only dissolve in water above pH 5.0–6.0. Most of these materials are synthetic or semi-synthetic (Porter et al., 2009). Enteric polymers can be divided into three categories: (i) modified cellulosic derivatives (*e.g.*, cellulose acetate phthalate, hypromellose phthalate, hypromellose acetate succinate) and (ii) methyl acrylate—methacrylic acid copolymers and (iii) other materials (*e.g.*, Shellac, polyvinyl acetate phthalate). Despite their efficiency, synthetic or semi-synthetic polymers show several limitations. First of all, these polymers need the use of hazardous, toxic and environmentally harmful chemicals such as, for instance, chloroethane, chloromethane, propylene oxide or phthalate moieties during their manufacture. Moreover, these coatings are not biodegradable and have strict daily intake limits (Czarnocka and Alhnan, 2015). Finally, most of these polymers are not approved for nutraceutics and dietary supplements (Czarnocka and Alhnan, 2015).

Recently, a Canadian company developed a new enteric coating for capsules using food proteins as raw material. This coating consists in highly purified proteins where succinoyl moieties are introduced (Caillard, 2014). Since these proteins are food by-products and succinoyl moieties are grafted using succinic anhydride, a food additive, this coating can be rightfully considered as a natural, potentially harmless and "eco-friendly" coating.

In this work, we studied the efficiency of this new material as an enteric coating for capsules. Some of its physical–chemical properties (mechanical properties and swelling in acidic conditions) were compared to a commonly used enteric coating (Eudragit™, commercialized by Evonik Industries). The effect of plasticizer type/concentration on these parameters was also studied. In addition, *in vitro* efficiency of the enteric coating was evaluated as a function of capsule weight gain. Three different sealing strategies and their impact on coating *in vitro* performances were also studied: direct coating using a standard spray gun configuration, chemical sealing using a hydroxypropylcellulose (HPC) sub-coat and sealing using an "inverted" spray gun configuration.

2. Materials and methods

2.1. Materials

Eudragit® L 30 D-55 was obtained from Evonik Industries (Essen, Germany). Succinylated food proteins were provided by Biovelia (Lévis, QC, Canada). Hydroxypropylcellulose (HPC) was obtained from American Chemicals Ltd. (Saint-Laurent, QC, Canada). Glycerol, polyethylene 400 (PEG 400), triethyl citrate (TEC), HCl 37%, sodium hydroxide, monobasic potassium phosphate, pepsin and pancreatin were purchased from Alfa Aesar (Ward Hill, MA, USA). Hypromellose (HPMC) "Vcaps" Plus Capsules were obtained from Capsugel Canada Corp. (Kirkland, QC, Canada). Lactose monohydrate was purchased from Chemroy Canada Inc. (Laval, QC, Canada), sodium croscarmellose was obtained from FMC Biopolymer (Newark, DE, USA), magnesium stearate was purchased from Mallinckrodt (St-Louis, MO, USA) and caffeine was obtained from EMD Millipore Corporation (Chicago, IL, USA).

2.2. Characterization of the films

2.2.1. Preparation of the films

Films were prepared by casting from their film-forming solutions. All chemicals were mixed under constant stirring for 60 min at room temperature. Dispersions were subsequently poured into Petri dishes equipped with Teflon frames. The same volume of film dispersion (14 mL) was casted for each tested formulation. Water was evaporated in an air-circulating oven (Thermo Fisher Scientific, Waltham, MA, USA) at 50 °C for 6 h. Films were subsequently transferred into a desiccator containing a saturated magnesium chloride solution (35% RH), at room temperature, for 24 h, until films reached constant moisture content. Once reached, films were peeled-off from their moulds and studied. The composition of tested film-forming formulations is given in Table 1.

Table 1
Composition of tested film-forming formulations expressed in % (w/w).

	Polymer	TEC	Glycerol	PEG400	Ethanol	Water	Solids
Eudragit™	12.5	2.5	–	–	–	85	15
Form. 1	8.5	–	2.55	–	17.7	71.3	11.1
Form. 2	8.5	–	3.4	–	17.7	70.4	11.9
Form. 3	8.5	–	4.25	–	17.7	69.8	12.8
Form. 4	8.5	–	–	2.55	17.7	71.3	11.1
Form. 5	8.5	–	–	3.4	17.7	70.4	11.9
Form. 6	8.5	–	–	4.25	17.7	69.8	12.8

2.2.2. Mechanical properties

The thickness of each film sample was measured using a digital thickness gauge (Mitutoyo, Japan). Then, films mechanical characterization was performed using a texture analyser TA-XT2 equipped with a 25 kg load cell (Stable Micro Systems, Scarsdale, NY, USA).

A flat-end, round cylindrical stainless steel probe (⌀ 4 mm × L 35 mm) was used to measure films mechanical properties. Films samples (⌀ 85 mm) were fixed in the apparatus. Probe penetrated the samples at a speed of 0.1 mm s^{-1} until films were pierced. For each film, puncture strength at break (PS), elongation at break (*E*), elastic modulus (EM) and puncture energy (PE) were measured. All parameters were calculated following equations given by Radebaugh et al. (1988) and Ciper and Bodmeier (2005). Typical stress–strain curve is given in Fig. 1. All experiments were performed in triplicate.

2.2.3. Swelling kinetics in simulated gastric fluid

Films swelling kinetics in simulated gastric fluid were measured as follows. Film samples of approximately 4 cm^2 (2 cm × 2 cm) were immersed in 50 mL of simulated gastric mediums (HCl solution pH 1.0; NaCl 2 g L^{-1}) and were briefly blotted and weighed at several time intervals. Films swelling ratios were determined from the weight changes before and after

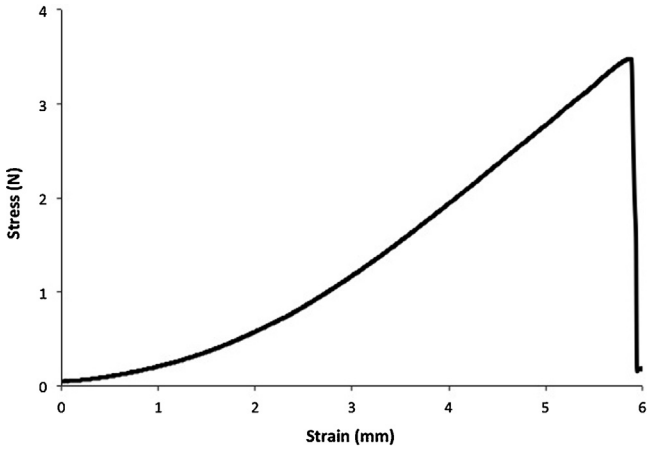

Fig. 1. Example of stress-strain curve (Formulation 1).