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Novel cellulose-based amorphous solid dispersions enhance quercetin solution concentrations *in vitro*

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ABSTRACT

Quercetin (Q) is a bioactive flavonol with potential to benefit human health. However, Q bioavailability is relatively low, due to its poor aqueous solubility and extensive phase-II metabolism. Strategies to increase solution concentrations in the small intestinal lumen have the potential to substantially increase Q bioavailability, and by extension, efficacy. We aimed to achieve this by incorporating Q into amorphous solid dispersions (ASDs) with cellulose derivatives. Q was dispersed in matrices of cellulose esters including 6-carboxycellulose acetate butyrate (CCAB), hydroxypropylmethylcellulose acetate succinate (HPMCAS) and cellulose acetate suberate (CASub) to afford ASDs that provided stability against crystallization, and pH-triggered release. Blends of CASub and CCAB with the hydrophilic polyvinylpyrrolidone (PVP) further enhanced dissolution. The ASD 10% Q:20% PVP:70% CASub most significantly enhanced Q solution concentration under intestinal pH conditions, increasing area under the concentration/time curve (AUC) 18-fold compared to Q alone. This novel ASD method promises to enhance Q bioavailability *in vivo*.

1. Introduction

Q (Fig. 1) is a dietary flavonol (a subclass of flavonoids) present at high levels in foods including apples, onions, and broccoli (Caridi et al., 2007; Price, Casuscelli, Colquhoun, & Rhodes, 1998). Q intake has been associated with many potential health benefits, including reduced risk of cardiovascular disease (Russo, Spagnuolo, Tedesco, Bilotto, & Russo, 2012), cancer (Firdous et al., 2014; Jaganathan, 2011; Zhou et al., 2010), and diabetes and obesity (Chiş, Baltaru, Maier, Mureşan, & Clichici, 2013; Gutierrez, Prater, & Holladay, 2014; Song, 2005).

Poor Q oral bioavailability severely limits its potential to benefit health. This low bioavailability is largely due to its crystallinity, and hence poor solubility (ranging from 2.15 to 7.7 μg/mL at 25 °C (Lauro et al., 2002; Srinivas, King, Howard, & Monrad, 2010)) in the aqueous milieu of the gut lumen, as well as extensive metabolism and subsequent luminal efflux by gut epithelial cells (Phase-II and Phase-III xenobiotic metabolism, respectively). Improved Q solubility may increase bioavailability by increasing the amount available for absorption, and by saturating Phase-II and Phase-III metabolic enzymes; both effects are likely to result in increased net flux into circulation.

Many techniques have been employed to improve Q oral bioavailability, such as protein- or cellulose-based nanoparticles (Fang et al., 2011; Kakran, Sahoo, Li, & Judeh, 2012; Sahu, Saraf, Kaur, & Saraf, 2013), encapsulation (Dian et al., 2014), nanoemulsi-

Abbreviations: ASD, amorphous solid dispersion; CCAB, carboxycellulose acetate butyrate; CASub, cellulose acetate suberate; EC, epicatechin; HPMCAS, hydroxypropylmethyl cellulose acetate succinate; PVP, polyvinylpyrrolidone.

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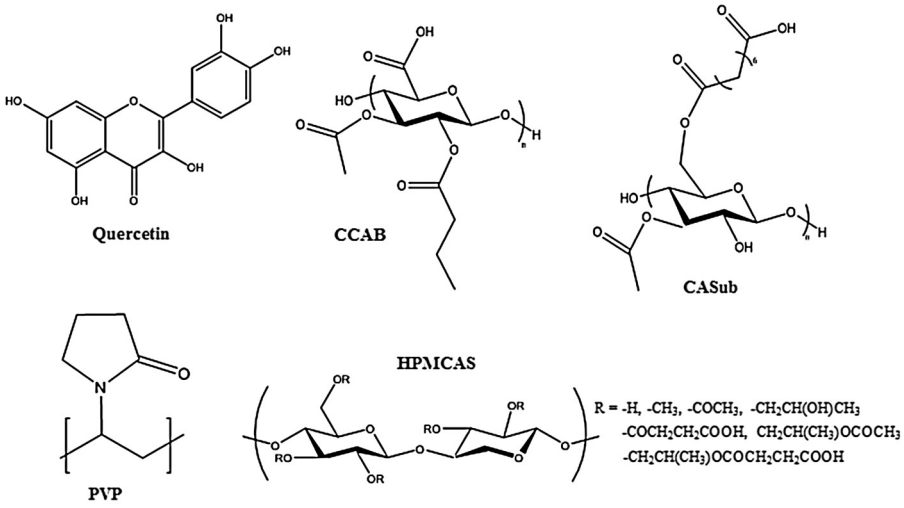

Fig. 1. Chemical structures of Q, CCAB, CASub, PVP, and HPMCAS. The cellulosic structures are not meant to convey regioselective substitution; depictions of substituent location are merely for convenience and clarity of depiction.

fying drug delivery systems (Tran, Guo, Song, & Bruno, 2016), and ASD (Ilevbare, Liu, Edgar, & Taylor, 2012; Li et al., 2013; Pereira et al., 2013). ASD preparation with polymer dispersants is an attractive way to stabilize the high energy, amorphous drug in a glassy polymeric matrix. Exposure of the ASD to the GI lumen not only provides supersaturated drug solutions, but also enhances permeation by increasing the drug concentration gradient across the enterocytes. Polymer selection is key for ASD performance because the dispersion must be miscible, with strong polymer-drug interactions (*e.g.* hydrogen bonding) for stability against crystallization (Pereira et al., 2013; Vasconcelos, Sarmento, & Costa, 2007). Amphiphilic polymers possessing carboxylic acid functionality perform well in ASD due to strong polymer-drug interactions; their pH responsiveness is also valuable. At gastric pH, the protonated form protects the drug and minimizes release, while deprotonation at near-neutral intestinal pH swells the polymer and triggers drug release (Li et al., 2013; Pereira et al., 2013). Cellulose derivatives are popular ASD polymers due to their generally benign nature and high T_g values. CASub and cellulose acetate adipate propionate (CAAdP) were synthesized in the Edgar lab and show high promise for ASD (Li et al., 2013; Liu et al., 2014). Novel ASD polymers are needed to go beyond the performance of currently used polymers like PVP and HPMCAS that were not designed for ASD, and cellulosic polymers are ideal candidates due to their generally low toxicity and lack of oral bioavailability.

ASD has been only lightly explored for Q dissolution enhancement. Lauro et al. achieved slight dissolution enhancement using ASDs prepared with cross-linked sodium carboxymethylcellulose and sodium starch glycolate (Lauro et al., 2002). Similarly, Lauro et al. used spray dried dispersions with cellulose acetate trimellitate and cellulose acetate phthalate to improve Q release at pH 6.8 (Lauro, Maggi, Conte, De Simone, & Aquino, 2005). Recently, several polymers were evaluated for their ability to improve Q dissolution *in vitro* (Li et al., 2013). HPMCAS afforded ASDs containing up to 50% Q content; enhanced dissolution was obtained from 10% Q ASDs, optimally in polymer blends containing 10% of the water-soluble (PVP) (Gupta, Kakumanu, & Bansal, 2004; Konno, Handa, Alonzo, & Taylor, 2008; Van den Mooter et al., 2001). Employing PVP in blends with other cellulosic polymers may generally enhance drug release, while retaining the excellent stabilization from the cellulosic polymer (Marks, Wegiel, Taylor, & Edgar, 2014).

The objective of this study was to assess the performance of the novel polymer CASub for making Q ASDs and creating supersaturated Q solutions at physiological pH, vs. crystalline Q as negative control and HPMCAS/Q ASD as positive control. We hypothesized that 1) CASub would provide enhanced solution concentration and preferable dissolution kinetics compared to HPMCAS, and 2) that blending CASub with PVP would further enhance Q dissolution.

2. Experimental

2.1. Materials

Quercetin (≥95% by HPLC), epicatechin (EC) (≥90% by HPLC), and KCl (solid, anhydrous, ≥99%) were purchased from Sigma-Aldrich. Cellulose acetate propionate (CAP-504-0.2; degree of substitution (DS) (acetate) = 0.04, DS (propionate) = 2.09; M_n = 15,000); CCAB; DS (butyrate) = 1.62, DS (acetate) = 0.06, DS (carboxylic acid) = 0.28; Mw = 252,000 and cellulose acetate (CA 320S, DS (acetate) = 1.82) M_n = 50,000 were from Eastman Chemical Company. HPMCAS (wt%: methoxyl 20–24%, hydroxypropyl 5–9%, acetyl 5–9%, succinoyl 14–18%; Mw = 18,000) was from Shin-Etsu Chemical Co., Ltd. Chemical structures of ASD polymers used (HPMCAS, PVP, CCAB, and CASub) are provided in Fig. 1. Acetonitrile (ACN, HPLC-grade), methylene chloride (HPLC-grade), tetrahydrofuran (THF), reagent ethanol, sodium phosphate monobasic, and sodium hydroxide (NaOH) were purchased from Fisher Scientific and used as received. HCl (12.1 M) was obtained from Macron Chemicals. Suberic acid, adipic acid, methyl ethyl ketone (MEK), *p*-toluenesulfonic acid (PTSA), triethylamine (Et_3N), and oxalyl chloride were purchased from ACROS Organics. 1,3-Dimethyl-2-imidazolidinone (DMI) was purchased from ACROS Organics and dried over 4 Å molecular sieves. Water was purified by reverse osmosis and ion exchange using a Barnstead RO pure ST (Barnstead/Thermolyne) purification system. LCMS grade ACN, water and formic acid were obtained from VWR.

2.2. Synthesis of CASub

CASub was synthesized as previously reported (Liu et al., 2014). See Supplemental Information for full details.

2.3. Preparation of ASDs via spray drying

Supplemental Information contains a full description of preparation of ASDs containing Q. Our convention for naming treatments is to list the % polymer(s), with the remainder being Q. For example, 10% Q/90% CCAB is referred to as 90 CCAB in the text, figures