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Cellulose-based amorphous solid dispersions enhance rifapentine delivery characteristics *in vitro*

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Rifapentine (PubChem CID: 6323497)
Rifampicin (PubChem CID: 5458213)
3-Formylrifamycin (PubChem CID: 6438444)
Hydroxypropylmethylcellulose acetate succinate (PubChem CID: 121950)

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ABSTRACT

The efficacy of rifapentine, an oral antibiotic used to treat tuberculosis, may be reduced due to degradation at gastric pH and low solubility at intestinal pH. We hypothesized that delivery properties would be improved *in vitro* by incorporating rifapentine into pH-responsive amorphous solid dispersions (ASDs) with cellulose derivatives including: hydroxypropylmethylcellulose acetate succinate (HPMCAS), cellulose acetate suberate (CASub), and 5-carboxypentyl hydroxypropyl cellulose (CHC). ASDs generally reduced rifapentine release at gastric pH, with CASub affording > 31-fold decrease in area under the curve (AUC) compared to rifapentine alone. Critically, reduced gastric dissolution was accompanied by reduced degradation to 3-formylrifamycin. Certain ASDs also enhanced apparent solubility and stabilization of supersaturated solutions at intestinal pH, with HPMCAS providing nearly 4-fold increase in total AUC vs. rifapentine alone. These results suggest that rifapentine delivery via ASD with these cellulosic polymers may improve bioavailability *in vivo*.

1. Introduction

Rifapentine (RPT, Fig. 1) is a semi-synthetic macrolide antibiotic used to treat tuberculosis (TB) (Anderson, Groundwater, Todd, & Worsley, 2012). Though rifampin (rifampicin, RIF, Fig. 1) is currently used in first-line TB treatment, RPT has several advantages vs. RIF. RPT has less potential to promote bacterial resistance, persists longer in the blood (less frequent dosing and increased patient compliance), and requires shorter treatment times (Dooley et al., 2012; Duanmu, Liu, Jiang, Wang, & Fu, 2005; Emary, Toren, Mathews, & Huh, 1998; Hastings, Watkins, & White, 2002; He et al., 1996; Lemke, 1995; Rosenthal et al., 2006). One challenge in RPT delivery is its gastric instability due to the acid-labile hydrazone linkage (Fig. 1) (Agrawal & Panchagnula, 2005; Kalia & Raines, 2008; Pereira et al., 2013; Prasad, Bhutani, & Singh, 2006). Acid degradation of RPT produces 3-formylrifamycin (3-FR, Fig. 1).

RPT is poorly soluble at near-neutral small intestine pH, limiting its absorption (Agrawal, 2003; Ostrovskii et al., 2016). Strategies to enhance intestinal dissolution may, however, be counterproductive by also enhancing acid solubility and degradation. An attractive strategy would be to inhibit acidic dissolution while enhancing dissolution at intestinal pH. Various strategies (solid dispersions, inclusion complexes, melt granulation and hydrophobic carriers) have been employed successfully to enhance RPT dissolution (Kalra, Sharma, & Jain, 2012; Pathak, Swati, Sharma, Jain, & Thoke, 2013). However, these techniques all enhanced RPT dissolution in acid, which is not optimal for RPT delivery. Strategies have not yet been developed to selectively provide pH-responsive dissolution to protect RPT from acidic degradation and release RPT at the near-neutral pH of the small intestine.

Amorphous solid dispersion (ASD) can enhance delivery of

Abbreviations: ASD, amorphous solid dispersion; AUC, area under the curve; CASub, cellulose acetate suberate; DSC, differential scanning calorimetry; Tg, glass transition temperature; Tm, melting point; HPMCAS, hydroxypropyl methylcellulose acetate succinate; LLOD, lower limit of detection; LLOQ, lower limit of quantification; Mw, molecular weight; Mn, average molecular weight; Cmax, maximum concentration; PVP, polyvinylpyrrolidone; PXRD, X-ray powder diffraction; RPT, rifapentine; RIF, rifampin; SI, supplementary information; TB, tuberculosis; 3-FR, 3-formylrifamycin; CHC, 5-carboxypentyl hydroxypropyl cellulose

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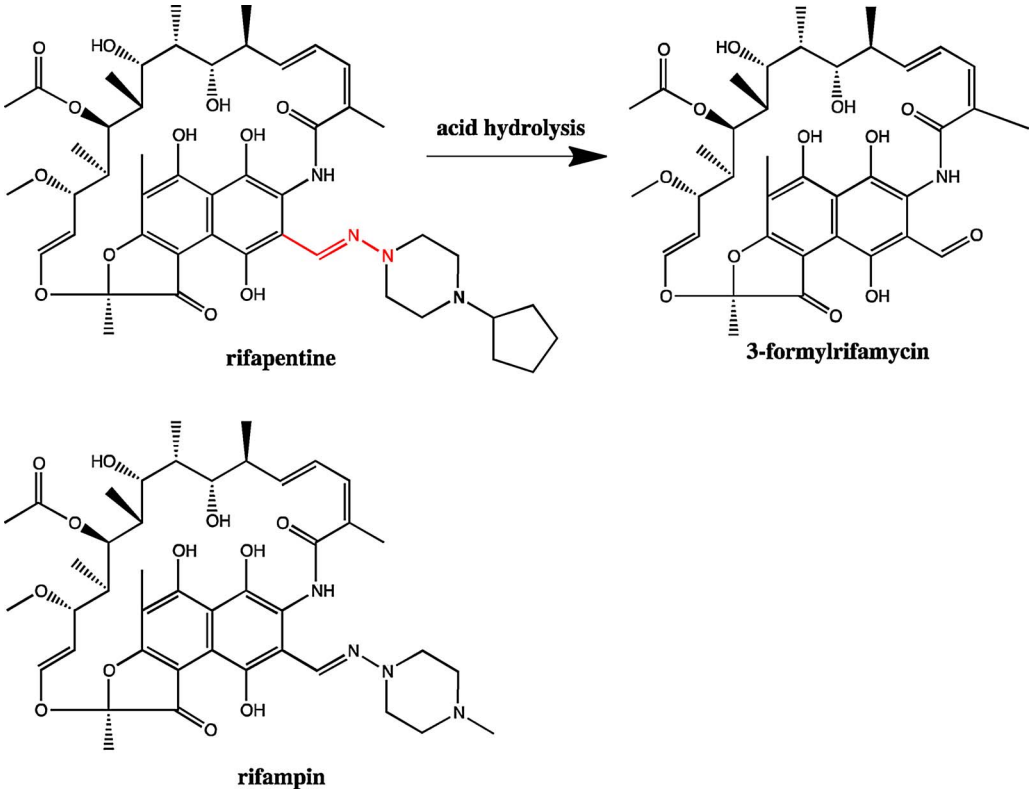

Fig. 1. Rifampin and rifapentine structures. Acid-labile hydrazone highlighted in red. pK_a values for rifampin are 1.7 and 7.9 (Budha, Lee, & Meibohm, 2008).

bioactive molecules with poor water solubility due at least in part to crystallinity (Gilley et al., 2017; Konno, Handa, Alonzo, & Taylor, 2008; Pereira et al., 2013). ASD holds the drug in amorphous form in a polymeric matrix, preventing crystallization during storage and transport (Konno et al., 2008). Eliminating the energy required to disrupt the crystal lattice can lead to rapid release and supersaturation upon exposure to aqueous media. Critically, the polymer must also prevent drug crystallization from the supersaturated solution for the duration of transport through the absorptive zones of the gastrointestinal (GI) tract. *In vivo*, intestinal supersaturation is likely to enhance absorption by substantially increasing the epithelial transmembrane concentration gradient, directly proportional to the achieved supersaturation ratio (Borbás et al., 2016).

Polymer selection is critical for ASD development. The polymer must be compatible with the drug and provide favorable drug-polymer interactions (Gilley et al., 2017; Liu, Taylor, & Edgar, 2015; Pereira et al., 2013; Vasconcelos, Sarmento, & Costa, 2007). Cellulose derivatives are attractive for ASDs because of their availability, stability, high glass transition temperatures (T_g, limiting drug mobility), ease of modification, and biocompatibility (Gilley et al., 2017; Liu, 2014; Li et al., 2013a,b; Liu et al., 2015; Shah et al., 2014). Attachment of ω-carboxyalkanoyl groups to the cellulose scaffold can improve ASD performance by enhancing specific polymer-drug interactions and pH responsiveness (Gilley et al., 2017; Li et al., 2009; Shah et al., 2014). At gastric pH (ca. 1.2), carboxylic acids are essentially 100% protonated, resulting in a net neutral species; therefore, the ASD remains intact due to lack of electrostatic repulsion and low polymer solubility (Gilley et al., 2017; Li et al., 2009; Pereira et al., 2013). At intestinal pH, acid residues are largely deprotonated, resulting in a net negative charge (Gilley et al., 2017; Li et al., 2009; Pereira et al., 2013). The resulting electrostatic repulsion causes swelling, releasing the drug into solution (Gilley et al., 2017; Li et al., 2009; Pereira et al., 2013). When properly designed, these cellulosic ASD polymers also partially dissolve (to concentrations ranging from tens of μg to mg/mL), creating the possibility for solution interaction with dissolved drug or drug nanodroplets (Ilevbare, Liu, Pereira, Edgar, & Taylor, 2013), and thus stabilization against crystallization from solution. Therefore, pH-responsive modified cellulose can potentially inhibit drug release in acid and enhance dissolution at near-neutral pH, promising for RPT (Li et al., 2013a,b).

We hypothesized that ASDs using three amphiphilic ASD polymers derived from cellulose [hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate suberate (CASub), and 5-carboxypentyl hydroxypropyl cellulose (CHC), Fig. 2] would protect RPT from degradation at gastric pH, and form stabilized supersaturated RPT solutions at intestinal pH *in vitro*.

2. Experimental

2.1. Materials

For a list of materials, see Supplementary Information (SI).

2.2. Polymer synthesis

CASub (Mw 22,500 g/mol, DS 2.72) and CHC (Mw 70,400 g/mol, DS 2.20) were synthesized as reported in Liu et al., 2014 and Dong et al., 2016, respectively. Molecular weights were determined by SEC and DS by ^{1}H NMR spectroscopy, as described in the references. See SI for full details. Polymer properties summarized in Table S1.

2.3. ASD preparation and characterization

ASDs formulations (90:10, 75:25, and 50:50, polymer:RPT) were prepared using HPMCAS, CASub, and CHC. ASDs and RPT alone were in powdered forms, which were used for all subsequent characterization and dissolution experiments. Due to the known impact of polymer/drug ratios on ASD performance, variations were employed in order to identify ratios providing optimum dissolution parameters. Our convention for naming formulations is to list the % polymer, with the remainder being drug. For example, 90% HPMCAS/10% RPT is referred to as “90 HPMCAS” in most of the text, or simply “90” in most figures. RPT-only formulations are referred to as RPT in the text and figures.