



Novel salicylic acid-based chemically crosslinked pH-sensitive hydrogels as potential drug delivery systems



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ABSTRACT

In this work, salicylic acid (SA), a non-steroidal anti-inflammatory, was chemically incorporated into hydrogel systems to achieve sustained SA release profiles. With its anti-inflammatory properties, sustained release of SA would be relevant for treating diseases such as diabetes and cancer. In this work, SA was chemically incorporated into hydrogel systems via covalent attachment to an itaconate moiety followed by UV-initiated crosslinking using acrylic acid and poly(ethylene glycol) diacrylate. The chemical composition of the hydrogel system was confirmed using FT-IR spectroscopy. The SA-based hydrogels were designed as pH-responsive hydrogels, collapsing at acidic pH (1.2) values and swelling at higher pH (7.4) values for gastrointestinal-specific delivery. The hydrogel systems exhibited a pH-dependent SA release profile: SA release was much slower at pH 1.2 compared to pH 7.4. Under acidic pH conditions, 30 wt% SA was released after 24 h, whereas 100 wt% SA was released in a sustained manner within 24 h in pH 7.4 PBS buffer. The pore structure of the gel networks were studied using SEM and exhibit appropriate pore sizes (15–60 μm) for physically encapsulating drugs. In addition, rheological studies of the hydrogels proved that these systems are mechanically strong and robust. Mucoadhesive behaviors were confirmed using a Texture Analyzer, the work of adhesion for the hydrogels was around 290 g·mm and the maximum detachment force was around 135 g. The SA-based hydrogels demonstrate great potential for oral delivery of bioactives in combination with SA to treat serious diseases such as cancer and diabetes.

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1. Introduction

Salicylic acid (SA) is the active compound of the low cost anti-inflammatory drug aspirin, which hydrolyzes *in vivo* to yield SA. SA has been used as anti-inflammatory drug for decades and recent studies indicate that salicylic acid can be used to treat cancer (Bastiannet et al., 2012), arthritis (Yamazaki et al., 2002), and fungal infections (Amborabe et al., 2002). Furthermore, studies have shown that inflammation exacerbates type 2 diabetes and that salicylates can reduce insulin resistance (Golfinet et al., 2011; Hundal et al., 2002; Nixon et al., 2012; Raghavan et al., 2014; Reid and Lightbody, 1959; Shoelson et al., 2006), suggesting that SA may affect oxidative stress, insulin resistance, and vascular inflammation (Raghavan et al., 2014).

Oral administration is the most common drug route as it is the cheapest, safest, and most patient-friendly. The most common oral drug delivery systems are hydrogels because of their ability to

protect drug and/or protein structures during the encapsulation process, as the encapsulation can be performed at low temperatures and in aqueous environments (Peppas et al., 2000). Hydrogels are chemically or physically crosslinked networks of water-soluble polymers that are capable of imbibing high concentrations of water or biological fluids (Brannon-Peppas and Harland, 1990; Lopérgolo et al., 2003; Park and Park, 1996; Peppas et al., 2000; Peppas and Mikos, 1986; Sri et al., 2012). When using hydrogels for drug delivery, the release profile is modified by changing the crosslinking density as well as the functional groups (Qi et al., 2015, 2017a, 2017b). pH-sensitive hydrogels are often utilized for oral delivery systems to target the different pH ranges of the digestive tract, as the pH ranges from 1 to 2.5 in the stomach to 6.4–7.5 in the intestine. Acrylic acid (AA) moieties have attracted considerable interest for oral delivery due to their responsiveness to pH shifts in the gastro-intestinal (GI) tract (Gao et al., 2012; Myung et al., 2007; Sutar et al., 2008; Wu et al., 2008). Hydrogels comprised of polyanions swell minimally in the stomach (pH 1–2.5) (Evans et al., 1988), with increased swelling in the intestine (pH 6.4–7.5) (Evans et al., 1988). In addition, poly(acrylic acid) (PAA) exhibits mucoadhesive behavior, which can adhere to mucosal

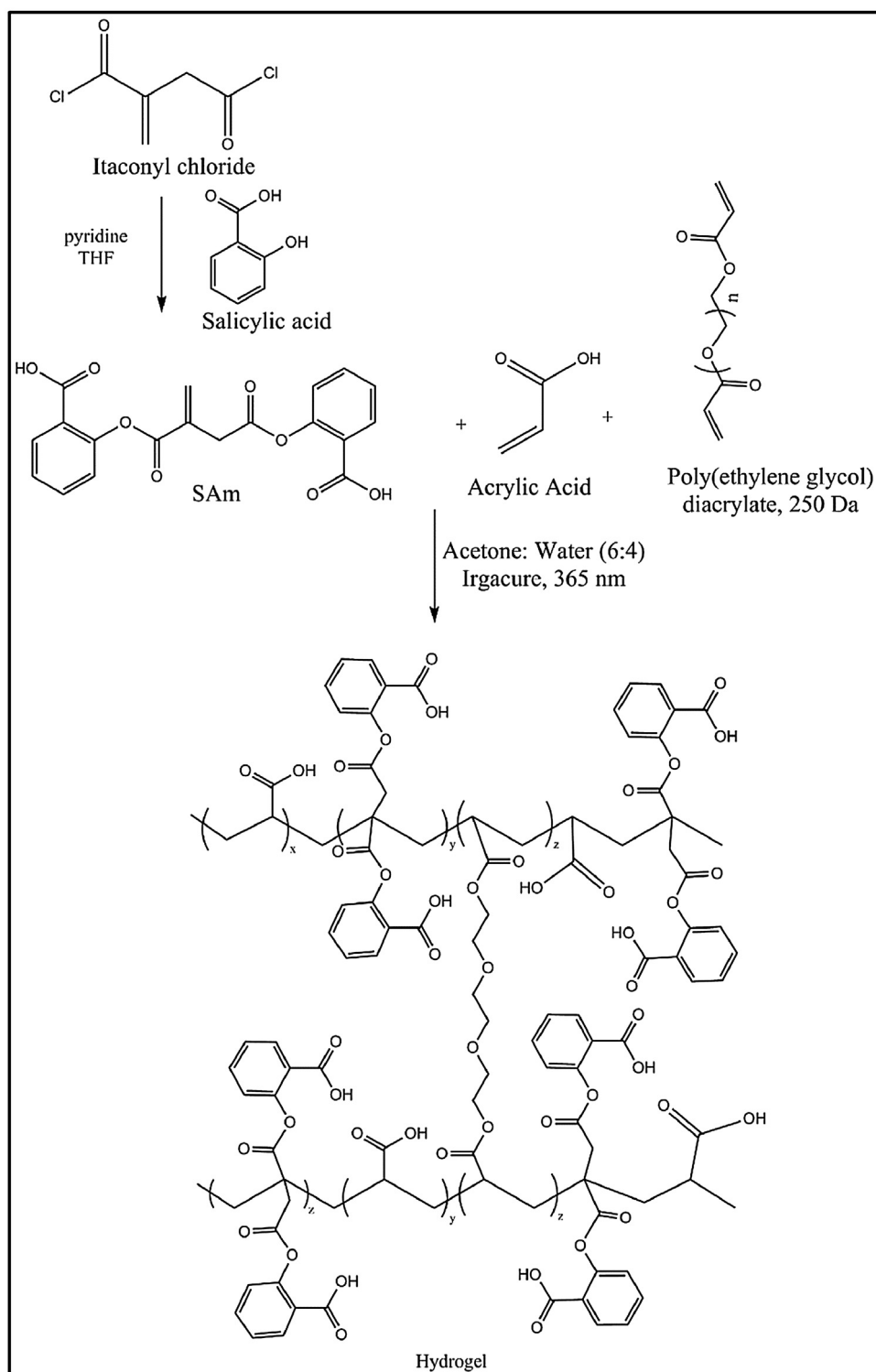
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membranes, further improving bioavailability by enhancing time *in vivo* (Lehr, 1994; Renukuntla et al., 2013; Shaji and Patole, 2008).

Previously, SA has been chemically incorporated into poly (anhydride-esters) *via* biodegradable linker to achieve higher drug loading (greater than 85%) (Schmeltzer et al., 2003, 2005) and shown to deliver SA from days to months for desired applications and drug administration routes (e.g., injectable vs oral) (Demirdirek and Uhrich, 2015; Erdmann et al., 2000; Prudencio et al.,

2005). In this research, pH-dependent, chemically crosslinked SA-based hydrogels were developed for oral delivery of bioactives in combination with SA to treat serious diseases such as cancer and diabetes. SA-based monomer was prepared using an itaconic acid linker followed by free radical polymerization with acrylic acid and poly(ethylene glycol) diacrylate (PEGDA) as the crosslinking agent (Scheme 1). Two hydrogel systems were prepared and evaluated: hydrogel L and hydrogel H, which have low and high crosslinking



Scheme 1. Synthesis of salicylic acid (SA)-based monomer (SAM) and hydrogel. Hydrogels were crosslinked with varying amounts of crosslinker (PEGDA) to yield low and high crosslinked gels.

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