International Journal of Pharmaceutics 546 (2018) 106–114

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Amphiphilic polyurethane hydrogels as smart carriers for acidic hydrophobic drugs

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ARTICLE INFO

Keywords:
Amphiphilic polyurethane
Hydrogel
Drug delivery
Controlled release
Hydrophobic drugs

ABSTRACT

Amphiphilic hydrogels are widely reported as systems with great potential for controlled drug release. Nevertheless, the majority of studies make use of functionalization or attachment of drugs to the polymer chains. In this study, we propose a strategy of combining amphiphilic polyurethanes with pH-responsive drugs to develop smart drug carriers. While the amphiphilic character of the polymer imparts an efficient load of hydrophobic and hydrophilic drugs, the drug's characteristics determine the selectivity of the medium delivery. Drug loading and release behavior as well as hydrolytic degradation of chemically crosslinked polyurethane hydrogels based on PEG and PCL-triol (PU (polyurethane) hydrogels) synthesized by an easy one-pot route were studied. PU hydrogels have been shown to successfully load the hydrophobic acidic drug sodium diclofenac, reaching a partition coefficient of 8 between the most hydrophobic PU and diclofenac/ethanol solutions. Moreover, an oral administration simulation was conducted by changing the environment from an acidic to a neutral medium. PU hydrogels release less than 5% of the drug in an acidic medium; however, in a PBS pH 7.4 solution, diclofenac is delivered in a sustained fashion for up to 40 h, achieving 80% of cumulative release.

1. Introduction

Controlling the rate and location of drug release is a promising strategy to improve drug efficiency and reduce harmful side effects (Caló and Khutoryanskiy, 2015; Li and Mooney, 2016; Loiola et al., 2017; Peppas et al., 2000). One way to achieve this goal is to explore differences in pH, ionic strength, and composition of physiological environments to trigger drug release at specific regions such as the stomach, intestine, blood, lymphatic fluid and so on (Charifson and Walters, 2014; Chen et al., 2017; Liu et al., 2015; Ullah et al., 2015). To take advantage of these physiological differences, not only does the carrier's chemical structure need to be considered but also the drug's chemical structure. Nearly 70% of drugs are ionizable and present themselves in the form of weak acids or bases, and therefore their solubility depends on pH. This solubility feature can be useful for drug delivery at specific sites (Kalepu and Nekkanti, 2015). Nevertheless, the interactions between the drug and the carrier as well as the carrier's permeability play an important role on rate and location of drug release (Li and Mooney, 2016).

A wide variety of drugs are weak acids, for instance, furosemide, cromoglicic acid, and all the nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, ibuprofen, naproxen and aspirin. Among them, diclofenac has been extensively studied as a drug model in carrier systems (Aminabhavi et al., 2015; de Menezes et al., 2017; du Toit et al., 2016; Kalepu and Nekkanti, 2015; Kim et al., 2017). These drugs present in their structure pendant carboxylic acid, carboxylates or sulfate groups, and the majority are hydrophobic (Charifson and Walters, 2014).

Hydrogels are studied as drug carriers for NSAIDs as an alternative to commonly adopted coated tablets which present undesirable release in stomach due to unexpected pH variations. Therefore, the use of hydrogels aim for more precise enteric drug release and side effect reduction as well as delivery at specific inflammation sites (Barba et al., 2009; Barron et al., 2016; Cascone et al., 2011; Chen et al., 2017; Chronopoulou et al., 2017; Demirdirek and Uhrich, 2017; Fan et al., 2017; Jensen et al., 2017; Kostova et al., 2017). Hydrogels are three-dimensional polymer networks capable of swelling a large amount of water due to the presence of hydrophilic functional groups along the polymer backbone or as pendant groups, such as hydroxyls, amines or ethers. Their mechanical properties range from tough elastomeric materials to viscous liquids, and usually, these properties are determined by their crosslinking nature. For example, physical interactions such as hydrogen bonding and the presence of a crystalline phase can act as crosslinkers, and the resulting water swollen material is called physically crosslinked hydrogel. These kinds of hydrogels present themselves as highly viscous liquids or soft solids and are suitable for several

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https://doi.org/10.1016/j.ijpharm.2018.05.034
Received 22 March 2018; Received in revised form 25 April 2018; Accepted 13 May 2018
Available online 14 May 2018
0378-5173/

applications, mainly in biomedicine. On the other hand, chemically crosslinked hydrogels are constituted by a permanent polymer network resulting from covalent bonds among polymer chains. This makes them tougher and more mechanically resistant compared with physically crosslinked hydrogels (Zhu and Marchant, 2011). In addition, they fit in a wide range of applications including agriculture, food industry, separation technologies, and also biomedicine (Hoffman, 2012).

Recently, Demirdirek and Uhrich (2017) reported that chemically crosslinked hydrogels based on acrylic acid, poly(ethylene glycol) diacrylate and an acrylic monomer derivate from itaconyl chloride and salicylic acid (IC-SA), presented a sustained release of salicylic acid in neutral or basic pH due to the hydrolysis of the IC-SA segments in the polymer chain. However, in acidic media these hydrogels shrink due to the protonation of carboxylic acid pendant groups in the polymer network. This feature allows the control of salicylic acid release in the intestinal environment. Nevertheless, these hydrogels require a covalent bond between the NSAID and the polymer matrix, which represents an additional synthetic step that may have to be adopted depending on the drug.

Water swelling capability is the main feature of hydrogels. In biomedical applications, for instance, the water content in hydrogels allows the transport of important substances such as oxygen, proteins, drugs and carbohydrates, through the network as well as through their integration with biological tissues (Hoffman, 2012). However, high hydrophilicity hinders or limits sorption of hydrophobic compounds into the hydrogel network, which is inconvenient for several applications such as hydrophobic drug loading and delivery (Barron et al., 2016). Therefore, the insertion of hydrophobic segments in the polymer backbone or as pendant groups is a strategy widely reported in the literature to develop amphiphilic hydrogels that can swell in both water and non-polar solvents, and also present mechanical resistance and water swelling coefficient modulated by the hydrophobic domains, that can also act as additional crosslinkers (Colinet et al., 2009; Grossen et al., 2017; Gu et al., 2017; Ward and Georgiou, 2011; Zhang et al., 2008; Zhou et al., 2011).

Hydrophobicity should also be controlled in order to modulate water content and drug release kinetics in hydrogels (Ullah et al., 2015; Ward and Georgiou, 2011). One advantage of the presence of hydrophobic domains in hydrogels is the thermosensitive behavior induced by them, leading to hydrogel swelling or shrinkage depending on the temperature of the medium (Kim and Matsunaga, 2017; Luo et al., 2016; Polo Fonseca et al., 2016; Sardon et al., 2015; Ward and Georgiou, 2011). Thermosensitive behavior is also an interesting feature for drug release systems because temperature can be used as a trigger for releasing drug at specific sites.

Amphiphilic polyurethanes are ideal candidates to produce hydrogels with properties that can be easily tuned by composition (Ghobril and Grinstaff, 2015; Guan et al., 2017; Kim et al., 2017; Kim and Matsunaga, 2017; Polo Fonseca et al., 2016; Sardon et al., 2015; Wei et al., 2017). Amphiphilic polyurethanes based on hydrophilic and hydrophobic segments such as poly(ethylene glycol) (PEG), polycaprolactone (PCL) or poly(propylene glycol) (PPG), respectively, and aliphatic diisocyanates have been reported in the literature as biocompatible polymers, which generates low toxicity metabolites *in vivo* (Barrioni et al., 2015; Polo Fonseca et al., 2016; Sardon et al., 2015). Luo et al. (2016) reported the synthesis and characterization of thermosensitive hydrogels based on triblock copolymers of PCL as the central block and PEG as the lateral chains bounded by the aliphatic diisocyanate isophorone diisocyanate (IPDI). These hydrogels presented a typical low critical solution temperature (LCST) at 37 °C (sol-gel transition), and sustained release of sodium diclofenac in PBS solution at 37 °C. However, the hydrogels release profiles are highly dependent on the concentration of sodium diclofenac: concentrations higher than 0.1% (w/v) of diclofenac in the hydrogel led to a significant reduction of the release rate, reaching only 60% of cumulative release after 168 h.

Hydrogels based on PEG and PCL have been studied with respect to their potential application in biomedicine, mainly due to their biocompatibility, PCL susceptibility to hydrolytic degradation, and also the potential thermosensitive behavior achieved by combining this two polymers (Boffito et al., 2015; Gong et al., 2009; Hatamzadeh et al., 2016; Peng et al., 2017). Nevertheless, little has been reported in the literature about chemically crosslinked polyurethane hydrogels containing PEG and PCL and their potential applications as drug carriers or scaffolds. Barrioni et al. (2015) reported the synthesis of crosslinked polyurethane hydrogels based on PEG (M_n ~600 g mol^{-1}), PCL-triol of (M_n ~900 g mol^{-1}), hexamethylene diisocyanate (HDI) as isocyanate and glycerol as a chain extender. PU films presented good mechanical properties and susceptibility to hydrolytic degradation. However, no drug release studies were conducted using these hydrogels.

Recently, we reported the synthesis and characterization of chemically crosslinked polyurethane hydrogels based on PEG of M_n ~2000 g mol^{-1} and PCL-triol of M_n ~900 g mol^{-1} as hydrophobic crosslinking agents and HDI as diisocyanate (Polo Fonseca et al., 2016). The hydrogels presented high mechanical resistance and high resilience as well as tunable swelling coefficients and thermosensitive behavior. In the present study, we report the hydrogel properties regarding drug loading and release of sodium diclofenac as well as their hydrolytic degradation at different pH's.

2. Experimental

The procedure for synthesis of PU is detailed elsewhere (Polo Fonseca et al., 2016). Briefly, previously dried precursors, PEG, PCL-triol and 50 μL of catalyst dibutyltin dilaurate were solubilized in dry dichloroethane at 45 °C under stirring and argon atmosphere. After solubilization, HDI was added in the molar ratio of isocyanate and hydroxyl groups (-NCO:-OH = 1:1). Reactions were conducted for 48 h at 45 °C and then finished by adding ethanol in excess. PU networks were purified by immersion in ethanol and changing the solvent several times, to ensure the extraction of all unreacted materials and catalysts. After that, PU networks were dried under nitrogen flow, followed by vacuum to ensure ethanol removal.

Differential scanning calorimetry (DSC) was conducted under argon flow for around 10 mg of dry PU samples on *TA Instruments Q2000* DSC equipment under the following procedure: 1) Heating to 200 °C at the rate of 20 °C/min, followed by 3 min isotherm; 2) Cooling to −100 °C at the rate of 10 °C/min, followed by 3 min isotherm and then 3) Heating to 200 °C at 10 °C/min.

^{13}C NMR analysis was performed on *Bruker Advance 500 MHz* equipment under the following conditions: without the nuclear Overhauser effect, 25 °C, 11.7 T, pulse delay of 1 s, 3572 scans and FID resolution of 0.5 Hz. Around 20 mg of dry PU was ground and swollen with 600 μL of $CDCl_3$ and then analysed.

Water swelling experiments were performed in triplicate. Around 20 mg of dry PU was weighed and immersed in a phosphate buffer saline solution (PBS) of pH 7.4 at 37.5 °C in a *Julabo F12* thermostatic bath. The samples were periodically weighed until swelling equilibrium was achieved. Swelling coefficient ($Q_{\%}$) was then calculated using Eq. (1).

$$Q_{\%} = (m_s/m_d) \times 100(\%) \quad (1)$$

where m_s and m_d are the mass of the swollen PU at equilibrium and dry mass of PU, respectively.

Hydrolytic degradation studies were conducted in triplicate at 37.5 °C in pH 7.4 (PBS) and pH 1.6 (HCl/KCl) solutions in a *Julabo F12* thermostatic bath. Around 50 mg of dry PU was weighed and immersed in pH 7.4 PBS solutions, which were changed every day. The hydrogel samples were removed from the PBS solutions, extensively washed with deionized water, weighed and then dried and weighed again after 2 and 4 weeks of experiment for PBS solutions and 1, 2 and 3 days for HCl/KCl solutions. Hydrolytic degradation was also conducted for diclofenac loaded PU at pH 1.6. In this case, drug loaded PU was immersed in pH