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Synthesis and chemical modification of poly(butylene succinate) with rutin useful to the release of silybin

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ABSTRACT

Poly (butylene succinate) (PBS) is a biodegradable polyester, which can be obtained from renewable sources. The chain extension technique was used, aiming to promote an increase in the molecular weight of PBS, besides improving its thermal, mechanical and rheological properties. To the best of our knowledge, the use of rutin as a natural chain extender has never been tested. In addition, this chain extension was compared to the ordinary one, using castor oil. Thus, the present work aimed to prepare and compare the properties of PBS extended by the addition of these mentioned chain extenders. In addition, different reaction conditions were tested and the obtained results allowed us to infer that both chain extenders produced an increase of molecular weight, viscosity and thermal resistance. In spite castor oil be a more efficient chain extender, the use of a small amount of rutin (1 wt%) produced an increase in the viscosity of PBS of around 100%. In addition, the molecular weight increased by 36% and the crystallinity presented a reduction of 7%. In addition, the polymer modified with rutin was tested as a silybin release system. The material extended using rutin was able to reduce the release of silybin, in comparison to the one from PBS, in 25.7%.

1. Introduction

The development of "green" technologies using products and processes of low environmental impact are being widely exploited, and considerable investments are being centered in the biopolymer area (Elias et al., 2015; Grance et al., 2012; Lopes et al., 2010; Marques et al., 2016; Péres et al., 2014; Souza et al., 2014, 2013, 2011, 2010a,b, 2009a,b, 2008a,b, 2006). Among synthetic biopolymers, poly (butylene succinate) (PBS),which is synthesized from succinic acid and 1, 4-butanediol (Luo et al., 2010, 2013; Ray et al., 2005; Wang et al., 2014, 2012a), attracts considerable attention (Bourmaud et al., 2015; Cao et al., 2002a,b; Chen et al., 2009; Dong et al., 2006; Frollini et al., 2013; Hexig et al., 2005; Li et al., 2014; Liang et al., 2010; Luzi et al., 2016; Ma et al., 2012; Mecking, 2004; Pang et al., 2008; Papageorgiou and Bikiaris, 2007; Soccio et al., 2008; Tachibana et al., 2010; Velmathi et al., 2005; Wang et al., 2011, 2012b; Xu and Guo, 2010; Xu et al., 2008; Zeng et al., 2009; Zhang et al., 2012) due to the possibility of obtaining this polymer from totally renewable sources (Ferreira et al., 2015).

PBS presents good thermal and mechanical properties (Chen et al., 2016; Chikh et al., 2016; Chiu, 2016; Du et al., 2016; Liverani et al., 2016; Pivsa-Art et al., 2016a,b; Ruan et al., 2016; Voznyak et al., 2016; Zhang et al., 2016c,d; Zhou et al., 2016), which allow the processing of this polymer in conventional equipments, such as extruders (Charlon et al., 2016; Kim et al., 2016; Lu et al., 2016; Pivsa-Art et al., 2016b; Voznyak et al., 2016) and injectors (Bourmaud et al., 2016, 2015; Oliviero et al., 2015; Pivsa-Art et al., 2016a; Sheikholeslami et al., 2016). According to literature, PBS can be compared to those of the commodities ordinarily used in the industry, such as polyethylene and polypropylene (Duan et al., 2016; Kim et al., 2005; Miyata et al., 2007; Muthuraj et al., 2014; Vroman and Tighzert, 2009).

PBS is one of the main representative biodegradable biopolymers (Bourmaud et al., 2016; Genovese et al., 2016; Thirunavukarasu et al., 2016; Totaro et al., 2016; Wu et al., 2016), due to its susceptibility to hydrolytic, enzymatic or biological degradation in a reasonable period of time (Tokiwa et al., 2009; Tokiwa and Suzuki, 1977). PBS is biocompatible, which enables

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its use in biomedical applications, such as the production of biocompatible materials (Debuissy et al., 2016; Genovese et al., 2016; Gigli et al., 2016; Toso et al., 2016; Zhang et al., 2016b) and drug delivery systems (Brunner et al., 2011; Cottaz et al., 2016; Gigli et al., 2016; He et al., 2013; Llorens et al., 2015; Sheikholeslami et al., 2016; Souza et al., 2017; Teo et al., 2016; Zhuang and Chena, 2016).

Despite the advantages, the PBS polymerization leads to polymers with relatively low molecular weight (Ikada et al., 2000; Kim et al., 2006; Sugihara et al., 2006). Thus, chemical methods have been studied, aiming to improve the properties of polycondensation polymers. Among them, the chain extension is a rapid and efficient method for the improvement of molecular weight and certain physical properties of polyesters such as toughness, viscosity and thermal stability (Bikiaris and Karayannidis, 1995; Li and Yang, 2006; Manjula et al., 2010). In addition, the use of this method is economically advantageous, since small amounts of the chain extenders are required (Raffa et al., 2012).

Among the most used chain extenders, those containing epoxy or isocyanate groups are very reactive (Xanthos and Dagli, 1991). However, the use of extenders containing hydroxyl groups cannot be discarded. Among these compounds, castor oil and rutin are studied in this work.

Castor oil, from the *Ricinus communis* plant seed (Alexopoulou et al., 2015; Bateni and Karimi, 2016; Campbell et al., 2015; Grichar et al., 2015; Hajar and Vahabzadeh, 2016, 2014; Horn et al., 2016; Kanwar et al., 2016; Kumar et al., 2016; Liu et al., 2014; McKeon et al., 2016; Pourzolfaghar et al., 2016; Singh, 2011; Uzoh and Nwabanne, 2016; Zhang et al., 2016a), presents a large amount of hydroxyl groups, especially those of ricinoleic acid, which corresponds to 80–90 wt% of the oil content. It is available at low cost and the plant is able to tolerate adverse weather conditions. Castor oil is a common chain extender of polymers (Allauddin et al., 2013; Badri et al., 2000; Bueno-Ferrer et al., 2012; Corcuera et al., 2010; Dawson et al., 1970; De et al., 2013; Galià et al., 2010; Gurunathan et al., 2015; Karak et al., 2009; Kendagannaswamy, 2002; Kong and Narine, 2007; Madbouly et al., 2013; Manjula et al., 2010; Miao et al., 2014, 2012; Mutlu and Meier, 2010; Oprea, 2011, 2010; Pandya et al., 1988; Rafienia et al., 2006; Saralegi et al., 2014; Saxena et al., 1992; Septevani et al., 2015; Thakur and Karak, 2014; Yeganeh and Mehdizadeh, 2004; Yu et al., 1999; Zhang and Huang, 2001).

Rutin, also known as “vitamin P”, belongs to the class of flavonoids (AlSharari et al., 2016; Bondarev et al., 2016; Ismail et al., 2016; Jadav, 2016a,b; Roushani and Shahdost-fard, 2016), being found in plants such as: *Sophora japonica*, *Fagopyrum esculentum*, *Eucalyptus macrorrhyncha,* in the fruit of the Brazilian tree Fava d’anta (*Dimorphandra mollis*); and in certain foods such as: oranges, grapefruits, lemons and limes, berry fruits and buckwheat (Amarowicz et al., 2009; Merken and Beecher, 2000; Pękal et al., 2012; Pérez-Jiménez et al., 2010; Sethiya et al., 2014; Solayman et al., 2016). Rutin presents dozens of biochemical and pharmacological activities including antioxidant, anti-inflammatory, anti-allergic, anti-viral and anti-carcinogenic effects, and stimulates of the immune system (Argentieri et al., 2012; Cui et al., 2016; Hyun et al., 2015; Kicel et al., 2015; Nunes et al., 2016; Radusiene et al., 2015; Singh and Kumari, 2015). Rutin presents two different hydroxyl groups, phenolic (flavonoid skeleton) and alcoholic (glycosyl radical) ones (Da Silva et al., 2002; Kreft et al., 1999). Due to its chemical structure, rutin can produce irregularity in the arrangement of the polyesters, reducing the crystalline degree of the macromolecular material. Fig. 1 shows the chemical structures and natural sources of these castor oil and rutin.

Fig. 1 Over the last years, the use of biodegradable polymers for the administration of pharmaceuticals and biomedical devices has increased expressively. In this context, poly(butylene succinate) (PBS) is one of the most promising biodegradable polyesters studied, since its hydrolytic and/or enzymatic degradation products can be naturally metabolized into nontoxic substances (Ahn et al., 2001; Ali Akbari Ghavimi et al., 2015; Chinsirikul et al., 2015; Costa-Pinto et al., 2012; Guo et al., 2013; Hao et al., 2013; Ikada and Tsuji, 2000; Jamshidian et al., 2010; Mohanraj et al., 2013; Patntirapong et al., 2015; Rossi et al., 2015; van Dijkhuizen-Radersma et al., 2004). In addition, PBS also can be used as an efficient carrier to hydrophobic drugs, such as silybin.

Silybin is a naturally occurring polyphenolic flavonoid obtained from the seed of the milk thistle (*Silybum marianum*), and has been widely used in the treatment of certain liver disorders, such as chronic active hepatitis, hepatic cirrhosis, as well as alcohol-induced and various types of drug-induced and toxin-induced liver damage (AbouZid et al., 2016; Ahmad et al., 2013; de Oliveira et al., 2015; Lucini et al., 2016). However, the effectiveness of silybin as a liver disease remedy was discounted by its poor water solubility and low bioavailability (Karkanis et al., 2011). In order to improve the dissolution and bioavailability of silybin, several approaches have been employed, such as incorporating into solid dispersion (Tang et al., 2007; Vasconcelos et al., 2007; Wang et al., 2010; Wei et al., 2012; Woo et al., 2007; Wu et al., 2006; Yan-Yu et al., 2006; Yanyu et al., 2006).

Therefore, the goal of this work is to evaluate the changes on the properties of PBS produced by the use of rutin and castor oil as chain extenders. In addition, the obtained material modified with rutin was tested as a drug delivery system. To the best of our knowledge, rutin was never tested as chain extenders for PBS or even to any other polyester. Furthermore, PBS was never tested as a vehicle to the silybin release. Main results presented here prove that the modification of PBS with rutin reduces the release of silybin from the drug delivery system.

2. Experimental

2.1. Materials

Succinic acid PA ACS (99.0%) and 1,4 butanediol PS (99.3%) were supplied by Sigma-Aldrich Brazil. Rutin was supplied by Merck, and castor oil was supplied by Petrobras. Titanium (IV) butoxide ($Ti(OBu)_4$) and silybin (primary pharmaceutical reference standard) were supplied by Sigma-Aldrich. All of these chemicals were used as received without further purification.

2.2. Synthesis of PBS

The synthesis of PBS was performed in two stages. The first step involved the preparation of a prepolymer by direct esterification, in which a three neck reactor was immersed in a silicone bath with the reaction medium temperature controlled at 150 °C with the aid of a thermocouple connected to a heating system. The reactor was connected to a condenser where water circulated at 10 °C, generated by an external bath, to facilitate the removal of the vapor generated from the reaction. Magnetic stirring and a nitrogen flow were applied to the system. The reaction mixture contained the monomers 1,4-butanediol and succinic acid in the ratio 1.1:1.0. Water, a byproduct of the reaction, was removed and collected. The reaction conditions were maintained for 5 h. In the second stage, polycondensation of the prepolymer by a transesterification reaction occurred. The catalyst, ($Ti(OBu)_4$), at 0.1 mol% concentration was added to the reaction medium at 150 °C and then the temperature was gradually increased to 200 °C and maintained for a further 12 h. In this system, a reduced pressure was applied with the aid of a suction pump. After complete synthesis in the reactor, a further step was carried out of polycondensation in the solid state