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Sodium alginate as a potential carrier in solid dispersion formulations to enhance dissolution rate and apparent water solubility of BCS II drugs

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ABSTRACT

The solid dispersion technique is the most effective method for improving the dissolution rate of poorly water-soluble drugs, however it depends on a suitable carrier selection. The work explored the use of the biopolymer sodium alginate (SA) as a potential carrier in solid dispersions (SD). The data demonstrated that SA was able to improve the biopharmaceutical properties of the BCS II drug telmisartan (TEL) of low solubility even using relative small drug:polymer ratio. A solid state grinding process was used to prepare the solid dispersions (SD) during 45 min. The SD were prepared in different proportions of drug and carrier of 1:1, 1:3, 1:5, 1:7 and 1:9 (mass/mass). DSC, XRPD, FTIR and Raman confirmed the presence of molecular interactions between TEL and the carrier. FTIR supports the presence of hydrogen bonds between TEL and the carrier. SD_1:5, SD_1:7 and SD_1:9 enhanced the dissolution rate of the drug releasing more than 80% of the drug in just 30 min (83%, 84% and 87%). The the *t*-test results demonstrated equal dissolution efficiency values for SD_1:7 and Micardis®, however the similarity ($f2$) and difference ($f1$) fit factors showed that the SD and Micardis® are statistically different. The physical stability studies demonstrated that SD using sodium alginate as a carrier remained unchanged during the period of 90 days at room temperature, showing that the sodium alginate acts as a good anti plasticizer agent, preventing the drug recrystallization.

1. Introduction

Sodium alginate (SA) is a hydrophilic polysaccharide which is mainly isolated from the cell walls of brown seaweeds (George & Abraham, 2006; Yang, Xie, & He, 2011). This biopolymer is considered biocompatible, biodegradable, non-toxic and its use as food additive has been generally recognized as safe (GRAS) by Food and Drug Administration (FDA) since 1982 (21CFR184.1724) (Andersen, Strand, Formo, Alsberg, & Christensen, 2012; Brownlee, Seal, Wilcox, Dettmar, & Pearson, 2009; George & Abraham, 2006).

The physicochemical properties of alginates are directly related with its molecular structure (Fig. 1A). Its general structure consists of 1 → 4 linked α-L-guluronic acid (G) and β-D-mannuronic acid (M) in alternating blocks of GG, MM and MG arranged in an irregular pattern (Brownlee et al., 2009; George & Abraham, 2006; Yang et al., 2011; Zia, Zia, Zuber, Rehman, & Ahmad, 2015). This chemical conformation is suitable for chemical reactions and linkages due to the presence of reactive sites, such as hydroxyl and carbonyl groups along the backbone (Zia et al., 2015).

In this sense, alginates have been widely used in several areas such as in bioengineering (Andersen et al., 2012), in food (Brownlee et al., 2009) and textile industries. In the pharmaceutical field, SA has been used as hydrogel former and it is also has been widely reported in the development of microparticles (Ahmed, El-Rasoul, Auda, & Ibrahim, 2013; Devi & Kakati, 2013; Lacerda, Parize, Fávere, Laranjeira, & Stulzer, 2014; Mladenovska et al., 2007; Tu et al., 2005) and for drug delivery of several drugs, such as gatifloxacin and risperidone (Bera, Goud, Kumar, & Boddupalli, 2015; Motwani et al., 2008). Recently, the use of ester alginates derivatives have been reported as promising solid dispersions carriers to enhance the aqueous solubility of a poorly soluble compound by classical hot melt method (Pawar & Edgar, 2013). In the same way, the

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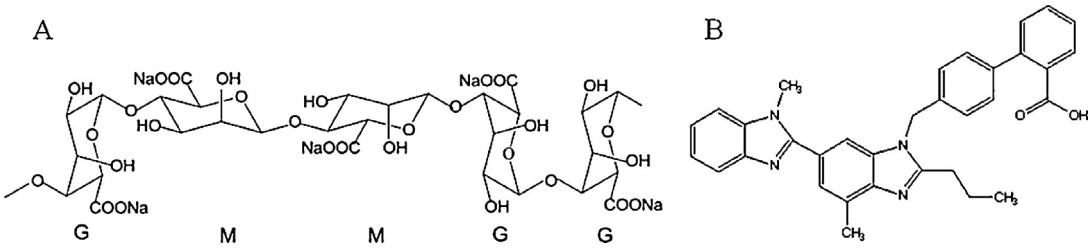

Fig. 1. Molecular structure of sodium alginate (A) (Yang et al., 2011) and chemical structure of telmisartan (B).

combination of sodium alginate with the alkalizer sodium carbonate demonstrated to be an effective carrier to enhance the solubility and dissolution of poorly soluble drugs in solid dispersions prepared by spray drying technique (Pradhan et al., 2014). In the present study, SA was selected as a promising carrier and telmisartan (TEL) as a model API aiming the development of solid dispersions *via* ball milling process, without solvent addition.

TEL is a potent and selective angiotensin II type 1 (AT1) receptor blocker, which is widely used in the treatment of hypertension (Goodman & Gilman, 2008). This drug is classified as class II by the Biopharmaceutical Classification System and was used as a model drug targeting the improvement of its poor aqueous solubility (Lobenberg & Amidon, 2000; Yang, Shao, & Han, 2014).

In accordance with TEL structure, this compound has four hydrogen acceptor and one hydrogen donor, which make it an interesting compound to be loading in SDs. In addition, its solubility is pH-dependent, being practically insoluble in strong acid solutions and spontaneously soluble in highly alkaline solutions (British Pharmacopoeia, 2012; Tran, Tran, & Lee, 2008; Wienen et al., 2000).

It is widely known that the conversion of crystalline drug in its amorphous form is one of the most promising strategies in order to increase solubility and dissolution rate of poorly soluble drugs (Guo, Shalaev, & Smith, 2013; Serajudidin, 2007). The amorphous state has higher intermolecular energy levels and has a higher molecular mobility than crystalline compounds, and thereby presents improvements in parameters as solubility and dissolution rate (Guo et al., 2013; Laitinen, Löbmann, Strachan, Grohganz, & Rades, 2013; Shan-Yang & Chun-Sen, 1989). However, the amorphous state is energetically less stable, tending to recrystallization. Taking into consideration that recrystallization can occur during production, storage or dissolution of amorphous solid (Aaltonen & Rades, 2009; Hancock & Parks, 2000; Laitinen et al., 2013), methods capable of stabilizing the amorphous form are promising to maintain the biopharmaceutical properties of drugs that have solubility problems in the crystalline state.

Solid dispersions (SD) have been shown to be one of the most effective technological strategies for the improvement of the dissolution rate/bioavailability of aqueous poorly soluble drugs, standing out among other techniques for promoting best results (Leuner & Dressman, 2000; Serajuddin, 1999; Vasconcelos, Sarmento, & Costa, 2007). The SD term refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles generally by melting or solvent method (Guo et al., 2013; Huang & Dai, 2014; Kim et al., 2006).

The mechanical grinding technique using ball mill is able to amorphize particles on a large scale and thus improve biopharmaceutical characteristics of drugs, outstanding among other techniques due to its low cost, easy handling and possibility of scaling up (Barzegar-Jalali et al., 2010; Lim, Ng, & Tan, 2013). Furthermore, this process is able to provide interactions between drug and carrier that results in changes in the physicochemical properties of the drug crystalline structure to its amorphous state, resulting in improvement of solubility, dissolution and bioavailability properties of drug (Crowley & Zografi, 2002). This technique is considered one of the simplest and common unit operations in the pharmaceutical industry, which does not require the use of solvents in the process, being considered clean and environmentally friendly (Barzegar-Jalali et al., 2010).

Based in the advantages described above, the present study proposes the development of SD using SA as the hydrophilic carrier and TEL as a model drug using mechanical grinding process *via* ball milling technique, in the solid state and without the addition of solvent.

All SD were evaluated in terms of solubility and dissolution rate. The physicochemical properties were assessed applying solid state techniques such as DSC, XRPD, FTIR, Raman and SEM. The physical stability of the system was analyzed during 90 days.

2. Experimental

2.1. Materials

TEL (PubChem CID: 65999) was purchased from Haohua Industry Co. Ltd. (China), characterized and evaluated in terms of quality control (purity ≥ 96%, form A) (Borba et al., 2014). SA (200.000 g mol), 99% of purity and ratio M/G = 1/2) PubChem CID: 6850754 was obtained from Sigma-Aldrich (Germany). Micardis® 40 mg, Boehringer Ingelheim (batch 6424), the reference medicine for TEL, was obtained in the market. All others chemicals and solvents were of analytical or HPLC grade.

2.2. Methods

2.2.1. Preparation of ball milled SD

The solid dispersions (SD) of TEL were obtained by solid state grinding method, using sodium alginate (SA) as a carrier. TEL-SA SD were prepared in different ratios and all formulations were accurately weighed to give a final mass of 2.0 g. Details regarding the composition of all SD obtained are shown in Table 1.

The samples were milled at room temperature for 45 min without addition of solvents in a Spex Dual Mixer 8000 D (New Jersey, USA) in a 40 mL steel jars with three steel balls (two with external diameter of 6.4 mm and one of 12.8 mm) at a constant ball:powder ratio of 3.7 (w/w).

Table 1
Composition of TEL solid dispersions.

Denomination	Proportion TEL:SA (w/w)	Grinding time (min)
SD_1:1	1:1	45
SD_1:3	1:3	45
SD_1:5	1:5	45
SD_1:7	1:7	45
SD_1:9	1:9	45