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A simple and effective method to improve bioavailability of glimepiride by utilizing hydrotropy technique

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ABSTRACT

The purpose of this study was to improve the solubility and bioavailability of glimepiride (GLMP) by utilizing hydrotropy technique. Meglumine (MU) as a hydrotrope could form the stable complex with glimepiride. The optimal glimepiride and meglumine (GLMP–MU) complex powder was obtained by using lyophilization. GLMP–MU powder was characterized by Fourier transform infrared spectroscopy (FT IR), X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC). The formation of hydrogen bond between glimepiride and meglumine was confirmed by FT IR. The XRD studies indicated the amorphous state of glimepiride was appeared in the GLMP–MU. The DSC results were further confirmed GLMP–MU complex was prepared successfully. Moreover, the *in vitro* drug release rate of GLMP–MU powder was dramatically faster than that of glimepiride. Meanwhile, the AUC of GLMP–MU solution at an *i.g.*/or *i.v.* dose of 5 mg/kg in rat was significantly higher than that of the glimepiride suspensions. Together our results showed that hydrotropy technique was a simple and effective method to increase the solubility of glimepiride.

1. Introduction

It is estimated that 40% of marketed drugs are poorly water-soluble, among the US pharmacopeia, this share is almost 30% (Fahr and Liu, 2007). Based on the biopharmaceutics classification system (BCS), drug substances are classified into four categories according to their solubility and permeability properties. For the drugs of BCS class II, the rate-limiting process of absorption is the drug dissolution step (Taupitz et al., 2013). Therefore, even though such compounds have powerful pharmacological activity, the expected clinical efficacy is sometimes not experienced (Kawabata et al., 2011). Dosage forms play a major role in determining the rate and extent of absorption of such drugs from the gastrointestinal tract (Pouton, 2006). Glimepiride exhibits very poor solubility at 37 °C (<0.004 mg/mL) in acidic and neutral media and relatively high permeability (30.4×10^6 cm/s) through Caco-2 cell monolayers. Thus, glimepiride is categorized as a Class II drug by the Biopharmaceutics Classification System (Iwata et al., 2009; Semalty, 2014).

Glimepiride (GLMP) is a white to yellowish crystalline powder and insoluble in water (Siddiqui et al., 2013). Chemically it is 1-[[4-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)-ethyl] phenyl] sulfonyl]-3-trans-(4-methylcyclohexyl) urea (Fig. 1a) (Salem et al., 2004; Song et al., 2004), and it is a third-generation sulfonylurea oral hypoglycemic agent used for the treatment of patients with type II non-insulin-dependent diabetes mellitus (Ammar et al., 2006a; Du et al., 2013). Preclinical investigation of glimepiride suggested a number of potential benefits over sulfonylurea currently available including lower dosage, rapid onset, longer duration of action and lower insulin C-peptide levels, possibly due to less stimulation of insulin secretion and more pronounced extrapancreatic effects (Ammar et al., 2006a; Song et al., 2004). Glimepiride has poor solubility and slow dissolution rate that lead to irreproducible clinical response or therapeutic failure in some cases due to subtherapeutic plasma drug levels (Ammar et al., 2006a). The poor solubility of GLMP leads to difficulties in the dosage form design. Concerning the drawbacks associated with the GLMP treatment, the use of suitable strategies to increase its water solubility or gastrointestinal absorption could reduce the undesirable side effects by the administration of lower doses (Aloisio et al., 2013). To overcome these obstacles, a lot of new pharmaceutical technologies, such as inclusion complexes (Ammar et al., 2006a,b), solid dispersions (Ahuja et al., 2007; Mohamed et al., 2012; Pahovnik et al., 2011), cosolvent (Seedher

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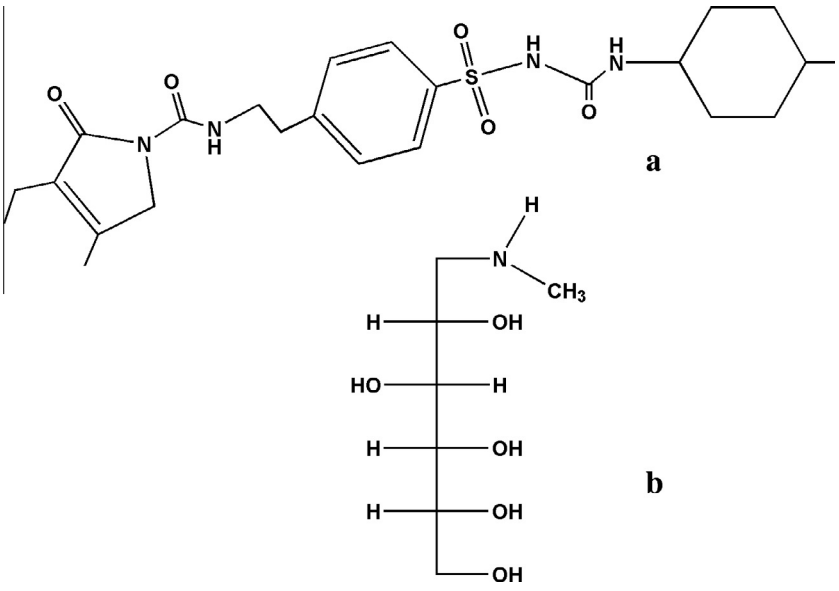

Fig. 1. The molecule structure of glimepiride (a) and meglumine (b).

and Kanojia, 2009), self-nanoemulsifying system (Mohd et al., 2014; Shah et al., 2013), nanocrystal (Du et al., 2013; Ning et al., 2011), and micelles (Reven et al., 2010, 2013; Seedher and Kanojia, 2008) have been used for increasing the solubility of glimepiride. Although those technologies improved the solubility of glimepiride to some extent, the improvement of clinical efficacy was not clear or the complex preparation was not suitable for industrial production.

Using hydrotrope to improve the solubility of undissolved drug has been reported (Agrawal et al., 2004; Lee et al., 2003). Hydrotropy, the process whereby the presence of a large quantity of one solute enhances the solubility of another solute, is an important technique to solubilize poorly water-soluble pharmaceutical compounds (Hodgdon and Kaler, 2007; Kim et al., 2010). It is also an important strategy being considered to prepare hydrophobic substances aqueous solution (Eastoe et al., 2011). Fluctuation Theory of Solutions (FTS) is employed to explain the mechanisms of hydrotropic drug solubilization (Shimizu et al., 2013). FTS has identified two major factors of hydrotrope-induced solubilization, one is preferential hydrotrope–solute interaction (Durand et al., 2009; Suzuki and Sunada, 1998) and the other is water activity depression (Badwan et al., 1982; Balasubramanian et al., 1989; Coffman and Kildsig, 1996; Cui, 2010; Cui et al., 2010; da Silva et al., 1999; Friberg et al., 1986). The former is dominated by hydrotrope–solute association, and the latter is enhanced by ionic dissociation and hindered by the self-aggregation of the hydrotrope (Booth et al., 2012). According to the literature, a suitable hydrotrope can increase the solubility of the drug a thousand times (Agrawal et al., 2004), which inspires us to study the possibility of using hydrotrope to increase the solubility of glimepiride and improve its bioavailability.

Meglumine, chemically designated as 1-deoxy-1-(methylamino)-D-glucitol (Fig. 1b), is an amino sugar used as organic alkaline hydrotrope (Aloisio et al., 2013; Gupta and Bansal, 2005b). Meglumine consists of several electron-accepting centers in the form of –OH and –NH groups, which provide varied possibilities for hydrogen bond (Gupta and Bansal, 2005b). Meglumine could form stable salt formation with weak acidic drugs, which is a well-established and effective technique for increasing solubility and bioavailability of acidic drugs (Aloisio et al., 2013; Gupta and Bansal, 2005a,b; Sharma et al., 2010). In recent years, some reports used meglumine and cyclodextrin (Aloisio et al., 2013; Basavaraj et al., 2006) or poly(vinyl pyrrolidone) (PVP) (Gupta and Bansal, 2005a; Telang et al., 2009) added to drug, which formed ternary system led to obviously increase of solubility of weak acidic drugs.

The present study was to deal with formulation of aqueous solution based on hydrotropy techniques of an undissolved drug. Glimepiride and meglumine (GLMP–MU) complexes were prepared and characterized by FT IR, XRD and DSC. Moreover, the lyophilized GLMP–MU complex *in vitro* drug release and its pharmacokinetics *in vivo* were also studied.

2. Materials and methods

2.1. Materials

Glimepiride was obtained from Hubei Kangbao Fine Chemical Co., LTD. Meglumine was purchased from Suzhou Jingye Medicine and Chemical Co., LTD. All other chemicals used were analytical grade. Wistar rats (200 ± 20 g) were purchased from Beijing Vital River Laboratory Animal Technology Co. Ltd. (Beijing, China). All animal experiments were performed in compliance with the requirements of the National Act of the People's Republic of China on the use of experimental animals and approved by the University Ethics Committee.

2.2. Preliminary hydrotropy ability of meglumine

A certain amount of glimepiride was added to 2 mL vials containing different weight ratio of meglumine (GLMP:MU = 1:0, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 and 1:10), and the mixture was added equal volume of distilled water. The vials were shaken vigorously for 10 min on a vortex mixer, and then the solution was allowed to equilibrate with mechanically shaking for 72 h at 37 ± 0.2 °C in an air-bath shaker (HZ-82, Jintan, China). After completion of 72 h, each vial was centrifuged at 3000 rpm for 10 min and then the samples were determined by HPLC.

An equal amount of glimepiride was added to 2 mL vials containing different weight ratio of meglumine (GLMP:MU = 1:2, 1:3, 1:5 and 1:10), and the mixture was added equal volume of distilled water. The vials were in a water bath at 80 °C for 30 min, and the vials transferred to refrigerator store at 4 °C for 24 h. Then the vials