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Application of a ternary HP-β-CD-complex approach to improve the dissolution performance of a poorly soluble weak acid under biorelevant conditions

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ABSTRACT

Over the last decades the poor solubility of new drugs has become an important issue, with one of the main challenges being to develop oral dosage forms with acceptable bioavailability for such compounds. The specific purpose of our study was to combine the advantages of cyclodextrins with those of solid dispersion approaches to improve the bioavailability of poorly soluble weak acids. Glyburide, an antidiabetic, was used as a model drug. First, binary drug inclusion complexes were prepared with 2-hydroxypropyl-β-cyclodextrin. Next, solid glyburide dispersions were prepared with polyvinylpyrrolidone (PVP) and a relatively new hydrophilic copolymer, Kollicoat® IR. Finally, to check for potential synergistic effects of the two types of excipients, ternary inclusion complexes were formulated by keeping the 1:2 drug:CD ratio constant but varying the polymer concentration (5–20%). The formulations were analyzed by differential scanning calorimetry and subjected to solubility and dissolution experiments in compendial and biorelevant media. The results of the study clearly indicate that all formulations result in better in vitro performance of the drug. Best results were obtained with the ternary inclusion complexes containing 10% Kollicoat® IR or 20% PVP K30. This formulation approach, particularly with the new polymer, appears to be promising in terms of enhancing the bioavailability of BCS class II drugs.

1. Introduction

In the early 1990s, a new era in drug discovery, characterized by the extensive use of combinatorial chemistry and high-throughput screening methodologies, was initiated. Since these methods make it possible to identify a huge number of potential new drugs within a short time frame, they have become standard methodologies in the field.

In order to classify marketed drug substances and new chemical entities (NCEs) according to their solubility and permeability through biological membranes, the Biopharmaceutics Classification System (BCS) was established in 1995 (Amidon et al., 1995). The BCS classifies drugs into four classes: BCS class I drugs have high solubility and high permeability, whereas drugs belonging to BCS class II have high permeability, but are burdened with poor solubility. Drugs with high solubility and poor permeability can be found in BCS class III and finally, drugs with poor solubility and poor permeability represent BCS class IV compounds. Unfortunately, as a result of the newer screening methods of drug discovery, NCEs often have high potency but, due to their high log *P* values, are characterized by poor solubility in aqueous fluids and often also have poor permeability due to high molecular weight (Lipinski, 2000). Thus, they tend to be classified as BCS class II or IV drugs. Whereas it is more difficult to make oral drug formulations of BCS class IV drugs, there is often a good chance of obtaining sufficient oral bioavailability of a BCS class II drug when the right formulation approach is used. For BCS class II drugs, the dissolution performance is the rate limiting step to drug absorption. Therefore, formulation strategies that improve dissolution properties can greatly enhance the bioavailability of these compounds.

Within the last decades, various strategies have been established to enhance the solubility of drugs (e.g. particle size reduction, salt formation, solid dispersions (SD), lipid based formulations and complex formation with cyclodextrins) (Leuner and Dressman, 2000; Li et al., 2001; Loftsson and Brewster, 1996). Solid dispersions are a well known method for improving solubility, with examples like griseofulvin (Saito et al., 2002), piroxicam (Wu et al., 2009) and tacrolimus (Yamashita et al., 2003) described in the open literature. As early as the middle of the last century, Sekiguchi and Obi had reported that formulations of eutectic mixtures lead to an increase in the solubility of poorly soluble drugs (Sekiguchi and Obi, 1961). Other research groups then also focused their activities on manufacturing solid dispersions (Joshi et al., 2004; Sethia and Squillante, 2004). Various formulation techniques intended to improve the efficiency in achieving glassy solid dispersions, i.e.

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formulations, where the poorly soluble drug is embedded in an amorphous state in a carrier, were investigated. These new technologies, such as solvent evaporation, spray drying, freeze-drying and hot melt extrusion (Leuner and Dressman, 2000; Vasconcelos et al., 2007), resulted in formulations that showed a significant increase in drug dissolution rate.

In addition to the preparation of solid dispersions, complexation with cyclodextrins (CDs) has become an important element of formulation development (Loftsson and Duchene, 2007; Stella and He, 2008). Natural CDs are α-1,4 linked oligosaccharides, consisting of 6, 7 or 8 glucose monomers which according to the number of glucose-units are called α-, β- or γ-CDs, respectively. The molecular structure of these glucose derivatives, which approximates a truncated cone or torus, generates a hydrophilic exterior surface and a nonpolar cavity interior. As such, CDs can interact with appropriately sized molecules to result in the formation of inclusion complexes (Loftsson and Brewster, 1996). Depending on the molecular capability (polarity, size and three-dimensional structure) of the guest molecule to form a non-covalent complex, CDs can either host the whole drug molecule or the non-polar part. By doing so, they can increase the aqueous solubility of sparingly soluble guest molecules by orders of magnitude in favorable cases. In addition, CD complexation is often accompanied by a variety of additional physicochemical advantages for the drug-molecule, most notably the stability of the drug or taste masking (Loftsson and Duchene, 2007; Szejtli, 1982). One of the few disadvantages of the natural CDs has been their limited water solubility (1.85 g/100 mL for β-CD) (Loftsson and Brewster, 1996). Despite its suboptimal aqueous solubility, β-CD is currently the most extensively used native CD in marketed products. The main reason for this is the dimensions of its inner cavity which appear to be optimal for many of the currently marketed drugs. However, nowadays the tendency is to modify the parent β-CD resulting in derivatives with increased aqueous solubility (Szejtli, 1998). To date only very few of these derivatives, i.e. methyl- (>50 g/100 mL), hydroxypropyl- (>60 g/100 mL), sulfobutylether- (>50 g/100 mL) derivates of β-CD and hydroxypropyl-γ-CD (>50 g/100 mL) can be found in pharmaceutical products (Brewster and Loftsson, 2007; Davis and Brewster, 2004; Loftsson et al., 2004; Loftsson and Duchene, 2007; Thompson, 1997).

Whereas the natural β-CD is generally recognized as safe (GRAS) by the FDA, approved as a food additive in Europe and Japan and listed in the European- (Ph.Eur.), the United States- (USP/NF) and the Japanese Pharmacopoeia (JP), several of the CD derivatives are cited in the FDA's list of Inactive Pharmaceutical Ingredients but do not enjoy GRAS status (Loftsson and Duchene, 2007). Currently only 2-hydroxypropyl-β-cyclodextrin (Hydroxypropyl Betadex, HP-β-CD) is listed in both Ph.Eur. and USP/NF. The available literature shows that the toxicity of HP-β-CD has been extensively studied. HP-β-CD is well tolerated in most species and humans, particularly if dosed orally. It shows limited toxicity, depending upon dose and route of administration. The main adverse effect observed in humans is diarrhoea. However, to date no effects on kidney have been reported (Gould and Scott, 2005; Irie and Uekama, 1997).

Despite its use in commercially available drug products such as intravenous voriconazole, sulfobutylether-β-cyclodextrin (SBE-β-CD) is not yet listed in any pharmacopoeial monograph. However, studies published recently indicate that in its toxicity is also limited and dependent upon dose and route of administration (Luke et al., 2010). In addition to HP-β-CD and SBE-β-CD, various chemically modified CDs have been described in the literature.

Some of the natural, non-modified CDs have either been associated with hepatotoxicity (Yong et al., 2007) or nephrotoxicity (Frijlink et al., 1991). By contrast, the chemical modifications applied to obtain the various CD derivatives have often greatly reduced the toxicity of the newer CD derivatives (Frijlink et al., 1991; Luke et al., 2010). It is thus likely that the regulatory status of CDs will evolve further, facilitating more frequent use of CD derivatives in pharmaceutical products in the future.

In order to act as a guest molecule in CDs, the drug compound has to fulfill some requirements such as a linear molecular structure and the ability to establish hydrophobic interactions with the CD molecule. Based on its molecular properties, its linear structure and its hydrophobic character, which appeared be ideal to interact with the cavity of CDs, glyburide was deemed to be an appropriate guest molecule. The drug has physicochemical properties typical of poorly water soluble drugs: a high molecular weight (M_W) (494 g/mol), a log P value of 4.8 and a high melting point of 172–174 °C (Lipinski, 2000; Yalkowsky, 1981). The aqueous solubility of glyburide has been reported as 0.06 μg/mL (Avdeef, 2007). Based on its poor solubility in aqueous fluids but high permeability through physiological membranes (Wei and Lobenberg, 2006) glyburide has been categorized as a BSC class II compound (Lindenberg et al., 2004). Since improving the rate and extent of in vivo dissolution typically results in an increased bioavailability of BCS class II compounds, glyburide represented a good candidate for our study. Complex formulation with natural β-CDs has been reported for glyburide previously. Literature data (Buchanan et al., 2002; Savolainen et al., 1998) suggest that glyburide forms 1:2 (mol:mol) drug:CD-complexes with β-CDs and its derivatives. The low single dose of glyburide (1.0–5.0 mg) widely used in the oral treatment of type-2 diabetes mellitus is very suitable for CD complexation since a 1:2 (drug:CD) complex with a CD derivate of high molecular weight (>1000 g/mol) can still be easily administered as an oral drug formulation.

In the present study glyburide was used as a model drug to evaluate the impact of different formulation technologies, including solid dispersions, binary CD inclusion complexes with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) and the combination of both methods (ternary CD complexes), on its solubility and dissolution rate. Particular attention was given to the performance of ternary complexes. It has been reported that addition of water-soluble polymers can significantly increase the apparent stability constant of a drug:CD complex (Loftsson and Brewster, 1996). Thus, it was hypothesized that the combination of a CD-derivate and a hydrophilic polymer might increase the HP-β-CD complexation efficacy for glyburide and therefore result in an even better drug dissolution than a simple, binary system. Such a performance could then be beneficial in terms of achieving an even higher bioavailability after oral administration of the drug and could also result in reduction of the dose required to achieve the desired pharmacological effect. This effect could be of particular importance for higher dosed poorly soluble NCEs.

Two water-soluble polymers were selected to prepare solid dispersions and also to act as the ternary component in the glyburide:HP-β-CD:polymer complex. The first polymer was polyvinylpyrrolidone (PVP) K30 which, after addition to binary CD complexes, has already been shown to facilitate dissolution of poorly soluble compounds (Fouad et al., 2011; Mura et al., 2001). The second polymer was Kollicoat® IR, a relatively new commercial hydrophilic polyvinyl alcohol–polyethylene glycol graft copolymer, which has been developed to be used for instant release (IR) coatings (Bühler, 2007). The aim of using Kollicoat® IR was to study the feasibility of this novel polymer for preparing ternary CD complexes. In general, Kollicoat® IR is associated with several promising properties. It is a pharmaceutical grade polymer, dissolves rapidly and has an exceptional solubility in water. Aqueous solutions with a concentration of up to 50% can be easily obtained (Bühler, 2007). Moreover, its chemical structure is not ionizable and therefore provides distinct advantages for a drug release that is independent on the pH of the release medium (Fouad et al., 2011). Even though it was originally developed for coating purposes, Kollicoat® IR has