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Article

Physicochemical Characterization, Molecular Docking, and *In Vitro* Dissolution of Glimepiride–Captisol Inclusion Complexes

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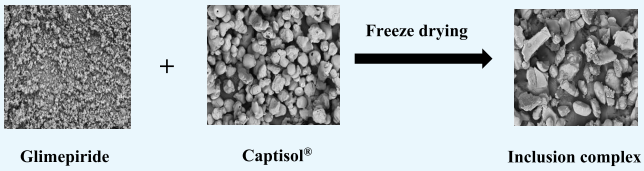
ABSTRACT: This present study investigated the effect of Captisol, a chemically modified cyclodextrin, on the in vitro dissolution of glimepiride. We prepared glimepiride–Captisol complexes of different mass ratios (1:1, 1:2, and 1:3 w/w) by a physical mixing or freeze-drying technique, and found that complexation with Captisol enhanced the water solubility of glimepiride. Molecular docking and dynamic simulation predicted complex formation; at the same time, Fourier transform infrared spectroscopy, differential scanning calorimetry, powder X-ray diffractometry, and scanning electron microscope indicated molecular interactions that support complexation. We also found that an inclusion complex was better than a physical mixture in enhancing the complexation of glimepiride with Captisol and enhancing water solubility. Phase solubility study of the glimepiride–Captisol complex showed an A_L-type profile, implying the formation of a 1:1 inclusion complex. The study also revealed that pH influenced the stability of the complex because the stability constant of the glimepiride–Captisol complex was higher in distilled water of pH ∼6.0 than in phosphate buffer of pH 7.2.



INTRODUCTION

Glimepiride (Figure 1) is a long-acting, second-generation sulfonylurea drug indicated for type 2 diabetes mellitus.[1] The drug is poorly water-soluble, which limits its bioavailability and, ultimately, efficacy[2,3] and therefore creates a critical need to enhance the water solubility of the drug. In this regard, there are intensive efforts to apply solubility enhancement techniques such as encapsulation within cavitands to improve glimepiride solubility. Well-known cavitands are cyclodextrins (Figure 1), which encapsulate poorly water-soluble drugs within their hydrophobic cavity and, through their hydrophilic exterior, enhance water solubility.[4−9] Ammar's group, for instance, designed different drug–cyclodextrin–polymer ternary systems to enhance the solubility of glimepiride,[8−10] and Uekama's group integrated cyclodextrin into drug carriers to improve the solubility of the drug.[11] In the ternary system, the cyclodextrin forms both inclusion and noninclusion complexes with glimepiride, leading to an increase in the drug's solubility.[8,9] Depending on the concentration of cyclodextrin in the system, aggregates of 1:1 or 1:2 glimepiride–cyclodextrin inclusion complexes are assembled, which can further solubilize the drug via noninclusion complexation or micelle-like structure.[7−10]

The structure of the cyclodextrin plays a critical role in drug solubilization. Uekama's group found that glimepiride forms more water-soluble complexes with α- and β-cyclodextrins than with γ-cyclodextrin,[11] implying that structural and functional modifications could fine-tune drug solubilization properties. Sulfobutylether-β-cyclodextrin (SBE_7-β-CD) (Figure 1) typifies a chemically modified cyclodextrin with improved solubility and reduced systemic toxicity.[12] Recently, Captisol, a chemically modified β-cyclodextrin (Figure 1), was designed to maximize safety and enhance drug solubility, stability, and bioavailability.[13] Preclinical and clinical evaluations suggest that Captisol is less toxic than β-cyclodextrin and provides more interactions to enhance water solubility of poorly water-soluble drugs.[14] These superior properties have triggered an interest in using Captisol to solubilize and stabilize poorly water-soluble drugs.[15−17] Here, we hypothesize that Captisol complexes glimepiride within the hydrophobic cavity to enhance the drug's solubility in aqueous media.

The goal of this study is to test the hypothesis by formulating a glimepiride–cyclodextrin solid dispersions, physical mixture and inclusion complex, and then study the drug's solubility. The solid dispersions were prepared using freeze-drying and physical mixing techniques. We carried out phase solubility studies to understand how temperature and pH affect the solubility of the glimepiride–Captisol inclusion complex. We also conducted molecular docking and simulation experiments to predict complex formation and stability. Powder X-ray diffractometry

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