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Improving furosemide polymorphs properties through supramolecular complexes of β-cyclodextrin

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ABSTRACT

In this work, complexes of β-cyclodextrin and the two solid forms of furosemide were prepared and characterized for their potential pharmaceutical applications, with the interactions between the two compounds being studied in the solution and solid states. The solubility studies revealed different behaviors of the polymorphs. In particular, it was observed that the binary complex significantly increased the solubility of furosemide form I in the gastric simulated fluid, which resulted in a rise in the bioavailability of this formulation after oral administration. In addition, results using ssNMR, FT-IR, DSC, TGA, SEM and XRPD provided evidence of the formation of complexes after utilizing kneading and freeze-drying methods. A comparison with previous developed complexes that used maltodextrin as the ligand was performed. Our results suggest that these novel supramolecular complexes showed promise to be used in drug delivery systems with an application in pharmaceutical formulations.

1. Introduction

It is well known that pharmaceutical solids can exist in various solid-state forms which have different physicochemical properties that affect their performance. In particular, polymorphic changes in the active pharmaceutical ingredient (API), may lead to significant effects on the bioavailability of the final product after oral administration [1].

Pharmaceutical complexes in solid state are usually developed in order to improve the profile of a single organic molecule, in terms of solubility, stability, bioavailability and organoleptic properties [2–4]. For example, supramolecular complexation is a commonly used technique to increase the solubility of poorly water-soluble drugs. Among the macromolecules utilized to solubilize drugs, the cyclodextrins (CDs) are the most widely used as they are an effective alternative. CDs are able to form inclusion complexes with many different types of appropriately sized and preferential non-polar molecules, both in solution and solid state [5–7].

Furosemide (FUR, Fig. 1) is widely applied as a strong loop diuretic in the treatment of edematous states associated with cardiac, renal, and hepatic failure, and also in the treatment of hypertension [8]. It is known to exist in seven polymorphic forms: four true polymorphs (I, II, III, IV), two solvates (IV – DMS and V – dioxane) and one amorphous form [9–11]. Since FUR has a low water solubility and low permeability, it belongs to Class IV in the Biopharmaceutics Classification System [12]. The relatively poor and variable oral absorption of FUR (60–70% [8]), which occurs site-specifically in the stomach and upper small intestine [13], has been ascribed to the poor dissolution of FUR at low pH as well as to the involvement of intestinal efflux proteins [14].

In previous reports, several approaches, including CDs, have been developed to increase the solubility and/or the dissolution rate of FUR [15–17]. However, to date, the effect of excipients on the performance of different solid-state forms has not been widely studied. A recent investigation of ours focused on supramolecular complexes of different polymorphs of FUR and maltodextrin [18], which certainly showed better solubility properties than their precursors.

Based on these above considerations, the aim of the present investigation was to prepare and characterize new supramolecular systems of FUR polymorphs I and II with β-cyclodextrin (βCD, Fig. 1). The objective of producing these complexes was to enhance the low solubility of FUR, which represents a limiting factor that is responsible for its poor and highly variable human bioavailability, and also to compare these complexes with the supramolecular ones with maltodextrin. Complexation was studied using solubility analysis, solid-state Nuclear Magnetic

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