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Research Article

Influence of β-cyclodextrin on the Properties of Norfloxacin Form A

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Abstract. Cyclodextrins are able to form host–guest complexes with hydrophobic molecules to result in the formation of inclusion complexes. The complex formation between norfloxacin form A and β-cyclodextrin was studied by exploring its structure affinity relationship in an aqueous solution and in the solid state. Kneading, freeze-drying, and physical mixture methods were employed to prepare solid complexes of norfloxacin and β-cyclodextrin. The solubility of norfloxacin significantly increased upon complexation with β-cyclodextrin as demonstrated by a solubility isotherm of the A_L type along with the results of an intrinsic dissolution study. The complexes were also characterized in the solid stated by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Fourier-transform infrared (FT-IR) spectroscopy, X-ray diffractometry, scanning electron microscopy (SEM), and solid-state nuclear magnetic resonance (ssNMR) spectrometry. The thermal analysis showed that the thermal stability of the drug is enhanced in the presence of β-cyclodextrin. Finally, the microbiological studies showed that the complexes have better potency when compared with pure drug.

KEY WORDS: bioassay; complexation; intrinsic dissolution; norfloxacin; β-cyclodextrin.

INTRODUCTION

Norfloxacin (NFLX), a second-generation fluoroquinolone antimicrobial agent, has been widely used in human and veterinary medicine and demonstrates a wide spectrum of activity against aminoglycoside-resistant *Pseudomonas aeruginosa* and beta-lactamase-producing organisms (1). This drug inhibits DNA gyrase by interfering with the DNA-rejoining reaction (2). It is effective in the treatment of urinary tract infections, gonococcal urethritis, and infections diarrhea (3).

Chemically, it is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid (Fig. 1) (4). It is freely soluble in glacial acetic acid and very slightly soluble in methanol, ethanol, and water at a pH of 6–10, and it has a relatively slow rate of dissolution (2,5). NFLX exists in several solid forms: three anhydrous polymorphs (forms A, B, and C), an amorphous form, a methanol solvate, several hydrate forms, salts, and cocrystals (6–8).

Cyclodextrins (CDs) are water-soluble cyclic oligosaccharides composed of 6, 7, or 8 glucopyranose units (α-, β-, or γ-CD) with a relatively hydrophobic central cavity and a hydrophilic outer surface, which differ in their ring size and solubility according to the number of glucopyranose units (9,10). One of the most important applications of CDs in the pharmaceutical sciences is the enhancement of the aqueous solubility of drugs through complexation. Hydrophilic CDs can increase the release rate of poorly water-soluble drugs and ultimately enhance drug absorption across biological barriers (11). β-cyclodextrin (β-CD) has been widely used in the early stages of pharmaceutical development due to its ease of availability and a cavity size which is suitable for the widest range of drugs (Fig. 1) (12,13).

The hydrophobic nature of the internal cavity of CDs is the key feature which is responsible for its ability to form complexes with guest molecules. The CD inclusion is a stoichiometric molecular phenomenon in which usually only one molecule interacts and gets entrapped inside the cavity of the CD (14). In the pharmaceutical industry, CDs are used as complexing agents to increase the aqueous solubility of poorly soluble drugs and subsequently to enhance bioavailability and stability (15–17).

The solubility of NFLX in water is pH dependent, increasing sharply either with a decrease in pH below 5 or with an increase in pH above 10. This is why only 35–45% of the drug is absorbed when orally administered. It is therefore to improve the aqueous solubility of NFLX to enhance its extent of absorption (18–20). One study on inclusion complexes of NFLX investigated the influence of dispersion in PEG 6000 and complexation with hydroxypropyl-β-cyclodextrin (HP-β-CD) in systems obtained

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