TFC050

Solubility improvement of ursolic acid complexed with hydroxypropil-β-cyclodextrin

Mayara Garcia Trevisani[1*]; Josimar de Oliveira Eloy[1]; Érika Cristina Vargas de Oliveira[1]; Juliana Palma Abriata Barcellos[1]; Juliana Maldonado Marchetti[1].

[1]Faculdade de Ciências Farmacêuticas, Universidade de São Paulo. [*]mayaragt@fcfrp.usp.br.

Introduction: Ursolic acid (UA) is a relatively nontoxic pentacyclic triterpenoid, naturally occurring in many medicinal plants such as *Panax ginseng*. This monohidroxylated triterpene acid has been widely investigated due to its broad spectrum of biological activities, such as antinflammatory, anticancer, antiviral, antibacterial, antiparasitic, hepatoprotective, among others. In recent years, several studies have shown trypanocidal activity of triterpene compounds like UA. However, the use of this compound is still limited due to its hydrophobicity, compromising the bioavailability. Several techniques have been studied to solve this limitation. Due to their complexation ability and other versatile characteristics, cyclodextrins (CDs) have been recognized as an important strategy to increase the drug stability and aqueous solubility and have a wide range of applications in different areas of drug delivery and pharmaceutical industry. CDs are natural cyclic macromolecules consisting of 6, 7 and 8 α-(1.4) linked glucopyranose units, named, respectively α-, β- and γ-CD. But their pharmaceutical use has been gradually replaced by semi-synthetic derivatives, in which additional chemical modifications in the original cyclodextrin results in changes of complexation degree, increasing the drug interaction, as the hydroxypropyl-β-CD case. CDs are able to form inclusion complexes with many drugs by taking up the drug molecule or some lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during complex formation, and the drug molecules in complex are in rapid equilibrium with free molecules in the solution. In the field of pharmaceutical technology, these oligosaccharides have been mainly used as complexing agents for promoting the increase in rate and extent of dissolution of hydrophobic drugs, consequently increasing the solubility and wettability in crystalline state. **Objective:** The purpose of this study was to evaluate the influence of the concentration of HP-β-cyclodextrin on the total solubility of ursolic acid. **Methods:** Samples were prepared varying the concentration of CD and adding excess UA in amber vials containing 5 mL of milli-Q water. Each vial received a defined amount of CD in a range from 20 to 60 mM. The samples were subjected to magnetic stirring in a controlled temperature of 25°C for seven days. After this period, the samples remained at rest for 2 h and then centrifuged at 350 g for 30 min and the supernatant was filtered through regenerated cellulose membrane of 0.45 micrometers. Samples were diluted and quantified by HPLC, using previously validated method. **Results:** There was a linear relationship between the concentration of HP-β-CD and the concentration of soluble UA. The higher increase in solubility achieved for the drug employed 60 mM HP-β-CD, which corresponded to 2.4% solubility of the total amount of UA. **Conclusion:** The CD complexation appears to be a viable strategy for increasing the solubility of poorly soluble drugs in water, but further studies are needed to determine the stability constant (Kc) of complex formation.

Keywords: Cyclodextrins, Ursolic acid, Inclusion complexes, Drug delivery systems, Chagas disease.

Financial support: CNPq, FAPESP