COMPUTATIONAL STUDY OF PHARMACEUTICAL COCRYSTAL

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INTRODUCTION

The Biopharmaceutics Classification System (BCS) is a system to differentiate the drugs on the basis of their solubility and permeability, in order to establish its potential absorption properties after their administration by extravascular, primarily orally.This classification takes into account the dose of drug to be administered to achieve therapeutic effects as it relates to the dissolution in aqueous media, which to be acceptable must not exceed the saturation concentration. This is because the drug must be dissolved to be absorbed state. However, there are drugs that have low solubility, low permeability and high hygroscopicity. Consequently significantly decreases the bioavailability of the drug. The solubility is one of the parameters that determine the bioavailability of a drug. Hence in the pharmaceutical industry provides the ability to alter their physicochemical properties without compromising the structural integrity of IFA, the latter responsible for the therapeutic effect on the body.

In this paper a methodology is shown in order to understand the stability and try to predict the formation of a cocrystal. We will use own programs and Gromacs MD simulations to develop as a starting point and potential parameters OPLS / AA (Optimized Potentials for Liquid Simulations). The formation of cocrystals is due to the formation of hydrogen bonds, so it is convenient to analyze whether OPLS / AA parameters correctly describe electrostatic interactions. The macroscopic fluid property that is related to these interactions is the dielectric constant was verified that this potential does not reproduce this property. Therefore loads, geometry and parameters of Lennard-Jones (LJ) was modified to reproduce the properties of the liquid-vapor equilibrium and surface tension. This study was conducted for the cocrystal formic acid/pyridine, isonicotinamide/formamide and nifedipine/dimethylsulfoxide. To observe the formation of the crystal, the radial distribution function was used to measure the distances of the atoms that form hydrogen bonds and angles formed by the molecular species. On the other hand, it is possible to stabilize cocrystal with force field parameters developed to simulate liquids. The dielectric constant of the components, wich is important to simulate polar systems, does not play a key role in the simulation cocrystal althought the hydrogen bonding interactions are the driving force to form these systems. The advantage of the new force fields parameters that reproduce the dielectric constant will be seen in simulations of cocrystal in contact with polar solvents in liquids, that is the case of several drugs which are prepared as cocrystals and then mixed with a solvent such as water.