Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 168 (2016) 45–51

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Theoretical and experimental studies of the stability of drug-drug interact

Monica F.R. Soares, Lariza D.S. Alves, Daniela Nadvorny *, José L. Soares-Sobrinho, Pedro J. Rolim-Neto

Department of Pharmaceutical Sciences, Pernambuco Federal University, Brazil

ARTICLE INFO

Article history:
Received 5 December 2015
Received in revised form 22 April 2016
Accepted 9 May 2016
Available online 26 May 2016

Keywords:
Density Functional Theory
Molecular dynamics
Drugs compatibility

ABSTRACT

Several factors can intervene in the molecular properties and consequently in the stability of drugs. The molecular complexes formation often occur due to favor the formation of hydrogen bonds, leading the system to configuration more energy stable. This work we aim to investigate through theoretical and experimental methods the relation between stability and properties of molecular complexes the molecular complex formed between the drugs, efavirenz (EFV), lamivudine (3TC) and zidovudine (AZT). With this study was possible determining the most stable complex formed between the compounds evaluated. In addition the energy and structural properties of the complex formed in relation to its individual components allowed us to evaluate the stability of the same.

1. Introduction

The stability of drugs is a crucial factor so that they do not lose their individual characteristics and, consequently, their activities. In this sense, external factors that are able to cause physical and/or chemical structural modifications can cause changes in the stability of a specific drug. These factors can be, for example, the interaction between a solvent, hydrogen bond formation, temperature variation and others. Furthermore, some treatments are performed by using more than one drug and the interaction between them should be taken into consideration. Thus, despite that experimental methods were able to show the occurrence of interactions, this does not often occur. Within this context, computational tools such as electronic structure and molecular dynamic methods appear as an alternative in realistically understanding the interactions present in systems composed of different drugs or in the evaluation of drug interaction with different solvents.

Efavirenz (EFV), lamivudine (3TC) and zidovudine (AZT) (Fig. 1) are compounds that present functional groups and are able to result in interactions between them, such as hydrogen complexes. Hydrogen bond formation causes significant changes in several molecular aspects such as vibrational properties and charge transfer [1,2].

Thus, in this study we investigated changes in energy and vibrational properties arising from molecular interactions formed between complex hydrogen and EFV, 3TC and AZT molecules with theoretical and experimental methods.

Thus, we intend to evaluate how the interactions among these compounds influence the stability thereof. For this reason computational studies of electronic structure and molecular dynamics complemented by experimental methods were performed.

2. Methodology

2.1. Computational methods

2.1.1. Electronic structure calculation

Initially, the geometry of minimum energy of each monomer, such as their frequencies in the harmonic approach using the Gaussian 09 program with Density Functional Theory (DFT) and the B3LYP/6-31++G(d,p) basis set [3,4] were calculated. Then the sites of possible interactions in each structure were identified which generated different hydrogen complexes.

Complexation energy is represented according to the following equation:

$$\Delta E_{complexation} = E_{hydrogencomplex} - \sum E_{monomer} \quad (1)$$

All electronic structure calculations that use a finite base is called a Basis Set Superposition Error (BSSE), which results in considerable errors in the calculation of stability of the complexes formed. One of the methods most used to correct this error is the method called *counterpoise* [5]. According to this method, the energy of the complex is corrected according to the following equation:

$$\Delta E^{Corr} = \lfloor E(HX) + E(R) \rfloor - E(R\cdots HX) \quad (2)$$

Where, *HX* and *R* are the monomeric units forming the complex $R\cdots HX$. BSSE is calculated as the difference between the hydrogen

* Corresponding author.
E-mail address: nady@ufpe.br (D. Nadvorny).

http://dx.doi.org/10.1016/j.saa.2016.05.009
1386-1425/

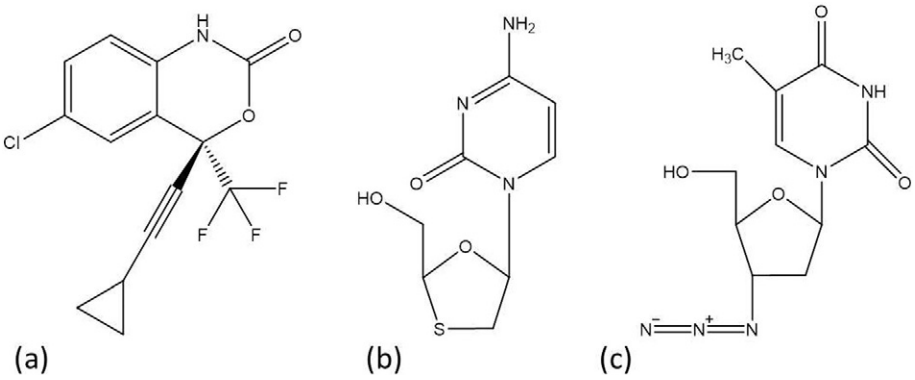

Fig. 1. Molecular structure of (a) EFV, (b) 3TC and (c) AZT.

bond ΔE according to the following equation:

$$BSSE = \Delta E - \Delta E^{Corr} \quad (3)$$

In addition to BSSE, including Zero Point Energy (ZPE) correction whose values are obtained from vibrational calculations, monomers as well as complexes are formed. Thus, the stability of the complex as a whole was obtained by varying the energy of the complex formed in relation to its monomers considering the energy of ZPE and BSSE by the counterpoise method [6]. A vibrational analysis was performed according to the chemical shifts observed in the complex in relation to isolated molecules and compared to the experimental infrared spectrum. The figures shown in the electronic structure step were designed by Chimera [7] while those shown in the molecular dynamics step were developed with VMD [8].

2.1.2. Molecular dynamics calculations

EFV, 3TC and AZT atomic coordinates were generated with GaussView and subsequently optimized by electronic structure methods the B3LYP/6-31++G(d,p) level with Gaussian 09 [9]. The system was solvated using the SPC water model. Initial system dimensions were set to $40 \times 40 \times 40$ Å^3. The system was submitted to molecular dynamics simulations using GROMACS 4.6.5, which is free, open source released under the GNU General Public License, in conjunction with the GROMOS force field parameter set to 53A6 [10–13]. The temperature was kept at 298 K via a v-rescale thermostat with a relaxation time of 0.1 ps coupled separately for solvent and solute. The pressure was maintained at 1 bar using the Berendsen barostat with a coupling constant of 1.0 ps and compressibility of 4.5×10^{-5} bar^{-1}. Periodic boundary conditions were applied in all dimensions and a 14 Å cut-off fixed for all nonbonded interactions. The computer simulation was performed for 50 ns containing 10 molecules of EFV, 7 of 3TC, 11 of AZT and 1700 water molecules, following the experimental concentration.

2.2. Experimental methodology

2.2.1. Materials

Active raw materials were provided by LAFEPE, Brazil: AZT (Northeast®,

lot DY070041), 97.9% purity; 3TC (Hangzhou®, lot 071,208), 100.0% purity e EFV (Cristália®, lot 1289/07) 98.0% purity.

2.2.2. Sample preparation

Binary and ternary physical mixtures were prepared in 1:1 and 1:1:1 (w/w) proportions by stirring in a vortexer (Barnstead Thermolyne Maxi Mix II, 37600, Lote 39296EJ) for 15 min, for general analysis. Varying proportions were used in evaluating the eutectic point of the binary mixtures. The 1:1:1 (w/w) proportion was chosen to maximize the probability of interactions between the materials with AZT, 3TC and EFV pharmacological proportions (2:1:2) (w/w) , respectively.

2.2.3. Fourier transform infrared spectroscopy and attenuated total reflectance (FTIR-ATR)

The infrared spectrum of the sample was obtained by the use of PerkinElmer®(Spectrum 400) equipment with an attenuated total reflectance (ATR) device with a selenide zinc crystal. The samples analyzed were transferred directly to the ATR device compartment. The result was obtained by the average of 4 sweeps obtained from 650 to 4000 cm^{-1} in a resolution of 4 cm^{-1}.

2.2.4. Solid state nuclear magnetic resonance (NMR)

All CP/MAS ^{13}C NMR spectra were acquired at 75.4 MHz to 13C using a Chemagnetics CMX-300 and a Chemagnetics spectrometer probe

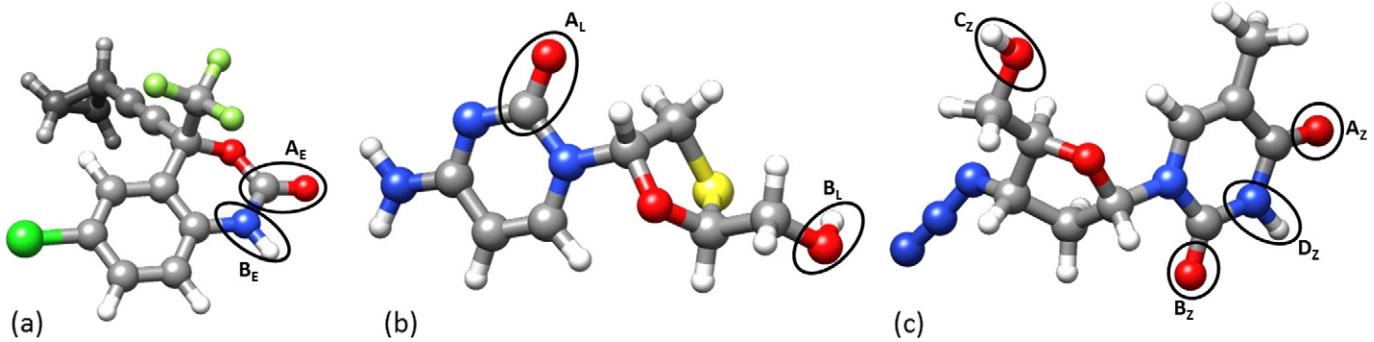

Fig. 2. Monomer molecular structures (a) EFV, (b) 3TC and (c) AZT, calculated by the B3LYP/6-31++G(d,p) level.