XIX SBQT
Simpósio Brasileiro de Química Teórica 2017
12 a 17/Nov, 2017, Águas de Lindóia/SP, Brasil

Competition for βCD cavity on inclusion complex of antihypertensive drugs and Excipient

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Abstract: Excipients, as Sodium Dodecyl Sulfate (SDS), are often present in drug compositions and they can improve the active molecule stability as well as modulate its pharmacological properties. Atenolol (ATE) and Losartan (LOS) are antihypertensive drugs, and in this work the competition between them and SDS for the β-cyclodextrin (βCD) cavity is evaluated. Molecular Dynamics were performed using GROMACS[1] for binary systems as control: ATE:βCD, LOS:βCD and SDS:βCD. Topology files were obtained from *The Automated Topology Builder (ATB) and Repository*[2], as βCD ID= 23854, ATEID= 36896, LOS ID=4615 and SDS ID=20332; geometries were all optimized with Gaussian 09[3] by DFT-M062X[4] and 6-31+g(d,p)[5]. The local minima were assured by vibrational analysis. To properly use GROMACS with ATB files, gromos53a6[6] force field was updated before MD run. Virtual boxes (7,0nm x 5,0nm x 5,0nm) were defined and filled with 5631 water molecules each, using the SCP216 force field[7]. For all systems, a 20ps NPT equilibration step, using a modified Berendsen thermostat denominated V-rescale[8], as well as a pressure coupling with Berendsen barostate[9]. The simulation stage was done during 10 ns at NPT ensemble at 300K and1.01325 bar. For all simulations, bonds were constrained by LINCS[10] and long range interactions were described by PME method[11]. The inclusion competition along MD simulation is represented in the Figure 1.

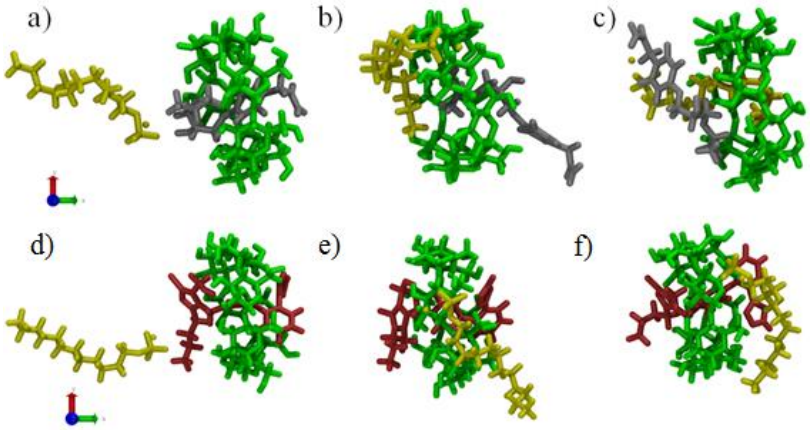

Figure 1 – Molecular dynamics frames for: First row ATE:βCD:SDS. a)t=0.00ns; b)t=5.19ns and c)t=9.35ns; second row LOS: βCD:SDS. d)t=0.00ns; e)t=2.16ns and f)t=9.46ns.Watermolecules representations were neglected. ATE:grey; SDS:yellow, BCD:green and LOS:red.

In reference system SDS:βCD Center of Masses (CoM...CoM) distances varies approximately between 1,5-6Å along the simulation. In ATE:βCD:SDS system, SDS-βCD d(CoM...CoM) decreases to values close to those verified for the binary system (2-5,5Å), while ATE:βCD d(CoM...CoM) arises along the simulation. This result means that excipient would win the competition, being held inside cavity. In LOS:βCD:SDS system, SDS:βCD d(CoM...CoM) varies (13,8-7,5Å), but distance does not reach binary system levels, indicates that LOS does not allow SDS to get into βCD. Distances between hydrogen atoms of guests and βCD were estimated using the software ILIAAD - Import and List Individual or Average Atomic Distances, developed by us for this purpose, aiming to help the ROESY experimental data analysis. Using a 5Å distance as cutoff, correlation maps similar to NMR 2D were obtained and are presented in Figure 2. The circles diameters were settled to indicate the occurrence frequency while the color scale refers to the average of hydrogen atoms distance.

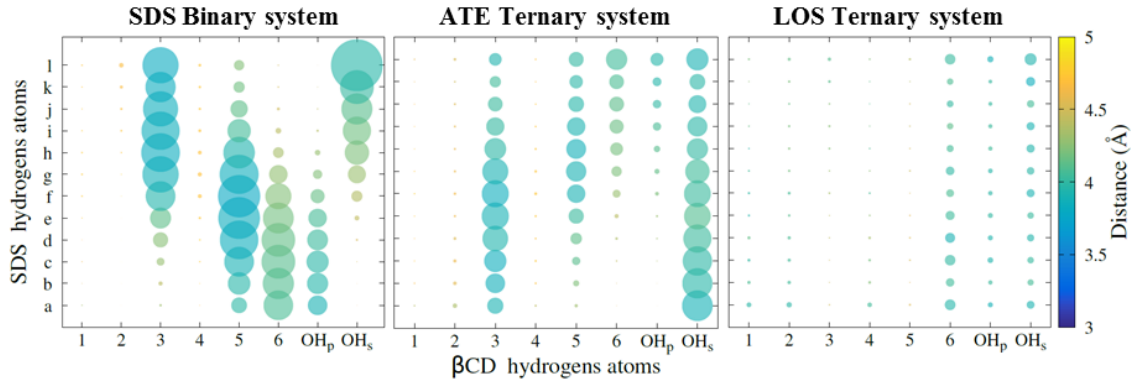

Figure 2 – Correlation Maps between SDS andβCD hydrogen atomson three systems types.

ATE:βCD:SDS system, shows a pattern distribution similar to the reference βCD:SDS system. Also, the inner βCD hydrogen atoms are statistically correlated with the guest ones, while for LOS:βCD:SDS system, there are no these correlations types. This result illustrates the competition for the βCD cavity through the molecular dynamics which was also experimentally observed by our coworkers on ITC as well as NMR experiments.

Key-words: Molecular dynamics, Losartan, Atenolol, Cyclodextrin, Inclusion complex
Support: This work has been supported by CAPES, CNPQ e FAPEMIG.

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