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Computational modeling of praziquantel drug release from montmorillonite clay using enhanced sampling method

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1. Introduction

A good drug delivery system is an important part of any new drug development process. In fact, an efficient delivery system would help optimizing the drug pharmacological effects and reducing its adverse reactions.

We examine here the case of the drug of choice for the treatment of the schistosomiasis disease. This molecule is poorly soluble in water and its efficacy would benefit from an improved dosage and an accelerated release of the drug. One of us has investigated experimentally the possibility of using clay minerals as excipients for praziquantel. These studies have shown that these low-cost biocompatible materials lead to an increased solubility and an improved dissolution profile [1-3].

In this presentation, we study computationally the praziquantel release from montmorillonite clay, with the aim of better understanding the dissolution process and to improve drug delivery, guide new experimental studies, and possibly replace them.

Eventually we would like to establish well defined computational strategy to alleviate the need for time consuming experiments for the study of drug delivery from clays.

2. Methodology

We modeled the montmorillonite with a two layer system as shown in Figure 1. The number of water molecules was chosen so as to reproduce as much as possible the experimental concentration. Periodic boundary conditions were applied. We use the LAMMPS program [4] interfaced to PLUMED [5] and the interatomic interactions were described by CVFF Interface force field [6].

Given the long-time scales involved in the process, we used the recently developed Gaussian Mixture-Based Enhanced Sampling (GAMBES) method [7] that allows not only to enhance sampling but are to obtain residence times.

3. Results and Discussion

The structure displayed in Figure 1 was used to model the water solvated praziquantel-montmorillonite system. After equilibration, in a set of GAMBES based simulations the molecule was seen to go out from the clay into the water, via a multi-step mechanism and a very high desorption rate in accordance with previous experimental studies that revealed a fast drug release.

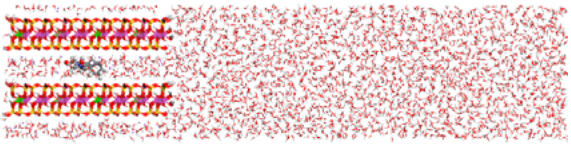

Fig. 1. Praziquantel-montmorillonite system in aqueous solution.

4. Conclusions

In this work, the praziquantel release from montmorillonite in aqueous solution has

been studied with atomistic simulation. The GAMBES method has allowed find out the release mechanism predicting a fast release time in agreement with experiments. It is to be hoped that this initial positive performance could eventually lead useful pharmaceutical applications.

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