Microporous and Mesoporous Materials 221 (2016) 117–122

Contents lists available at ScienceDirect

Microporous and Mesoporous Materials

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

Pore size effect on the stabilization of amorphous drug in a mesoporous material: Insights from molecular simulation

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ARTICLE INFO

Article history:
Received 9 June 2015
Received in revised form
26 August 2015
Accepted 16 September 2015
Available online 28 September 2015

Keywords:
Molecular dynamics simulation
Stability
Amorphous
Mesoporous material

ABSTRACT

In this work, molecular dynamics simulation techniques are employed to study the effect of mesoporous MCM41 material in stabilizing ibuprofen amorphous drug. Our simulation results show that the intermolecular interaction occurring between ibuprofen amorphous drugs and mesoporous material decreases the possibility of self-organization of ibuprofen molecules and therefore prevents recrystallization. The maximum pore diameter of mesoporous MCM41 found to be effective in stabilizing the amorphous ibuprofen was about 20 nm. The methodology used in this study provides valuable insight towards molecular level understanding of confined amorphous active pharmaceutical ingredients (APIs).

1. Introduction

Poor aqueous solubility of active pharmaceutical ingredients (APIs) is the most challenging issue in developing a pharmaceutical product. The poor solubility yields to low bioavailability of the drugs. There are a few formulation methods to improve the dissolution rate of poorly water-soluble drugs, for example, by co-crystallization [1], particle size mediation [2,3], formation of nanocrystalline particles [4] and the use of amorphous form of the APIs in solid dispersion [5–7]. While the amorphous form effectively improves the solubility, it is a great challenge to stabilize it to achieve an acceptable shelf life. As the amorphous materials are generally thermodynamically unstable, there is a high tendency for them to revert back to the crystalline forms and thus losing their solubility advantage upon storage or during transport [8].

Several studies [6,9–11] have shown that amorphous drugs may reside in an amorphous state in the mesoporous silica materials, such as MCM-41 and SBA-15. Shen et al. [6] employed co-spray drying method to stabilize the amorphous ibuprofen with mesoporous SBA-15. They have shown that the nanosized mesoporous channels entrapped the amorphous state of ibuprofen molecules and exhibited excellent physical stability at severe storage condition for 12 months. The pore wall of SBA-15 material prevented the re-crystallization of amorphous ibuprofen. However, it has also been reported that crystallization may happen in mesoporous material with large pore size (>20 nm) [12].

It was observed that there is a correlation between molecular mobility and stability in many amorphous drugs [13–16]. Physical stability often improves when the molecular mobility is reduced. Bhardwaj et al. [8] employed dynamic dielectric spectroscopy [17] to study the different modes of mobility in amorphous itraconazole. They observed that α-relaxation time correlated to both crystallization onset and kinetics, indicating the role of this mobility mode in physical instability of the supercooled itraconazole. Bras et al. [5] investigated the molecular mobility of ibuprofen confined in nanostructured silica material, SBA-15, using dielectric relaxation spectroscopy. Their results showed the existence of two families of molecules with different molecular mobilities. Molecules close to the pore centre have high mobility at low temperatures, whereas molecules interacting with the pore walls have low mobility. The interaction between molecules at the pore walls and molecules of amorphous ibuprofen might have prevented the amorphous ibuprofen from crystallizing, thereby yielding a stabilized amorphous drug.

Molecular simulation is a powerful tool to probe into such interaction due to its ability to provide a direct insight into the

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http://dx.doi.org/10.1016/j.micromeso.2015.09.029
1387-1811/

confined amorphous drug at the molecular level. Busselez et al. [18] studied the prototypical glass-forming liquid glycerol confined in a nanoporous silica channel by employing all-atoms MD simulations. Their simulations showed that there was formation of interfacial hydrogen bonds between glycerol and the pore wall of nanoporous silica channel. They also observed that the lifetimes of interfacial glycerol-silanol hydrogen bonds were longer than those of glycerol–glycerol hydrogen bonds. This observation implied that the glycerol molecules engaged at the silica wall were less available to contribute to the formation of bulk-like network with other glycerol molecules. Affouard et al. [19] and Bras et al. [20] performed molecular dynamics (MD) simulations of racemic ibuprofen in the liquid state. The simulation data showed various hydrogen bonded aggregates formed between the ibuprofen molecules. They observed that the long time dipole–dipole auto correlation function was dominated by the internal cis-trans conversion of O=C–OH group coupled with the change in the intermolecular linear/cyclic hydrogen bond structures [19].

Molecular model of mesoporous (SBA-15) matrix functionalized with non-polar chains [21] and polar molecule 3-aminopropyl-triethoxy-silane (APTES) [22] was studied using molecular dynamics and docking method to predict the release kinetic of drugs. The simulation model showed various interactions occurred between drug and mesoporous matrix that affect the release process. In this work, MD simulation is employed to study the effect of nanostructured materials (MCM-41) in stabilizing ibuprofen amorphous drug. Previous experimental work [12] has shown that mesoporous material was able to stabilize ibuprofen amorphous drug, however, their results also showed the appearance of nanocrystals when ibuprofen was co-spray dried with mesoporous material with larger pores (pore size above 20 nm). With MD simulation technique, we aim to study the dynamics of interaction between ibuprofen molecules and mesoporous material so as to provide direct support to the experimental works of confined amorphous drug.

2. Computational details

MD simulations were carried out using the Accelrys Materials Studio (Version 7.0) [23] for ibuprofen molecules. An amorphous silica in a rectangular parallelepiped of 21.4 nm × 21.4 nm × 2.14 nm shown in Fig. 1 was created and a cylinder was carved along the *z* direction by removing the atoms within to represent the pore. Four different pore sizes, diameters of 16.4 nm, 18.4 nm, 20.0 nm and 20.4 nm, are considered. The range of pore diameters is chosen to obtain the maximum size of mesoporous material to be able to stabilize ibuprofen drug. The oxygen dangling bonds at the wall are saturated with hydrogen atoms to form silanol groups. The positions of silicon and oxygen atoms of the porous silica are fixed, and the hydroxyl groups at the wall are allowed to rotate. The model leads to a realistic cylindrical channel of silica that mimics MCM-41 mesoporous materials [18]. There are random 508 number of ibuprofen molecules confined in the straight cylindrical channel and the molecules are allowed to move. The COMPASS [24] (condensed-phase optimized molecular potentials for the atomistic simulation studies) force field was used to model the atomic interactions. COMPASS force field has been known to be able to predict various solid-state properties [25,26] (e.g. lattice energies, unit cell structures).

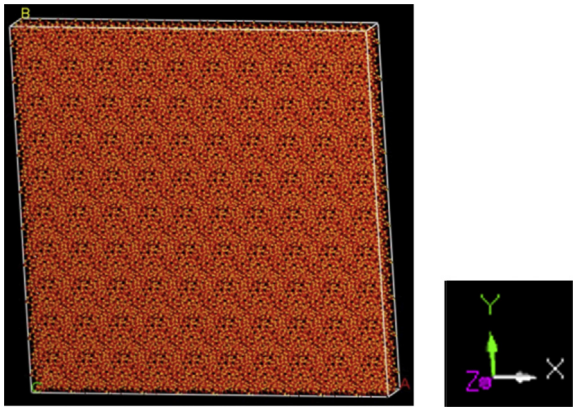

Fig. 1. Amorphous silica in a rectangular parallelepiped.

The confined ibuprofen system was first minimized with a geometry optimization procedure before an MD simulation was carried out. The velocity Verlet integrator was used to integrate the equations of motion. The integration timestep used was 1 fs. Ewald summation was used to enable the long range interactions. A cutoff radius of 1.25 nm was used for both non-bonded and electrostatic interactions. Simulation in the NVE (constant number of particle, constant volume, and constant energy) ensemble was conducted at initial temperature of 298 K for at least 300 ps to ensure that the ibuprofen systems have equilibrated. Equilibration was determined by observing the change in the thermodynamic properties (energies, temperatures, and densities) as a function of time. Each system was concluded to have reached equilibration condition if these properties showed sufficiently small variations over time. The required time was about 100–150 ps depending on the system. Fig. 2 shows the equilibrated ibuprofen molecules confined in four different sizes of mesoporous material.

The equilibrated structures were again minimized with a geometry optimization procedure by allowing all atoms to relax, and the interaction energies between ibuprofen molecules and mesoporous material are obtained by the following expression:

$$E_{interaction} = E_{total} - \left(E_{meso} + E_{ibuprofen}\right) \quad (1)$$

in which, E_{total} is the total interaction energy of the system (includes all atoms of the mesoporous material and the ibuprofen molecule), E_{meso} is the interaction energy of the atoms of mesoporous material, $E_{ibuprofen}$ is the interaction energy of the atoms of ibuprofen molecules. The energy is calculated using COMPASS [24] force field approximation. It is expressed by a potential, $V(r)$, which consists of the various interactions between bonded and non-bonded atoms as a function of their coordinates r.

3. Results and discussions

3.1. Solid-state and density properties for ibuprofen

To justify the use of COMPASS force field for this work, molecular dynamics simulation and energy minimization of ibuprofen crystal structures are performed. The crystal structure was obtained from the Cambridge Structural Database (CSD), Ver. 5.26. The space group of the crystal is P21/c (monoclinic with the unit cell dimensions of a = 1.467 nm, b = 0.7886 nm, c = 1.073 nm, β = 99.36°, and Z = 4). The unit cell parameters obtained from the simulation using COMPASS force field are a = 1.469 nm, b = 0.770 nm, c = 1.038 nm, and β = 101.2°. Another justification for the use of COMPASS force field was done by comparing the simulated and experimental density of ibuprofen. The ibuprofen crystal structure was extended to 5 × 5 × 5 unit cells and molecular dynamics simulation was performed. Simulation in the NPT (constant number of particle, constant pressure, and constant temperature)