Carbohydrate Research 401 (2015) 89–95

Contents lists available at ScienceDirect

Carbohydrate Research

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

Predict the glass transition temperature and plasticization of β-cyclodextrin/water binary system by molecular dynamics simulation

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ARTICLE INFO

Article history:
Received 30 July 2014
Received in revised form 22 October 2014
Accepted 27 October 2014
Available online 4 November 2014

Keywords:
Molecular dynamics simulation
β-Cyclodextrin
Glass transition
Plasticization

ABSTRACT

The glass transition temperature, diffusion behavior and plasticization of β-cyclodextrin (β-CD), and three amorphous β-CD/water mixtures (3%, 5% and 10% [w/w] water, respectively) were investigated by molecular dynamics simulation, which were performed using Condensed-phase Optimized Molecular Potentials for Atomistic Simulation Studies (COMPASS) force field and isothermal–isobaric ensembles. The specific volumes of four amorphous cells were obtained as a function of temperature. The glass transition temperatures (T_g) were estimated to be 334.25 K, 325.12 K, 317.32 K, and 305.41 K for amorphous β-CD containing 0%, 3%, 5% and 10% w/w water, respectively, which compares well with the values observed in published literature. The radial distribution function was computed to elucidate the intermolecular interactions between amorphous β-CD and water, which acts as a plasticizer. These results indicate that the hydrogen bond interactions of oxygen in hydroxyl ions was higher than oxygen in acetal groups in β-CD amorphous mixtures with that in water, due to less accessibility of ring oxygens to the surrounding water molecules. The mobility of water molecules was investigated over various temperature ranges, including the rubbery and glassy phases of the β-CD/water mixtures, by calculating the diffusion coefficients and the fractional free volume. In β-CD amorphous models, the higher mobility of water molecules was observed at temperatures above T_g, and almost no change was observed at temperatures below T_g.

1. Introduction

A majority of drugs and food matrices are hydrophobic and have poor aqueous solubility, because of their physicochemical properties and manufacturing processes.[1,2] Currently, the major challenge for scientists is identify ways to promote the aqueous solubility, stability and bioavailability of such food products. Several approaches such as salt formation, cocrystallization, particle size reduction, and solubilization have been explored for improving their properties.[3] Currently, novel uses of active ingredients that are wrapped in carbohydrates in an amorphous state are one of the most promising and actively pursued approaches. Amorphous carbohydrates possess several useful properties such as high purity, low toxicity, good glass formers, and high glass transition temperatures (T_g), which are often used in modern pharmaceutical and food industries.[4,5] Amorphous systems possess the lowest molecular mobility and high viscosity at temperatures below T_g in the glassy state, which dramatically slows down the relaxation time.[6] Therefore, when encased in an amorphous carbohydrate with high T_g and excellent solubility, the sensitive active ingredients are stored at room temperatures, in order to retain their high solubility, fast dissolution rate, and bioavailability.[7]

Cyclodextrins(CDs) are commonly used, amorphous carbohydrates with unique characteristics, are water-soluble cyclic oligosaccharides containing a few D-glucopyranose units linked by α-(1–4) glycosidic bonds. Hydrophilic CDs that consist of six, seven, or eight glucose rings are called α-, β-, and γ-cyclodextrins, respectively, and have a remarkable capacity to form inclusion complexes.[8–10] The numerous and specific properties of CDs lead to a wide range of interesting applications in pharmaceuticals, separation science or packaging materials, as well as in toiletries and food additives.[11] The β-CD, a particular CD, appears most useful as a pharmaceutical complexing agent and food additive, because of its ability to form complexes, availability at a low cost, and better cavity dimension and other properties as compared to α- and γ-CD.[12,13]

Molecular dynamics (MD) simulation is an ideal method for exploring various atomic structures and certain dynamic processes of amorphous carbohydrate matrices, which cannot be easily

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http://dx.doi.org/10.1016/j.carres.2014.10.026
0008-6215/

investigated experimentally, but may be important in predicting properties.[14] In this study, the atomistic MD was performed on a β-CD/H_2O binary system to predict the T_g of amorphous models, by exploring the relation between structure and properties of the whole system, and by elucidating the effect of plasticizer, that is, water on the T_g of the model compound. For this purpose, we prepared a series of 0%, 3%, 5% and 10% β-CD/H_2O mixtures in water. These matrices were investigated using the COMPASS force fields to analyze the detailed interactions of the model.

2. Results and discussion

2.1. Glass transition temperature

A bulk of amorphous cell models of β-CD containing 0%, 3%, 5% and 10% w/w water were constructed. Each β-CD/water system was constructed based on conjugate gradient principle, and their geometry was optimized using the smart minimization method.[15] The cells with ban energy minimized structure were the starting point for the MD simulations. The simulations were carried out in two stages (NVT followed by NPT) to provide thermal energies to cross energy barriers between local minima and to prevent entrapment of simulated systems in a unstable state of local high-energy minima.

At constant temperature, the thermodynamic constants of variables such as heat capacity, volume, and specific volume and density changes. In this biphasic system, the transfer from one phase to another is associated with a discontinuity, and hence, the abrupt change was utilized to estimate the T_g via a curve plotted with any of these variables versus temperature.[16,17] In this study, we demonstrated the procedure to determine the T_g from MD simulations by plotting specific volume as a function of temperature of four independent β-CD/H_2O amorphous models (Fig. 1). The regression lines employed to determine the T_g values are indicated: 334.25 K, 325.12 K, 317.32 K, and 305.41 K for β-CD containing 0%, 3%, 5%, and 10% w/w water, respectively. The decrease in T_g of amorphous β-CD was seen with an increase in the moisture content. This observation is similar to that reported by other researchers, who studied glass transitions and plasticization for methanol, trehalose and sucrose.[3,18,19,39] This effect is because water is reported to have a T_g of about −138, and acts as an effective plasticizer by enhancing the molecular mobility and increasing the free volume, thereby, resulting in the decrease of viscosity of amorphous matrix–water mixtures.[20,21] Additionally, the plasticization effect of water may form stable bridges through hydrogen bonding and the dipole–dipole intra- and inter-molecular interactions between water and amorphous matrices. The interactions and hydrogen bonding of the β-CD/H_2O binary system have been studied and described in detail in Section 2.3.

2.2. Comparison of molecular dynamics values at glass transition temperatures: simulated and theoretical

It is well known that water is one of the important factors that govern the stability of amorphous carbohydrates during shelf life, due to which water plasticizes amorphous carbohydrates materials

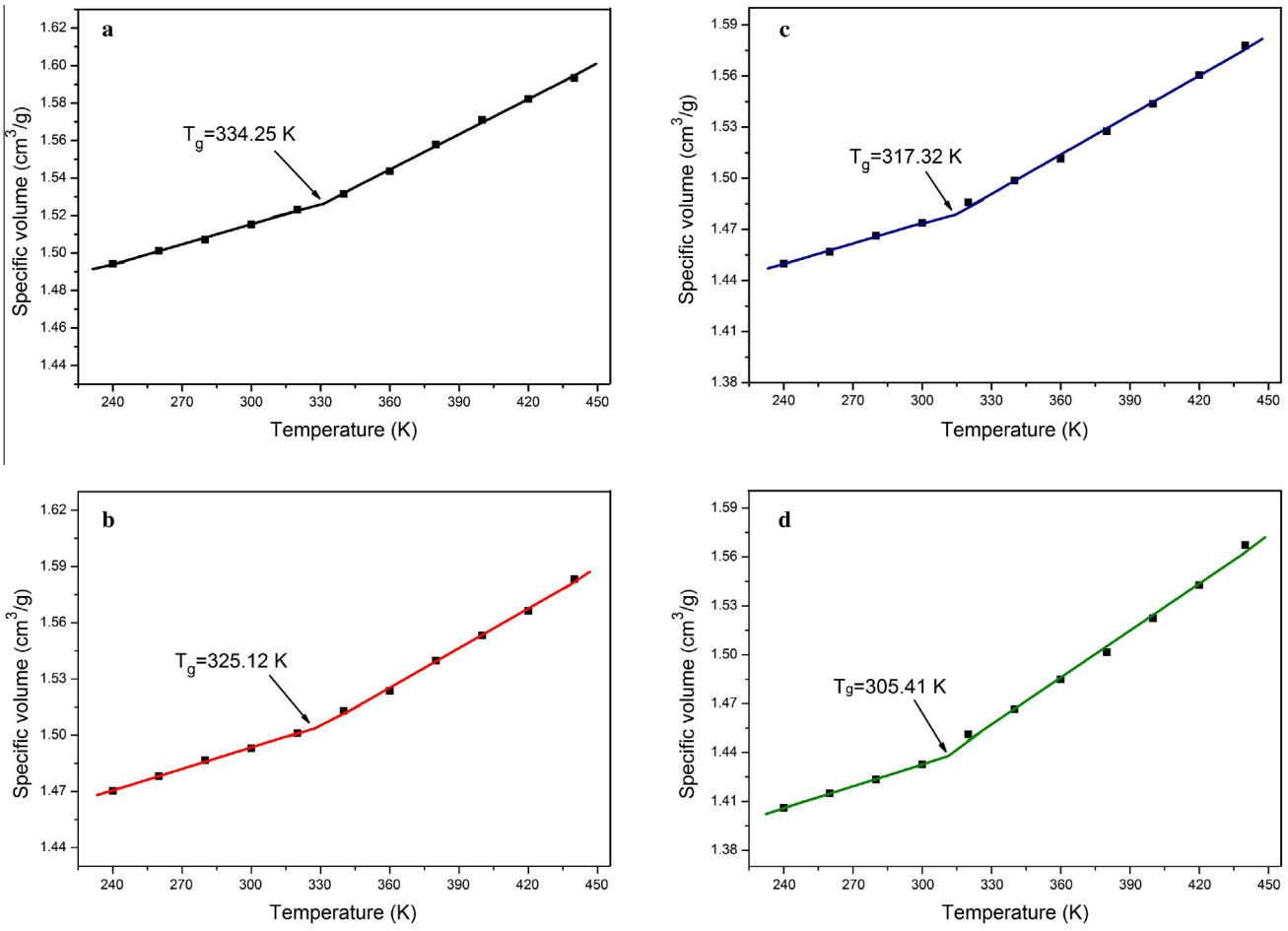

Figure 1. Specific volume versus temperature using MD simulations for β-CD/H_2O binary system, the glass transition temperature (T_g) is estimated at 334.25 K, 325.12 K, 316.32 K, and 305.41 K for 0%, 3%, 5% and 10%.