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ORIGINAL ARTICLE

The role of maltosyl residue of maltosyl-β-cyclodextrin in the inclusion with dehydrocholic acid

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Abstract Maltose substituted β-cyclodextrin (M-β-CD) is an important drug carrier due to its excellent water solubility and good compatibility. In this work, dehydrocholic acid (DHA) was taken as the model drug; the inclusion of M-β-CD/DHA was studied through molecular dynamics simulations. The effect of the maltosyl residue of M-β-CD on the interactions of M-β-CD with DHA, M-β-CD with water, and DHA with water were analyzed. Based on the results, the difference between the complex of M-β-CD/DHA and that of β-CD/DHA can be explained and understood.

Keywords β-cyclodextrin · Maltosyl residue · Molecular dynamics simulation

Introduction

β-cyclodextrin (β-CD) is cyclic (1 → 4)-linked oligosaccharide constructed from seven units of glucose [1, 2]. The most notable feature of β-CD is its ability to form solid inclusion complexes with a very wide range of compounds by a molecular complexation [3]. β-CD and its derivatives have been investigated as drug carriers [1, 2]. Inclusion in β-CDs has an effect on the physicochemical properties of drug molecules, including enhanced aqueous solubility, chemical stability, and bioavailability, which are not achievable otherwise [4]. However, β-cyclodextrin has relatively low solubility, both in water and organic solvents, which limits its use in pharmaceutical formulations. The derivative of β-CD, such as 6-*O*-maltosyl-β-cyclodextrin (M-β-CD), has been prepared as drug carrier [2]. M-β-CD has much higher solubility than β-CD itself in water [5–7]; the derivative has been used as drug carrier for various kinds of drugs [8]. M-β-CD has higher affinity to drugs having steroid skeletons such as dehydrocholic acid (DHA) [2]. They form inclusion complexes of the host–guest type through noncovalent interactions. M-β-CD is a useful functional excipient in the pharmaceutical industry.

Molecular dynamics (MD) simulation has been a useful method to investigate the inclusion of cyclodextrins with guest compounds [9–14]. MD simulation methods are frequently used for deriving information on the geometry and energy interaction of the inclusion compounds, the energetic properties of formation of the inclusion complex along four different pathways [9], different interaction energy due to orientations of the guest within the host [12], the detailed structures of the permethrin/β-CD inclusion complexes [13], investigation of the inclusions of puerarin and daidzin with β-cyclodextrin for the separation of puerarin from daidzin [14], chiral recognition for amino acids with permethylated β-cyclodextrin [15], the specificity of guest:β-CD association [16], competitive and reversible binding of guest molecules to their hosts in aqueous solution [17]. However, few research reports the inclusion of M-β-CD with drugs by MD simulation. In this work, MD simulations will be carried out to study the inclusion of M-β-CD with DHA. DHA is taken as a model drug; it is not water soluble. DHA acts as a hydrococholeretic, increasing bile output to clear increased bile acid load [18]. The role of maltosyl residue of M-β-CD in the interactions will be investigated.

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Methods

MD simulation was performed with the GROMACS 4.02 software package [19, 20]. The topology parameters of DHA (Fig. 1) and M-β-CD were built by the Dundee PRODRG server [21], which has been widely used to generate the molecular topology file for various compounds, including nicotine [22], puerarin and daidzin [14], β-cyclodextrin [14], amino acids [23], stepholidine [24], and *P*-glycoprotein [25]. GROMACS software package has also been proved to be powerful for the simulations of drugs and β-CD. The simulation results are in accordance with the experimental results [14, 26]. In this work, before the MD simulations, one drug molecule was docked into the cavity of M-β-CD using AutoDock 4.0 [27]. The docking results were obtained per 100 docking rounds. The conformation of a complex with the lowest docking energy was selected as the starting structure for further MD simulation. The MD simulation of the complex in aqueous solution was carried out using the GROMOS-96 force field. The NPT ensemble was set at $T = 300$ K, $P = 1$ atm. The complex was put in the center of a truncated octahedron box using periodic boundary conditions and solvated with SPC water models. The box length was set with image distance 5 nm. The classical Newton's equations of motion were integrated using the Leap-frog algorithm with the weak coupling to temperature and pressure baths utilizing the Berendsen methods. Before MD simulation started, the energy minimization using Steepest Descent and Quasi-Newtonian algorithms was performed to gain the maximum force smaller than 10 kJ mol^{-1} nm^{-1} in order to avoid improper structures. The electrostatic interactions were taken into account using the particle mesh Ewald (PME) approach with a cutoff distance equal to 1.2 nm. The Lincs procedure was implemented to maintain rigid bond lengths. All simulations were computed with time step of 0.002 ps, and coordinates were recorded every 500 steps (1 ps) to disks for data analyzing. The whole simulations were carried out for 20 ns.

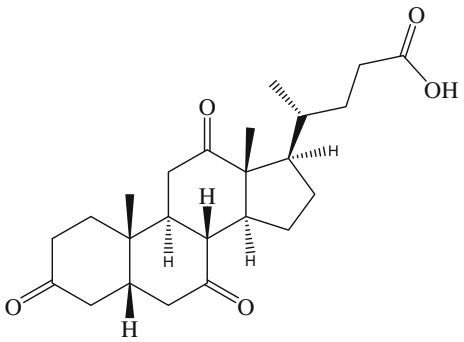

Fig. 1 Molecular structure of dehydrocholic acid

Results and discussion

The ability of M-β-CD to form an inclusion complex with DHA is a function of the interactions between the different components of the system (M-β-CD, DHA, water). M-β-CD is a derivative of β-CD by substitution of 6-OH group with maltose. To elucidate the role of maltosyl residue in the interactions, β-CD is taken as a reference host.

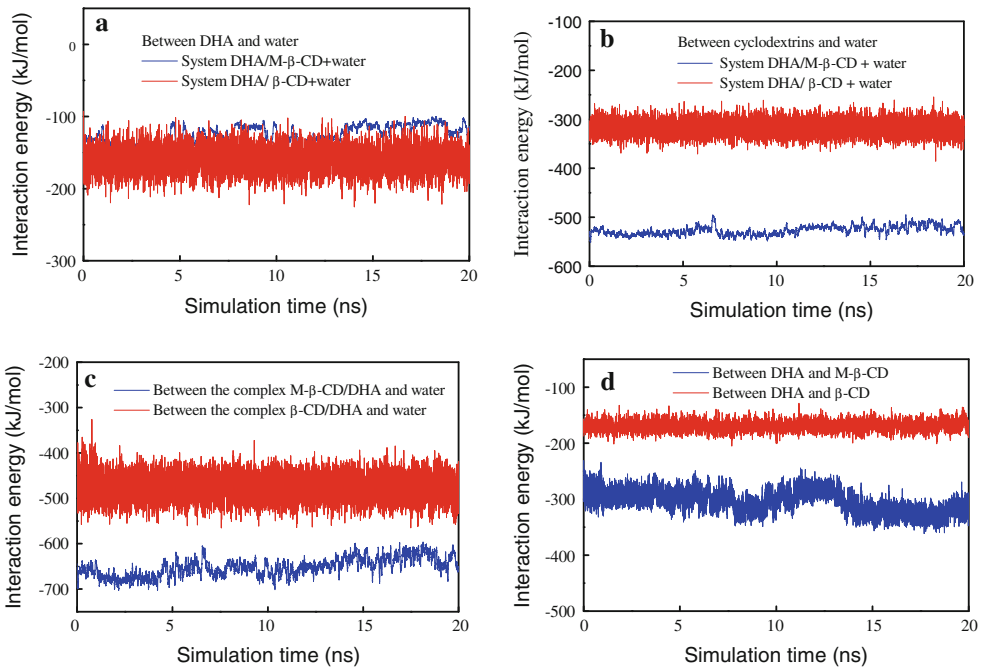

Fig. 2 Interaction energy. **a** Between DHA with water, **b** between cyclodextrins and water, **c** between complexes and water, and **d** between DHA and cyclodextrins

Equation (1) is used for the interaction energy, which is the summation of electrostatic interaction energy (ΔE_{Coul}) and van der Waals interaction energy (ΔE_{LJ}) [28].

$$\Delta E = \Delta E_{\mathrm{Coul}} + \Delta E_{\mathrm{LJ}} \quad (1)$$

Figure 2 shows the interaction energies. As can be seen, the interaction energy between the DHA included in M-β-CD and water is almost same as that between the DHA included in β-CD and water (Fig. 2a). The interaction energy of M-β-CD with water is larger than that of β-CD with water (Fig. 2b). Obviously, the maltosyl residue contributes to the larger interaction energy. As a result, the interaction energy of the complex M-β-CD/DHA with water is larger than that of the complex β-CD/DHA with water (Fig. 2c). The results imply that M-β-CD included with DHA has a higher water solubility than the complex of β-CD/DHA. The interaction energy between DHA and M-β-CD is larger than that between DHA and β-CD (Fig. 2d). This is due to the contribution of the interaction energy of the maltosyl residue with DHA. These results indicate that, due to the interactions involved by the maltosyl residue, the complex M-β-CD/DHA exists in a more stable state than the complex β-CD/DHA.

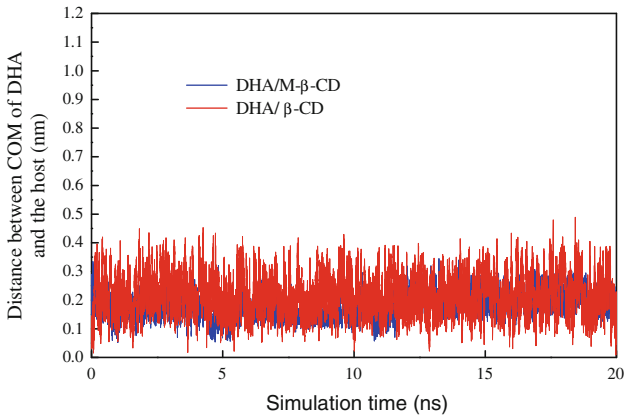

Fig. 5 Distance between the centers of the mass

Figure 3 shows the root mean square deviation (RMSD) of backbone atoms from the crystal structure. In comparison to β-CD, M-β-CD has a larger conformation change. This is due to the combined effect of the interaction

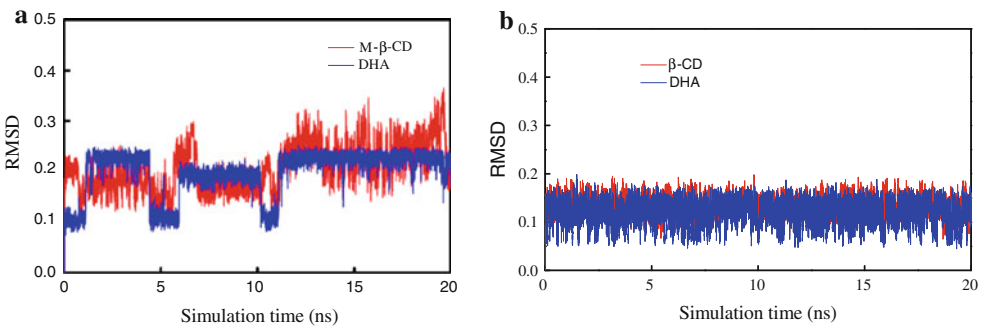

Fig. 3 RMSD of the complexes M-β-CD/DHA (**a**) and β-CD/DHA (**b**)

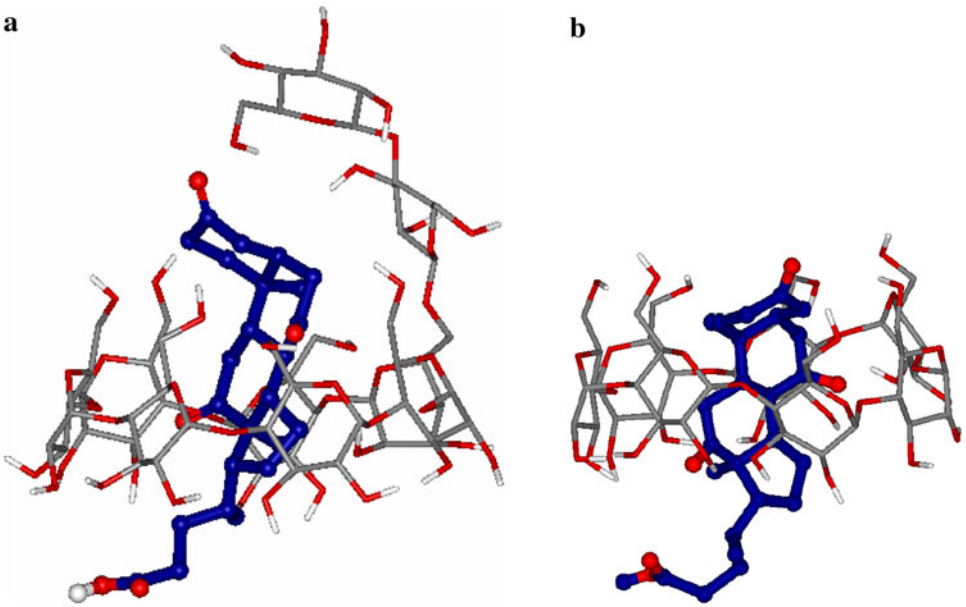

Fig. 4 Snapshots of the inclusion complexes of M-β-CD/DHA (**a**) and β-CD/DHA (**b**)

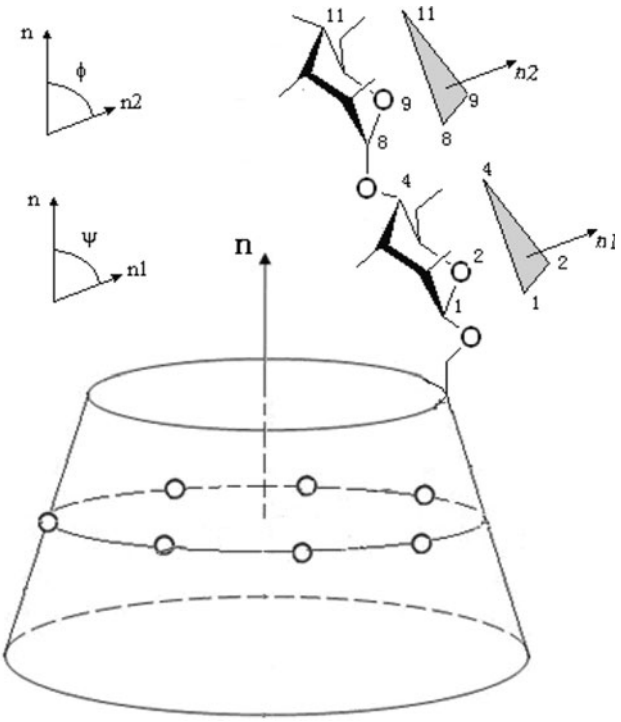

Fig. 6 Schematic presentation of angles ψ and ϕ in M-β-CD

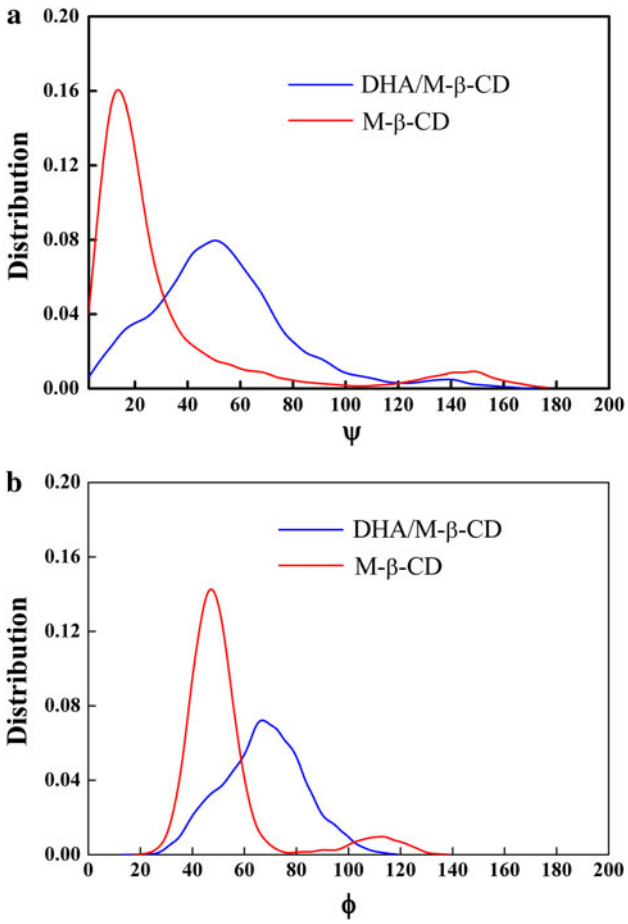

Fig. 7 Distribution of angles ψ and ϕ with and without DHA included in M-β-CD

between hosts and DHA and the interaction between hosts and water. Due to the interactions involved by the maltosyl residue, the interaction energy of M-β-CD with DHA is larger than that of β-CD with DHA; the interaction energy of M-β-CD with water is larger than that of β-CD with water. In addition, as illustrated by Fig. 4, the maltosyl residue waving outside the cavity frequently also contributes to that the RMSD of M-β-CD has a larger conformation change. While for the complex of β-CD/DHA, the RMSD of β-CD does not change so much. The interaction of maltosyl residue with DHA has some effect on the position of DHA inside the cavity of cyclodextrin, but not so much, as illustrated in Fig. 4. The results of the distance between the center of mass (COM) are presented in Fig. 5. It shows that the distance between the COM of DHA and that of M-β-CD is comparable with the distance between the COM of DHA and that of β-CD.

Figure 6 shows the definition of the angles ψ and ϕ. The normal vector, n, is for the plane through the seven glycosidic oxygen atoms. The normal vectors, $n1$ and $n2$, are for the planes through atoms 1-2-4 and 8-9-11, respectively. ψ is the angle between n and $n1$; ϕ is the angle between n and $n2$. The binding of DHA within M-β-CD is not fixed but rather is a dynamic equilibrium. These angles can reflect the movement of the maltosyl residue when DHA is included in M-β-CD. As illustrated in Fig. 7, the distributions of the angle ψ are from 0 to 40° (without DHA included) and from 20 to 80° (with DHA included), the distributions of the angle ϕ are from 30 to 70° (without DHA included) and from 40 to 100° (with DHA included). These results indicate that, when DHA is included, due to the interaction of the maltosyl residue with DHA, the maltosyl residue moves toward larger angles of ψ and ϕ, M-β-CD becomes more open.

Conclusions

Through molecular dynamics simulation, the inclusion of M-β-CD with DHA has been studied. The role of maltosyl residue in the interactions between the different components of the system (M-β-CD, DHA, and water) has been analyzed. The maltosyl residue contributes to the larger interaction energies between M-β-CD and DHA, between M-β-CD and water, between the complex M-β-CD/DHA and water. The maltosyl residue also contributes the stable complex of M-β-CD/DHA.

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