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Mesoscale simulation of drug molecules distribution in the matrix of solid lipid microparticles (SLM)

Chunxia Long, Lijuan Zhang, Yu Qian *

School of Chemical Engineering, South China University of Technology, Guangzhou 510640, PR China

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Abstract

Dissipative particle dynamics (DPD) simulation is used in this work to model the distribution of ibuprofen molecules in the carrier of solid lipid microparticles (SLM). It is shown from DPD simulation that the aggregating morphology of SLM is different at different oil content levels. At lower oil contents, the oil phase aggregates as spherical particles, while, columnar structure and lamellar structure are observed at higher oil contents. For SLM made from tristearin, ibuprofen molecules are adsorbed on the surface of the carrier. For glyceryl behenate SLM, ibuprofen molecules are distributed in the outer area of the carrier matrix. In cetyl alcohol SLM, however, part of the ibuprofen molecules locate at the outer area of the carrier matrix, while the remaining is distributed in the inner area of the matrix. The mesoscale simulation results are satisfactorily verified by the in vitro experiments and tests. For the three SLM, an initial burst release happens since ibuprofen molecules locate at the surface or the outer area of the carrier matrixes. While the extent of burst release is much reduced in glyceryl behenate SLM and cetyl alcohol SLM for ibuprofen molecules are distributed in the carrier matrixes.
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Keywords: Dissipative particle dynamics simulation; Drug release; Solid lipid microparticles

1. Introduction

During the last few decades, increasing attention has been paid to the sustained release of various drugs. Encapsulating drug in microspheres is a common approach to sustain drug release. Drug release is controlled and sustained at a proper rate over prolonged time, which will improve its efficiency and reduce its side effect [1,2]. In addition, for the drugs with short half-life and low solubility, their physical stability and dissolution properties are improved being embedded in micro-size drug carriers, which enhance the therapeutic efficiency of the drugs [3–5]. Microparticles made from solid lipid (SLM), such as fatty acid, glyceride, fatty alcohol and solid wax, are micro-size carrier systems and suitable for the corporation of lipophilic drugs. They are characteristic of better bio-compatibility than polymeric microparticles and can control and sustain drug release effectively [6–8]. SLM are complex multi-phase systems and their properties are determined not only with their composition but also with their microstructures. Therefore, it is important to investigate the relationship between their microstructures and properties, which would be helpful to obtain desired properties of SLM from optimizing their microstructures. The distribution of drug molecules in a carrier is an essential characteristic of the microstructure, thus directly determines their stability and release performance. For a drug carrier in microsize, it is difficult to observe its drug distribution by experiments. Computer simulation provides us a convenient approach to investigate its drug distribution.

Atomistic simulation can provide detailed information on the behaviour of the system. It is, however, typically limited to a few 100 molecules and nanosecond timescale [9]. Although computational fluid dynamics (CFD) is a macroscopic simulation technique, it ignores the microscopic effects. Actually, many processes of interest occur over a system of thousands of molecules within a timescale of microseconds, such as emulsion, colloid, polymer mixture and submicron drug carrier. Dissipative particle dynamics (DPD) is a mesoscopic simulation technique to simulate complex fluid dynamical phenomena suitable for these systems. It regards clusters of atoms or fluid packets as fluid particles or beads which move according to the Newton's equations of motion. The method was proposed by Hoogerbrugge and Koelman initially for polymeric systems

* Corresponding author. Tel.: +86 20 87112046; fax: +86 20 87112046.
E-mail address: ceyuqian@scut.edu.cn (Y. Qian).

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by introducing bead-and-spring type particles [10]. In 1995, Espaňol and Warren carried out detailed formulation by connecting fluctuation–dissipation theorem with the method [11]. Later, Groot and Warren established a link between DPD parameters and Flory-Huggins parameters for polymer systems, which open a way to bridge the gap between atomistic simulations and mesoscopic simulations [12]. Since then, the application of DPD simulation has been extended to study the behaviour of surfactants at the water/oil interface [13,14], the lipid membrane and vesicles [15–18], and surface tension calculations [12,19]. In addition, DPD simulation technique was used to simulate systems consisting of polymer, surfactant, and water. The aggregating morphology of surfactant and polymer in the solution and the way of the surfactant connecting with the polymer are discussed [20,21]. However, DPD method has not been applied in a real drug delivery system.

In this paper, DPD simulation technique is employed to explore the distribution of drug molecules in the matrixes of SLM, in which tristearin, glyceryl behenate and cetyl alcohol are chosen as the carrier materials, ibuprofen as the model drug, while polyvinyl alcohol (PVA) as the stabilizer. Ibuprofen is a nonsteroidal anti-inflammatory drug with a low solubility and short half-life. Its bioavailability is low after oral administration and it causes irritation in the gastrointestinal mucous membrane. Embedding ibuprofen in the solid matrixes of SLM can sustain its release and improve its physical stability as well as reduce the gastrointestinal adverse effect. SLM are produced for oral administration and their in vitro release performance is also studied. The relationship of the microstructures of SLM and their release performance are further investigated.

2. DPD simulation

2.1. The DPD method

In DPD simulations, a set of beads move according to the Newton's equations of motion [12]:

$$\frac{\mathrm{d}\boldsymbol{r}_i}{\mathrm{d}t} = \boldsymbol{v}_i, \qquad m_i\frac{\mathrm{d}\boldsymbol{v}_i}{\mathrm{d}t} = \boldsymbol{f}_i \tag{1}$$

where $\boldsymbol{r}_i$, $\boldsymbol{v}_i$ and $\boldsymbol{f}_i$ are the position vector, velocity, and the total force on the ith bead, respectively. All bead masses m_i are assumed to be the same and set equal to unity for simplicity. Each bead is subject to three non-bonded forces from its neighbours: a conservative force ($\boldsymbol{F}_{ij}^{\mathrm{C}}$), a random force ($\boldsymbol{F}_{ij}^{\mathrm{R}}$), and a dissipative force ($\boldsymbol{F}_{ij}^{\mathrm{D}}$). The total force on a bead $\boldsymbol{f}_i$ is showed as

$$\boldsymbol{f}_i = \sum_{i\neq j}(\boldsymbol{F}_{ij}^{\mathrm{C}} + \boldsymbol{F}_{ij}^{\mathrm{D}} + \boldsymbol{F}_{ij}^{\mathrm{R}}) \tag{2}$$

where the sum runs over all other particles within a certain cutoff radius r_{c}. The cutoff radius r_{c} is set as an unit of length in calculation. The conservative force ($\boldsymbol{F}_{ij}^{\mathrm{C}}$) is a soft repulsion acting along the line of centres given by

$$\boldsymbol{F}_{ij}^{\mathrm{C}} = \begin{cases} a_{ij}(1-r_{ij})\hat{\boldsymbol{r}}_{ij} & r_{ij} < 1 \\ 0 & r_{ij} \geq 1 \end{cases} \tag{3}$$

where a_{ij} is a repulsion parameter between particle i and j. The term $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$, $r_{ij} = |\boldsymbol{r}_{ij}|$, $\hat{\boldsymbol{r}}_{ij} = \boldsymbol{r}_{ij}/|\boldsymbol{r}_{ij}|$. The random force ($\boldsymbol{F}_{ij}^{\mathrm{R}}$) and dissipative force ($\boldsymbol{F}_{ij}^{\mathrm{D}}$) are given by

$$\boldsymbol{F}_{ij}^{\mathrm{R}} = \begin{cases} \sigma\omega^{\mathrm{R}}(r_{ij})\theta_{ij}\hat{\boldsymbol{r}}_{ij} & r_{ij} < 1 \\ 0 & r_{ij} > 1 \end{cases} \tag{4}$$

$$\boldsymbol{F}_{ij}^{\mathrm{D}} = \begin{cases} -\gamma\omega^{\mathrm{D}}(r_{ij})(\hat{\boldsymbol{r}}\cdot\boldsymbol{v}_{ij})\hat{\boldsymbol{r}}_{ij} & r_{ij} < 1 \\ 0 & r_{ij} > 1 \end{cases} \tag{5}$$

where θ_{ij} is a randomly fluctuating variable between 0 and 1. The terms $\boldsymbol{v}_{ij} = \boldsymbol{v}_i - \boldsymbol{v}_j$, ω^{R} and ω^{R} are r-dependent weight functions vanishing for $r > r_{\mathrm{c}}$. One of the two weight functions can be chosen arbitrarily and the other is fixed [11]. The relations of the parameters are

$$\omega^{\mathrm{D}}(r) = [\omega^{\mathrm{R}}(r)]^2, \qquad \sigma^2 = 2\gamma k_{\mathrm{B}}T \tag{6}$$

where T is the absolute temperature and k_{B} is the Boltzmann's constant. In addition, beads connected in a molecule experience a spring force due to bonded neighbours [11]. The spring force is

$$\boldsymbol{F}_i^{\mathrm{S}} = \sum_j C\boldsymbol{r}_{ij} \tag{7}$$

where C is the spring constant.

2.2. Simulation parameter calculation

In DPD simulations, the coarse-grained approach is used where one DPD bead represents a group of atoms or a liquid volume. The coarse-graining procedure is given as follows. A water molecule and a monomer of PVA are represented with a single bead denoted with w and p, respectively. The molecular structure of ibuprofen is shown in Fig. 1(a). Each part separated by dashed lines is represented with a single bead named da, db and dc, respectively. The molecular structure of tristearin is shown in Fig. 1(b). The group in the dashed line box is represented with a bead named f. The hydrocarbon chain are represented with

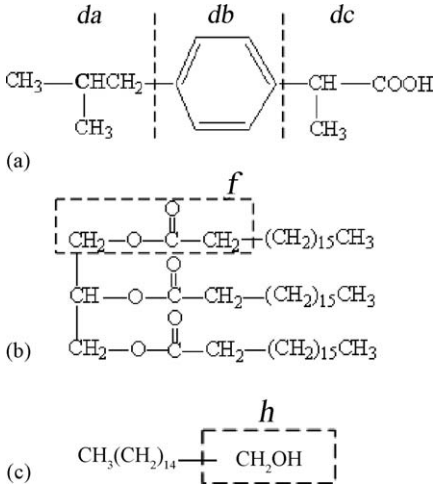

Fig. 1. The molecular structures of (a) ibuprofen, (b) tristearin, and (c) cetyl alcohol.

Table 1
The interaction parameters a_{ij} used in DPD simulations

Parameter	*w*	*a*	*f*	d*a*	d*b*	d*c*	*p*	*h*
w	25							
a	100.59	25						
f	79.69	28.00	25					
d*a*	118.17	25.03	29.06	25				
d*b*	83.83	28.16	25.00	29.25	25			
d*c*	57.11	38.32	28.83	41.37	29.00	25		
p	54.81	34.33	27.01	36.72	27.10	25.22	25	
h	39.03	43.45	32.91	47.89	33.38	26.12	26.95	25

several beads named *a*. The molecular structure of cetyl alcohol is shown in Fig. 1(c). The atom group in the dashed line box is represented with a bead denoted as *h*. The hydrocarbon chain is also represented with several beads named *a*, which is the same as that in the tristearin molecule. Glyceryl behenate is a mixture of mono-, di- and triglycerides of behenic acid (C22). The coarse-grained molecular structure of the triglyceride is similar with that of tristearin. For the mono- and diglycerides in the mixture, the group with a hydroxyl is presented with a bead named *h* which is the same as that in the cetyl alcohol molecule.

Since the coarse-grained model of each molecule has been developed, the repulsion parameters a_{ij} between every two of the beads are calculated. The repulsion parameters between beads of the same type are as follows [12]:

$$a_{ii} = \frac{75k_BT}{\rho} \tag{8}$$

The compressibility of pure fluid is chosen as $\rho = 3$, which is close to that of water [12], thus $a_{ii} = 25k_BT$. As Hoogerbrugge and Koelman did [10], we choose the conservative interaction potential $k_BT = 1$. The repulse parameters between different types of particles are as follows [12]:

$$a_{ij} \approx a_{ii} + 3.27\chi_{ij} \tag{9}$$

where χ_{ij} is the Flory-Huggins parameter, obtained from two approaches of experiment and molecular simulation. Flory-Huggins parameter χ_{ij} is calculated from solubility parameters [19]

$$\chi_{ij} = \frac{(\delta_i - \delta_j)^2 V}{RT} \tag{10}$$

where δ_i and δ_j are the solubility parameters of *i* and *j*, respectively, while *V* is the molar volume of the bead. The solubility parameter is calculated using Discover and Amorphous Cell program in the commercial software Materials Studio (Accelrys) with the COMPASS force field. The calculated DPD repulsion parameters a_{ij} are listed in Table 1.

The simulation is performed in a $20 \times 20 \times 20\ r_c$ box with a periodic boundary condition in all three directions. The beads of the same molecule are connected by a harmonic spring and the spring constant $C = 4$ [22]. Each DPD simulations run 10 000 steps with a time step of 0.05 ns. Glyceryl behenate is a mixture of mono-, di- and triglycerides with a molar fraction of 15%, 45% and 40%, respectively. All the components are considered in the simulation system. The simulations are performed using DPD program in the commercial software Materials Studio (Accelrys).

3. Experiments

To investigate the relationship of the microstructures of SLM and their release performance, SLM were produced and their in vitro release properties were studied. The materials used in this work were listed as follows: glyceryl behenate (Gattefossé, France) is a mixture of 13–21% mono-, 40–60% di- and 21–35% triglycerides of behenic acid (C22). Other materials were tristearin (90% purity, Yihe chemical Ltd., China), cetyl alcohol (C.P. Shantou Guanghua chemical Ltd.), ibuprofen (Shanghai Yuanji chemical Ltd.) and Polyvinyl alcohol (PVA, MW = 13 000–23 000, 87–89% hydrolysed, Sigma–Aldrich, Inc.).

An emulsion-congealing technique was used to prepare SLM, which was described in detail in literatures [6,23]. The formulation consisted of 15% lipid, 8% PVA (wt.), 10% ibuprofen (wt., relative to lipid only) and water. Particle size and its polydispersity index was analysed with a photo correlation spectroscopy (PCS, Mastersize-2000, Malvern Instruments, UK). The morphology of SLM was examined by scanning electronic microscope (SEM, FEI-XL30, Philips, Netherlands). Suspension samples were spread on copper stubs for 3 days till they were totally dried. The dried samples were then coated with gold and examined by SEM at 15 kV. The drug entrapment efficiency was determined by measuring the free drug concentration in the aqueous phase. The suspension was centrifuged for 15 min at $13\,000 \times g$ (TGL-20M, Changsha Xiangyi Centrifuge Instrument Co., Ltd., China). The aqueous phase was then filtered through a 0.22 μm membrane. The drug content of the filtrate was measured by spectrophotometry (751-GW spectrophotometer, HP Analytical Apparatus Ltd., Shanghai). The amount of incorporated drug was determined as the result of the initial drug minus the free drug.

To study the drug release from SLM with different carrier materials, the paddle method of the China Pharmacopoeia (2000) was employed. Drug release was investigated at $37.2 \pm 0.5\ ^\circ C$ in phosphate buffer (pH 7.2), which was similar with the intestinal environment. The dissolution media of simulated gastric fluid with acidic environment was not taken into account to minimize the influence of other factors. At fixed time intervals, samples were drawn from the receiver compartment and measured spectrophotometrically at a wave length of 222 nm. Drawn samples were replaced immediately with fresh dissolution medium.

4. Results and discussion

4.1. The aggregating morphology of SLM at different oil contents

As shown in Fig. 2 is the snap shots of phase separation of tristearin SLM during the simulation. In the simulation system, the molar fraction of tristearin, PVA, ibuprofen, and water are 9%, 4.5%, 4.5%, and 82%, respectively. To display

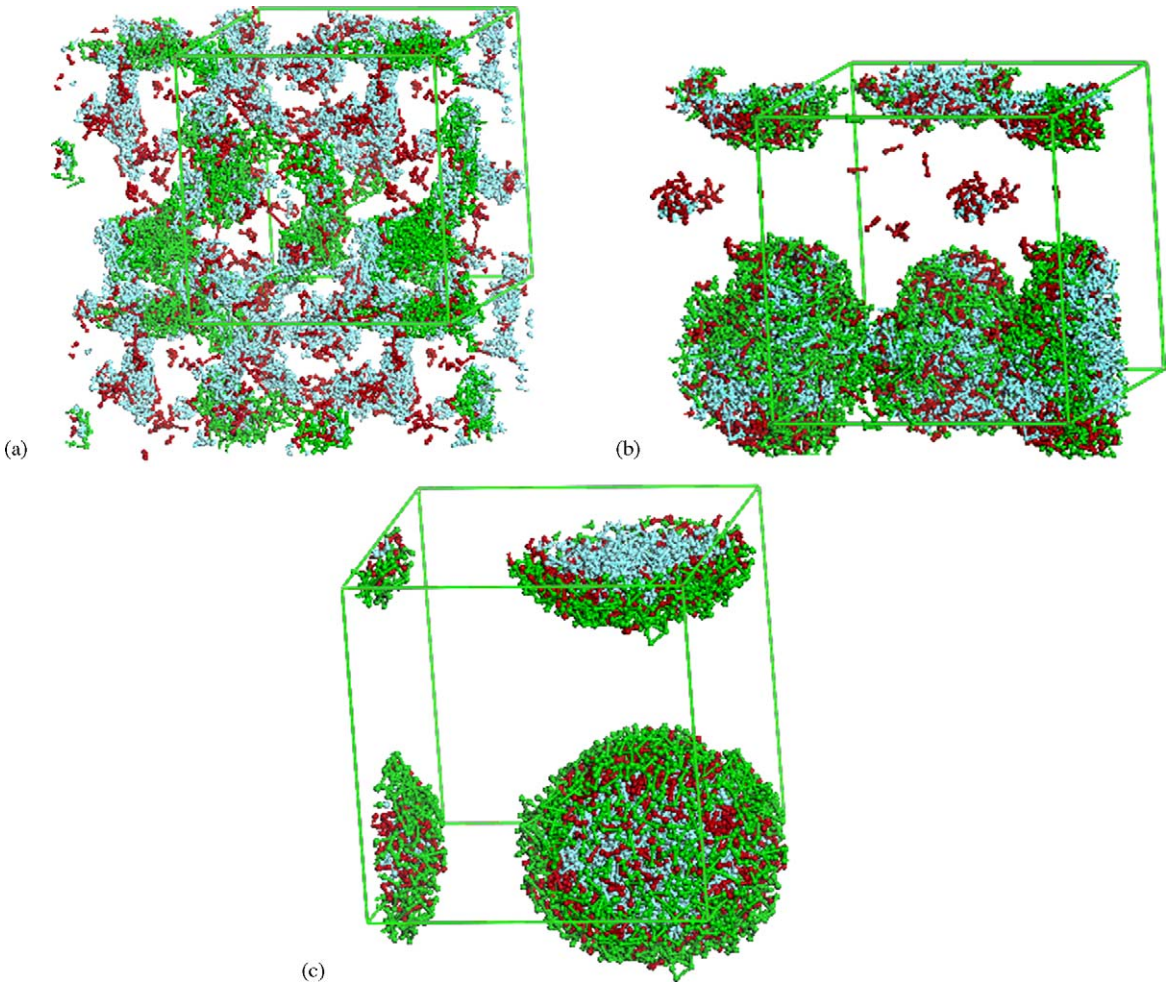

Fig. 2. Phase separation of tristearin SLM at different simulation steps. (a) 100 steps, (b) 2000 steps, (c) 10 000 steps (PVA, tristearin, ibuprofen). *Note*: coloured pictures of Figs. 2–4 are available upon request for clear view.

the molecular arrangement of the drug delivery system clearly, water molecules are not shown here. As shown in Fig. 2(a), all the components are mixed together at the beginning. After 2000 simulation steps, tristearin, ibuprofen and PVA congregate and the phase separation is obvious. With the simulation time increasing, the separated congeries unite and become a larger one. The system reaches equilibrium after 5000 steps. No obvious changes are observed for the system with increasing simulation time. It is seen in Fig. 2(c), at the 10 000 steps, in the final equilibrium state, a spherical particle is formed with PVA molecules enwrapping on the surface of the drug carrier and serving as the stabilizer. To obtain the statistical results of the simulated system, the simulation time is set to 10 000 steps.

The aggregating morphology of the oil phase at different oil contents is investigated. In the simulation system, the molar ratio of tristearin, PVA and ibuprofen is fixed as 2:1:1 according to that in the experiment. Tristearin, PVA and ibuprofen are regarded as the oil phase. Several small spherical particles are observed in the simulation box when the oil molar fraction is 6%, as shown in Fig. 3(a). Similar results are observed when the oil contents are lower except that the particles are smaller. With the oil contents growing up to 12% and 18%, as seen in Fig. 3(b) and (c), the small spherical particles unite to be a larger one. Because when the oil content is high, the separated oil phases are easier to collide and joint together. When the oil molar fraction is up to 20%, the aggregating morphology of SLM is not a spherical particle any more and a columnar structure is formed. This phenomenon is often observed in the surfactant solution when the surfactant concentration is above 10 times of its critical micelle concentration [24]. The columnar structure ensures that the area of hydrophobic groups contacting with water is minimal, which keeps the system stable. The aggregating morphology of the oil phase is complex when the oil molar fraction is higher than 20%. A lamellar structure is observed when the oil molar fraction is increased to 45%. The aggregating morphology of the oil phase at high oil contents will be discussed in detail in a later report. Similar results are obtained when glyceryl behenate SLM and cetyl alcohol SLM are simulated. The DPD simulation results show qualitatively the changes of the aggregating morphology at different oil contents. To produce spherical drug carriers, the oil content has been controlled in a low level. During the sample preparation, the oil molar fraction is below 1% to keep the system stable.

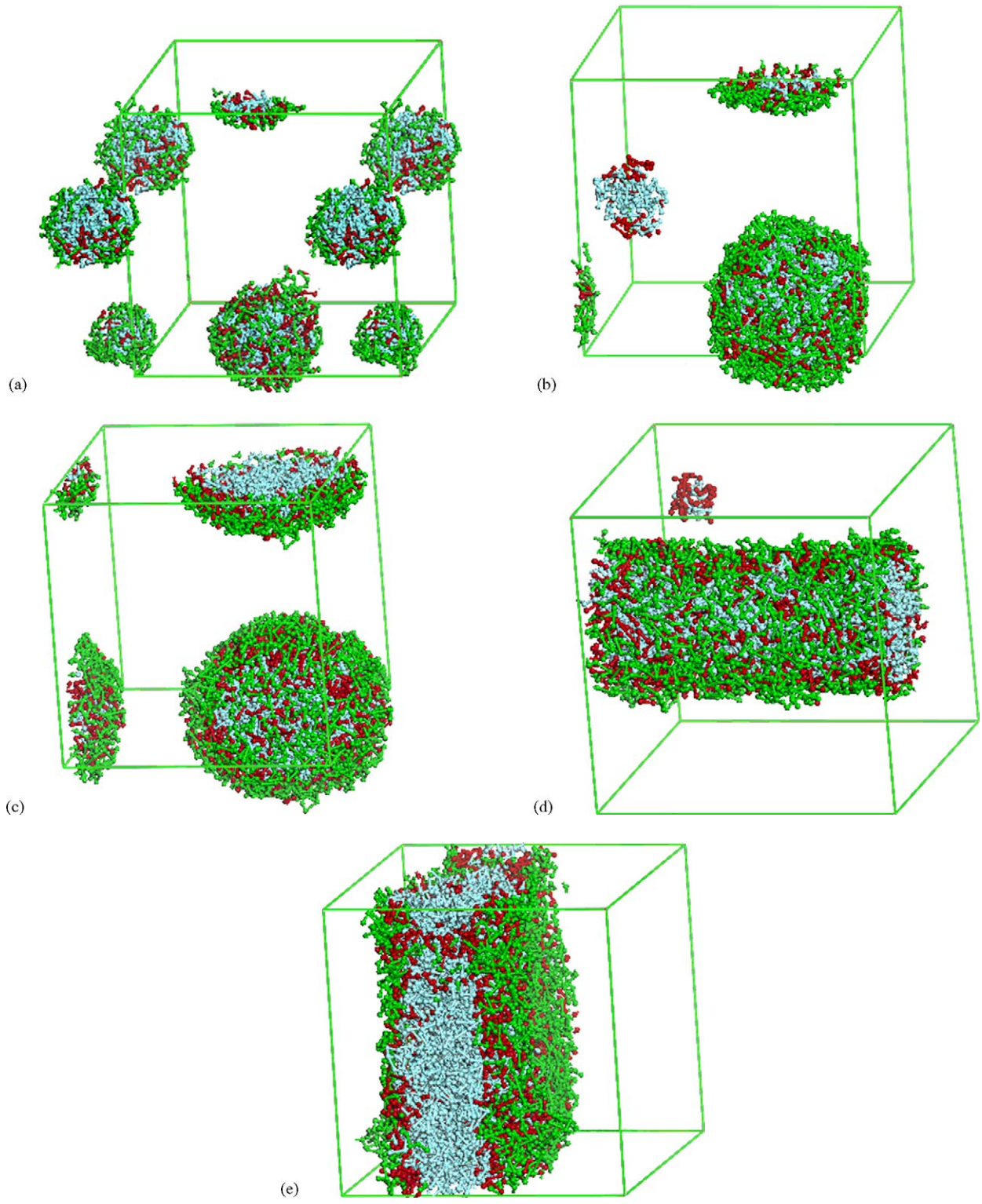

Fig. 3. Aggregating morphology of SLM at different oil contents. (a) 6%, (b) 12%, (c) 18%, (d) 20%, (e) 45% (PVA, tristearin, ibuprofen).

4.2. Simulation results of ibuprofen distribution in SLM

Ibuprofen molecules distribution in the drug carrier is analysed from the simulation results when the oil molar fraction is 18% in which the molar ratio of carrier material, ibuprofen, and stabilizer is 2:1:1. To reveal how ibuprofen molecules are distributed in the carrier, section views of SLM are shown in Fig. 4 without PVA. It is shown in Fig. 4(a) that, in the tristearin SLM, ibuprofen molecules are adsorbed on the surface of the carrier with their polar groups towards the water phase and non-polar groups to the carrier, and a shell-spherical structure is formed. However, in the glyceryl behenate SLM, as shown in

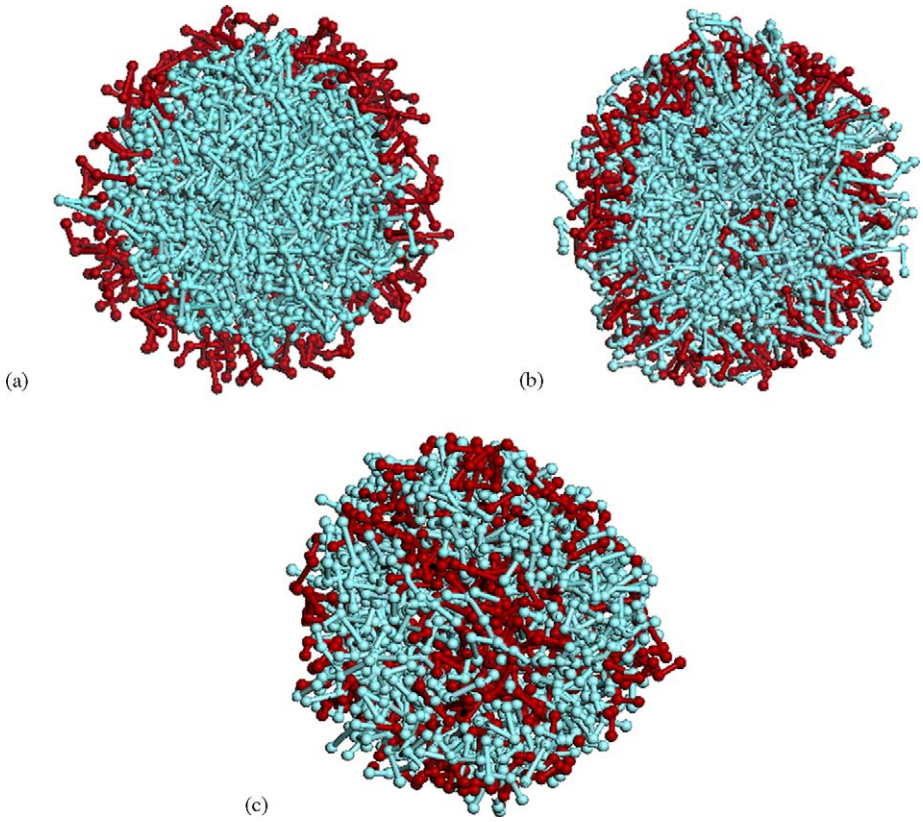

Fig. 4. The section views of SLM. (a) Tristearin SLM, (b) glyceryl behenate SLM, (c) cetyl alcohol SLM (carrier material, ibuprofen).

Fig. 4(b), ibuprofen molecules are not adsorbed on the surface of the carrier, but are distributed in the outer area of the carrier matrix. This is because the mono- and diglycerides of glyceryl behenate possess hydrophilic hydroxyl groups which have polar interaction with the carboxyl groups of the ibuprofen molecules. Hence, in the glyceryl behenate SLM, the hydrophobic groups of the ibuprofen molecules remain in the body of the carrier with their carboxyl groups at the oil/water interface along with the hydroxyl groups of the glyceryl behenate molecules. In the cetyl alcohol SLM, however, part of the ibuprofen molecules are distributed in the outer area of the carrier matrix, as shown in Fig. 4(c), which is similar with that in the glyceryl behenate SLM. While the remaining ibuprofen molecules are distributed in the inner area of the matrix. This is because part of the hydroxyl groups in the cetyl alcohol molecules are distributed at the oil/water interface, while other part of the hydroxyl groups remain in the inner area of the matrix. Polar interaction exists between the hydroxyl groups of the cetyl alcohol molecules and the carboxyl groups of the ibuprofen molecules, which keep part of the ibuprofen molecules remain in the inner area of the carrier matrix. The SLM with lower drug contents are also simulated, and the drug distribution in the carriers is similar.

4.3. In vivo release performance of SLM

To investigate the effect of the drug distribution in SLM on the release performance and verify the simulation results simultaneously, ibuprofen loaded SLM are produced with tristearin, glyceryl behenate and cetyl alcohol as the carrier materials. To keep the three SLM systems with similar sizes, the homogenization power is different in producing these three SLM systems. The homogenization power in producing tristearin SLM is highest, while that of producing cetyl alcohol SLM is the lowest. As shown in Table 2, however, the mean particle size of tristearin SLM is slightly larger than that of glyceryl behenate SLM and cetyl alcohol SLM. That is because surfactant cetyl alcohol reduces the surface tension, so do smaller particles. For glyceryl behenate SLM, the mono- and diglycerides in glyceryl behenate possess the properties of a surfactant (HLB 2–5) which also reduce the surface tension of the system. The SEM micrographs of SLM are shown in Fig. 5.

The drug release profiles of tristearin SLM, glyceryl behenate SLM, and cetyl alcohol SLM are shown in Fig. 6. A sustained release of ibuprofen can be experimentally achieved in the SLM. Ibuprofen crystal exhibits a 100% release within 3 h, while full release of ibuprofen in tristearin SLM and glyceryl behenate

Table 2
The particle size and entrapment efficiency of SLM

Carrier material	Mean size (μm)	Polydispersity index	Entrapment efficiency (%)
Tristearin	5.38 ± 0.63	0.550 ± 0.032	75.1
Glyceryl behenate	4.67 ± 0.42	0.381 ± 0.021	85.3
Cetyl alcohol	4.24 ± 0.31	0.651 ± 0.038	78.4

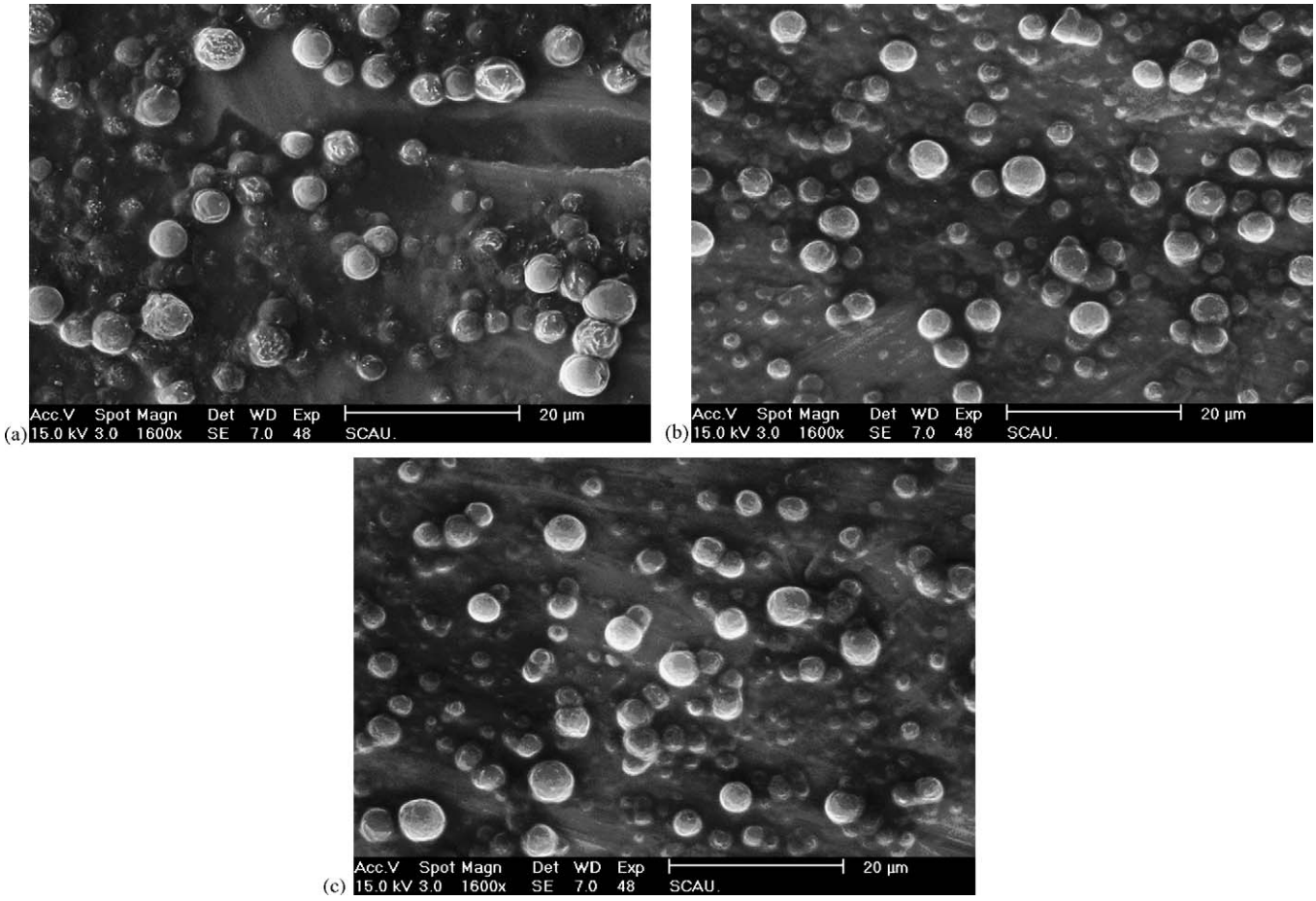

Fig. 5. The SEM micrographs of SLM. (a) Tristearin SLM, (b) glyceryl behenate SLM, (c) cetyl alcohol SLM.

SLM are delayed to 7 and 10 h, respectively. Full release of ibuprofen in cetyl alcohol SLM lasts for even longer. An initial burst release happens for all these three SLM. For tristearin SLM, 90% drug is released within 4 h, while only 75% drug is released for glyceryl behenate SLM and cetyl alcohol SLM in the time. A better sustained release of ibuprofen is obtained for glyceryl behenate SLM and cetyl alcohol SLM. However, the drug release profiles in glyceryl behenate SLM and cetyl alcohol SLM are different. The drug release rate of cetyl alcohol SLM is much reduced after 4 h.

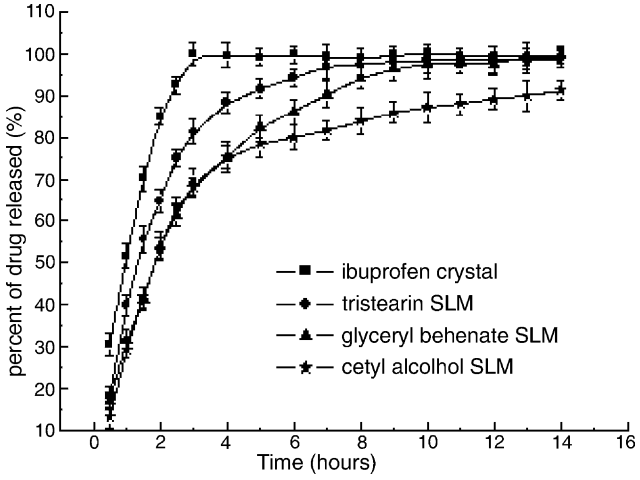

Fig. 6. Release profiles of ibuprofen crystal and ibuprofen loaded SLM.

The drug release performance agrees well with the simulation results. From the simulation results above, in tristearin SLM and glyceryl behenate SLM, ibuprofen molecules are adsorbed on the surface and locate at the outer area of the carrier. While in cetyl alcohol SLM, part of the ibuprofen molecules locate at the outer area of the carrier and the remaining is kept in the inner area of the matrix. This induces a burst release happen for these three SLM systems. However, the extent of their burst release is different. In the tristearin SLM, ibuprofen molecules are adsorbed on the surface of the carrier and the resistance of drug release is the stabilizer layer. However, in the glyceryl behenate SLM drug molecules are distributed in the outer area of the carrier matrix. During the release process, drug molecules firstly diffuse through the carrier matrix and then pass through the stabilizer layer. The drug release rate is thus much reduced. In addition, in the cetyl alcohol SLM, part of the ibuprofen molecules locate in the inner area of the carrier matrix. The ibuprofen molecules should diffuse through the carrier matrix for a long distance before they get to the oil/water interface and the drug release rate is much reduced later.

Basing on the above analysis, the distribution of drug molecules in SLM is proved to influence its release performance directly. A better sustained release is obtained when drug molecules locate in the carrier matrix. Although no satisfied sustained release of ibuprofen is achieved in our work now, and the selection of better excipient for ibuprofen is going on. The method of predicting drug release performance from DPD simulation results should be convenient in carrier material selection. Hence, an SLM system with desired properties can be achieved by choosing and designing a proper carrier material for a certain drug, which is attractive in drug carrier design.

5. Conclusions

The DPD simulation is used to model the SLM with tristearin, glyceryl behenate and cetyl alcohol as the carrier materials. The simulation shows that the aggregating morphology of SLM is spherical at low oil contents, a columnar structure at the oil molar fraction of 20%, and a lamellar structure at the oil molar fraction over 45%. The ibuprofen distribution in the carriers is further investigated at a low oil content. For the tristearin SLM, ibuprofen molecules are adsorbed on the surface of the drug carrier and a shell-spherical structure is formed. While ibuprofen molecules are mainly distributed in the outer area of the matrix of the glyceryl behenate SLM. In the cetyl alcohol SLM, however, part of the ibuprofen molecules locate at the outer area of the matrix, while the remaining is distributed in the inner area of the carrier matrix. The in vitro release profiles of the SLM validate the simulation results. An initial burst release happens for these three SLM. However, the difference of the drug distribution in the carriers induces different release performance of SLM made from different materials. Since ibuprofen molecules are distributed in the matrix of the glyceryl behenate SLM and the cetyl alcohol SLM, a better sustained release is achieved in these two SLM than the tristearin SLM. Meanwhile, the ibuprofen release rate in cetyl alcohol SLM is much reduced after 4 h since part of the ibuprofen molecules locate in the inner area of the matrix.

The microstructure of a drug carrier can be shown by the mesoscopic simulation method DPD directly. The DPD simulation provides us an insight into the microstructure of a drug carrier and predicts its property. Desired properties of a drug carrier can be obtained from correlating and optimizing its microstructure. In this way, the new product can be better understood and designed, development expenses in terms of cost and time would be much reduced.

Acknowledgments

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