

Available online at www.sciencedirect.com

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

Original Research Paper

Investigating the molecular dissolution process of binary solid dispersions by molecular dynamics simulations

Tenglan Chan, Defang Ouyang *

State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China

ARTICLE INFO

Article history:

Received 16 June 2016

Received in revised form 17 July 2017

Accepted 26 July 2017

Available online 23 October 2017

Keywords:

Solid dispersion

Molecular modeling

Dissolution process

Ibuprofen

ABSTRACT

Dissolution molecular mechanism of solid dispersions still remains unclear despite thousands of reports about this technique. The aim of current research was to investigate the molecular dissolution mechanism of solid dispersions by molecular dynamics simulations. The formation of ibuprofen/polymer solid dispersions was modeled by the simulated annealing method. After that, the models of solid dispersions were immersed into the water box with 25–30 Å thicknesses and 50–100 ns MD simulations were performed to all systems. Simulation results showed various dissolution behaviors in different particle sizes and various polymers of solid dispersions. Small-sized particles of solid dispersions dissolved quickly in the water, while the large particles of PEG or PVP-containing solid dispersions gradually swelled in the dissolution process and drug molecules may aggregate together. In the dissolution process, the carboxylic groups of ibuprofen molecules turned its direction from polymer molecules to external water box and then the drug molecules left the polymer coils. At the same time, polymer coils gradually relaxed and became free polymer chains in the solution. In addition, solid dispersion with poloxamer could prevent the precipitate of drug molecules in the dissolution process, which is different from those of PEG or PVP-containing systems. This research provided us clear images of dissolution process of solid dispersions at the molecular level.

© 2018 Shenyang Pharmaceutical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Solubilization of poorly soluble drugs attracts high attentions from formulation scientists in the pharmaceutical industry [1]. Amorphous solid dispersion is one of important drug de-

livery techniques to enhance the solubility and dissolution rate for crystalline drugs with low solubility [2]. In the system of solid dispersions, the crystalline structure of drugs was changed to amorphous state and resulted in higher bioavailability [3]. The first solid dispersion (SD) was reported by Sekiguchi and Obi in 1961 [4]. Several products with solid dispersion techniques

* Corresponding author. University of Macau, Avenida da Universidade, N22, Taipa, Macau, China. Tel.: +853 8822 4514.

E-mail address: defangouyang@umac.mo (D. Ouyang).

Peer review under responsibility of Shenyang Pharmaceutical University.

<https://doi.org/10.1016/j.ajps.2017.07.011>

1818-0876/© 2018 Shenyang Pharmaceutical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1 – Recent progress of molecular modeling in solid dispersions.

Drugs	Polymers	Simulation methods	References
Lafutidine (LAFT)	Soluplus, PEG 400, Lutrol F127, Lutrol F68	Molecular dynamics (MD) simulation; Gaussian program in Schrodinger, Maestro software program	[10]
Artemisinin	PEG, PVP	Molecular dynamics (MD) simulation; Materials Studio 6.0; COMPASS force field;	[11]
Carbamazepine	Poloxamer 188	Molecular dynamics (MD) simulation; XenoView software; PCFF force field parameters and charges;	[3]
Posaconazole	Soluplus, PEG 400, Lutrol F127, Lutrol F68, TPGS	Molecular dynamics (MD) simulation; Gaussian program in Schrodinger, Maestro software program;	[12]
Curcumin	MPEG-PCL	Molecular dynamics (MD) simulation; HyperChem software (HyperChem Professional 80); CHARMM27 force field; Simulating anneal method;	[13]
Paclitaxel	PEG, PCL, MPEG-PCL	Molecular dynamics (MD) simulation and molecular docking; HyperChem software (HyperChem Professional 80); CHARMM27 force field; simulating anneal method; AutoDock Vina	[14]
Propranolol HCl, diphenhydramine HCl, paracetamol, ibuprofen, dichlofenac Na, hydrocortisone	Eudragit L100, Eudragit EPO, Eudragit L100-55, Kollidon VA64	Computational model based on quantum mechanical (QM) calculations; GaussView software; Gaussian 09 program;	[15]
Lumefantrine	Soluplus, Kollidone VA64, Plasdone S630	Molecular dynamics (MD) simulation; Gaussian program in Schrodinger; Maestro software program;	[16]
Indomethacin (IMC)	PVP	Molecular dynamics (MD) simulation; AMBER software; AMBER-ff03 forcefield; Gaussian 03 program;	[17]
Cetirizine HCl, verapamil HCl,	Eudragit L100 and L100-55	Molecular dynamics (MD) simulation; Gaussian 09 program in Schrodinger;	[18]

have been commercialized in the pharmaceutical market [5]. In recent two decades, publications in solid dispersion area increase sharply. However, there are still four key problems about solid dispersions to be answered: the solid state structure of solid dispersions; the mechanism of dissolution enhancement; the aging issue during storage period; and the understanding of the *in vitro/in vivo* correlation [6]. Recent review has raised three possible assumptions of how polymeric amorphous solid dispersions (PASD) dissolve in aqueous solution: (a) PASD nano-clusters dissolve quickly into the solution; (b) the PASD particles gradually dissolve and the drug molecules remain amorphous state in the undissolved particles; (c) the PASD particles gradually dissolve, but the recrystallization of drugs may happen at the surface of the undissolved particles [7]. However, there is still lack of direct and clear evidence for dissolution molecular mechanism of solid dispersions in aqueous environment.

Molecular dynamics (MD) simulation describes the molecular systems by mimicking the behavior of molecules at the atomistic level [8]. Meanwhile, molecular simulation is able to calculate the physical properties of drug/excipient systems without costly experiments [9]. Recent progress about molecular modeling studies for solid dispersions was summarized in Table 1. Our previous study used molecular modeling to investigate the solid state structure of ibuprofen/polymer SD by the simulated annealing method and provided an *in silico* protocol to the preparation of SD [19]. Three polymers were selected as the carriers, including polyethylene glycol (PEG), poloxamer and polyvinylpyrrolidone (PVP). Simulation results showed linear polymer chains form the random coils under heat and the drug molecules stick on the surface of polymer coils. This research provided more reasonable molecular images of solid dispersions than the existing theory.

Following our previous study [19], the aim of our study was to further investigate the dissolution molecular mechanism of

SD by MD approach. Ibuprofen (IBU), an anti-inflammatory drug for moderating pain and fever, was still chosen as the model drug, and PEG, PVP and poloxamer were selected as the polymeric carriers.

2. Material and simulation details

2.1. Model establishing

The model of the selected polymer and drug molecules were built by Discovery Studio Visualizer 3.1 (<http://accelrys.com/products/discovery-studio/>). The molecular structures of the polymers (PEG, PVP, poloxamer 188) were same as our previous publication [19]. The model of PEG contains 20 repeating units of ethylene oxide. The PVP model contains nine repeating units of vinylpyrrolidone. The model of poloxamer was composed of a central chain with three repeating units of propylene oxide, flanked by two chains with 8 repeating units of ethylene oxide. Ibuprofen was used as a model drug. The structure of ibuprofen lattice was downloaded from Cambridge Structural Database and crystal structure of racemate and enantiomer (S)-(+)-ibuprofen was selected [20]. These SD models with the Packmol program were further optimized from previous manual-built models in our previous publication [19]. Packmol program [21] (<http://www.ime.unicamp.br/~martinez/packmol/>) was used to obtain random distribution of polymers with a tolerance distance of 3.0 Å in a limited boundary box. The details of all systems were shown in Table 2.

2.2. Preparation process modeling of solid dispersions by the simulated annealing method

The molecular dynamics (MD) simulations utilized the AMBER14 software package with the general AMBER force field (gaff) for

Table 2 – The details of solid dispersion systems in the simulation process.

SD system no.	Weight ratio	Molar ratio	Numbers of ibuprofen	Numbers of polymer chains	Numbers of water molecules (water box)	Total atom number in the systems	Initial gyration radius
IBU/PEG	1:5	4:5	4	5	29,529 (30 Å)	89,434	13.37 Å
IBU/PVP	1:10	4:8	4	8	30,894 (30 Å)	94,012	13.75 Å
IBU/POL	1:10	4:10	4	10	36,036 (30 Å)	109,690	14.81 Å
IBU/PEG-2	1:5	16:20	16	20	22,579 (25 Å)	71,125	15.37 Å
IBU/PVP-2	1:10	16:32	16	32	32,480 (25 Å)	103,120	18.82 Å
IBU/POL-2	1:10	16:40	16	40	30,771 (25 Å)	98,641	19.12 Å

all carriers and drugs. The models of all systems were built using the LEAP module in AmberTools 1.5. The simulated annealing method was similar to our previous publication [19]. After minimization, 2 ns annealing simulation was performed. Firstly, the system was gradually heated from 0 to 500 K in 200 ps, and then kept at a temperature of 500 K for 1000 ps to equilibrate the systems. Next, the system was quickly cooled down from 500 to 300 K in 100 ps and finally the systems were kept at a temperature of 300 K for 700 ps for equilibration.

2.3. Dissolution process modeling of solid dispersions by MD simulations

After the simulated annealing process, the solid dispersion system was immersed in a water box with a solvation shell of 25 or 30 Å thickness using TIP3P model for water with the general AMBER force field (gaff) and the ff14SB force field. In the minimization procedure, the structures of drugs and polymers were subjected to 2000 steps of steepest descent minimization followed by 2000 steps of conjugate gradient minimization. The whole system was subjected to 2000 steps of conjugate gradient minimization followed by 3000 steps of conjugate gradient minimization. After minimization, the system was heated at 300 K while keeping the structure of the solid dispersion fixed with weak restraints. The non-bonded cutoff distance was 8.0 Å. Then, 50 or 100 ns MD simulation at 300 K was performed in the solvated system to simulate the dissolution process of the solid dispersion. The Langevin Dynamics was used to control the temperature using a collision frequency of 1.0 ps^{-1} . In these simulations, the parameter $iwrap = 1$ of MD input files were used to wrap all molecules into a primary box. Constant pressure periodic boundary with an average pressure of 1 atm was also applied. Initial Gyration Radius gave the reference of the particle size for different SD systems after simulated anneal process.

3. Results and discussion

During simulated annealing process, the polymer chains formed random coils, the crystal structure of ibuprofen was broken and the drug molecules were stuck or inserted to the surface of the polymer coils to form an amorphous solid dispersion, the drugs molecules were molecularly dispersed in the SDs matrix. SD system of ibuprofen with polymers (e.g. PEG, poloxamer and PVP) also showed similar results. Various SD systems with polymers in different lengths and different weight ratios gained

similar results (data not shown). The temperature change during the simulated annealing process was shown in Fig. 1. It was not surprising that these results were similar to our previous report.

3.1. Simulation results of small particle systems

Fig. 2, Fig. 3 and Fig. 4 indicated the dissolution process of small particles of solid dispersions with three polymers. In the dissolution process, the carboxylic group of ibuprofen molecules turned its direction from polymer molecules to external water molecules and ibuprofen molecules slowly left the surface of the polymer coils. At the same time, all three polymer coils including PEG, POL and PVP became quickly relaxed and the polymer chains were released in the solution, which was in agreement with the assumption (a) [7]. Due to the less numbers of the polymer chain, the interaction between the chain-chain and chain-drug was weaker compare to larger particle system. When the particle was immersed in the aqueous condition, the polymer matrix had easily disentangled the random coils. At the same time, the water molecules quickly permeated into the carrier matrix, while the polymer and drug molecules rapidly dispersed and diffused into the water.

3.2. Simulation results of large particle systems

Fig. 5, Fig. 6 and Fig. 7 indicated the dissolution process of large particles of solid dispersion with three polymers. In the dis-

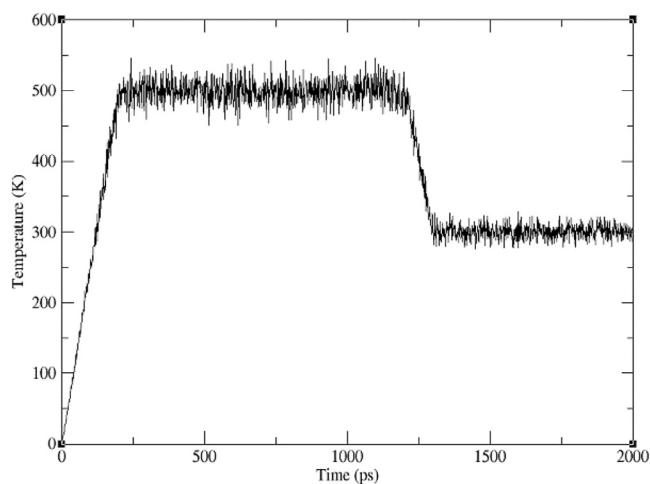


Fig. 1 – Temperature change vs time for the systems in the simulated annealing method.

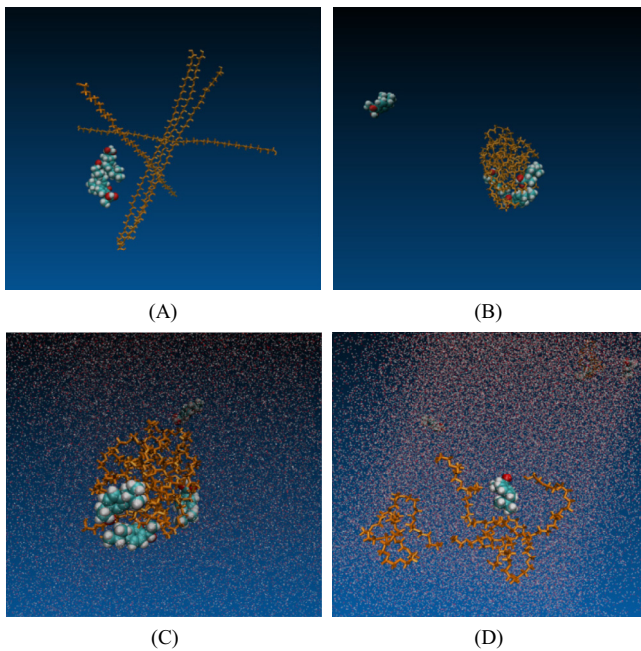


Fig. 2 – Simulation process of IBU-PEG small particle system (drug-polymer unit ratio 4:5, weight ratio 1:5). (A) Initial model of ibuprofen crystal and PEG system, (B) the solid dispersion system after simulated annealing process, (C) solid dispersion in aqueous phase at 0 ns, (D) solid dispersion in aqueous phase after 50 ns.

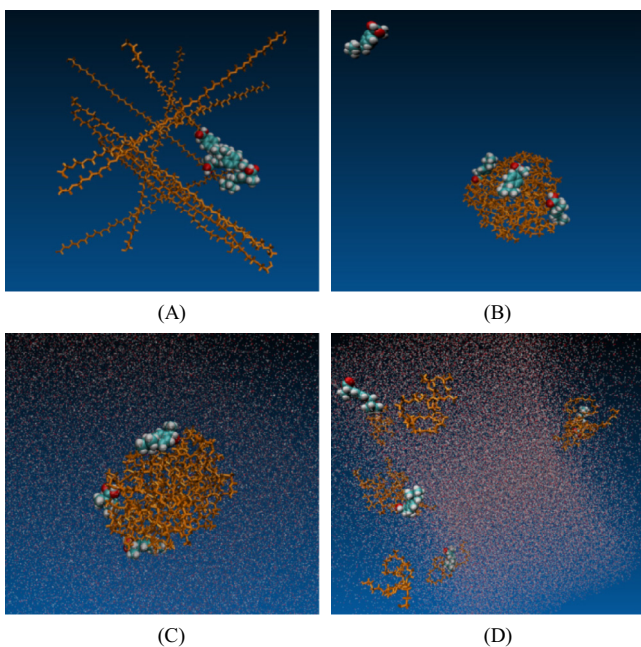


Fig. 3 – Simulation process of IBU-POL small particle system (drug-polymer unit ratio was 4:10, weight ratio 1:10). (A) Starting model of ibuprofen crystal and POL system, (B) the solid dispersion system after simulated annealing process, (C) solid dispersion in aqueous phase, (D) solid dispersion in aqueous phase after 50 ns.

solution process, more and more ibuprofen molecules in the large particles were gradually released from solid dispersion systems and the polymer coils increased the relaxed state with the time. However, large SD particles with different polymers presented various dissolution behaviors, which was different from small SD particles. The larger particle system of IBU-PEG and IBU-PVP showed the aggregation of drug molecules at the later stage of dissolution process, which may result in further recrystallization and low dissolution rate. In the preparation process of solid dispersions, it is clearly shown that the drug molecules were randomly dispersed on the surface of amorphous polymer coils by the simulated annealing method. However, the drug aggregation in the dissolution process indicated that the solid dispersion systems with PEG or PVP may have the recrystallization problem in the GI tract and then lead to the bioavailability issue. Previous studies investigated the reprecipitation inhibitory effect of three polymers (PEG 6000, PVP K30 and Eudragit) for patchouli alcohol supersaturated solutions [22]. The results showed that the inhibitory effect of PEG 6000 and PVP K30 was less effective than that of Eudragit.

3.3. Discussion of two dissolution behaviors in large particle systems

PEGs are semi-crystalline polymers of ethylene oxide and widely used in solid dispersions. However, it is quite interesting that PEG promotes crystallization for some compounds (e.g. ibuprofen, fenofibrate), which is different from other polymers for crystallization hindrance [23]. For PVP, recent research with ATR (Attenuated Total Reflection)-FTIR (Fourier-Transform-Infrared) spectroscopic imaging indicated that too fast dissolution of PVP/Aprepitant solid dispersion could negatively influence the bioavailability due to high local super-saturation and consequent recrystallization [24]. The good water affinity of PVP solid dispersions makes the polymer fast dissolving, which leads to phase separation and local recrystallization of the drug molecules [25]. Fig. 8B also showed that the gyration radius of IBU-PVP system increased much faster than another two systems after 20 ns, which also indicated that the PVP system dissolved more quickly than PEG and POL systems. Moreover, Fig. 9B showed that the overall mean square displacement plot of PVP was clearly increased sharply compared to PEG and POL systems, which also indicated that the displacement of the whole atoms in PVP system moved faster. The simulation results gave a clear molecular image of the aggregation and/or recrystallization process in solid dispersion systems with PEG or PVP.

For large particles with poloxamer, the drug and polymer molecules of poloxamer SD particles were gradually released and the drug remains amorphous form in the undissolved particles in 100 ns simulations, which is different from the systems with PEG and PVP. The possible reason is that amphiphilic property of poloxamer, as a nonionic surfactant, could effectively hinder the aggregation of drug molecules in the dissolution process. This result was also observed in the experimental studies. For example, solubility and dissolution rate of nifedipine/poloxamer solid dispersion were better than those of the systems with PEGs or cyclodextrin complex [26]. Furthermore, the increasing amount of Soluplus in the Aprepitant-Soluplus-PVP ternary solid dispersion systems could effectively

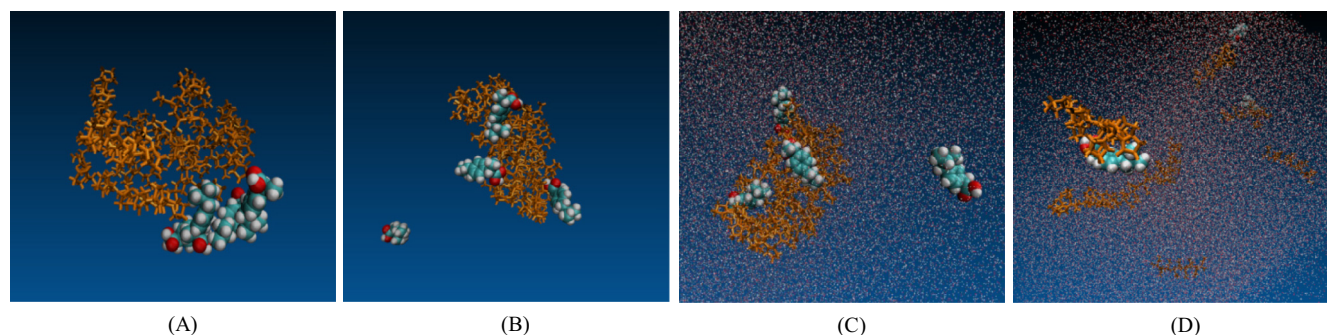


Fig. 4 – Simulation process of IBU-PVP small particle system (drug-polymer unit ratio was 4:8, weight ratio 1:10). (A) Starting model of ibuprofen crystal and PVP system, (B) the solid dispersion system after simulated annealing process, (C) solid dispersion in aqueous phase, (D) solid dispersion in aqueous phase after 50 ns.

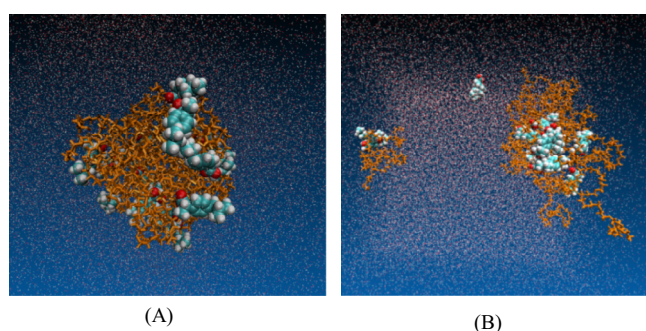


Fig. 5 – Simulated dissolution process of IBU-PEG large particle system (drug-polymer unit ratio was 16:20, weight ratio was 1:5). (A) IBU-PEG SD system in aqueous phase, (B) IBU-PEG SD system in aqueous phase after 100 ns.

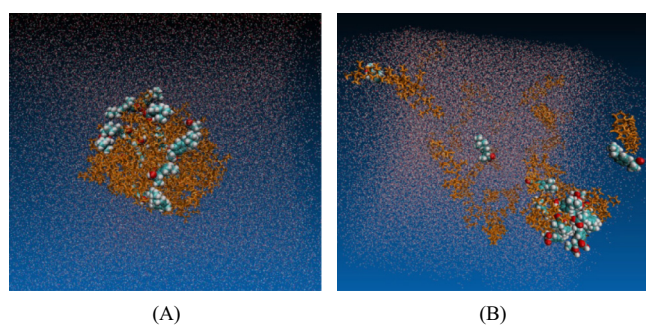


Fig. 6 – Simulated dissolution process of IBU-PVP large particle system (drug-polymer unit ratio was 16:32, weight ratio was 1:10). (A) IBU-PVP SD system in aqueous phase, (B) IBU-PVP SD system in aqueous phase after 100 ns.

delay the onset of recrystallization due to the amphiphilic nature of Soluplus [27]. Another experimental study indicated that hypromellose acetate succinate (HPMCAS) with the amphiphilic nature showed better stabilization of solid dispersions than that of hypromellose systems [28]. Thus, we can see that the amphiphilic polymer (e.g. poloxamer, Soluplus or HPMCAS) could effectively prevent the recrystallization in the dissolution process and may enhance the bioavailability of poorly soluble drugs in solid dispersions.

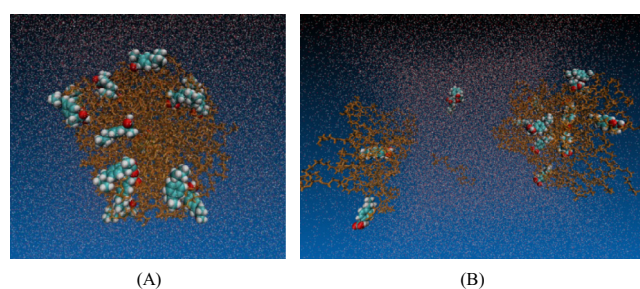


Fig. 7 – Simulated dissolution process of IBU-POL large particle system (drug-polymer unit ratio was 16:40, weight ratio was 1:10). (A) IBU-POL SD system in aqueous phase, (B) IBU-POL SD system in aqueous phase after 100 ns.

3.4. Combination of our simulation results and the three dissolution assumptions

Our simulation results indicated that the dissolution process of small SD particles agrees with the hypothesis (a), while large SD particles agreed with the hypotheses (b) and (c) [7]. The hypothesis (a) assumed that the drug and polymer molecules rapidly dissolved and dispersed in the aqueous solution. However, large SD particles with different polymers showed different dissolution behaviors. In the dissolution process, the drug molecules in the large particles with PEG or PVP easily shift and aggregate together, which was in consistency with the hypothesis (c) of drug recrystallization in the dissolution process [24,25,29]. The large SD particles with poloxamer could effectively hinder the aggregation of drug molecules in the dissolution process, indicated in hypothesis (b). Therefore, our simulations could effectively mimic the dissolution process of solid dispersion.

4. Conclusion

This research investigated the dissolution process of solid dispersion particles at molecular level. The results agreed with recent hypotheses of different dissolution mechanism of solid dispersions [7]. Our research will provide useful clues for future formulation development of solid dispersions.

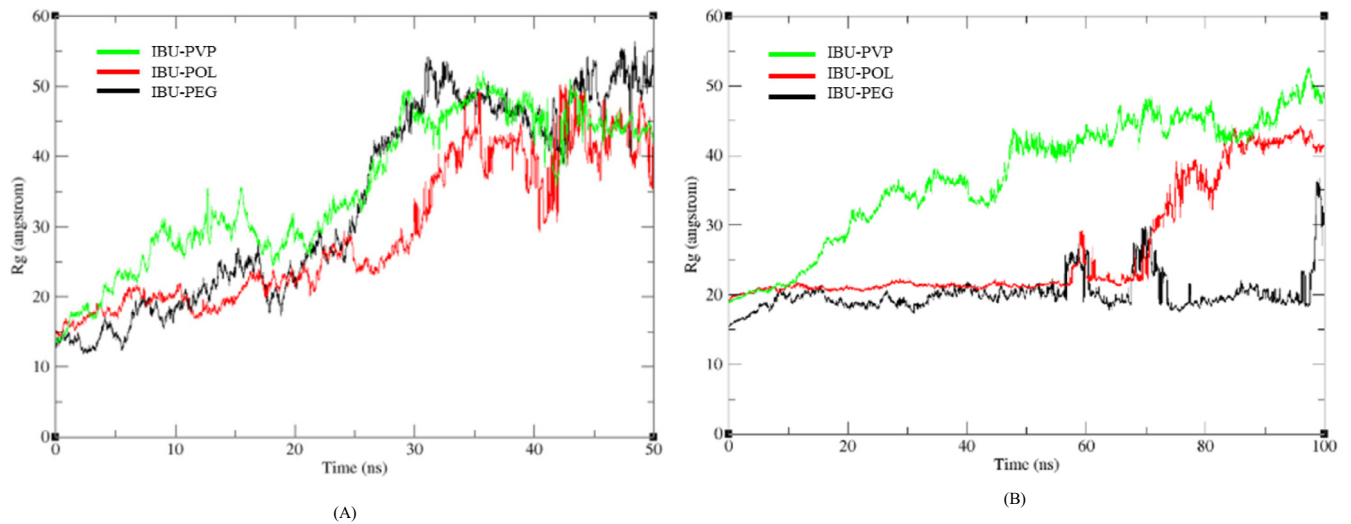


Fig. 8 – The mass-weighted radius of gyration of SD system in different size scale, with fluctuation as a function of time. (A) Small particle size system, (B) larger particle size system.

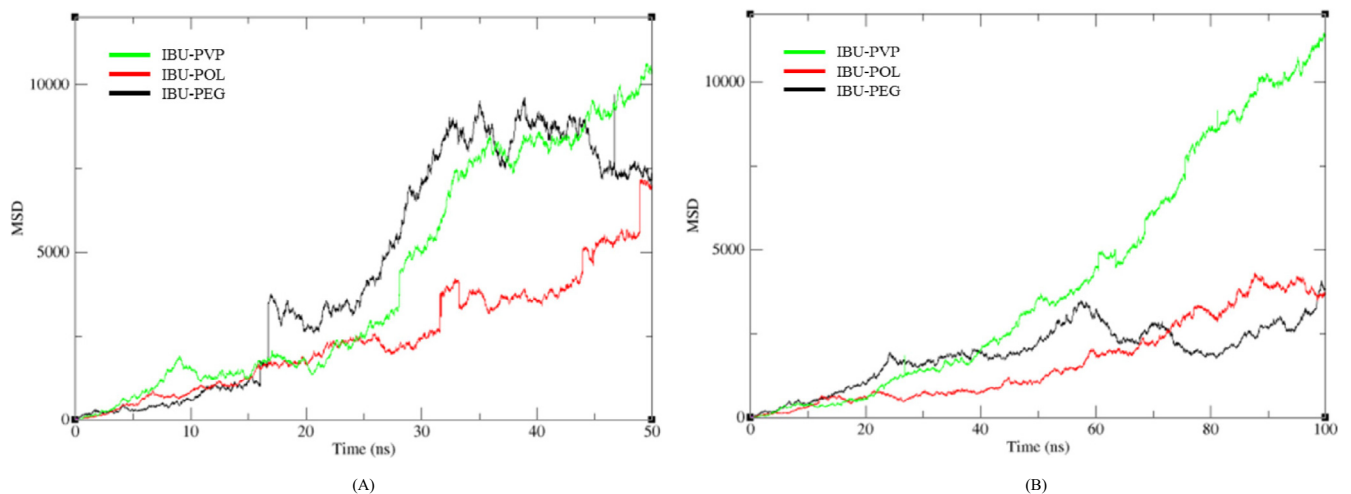


Fig. 9 – The overall mean square displacement plot of SD system in different size scale, with fluctuation as a function of time. (A) Small particle size system, (B) larger particle size system.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Acknowledgment

University of Macau research grants (MYRG2016-00038-ICMS-QRCM and MYRG2016-00040-ICMS-QRCM) are gratefully acknowledged for providing financial support.

REFERENCES

- [1] Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discov Today* 2007;12:1068–75.
- [2] Lakshman JP, Cao Y, Kowalski J, et al. Application of melt extrusion in the development of a physically and chemically stable high-energy amorphous solid dispersion of a poorly water-soluble drug. *Mol Pharm* 2008;5:994–1002.
- [3] Medarević DP, Kachrimanis K, Mitrić M, et al. Dissolution rate enhancement and physicochemical characterization of carbamazepine-poloxamer solid dispersions. *Pharm Dev Technol* 2016;21:268–76.

- [4] Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem Pharm Bull* 1961;9:866–72.
- [5] Mitra A, Li L, Marsac P, et al. Impact of polymer type on bioperformance and physical stability of hot melt extruded formulations of a poorly water soluble drug. *Int J Pharm* 2016;505:107–14.
- [6] Craig DQ. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int J Pharm* 2002;231:131–44.
- [7] Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. *J Pharm Sci* 2016;105:2527–44.
- [8] Leach AR. *Molecular modelling: principles and applications*. 2nd ed. Prentice Hall; 2001. p. 1–25 [Chapter 1].
- [9] Maus M, Wagner KG, Kornherr A, et al. Molecular dynamics simulations for drug dosage form development: thermal and solubility characteristics for hot-melt extrusion. *Mol Simul* 2008;34:1197–207.
- [10] Fule R, Amin P. Development and evaluation of lafutidine solid dispersion via hot melt extrusion: investigating drug-polymer miscibility with advanced characterisation. *Asian J Pharm Sci* 2014;9:92–106.
- [11] Shahzad Y, Sohail S, Arshad MS, et al. Development of solid dispersions of artemisinin for transdermal delivery. *Int J Pharm* 2013;457:197–205.
- [12] Fule R, Amin P. Hot melt extruded amorphous solid dispersion of posaconazole with improved bioavailability: investigating drug-polymer miscibility with advanced characterisation. *Biomed Res Int* 2014;doi:10.1155/2014/146781.
- [13] Gong C, Deng S, Wu Q, et al. Improving antiangiogenesis and anti-tumor activity of curcumin by biodegradable polymeric micelles. *Biomaterials* 2013;34:1413–32.
- [14] Gong C, Xie Y, Wu Q, et al. Improving anti-tumor activity with polymeric micelles entrapping paclitaxel in pulmonary carcinoma. *Nanoscale* 2012;4:6004–17.
- [15] Maniruzzaman M, Pang J, Morgan DJ, et al. Molecular modeling as a predictive tool for the development of solid dispersions. *Mol Pharm* 2015;12:1040–9.
- [16] Fule R, Meer T, Sav A, et al. Solubility and dissolution rate enhancement of lumefantrine using hot melt extrusion technology with physicochemical characterisation. *J Pharm Investig* 2013;43:305–21.
- [17] Xiang TX, Anderson BD. Molecular dynamics simulation of amorphous indomethacin-poly (vinylpyrrolidone) glasses: solubility and hydrogen bonding interactions. *J Pharm Sci* 2013;102:876–91.
- [18] Maniruzzaman M, Snowden MJ, Bradley MS, et al. Studies of intermolecular interactions in solid dispersions using advanced surface chemical analysis. *RSC Adv* 2015;5:84936.
- [19] Ouyang D. Investigating the molecular structures of solid dispersions by the simulated annealing method. *Chem Phys Lett* 2012;554:177–84.
- [20] Hansen LK, Perlovich GL, Bauer-Brandl A. Redetermination and H-atom refinement of (S)-(+)-ibuprofen. *Acta Crystallogr Sect E Struct Rep Online* 2003;59:o1357–8.
- [21] Martinez L, Andrade R, Birgin EG, et al. PACKMOL: a package for building initial configurations for molecular dynamics simulations. *J Comput Chem* 2009;30:2157–64.
- [22] Chen YL, Liao JB, Liang YZ, et al. Characterization of solid dispersions of Patchouli alcohol with different polymers: effects on the inhibition of reprecipitation and the improvement of dissolution rate. *Drug Dev Ind Pharm* 2015;41:436–44.
- [23] Zhu Q, Harris MT, Taylor LS. Modification of crystallization behavior in drug/polyethylene glycol solid dispersions. *Mol Pharm* 2012;9:546–53.
- [24] Punčochová K, Ewing AV, Gajdošová M, et al. Identifying the mechanisms of drug release from amorphous solid dispersions using MRI and ATR-FTIR spectroscopic imaging. *Int J Pharm* 2015;483:256–67.
- [25] Punčochová K, Vukosavljevic B, Hanuš J, et al. Non-invasive insight into the release mechanisms of a poorly soluble drug from amorphous solid dispersions by confocal Raman microscopy. *Eur J Pharm Biopharm* 2016;101:119–25.
- [26] Chutimaworapan S, Ritthidej GC, Yonemochi E, et al. Effect of water-soluble carriers on dissolution characteristics of nifedipine solid dispersions. *Drug Dev Ind Pharm* 2000;26:1141–50.
- [27] Punčochová K, Ewing AV, Gajdošová M, et al. The combined use of imaging approaches to assess drug release from multicomponent solid dispersions. *Pharm Res* 2017;34:990–1001.
- [28] DiNunzio JC, Hughey JR, Brough C, et al. Production of advanced solid dispersions for enhanced bioavailability of itraconazole using KinetiSol Dispersing. *Drug Dev Ind Pharm* 2010;36:1064–78.
- [29] Qian F, Wang J, Hartley R, et al. Solution behavior of PVP-VA and HPMC-AS-based amorphous solid dispersions and their bioavailability implications. *Pharm Res* 2012;29:2766–76.