Molecular Simulation of Structure and Loading-Drug Character of Poly(propylene-*co*-γ-butyrolactone carbonate)

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ABSTRACT: Based on COMPASS forcefield, the relationship between microstructure and macroscopic properties of poly(propylene-*co*-γ-butyrolactone carbonate) (PPCG) was investigated by ''Materials Studio'' simulation soft successfully for the first time. The results of simulation showed that the molecular chain of PPCG was flexible. Degradable carbonic and carboxylic ester groups were distributed outside the PPCG cell. Furthermore, the structure of microphase separation was observed in PPCG cell. The ''Materials Studio'' also simulated and calculated the reciprocity between PPCG and caffeine molecule. It was further found that the caffeine molecule was selectively distributed among the segment of carbon dioxide (CO_2) rather than the segment of γ-butyrolactone (GBL). So the microphase separation structure of PPCG can be applied to the self-assembly of drug molecule. And the conclusion offered a theoretical basis for the self-assembly behavior of drug molecule. In a word, the results of molecular simulation not only verified the experimental conclusions, but also showed a clear description of the relationships between molecular structure and macroscopic properties of PPCG. Moreover, it offered a reference for studying the reciprocity between carrier and drug molecule further. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 872–880, 2008

Key words: poly(propylene-*co*-γ-butyrolactone carbonate); molecular modeling; structure–property relations

INTRODUCTION

In the polymer carrier, the sites of drug molecules are affected by many factors such as microphase structure, compatibility between drug and monomer, solubility of drug in the polymer, and so on. The microphase structure is the key factor in loading and control-releasing drug.[1] Hence, the study on the reciprocity between drug and carrier is very important for discovering the releasing characters of drug from carriers and for achieving control-releasing drug. Molecular simulation is a useful tool to understand the relationship between microstructure and functions of materials. It can discover the relationship between microstructure and macroscopic properties of materials and offer necessary and reliable proofs. Besides theoretical analysis and experimental test, molecular simulation computation has also become one of the effective methods in present science research.[2]

In this article, poly(propylene-*co*-γ-butyrolactone carbonate) (PPCG), which had been successfully synthesized in our previous experiment, became the object of molecular simulation using the molecular simulation soft ''Materials Studio 3.0'' (MS Modeling). The basic molecular structure of PPCG was shown in Figure 1. The relationship between PPCG structure and properties was found by molecular simulation from the micropoint of view. Moreover, based on PPCG loading-caffeine successfully in our previous experiment,[3] the loading-drug character of PPCG was probed into further by the molecular simulation with caffeine as the drug model. The relationship between PPCG structure and loading-drug character was discovered from a micropoint of view.

PRINCIPLE AND METHOD OF SIMULATION

MS Modeling allows you to easily create and study models of molecular structures to perform atomistic simulations on complex systems and predict main properties. The modules ''Discover'' and ''Amorphous Cell'' of MS Modeling were applied in simulation and analytical computation of the polymer structure and properties in our study. In the process of simulation, the forcefield of molecular mechanics (MM) and molecular dynamics (MD) is COMPASS forcefield. COMPASS is a powerful forcefield that can support atomistic simulations of condensed phase materials. COMPASS is short for Condensed-phase

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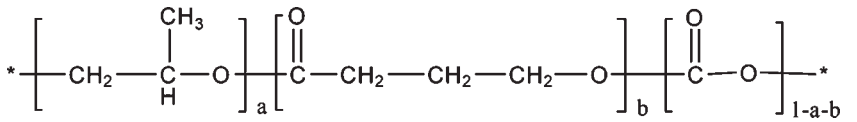


Figure 1 Basic structure and linkage type of random tricopolymer PPCG.

Optimized Molecular Potentials for Atomistic Simulation Studies. COMPASS is the first *ab initio* forcefield that has been parameterized and validated using condensed-phase properties in addition to various *ab initio* and empirical data for molecules in isolation. Consequently, this forcefield enables accurate and simultaneous prediction of structural, conformational, vibrational, and thermophysical properties for a broad range of molecules in isolation and in condensed phases and under a wide range of conditions of temperature and pressure.

Utilizing ''Theodorou and Suter''' method,[4,5] the model of amorphous polymer structure was built up by the minimum reflection measure and the periodic border condition.[6] The model was validated by XRD and glass transition temperature (T_g). To reduce the simulating time during which the balance was obtained and get effective statistical average of computational properties, firstly various models whose density was lower than experimental were built up. And then the model, whose ultimate optimize energy was lowest, was selected as the next researched object. The selected model was processed with the rotative MM and MD about 5–10 times at a high temperature (370 K). The aim was to make the structure achieve optimization gradually through the repeating high temperature process, and underwent some times high temperature relaxation and minimizing energy. The cohesion energy density (CED) of the model was calculated after each circulation until CED was stabile at some extent without increase. Then the above process was repeated at room temperature (298 K), whereas the density of the model was changed to the experimental data. The CED was also calculated and analyzed by the same means. Ultimately the optimized and stabile model was obtained. Based on the reasonable and proper model, the structure and properties of PPCG model were analyzed. Moreover the structure and properties of PPCG loading-caffeine (PPCG-caffeine) system were also analyzed, and the reciprocity between PPCG and caffeine was discussed.

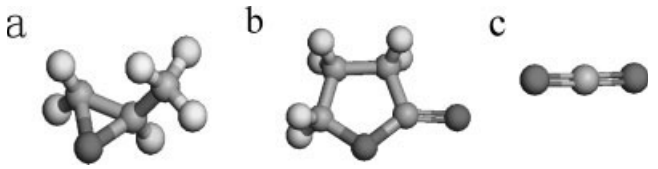


Figure 2 3D models of propylene oxide (a), γ-butyrolactone (b), and carbon dioxide (c) molecular structures. (Gray: carbon atom; white: hydrogen atom; black: oxygen atom).

RESULTS

Simulation of PPCG molecular structure

Build of the PPCG cell

The PPCG, which was simulated by computer as the ratio of three monomers propylene oxide (PO), γ-butyrolactone(GBL), carbon dioxide(CO_2) was 48:36:16. The 3D molecular models of PO, GBL, and CO_2 were shown in Figure 2.

The PPCG amorphous random copolymer chain whose length was 20 was built by MS Modeling as shown in Figure 3. Besides C—C bonds, the chain were mainly composed of carbonic ester group and carboxylic ester group. Otherwise, there were a few ether linkages which were formed by the copolymerization or homopolymerization of PO and GBL. The structural character of PPCG chain was consistent

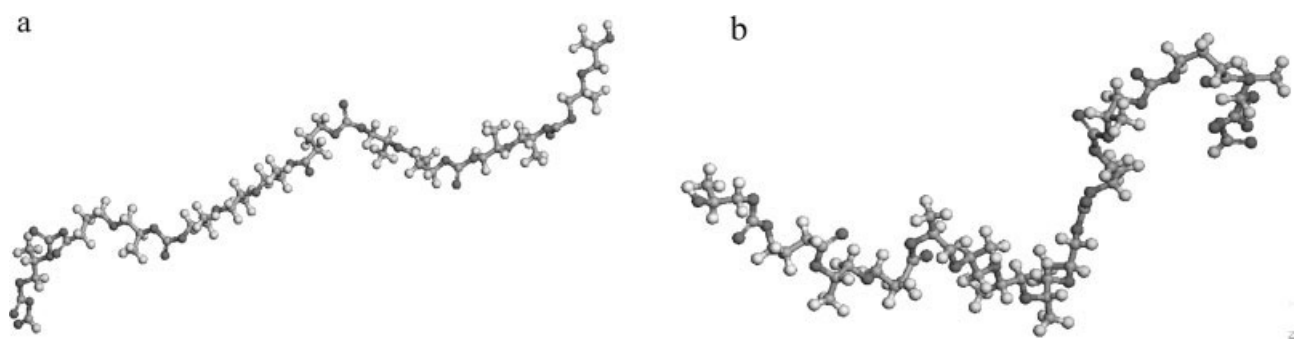


Figure 3 3D models of primal (a) and optimized (b) PPCG molecular chain in length 20. (Gray: carbon atom; white: hydrogen atom; black: oxygen atom).

TABLE I
Energy Distribution of Optimized PPCG Structure Unit

Total potential energy at −375.84 kcal/mol				Total nonbond at −278.30 kcal/mol			
Electrostatic	vdW repulsive	vdW dispersive	Hydrogen bond	Angle	Bond	Torsion	Out-of-plane
−303.98	232.12	−206.44	0.00	68.93	7.75	−147.73	0.57

with the experimental conclusion in previous research.[7,8]

After MM and MD circulation and optimization several times, the structure model of Figure 3(a) was turned into the stabile PPCG chain model, as shown in Figure 3(b). Its energy distribution and value were listed in Table I. It can be inferred form Table I that PPCG molecular chain had good extendibility, good flexibility, and yield. This result was consistent with the result observed from experimental sample.

The PPCG cell was composed of the optimized PPCG chain model. The PPCG cell model also underwent MM and MD circulation for several times. Then its CED increased and reached a stabile value of 12,242.68 J/cm^3. Thus, the stabile and optimized PPCG cell model was obtained (as shown in Fig. 4).

Validation of the PPCG cell model

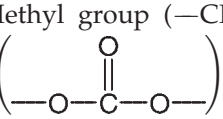
The XRD spectrum and glass transition temperature of the PPCG cell model were calculated by computer. The contrast of this result and the experimental data could verify the validity of the model.

The calculated XRD spectrum of the optimized PPCG cell model was as shown in Figure 5(b). The shape and the main shifts of the calculated XRD spectrum were very close to the experimental XRD spectrum as shown in Figure 5(a). The main 2θ shifts of the experimental and the calculated XRD spectrum were 21.26° and 23.62°, respectively. The main difference between the two spectra was the intensity of peaks because of the difference of the quantity.

The optimized PPCG cell model, which was obtained at 298 K, experienced a process during which the temperature decreased from 400 to 200 K. Thus the specific volume of the PPCG cell with the change of temperature was recorded (as shown in Fig. 6). The junction of two lines showed that the T_g of the PPCG cell was 307 K, which was very close to the experimental T_g 303.55 K.

Therefore, according to the validation with XRD and T_g, the simulative PPCG cell model by computer was consistent with the actual PPCG cell.

Concentration distribution function

To find out structural characters of PPCG, the concentration distribution functions (CDF) of three monomers in the PPCG cell were calculated and analyzed. The distributions of three monomers in the PPCG cell were discussed. Methyl group (—CH_3) of PO, carbonic ester group  including CO_2, and C4 chain (—CH_2—CH_2—CH_2—CH_2—) of GBL were selected as the observed points. The CDFs of PO, CO_2, and GBL were shown in Figure 7 respectively. From Figure 7, it was observed that the surface of the PPCG cell was full of CO_2 monomers, while the quantity of GBL monomer was small, and there were mainly PO monomers inside the PPCG cell. GBL and CO_2 monomers, which offered PPCG polymer good degradability, were distributed at the surface of the PPCG cell and could meet with the outside media sufficiently. The structural character provided good degradability to PPCG polymer. In our previous experimental research, it had been verified that PPCG with GBL monomer had better degradability than polypropylene carbonate (PPC) that polymerized with only PO and CO_2.[7,8]

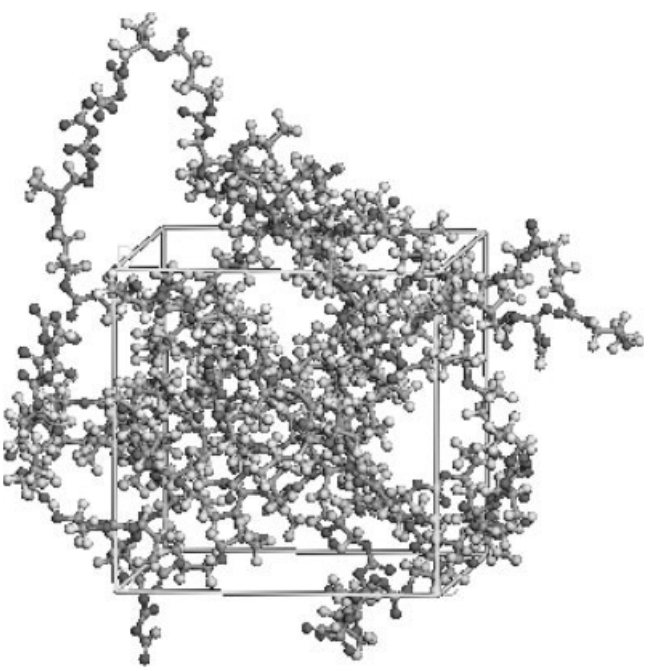


Figure 4 3D structural model of the PPCG cell. (Gray: carbon atom; white: hydrogen atom; black: oxygen atom).

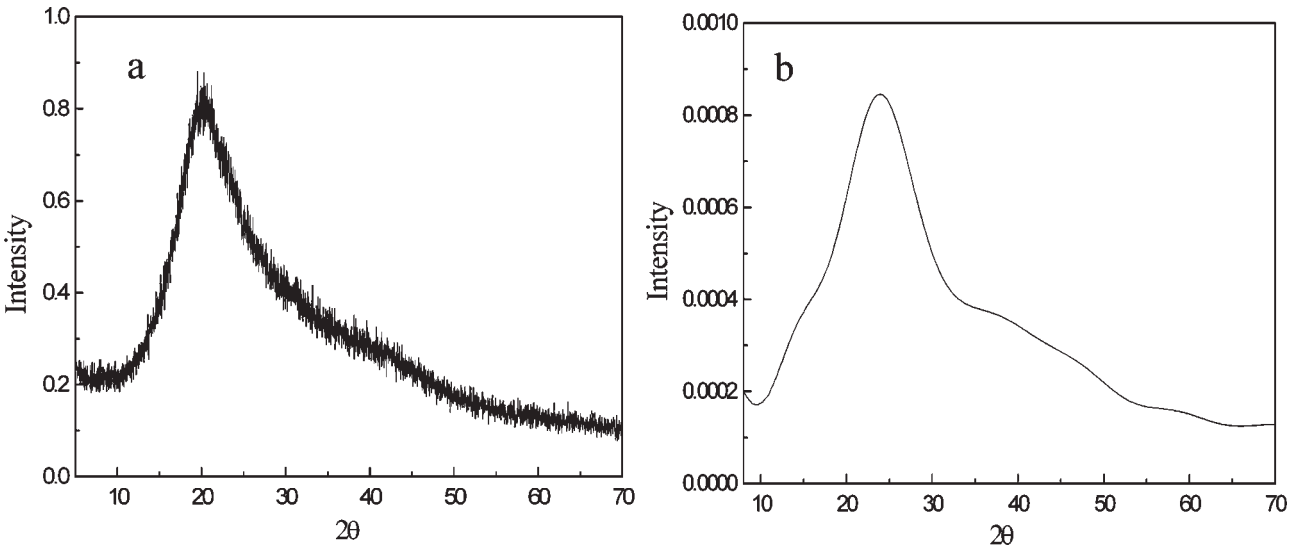


Figure 5 Experimental (a) and calculated (b) XRD spectra.

Pair correlation function

Pair correlation function (PCF) can reflect the microstructure of polymer directly. According to PCF, the relative position of two parts in the polymer cell, such as atoms, structural fractions, and molecular chains, can be observed. Consequently the structural character of the polymer cell can be theoretically estimated.

The observed points of three monomers in PCF were similar to that in CDF. PCF of PO and CO_2, PCF of PO and GBL, and PCF of CO_2 and GBL were calculated, respectively. The results were shown in Figures 8–10. In these figures, (b) was the local enlarged image of (a).

Figure 8(a) showed that there were mainly PO monomer units around PO within 2 Å and there were mainly CO_2 monomer units around CO_2 within 2.5 Å. But in Figure 8(b), the probability of CO_2 was larger than that of PO around PO in the range of 7–10 Å. The probability of CO_2 reached maximum at 7.7 Å. In Figure 9(a), there were mainly PO monomer units around PO within 2 Å, and there were mainly GBL monomer units around GBL within 3 Å. But in Figure 9(b), it was observed that the probability of GBL around PO increased from 2.8 Å and extended the probability of PO around PO in the range of 3–6.5 Å.

Figure 10(a) was similar to Figure 8(a) and Figure 9(a). There were mainly GBL monomer units around GBL within 3 Å and there were mainly CO_2 monomer units around CO_2 within 2.5 Å. In Figure 10(b), the probability of CO_2 around GBL increased from 2 to 6 Å and reached a maximum at 2.4 Å. The probability was comparatively large, from 3.2 to 6 Å.

According to the above discussion, we could find out that in the short distance (less than 3 Å), the tricopolymer PPCG was composed of PO homopolymer segment, GBL homopolymer segment, CO_2 homopolymer segment, and tricopolymer of three monomers, whose proportions in the tricopolymer PPCG went from the highest to the lowest.

However, the appearance probability of tricopolymer increased a lot in the range of 3–6 Å, and the tricopolymer structure became the main structure of the PPCG cell. The copolymer structure of PO and CO_2 increased from 7 to 10 Å, and its probability reached maximum in 7.7 Å, which was still less than that of other copolymers. Therefore it could be deduced that there were mainly tricopolymer structures of PO, CO_2, and GBL in PPCG copolymer. And there were also aggregations of some monomers' structures, especially the aggregation of PO structure. Hence, the

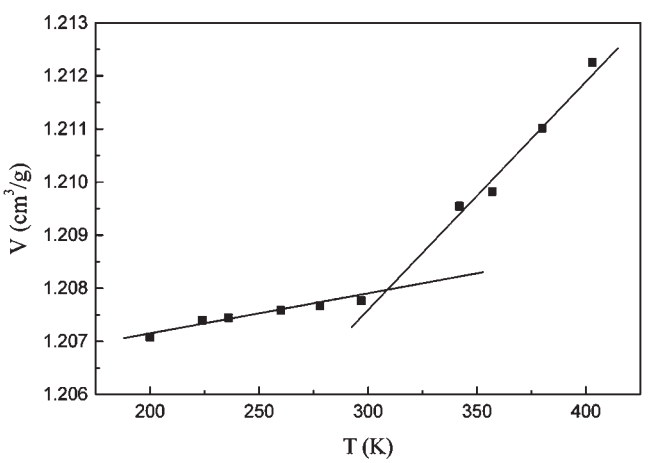


Figure 6 Relation curve between specific volume and temperature of PPCG unit model.

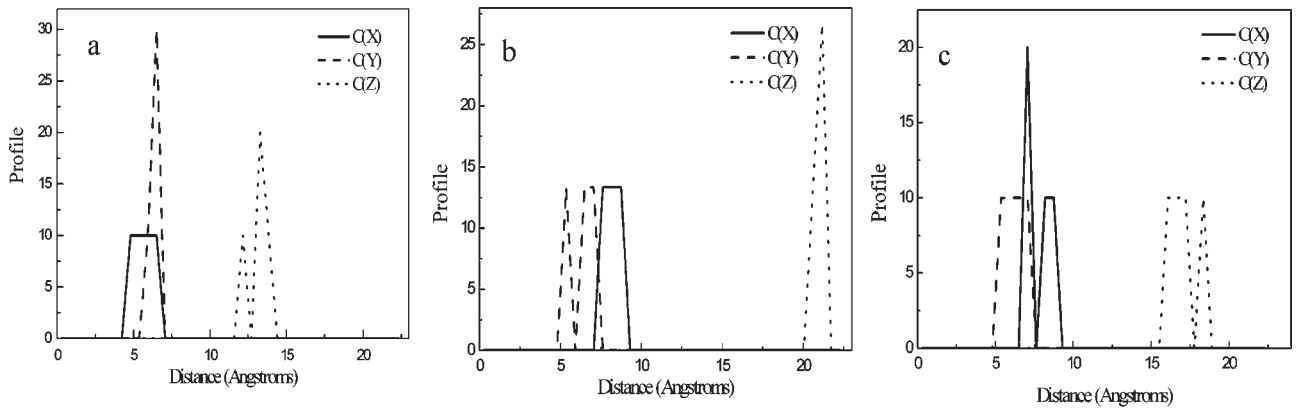


Figure 7 Concentration distribution functions of PO (a), CO_2 (b), GBL (c) in PPCG unit.

PPCG cell had the structural character of the microphase separation.

The research of Shen et al.[9] indicated that drug controlling–releasing system of polyanhydrides could present the structural character of the microphase separation at some condition. Moreover, because of the difference of two monomers in the copolymer, various drugs can be selectively distributed among the special microphase separation regions. Thereby a new drug controlling–releasing technology becomes possible, by which a carrier can transport two various drugs at the same time. Therefore the scientific significance of the copolymers with the structural character of the microphase separation is overwhelming. Consequently PPCG, as a new copolymer, would have the most important practical benefit and great potential in the field of the drug controlling–releasing technology.

Molecular simulation of the loading drug system PPCG–caffeine

The 3D structure of the caffeine molecule was shown in Figure 11. The balance stable models of PPCG–caffeine[51] system (the ratio of PPCG molecule and caffeine molecule was 5 : 1) and PPCG–caffeine12 system (the ratio of PPCG molecule and caffeine molecule was 1 : 2) were built respectively, with the same method as used before, and were shown in Figure 12.

The reciprocity between PPCG and caffeine were investigated by CDF and PCF. The whole molecule of caffeine and PPCG chain were selected as the observed points. Other observed points of three monomers (PO, CO_2, and GBL) were the same as previous. The PCF of caffeine and PPCG, and three monomers and caffeine, and the CDF of caffeine in the PPCG cell were calculated and analyzed respectively.

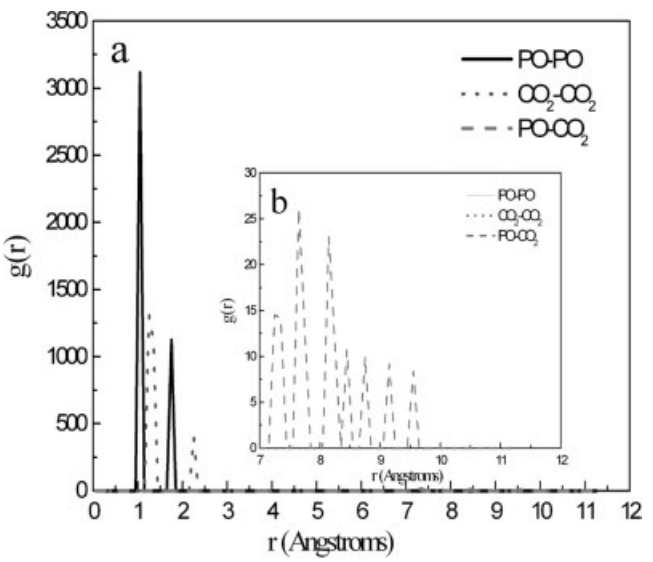


Figure 8 PCF of PO and CO_2.

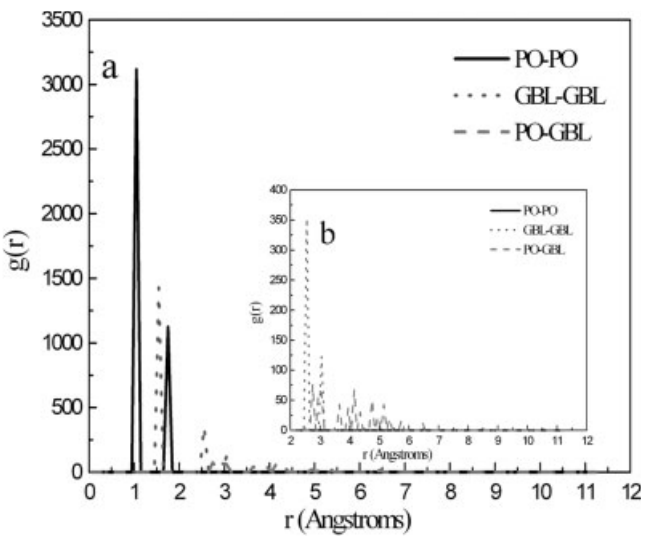


Figure 9 PCF of PO and GBL.

The PCF between caffeine and PPCG of two systems were shown in Figures 13 and 14. In these figures, (b) was the local enlarged image of (a).

It was observed from Figure 13 and Figure 14 that the probability of caffeine molecule around caffeine molecule was higher than PPCG around caffeine molecule in the 0–7 Å range, whether the caffeine concentration was high or low. Up to 8 Å there was never simple reciprocity among caffeine molecules, but both the reciprocity among PPCG molecules and the reciprocity between PPCG molecule and caffeine molecule increased evidently. In the low caffeine concentration system, the probability of caffeine around PPCG was higher than that of PPCG around PPCG. It meant that the reciprocity between PPCG and caffeine was greater than that between PPCG and PPCG. Although in the high caffeine concentration system, the probability of caffeine around PPCG was almost equal to the probability of PPCG around PPCG, it meant that the two reciprocities were similar. Consequently it could be deduced that the dispersed extent of caffeine in the high concentration system was greater than that in the low concentration system. As shown in Figure 15, it could also be observed that the dispersed extent of caffeine in the low concentration system was more convergent than that in the high concentration system.

Taking the PPCG-caffeine12 system as the example, PCF of caffeine molecule and three monomers in PPCG was calculated and the results were shown in

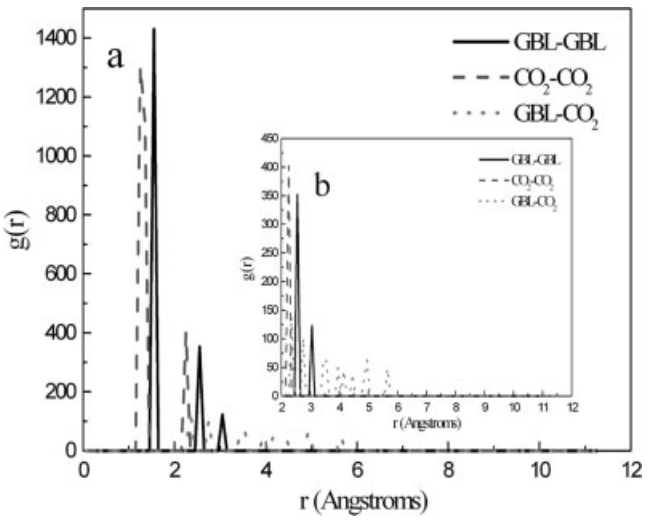


Figure 10 PCF of GBL and CO_2.

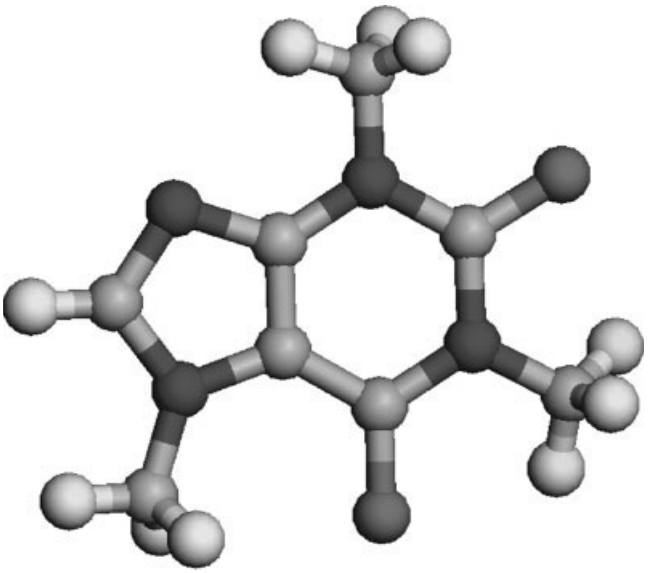


Figure 11 3D model of caffeine molecule. (Gray: carbon atom; white: hydrogen atom; black: oxygen atom; leaden: nitrogen atom).

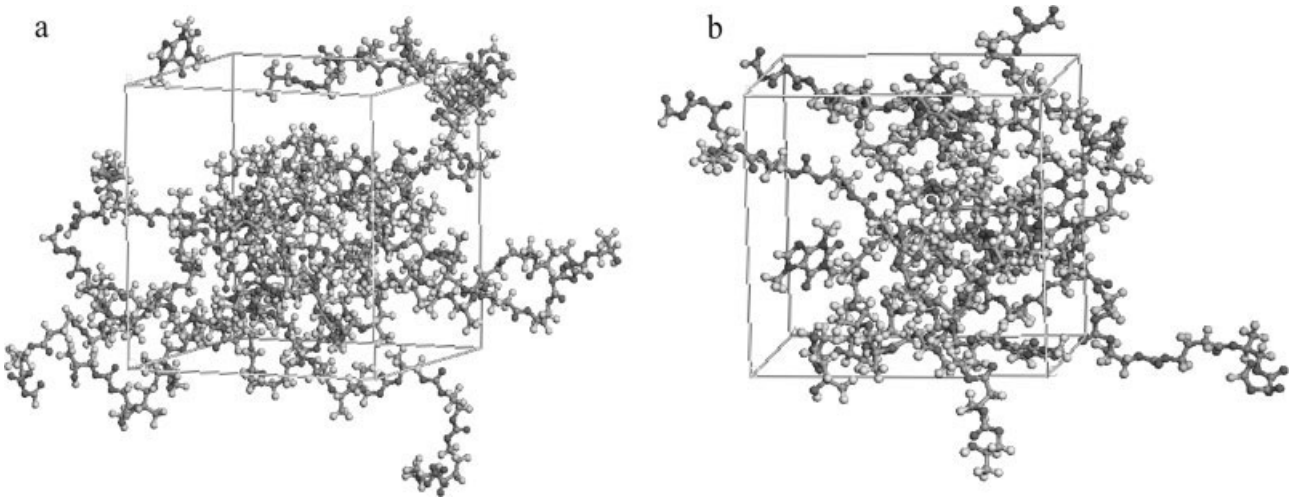


Figure 12 3D models of PPCG-caffeine51 (a) and PPCG-caffeine12 (b). (Gray: carbon atom; white: hydrogen atom; black: oxygen atom; leaden: nitrogen atom).

Figures 16–18. In these figures, (b) was the local enlarged image of (a). It could be observed that in the range of 11.5–12.5 Å there were three interaction peaks of PO-caffeine, and the largest peak value was 1.7. And many interaction peaks of CO_2-caffeine appeared in the range of 8–12.5 Å, and its largest peak value was 5.2. Hence, the interaction peak of CO_2-caffeine was larger than that of PO-caffeine, and the probability of caffeine around CO_2 was far higher than that of caffeine around PO. Otherwise, the obvious interaction peak of GBL-caffeine could not be observed in the PCF between GBL and caffeine (Fig. 18).

Thereby, it could be confirmed that the caffeine molecule distributed in the PPCG cell and the segment CO_2 interacted with each other. At the same time some caffeine molecules and the segment of PO also interacted with each other. But few caffeine molecules and the segment of GBL interacted with each other. So the interaction between CO_2 and caffeine was strongest, whereas the interaction between PO and caffeine was weakest. Because of the local aggregations of some monomer structures in PPCG (that was the structural character of the microphase separation) and the rich phase PO in the PPCG cell, there must be some PO that appeared at the CO_2 segment,

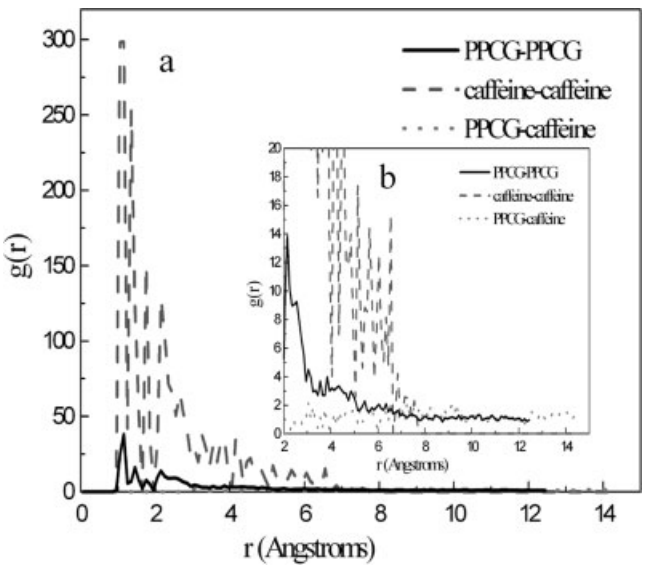


Figure 13 PCF between PPCG and caffeine in PPCG-caffeine51 system.

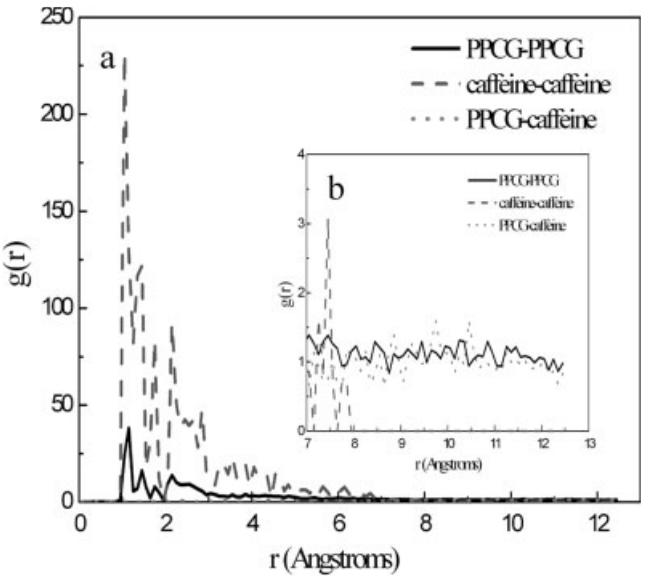


Figure 14 PCF between PPCG and caffeine in PPCG-caffeine12 system.

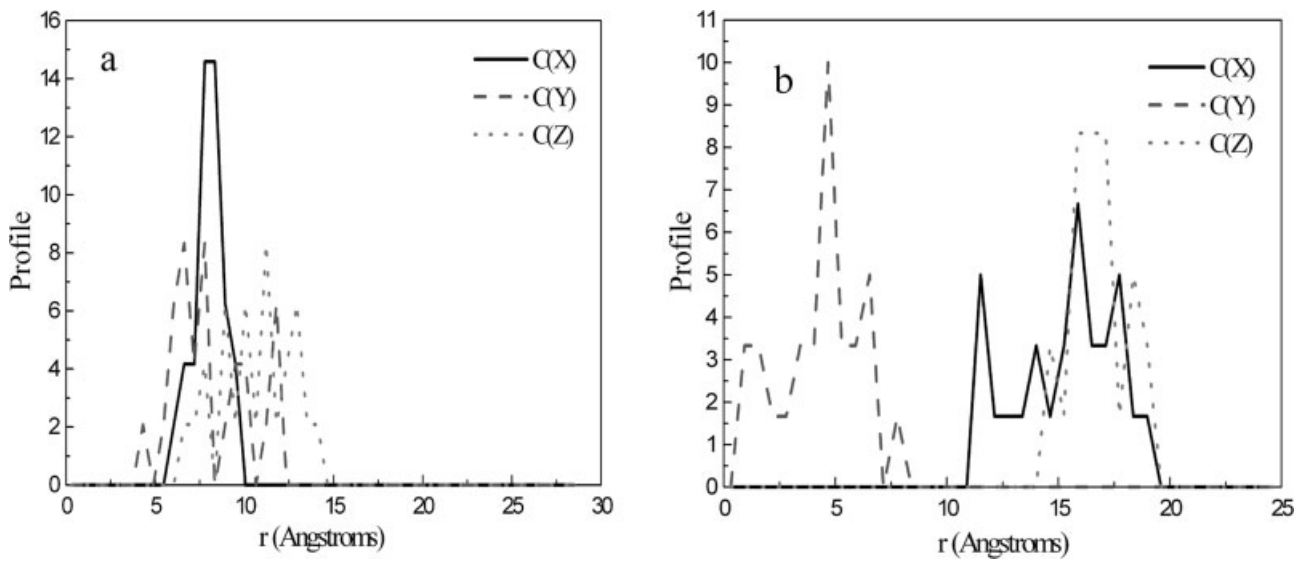


Figure 15 CDF of caffeine in PPCG-caffeine51 (a) and PPCG-caffeine12 (b), respectively.

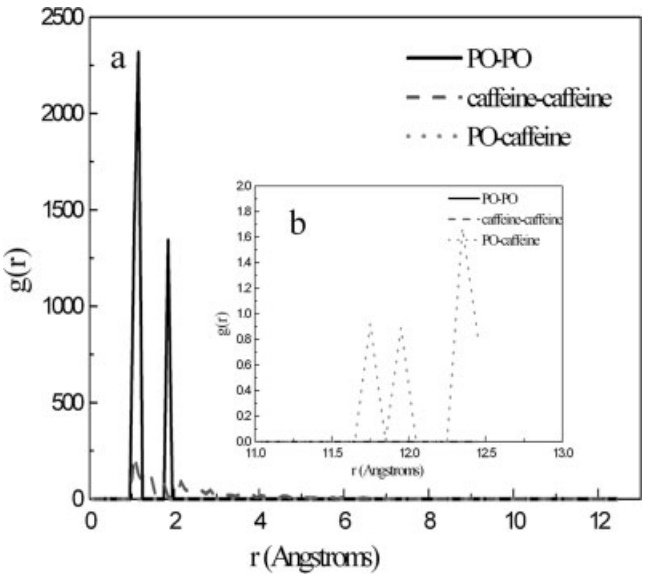


Figure 16 PCF of PO and caffeine.

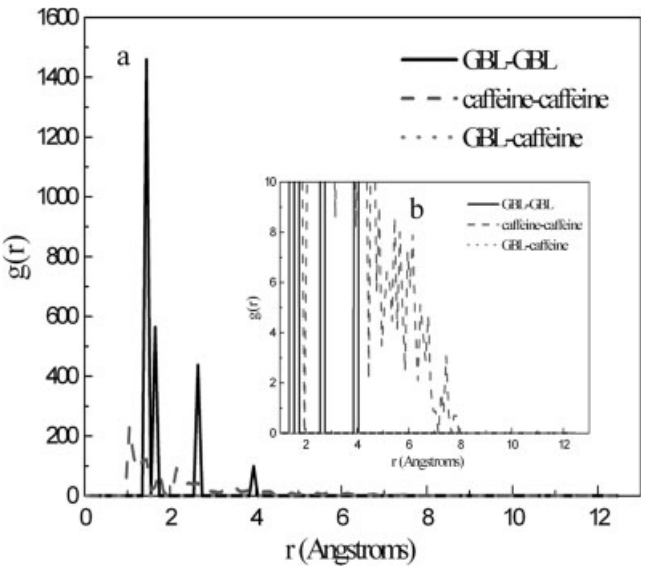


Figure 18 PCF of GBL and caffeine.

and PO was the lean phase comparatively in the CO_2 segment. In this region, a few PO structures bedded themselves in the CO_2 structural segment. Thus a few PO were distributed around caffeine. It is the reason why a few weak peaks of PO-caffeine appeared on the site where CO_2 and caffeine interacted with each other.

According to the above discussion, drug molecules, caffeine aggregated mainly at the CO_2 segment of the PPCG cell, and almost never at the GBL segment. But a few drug molecules aggregated at the PO segment. So it could be confirmed that caffeine molecules were selectively distributed in the CO_2 segment in the PPCG cell. And the GBL segment without caffeine molecules could be used to carry the other drug molecule. Consequently different drugs could be distributed into different positions in a PPCG carrier. It meant that a carrier could transport two different drugs at the same time. This offered a new direction for the drug controlling–releasing system.[9]

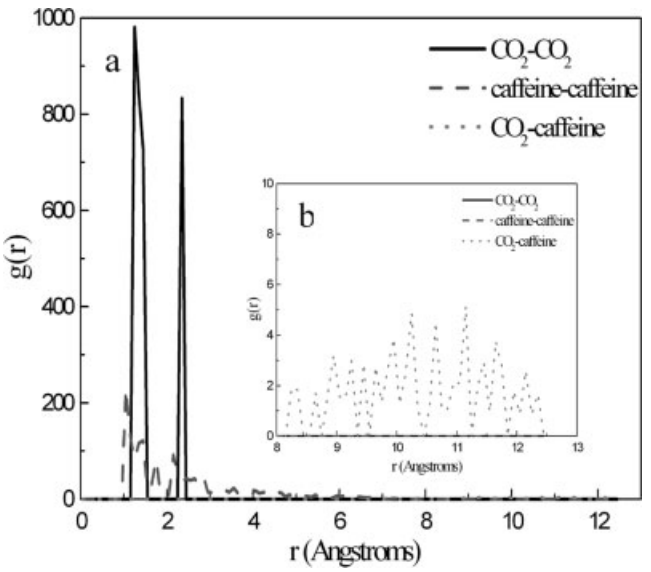


Figure 17 PCF of CO_2 and caffeine.

CONCLUSION

Based on previous experiments, the new tricopolymer PPCG was simulated by the soft ''Materials Studio'' and its characters, such as structure, degradability, and drug loading property, were analyzed deeply. Through simulation and analyses, it can be validated in theory that PPCG molecular chain was flexible and linear. And the molecular chain was composed of degradable carbonic and carboxylic ester groups, which made PPCG polymer degradable and were distributed at the surface of the PPCG cell. The copolymer structure was mainly composed of PO–CO_2–GBL linkage as well as aggregation of some monomers, such as PO aggregation. Hence, the PPCG cell had the structural character of the microphase separation. Because of this character, most caffeine molecules were selectively distributed among the CO_2 segment, and none in the GBL segment. Therefore, it is hopeful to realize the self-assembly of drugs and the synchronized carry of different drugs with the microphase separation structure of PPCG. The simulative result by computer is not only consistent to experimental conclusion, but also shows a clear description of the relationships between molecular structure and macroscopic properties of PPCG. Moreover, it offered the theoretical base and method for studying the reciprocity between carrier and drug molecule further.

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