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RESEARCH ARTICLE

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Synthesis of AB_2 star-shaped miktoarm copolymers and their crystallization behavior

Abstract A small molecule (GMS-SA_2) with one alkyl chain and two terminal carboxyl groups was synthesized successfully by the reaction of glyceryl monostearate (GMS) with excess succinic anhydride (SA). Then, GMS-SA_2 was used as a coupling agent to condensate with polyethylene glycols (PEG) of different molecular weight or polyethylene glycol monomethyl ether (PEGm) in the presence of stannous octoate as catalyst and diphenyl ether as azeotropic agent. The AB_2 star-shaped miktoarm copolymers were obtained successfully and were characterized by ^{1}H-NMR, DSC, GPC, XRD, FTIR and polarizing microscopy. The results of DSC and XRD measurements indicate that the crystallization temperature and the melting temperature of the AB_2 star-shaped miktoarm copolymers are different from those of the corresponding linear PEGs, because the existing of GMS-SA_2 alters their crystalline growth velocity and the perfect degree of crystals. It is very important to control the crystal morphology of star-shaped copolymers by introducing the miktoarm into the star-shaped polymers and adjusting its content in star-shaped polymers.

Keywords star-shaped polymer, miktoarm, glyceryl monostearate, polyethylene glycol, crystallization

1 Introduction

The concept of star-shaped polymers was first provided by Flory in 1948 [1], which was defined as a kind of polymer containing several or multiple polymer chains from a branched point or a core. However, the star-shaped miktoarm polymers are a special kind of star-shaped ones because they join different kinds of polymer chains at a branched point different from the traditional star-shaped polymer. They can be used as model copolymers to investigate their various properties in solution or in bulk affected by their two or more thermodynamically incompatible components. Furthermore, the phase separation of incompatible chain segments on the molecular level often drives them to form some complicated nanostructure. Unlike in linear copolymers, little changes in composition or structure of nonlinear star-shaped miktoarm copolymers can induce tremendous changes in their morphologies. These polymers have attracted much attention in science and industry due to their many potential applications [2].

There are two methods to synthesize star-shaped polymers [3]. The first is defined as 'core-first' where the initiator containing multiple functional groups is used to initiate polymerization. The arm number of star-shaped polymers is confirmed by the number of functional groups in the core. The second method is defined as 'arm-first' where the chain segments as arms are synthesized first (usually produced by active polymerization), and then are made to connect with each other using a coupling agent containing multiple functional groups to produce star-shaped polymers. To our knowledge, most of the star-shaped polymers synthesized at present often contain the same arms. There are few studies on star-shaped miktoarm copolymers because most of them are synthesized by active ionic polymerization [4–13]. Major disadvantages such as the need for high vacuum technology, rigorous polymerization conditions, and rare optional monomers limit these studies.

Linear PEG is a kind of biocompatible crystalline polymer widely used in scientific researches, especially in biotechnology and pharmacology. Some recent researches [14–23] show that the viscosities of the branched polymers are lower than those of the linear polymers, but their degradation rates are higher than those of the linear polymers. This property of branched polymers is favorable for

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encapsulation and delivery of drugs. Star-shaped polyethylene glycol (PEG) or miktoarm PEG has been synthesized by the anionic or cationic ring opening polymerization of ethylene oxide using hyperbranched polyether polyhydric alcohol or the hyperbranched polymer with hydroxyl terminals as a core [24,25]. In this paper, a small molecule (GMS-SA_2) with one alkyl chain and two terminal carboxyl groups was synthesized successfully by the reaction of glyceryl monostearate (GMS) with excessive succinic anhydride (SA). Then, GMS-SA_2 was used as a coupling agent to condensate with PEG of different molecular weights or polyethylene glycol monomethyl ether (PEGm) in the presence of stannous octoate as catalyst and diphenyl ether as azeotropic agent, and AB_2 star-shaped miktoarm copolymers were produced successfully. In addition, we found that it was difficult to obtain the star-shaped miktoarm copolymers if GMS was used as a coupling agent directly. The core molecule must be modified by introducing some interval segments to decrease the density of functional groups in space and further produce the expected star-shaped miktoarms effectively. Introduction of interval segments into the core molecules, which is important in the synthesis of star-shaped miktoarms, can be done by using a small molecule containing multiple functional groups as a core. At the same time, not only the crystallization rate, but also the quality of the crystal of star-shaped miktoarm copolymers was affected by the alkyl arms in GMS, and they may further induce the change of crystallization temperature, melting temperature and crystal morphology.

2 Experimental

2.1 Materials

Hydroxyl terminated PEG (Acros Co.) with average molecular weights of 800, 2000 and 4000, PEGm (Acros Co.) with an average molecular weight of 750, and GMS (Shanghai Reagent Co.) were used. All the above reagents were dried at 75°C for 12 h and kept in a vacuum oven. SA was purified according to reference [25]. Dimethyl sulfoxide (DMSO), 1,4-dioxane and N,N-dimethyl formamide (DMF) were dried using anhydrous magnesium sulfate and then purified by vacuum distillation. Diphenyl ether was dried by molecular sieve (3 Å). Acetone, toluene, tetrachloromethane, ethylether, chloroform and stannous octoate were purchased in the domestic market and used without further purification.

2.2 Measurements

^{1}H nuclear magnetic resonance (^{1}H-NMR) measurements were carried out on a 400 MHz Mercury Plus NMR spectrometer (Varian Co.) with $CDCl_3$ or DMSO-d_6 as solvents. IR spectra were recorded on a Perkin-Elmer FT/IR spectrometer. DSC measurements were performed on a Perkin-Elmer Pyris-1 differential scanning calorimeter at a heating rate of 10°C min^{-1} in N_2. The crystallization and melting of AB_2 star-shaped miktoarm copolymers were observed *in situ* using a Leica DM LP micropolariscope.XRD measurements were performed on a D/MAX-2200/PC diffractometer, and XRD patterns were recorded at a scanning rate of 4° min^{-1} with Cu Kα radiation ($\lambda = 1.54178$ Å).

2.3 Syntheses

2.3.1 Synthesis of GMS-SA_2

In a 150 mL conical flask, 18 g (0.05 moL) GMS was dissolved in 40 mL anhydrous acetone with constant stirring. 20 g (0.20 mol) SA was added in several batches. When most of SA solid dissolved, the mixture was heated to 60°C and continuously stirred for 12 h. The mixture in conical flask was evaporated at 120°C in a rotary evaporator under vacuum (0.09 MPa) until it became transparent. After it was cooled to room temperature, the resulting solid was dissolved in 50 mL acetone and filtered. Then the filtrate was poured into 400 mL deionized water, stirred for 0.5 h and then refrigerated for 12 h. Upon filtration, a white solid was obtained . This was dried under vacuum for 12 h resulting in a yield of 88%.

FTIR(KBr), ν : 2955, 2918, 2850, 2657, 1729, 1714, 1693, 1471, 1419, 1311, 1247, 1196, 1180, 1115, 1045, 942, 801, 717, 640, 581 cm^{-1}

^{1}H-NMR(400 MHz, DMSO-d_6), δ = 0.82, 1.20, 1.48, 2.26, 2.48, 3.30(H2O), 4.15, 5.25, 12.10

2.3.2 Synthesis of AB_2 star-shaped miktoarm copolymers

The synthesis of GMS-(SA-PEG2000)$_2$) is given as an example, and the typical process is as follows: In a 150 mL conical flask, 1.395 g (0.002 mol) GMS-SA_2 and 11 g (0.0055 mol) PEG2000 were dissolved in a mixture of 20 mL acetone and 5 mL DMSO. Then 0.02 g stannous octoate as catalyst and 10 mL diphenyl ether as azeotropic agent were also added into the conical flask. The mixture in the conical flask was evaporated in a rotary evaporator at 160°C under 0.09 MPa for 3 h and further at 160°C under 200 Pa for another hour. After it was cooled to room temperature, the resulting solid was dissolved in 15 mL chloroform and precipitated in 300 mL anhydrous ethylether. A white solid, obtained by filtration, was dried under vacuum at 80°C for 12 h. The yield was 89%.

FTIR(KB), *v* : 3456, 2889, 1968, 1732, 1644, 1468, 1360, 1343, 1281, 1241, 1147, 1112, 1060, 962, 842, 752, 693, 529 cm^{-1}

^{1}H-NMR(400 MHz, $CDCl_3$) $\delta = 0.76$, 1.15, 1.51, 2.21, 2.53, 3.48, 4.14, 5.16, 7.3

Table 1 The molar ratio in feed

samples	GMS-SA_2			PEG			PEGm			yield/%
	F_W[a]	mol	g	M_W[b]	mol	g	M_W[b]	mol	g	
1	558	0.005	2.79				750	0.011	8.25	82
2	558	0.005	2.79	800	0.011	8.8				84
3	558	0.0025	1.395	2000	0.0055	11				89
4	558	0.00125	0.698	4000	0.00275	11				88

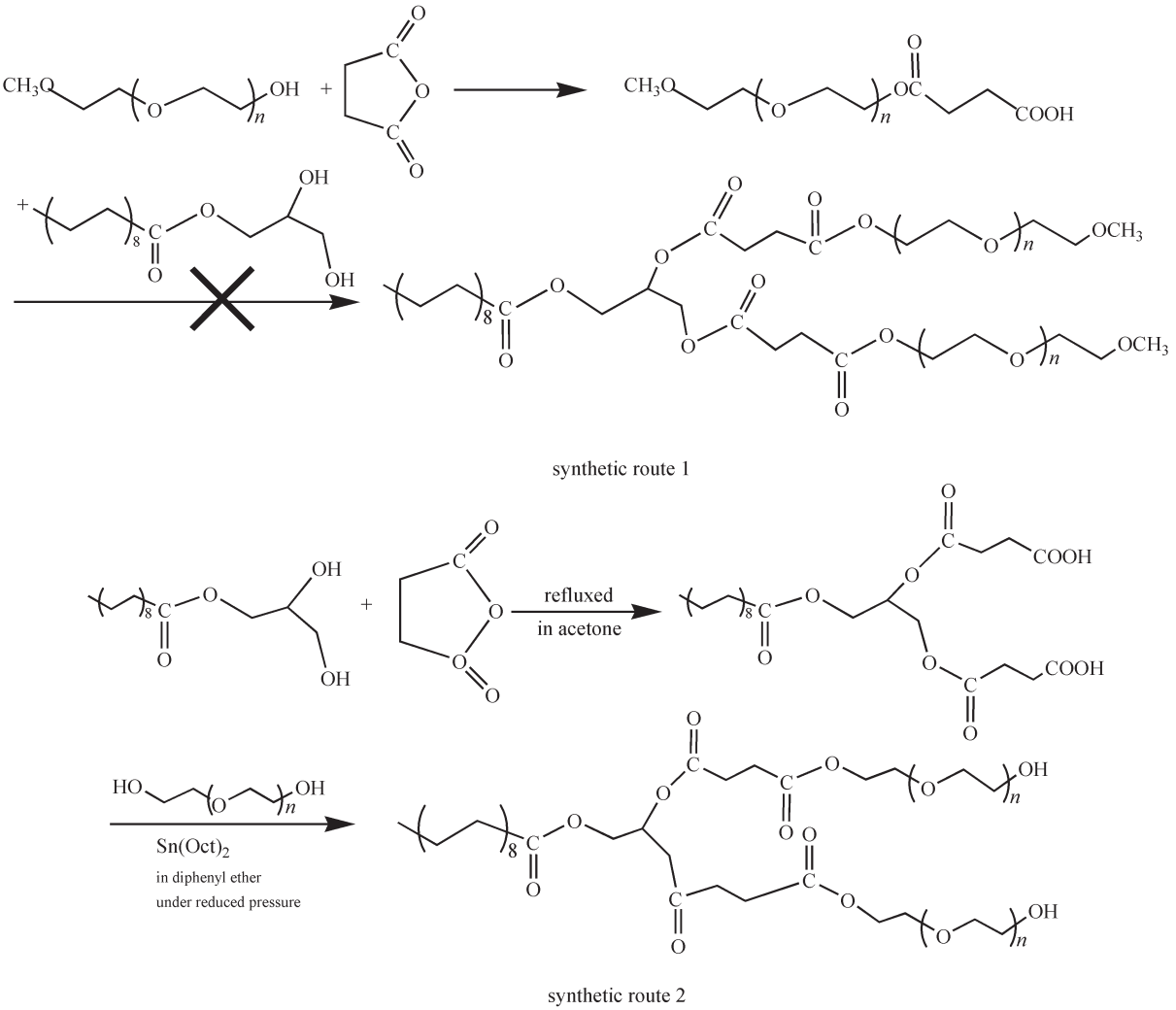
[a]Formula weight; [b]Average molecular weight

3 Results and discussion

3.1 Synthesis and characterization of AB_2 star-shaped miktoarm copolymers

The synthetic route 1 in Scheme 1 was used first to synthesize AB_2 star-shaped miktoarm copolymers, that is, the hydroxyl group of the PEGm (average molecular weight = 750) was first changed into carboxyl group by reacting with SA, then it was coupled with GMS to produce AB_2 star-shaped miktoarm copolymers. However, NMR results showed that the anticipated AB_2 star-shaped miktoarm copolymer was not obtained in this process. We believe that the steric hindrance presented by the two hydroxyl groups in GMS was significant and this made it difficult for them to couple with the chain segments (SA-PEGm with relatively high molecular weight) as arms. The polymer was not obtained even under the severe reaction conditions.

So the synthetic route 2 in Scheme 1 was adopted, that is, excess SA was used to react with GMS, and the two hydroxyl groups in GMS were changed into two carboxyl groups. This modification can simultaneously increase the



Scheme 1 Synthesis of AB_2 star-shaped miktoarm copolymers

distance between the two functional groups in the coupling agent and decrease the steric hindrance among the functional groups in the next coupling reaction. Then GMS-SA_2 was coupled with PEGm directly, and the NMR results showed that the AB_2 star-shaped miktoarm copolymer was prepared successfully (see Fig. 1). The same coupling agent, GMS-SA_2,was coupled with PEG of different molecular weights to produce AB_2 star-shaped miktoarm copolymers with different arm lengths.

^{1}H-NMR spectra of the intermediate (GMS-SA_2) and the AB_2 star-shaped miktoarm copolymers (GMS-(SA-PEGm750)$_2$, GMS-(SA-PEG800)$_2$) are shown in Fig. 1. The ^{1}H-NMR signals were assigned to various kinds of protons and labeled by the letters a to k. In the ^{1}H-NMR spectrum of GMS-SA_2, the ratio of peak area between the end carboxyl group (i) and the methyl group (a) is close to 2/3, and the ratios of peak area between the other peaks and the methyl group are consistent with theoretical values. This means that the two hydroxyl groups of GMS were esterified successfully by SA, and an intermediate (GMS-SA_2) containing two carboxyl groups was formed.

In the ^{1}H-NMR spectrum of GMS-(SA-PEGm750)$_2$, the original peak (i) attributed to the carboxyl group of the intermediate (GMS-SA_2) is absent but the other peaks can still be seen with their chemical shifts slightly changed. In addition, a new strong peak and a new weak peak appeared at $\delta = 3.7$ and $\delta = 3.4$ respectively. The first one can be attributed to the protons of PEGm arms (–CH_2CH_2O–), and the latter to the protons of methoxyl groups at the end of the arms. Similarly, in the ^{1}H-NMR spectrum of GMS-(SA-PEG800)$_2$, only one new peak appeared around $\delta = 3.7$. This can be attributed to the protons of PEG800 arms (–CH_2CH_2O–). Thus it can be seen that the AB_2 star-shaped miktoarm copolymers can be prepared successfully according to synthetic route 2 in Scheme 1 and that it is very important to introduce some interval segments into the small core molecule.

3.2 The molecular weight of AB_2 star-shaped miktoarm copolymers

The molecular weight of AB_2 star-shaped miktoarm copolymers can be calculated according to their ^{1}H-NMR spectra, and the results are shown in Table 2. There is only one methyl group in the alkyl arm of each AB_2 star-shaped miktoarm copolymer. So the integral area of its proton signals can be used as a base to calculate their molecular weight. The calculation is as follows:

For AB_2 star-shaped miktoarm copolymers containing terminal hydroxyl groups:

$$M_{n,\mathrm{NMR}} = \frac{S_b}{S_a} \times \frac{3}{2} \times 14 + 15 + \frac{S_j}{S_a} \times \frac{3}{4} \times 44 + 313$$

For AB_2 star-shaped miktoarm copolymers containing terminal methoxyl groups:

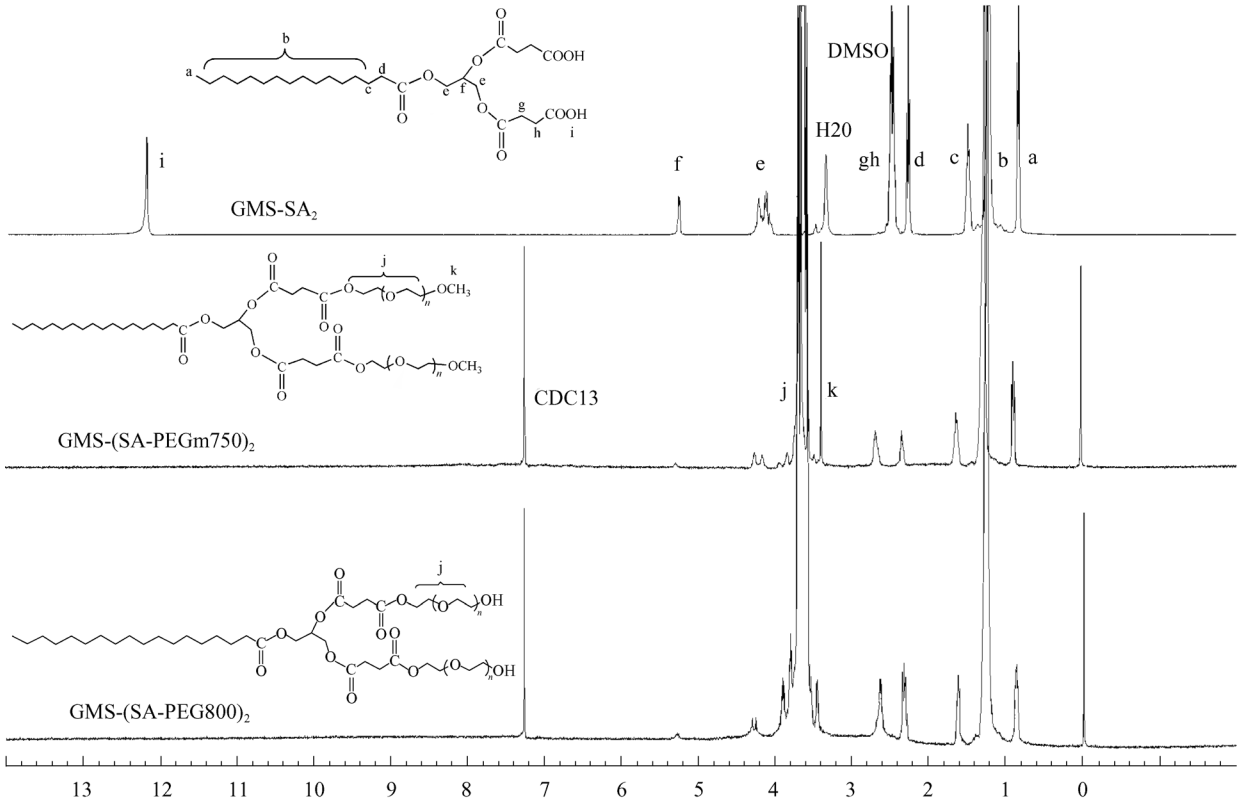


Fig. 1 The ^{1}H-NMR spectra of GMS-SA_2 and AB_2 star-shaped miktoarm copolymers

Table 2 The molecular weights of AB_2 star-shaped miktoarm copolymers

samples	$M_{n,\ th}$	$M_{n,\ NMR}$
GMS-(SA-PEGm750)$_2$	2000	1800
GMS-(SA-PEG800)$_2$	2100	2200
GMS-(SA-PEG2000)$_2$	4500	4100
GMS-(SA-PEG4000)$_2$	8500	7800

$$M_{n\mathrm{NMR}} = \frac{S_b}{S_a} \times \frac{3}{2} \times 14 + 15 + \frac{S_j}{S_a} \times \frac{3}{4} \times 44 + \frac{S_k}{S_a} \times 15 + 313$$

In the equation above, S_a is the integral area of the methyl proton signals in the alkyl arm of GMS, S_b is the integral area of the methylene proton signals in the alkyl arm of GMS, S_j is the integral area of the proton signals in the PEG arm, S_k is the integral area of the methoxyl proton signals. The formula weight of the PEG structural unit is 44, that of the branched unit (disuccinic glyceride) is 313 and that of methyl is 15.

According to the results in Table 2, the molecular weights calculated from ^{1}H-NMR spectra are consistent with the theoretical values of AB_2 star-shaped miktoarm copolymers. This means that the design and synthesis of AB_2 star-shaped miktoarm copolymers were successful.

3.3 The crystallization behavior of AB_2 star-shaped miktoarm copolymers

The crystallization behavior of AB_2 star-shaped miktoarm copolymers was characterized by DSC, XRD and polarizing microscopy.

The DSC programmed temperature curves of linear PEG800, PEG2000, PEG4000 and their corresponding AB_2 star-shaped miktoarm copolymers GMS-(SA-PEG800)$_2$, GMS-(SA-PEG2000)$_2$, GMS-(SA-PEG4000)$_2$ are shown in Fig. 2. Two melting peaks were observed in the thermograms of GMS-(SA-PEG800)$_2$ and GMS-(SA-PEG2000)$_2$, respectively. The sharp melting peak around 25°C can be attributed to the melting of the alkyl arm crystals in GMS and the relatively broad melting peak to the melting of PEG arm crystals. However, the sharp melting peak around 25°C was not observed for GMS-(SA-PEG4000)$_2$. We believe it was not detected because the molecular weight of the PEG arm is relatively high compared to the alkyl arm. Thus it can be seen that the crystallization of both alkyl arm and PEG arm in AB_2 star-shaped miktoarm copolymers did occur. In addition, the melting temperature of the PEG arm in AB_2 star-shaped miktoarm copolymers was lower than that of the linear PEG because of the influence of the alkyl arm of GMS and the branched structure. The melting point decreased with increasing molecular weight of the PEG arm and the average temperature decrease was about 5–10°C.

The XRD spectra of the linear PEG2000, the intermediate GMS-SA_2 and the AB_2 star-shaped miktoarm copolymer GMS-(SA-PEG2000)$_2$ are shown in Fig. 3. Analyzing the spectra, we find that GMS-SA_2 itself is a kind of crystallizing material. In the XRD spectrum of GMS-(SA-PEG2000)$_2$, the weak crystal diffraction peaks attributed to GMS-SA_2 were still observed (for example the peaks indicated by arrows in Fig. 3). As a whole, the XRD spectrum of GMS-(SA-PEG2000)$_2$ is similar to that of the linear PEG2000 indicating that the crystallization behavior of these AB_2 star-shaped miktoarm copolymers is determined by their PEG arms.

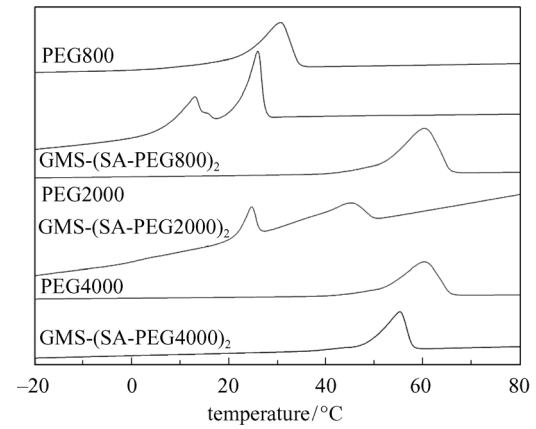


Fig. 2 The DSC curves of AB_2 star-shaped miktoarm copolymers and the corresponding linear PEG of different molecular weight at a heating rate of 10 K/min

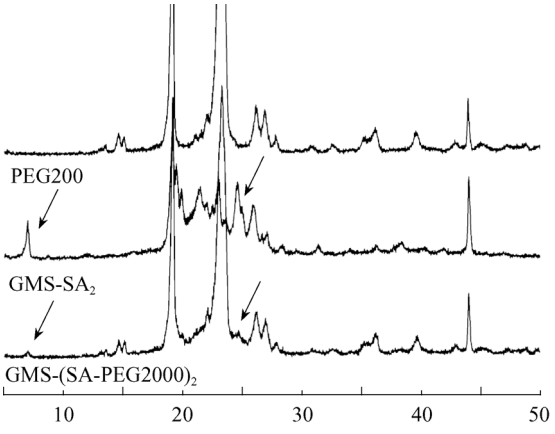


Fig. 3 XRD spectra of PEG, 2000GMS-SA_2 and GMS-(SA-PEG2000)$_2$

The bar is equivalent to 10 microns. The crystal morphology was obtained at different crystallization times (s): (a) 15, 17, 19, 21, 23; (b) 240, 243, 249, 255, 265; (c) 212, 222, 227, 232, 237; (d) 21, 56, 105, 133, 158.

In order to further investigate the crystallization behavior affected by miktoarm structure, a polarizing microscope was used to observe the crystallization process of linear PEG4000 and AB_2 star-shaped miktoarm copolymers (GMS-(SA-PEG2000)$_{20}$ and GMS-(SA-PEG4000)$_2$) *in situ*. The results are shown in Fig. 4. The crystallization

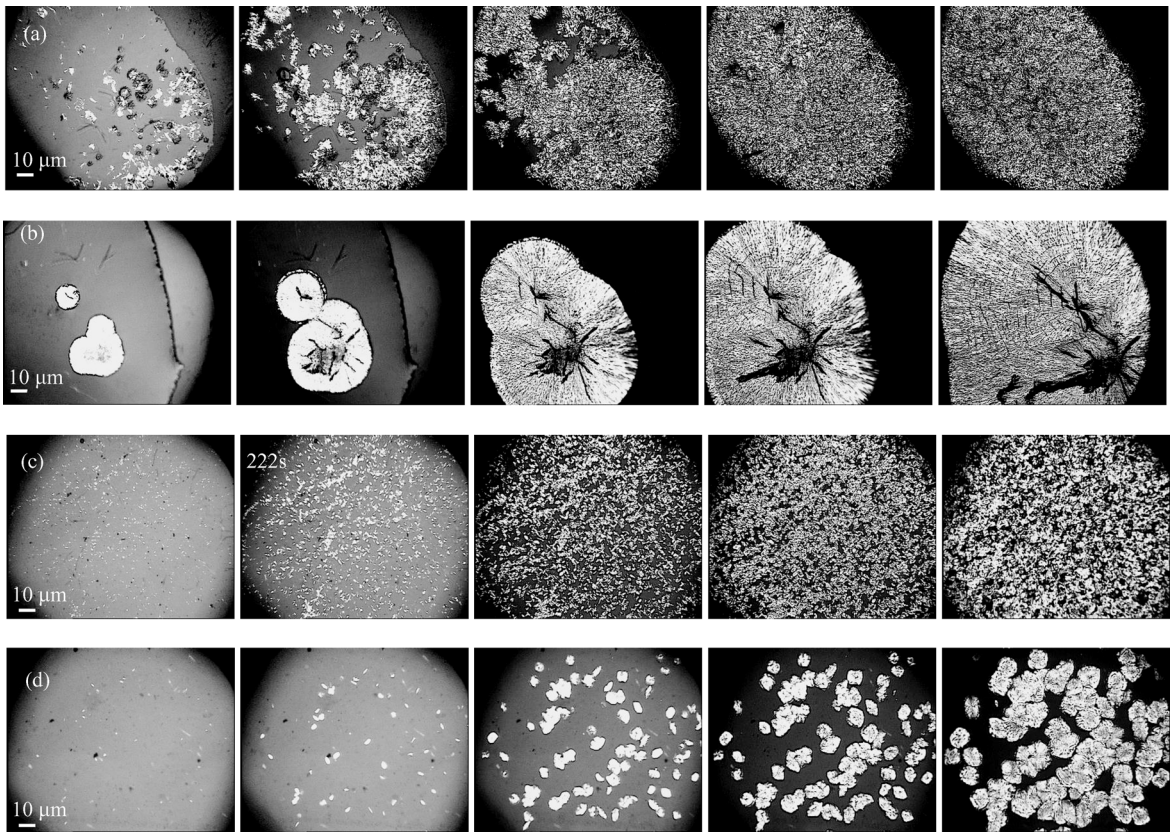


Fig. 4 Crystallization process in situ of GMS(a), linear PEG4000(b), GMS-(SA-PEG2000)$_2$(c) and GMS-(SA-PEG4000)$_2$(d)

process after complete melting showed that some fine irregular cluster crystals were formed mainly for GMS. However, some large spherulites were formed for linear PEG, that is, crystals grew from crystal nuclei to form large regular spherulites. The crystallization behavior of AB_2 star-shaped miktoarm copolymers made from GMS and linear PEG by molecular design became very interesting due to the alkyl arm. When the molecular weight of the PEG arm was relatively low (such as GMS-(SA-PEG2000)$_2$), the morphology of the crystals formed at the beginning was very similar to that of GMS. So we concluded that the alkyl arms of GMS in AB_2 star-shaped miktoarm copolymers crystallized first to form crystal nuclei and then induced the crystallization of PEG to form small irregular crystals. Their morphology was between fine irregular cluster crystals and spherulites. When the molecular weight of PEG arm was relatively high (such as GMS-(SA-PEG4000)$_2$), the content ratio of the alkyl arm in AB_2 star-shaped miktoarm copolymers was low. Although some fine irregular cluster crystal nuclei appeared at the beginning of crystallization, there were evidently fewer of these nuclei than in the low-molecular-weight-PEG counterparts. They formed small spherulites quickly and further grew in size. Linear PEG polymers, however, formed much larger final crystals than GMS-(SA-PEG2000)$_2$ or GMS-(SA-PEG4000)$_2$. So, we can control the crystal morphology and size of the star-shaped multiple arm polymers by introducing miktoarms or adjusting the content of the miktoarm. In our study the crystallization behavior of PEG was changed obviously by introducing GMS miktoarms, that is, fine irregular cluster crystals were formed when the content ratio of GMS was relatively high. When the GMS content was low, irregular spherulites were formed.

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