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Liquid-crystalline behaviours of novel chitosan derivates containing singular and cholesteryl groups

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A series of esters of chitosan with cholesteryl hexanoate and cholesteryl decanoate side chains were synthesised. These compounds had higher solubilities than chitosan itself and all formed cholesteric lyotropic liquid crystalline phases. They had enhanced mesogenic properties as compared with the parent polymer. We consider that these compounds may prove to be of value as vehicles for drug delivery.

Keywords: chitosan; lyotropic liquid crystal; cholesteric; solubility

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1. Introduction

After cellulose, chitin is the most abundant natural polymer. It is the linear polymer of N-acetylglucosamine units. It fills more or less the same role as cellulose in plants and collagen in higher animals. The shells of shrimps, crabs and molluscs, the cuticles of insects and the cell walls of fungi all contain chitin as one of their major structural components.

Chitosan is obtained by the deacetylation of chitin by hydrolysis in a base solution. It has a random distribution of glucosamine and N-acetylglucosamine units. It is non-toxic, biodegradable and biocompatible (*1*, *2*); hence it has a wide range of applications in food, agriculture, cosmetics, textiles, nanotechnology, water engineering and in particular in medicine (as a drug carrier) (*3–10*).

Chitosan forms a chiral lyotropic mesophase – but it is only soluble in an acid solution. The aim of this investigation is to synthesise chitosan derivatives with enhanced solubility and mesogenic properties, with the production of improved drug carriers in mind.

2. Experimental

2.1 Materials and measurements

Hexanedioic acid, cholesterol and decanedioic acid were obtained from the Jilin Chemical Industry Company and thionyl chloride, toluene, ethanol, chloroform, tetrahydrofuran (THF) and methanol were purchased from the Shenyang Chemical Company. Chitosan (M_W = 5000–10,000, DD = 85%) were purchased from the JiNan Bioengineering Company. All solvents and reagents were used as received. Pyridine was purified by distillation over KOH before using.

2.2 Characterisation

Fourier transform infrared spectroscopy (FTIR) spectra of the synthesised polymers and monomers in solid state were obtained by the KBr method performed on a PerkinElmer instruments Spectrum One Spectrometer (PerkinElmer, Foster City, CA). ^{1}H NMR (300 MHz) spectra and ^{13}C NMR (75.4 MHz) spectra were obtained with a Varian WH-90PFT NMR Spectrometer (Varian Associates, Palo Alto, CA) with CF_3COOD as the solvent and tetramethylsilane (TMS) as an internal standard. The thermal transition properties were characterised by a NETZSCH instruments DSC 204 (Netzsch, Wittelsbacherstr, Germany) at a heating rate of 10°C min^{-1} under a nitrogen atmosphere. Phase transition temperatures were measured during the first heating and cooling scans. Visual observation of liquid crystalline transitions and optical textures under cross-polarised light was made by a Leica DMRX (Leica, Wetzlar, Germany) polarised optical microscope equipped with a Linkam THMSE-600 (Linkam, Surrey, England) hot stage. Measurement of the optical rotation (α) was carried out with a PerkinElmer instrument Model 341 Polarimeter at different temperatures on the heating and cooling cycles, using a sodium light source (λ = 589 nm).

2.2 Synthesis

2.2.1 Synthesis of hexanedioic acid mono-cholesteryl ester (M_1)

Hexanedioic chloride (184 g, 1.0 mol), which was prepared by hexanedioic acid and excess thionyl chloride using the normal method, was dissolved in 205 ml chloroform. The solution of cholesterol (27.6 g, 0.20 mol) in dry chloroform (150 ml) and pyridine (15 ml) was added

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dropwise into the solution of acid chloride in the chloroform. The reaction mixture was stirred at 65°C for 24 h. The solvent was removed under reduced pressure. After cooling to room temperature, the rest of the reaction mixture was poured into 1000 ml cold water and acidified with 6 N sulfuric acid. The precipitates were isolated by filtration, washed with hot water and recrystallised in alcohol, then dried in a vacuum oven to obtain white crystals of hexanedioic acid mono-cholesteryl ester (M1). Yield: 57%. m.p.: 135.2°C. IR (KBr, cm^{-1}): 3056, 2959, 2875 (–CH_3, –CH_2– and –CH–), 2642–2530 (–OH in –COOH), 1722, 1690 (C=O), 1172 (C–O–C).

^{1}H NMR ($CDCl_3$, TMS, d, ppm): 0.68–2.35 (m, 43H, cholesteryl-H); 1.60 (m, 4H, –CH_2–); 2.40 (m, 4H, –CH_2–); 3.96 (t, 1H, COOCH$\diagup\!\!\diagdown$ in cholesteryl); 5.37 (d, 1H, =CH– in cholesteryl).

2.2.2 *Synthesis of decanedioic acid mono-cholesteryl ester (M_2)*

Decanedioyl chloride (239 g, 1.0 mol), which was prepared using decanedioic acid and excess thionyl chloride, was dissolved in 200 ml chloroform. The solution of cholesterol (27.6 g, 0.20 mol) in dry chloroform (150 ml) and pyridine (15 ml) was added dropwise into the solution of acid chloride in the chloroform. The reaction mixture was stirred at 65°C for 24 h. The solvent was then removed under reduced pressure. After cooling to room temperature, the mixture was poured into 1000 ml cold water and acidified with 6 N sulfuric acid. The precipitates were isolated by filtration, washed with hot water, recrystallised in alcohol and dried in a vacuum oven to obtain white crystals of decanedioic acid mono-cholesteryl ester (M_2). Yield: 62%. m.p.: 115.8°C. IR (KBr, cm^{-1}): 3054, 2955, 2875 (–CH_3, –CH_2– and –CH–), 2642–2560 (–OH in –COOH), 1728, 1694 (C=O), 1171 (C–O–C).

^{1}H NMR ($CDCl_3$, TMS, d, ppm): 0.68 – 2.35 (m, 43H, cholesteryl-H); 1.30 (m, 8H, –CH_2–); 1.61 (m, 4H, –CH_2–); 2.40 (m, 4H, –CH_2–); 3.96 (t, 1H, COOCH$\diagup\!\!\diagdown$ in cholesteryl); 5.37 (d, 1H, =CH– in cholesteryl).

2.2.3 *Synthesis of the polymers derived from chitosan*

For synthesis of the polymers, the generic method was adapted, as shown in Scheme 1. The polymerisation experiment is summarised in Table 1. The synthesis of polymer P_{1-1} was given as an example. The solution of chitosan (1.0 g) in methane sulfonic acid was added dropwise into the solution of M1 (1.48 g) in 35 ml chloroform under stirring and cooled to 0°C to react for 18 h under nitrogen and anhydrous conditions. The mixture was then poured into cool acetone to allow the formation of precipitate. After filtration, the product was dried at 80°C for 2 h under vacuum to obtain polymer P_{1-1} in the yield of 70%. IR (KBr, cm^{-1}): 2964 – 2874 (–CH_3 and –CH_2–), 1754 – 1720 (C=O), 1261, 1191 – 1084 (C-O).

^{1}H NMR(CF_3COOD, TMS, d, ppm): 0.68–2.35 (m,43H, cholesteryl-H); 3.96 (t, 1H, COOCH$\diagup\!\!\diagdown$ in cholesteryl); 1.31 (m,8H, –CH_2–); 1.61 (m,4H, –CH_2–); 2.25 (m, 4H, –CH_2–); 3.0–5.28 (m, 168H, chitosan-H), 5.37 (d, 1H, =CH– in cholesteryl).

^{13}C NMR(CF_3COOD, TMS, d, ppm): 18.3, 18.5, 20.3, 22.3 (CH_3); 26.73, 30.81, 30.85, 35.9, 37.9, 40.9 (methylene-C); 51.9, 58.90, 62.30, 65.6, 67.57, 75.77, 99.26 (tertiary C in chitosan); 39.2, 40.6 (quaternary C in cholesteryl); 75.9 (tertiary C in cholesteryl); 130.20 (=CH— in cholesteryl); 150.0 (=C$\diagup\!\!\diagdown$ in cholesteryl); 160.6, 161.2, 162.9 (C=O).

3. Results and discussion

3.1 *Synthesis*

The synthetic routes for the target polymers are shown in Scheme 1. Their structures were characterised by IR, ^{1}H NMR and ^{13}C NMR spectra. The result of the molar ratio of the monomers introduced into the chitosan chain, which was determined by ^{1}H NMR, is shown in Table 1.

Polymers were prepared by one-step acylating reaction between O–H or N–H groups of chitosan and acyl chloride of monomers. Different from chitosan, the obtained polymers were soluble in THF, chloroform, acid solution and so forth. The improvement of solubility of chitosan is of benefit for further synthesis. The change of liquid crystal polymer (LCP) solubility may be attributed to the hydrogen bonds disturbance, owing to the introduction of cholesteric monomers in the chitosan chain.

Chitosan and the polymers were characterised by FTIR. The representative curves of chitosan, P_{1-1} and P_{1-2} are shown in Figure 1 to identify the changes to the structure. The chitosan showed a distinct carbonyl groups stretching vibration at 1648 and 1605 cm^{-1}; N–H stretching and O–H stretching vibrations can be characterised by the broad peak between 3200 and 3600 cm^{-1}. When the ω-alkyl diacid monocholesterol ester was grafted onto the amine groups of chitosan, the strong absorption peak of 1648 and 1605 cm^{-1} almost disappeared, while prominent bands at 1634 and 1527 cm^{-1} were observed, which were assigned to the carbonyl stretching of the amnide I and amide II bands, respectively. As M_1 increased, the intensity of the carbonyl stretching of amnide I, amide II and ester increased obviously, while the intensity of the peak at 3442 weakened. The peak at 58.9 ppm, showing in the

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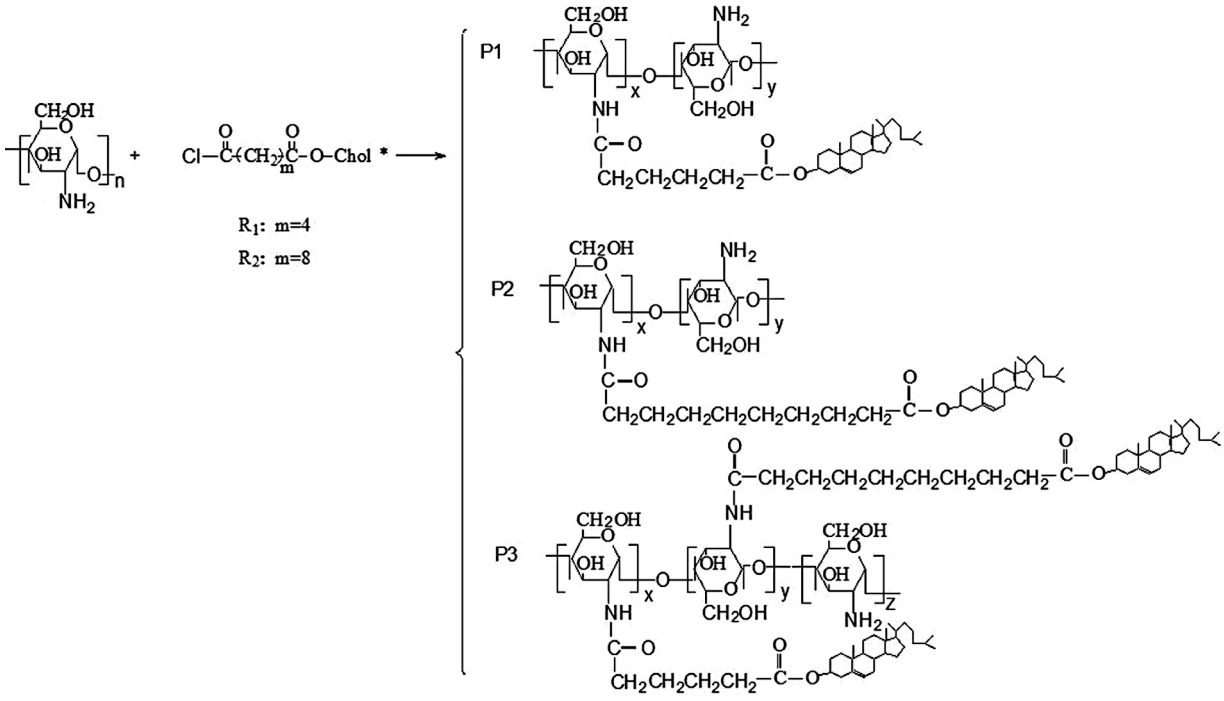

Scheme 1. The synthesis of the polymers.

Table 1. Polymerisation, specific rotation, decomposition temperatures and critical centration of the polymers.

Sample	Chitosan /g	M_1 /g	M_1 /mmol	M_2 /g	M_2 /mmol	B[a]	a[b] /°	Td[c] /°C	C*[d] /%
P_{1-1}	1	0.74	1.39	–	–	24:1	–5.476	201.0	51
P_{1-2}	1	1.48	2.78	–	–	12:1	–13.67	198.5	49
P_{2-1}	1	–	–	0.82	1.39	24:1	–22.73	229.8	58
P_{2-2}	1	–	–	1.64	2.78	12:1	–5.667	184.4	60
P_3	1	0.74	1.39	0.82	1.39	12:1	–10.00	187.6	54
Chitosan	–	–		–			–26.52	285.2	40

[a]B = mol (pyranose): mol (M_1 or M_2) measured by 1H NMR.
[b]Specific rotation of the polymers (0.1 g in 10 ml $CHCl_3$) and chitosan (0.1 g in 10 ml acetic acid).
[c]Temperature at which 5% weight loss occurred.
[d]The critical concentration in chloroform solution.

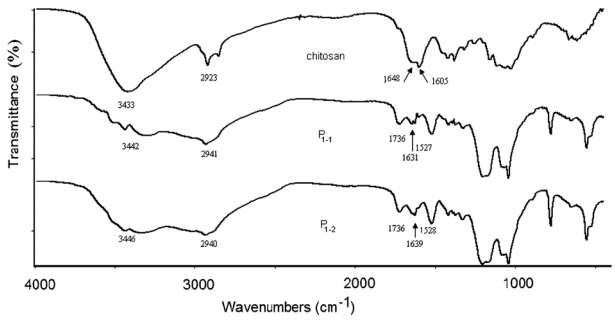

Figure 1. The infrared curves of chitosan, P_{1-1} and P_{1-2}.

^{13}C NMR spectra of P_{1-1}, indicated that esterification had taken placed in C_2. These results clearly identified that N-acylated derivatives were obtained.

^1H NMR spectra of P_{1-1} showed multiplets at 0.68–3.96, 3.0–5.28 and 5.37 ppm, corresponding to methyl and methylene protons, chitosan protons and olefinic protons, respectively.

3.2 Thermal analysis

Differential scanning calorimetry (DSC) curves of M_1 showed a melting transition and a cholesteric–

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isotropic phase transition at 135.2 and 148.3°C on heating, and displayed an isotropic–cholesteric phase transition and crystallisation process at 145.2 and 96.7°C on cooling, respectively. Two endothermic phase transitions were observed on the DSC heating curve of M_2, which represents the melting transition at 115.8°C and the cholesteric–isotropic phase transition at 123.3°C, respectively. On the cooling scans of M_2, at 118.7°C, an isotropic–cholesteric phase transition was detected and the crystallisation temperature appeared at 98.2°C. Their DSC curves are presented in Figure 2.

Thermogravimetric analysis (TGA) thermograms of the chitosan and polymers measured using a nitrogen atmosphere are shown in Figure 3 and the decomposition temperatures, at which there was 5% weight loss, are summarised in Table 1. Compared with chitosan, the thermal stability of the LCPs decreased evidently. With cholesteric monomers increased in the feed, the decomposition temperatures decreased. This may be attributed to the loss of hydrogen bonds between the chitosan molecules, owing to the introduction of the cholesteric monomers.

3.3 Determining critical concentration of the LCPs

Chitosan and the LCPs all exhibited lytropic liquid crystal (LC) properties in the chloroform solution. A series of the LCPs' solutions in the chloroform with different concentrations were prepared. Their critical concentrations were determined by observing the optical textures using polarised optical microscopy (POM). The results of the critical concentration are summarised in Table 1.

3.4 Texture analysis

The optical textures of the monomers and the polymers were studied by means of POM with a hot stage, which are shown in Figures 4 and 5. The POM results showed that M_1 and M_2 exhibited a cholesteric phase on the heating and cooling cycles. When M_1 was heated to 135.2°C, the typical cholesteric oily streak texture appeared. When the isotropic was cooled to 145.2°C, it displayed a broken focal-conic texture. When M_2 was heated to 119°C, the sample began to melt, an oily streak texture appeared, and mesomorphic behaviour disappeared at 123.3°C. When the isotropic state was cooled, the cholesteric broken focal-conic texture appeared, and it crystallised at 98°C. The optical textures of M_1 and M_2 are shown in Figure 4.

Chitosan and the polymers all exhibited a cholesteric lytropic LC phase. Above the critical concentration, chitosan exhibited a finger texture, which is the typical cholesteric texture, and the sample P_{1-1} showed

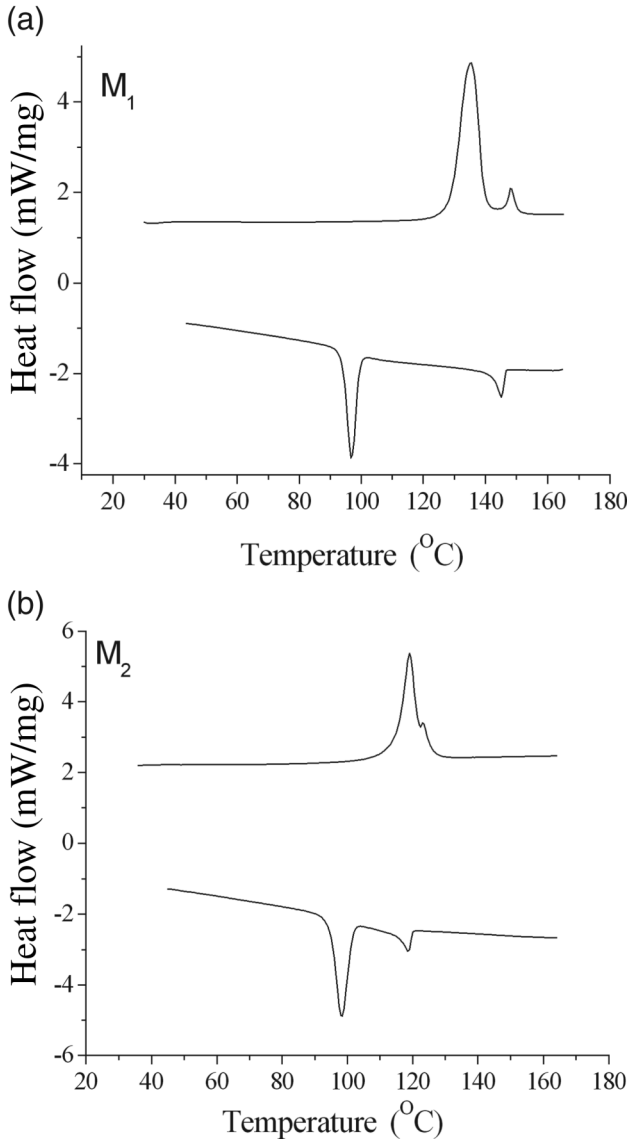

Figure 2. DSC thermograms of $M_1$and M_2.

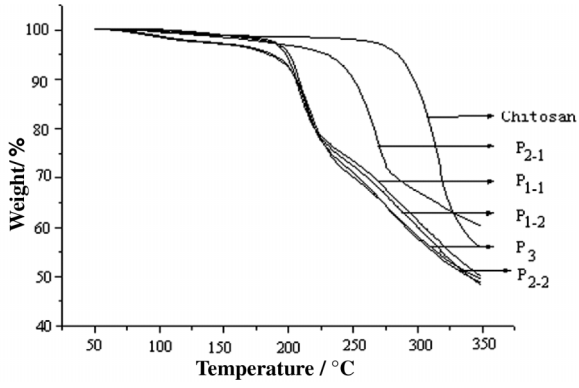

Figure 3. Thermogravimetric analysis thermographs of the chitosan and the LCPs.

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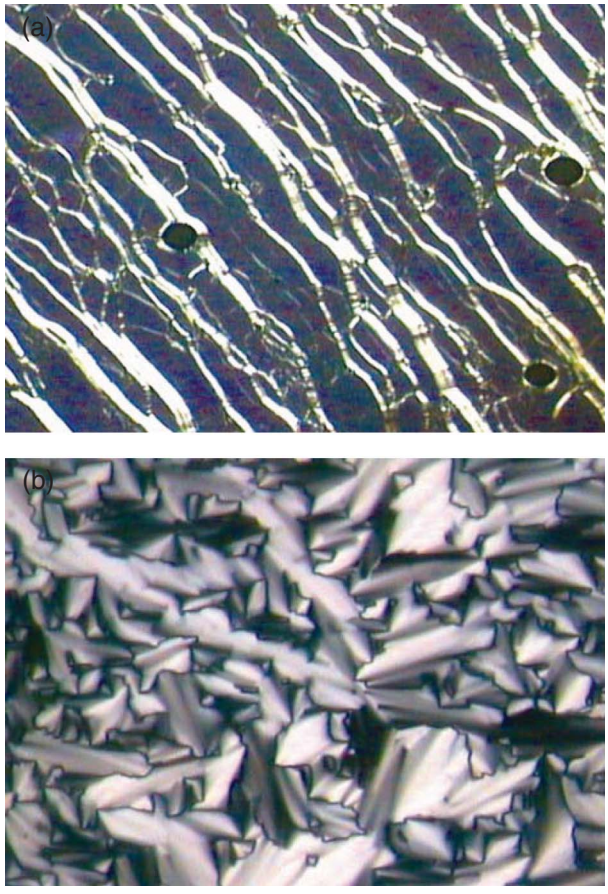

Figure 4. Optical texture of the monomers (200×): (a) cholesteric oily streaks of monomer M_1 on heating to 138°C; (b) broken focal conic texture of monomer M_2 on cooling to 115°C.

the cholesteric focal-conic texture of a common cholesteric texture. The other polymers display the Grandjean texture of a cholesteric phase. Optical textures of the polymers are shown in Figure 5. As shown in Figure 5, the LC property of chitosan was very weak, while the chitosan derivates containing the cholesteric monomers exhibited a clear focal-conic texture and the colour of a Grandjean texture. This suggested that the introduction of cholesteric monomers intensified the LC property.

3.5 Circular polarisation spectra

The unique optical properties of cholesteric liquid crystalline are related to the helical supermolecular structure of the cholesteric phase. The periodic helical structure of the cholesteric phase selectively reflects visible light like an ordinary diffraction grating, the pitch of which controls the wavelength of a selective reflection of light. If the reflected wavelength lies in the visible range of the spectrum, the cholesteric phase

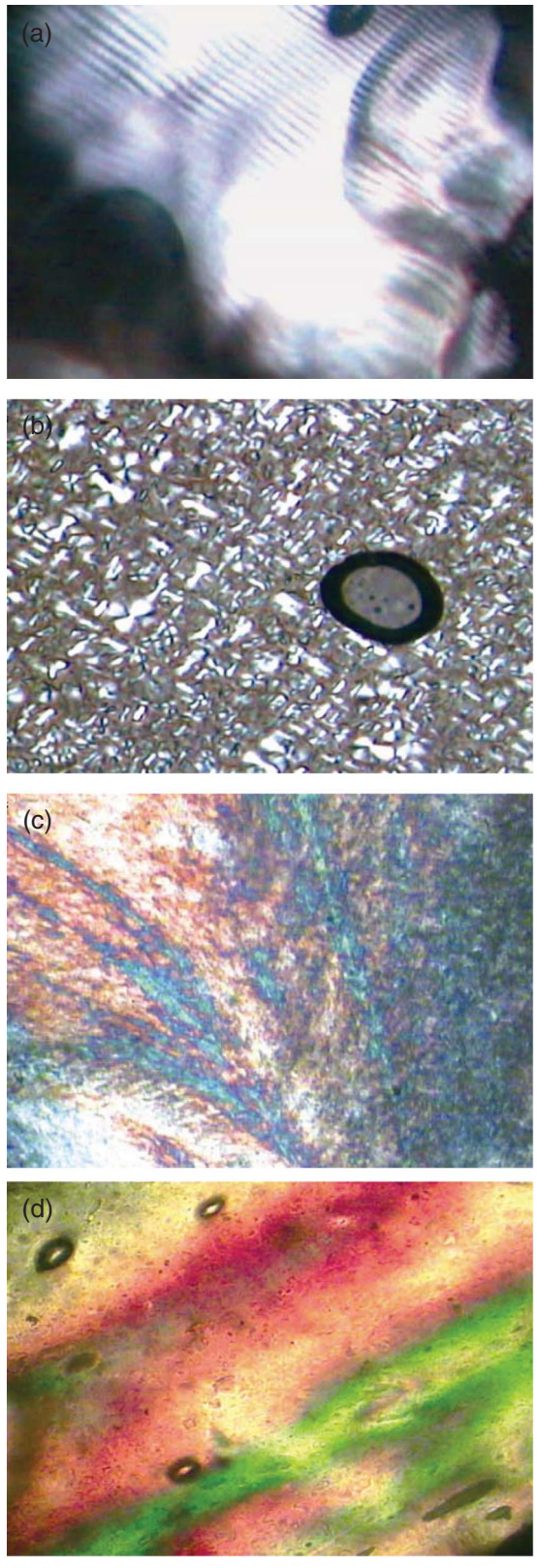

Figure 5. Optical texture of the chitosan and the polymers (200×): (a) cholesteric finger texture of chitosan; (b) cholesteric focal-conic texture of P_{1-1}; (c) Grandjean texture of P_{2-1}; (d) Grandjean texture of P_3.

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exhibits brilliant colours. The transmitted light shows complementary colour. The wavelength of the selective reflection of light λ_m obeys the Bragg condition

$$\lambda_m = n \cdot P \quad (1)$$

where n is the average index of refraction and P is the pitch of the cholesteric phase, defined as the spatial distance over which the director rotates 360°.

The helical pitch is an important parameter in connection with the optical properties of the cholesteric phase. Although the microscopic origins of the helical pitch are still a subject of study, it is known that the helical pitch and the optical properties of side-chain cholesteric liquid crystalline polymers mainly depend on the polymer backbone, the rigidity of the mesogenic units, the length of the flexible spacer and the outer conditions (such as concentration, temperature, force field, electric field and magnetic field). In this paper, these lytropic LC polymers did not exhibit selective reflects in the visible light range.

3.6 Optical rotation analysis

The optical properties of the chiral LCPs derived from chitosan and cholesteric monomers in the liquid crystalline state induce a twist in the director of the adjacent molecules, thereby forming a supermolecular helical structure. Therefore, it is interesting to study the variation of optical rotation (α) due to introduction of different chiral groups in the side-chain chitosan derivates.

The specific rotations of the polymers are all negative values; the cleavage of the O–H bond and the binding of two monomers to the chitosan main chains seemed to significantly affect the chirality of the compounds, as shown in Table 1. As compared with chitosan, the polymers showed significantly lower specific rotations. The results suggest that the existence of side chains affects the molecular polarity leading to the decrease of the specific rotations.

4. Conclusions

A series of esters of chitosan with cholesteryl hexanoate and cholesteryl decanoate side chains were synthesised. The cholesteryl monomers M_1 and M_2 displayed thermotropic liquid-crystalline properties, an oily texture and a focal-conic texture. All chitosan derivatives formed cholesteric lyotropic liquid crystalline phases. The critical concentrations were 40% for chitosan and 51%, 49%, 58%, 60% and 54% for the chitosan derivates P_{1-1}, P_{1-2}, P_{2-1}, P_{2-2} and P_3, respectively. Different from the blur finger texture of chitosan, the chitosan derivatives displayed a clear focal-conic texture and the colour of a Grandjean texture. The thermal decomposition temperatures of the chitosan derivatives were lower than that of the parent polymer, obviously. These compounds had enhanced mesogenic properties as compared with the parent polymer and had higher solubilities than chitosan itself, which provided the potential possibility to further synthesise LC drug carriers. This may be attributed to the weakening of hydrogen bonds between the chitosan molecules by the introduction of cholesteryl monomers.

The most likely structure of the mesogenic units is that of a central chitosan strand surrounded by an inner shell of alkyl chains and an outer shell of sterol units. Since alkyl chains are flexible and non-chiral, one would expect it to be the chirality of the cholesteryl groups (rather than that of the chitosan mainchain) that determines the bulk chirality of the mesophase.

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