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Oil Gels with Chemically Cross-linked Copolymer of Trimethylene Carbonate Derivative and L-Lactide: Preparation and Stereocomplex Formation within Gels

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Oil gels made of low-toxic components were prepared using chemically cross-linked copolymer, which was composed of poly(trimethylene carbonate) derivative and poly(L-lactide). The poly(L-lactide) moiety in gels could form stereocomplexes with poly(D-lactide).

Oil gels are semi-solid systems, in which an organic liquid phase is immobilized within a three-dimensional network. Oil gels can be used as chemomechanical materials,[1] oil absorbant[2] and so on. Oil gels can retain and release water-insoluble drugs, such as indomethacin[3] hydrocortisone[4] and testosterone[5]. In particular, many drugs, such as hormones, cancer drugs and so on, are hydrophobic; therefore, oil gels could be useful in drug delivery research or as drug delivery vehicles. However, the use of oil gels in drug delivery systems have been limited due to a lack of insight on the biocompatibility and toxicity of solvents and gelators.[6] Furthermore, physical gels may demonstrate difficulty in retaining drugs because of lack of stability that leads to collapse. While there are many reports in the literature regarding physical gels composed of low molecular weight organogelators, including fatty and amino acids,[7] nucleotides[8] and organometallic compounds[9]. There is a lack of literature on biodegradable oil gels with chemically cross-linked polymer networks; these biodegradable hydrophobic gels would serve an unmet need.

Polylactide (PLA) is a popular semicrystalline polymer with a unique characteristic; the stereocomplexation between poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA) has been well characterized.[10] Detailed mechanisms regarding stereocomplexation and the application of stereocomplexed PLA have been reported.[11] Additionally PLA is biodegradable and biocompatible, so it is studied for use in biomedical material applications (e.g. drug carriers,[12] resorbable sutures,[13] and nanosheets for burn wounds[14]). PLA has an affinity for several organic solvents, therefore, PLA is a good candidate for oil gels. Since PLA does not have cross-linking points, an additional compound is necessary to construct polymer networks.

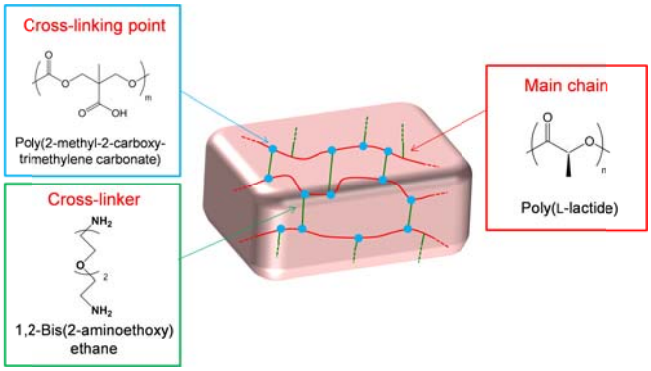
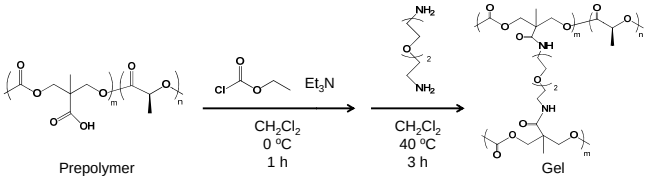


Figure 1. Schematic illustration of oil gel with three-dimensional polymer network.

In this study, we selected a trimethylene carbonate (TMC) derivative as introducing cross-linking points when preparing polylactide oil gels. Poly(TMC) (PTMC) is a biodegradable and biocompatible synthetic polymer[15], and PTMC can introduce several functional side chains groups[16]. Therefore, PTMC derivative introduces useful cross-linking points. Then, Oil gels composed of PLA were prepared with chemically cross-linked polymer networks (Figure 1). Three-dimensional polymer networks were created by chemically cross-linking copolymers composed of PLA and PTMC, and we tried to control gel structure by stereocomplexation with PDLA. Organic solvents with low-toxicity were absorbed by polymer networks. To the best of our knowledge, this is the first report of chemical gels composed of PLA with low-toxic organic solvents.



Scheme 1. Cross-linking reaction of copolymers using 1,2-bis(2-aminoethoxy)ethane.

We synthesized random copolymers, with carboxylic side chain groups, composed of PLLA and poly(2-methyl-2-carboxytrimethylene carbonate) according to a the previously reported method[17, 18].Copolymer is considered to have random sequence of lactic acid and one polymer chain had 74 units of PTMC derivative and 296 units of lactic acid (m : n = 86 : 258) (see Supporting Information, Section 1-3). A lot of PTMC derivative are introduced as cross-linking points for successful cross-linking reactions. Then, we prepared gels by reacting copolymers and 1,2-bis(2-aminoethoxy)ethane as cross-linkers (Scheme 1). We used a similar compound, with amino end groups, to cross-link polymers[19]. This cross-linker contains oligo(ethylene glycol) groups, which resemble poly(ethylene glycol), a known biocompatible polymer[20]. Here, we changed the amount of the cross-linker to probe its effect on reaction yields. 1,2-Bis(2-aminoethoxy)ethane was dried by distillation and stored as solution with molecular sieves 4A just before use. Table 1 shows reaction conditions resulting yields. These results suggest that more products can be obtained with lower amount of cross-linker. We hypothesize that more graft copolymers are synthesized when a large amount of cross-linker is used. The presence of the graft copolymer was confirmed by ^{1}H NMR (see Supporting Information, Figure S5). Table 1 shows that yields under these reaction conditions are about 20%. We think that these values are low due to the steric hindrance of the main polymer chain and some graft copolymer made of prepolymers and cross-linkers. Furthermore, the longer reaction time resulted in the lower yields, which implied the hydrolysis of ester groups in PLA under alkaline condition (see Supporting Information, Table S2). Prepolymers have the quaternary carbon atoms next to carboxy groups. The carboxy group next to the quaternary carbon is not reactive. Henceforth, we use oil gels made by cross-linking copolymers and cross-linkers, where the molar ratio of amino groups of cross-linkers to TMC derivative is 0.5 (Table 1, entry 1) with regard to swelling ratio (Figure 2), because of the high yield under these conditions. After the reaction, an excess amount of chloroform was added to the product in order to remove the unreacted compounds. After over 12 hours, chloroform was removed to obtain oil gel in chloroform. We confirmed reactions by FT-IR spectra (see Supporting Information, Figure S7). Unfortunately, the peaks derived from carbonyl groups of PTMC derivatives and PLA were overlapped each other. However, spectra from dry gels peak around 1664 cm^{-1} and 1540 cm^{-1}, which are representative of amide groups, that were not present before reaction. Therefore, carboxy groups of prepolymers react with amine groups of cross-linkers in successful cross-linking reactions.

Table 1 Results of cross-linking reaction.

Entry	[NH_2] /[COOH] [a]	Product (mg)	Yield[b] (%)	Reacted TMC derivatives[c] (%)
1	0.5	85	27	44
2	1	71	20	>100
3	2	46	11	64
4	3	56	12	>100

[a] Molar ratio of amino groups of cross-linkers to TMC derivatives. [b] The yield of reaction was calculated from the weight of dry gel. Dry gel was obtained by vacuum-drying of the oil gel in $CHCl_3$ over 3 hours at room temperature. [c] Calculated from elemental analysis.

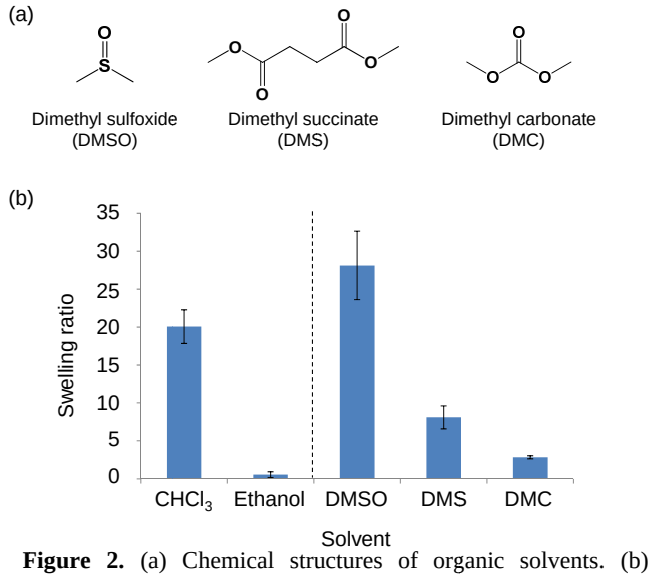


Figure 2. (a) Chemical structures of organic solvents. (b) Swelling ratios of oil gels in various organic solvents.

Next, we checked whether dry gels absorbed various organic solvents. Figure 2a shows the chemical structures of solvents used in this study. We choose comparatively low toxic organic solvents as dispersion media. i.e.; dimethyl sulfoxide (DMSO), dimethyl carbonate (DMC) and dimethyl succinate (DMS). Orl-rat LD_{50} of these solvents is comparable to ethanol, which is considered to display low toxicity (DMSO : 14500 mg/kg[21], DMC : >5000 mg/kg[22], DMS : >5 g/kg[21], ethanol : 6.2-17.8 g/kg[23]). Figure 2b shows gel swelling ratios in these solvents. Swelling ratios were calculated as follows: (W_s – W_d)/W_d, where W_s is the weight of the swollen oil gel at room temperature and W_d is the weight of the dry gel. To compare swelling ratios of the aforementioned solvents, we measured swelling ratios of chloroform and ethanol. Chloroform is a good solvent and ethanol is a poor solvent for PLA. Figure 2b suggests that the swelling ratio in ethanol is lower than that in other solvents because ethanol is a poor solvent for PLA. In contrast, swelling ratios in good solvents for PLA such as chloroform and DMSO are relatively high. When it comes to DMSO, DMC and DMS, the swelling ratio is about 28, 3 and 8, respectively. Differences in swelling ratios are considered

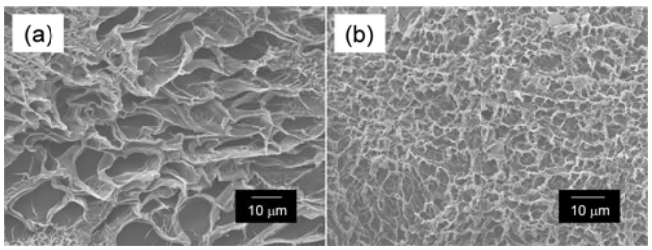


Figure 3. SEM images of oil gel in DMC after freeze-drying. (a) before and (b) after introducing PDLA.

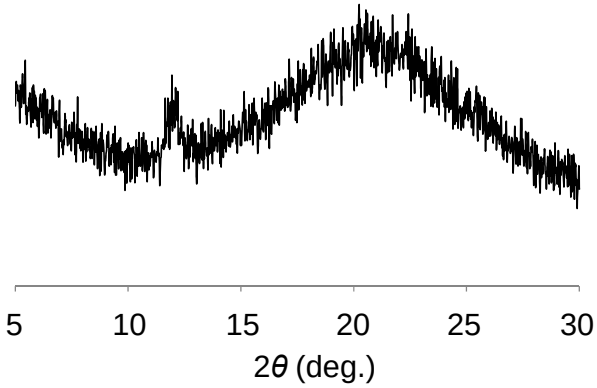


Figure 4. XRD pattern of freeze-dried oil gel after introducing PDLA.

relevant to solubility parameters (Supporting Information, Table S3).

In order to investigate the morphology of oil gels, we freeze-dried gels in DMC and observed them under a Scanning Electron Microscope (SEM). Figure 3a shows an SEM micrograph of a freeze-dried oil gel, which confirms that the oil gel had three- dimensional polymer networks and suggests that the pore size of the oil gel is about 10 μm.

Next, we tried to form stereocomplexes inside the oil gels, because we have confirmed that the prepolymer could form stereocomplexation with PDLA (Supporting Information, Figure S12). It is noteworthy that the solubility of stereocomplexed PLA is lower than enatiomeric PLA.[11b] Therefore, we assume that an oil gel shrinks by forming stereocomplexes between PLLA within polymer networks and PDLA. The oil gel in DMC was immersed into a solution containing PDLA (M_n = 4300, polydispersity = 2.24, 50 mg/mL). After 24 hours, the oil gel was freeze-dried in order to preserve the structure of the polymer network. We vertified the stereocomplexation by SEM images and X-ray diffraction (XRD) measurements. Figure 3b shows an SEM image after introducing PDLA; as compared with the pore sizes before introducing PDLA (Figure 3a), pore size was reduced after introducing PDLA, suggested that the oil gel might shrink by stereocomplexation of PLA. XRD pattern is shown in Figure 4. Strong peak is observed at 2θ = 12 °, which are in agreement with previously reported values of PLA stereocomplexes.[11b] . The amount of introduced PDLA was 0.9±0.2 mg (n = 3) (see Supporting Information, Table S1). We think that the oil gel might shrink due to the lowering of solubility of polymers caused by stereocomplexation. And it is also conceivable that PDLA cross-link prepolymers by sterecomplexation between PDLA and block sequence of L-lactic acid, leading the shrinking of polymer network. However, shrinking of oil gels was not made sure by the change of swelling ratio (see Supporting Information, Figure S10). If PDLA with more high molecular weight was used, swelling ratio might decrease by stereocomplexation. Therefore, it suggests that stereocomplexes might form in oil gels and the oil gel shrunk. Detail investigations are currently underway with various conditions

Conclusions

In conclusion, this is the first reported instance describing the preparation of chemical gels composed of PLA with low-toxic organic solvents. Copolymers composed of PLLA and PTMC derivative were cross-linked using oligo(ethylene glycol) containing amino groups. The yield of the cross-linking reaction is about 20%. This value is considered to be low because of steric hindrance of the main polymer chain and synthesis of graft copolymers from prepolymers and cross-linkers. The obtaind chemically cross-linked polymer network absorbed DMSO, DMC and DMS, leading to oil gels. Swelling ratios of these solvents are 28, 3, 8, respectively, which revealed that stereocomplexation between PLLA of three-dimensional polymer networks and PDLA occurred and the oil gel shrank. These oil gels can be investigated as vehicles for lipophilic drug delivery systems (under investigation and published in the future) and gel shrinking upon stereocomplexation has potential applications in stimuli-responsive materials. For example, the size of oil gels with nano size can be changed by stereocomplexation when the swelling ratios of them are low (the distances among the sequences of PLLA are short, so it is easy to cross-link by stereocomplexation).And we found out that stereocomplexes between PLLA and PDLA is easy to degrade than homopolymer.[24, 25] Therefore, degradation of oil gels can be changed by making stereocomplexation.

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