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(54) Title: BIODEGRADABLE THERMORESPONSIVE HYDROGELS

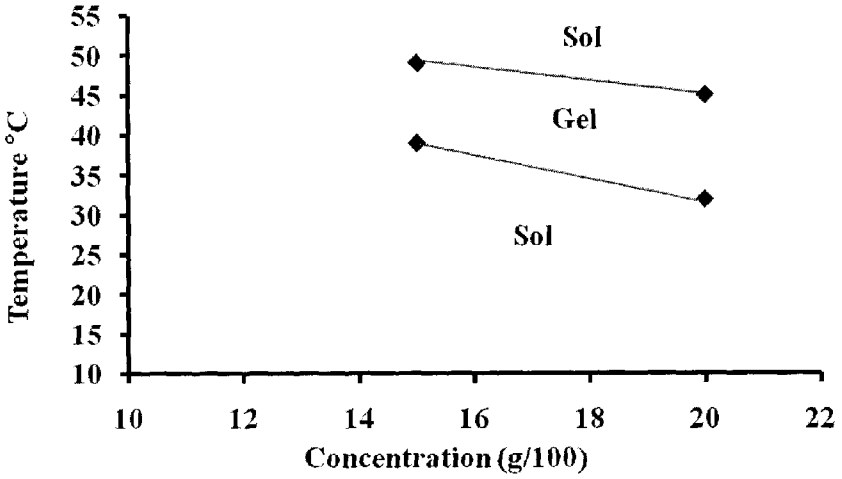


Figure 9

(57) Abstract: Gel-forming compositions of block copolymers for use as thermoresponsive, biodegradable, hydrogels for sustained delivery of a bioactive agent are provided. The copolymers can comprise block copolymers of poly(ethylene glycol) (PEG) and poly(α-benzyl caboxylate ε-caprolactone (PBCL), poly(α-carboxyl-ε-caprolactone) (PCCL), or both PBCL and PCCL functionalities poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε- caprolactone)] (PCBCL).

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TITLE: BIODEGRADABLE THERMORESPONSIVE HYDROGELS

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FIELD OF THE INVENTION:

The present disclosure relates to hydrogel-forming block copolymers comprising polyethylene glycol (PEG) and poly-ε-caprolactone (PCL), and particularly to copolymers comprising PEG-PCL wherein the block copolymer comprises pendant functional groups permitting hydrophobic, ionic and covalent bonding on the PCL block. The present disclosure also relates to methods of use thereof for delivering drugs and other bioactive agents to an individual.

BACKGROUND:

It is known that amphiphilic (i.e. compounds having both hydrophobic and hydrophilic properties) block copolymers can self-assemble into micellar structures. At high concentrations, the micellar structures can further self-assemble to form a diphasic (liquid/solid) gel-like structure or network via a process known as "sol-gel" transition. The process of sol-gel transition by block copolymers (or "hydrogels") may be triggered by environmental factors, such as, for example, changes in temperature. In that regard, the sol-gel transition may also be reversible. By way of example, block copolymers are known to form a sol at room temperature, thereby becoming injectable, and to form a gel upon an increase in temperature, such as that which may occur upon injection of the copolymer into a patient (i.e. as the sol adjusts to the patient's higher body temperature).

The thermoresponsive and reversible sol-gel transition of block copolymers such as poly(ethylene glycol) (PEG) and poly(ester)s (for example poly(lactide-co-glycolide) (PLGA), poly(D,L-lactide) (PDLA) and poly(ε-caprolactone) (PCL)) is known. Depending upon the structure of the block copolymer, the temperature dependent sol-gel transition may allow block copolymers to be utilized as, *inter alia*:

- a sustained-release matrix for the systemic or regional delivery of water soluble or water insoluble drugs and proteins, and/or
- a product for topical administration in the surgical field for prevention of tissue adhesion or scarring.

While the thermoresponsive and reversible nature of block copolymers are known, the ability and extent of which block copolymer hydrogels may be utilized as injectable implants for depot drug delivery remains unclear. For instance, known PEG-PCL block copolymer hydrogels are not amenable to chemical engineering due to the lack of functional groups on the polyester block, and they are also restricted in the types of drugs that can be incorporated into the block copolymer (i.e. known PEG-PCL block copolymers are limited to hydrophobic drugs only).

It may be desirable to have aromatic groups, reactive groups, or conjugated drugs on the PCL block. The presence of such functional and aromatic groups on the PCL block may provide the appropriate template for fine-tuning of copolymer delivery systems (i.e. to tailor the sol-gel transition of the copolymers), to increase drug encapsulation, to enhance micellar stability, thereby improving control and the rate of drug release from the copolymer

hydrogel carrier, or to chemically attach different drugs, drug compatible moieties or diagnostic agents to the core-forming structure.

There is a need for thermoresponsive PEG-PCL block copolymer hydrogels that are capable of temperature dependent sol-gel transition, being soluble at room temperature and becoming gel upon injection into a patient, and that can serve as injectable implants or topical formulations for sustained drug delivery of a wide variety of drugs, including non-hydrophobic drugs, after subcutaneous or local administration to a host. There is a further need for such thermoresponsive hydrogel copolymers to be biodegradable upon injection, thereby obviating the need to clear the gel from the injection site by surgical retrieval of an exhausted depot.

SUMMARY:

The present disclosure relates to gel forming compositions of block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), and particularly to PEG-PCL block copolymers having optional pendant functional groups on the PCL block. More specifically, the present disclosure relates to PEG-PCL block copolymers, wherein the PCL block further comprises benzyl carboxylate (PBCL), such as poly(α-benzyl carboxylate ε-caprolactone), carboxyl side groups (PCCL), such as poly(α-carboxyl-ε-caprolactone), or both PBCL and PCCL functionalities (PCBCL), such as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)]. The PEG-PCL block copolymers may further comprise optional substituents on the PCL block selected from the group consisting of halo, OH, OC_{1-4}alkoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkenyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, CN, NO_2,

$C(O)C_{1-4}$alkyl, $C(O)OC_{1-4}$alkyl, SO_2C_{1-4}alkyl, SO_2NH_2, SO_2NHC_{1-4}alkyl, phenyl, C_{1-4}alkylenephenyl, cholesteryl, poly(amine)s, protected poly(amines), polyamine-CF_3, and hydrazone.

The present disclosure also relates to methods of producing the foregoing block copolymers, and the use thereof as biodegradable hydrogels for sustained drug delivery. Specifically, the present disclosure relates to a PEG-PCL copolymer wherein the PCL block comprises functional groups and a bioactive agent in which the block copolymer forms a micelle around the bioactive agent and the micelles may form a gel.

The present disclosure also relates to hydrogels that may form an "implant" *in situ* following injection into a host, or that may form a "film" following topical administration to a host. One advantage of the formation of an implant or film may be that the hydrogel can be used as a delivery system, wherein the implant or film comprises a bioactive agent that is slowly released, *in vivo*, from the implant or film. Another advantage may be that the implant or film is mucoadhesive, a feature that may depend upon the nature and number of pendant functional groups on the PCL block of the copolymer. A further advantage of the implant or film may be that as the micelles and bioactive agent(s) are released from the hydrogel, the polymers (implants or films) may biodegrade into materials that are harmless to the host.

The present disclosure relates to PEG-PCL, PEG-PBCL and PEG-PCCL block copolymers which may provide hydrogels that:

- have decreased critical gelation concentration,

- may be soluble at room and elevated temperature (i.e. above 40°C),
- may form a gel within a desired temperature range, such as that which may occur upon injection into a patient (i.e. body temperature) or upon administration to the surface of the body, e.g. the eye or mucosal surface,
- may have mucoadhesive properties,
- may be capable of incorporating effective drugs and other biological agents and concentrations thereof, particularly insoluble (hydrophobic) drugs or drugs having reduced solubility, and
- may sustain their rate of release upon injection or administration to the host.

The present disclosure further relates to means for optimizing the foregoing characteristics by, among other things, varying factors such as changes in the molecular weight (or length) of the block copolymer hydrogels and by altering the hydrophilic/lipophilic balance and level of benzyl caboxylate and carboxylic acid substitution on the PCL block.

Broadly stated, a gel forming composition is provided comprising a block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), the PCL block further comprising pendant functional groups selected from the group consisting of benzyl carboxylate as poly(α-benzyl carboxylate ε-caprolactone) (PBCL), carboxyl side groups as poly(α-carboxyl-ε-

caprolactone) (PCCL), and a combination thereof as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)] (PCBCL).

Broadly stated, a method is provided for producing a gel forming composition comprising a block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), the PCL block further comprising pendant functional groups selected from the group consisting of benzyl carboxylate as poly(α-benzyl carboxylate ε-caprolactone) (PBCL), carboxyl side groups as poly(α-carboxyl-ε-caprolactone) (PCCL), and a combination thereof as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)] (PCBCL), the method comprising: preparing an α-benzyl carboxylate-ε-caprolactone (BCL) monomer; and performing a ring opening polymerization reaction of the monomer.

Broadly stated, a method is provided for the delivery of a bioactive agent to an individual, the method comprising: providing a carrier comprising a gel forming composition comprising a block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), the PCL block further comprising pendant functional groups selected from the group consisting of benzyl carboxylate as poly(α-benzyl carboxylate ε-caprolactone) (PBCL), carboxyl side groups as poly(α-carboxyl-ε-caprolactone) (PCCL), and a combination thereof as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)] (PCBCL); interacting the carrier and the bioactive agent together such that the block copolymer forms micelles around the bioactive agent; and administering the carrier and bioactive agent to an individual.

Broadly stated, a system is provided for the delivery of a bioactive agent to an individual, the system comprising a carrier and a bioactive agent, the carrier comprising a gel forming composition comprising a block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), the PCL block further comprising pendant functional groups selected from the group consisting of benzyl carboxylate as poly(α-benzyl carboxylate ε-caprolactone) (PBCL), carboxyl side groups as poly(α-carboxyl-ε-caprolactone) (PCCL), and a combination thereof as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)] (PCBCL), wherein the block polymer is capable of incorporating the bioactive agent into the carrier and the bioactive agent is released from the carrier when delivered to an individual.

Broadly stated, a method is provided for optimizing characteristics of a gel forming composition comprising a block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), the PCL block further comprising pendant functional groups selected from the group consisting of benzyl carboxylate as poly(α-benzyl carboxylate ε-caprolactone) (PBCL), carboxyl side groups as poly(α-carboxyl-ε-caprolactone) (PCCL), and a combination thereof as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)] (PCBCL), the method comprising varying properties of the block copolymer, the properties selected from the group consisting of the molecular weight of the block copolymer, the length of the block copolymer, altering the hydrophilic/lipophilic balance and level of benzyl caboxylate and carboxylic acid substitution on the PCL block, the ratio of PEG to PCBCL,

PCCL, or PBCL, the orientation of PEG to PCBCL, PCCL, or PBCL, and the extent of debenzylation within the PCL block.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1 shows the synthetic scheme for the preparation of α-benzyl carboxylate-ε-caprolactone (PBCL; α-carbon-substituted monomer);

Figure 2 shows the synthetic scheme for the preparation of PCBCL-PEG-PCBCL;

Figure 3 shows the ^{1}H NMR spectrum of PCBCL-PEG-PCBCL block copolymers;

Figure 4 shows the percent of conversion of monomer to polymer as a function of increasing the molar ratio of PEG to catalyst;

Figure 5 shows the shows the synthetic scheme for the preparation of PEG-PBCL-PEG;

Figure 6 shows the ^{1}H NMR spectrum of PEG-PBCL-PEG block copolymers;

Figure 7 shows the GPC chromatograph of block copolymers A) PBCL-PEG-PBCL B) PCBCL-PEG-PCBCL 27% reduced C) PCBCL-PEG-PCBCL 50% reduced D) PCBCL-PEG-PCBCL 75% reduced E) PCCL-PEG-PCCL;

Figure 8 shows the MALDI mass spectra of 8A) PBCL-PEG-PBCL 8B) PCBCL-PEG-PCBCL 27% reduced 8C) PCBCL-PEG-PCBCL 50% reduced 8D) PCBCL-PEG-PCBCL 75% reduced 8E) PCCL-PEG-PCCL (100 % reduced) block copolymers;

Figure 9 shows the sol-gel transition behaviour of 15% and 20% (W/W concentration) aqueous solution of 27.3% debenzylated copolymer;

Figure 10 shows the DSC determination of transition temperature of aqueous solution of 27.3% debenzylated copolymer;

Figure 11 shows the CMC of block copolymers at 25°C;

Figure 12 shows the comparison of thermoresponsive behavior of block copolymers with different percentages of debenzylation;

Figure 13 shows particle size change as a function of percentage of debenzylation;

Figure 14A shows particle size change as a function of temperature for different concentration of 27% debenzylated PCBCL-b-PEG-b-PCBCL;

Figure 14B shows the particle size change as a function of temperature for different concentration of 50% debenzylated PCBCL-b-PEG-b-PCBCL;

Figure 15 shows the changes in particle size as a function of pH value of solution at room temperature; and

Figures 16A - 16E show the effect of pH on changes in the size of micelles (1 mg/ml) as a function of temperature on polymeric micelles.

DETAILED DESCRIPTION OF EMBODIMENTS:

Gel forming block copolymers of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), and particularly to PEG-PCL block copolymers having optional pendant functional groups on the PCL, which can serve as implants for drug delivery into a host or as topical gels for regional drug release are provided. More specifically, the present disclosure relates to PEG-PCL block copolymers, wherein the PCL block further comprises benzyl carboxylate (PBCL), such as poly(α-benzyl carboxylate ε-caprolactone), carboxyl side groups (PCCL), such as poly(α-carboxyl-ε-caprolactone), or

both PBCL and PCCL functionalities (PCBCL), such as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)]. In some embodiments, the PEG-PCL block copolymer further comprises optional substituents selected from the group consisting of halo, OH, OC_{1-4}alkoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkenyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, CN, NO_2, $C(O)C_{1-4}$alkyl, $C(O)OC_{1-4}$alkyl, SO_2C_{1-4}alkyl, SO_2NH_2, SO_2NHC_{1-4}alkyl, phenyl, C_{1-4}alkylenephenyl, cholesteryl, poly(amine)s, protected poly(amines), polyamine-CF_3, and hydrazone.

Some embodiment can comprise a PEG-PCL copolymer wherein the PCL block can further comprise a functional group and a bioactive agent in which the block copolymer can form a micelle around the bioactive agent and the micelles can further form a gel. The bioactive agent may be selected from the group consisting of nucleic acid, protein, peptide and/or drug. Additionally, the bioactive agent may be selected from the group consisting of steroids, analgesics, anti-infectives, anti-inflammatories, anti-psychotics, anti-histamines, immunosuppressives, anti-angiogenics, antihypertensives, and oncolytics. The PEG-PBCL, PEG-PCCL or PEG-PCBCL block copolymer can form a micelle around the bioactive agent by chemical conjugation, electrostatic complexation and physical encapsulation.

In some embodiments, the gel forming copolymers and bioactive agent can be administered to an individual in any manner appropriate as known by those skilled in the art. For example the composition can be administered as an intra-operative spray in the surgical field, or as subcutaneous depots, or by intra-articular (joints) & intra-cavity (rectal, buccal, vaginal) routes.

One feature of the block copolymers of the present disclosure, which can be a function of their structural makeup, is the ability to manipulate or control the sol-gel transition of their respective hydrogels, including, for example, the ability to optimize the temperature at which the sol-gel transition occurs and/or to prolong the rate of release of several poorly soluble drugs. In other words, by modifying the structure or the overall length of the hydrophobic and hydrophilic blocks of the copolymer, one can improve the ability of the copolymers to serve as delivery systems. In some embodiments, the structure of the copolymer can comprise PEG-PCL polymers ranging from between 500-5000 g/mol for the PEG hydrophilic block, and between 1000 – 4000 g/mol for the PCL/functionalized-PCL hydrophobic block. In addition to the length of the copolymer, modification of the chemical structure of the functional side chains and the level of substitution upon said side chains on the copolymer can provide further advantages of the present disclosure, such as:

- to further optimize the temperature of the sol-gel transition;
- to further optimize the pH of the sol-gel transition;
- to achieve a desired stability of the copolymer; and
- to obtain optimum biodegradation, drug loading, and release or activation properties of the copolymer.

By way of example, the ratio of PEG to PCBCL, PCCL or PBCL may be manipulated to effect changes in sol/gel profile. The extent of debenzylation within the functionalized PCL block (ratio of PCCL to PBCL blocks) can also be used to change sol/gel profile.

EXPERIMENTAL EXAMPLES:

The following examples and figures are provided to aid the understanding of the present disclosure, the true scope of which is set forth in the claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit or scope of the invention.

Example 1: Synthesis of block copolymers

Hydroxyl-poly(ethylene glycol) (PEG) (Mw = 1450), diisopropylamine (99%), benzyl chloroformate (tech 95%), sodium (in kerosin), butyllithium (Bu-Li) in hexane (2.5 M solution), and palladium-coated charcoal can be purchased from Sigma, St. Louis, MO. ε-*Caprolactone* can be purchased from Lancaster Synthesis, UK. Stannous octoate was purchased from MP Biomedicals Inc., Germany.

Synthesis of block copolymers can be accomplished in three steps: i) preparation of α-benzyl carboxylate-ε-caprolactone (BCL) monomer; ii) ring opening polymerization of benzyl substituted monomer using dihydroxy PEG as initiator leading to the formation of poly (α-benzyl carboxylate-ε-caprolactone)-b-PEO-b-poly (α-benzyl-carboxylate-ε-caprolactone) (PBCL-b-PEO-b-PBCL) block copolymers; iii) partial or complete debenzylation (the reduction of benzyloxy carboxylate to a carboxyl group) of block copolymer at three different degrees leading to the preparation of poly[(α-carboxyl-ε-caprolactone)-co-(α-benzylcarboxylate-ε-caprolactone)]-b-PEO-b-poly[(α-carboxyl-ε-caprolactone)-co-(α-benzylcarboxylate-ε-caprolactone)] (PCBCL-b-PEO-b-PCBCL) block copolymers and poly (α-carboxy-ε-caprolactone)-b-PEO-b-poly(α-carboxy-ε-caprolactone).

Synthesis of a benzyl substituted monomer is known in the art and is described in Mahmud, A., X.B. Xiong, and A. Lavasanifar, Novel self-associating poly(ethylene oxide)-block-poly(epsilon-caprolactone) block copolymers with functional side groups on the polyester block for drug delivery. Macromolecules, 2006. 39(26): p. 9419-9428, herein incorporated by reference in its entirety.

Referring now to Figure 1, BCL can be synthesized by anionic activation of ε-caprolactone (3.1 mL) and further treatment with benzyl chloroformate (4.3 mL). Successful substitution of benzyl carboxylate on ε-caprolactone monomer can be evidenced by ^{1}H NMR spectroscopy.

Referring now to Figure 2, block copolymers of PBCL-*b*-PEG-*b*-PBCL can be synthesized through ring opening polymerization of α-benzyl carboxylate-ε-caprolactone by dihydroxylated PEG at different molecular weight ratios of PEG to PBCL. Ring-opening polymerization of BCL (1 g) with hydroxy PEG as initiator (0.5 g) and stannous octoate (16 mg) as catalyst can be used to prepare PBCL-b-PEO-b-PBCL. The debenzylation can be conducted on PBCL-*b*-PEG-*b*-PBCL in the presence of hydrogen gas to transform PBCL. Incomplete reduction of PBCL can lead to the formation of PCBCL in the blocks. The percentage of α-benzyl carboxylate-ε-caprolactone conversion to PBCL-b-PEO-b-PBCL can be determined by comparing the degree of polymerization of PBCL-b-PEO-b-PBCL measured by ^{1}H NMR to theoretical degree of polymerization. Partial catalytic debenzylation of PBCL-b-PEO-b-PBCL at different conditions can be accomplished using palladium, 10 wt. % on activated carbon to produce PCBCL-b-PEO-b-PCBCL with 27,

50, and 75 % of PBCL benzyl groups reduced to carboxyl groups, respectively. Complete debenzylation of 1 g of PCBCL-b-PEO-b-PCBCL can be accomplished by 250 mg of activated charcoal. Overall, five different block copolymers (PBCL-PEG-PBCL, PCBCL-PEG-PCBCL 27 % reduced, PCBCL-PEG-PCBCL 50% reduced, PCBCL-PEG-PCBCL 75% reduced, and PCBCL-PEG-PCBCL 100% reduced) were synthesized and used for further characterization studies. The characteristics are summarized in Table 1.

TABLE 1-Characteristics of synthesized block copolymers

polymer	[a] Percent of Reduction	Theoretical Mw	[b] Mw	[c] Mw	[b] Degree of polymerization		[c] Degree of polymerization	
					CCL Block	CCL Block	CCL Block	BCL Block
PBCL-PEG-PBCL	0	4428	3683	3435.1	N/A	9.0	N/A	8
PCBCL-PEG-PCBCL	27	4136	3506	3503	1.9	7.1	2	7
PCBCL-PEG-PCBCL	50	3887	3206	------	4.3	4.4	4	------
PCBCL-PEG-PCBCL	75	3618	3303	-------	8.0	2.0	8	------
PCBCL-PEG-PCBCL	100	3350	2367	2240.7	5.8	N/A	5	N/A

a - The number shown indicates the percent of debenzylation (reduction of benzyloxy carboxylate to carboxyl group) in each block copolymer determined by ^{1}H NMR spectroscopy.

b - Measured by ^{1}H NMR.

c - Measured by MALDI-TOF. N/A (not applicable)

^{1}H NMR spectroscopy of polymers in $CDCl_3$ as solvent can be used to study the composition of copolymers. The degree of polymerization for PBCL-b-PEO-b-PBCL, comparing peak intensity of CH2-O- (δ=4.1 ppm) to the

methylene protons of the benzyl carboxylate group (δ=5.15). Percentage of conversion can be calculated using the following equation:

$$\frac{Degree\,of\,Polymerization\,of\,PBCL-b-PEO-b-PBCL}{Theoretical\,Degree\,of\,Polymerization\,of\,PBCL-b-PEO-PBCL} \times 100$$

Referring now to Figure 3, the ^{1}H NMR spectrum of PCBCL-PEG-PCBCL block copolymers is shown. The number-average molecular weight of block copolymers was determined from the ^{1}H NMR spectrum comparing peak intensity of PEO (-CH2CH2O-, δ= 3.65 ppm) to that of PBCL or PCCL (-OCH2-, δ= 4.05 ppm) considering a 1450 g/mol molecular weight for PEO.

As further shown in Table 1 and Example 2, the molecular weight of synthesized copolymers can also be determined by Matrix-assisted laser desorption/ionisation-time of flight (MALDI-TOF) analysis. The comparison of the result of molecular weight and degree of polymerization obtained by two methods are summarized in the Table 1. The results were comparable to the copolymer's respective nominal molecular weights.

The polymerization can be performed with different ratio of PEG to catalyst while the ratio of monomer to PEG can be kept constant to investigate the effect of amount of PEG and catalyst on the percentage of monomer conversion of polymer. The ratio of polyethylene glycol to catalyst can be changed within a range of 2.6 to 6.4 to optimize the reaction condition. Referring now to Figure 4, the percent of monomer conversion to polymer is shown as a function of changes of the ratio of PEG to catalyst. Figure 4 shows that optimum conversion can occur at the molar PEG/catalyst ratio of 5.8.

Additionally, further alternate block copolymers can be synthesized for the purpose of micelle and gel forming compositions. For example and referring now to Figure 5, the synthesis pathway of PEG-PBCL-PEG is shown.

A PEO-b-PBCL block copolymer can be synthesized by ring opening polymerization of α-benzyl carboxylate-ε-caprolactone using methoxy-PEO as initiator and stannous octoate as catalyst as described in Mahmud, A., X.B. Xiong, and A. Lavasanifar, 2006, *supra*.

PEG-PBCL (2.2 mmole) and 4-Dimethylaminopyridine (DMAP) (2.2 mmole) can be dissolved in 50 mL anhydrous CH_2Cl_2, and the solution can be cooled down to 0 °C in ice-water bath. Adipoyl chloride (1.05 mmol) can be dissolved in 20 mL of anhydrous CH_2Cl_2 and added drop-wise into the solution. The reaction can be allowed to proceed under refluxing for 48 hours. The solution can be then washed twice with 1 N HCl and twice with water as described in Li, F., et al., Synthesis and gelation properties of PEG-PLA-PEG triblock copolymers obtained by coupling monohydroxylated PEG-PLA with adipoyl chloride. Langmuir, 2007. 23(5): p. 2778-83, herein incorporated by reference in its entirety.

Figure 6 shows the ^1H NMR spectrum of PEG-PBCL-PEG and the corresponding peak assignments.

Example 2: Characterization of prepared block copolymers

The gel permeation chromatography (GPC) system (HEWLETT PACKARD series 1100) with a refractive index detector (Waters 410) can be used to investigate the molecular weight and molecular weight distributions of

prepared block copolymers. A polymer solution (20 uL of 20 mg/mL in tetrahydrofuran (THF)) can be manually injected into a 7.8 × 300 mm Styragel HMW 6E column (Waters Inc. Milford, MA), which can be attached to an HP 1100 pump. The column can be eluted with 1 mL/min THF. The elution pattern can be detected by refractive index (model 410; Waters Inc.) using Poly(ethylene glycol)s in a molecular weight range of 985-3700 Da as molecular weight standards.

GPC can be used to investigate the polydispersity of copolymers and the effect of percentage of debenzylation on polydispersity. The polydispersity of five copolymers with different percentages of debenzilation can be determined by GPC. Figure 7 shows the chromatographs obtained for each of these copolymers: a) PBCL-PEG-PBCL b) PCBCL-PEG-PCBCL 27% reduced c) PCBCL-PEG-PCBCL 50% reduced d) PCBCL-PEG-PCBCL 75% reduced e) PCCL-PEG-PCCL. Comparison of the graphs with different degree of debenzilation shows that copolymers with complete debenzylation and one without any debenzylation can have a monodisperse chromatograph with polydispesity range between 1.3-1.6. On the other hand, incomplete debenzylation produces bimodal distribution of polymers. In other words, GPC assessment of block copolymers can show bimodal chromatograph for partially debenzylated polymers where as PCCL-b-PEG-b-PCCL and PBCL-b-PEG-b-PBCL copolymers were monodispersed. This observation can be interpreted as demonstrating the existence of the mixture of PBCL-PEG-PBCL and PCCL-PEG-PCCL in the partially debenzylated block copolymers.

MALDI-TOF can be used to determine the molecular weight and degree of polymerization of synthesized copolymers. 2, 5-dihydroxybenzoic acid (DHB) can be used as matrix, the polymer samples can be dissolved in methanol at a concentration of 5 mg/mL. Sodium chloride (2 mg/ml in methanol) can be used as cationization agent. Solutions of polymer, matrix, and salt can be mixed in a 2:2:1 volume ratio (polymer/matrix/salt) and the mixture was thoroughly vortexed. The sample mixture can be then added on a stainless steel target plate and the spots can be dried at room temperature prior to insert into the instrument.

Referring now to Figures 8A-E, the results of the MALDI mass spectra are shown for a) PBCL-PEG-PBCL; b) PCBCL-PEG-PCBCL 27% reduced; c) PCBCL-PEG-PCBCL 50% reduced; d) PCBCL-PEG-PCBCL 75% reduced; and e) PCCL-PEG-PCCL (100 % reduced) block copolymers respectively. The spectrum of incomplete debenzylated copolymers shows polydisperse polymer samples which can be confirmed by GPC results. The peak intensities decrease with increasing mass-to-charge ratio (m/z) values until the signal is indistinguishable from the baseline value at approximately m/z 3200 Da. Due to the rather broad molar mass distribution, there can be mass discrimination effects causing a decreasing detection response at higher masses. Lighter molecules can be preferentially desorbed and ionized in the MALDI process, suppressing desorption and ionization of higher molar mass molecules. The peaks corresponding to each block series observed in the MALDI mass spectrum of block copolymers can be compared with the MALDI mass spectrum of PEG, α-benzylcarboxylate-ε-caprolactone (BCL) blocks

which show a peak-to-peak increment of 248, and α-carboxyl-ε-caprolactone (CCL) which show a peak-to-peak increment of 158 after subtraction of PEG and sodium cation mass, which corresponds to the mass of BCL and CCL respectively.

Example 3: Characterization of PCBCL-PEG-PCBCL hydrogels

The phase transition of aqueous colloidal solutions at different block copolymer concentrations and temperatures can be followed using test tube inversion method and differential scanning calorimetry (DSC).

By Inverse Flow Method

The test tube inversion method can be used to determine the sol-gel transition of synthesized block copolymers. The copolymers can be dissolved in distilled water at concentrations of 15 (w/w) in a vial (volume: 4 mL). The vials can be immersed in a water bath with the temperature set at 20°C. The temperature of the water bath can be allowed to increase by 10°C every 5 min up to 60°C. Phase transition (flow/no flow) can be assessed by inverting the incubated tube containing polymer aqueous solutions, vertically. The copolymer solution can be considered to be gel when the solution does not flow at all when the vial was inverted. The incubation temperature at which this phenomenon is observed can be recorded as the transition temperature for that block copolymer.

Referring now to Figure 9, the results of a test tube inversion show sol-gel transition behaviour of 15% and 20% concentration (W/W) aqueous solution of 27.3% debenzylated copolymers. At 15% the composition is in sol phase up to approximately 35°C and becomes a gel as the temperature

increases until approximately 48°C where is becomes a sol again. At 20% the composition is in sol phase up to approximately 30°C and becomes a gel as the temperature increases until approximately 44°C where is becomes a sol again.

TABLE 2: Characterization of the sol-gel behaviour Inverse Flow Method

Percentage of Debenzylation	Ratio of PCBCL/PEG	Gelation Starting Point [1]	Gelation Ending Point [2]
13.5	0.18	29	43
18.4	0.25	30	51
23.0	0.22	38	48
27.3	0.28	39	51
29.2	0.26	30	43
60.7	0.25	36	----

[1] Temperature in °C corresponding to the starting point of transition from sol to gel of copolymers aqueous solutions

[2] Temperature in °C at which free standing gels starts to become solution

By Differential Scanning Calorimetry (DSC)

The thermal behaviour, or lower critical solution temperature (LCST), of both hydrous copolymer and copolymers in the solid state can be determined using a differential scanning calorimeter. Samples (dry copolymers and hydrogels) can be first heated from -90 to 80°C at a heating rate of 1°C/min, then cooled to -90°C, and then reheated again to 80°C at the same rate. The sample pans for hydrogels can be filled with distilled water and for dry copolymers empty pans can be used as reference.

Referring now to Figure 8, the determination by DSC of transition temperature of an aqueous solution of 27.3% debenzylated copolymer is shown as approximately 30°C. This confirms the test tube inversion results of Figure 9.

The ^{1}H NMR results shown in Table 3 confirmed the preparation of block copolymers. PCBCL-*b*-PEG-*b*-PCBCL block copolymers displayed sol to gel transition behaviour as a result of an increase in temperature. Variations in the level of benzyl/carboxyl substitution on the PCBCL block can affect the transition temperature of PCBCL-*b*-PEG-*b*-PCBCL block copolymers. For example, referring to Table 2, PCBCL-*b*-PEG-*b*-PCBCL block copolymers with a PEG/PCBCL ratio of 0.26 and 29% level of benzyl/carboxyl substitution can show an appropriate sol to gel transition (~30°C) for the preparation of an injectable implants.

TABLE 3: Characterization of Synthesized Copolymers by ^{1}H NMR

Number Average Molecular weight	**Ratio of PCBCL/PEG**	**Percentage of Debenzylation**
1699.5	0.22	13.1
1446.4	0.18	13.5
1944.9	0.25	18.4
1683.2	0.22	23.0
2090.6	0.28	27.3
1943.3	0.26	29.2
1614.1	0.25	60.7

Example 4: Self assembly of block copolymers and the characterization of self assembled structures

Self-assembly of block copolymers can be carried out by dissolving the copolymers in water. Aqueous samples can be kept in 8 °C overnight. A change in the fluorescence excitation spectra of pyrene in the presence of varied concentrations of block copolymers can be used to measure the critical micellar concentration (CMC) of prepared block copolymers. Pyrene can be dissolved in acetone and can be added to 5 mL volumetric flasks to provide a concentration of 6×10^{-7} M in the final solutions. Acetone can then be evaporated and replaced with aqueous polymeric micellar solutions with concentrations ranging from 0.05 to 1000 µg/mL. Samples can be heated at 65 °C for an hour, cooled to room temperature overnight, and deoxygenated with nitrogen gas prior to fluorescence measurements. The excitation spectrum of pyrene for each sample can be obtained at room temperature using a Varian Cary Eclipse fluorescence spectrophotometer (Victoria, Australia). Emission wavelength and excitation/emission slit can be set at 390 and 5 nm, respectively. The intensity ratio of peaks at 338 nm to those at 333 nm can be plotted against the logarithm of copolymer concentration. The CMC can be measured from a sharp rise in intensity ratios (I338/I333) at the onset of micellization.

Referring now to Figure 11, CMC values of block copolymers with different percentages of debenzylation can be determined by fluorescence spectroscopy using pyrene as a fluorescence probe at 25°C. Table 4

summarizes the CMC values of copolymers with different percentages of debenzylation.

TABLE 4 Characterization of the self assembly of different block copolymers

Percentage of Debenzylation	CMC values (μg/mL)	Lower Critical Solution temperature (2mg/ml concentration)	Lower Critical Solution pH (2mg/ml concentration)
0	0.79	N/A	N/A
27	0.65	35	4.5
50	0.86	40	4.5
75	1.18	40	4.5

The micelle formation of block copolymers can be assessed by CMC measurement. As would be understood by one skilled in the art, low CMC values shown in Table 4 can indicate that micelles formed from block copolymers can be thermodynamically stable and can be stable even following dilution. The hydrophilicity of block copolymers can depend on the percentage of debenzylation of polymers and the PEG/PCBCL ratio. A higher percentage of debenzylation can mean more carboxylic groups and less benzyl groups on the polymer, therefore increasing the percentage of debenzylation can cause an increase in hydrophilicity. The values shown in Table 4 can suggest that increasing hydrophilicity reduces the ability of self assembling micelles, and can therefore lead to increases in CMC values. As shown in Table 4, the CMC value for the 75% debenzylated copolymer is

higher than the other copolymers which are more hydrophobic in nature than the 75% debenzylated copolymer.

Example 5: Assessing the effect of temperature on the self assembly of block copolymers

The thermoresponsive behavior of polymeric micelles can be assessed by Dynamic Light Scattering (DLS) at different temperatures. The changes in the size of micelles as a function of increasing the temperature between 25-55°C can be assessed using a ZETA-SIZER, MALVERN Nano-ZS90 (Malvern Instrument Ltd., Malvern, U.K.). Copolymers can be dissolved in distilled water at 1, 2, 3, and 5 mg/mL concentrations. Samples can be filtered through Fisherbrand 0.20 µm Nylon filter before measurement.

The thermoresponsive size change of polymeric micelles can be studied by DLS. Figure 12 summarizes the changes in the diameter of five block copolymer micelles with different percentages of debenzylation as a function of temperature. As shown in figure 12, micelle size of most partially debenzylated copolymers decreased by increasing temperature. As an exception, the 27 % partially debenzylated copolymer demonstrated an increase in micelle size as temperature increased. In addition, PBCL-PEG-PBCL does not contain carboxylic groups on the caprolactone chain and does not show any changes in micellar size at different temperatures and is not thermoresponsive. The micellar size of synthetized copolymers at room temperature are summarized in figure 13.

Increasing temperature can promote the release of water molecules from water clusters surrounding carboxylic groups on hydrophobic

caprolactone chains and PEG. At 27% partial debenzylation, this phenomena can lead to micellar tendency to aggregate by strengthened hydrophobic interaction at increased temperatures as the micellar outer and inner surfaces can be more hydrophobic (as is known in the art and described in Wei, H., et al., Self-assembled thermoresponsive micelles of poly(N-isopropylacrylamide-b-methyl methacrylate). Biomaterials, 2006. 27(9): p. 2028-34.). As such, by increasing the temperature, the measured micellar diameter can be increased. In the case of 50 and 75 % partially debenzylated copolymers, 50% or more of the benzyl groups on the polymer chain have been converted to carboxylic groups. The more carboxylic groups in the structure of polymer can lead to more water molecules involved in the structure of polymer micelles in water. With an increasing temperature, dehydration can happen, but because polymers more hydrophilic than the 27% debenzylated copolymer do not contain enough inter-micellar hydrophobic interaction to create an increase in size, the decrease in amount of water cluster surrounding PEG and carboxylic groups can lead to shrinkage in the size of micelles.

Block copolymers with complete debenzylation (100%) contain the highest amount of carboxylic groups sitting on the caprolactone chain, meaning more water molecules can become involved in the structure of polymeric micelle in water. As depicted in Figure 12, the 100% debenzylated copolymer can have the sharpest decrease in micelle size by increasing the temperature. Figure 13 shows the comparison of micellar size of five different copolymers at room temperature and it can be noted that by increasing the

amount of carboxylic groups in the structure of block copolymers, measured micellar size increases, which suggests the existence of water clustering around carboxylic groups.

The effect of concentration of polymeric aqueous solution on thermoresponsive self assembly of block copolymers with 27 and 50% debenzylated can be also investigated using DLS. Figures 14A and 14B summarize the micellar size changes as a function of temperature for different polymer concentrations of 27% debenzylated PCBCL-b-PEG-b-PCBCL and 50% debenzylated PCBCL-b-PEG-b-PCBCL respectively. It can be noted that by increasing the concentration, the thermoresponsive behavior of micelles can become more noticeable.

Referring to Figure 14B, solutions of 5 mg/mL block copolymers with 50% carboxylic group content can become turbid by increasing the temperature. The higher content of carboxylic groups can be the reason for turbidity at higher temperature, as increasing the temperature can cause dehydration of carboxylic groups, which increase the hydrophobicity of block copolymers. The greater amount of carboxylic groups on 50% debenzylated copolymers as compared to 27%, can lead to higher hydrophobic interaction between caprolacton blocks by increasing the temperature. This can be a cause of occurance of turbidity for fifty percent debenzylated polymeric micelle at higher concentrations. The 50% debenzylated polymer has more carboxcylic groups than 27% debenzylated polymer; therefore the chance of hydrophobic interactions can occur more often in 50% debenzylated the former block copolymer, which can lead to turbidity in solution by increasing

the temperature. In addition, the lower critical solution temperature (LCST) can be obtained from the break point in size change from Figures 14A and 14B. The LCST for the 27% debenzylated polymer can be approximately 35 °C, while for the 50% debenzylated polymer, the LCST can be approximately 41 °C. As such, carboxylic content can have an influence on LCST and LCST can differ for different polymeric micelle solutions based on carboxylic group content.

Polymeric micelles can show thermoresponsive behavior by increasing temperature, which is affected by carboxylic group content of the block copolymers, and the concentration of polymeric micellar solution.

Example 6: Assessing the effect of pH on the self assembly of block copolymers

The pH-sensitivity of the self-assembly process can be examined by measuring particle size change as a function of pH using DLS. To determine whether aqueous solution of block copolymers exhibit a pH response, the change of the average diameter as a function of pH can also be confirmed at the polymer concentration of 1 mg/ml by DLS at different temperatures. The pH of aqueous solution of block can be changed by adding 1 N HCL, and 1% V/V Triethylamine as needed.

Figure 15 depicts that polymeric micelles of room temperature copolymers with different carboxylic content can have significant size change at pH 4.5, while micelles made of copolymer with no carboxyl group can have negligible size changes as a function of pH. Figure 15 shows a sharp increase in micellar size at pH 4.5 which is near the pKa of a carboxylic group,

which means that at pH 4.5 carboxylic groups become half-deionized or in other words become more hydrophobic. In contrast, polymeric micellar size of PBCL-b-PEG-b-PBCL copolymers can show insignificant changes by increasing the pH.

Partial conversion of α-benzyl carboxylate groups sitting on caprolactone chains to carboxylic groups by debenzylation can introduce a pH sensitivity potential to a block copolymers. By decreasing the pH of polymeric solutions, carboxylic group of copolymers can become deionized. Therefore, caploracton blocks in block copolymers can become more hydrophobic, similar to the way an increase in temperature can cause an increase in hydrophobic interaction. In addition, micelles tend to aggregate by strengthened hydrophobic interactions. This behaviour can rely on the transition of the micelles from hydrophilic to hydrophobic due to the deionization of carboxylic group by decreasing the pH.

In addition, thermoreversible behaviour of polymeric micelles at different pH levels can be assessed for each copolymer by increasing the temperature. Referring now to Figures 16A-16E, polymeric micelles can keep their thermoresponsive behaviour as pH varies. The point at which a curve begins to sharply increase can be reflective of the sol-gel transition temperature for that copolymer at that pH. In a pH 3 solution (not shown), an increase in temperature can cause the micellar solution become turbid, which can be a result of the deionization of carboxylic groups and increased hydrophobicity of the polymeric micelles. In Figure 16A, micelle size of a 27% debenzylated polymer is shown as a function of temperature for pH 4.5, pH 7,

and pH 9. In Figure 16B, micelle size of a 50% debenzylated polymer is shown as a function of temperature for pH 4.5, pH 7, and pH 9. In Figure 16C, micelle size of a 75% debenzylated polymer is shown as a function of temperature for pH 4.5, pH 7, and pH 9. In Figure 16D, micelle size of a 27% debenzylated polymer, a 50% debenzylated polymer, and a 75% debenzylated polymer are shown as a function of temperature for pH 9. In Figure 16E, micelle size of a 27% debenzylated polymer, a 50% debenzylated polymer, and a 75% debenzylated polymer are shown as a function of temperature for pH 7.

Although a few embodiments have been shown and described, it will be appreciated by those skilled in the art that various changes and modifications might be made without departing from the scope of the invention. The terms and expressions used in the preceding specification have been used herein as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited only by the claims that follow.

WE CLAIM:

1. A gel forming composition comprising a block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), the PCL block further comprising pendant functional groups selected from the group consisting of benzyl carboxylate as poly(α-benzyl carboxylate ε-caprolactone) (PBCL), carboxyl side groups as poly(α-carboxyl-ε-caprolactone) (PCCL), and a combination thereof as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)] (PCBCL).
2. The composition of claim 1 wherein the block copolymer is partially debenzylated at 27% debenzylation.
3. The composition of claim 1 wherein the PCL block further comprises pendant functional groups selected from the group consisting of halo, OH, OC_{1-4}alkoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkenyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, CN, NO_2, $C(O)C_{1-4}$alkyl, $C(O)OC_{1-4}$alkyl, SO_2C_{1-4}alkyl, SO_2NH_2, SO_2NHC_{1-4}alkyl, phenyl, C_{1-4}alkylenephenyl, cholesteryl, poly(amine)s, protected poly(amines), polyamine-CF_3, hydrazone, and any combination thereof.
4. The composition of claim 1 wherein the block copolymer comprises at least one hydrophilic block and at least one hydrophobic block.
5. The composition of claim 4 wherein the at least one hydrophilic block comprises PEG polymers ranging between 500-5000 g/mol.
6. The block copolymer of claim 4 wherein the at least one hydrophobic block comprises PCL and functionalized PCL polymers ranging between 1000 – 4000 g/mol.

7. A method of producing a gel forming composition comprising a block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), the PCL block further comprising pendant functional groups selected from the group consisting of benzyl carboxylate as poly(α-benzyl carboxylate ε-caprolactone) (PBCL), carboxyl side groups as poly(α-carboxyl-ε-caprolactone) (PCCL), and a combination thereof as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)] (PCBCL), the method comprising:

   preparing an α-benzyl carboxylate-ε-caprolactone (BCL) monomer; and

   performing a ring opening polymerization reaction of the monomer.

8. The method of claim 7 wherein the method further comprises performing a debenzylation reaction on the block copolymer.

9. The method of claim 8 wherein the debenzylation of the block copolymer is partial debenzylation.

10. The method of claim 8 wherein the debenzylation of the block copolymer is complete debenzylation.

11. The method of claim 7 using dihydroxy PEG as an initiator for the ring opening polymerization.

12. The method of claim 11 wherein the ring opening polymerization is performed with a ratio of 5.8 PEG to a catalyst.

13. The method of claim 7 wherein the method further comprises adding pendant functional groups to the PCL block, the pendant functional groups selected from the group consisting of halo, OH, OC_{1-4}alkoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkenyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, CN,

NO_2, $C(O)C_{1-4}$alkyl, $C(O)OC_{1-4}$alkyl, SO_2C_{1-4}alkyl, SO_2NH_2, SO_2NHC_{1-4}alkyl, phenyl, C_{1-4}alkylenephenyl, cholesteryl, poly(amine)s, protected poly(amines), polyamine-CF_3, hydrazone, and any combination thereof.

14. A method of delivery of a bioactive agent to an individual, the method comprising:

providing a carrier comprising a gel forming composition comprising a block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), the PCL block further comprising pendant functional groups selected from the group consisting of benzyl carboxylate as poly(α-benzyl carboxylate ε-caprolactone) (PBCL), carboxyl side groups as poly(α-carboxyl-ε-caprolactone) (PCCL), and a combination thereof as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)] (PCBCL);

interacting the carrier and the bioactive agent together such that the block copolymer forms micelles around the bioactive agent; and

administering the carrier and bioactive agent to an individual.

15. The method of claim 14 wherein the micelles form a hydrogel.

16. The method of claim 14 wherein the block copolymer forms micelles around the bioactive agent in a manner selected from the group consisting of chemical conjugation, electrostatic complexation, and physical encapsulation.

17. The method of claim 14 wherein the bioactive agent is hydrophobic.

18. The method of claim 14 wherein the bioactive agent is non-hydrophobic.

19. The method of claim 14 wherein the bioactive agent is selected from the group consisting of nucleic acid, protein, peptide, and drug.

20. The method of claim 14 wherein the bioactive agent is selected from the group consisting of steroids, analgesics, anti-infectives, anti-inflammatories, anti-psychotics, anti-histamines, immunosuppressives, anti-angiogenics, antihypertensives, and oncolytics.

21. The method of claim 14 wherein administration of the carrier and bioactive agent to an individual is done locally.

22. The method of claim 14 wherein administration of the carrier and bioactive agent to an individual is done subcutaneously.

23. The method of claim 14 wherein manner of administration of the carrier and bioactive agent to an individual is selected from the group consisting of intra-operative spray, subcutaneous depot, intra-articular routes, and intra-cavity routes.

24. The method of claim 14 wherein the PCL block further comprises pendant functional groups selected from the group consisting of halo, OH, OC_{1-4}alkoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkenyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, CN, NO_2, $C(O)C_{1-4}$alkyl, $C(O)OC_{1-4}$alkyl, SO_2C_{1-4}alkyl, SO_2NH_2, SO_2NHC_{1-4}alkyl, phenyl, C_{1-4}alkylenephenyl, cholesteryl, poly(amine)s, protected poly(amines), polyamine-CF_3, hydrazone, and any combination thereof.

25. A system for the delivery of a bioactive agent to an individual, the system comprising a carrier and a bioactive agent, the carrier comprising a gel forming composition comprising a block copolymer of poly(ethylene glycol)

(PEG) and poly(ε-caprolactone) (PCL), the PCL block further comprising pendant functional groups selected from the group consisting of benzyl carboxylate as poly(α-benzyl carboxylate ε-caprolactone) (PBCL), carboxyl side groups as poly(α-carboxyl-ε-caprolactone) (PCCL), and a combination thereof as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)] (PCBCL), wherein the block polymer is capable of incorporating the bioactive agent into the carrier and the bioactive agent is released from the carrier when delivered to an individual.

26. The system of claim 25 wherein the carrier is capable of a temperature dependent sol-gel transition.

27. The system of claim 25 wherein the carrier is capable of a pH dependent sol-gel transition.

28. The system of claim 25 wherein the carrier is soluble at room temperature and gel at body temperature.

29. The system of claim 25 wherein the carrier forms an in situ implant upon delivery to an individual by injection.

30. The system of claim 25 wherein the carrier forms a film upon topical delivery to an individual.

31. The system of claim 25 wherein the carrier has decreased critical gelation concentration.

32. The system of claim 25 wherein the carrier has mucoadhesive properties.

33. The system of claim 25 wherein the PCL block further comprises pendant functional groups selected from the group consisting of halo, OH, OC_{1-4}alkoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkenyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-}$

$_4$alkyl)(C_{1-4}alkyl), CN, NO_2, C(O)C_{1-4}alkyl, C(O)OC_{1-4}alkyl, SO_2C_{1-4}alkyl, SO_2NH_2, SO_2NHC_{1-4}alkyl, phenyl, C_{1-4}alkylenephenyl, cholesteryl, poly(amine)s, protected poly(amines), polyamine-CF_3, hydrazone, and any combination thereof.

34. A method for optimizing characteristics of a gel forming composition comprising a block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL), the PCL block further comprising pendant functional groups selected from the group consisting of benzyl carboxylate as poly(α-benzyl carboxylate ε-caprolactone) (PBCL), carboxyl side groups as poly(α-carboxyl-ε-caprolactone) (PCCL), and a combination thereof as poly[(a-carboxyl-ε-caprolactone)-co-(α-benzyl carboxylate ε-caprolactone)] (PCBCL), the method comprising varying properties of the block copolymer, the properties selected from the group consisting of the molecular weight of the block copolymer, the length of the block copolymer, altering the hydrophilic/lipophilic balance and level of benzyl caboxylate and carboxylic acid substitution on the PCL block, the ratio of PEG to PCBCL, PCCL, or PBCL, the orientation of PEG to PCBCL, PCCL, or PBCL, and the extent of debenzylation within the PCL block.

35. The method of claim 34 wherein the characteristic of the gel forming composition to be optimized is selected from the group consisting of the temperature of sol-gel transition, pH of sol-gel transition, stability of the copolymer, biodegradation, bioactive agent loading, bioactive agent release, and activation properties of the copolymer.

36. The method of claim 34 wherein the properties further comprise the addition of pendant functional groups to the PCL block, the pendant functional groups selected from the group consisting of halo, OH, OC_{1-4}alkoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkenyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, CN, NO_2, $C(O)C_{1-4}$alkyl, $C(O)OC_{1-4}$alkyl, SO_2C_{1-4}alkyl, SO_2NH_2, SO_2NHC_{1-4}alkyl, phenyl, C_{1-4}alkylenephenyl, cholesteryl, poly(amine)s, protected poly(amines), polyamine-CF_3, hydrazone, and any combination thereof.

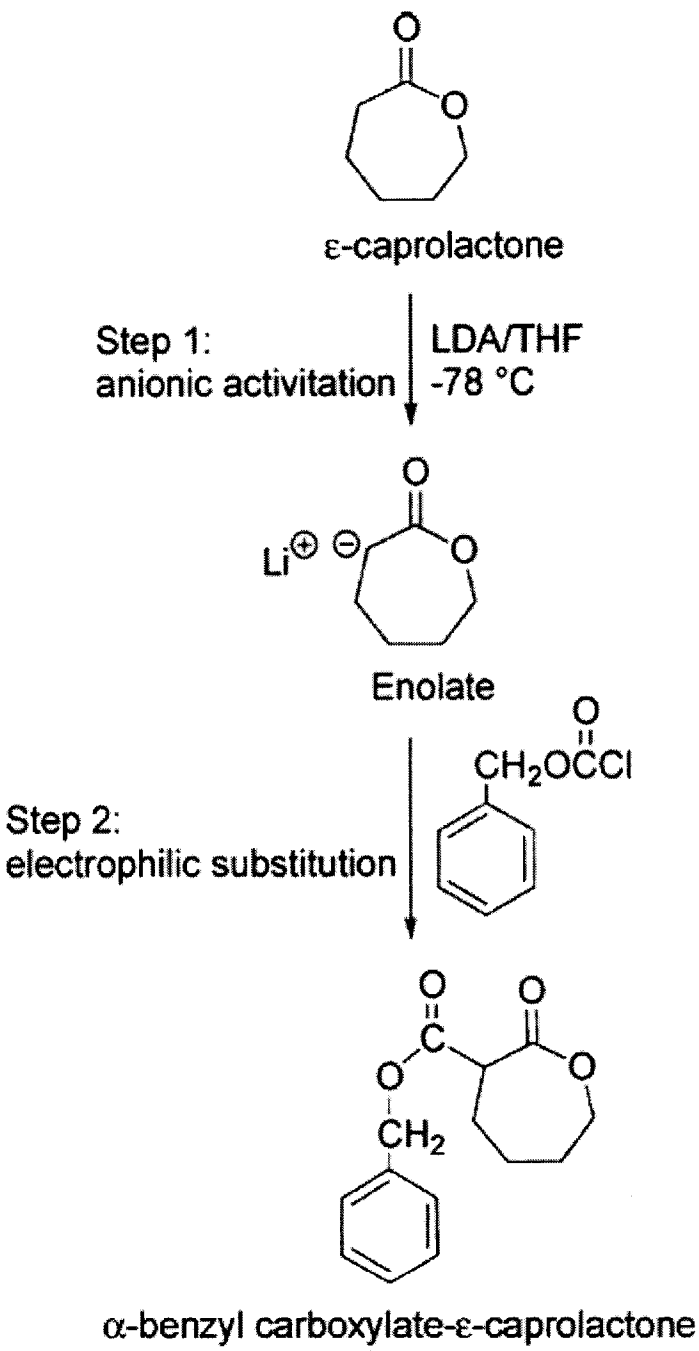

ε-caprolactone
Step 1:
anionic activitation
LDA/THF
-78 °C
Li
Enolate
Step 2:
electrophilic substitution
CH2OCCl
α-benzyl carboxylate-ε-caprolactone

Figure 1

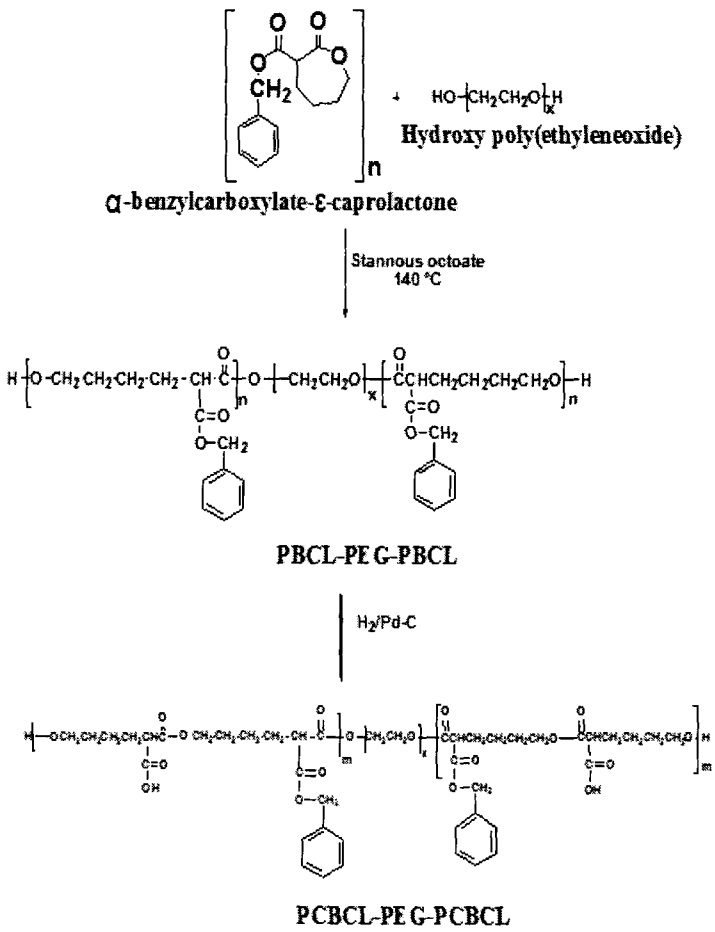

Hydroxy poly(ethyleneoxide)
α-benzylcarboxylate-ε-caprolactone
Stannous octoate
140 °C
PBCL-PEG-PBCL
H2/Pd-C
PCBCL-PEG-PCBCL

Figure 2

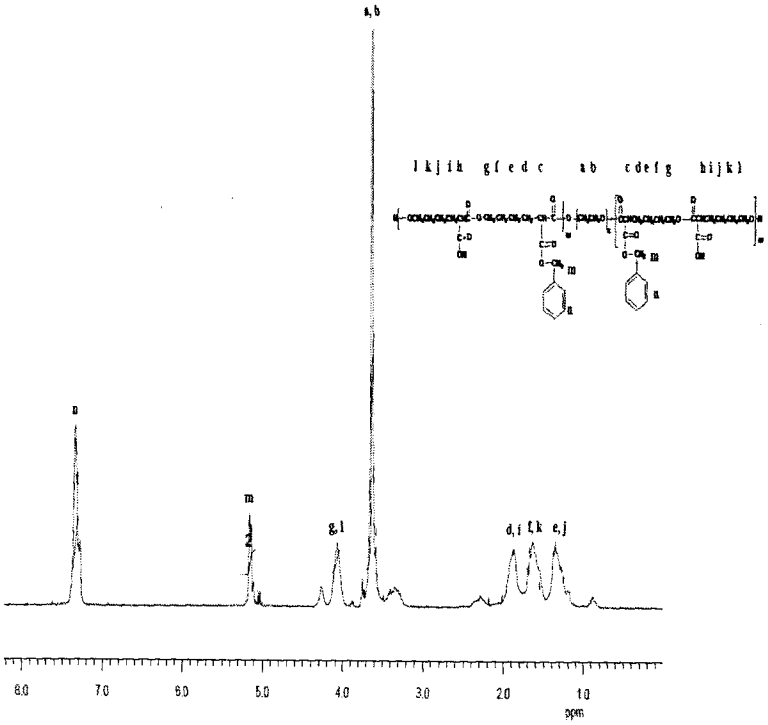

a,b
l k j i h g f e d c a b c d e f g h i j k l
n
m
g,l
d,j f,k e,j
8.0
7.0
6.0
5.0
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3.0
2.0
1.0
ppm

Figure 3

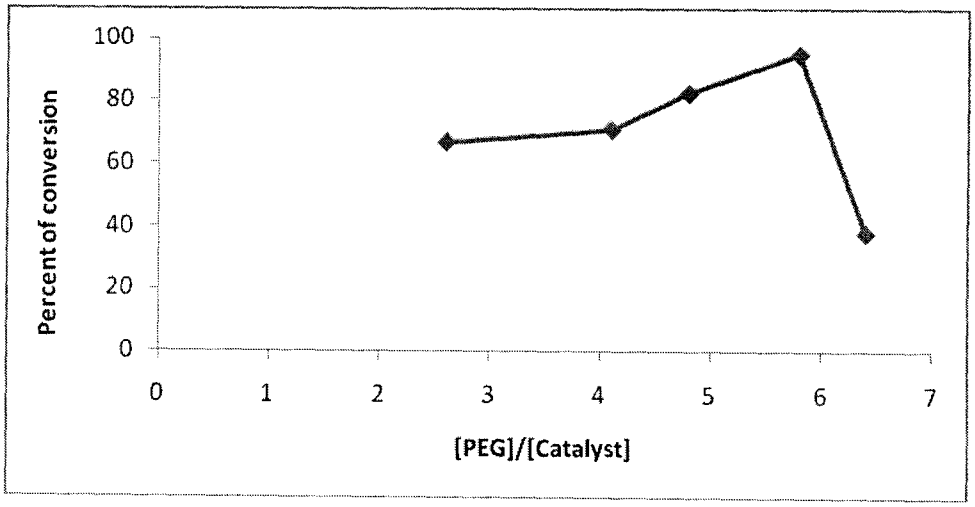
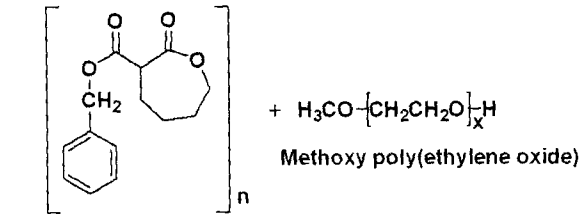
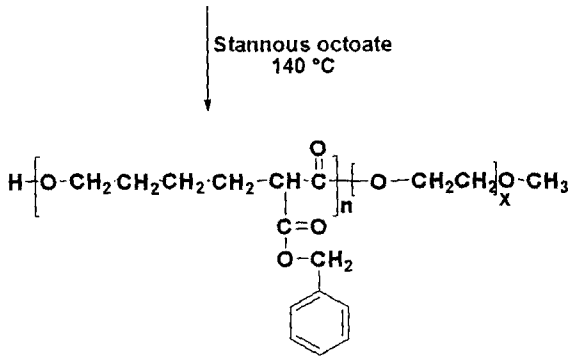

Percent of conversion
100
80
60
40
20
0
0
1
2
3
4
5
6
7
[PEG]/[Catalyst]

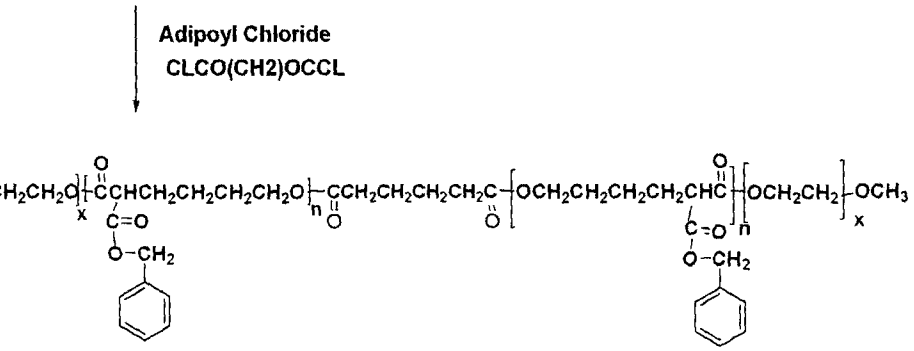
Figure 4



α-benzylcarboxylate-ε-caprolactone



PBCL-PEG



PEG-PBCL-PEG

Figure 5

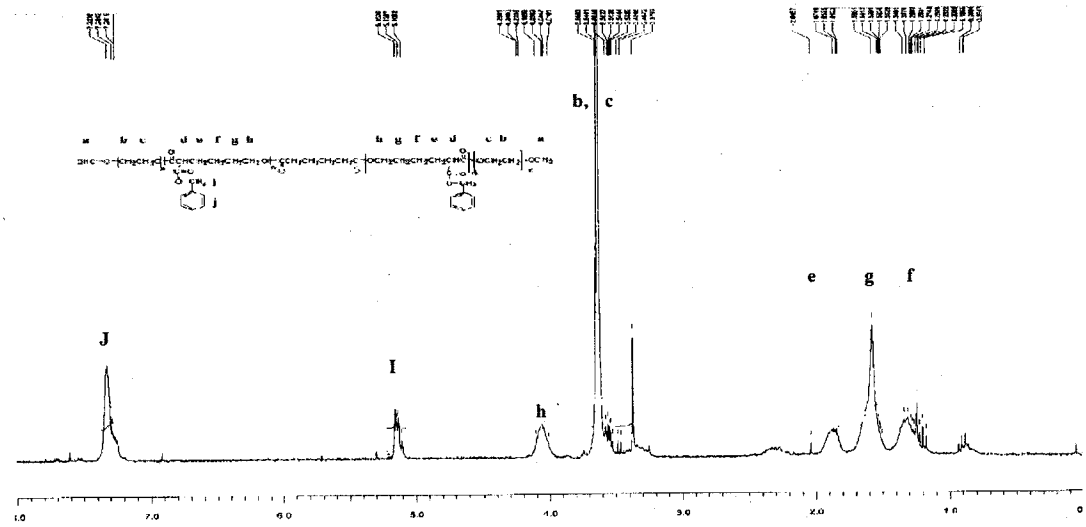


Figure 6

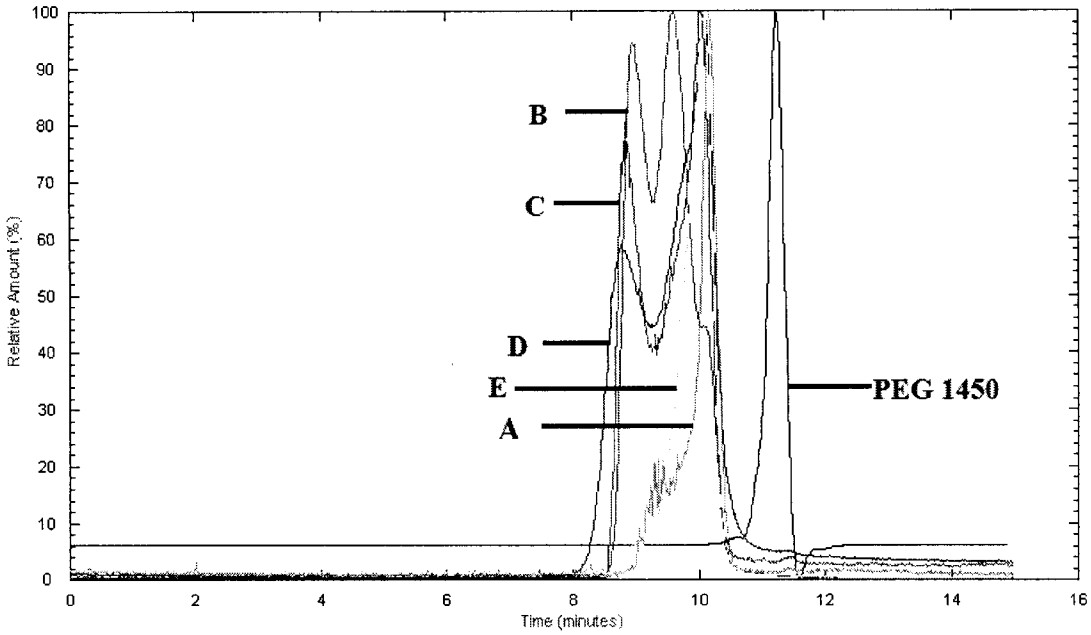


Figure 7

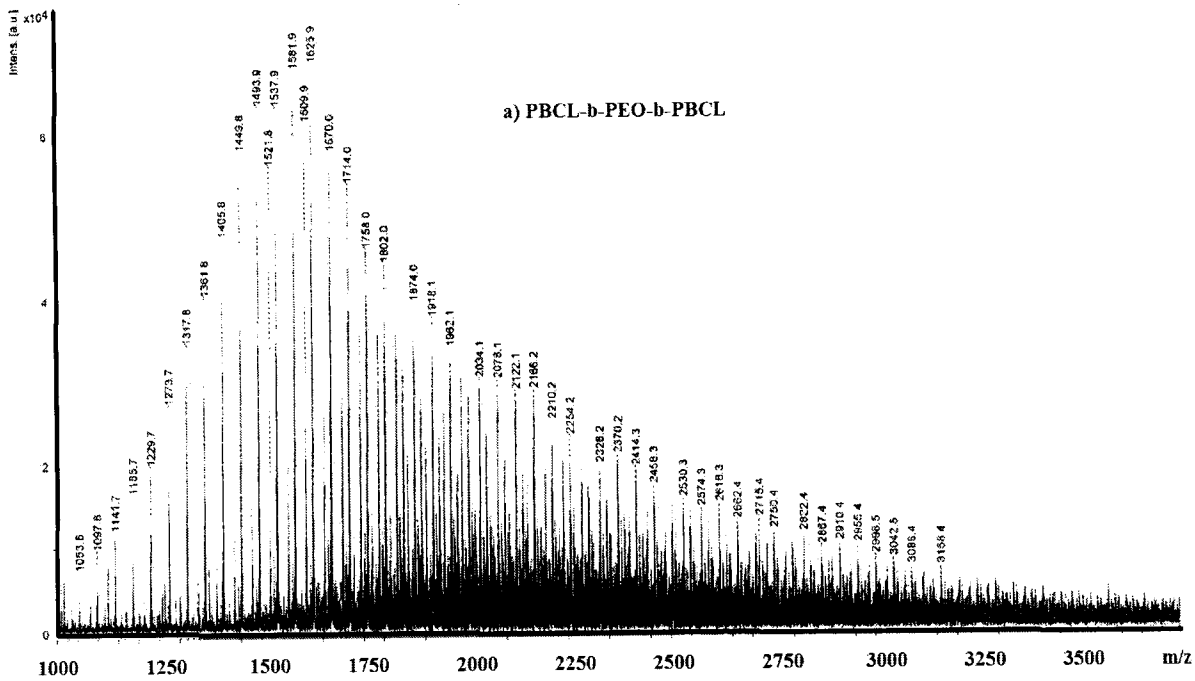

a) PBCL-b-PEO-b-PBCL
Intens. [a.u.]
x10^4
0
2
4
6
1000
1250
1500
1750
2000
2250
2500
2750
3000
3250
3500
m/z

Figure 8A

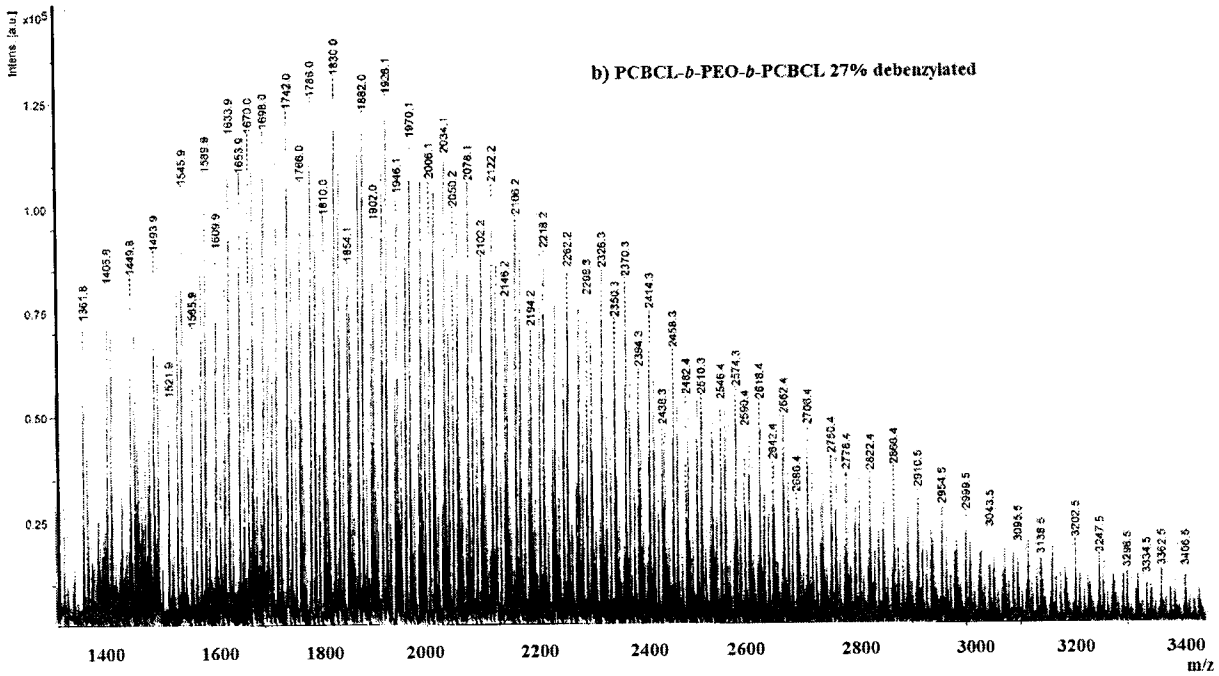

b) PCBCL-b-PEO-b-PCBCL 27% debenzylated
Intens. [a.u.]
x10^5
1.25
1.00
0.75
0.50
0.25
1400
1600
1800
2000
2200
2400
2600
2800
3000
3200
3400
m/z

Figure 8B

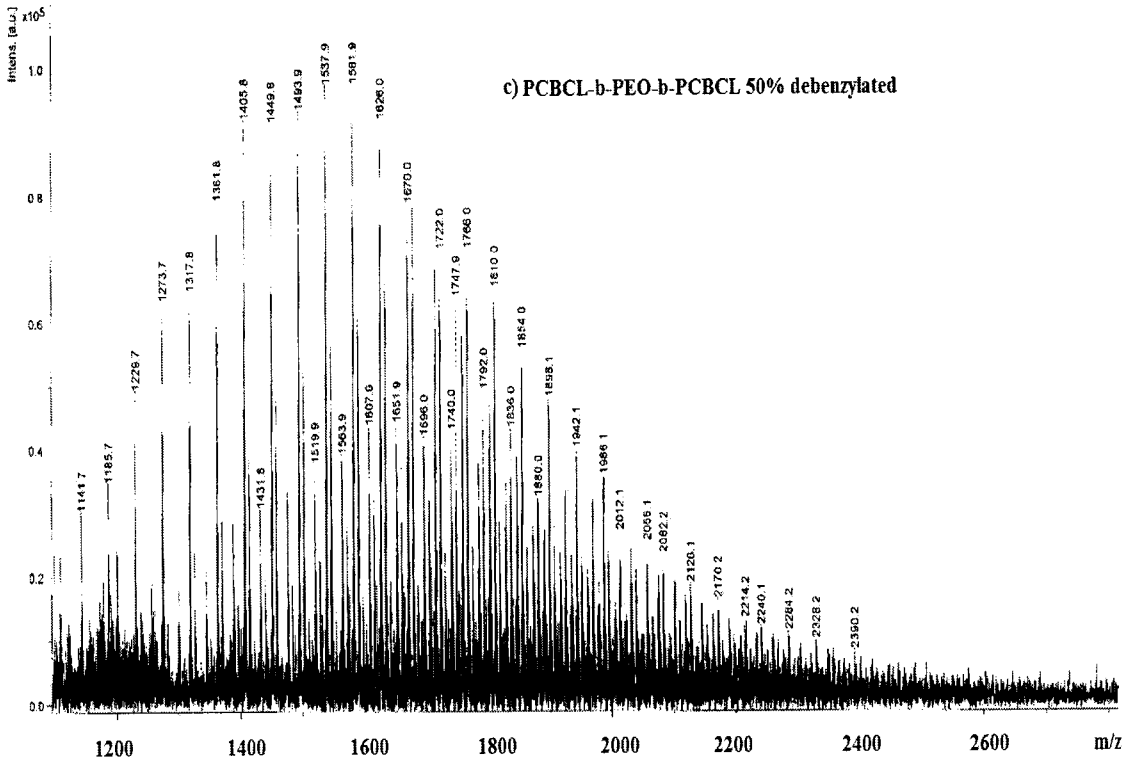

c) PCBCL-b-PEO-b-PCBCL 50% debenzylated
Intens. [a.u.]
x10^5
1.0
0.8
0.6
0.4
0.2
0.0
1200
1400
1600
1800
2000
2200
2400
2600
m/z
1141.7
1185.7
1226.7
1273.7
1317.8
1361.8
1405.8
1431.8
1449.8
1493.9
1519.9
1537.9
1563.9
1581.9
1607.9
1626.0
1651.9
1670.0
1696.0
1722.0
1740.0
1747.9
1766.0
1792.0
1810.0
1836.0
1854.0
1880.0
1898.1
1942.1
1968.1
2012.1
2056.1
2082.2
2120.1
2170.2
2214.2
2240.1
2284.2
2328.2
2390.2

Figure 8C

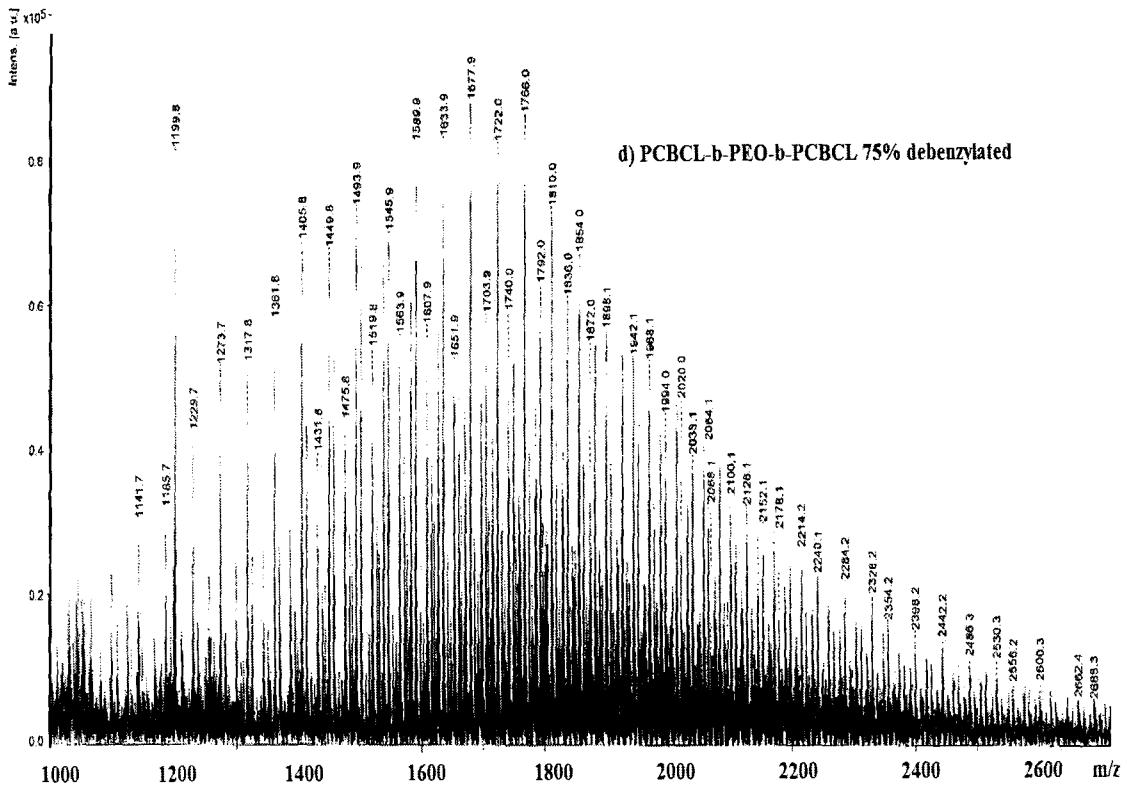

d) PCBCL-b-PEO-b-PCBCL 75% debenzylated
Intens. [a.u.]
x10^5
0.0
0.2
0.4
0.6
0.8
1000
1200
1400
1600
1800
2000
2200
2400
2600
m/z
1141.7
1185.7
1199.8
1229.7
1273.7
1317.8
1361.8
1405.8
1431.6
1449.6
1475.8
1493.9
1519.8
1545.9
1563.9
1589.8
1607.9
1633.9
1651.9
1677.9
1703.9
1722.0
1740.0
1766.0
1792.0
1810.0
1836.0
1854.0
1872.0
1898.1
1942.1
1968.1
1994.0
2020.0
2039.1
2064.1
2088.1
2100.1
2126.1
2152.1
2178.1
2214.2
2240.1
2264.2
2326.2
2354.2
2398.2
2442.2
2486.3
2530.3
2556.2
2600.3
2662.4
2688.3

Figure 8D

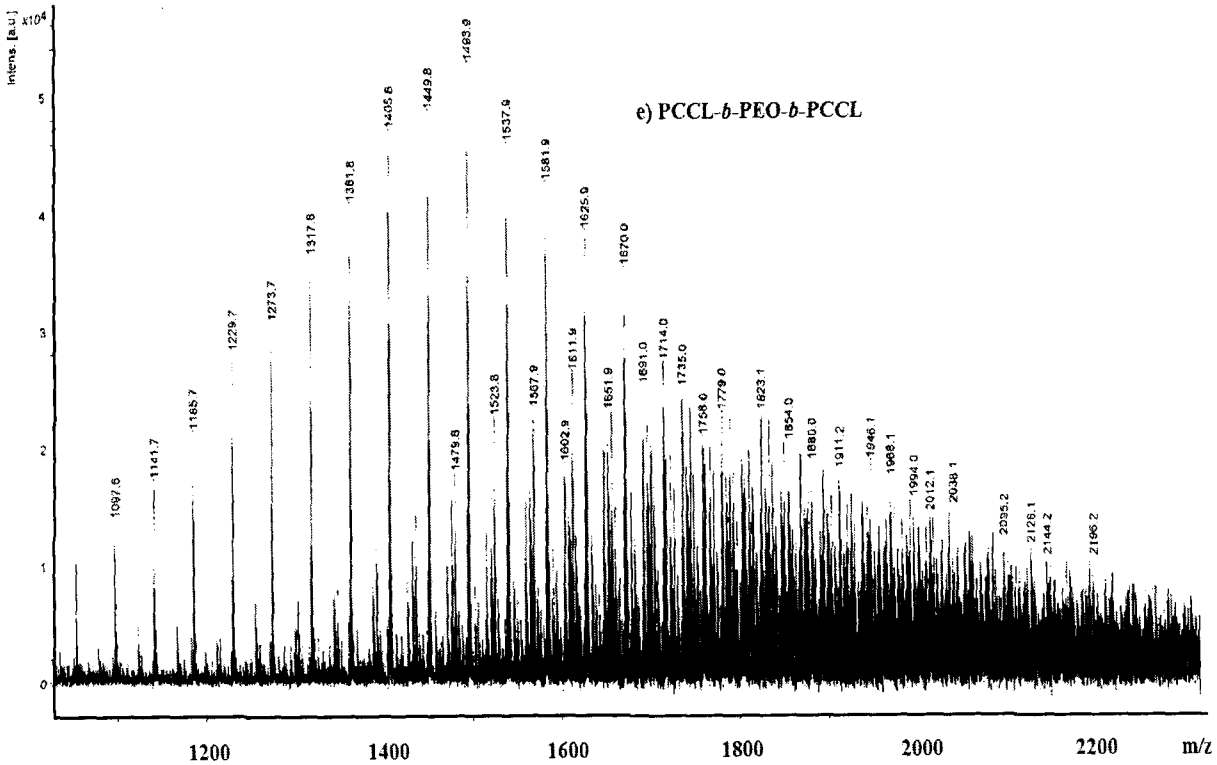

e) PCCL-b-PEO-b-PCCL
Intens. [a.u.]
x10^4
m/z
1200
1400
1600
1800
2000
2200
1097.6
1141.7
1185.7
1229.7
1273.7
1317.8
1361.8
1405.8
1449.8
1493.9
1537.9
1581.9
1625.9
1670.0
1479.8
1523.8
1567.9
1602.9
1611.9
1651.9
1691.0
1714.0
1735.0
1758.0
1779.0
1823.1
1854.0
1880.0
1911.2
1946.1
1988.1
1994.0
2012.1
2038.1
2095.2
2126.1
2144.2
2196.2

Figure 8E

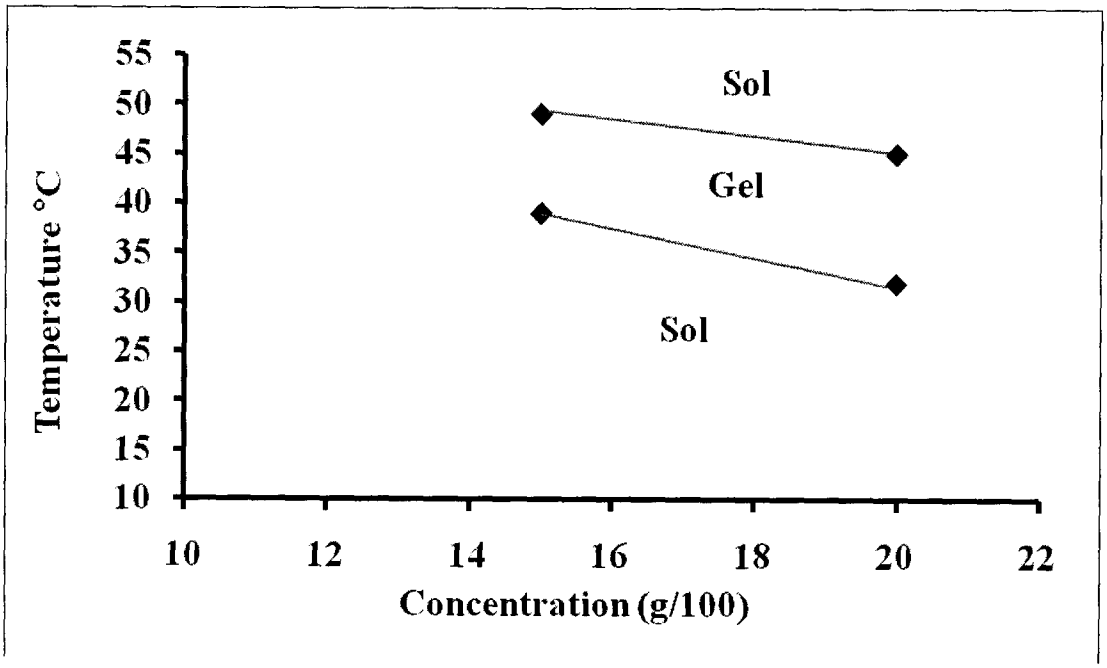

Temperature °C
55
50
45
40
35
30
25
20
15
10
10
12
14
16
18
20
22
Concentration (g/100)
Sol
Gel
Sol

Figure 9

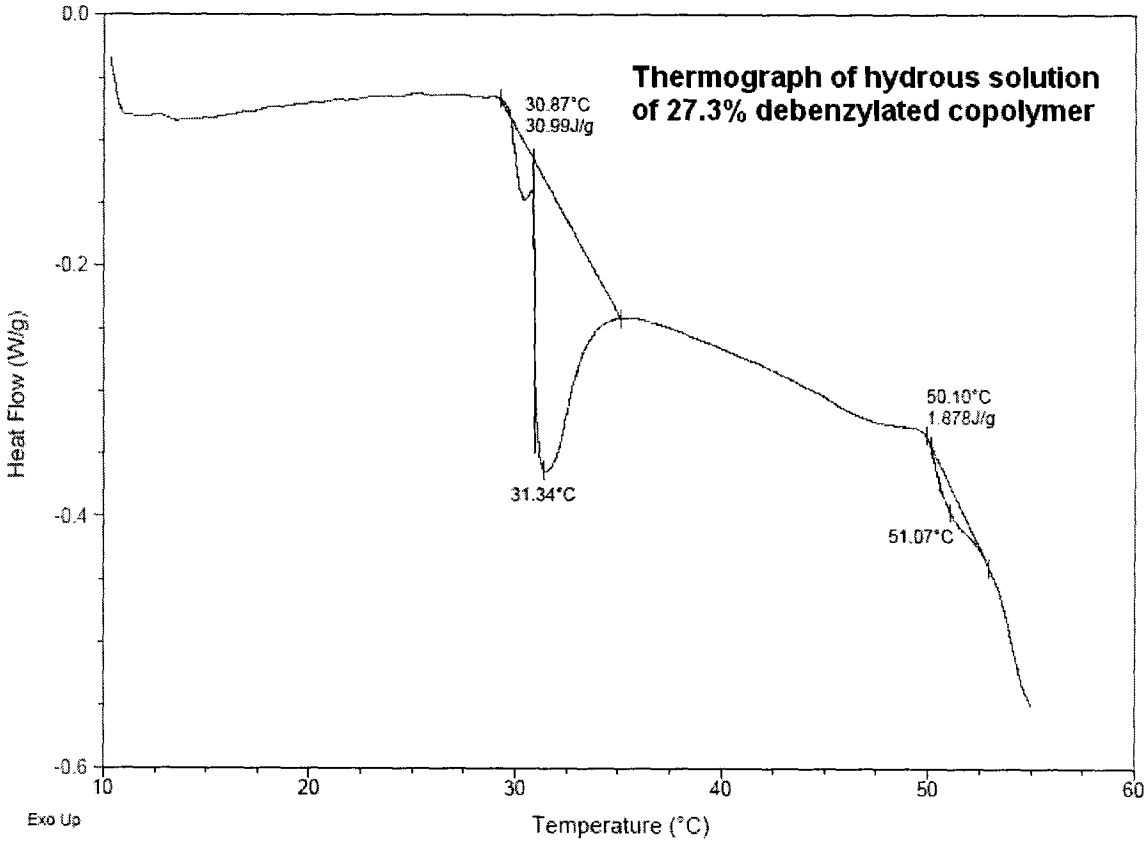

Thermograph of hydrous solution
of 27.3% debenzylated copolymer
30.87°C
30.99J/g
31.34°C
50.10°C
1.878J/g
51.07°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
0.0
-0.2
-0.4
-0.6
10
20
30
40
50
60

Figure 10

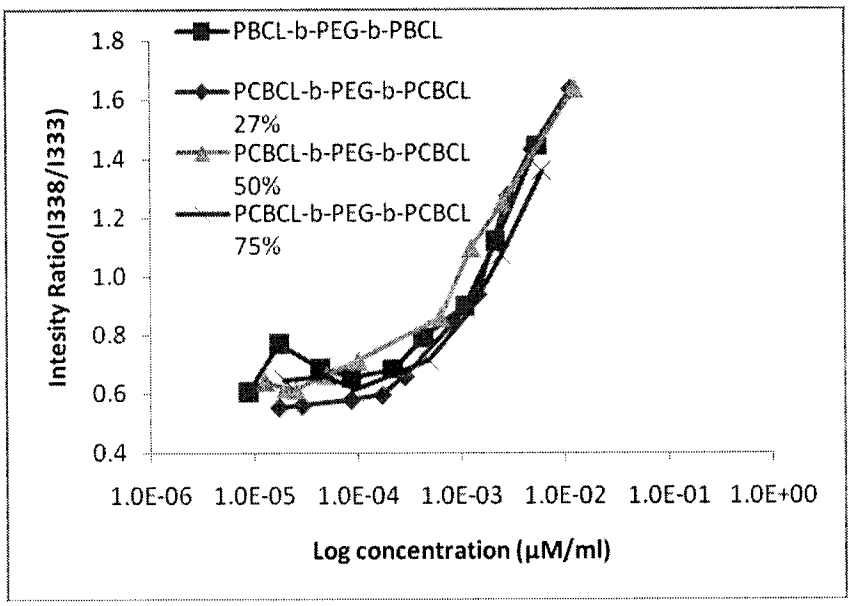

PBCL-b-PEG-b-PBCL
PCBCL-b-PEG-b-PCBCL 27%
PCBCL-b-PEG-b-PCBCL 50%
PCBCL-b-PEG-b-PCBCL 75%
Intesity Ratio(I338/I333)
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
1.0E-06 1.0E-05 1.0E-04 1.0E-03 1.0E-02 1.0E-01 1.0E+00
Log concentration (µM/ml)

Figure 11

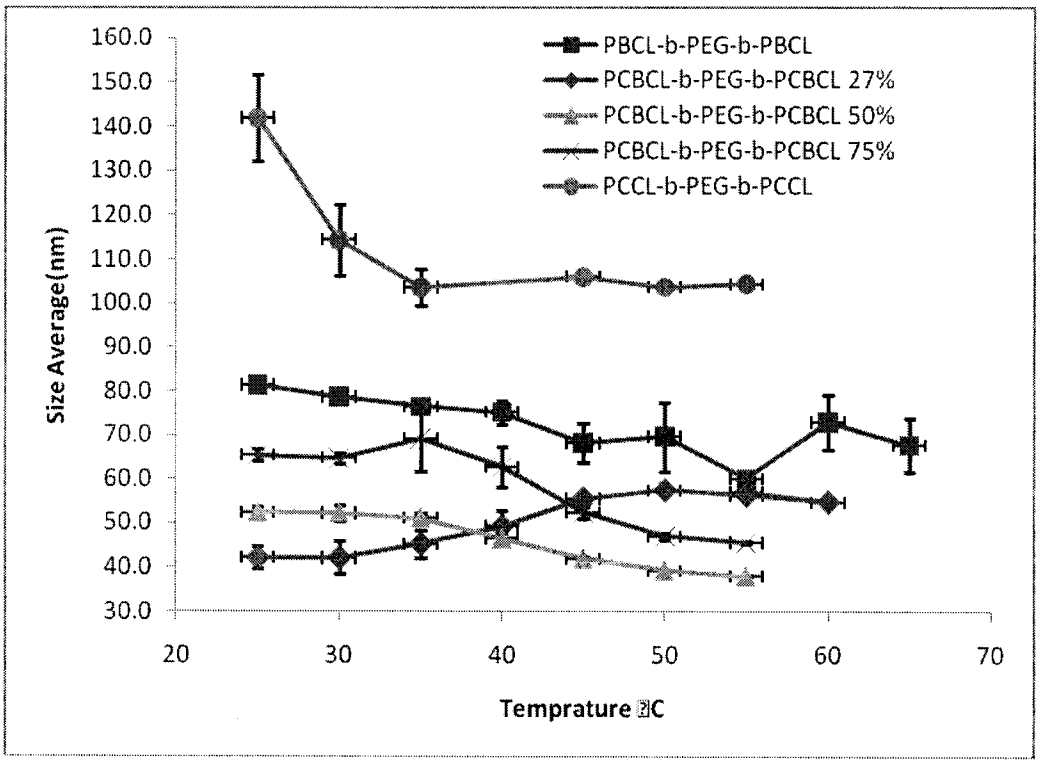

160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
Size Average(nm)
20
30
40
50
60
70
Temprature ℃
PBCL-b-PEG-b-PBCL
PCBCL-b-PEG-b-PCBCL 27%
PCBCL-b-PEG-b-PCBCL 50%
PCBCL-b-PEG-b-PCBCL 75%
PCCL-b-PEG-b-PCCL

Figure 12

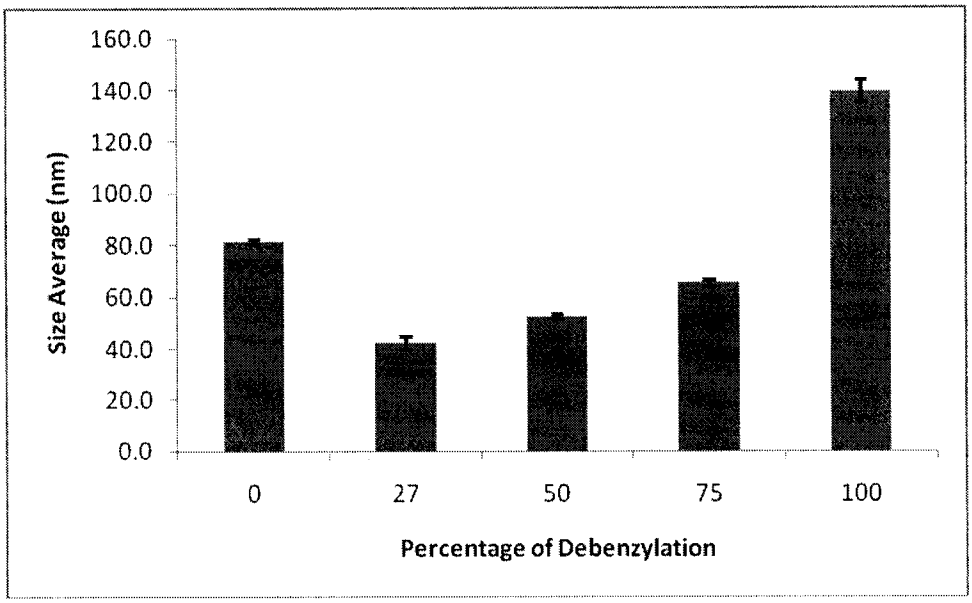

160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Size Average (nm)
0
27
50
75
100
Percentage of Debenzylation

Figure 13

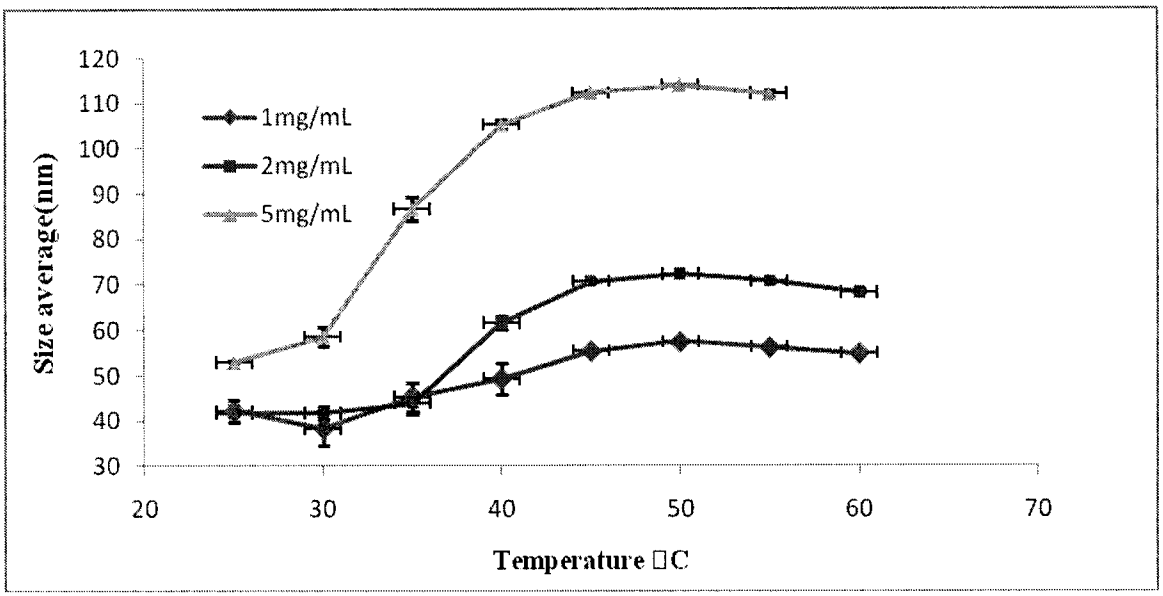

120
110
100
90
80
70
60
50
40
30
Size average(nm)
1mg/mL
2mg/mL
5mg/mL
20
30
40
50
60
70
Temperature □C

Figure 14A

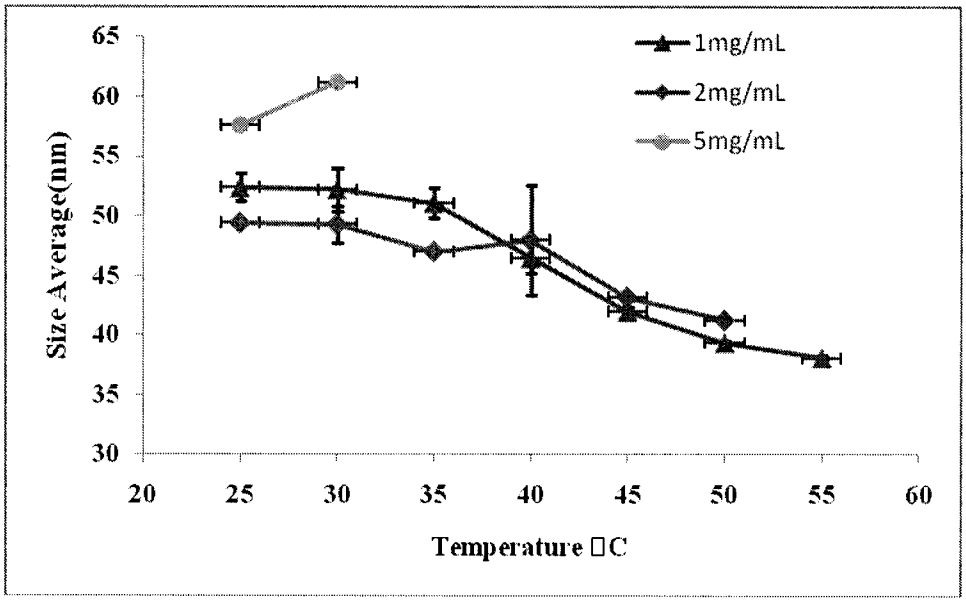

65
60
55
50
45
40
35
30
Size Average(nm)
20
25
30
35
40
45
50
55
60
Temperature □C
1mg/mL
2mg/mL
5mg/mL

Figure 14B

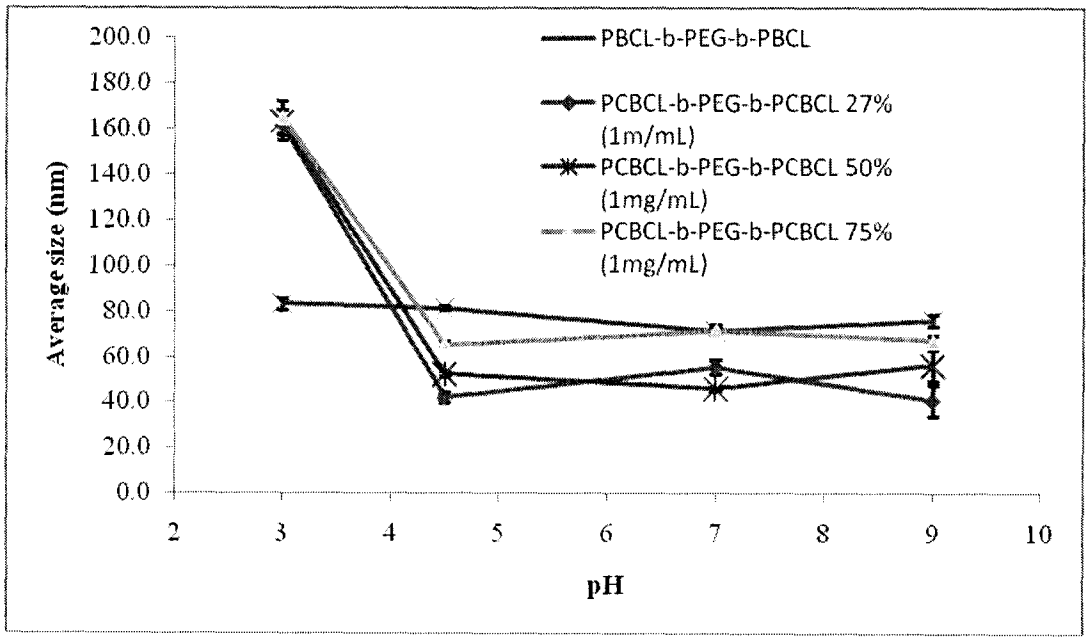

200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Average size (nm)
2
3
4
5
6
7
8
9
10
pH
PBCL-b-PEG-b-PBCL
PCBCL-b-PEG-b-PCBCL 27% (1m/mL)
PCBCL-b-PEG-b-PCBCL 50% (1mg/mL)
PCBCL-b-PEG-b-PCBCL 75% (1mg/mL)

Figure 15

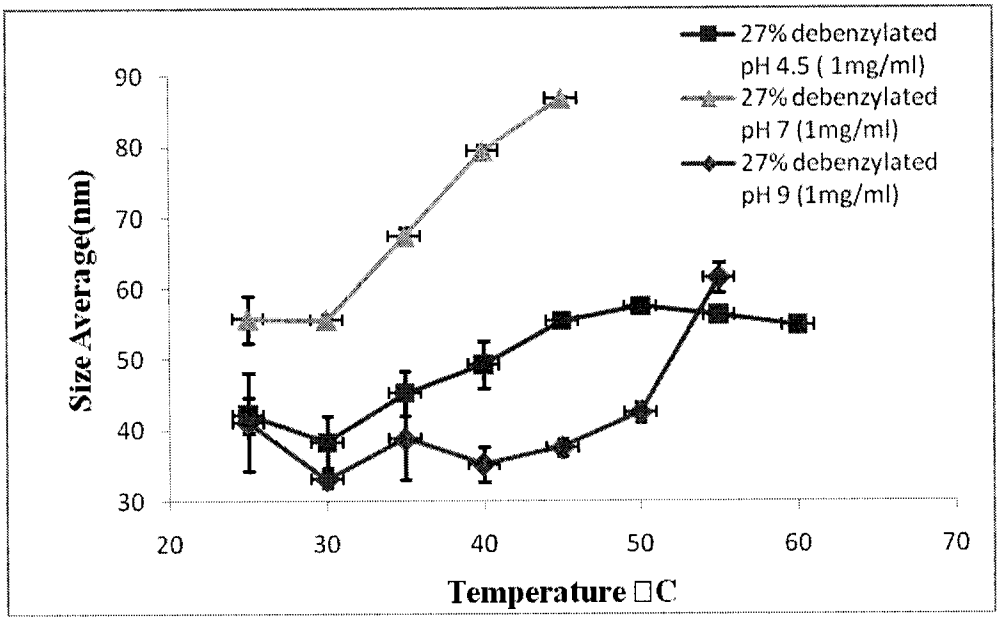

27% debenzylated pH 4.5 (1mg/ml)
27% debenzylated pH 7 (1mg/ml)
27% debenzylated pH 9 (1mg/ml)
Size Average(nm)
90
80
70
60
50
40
30
20
30
40
50
60
70
Temperature □C

Figure 16A

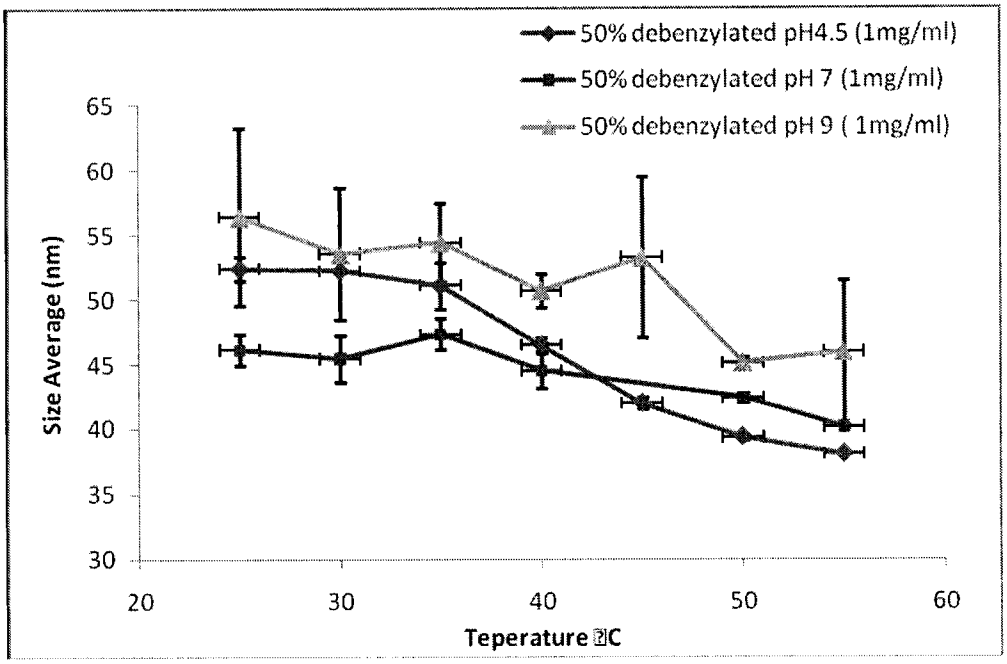

50% debenzylated pH4.5 (1mg/ml)
50% debenzylated pH 7 (1mg/ml)
50% debenzylated pH 9 (1mg/ml)
Size Average (nm)
65
60
55
50
45
40
35
30
20
30
40
50
60
Teperature ⍰C

Figure 16B

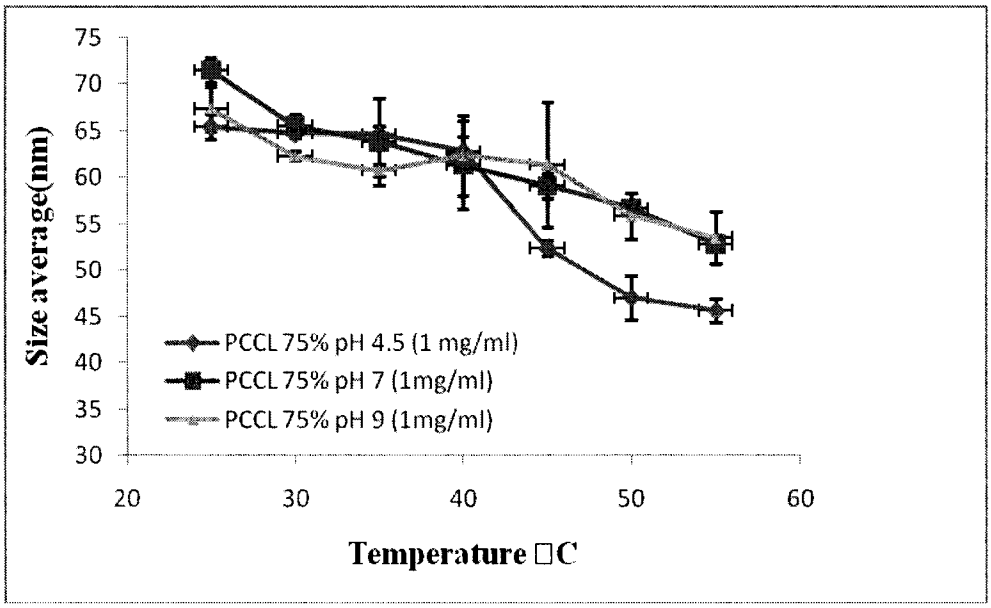

75
70
65
60
55
50
45
40
35
30
Size average(nm)
PCCL 75% pH 4.5 (1 mg/ml)
PCCL 75% pH 7 (1mg/ml)
PCCL 75% pH 9 (1mg/ml)
20
30
40
50
60
Temperature □C

Figure 16C

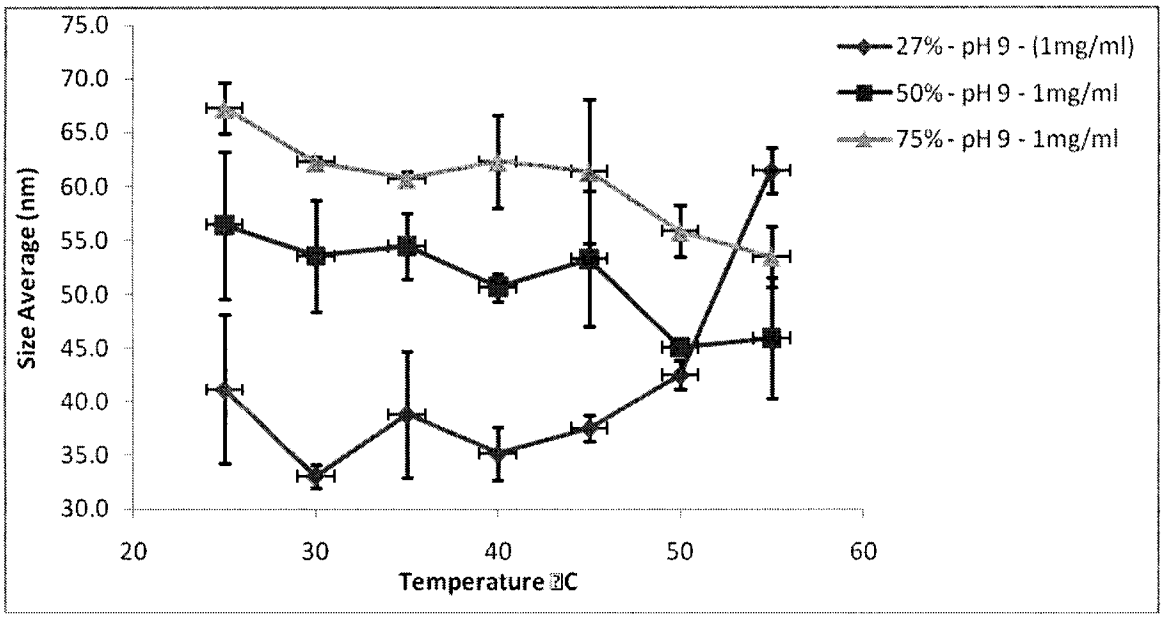

75.0
70.0
65.0
60.0
55.0
50.0
45.0
40.0
35.0
30.0
Size Average (nm)
20
30
40
50
60
Temperature ⍰C
27% - pH 9 - (1mg/ml)
50% - pH 9 - 1mg/ml
75% - pH 9 - 1mg/ml

Figure 16D

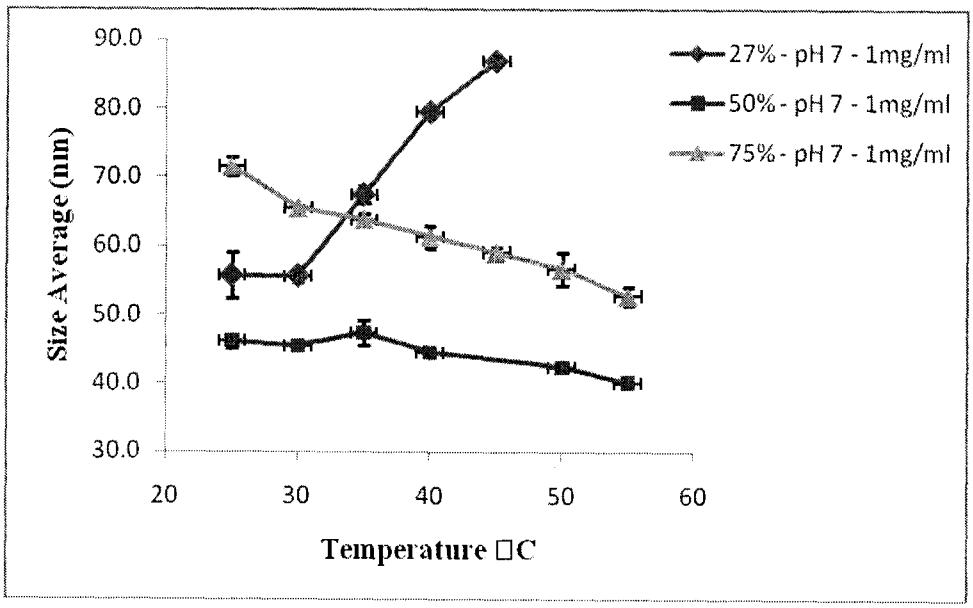

90.0
80.0
70.0
60.0
50.0
40.0
30.0
Size Average (nm)
20
30
40
50
60
Temperature □C
27% - pH 7 - 1mg/ml
50% - pH 7 - 1mg/ml
75% - pH 7 - 1mg/ml

Figure 16E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/001693

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C08L 71/02*** (2006.01) , ***A61K 47/34*** (2006.01) , ***A61K 9/10*** (2006.01) , ***C08J 3/075*** (2006.01) , ***C08L 67/04*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C08L 71/02 (2006.01) , ***A61K 47/34*** (2006.01) , ***A61K 9/10*** (2006.01) , ***C08J 3/075*** (2006.01) , ***C08L 67/04*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Canadian Patent Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D1:MAHMUD A. ET AL., Macromolecules. 2006, 39, 9419-9428.	1, 2, 4-12, 14-23, 25-32

[ ] Further documents are listed in the continuation of Box C.

[ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2010 (20-12-2010)	13 January 2011 (13-01-2011)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Rebecca Gardner (819) 956-4117

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/001693

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 14-33

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 14-33 are directed to a method for treatment of the human or animal body by surgery or therapy, are not required to be searched nor is a written opinion required by this Authority. Regardless, this Authority has established a written opinion based on the alleged effect or purpose/use of the product defined in claims 14-33.

2. [X] Claim Nos. : 3, 13, 24 and 33, 34-36

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

Claims 3, 13, 24 and 33 relate to an extremely large number of possible polymers and attempt to define the subject matter to encompass the specific examples along with other possibilities including those not contemplated by the applicant. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is not found. Continued on page 4.

3. [ ] Claim Nos. :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

continued from Box II:

Claims 34-36-36 are directed to a method for optimizing characteristics of a gel forming composition which is achieved by varying the properties of the compostions and do not comply with Article 6 of the PCT. Applicant is claiming a method or process without fully defining it in the claims. A method is a series of steps to be followed and applied to a defined substance or compound in order to achieve a desired result.