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(54) Title: THERMALLY RESPONSIVE POLYMERS

(57) Abstract: A therapeutic composition comprising particles comprising a biodegradable thermally responsive vinyl ether polymer or co-polymer in a physiologically acceptable fluid, the particles comprising an entrapped bioactive substance releasably bound to the polymer, the polymer particles forming a stable colloidal suspension at a first temperature  $T_1$  wherein  $T_1$  is less than  $37^\circ\text{C}$ , and forming a gel at a temperature  $T_2$ , wherein  $T_2$  is not greater than  $37^\circ\text{C}$ , and wherein  $T_2 - T_1 = 5^\circ\text{C}$  and wherein  $37^\circ\text{C} - T_2 < 5^\circ\text{C}$ , the polymer gel being adapted to permit controlled release of the bioactive substance when in its gel form.



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## THERMALLY RESPONSIVE POLYMERS

5 This invention relates to thermally responsive polymers, and more particularly to thermally responsive biodegradable polymers suitable for use in a composition for the controlled release of bioactive substances, to therapeutic compositions comprising such polymers and to a method of controlled delivery of bioactive substances using thermally responsive biodegradable polymers .

10 It is known to obtain controlled release of a bioactive substance, e.g. a pharmaceutically active substance, by embedding it in a matrix of an insoluble substance from which the active substance will gradually diffuse. Controlled release of an active substance contained in a tablet core may also be achieved by applying to the core a semi-permeable coating through which water and dissolved active  
15 substance may diffuse or an insoluble coating provided with a hole through which the active substance is released. Gradual release of an active substance may furthermore be obtained by microencapsulating particles of an active substance in one or more layers of film which may be of different types, e.g. of a type which mediates diffusion of the active substance or release thereof in the intestines.

20 These conventional ways of providing controlled release of an active substance have certain drawbacks, in that it is difficult to maintain a constant concentration of the active substance, for example a constant concentration of a pharmaceutically active substance in plasma for the entire period when the dosage form is present in the body.  
25 In particular, this may be the problem with drugs which have a brief half-life in the body. Furthermore, the penetration of water through diffusion coatings may cause hydrolysis of active substances which are unstable in an aqueous environment.

Biodegradable polymers have been used in parenteral controlled release formulations  
30 of bioactive compounds. In one approach the polymer is fabricated into microspheres that may be injected via syringe, and the bioactive compound is entrapped within the microspheres. This approach has not proved to be practical in part due to difficulties in the manufacturing procedure for producing sterile and reproducible products, and the high cost of manufacturing. In another approach the biodegradable polymer and

the bioactive material are dissolved in a biocompatible water-miscible solvent to provide a liquid composition. When the liquid composition is injected into the body, the solvent dissipates into the surrounding aqueous environment, and the polymer forms a solid depot from which the bioactive material is released.

5

European Patent Application 0537559 concerns polymeric compositions having a thermoplastic polymer, rate modifying agent, water soluble bioactive material and water-miscible organic solvent. Upon exposure to an aqueous environment (e.g. body fluids) the liquid composition is capable of forming a biodegradable microporous,  
10 solid polymer matrix for controlled release of water soluble or dispersible bioactive materials over about four weeks. The thermoplastic polymer may be, among many others listed, polylactide, polyglycolide, polycaprolactone or copolymers thereof, and is used in high concentration (45 to 50%).

15 Other patent documents providing compositions that form a solid, gel or coagulated mass, akin to European Patent Application 0537559, include US patents:

4,150,108, 4,329,332, 4,331,652, 4,333,919, 4,389,330, 4,489,055,  
4,526,938, 4,530,840, 4,542,025, 4,563,489, 4,675,189, 4,677,191,  
4,683,288, 4,758,435, 4,857,335, 4,931,287, 5,178,872, 5,252,701,  
20 5,275,820, 5,478,564, 5,540,912, 5,447,725, 5,599,852, 5,607,686,  
5,609,886, 5,631,015, 5,654,010, 5,700,485, 5,702,717, 5,711,968,  
5,733,566, 4,938,763, 5,077,049, 5,278,201, 5,278,202, 5,288,496,  
5,324,519, 5,324,520, 5,340,849, 5,368,859, 5,401,507, 5,419,910,  
5,427,796, 5,487,897, 5,599,552, 5,632,727, 5,643,595, 5,660,849,  
25 5,686,092, 5,702,716, 5,707,647, 5,717,030, 5,725,491, 5,733,950,  
5,736,152, 5,744,153, 5,759,563, 5,780,044,

US 6790460 describes a controlled release delivery system for delivery to biological surfaces comprising an oral cavity or mucous membranes of various tissues, said  
30 system comprising a plurality of solid nano-particles, each of said solid nano-particles comprising a core formed of a hydrophobic material and an effective amount of a first active agent contained therein and a bioadhesive positively charged surfactant entrapped on a surface of each of said solid nano-particles surrounding said core

wherein the positively charged surfactant is cetylpyridinium chloride, and the hydrophobic material comprises carnauba wax.

5 In Rimmer et al ACS Polym. Preprints (2002) 43; 971 there is described a synthesis of poly(methyl vinyl ether) oligomers by ab initio cationic polymerisation with silyl ketal ethers. In Rimmer et al ACS Polym. Preprints (2002) 43, 1075 there is described a synthesis of end-functionalised oligo (vinyl ether)s via alkylation of silyl enol ethers in an ab initio cationic polymerisation. These syntheses result in the formation of poly(methyl vinyl ether) oligomers with ester end groups.

10

Despite the vast amount of work that has been carried out hitherto, difficulties in delivery of bioactive substances still subsist and relatively few site-specific controlled release systems have been developed. Accordingly there remains a need for a long term site-specific sustained-release composition, especially for parenteral  
15 administration.

20

The present invention provides polymers and polymer compositions and methods of manufacturing and administering such compositions, wherein a thermally responsive colloidal suspension is converted into a biodegradable gel capable of permitting controlled release of a bioactive substance.

25

In a first aspect, the present invention provides a therapeutic composition comprising particles of a biodegradable thermally responsive vinyl ether polymer or copolymer in a physiologically acceptable fluid, the particles comprising an entrapped bioactive substance releasably bound to the polymer, the polymer forming a stable colloidal suspension at a first temperature  $T_1$ , wherein  $T_1$  is less than  $37^\circ\text{C}$ , and forming a gel at a temperature  $T_2$ , wherein  $T_2$  is not greater than  $37^\circ\text{C}$ , and wherein  $T_2 - T_1 \geq 5^\circ\text{C}$  and wherein  $37^\circ\text{C} - T_2 < 5^\circ\text{C}$ , the polymer in use permitting controlled release of the bioactive substance when in its gel form.

30

In a second aspect, the present invention provides a method for administration of a bioactive substance, which comprises forming a stable colloidal suspension of particles of a biodegradable thermally responsive vinyl ether polymer or copolymer in

a physiologically acceptable fluid at a first temperature  $T_1$ , wherein  $T_1$  is less than 37°C, the particles comprising an entrapped bioactive substance releasably bound to the polymer, administering the colloidal suspension to a subject such that after administration the suspension is warmed by body heat to a temperature  $T_2$  at which the polymer forms a gel, the polymer gel in use permitting controlled release of the bioactive substance.

In this specification, a "stable colloidal suspension" is one that is stable at a temperature  $T_1$  which is below normal body temperature, but which at a temperature  $T_2$ , which is greater than  $T_1$  but not greater than body temperature, is converted to an insoluble gel.

"Thermally responsive" means that the polymer, or some component of the polymer, responds to a change in temperature by a steric or conformational change, by a change in protonation, by a change in solvation, or by a change in hydration, such that it can no longer maintain a colloidal suspension.

"Controlled release of a bioactive substance" means that the bioactive substance is released into a biological environment over a prolonged period of time.

"Biodegradable" means that the polymer breaks down over a prolonged period of time into inert or physiologically acceptable components.

"Releasably bound" means that the bioactive substance is entrapped within or on the surface of the polymer by ionic or covalent bonds, or by Van der Waals forces, or by physical entanglement, but can be released when the polymer is contacted with a biological environment.

The expression "alkyl group" is intended to include alkyl groups having either a straight or a branched chain configuration. Alkyl groups having up to 30 carbon atoms in the alkyl chain can be used, although lower alkyl groups having up to six carbon atoms are generally preferred. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl,

isohexyl and the like. The expression "alkylene group" is intended to include divalent alkyl groups having either a straight or a branched chain configuration. Alkylene groups having up to 30 carbon atoms in the alkylene chain can be used, although lower alkylene groups having up to six carbon atoms are generally preferred.

- 5 Exemplary of such alkylene groups are methylene, ethylene, propylene, isopropylene, butylene, sec-butylene, tertiary butylene, pentylene, isopentylene, hexylene, isohexylene and the like.

- 10 In a third aspect, the present invention provides certain novel poly (alkyl vinyl ether) block co-polymers, graft co-polymers, and micro- and nano-suspensions thereof, suitable for use in the compositions and method of the first and second aspects of the invention.

- 15 Suitable vinyl ether polymers and copolymers for use in the present invention can be prepared by known methods, for example, by solution, suspension or emulsion polymerisation of the appropriate monomers and/or oligomers. Preferred vinyl ether polymers and copolymers for use in the present invention include polymers and copolymers of alkyl vinyl ethers, especially C<sub>1-6</sub> alkyl vinyl ethers, for example methyl vinyl ether, ethyl vinyl ether, n-propyl vinyl ether, isopropyl vinyl ether, n-  
20 butyl vinyl ether, isobutyl vinyl ether, t-butyl vinyl ether, n-pentyl vinyl ether and n-hexyl vinyl ether. Copolymers of alkyl vinyl ethers can also be used, for example, copolymers of any of the above alkyl vinyl ethers with styrene,  $\alpha$ -methyl styrene, 2-methyl styrene, 3-methyl styrene, 4-methyl styrene, isobutylene, vinyl caprolactam or any other suitable monomer capable of being copolymerized by cationic  
25 polymerization..

- Other copolymers that may be used include graft co-polymers in which poly (alkyl vinyl ether) side chains are introduced onto a second polymer backbone comprising, for example, polymer backbones formed from polystyrenes, polymethacrylates,  
30 polyacrylates, poly(vinyl alkonate)s, poly( N-vinyl pyrrolidinone), polyacrylamide, polyamides, or polyesters. Such modified alkyl vinyl ether copolymers are new materials and are accordingly also included within the invention.

In colloidal suspension such co-polymers can form thermally responsive micelle particles or larger particles (with diameters from 100 nm to 5mm) in which the poly (alkyl vinyl ether) side chains form a thermally responsive outer shell and the second polymer component forms an inner core that releasably binds the bioactive substance.

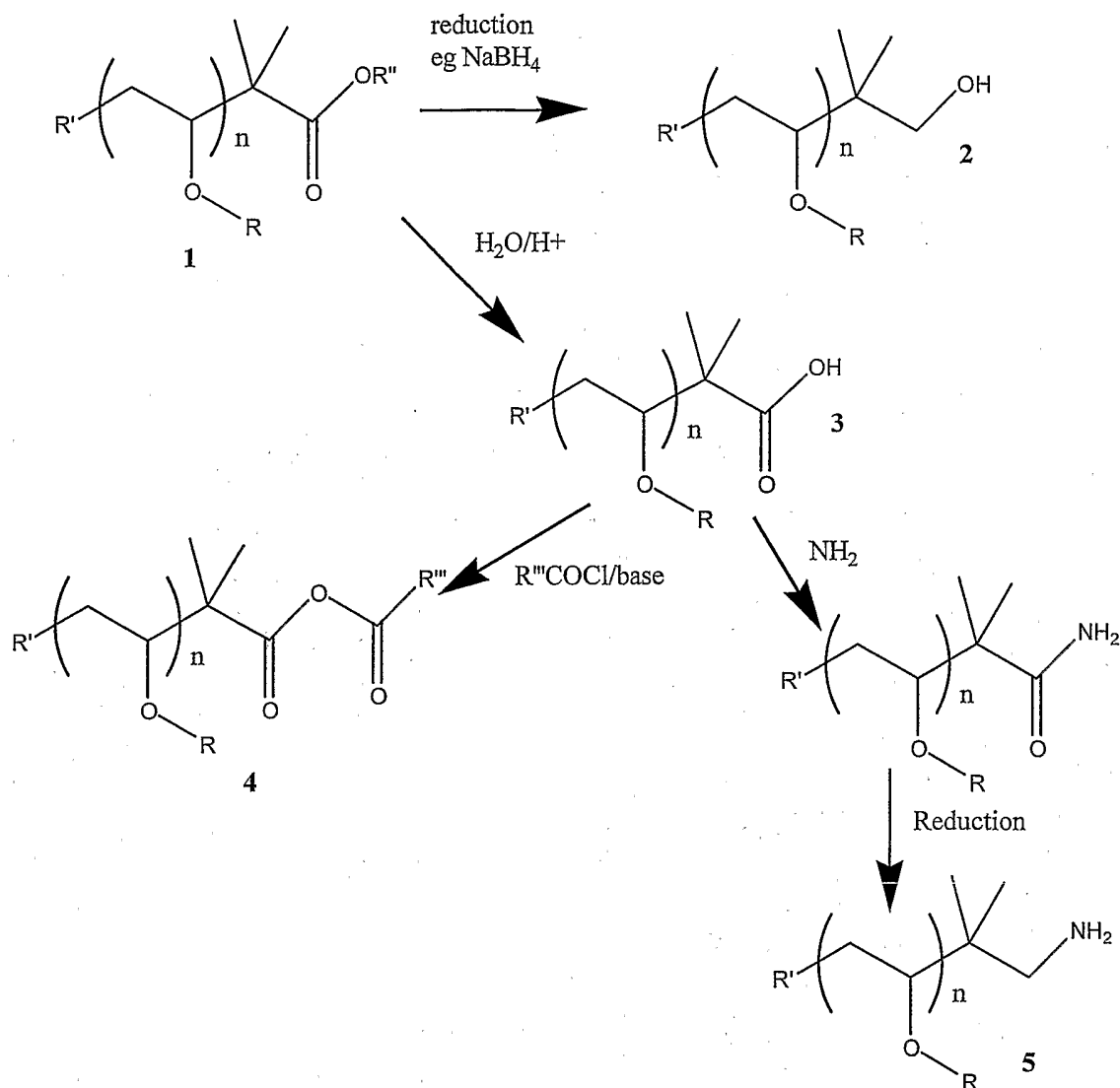
- 5 On warming, the poly (alkyl vinyl ether) side chains can no longer stabilise the colloidal suspension and the suspension collapses to form an insoluble gel. In another aspect the poly (alkyl vinyl ether) side chains can also, or alternatively, form thermally responsive arms that can be used to regulate the diffusion of bioactive substances from out of the particle outer shell or inner core.

10

- Another especially preferred class of vinyl ether polymers for use in the present invention includes block copolymers based on poly (alkyl vinyl ether) oligomers. Such block copolymers wherein the poly (alkyl vinyl ether) oligomer is copolymerised with a peptide or a poly (alkyl carbonate) are also new materials and
- 15 are also included within the scope of the invention, together with methods for manufacturing such block copolymers by reacting a poly (alkyl vinyl ether) oligomer with another polymer or oligomer, for example, a peptide, or by polymerising a monomer, for example, a N-carboxy anhydride, a cyclic carbonate or a diol and an activated formate (where the latter are the components of polycarbonate
- 20 polycondensation) in the presence of a poly (alkyl vinyl ether) oligomer.

- Syntheses of preferred reactive poly (alkyl vinyl ether) oligomers are set out in Scheme 1 below. The starting material, compound (1), can be prepared as described in "Ab initio cationic polymerization of vinyl ethers" Stephen Rimmer, Weihong
- 25 Lang, Prodip Sarker, ACS Polym. Preprints 43, 971 (2002) and "Synthesis of end-functionalised oligo(vinyl ether)s via alkylation of silyl enol ethers in an ab initio cationic polymerization" Prodip Kumar Sarker, Stephen Rimmer, ACS Polym. Preprints 43, 1075 (2). The reactive end groups of the oligomers are respectively alcohol (2), carboxylic acid (3), anhydride (4) and amine (5).

30



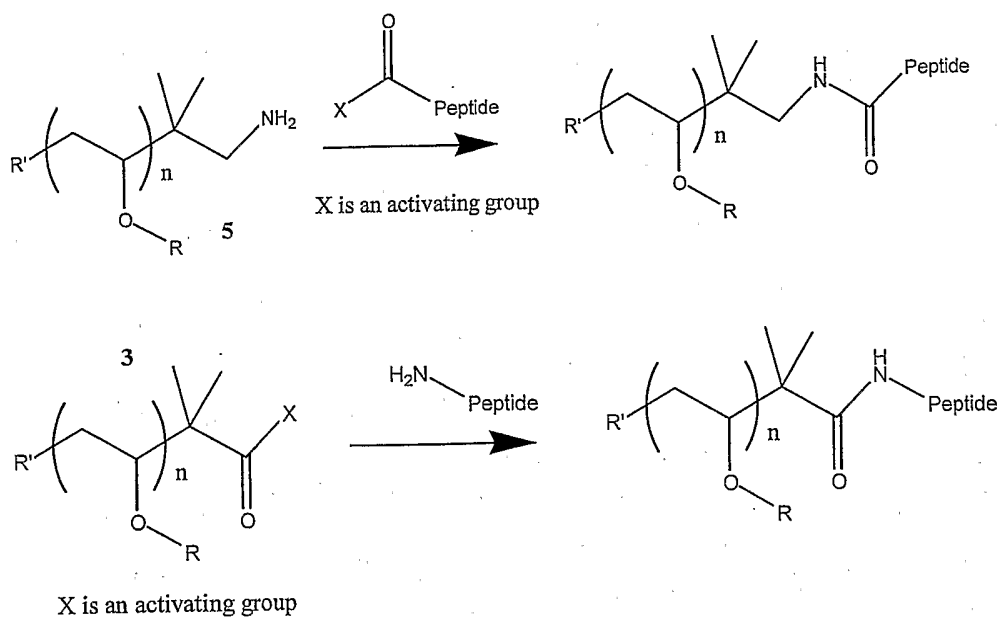
wherein  $\text{R}$ ,  $\text{R}^{\text{I}}$ ,  $\text{R}^{\text{II}}$  and  $\text{R}^{\text{III}}$  are each independently an alkyl group, and wherein  $n$  is an integer.

5

### Scheme 1

Two syntheses of preferred poly (alkyl vinyl ether) - peptide block copolymers using the oligomers prepared in *Scheme 1* are set out in *Scheme 2* below.

10

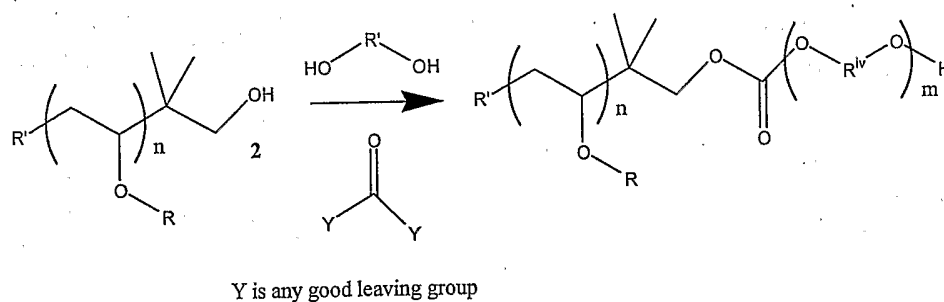


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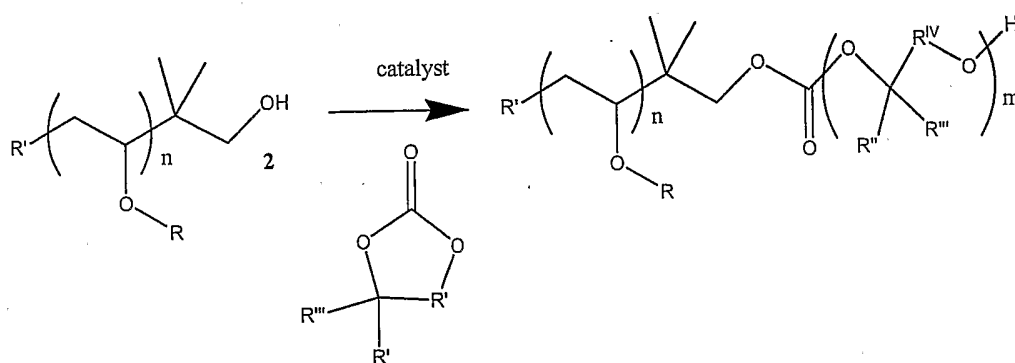
wherein R and R<sup>I</sup> are each independently an alkyl group, and wherein n is an integer.

### Scheme 2

- 10 Two syntheses of preferred poly (methyl vinyl ether) – poly(alkyl carbonate) block copolymers using the oligomers prepared in *Scheme 1* are set out in *Scheme 3* below.



15



wherein R, R<sup>I</sup>, R<sup>II</sup> and R<sup>III</sup> are each independently an alkyl group and R<sup>IV</sup> is an alkylene group, and wherein m and n are integers that can be the same or different.

### 5 *Scheme 3*

The vinyl ether polymers and copolymers used in the present invention preferably form stable colloidal suspensions at ambient temperatures and, for example, T<sub>1</sub> is preferably in the range of from 0 to 30°C, more preferably from 4°C to 25°C, and  
10 most preferably from 8°C to 20°C. The particle size of the polymer particles is preferably in the range of from 10 to 5000 nm, more preferably from 20 to 1000 nm, most preferably from 100 to 500 nm.

The therapeutic composition can be formulated to be compatible with its intended  
15 route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. Suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine,  
20 propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric  
25 acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Therapeutic compositions suitable for injectable use include sterile aqueous dispersions and sterile powders for the extemporaneous preparation of sterile  
30 injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It

should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a suspension medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the suspension and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. An increase in the time for absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Generally, suspensions are prepared by incorporating the polymer and bioactive substance into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the polymer and bioactive substance plus any additional desired ingredient from a previously sterile-filtered solution thereof.

It is advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of bioactive substance calculated to produce the desired therapeutic effect in association with the polymer gel.

Toxicity and therapeutic efficacy of such compositions can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio

LD<sub>50</sub>/ED<sub>50</sub>. Bioactive substances which exhibit high therapeutic indices are preferred. An advantage of the present invention is that substances that exhibit toxic side effects may be used, since the invention can provide a delivery system that targets such substances to the site of affected tissue in order to minimize potential damage to  
5 uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating compositions for use in humans. The delivered dosage of such compositions lies preferably within a range of circulating concentrations that include  
10 the ED<sub>50</sub> with little or no toxicity. The dosage may vary within this range depending upon the bioactive substance employed and the route of administration utilized. For any bioactive substance used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that  
15 includes the IC<sub>50</sub> (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

20 When the temperature of the colloidal suspension is raised from T<sub>1</sub> to T<sub>2</sub> the temperature responsive polymer loses its ability to remain as a colloid and the particles coalesce to form a gel. T<sub>2</sub> is preferably at or close to normal body temperature, but does not significantly exceed normal body temperature, which in this specification is defined as 37°C. T<sub>2</sub> can, for example, be 33°C, 34°C, 35°C, 36°C or  
25 37°C. In gel form the polymer is swollen with a physiologically acceptable fluid, and molecules of the bioactive substance can migrate from the polymer as they are released. The release mechanism can be activated by the influence of the biological environment or can result from the biodegradation of the polymer, or both.

30 A particular advantage of the therapeutic compositions of the invention is that when administered to a particular site in a human or animal body the colloidal suspension rapidly breaks down, forming a gel mass which can remain at the administration site and is not dissipated throughout the body. Thus the therapeutic composition can

release the bioactive substance at the site of administration over lengthy periods. The therapeutic compositions of the invention find particular application in the administration of bioactive substances to the eye, and especially the vitreous humour, which has proved very difficult to treat in the past. The therapeutic composition can  
5 be injected into the vitreous humour and can form a gel mass that remain at the site of injection, delivering a therapeutic substance, for example, to the retina, for prolonged periods. In another preferred embodiment of a method according to the invention, the therapeutic composition can be injected into a lymph gland to deliver, for example, an anti-cancer drug.

10

Therapeutic compositions in accordance with the invention can be used to treat a wide variety of diseases and conditions, including, but not limited to, macular degeneration and other retinal diseases, and cell proliferation diseases including cancer, especially lymphatic cancer.

15

Embodiments of vinyl ether polymers and colloidal polymer suspensions in accordance with the invention will now be described and illustrated in the following Examples:

## 20 EXAMPLE 1

A polystyrene with a poly (methyl vinyl ether) shell

A suspension of styrene copolymer particles containing a monomer feed of styrene  
25 (80 mol%), divinyl benzene (10 mol%) and chloromethyl styrene (10 mol %) are produced using the known suspension polymerization art. These are then used to initiate a polymerization of methyl vinyl ether. The polymerization was conducted at -78°C in dichloro methane. (1-Methoxy-2-methyl-propenyloxy)-trimethyl-silane is added together with the methyl vinyl ether at the start of the polymerization, which is  
30 initiated by the addition of titanium tetrachloride. The reaction is run for 1.5 hours before quenching with ammonia in methanol (2.0 mol dm<sup>-3</sup>). The presence of poly (methyl vinyl ether) at the surface of the particles is demonstrated using XPS.

## EXAMPLE 2

A polystyrene with a poly (ethyl vinyl ether) shell

5 The procedure of Example 1 is repeated replacing methyl vinyl ether with ethyl vinyl ether.

#### EXAMPLE 3

10 A polystyrene with a poly (isobutyl vinyl ether) shell

The procedure of Example 1 is repeated replacing methyl vinyl ether with isobutyl vinyl ether.

15 In all the above examples, XPS showed unequivocal evidence for poly (vinyl ether) formation due to the presence of oxygen at the surface of the styrene copolymer particles that was not present prior to polymerization.

#### EXAMPLE 4

20 Gel formation

The polymer suspensions of Examples 1 to 3 are stable at temperatures below 30 °C. In each case the suspension is warmed to body temperature (37°C) whereupon the polymer precipitates as an insoluble gel.

25

#### EXAMPLE 5

Release of a bioactive substance.

30 5-fluorouracil is added to the polymer suspensions of Examples 1 to 3 at a temperature below 30 °C, for example, ambient temperature, and absorbed into the polymer particles. The suspensions are then warmed to body temperature (37°C) and the formation of an insoluble gel precipitate is observed. The gel precipitate degrades

and releases the 5-fluorouracil into a physiologically acceptable phosphate buffered saline solution over an extended period.

5 The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

10 All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the combination, except combinations where at least some of such features and/or steps are mutually exclusive.

15 Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

20 The invention is not restricted to the details of the foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

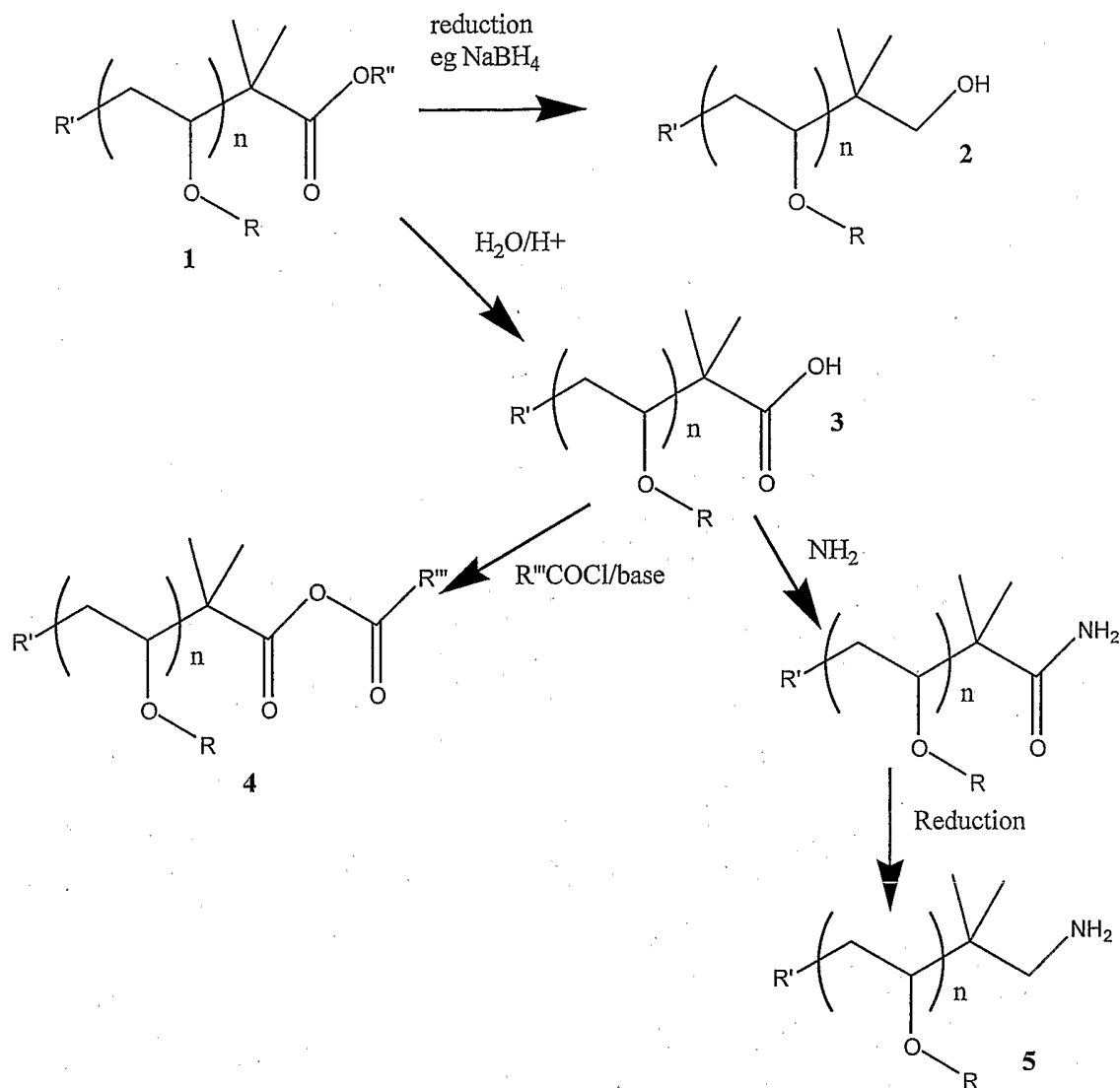
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## CLAIMS

1. A therapeutic composition comprising particles comprising a biodegradable  
5 thermally responsive vinyl ether polymer or copolymer in a physiologically acceptable fluid, the particles comprising an entrapped bioactive substance releasably bound to the polymer, the polymer particles forming a stable colloidal suspension at a first temperature  $T_1$  wherein  $T_1$  is less than  $37^\circ\text{C}$ , and forming a gel at a temperature  $T_2$ , wherein  $T_2$  is not greater than  $37^\circ\text{C}$ , and wherein  $T_2 - T_1 \geq 5^\circ\text{C}$  and wherein  $37^\circ\text{C}$   
10  $- T_2 < 5^\circ\text{C}$ , the polymer in use permitting controlled release of the bioactive substance when in its gel form.
2. A composition according to claim 1, wherein the polymer or copolymer is  
15 polymerised on the surface of a second polymer or copolymer.
3. A composition according to claim 1 or 2, wherein the vinyl ether polymer or  
copolymer comprises a polymer or copolymer of a  $\text{C}_{1-6}$  alkyl vinyl ether.
4. A composition according to claim 3, wherein the vinyl ether polymer or  
20 copolymer comprises a polymer or co-polymer of methyl vinyl ether, ethyl vinyl ether, n-propyl vinyl ether, isopropyl vinyl ether, n-butyl vinyl ether, isobutyl vinyl ether, t-butyl vinyl ether, n-pentyl vinyl ether or n-hexyl vinyl ether.
5. A composition according to any one of the preceding claims, wherein the vinyl  
25 ether copolymer comprises a copolymer of an alkyl vinyl ether with a second monomer capable of being polymerized by cationic polymerization.
6. A composition according to any one of the preceding claims, wherein the vinyl  
ether or copolymer comprises a polymer in which poly (alkyl vinyl ether) side chains  
30 are introduced onto a polymer backbone comprising a second polymer or copolymer.
7. A composition according to claim 6, which comprises a colloidal suspension wherein the polymer or copolymer forms thermally responsive micelle particles in

which the poly (alkyl vinyl ether) side chains form a thermally responsive outer shell and the second polymer or co-polymer forms an inner core.

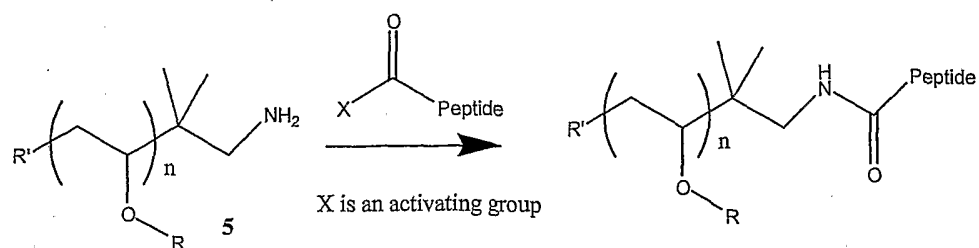
8. A composition according to claim 7, wherein the inner core releasably binds  
5 the bioactive substance.
9. A composition according to any one of the preceding claims, wherein the vinyl  
ether co-polymer comprises a block co-polymer based on a poly (alkyl vinyl ether)  
oligomer.
- 10
10. A composition according to claim 9, wherein the poly (alkyl vinyl ether)  
oligomer is co-polymerised with a peptide or a poly (alkyl carbonate).
11. A composition according to claim 9, wherein the oligomer comprises reactive  
15 end groups selected from alcohol, carboxylic acid, anhydride and amine.
12. A composition according to claim 9, wherein the oligomer is prepared  
according to reaction *scheme I*:



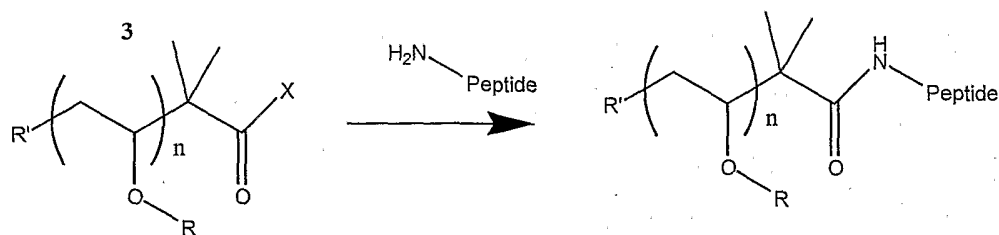
Scheme I

wherein R, R<sup>I</sup>, R<sup>II</sup> and R<sup>III</sup> are each independently an alkyl group, and wherein n is an integer.

13. A composition according to claim 10, wherein the poly (alkyl vinyl ether)-peptide block copolymer is prepared in accordance with reaction *scheme II*:



or



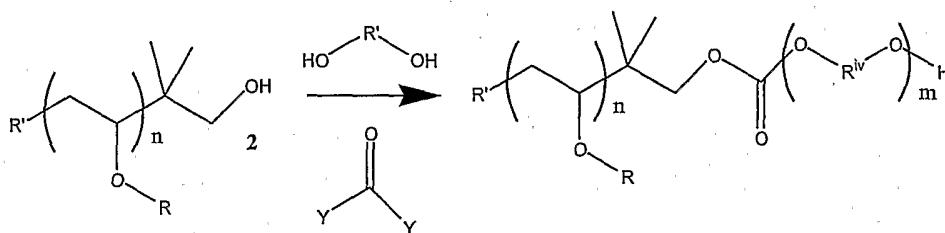
5

*Scheme II*

wherein R and R<sup>I</sup> are each independently an alkyl group, and wherein n is an integer.

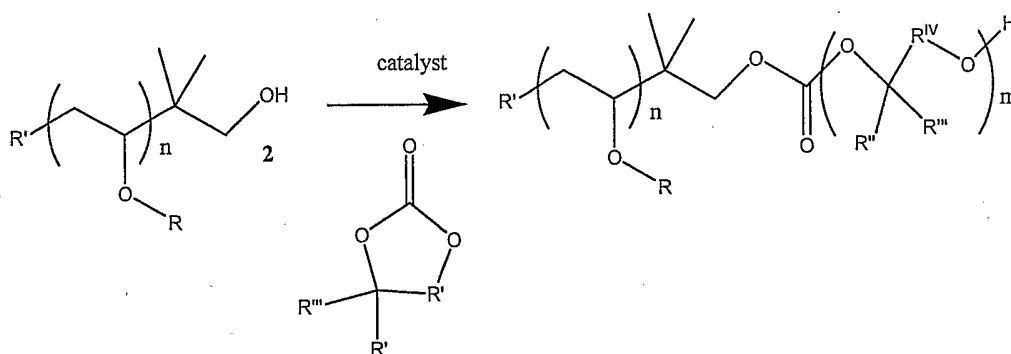
10

14. A composition according to claim 10, wherein the poly (ethyl vinyl ether)-poly (alkyl carbonate) block copolymer is prepared in accordance with reaction *scheme III*:



15

or



wherein  $R$ ,  $R^I$ ,  $R^{II}$  and  $R^{III}$  are each independently an alkyl group and  $R^{IV}$  is an  
 5 alkylene group, and wherein  $m$  and  $n$  are integers that can be the same or different.

15. A composition according to any one of the preceding claims, in which  $T_1$  is in the range of from  $4^\circ\text{C}$  to  $25^\circ\text{C}$ .

10 16. A composition according to any one of the preceding claims, wherein the particles size of the colloidal polymer particles is in the range of from 20 to 1000 nm.

17. A composition according to any one of the preceding claims, formulated for parenteral administration.

15

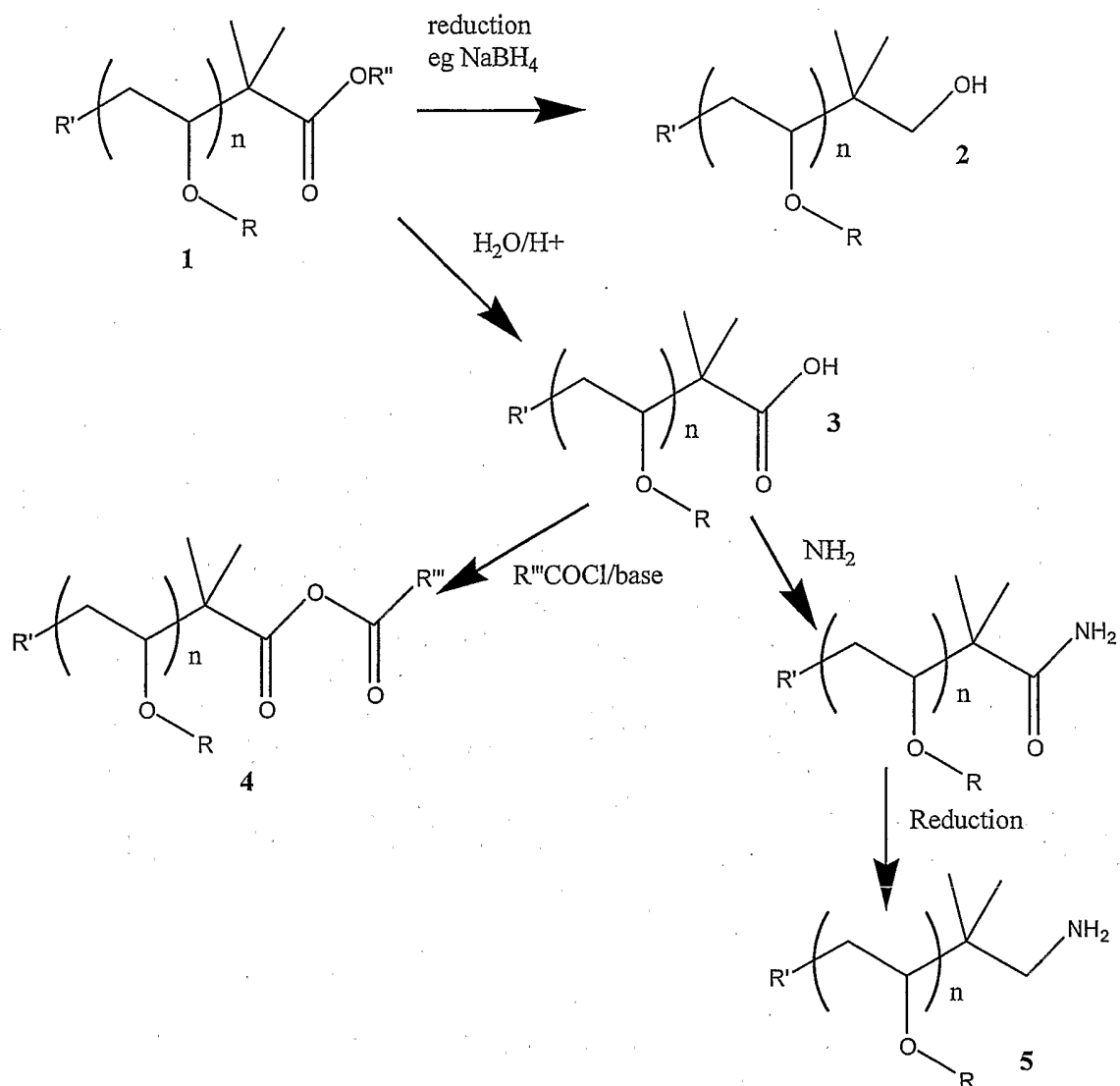
18. A composition according to any one of the preceding claims, wherein  $T_2$  is in the range of from  $33^\circ\text{C}$  to  $37^\circ\text{C}$ .

19. A composition according to any one of the preceding claims, formulated for  
 20 injection into the vitreous humour of the eye.

20. A composition according to any one of the preceding claims substantially as described in the examples.

25 21. A controlled release composition according to any one of the preceding claims formulated for parenteral administration substantially as hereinbefore described.

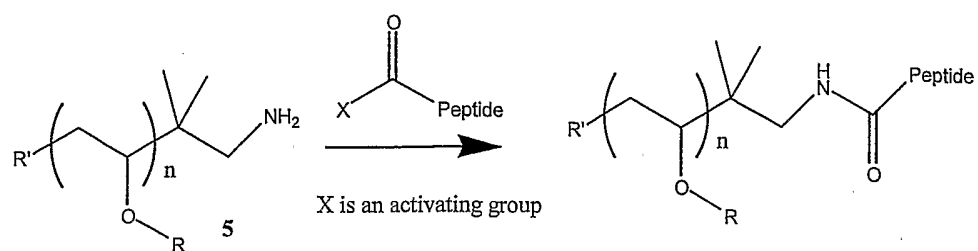
22. A method for administration of a bioactive substance, which comprises forming a stable colloidal suspension of particles comprising a biodegradable thermally responsive vinyl ether polymer or copolymer in a physiologically acceptable fluid at a first temperature  $T_1$ , wherein  $T_1$  is less than 37° C, the particles  
5 comprising an entrapped bioactive substance releasably bound to the polymer, administering the colloidal suspension to a subject such that after administration the suspension is warmed by body heat to a temperature  $T_2$  at which the polymer particles form a gel, the polymer gel in use permitting controlled release of the bioactive substance.
- 10 23. A method according to claim 22, wherein there is used a composition according to any one of claims 1 to 21.
24. A poly (alkyl vinyl ether) block co-polymer, or a micro-or nano-suspension  
15 comprising particles comprising a poly (alkyl vinyl ether) block co-polymer.
25. A method of making a block co-polymer or suspension according to claim 24, which comprises co-polymerising a poly (alkyl vinyl ether) oligomer with a second monomer or oligomer.
- 20 26. A method according to claim 25, wherein the poly (alkyl vinyl ether) oligomer is co-polymerised with a peptide or a poly (alkyl carbonate).
27. A method according to claim 25 or 26, wherein the oligomer comprises  
25 reactive end groups selected from alcohol, carboxylic acid, anhydride and amine.
28. A method according to any one of claims 25 to 27, wherein the oligomer is prepared according to reaction *scheme I*:



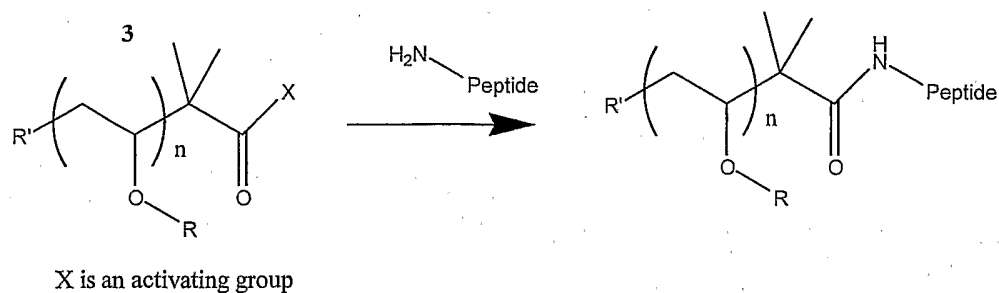
Scheme I

wherein  $R$ ,  $R^I$ ,  $R^{II}$ , and  $R^{III}$  are each independently an alkyl group, and wherein  $n$  is an integer.

29. A method according to claim 26, wherein the poly (alkyl vinyl ether)-peptide block co-polymer is prepared in accordance with reaction *scheme II*:



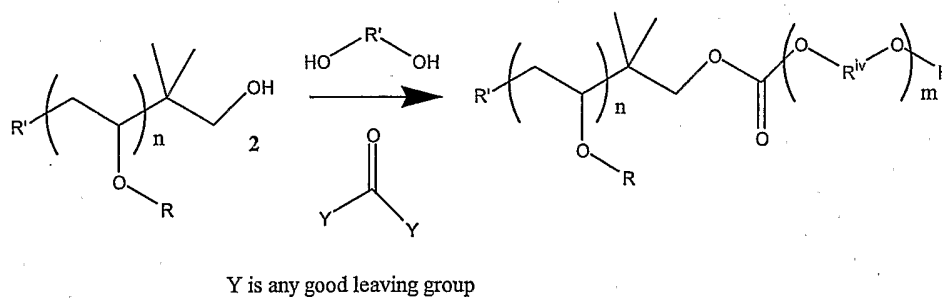
OR

*Scheme II*

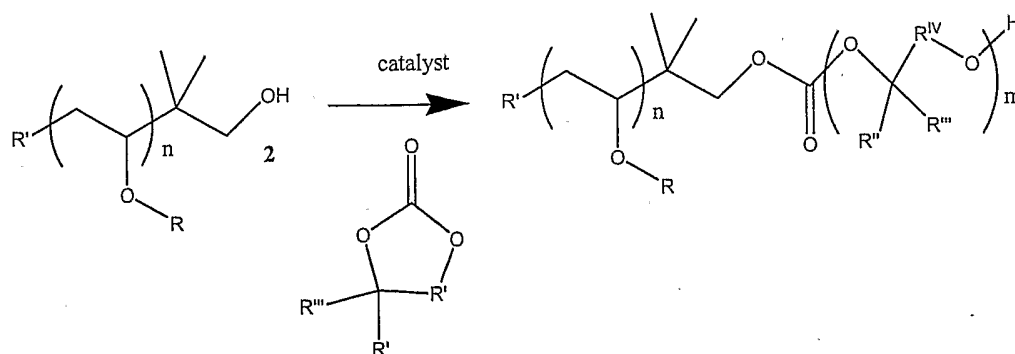
wherein R and R<sup>I</sup> are each independently an alkyl group, and wherein n is an integer.

10

30. A method according to claim 26, wherein the poly (ethyl vinyl ether)-poly (alkyl carbonate) block co-polymer is prepared in accordance with reaction *scheme III*:



OR



wherein R, R<sup>I</sup>, R<sup>II</sup>, and R<sup>III</sup> are each independently an alkyl group and

5 R<sup>IV</sup> is an alkylene group, and wherein m and n are integers.

31. A poly (alkyl vinyl ether) graft co-polymer or a micro-or nano-suspension comprising particles comprising a poly (alkyl vinyl ether) graft co-polymer, wherein the graft co-polymer has been formed by introducing poly (alkyl vinyl ether) side chains onto a backbone of a second polymer.

32. A graft co-polymer or suspension according to claim 31, wherein the second polymer is a polystyrene, polymethacrylate, polyacrylate, polyamide, polyester, or polypeptide.

33. A colloidal suspension of particles comprising thermally responsive micelle particles comprising a graft co-polymer according to claim 31 or 32, wherein the poly (alkyl vinyl ether) side chains form a thermally responsive outer shell and the second polymer forms an inner core.

34. A block co-polymer or suspension according to claim 24, or a graft co-polymer or suspension according to any one of claims 31 to 33, formulated for parenteral administration.

35. A block co-polymer or suspension according to claim 24, or a graft co-polymer or suspension according to any one of claims 31 to 33 substantially as hereinbefore described.

36. A method according to any one of claims 25 to 30 substantially as herein before described.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB2005/004020

## A. CLASSIFICATION OF SUBJECT MATTER

A61K9/00 A61K31/00 A61K47/34 C08F2/00 C08G83/00

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)

A61K C08F C08G

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                     | Relevant to claim No.         |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| X          | US 4 997 643 A (PARTAIN, III ET AL)<br>5 March 1991 (1991-03-05)<br><br>column 4<br>column 5, line 51 - line 53<br>column 9, line 35 - line 43<br>column 10, line 1 - line 26<br>examples 2,3<br>----- | 1-5, 22,<br>24, 25,<br>31, 33 |
| X          | EP 0 537 559 A (ATRIX LABORATORIES, INC)<br>21 April 1993 (1993-04-21)<br>cited in the application<br>page 4, line 9 - line 45; claims 1,5<br>page 8, line 54 - line 56<br>-----                       | 1, 22, 24,<br>25, 31, 33      |
| X          | US 5 663 260 A (FRECHET ET AL)<br>2 September 1997 (1997-09-02)<br>claims 26, 31, 43; examples V, VI<br>-----<br>-/-                                                                                   | 24, 25,<br>31, 33             |



Further documents are listed in the continuation of box C.



Patent family members are listed in 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 document 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.

\*G\* document member of the same patent family

Date of the actual completion of the international search

28 December 2005

Date of mailing of the international search report

17/01/2006

Name and mailing address of the ISA

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Kardas-Llorens, E

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB2005/004020

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages                                                                       | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | US 2003/147956 A1 (SHEFER ADI ET AL)<br>7 August 2003 (2003-08-07)<br>cited in the application<br>paragraphs '0010!, '0072!, '0084!; claim<br>1<br>----- | 1,22,24,<br>25,31,33  |
| X          | US 4 250 289 A (CORDES, CLAUS ET AL)<br>10 February 1981 (1981-02-10)<br>claim 1; examples 1-6<br>-----                                                  | 24,25,<br>31,33       |

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box II.1

Although claims 22 and 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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## Continuation of Box II.2

Claims Nos.: 20,21, 35, 36

Claims 20,21,35 and 36 are not clear (Art. 6 and Rule 6.2(a) PCT).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2005/004020

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of 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. ☒ Claims Nos.: 20, 21, 35, 36  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 22 and 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 20, 21, 35, 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:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box 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:

see additional sheet

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 an additional fee, this Authority did not invite payment of any additional fee.
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 claims 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 claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-19, 22, 23

Therapeutic composition comprising particles comprising a vinyl ether polymer or copolymer and an entrapped bioactive substance.

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2. claims: 24,25-31-33 and 34

Poly(alkyl vinyl ether) co-polymers

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2005/004020

| Patent document<br>cited in search report |    | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|----|---------------------|----------------------------|---------------------|
| US 4997643                                | A  | 05-03-1991          | CA 2020966 A1              | 13-01-1991          |
| EP 0537559                                | A  | 21-04-1993          | AT 162398 T                | 15-02-1998          |
|                                           |    |                     | AU 2605592 A               | 22-04-1993          |
|                                           |    |                     | CA 2079830 A1              | 16-04-1993          |
|                                           |    |                     | DE 69224131 D1             | 26-02-1998          |
|                                           |    |                     | DE 69224131 T2             | 30-04-1998          |
|                                           |    |                     | ES 2113906 T3              | 16-05-1998          |
|                                           |    |                     | JP 5286850 A               | 02-11-1993          |
|                                           |    |                     | KR 260672 B1               | 01-08-2000          |
| US 5663260                                | A  | 02-09-1997          | EP 0791022 A1              | 27-08-1997          |
|                                           |    |                     | WO 9614345 A1              | 17-05-1996          |
| US 2003147956                             | A1 | 07-08-2003          | AU 3977602 A               | 03-06-2002          |
|                                           |    |                     | EP 1328257 A2              | 23-07-2003          |
|                                           |    |                     | WO 0241765 A2              | 30-05-2002          |
|                                           |    |                     | US 6565873 B1              | 20-05-2003          |
| US 4250289                                | A  | 10-02-1981          | CA 1148297 A1              | 14-06-1983          |
|                                           |    |                     | DE 2840501 A1              | 27-03-1980          |
|                                           |    |                     | EP 0009169 A2              | 02-04-1980          |
|                                           |    |                     | JP 1414915 C               | 10-12-1987          |
|                                           |    |                     | JP 55040797 A              | 22-03-1980          |
|                                           |    |                     | JP 62019762 B              | 01-05-1987          |