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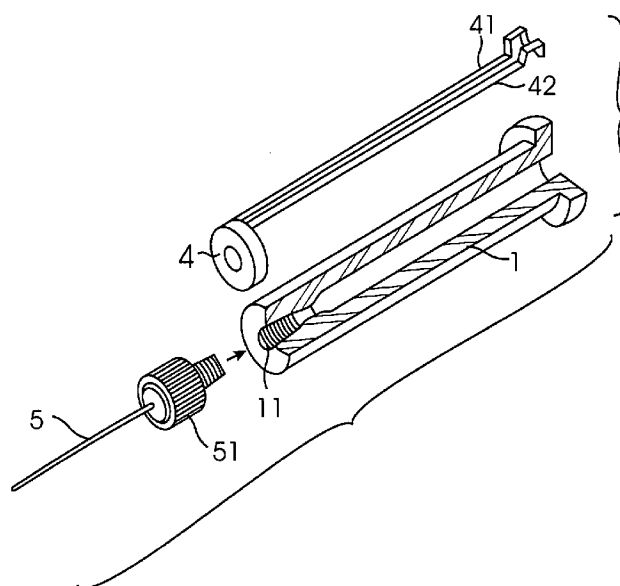
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(54) Title: COMPOSITIONS, DEVICES AND METHODS FOR MODIFYING SOFT TISSUE



(57) Abstract: Compositions which comprise side chain crystalline (SCC) polymers and which are useful for modifying the soft tissue of human beings and other mammals. The modification can result in cosmetic and/or reconstructive improvement of the soft tissue. The compositions can remain effective for extended periods of time, or if desired, for selected shorter periods. Injection devices which are particularly suitable for dispensing such compositions include a reservoir (1) having an outlet (2) to which a needle is fixed, a piston (3) which is movable within the reservoir so that composition within the reservoir can be urged towards the outlet, and a heater (4) for heating composition near the outlet to a temperature substantially higher than composition relatively remote from the outlet.

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Title COMPOSITIONS, DEVICES AND METHODS FOR MODIFYING SOFT
TISSUE

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CROSS-REFERENCE TO RELATED APPLICATIONS

This application is related to, and claims priority from, (1) United States
Provisional Application No. 60/856,430, filed November 3, 2006, by Edward E. Schmitt
(Docket 16971), (2) United States Provisional Application No. 60/857,546, filed November
8, 2006, by Edward E. Schmitt (Docket 16971-1), and (1) United States Provisional
Application No. 60/857, 755, filed November 8, 2006, by John F. Krumme and Christian
Walton (Docket 17311). The entire disclosure of each of those applications is
incorporated herein by reference for all purposes.

FIELD OF THE INVENTION

This invention relates to compositions, methods and devices for modifying soft
tissue in human beings and other mammals.

BACKGROUND

It is known to use polymeric compositions to modify the soft tissue of human beings
for cosmetic and/or reconstructive purposes. Compositions known for this purpose
comprise for example collagen or a derivative thereof, hyaluronic acid, polylactic acid,
hydroxymethylcellulose, hydroxyapatite and expanded polytetrafluoroethylene. Devices for
dispensing such compositions are also known. Reference may be made for example to
United States Patents Nos. 4,140,537, 4,424,208, 4,582,640, 4,725,671, 4,803,075,
4,481,001, 5,295,980, 5,366,498, 5,383,930, 5,523,291, 5,705,488, 5,827,937, 7,004,977
and 7,083,611, the entire disclosures of which are incorporated herein by reference for all
purposes.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides novel compositions which comprise
side chain crystalline (SCC) polymers (as hereinafter defined) and which are suitable for
use in the modification of the soft tissue of mammals. The novel compositions, unlike the

known compositions, can remain effective for extended periods of time, or, if desired, for selected shorter periods. In another aspect, the invention provides novel injection devices suitable for dispensing such compositions, and other purposes. In further aspects, the invention provides novel SCC copolymers, novel intermediates for making SCC polymers, novel methods of making SCC copolymers, and novel components for use in injection devices.

The invention also includes methods which comprise placing a composition comprising an SCC polymer in a human being. The composition can for example be placed in or close to the stratum corneum to change the contours of the skin for cosmetic and/or reconstructive purposes (the term skin being used herein to include skin defects such as, for example, acne scars); or it can be placed at another location for reconstructive purposes, for example to modify a sphincter, e.g. to control urinary or fecal incontinence.

Preferred aspects of the present invention include: --

(A) Compositions which

- (a) comprise a side chain crystalline (SCC) polymer,
- (b) at the body temperature of a human being, have a substantially stable equilibrium shape, and
- (c) at an elevated temperature which can be tolerated by a human being, can be dispensed through a hypodermic needle.

(B) Injection devices which comprise

- (1) a reservoir for a composition to be dispensed, the reservoir having an outlet to which a needle can be, or is, fixed,
- (2) a piston which is movable within the reservoir so that composition within the reservoir can be urged towards the outlet, and
- (3) a heater for heating composition which is relatively near the outlet to a temperature which is substantially higher than composition which is relatively remote from the outlet.

(C) SCC polymers which

- (1) comprise
 - (a) 3 to 15%, by weight, based on weight of the polymer, of one or more first polymer blocks each of which

- (i) has a number average molecular weight (M_n) of less than 5000, and
- (ii) comprises at least 70%, based on the weight of the block, of repeating units having the formula $-Y(R_c)-$, wherein each of the Y radicals is a radical forming part of the backbone of the polymer, and each of the $-Y(R_c)-$ radicals contains a side chain R_c radical which is a high temperature crystallizable (HTC) radical (as hereinbefore defined), and
- (b) 85 to 97%, based on the weight of the polymer, of one or more second polymer blocks comprising at least 70% of repeating units which have the formula $-Z(R_z)-$, where Z is a radical forming part of the polymer backbone, and $-Z(R_z)-$ does not contain an HTC radical; and
- (2) have a T_p of 33 to 48°C.
- (D) SCC polymers which comprise linking groups which are bio-erodable.
- (E) Methods of making SCC polymers as defined in (C) which comprise
- (A1) providing a hard block oligomer corresponding to the first block, and
- (B1) forming the second block on the oligomer by polymerization of a monomer corresponding to the repeating units of the formula $-Z(R_z)-$;
- or
- (A2) providing a soft block precursor corresponding to the second block in the SCC polymer, and
- (B2) forming the first block on the soft block precursor by polymerization of a monomer corresponding to the repeating units of the formula $-Y(R_c)-$;
- or
- (A3) reacting together (i) a hard block oligomer corresponding to the first block and (ii) a soft block precursor corresponding to the second block.
- (F) Hard block oligomers which are suitable for use in step (A1) or (A3) of (E); which have an M_n of less than 5,000 and a polydispersity less than 3; and which contain a reactive linking group through which the oligomer can be joined to the second blocks (the soft blocks), or a functional group which can be converted into such a reactive linking group.

(G) Soft block precursors which are suitable for use in step (A2) or (A3) of (E), and which comprises a plurality of repeating units of the formula $-Z(Rz)-$, at least one of the Z radicals including a bioerodable linking group and/or a functional group which can be reacted to form a linking radical which is bioerodable.

(H) Novel components which can form part of an injection device as in (B), for example

(i) a reservoir which comprises an electrical heater adjacent the outlet; or

(ii) a needle comprising a fitting which can be fixed to the outlet of a reservoir, and an electrical heater substantially surrounding the fitting;

(iii) a reservoir which comprises an outlet, and, adjacent to the outlet, a component composed of a magnetically permeable material; or

(iv) a needle which comprises a fitting for securing the needle to a reservoir, the fitting comprising a magnetically permeable material.

(I) A method of treating a human being or other mammals which comprise placing a composition comprising an SCC polymer in the mammal, the composition preferably being a composition as defined in (A), and/or comprising an SCC polymer as defined in (C) or (D), and/or the composition being placed in the mammal by means of an injection device as defined in (B).

The term SCC polymer is used herein to denote a polymer which comprises a plurality of repeating units having the formula $-Y(Rc)-$, wherein each of the Y radicals is a radical forming part of the backbone of the polymer, and each of the $-Y(Rc)-$ radicals contains a crystallizable side chain Rc radical such that the Rc radicals can crystallize together. The resulting polymer has a crystalline melting point which results from the melting of Rc radicals which have crystallized together. Many SCC polymers also contain a plurality of repeating units having the formula $-Z(Rz)-$, where Z is a radical forming part of the polymer backbone and $-Z(Rz)-$ does not contain an Rc radical; thus, Rz is not an Rc radical. As further discussed below, a wide variety of Y, Rc, Z and Rz radicals can be present in an SCC polymer.

SCC polymers melt over a narrow temperature range, and at a temperature which is chiefly determined by the Rc radicals. The melting point is little influenced by the molecular weight of the polymer (unlike conventional crystalline polymers, whose crystallinity results from crystallization of main polymer backbone). For example, homopolymers of n-alkyl acrylates in which the n-alkyl group contains 14, 16, 18, 20, 22,

30, 40 and 50 carbon atoms typically have peak melting points (T_p , as defined below) of about 20, 36, 49, 60, 71, 76, 96 and 102°C respectively, while the homopolymers of the corresponding n-alkyl methacrylates typically have T_p 's of about 10, 26, 39, 50, 62, 68, 91 and 90 °C respectively. Random polymers containing

5 $-Z(R_z)-$ units typically have somewhat lower melting points; block copolymers in which the $Y(R_c)$ units are grouped together typically have intermediate T_p 's.

The SCC polymer, and the other ingredients, if any, of the composition to be placed in a human being or other mammal, are preferably such that

- (1) the composition can be maintained at a relatively high temperature which
 - 10 (i) is above the body temperature of the mammal at the location into which the composition is to be placed, but is not too hot to be tolerated by the mammal, and
 - (ii) is above the temperature at which the melting of the SCC polymer is complete (T_L as defined below); and
- 15 (2) when the composition is at equilibrium within the mammal, the composition is substantially less mobile than at said relatively high temperature, so that its shape within the mammal is substantially stable (throughout this specification, the term "shape" refers to the shape of the composition in three dimensions).

20 In some embodiments of the invention, the composition is such that, after it has been placed within the mammal, it takes a substantial time, e.g. at least 5 minutes, to reach equilibrium within the mammal. During this time, even if the composition has cooled to below its melting point, there is little or no crystallization of the SCC polymer. This makes it possible for the shape of the composition under the skin, and in consequence the shape of the skin over the composition, to be changed by pressure exerted selectively on

25 the exterior of the skin.

The SCC polymers defined in (C) above are novel per se. They

- (1) comprise, e.g. consist essentially of,
 - 30 (a) 3 to 15%, e.g. 7 to 11%, particularly about 9%, by weight, based on weight of the polymer, of one or more first polymer blocks (often referred to herein as hard blocks), each of the first polymer blocks (i) having a number average molecular weight (M_n) of less than 5000, preferably less than 3000, e.g. less than 1500, and (ii) comprising at least 70%, preferably at least 85%,

based on the weight of the first polymer block, e.g. consisting essentially of, repeating units having the formula $-Y(Rc)-$, wherein each of the Y radicals is a radical forming part of the backbone of the polymer, and each of the $-Y(Rc)-$ radicals contains a side chain Rc radical which is a high temperature crystallizable (HTC) radical (as hereinafter defined), and

(b) 85 to 97%, e.g. 89 to 93%, particularly about 91%, by weight, based on the weight of the polymer, of one or more second polymer blocks (often referred to herein as soft blocks) comprising at least 70%, preferably at least 85%, based on weight of the second polymer block, e.g. consisting essentially of, repeating units which have the formula $-Z(Rz)-$, where Z is a radical forming part of the polymer backbone and $-Z(Rz)-$ does not contain an HTC radical; and

(2) have a peak melting point (T_p) of 33 to 48°C, preferably 35 to 46%, e.g. 37 to 43°C.

The term high temperature crystallizable (HTC) radical is used herein to denote a radical such that a homopolymer consisting essentially of repeating units of the formula $-Y(Rc)-$ has a melting point of at least 34°C.

The polydispersity of the novel copolymers (i.e. the ratio M_w/M_n) is preferably less than 3, particularly less than 2.

The SCC polymers defined in (D) above are novel per se. In these SCC polymers, at least some of the Y radicals, and/or at least some of the Z radicals, when present, comprise a linking group which is bio-erodable, i.e. which, when the SCC polymer is present in a human body, can be weakened or destroyed, e.g. by hydrolysis, by substances which are present in the human body, particularly aqueous fluids. The nature, positioning and number, of such bio-erodable linking groups can be controlled in the preparation of the polymer, in order to make an SCC polymer which has a desired erodability over the course of time. Examples of such bioerodable linkages include ether linkages and phosphorus-containing linkages, e.g. phosphates. The polydispersity of these bio erodible polymers is preferably less than 6, particularly less than 4. At least some of the linkages between the hard blocks and the soft blocks, and/or within the soft blocks of the SCC polymers as defined in (C) can be bioerodable.

In preferred embodiments, the compositions as defined in (A) contain one or more SCC polymers which

- (1) have a peak melting point (T_p) of 33 to 48°C, preferably 35 to 46°C, e.g. 37 to 43°C; and/or
- (2) are as defined in (C) and/or (D) above.

As further explained below, the SCC polymer can be selected so that the composition retains its desired shape for a desired period of time, for example for a time which is substantially longer than the time for which many of the compositions now in use are effective, and/or for a time which depends upon the bioerodability of the polymer.

An advantage of the SCC polymer compositions is that, after they have been placed in a human being and have assumed a substantially stable shape, that shape can be changed, or some or all of the composition can be extracted, by (A) heating the composition to a temperature above its melting point, and (B) exerting pressure on the skin to change the shape of the composition and/or extracting at least a portion of the composition through an opening in the skin.

In steps (B1) and (B2) of the method described in (E), the formation of the polymeric block on the oligomer or precursor can be effected by addition or condensation polymerization.

The oligomers described in (F) above correspond to the first polymeric blocks (the hard blocks) in the SCC polymers disclosed in (C) above. The oligomer (i) has an M_n of less than 5,000, preferably less than 3,000, e.g. less than 1,500, (ii) comprises at least 70%, preferably at least 85%, based on the weight of the oligomer, e.g. consists essentially of, repeating units having the formula $-Y(R_c)-$, wherein each of the Y radicals is a radical forming part of the backbone of the polymer, and each of the $-Y(R_c)-$ radicals contains a side chain R_c radical which is an HTC radical as hereinbefore defined, and (iii) comprises a reactive linking group through which the oligomer can be joined to the second polymeric blocks (the soft blocks), or a functional group which can be converted into such a reactive linking group. The polydispersity of the oligomers is preferably less than 3, particularly less than 2.0, e.g. less than 1.7, preferably less than 1.4.

The soft block precursors described in (G) correspond to the second polymeric blocks in an SCC polymer as disclosed in (C), the precursor comprising a plurality of

repeating units of the formula $-Z(R_z)-$, at least one of the Z radicals including a bioerodable linking group and/or a functional group which can be reacted to form a linking radical which is bioerodable.

5 The SCC block copolymers described in (C) contain only a small proportion of the $-Y(R_c)-$ radicals which could give rise to crystallinity. However, it has been found that the copolymers nonetheless have an unexpectedly useful degree of crystallinity. It has also been found that such a copolymer, if cooled beneath the skin from above its melting point to a temperature below, but not very far below, e.g. less than 10°C below, its melting point, e.g. to human body temperature, takes a substantial time, e.g. at least 5 or at least 10
10 minutes, and sometimes substantially longer, to crystallize. During this time, the composition remains in a state in which it will not flow easily, but its shape can be changed by pressure, for example pressure exerted on the composition through the skin. This hysteresis is very valuable in the methods of the invention, since it gives the practitioner time in which to change the shape of the composition so that the desired aesthetic or other
15 effect is obtained.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated in the accompanying drawings, which are diagrammatic and not to scale, and in which Figure 1 is an exploded perspective view of a device of the invention, Figure 2 is a perspective view of the device off Figure 1 when assembled, Figure
20 3 is a cross-sectional view of the heated hub in one device of the invention, and Figure 4 is a cross-sectional view of the heated hub in another device of the invention.

DETAILED DESCRIPTION OF THE INVENTION

In this specification, reference is made to particular features (including for example components, ingredients, elements, devices, apparatus, systems, groups, ranges, method
25 steps, test results, etc.) of the invention. It is to be understood that the disclosure of the invention in this specification includes all possible combinations of such particular features. For example, where a particular feature is disclosed in the context of a particular aspect, a particular embodiment, a particular claim, or a particular Figure, that feature can also be used, to the extent appropriate, in the context of other particular aspects, embodiments,
30 claims and Figures, and in the invention generally. The invention disclosed herein includes embodiments not specifically described herein and can for example make use of

features which are not specifically described herein, but which provide functions which are the same, equivalent or similar to, features specifically disclosed herein.

The term "comprises" and grammatical equivalents thereof are used herein to mean that, in addition to the features specifically identified, other features are optionally present. For example, a composition "comprising" (or "which comprises") ingredients A, B and C can contain only ingredients A, B and C, or can contain not only ingredients A, B and C but also one or more other ingredients. The term "consisting essentially of" and grammatical equivalents thereof is used herein to mean that, in addition to the features specifically identified, other features may be present which do not materially alter the claimed invention. The term "at least" followed by a number is used herein to denote the start of a range beginning with that number (which may be a range having an upper limit or no upper limit, depending on the variable being defined). For example "at least 1" means 1 or more than 1, and "at least 80%" means 80% or more than 80%. The term "at most" followed by a number is used herein to denote the end of a range ending with that number (which may be a range having 1 or 0 as its lower limit, or a range having no lower limit, depending upon the variable being defined). For example, "at most 4" means 4 or less than 4, and "at most 40%" means 40% or less than 40 %. When, in this specification, a range is given as "(a first number) to (a second number)" or "(a first number) - (a second number)", this means a range whose lower limit is the first number and whose upper limit is the second number. For example, "from 8 to 20 carbon atoms" or "8-20 carbon atoms" means a range whose lower limit is 8 carbon atoms, and whose upper limit is 20 carbon atoms. The terms "plural", "multiple", "plurality" and "multiplicity" are used herein to denote two or more than two features.

Where reference is made herein to a method comprising two or more defined steps, the defined steps can be carried out in any order or simultaneously (except where the context excludes that possibility), and the method can optionally include one or more other steps which are carried out before any of the defined steps, between two of the defined steps, or after all the defined steps (except where the context excludes that possibility). Where reference is made herein to "first" and "second" features, this is generally done for identification purposes; unless the context requires otherwise, the first and second features can be the same or different, and reference to a first feature does not mean that a second feature is necessarily present (though it may be present). Where reference is made herein

to "a" or "an" feature, this includes the possibility that there are two or more such features (except where the context excludes that possibility). Where reference is made herein to two or more features, this includes the possibility that the two or more features are replaced by a lesser number or greater number of features providing the same function (except where the context excludes that possibility). The numbers given herein should be construed with the latitude appropriate to their context and expression; for example, each number is subject to variation which depends on the accuracy with which it can be measured by methods conventionally used by those skilled in the art.

In this specification, parts and percentages are by weight, except where otherwise noted. Temperatures are in degrees Centigrade ($^{\circ}\text{C}$). Molecular weights are expressed in Daltons, measured in tetrahydrofuran using size exclusion chromatography, configured with a Wyatt laser light scattering detector. The term M_n denotes the number average molecular weight, and the term M_w denotes the weight average molecular weight. The term T_o denotes the onset of melting temperature, the term T_p denotes the peak melting temperature, and the term T_L denotes the temperature at which melting is complete, of a polymer, determined using a DSC calorimeter at a rate of temperature change of $10^{\circ}\text{C}/\text{min}$, on the second heat cycle, and typically from -10 to 150°C . T_o is the temperature at the intersection of the baseline of the DSC peak and the onset line, the onset line being defined as the tangent to the steepest part of the DSC curve below T_p . T_p is the temperature at the peak of the DSC curve. T_L is the intersection of the baseline of the DSC curve and the descent line of the DSC curve (defined as the tangent to the steepest part of the DSC curve above T_p).

This specification incorporates by reference all documents referred to herein and all documents filed concurrently with this specification or filed previously in connection with this application, including but not limited to such documents which are open to public inspection with this specification.

For details of SCC polymers in general, reference can be made for example to J. Poly. Sci. 60, 19 (1962); J. Poly. Sci. (Polymer Chemistry) 7, 3053 (1969), 9, 1835, 3349, 3351, 3367, 10, 1657, 3347, 18, 2197, 19, 1871; J. Poly. Sci, Poly-Physics Ed 18 2197 (1980); J. Poly. Sci, Macromol. Rev, 8, 117 (1974); Macromolecules 12, 94 (1979), 13, 12, 15, 18, 2141, 19, 611; JACS 75, 3326 (1953), 76; 6280; Polymer J 17, 991 (1985); and Poly. Sci USSR 21, 241 (1979); United States Patents Nos. 4,830,855, 5,120,349,

5,129,180, 5,156,911, 5,254,354, 5,387,450, 5,412,035, 5,469,867, 5,665,822, 5,752,926, 5,783,302, 6,013,293, 6,060,540, 6,199,318, 6,210,724, 6,224,793, 6,255,367, 6,376,032, 6,492,462, 6,540,984, 6,548,132, 6,831,116, 6,989,417, and 7,101,928 ; and US Patent Application Publications Nos. 2001/0018484 2002/0090425 and 2002/0127305. The entire disclosure of each of those publications, patents and patent publications is incorporated herein by reference for all purposes.

In the SCC polymers used in this invention, substantially all the repeating units of the formula $-Y(R_c)-$ can be the same, or there can be a plurality of different types of repeating unit which differ from each other in Y, or in R_c , or in both Y and R_c . When the SCC polymer also contains repeating units of the formula $-Z(R_z)-$, those repeating units can all be the same, or there can be a plurality of different types of repeating unit which differ from each other in Z, or in R_z , or in both Z and R_z . The Y and Z radicals can be the same or different. The $-Y(R_c)-$ and $-Z(R_z)-$ radicals can be in any desired distribution, for example randomly, or in first blocks containing only $-Y(R_c)-$ radicals and in second blocks containing only $-Z(R_z)-$ radicals.

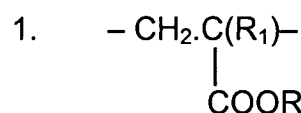
In the $-Y(R_c)-$ radicals, the R_c radical will often have the general formula $-S(C_y)-$, where C_y is the radical which results in crystallinity, and S is a bond or a linking radical, for example a covalent bond or a divalent organic or inorganic radical, e.g. an ester, carbonyl, amide, amine oxide, hydrocarbon (for example phenylene), amino or ether radical.

The Y (and Z radicals, if present) which form the backbone of the polymer can be derived from any type of polymerization, e.g. addition and/or condensation polymerization of suitable monomers. For example, the SCC polymer can be, or can comprise sections which are, polyacrylates, polyolefins, polyethers, polyurethanes, polyesters, polyamides, polysilanes, or polysiloxanes. Thus, each of the Y radicals (and each of the Z radicals, if present) normally comprises a plurality of "backbone atoms", i.e. atoms which form part of the backbone of the polymer. In each Y radical (and in each Z radical, if present) there is a backbone atom which is at least trivalent, generally carbon, and which carries the substituent R_c (or R_z). Generally, each Y (or Z) radical includes at least one other backbone atom. The other backbone atoms have a valence of at least 2. Examples of divalent backbone atoms are oxygen and sulfur. Nitrogen is an example of a trivalent backbone atom. Carbon is an example of a 4-valent atom. Any valencies of the backbone

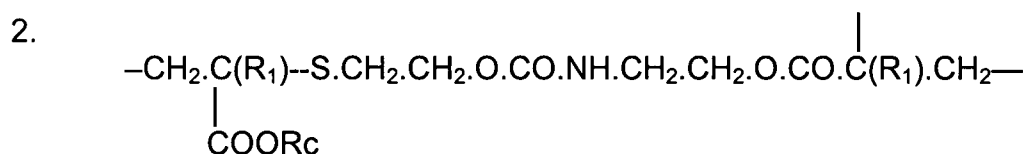
atoms which are not satisfied by the R_c (or R_z) radical can be satisfied by hydrogen radicals or other radicals. In the -Z(R_z)- radicals, the R_z radical can be a hydrogen radical.

The nature of the Y and Z radicals will be determined by the monomers from which the polymers are derived and by the mechanism of the polymerization (e.g. addition or condensation polymerization). In some cases, all the Y and Z radicals will be the same, at least in the backbone atoms.

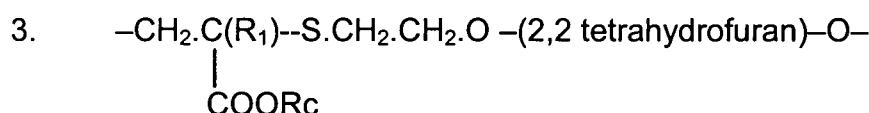
Examples of --Y(R_c)-- include, without limitation, radicals having the formula:



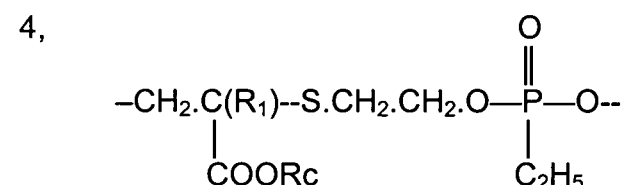
where R₁ is hydrogen or methyl, and R_c is an HTC radical, e.g. derived from an n-alkyl or fluorinated n-alkyl acrylate or methacrylate in which the n-alkyl group contains 12 to 50 carbon atoms, e.g. one or more of octadecyl acrylate or methacrylate and behenyl acrylate or methacrylate;



where R₁ is hydrogen or methyl, and R_c is an HTC radical, e.g. derived from an n-alkyl or fluorinated n-alkyl acrylate or methacrylate in which the n-alkyl group contains 12 to 50 carbon atoms, e.g. one or more of octadecyl acrylate or methacrylate and behenyl acrylate or methacrylate;

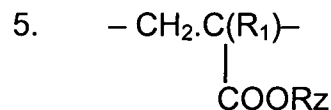


where R₁ is hydrogen or methyl, and R_c is an HTC radical, e.g. derived from an n-alkyl or fluorinated n-alkyl acrylate or methacrylate in which the n-alkyl group contains 12 to 50 carbon atoms, e.g. one or more of octadecyl acrylate or methacrylate and behenyl acrylate or methacrylate; and



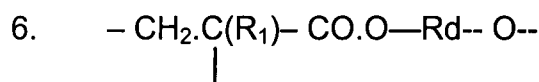
where R_1 is hydrogen or methyl, and R_c is an HTC radical, e.g. derived from an n-alkyl or fluorinated n-alkyl acrylate or methacrylate in which the n-alkyl group contains 12 to 50 carbon atoms, e.g. one or more of octadecyl acrylate or methacrylate and behenyl acrylate or methacrylate.

Examples of $--Z(R_z)--$ include, without limitation, radicals having the formula:

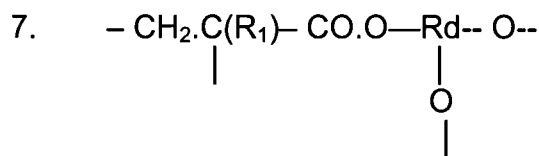


where R_1 is hydrogen or methyl, and R_z is an n-alkyl or branched chain alkyl or n-fluoroalkyl or branched chain fluoroalkyl radical containing 1-6 carbon atoms, e.g. derived from n-butyl acrylate or methacrylate.

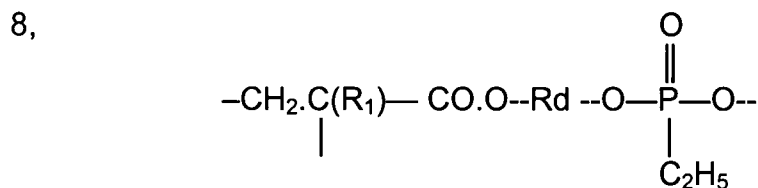
Examples of linking radicals that may form part of $--Z(R_z)--$ radicals include, without limitation, radicals having the formula:



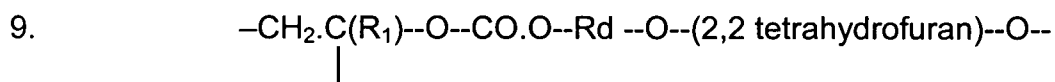
where R_1 is hydrogen or methyl, and R_d is a divalent radical, e.g. $-CH_2.CH_2--$.



where R_1 is hydrogen or methyl, and R_d is a trivalent radical,



where R_1 is hydrogen or methyl, and R_z is an n-alkyl or branched chain alkyl group containing 1-10 carbon atoms; and

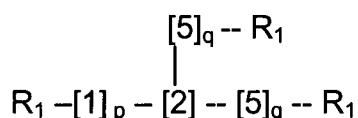


where R_1 is hydrogen or methyl, and R_d is a divalent radical, e.g. $-CH_2, CH_2--$.

Polymers (including oligomers) comprising the repeating units of formula Y(Rc) and, if present, repeating units of formula Z(Rz), will also contain terminal radicals, for example hydrogen or methyl.

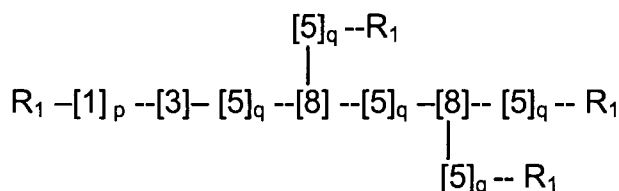
Radicals 1 and 5 above are representative of radicals repeated multiple times adjacent to each other; the other radicals above are representative of radicals which can be at the end of a chain of multiple radicals, e.g. multiple radicals 1 and/or 5 above, or which can link two or more blocks of radicals of the same or different kinds, for example so as to provide a bioerodable link between those blocks.

Thus, one type of polymer (the polymer produced in Example 37 being an example of this type) has the formula



wherein p is for example 2-5, the q's may be the same or different, and the total of the q's is for example 40 to 240

Another type of polymer (the polymer produced in Example 62 being an example of this type) has the formula



wherein p is for example 2-5, the q's may be the same or different, and the total of the q's is for example 40 to 240.

In some embodiments, some or all of the Z radicals can include a linking unit which is selected for its ability to provide the SCC polymer with a desired property, e.g. to make the SCC polymer bio-erodable. For example, dihydroxy-terminated monomers, or dihydroxy-terminated oligomers or polymers which are precursors for polymeric blocks in a block copolymer, can be linked to each other through a difunctional reagent such as 2-,2-diethoxy tetrahydrofuran or dichloro ethyl phosphate which results in bioerodable linkages. In this way, SCC polymers, which are normally hydrophobic and highly resistant to water,

can be made selectively sensitive to water. By selecting the number and type of such linkages, it is possible to impart to the polymer a wide range of hydrolytic stability, and a correspondingly wide, but predetermined, variation in the stability of the composition in the human body. Because the bulk of the SCC polymer is hydrophobic, any bio-erosion of the SCC polymer will take place gradually, starting and continuing at the surface of the SCC polymer which is exposed to aqueous body fluids.

In some preferred embodiments, the first polymeric blocks (and the oligomers from which they can be derived) consist essentially of (i) units in which the Rc radical comprises an n-alkyl radical containing 16-20 carbon atoms, e.g. an n-octadecyl (also known as stearyl) radical, for example derived from the corresponding n-alkyl acrylate or methacrylate, e.g. n-octadecyl methacrylate, and (ii) units in which the Rc radical comprises an n-alkyl radical containing 21-30, or more, carbon atoms, e.g. a behenyl radical (i.e. a linear polymethylene radical containing 22 carbon atoms), for example derived from the corresponding n-alkyl acrylate or methacrylate, e.g. behenyl methacrylate. The radicals (i) and (ii) can be randomly distributed in the first polymeric block. Each of the first (hard block) polymeric blocks can for example contain 1-4 of the repeating units (i) and 1-4 of the repeating units (ii). The first polymeric blocks can, for example, contain on average 50-70%, e.g. 55-63%, of the behenyl radicals, based on the weight of the first polymeric blocks.

The SCC compositions comprising the SCC polymer (hereinafter referred to as the SCC polymer composition) can consist of the SCC polymer, or can also contain other ingredients which do not adversely affect the functionality of the composition. In many cases, it is preferred that the composition should contain less than 5% by weight of water, preferably substantially no water. The compositions can be sterilized, before being placed in the human body, e.g. by radiation.

In some embodiments, the SCC polymer composition is preferably selected so that, at a temperature above T_L , but at or below the temperature which can be comfortably tolerated by the human being into which the composition is to be placed, e.g. about 44°C, preferably at a temperature below 43°C or 42°C, the SCC composition has a viscosity such that it can be subcutaneously injected into the human being through a hypodermic needle having a gauge between 25 and 32, preferably between 27 and 30.

The rheological properties of an SCC polymer depend upon, among other things, the extent of the crystallization of the SCC polymer. When all the polymer has melted, which may be for example at a temperature which is 1-7°C above T_p , there is no crystallinity and the polymer is a fluid. In some embodiments of the invention, the SCC polymer, at the time when it is placed in the human body, is preferably a fluid having a viscosity such that it can be passed through a small tube, e.g. a tube having a gauge of 25 to 32. When the SCC polymer is at equilibrium at a temperature below T_o , all the crystallizable radicals are in crystalline form. When the SCC polymer is at equilibrium at a temperature between T_o and T_p , some, but not all, of the crystallizable radicals are in crystalline form. Therefore, when the SCC polymer is at equilibrium at a temperature below T_p , it will not flow and will not change shape permanently (though it may undergo elastic deformation) when subjected to tolerable pressure through the skin. If the equilibrium temperature is between T_o and T_p , the cooled composition will often more readily undergo elastic deformation.

The rheological properties of the SCC polymer, at equilibrium under the skin, are also important to the "feel" of the skin over the SCC polymer (i.e. the tactile impression to a person feeling the skin). I have found that SCC polymers having relatively large proportions of soft blocks contribute to an attractive palpability, and I believe that this is because such SCC polymers have a soft, gel-like consistency. In some embodiments of the invention, therefore, it is preferred to use an SCC polymer in which the proportion of soft blocks is at least 70%, e.g. at least 85%, preferably at least 84%, e.g. 70 to 98%, or 85 to 97%, or 89 to 93%, e.g. about 91%. The low glass transition temperature of the soft block enhances the palpability of the skin over the composition. For some embodiments, the glass transition temperature of the soft blocks is less than 0°C, particularly less than -20°C, e.g. -32 to -50°C.

After the SCC polymer has been placed under the skin, it begins to cool, but there is a delay in reaching equilibrium. Thus, when the polymer has first cooled to below T_o , and has not reached equilibrium, few or none of the crystallizable groups may have crystallized. This hysteresis effect is valuable in many embodiments of the present invention, because the SCC polymer, after having been placed under the skin, remains for a time in a rheological state which is between the fluid state of the polymer as it was placed under the skin and the equilibrium shape-retaining state. During that time, which is

preferably at least 5 minutes, particularly at least 10 minutes, little or none of the polymer will flow away from the location in which it was initially placed, but the shape of the polymer can be changed by pressure on the skin over the polymer. That pressure can be provided by the fingers of a practitioner and/or by a practitioner-controlled mechanical instrument which optionally supplies heat to the skin in order to prolong the time during which the polymer can be shaped.

Under appropriate conditions, this invention can change the appearance of skin in a desired way, e.g. to increase the volume of lips or another part of the body, or to reduce or remove skin blemishes, for example dermal volume loss (DVL), caused by natural aging, disease, or mal-formed skin blemishes such as acne, vermillion border, vermillion, fine lines and wrinkles, folds, furrows and deep wrinkles.

The SCC polymer composition can be delivered to the site in any appropriate way. In one preferred method, the composition, while it is as a temperature of T_L or above (which may be 1-7°C above T_p), is injected subcutaneously through a hypodermic needle or the like having a relatively small size, for example a gauge between 25 and 32.

The temperature of the SCC polymer composition when it first contacts the human being (or other mammal) must be tolerable to the human being. Since the tissue surrounding the composition will act as a heat sink, the composition has low heat transmissibility, and, in many cases, the fact that the quantity of the composition is small compared to the surrounding tissue, that temperature may be substantially above the temperature that can be tolerated on a continuous basis over a large area. Thus the temperature of the composition when it first contacts the human being can for example be as high as 52°C, though lower temperatures, e.g. less than 48°C, may be preferred.

Only a little thermal energy is needed to remelt an SCC polymer composition which has been placed in a human body. A composition directly under the skin can be melted by applying heat to the outside of the skin, e.g. by means of a thermal wand whose tip is at about 46°C plus or minus 3°C (when touching the skin). The melted composition can then be reshaped by applying pressure to the outside of the skin, e.g. with the thermal wand and/or the practitioner's fingers. Alternatively or additionally, some or all of the melted composition can be removed by inserting a hypodermic syringe into the melted composition and applying suction. After removal of the heat, the composition cools back to its body temperature state.

Any suitable device can be used to deliver the SCC polymer composition to the desired site. However, it is preferred to use a novel device as described in (B) above. In one embodiment of such a device, the reservoir comprises a hub at the outlet and an electrical heater which substantially surrounds the hub. In another embodiment, an electrical heater is placed at the outlet so that, when a needle is attached to the outlet, the heater lies between a fitting on the end of the needle and the parts of the reservoir defining the outlet. In another embodiment, the needle comprises a fitting which is fixed to the outlet of the reservoir, and an electrical heater which substantially surrounds the fitting. In other embodiments, the needle, and/or the reservoir, and/or a component adjacent to the outlet, comprises a magnetically permeable material which can be heated inductively, e.g. by a coil which is part of the device. Suitable magnetically permeable materials include for example nickel-iron alloys and ferrite-filled ceramics. The novel devices are particularly useful for dispensing SCC polymer compositions, but also useful for dispensing other compositions, for example when the human being into which the composition is to be injected derives some benefit, for example improved performance during or after the injection or greater comfort during or after the injection.

The piston in the injection device of the invention can be powered manually, hydraulically or pneumatically. Preferred devices are capable of precise volume, flow rate, and temperature control of the composition and/or can operate at high pressures, for example up to and exceeding 5000psi (350 kg per square centimeter), when such pressures are needed to deliver a viscous composition (e.g. an SCC polymer composition as described in (A) above) through a small gauge (for example 23-30 gauge) needle. Flow rates of 0.3 to 3, e.g. 0.5 to 2, cc /min can be used in some cases.

The reservoir is preferably constructed from a thermally insulating material, for example a polymeric material such as polycarbonate or Ultem.

The device preferably includes a hub constructed from a thermally conductive material, for example metal, e.g. brass or stainless steel. The hub may be secured to the reservoir, at or near the outlet of the reservoir, or to the end of the needle which is secured to the outlet of the reservoir.

The needle is preferably removably attached to the outlet of the reservoir, so that if desired a new needle can be used for successive uses of material from the same

reservoir. The needle can include a fitting of substantial thermal mass through which the needle is secured to the outlet.

The heating of the composition can be carried out in any way, but is preferably carried out by means of an electrically powered heater. The heater preferably mates geometrically with the hub. The hub can for example be heated to a temperature of 40 to 100°C., e.g. 45 to 70°C. The hub delivers heat to the composition as it passes from the reservoir into the needle. The amount of the composition which is heated at any one time can for example be at most 10%, preferably less than 5%, for example less than 2%, of the total capacity of the reservoir. However, amounts greater than 10% can be heated, for example by heat conducted away from the heater to other parts of the reservoir, e.g. by metal strips extending longitudinally towards the rear end of the reservoir. The heater can for example generate 5-15, e.g. about 10, watts

In a preferred embodiment the injection device comprises a hand piece containing a piston in a cylinder that is driven by either hydraulic or pneumatic pressure from a remote pressure source and controller. The drive piston of the hand piece in turn is attached to a piston rod of smaller diameter than the drive piston. This rod mechanically engages and drives a second piston sliding in a thermally insulating, (e.g. a polymeric material such as polycarbonate or Ultem) disposable syringe. The disposable syringe mates removably with the hand piece and is provided with a metal hubbed needle. The needle is designed to be easily replaceable (by simple threading or via a twist-on fitting, e.g. a Leur-Lock fitting).

The volume of material delivered by the device is a function of the product of the pressure and the length of time that the pressure is applied by the dispenser, i.e. the person controlling the device. The flow rate of material for a given pressure generally goes up with the temperature of the material ((since high temperatures yield lower viscosities, and, therefore, higher flow rates), and goes down a sharply with a decrease in the needle lumen diameter. The flow rate goes down with an increase in the needle length. The needle lumen diameter is generally fixed for a given needle size and length. For a given device and polymer composition, the dispenser should balance pressure, time, and temperature of the polymer to achieve optimum performance.

For optimum results, the design of the device will consider, among other things, (a) the thermal conductivity of the hub and needle, (b) the diameter and length of the hub, (c)

the length and wall thickness of the needle extending beyond the end of the hub, and (d) heater to hub thermal contact efficiency.

Preferred features of the invention can optionally include the following.

(1) A hydraulically or pneumatically powered hand piece (which may be disposable or non-disposable) which cooperates with an optionally disposable pre-filled reservoir, in order to provide control of pressure on the material in the prefilled reservoir, and which thus allows precise delivery of polymeric implant materials, in particular compositions which are too viscous for convenient manual injection. Remote hydraulic or pneumatic control can be provided by modification of commercially available pressurized dispenser equipment, e.g. an EFD (Nordson Corp.) 2400 pneumatic or 2800 hydraulic controller.

(2) A pre-filled reservoir with thermal insulating properties which allow it to be handled manually even while heated polymer is being dispensed from the outlet of the reservoir. The reservoir can have a shape such that it can conveniently be equipped by the dispenser's fingers. The reservoir is preferably thick-walled so that it will resist high pressures. The reservoir can be optically clear, or can include inspection windows, so that the dispenser can see how much polymer is in the reservoir. The reservoir can include markings to see how much polymer has been dispensed, in total and/or in a particular injection.

(3) An electrical heater (which can be disposable or reusable) in combination with a disposable hubbed needle, thus allowing efficient heating of the polymeric composition during delivery and control of the viscosity of the composition. The material and shape of the needle and needle hub material are preferably selected to provide high thermal conductivity while preserving normal needle parameters.

Referring now to the drawings, Figures 1-4 show a reservoir 1 having a threaded outlet 11; a needle 5 having a threaded terminal 51 which can be screwed into the outlet 11; and an electrical heater 4 having insulated leads 41 and 42. A piston, not shown, fits into the reservoir 1.

The invention is illustrated by the following Examples.

Example 1

In this Example, a hard block oligomer as disclosed in (F) was prepared.

259.5 g (0.766 moles) of octadecyl methacrylate, 317.0 g (0.803 moles) of behenyl methacrylate and 959 g of toluene were introduced into glass reaction vessel. The vessel

was purged with nitrogen to eliminate the bulk of dissolved oxygen. The rate of introduction was slow enough that discrete bubbles could be observed. The reaction mixture was stirred with a mechanical stirrer and was heated, keeping the temperature below about 60°C. When most of the monomer had dissolved, 92.4 g (1.183 moles) of mercaptoethanol and 1.795 g of azobisisobutyronitrile (hereinafter AIBN) were added in that order. The molar ratio of the methacrylate monomer to the mercapto ethanol was 1.33. The reaction mixture was stirred at about 100 RPM and the temperature was maintained at about 60°C. All fluorescent lights in the hood and surrounding area were then turned off and the reaction allowed to proceed for approximately 72 hours. When the reaction was complete, the lights were turned back on and a distillation adapter was attached to the reaction vessel. A gentle stream of nitrogen flow was maintained. Most of the toluene was flash-distilled off under partial vacuum and the temperature was then gradually raised to about 60°C. When about 2/3rds of the original volume of toluene had been flash-distilled out of the reaction vessel, 1584 g of acetonitrile was added to the warm flask and stirred until all of the material has been dissolved or suspended. The vessel and its contents were chilled to about 5°C. In time, a crystalline phase formed at the bottom of the reaction vessel. The product was isolated by decanting off the clear supernatant solution. The purification process was repeated several times until the product was isolated as a crystalline solid. The crystalline product was air dried and, finally, vacuum-dried. The product had an Mn of about 1067 and an Mw of about 1263 and a Tp of about 43°C.

Examples 2-35

In Examples 2-35, the procedure of Example 1 was followed except that the ratio of the methacrylate monomer to the mercaptoethanol was varied, thus changing the Mn and Mw of the product. The results are summarized in the table below. All the products had a Tp of about 43°C.

	Ratio	Mn	Mw	Poly-dispersity
Example 2	5.934	2,554	3,411	1.34
Example 3	5.934	2,599	3,403	1.31
Example 4	5.934	3,015	3,873	1.28
Example 5	5.934	2,622	3,460	1.32
Example 6	5.940	3,140	4,039	1.29
Example 7	5.940	2,835	3,783	1.33
Example 8	5.940	3,209	4,025	1.25
Example 9	5.940	3,429	4,298	1.25
Example 10	4.240	2,410	3,072	1.27
Example 11	4.240	2,405	3,244	1.35
Example 12	3.710	2,505	3,560	1.42
Example 13	3.710	2,484	3,162	1.27
Example 14	3.000	1,702	2,224	1.31
Example 15	3.000	1,770	2,348	1.33
Example 16	3.000	1,907	2,258	1.18
Example 17	3.000	1,836	2,191	1.19
Example 18	12.953	5,143	6,941	1.35
Example 19	12.953	4,821	6,738	1.40
Example 20	7.000	3,233	4,065	1.26
Example 21	7.000	3,695	4,428	1.20
Example 22	7.000	3,203	4,052	1.27
Example 23	7.000	3,146	3,943	1.25
Example 24	7.000	3,557	4,123	1.16
Example 25	7.000	3,634	4,249	1.17
Example 26	2.500	1,630	2,113	1.30
Example 27	2.500	1,813	2,325	1.28
Example 28	2.500	1,872	2,602	1.39
Example 29	2.500	1,664	1,994	1.20
Example 30	2.500	1,735	1,997	1.15
Example 31	2.500	1,749	2,027	1.16
Example 32	1.500	1,189	1,390	1.17
Example 33	1.500	1,132	1,397	1.23
Example 34	1.330	1,093	1,399	1.28
Example 35	1.330	981	1,171	1.19
mean				1.27
stand dev				0.07

In Example 36, the hydroxyl group in the hydroxy-terminated hard block oligomer prepared in Example 1 was converted into a methacrylate derivative, thus preparing another hard block oligomer.

375.6 g (0.327 moles) of the hydroxy-terminated hard block oligomer prepared in Example 1, 65.78 g (0.4239 moles) of isocyanatoethyl methacrylate (IEMA), and 680 g of toluene were added to a reaction vessel. The system was not purged with nitrogen because dissolved oxygen was needed to inhibit any unwanted polymerization. The reaction mixture was stirred with a motorized paddle and heat was applied, keeping the temperature of the reaction mixture at or below about 30°C. When most of the methacrylate monomer had dissolved, 1.022 g (0.424 moles) of dibutyl tin dilaurate (a catalyst for the desired reaction) was added, while stirring the mixture at about 100 RPM. The fluorescent lights in the hood were turned off, and the reaction was allowed to proceed for about 16 hours. When the reaction was complete, 35.1 g (0.3272 moles) of ethanol was added to the reaction mixture to consume any unused IEMA. The reaction mixture was stirred for an additional 4 hours. The product was isolated and purified in the way described in Example 1, and had an Mn of 2,368.

Example 37

In this Example, a block copolymer as disclosed in (C) above was made by polymerizing n-butyl acrylate (referred to below as C4A) on the methacrylate-containing hard block oligomer prepared in Example 36, which is referred to below as FHB (an abbreviation for functionalized hard block).

162g (1.26 moles) of C4A, 8.44g (0.0036 mole) of FHB and 444 g of methyl acetate were introduced into a glass reaction flask. The system was purged with nitrogen to eliminate the bulk of dissolved oxygen. The rate of introduction was slow enough that discrete bubbles could be observed. The reaction mixture was stirred with a motorized paddle and was heated, while keeping the temperature of the mixture at or below about 60°C. When most of the FHB had dissolved, 0.507g (0.0025 mole) of 1-dodecanethiol (C12SH) and 0.159 g (0.001 mole) of AIBN were added to the reaction flask in that order. The molar ratio of butyl acrylate monomer to dodecanethiol was 505. The stirrer was maintained at about 100 RPM and the temperature of the reaction mixture at about 60°C. All fluorescent lights in the hood and surrounding area were turned off. The reaction was allowed to proceed for approximately 24 hours. The lights were then turned back on and a

distillation adapter was attached to the reaction vessel. A gentle stream of nitrogen was maintained. Most of the methyl acetate was flash-distilled off under partial vacuum and the temperature was gradually raised to about 60°C. When most of the methyl acetate had been flash-distilled out of the reaction vessel, 1584 g of acetonitrile was added to the warm flask and stirred until all of the material has been dissolved or suspended. The vessel and its contents were chilled to about 5°C. A hazy white gel phase formed in time at the bottom of the reaction vessel. The product was isolated by decanting off the clear supernatant solution on the top. The purification process was repeated several times until the product was isolated as a hazy viscous soft gel. The product was air dried and, finally, vacuum-dried. Approximately, 245g of material was produced. The resulting product had an Mn of 48,505, a To of about 34.8°C, a Tp of about 38.7°C, and a T_L of about 41.2°C. Because 95.05% of the monomeric reaction mixture was n-butyl acrylate, we calculated that the soft block component had an Mn of 46,103.

Examples 38-60

In Examples 38-60, the procedure of Example 37 was followed, except that the quantity of C12SH was changed so that the molar ratio of C4A to C12SH was as stated below. The Tp of all the products was about the same. These Examples show that by adjusting the molar ratio between the C4A and C12SH, block copolymers of various molecular weights can be prepared.

	Molar Ratio C4A /C12SH	Mn (1)	Mn (2)	Hard Block Units
Example 38	399.5	29,827	34,590	2.01
Example 39	1423.4	101,165	106,450	2.23
Example 40	856.0	77,180	86,060	3.75
Example 41	760.1	71,675	81,230	4.52
Example 42	1542.3	143,467	153,150	4.09
Example 43	1033.0	106,327	114,350	3.39
Example 44	504.6	48,161	50,670	1.06
Example 45	504.6	46,103	48,505	1.01
Example 46	1300.8	103,067	108,100	1.77
Example 47	413.2	40,513	43,330	1.10
Example 48	825.1	79,193	84,700	2.15
Example 49	336.6	33,314	35,630	1.22
Example 50	588.0	64,430	68,910	2.37
Example 51	174.0	27,087	28,970	1.00
Example 52	319.2	54,416	58,200	2.00
Example 53	173.8	15,082	16,130	0.56
Example 54	317.5	32,234	34,475	1.19
Example 55	62.9	10,128	11,350	0.55
Example 56	202.1	26,330	29,495	1.44
Example 57	138.7	20,503	22,530	1.44
Example 58	126.7	17,480	18,650	1.15
Example 59	126.7	16,670	17,990	1.11
Example 60	126.7	16,130	15,870	1.02

When the molar ratio between C4A and C12SH was plotted against the measured soft block molecular weight number average (Mn; ordinate), a mathematical relationship was discovered that is represented by the equation: $348.23 \times \text{ratio}^{0.8009} = \text{Mn}$. This power fit had a variance confidence factor of 95%.

Example 61

This Example shows the preparation of an oligomeric diol corresponding to part of a soft block. To a glass reaction flask was added 2100g of methyl acetate, 929.3g (7.251 moles) of C4A, 92.9g (0.714 moles) of hydroxy ethyl methacrylate, 48.23g (0.617 mole) of mercaptoethanol and 7.54g (0.046 mole) of AIBN. The molar ratio of the methacrylate monomer to the mercaptoethanol was 12.90. The reaction mixture was heated to between 58° and 61°C for about 70 hours. The mechanical stirrer was maintained at about 100 RPM. All fluorescent lights in the hood and surrounding area were turned off. When the reaction was complete, the lights were turned back on and a distillation adapter was attached to the reaction vessel. A gentle stream of nitrogen was maintained. Most of the

methyl acetate was flash-distilled off under partial vacuum and the temperature was gradually raised to about 60°C. When about 4/5ths of the original volume of methyl acetate had been flash-distilled out of the reaction vessel, 1584 g of acetonitrile was added to the warm flask and stirred until all of the material has been dissolved or suspended.

5 The vessel and its contents were chilled to about 5°C. In time, a viscous liquid phase formed at the bottom of the reaction vessel. The product was isolated by decanting off the clear supernatant solution on the top. The purification process was repeated several times until the product was isolated as a water-clear viscous liquid. The product was air dried and, finally, vacuum-dried. The resulting product had an Mn of 1,842 and an Mw of 2,565,
10 i.e. a polydispersity of about 1.4.

Example 62

In this Example, a bioerodable block copolymer containing tetrahydrofuran linkages within the soft block and between the soft and hard blocks was prepared.

To an oven-dried, glass reaction flask was added 30g (0.0163 mole) of the
15 oligomeric diol described in Example 61, 3.33g (0.0034 mole) of the hydroxy-terminated hard block oligomer described in Example 1 and having an Mn of 969, 3.149 g (0.01938 mole) of diethoxytetrahydrofuran (DETHF), and 0.03 g of polyphosphoric acid catalyst. The system was purged with nitrogen to eliminate most of dissolved oxygen and to carry away any produced ethanol. The rate of introduction was slow enough that discrete bubbles
20 could be observed. The reaction mixture was stirred with a motorized paddle and was heated but not to the extent that the mixture exceeded about 120°C. After about 3 hours, vacuum was applied for about 30 minutes. The temperature was then raised to about 150°C for an additional 3 hours. A small sample of the orthoester linked polymer was taken from the reaction mixture. Its Mn was 5,583 and its Mw was 64,414. A small drop of
25 DETHF was added and the reaction was continued for another 5 hours at 120°C under full vacuum. The Mn rose to 18,250 and the Mw to 574,200. It was concluded that a variety of molecular weight materials could be produced and depended on the stoichiometry, temperature, and the length of time that the reaction is under vacuum.

Example 63

30 In this Example, a bioerodable block copolymer having bioerodable phosphate linkages within the soft block and between the soft and hard blocks was prepared using

the oligomeric diol prepared in Example 61 and a hydroxy-terminated hard block oligomer prepared according to the procedure of Example 1 but having an Mn of 969.

Approximately equimolar amounts of ethyl dichlorophosphate and the oligomeric diol were reacted in the presence of an organic base such as triethylamine or the like. The reaction product is then reacted with the hydroxy-terminated hard block oligomer, thus preparing a block copolymer in which the blocks are linked together through a phosphate linkage.

Example 64

The block copolymer produced in Example 59 was heated to about 75°C and drawn into a dozen 1cc syringes. Any air bubbles trapped in the polymer were allowed to migrate to the surface, after which the filled syringes were sterilized by radiation.

A small Yorkshire pig was anesthetized, stabilized and prepped. The breathing and heart rate of the pig were monitored. Several dozen implant sites were marked with a black indelible marker pen. The injection sites were shared between injections of two commercial filler materials (Restylan® and Radiesse®) and the sterile block copolymer of Example 59. Sterile needles (selected from among several 25 to 27 gauge 0.5" needles) were attached to the end of the syringes by means of a Leur-Lock fitting. The tip of the needle was angled at about a 20° angle before it pierced the skin. The needle was inserted approximately 11mm into the tissue. The depth was estimated to be 4 mm below the surface. Using calibrated markings on the barrel, the piston in the syringe was used to inject approximately 0.2 cc of each of the different materials into randomly selected sites. The block copolymer of Example 59 was at a temperature of about 45-48°C when it was injected.

When all the implantations were complete, a team of 5 knowledgeable individuals wearing clean nitrile gloves were ask to subjectively rate the palpability of the individual implant sites. The block copolymer of Example 59 was rated between the two commercial products.

Example 65

Using another anesthetized pig, the procedure of Example 64 was followed using a polymer which was the same as the polymer of example 59 except that the ratio of behenyl methacrylate to octadecyl methacrylate was 55:42 (instead of 62: 38) and about 0.1 cc of the polymer was injected. The polymer used in this Example had a T_p of about 38°C and

a T_L of about 41.2°C. Those injected polymer formed small raised lumps about 6mm in diameter. After about 15 minutes, three of these sites were massaged and the lumps flattened out over a broader area. The other sites were cooled to about 25°C either by a stream of cool air or by ice contained in a sterile latex glove. Three of the cooled sites were massaged, but the raised lumps failed to spread out. A thermal wand about the size of a large pen and designed to maintain a 80 sq mm tip at a temperature of 46 to 49°C was applied to the stratum corneum directly above each of the now immobile raised lumps. With the heat and pressure applied by the wand the lump was easily flattened out. This procedure was repeated three more times. The areas that were flattened out were chilled by cool air to set the material and prevent further migration.

Example 66

A removal device was constructed as follows. An empty syringe fitted with a sterile stainless steel 16 gauge needle (0.5" long, and fitted with a nickel plated brass Leur-Lock® hub) was attached to a vacuum line that achieved a negative pressure of 28.5 inches of mercury. The syringe and needle were heated so that the temperature at the tip of the needle was about 45 to 47°C (in air).

The 5 remaining raised lumps in Example 65 were treated as follows. First, the warm thermal wand was placed directly on top of the lump, thus melting the block copolymer in the lump. Second, the needle of the removal device (without vacuum) was inserted into the center of the raised lump. Third, vacuum was applied to the needle. Melted copolymer was drawn up into the empty syringe. Gentle massaging of the lump helped to drive additional material into the syringe. The other four sites were treated in like manner. It was estimated that between 1/3 and 2/3 of the filler material had been removed.

Claims

1. A composition which
 - (a) comprises a side chain crystalline (SCC) polymer,
 - (b) at the body temperature of a human being, has a substantially stable equilibrium shape, and
 - (c) at an elevated temperature which can be tolerated by a human being, can be dispensed through a hypodermic needle.
2. A composition according to claim 1 which, when cooled from (a) a first temperature which is 1-7°C above the T_L of the SCC polymer to (b) a second temperature which is below the T_p of the SCC polymer, takes at least five minutes to assume the substantially stable equilibrium shape.
3. A composition according to claim 2 wherein the first temperature is less than 48°C and the T_p of the SCC polymer is 37 to 43°C..
4. A composition according to any of claims 1-3 wherein the SCC polymer
 - (1) comprises
 - (a) 3 to 15%, by weight, based on weight of the polymer, of one or more first polymer blocks each of which
 - (i) has a number average molecular weight (M_n) of less than 5000, and
 - (ii) comprises at least 70%, based on the weight of the block, of repeating units having the formula $-Y(R_c)-$, wherein each of the Y radicals is a radical forming part of the backbone of the polymer, and each of the $-Y(R_c)-$ radicals contains a side chain R_c radical which is a high temperature crystallizable (HTC) radical (as hereinbefore defined), and
 - (b) 85 to 97%, based on the weight of the polymer, of one or more second polymer blocks comprising at least 70% of repeating units which have the formula $-Z(R_z)-$, where Z is a radical forming part of the polymer backbone, and $-Z(R_z)-$ does not contain an HTC radical; and
 - (2) has a T_p of 33 to 48°C.

5. A composition according to claim 4 wherein the SCC polymer
 - (a) comprises 7 to 11% of the first blocks and 89 to 93% of the second blocks,
 - (b) has a T_p of 37 to 43°C., and
 - (c) has a polydispersity less than 3.
- 5 6. A composition according to any of claims 1-5 wherein the SCC polymer comprises linking groups which are bio-erodable.
7. A composition according to claim 6 wherein the SCC polymer has a polydispersity of less than 6 and the linking groups comprise phosphate or ether linkages.
8. An injection device which is suitable for dispensing a composition as claimed in any
10 of claims 1-7, and which comprises
 - (1) a reservoir for the composition, the reservoir having an outlet to which a needle can be, or is, fixed,
 - (2) a piston which is movable within the reservoir so that composition within the reservoir can be urged towards the outlet, and
 - 15 (3) a heater for heating composition which is relatively near the outlet to a temperature which is substantially higher than composition which is relatively remote from the outlet.
9. A device according to claim 8 wherein
 - (1) the reservoir comprises a hub at the outlet and a heater which substantially
20 surrounds the hub;
or
 - (2) a hypodermic needle is attached to the outlet of the reservoir, and a heater lies between the needle and the outlet of the reservoir.
10. A device according to claim 8 or 9 wherein the heater is an electrical heater.
- 25 11. A device according to claim 8 or 9 wherein the heater comprises magnetically permeable material which can be heated inductively.
12. A method of treating a mammal which comprises placing in the mammal a composition as claimed in any of claims 1-7.
13. A method according to claim 12 wherein the composition is dispensed through a
30 device as claimed in any of claims 8-11.
14. A side chain crystalline (SCC) polymer which is suitable for use in a composition according to any of claims 1-7 and which

(1) comprises

(a) 3 to 15%, by weight, based on weight of the polymer, of one or more first polymer blocks each of which

(i) has a number average molecular weight (M_n) of less than 5000, and

(ii) comprises at least 70%, based on the weight of the block, of repeating units having the formula $-Y(R_c)-$, wherein each of the Y radicals is a radical forming part of the backbone of the polymer, and each of the $-Y(R_c)-$ radicals contains a side chain R_c radical which is a high temperature crystallizable (HTC) radical (as hereinbefore defined), and

(b) 85 to 97%, based on the weight of the polymer, of one or more second polymer blocks comprising at least 70% of repeating units which have the formula $-Z(R_z)-$, where Z is a radical forming part of the polymer backbone, and $-Z(R_z)-$ does not contain an HTC radical; and

(2) has a T_p of 33 to 48°C.

13. An SCC polymer according to claim 12 which

(a) comprises 7 to 11% of the first blocks and 89 to 93% of the second blocks,

(b) has a T_p of 37 to 43°C., and

(c) has a polydispersity less than 3.

14. A side chain crystalline (SCC) polymer which is suitable for use in a composition according to any of claims 1-7 and which comprises linking groups which are bio-erodable.

15. An SCC polymer according to claim 14 which has a polydispersity of less than 6 and wherein the linking groups comprise phosphate or ether linkages.

16. A method of making an SCC polymer as defined in claim 14 or 15, the method comprising

(A1) providing a hard block oligomer corresponding to the first block, and

(B1) forming the second block on the oligomer by polymerization of a monomer corresponding to the repeating units of the formula $-Z(R_z)-$;

or

(A2) providing a soft block precursor corresponding to the second block in the SCC polymer, and

(B2) forming the first block on the soft block precursor by polymerization of a monomer corresponding to the repeating units of the formula $-Y(R_c)-$;

or

(A3) reacting together (i) a hard block oligomer corresponding to the first block and
(ii) a soft block precursor corresponding to the second block.

17. A hard block oligomer which is suitable for use in step (A1) or (A3) of claim 16, which has an M_n of less than 5,000 and a polydispersity less than 3; and which contains a reactive linking group through which the oligomer can be joined to the second blocks (the soft blocks), or a functional group which can be converted into such a reactive linking group.

18. A soft block precursor which is suitable for use in step (A2) or (A3) of claim 16, and which comprises a plurality of repeating units of the formula $-Z(R_z)-$, at least one of the Z radicals including a bioerodable linking group and/or a functional group which can be reacted to form a linking radical which is bioerodable.

19. A novel component which can form part of an injection device as claimed in any of claims 8-11 and which is

- (i) a reservoir which comprises an electrical heater adjacent the outlet; or
- (ii) a needle comprising a fitting which can be fixed to the outlet of a reservoir, and an electrical heater substantially surrounding the fitting;
- (iii) a reservoir which comprises an outlet, and, adjacent to the outlet, a component composed of a magnetically permeable material; or
- (iv) a needle which comprises a fitting for securing the needle to a reservoir, the fitting comprising a magnetically permeable material.

1/2

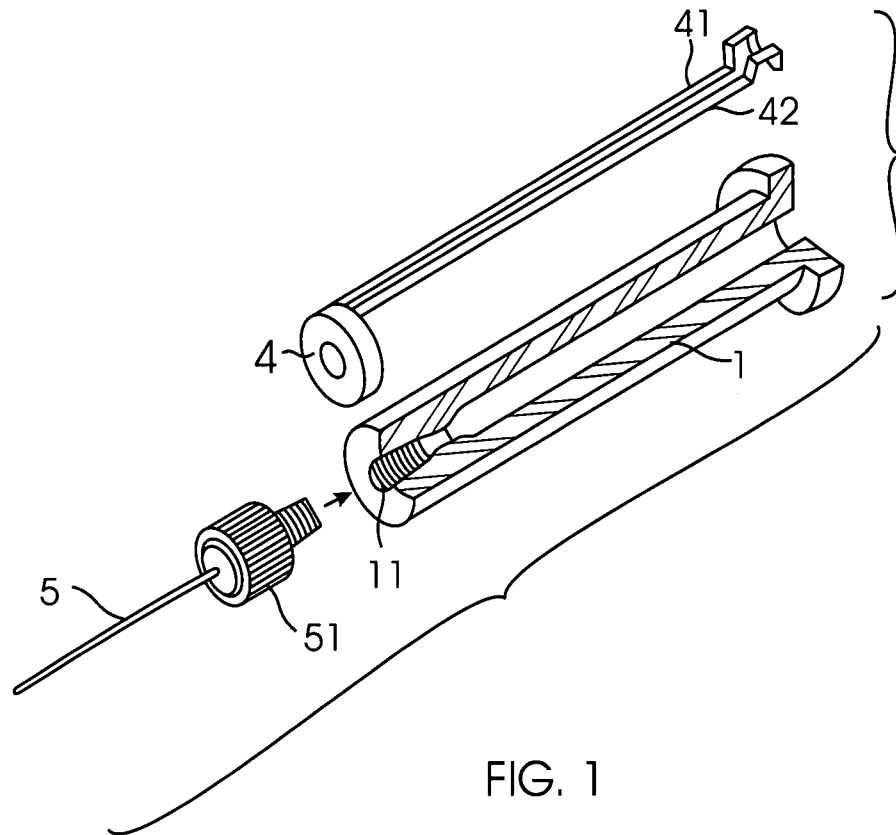


FIG. 1

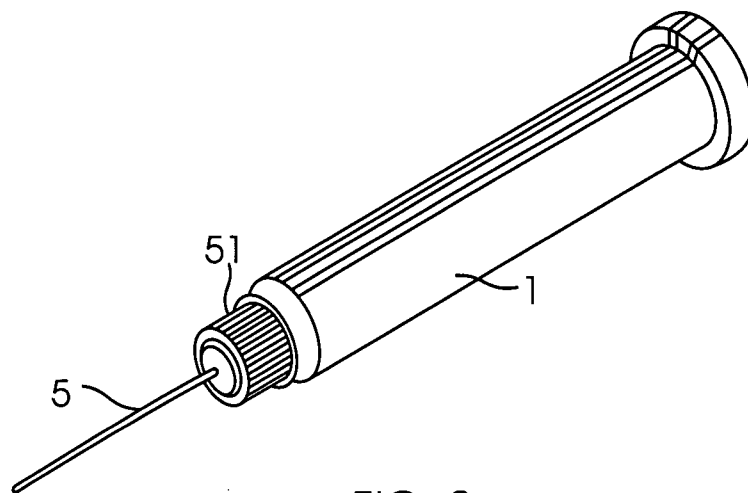


FIG. 2

2/2

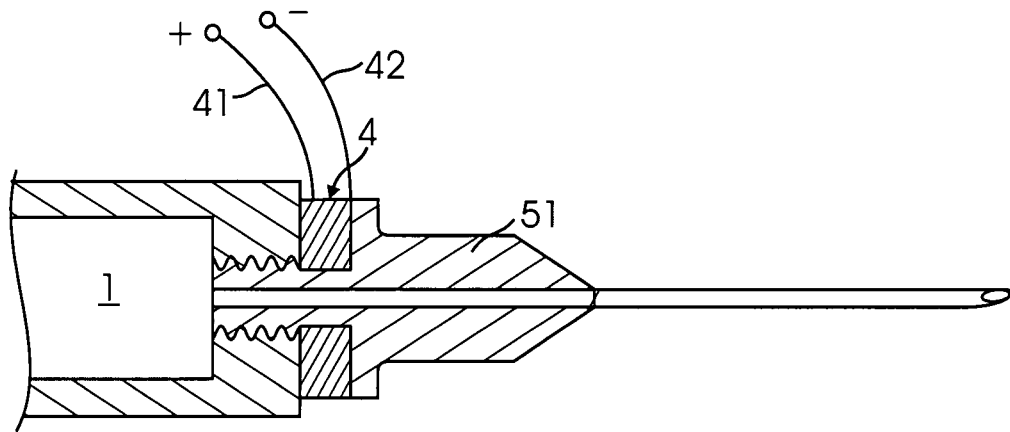


FIG. 3

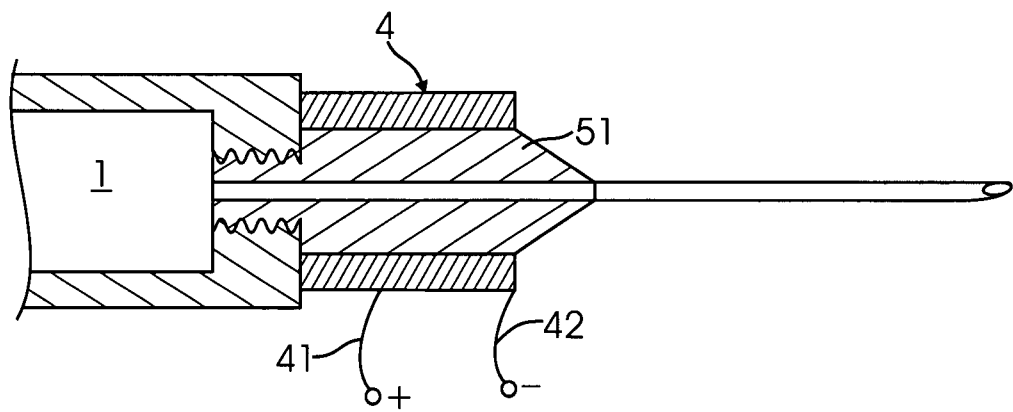


FIG. 4