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Fortsættes ...

TOMOKO FUJIWARA ET AL: "Novel Thermo-Responsive Formation of a Hydrogel by Stereo-Complexation between PLLA-PEG-PLLA and PDLA-PEG-PDLA Block Copolymers", MACROMOLECULAR BIOSCIENCE, vol. 1, no. 5, 1 July 2001 (2001-07-01), DE, pages 204 - 208, XP055514006, ISSN: 1616-5187, DOI: 10.1002/1616-5195(20010701)1:5<204::AID-MABI204>3.0.CO;2-H

DESCRIPTION

Description

FIELD OF THE INVENTION

[0001] The present invention relates to biodegradable drug delivery compositions comprising a mixture of at least three block copolymers taken among triblock and diblock copolymers composed of polyester and poly(ethylene oxide) blocks, a triblock copolymer comprising one poly(ethylene oxide) block between two polyester blocks and a diblock copolymer comprising a polyester block and an one end-capped poly(ethylene glycol), as well as at least one pharmaceutically active ingredient. The weight ratio of triblock copolymers to diblock copolymers in this formulation is 1:19 to 5:1 for modulating drug release kinetics of at least one active ingredient. When incorporated into a block copolymer, poly(ethylene oxide) or polyoxyethylene (PEO) is also frequently referred to as poly(ethylene glycol) (PEG) and the terms can be used interchangeably for the purposes of this invention.

BACKGROUND OF THE PRESENT INVENTION

[0002] In the domain of sustained drug delivery, systems based on diblock or triblock copolymers have been used to deliver a variety of drugs and are generally formulated to deliver specific drugs whether they are hydrophobic drugs or hydrophilic drugs. Depending on the drug physico-chemical characteristics, the drug formulations differ in polymer concentrations, types of polymers utilized, molecular weights of the polymers and solvents used in the formulations.

[0003] Also the type of environment in which the drug is delivered is an important consideration in formulating a drug delivery system. Thus, there exist drug delivery compositions that are prepared using temperature sensitive polymers, phase sensitive polymers, pH sensitive polymers and photosensitive polymers. See, for example, K. Al-Tahami and J. Singh "Smart Polymer Based Delivery Systems for Peptide and Proteins," Recent Patents on Drug Delivery & Formulation, 1: pages: 65-71 Bentham Science Publishers, LTD. 2007.

[0004] U.S. Patent No. 6,592,899 describes a PLA/PLGA oligomer combined with a block copolymer for enhancing the solubility of a hydrophobic drug into a hydrophilic environment.

[0005] U.S. Patent 6,541,033 describes a sustained release pharmaceutical composition based on thermosensitive, biodegradable hydrogels, consisting of a block copolymer of PLA or PLGA and PEG, for the sustained delivery of biologically active agents.

[0006] Hydrogels containing triblock copolymers are described in U.S. Patent 6,350,812.

[0007] U.S. Patent 9,023,897 B2 describes biodegradable drug compositions comprising a triblock copolymer and a diblock copolymer and a pharmaceutically active ingredient.

[0008] WO 2012/090070 A2 describes biodegradable drug delivery compositions comprising a triblock copolymer containing a polyester and a polyethylene glycol and a diblock copolymer containing a polyester and an end-capped polyethylene glycol, as well as a pharmaceutically active principle.

[0009] WO 2014/001904 A1 describes biodegradable drug delivery compositions comprising a triblock copolymer containing a polyester and a polyethylene glycol and a diblock copolymer containing a polyester and an end-capped polyethylene glycol, as well as at least one pharmaceutically active principle or hydrophobic active principle.

[0010] WO 01/82970 A1 describes a water soluble, biodegradable reverse thermal gelation system comprising a mixture of at least two types of tri-block copolymer components is disclosed. The tri-block copolymer components are made of a hydrophobic biodegradable polyester A-polymer block and a hydrophilic polyethylene glycol B-polymer block. The drug release and gel matrix erosion rates of the biodegradable reverse thermal gelation system may

be modulated by various parameters such as the hydrophobic/hydrophilic component contents, polymer block concentrations, molecular weights and gelation temperatures, and weight ratios of the tri-block copolymer components in the mixture.

[0011] WO 2017/085561 A1 describes a method of targeting to the synovial tissue biodegradable drug delivery compositions or morselizing biodegradable drug delivery compositions comprising a triblock copolymer containing a polyester and a polyethylene glycol and a diblock copolymer containing a polyester and an end-capped polyethylene glycol, as well as at least one pharmaceutically active principle.

[0012] WO 2012/131106 A1 describes a composition comprising (a) an active ingredient, preferably a pharmaceutically active ingredient (b) a solvent and (c) a mixture of at least two types of tri-block copolymers of formula (1) B-A-B (1) wherein B stands for a hydrophobic block and wherein A stands for a hydrophilic block, wherein the mixture is prepared by mixing at least two types of tri-block copolymers having a degree of modification of 100% and wherein the at least two types of B-A-B types of tri-block copolymers differ only on the type of end-group or wherein the mixture is prepared by mixing at least two types of tri-block copolymers, wherein one of the at least two tri-block copolymers has a degree of modification of 100% and one of the at least two tri-block copolymers has a degree of modification of 0% and wherein the at least two types of B-A-B types of tri-block copolymers differ only on the degree of modification of the end-groups.

[0013] Macromol. Biosci. 2003, 3, pages 657-661 discloses bioresorbable hydrogels prepared through stereocomplexation between poly (L-lactide) and poly(D-lactide blocks attached to poly (ethylene glycol).

[0014] Macromol. Biosci. 2001, 1, pages 204-208 discloses thermo-responsive formation of a hydrogel by stereo-complexation between PLLA-PEG-PLLA and PDLA-PEG-PDLA block copolymers.

[0015] However there remains a need to provide biodegradable drug delivery compositions comprising diblock and triblock copolymers with improved properties regarding the modulation of the rate of release of the at least one active ingredient. For example, it may be desirable to provide compositions with an increased rate of release of the active ingredient relative to known drug delivery compositions comprising diblock and triblock copolymers. The composition should enable the release of the at least one active ingredient to be controlled over a time period without adversely affecting the physical parameters of the formulation.

[0016] Furthermore, the biodegradable drug delivery compositions of the present invention can be formulated to be long acting formulations, which reduce the initial burst release of the drug and modulate the release rate of the drug over time according to first order or zero order or pseudo zero order kinetics. This phenomenon is illustrated in the flattening of the drug release curves.

[0017] Moreover, the biodegradable drug delivery composition can be modulated without adversely impacting the injectability of this composition.

[0018] Thus, one of the objects of the present invention is how to modulate the release kinetics of at least one pharmaceutically active ingredient from a triblock / diblock biodegradable depot without adversely impacting or by improving the physical parameters of the formulation before and/or after injection.

[0019] By "improving" means the decrease of either or both the injectability and viscosity of the formulation.

SUMMARY OF THE INVENTION

[0020] The present invention provides a biodegradable drug delivery composition comprising:

1. (i) a mixture of at least three different block copolymers, wherein each block copolymer is:
    1. (a) a biodegradable triblock copolymer having the formula:

$$A_V\text{-}B_W\text{-}A_X$$

wherein A is a polyester and B is polyethylene glycol and v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x; or

2. (b) a biodegradable diblock copolymer having the formula:

$$C_y\text{-}A_z$$

wherein A is a polyester and C is an end-capped polyethylene glycol and y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000; and

wherein the mixture comprises at least one (a) and at least one (b); and the weight ratio between (a) and (b) is 1:19 to 5:1; and

2. (ii) at least one pharmaceutically active ingredient.

[0021] In a preferred embodiment said polyester A is selected from the group of, polylactic acid, polyglycolic acid, polycaprolactone, polyethylene adipate, polyhydroxyalkanoate and mixtures thereof and optionally wherein the end-capped polyethylene glycol is methoxy polyethylene glycol.

[0022] In one embodiment the composition further comprises at least one organic solvent. Typically the organic solvent is a pharmaceutically acceptable solvent. This organic solvent can be retained in the composition or evaporated off prior to administration.

[0023] In one embodiment of the biodegradable drug delivery composition, for at least one biodegradable triblock copolymer (a) A is PLA.

[0024] In one embodiment of the biodegradable drug delivery composition, for at least one biodegradable diblock copolymer (b) A is PLA.

[0025] In one embodiment the composition further comprises:

1. (a) a biodegradable triblock copolymer having the formula:

$$PLA_v\text{-}PEG_w\text{-}PLA_x$$

wherein v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x; and/or

2. (b) a biodegradable diblock copolymer having the formula:

$$mPEG_y\text{-}PLA_z$$

wherein y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000.

[0026] In some embodiments the composition comprises:

1. (a) a biodegradable triblock copolymer having the formula:

$$PLA_v\text{-}PEG_w\text{-}PLA_x$$

wherein v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x; and

2. (b) 2, 3 or 4 different biodegradable diblock copolymers each having the formula:

$$mPEG_y\text{-}PLA_z$$

wherein y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000;

and wherein the weight ratio between (a) and (b) is 1:19 to 5:1.

[0027] In some embodiments the composition comprises: (a) two different biodegradable triblock copolymers each having the formula:

$$PLA_v\text{-}PEG_w\text{-}PLA_x$$

wherein v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x; and

(b) 1, 2, 3 or 4 different biodegradable diblock copolymer(s) each having the formula:

$$mPEG_y\text{-}PLA_z$$

wherein y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000 ;

and wherein the weight ratio between (a) and (b) is 1:19 to 5:1.

[0028] Typically the composition is an injectable liquid and is suitable for forming a depot when injected into the body or are small solid particles or rod implants or spatial formulations.

[0029] Typically the mass of the polyethylene glycol chain ranges from 180 g/mol to 12 kg/mol or 194 g/mol to 12 kg/mol or 200 g/mol to 12 kg/mol or from 100 g/mol to 4 kg/mol and the molecular weight of the end-capped polyethylene glycol chain ranges from 100 g/mol to 2 kg/mol or 164 g/mol to 10 kg/mol.

[0030] The biodegradable drug delivery composition may also further comprise a pharmaceutically acceptable vehicle, such as a solvent.

[0031] In one embodiment the pharmaceutically active ingredient is hydrophobic.

[0032] In one embodiment the pharmaceutically active ingredient is risperidone, bupivacaine, ivermectin, octreotide, meloxicam, or combinations thereof.

[0033] In another embodiment the at least one pharmaceutically active ingredient is present in an amount of from 0.05 % to 60% (w/w%), optionally 0.05% to 40%, optionally 0.05% to 30%, optionally 0.05% to 10%, optionally 0.05% to 7%, optionally 0.05% to 2% of the total composition.

[0034] In one embodiment the biodegradable drug delivery composition is an injectable liquid and the at least one pharmaceutically active ingredient is present in an amount of 0.05% to 60% (w/w%).

[0035] In an alternative embodiment the biodegradable drug delivery composition is a rod implant and the at least one pharmaceutically active ingredient is present in an amount of from 50% to 80% (w/w%).

[0036] In a further embodiment, the copolymers are present in an amount of 2% to 60% (w/w%) of the total composition, optionally 10% to 50%, optionally 20% to 40%, optionally 20% to 35%, optionally 30% to 50%.

[0037] In one embodiment the one or more triblock copolymers are present in an amount of 1% to 50% (w/w%), optionally 5% to 40% of the total composition.

[0038] In one embodiment the one or more diblock copolymers are present in an amount of 1% to 57% (w/w%), 2.5% to 45% of the total composition.

[0039] In an additional embodiment the weight ratio of the sum of the biodegradable triblock copolymers of (a) over the sum of the biodegradable diblock copolymers of (b) in said biodegradable drug delivery composition is 1:5 to 3:1.

[0040] Typically the polyester repeat unit to ethylene oxide molar ratio in the composition is between 0.5 to 22.3, optionally 0.5 to 10, optionally 0.5 to 3.5 in the triblock and 0.8 to 15, optionally 1 to 10 in the diblock.

[0041] The composition may comprise three different block copolymers as defined above or four different block copolymers as defined above or five different block copolymers as defined above or six different block copolymers as defined above.

[0042] The composition may comprise one biodegradable triblock copolymer as defined above, or two different biodegradable triblock copolymers as defined above, or three different biodegradable triblock copolymers as defined above, or four different biodegradable triblock copolymers as defined above.

[0043] The composition may comprise one biodegradable diblock copolymer as defined above, or two different biodegradable diblock copolymers as defined above, or three different biodegradable diblock copolymers as defined above, or four different biodegradable diblock copolymers as defined above.

[0044] In one embodiment the composition comprises a triblock copolymer present in an amount of 1% to 50% (w/w%) of the total composition, a diblock copolymer present in an amount of 1% to 57% (w/w%) of the total composition, and one or more further diblock or triblock copolymers each present in an amount of 0.5 to 20 (w/w%) of the total composition.

[0045] In preferred embodiments the biodegradable drug delivery composition is a composition as defined in any of Tables 1 to 6 (excluding the comparative examples marked *).

[0046] Typically the release of at least one active ingredient is modulated by the composition.

[0047] In one embodiment the composition is suitable to deliver the active ingredient, optionally a therapeutically effective amount of the active ingredient, to a subject for at least 1 day, optionally at least 3 days, optionally at least 7 days, optionally at least 30 days, optionally at least 90 days, optionally at least 1 year.

[0048] In one embodiment the composition is suitable for parenteral administration.

[0049] In one embodiment the block copolymers are substantially insoluble in an aqueous solution, optionally wherein the block copolymers have less than 5%, optionally less than 1% (w/w) solubility in an aqueous solution.

[0050] In a further aspect, the invention provides a biodegradable drug delivery composition as defined above for use in medicine.

[0051] In one embodiment of the composition for use, the use comprises modulating the kinetics of release of at least one active ingredient, said use comprising administering a biodegradable drug delivery composition as defined above to a subject, wherein the release kinetics of said at least one active ingredient from said biodegradable drug delivery composition are modulated without affecting one or more physical parameters of said biodegradable drug composition.

[0052] Typically the one or more physical parameters are injectability and viscosity before injection of the biodegradable drug delivery composition and depot robustness after injection of the biodegradable drug delivery composition.

BRIEF DESCRIPTION OF THE DRAWINGS

[0053]

Fig. 1 is a graph showing the percentage total in vitro cumulative release of risperidone over time from three different formulations. Formulation F28 (○) has a weight ratio of the sum of triblock to diblock of 5 containing 25.00% of P1R6 triblock copolymer, 1.25% of dP2R3 diblock copolymer, 1.25% of dP0.35R8.5 diblock copolymer, 1.25% of dP0.35R5 diblock copolymer, 1.25% of dP2R0.5 diblock copolymer with 10.00% active ingredient (API) and 60.00% of DMSO. Formulation F29 (⊗) has a weight ratio of the sum of triblock to diblock of 0.05 containing 1.50% of P1R6 triblock copolymer, 7.125% of dP2R3 diblock copolymer, 7.125% of dP0.35R8.5 diblock copolymer, 7.125% of dP0.35R5 diblock copolymer, 7.125% of dP2R0.5 diblock copolymer with 10.00% active ingredient (API) and 60.00% of DMSO. Formulation F16 (□) has a weight ratio of the sum of triblock to diblock of 1 containing 1.00% of P1R4 triblock copolymer, 1.50% of P1R6 triblock copolymer, 1.50% of dP2R3 diblock copolymer and 1.00% of dP0.35R8.5 diblock copolymer with 60.00% active ingredient (API) and 35.00% of DMSO. The specific block copolymer formulations are set forth in Table 1 below.

The weight ratio of the sum of triblock to diblock has an impact on the release modulation. Indeed, F28 and F29 curves show two distinct release profiles.

Interestingly, an important amount of API (60.00%) associated with a small proportion of polymer content (5.00%) yielded a pseudo-zero order kinetic profile. Indeed, F16 curve shows a pseudo-zero order release profile.

Fig. 2 is a graph showing the percentage total in vitro cumulative release of bupivacaine over time from four different formulations. Formulation F289 (not according to the invention) (○) has a weight ratio of the sum of triblock to diblock of 1 containing 20.00% of P1R4 triblock copolymer and 20.00% of dP1R4 diblock copolymer with 2.00% active ingredient (API) and 58.00% of DMSO. Formulation F290 (△) has a weight ratio of the sum of triblock to diblock of 1 containing 20.00% of P1R4 triblock copolymer, 10.00% of dP1R4 diblock copolymer and 10.00% of dP0.35R8.5 diblock copolymer with 2.00% active ingredient (API) and 58.00% of DMSO. Formulation F291 (not according to the invention) (□) has a weight ratio of the sum of triblock to diblock of 1 containing 20.00% of P1R4 triblock copolymer and 20.00% of dP0.35R8.5 diblock copolymer with 2.00% active ingredient (API) and 58.00% of DMSO. Formulation F292 (not according to the invention) (◇) has a weight ratio of the sum of triblock to diblock of 1 containing 25.00% of P1R4 triblock copolymer and 25.00% of dP1R4 diblock copolymer with 2.00% active ingredient (API) and 48.00% of DMSO. The specific block copolymer formulations are set forth in Table 2 below.

The addition of an additional biodegradable block copolymer has an impact on the release modulation without adversely impacting the injectability of the formulation as indicated in Table 7. Indeed, F289 (not according to the invention) and F290 curves show two distinct and modulated release profiles. Moreover, this additional biodegradable diblock copolymer allows a better control of the release. Indeed, F289 (not according to the invention) curve shows an uncontrolled initial burst highlighted by an important variability between replicates. Standard deviation values of F289 (not according to the invention) and F290 are 13.3 and 2.8 respectively, two days after depot formation.

The use of this additional biodegradable block copolymer mentioned above as the unique diblock copolymer results on release modulation compared to the initial formulation. F289 (not according to the invention) and F291 (not according to the invention) curves show two distinct release profiles. However, depot from F291 formulation shows non-optimal robustness with a significant depot fragmentation at early time point. This non-optimal robustness induces an important variability between each replicate due to an unwanted and early depot fragmentation. Indeed, F290 and F291 (not according to the invention) show standard deviation values of 5.7 and 9.7 respectively, ten days after depot formation.

The increase of the total polymer content has an impact on the release modulation. F292 (not according to the invention) shows a modulated release profile compared to F289 (not according to the invention). However, the increasing of the total polymer content has an impact on the injectability of the formulation as indicated in Table 7. Consequently, F289 and F292 have injectability values of 4.8 N and 14.5 N respectively.

Despite the modulation obtained with F291 (not according to the invention) and F292 (not according to the invention), reformulation had a negative impact on the physical parameters of depot and formulation respectively. Thus, these data imply that the addition of an additional biodegradable block copolymer, as in F290, is an efficient way to provide a predictable modulation.

Figure 3 is a graph showing the percentage total in vitro cumulative release of bupivacaine over time from four different formulations. Formulation F289 (not according to the invention) (○) has a weight ratio of the sum of triblock to diblock of 1 containing 20.00% of P1R4 triblock copolymer and 20.00% of dP1R4 diblock copolymer with 2.00% active ingredient (API) and 58.00% of DMSO. Formulation F290 (△) has a weight ratio of the sum of triblock to diblock of 1 containing 20.00% of P1R4 triblock copolymer, 10.00% of dP1R4 diblock copolymer and 10.00% of dP0.35R8.5 diblock copolymer with 2.00% active ingredient (API) and 58.00% of DMSO. Formulation F293 (not according to the invention) (⊗) has a weight ratio of the sum of triblock to diblock of 1 containing 20.00% of P1R4 triblock copolymer and 20.00% of dP1R4 diblock copolymer with 4.00% active ingredient (API) and 56.00% of DMSO. Formulation F294 (not according to the invention) (X) has a weight ratio of the sum of triblock to diblock of 1 containing 20.00% of P1R4 triblock copolymer and 20.00% of dP1R4 diblock copolymer with 6.00% active ingredient (API) and 54.00% of DMSO. The specific block copolymer formulations are set forth in Table 2 below.
The increase of the total API loading has an impact on the release modulation. F293 (not according to the invention) and F294 (not according to the invention) containing 4.00% and

6.00% of API respectively show different release profiles compared to F289 (not according to the invention) and F290. The release kinetics decrease with increasing amount of API in the formulation. However, the obtained profiles show similar undesirable release trends with high initial burst. In addition, this is not a valid strategy as the injectability also increases with API content as shown in Table 7.

Figure 4 is a graph showing the percentage total in vitro cumulative release of bupivacaine over time from four different formulations. Formulation F45 (○) has a weight ratio of the sum of triblock to diblock of 5 containing 41.70% of P1R4 triblock copolymer, 4.15% of dP2R0.5 diblock copolymer and 4.15% of dP0.35R8.5 diblock copolymer with 1.00% active ingredient (API) and 49.00% of DMSO. Formulation F46 (⊗) has a weight ratio of the sum of triblock to diblock of 0.05 containing 2.50% of P1R4 triblock copolymer, 23.75% of dP2R0.5 diblock copolymer and 23.75% of dP0.35R8.5 diblock copolymer with 1.00% active ingredient (API) and 49.00% of DMSO. Formulation F49 (□) has a weight ratio of the sum of triblock to diblock of 0.05 containing 3.00% of P1R4 triblock copolymer, 28.50% of dP2R0.5 diblock copolymer and 28.50% of dP0.35R8.5 diblock copolymer with 1.00% active ingredient (API) and 39.00% of DMSO. Formulation F64 (*) has a weight ratio of the sum of triblock to diblock of 0.05 containing 3.00% of P1R4 triblock copolymer, 28.50% of dP0.35R5 diblock copolymer and 28.50% of dP0.35R8.5 diblock copolymer with 1.00% active ingredient (API) and 39.00% of DMSO. The specific block copolymer formulations are set forth in Table 3 below.

The weight ratio of the sum of triblock to diblock has an impact on the release modulation. Indeed, F45 and F46 curves show two distinct and modulated release profiles.

The substitution of a block copolymer in the formulation composition has a significant impact on the release modulation. Indeed, F49 and F64 curves show two distinct and modulated release profiles.

Thus, results indicate that the addition of an additional biodegradable block copolymer is an efficient way to modulate the release kinetics.

Figure 5 is a graph showing the percentage total in vitro cumulative release of ivermectin over time from six different formulations. Formulation F105 (not according to the invention) (○) has a weight ratio of the sum of triblock to diblock of 0.67 containing 20.00% of P2R3.5 triblock copolymer, and 30.00% of dP0.35R8.5 diblock copolymer with 1.00% active ingredient (API) and 49.00% of DMSO. Formulation F119 (⊗) has a weight ratio of the sum of triblock to diblock of 0.67 containing 10.00% of P12R0.7 triblock copolymer, 10.00% of P0.19R18 triblock copolymer and 30.00% of dP0.35R8.5 diblock copolymer with 1.00% active ingredient (API) and 49.00% of DMSO. Formulation F124 (△) has a weight ratio of the sum of triblock to diblock of 0.5 containing 4.20% of P1R4 triblock copolymer, 4.20% of P1R6 triblock copolymer, 5.50% of dP0.35R5 diblock copolymer 5.50% of dP2R3 diblock copolymer and 5.50% of dP0.35R8.5 diblock copolymer with 1.00% active ingredient (API) and 74.10% of DMSO. Formulation F126 (V) has a weight ratio of the sum of triblock to diblock of 0.5 containing 2.80% of P1R4 triblock copolymer, 2.80% of P1R6 triblock copolymer, 2.80% of P2R3.5 triblock copolymer 5.50% of dP0.35R5 diblock copolymer 5.50% of dP2R3 diblock copolymer and 5.50% of dP0.35R8.5 diblock copolymer with 1.00% active ingredient (API) and 74.10% of DMSO. Formulation F115 (□) has a weight ratio of the sum of triblock to diblock of 0.5 containing 8.30% of P2R3.5 triblock copolymer, 8.30% of dP0.16R1 diblock copolymer and 8.30% of dP2R10 diblock copolymer with 1.00% active ingredient (API) and 74.10% of DMSO. Formulation F110 ( ) has a weight ratio of the sum of triblock to diblock of 0.5 containing 8.30% of P2R3.5 triblock copolymer, and 16.70% of dP2R3 diblock copolymer with 1.00% active ingredient (API) and 74.10% of DMSO. The specific block copolymer formulations are set forth in Table 4 below.

The substitution of the P2R3.5 triblock of 12700 g/mol molecular weight by the same amount of a mixture of two triblock copolymers, P12R0.7 and P0.19R18 having respectively 25700 g/mol and 5800 g/mol molecular weight has an impact on the release kinetics. Here the molecular weight of the sum of triblock from F119 is approximately on the same range as F115 one (15800 g/mol vs 12700 g/mol).

Similarly, the substitution of the dP2R3 of 11800 g/mol molecular weight by the same amount of a mixture of two diblock copolymers, dP2R10 and dP0.16R1 having respectively 34700 g/mol and 420 g/mol molecular weight impacts on the release kinetics. Indeed, the F110 and F115 curves show two distinct and modulated release profiles.

The addition of an additional biodegradable triblock copolymer induces a modulation of the release kinetics profile. Indeed, the F126 curve shows a slower release compared to the F124 curve.

Thus, data show that the substitution of one block copolymer by two others of an approximately equivalent total molecular weight is an efficient way to modulate the release

kinetics.

Figure 6 is a graph showing the percentage total in vitro cumulative release of octreotide acetate over time from three different formulations. Formulation F163 (○) has a weight ratio of the sum of triblock to diblock of 1 containing 10.00% of P1R4 triblock copolymer, 10.00% of P1R6 triblock copolymer, 10.00% of dP1R4 diblock copolymer, and 10.00% of dP0.35R8.5 diblock copolymer with 4.00% active ingredient (API) and 56.00% of DMSO. Formulation F165 (not according to the invention) (□) has a weight ratio of the sum of triblock to diblock of 1 containing 20.00% of P1R6 triblock copolymer, 20.00% dP0.35R8.5 diblock copolymer with 4.00% active ingredient (API) and 56.00% of DMSO. Formulation F166 (not according to the invention) (△) has a weight ratio of the sum of triblock to diblock of 1 containing 20.00% of P1R4 triblock copolymer, 20.00% dP1R4 diblock copolymer with 4.00% active ingredient (API) and 56.00% of DMSO. The specific block copolymer formulations are set forth in Table 5 below.
F163 shows that the combination of the two triblocks and the two diblocks from F165 and F166 yields an intermediate release kinetics, meaning the observed modulation based on four block copolymers composition appears to arise from the contribution of F165 and F166.

Figure 7 displays the in vitro cumulative release of meloxicam over time from two different formulations. Formulation F197 (not according to the invention) (□) has a weight ratio of the sum of triblock to diblock of 5 containing 50.00% of P0.19R2 triblock copolymer and 10.00% of dP0.35R8.5 diblock copolymer with 2.00% active ingredient (API) and 38.00% of DMSO. Formulation F199 (V) has a weight ratio of the sum of triblock to diblock of 5 containing 25.00% of P0.19R2 triblock copolymer, 25.00% of P2R3.5 triblock copolymer and 10.00% of dP0.35R8.5 diblock copolymer with 2.00% active ingredient (API) and 38.00% of DMSO. Formulation F365 (not according to the invention) has a weight ratio of the sum of triblock to diblock of 5 containing 50.00% of P2R3.5 triblock copolymer and 10.00% of dP0.35R8.5 diblock copolymer with 2.00% active ingredient (API) and 38.00% of DMSO. F365 has not been tested in vitro as it presented a very high injectability (53.6 N) hindering its manipulation. The specific block copolymer formulations are set forth in Table 6 below.
F199 release kinetics is modulated compared to that of F197. The substitution of 25.00% of P0.19R2 initially present at 50.00% in F197 by the same amount of P2R3.5 induces a strong modulation of release kinetics. Indeed, the addition of P2R3.5 triblock copolymer as an additional biodegradable block copolymer in F199 leads to an increase of the total duration of release. Additionally, the initial burst is significantly decreased and there is no reacceleration of the kinetics after 100 days of release in F199 release profile.

Figure 8 is a representation of injectability data measured from F197 (not according to the invention), F199, and F365 (not according to the invention). Data show that the complete substitution of P0.19R2 by P2R3.5 in F365 drastically impacts the injectability of initial F197 formulation, leading to a formulation hardly injectable whereas the partial substitution of P0.19R2 by P2R3.5 in F199 yields an acceptable increase of the injectability. Indeed, F365 has much higher injectability compared to F197. Table 8 presents the injectability values of these formulations.
These results confirm that the addition of an additional biodegradable block copolymer is an efficient way to modulate the release kinetics without significantly changing the physical parameters of the formulation such as the injectability. These results also demonstrate that modulating the release kinetics can be highly challenging when dealing with only two block copolymers at high loading. Therefore, the addition of at least one block copolymer to the formulation can be a useful formulation tool for achieving this modulation in an efficient manner.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0054] As used herein the term "biodegradable" means that the polyesters undergo hydrolysis to form their constituent oligomers or monomers in vivo, for example PLA undergoes hydrolysis to form lactic acid.

[0055] The term "parenteral administration" encompasses intramuscular, intraperitoneal, intra-abdominal, subcutaneous, intravenous and intraarterial. It also encompasses intradermal, intracavernous, intravitreal, intracerebral, intrathecal, epidurall and intraosseous administration.

[0056] The term "animals" encompasses all members of the Kingdom Animalia. The animal

may be a human or non-human animal.

[0057] As used herein the term "plant" encompasses all members of the Plant Kingdom.

[0058] "Active ingredient" means a drug or medicine for treating or preventing various medical illnesses. For the purposes of the present application the term "active principle" has the same meaning as "active ingredient" Thus the terms active ingredient, active principle, drug or medicine are used interchangeably. The term Active Pharmaceutical Ingredient, or "API" is also used. The term drug or active ingredient as used herein includes without limitation physiologically or pharmacologically active substances that act locally or systemically in the body of an animal or plant. At least one active ingredient is present in the biodegradable drug composition of the invention.

[0059] As used herein "disease" means any disorder in a human, animal or plant caused by infection, diet, or by faulty functioning of a process.

[0060] The term "implant" means any solid object, which is formed outside the body and is placed into the body by a surgical procedure. Implants can be placed permanently or they can be removed, if necessary and depending on the circumstances. These procedures include, but are not limited to making a small cut in the body of an animal and inserting a solid or a trochar. A trochar is medical device that is made up of an obturator (which may be a metal or plastic sharpened or non-bladed tip), a cannula and a seal. The trocar functions as a portal for the subsequent placement of the implant into the body of the animal.

[0061] The term "depot injection" is an injection of a flowing pharmaceutical composition, usually subcutaneous, intradermal or intramuscular that deposits a drug in a localized mass, such as a solid mass, called a "depot". The depots as defined herein are in situ forming upon injection. Thus, the formulations can be prepared as liquids or micro particles and can be injected into the body.

[0062] There are several methods of injection or infusion used in humans, including intradermal, subcutaneous, intramuscular, intravenous, intraosseous, intraperitoneal, intrathecal, epidural, intracardiac, intraarticular, intracavernous, and intravitreal.

[0063] The term "spatial formulation" encompasses any formulation that can be applied on or into the animal or plant body and do not necessarily have to be administered through a syringe.

[0064] As used herein "repeat units" are the fundamental recurring units of a polymer.

[0065] By "end-capped polyethylene glycol" (cPEG) refers to PEG's in which one terminal hydroxyl group is reacted and includes alkoxy-capped PEG's, urethane-capped PEG's ester-capped PEG's and like compounds. The capping group is a chemical group which does not contain a chemical function susceptible to react with cyclic esters like lactide, glycolactide, caprolactone and the like or other esters and mixtures thereof. The reaction of an end-capped PEG polymer with lactide generates a diblock cPEG-PLA copolymer.

[0066] As used herein "polyethylene glycol", as abbreviated PEG throughout the application, is sometimes referred to as poly(ethylene oxide) or poly(oxyethylene) and the terms are used interchangeably in the present invention.

[0067] The abbreviation of "PLA" refers to poly(lactic acid).

[0068] The abbreviation of "PLGA" refers to poly(lactic-co-glycolic acid).

[0069] The abbreviation of "PCLA" refers to poly(ε-caprolactone-*co*-lactide).

[0070] The abbreviation "PE" refers to polyester.

[0071] The abbreviation "T" or "TB" refers to a triblock copolymer(s), while the abbreviation "D" or "DB" refers to a diblock copolymer(s).

[0072] The term "diblock" as used herein refers, for example, to an end-capped PEG-polyester coplymer. "mPEG" refers to methoxy polyethylene glycol.

[0073] The term "triblock" refers, for example, to a polyester-PEG-polyester copolymer.

[0074] The R molar ratio refers to the number of polyester (PE) units to a number of ethylene oxide units (EO) that is present in the biodegradable drug delivery composition. For example, the number of polyester units can refer to the number of lactoyl units (LA) or the number of glycolide units (G) or the number of caprolactone units (CL) or mixtures thereof.

[0075] This R molar ratio is determined experimentally by NMR. The R molar ratio of the triblock copolymer can range from, 0.5 to 22.3, optionally 0.5 to 10, optionally 0.5 to 3.5. In another aspect the R molar ratio in the triblock can range from 0.5 to 2.5 in the biodegradable drug delivery composition described herein.

[0076] The R molar ratio in the diblock can range from 0.8 to 15, optionally 1 to 10, optionally 2 to 6, optionally from 3 to 5 in the biodegradable drug delivery composition.

[0077] The degree of polymerization or DP is the number of repeat units in an average polymer chain at time t in a polymerization reaction. For example, the degree of polymerization for PEG for the triblock is between 3 to 300 and for the diblock the degree of polymerization of PEG is between 2 to 250. For PLA, the degree of polymerization for the triblock is between 1 to 3,000 and has the same value of between 1 to 3,000 for the diblock.

[0078] As used herein "at least three" block copolymers may mean a mixture of 3, 4, 5, 6, 7, 8, 9 or 10 different block copolymers in the biodegradable drug delivery composition. In an embodiment of the invention, any combination of 3 to 10 triblock and diblock copolymers can be formulated, provided that at least one triblock copolymer and at least one diblock copolymer are present in the mixture. Other examples include 3 to 5 or 4 to 8 or 4 to 6, 3 to 7, 4 to 9 and the like mixtures of triblock and diblock copolymers can be used in the biodegradable drug compositions as described herein.

[0079] "Modulating the kinetics of the release of the at least one active ingredient" means regulating the release rate of the at least one active ingredient from the depot after it is administered *in vivo.* In this respect, the kinetics may be first order kinetics or pseudo-zero order kinetics depending on the formulations fabricated.

[0080] "Release modulation", as used herein, is defined as the variation of the at least one active ingredient quantity discharged over time from the depot. This required variation can be an increase or a decrease of the release from an initial kinetics, immediately or sustained long-term over the time period. Modification of the release profile may affect several periods; in the very first hours of release, for example, inducing an increase or a decrease of the initial "burst", or in more advanced periods to avoid a re-acceleration or a steep decrease of the release or for the duration of the release. Formulation modulation is a process in which particular release profiles and an optimized total release duration for a certain therapeutic application can be obtained.

[0081] As used herein, "first order kinetics" means that the process of release of the drug is directly proportional to the drug concentration involved in the process.

[0082] "Pseudo-zero order kinetics," as used herein, means that the process of the release of the drug takes place at a constant rate.

[0083] The term "physical parameters," as used herein, is intended to refer to physical properties of the composition which are important for clinical utilization of the formulations. Among them, viscosity, more specifically dynamic viscosity of the formulation, swelling and robustness of the depot after injection of the formulation are important parameters to be controlled during the optimization of the formulations. A key physical parameter of the formulations is their injectability, i.e. their suitability for administration by injection.

[0084] A depot has a "lack of robustness" if it undergoes early fragmentation into a plurality of pieces. This fragmentation can lead to unexpected and uncontrolled change of release such as burst and variability. This fragmentation may be determined in the depot visually *in vitro.* A lack of robustness due to early physical fragmentation of the depot is distinguished from normal degradation of the polymers in the depot, for example hydrolysis of the polymers which is a key mechanism to allow release of the active ingredient, along with diffusion of the active ingredient through the pores of the polymer matrix. Preferably, complete hydrolysis of the polymers forming the depot does not occur until all, or substantially all, for example 90 wt%, or 99 wt% of the active ingredient has been released from the depot.

[0085] As used herein, "swelling" is an increase in volume of the formed depot related to the

water uptake. The volume of the initial depot can be increased 3 times to 5 times or 1.1 times to 3 times when injected into the body of an animal. This swelling is determined visually *in vitro.*

[0086] The "injectability" of a formulation, as used herein, is defined by the force needed in Newtons (N) to inject a formulation using pre-determined parameters. These parameters include: injection speed, injection volume, injection duration, syringe type or needle type and the like. These parameters may vary based on the at least one pharmaceutically active ingredient used, or the desired method of administration such as sub cutaneous, intra ocular, intra articular and the like. They will be adjusted based on the at least one pharmaceutically active ingredient present within the formulations, to be able to observe the differences and fluctuations between the formulations. The injectability must be kept low such that the formulation can be easily administered by a qualified healthcare professional in an acceptable timeframe. An ideal injectability value may be from 0.1 N to 10N with the measurement method described below. An acceptable injectability value may be from 10 N to 20 N. A non-optimal injectability may be from 20 N to 30 N. Formulations are hardly injectable from 30 to 40 N and non-injectable above 40 N. Injectability may be measured using a texturometer, preferably a Lloyd Instruments FT plus texturometer, using the following analytical conditions: 500 µL of formulation are injected through a 1 mL syringe, a 23G 1" Terumo needle with a 1 mL/min flow rate.

[0087] "Viscosity," by definition and as used herein, is a measure of a fluid's resistance to flow and gradual deformation by shear stress or tensile strength. It describes the internal friction of a moving fluid. For liquids, it corresponds to the informal concept of "thickness;" By 'dynamic viscosity" is meant a measure of the resistance to flow of a fluid under an applied force. The dynamic velocity can range from 1 mPa.s. to 3000 mPa.s or 5 mPa.s to 2500 mPa.s or 10 mPa.s to 2000 mPa.s or 20 mPa.s to 1000 mPa.s. Dynamic viscosity is determined using an Anton Paar Rheometer equipped with cone plate measuring system. Typically, 250µL of studied formulation are placed on the measuring plate. The temperature is controlled at +25°C. The measuring system used is a cone plate with a diameter of 25 mm and a cone angle of 2 degrees (CP25-2/S). The working range is from 10 to 1000 s^{-1}. After being vortexed for 10 seconds, formulations are placed at the center of the thermo-regulated measuring plate using a spatula. The measuring system is lowered down and a 0.051 mm gap is left between the measuring system and the measuring plate. Eleven viscosity measurement points are determined across the 10 to 1000 s^{-1} shear rate range. Given values are the ones obtained at 100 s^{-1}.

[0088] The present invention relates to the modulation of the release kinetics of at least one active ingredient from a triblock /diblock biodegradable pharmaceutical composition without adversely impacting critical formulation characteristics such as the physical parameters. The addition of at least one additional biodegradable block copolymer to the initial TB/DB mixture allows tuning the release kinetics without impacting the injectability, which if not, may result in preventing the compositions to be injectable through standard devices. The combination of at least three block copolymers substantially amplifies the range of attainable release of the at least one active ingredient and does so in a more efficient modulating manner.

[0089] The present invention thus relates to a biodegradable drug composition comprising a mixture of at least three copolymers taken among triblock copolymers and diblock copolymers. The biodegradable triblock copolymer has the formula: A_v-B_w-A_x, wherein A is a polyester and B is polyethylene glycol and v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x. The degree of polymerization for DP-PEG is calculated by dividing the PEG molecular weight by the EO unit molecular weight (44 g/mol). v + x equals the degree of polymerization (number of repeat units) for PLA. DP-PLA is calculated by multiplying DP-PEG by the R ratio.

[0090] However, the number of repeat units of v, w and x in the triblock composition may vary due to the targeted time of release of the active ingredient and the type of active ingredient itself. Therefore the number of repeat units in the triblock of v, w and x can range from 1 to 3,300 or from 60 to 2,800 or from 300 to 1,700 or from 500 to 1, 250 and v=x or v≠x. For instance, w can be 273, while v + x can be 682 or w can be 136 and v + x can be 273 or w can be 45.5 and v + x can be 546 or w can be 273 and v +x can be 136.

[0091] The molecular weight of the PEG in the triblock can range from 180 g/mol to 12,000 g/mol.

[0092] The polyester in the triblock can be polylactic acid (PLA), polycaprolactone (PCL), polyethylene adipate (PEA), polyglycolic acid (PGA), polyhydroxyalkanoate (PHA) and mixtures

thereof. In one embodiment the polyester that is used is polylactic acid. In another embodiment the polyester is poly(lactic-co-glycolic acid).

[0093] The biodegradable triblock copolymers are then combined with the biodegradable diblock copolymers having the formula: C_y-A_z, wherein A is a polyester and C is an end-capped polyethylene glycol and y and z are the number of repeat units with y ranging from 1 to 3,000 and z ranging from 1 to 300. This combination has a weight ratio of the sum of triblock copolymer to diblock copolymer ranging from 1:19 to 5:1.

[0094] Examples of end-capped polyethylene glycols include alkoxy capped PEG's such as methoxyPEG or ethoxyPEG, urethane-capped PEG's, ester-capped PEG's, amine-capped PEG's and amide-capped PEG's. This list of end-capped PEG's is not exhaustive and a person skilled in the art would recognize additional end-capped PEG's, which are not listed.

[0095] Moreover, the number of repeat units (degree of polymerization (DP)) of y and z in the diblock composition may also vary. Thus, y can, for example, range from 8 to 500 or 150 to 850 or 200 to 500 or 30 to 1,200 and z can range from 32 to 123 or 7 to 250. For example, y be 32. The degree of polymerization for DP-PEG is calculated by dividing the PEG molecular weight of the capped PEG by the EO unit molecular weight (44 Da). The DP-PLA is calculated by multiplying DP-PEG by the R ratio.

[0096] The polyester in the diblock can be polylactic acid (PLA), polycaprolactone (PCL), polyethylene adipate (PEA), polyglycolic acid (PGA), or polyhydroxyalkanoate

[0097] (PHA) and mixtures thereof. In one embodiment the polyester that is used is polylactic acid. In another embodiment the polyester is poly(lactic-co-glycolic acid).

[0098] Preferred embodiments of the invention comprise any of the following combinations of polymers:

1. 1) (a) a biodegradable triblock copolymer having the formula:

   $$PLA_v\text{-}PEG_w\text{-}PLA_x$$

   wherein v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x; and

   (b) 2, 3 or 4 different biodegradable diblock copolymers each having the formula:

   $$mPEG_y\text{-}PLA_z$$

   wherein y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000;

   and wherein the weight ratio between (a) and (b) is 1:19 to 5:1.

2. 2)
   1. (a) two different biodegradable triblock copolymers each having the formula:

      $$PLA_v\text{-}PEG_w\text{-}PLA_x$$

      wherein v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x; and
   2. (b) 1, 2, 3 or 4 different biodegradable diblock copolymer(s) each having the formula:

      $$mPEG_y\text{-}PLA_z$$

      wherein y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000 ;

   and wherein the weight ratio between (a) and (b) is 1:19 to 5:1.

[0099] The at least three block copolymer(s) are combined by dissolving them together at room temperature in a pharmaceutically acceptable solvent. They are combined such that these at least three block copolymers are in a final concentration of 2% to 60% (w/w%) of the

total composition or optionally 10% to 50%, optionally 20% to 40%, optionally 20% to 35%, optionally 30% to 50% of the total composition. In one aspect the pharmaceutically acceptable solvent is an organic solvent. This organic solvent can be retained in the composition or evaporated off prior to administration.

[0100] A "small quantity," as used herein, is defined as an amount of copolymer lower than the combined amount of the other two block copolymers in the biodegradable drug composition. This small quantity of the at least one additional biodegradable block copolymer is not an addition to the total polymer content but added as an addition of a substitute block copolymer from the existing classical two block copolymer composition. This addition of an at least one additional biodegradable block copolymer to the formulation composition, without changing either the total amount of block copolymers within the formulation or the TB/DB ratio, is an appropriate way to modify the release profile without affecting relevant physical parameters. For example, the at least one additional biodegradable block copolymer can be less than 25% of the total block copolymer content or can be, for example, less than 5%. In another embodiment a 'small quantity' can range from 1% to 25% of the total block copolymer content or 2.5% to 15% of the total block copolymer content or 3.5% to 12% of the total block copolymer content.

[0101] The present invention relates to the modulation of the release kinetics of at least one active ingredient from a triblock / diblock biodegradable pharmaceutical composition without adversely impacting critical formulation characteristics, including physical parameters such as robustness of the depot, or injectability or viscosity of the formulation. The presence of an additional biodegradable block copolymer to the initial TB / DB mixture allows tuning of the release kinetics without impacting the injectability, which if not, may prevent the compositions from being injectable through standard devices.

[0102] In a preferred embodiment, the combination of at least three block copolymers substantially amplifies the range of attainable release of the at least one active ingredient and does so in a more efficient modulating manner.

[0103] This formulation allows modulation of the release profile of the at least one active ingredient inducing an increase or a decrease of the release kinetic over time without significantly impacting the physical parameters of the initial formulation. The total polymer content as well as the total of at least one active ingredient content of the formulation is still unchanged and gives to the formulation the same relevant parameters such as injectability or depot robustness. The goal of this approach is to modify the release kinetics keeping the benefits provided by the initial triblock and diblock PEG-PLA copolymer (injectability, depot robustness etc.)

[0104] The release modulation by keeping a two block copolymers formulation differs from the addition of at least one additional block copolymer since the physical parameters can significantly differ from the two block copolymer formulation. In this respect, there may be an impact on the physical parameters.

[0105] The mixtures of at least three triblock copolymers and diblock copolymers can contain any polyester such as polylactic acid (PLA), polycaprolactone (PCL), polyethylene adipate (PEA), polyglycolic acid (PGA), polyhydroxyalkanoate (PHA) and mixtures thereof. Thus, the triblock can contain, for example, PCL-PEG-PCL or PEA-PEG-PEA or PGA-PEG-PGA or PHA-PEG-PHA or PLA-PEG-PLA or PLA-PEG-PCL, PCL_y-PEG_w-$PCLA_x$ or PHA-PEG-PEA. The diblock can contain, for example, end-capped PEG-PLA or end-capped PEG-PCL or end-capped PEG-PEA or end-capped PEG-PGA or end-capped PEG-PLGA or end-capped PEG-PHA or end-capped PEG-PCLA.

[0106] Therefore, in particular embodiments the biodegradable drug delivery composition comprising the mixtures of at least three triblock copolymer and diblock copolymers may comprise a triblock copolymer of PLA-PEG-PLA and a diblock copolymer of mPEG-PLGA mixed with a triblock copolymer of PCL-PEG-PCL and a diblock copolymer of mPEG-PLA. Another example is a triblock of copolymer PEA-PEG-PEA and a diblock copolymer of mPEG-PEA mixed with a triblock copolymer of PLA-PEG-PLA and a diblock copolymer of m-PEG-PLGA. Yet another example is a triblock copolymer of PLA-PEG-PCL and diblock copolymer having end-capped PEG-PCL and a triblock copolymer of PLA-PEG-PLA or a triblock copolymer of PLA-PEG-PLA and a diblock copolymer of end-capped PEG-PLA and a diblock copolymer of an end-capped PEG-PLGA or a triblock copolymer of PCLA-PEG-PCLA and a diblock copolymer of end-capped PEG-PLA and a diblock copolymer of an end-capped PEG-PCLA.

[0107] The weight ratio of the sum of the biodegradable triblock copolymer and the biodegradable diblock copolymer in the biodegradable drug delivery composition is from 1:19 to 5:1, optionally from 1:5 to 3:1, optionally from 1:2 to 3:1. Therefore this ratio can be, for example, 1:5, 1:10, 1:19, 4:1, 3:1 or 2:1.

[0108] The length of the polyester chain is defined by its polyester to ethylene oxide molar ratio, which is between 0.5 to 22.3, optionally 0.5 to 10, optionally 0.5 to 3.5, optionally 0.5 to 2.5 or for the triblock copolymer and 0.8 to 15, optionally 0.8 to 13, optionally 1 to 10, optionally 3 to 5, optionally 2 to 6 for the diblock copolymer. Thus, for example, if polylactic acid is used the chain length is defined by the lactic acid/ethylene oxide molar ratio. Similarly if polyglycolic acid is used, the chain length is defined by the polyglycolic acid/ethylene oxide molar ratio or the polycaprolactone/ ethylene oxide molar ratio or the polyhydroxyalkanoate/ethylene oxide molar ratio. If poly(lactic-co-glycolic) acid is used the chain length is defined by the R ratio.

[0109] The weight of the end-capped polyethylene glycol can range from 120 g/mol to 10,000 g/mol or 164 g/mol to 2,000 g/mol or from 100 g/mol to 2 kg/mol or from 200 g/mol to 8,000 g/mol or from 194 g/mol to 7,500 g/mol or from 100 g/mol to 6,500 g/mol or from 164 g/mol to 9,500 g/mol. It can range in the lower 130 to 300 g/mol range or in the 125 g/mol to 800 g/mol range.

[0110] The molecular weight of the polyethylene glycol chain ranges from 180 g/mol to 12 kg/mol in the biodegradable drug delivery composition or it can range from 400 g/mol to 12 kg/mol or 194 g/mol to 12 kg/mol.

[0111] The polymer total amount is in a range from 2% to 60% (w/w%), optionally 1% to 50% (w/w%), optionally 10% to 50%, optionally 20% to 40%, optionally 20% to 35%, optionally 30% to 50% of the total weight of the composition. In another embodiment the total weight of the polymers present in the biodegradable drug composition is 30% to 50% (w/w%) or 10% to 35% (w/w%) of the total weight of the composition. In yet another embodiment the polymers are present in the biodegradable drug composition at 40% to 50% (w/w%) or 20% to 45% (w/wt%) of the total weight of the composition.

[0112] Thus, the triblock copolymer is present in an amount of 1% to 50% (w/w%) or 3% to 45% (w/w%) of the total weight of the composition. In another aspect the triblock copolymer is present in an amount of 6% to 10% (w/w%) of the total weight of the composition. In yet another aspect the triblock copolymer is present in an amount of 20% to 40 % (w/w%) of the total weight of the composition. In yet another aspect the triblock is present in an amount of 5% to 40% (w/w%) of the total composition.

[0113] Likewise the diblock copolymer can be present in the biodegradable drug composition in an amount of 1% to 57% (w/w%) of the total weight of the composition. In another aspect the diblock copolymer is present in an amount of 2.5% to 45% (w/w%) of the total weight of the composition. In yet another aspect the diblock copolymer is present in an amount of 5% to 40% (w/w%) of the total weight of the composition. In yet another aspect the diblock is present in an amount of 8% to 20% (w/w%) of the total composition.

[0114] The third or further biodegradable block copolymer may be present in the biodegradable drug composition in an amount of at least 0.5 to 20, optionally 0.2 to 20 (w/w%) of the total composition. In another example, it can be present in a range of 1 to 10 (w/wt%); in yet another it can be in the range of 2 to 8 (w/w%) of the total composition. In yet another aspect, the at least one additional biodegradable block copolymer can be present in an amount of 3 to 5 (w/w%) of the total composition.

[0115] The at least one pharmaceutically active ingredient is entrapped in the mixture of the at least three triblock and diblock biodegradable drug delivery compositions. Representative drugs and biologically active agents to be used in the invention include, without limitation, peptide drugs, protein drugs, desensitizing agents, antigens, vaccines, vaccine antigens, anti-infectives, antidepressants, stimulants, opiates, antipsychotics, atypical antipsychotics, glaucoma medications, antianxiety drugs, antiarrhythmics, antibacterials, anticoagulents, anticonvulsants, antidepressants, antimetics, antifungals, antineoplastics, antivirals, antibiotics, antimicrobials, antiallergenics, anti-diabetics, steroidal anti-inflammatory agents, decongestants, miotics, anticholinergics, sympathomimetics, sedatives, hypnotics, psychic energizers, tranquilizers, androgenic steroids, estrogens, progestational agents, humoral agents, prostaglandins, analgesics, corticosteroids, antispasmodics, antimalarials, antihistamines, cardioactive agents, non-steroidal anti-inflammatory agents, antiparkinsonian agents, antihypertensive agents, beta-adrenergic blocking agents, nutritional agents,

gonadotrophin releasing hormone agonists, insecticides, anti-helminthic agents or combinations thereof.

[0116] The pharmaceutically active ingredient may be risperidone, bupivacaine, ivermectin, octreotide, meloxicam, or combinations thereof.

[0117] Combinations of drugs can be used in the biodegradable drug delivery composition of this invention. For instance, if one needs to treat Lupus erythematosis, non-steroidal anti-inflammatory agents and corticosteroids can be administered together in the present invention.

[0118] Veterinary medicaments such as medicines for the treatment of worms or vaccines for animals are also part of the present invention.

[0119] Viral medicaments for plants such as those viruses from *Potyviridae, Geminiviridae,* the *Tospovirus* genus of *Bunyaviridiae and Banana streak virus* are also encompassed by the present invention. Also medicaments for tobacco mosaic virus, turnip crinkle, barley yellow dwarf, ring spot watermelon and cucumber mosaic virus can be used in the biodegradable drug delivery composition of the invention.

[0120] To those skilled in the art, other drugs or biologically active agents that can be released in an aqueous environment can be utilized in the described delivery system. Also, various forms of the drugs or biologically active agents may be used. These include without limitation forms such as uncharged molecules, molecular complexes, salts, ethers, esters, amides, etc., which are biologically activated when injected into the animal or plant or used as a spatial formulation such that it can be applied on or inside the body of an animal or plant or as a rod implant.

[0121] The pharmaceutically effective amount of an active ingredient may vary depending on the active ingredient, the extent of the animal's or plants medical condition and the time required to deliver the active ingredient. There is no critical upper limit on the amount of active ingredient incorporated into the polymer solution except for that of an acceptable solution or dispersion viscosity for injection through a syringe needle and that it can effectively treat the medical condition without subjecting the animal or plant to an overdose. The lower limit of the active ingredient incorporated into the delivery system is dependent simply upon the activity of the active ingredient and the length of time needed for treatment.

[0122] Generally the pharmaceutically active ingredient is present in an amount of 0.05% to 60% (w/w%) of the total weight of the composition. In another embodiment the active ingredient is present in 1% to 40% (w/w%) of the total weight of the composition. In another embodiment the active ingredient is present in 2% to 4% (w/w%) of the total weight of the composition. In yet another embodiment the active ingredient, which is a small molecule, is present in an amount of 1% to 20% (w/w%) of the total weight of the composition.

[0123] In the biodegradable drug delivery composition of the present invention, the pharmaceutically effective amount can be released gradually over an extended period of time. This slow release can be continuous or discontinuous, linear or non-linear and can vary due to the composition of the triblock copolymer and diblock copolymer.

[0124] The active ingredient can be released for a duration of between 1 day to 1 year or longer depending upon the type of treatment needed and the biodegradable drug delivery composition used. In one embodiment the biodegradable drug delivery composition can deliver the active ingredient for at least 1 day, optionally at least 3 days, optionally at least 7 days. In another embodiment the biodegradable drug delivery composition can deliver the active ingredient for at least 30 days. In one embodiment the biodegradable drug delivery composition can deliver the active ingredient for at least 90 days. In yet another embodiment the biodegradable drug delivery composition can deliver an active ingredient for 1 year or longer.

[0125] The biodegradable drug delivery composition can be an injectable liquid, preferably at room temperature, and can be injected through a syringe without excessive force. These biodegradable drug delivery compositions are also *in situ* forming and biodegradable and turn into solid depots when injected into the animal or plant. It can also be prepared as microparticles that can be injected via a syringe.

[0126] Alternatively, the biodegradable drug composition is produced as a solid, prepared as small particles (that are not injectable due to their size) and prepared as a powder which is sprinkled on the injured site. The solid implants can be formulated in any shape that I desirable

for its application into the body.

[0127] In another aspect the drug delivery composition is a rod implant, which can be implanted under the skin or in another compartment in the body. In another aspect the drug delivery composition can be prepared and applied as a film. In yet another aspect the biodegradable drug delivery composition can be used as a spatial formulation such that it can be applied onto or inside the body of an animal or plant. It can be applied anywhere on the body, including in the eye.

[0128] The biodegradable drug delivery composition can further comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. An acceptable carrier can be saline, buffered saline and the like. It can be added to the biodegradable drug delivery composition after its formulation with the drug and a mixture of at least three copolymers taken among triblock copolymers and diblock copolymers.

[0129] The adjuvant can be formulated simultaneously when mixing the drug. In this regard the adjuvants that can be used are alum, aluminum phosphate, calcium phosphate, MPL™, CpG motifs, modified toxins, saponins, endogenous stimulatory adjuvants such as cytokines, Freunds complete and incomplete adjuvants, ISCOM type adjuvants, muramyl peptides and the like.

[0130] The vehicle can be any diluent, additional solvent, filler or binder that may alter the delivery of the active ingredient when needed in the biodegradable drug delivery composition. Examples include small amounts of triglycerides such as triacetin or tripropionin. The amount that can be used in the present biodegradable drug delivery compositions of the present invention can vary from 12% to 20% (w/w%). In one aspect a triacetin can be added in the formulation at 17% (w/w%). In another aspect tripropionin (abbreviated herein as Tripro) can be added at 16% (w/w%).

[0131] In one embodiment the composition may comprise an organic solvent. The organic solvent may be selected from the group of: benzyl alcohol, benzyl benzoate, dimethyl isosorbide (DMI), dimethyl sulfoxide (DMSO), ethyl acetate, ethyl benzoate, ethyl lactate, glycerol formal, methyl ethyl ketone, methyl isobutyl ketone, N-ethyl-2-pyrrolidone, N-methyl-2-pyrrolidinone(NMP), pyrrolidone-2, tetraglycol, triacetin, tributyrin, tripropionin (tripro), and mixtures thereof. In one embodiment DMSO, NMP, tripro or mixtures thereof can be used as solvents.

[0132] In a further described example, provided is a method for preparing the biodegradable drug delivery composition comprising a mixture of at least three block copolymers taken among triblock copolymers and diblock copolymers is also encompassed by the invention. This method comprises:

1. (i) dissolving in an organic solvent at least three triblock and diblock copolymers comprising:
    1. (a) a biodegradable triblock copolymer comprising the formula:

        $$A_v\text{-}B_w\text{-}A_x,$$

        wherein A is a polyester and B is polyethylene glycol and v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x; and
    2. (b) a biodegradable diblock copolymer comprising the formula:

        $$C_y\text{-}A_z,$$

        wherein A is a polyester and C is an end-capped polyethylene glycol y and z are the number of repeat units and with y ranging from 2 to 250 and z ranging from 1 to 3,000 to form a polymer mixture;

        wherein the weight ratio between (a) and (b) is 1:19 to 5:1; and
2. (ii) adding at least one pharmaceutically active ingredient to said polymer mixture.

[0133] In this method, combinations of at least three block copolymers comprising at least one

diblock and at least one triblock, for example 3 to 10 block copolymers can be formulated. For instance, two triblock copolymers can be combined with one diblock or one triblock copolymer can be combined with two diblocks. Five triblock copolymers can be combined with five diblocks or three triblock copolymers can be combined with seven diblock copolymers. Four triblocks can be combined with three diblocks and the like.

[0134] The polyester in the triblock can be polylactic acid (PLA), polycaprolactone (PCL), polyethylene adipate (PEA), polyglycolic acid (PGA), polyhydroxyalkanoate (PHA) and mixtures thereof. In one embodiment the polyester that is used is polylactic acid.

[0135] The polyester in the diblock can be polylactic acid (PLA), polycaprolactone (PCL), polyethylene adipate (PEA), polyglycolic acid (PGA), or polyhydroxyalkanoate (PHA) and mixtures thereof. In one embodiment the polyester that is used is polylactic acid. In another embodiment the polyester is poly(lactic-co-glycolic acid).

[0136] The organic solvent that can be used in the method described herein may be selected from the group of: benzyl alcohol, benzyl benzoate, dimethyl isosorbide (DMI), dimethyl sulfoxide (DMSO), ethyl acetate, ethyl benzoate, ethyl lactate, glycerol formal, methyl ethyl ketone, methyl isobutyl ketone, N-ethyl-2-pyrrolidone, N-methyl-2-pyrrolidinone(NMP), pyrrolidone-2, tetraglycol, triacetin, tributyrin, tripropionin (tripro), and mixtures thereof. In one embodiment DMSO, NMP, tripro or mixtures thereof can be used as solvents.

[0137] The organic solvent is typically present in an amount of 35% to 75% (w/w%) of the total composition. In another embodiment the organic solvent used in the preparation of the biodegradable drug delivery composition is present in an amount of 50% to 60% (w/w%) of the total composition. In yet another embodiment the solvent used in the preparation of the biodegradable drug delivery composition is present in an amount of 25% to 90% (w/w%) of the total composition. The amount of organic solvent in another embodiment can be 0% if it is evaporated.

[0138] This organic solvent can be retained in the composition or evaporated off prior to administration.

[0139] Some mPEG-OH may be contaminated with a small amount of OH-PEG-OH. By following the methods of the present invention and using the contaminated mPEG-OH the final product may be mPEG-PLA contaminated with a small amount of PLA-PEG-PLA, which is encompassed by the present invention.

[0140] In an additional aspect, the present invention provides a biodegradable drug delivery composition for use in modulating the kinetics of release of at least one active ingredient said use comprising administering a biodegradable drug delivery composition comprising a mixture of at least three different block copolymers taken among triblock and diblock copolymers comprising:

1. (a) a biodegradable triblock copolymer having the formula:

   $$A_v\text{-}B_w\text{-}A_x$$

   wherein A is a polyester and B is polyethylene glycol and v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x;
2. (b) a biodegradable diblock copolymer having the formula:

   $$C_y\text{-}A_z$$

   wherein A is a polyester and C is an end-capped polyethylene glycol and y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000;
   wherein the weight ratio between (a) and (b) is 1:19 to 5:1; and
3. (c) at least one pharmaceutically active ingredient.

[0141] In this composition for use the triblock and diblock can be selected from the group of a polylactic acid, polyglycolic acid, polycaprolactone, poly(ε-caprolactone-*co*-lactide), polyethylene adipate, poly(lactide-co-glycolide) acid, polyhydroxyalkanoate and mixtures thereof and the end-capped polyethylene glycol can be methoxy polyethylene glycol. In one aspect the triblock is PLA-PEG-PLA and the diblock is mPEG-PLA, as described herein, for the

biodegradable drug compositions.

[0142] In this composition for use the kinetics of release of at least one active ingredient the molecular weight of the polyethylene glycol chain can range from 180 g/mol to 12 kg/mol or 194 g/mol to 12 kg/mol and the molecular weight of the end-capped polyethylene glycol chain ranges from 100 g/mol to 4 kg/mol or 164 g/mol to 10 kg/mol.

[0143] In another embodiment of the composition for use the at least one pharmaceutically active ingredient used in the method is present in an amount of from 0.05 % to 60% (w/w%), optionally 0.05% to 40%, optionally 0.05% to 30%, optionally 0.05% to 10%, optionally 0.05% to 7%, optionally 0.05% to 2% of the total composition.

[0144] In one embodiment of the composition for use the biodegradable drug delivery composition is an injectable liquid and the at least one pharmaceutically active ingredient is present in an amount of 0.05% to 60% (w/w%).

[0145] In an alternative embodiment of the composition for use the biodegradable drug delivery composition is a rod implant and the at least one pharmaceutically active ingredient is present in an amount of from 50% to 80% (w/w%).

[0146] In a further embodiment of the composition for use, the copolymers are present in an amount of 2% to 60% (w/w%) of the total composition, optionally 10% to 50%, optionally 20% to 40%, optionally 20% to 35%, optionally 30% to 50%.

[0147] In one embodiment of the composition for use the one or more triblock copolymers are present in an amount of 1% to 50% (w/w%), optionally 5% to 40% of the total composition.

[0148] In one embodiment of the composition for use the one or more diblock copolymers are present in an amount of 1% to 57% (w/w%), 2.5% to 45% of the total composition.

[0149] In an additional embodiment of the composition for use the weight ratio of the sum of the biodegradable triblock copolymers of (a) over the sum of the biodegradable diblock copolymers of (b) in said biodegradable drug delivery composition is 1:5 to 3:1.

[0150] Typically the polyester repeat unit to ethylene oxide molar ratio in the composition used is between 0.5 to 22.3, optionally 0.5 to 10, optionally 0.5 to 3.5 in the triblock and 0.8 to 15, optionally 1 to 10 in the diblock.

[0151] In the composition for use in modulating the kinetics of release of at least one active ingredient, the composition can be an injectable liquid or microparticles and form a depot when injected into the body or a solid or are small solid particles or rod implants or spatial formulations that can be formulated as solids and placed into the body using a trocar, for example.

[0152] Provided is a drug delivery composition comprising:

1. (i) a mixture of at least three different block copolymers, wherein each block copolymer is:
    1. (a) a triblock copolymer having the formula:

        $$A_v\text{-}B_w\text{-}A_x$$

        wherein A is a polyester and B is polyethylene glycol and v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x; or
    2. (b) a diblock copolymer having the formula:

        $$C_y\text{-}A_z$$

        wherein A is a polyester and C is an end-capped polyethylene glycol and y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000; and

        wherein the mixture comprises at least one (a) and at least one (b); and the weight ratio between (a) and (b) is 1:19 to 5:1; and
2. (ii) at least one pharmaceutically active ingredient.

[0153] Also provided is a composition for use in modulating the kinetics of release of at least one active ingredient, said use comprising administering a drug delivery composition as defined above to a subject, wherein the release kinetics of said at least one active ingredient from said drug delivery composition are modulated without affecting one or more physical parameters of said drug delivery composition.

[0154] Described is a biodegradable drug delivery composition comprising a mixture of at least three triblock copolymers and diblock copolymers comprising:

1. (a) a biodegradable triblock copolymer having the formula:

   A_v-B_w-A_x

   wherein A is a polyester and B is polyethylene glycol and v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x;
2. (b) a biodegradable diblock copolymer having the formula:

   C_y-A_z

   wherein A is a polyester and C is an end-capped polyethylene glycol and y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000, wherein the weight ratio of the sum of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1:19 to 5:1 in said biodegradable drug composition;
3. (c) at least one additional biodegradable block copolymer; and
4. (d) at least one pharmaceutically active principle, wherein the release kinetics of said at least one active principle from said biodegradable drug delivery composition is modulated without affecting physical parameters of said biodegradable drug composition.

[0155] Described is a biodegradable drug delivery composition comprising a mixture of at least three triblock copolymers and diblock copolymers comprising:

1. (a) a biodegradable triblock copolymer having the formula:

   A_v-B_w-A_x

   wherein A is a polyester and B is polyethylene glycol and v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300, v and x being ester repeat units and w being ethylene oxide repeat units and v=x or v≠x;
2. (b) a biodegradable diblock copolymer having the formula:

   C_y-A_z

   wherein A is a polyester and C is an end-capped polyethylene glycol and y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000, y being the number of ethylene oxide repeat units and z the number of ester repeat units wherein the weight ratio of the sum of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1:19 to 5:1 in said biodegradable drug composition;
3. (c) at least one additional biodegradable block copolymer;and
4. (d) at least one pharmaceutically active principle, wherein the release kinetics of said at least one active principle from said biodegradable drug delivery composition is modulated without affecting physical parameters of said biodegradable drug composition.

[0156] Described is biodegradable drug delivery composition comprising a mixture of at least three triblock copolymers and diblock copolymers comprising:

1. (a) a biodegradable triblock copolymer having the formula:

$$PLA_v\text{-}PEG_w\text{-}PLA_x$$

wherein v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x;
2. (b) a biodegradable diblock copolymer having the formula:

$$mPEG_y\text{-}PLA_z$$

wherein y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000, wherein the weight ratio of the sum of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1:19 to 5:1 in said biodegradable drug composition;
3. (c)at least one additional biodegradable block copolymer; and
4. (d) at least one pharmaceutically active principle, wherein the release kinetics of said at least one active principle from said biodegradable drug delivery composition is modulated without affecting physical parameters of said biodegradable drug composition.

[0157] Described is a biodegradable drug delivery composition comprising a mixture of at least three triblock copolymers and diblock copolymers comprising:

1. (a) a biodegradable triblock copolymer present in an amount of 1% to 50% (w/w%) of the total composition having the formula:PLAv-PEGw-PLAx
wherein and v and x are the number of repeat units ranging from 1 to 3,000 and w is the number of repeat units ranging from 3 to 300 and v=x or v≠x;
2. (b) a biodegradable diblock copolymer present in an amount of 1% to 57% (w/w%) of the total composition having the formula:

$$mPEG_y\text{-}PLA_z$$

wherein y and z are the number of repeat units with y ranging from 2 to 250 and z ranging from 1 to 3,000, wherein the weight ratio of the sum of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1:19 to 5:1 in said biodegradable drug composition;
3. (c) at least one additional biodegradable block copolymer; and
4. (d) at least one pharmaceutically active principle present in an amount of 0.05% to 60% (w/w%) of the total composition, wherein the release kinetics of said at least one active principle from said biodegradable drug delivery composition is modulated without affecting physical parameters of said biodegradable drug composition.

EXAMPLES

Preparative Example 1-Polymer Synthesis

[0158] Block copolymers were synthesized according to the method described in U.S. Patent No. 6,350,812, with minor modifications. Typically the necessary amount of PEG (in the triblock copolymer) or methoxy-PEG (in the diblock copolymer) was heated at 80°C and dried under vacuum for 30 minutes in a reactor vessel. DL-lactide (corresponding to the targeted LA/EO molar ratio) and zinc lactate (1/1000 of amount of lactide) were added. The reaction mixture was first dehydrated by two short vacuum/N_2 cycles. The reaction was heated at 140°C under constant nitrogen flow (0.2 bar). After the reaction stopped, the block copolymer was discharged from the vessel and left to stand at room temperature until solidification. The product obtained was characterized by ^{1}H NMR for its lactate content. 1H NMR spectroscopy was performed using a Brucker advance 300 MHz spectrometer.

[0159] For all 1H NMR spectrograms, MestReNova software was used for the integration of peaks and their analyses. Chemical shifts were referenced to the Δ= 7.26ppm solvent value for $CDCl_3$.

[0160] For the determination of the R ratio, that describes the ratio between lactic acid units over ethylene oxide units (LA/EO), all peaks were separately integrated. The intensity of the signal (integration value) is directly proportional to the number of hydrogens that make the signal. So to determine the R ratio (LA/EO ratio), the integration values need to be homogenous and representative of the same number of protons (e.g. all signal values are determined for 1H). A characteristic peak of PLA and one of PEG are then used to determine the LA/EO ratio. This method is valid for molecular weight of PEGs above 1000 g/mol where the signal obtained for the polymer end-functions can be neglected.

[0161] The triblock polymers described herein were labelled PxRy where x represents the molecular weight of the PEG chain in kDa and y is the polyester monomer/ethylene oxide molar ratio, for example the lactic acid/ethylene oxide (LA/EO) molar ratio. The diblock mPEG-PLA polymers described herein where labelled dPxRy where x represents the molecular weight of the PEG chain in kDa and y is the polyester monomer/ethylene oxide molar ratio, for example the lactic acid/ethylene oxide (LA/EO) molar ratio.

Example 2- Preparation of a Specific Formulation for meloxicam

[0162] The formulation F197 (not according to the invention), described herein, was based on an organic solution of block copolymers containing meloxicam as API. 1800 milligrams of the block copolymers corresponding to a mix of diblock and triblock copolymers in defined weight ratio of the sum of triblock to the sum of diblock as indicated in Table 6 were dissolved in 1140 milligrams of DMSO at room temperature over-night and under constant magnetic stirring. The next day 60 milligrams of drug were added to this block copolymer solution and stirred until complete homogenization of the solution obtained. The formulation was loaded in a syringe before use.

Example 3- Formulation Preparation

[0163] Following Examples 1 and 2, the following formulations were prepared as set forth in Tables 1 to 6 below:
All the compositions in Tables 1 to 6 are completed up to 100% using DMSO as a solvent.

TABLE 1

			Triblock copolymer 1		mPEG-PLA		Triblock copolymer 2				mPEG-PLA			
		Risperidone	PLA-PEG-PLA		Diblock copolymer 1		PLA-PEG-PLA		Diblock copolymer 2		Diblock copolymer 3		Diblock copolymer 4	
	TB:DB													
N°	Weight ratio	% (w/w)	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code
16	1.00	60	1.00	P1R4	1.50	dP2R3	50	P1R6	1.00	dP0.35R8.5	-	-	-	-
28	5.00	10	25.00	P1R6	1.25	dP2R3	-	-	1.25	dP0.35R8.5	1.25	dP0.35R5	1.25	dP2R0.5
29	0.05	10	1.50	P1R6	7.125	dP2R3	-	-	7.125	dP0.35R8.5	7.125	dP0.35R5	7.125	dP2R0.5

TABLE 2

			Triblock copolymer 1		mPEG-PLA			
		Bupivacaine	PLA-PEG-PLA		Diblock copolymer 1		Diblock copolymer 2	
N°	TB:DB Weight ratio	%(w/w)	%(w/w)	Code	% (w/w)	Code	% (w/w)	Code
289*	1.00	2.00	20.00	P1R4	20.00	dP1R4	-	-
290	1.00	2.00	20.00	P1R4	10.00	dP1R4	10.00	dP0.35R8.5
291*	1.00	2.00	20.00	P1R4	-	-	20.00	dP0.35R8.5
292*	1.00	2.00	25.00	P1R4	25.00	dP1R4	-	-
293*	1.00	4.00	20.00	P1R4	20.00	dP1R4	-	-
294*	1.00	6.00	20.00	P1R4	20.00	dP1R4	-	-
*** = comparative example not in accordance with the invention.**								

TABLE 3

			Triblock copolymer 1		mPEG-PLA			
		Bupivacaine	PLA-PEG-PLA		Diblock copolymer 1		Diblock copolymer 2	
N°	TB:DB Weight ratio	% (w/w)	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code
45	5.00	1.00	41.70	P1R4	4.15	dP0.35R8.5	4.15	dP2R0.5
46	0.05	1.00	2.50	P1R4	23.75	dP0.35R8.5	23.75	dP2R0.5
49	0.05	1.00	3.00	P1R4	28.50	dP0.35R8.5	28.50	dP2R0.5
64	0.05	1.00	3.00	P1R4	28.50	dP0.35R8.5	28.50	dP0.35R5

TABLE 4

*** = comparative example not in accordance with the invention.**

			Triblock copolymer 1		mPEG-PLA		Triblock copolymer 2		mPEG-PLA				Triblock copolymer 3	
		Ivermectin	PLA-PEG-PLA		Diblock copolymer 1		PLA-PEG-PLA		Diblock copolymer 2		Diblock copolymer 3		PLA-PEG-PLA	
N°	TB: DB Weight ratio	%(w/w)	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code
105*	0.67	1.00	20.00	P2R3.5	30.00	dP0.35R8.5	-	-	-	-	-	-	-	-
110*	0.50	1.00	8.30	P2R3.5	16.70	dP2R3	-	-	-	-	-	-	-	-
115	0.50	1.00	8.30	P2R3.5	8.30	dP0.16R1	-	-	8.30	dP2R10	-	-	-	-
119	0.67	1.00	10.00	P12R0.7	30.00	dP0.35R8.5	10.00	P0.19R18	-	-	-	-	-	-
124	0.50	1.00	4.20	P1R4	5.50	dP2R3	4.20	P1R6	5.50	dP0.35R8.5	5.50	dP0.35R5	-	-
126	0.50	1.00	2.80	P1R4	5.50	dP2R3	2.80	P1R6	5.50	dP0.35R8.5	5.50	dP0.35R5	2.80	P2R3.5

TABLE 5

			Triblock copolymer 1		mPEG-PLA		Triblock copolymer 2		mPEG-PLA	
		Octreotide acetate	PLA-PEG-PLA		Diblock copolymer 1		PLA-PEG-PLA		Diblock copolymer 2	
N°	TB:DB Weight ratio	%(w/w)	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code
163	1.00	4.00	10.00	P1R4	10.00	dP1R4	10.00	P1R6	10.00	dP0.35R8.5
165*	1.00	4.00	20.00	P1R6	20.00	dP0.35R8.5	-	-	-	-
166*	1.00	4.00	20.00	P1R4	20.00	dP1R4	-	-	-	-

*** = comparative example not in accordance with the invention.**

44

TABLE 6

			Triblock copolymer 1		Triblock copolymer 2		mPEG-PLA	
		Meloxicam	PLA-PEG-PLA				Diblock copolymer 1	
N°	TB:DB Weight ratio	%(w/w)	% (w/w)	Code	% (w/w)	Code	% (w/w)	Code
197*	5.00	2.00	50.00	P0.19R2	-	-	10.00	dP0.35R8.5
199	5.00	2.00	25.00	P0.19R2	25.00	P2R3.5	10.00	dP0.35R8.5
365*	5.00	2.00	50.00	P2R3.5	-	-	10.00	dP0.35R8.5

*** = comparative example not in accordance with the invention.**

45

Example 4-Injectability of differing compositions

[0164] Injectability measurements are performed using the Lloyd Instruments FT plus texturometer, using the following analytical conditions:

- Set-up 1:
  500 µL of studied formulation are injected through a 1 mL Codan syringe, a 23G 1" Terumo needle with a 1 mL/min flow rate. Samples are analyzed in six replicates.

[0165] The obtained value in N (Newton) is correlated with the needed force to inject the formulation with the described conditions.

- Set-up 2:
  500 µL of studied formulation are injected through a 1 mL Codan syringe, a 23G 5/8" BD needle with a 1 mL/min flow rate. Samples are analyzed in six replicates.

[0166] The obtained value in N (Newtons) is correlated with the needed force to inject the formulation with the described conditions.

[0167] Example from Figure 2 and Figure 3:
F289 (not according to the invention), F290 and F291 (not according to the invention) are mixtures of triblock (TB) P1R4 and diblock (DB) dP1R4 or mixtures of triblock (TB) P1R4, diblock (DB) dP1R4 and dP0.35R8.5 or mixtures of triblock (TB) P1R4 and diblock (DB) dP0.35R8.5 respectively for a total polymer content of 40% as indicated in Table 3. Injectability average values for F289, F290 and F291 are 4.8N and 4.4N and 4.3N respectively as indicated in Table 7. Injectability measurement has been performed following the set up 1.

[0168] Data show that the addition of an additional biodegradable block copolymer induces a release modulation, as shown in Figure 2, without having an impact on injectability.

[0169] F292 (not according to the invention), is a mixture of triblock (TB) P1R4 and diblock (DB) dP1R4 for a total polymer content of 50% as indicated in Table 2. Injectability average value for F292 is 14.5N as indicated in Table 7.

[0170] Data show that an increase of the total polymer content from 40% to 50% induces a release modulation, as shown in Figure 2. However, this increase leads a raise of injectability value from 4.8N to 14.5N for F289 (not according to the invention) and F292 (not according to the invention) respectively.

[0171] F293 (not according to the invention), and F294 (not according to the invention) are mixture of triblock (TB) P1R4 and diblock (DB) dP1R4 for a total polymer content of 40% containing respectively 4% and 6% of API loading as indicated in Table 2. Injectability average values for F293 and F294 are 4.8N and 5.3N as indicated in Table 7.

[0172] Data show that an increase of the total API loading from 4% to 6% induces a release modulation, as shown in Figure 3. However this modulation is sub-optimal due to a high initial burst.

TABLE 7

	Bupivacaine					
N°	%(w/w)	Total copolymer content (%)	Number of copolymers	Number of replicates	Injectability (N)	Standard deviation
289*	2.00	40.00	2	6	4.8	0.5
290	2.00	40.00	3	6	4.4	0.4
291*	2.00	40.00	2	6	4.3	0.4
292*	2.00	50.00	2	6	14.5	0.6
293*	4.00	40.00	2	6	4.8	0.4
294*	6.00	40.00	2	6	5.3	0.2
*** = comparative example not in accordance with the invention.**						

[0173] Example from Figures 7 and 8:
F197 (not according to the invention), F199 and F325 (not according to the invention) are mixtures of diblock (DB) dP0.35R8.5 and triblock (TB) P0.19R2 and/or P2R3.5 for a total

polymer content of 60%, as indicated in Table 8. Injectability average values for F197, F199 and F325 are 2.5N, 8.6N and 53.6N respectively, as detailed in Table 8.

[0174] Data show that the addition of an additional biodegradable block copolymer induces a release modulation, as shown in Figure 7, while keeping a formulation injectable.

[0175] Injectability measurement has been performed following the set up 2.

TABLE 8

	Meloxicam					
N°	%(w/w)	Total copolymer content (%)	Number of copolymers	Number of replicates	Injectability (N)	Standard deviation
197*	2.00	60.00	2	6	2.5	0.2
199	2.00	60.00	3	6	8.6	0.7
365*	2.00	60.00	2	3	53.6	2.8
*** = comparative example not in accordance with the invention.**						

Example 5 - Viscosity measurements

[0176] Dynamic viscosity is determined using an Anton Paar Rheometer equipped with cone plate measuring system. The following set-up is typically used to measure viscosity:
250µL of studied formulation are placed on the measuring plate. The temperature is controlled at +25°C. The measuring system used is a cone plate with a diameter of 25 mm and a cone angle of 2 degrees (CP25-2/S).

[0177] The working range is from 10 to 1000 s^{-1}.

[0178] After being vortexed for 10 sec, formulations are placed at the center of the thermo-regulated measuring plate using a spatula. The measuring system is lowered down and a 0.051 mm gap is left between the measuring system and the measuring plate.

[0179] Eleven viscosity measurements points are determined across the 10 to 1000 s^{-1} shear rate range. Given values are the ones obtained at 100 s^{-1}.

Example 6 - *In vitro* Release Assay

[0180] 50 mg of bupivacaine formulation is added to 50 ml of physiological buffer. The physiological buffer that is used is KRT containing 50 ml Krebs / Ringer / Tris (KRT) buffer pH 7.4, which is 143 mM Sodium Chloride, 5.1 mM Potassium Chloride, 2.7 mM Calcium Chloride, 1.34 mM Magnesium Sulfate, 25 mM Tris-Cl pH 7.4 and 0.1% sodium azide. Upon injection, the solvent diffuses away from the formulation and the remaining polymer forms an *in situ* depot within the aqueous environment.

[0181] In order to maintain sink conditions, for drug release, the release medium is maintained under constant shaking at 180 rpm (Unimax 1010 apparatus, Heidolph) at 37°C. At pre-determined time intervals, media are collected and analyzed by UPLC. The amount of bupivacaine released from the formulation is calculated from a calibration curve. The concentration of bupivacaine ranges between 0 and 150 µg/ml.

[0182] The bupivacaine incorporated into the polymer solution is encapsulated within the polymer matrix as it solidifies.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not

form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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- US6541033B [0005]
- US6350812B [0006] [0158]
- US9023897B2 [0007]
- WO2012090070A2 [0008]
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Non-patent literature cited in the description

- Smart Polymer Based Delivery Systems for Peptide and Proteins**K. AL-TAHAMIJ. SINGH**Recent Patents on Drug Delivery & FormulationBentham Science Publishers, LTD.20070000vol. 1, 65-71 [0003]
- Macromol. Biosci., 2003, vol. 3, 657-661 [0013]
- Macromol. Biosci., 2001, vol. 1, 204-208 [0014]

Patentkrav

1. Biologisk nedbrydelig sammensætning til lægemiddeladministration, som omfatter:
(i) en blanding af mindst tre forskellige blok-copolymerer, hvor hver blok-copolymer er:
(a) en biologisk nedbrydelig triblok-copolymer med formlen:
A_v-B_w-A_x
hvor A er en polyester, og B er polyethylenglycol, og v og x er antallet af gentagne enheder, der ligger i intervallet fra 1 til 3.000, og w er antallet af gentagne enheder, der ligger i intervallet fra 3 til 300, og v=x eller v≠x; eller
(b) en biologisk nedbrydelig diblok-copolymer med formlen:
C_y-A_z
hvor A er en polyester, og C er en endecappet polyethylenglycol, og y og z er antallet af gentagne enheder, idet y ligger i intervallet fra 2 til 250, og z ligger i intervallet fra 1 til 3.000; og
hvor blandingen omfatter mindst én (a) og mindst én (b); og vægtforholdet mellem (a) og (b) er 1:19 til 5:1; og
(ii) mindst én farmaceutisk aktiv bestanddel.

2. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge krav 1, som omfatter en copolymer som defineret i (a) eller (b), hvor polyesteren A er valgt fra gruppen, der består af polymælkesyre (PLA), polyglycolsyre, polycaprolacton, polyethylenadipat, polyhydroxyalkanoat og blandinger deraf, og eventuelt hvor den endecappede polyethylenglycol er methoxypolyethylenglycol.

3. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge krav 1 eller krav 2, som yderligere omfatter mindst ét organisk opløsningsmiddel.

4. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af ovennævnte krav, hvor det for mindst én biologisk nedbrydelig triblok-copolymer gælder, at (a) A er PLA, og/eller det for

mindst én biologisk nedbrydelig diblok-copolymer gælder, at (b) A er PLA.

5. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af ovennævnte krav, hvilken sammensætning yderligere omfatter:
(a) en biologisk nedbrydelig triblok-copolymer med formlen:
PLA_v-PEG_w-PLA_x
hvor v og x er antallet af gentagne enheder, der ligger i intervallet fra 1 til 3.000, og w er antallet af gentagne enheder, der ligger i intervallet fra 3 til 300, og v=x eller v≠x; og/eller
(b) en biologisk nedbrydelig diblok-copolymer med formlen:
mPEG_y-PLA_z
hvor y og z er antallet af gentagne enheder, idet y ligger i intervallet fra 2 til 250, og z ligger i intervallet fra 1 til 3.000.

6. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af kravene 1 til 4, som omfatter:
(a) en biologisk nedbrydelig triblok-copolymer med formlen:
PLA_v-PEG_w-PLA_x
hvor v og x er antallet af gentagne enheder, der ligger i intervallet fra 1 til 3.000, og w er antallet af gentagne enheder, der ligger i intervallet fra 3 til 300, og v=x eller v≠x; og
(b) 2, 3 eller 4 forskellige biologisk nedbrydelige diblok-copolymerer hver med formlen:
mPEG_y-PLA_z
hvor y og z er antallet af gentagne enheder, idet y ligger i intervallet fra 2 til 250, og z ligger i intervallet fra 1 til 3.000;
og hvor vægtforholdet mellem (a) og (b) er 1:19 til 5:1.

7. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af kravene 1 til 5, som omfatter:

(a) to forskellige biologisk nedbrydelige triblok-copolymerer hver med formlen:

PLA_v-PEG_w-PLA_x

hvor v og x er antallet af gentagne enheder, der ligger i intervallet fra 1 til 3.000, og w er antallet af gentagne enheder, der ligger i intervallet fra 3 til 300, og v=x eller v≠x; og

(b) 1, 2, 3 eller 4 forskellige biologisk nedbrydelige diblok-copolymerer hver med formlen:

mPEG_y-PLA_z

hvor y og z er antallet af gentagne enheder, idet y ligger i intervallet fra 2 til 250, og z ligger i intervallet fra 1 til 3.000;

og hvor vægtforholdet mellem (a) og (b) er 1:19 til 5:1.

8. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen er en injicerbar væske, der er egnet til dannelse af et depot, når den injiceres i kroppen, eller er små faste partikler eller stavimplantater eller rumlige formuleringer.

9. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af ovennævnte krav, hvor massen af polyethylenglycolkæden ligger i intervallet fra 180 g/mol til 12 kg/mol eller 194 g/mol til 12 kg/mol eller 200 g/mol til 12 kg/mol eller fra 100 g/mol til 4 kg/mol, og molekylvægten af den endecappede polyethylenglycolkæde ligger i intervallet fra 100 g/mol til 2 kg/mol eller 164 g/mol til 10 kg/mol; og/eller som yderligere omfatter et farmaceutisk acceptabelt vehikel, eventuelt hvor det farmaceutisk acceptable vehikel er et opløsningsmiddel; og/eller hvor den farmaceutisk aktive bestanddel er hydrofob; og/eller hvor den farmaceutisk aktive bestanddel er risperidon, bupivacain, ivermectin, octreotid, meloxicam eller kombinationer deraf.

10. Biologisk nedbrydelig sammensætning til

lægemiddeladministration ifølge et hvilket som helst af ovennævnte krav, hvor den mindst ene farmaceutisk aktive bestanddel er til stede i en mængde på fra 0,05 % til 60 % (vægt/vægt-%), eventuelt 0,05 % til 40 %, eventuelt 0,05 % til 30 %, eventuelt 0,05 % til 10 %, eventuelt 0,05 % til 7 %, eventuelt 0,05 % til 2 % af den samlede sammensætning.

11. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge krav 10, som er en injicerbar væske, hvor den mindst ene farmaceutisk aktive bestanddel er til stede i en mængde på 0,05 % til 60 % (vægt/vægt-%), eller er et stavimplantat, hvor den mindst ene farmaceutisk aktive bestanddel er til stede i en mængde på fra 50 % til 80 % (vægt/vægt-%).

12. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af ovennævnte krav, hvor copolymererne er til stede i en mængde på 2 % til 60 % (vægt/vægt-%) af den samlede sammensætning, eventuelt 10 % til 50 %, eventuelt 20 % til 40 %, eventuelt 20 % til 35 %, eventuelt 30 % til 50 %; og/eller hvor den ene eller de flere triblok-copolymerer er til stede i en mængde på 1 % til 50 % (vægt/vægt-%), eventuelt 5 % til 40 % af den samlede sammensætning; og/eller hvor den ene eller de flere diblok-copolymerer er til stede i en mængde på 1 % til 57 % (vægt/vægt-%), eventuelt 2,5 % til 45 % af den samlede sammensætning; og/eller hvor vægtforholdet mellem summen af de biologisk nedbrydelige triblok-copolymerer ifølge (a) og summen af de biologisk nedbrydelige diblok-copolymerer ifølge (b) i den biologisk nedbrydelige sammensætning til lægemiddeladministration er 1:5 til 3:1; og/eller hvor molforholdet mellem den gentagne polyesterenhed og ethylenoxid i sammensætningen er mellem 0,5 og 22,3, eventuelt 0,5 og 10, eventuelt 0,5 og 3,5 i triblokken og 0,8 til 15, eventuelt 1 til 10 i diblokken.

13. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af

ovennævnte krav, hvilken sammensætning omfatter tre forskellige blok-copolymerer som defineret i et hvilket som helst af ovennævnte krav eller fire forskellige blok-copolymerer som defineret i et hvilket som helst af ovennævnte krav eller fem forskellige blok-copolymerer som defineret i et hvilket som helst af ovennævnte krav eller seks forskellige blok-copolymerer som defineret i et hvilket som helst af ovennævnte krav.

14. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af ovennævnte krav, som omfatter én biologisk nedbrydelig triblok-copolymer som defineret i et hvilket som helst af ovennævnte krav eller to forskellige biologisk nedbrydelig triblok-copolymerer som defineret i et hvilket som helst af ovennævnte krav eller tre forskellige biologisk nedbrydelig triblok-copolymerer som defineret i et hvilket som helst af ovennævnte krav eller fire forskellige biologisk nedbrydelig triblok-copolymerer som defineret i et hvilket som helst af ovennævnte krav.

15. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af ovennævnte krav, som omfatter én biologisk nedbrydelig diblok-copolymer som defineret i et hvilket som helst af ovennævnte krav eller to forskellige biologisk nedbrydelig diblok-copolymerer som defineret i et hvilket som helst af ovennævnte krav eller tre forskellige biologisk nedbrydelig diblok-copolymerer som defineret i et hvilket som helst af ovennævnte krav eller fire forskellige biologisk nedbrydelig diblok-copolymerer som defineret i et hvilket som helst af ovennævnte krav.

16. Biologisk nedbrydelig sammensætning til lægemiddeladministration ifølge et hvilket som helst af ovennævnte krav, som er egnet til administration af den aktive bestanddel til et individ, eventuelt en terapeutisk effektiv mængde af den aktive bestanddel, i mindst 1 dag, eventuelt mindst 3 dage, eventuelt mindst 7 dage, eventuelt mindst 30 dage,

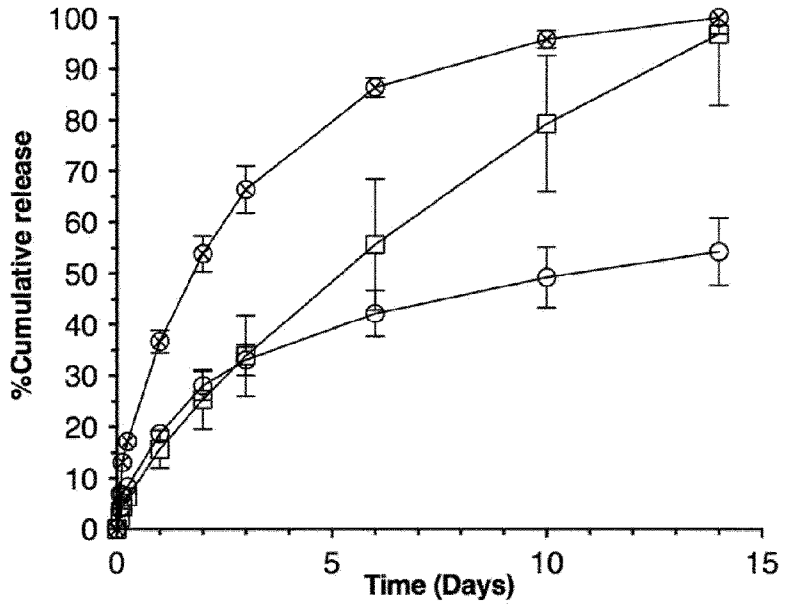
eventuelt mindst 90 dage, eventuelt mindst 1 år; og/eller som er egnet til parenteral administration; og/eller hvor blok-copolymererne har mindre end 5 %, eventuelt mindre end 1 % (vægt/vægt) opløselighed i en vandig opløsning.

17. Biologisk nedbrydelig sammensætning til lægemiddeladministration som defineret i et hvilket som helst af ovennævnte krav til anvendelse i medicin, eventuelt hvor anvendelsen omfatter modulering af kinetikken for frigivelse af mindst én aktiv bestanddel, hvilken anvendelse omfatter administrering af en biologisk nedbrydelig sammensætning til lægemiddeladministration som defineret i et hvilket som helst af ovennævnte krav til et individ, hvor frigivelseskinetikken for den mindst ene aktive bestanddel fra den biologisk nedbrydelige sammensætning til lægemiddeladministration moduleres uden påvirkning af en eller flere fysiske parametre for den biologisk nedbrydelige sammensætning til lægemiddeladministration, eventuelt hvor den ene eller de flere fysiske parametre er injicerbarhed og viskositet før injektion af den biologisk nedbrydelige sammensætning til lægemiddeladministration og depotrobusthed efter injektion af den biologisk nedbrydelige sammensætning til lægemiddeladministration.

DRAWINGS

Drawing

Figure 1



F28: 30.00%Pol(5)_TB:DB,5:1_25.00%P1R6_1.25%dP2R3_1.25%dP0,35R8,5_1.25%dP0,35R5_1.25%dP2R0,5 _10.00%API

F16: 5.00%Pol(4)_TB:DB,1:1_1.00%P1R4_1.50%P1R6_1.50%dP2R3_1.00%dP0,35R8,5_60.00%API

F29: 30.00%Pol(5)_TB:DB,1:19_1.50%P1R6_7.125%dP2R3_7.125%dP0,35R8,5_7.125%dP0,35R5_7.125%dP2R0,5_10.00%AP

Figure 2

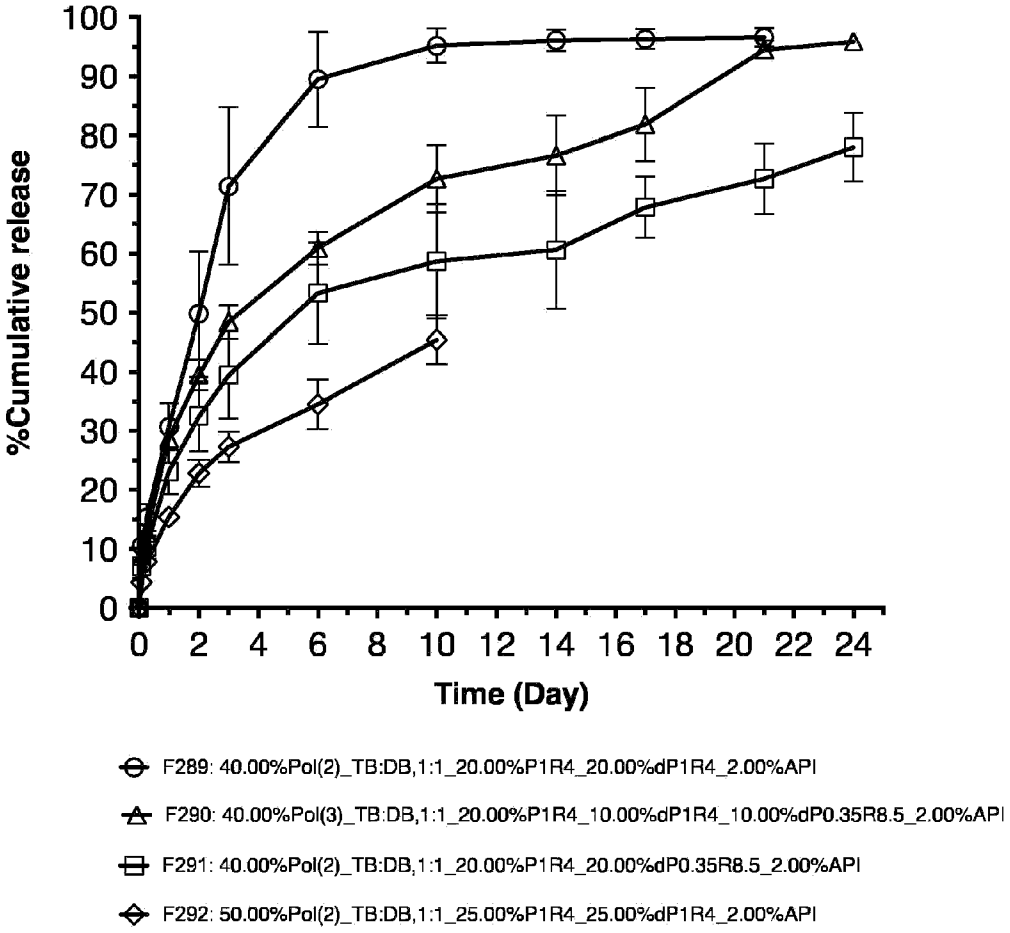
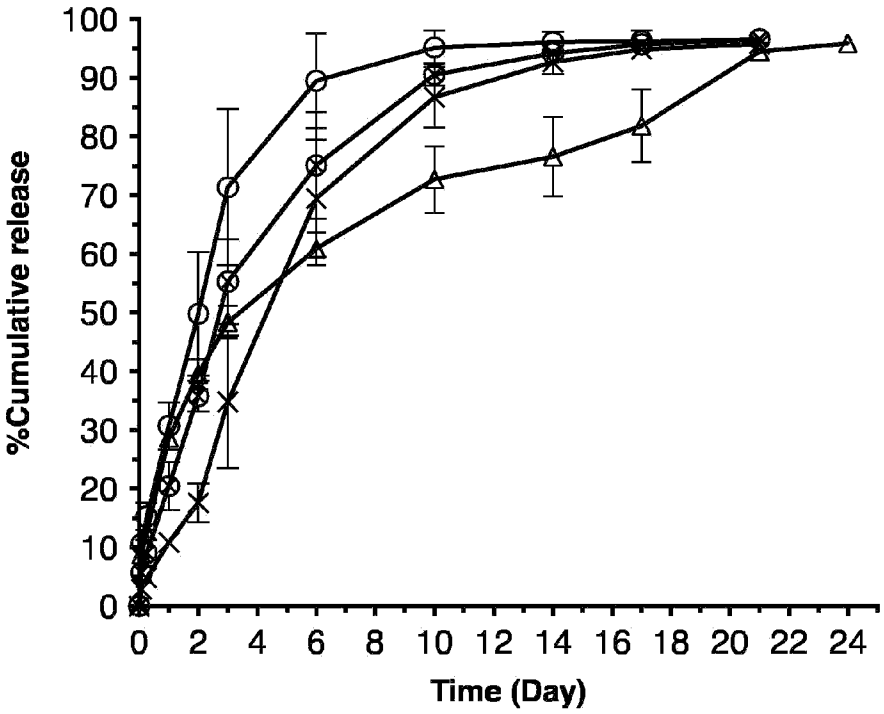

%Cumulative release
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (Day)
F289: 40.00%Pol(2)_TB:DB,1:1_20.00%P1R4_20.00%dP1R4_2.00%API
F290: 40.00%Pol(3)_TB:DB,1:1_20.00%P1R4_10.00%dP1R4_10.00%dP0.35R8.5_2.00%API
F291: 40.00%Pol(2)_TB:DB,1:1_20.00%P1R4_20.00%dP0.35R8.5_2.00%API
F292: 50.00%Pol(2)_TB:DB,1:1_25.00%P1R4_25.00%dP1R4_2.00%API

Figure 3



F289: 40.00%Pol(2)_TB:DB,1:1_20.00%P1R4_20.00%dP1R4_2.00%API

F290: 40.00%Pol(3)_TB:DB,1:1_20.00%P1R4_10.00%dP1R4_10.00%dP0.35R8.5_2.00%API

F293: 40.00%Pol(2)_TB:DB,1:1_20.00%P1R4_20.00%dP1R4_4.00%API

F294: 40.00%Pol(2)_TB:DB,1:1_20.00%P1R4_20.00%dP1R4_6.00%API

Figure 4

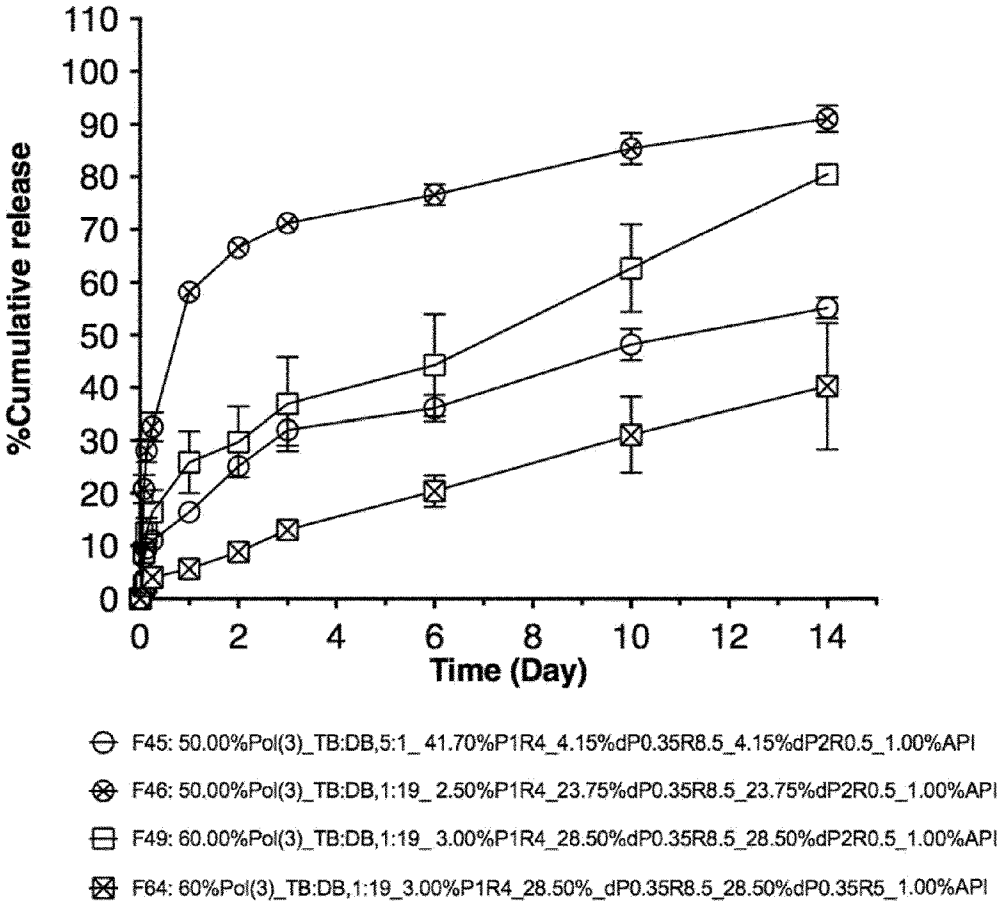
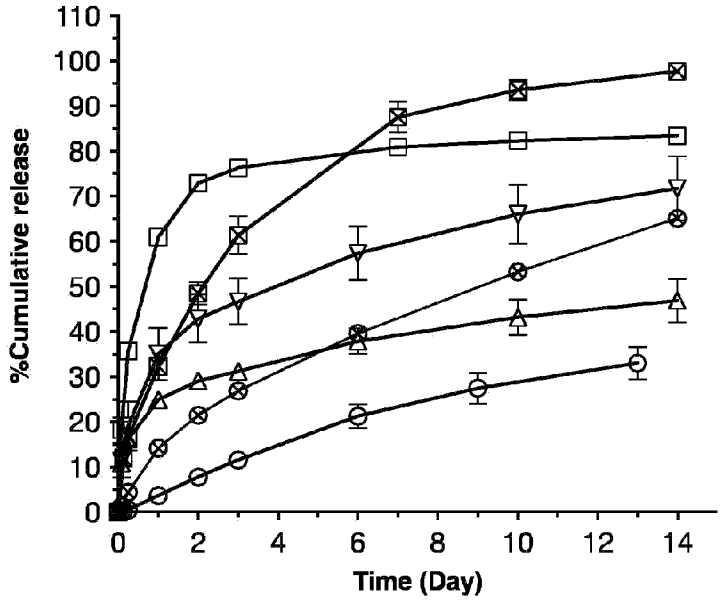

%Cumulative release
110
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
Time (Day)
F45: 50.00%Pol(3)_TB:DB,5:1_ 41.70%P1R4_4.15%dP0.35R8.5_4.15%dP2R0.5_1.00%API
F46: 50.00%Pol(3)_TB:DB,1:19_ 2.50%P1R4_23.75%dP0.35R8.5_23.75%dP2R0.5_1.00%API
F49: 60.00%Pol(3)_TB:DB,1:19_ 3.00%P1R4_28.50%dP0.35R8.5_28.50%dP2R0.5_1.00%API
F64: 60%Pol(3)_TB:DB,1:19_3.00%P1R4_28.50%_dP0.35R8.5_28.50%dP0.35R5_1.00%API

Figure 5



F105: 50.00%Pol(2)_TB:DB, 1:1.5_20.00%P2R3.5_30.00%dP0.35R8.5_1.00%API

F110: 25.00%Pol(2) TB:DB, 1:2 8.30%P2R3.5 16.70%dP2R3 1.00%API

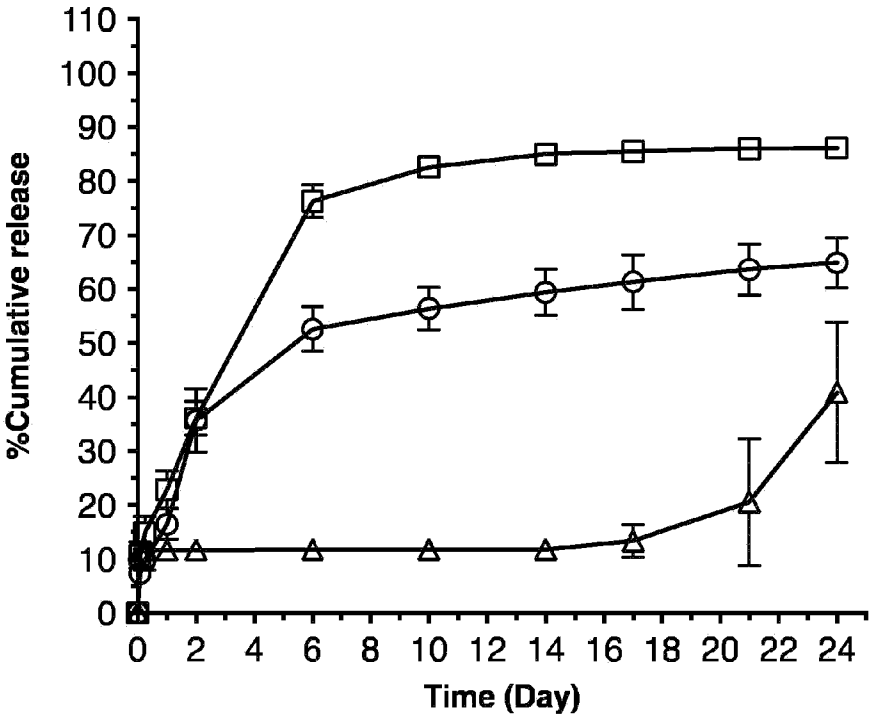
F115: 25.00%Pol(3)_TB:DB, 1:2_8.30%P2R3.5_8.30%dP0.16R1_8.30%dP2R10_1.00%API

F119: 50.00%Pol(3)_TB:DB, 1:1.5_10.00%P12R0.7_10.00%dP0.19R18_30.00%dP0.35R8.5_1.00%API

F124: 50.00%Pol(5)_TB:DB, 1:2_4.20%P1R4_4.20%P1R6_5.50%dP2R3_5.50%dP0.35R8.5_5.50%dP0.35R5_1.00%API

F126: 50.00%Pol(6)_TB:DB, 1:2_2.80%P1R4_2.80%P1R6_2.80%P2R3.5_5.50%dP2R3_5.50%dP0.35R8.5_5.50%dP0.35R5_1.00%API

Figure 6



F163: 40.00%Pol(4)_TB:DB, 1:1_10.00%P1R4_10.00%P1R6_10.00%dP1R4_10.00%dP0.35R8.5_4.00%API

F165: 40.00%Pol(2)_TB:DB, 1:1_20.00%P1R6_20.00%dP0.35R8.5_4.00%API

F166: 40.00%Pol(2)_TB:DB, 1:1_20.00%P1R4_20.00%dP1R4_4.00%API

Figure 7

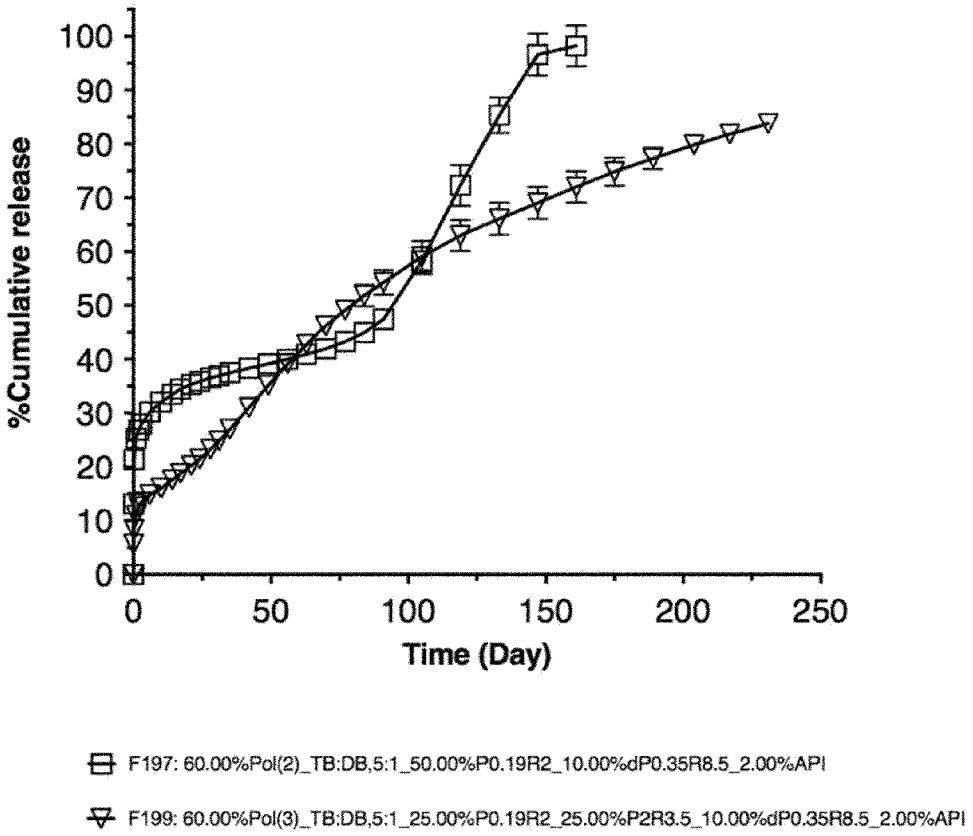
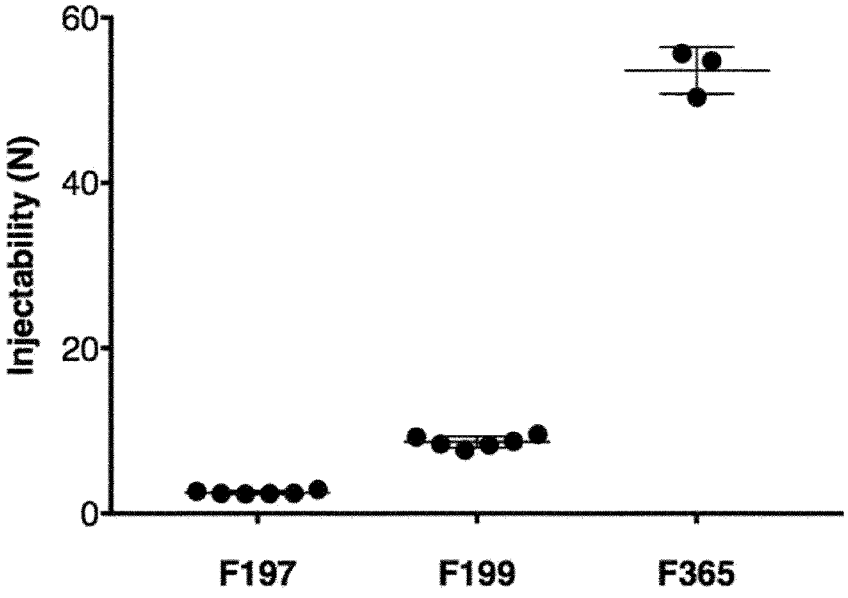

%Cumulative release
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
Time (Day)
F197: 60.00%Pol(2)_TB:DB,5:1_50.00%P0.19R2_10.00%dP0.35R8.5_2.00%API
F199: 60.00%Pol(3)_TB:DB,5:1_25.00%P0.19R2_25.00%P2R3.5_10.00%dP0.35R8.5_2.00%API

Figure 8



F197: 60.00%Pol(2)_TB:DB,5:1_50.00%P0.19R2_10.00%dP0.35R8.5_2.00%API

F199: 60.00%Pol(3)_TB:DB,5:1_25.00%P0.19R2_25.00%P2R3.5_10.00%dP0.35R8.5_2.00%API

F365: 60.00%Pol(2)_TB:DB,5:1_50.00%P2R3.5_10.00%dP0.35R8.5_2.00%API