BIODEGRADABLE DRUG DELIVERY FOR HYDROPHOBIC COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to 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 hydrophobic active principle one of which is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine. The ratio of triblock copolymer to diblock copolymer in this formulation is 1:3 to 1:8 or 1:1 to 1:19 or 3:2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1. Methods for producing these biodegradable drug compositions using organic solvents are also disclosed.

BACKGROUND OF THE PRESENT INVENTION

Drug delivery systems such as diblock and 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 solubility these drug formulations differ in polymer concentrations, types of polymers utilized, molecular weights of the polymers and solvents used in the formulations.

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.

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. More specifically this polymer composition has a polyester oligomer

having a molecular weight of between 400 and 10,000 daltons and a biodegradable AB-type, ABA-type or BAB type block copolymer. The hydrophobic A part is a polyester, while the hydrophilic B part is a polyethylene glycol having a molecular weight of between 2,400 and 4,999 daltons. This polymeric composition is soluble in an aqueous environment.

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, such as leptin. The sustained release is for a period of a week or more and preferably up to one month.

Hydrogels containing triblock copolymers are described in U.S. Patent 6,350,812. These hydrogels retain water weight at least equal to the water weight of the copolymer and are soft hydrogels.

U.S. Patent 7,875,677 provides micelle-forming compositions comprising a hydrophobic drug, a biocompatible block copolymer, which has a hydrophilic protein comprising a polyethylene oxide and a hydrophobic portion having a polyester and a biocompatible water soluble polymer, wherein the water soluble polymer is present in a sufficient amount to make the micelle-forming composition injectable.

It is well known in the art that poorly water soluble or hydrophobic drugs often result in slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. Hence, formulating hydrophobic drugs is a challenge well known in this art.

None of the patents nor the literature cited above describes drug delivery compositions that are injectable, *in situ* forming and are biodegradable and turn into solid implants when injected into the body and deliver pharmaceutically hydrophobic active principles . The biodegradable drug compositions of the present invention comprise triblock copolymers and diblock copolymers formulated in such a manner that the diblock copolymer serves as a reservoir while the triblock copolymer acts as a frame in the formulations and increases the lifespan of the diblock copolymer.

Furthermore, the biodegradable drug delivery compositions of the present invention can be long acting formulations, which reduce the initial burst release of the drug and modulate the release rate of the drug or hydrophobic drug over time. This phenomenon is illustrated in the flattening of the drug release curves.

SUMMARY OF THE INVENTION

The present invention provides a biodegradable drug delivery composition comprising(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, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (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 ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1:3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 in said biodegradable drug composition; and (c) at least one pharmaceutically active principle.

The present invention provides a biodegradable drug delivery composition comprising(a) a biodegradable triblock copolymer having the formula:

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wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (b) a biodegradable diblock copolymer having the formula:

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The present invention provides a biodegradable drug delivery composition comprising(a) a biodegradable triblock copolymer having the formula:

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The present invention provides a biodegradable drug delivery composition comprising(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, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units and v=x or v≠x; (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1: 3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 in said biodegradable drug composition; and (c) at least one pharmaceutically active principle.

The present invention provides a biodegradable drug delivery composition comprising(a) a biodegradable triblock copolymer having the formula:

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wherein A is a polyester and C is an end-capped polyethylene glycol and y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1: 3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 in said biodegradable drug composition; and (c) at least one pharmaceutically active principle.

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wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090, v and x being ester repeat units

and w being ethylene oxide repeat units and v=x or v≠x; (b) a biodegradable diblock copolymer having the formula:

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wherein A is a polyester and C is an end-capped polyethylene glycol and y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1: 3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 in said biodegradable drug composition; and (c) at least one pharmaceutically hydrophobic active principle.

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A biodegradable drug delivery composition comprising:(a) a biodegradable triblock copolymer having the formula:

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

wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (b) a biodegradable diblock copolymer having the formula:

$$PEG_y\text{-}PLA_z$$

wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1:3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 in said biodegradable drug composition and wherein the PEG in the diblock is end-capped; and (c) at least one pharmaceutically active principle.

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wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (b) a biodegradable diblock copolymer having the formula:

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wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1:3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 in said biodegradable drug composition and wherein the PEG in the diblock is end-capped; and (c) at least one pharmaceutically active principle.

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PEG_y-PLA_z

wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1:3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 in said biodegradable drug composition and wherein the PEG in the diblock is end-capped; and (c) at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine.

A biodegradable drug delivery composition comprising:(a) a biodegradable triblock copolymer having the formula:

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wherein v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090 v and x being ester repeat units and w being ethylene oxide repeat units and v=x or v≠x; (b) a biodegradable diblock copolymer having the formula:

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wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1:3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 in said biodegradable drug composition and wherein the PEG in the diblock is end-capped; and (c) at least one pharmaceutically active principle

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wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the

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In yet another aspect a biodegradable drug delivery composition is provided, which comprises:(a) a biodegradable triblock copolymer present in an amount of 3% to 45% (w%/w%) of the total composition having the formula:

PLA_v-PEG_w-PLA_x

wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (b) a biodegradable diblock copolymer present in an amount of 8.0% to 50% (w%/w%) of the total composition having the formula:

PEG_y-PLA_z

wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1:3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 in said biodegradable drug composition and wherein the PEG in the diblock is end capped and (c) at least one pharmaceutically active principle is present in an amount of 1% to 20% (w%/w%) of the total composition or the at least one pharmaceutically active principle is present in an amount of 1 to 200 mg/ml.

In yet another aspect a biodegradable drug delivery composition is provided, which comprises:(a) a biodegradable triblock copolymer present in an amount of 3% to 45% (w%/w%) or 2% to 45% (w%/w%) or 1.2% to 30% (w%/w%) of the total composition having the formula:

PLA_v-PEG_w-PLA_x

wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (b) a biodegradable diblock copolymer present in an amount of 8.0% to 50% (w%/w%) or 1% to 28% (w%/w%) of the total composition having the formula:

PEG_y-PLA_z

wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1:3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 in said biodegradable drug composition and wherein the PEG in the diblock is end capped and (c) at least one pharmaceutically active principle is present in an amount of 1% to 20% (w%/w%) of the total composition or the at least one pharmaceutically active principle is present in an amount of 1 to 200 mg/ml.

In yet another aspect a biodegradable drug delivery composition is provided, which comprises:(a) a biodegradable triblock copolymer present in an amount of 3.0% to 45% (w%/w%) or 2% to 45% (w%/w%) or 1.2% to 30% (w%/w%)of the total composition having the formula:

PLA_v-PEG_w-PLA_x

wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (b) a biodegradable diblock copolymer present in an amount of 8.0% to 50% (w%/w%) or 1% to 28% (w%/w%) of the total composition having the formula:

PEG_y-PLA_z

wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1:3 to 1:8 or 1: 1 to 1:19 or 3:2 to 1:19 or 2:3 or 4:1 in said biodegradable drug composition and wherein the PEG in the diblock is end capped and (c) at least one pharmaceutically hydrophobic active principle is present in an amount of 1% to 20% (w%/w%) of the total composition or the at least one pharmaceutically active principle is present in an amount of 1 to 200 mg/ml.

In yet another aspect a biodegradable drug delivery composition is provided, which comprises:(a) a biodegradable triblock copolymer present in an amount of 3.0% to 45% (w%/w%) or 2.0% to 45% (w%/w%) or 1.2% to 30% (w%/w%)of the total composition having the formula:

PLA_v-PEG_w-PLA_x

wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (b) a biodegradable diblock copolymer present in an amount of 8.0% to 50% (w%/w%) or 1% to 28% (w%/w%) of the total composition having the formula:

PEG_y-PLA_z

wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1: 3 to 1:8 or 3:2 to 1:19 or 1:1 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 in said biodegradable drug composition and wherein the PEG

in the diblock is end capped and (c) at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine. is present in an amount of 10% to 40% (w%/w%) or 1% to 40% (w%/w%)of the total composition or the at least one pharmaceutically active principle is present in an amount of 1 to 200 mg/ml or 0.1 to 200 mg/ml.

The biodegradable drug delivery compositions of the invention can have a lactic acid to ethylene oxide molar ratio in the composition of between 0.5 to 3.5 or from 0.5 to 2.5 or 0.5 to 22.3 for the triblock copolymer and between 2 to 6 or 0.8 to 13 for the diblock copolymer.

In another aspect the biodegradable drug delivery compositions of the invention can have a lactic acid to ethylene oxide molar ratio in the composition of between 0.5 to 22.3 for the triblock copolymer and between 0.8 to 13 for the diblock copolymer.

In yet another aspect the biodegradable drug delivery compositions of the invention can have a lactic acid to ethylene oxide molar ratio in the composition of between 0.5 to 2.5 for the triblock copolymer and between 3 to 5 for the diblock copolymer.

In one aspect the biodegradable drug delivery composition is an injectable liquid that when it is inserted into the body of an animal or plant becomes a hardened implant.

In yet another aspect the biodegradable delivery drug composition can be used as a spatial formulation such that it can be applied onto or inside the body of an animal or plant. For example, it can be dispensed during surgery to treat a wound or inside a plant to treat a virus.

In another aspect the biodegradable drug composition is prepared as small solid particles, which are placed directly on the injured site of the body of an animal or plant.

In another aspect the biodegradable drug composition is in the form of a rod implant.

A method for preparing the biodegradable drug delivery composition of the invention, said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090 wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1:19 (a):(b) to form a polymer mixture; and
(ii) adding at least one pharmaceutically active principle to said polymer mixture, is yet another aspect of the invention.

A method for preparing the biodegradable drug delivery composition of the invention, said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090 wherein v=x or v≠x; and (b) a biodegradable diblock copolymer having the formula:

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wherein A is a polyester and C is an end-capped polyethylene glycol and y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3.2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 (a):(b) to form a polymer mixture; and

(ii) adding at least one pharmaceutically hydrophobic active principle to said polymer mixture, is yet another aspect of the invention.

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wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090 wherein v=x or v≠x; and (b) a biodegradable diblock copolymer having the formula:

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wherein A is a polyester and C is an end-capped polyethylene glycol and y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3.2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 (a):(b) to form a polymer mixture; and

(ii) adding at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine to said polymer mixture, is yet another aspect of the invention.

Yet another aspect of the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1060 wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3.2 to 1:19 in (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically active principle to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect of the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1060 wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3.2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 in (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically active principle to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect of the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method

comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1060 wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3.2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 in (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically hydrophobic active principle to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect of the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090 wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3.2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 in (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect of the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3.2 to 1:19 (a):b) to form a polymer mixture; (ii) adding at least one pharmaceutically active principle to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect of the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3.2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 (a):b) to form a polymer mixture; (ii) adding at least one pharmaceutically active principle to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect of the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3.2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 (a):b) to form a polymer mixture; (ii) adding at least one pharmaceutically hydrophobic active principle to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect of the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090 or 4 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3.2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1 (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine to said polymer mixture; and (iii) evaporating said solvent.

In the above methods the organic solvent can be present in an amount of 40% to 74% (w%/w%) or 30% to 70% (w%/w%) or 26% to 90% (w%/w%) of the total composition. Mixtures of solvents can also be used.

Other aspects and embodiments are set forth below, or will readily arise from the following description of the preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the *in vitro* release rate of the drug from formulations based on 40% P6R1(TB):dP2R4(DB) in ratios of 1:0 (-○-), 1:2 (-Δ-), 1:4 (-●-), 1:6 (-▼-) and 1:9 (-*-) over time in days. This graph shows that formulations based on TB:DB are sustaining the release for more than 30 days.

Fig. 2 is a graph showing the *in vitro* cumulative percent release curve from candidate formulations of Figure 1 over time (days). This graph illustrates that the initial burst is reduced and the drug release curve is flattened in the combination of triblock copolymer and diblock copolymer compositions compared to the triblock copolymer composition alone. It should be noted that the 1:9 curve is overlapping the 1:4 curve.

Fig. 3 is a graph showing the injectability of formulations based on 40% P6R1 (TB);dP2R4(DB) in various ratios ranging from 1:0 triblock copolymer to diblock copolymer to 0:1 triblock copolymer to diblock copolymer. This graph illustrates that all formulations are injectable using a classical injection device.

Fig. 4 is a graph showing the *in vitro* cumulative percentage release curve from candidate formulations over time (days) of various compositions of the invention. The compositions described as numbers 177, 246, 224, 225 and 250 are described in Table1.

Fig. 5 is a graph showing the *in vitro* release rate from candidate formulations in micrograms per hour per gram of formulation (µg/h/gr of formulation) The compositions described as numbers 177, 246, 224, 225 and 250 are described in Table1.

Fig. 6 is a graph showing the M53 plasma concentration in nanograms per milliliter (ng/ml) over time in days. Day zero is the day that the composition was

administered subcutaneously. The compositions indicated as numbers 177, 246, 224, 225 and 250 are described in Table1.

Fig. 7 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P0.2R5 (4 units of ethylene oxide and 24 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 8 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P0.2R14 (4 units of ethylene oxide and 58 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 9 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P0.2R22 (4 units of ethylene oxide and 89 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 10 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P0.4R4 (9 units of ethylene oxide and 41 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 11 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P0.4R7 (9 units of ethylene oxide and 67 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 12 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P0.6R1 (13 units of ethylene oxide and 26 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 13 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P0.6R3 (13 units of ethylene oxide and 40 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 14 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P0.6R4 (13 units of ethylene oxide and 55 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 15 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P1R2 (22 units of ethylene oxide and 47 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 16 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P1R3 (22 units of ethylene oxide and 68 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 17 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P1R4 (22 units of ethylene oxide and 88 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 18 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P2R2 (45 units of ethylene oxide and 88 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 19 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblockco polymer P2R3 (45 units of ethylene oxide and 157 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 20 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P2R5 (45 units of ethylene oxide and 216 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 21 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P3R1 (68 units of ethylene oxide and 66 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 22 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P3R2 (68 units of ethylene oxide and 154 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 23 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P3R3 (68 units of ethylene oxide and 218 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 24 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P6R0.9 (136 units of ethylene oxide and 125 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 25 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P6R1.6 (136 units of ethylene oxide and 218 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 26 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer

P6R2 (136 units of ethylene oxide and 272 units of lactic acid) mixed with various diblock copolymers (see Table 2 for details).

Fig. 27 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P2R4 (45 units of ethylene oxide and 157 units of lactic acid) mixed with diblock copolymer dP0.4R6 (7 units of ethylene oxide and 42 units of lactic acid) at different ratios (see Table 2 for details).

Fig. 28 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P2R4 (45 units of ethylene oxide and 157 units of lactic acid) mixed with diblock copolymer dP0.6R5 (12 units of ethylene oxide and 54 units of lactic acid) at different ratios (see Table 2 for details).

Fig. 29 is a graph showing the *in vitro* cumulative percent release of acetaminophen over time (days) from formulations based on triblock copolymer P2R5 (45 units of ethylene oxide and 216 units of lactic acid) mixed with diblock copolymer dP0.2R13 (3 units of ethylene oxide and 39 units of lactic acid) at different ratios (see Table 2 for details).

Fig. 30 is a graph showing the *in vitro* release rate of buprenorphine over time (days) from formulations n°33 (10%BN/ 8%P2R2/ 32%dP0.4R10), n°47 (10%BN/ 8%P2R2/ 32%dP1R3) and n°58 (10%BN/ 10%P0.4R8/ 40%dP1R2).

Fig. 31 is a graph showing the plasma concentration of buprenorphine over time (days) in rats injected with formulations n°33 (10%BN/ 8%P2R2/ 32%dP0.4R10), n°47 (10%BN/ 8%P2R2/ 32%dP1R3) and n°58 (10%BN/ 10%P0.4R8/ 40%dP1R2).

Fig. 32 is a graph showing the *in vitro* release rate of risperidone over time (days) from formulations based on triblock polymer P2R5 (45 units of ethylene oxide and 216 units of lactic acid) mixed with diblock polymer dP0.2R13 (3 units of ethylene oxide and 39 units of lactic acid) at different ratios (see Table 2 for details).

Fig. 33 is a graph showing the plasma concentration of risperidone and 9-OH risperidone over time (days) in rats injected with formulations n°10 (5%RSP/ 16%P2R2/ 24%dP2R2/ DMSO), n°29 (10%RSP/ 24%P1R4/ 16%dP0.4R5/ DMSO) and n°31 (10%RSP/ 18%P2R4/ 12%dP0.4R5/ DMSO).

Fig. 34 is a graph showing the plasma concentration of ivermectin over time (days) in dogs injected with formulations n°7 (5%IVM/ 15%P3R3/ 25%dP0.4R5/ DMSO), n°9 (5%IVM/ 15%P2R4/ 25%dP2R3/ DMSO) and n°10 (5%IVM/ 15%P2R5/ 25%dP2R2/ DMSO).

Fig. 35 is a graph showing the *in vitro* release rate of medroxyprogesterone acetate (MPA) from candidate formulations in milligrams per gram of formulation per day (mg MPA/gr of formulation/day) The formulations described as numbers 33, 34 and 49 as described in Table 6. *In vitro* release obtained with Depo-SubQ Provera is shown as a control.

Fig. 36 is a graph showing the *in vitro* cumulative percent release of medroxyprogesterone acetate over time (days) from formulations described 33, 34 and 49 as described in Table 6. *In vitro* release obtained with Depo-SubQ Provera is shown as a control.

Fig. 37 is a graph showing the *in vitro* release rate of medroxyprogesterone acetate from candidate formulations in milligrams per gram of formulation per day (mg/gr of formulation/day) The formulations described as numbers 12, 32 and 36 are described in Table 6. In vitro release obtained with Depo-SubQ Provera is shown as a control.

Fig. 38 is a graph showing the *in vitro* cumulative percent release of medroxyprogesterone acetate from formulations described 12, 32 and 36 per days are described in Table 6. *In vitro* release obtained with Depo-SubQ Provera is shown as a control.

Fig. 39 is a graph showing the plasma concentration of medroxyprogesterone acetate (MPA) in female dogs over time (days) injected with formulations 33, 34 and 49 described in Table 6. Each dog received a single 3 mg/kg dose of MPA.

Fig. 40 is a graph showing the plasma concentration of medroxyprogesterone acetate (MPA) in dogs over time (days) injected with formulations 12, 32 and 36 are described in Table 6. For formulations 32, 36 and the control group (receiving Depo-subQ-Provera), each dog received a single 3 mg/kg MPA dose. The group receiving formulation 12 was dosed at 6 mg/kg MPA.

Fig. 41 is a graph showing the *in vitro* percent total release of medroxyprogesterone acetate (MPA) over time (days) from formulations 7, 10 and 13 described in Table 6.

Fig. 42 is a graph showing the *in vitro* percent total release of medroxyprogesterone acetate (MPA) over time (days) from formulations 32 and 33 described in Table 6.

Fig 43 is a graph showing the *in vitro* percent total release of medroxyprogesterone acetate (MPA) over time (days) from formulations 25, 27 and 30 described in Table 6.

Fig 44 is a graph showing the *in vitro* percent total release of progesterone (Pro) over time (days) from formulations 11, 13 and 7 described in Table 7.

Fig. 45 is a graph showing the *in vitro* percent total release of progesterone (Pro) over time (days) from formulations 10, 12 and 5 described in Table 7 .

Fig. 46 is a graph showing the *in vitro* percent total release of Levonorgestrel (Levo) over time (days) from formulations 7, 8 and 9 described in Table 8.

Fig 47 is a graph showing the *in vitro* percent total release of Levonorgestrel (Levo) over time (days) from formulations 4, 5 and 6 described in Table 8.

Fig. 48 Fig 42 is a graph showing the *in vitro* percent total release of cyclosporine (CSP) over time (days) from formulations 19, 20, 21, 22, 23 and 24 described in Table 9.

Fig. 49 is a graph showing the *in vitro* percent total release of Bupivacaine base (Bupi) over time (days) from formulations based on formulations 42, 47, 37, 35 and 34 described in Table 10.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

As used herein the term "biodegradable" means that the triblock and diblock copolymers will after a period of time erode or degrade *in vivo* to form smaller non-toxic components.

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.

The term "animals" encompasses all members of the Kingdom Animalia.

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

"Active principle" means a drug or medicine for treating various medical illnesses. Thus active principles, drugs and medicines are used interchangeably. The term drug or active principle 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 principle is present in the biodegradable drug composition of the invention.

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

The term "implant" means that the drug delivery compositions are injectable, are *in situ* forming and are biodegradable and turn into solid implants when injected into the body. Thus, that the formulations that are synthesized are liquids such that they can be easily injected through a syringe without excessive force.

The term "spatial formulations" encompass any formulations that can be applied on or into the animal or plant body and do not necessarily have to be administered through a syringe.

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

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.

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.

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

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

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

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

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

As used herein the term "partial suspension" means that the pharmaceutically active principle is in a partly soluble and partly solid form.

As used herein "hydrophobic" when referring to the pharmaceutically active principles means drugs that have poor solubility in aqueous solutions. The International Union of Pure and Applied Chemistry (IUPAC) defines solubility as "the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent." A substance is said to be soluble if more than 0.1 g of that substance dissolves in 100 ml of distilled water at 250°C. If less than 0.1 g dissolves in 100 ml of distilled water at 250°C the substance is sparingly soluble or insoluble at a particular temperature.

The LA/EO ratio refers to the molar ratio of lactic acid units to ethylene oxide units that is present in the biodegradable drug delivery composition. It is determined experimentally by NMR. The LA/EO molar ratio of the combined triblock copolymer can range from 0.5 to 3.5. In another aspect the LA/EO molar ratio in the triblock can range from 0.5 to 2.5 in the biodegradable drug delivery composition described herein. In yet another aspect the LA/EO ratio in the triblock can range from 0.5 to 22.3.

The LA/EO ratio in the diblock can range from 2 to 6. In another aspect the LA/EO ratio in the diblock can range from 3 to 5 in the biodegradable drug delivery composition. In another aspect the LA/EO ratio in the diblock can range from 0.8 to 13.

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 is about 45 to 170 or it can be 4 to 273 or 3 to 45 or 0.55 to 68, while for PLA it can range from about 84 to 327 or it can be 24 to 682 or 7 to 327 or 39.9 to 170.

The present invention thus relates to a biodegradable drug composition comprising a triblock copolymer and a diblock copolymer. 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, w and x are the number of repeat units ranging, for example, from 4 to 1090 or from 6 to 1090 and v=x or v≠x. w is the degree of polymerization (number of repeat units) for PEG. The degree of polymerization for DP-PEG is calculated by dividing the PEG molecular weight by the EO unit molecular weight (44 Da). v + x equals the degree of polymerization (number of repeat units) for PLA. DP-PLA is calculated by multiplying DP-PEG by the LA/EO ratio.

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 principle and the type of active principle itself. Therefore the number of repeat units in the triblock of v, w and x can range from 4 to 1090 or from 6 to 1090 or from 8 to 1090, from 10 to 850, from 20 to 700, from 30 to 650 and v=x or v≠x. For instance, w can be 273, while x + y can be 682 and v=x or v≠x or w can be 136 and x + y can be 273 and v=x or v≠x or w can be 45.5 and x + y can be 546 or w can be 273 and x + y can be 136.

The size of the PEG in the triblock can range from 194 Da to 12,000 Da.

The polyester in the triblock can be polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA) or polyhydroxyalkanoate (PHA). In one embodiment the polyester that is used is polylactic acid.

The triblock copolymer is then combined with 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 ranging from 7 to 371 or from 3 to 327 or 3 to 237. This combination has a ratio of triblock copolymer to diblock copolymer ranging from 1:3 to 1:8 or 1:1 to 1:19 or 3:2 to 1:19 or 2:3 or 4:1 or 2.3 to 4.1.

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.

However 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 7 to 43 or 3 to 45 or 0.55 to 68 and z can range from 32 to 123 or 7 to 327 or 39.9 to 170. For example, y can be 25 and z can be 123, y can be 34.5 and z can be 123 or y can be 45 and z can 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 LA/EO ratio.

The polyester in the diblock can be polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA) or polyhydroxyalkanoate (PHA). In one embodiment the polyester that is used is polylactic acid. In another embodiment the polyester is poly(lactic-co-glycolic acid).

In another aspect the present invention provides a biodegradable drug delivery composition comprising(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, w and x the number of are repeat units ranging from 4 to 1090 or from 6 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units and v=x or v≠x; (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 in said biodegradable drug composition; and (c) at least one pharmaceutically active principle.

In another aspect the present invention provides a biodegradable drug delivery composition comprising(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, w and x the number of are repeat units ranging from 4 to 1090 or from 6 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units and v=x or v≠x; (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 or 2:3 or 4:1 or 2.3 to 4.1 in said biodegradable drug composition; and (c) at least one pharmaceutically hydrophobic active principle.

In another aspect the present invention provides a biodegradable drug delivery composition comprising(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, w and x the number of are repeat units ranging from 4 to 1090 or from 6 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units and v=x or v≠x; (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 or 2:3 or 4:1 or 2.3 to 4.1 in said biodegradable drug composition; and (c) at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine.

In another aspect the present invention provides a biodegradable drug delivery composition comprising a biodegradable triblock copolymer having the formula: PLA_v-PEG_w-PLA_x, wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; a biodegradable diblock copolymer having the formula: $mPEG_y$-PLA_z, wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 327, wherein the ratio of the biodegradable triblock copolymer and the biodegradable diblock copolymer is 1: 6 in said biodegradable drug composition; and at least one pharmaceutically active principle.

In another aspect the present invention provides a biodegradable drug delivery composition comprising a biodegradable triblock copolymer having the formula: PLA_v-PEG_w-PLA_x, wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; a biodegradable diblock copolymer having the formula: $mPEG_y$-PLA_z, wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 327, wherein the ratio of the biodegradable triblock copolymer and the biodegradable diblock copolymer is 1: 6 in said biodegradable drug composition; and at least one pharmaceutically hydrophobic active principle.

In another aspect the present invention provides a biodegradable drug delivery composition comprising a biodegradable triblock copolymer having the formula: PLA_v-PEG_w-PLA_x, wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; a biodegradable diblock copolymer having the formula: $mPEG_y$-PLA_z, wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 327, wherein the ratio of the biodegradable triblock copolymer and the biodegradable diblock copolymer is 1: 6 or 2:3 or 3:2 or 4:1 or 2.3 to 4.1 in said biodegradable drug composition; and at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate levonorgestrel, cyclosporine, progesterone or bupivacaine.

In another aspect a biodegradable drug delivery composition comprising:(a) a biodegradable triblock copolymer having the formula:

PLA_v-PEG_w-PLA_x

wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (b) a biodegradable diblock copolymer having the formula:

$mPEG_y$-PLA_z

wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1: 4 in said biodegradable drug composition; and (c) at least one pharmaceutically active principle.

In another aspect a biodegradable drug delivery composition comprising:(a) a biodegradable triblock copolymer having the formula:

PLA_v-PEG_w-PLA_x

wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (b) a biodegradable diblock copolymer having the formula:

$mPEG_y$-PLA_z

wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1: 4 in said biodegradable drug composition; and (c) at least one pharmaceutically hydrophobic active principle.

In another aspect a biodegradable drug delivery composition comprising:(a) a biodegradable triblock copolymer having the formula:

PLA_v-PEG_w-PLA_x

wherein v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x; (b) a biodegradable diblock copolymer having the formula:

$mPEG_y$-PLA_z

wherein y and z are the number of repeat units ranging from 7 to 371 or 3 to 237, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 1: 4 or 2:3 or 3:2 or 4:1 or 2.3 to 4.1 in said biodegradable drug composition; and (c) at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine.

The ratio of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1: 3 to 1: 8 or 1:1 to 1:19 or 3:2 to 1:19 in said biodegradable drug composition. In one embodiment the ratio of the biodegradable triblock copolymer of and the biodegradable CA diblock copolymer is selected from the group of 1:3, 1:4, 1:5, 1:6, 1:7 and 1:8 or 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:11, 1:12, 1:13, 1:14, 1:15, 1:16, 1:17, 1:18 and 1:19. It can also be 3:2 or 2:3 or 4:1. In another aspect the ratio of the triblock to the diblock is 1:6.

The length of the polyester chain is defined by its polyester to ethylene oxide molar ratio, which is between 0.5 to 3.5 or 0.5 to 2.5 or 0.5 to 22.3 for the triblock copolymer and 3 to 5 or 2 to 6 or 0.8 to 13 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 ratio of LA + G/EO.

The mass of the end-capped polyethylene glycol can range from 164 Da to 2,000 Da or from 100 Da to 2 kDa. It can range in the lower 100 to 300 Da range or in the 1 kDa to 2 kDa range.

The size of the polyethylene glycol chain ranges from 200 Da to 12 kDa in the biodegradable drug delivery composition or it can range from 400 Da to 12 kDa or 194 Da to 12 kDA.

The polymers are present in an amount of 20% to 50% (w%/w%) of the total weight of the composition. In another aspect the total weight of the polymers present in the biodegradable drug composition is 30% to 50% (w%/w%) of the total weight of the composition. In yet another aspect the polymers are present in the biodegradable drug composition at 40% to 50% (w%/w%) of the total weight of the composition. In another aspect the polymers are present in an amount of 5% to 40% (w%/w%) of the total composition or 5% to 50% (w%/w%) of the total composition. In yet another aspect the polymers are present in the biodegradable drug composition

at 2.5% to 40% (w%/w%) or 2.5% to 50% (w%/w%) of the total weight of the composition.

Thus, the triblock copolymer is present in an amount of 3.0% 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 copolymer is present in an amount of 1.2 % to 30% (w%/w%) of the total weight of the composition or 1.2% to 45% (w%/w%) of the total weight of the composition.

In another embodiment the triblock copolymer is present in 3.3% to 4.0% (w%/w%) or 3.5% (w%) or 4.0% (w%) or 1.9% to 4.0%(w%/w%) of the total weight of the composition.

Likewise the diblock copolymer can be present in the biodegradable drug composition in an amount of 8% to 50% (w%/w%) of the total weight of the composition. In another aspect the diblock copolymer is present in an amount of 10% to 20% (w%/w%) of the total weight of the composition. In yet another aspect the diblock copolymer is present in an amount of 20% to 40% (w%/w%) of the total weight of the composition. In yet another aspect the diblock copolymer is present in an amount of 1% to 28% (w%/w%) of the total weight of the composition or 1% to 50% (w%/w%) of the total weight of composition.

In yet another embodiment the diblock is present in an amount of 2.48% to 5.02% (w%/w%) or 2.3% to 5.4% (w%/w%) or 2.5% to 5.1% (w%/w%) or 2.3% (w%) or 2.3% to 5.8% (w%/w%) of the total weight of the composition.

The at least one pharmaceutically active principle is entrapped in the triblock:diblock biodegradable drug delivery composition. 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, antibiotics, antimicrobials, antiallergenics, anti-diabetics,

steroidal anti-inflammatory agents, decongestants, miotics, anticholinergics, sympathomimetics, sedatives, hypnotics, psychic energizers, tranquilizers, androgenic steroids, estrogens, progestational agents, medroxyprogesterone acetate, 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 and the benzophenanthridine alkaloids.

Thus combinations of drugs can also 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.

In an embodiment the pharmaceutically active principle is a hydrophobic drug having a low solubility or is insoluble in aqueous solutions. Hydrophpbioc drugs are described herein and include, for example, amphotericin, anthralin, beclomethasone, betamethasone, camptothecin, curcumin, dexamethasone, genistein, indomethacin, lidocaine, taxol, tetracycline, tretinoin, therapeutic proteins that are insoluble in water and the like. In one embodiment the pharmaceutically active principle is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine.

Veterinary medicaments such as medicines for the treatment of worms or vaccines for animals are also part of the present invention. Hydrophobic veterinary drugs can also be formulated in the biodegradable drug compositions as described herein.

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.

Hydrophobic viral medicaments for plants can also be formulated in the biodegradable drug compositions as described herein.

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.

The pharmaceutically effective amount of an active principle or hydrophobic active principle may vary depending on the active principle, the extent of the animal's or plants medical condition and the time required to deliver the active principle or hydrophobic active principle. There is no critical upper limit on the amount of active principle or hydrophobic active principle 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 principle or hydrophobic active principle incorporated into the delivery system is dependent simply upon the activity of the active principle or hydrophobic active principle and the length of time needed for treatment.

For instance some active principles or hydrophobic active principles may be present in the biodegradable drug delivery composition from 10 to 200 mg/ml. In another aspect the drugs should be present in the amount of 10 to 40 µg/ml. . In another aspect the drugs should be present in the amount of 10 to 500 mg/ml. For a small molecule, for instance, the active principle can be loaded as high as 100 to 200 mg per ml.

Generally the pharmaceutically active principle is present in an amount of 1 % to 20% (w%/w%) of the total weight of the composition. In another aspect the active principle is present in 1% to 4% (w%/w%) of the total weight of the composition. In another aspect the active principle is present in 2% to 4% (w%/w%) of the total

weight of the composition. In yet another aspect the active principle, which is a small molecule, is present in an amount of 10% to 20% (w%/w%) of the total weight of the composition. In another aspect the active principle is present in an amount of 10% to 40% (w%/w%) of the total composition. In another embodiment the pharmaceutically active hydrophobic active principle is present in the amounts of 1% to 40% (w%/w%).

As examples, the medroxyprogesterone acetate can be present in an amount of 10% to 40% (w%/w%) of the total weight of the biodegradable drug delivery compositions; the progesterone can be present in an amount of 20% to 40% (w%/w%) of the total weight of the biodegradable drug delivery compositions; the cyclosporine can be present in an amount of 5% to 21.1% (w%/w%) of the total weight of the biodegradable drug delivery compositions; levonorgestrel can be present in an amount of 10% to 20% (w%/w%) of the total weight of the biodegradable drug delivery compositions; and the bupivacaine can be present in an amount of 1% to 15% (w%/w%) of the total weight of the biodegradable drug delivery compositions.

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. Thus, the higher the lactic acid content of the triblock and diblock copolymers in comparison with the polyethylene glycol content, as well as the amount of triblock and diblock copolymers present in the biodegradable drug composition the longer the release of the active principle or hydrophobic active principle or drug. In other words, the higher the LA/EO molar ratio and the greater weight percentage of the triblock and diblock copolymers, the longer it will take for the active principle or hydrophobic active principle to be released from the drug composition.

The active principle or hydrophobic active principle can be released for a duration of between 7 days to 1 year or longer depending upon the type of treatment needed and the biodegradable drug delivery composition used. In one aspect the biodegradable drug delivery composition can deliver the active principle or

hydrophobic active principle for at least 7 days. In another aspect the biodegradable drug delivery composition can deliver the active principle or hydrophobic active principle for at least 30 days. In one aspect the biodegradable drug delivery composition can deliver the active principle or hydrophobic active principle for at least 90 days. In yet another aspect the biodegradable drug delivery composition can deliver an active principle or hydrophobic active principle for 1 year or longer.

The biodegradable drug delivery composition can be an injectable liquid or a partial suspension at room temperature and be injected through a syringe without excessive force. But these biodegradable drug delivery compositions are also *in situ* forming and biodegradable and turn into solid implants when injected into the animal or plant. Alternatively the biodegradable drug composition is produced as a solid, prepared as small particles and used as a powder which is sprinkled on the injured site. 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 delivery drug 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. In another aspect the biodegradable drug composition can be produced as a partial suspension, the drug being in between the state of being partly soluble and partly solid.

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 diblock copolymer and triblock copolymer.

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.

The vehicle can be any diluent, additional solvent, filler or binder that may alter the delivery of the active principle 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 deliver 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 17.0% (w%/w%). In another aspect tripropionin (abbreviated herein as Tripro) can be added at 16% (w%/w%). In yet another aspect benzyl alcohol can be added at 15% to 35% (w%/w%).

A method for preparing the biodegradable drug delivery composition of the invention is also encompassed by the invention. This method comprises: (i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula: A_v-B_w-A_x, wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090; and (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 ranging from 7 to 371or 3 to 237 in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 triblock to diblock to form a polymer mixture; and adding at least one pharmaceutically active principle to said polymer mixture.

A method for preparing the biodegradable drug delivery composition of the invention is also encompassed by the invention. This method comprises: (i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula: A_v-B_w-A_x, wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090; and (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 ranging from 7 to 371or 3 to 237 in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 or 2:3 or 4:1 triblock to diblock to form a polymer mixture; and adding at least one pharmaceutically hydrophobic active principle to said polymer mixture.

A method for preparing the biodegradable drug delivery composition of the invention is also encompassed by the invention. This method comprises: (i)

dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090; and (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 ranging from 7 to 371or 3 to 237 in a ratio of1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 or 2:3 or 4:1 or 2.3 to 4.1triblock to diblock to form a polymer mixture; and adding at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine to said polymer mixture.

A method for preparing the biodegradable drug delivery composition of the invention, said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 (a):(b) to form a polymer mixture; and
(ii) adding at least one pharmaceutically active principle to said polymer mixture, is yet another aspect of the invention.

A method for preparing the biodegradable drug delivery composition of the invention, said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 or 2:3 or 4:1 or 2.3 to 4.1 (a):(b) to form a polymer mixture; and

(ii) adding at least one pharmaceutically hydrophobic active principle to said polymer mixture, is yet another aspect of the invention.

A method for preparing the biodegradable drug delivery composition of the invention, said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 or 2:3 or 4:1 or 2.3 to 4.1 (a):(b) to form a polymer mixture; and

(ii) adding at least one pharmaceutically active principle one of which is medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine to said polymer mixture, is yet another aspect of the invention.

Yet another aspect the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 137 in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically active principle to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 137 in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 or 2:3 or 4:1 or 2.3 to 4.1 (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically hydrophobic active principle to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method

comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 137 in a ratio of 1: 3 to 1:8 or 1:1 to 1:19 or 3:2 to 1 :19 or 2:3 or 4:1 or 2.3 to 4.1 (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate levonorgestrel, cyclosporine, progesterone or bupivacaine to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

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

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 1:4 (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically active principle to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 1:4 (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically hydrophobic active principle to said polymer mixture; and (iii) evaporating said solvent.

Yet another aspect the present invention provides a method for preparing the biodegradable drug delivery composition of the present invention said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 6 to 1090, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (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 ranging from 7 to 371 or 3 to 237, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 1:4 or 2:3 or 3:2 or 4:1 (a):(b) to form a polymer mixture; (ii) adding at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate levonorgestrel, cyclosporine, progesterone or bupivacaine to said polymer mixture; and (iii) evaporating said solvent.

Another embodiment provides a method for preparing the biodegradable drug delivery composition of the invention, said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

A_v-B_w-A_x, wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090; and (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 ranging from 7 to 371 or 3 to 237 in a ratio of 1:6 triblock to diblock to form a polymer mixture; adding at least one pharmaceutically active principle to said polymer mixture; and evaporating said solvent. In this aspect no solvent is present in the biodegradable drug delivery composition.

Another embodiment provides a method for preparing the biodegradable drug delivery composition of the invention, said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula: A_v-B_w-A_x, wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090; and (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 ranging from 7 to 371 or 3 to 237 in a ratio of 1:6 triblock to diblock to form a polymer mixture; adding at least one pharmaceutically hydrophobic active principle to said polymer mixture; and evaporating said solvent. In this aspect no solvent is present in the biodegradable drug delivery composition.

Another embodiment provides a method for preparing the biodegradable drug delivery composition of the invention, said method comprising:(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula: A_v-B_w-A_x, wherein A is a polyester and B is polyethylene glycol and v, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090; and (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 ranging from 7 to 371 or 3 to 237 in a ratio of 1:6 or 2:3 or 3:2 or 4:1 or 2.3 to 4.1 triblock to diblock to form a polymer mixture; adding at least one pharmaceutically hydrophobic active principle one of which is medroxyprogesterone acetate levonorgestrel, cyclosporine, progesterone or bupivacaine to said polymer mixture; and evaporating said solvent. In this aspect no solvent is present in the biodegradable drug delivery composition.

The organic solvent that can be used in the method decribed herein is selected from the group of: benzyl alcohol, benzyl benzoate, diethylene glycol dimethyl ether (Diglyme), diethylene glycol monoethyl ether (DEGMEE), dimethyl isosorbide (DMI), dimethyl sulfoxide (DMSO), ethyl acetate, ethyl benzoate, ethyl lactate, ethylene glycol monoethyl ether acetate, glycerol formal, methyl ethyl ketone, methyl isobutyl ketone, N-ethyl-2-pyrrolidone, N-methyl-2-pyrrolidone(NMP), pyrrolidone-2, tetraglycol, triacetin, tributyrin, tripropionin (tripro), or triethylene glycol dimethyl ether (triglyme) and mixtures thereof.

The organic solvent is present in an amount of 40% to 74% (w%/w%) of the total composition. In another aspect 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 aspect the solvent used in the preparation of the biodegradable drug delivery composition is present in an amount of 60% to 70% (w%/w%) of the total composition. In yet another aspect, the solvent used in the preparation of the biodegradable drug delivery system is present in the amount of 30%% to 70% (w%/w%) of the total composition. In another embodiment the organic solvent is present in the amount of 30% to 90% (w%/w%) of the total composition.

As examples, when medroxyprogesterone acetate is the active principle 30% to 70% (w%/w%) of the total composition of solvent is used; when progesterone is the active principle 40% to 80% (w%/w%) of the total composition of solvent is used; when cyclosporine is the active principle 55% to 72.9% (w%/w%) of the total composition of solvent is used; when levonorestrel is the active principle 70% to 90% (w%/w%) of the total composition of solvent is used; and when bupivacaine base is the active principle 62.5 % to 80% (w%/w%) of the total composition of solvent is used.

Some mPEG-OH are 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 would be mPEG-PLA contaminated with a small amount of PLA-

PEG-PLA, which is encompassed by the present invention. This contamination is less than 2%.

Another aspect of the present invention is the use of diblock and triblock copolymers for the manufacture of a biodegradable drug composition. In this respect 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, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x. The polyester can be polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA) or polyhydroxyalkanoate (PHA). In one embodiment the polyester that is used is poly(lactic) acid.

The triblock copolymer is then combined with 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 ranging from 7 to 371 or 3 to 237. The polyester can be polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA), poly(lactic-co-glycolic acid (PLGA) or polyhydroxyalkanoate (PHA). In one embodiment the polyester that is used is poly(lactic) acid.

The pharmaceutically active principle is then combined with the triblock and diblock

In yet another aspect of the present invention is the use of diblock and triblock copolymers for the manufacture of a biodegradable drug composition. In this respect 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, w and x are the number of repeat units ranging from 4 to 1090 or 6 to 1090 and v=x or v≠x. The polyester can be polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA) or polyhydroxyalkanoate (PHA). In one embodiment the polyester that is used is poly(lactic) acid.

The triblock copolymer is then combined with 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 ranging from 7 to 371 or 3 to 237. The polyester can be polylactic acid (PLA), polycaprolactone

(PCL), polyglycolic acid (PGA), poly(lactic-co-glycolic acid (PLGA) or polyhydroxyalkanoate (PHA). In one embodiment the polyester that is used is poly(lactic) acid.

. The pharmaceutically hydrophobic active principle is then combined with the triblock and diblock and can be medroxyprogesterone acetate levonorgestrel, cyclosporine, progesterone or bupivacaine base.

The ratio of the biodegradable triblock copolymer of (a) and the biodegradable CA diblock copolymer of (b) is 1: 3 to 1: 8 in said biodegradable drug composition. In one embodiment the ratio of the biodegradable triblock copolymer of and the biodegradable CA diblock copolymer is selected from the group of 1:3, 1:4, 1;5, 1:6, 1:7 and 1:8. or 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:11, 1:12, 1:13, 1:14, 1:15, 1:16, 1:17, 1:18 and 1:19. In another aspect the ratio of the triblock to the diblock is 1:6. It can also be 3:2 or 2:3 or 4:1 or 2.3 to 4.1.

The length of the polyester chain is defined by its polyester to ethylene oxide molar ratio, which is between 0.5 to 3.5 or 0.5 to 2.5 or 0.5 to 22.3 for the triblock and 3 to 5 or 2 to 6 or 0.8 to 13 for the diblock.

The mass of the end-capped polyethylene glycol can range from 100 Da to 2 kDa or 164 Da to 2 kDa. It can range in the 100 to 300 Da range or in the 1 kDa to 2 kDa range.

The size of the polyethylene glycol chain ranges from 200 Da to 12 kDa in the biodegradable drug delivery composition or it can range from 400 Da to 12 kDa or 194 Da to 12 kDa.

A number of embodiments and/or aspects of the invention have been described. Nevertheless it will be understood that various modifications may be made without departing from the spirit and scope of the invention.

EXAMPLES

Example 1- Polymer synthesis

Copolymers were synthesized according to the method described in the U.S. Patent No. 6,350,812, incorporated herein by reference, with minor modifications. Typically, the necessary amount of PEG (gives the triblock coploymer) or methoxy-PEG (gives the diblock copolymer) was heated at 65°C and dried under vacuum for 2 hours 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 three short vaccum/N2 cycles. The reaction mixture was heated at 140°C and rapidly degassed under vacuum. The reaction was conducted for four days at 140°C under constant nitrogen flow (0.2 bar). The reaction was cooled to room temperature and its content was dissolved in acetone and then subjected to precipitation with ethanol. The product obtained was subsequently dried under reduced pressure. The final product was characterized by ^{1}H NMR for its lactate content. The triblock PLA-PEG-PLA polymers described herein were labeled PxRy where x represent the size of the PEG chain in kDa and y is the LA/EO molar ratio. The diblock mPEG-PLA polymers described herein were labeled dPxRy where x represent the size of the PEG chain in kDa and y is the LA/EO molar ratio.

Example 2-Formulation Preparation Specific for the peptide M53

The formulations described herein were based on organic solution of polymers containing as the drug, the peptide M53, a GLP-1 analogue. Typically, 0.4 grams of polymers, corresponding to a mix of a diblock copolymer and a triblock copolymer in defined mass ratio, were dissolved in 0.57 grams of a biocompatible solvent at room temperature overnight under constant magnetic stirring. The solvent was either a single solvent or a combination of solvents. The next day, 20 mg of drug was added to the polymer solution and stirred until complete dissolution. When the drug was not soluble in the solvent, a suspension of the drug in a polymer solution was obtained. Alternatively, the drug was dissolved or suspended in the biocompatible solvent and the polymer(s) added subsequently. The formulations were loaded in a syringe before use.

Example 3-The Formulations that were prepared

Following Examples 1 and 2 various formulations were prepared, which are set forth in Table 1 for the peptide M53

Table 1

		M53	Triblock copolymer (TB)						Diblock copolymer (DB)						Solvent 1		Solvent 2	
N°	Ratio DB/TB	% (w/w)	% (w/w)	Code	PEG size (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	% (w/w)	Code	PEG size (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Name	% (w/w)	Name	% (w/w)
10	4,0	4,0	10,0%	P12R0.5	12	0,5	273	136	40,0%	dP2R3	2	3,2	45	143	DEGMEE	46,0%		
12	4,0	4,0	10,0%	P12R3	12	2,5	273	682	40,0%	dP2R3	2	3,2	45	143	DEGMEE	46,0%		
21	4,0	4,0	10,0%	P12R0.5	12	0,5	273	136	40,0%	dP2R3	2	3,2	45	143	Diglyme	46,0%		
23	4,0	4,0	10,0%	P12R3	12	2,5	273	682	40,0%	dP2R3	2	3,2	45	143	Diglyme	46,0%		
34	4,0	4,0	10,0%	P12R0.5	12	0,5	273	136	40,0%	dP2R3	2	3,2	45	143	DMI	46,0%		
45	4,0	4,0	10,0%	P12R3	12	2,5	273	682	40,0%	dP2R3	2	3,2	45	143	DMI	46,0%		
66	4,0	4,0	10,0%	P12R0.5	12	0,5	273	136	40,0%	dP2R3	2	3,2	45	143	Diglyme	46,0%		
68	4,0	4,0	10,0%	P12R3	12	2,5	273	682	40,0%	dP2R3	2	3,2	45	143	Diglyme	46,0%		
76	4,0	4,0	10,0%	P12R0.5	12	0,5	273	136	40,0%	dP2R3	2	3,2	45	143	DMSO	46,0%		
78	4,0	4,0	10,0%	P12R3	12	2,5	273	682	40,0%	dP2R3	2	3,2	45	143	DMSO	46,0%		
80	4,0	4,0	10,0%	P12R0.5	12	0,5	273	136	40,0%	dP2R3	2	3,2	45	143	Et Lactate	46,0%		
82	4,0	4,0	10,0%	P12R3	12	2,5	273	682	40,0%	dP2R3	2	3,2	45	143	Et Lactate	46,0%		
105	4,0	4,0	8,0%	P6R0.9	6	0,9	136	123	32,0%	dP2R4	2	4,4	45	200	Diglyme	56,0%		
116	4,0	4,0	8,0%	P6R0.9	6	0,9	136	123	32,0%	dP2R4	2	4,4	45	200	Diglyme	56,0%		
123	4,0	4,0	8,0%	P3R1	3	1,0	68	68	32,0%	dP2R4	2	4,3	45	195	DMSO	56,0%		
124	4,0	4,0	8,0%	P6R0.9	6	0,9	136	123	32,0%	dP2R4	2	4,3	45	195	DMSO	56,0%		
153	4,0	4,0	7,0%	P12R0.	12	0,5	273	136	28,0%	dP2R4	2	4,3	45	195	DMSO	61,0%		

				5														
159	4,0	4,0	7,0%	P12 R0. 5	12	0,5	273	136	28,0 %	dP2 R4	2	4,3	45	195	DM SO	44,0 %	Tra ceti n	17,0 %
169	5,7	2,0	6,0%	P6R 0.9	6	0,9	136	123	34,0 %	dP2 R4	2	4,3	45	195	DM SO	58,0 %		
177	5,7	2,0	7,5%	P6R 0.9	6	0,9	136	123	42,5 %	dP2 R4	2	4,3	45	195	DM SO	48,0 %		
198	9,0	4,0	4,0%	P6R 0.9	6	0,9	136	123	36,0 %	dP2 R4	2	4,3	45	195	Digl yme	37,0 %	Trip ro	19,0 %
200	9,0	2,0	5,0%	P6R 0.9	6	0,9	136	123	45,0 %	dP2 R3	2	3	45	136	DM SO	48,0 %		
203	4,0	2,0	10,0%	P6R 0.9	6	0,9	136	123	40,0 %	dP2 R7	2	7,2	45	327	DM SO	48,0 %		
207	5,7	4,0	6,0%	P6R 0.9	6	0,9	136	123	34,0 %	dP2 R4	2	4,3	45	195	Digl yme	40,0 %	Trip ro	16,0 %
209	4,0	2,0	9,0%	P6R 0.9	6	0,9	136	123	36,0 %	dP2 R7	2	7,2	45	327	DM SO	53,0 %		
210	4,0	2,0	8,0%	P6R 0.9	6	0,9	136	123	32,0 %	dP2 R7	2	7,2	45	327	DM SO	58,0 %		
221	9,0	4,0	5,0%	P6R 0.9	6	0,9	136	123	45,0 %	dP2 R4	2	4,3	45	195	Digl yme	33,0 %	Trip ro	13,0 %
224	5,7	2,0	6,0%	P6R 0.9	6	0,9	136	123	34,0 %	dP2 R4	2	4,3	45	195	Digl yme	41,4 %	Trip ro	16,6 %
225	9,0	2,0	5,0%	P6R 0.9	6	0,9	136	123	45,0 %	dP2 R4	2	4,3	45	195	Digl yme	34,0 %	Trip ro	13,6 %
230	5,7	2,0	7,5%	P6R 0.9	6	0,9	136	123	42,5 %	dP1 R5	1	5,4	23	123	DM SO	48,0 %		
234	5,7	2,0	6,0%	P6R 0.9	6	0,9	136	123	34,0 %	dP1 R5	1	5,4	23	123	Digl yme	41,4 %	Trip ro	16,6 %
241	5,9	2,0	6,5%	P6R 0.9	6	0,9	136	123	38,5 %	dP1 R5	1	5,4	23	123	DM SO	53,0 %		
245	5,9	2,0	6,5%	P2R 2	2	2	45	91	38,5 %	dP1 R5	1	5,4	23	123	DM SO	53 %		
246	5,7	2,0	7,5%	P2R 2	2	2	45	91	42,5 %	dP1 R5	1	5,4	23	123	DM SO	48,0 %		
247	9,0	2,0	5,0%	P2R 2	2	2	45	91	45,0 %	dP1 R5	1	5,4	23	123	DM SO	48,0 %		
250	9,0	4,0	5,0%	P6R 0.9	6	0,9	136	123	45,0 %	dP2 R4	2	4,3	45	195	Digl yme	33,2 %	Trip ro	12,8 %

Example 4-Acetaminophen's formulations preparation

The formulations described herein were based on organic solution of polymers prepared as in Example 1, containing as the drug, acetaminophen. Typically, 0.4 grams of polymers, corresponding to a mix of a diblock copolymer and a triblock copolymer in defined mass ratio, were dissolved in 0.55 grams of dimethyl sulfoxide at room temperature overnight under constant magnetic stirring. The next day, 50 mg of acetaminophen was added to the polymer solution and stirred until complete dissolution. The formulations were loaded in a syringe before use. The composition

of the various formulations is shown in Table 2 below, where the solvent used is DMSO.

Figures 7 to 26 illustrate the results of these formulations which show all possible combinations of 15 triblock copolymers with 20 diblocks copolymers.

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Table 2

		Triblock copolymer (TB)						Diblock copolymer (DB)						Solvent	
Exp n°	Ratio DB/TB	% (w/w)	Code	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	% (w/w)	Code	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Name	% (w/w)
1	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
2	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
3	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
4	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
5	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
6	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
7	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
8	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
9	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
10	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
11	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
12	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
13	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
14	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
15	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
16	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
17	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
18	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
19	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
20	4,0	8%	P2R	2,0	3,5	45	157	32%	dP2	2,0	2,8	45	125	DMS	55%

			3						R3					O	
21	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP0. 2R6	0,2	5,8	3	17	DMS O	55%
22	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
23	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP0. 6R5	0,6	4,6	12	54	DMS O	55%
24	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP1 R4	1,0	4,0	22	89	DMS O	55%
25	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP2 R3	2,0	2,8	45	125	DMS O	55%
26	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP0. 2R6	0,2	5,8	3	17	DMS O	55%
27	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
28	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP0. 6R5	0,6	4,6	12	54	DMS O	55%
29	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP1 R4	1,0	4,0	22	89	DMS O	55%
30	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP2 R3	2,0	2,8	45	125	DMS O	55%
31	4,0	8%	P0.2 R6	0,2	5,9	4	24	32%	dP0. 2R2	0,2	2,2	3	7	DMS O	55%
32	4,0	8%	P0.2 R6	0,2	5,9	4	24	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%

33	4,0	8%	P0.2 R6	0,2	5,9	4	24	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
34	4,0	8%	P0.2 R6	0,2	5,9	4	24	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	55%
35	4,0	8%	P0.2 R6	0,2	5,9	4	24	32%	dP0. 6R3	0,6	3,0	12	35	DMS O	55%
36	4,0	8%	P0.2 R6	0,2	5,9	4	24	32%	dP0. 6R5	0,6	5,1	12	60	DMS O	55%
37	4,0	8%	P0.2 R6	0,2	5,9	4	24	32%	dP1 R3	1,0	3,0	22	66	DMS O	55%
38	4,0	8%	P0.2 R6	0,2	5,9	4	24	32%	dP1 R5	1,0	5,4	22	119	DMS O	55%
39	4,0	8%	P0.2 R6	0,2	5,9	4	24	32%	dP2 R1	2,0	1,3	45	58	DMS O	55%
40	4,0	8%	P0.2 R6	0,2	5,9	4	24	32%	dP2 R5	2,0	5,3	45	237	DMS O	55%
41	4,0	8%	P0.2 R22	0,2	22,3	4	89	32%	dP0. 2R2	0,2	2,2	3	7	DMS O	55%
42	4,0	8%	P0.2 R22	0,2	22,3	4	89	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
43	4,0	8%	P0.2 R22	0,2	22,3	4	89	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
44	4,0	8%	P0.2 R22	0,2	22,3	4	89	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	55%
45	4,0	8%	P0.2 R22	0,2	22,3	4	89	32%	dP0. 6R3	0,6	3,0	12	35	DMS O	55%
46	4,0	8%	P0.2 R22	0,2	22,3	4	89	32%	dP0. 6R5	0,6	5,1	12	60	DMS O	55%
47	4,0	8%	P0.2 R22	0,2	22,3	4	89	32%	dP1 R3	1,0	3,0	22	66	DMS O	55%
48	4,0	8%	P0.2 R22	0,2	22,3	4	89	32%	dP1 R5	1,0	5,4	22	119	DMS O	55%
49	4,0	8%	P0.2 R22	0,2	22,3	4	89	32%	dP2 R1	2,0	1,3	45	58	DMS O	55%
50	4,0	8%	P0.2 R22	0,2	22,3	4	89	32%	dP2 R5	2,0	5,3	45	237	DMS O	55%
51	4,0	8%	P0.4 R5	0,4	4,7	9	41	32%	dP0. 2R2	0,2	2,2	3	7	DMS O	55%
52	4,0	8%	P0.4 R5	0,4	4,7	9	41	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
53	4,0	8%	P0.4 R5	0,4	4,7	9	41	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
54	4,0	8%	P0.4 R5	0,4	4,7	9	41	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	55%
55	4,0	8%	P0.4 R5	0,4	4,7	9	41	32%	dP0. 6R3	0,6	3,0	12	35	DMS O	55%
56	4,0	8%	P0.4 R5	0,4	4,7	9	41	32%	dP0. 6R5	0,6	5,1	12	60	DMS O	55%
57	4,0	8%	P0.4 R5	0,4	4,7	9	41	32%	dP1 R3	1,0	3,0	22	66	DMS O	55%
58	4,0	8%	P0.4 R5	0,4	4,7	9	41	32%	dP1 R5	1,0	5,4	22	119	DMS O	55%
59	4,0	8%	P0.4 R5	0,4	4,7	9	41	32%	dP2 R1	2,0	1,3	45	58	DMS O	55%
60	4,0	8%	P0.4 R5	0,4	4,7	9	41	32%	dP2 R5	2,0	5,3	45	237	DMS O	55%

61	4,0	8%	P0.4 R8	0,4	7,7	9	67	32%	dP0. 2R2	0,2	2,2	3	7	DMS O	55%
62	4,0	8%	P0.4 R8	0,4	7,7	9	67	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
63	4,0	8%	P0.4 R8	0,4	7,7	9	67	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
64	4,0	8%	P0.4 R8	0,4	7,7	9	67	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	55%
65	4,0	8%	P0.4 R8	0,4	7,7	9	67	32%	dP0. 6R3	0,6	3,0	12	35	DMS O	55%
66	4,0	8%	P0.4 R8	0,4	7,7	9	67	32%	dP0. 6R5	0,6	5,1	12	60	DMS O	55%
67	4,0	8%	P0.4 R8	0,4	7,7	9	67	32%	dP1 R3	1,0	3,0	22	66	DMS O	55%
68	4,0	8%	P0.4 R8	0,4	7,7	9	67	32%	dP1 R5	1,0	5,4	22	119	DMS O	55%
69	4,0	8%	P0.4 R8	0,4	7,7	9	67	32%	dP2 R1	2,0	1,3	45	58	DMS O	55%
70	4,0	8%	P0.4 R8	0,4	7,7	9	67	32%	dP2 R5	2,0	5,3	45	237	DMS O	55%
71	4,0	8%	P0.6 R2	0,6	1,9	13	26	32%	dP0. 2R2	0,2	2,2	3	7	DMS O	55%
72	4,0	8%	P0.6 R2	0,6	1,9	13	26	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
73	4,0	8%	P0.6 R2	0,6	1,9	13	26	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
74	4,0	8%	P0.6 R2	0,6	1,9	13	26	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	55%
75	4,0	8%	P0.6 R2	0,6	1,9	13	26	32%	dP0. 6R3	0,6	3,0	12	35	DMS O	55%
76	4,0	8%	P0.6 R2	0,6	1,9	13	26	32%	dP0. 6R5	0,6	5,1	12	60	DMS O	55%
77	4,0	8%	P0.6 R2	0,6	1,9	13	26	32%	dP1 R3	1,0	3,0	22	66	DMS O	55%
78	4,0	8%	P0.6 R2	0,6	1,9	13	26	32%	dP1 R5	1,0	5,4	22	119	DMS O	55%
79	4,0	8%	P0.6 R2	0,6	1,9	13	26	32%	dP2 R1	2,0	1,3	45	58	DMS O	55%
80	4,0	8%	P0.6 R2	0,6	1,9	13	26	32%	dP2 R5	2,0	5,3	45	237	DMS O	55%
81	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP0. 2R2	0,2	2,2	3	7	DMS O	55%
82	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
83	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
84	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	55%
85	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP0. 6R3	0,6	3,0	12	35	DMS O	55%
86	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP0. 6R5	0,6	5,1	12	60	DMS O	55%
87	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP1 R3	1,0	3,0	22	66	DMS O	55%

88	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP1 R5	1,0	5,4	22	119	DMSO	55%
89	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP2 R1	2,0	1,3	45	58	DMSO	55%
90	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP2 R5	2,0	5,3	45	237	DMSO	55%
91	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 2R2	0,2	2,2	3	7	DMSO	55%
92	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 2R1 3	0,2	13,0	3	39	DMSO	55%
93	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 4R2	0,4	2,0	7	14	DMSO	55%
94	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 4R8	0,4	8,4	7	61	DMSO	55%
95	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 6R3	0,6	3,0	12	35	DMSO	55%
96	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 6R5	0,6	5,1	12	60	DMSO	55%
97	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP1 R3	1,0	3,0	22	66	DMSO	55%
98	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP1 R5	1,0	5,4	22	119	DMSO	55%
99	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP2 R1	2,0	1,3	45	58	DMSO	55%
100	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP2 R5	2,0	5,3	45	237	DMSO	55%
101	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 2R2	0,2	2,2	3	7	DMSO	55%
102	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 2R1 3	0,2	13,0	3	39	DMSO	55%
103	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 4R2	0,4	2,0	7	14	DMSO	55%
104	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 4R8	0,4	8,4	7	61	DMSO	55%
105	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 6R3	0,6	3,0	12	35	DMSO	55%
106	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 6R5	0,6	5,1	12	60	DMSO	55%
107	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP1 R3	1,0	3,0	22	66	DMSO	55%
108	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP1 R5	1,0	5,4	22	119	DMSO	55%
109	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP2 R1	2,0	1,3	45	58	DMSO	55%
110	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP2 R5	2,0	5,3	45	237	DMSO	55%
111	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 2R2	0,2	2,2	3	7	DMSO	55%
112	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 2R1 3	0,2	13,0	3	39	DMSO	55%
113	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 4R2	0,4	2,0	7	14	DMSO	55%
114	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 4R8	0,4	8,4	7	61	DMSO	55%

115	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
116	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
117	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
118	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
119	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
120	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
121	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%
122	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
123	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
124	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
125	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
126	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
127	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
128	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
129	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
130	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
131	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%
132	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
133	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
134	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
135	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
136	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
137	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
138	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
139	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
140	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
141	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%

142	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
143	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
144	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
145	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
146	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
147	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
148	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
149	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
150	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
151	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%
152	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
153	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
154	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
155	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
156	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
157	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
158	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
159	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
160	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
161	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%
162	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
163	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
164	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
165	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
166	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
167	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
168	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP1R5	1,0	5,4	22	119	DMSO	55%

169	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
170	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
171	4,0	8%	P0.2R6	0,2	5,9	4	24	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
172	4,0	8%	P0.2R6	0,2	5,9	4	24	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
173	4,0	8%	P0.2R6	0,2	5,9	4	24	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
174	4,0	8%	P0.2R6	0,2	5,9	4	24	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
175	4,0	8%	P0.2R6	0,2	5,9	4	24	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
176	4,0	8%	P0.2R22	0,2	22,3	4	89	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
177	4,0	8%	P0.2R22	0,2	22,3	4	89	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
178	4,0	8%	P0.2R22	0,2	22,3	4	89	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
179	4,0	8%	P0.2R22	0,2	22,3	4	89	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
180	4,0	8%	P0.2R22	0,2	22,3	4	89	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
181	4,0	8%	P0.4R5	0,4	4,7	9	41	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
182	4,0	8%	P0.4R5	0,4	4,7	9	41	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
183	4,0	8%	P0.4R5	0,4	4,7	9	41	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
184	4,0	8%	P0.4R5	0,4	4,7	9	41	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
185	4,0	8%	P0.4R5	0,4	4,7	9	41	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
186	4,0	8%	P0.4R8	0,4	7,7	9	67	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
187	4,0	8%	P0.4R8	0,4	7,7	9	67	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
188	4,0	8%	P0.4R8	0,4	7,7	9	67	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
189	4,0	8%	P0.4R8	0,4	7,7	9	67	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
190	4,0	8%	P0.4R8	0,4	7,7	9	67	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
191	4,0	8%	P0.6R2	0,6	1,9	13	26	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
192	4,0	8%	P0.6R2	0,6	1,9	13	26	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
193	4,0	8%	P0.6R2	0,6	1,9	13	26	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
194	4,0	8%	P0.6R2	0,6	1,9	13	26	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
195	4,0	8%	P0.6R2	0,6	1,9	13	26	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
196	4,0	8%	P0.6R4	0,6	4,2	13	55	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
197	4,0	8%	P0.6R4	0,6	4,2	13	55	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%

198	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP0. 6R5	0,6	4,6	12	54	DMS O	55%
199	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP1 R4	1,0	4,0	22	89	DMS O	55%
200	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP2 R3	2,0	2,8	45	125	DMS O	55%
201	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 2R6	0,2	5,8	3	17	DMS O	55%
202	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
203	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 6R5	0,6	4,6	12	54	DMS O	55%
204	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP1 R4	1,0	4,0	22	89	DMS O	55%
205	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP2 R3	2,0	2,8	45	125	DMS O	55%
206	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 2R6	0,2	5,8	3	17	DMS O	55%
207	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
208	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 6R5	0,6	4,6	12	54	DMS O	55%
209	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP1 R4	1,0	4,0	22	89	DMS O	55%
210	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP2 R3	2,0	2,8	45	125	DMS O	55%
211	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 2R6	0,2	5,8	3	17	DMS O	55%
212	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
213	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 6R5	0,6	4,6	12	54	DMS O	55%
214	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP1 R4	1,0	4,0	22	89	DMS O	55%
215	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP2 R3	2,0	2,8	45	125	DMS O	55%
216	4,0	8%	P2R 5	2,0	4,8	45	216	32%	dP0. 2R6	0,2	5,8	3	17	DMS O	55%
217	4,0	8%	P2R 5	2,0	4,8	45	216	32%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
218	4,0	8%	P2R 5	2,0	4,8	45	216	32%	dP0. 6R5	0,6	4,6	12	54	DMS O	55%
219	4,0	8%	P2R 5	2,0	4,8	45	216	32%	dP1 R4	1,0	4,0	22	89	DMS O	55%
220	4,0	8%	P2R 5	2,0	4,8	45	216	32%	dP2 R3	2,0	2,8	45	125	DMS O	55%
221	4,0	8%	P3R 1	3,0	1,0	68	66	32%	dP0. 2R6	0,2	5,8	3	17	DMS O	55%
222	4,0	8%	P3R 1	3,0	1,0	68	66	32%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
223	4,0	8%	P3R 1	3,0	1,0	68	66	32%	dP0. 6R5	0,6	4,6	12	54	DMS O	55%
224	4,0	8%	P3R 1	3,0	1,0	68	66	32%	dP1 R4	1,0	4,0	22	89	DMS O	55%
225	4,0	8%	P3R 1	3,0	1,0	68	66	32%	dP2 R3	2,0	2,8	45	125	DMS O	55%
226	4,0	8%	P3R 3	3,0	3,2	68	218	32%	dP0. 2R6	0,2	5,8	3	17	DMS O	55%

227	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
228	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
229	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
230	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
231	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
232	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
233	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
234	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
235	4,0	8%	P6R0.9	6,0	0,9	136	125	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
236	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
237	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
238	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
239	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
240	4,0	8%	P6R2	6,0	2,0	136	272	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
241	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%
242	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
243	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
244	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
245	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
246	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
247	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
248	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
249	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
250	4,0	8%	P0.2R14	0,2	14,5	4	58	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
251	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%
252	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
253	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
254	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%

255	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
256	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
257	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
258	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
259	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
260	4,0	8%	P0.6R3	0,6	3,0	13	40	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
261	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%
262	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
263	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
264	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
265	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
266	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
267	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
268	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
269	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
270	4,0	8%	P1R3	1,0	3,1	22	68	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
271	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%
272	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
273	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
274	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
275	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
276	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
277	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
278	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
279	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
280	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
281	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%

282	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
283	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
284	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
285	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
286	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
287	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
288	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
289	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
290	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
291	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%
292	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
293	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP0.4R2	0,4	2,0	7	14	DMSO	55%
294	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
295	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP0.6R3	0,6	3,0	12	35	DMSO	55%
296	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
297	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP1R3	1,0	3,0	22	66	DMSO	55%
298	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP1R5	1,0	5,4	22	119	DMSO	55%
299	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP2R1	2,0	1,3	45	58	DMSO	55%
300	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP2R5	2,0	5,3	45	237	DMSO	55%
301	0,0	40%	P2R3	2,0	3,5	45	157	0%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
302	0,05	38%	P2R3	2,0	3,5	45	157	2%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
303	0,11	36%	P2R3	2,0	3,5	45	157	4%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
304	0,25	32%	P2R3	2,0	3,5	45	157	8%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
305	1,00	20%	P2R3	2,0	3,5	45	157	20%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
306	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
307	9,0	4%	P2R3	2,0	3,5	45	157	36%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
308	19,0	2%	P2R3	2,0	3,5	45	157	38%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
309	∞	0%	P2R3	2,0	3,5	45	157	40%	dP0.4R6	0,4	5,8	7	42	DMSO	55%

310	0,0	40%	P2R3	2,0	3,5	45	157	0%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
311	0,05	38%	P2R3	2,0	3,5	45	157	2%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
312	0,11	36%	P2R3	2,0	3,5	45	157	4%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
313	0,25	32%	P2R3	2,0	3,5	45	157	8%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
314	1,00	20%	P2R3	2,0	3,5	45	157	20%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
315	4,0	8%	P2R3	2,0	3,5	45	157	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
316	9,0	4%	P2R3	2,0	3,5	45	157	36%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
317	19,0	2%	P2R3	2,0	3,5	45	157	38%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
318	∞	0%	P2R3	2,0	3,5	45	157	40%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
319	0,0	40%	P0.4R8	0,4	7,7	9	67	0%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
320	0,05	38%	P0.4R8	0,4	7,7	9	67	2%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
321	0,11	36%	P0.4R8	0,4	7,7	9	67	4%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
322	0,25	32%	P0.4R8	0,4	7,7	9	67	8%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
323	1,00	20%	P0.4R8	0,4	7,7	9	67	20%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
324	4,0	8%	P0.4R8	0,4	7,7	9	67	32%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
325	9,0	4%	P0.4R8	0,4	7,7	9	67	36%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
326	19,0	2%	P0.4R8	0,4	7,7	9	67	38%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
327	∞	0%	P0.4R8	0,4	7,7	9	67	40%	dP0.4R8	0,4	8,4	7	61	DMSO	55%
328	0,0	40%	P1R2	1,0	2,1	22	47	0%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
329	0,05	38%	P1R2	1,0	2,1	22	47	2%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
330	0,11	36%	P1R2	1,0	2,1	22	47	4%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
331	0,25	32%	P1R2	1,0	2,1	22	47	8%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
332	1,00	20%	P1R2	1,0	2,1	22	47	20%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
333	4,0	8%	P1R2	1,0	2,1	22	47	32%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
334	9,0	4%	P1R2	1,0	2,1	22	47	36%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
335	19,0	2%	P1R2	1,0	2,1	22	47	38%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
336	∞	0%	P1R2	1,0	2,1	22	47	40%	dP0.6R5	0,6	5,1	12	60	DMSO	55%
337	0,0	40%	P2R5	2,0	4,8	45	216	0%	dP0.2R13	0,2	13,0	3	39	DMSO	55%

338	0,05	38%	P2R 5	2,0	4,8	45	216	2%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
339	0,11	36%	P2R 5	2,0	4,8	45	216	4%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
340	0,25	32%	P2R 5	2,0	4,8	45	216	8%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
341	1,00	20%	P2R 5	2,0	4,8	45	216	20%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
342	4,0	8%	P2R 5	2,0	4,8	45	216	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
343	9,0	4%	P2R 5	2,0	4,8	45	216	36%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
344	19,0	2%	P2R 5	2,0	4,8	45	216	38%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
345	∞	0%	P2R 5	2,0	4,8	45	216	40%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%

Example 5-Buprenorphine's formulations preparation

The formulations described herein were based on organic solution of polymers prepared as in Example 1, containing as the drug, buprenorphine. Typically, 0.4 grams of polymers, corresponding to a mix of a diblock copolymer and a triblock copolymer in defined mass ratio, were dissolved in 0.5 grams of dimethyl sulfoxide at room temperature overnight under constant magnetic stirring. The next day, 100 mg of buprenorphine was added to the polymer solution and stirred until complete dissolution. The formulations were loaded in a syringe before use.

Three different formulations were selected for *in vivo* experiments. The composition of these formulations is shown in Table 3 below. The formulations were injected subcutaneously in the interscapular space of male rats (200-250 gr) at a final dose of 100 mg/kg of buprenorphine. Blood samples were withdraw periodically and analyzed for buprenorphine concentrations by LC/MS/MS.

The formulations are shown in Table 3 below.

Table 3

		Triblock copolymer (TB)						Diblock copolymer (DB)						Solvent	
Exp n°	Ratio DB/TB	% (w/w)	Code	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	% (w/w)	Code	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Name	% (w/w)
1	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP0.4R10	0,35	9,8	8	78	DMSO	40,0 %
2	4,0	10,0%	P2R2	2	2,2	45	101	40,0 %	dP0.4R10	0,35	9,8	8	78	DMSO	40,0 %
3	4,0	10,0%	P2R3	2	3,3	45	150	40,0 %	dP0.4R10	0,35	9,8	8	78	DMSO	40,0 %
4	4,0	10,0%	P2R4	2	4,3	45	195	40,0 %	dP0.4R10	0,35	9,8	8	78	DMSO	40,0 %
5	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP1R4	1	4,2	23	95	DMSO	40,0 %
6	4,0	10,0%	P2R2	2	2,2	45	101	40,0 %	dP1R4	1	4,2	23	95	DMSO	40,0 %
7	4,0	10,0%	P2R3	2	3,3	45	150	40,0 %	dP1R4	1	4,2	23	95	DMSO	40,0 %
8	4,0	10,0%	P2R4	2	4,3	45	195	40,0 %	dP1R4	1	4,2	23	95	DMSO	40,0 %
9	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP1R5	1	5,4	23	123	DMSO	40,0 %
10	4,0	10,0%	P2R2	2	2,2	45	101	40,0 %	dP1R5	1	5,4	23	123	DMSO	40,0 %
11	4,0	10,0%	P2R3	2	3,3	45	150	40,0 %	dP1R5	1	5,4	23	123	DMSO	40,0 %
12	4,0	10,0%	P2R4	2	4,3	45	195	40,0 %	dP1R5	1	5,4	23	123	DMSO	40,0 %
13	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP2R3	2	2,7	45	120	DMSO	40,0 %
14	4,0	10,0%	P2R2	2	2,2	45	101	40,0 %	dP2R3	2	2,7	45	120	DMSO	40,0 %
15	4,0	10,0%	P2R3	2	3,3	45	150	40,0 %	dP2R3	2	2,7	45	120	DMSO	40,0 %
16	4,0	10,0%	P2R4	2	4,3	45	195	40,0 %	dP2R3	2	2,7	45	120	DMSO	40,0 %
17	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP2R4	2	4,1	45	186	DMSO	40,0 %
18	4,0	10,0%	P2R2	2	2,2	45	101	40,0 %	dP2R4	2	4,1	45	186	DMSO	40,0 %
19	4,0	10,0%	P2R3	2	3,3	45	150	40,0 %	dP2R4	2	4,1	45	186	DMSO	40,0 %
20	4,0	10,0%	P2R4	2	4,3	45	195	40,0 %	dP2R4	2	4,1	45	186	DMSO	40,0 %

21	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0%	dP2R5	2	5,3	45	241	DMSO	40,0%
22	4,0	10,0%	P2R2	2	2,2	45	101	40,0%	dP2R5	2	5,3	45	241	DMSO	40,0%
23	4,0	10,0%	P2R3	2	3,3	45	150	40,0%	dP2R5	2	5,3	45	241	DMSO	40,0%
24	4,0	10,0%	P2R4	2	4,3	45	195	40,0%	dP2R5	2	5,3	45	241	DMSO	40,0%
26	4,0	9,0%	P0.4R8	0,4	7,7	9	70	36,0%	dP0.4R10	0,35	9,8	8	78	DMSO	45,0%
27	4,0	9,0%	P2R2	2	2,2	45	101	36,0%	dP0.4R10	0,35	9,8	8	78	DMSO	45,0%
28	4,0	9,0%	P2R3	2	3,3	45	150	36,0%	dP0.4R10	0,35	9,8	8	78	DMSO	45,0%
29	4,0	9,0%	P0.4R8	0,4	7,7	9	70	36,0%	dP1R4	1	4,2	23	95	DMSO	45,0%
30	4,0	9,0%	P2R2	2	2,2	45	101	36,0%	dP1R4	1	4,2	23	95	DMSO	45,0%
31	4,0	9,0%	P2R2	2	2,2	45	101	36,0%	dP2R3	2	2,7	45	120	DMSO	45,0%
32	4,0	8,0%	P0.4R8	0,4	7,7	9	70	32,0%	dP0.4R10	0,35	9,8	8	78	DMSO	50,0%
33	4,0	8,0%	P2R2	2	2,2	45	101	32,0%	dP0.4R10	0,35	9,8	8	78	DMSO	50,0%
34	4,0	8,0%	P2R3	2	3,3	45	150	32,0%	dP0.4R10	0,35	9,8	8	78	DMSO	50,0%
35	4,0	8,0%	P0.4R8	0,4	7,7	9	70	32,0%	dP1R4	1	4,2	23	95	DMSO	50,0%
36	4,0	8,0%	P2R2	2	2,2	45	101	32,0%	dP1R4	1	4,2	23	95	DMSO	50,0%
37	4,0	8,0%	P2R2	2	2,2	45	101	32,0%	dP2R3	2	2,7	45	120	DMSO	50,0%
38	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0%	dP1R3	1	2,7	23	61	DMSO	40,0%
39	4,0	10,0%	P2R2	2	2,2	45	101	40,0%	dP1R3	1	2,7	23	61	DMSO	40,0%
40	4,0	10,0%	P2R3	2	3,3	45	150	40,0%	dP1R3	1	2,7	23	61	DMSO	40,0%
41	4,0	10,0%	P2R4	2	4,3	45	195	40,0%	dP1R3	1	2,7	23	61	DMSO	40,0%
42	4,0	9,0%	P0.4R8	0,4	7,7	9	70	36,0%	dP1R3	1	2,7	23	61	DMSO	45,0%
43	4,0	9,0%	P2R2	2	2,2	45	101	36,0%	dP1R3	1	2,7	23	61	DMSO	45,0%
44	4,0	9,0%	P2R3	2	3,3	45	150	36,0%	dP1R3	1	2,7	23	61	DMSO	45,0%
45	4,0	9,0%	P2R4	2	4,3	45	195	36,0%	dP1R3	1	2,7	23	61	DMSO	45,0%

46	4,0	8,0%	P0.4R8	0,4	7,7	9	70	32,0 %	dP1R3	1	2,7	23	61	DMSO	50,0 %
47	4,0	8,0%	P2R2	2	2,2	45	101	32,0 %	dP1R3	1	2,7	23	61	DMSO	50,0 %
48	4,0	8,0%	P2R3	2	3,3	45	150	32,0 %	dP1R3	1	2,7	23	61	DMSO	50,0 %
49	4,0	8,0%	P2R4	2	4,3	45	195	32,0 %	dP1R3	1	2,7	23	61	DMSO	50,0 %
51	4,0	10,0%	P2R2	2	2,2	45	101	40,0 %	dP0.4R8	0,35	7,9	8	63	DMSO	40,0 %
52	4,0	10,0%	P2R2	2	2,2	45	101	40,0 %	dP0.4R5	0,35	4,9	8	39	DMSO	40,0 %
53	4,0	10,0%	P2R2	2	2,2	45	101	40,0 %	dP1R2	1	2,1	23	48	DMSO	40,0 %
54	4,0	10,0%	P2R2	2	2,2	45	101	40,0 %	dP2R0.8	2	0,8	45	34	DMSO	40,0 %
55	4,0	10,0%	P2R2	2	2,2	45	101	40,0 %	dP2R2	2	1,5	45	68	DMSO	40,0 %
56	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP0.4R8	0,35	7,9	8	63	DMSO	40,0 %
57	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP0.4R5	0,35	4,9	8	39	DMSO	40,0 %
58	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP1R2	1	2,1	23	48	DMSO	40,0 %
59	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP2R0.8	2	0,8	45	34	DMSO	40,0 %
60	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP2R2	2	1,5	45	68	DMSO	40,0 %
61	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP0.4R10	0,35	9,8	8	78	DEGMEE	40,0 %
62	4,0	10,0%	P2R4	2	4,3	45	195	40,0 %	dP0.4R10	0,35	9,8	8	78	DEGMEE	40,0 %
63	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP1R3	1	2,7	23	61	DEGMEE	40,0 %
64	4,0	10,0%	P2R4	2	4,3	45	195	40,0 %	dP1R3	1	2,7	23	61	DEGMEE	40,0 %
65	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP2R4	2	4,1	45	186	DEGMEE	40,0 %
66	4,0	10,0%	P2R4	2	4,3	45	195	40,0 %	dP2R4	2	4,1	45	186	DEGMEE	40,0 %
67	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0 %	dP0.4R10	0,35	9,8	8	78	Diglyme	40,0 %
68	4,0	10,0%	P2R4	2	4,3	45	195	40,0 %	dP0.4R10	0,35	9,8	8	78	Diglyme	40,0 %

69	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0%	dP1R3	1	2,7	23	61	Diglyme	40,0%
70	4,0	10,0%	P2R4	2	4,3	45	195	40,0%	dP1R3	1	2,7	23	61	Diglyme	40,0%
71	4,0	10,0%	P0.4R8	0,4	7,7	9	70	40,0%	dP2R4	2	4,1	45	186	Diglyme	40,0%
72	4,0	10,0%	P2R4	2	4,3	45	195	40,0%	dP2R4	2	4,1	45	186	Diglyme	40,0%
73	4,0	9,0%	P0.4R8	0,4	7,7	9	70	36,0%	dP1R2	1	2,1	23	48	DMSO	45,0%
74	4,0	8,0%	P0.4R8	0,4	7,7	9	70	32,0%	dP1R2	1	2,1	23	48	DMSO	50,0%
75	3,0	10,0%	P0.4R8	0,4	7,7	9	70	30,0%	dP1R2	1	2,1	23	48	DMSO	50,0%
76	6,0	5,7%	P0.4R8	0,4	7,7	9	70	34,3%	dP1R2	1	2,1	23	48	DMSO	50,0%
77	4,0	8,0%	P0.4R5	0,4	4,7	9	43	32,0%	dP1R2	1	2,1	23	48	DMSO	50,0%
78	4,0	8,0%	P1R2	1	2,1	23	48	32,0%	dP1R2	1	2,1	23	48	DMSO	50,0%
79	4,0	8,0%	P1R3	1	2,8	23	64	32,0%	dP1R2	1	2,1	23	48	DMSO	50,0%
80	4,0	8,0%	P0.4R5	0,4	4,7	9	43	32,0%	dP1R3	1	2,7	23	61	DMSO	50,0%
81	4,0	8,0%	P1R2	1	2,1	23	48	32,0%	dP1R3	1	2,7	23	61	DMSO	50,0%
82	4,0	8,0%	P1R3	1	2,8	23	64	32,0%	dP1R3	1	2,7	23	61	DMSO	50,0%
83	4,0	8,0%	P0.4R5	0,4	4,7	9	43	32,0%	dP0.4R5	0,35	4,9	8	39	DMSO	50,0%
84	4,0	8,0%	P1R2	1	2,1	23	48	32,0%	dP0.4R5	0,35	4,9	8	39	DMSO	50,0%
85	4,0	8,0%	P1R3	1	2,8	23	64	32,0%	dP0.4R5	0,35	4,9	8	39	DMSO	50,0%
86	4,0	10,0%	P2R4	2	4,3	45	195	40,0%	dP2R4	2	4,1	45	186	DEGMEE	40,0%
87	4,0	8,0%	P0.4R5	0,4	4,7	9	43	32,0%	dP1R2	1	2,1	23	48	DEGMEE	50,0%
88	4,0	8,0%	P1R2	1	2,1	23	48	32,0%	dP1R2	1	2,1	23	48	DEGMEE	50,0%
89	4,0	8,0%	P1R3	1	2,8	23	64	32,0%	dP1R2	1	2,1	23	48	DEGMEE	50,0%
90	4,0	10,0%	P2R4	2	4,3	45	195	40,0%	dP2R4	2	4,1	45	186	Diglyme	40,0%

91	4,0	8,0%	P0.4R5	0,4	4,7	9	43	32,0 %	dP1R2	1	2,1	23	48	Diglyme	50,0 %
92	4,0	8,0%	P1R2	1	2,1	23	48	32,0 %	dP1R2	1	2,1	23	48	Diglyme	50,0 %
93	4,0	8,0%	P1R3	1	2,8	23	64	32,0 %	dP1R2	1	2,1	23	48	Diglyme	50,0 %
95	4,0	10,0%	P2R4	2	4,3	45	195	40,0 %	dP2R4	2	4,1	45	186	DMSO	40,0 %
96	4,0	8,0%	P0.4R5	0,4	4,7	9	43	32,0 %	dP1R2	1	2,1	23	48	DMSO	50,0 %
97	4,0	8,0%	P1R2	1	2,1	23	48	32,0 %	dP1R2	1	2,1	23	48	DMSO	50,0 %
98	4,0	8,0%	P1R3	1	2,8	23	64	32,0 %	dP1R2	1	2,1	23	48	DMSO	50,0 %

The results of these formulations are illustrated in Figures 30 and 31.

Example 6-Risperidone's formulations preparation

The formulations described herein were based on organic solution of polymers prepared as in Example 1, containing as the drug, risperidone. Typically, 0.4 grams of polymers, corresponding to a mix of a diblock copolymer and a triblock copolymer in defined mass ratio, were dissolved in 0.5 grams of dimethyl sulfoxide at room temperature overnight under constant magnetic stirring. The next day, 100 mg of risperidone was added to the polymer solution and stirred. The formulations were loaded in a syringe before use.

Three different formulations were selected for *in vivo* experiments. The composition of these formulations is shown in Table 4 below. The formulations were injected subcutaneously in the interscapular space of male rats (300 gr) at a final dose of 21 mg/kg of risperidone. Blood samples were withdraw periodically and analyzed for risperidone and 9-OH risperidone concentrations by LC/MS/MS.

The formulations are shown in Table 4 below.

Table 4

		Risp	Triblock copolymer (TB)						Diblock copolymer (DB)						Solvent	
Exp n°	Ratio DB/TB	% (w/w)	% (w/w)	Code	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	% (w/w)	Code	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Name	% (w/w)
5	1,5	2,5%	16,0%	P2R3	2	3,5	45	158,6	24,0%	dP2R3	2	2,7	45	122,7	DMSO	57,5%
6	1,5	2,5%	16,0%	P2R2	2	2,3	45	104,5	24,0%	dP1R3	1	2,7	23	61,4	DMSO	57,5%
10	1,5	5,0%	16,0%	P2R2	2	2,3	45	104,5	24,0%	dP2R3	2	2,7	45	122,7	DMSO	55,0%
11	1,5	5,0%	16,0%	P2R3	2	3,5	45	158,6	24,0%	dP2R3	2	2,7	45	122,7	DMSO	55,0%
12	1,5	5,0%	16,0%	P2R2	2	2,3	45	104,5	24,0%	dP1R3	1	2,7	23	61,4	DMSO	55,0%
16	0,7	5,0%	24,0%	P2R3	2	3,5	45	158,6	16,0%	dP0.4R5	0,35	4,9	8	39,0	DMSO	55,0%
17	1,5	5,0%	16,0%	P3R2	3	2,3	68	156,8	24,0%	dP2R3	2	2,9	45	131,8	DMSO	55,0%
19	1,5	5,0%	16,0%	P3R3	3	3,2	68	218,2	24,0%	dP2R3	2	2,7	45	122,7	DMSO	55,0%
20	1,5	5,0%	16,0%	P1R4	1	3,8	23	86,4	24,0%	dP2R3	2	2,9	45	131,8	DMSO	55,0%
21	0,7	5,0%	24,0%	P1R4	1	3,8	23	86,4	16,0%	dP0.4R5	0,35	4,9	8	39,0	DMSO	55,0%
22	1,5	10,0%	16,0%	P2R2	2	2,3	45	104,5	24,0%	dP2R3	2	2,7	45	122,7	DMSO	50,0%
23	1,5	10,0%	16,0%	P2R3	2	3,5	45	158,6	24,0%	dP2R3	2	2,7	45	122,7	DMSO	50,0%
25	0,7	10,0%	24,0%	P2R3	2	3,5	45	158,6	16,0%	dP0.4R5	0,35	4,9	8	39,0	DMSO	50,0%
26	1,5	10,0%	16,0%	P3R3	3	3,2	68	218,2	24,0%	dP2R3	2	2,7	45	122,7	DMSO	50,0%
27	1,5	10,0%	16,0%	P1R4	1	3,8	23	86,4	24,0%	dP2R3	2	2,9	45	131,8	DMSO	50,0%
28	0,7	5,0%	18,0%	P1R4	1	3,8	23	86,4	12,0%	dP0.4R5	0,35	4,9	8	39,0	DMSO	65,0%
29	0,7	10,0%	24,0%	P1R4	1	3,8	23	86,4	16,0%	dP0.4R5	0,35	4,9	8	39,0	DMSO	60,0%
30	0,7	10,0%	18,0%	P1R4	1	3,8	23	86,4	12,0%	dP0.4R5	0,35	4,9	8	39,0	DMSO	60,0%
31	0,7	10,0%	18,0%	P2R3	2	3,5	45	158,6	12,0%	dP0.4R5	0,35	4,9	8	39,0	DMSO	60,0%
32	1,5	10,0%	12,0%	P1R4	1	3,8	23	86,4	18,0%	dP2R3	2	2,9	45	131,8	DMSO	60,0%

33	1,5	10,0%	12,0%	P3 R3	3	3,2	68	218,2	18,0 %	dP2 R3	2	2,7	45	122,7	DMSO	60,0%
34	0,7	15,0%	18,0%	P1 R4	1	3,8	23	86,4	12,0 %	dP0 .4R 5	0,35	4,9	8	39,0	DMSO	55,0%
35	1,5	15,0%	12,0%	P2 R2	2	2,3	45	104,5	18,0 %	dP2 R3	2	2,7	45	122,7	DMSO	55,0%
36	0,7	15,0%	18,0%	P2 R3	2	3,5	45	158,6	12,0 %	dP0 .4R 5	0,35	4,9	8	39,0	DMSO	55,0%
40	0,7	10,0%	24,0%	P1 R4	1	3,8	23	86,4	16,0 %	dP0 .4R 5	0,35	5,02	8	39,9	DMSO	60,0%
41	0,7	10,0%	18,0%	P2 R3	2	3,5	45	158,6	12,0 %	dP0 .4R 5	0,35	5,02	8	39,9	DMSO	60,0%
42	0,7	10,0%	24,0%	P1 R4	1	4,0	23	89,8	16,0 %	dP0 .4R 5	0,35	5,02	8	39,9	DMSO	60,0%
43	0,7	10,0%	24,0%	P1 R4	1	3,8	23	86,4	16,0 %	dP0 .4R 5	0,35	5,02	8	39,9	DMSO	60,0%
44	0,7	10,0%	24,0%	P1 R4	1	4,0	23	89,8	16,0 %	dP0 .4R 5	0,35	5,02	8	39,9	DMSO	60,0%

The results of these formulations are illustrated in Figures 32 and 33.

Example 7-Ivermectin's formulations preparation

The formulations described herein were based on organic solution of polymers prepared as in Example 1, containing as the drug, ivermectin. Typically, 0.4 grams of polymers, corresponding to a mix of a diblock copolymer and a triblock copolymer in defined mass ratio, were dissolved in 0.55 grams of dimethyl sulfoxide at room temperature overnight under constant magnetic stirring. The next day, 50 mg of ivermectin was added to the polymer solution and stirred until complete dissolution. Three different formulations were selected for in vivo experiments. The composition of these formulations is shown in Table 5 below. The formulations were injected subcutaneously in the interscapular space of male dogs (10 to 17 kg) at a final dose of 0.6 mg/kg of ivermectin. Blood samples were withdraw periodically and analyzed for ivermectin concentrations by LC/MS/MS.

The formulations are shown in Table 5.

Table 5

		IVM	Triblock copolymer (TB)						Diblock copolymer (DB)						Solvent	
Exp n°	Ratio DB/TB	% (w/w)	% (w/w)	Code	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	% (w/w)	Code	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Name	% (w/w)
9	1,7	5,0%	15,0%	P3R3	3	3,2	68	218	25,0%	dP0.4R5	0,35	4,9	8	39	DMSO	55,0%
10	1,7	5,0%	15,0%	P2R3	2	3,5	45	159	25,0%	dP2R3	2	2,9	45	132	DMSO	55,0%
11	1,7	5,0%	15,0%	P2R5	2	5,3	45	241	25,0%	dP2R2	2	2,3	45	105	DMSO	55,0%

The results are illustrated in Figure 34.

Example 8-Methdroxyprogesterone Acetate's formulations preparations

The formulations as described herein are based on organic solutions of the polymers as described in Example 1, containing as the drug medroxyprogesterone acetate. Typically 0.4 grams of polymers corresponding to a mix of diblock and triblock copolymer in a defined mass ratio were dissolved in 0.3 grams of DMSO or a combination of DMSO and benzyl alcohol at room temperature overnight with constant magnetic stirring. The next day the polymer solution was filtered through a 0.22 µm filter and 0.3 grams of medroxyprogesterone acetate was added to the filtered polymer solution and stirred until a homogeneous suspension of the drug was obtained. The formulations were loaded into a syringe before use. The compositions are shown in Table 6 below. The formulations were injected subcutaneously in the interscapular space of female dogs (11.4 to 14.1 kg). Blood samples were withdrawn periodically and analyzed for medroxyprogesterone acetate concentrations by LC/MS/MS having a below limit of quantification of 0.25 ng/ml. The results are shown in Figure 35.

The formulations are shown in Table 6.

Table 6

Exp n°	Exp. Code	Experiment type	Duration (days)	Drug Type	Drug loading % (w/w)	Polymer % (w/w)	%Polymer 1 TRIBLOCK		Ratio (LA/EO)	DP-PEG	DP-PLA	% Polymer 2 DIBLOCK	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Solvent 1	% Solvant 1 (w /w)	Solvent 2	% Solvant2 (w/w°)	Solubilisaton Time Org phase
1	AR01.01	Dosing curve	9	Medroxyprogesterone																	
2	AR02.01	Solvent solubility	28	Medroxyprogesterone																	
3	AR03.01	Buffer solubility	4	Medroxyprogesterone																	
4	AR04.01	Buffer solubility	15	Medroxyprogesterone																	
5	AR05.01	In vitro release	195	Medroxyprogesterone	10%	35%	14%	1	3,95	23	89,8	21%	0,35	5,02	8	39,9	DMSO	55%			Stir Overnight @Room Temp
6	AR06.01	In vitro release	195	Medroxyprogesterone	20%	35%	14%	1	3,95	23	89,8	21%	0,35	5,02	8	39,9	DMSO	45%			Stir Overnight @Room Temp
7	AR07.01	In vitro release	195	Medroxyprogesterone	30%	35%	14%	1	3,95	23	89,8	21%	0,35	5,02	8	39,9	DMSO	35%			Stir Overnight @Room Temp
8	AR08.01	In vitro release	195	Medroxyprogesterone	10%	40%	16%	1	3,95	23	89,8	24%	0,35	5,02	8	39,9	DMSO	50%			Stir Overnight @Room Temp
9	AR09.01	In vitro release	195	Medroxyprogesterone	20%	40%	16%	1	3,95	23	89,8	24%	0,35	5,02	8	39,9	DMSO	40%			Stir Overnight @Room Temp
10	AR10.01	In vitro release	195	Medroxyprogesterone	30%	40%	16%	1	3,95	23	89,8	24%	0,35	5,02	8	39,9	DMSO	30%			Stir Overnight @Room Temp
11	BJ01.01	In vitro release	342	Medroxyprogesterone	10%	40%	16%	2	3,49	45	158,6	24%	2	2,7	45	122,7	DMSO	50%			Stir Overnight @Room Temp
12	BJ02.01	In vitro release	342	Medroxyprogesterone	20%	40%	16%	2	3,49	45	158,6	24%	2	2,7	45	122,7	DMSO	40%			Stir Overnight @Room Temp
13	BJ03.01	In vitro release	342	Medroxyprogesterone	30%	40%	16%	2	3,49	45	158,6	24%	2	2,7	45	122,7	DMSO	30%			Stir Overnight @Room Temp
14	AR11.01	In vitro release	146	Depot SubQ Provera																	
15	AR12.01	In vitro release	189	Medroxyprogesterone	20%	30%	12%	1	3,95	23	89,8	18%	0,35	5,02	8	39,9	DMSO	50%			Stir Overnight @Room Temp
16	AR13.01	In vitro release	189	Medroxyprogesterone	20%	30%	18%	1	3,95	23	89,8	12%	0,35	5,02	8	39,9	DMSO	50%			Stir Overnight @Room Temp
17	AR14.01	In vitro release	189	Medroxyprogesterone	20%	35%	21%	1	3,95	23	89,8	14%	0,35	5,02	8	39,9	DMSO	45%			Stir Overnight @Room Temp
18	AR15.01	In vitro release	189	Medroxyprogesterone	20%	40%	24%	1	3,95	23	89,8	16%	0,35	5,02	8	39,9	DMSO	40%			Stir Overnight @Room Temp
19	AR16.01	In vitro release	189	Medroxyprogesterone	20%	30%	18%	2	3,49	45	158,6	12%	0,35	5,02	8	39,9	DMSO	50%			Stir Overnight @Room Temp
20	BJ04.01	In vitro release	336	Medroxyprogesterone	20%	40%	24%	2	3,49	45	158,6	16%	0,35	5,02	8	39,9	DMSO	40%			Stir Overnight @Room Temp

21	BJ05.01	In vitro release	336	Medroxyprogesterone	20%	30%	12%	2	3,49	45	158,6	18%	2	2,7	45	122,7	DMSO	50%			Stir Overnight @Room Temp
22	BJ06.01	In vitro release	336	Medroxyprogesterone	20%	35%	14%	2	3,49	45	158,6	21%	2	2,7	45	122,7	DMSO	45%			Stir Overnight @Room Temp
23	AR17.01	In vitro release	182	Medroxyprogesterone	20%	20%	8%	1	3,95	23	89,8	12%	0,35	5,02	8	39,9	DMSO	60%			Stir Overnight @Room Temp
24	AR18.01	In vitro release	182	Medroxyprogesterone	20%	20%	12%	1	3,95	23	89,8	8%	0,35	5,02	8	39,9	DMSO	60%			Stir Overnight @Room Temp
25	AR19.01	In vitro release	182	Medroxyprogesterone	20%	20%	16%	1	3,95	23	89,8	4%	0,35	5,02	8	39,9	DMSO	60%			Stir Overnight @Room Temp
26	AR20.01	In vitro release	182	Medroxyprogesterone	20%	20%	12%	2	3,49	45	158,6	8%	0,35	5,02	8	39,9	DMSO	60%			Stir Overnight @Room Temp
27	AR21.01	In vitro release	182	Medroxyprogesterone	20%	20%	16%	2	3,49	45	158,6	4%	0,35	5,02	8	39,9	DMSO	60%			Stir Overnight @Room Temp
28	AR22.01	In vitro release	182	Medroxyprogesterone	20%	20%	8%	2	3,49	45	158,6	12%	2	2,7	45	122,7	DMSO	60%			Stir Overnight @Room Temp
29	BJ07.01	In vitro release	329	Medroxyprogesterone	20%	20%	12%	2	3,49	45	158,6	8%	2	2,7	45	122,7	DMSO	60%			Stir Overnight @Room Temp
30	BJ08.01	In vitro release	329	Medroxyprogesterone	20%	20%	16%	2	3,49	45	158,6	4%	2	2,7	45	122,7	DMSO	60%			Stir Overnight @Room Temp
31	BJ09.01	In vitro release	329	Medroxyprogesterone	20%	30%	30%	2	3,49	45	158,6						DMSO	60%			Stir Overnight @Room Temp
32	BJ10.01	In vitro release	55	Medroxyprogesterone	30%	10%	6%	2	3,49	45	158,6	4%	2	2,7	45	122,7	DMSO	60%			Stir Overnight @Room Temp
33	BJ11.01	In vitro release	55	Medroxyprogesterone	40%	5%	3%	2	3,49	45	158,6	2%	2	2,7	45	122,7	DMSO	55%			Stir Overnight @Room Temp
34	BJ12.01	In vitro release	55	Medroxyprogesterone	30%	10%	6%	2	3,49	45	158,6	4%	2	2,7	45	122,7	DMSO	30%	Benzyl Alcohol	30%	Stir Overnight @Room Temp
35	BJ13.01	In vitro release	55	Medroxyprogesterone	30%	10%						10%	2	2,7	45	122,7	DMSO	60%			Stir Overnight @Room Temp
36	BJ14.01	In vitro release	309	Medroxyprogesterone	20%	20%	12%	2	3,49	45	158,6	8%	0,35	5,02	8	39,9	DMSO	30%	Benzyl Alcohol	30%	Stir Overnight @Room Temp
37	BJ15.01	In vitro release	309	Medroxyprogesterone	20%	20%	12%	2	3,49	45	158,6	8%	0,35	5,02	8	39,9	DMSO	45%	Benzyl Alcohol	15%	Stir Overnight @Room Temp
38	AR23.01	In vitro release	191	Medroxyprogesterone	20%	20%	12%	2	3,49	45	158,6	8%	2	2,7	45	122,7	DMSO	30%	Benzyl Alcohol	30%	Stir Overnight @Room Temp
39	AR24.01	In vitro release	191	Medroxyprogesterone	20%	20%	12%	2	3,49	45	158,6	8%	2	2,7	45	122,7	DMSO	45%	Benzyl Alcohol	15%	Stir Overnight @Room Temp
40	AR25.01	In vitro release	191	Medroxyprogesterone	20%	20%	12%	2	3,3	45	150,0	8%	2	2,7	45	122,7	DMSO	30%	Benzyl Alcohol	30%	Stir Overnight @Room Temp

41	BJ16.01	In vitro release	49	Medroxyprogesterone	42%														DMSO	58%								
42	BJ17.01	In vitro release	267	Medroxyprogesterone	40%	5%	3%	2	3,49	45	168,6	2%	2	2,7	45	122,7	DMSO	55%										
43	AR26.01	In Vivo Study	165	Medroxyprogesterone Ir	30%	10%	6%	2	3,49	45	158,6	4%	2	2,7	45	122,7	DMSO	60%										
44	AR27.01	In Vivo Study	165	Medroxyprogesterone Ir	40%	5%	3%	2	3,49	45	158,6	2%	2	2,7	45	122,7	DMSO	55%										
45	AR28.01	In Vivo Study	165	Medroxyprogesterone Ir	30%	10%	6%	2	3,49	45	158,6	4%	2	2,7	45	122,7	DMSO	30%	Benzyl Alcohol	30%								
46	AR29.01	In Vivo Study		Medroxyprogesterone Ir	30%	10%	6%	2	3,49	45	158,6	4%	2	2,7	45	122,7	DMSO	60%										
47	AR30.01	In Vivo Study	143	Medroxyprogesterone Ir	20%	20%	12%	2	3,49	45	158,6	8%	0,35	5,02	8	39,9	DMSO	30%	Benzyl Alcohol	30%								
48	AR31.01	In Vivo Study	190	Medroxyprogesterone Ir	20%	40%	16%	2	3,74	45	170,0	24%	2	2,34	45	106,4	DMSO	40%										
49	AR32.01	In Vivo Study	115	Medroxyprogesterone Ir	20%	10%	6%	2	3,74	45	170,0	4%	2	2,34	45	106,4	DMSO	35%	Benzyl Alcohol	35%								
50	AR33.01	Solvent Solubility	2	Medroxyprogesterone																								
51	AR34.01	Dosing curve	2	Medroxyprogesterone																								
52	AR35.01	In vitro release	111	Medroxyprogesterone Ir	40%	5%	3%	2	3,6	45	163,6	2%	2	2,48	45	112,7	DMSO	54,5%										
53	AR36.01	In vitro release	111	Medroxyprogesterone Ir	30%	10%	6%	2	3,6	45	163,6	4%	2	2,48	45	112,7	DMSO	####	Benzyl Alcohol	####								
54	AR37.01	In vitro release	111	Medroxyprogesterone Ir	20%	10%	6%	2	3,6	45	163,6	4%	2	2,48	45	112,7	DMSO	####	Benzyl Alcohol	####								
55	AR38.01	In vitro release	111	Depot SubQ Provera																								
56	AR39.01	In vitro release	64	Medroxyprogesterone Ir	30%	10%	6%	2	3,6	45	163,6	4%	2	2,48	45	112,7	DMSO	30,0%	Benzyl Alcohol	30 ,0%								
57	AR40.01	In vitro release	64	Medroxyprogesterone Ir	20%	10%	6%	2	3,6	45	163,6	4%	2	2,48	45	112,7	DMSO	35,0%	Benzyl Alcohol	35,0%								
58	AR41.01	In vitro release	96	Medroxyprogesterone	40%	5%	3%	2	3,6	45	163,6	2%	2	2,48	45	112,7	DMSO	54,5%										
59	AR42.01	In vitro release	96	Medroxyprogesterone	40%	5%	3%	2	3,6	45	163,6	2%	2	2,48	45	112,7	DMSO	26,0%										
60	AR43.01	In vitro release	96	Medroxyprogesterone	20%	10%	6%	2	3,6	45	163,6	4%	2	2,48	45	112,7	DMSO	####	Benzyl Alcohol	####								
61	AR44.01	In vitro release	96	Medroxyprogesterone	20%	10%	6%	2	3,6	45	163,6	4%	2	2,48	45	112,7	DMSO	20,5%	Benzyl Alcohol	20,5%								
62	AR45.01	Solvent Solubility	1	Medroxyprogesterone													DMSO											
63	AR46.01	In vitro release	50	Medroxyprogesterone Ir	30%	10%	6%	2	3,6	45	163,6	4%	2	2,48	45	112,7	DMSO	30,0%	Benzyl Alcohol	30,0%								
64	AR47.01	In vitro release	50	Medroxyprogesterone Ir	20%	10%	6%	2	3,6	45	163,6	4%	2	2,48	45	112,7	DMSO	35,0%	Benzyl Alcohol	35,0%								

DRUG : MEDROXYPROGESTERONE (MPA)

Exp n°	Drug loading % (w/w)	Polymer % (w/w)	Ratio Pol1/Pol2	% Polymer 1	Polymer 1 code	Batch number	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	% Polymer 2	Polymer 2 code	Batch number	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Solvent 1	% Solvent 1 (w/w)	Solvent 2	% Solvent 2 (w/w)
5	10%	35%	0.7	14%	P1R4	MIC180-C	1	4.0	23	90	21%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	55.0%		
6	20%	35%	0.7	14%	P1R4	MIC180-C	1	4.0	23	90	21%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	45.0%		
7	30%	35%	0.7	14%	P1R4	MIC180-C	1	4.0	23	90	21%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	35.0%		
8	10%	40%	0.7	16%	P1R4	MIC180-C	1	4.0	23	90	24%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	50.0%		
9	20%	40%	0.7	16%	P1R4	MIC180-C	1	4.0	23	90	24%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	40.0%		
10	30%	40%	0.7	16%	P1R4	MIC180-C	1	4.0	23	90	24%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	30.0%		
11	10%	40%	0.7	16%	P2R3	MIC166-C	2	3.5	45	159	24%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	50.0%		
12	20%	40%	0.7	16%	P2R3	MIC166-C	2	3.5	45	159	24%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	40.0%		
13	30%	40%	0.7	16%	P2R3	MIC166-C	2	3.5	45	159	24%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	30.0%		
15	20%	30%	0.7	12%	P1R4	MIC180-C	1	4.0	23	90	18%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	50.0%		
16	20%	30%	1.5	18%	P1R4	MIC180-C	1	4.0	23	90	12%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	50.0%		
17	20%	35%	1.5	21%	P1R4	MIC180-C	1	4.0	23	90	14%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	45.0%		

18	20%	40%	1.5	24%	P1R4	MIC180-C	1	4.0	23	90	16%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	40.0%		
19	20%	30%	1.5	18%	P2R3	MIC166-C	2	3.5	45	159	12%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	50.0%		
20	20%	40%	1.5	24%	P2R3	MIC166-C	2	3.5	45	159	16%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	40.0%		
21	20%	30%	0.7	12%	P2R3	MIC166-C	2	3.5	45	159	18%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	50.0%		
22	20%	35%	0.7	14%	P2R3	MIC166-C	2	3.5	45	159	21%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	45.0%		
23	20%	20%	0.7	8%	P1R4	MIC180-C	1	4.0	23	90	12%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	60.0%		
24	20%	20%	1.5	12%	P1R4	MIC180-C	1	4.0	23	90	8%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	60.0%		
25	20%	20%	4.0	16%	P1R4	MIC180-C	1	4.0	23	90	4%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	60.0%		
26	20%	20%	1.5	12%	P2R3	MIC166-C	2	3.5	45	159	8%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	60.0%		
27	20%	20%	4.0	16%	P2R3	MIC166-C	2	3.5	45	159	4%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	60.0%		
28	20%	20%	0.7	8%	P2R3	MIC166-C	2	3.5	45	159	12%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	60.0%		
29	20%	20%	1.5	12%	P2R3	MIC166-C	2	3.5	45	159	8%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	60.0%		
30	20%	20%	4.0	16%	P2R3	MIC166-C	2	3.5	45	159	4%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	60.0%		
32	30%	10%	1.5	6%	P2R3	MIC166-C	2	3.5	45	159	4%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	60.0%		
33	40%	5%	1.5	3%	P2R3	MIC166-C	2	3.5	45	159	2%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	55.0%		
34	30%	10%	1.5	6%	P2R3	MIC166-C	2	3.5	45	159	4%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	30.0%	Benzyl Alcohol	30.0%
36	20%	20%	1.5	12%	P2R3	MIC166-C	2	3.5	45	159	8%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	30.0%	Benzyl Alcohol	30.0%
37	20%	20%	1.5	12%	P2R3	MIC166-C	2	3.5	45	159	8%	dP0.35R5	MIC173-C1	0.35	5.0	8	40	DMSO	45.0%	Benzyl Alcohol	15.0%
38	20%	20%	1.5	12%	P2R3	MIC166-C	2	3.5	45	159	8%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	30.0%	Benzyl Alcohol	30.0%

39	20%	20%	1.5	12%	P2R3	MIC166-C	2	3.5	45	159	8%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	45.0%	Benzyl Alcohol	15.0%
40	20%	20%	1.5	12%	P2R3	MIC205	2	3.3	45	150	8%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	30.0%	Benzyl Alcohol	30.0%
41	42%																	DMSO	58.0%		
42	40%	5%	1.5	3%	P2R3	MIC166-C	2	3.5	45	159	2%	dP2R3	MIC138-A	2	2.7	45	123	DMSO	55.0%		
58	40%	5%	1.5	3%	P2R4	MIC227	2	3.6	45	164	2%	dP2R2	MIC226	2	2.5	45	113	DMSO	54.5%		
59	40%	5%	1.5	3%	P2R4	MIC227	2	3.6	45	164	2%	dP2R2	MIC226	2	2.5	45	113	DMSO	26.0%		
60	20%	10%	1.5	6%	P2R4	MIC227	2	3.6	45	164	4%	dP2R2	MIC226	2	2.5	45	113	DMSO	34.8%	Benzyl Alcohol	34.8%
61	20%	10%	1.5	6%	P2R4	MIC227	2	3.6	45	164	4%	dP2R2	MIC226	2	2.5	45	113	DMSO	20.5%	Benzyl Alcohol	20.5%

Example 9-Progesterone formulations preparations

The formulations as described herein are based on organic solutions of the polymers as described in Example 1, containing as the drug progesterone. Typically 0.1 grams of polymers corresponding to a mix of diblock and triblock copolymer in a defined mass ratio were dissolved in 0.6 grams of DMSO at room temperature overnight with constant magnetic stirring. The next day the polymer solution was filtered through a 0.22 µm filter and 0.3 grams of progesterone was added to the filtered polymer solution and stirred until a homogeneous suspension of the drug was obtained. The formulations were loaded into a syringe before use. The compositions are shown in Table 7 below.

Table 7

DRUG : PROGESTERONE

Exp n°	Drug loading % (w/w)	Polymer % (w/w)	Ratio Pol1/Pol2	% Polymer 1 – Triblock	Polymer 1 code	Batch number	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	% Polymer 2 - Diblock	Polymer 2 code	Batch number	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Solvent 1	% Solvent 1 (w/w)
2	20%	40%	0.7	16%	P1R3	MIC239-C	2	3.5	45	159	24%	dP2R2	MIC238	2	2.3	45	106	DMSO	40.0%
3	30%	10%	1.5	6%	P1R3	MIC239-C	2	3.5	45	159	4%	dP2R2	MIC238	2	2.3	45	106	DMSO	60.0%
4	20%	20%	1.5	12%	P1R3	MIC239-C	2	3.5	45	158	8%	dP0.35R5	MIC251-C	0.35	5.4	8	43	DMSO	60.0%
5	40%	5%	1.5	3.0%	P1R3	MIC239-C	2	3.5	45	159	2.0%	dP2R2	MIC238	2	2.3	45	106	DMSO	55.0%
6	30%	10%	1.5	6%	P1R3	MIC239-C	2	3.5	45	159	4%	dP2R2	MIC238	2	2.3	45	106	DMSO	60.0%
7	20%	10%	1.5	6.0%	P1R3	MIC239-C	2	3.5	45	158	4.0%	dP2R2	MIC238	2	2.3	45	106	DMSO	70.0%
10	40%	0%																DMSO	60.0%
11	20%	0%																DMSO	80.0%
12	40%	2.5%	1.5	1.5%	P1R3	MIC239-C	2	3.5	45	159	1.0%	dP2R2	MIC238	2	2.3	45	106	DMSO	57.5%
13	20%	5%	1.5	3.0%	P1R3	MIC239-C	2	3.5	45	158	2.0%	dP2R2	MIC238	2	2.3	45	106	DMSO	75.0%

Example 10-Levonorgestrel formulations preparations

The formulations as described herein are based on organic solutions of the polymers as described in Example 1, containing as the drug Levonorgestrel. Typically 0.1 grams of polymers corresponding to a mix of diblock and triblock copolymer in a defined mass ratio were dissolved in 0.7 grams of DMSO at room temperature overnight with constant magnetic stirring. The next day the polymer solution was filtered through a 0.22 µm filter and 0.2 grams[of Levonorgestrel was added to the filtered polymer solution and stirred until a homogeneous suspension of the drug was obtained. The formulations were loaded into a syringe before use. The compositions are shown in Table 8 below.

Table 8

DRUG : LEVONORGESTREL

Exp n°	Drug loading % (w/w)	Polymer % (w/w)	Ratio Pol1/Pol2	% Polymer 1 - Triblock	Polymer 1 code	Batch number	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	% Polymer 2 - Diblock	Polymer 2 code	Batch number	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Solvent 1	% Solvent 1 (w/w)
4	20%	0%	-															DMSO	80%
5	20%	5%	1.5	3%	P2R3	MIC239-C	2	3.5	45	158	2%	dP2R2	MIC238	2	2.3	45	106	DMSO	75%
6	20%	10%	1.5	6%	P2R3	MIC239-C	2	3.5	45	158	4%	dP2R2	MIC238	2	2.3	45	106	DMSO	70%
7	10%	0%	-															DMSO	90%
8	10%	5%	1.5	3%	P2R3	MIC239-C	2	3.5	45	159	2%	dP2R2	MIC238	2	2.3	45	106	DMSO	87.5%
9	10%	10%	1.5	6%	P2R3	MIC239-C	2	3.5	45	159	4%	dP2R2	MIC238	2	2.3	45	106	DMSO	85%

Example 10-Cyclosporine formulations preparations

The formulations as described herein are based on organic solutions of the polymers as described in Example 1, containing as the drug cyclosporine. Typically 0.15grams of polymers corresponding to a mix of diblock and triblock copolymer in a defined mass ratio were dissolved in 0.65 grams of DMSO at room temperature overnight with constant magnetic stirring. The next day the polymer solution was filtered through a 0.22 µm filter and 0.2 grams of cyclosporine was added to the filtered polymer solution and stirred until a homogeneous suspension of the drug was obtained. The formulations were loaded into a syringe before use. The compositions are shown in Table 9 below.

Table 9

DRUG : CYCLOSPORINE

Exp n°	Drug loading % (w/w)	Polymer % (w/w)	Ratio Pol2/Pol1	% Polymer 1 - Triblock	Polymer 1 code	Batch number	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	% Polymer 2 - Diblock	Polymer 2 code	Batch number	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Solvent 1	% Solvent 1 (w/w)
12	5.0%	35.0%	4.0	7.0%	P1R4	MIC243-C	1.0	4.0	22	89	28.0%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	60.0%
13	5.0%	35.0%	4.0	7.0%	P1R4	MIC243-C	1.0	4.0	22	89	28.0%	dP2R2	MIC245-C	2.0	2.5	45	111	DMSO	60.0%
14	5.0%	35.0%	4.0	7.0%	P1R4	MIC243-C	1.0	4.0	22	89	28.0%	dP0.6R5	MIC187-C	0.55	5.1	12	60	DMSO	60.0%
16	10.0%	35.0%	4.0	7.0%	P1R4	MIC243-C	1.0	4.0	22	89	28.0%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	55.0%
17	12.8%	25.7%	4.0	5.0%	P1R4	MIC243-C	1.0	4.0	22	89	20.7%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	61.5%
18	15.9%	20.1%	4.0	4.1%	P1R4	MIC243-C	1.0	4.0	22	89	16.0%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	64.0%
19	17.7%	14.2%	4.0	2.9%	P1R4	MIC243-C	1.0	4.0	22	89	11.3%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	68.1%
20	18.8%	9.4%	4.0	1.9%	P1R4	MIC243-C	1.0	4.0	22	89	7.5%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	71.8%
21	21.1%	6.0%	4.0	1.2%	P1R4	MIC243-C	1.0	4.0	22	89	4.8%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	72.9%
22	20.0%	10.0%	4.0	2.0%	P1R4	MIC243-C	1.0	4.0	22	89	8.0%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	70.0%
23	20.0%	12.5%	4.0	2.5%	P1R4	MIC243-C	1.0	4.0	22	89	10.0%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	67.5%
24	20.0%	15.0%	4.0	3.0%	P1R4	MIC243-C	1.0	4.0	22	89	12.0%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	65.0%
25	20.0%	17.5%	4.0	3.5%	P1R4	MIC243-C	1.0	4.0	22	89	14.0%	dP1R4	MIC225-C	1.0	3.9	22	85	DMSO	62.5%

Example 11-Bupivacaine formulations preparations

The formulations as described herein are based on organic solutions of the polymers as described in Example 1, containing as the drug Bupivacaine base. Typically 0.1 grams of polymers corresponding to a mix of diblock and triblock copolymer in a defined mass ratio were dissolved in 0.75 grams of DMSO at room temperature overnight with constant magnetic stirring. The next day the polymer solution was filtered through a 0.22 µm filter and 0.15 grams of Bupivacaine base was added to the filtered polymer solution and stirred until a homogeneous suspension of the drug was obtained. The formulations were loaded into a syringe before use. The compositions are shown in Table 10 below.

Table 10

DRUG : BUPIVACAINE FORMULATIONS (BUPI)

Exp n°	Drug loading % (w/w)	Polymer % (w/w)	Ratio Pol1/Pol2	% Polymer 1	Polymer 1 - Triblock code	Batch number	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	% Polymer 2 - Diblock	Polymer 2 code	Batch number	PEG (kDa)	Ratio (LA/EO)	DP-PEG	DP-PLA	Solvent 1	% Solvent 1 (w/w)
2	1%	30.0%	2.0	20%	P1R4	MIC243-C	1	4.0	23	91	10%	dP0.35R6	MIC207-C	0.35	5.8	8	46	DMSO	69.0%
3	1%	30.0%	2.0	20%	P1R4	MIC243-C	1	4.0	23	91	10%	dP2R2	MIC238	2	2.3	45	106	DMSO	69.0%
4	1%	30.0%	2.0	20%	P2R3	MIC239-C	2	3.5	45	158	10%	dP0.35R6	MIC207-C	0.35	5.8	8	46	DMSO	69.0%
5	1%	30.0%	2.0	20%	P2R3	MIC239-C	2	3.5	45	158	10%	dP2R2	MIC238	2	2.3	45	106	DMSO	69.0%
6	1%	30.0%	2.0	20%	P3R2	MIC195-C	3	1.9	68	128	10%	dP0.35R6	MIC207-C	0.35	5.8	8	46	DMSO	69.0%
7	1%	30.0%	2.0	20%	P3R2	MIC195-C	3	1.9	68	126	10%	dP2R2	MIC238	2	2.3	45	106	DMSO	69.0%
9	5.0%	30.0%	2.0	20%	P1R4	MIC243-C	1	4.0	23	91	10%	dP0.35R6	MIC207-C	0.35	5.8	8	46	DMSO	65.0%
10	1.3%	30.0%	1.0	15%	P1R4	MIC243-C	1	4.0	23	91	15%	dP0.35R6	MIC207-C	0.35	5.8	8	46	DMSO	68.7%
11	1.3%	30.0%	2.0	20%	P1R4	MIC243-C	1	4.0	23	91	10%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	68.7%
12	1.3%	30.0%	1.0	15%	P1R4	MIC243-C	1	4.0	23	91	15%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	68.7%
13	1.3%	30.0%	2.0	20%	P2R2	MIC230	2	2.4	45	110	10%	dP0.35R6	MIC207-C	0.35	5.8	8	46	DMSO	68.7%

14	1.3%	30.0%	1.0	15%	P2R2	MIC230	2	2.4	45	110	15%	dP0.35R6	MIC207-C	0.35	5.8	8	46	DMSO	68.7%
15	1.3%	30.0%	2.0	20%	P2R2	MIC230	2	2.4	45	110	10%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	68.7%
16	1.3%	30.0%	1.0	15%	P2R2	MIC230	2	2.4	45	110	15%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	68.7%
30	5.0%	30.0%	2.0	20.0%	P1R4	MIC243-C	1	4.0	23	91	10.0%	dP0.35R5	MIC251-C	0.35	5.4	8	43	DMSO	65.0%
31	1.0%	30.0%	2.0	20.0%	P1R4	MIC243-C	1	4.0	23	91	10.0%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	69.0%
32	1.0%	30.0%	2.0	20.0%	P2R2	MIC230	2	2.4	45	110	10.0%	dP0.35R5	MIC251-C	0.35	5.4	8	43	DMSO	69.0%
33	5.0%	30.0%	1.0	15.0%	P1R4	MIC243-C	1	4.0	23	91	15.0%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	65.0%
34	10.0%	30.0%	1.0	15.0%	P1R4	MIC243-C	1	4.0	23	91	15.0%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	60.0%
35	10.0%	25.0%	1.0	12.5%	P1R4	MIC243-C	1	4.0	23	91	12.5%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	65.0%
36	12.5%	25.0%	1.0	12.5%	P1R4	MIC243-C	1	4.0	23	91	12.5%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	62.5%
37	10.0%	20.0%	1.0	10.0%	P1R4	MIC243-C	1	4.0	23	91	10.0%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	70.0%
38	12.5%	20.0%	1.0	10.0%	P1R4	MIC243-C	1	4.0	23	91	10.0%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	67.5%
39	15.0%	20.0%	1.0	10.0%	P1R4	MIC243-C	1	4.0	23	91	10.0%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	65.0%
40	15.0%	20.0%	2.0	13.3%	P1R4	MIC243-C	1	4.0	23	91	6.7%	dP2R3	MIC252-C	2	3.0	45	135	DMSO	65.0%
41	12.5%	15.0%	1.0	7.5%	P1R4	MIC243-C	1	4.0	23	91	7.5%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	72.5%
42	10.0%	10.0%	1.0	5.0%	P1R4	MIC243-C	1	4.0	23	91	5.0%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	80.0%
43	12.5%	10.0%	1.0	5.0%	P1R4	MIC243-C	1	4.0	23	91	5.0%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	77.5%
44	15.0%	10.0%	1.0	5.0%	P1R4	MIC243-C	1	4.0	23	91	5.0%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	75.0%

45	12.5%	15.0%	2.0	10.0%	P1R4	MIC243-C	1	4.0	23	91	5.0%	dP2R2	MIC238	2	2.3	45	106	DMSO	72.5%
46	15.0%	10.0%	2.0	6.7%	P1R4	MIC243-C	1	4.0	23	91	3.3%	dP2R2	MIC238	2	2.3	45	106	DMSO	75.0%
47	10.0%	15.0%	1.0	7.5%	P1R4	MIC243-C	1	4.0	23	91	7.5%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	75.0%
48	11.0%	15.0%	1.0	7.5%	P1R4	MIC243-C	1	4.0	23	91	7.5%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	74.0%
49	12.0%	15.0%	1.0	7.5%	P1R4	MIC243-C	1	4.0	23	91	7.5%	dP1R4	MIC225-C	1	3.9	23	88	DMSO	73.0%

Example 12-Injectability of differing compositions

Various formulations were tested for injectability using formulations with different ratios of triblock (TB) and diblock (DB). Different solutions in DMSO based on a mixture of the triblock copolymer P6R1(TB) and the diblock copolymer dP2R4(DB) were prepared.

A 50% weight%/weight % polymer/formulation mass was used in these viscosity experiments. The weight% / weight % of triblock to diblock that was used in this experiment were the following: 50 wt. %:0 wt. %, 45 wt. %:5 wt. %, 20 wt. %:5 wt. %, 35 wt. %:15 wt. %, 15 wt. %:10 wt. %, 25 wt. %:25 wt. %, 10 wt. %:15 wt. %, 15 wt. %:35 wt. %, 5 wt. %:20 wt. %, 5 wt. %:45 wt. % and 0 wt. %:50 wt. %.

The injectability results are shown in Figure 3.

Example 13- *In vitro* Release Assay

100 to 500 mg of formulation was added to 20 to 50 ml of physiological buffer. The physiological buffer that was used was 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 diffused away from the formulation and the remaining polymer formed a solid biodegradable implant within the aqueous environment.

In order to maintain sink conditions, for drug release, the release medium was 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 HPLC. The amount of the GLP-1 analogue peptide M53, released from the formulation was calculated from a calibration curve. The concentration of M53 ranged between 0 and 5 mg/ml or it ranged between 0 and 200 µg/ml.

The results are shown in Figure 4 and Figure 5. Figure 5 illustrates the release rate of formulations 177, 224, 225, 246 and 250 as shown in Table 1, while Figure 4 shows the cumulative release of drug from the indicated formulations.

When the GPL-1 analogue was incorporated into the polymer solution, it was encapsulated within the polymer matrix as it solidified. The drug was then released either by diffusion inside the matrix or by biodegradation of the matrix.

Example 14- Pharmacokinetic study

Several formulations were tested in a pharmacokinetic study in rats. Compositions containing 1 mg of drug per animal of the formulations of 177, 224, 225, 246 and 250, as set forth in Table 1 were subcutaneously administered to rats. Blood samples were collected into EDTA tubes at different time points, centrifuged and the plasma from each time point was retained. The plasma samples were analyzed by LC/MS/MS and quantified for drug content. Results are presented as ng/ml of plasma measured over time.

The results of one pharmacokinetic study are shown in Figure 6. As shown in this Figure three of the five formulations sustain plasma concentration higher than 0.1 ng/ml for more than 28 days while giving a moderate initial drug burst release below 30 ng/ml.

Example 15- Blood Glucose Levels

Blood glucose levels with patients suffering from diabetes type 2 are taken prior to treatment. A control group having no treatment is used for this study. Patients of either gender are used in this study provided that they have diabetes type 2 and are between the ages of 35 and 60.

A GPL-1 analogue is formulated according to Examples 1 and 2 and has the chemical characteristics of number 230 in Table 1. The injectable liquid that is obtained is then injected into several patients at a dosage of 8 mg/ml. The control group is given PBS.

The amount of blood sugar levels and fructosamine is then measured for a period of 30 days, twice weekly, before meals and 2 hours after meals. The amounts of blood glucose after treatment are measured and the results are averaged. The values are shown in Table 11:

Table 11

Week number	Patient number	Blood Glucose Level Before Meals in mmol/l	Blood Glucose Level After Meals In mmol/l	Fructosamine µmol
Prior to Treatment	1	150	190	300
	2	130	175	320
	3	200	230	330
	4	220	240	360
1	1	90	150	280
	2	98	110	290
	3	120	160	330
	4	215	240	365
2	1	92	120	275
	2	95	100	287
	3	118	158	300
	4	210	230	370
3	1	92	110	270
	2	98	101	275
	3	115	155	280
	4	211	222	385
4	1	93	110	260
	2	85	100	260
	3	110	150	265
	4	223	244	365

Normal results for the glucose levels before meals range from 80 to 120 mmol/l. Normal results for the glucose levels after meals should be 160 mmol/l or less. Normal fructosamine levels are under 265. Between 265 and 280 indicates excellent blood glucose control; 280 and 500 indicates good blood glucose control;, between 320 and 340 indicates fair blood glucose control; and over 350 indicates poor blood glucose control.

Patient 4 was administered the placebo.

These results show that when administered the biodegradable drug delivery compositions of the present invention are effective to treat diabetes type 2.

While the invention has been described in terms of various preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions and changes may be made without departing from the scope thereof. Accordingly, it is intended that the scope of the present invention be limited by the scope of the claims, including equivalents thereof.

CLAIMS

What is claimed is:

1. A biodegradable drug delivery composition comprising:

(a) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x; and

(b) a biodegradable diblock copolymer having the formula:

methoxy poly(ethylene glycol)$_y$-(polylactic acid)$_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 3:2 to 1:19 in said biodegradable drug composition; and (c) at least one pharmaceutically hydrophobic active principle, wherein said at least one pharmaceutically active hydrophobic principle is present in the amount of 21.1% to 40% (wt%/wt%).

2. The biodegradable drug delivery composition according to Claim 1, wherein the at least one pharmaceutically hydrophobic active principle one of which is risperidone, ivermectin, levonorgestrel, cyclosporine, progesterone, bupivacaine base or medroxyprogesterone acetate.

3. A biodegradable drug delivery composition comprising:

(a) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x, v and x being lactyl or lactoyl repeat units and w being ethylene glycol repeat units and v=x or v≠x; and

(b) a biodegradable diblock copolymer having the formula:

methoxy poly(ethylene glycol)y-(polylactic acid) $_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, y being the number of ethylene glycol repeat units and z the number of lactyl or lactoyl repeat units, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 3:2 to 1:19 in said biodegradable drug composition; and (c) at least one pharmaceutically hydrophobic active principle, wherein said at least one pharmaceutically active hydrophobic principle is present in the amount of 21.1% to 40% wt%/wt%.

4. The biodegradable drug composition according to Claim 3, wherein the at least one pharmaceutically hydrophobic active principle one of which is risperidone, ivermectin, levonorgestrel, cyclosporine, progesterone, bupivacaine base or medroxyprogesterone acetate.

5. A biodegradable drug delivery composition is provided, which comprises:

(a) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x; and

(b) a biodegradable diblock having the formula:

methoxy poly(ethylene glycol)$_y$-(polylactic acid)$_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, wherein the ratio of the biodegradable triblock copolymer of

(a) and the biodegradable diblock copolymer of (b) is 3:2 to 1:19 in said biodegradable drug composition and (c) at least one pharmaceutically hydrophobic active principle, wherein said at least one hydrophobic active principle is an homogenous suspension.

6. The biodegradable drug delivery composition according to Claim 5, wherein the at least one pharmaceutically hydrophobic active principle one of which is risperidone, ivermectin, levonorgestrel, cyclosporine, progesterone, bupivacaine or medroxyprogesterone acetate.

7. A biodegradable drug delivery composition, which comprises:

(a) a biodegradable triblock copolymer present in an amount of 3.0% to 45% (w%/w%) or 2% to 45% (w%/w%)of the total composition having the formula:

$$\text{poly(lactic acid)}_v\text{-poly(ethylene glycol)}_w\text{-poly(lactic acid)}_x$$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273; and

(b) a biodegradable diblock copolymer present in an amount of 8.0% to 50% (w%/w%) of the total composition having the formula:

$$\text{methoxy poly(ethylene glycol)}_y\text{-(polylactic acid)}_z$$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 3:2 to 1:19 in said biodegradable drug composition and (c) at least one pharmaceutically hydrophobic active principle which is in an amount of 21.1% to 40% (w%/w%) of the total composition and an organic solvent.

8. The biodegradable drug delivery composition according to Claim 7, wherein the

at least one pharmaceutically hydrophobic active principle one of which is risperidone, ivermectin, levonorgestrel, cyclosporine, progesterone, bupivacaine or medroxyprogesterone acetate.

9. The biodegradable drug delivery compositions according to Claim 1 or Claim 7, wherein a lactic acid to ethylene oxide molar ratio in said composition is between 0.5 to 3.5 or between 0.5 to 2.5 or between 0.5 to 22.3 for the triblock copolymer and between 2 to 6 or between 0.8 to 13 or between 3 to 5 for the diblock copolymer.

10. The biodegradable drug delivery compositions according to Claim 1 or Claim 7, wherein said compositions are an injectable liquid that when inserted into the body of an animal or plant becomes a hardened implant.

11. A method for preparing the biodegradable drug delivery composition of the invention, said method comprising:

(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

$$\text{poly(lactic acid)}_v\text{-poly(ethylene glycol)}_w\text{-poly(lactic acid)}_x$$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 wherein v=x or v≠x; and (b) a biodegradable diblock copolymer having the formula:

$$\text{methoxy poly(ethylene glycol)}_y\text{-(polylactic acid)}_z$$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, in a ratio of 3.2 to 1:19 to form a polymer mixture; and

(ii) adding at least one pharmaceutically hydrophobic active principle to said polymer mixture, wherein said at least one pharmaceutically active hydrophobic principle is present in the amount of 21.1% to 40% (wt%/wt%).

12. The method for preparing the biodegradable drug delivery compositions according to Claim 11, the at least one pharmaceutically hydrophobic active principle one of which is risperidone, ivermectin, levonorgestrel, cyclosporine, progesterone, bupivacaine or medroxyprogesterone acetate to said polymer mixture.

13. A method for preparing the biodegradable drug delivery composition of the present invention said method comprising:

(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 wherein v=x or v≠x; and (b) a biodegradable diblock copolymer having the formula:

methoxy poly(ethylene glycol)$_y$-(polylactic acid)$_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, in a ratio of 3.2 to 1:19 to form a polymer mixture;

(ii) adding at least one pharmaceutically hydrophobic active principle to said polymer mixture, wherein said at least one pharmaceutically active hydrophobic principle is present in the amount of 21.1% to 40% (wt%/wt%); and

(iii) evaporating said solvent.

14. The method according to Claim 13, wherein the at least one pharmaceutically hydrophobic active principle one of which is risperidone, ivermectin, levonorgestrel, cyclosporine, progesterone, bupivacaine or medroxyprogesterone acetate.

15. A method for preparing the biodegradable drug delivery composition of the

present invention said method comprising:

(i) dissolving in an organic solvent (a) a biodegradable ABA type block copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273, v and x being ester repeat units and w being ethylene oxide repeat units wherein v=x or v≠x; and (b) a biodegradable diblock copolymer having the formula:

methoxy poly(ethylene glycol)$_y$-(polylactic acid)$_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, y being the number of ethylene oxide repeat units and z the number of ester repeat units, in a ratio of 3.2 to 1:19 to form a polymer mixture;

(ii) adding at least one pharmaceutically hydrophobic active principle to said polymer mixture, wherein said at least one hydrophobic active principle is an homogenous suspension; and

(iii) evaporating said solvent.

16. The method according to Claim 15, wherein the at least one pharmaceutically hydrophobic active principle one of which is risperidone, ivermectin, levonorgestrel, cyclosporine, progesterone, bupivacaine or medroxyprogesterone acetate.

17. The method according to any one of Claims 11 to 16, the organic solvent is be present in an amount of 40% to 74% (w%/w%) or 30% to 70% (w%/w%) or 26% to 90% (w%/w%) of the total composition.

18. A biodegradable drug delivery composition comprising:

(a) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x; and

(b) a biodegradable diblock copolymer having the formula:

methoxy poly(ethylene glycol)$_y$-(polylactic acid)$_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, wherein the ratio of the biodegradable triblock copolymer of (a) and the biodegradable diblock copolymer of (b) is 2.0 to 4.0 in said biodegradable drug composition; and (c) at least one pharmaceutically hydrophobic active principle.

19. A biodegradable drug delivery composition comprising:

(a) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x; and

(b) a biodegradable diblock copolymer having the formula:

methoxy poly(ethylene glycol)$_y$-(polylactic acid)$_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, wherein said copolymers are present in an amount of 2.5% to 17.5% (w%/w%) of the total composition and (c) at least one pharmaceutically hydrophobic active principle.

20. A biodegradable drug delivery composition comprising:

(a) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x; and

(b) a biodegradable diblock copolymer having the formula:

methoxy poly(ethylene glycol)$_y$-(polylactic acid)$_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, wherein said triblock copolymer is present in an amount of 1.2% to 2.9% (w%/w%) of the total composition and (c) at least one pharmaceutically hydrophobic active principle.

21. A biodegradable drug delivery composition comprising:

(a) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x; and

(b) a biodegradable diblock copolymer having the formula:

methoxy poly(ethylene glycol)$_y$-(polylactic acid)$_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, wherein said diblock copolymer is present in an amount of 1.0% to 7.5% (w%/w%) of the total composition and (c) at least one pharmaceutically hydrophobic active principle.

22. A biodegradable drug delivery composition comprising:

(a) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$.poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x; and

(b) a biodegradable diblock copolymer having the formula:

methoxy poly(ethylene glycol)$_y$-(polylactic acid)$_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, further comprising an organic solvent, which is present in the amount of 75% to 87.5% (w%/w%) of the total composition and (c) at least one pharmaceutically hydrophobic active principle.

23. A biodegradable drug delivery composition comprising:

(a) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$.poly(ethylene glycol)$_w$-poly(lactic acid)$_x$

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x; and

(b) a biodegradable diblock copolymer having the formula:

methoxy poly(ethylene glycol)$_y$-(polylactic acid)$_z$

wherein y and z are the number of repeat units y ranging from 3 to 45 and z ranging from 7 to 327, wherein a lactic acid to ethylene oxide molar ratio in said composition is between 3.5 to 4.0 for the triblock copolymer and between 2.3 to 5.0 for the diblock copolymer and (c) at least one pharmaceutically hydrophobic active principle.