(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2014 (03.01.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/001905 A1

(51) International Patent Classification:
A61K 47/34 (2006.01) *A61K 31/57* (2006.01)

(21) International Application Number:
PCT/IB2013/001549

(22) International Filing Date:
27 June 2013 (27.06.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/665192 27 June 2012 (27.06.2012) US

(71) Applicant: **MEDINCELL** [FR/FR]; 1, avenue Charles Cros, F-34830 Jacou (FR).

(72) Inventors: **GAUDRIAULT, Georges**; 334, rue Louis-Martin Berthoud, F-34080 Montpellier (FR). **ROBERGE, Christophe**; 25, rue de la Garenne, F-34920 Le Crès (FR).

(74) Agents: **PARIS, Fabienne** et al.; Ernest Gutmann - Yves Plasseraud SAS, 3, rue Auber, F-75009 Paris (FR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2014/001905 A1

(54) Title: BIODEGRADABLE DRUG DELIVERY FOR HYDROPHOBIC COMPOSITIONS

(57) Abstract: A biodegradable drug delivery compositions comprising a triblock copolymer containing a polyester and a polyethylene glycol and a diblock copolymer containing a polyester and an end-capped polyethylene glycol, as well as at least one pharmaceutically active principle or hydrophobic active principle such as medroxyprogesterone acetate, levonorgestrel, cyclosporine, progesterone or bupivacaine is disclosed.

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:

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

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 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.

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

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, 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-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 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.

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

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, 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-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 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.

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

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, 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:

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 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 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.

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

A_v-B_w-A_x

wherein A is a polyester and B is polyethylene glycol and v, 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:

$$C_y\text{-}A_z$$

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.

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, 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.

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.

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 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.

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 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.

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-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:

PLA_v-PEG_w-PLA_x

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:

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

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 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:

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 active principle

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 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:

$$PEG_y\text{-}PLA_z$$

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 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

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 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:

$$PEG_y\text{-}PLA_z$$

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 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.

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:

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

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 (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:

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

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 (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:

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

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 (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.

5

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%	P3R2	3,0	2,3	68	154	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
22	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
23	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
24	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
25	4,0	8%	P3R2	3,0	2,3	68	154	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
26	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
27	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
28	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
29	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
30	4,0	8%	P6R2	6,0	1,6	136	218	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
31	4,0	8%	P0.2R6	0,2	5,9	4	24	32%	dP0.2R2	0,2	2,2	3	7	DMSO	55%
32	4,0	8%	P0.2R6	0,2	5,9	4	24	32%	dP0.2R13	0,2	13,0	3	39	DMSO	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	DMS O	55%
89	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP2 R1	2,0	1,3	45	58	DMS O	55%
90	4,0	8%	P0.6 R4	0,6	4,2	13	55	32%	dP2 R5	2,0	5,3	45	237	DMS O	55%
91	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 2R2	0,2	2,2	3	7	DMS O	55%
92	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
93	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
94	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	55%
95	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 6R3	0,6	3,0	12	35	DMS O	55%
96	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP0. 6R5	0,6	5,1	12	60	DMS O	55%
97	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP1 R3	1,0	3,0	22	66	DMS O	55%
98	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP1 R5	1,0	5,4	22	119	DMS O	55%
99	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP2 R1	2,0	1,3	45	58	DMS O	55%
100	4,0	8%	P1R 2	1,0	2,1	22	47	32%	dP2 R5	2,0	5,3	45	237	DMS O	55%
101	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 2R2	0,2	2,2	3	7	DMS O	55%
102	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
103	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
104	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	55%
105	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 6R3	0,6	3,0	12	35	DMS O	55%
106	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP0. 6R5	0,6	5,1	12	60	DMS O	55%
107	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP1 R3	1,0	3,0	22	66	DMS O	55%
108	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP1 R5	1,0	5,4	22	119	DMS O	55%
109	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP2 R1	2,0	1,3	45	58	DMS O	55%
110	4,0	8%	P1R 4	1,0	4,0	22	88	32%	dP2 R5	2,0	5,3	45	237	DMS O	55%
111	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 2R2	0,2	2,2	3	7	DMS O	55%
112	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
113	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
114	4,0	8%	P2R 2	2,0	2,0	45	88	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	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%	P0.6R4	0,6	4,2	13	55	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
199	4,0	8%	P0.6R4	0,6	4,2	13	55	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
200	4,0	8%	P0.6R4	0,6	4,2	13	55	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
201	4,0	8%	P1R2	1,0	2,1	22	47	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
202	4,0	8%	P1R2	1,0	2,1	22	47	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
203	4,0	8%	P1R2	1,0	2,1	22	47	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
204	4,0	8%	P1R2	1,0	2,1	22	47	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
205	4,0	8%	P1R2	1,0	2,1	22	47	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
206	4,0	8%	P1R4	1,0	4,0	22	88	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
207	4,0	8%	P1R4	1,0	4,0	22	88	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
208	4,0	8%	P1R4	1,0	4,0	22	88	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
209	4,0	8%	P1R4	1,0	4,0	22	88	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
210	4,0	8%	P1R4	1,0	4,0	22	88	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
211	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
212	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
213	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
214	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
215	4,0	8%	P2R2	2,0	2,0	45	88	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
216	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
217	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
218	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
219	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
220	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
221	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP0.2R6	0,2	5,8	3	17	DMSO	55%
222	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP0.4R6	0,4	5,8	7	42	DMSO	55%
223	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP0.6R5	0,6	4,6	12	54	DMSO	55%
224	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP1R4	1,0	4,0	22	89	DMSO	55%
225	4,0	8%	P3R1	3,0	1,0	68	66	32%	dP2R3	2,0	2,8	45	125	DMSO	55%
226	4,0	8%	P3R3	3,0	3,2	68	218	32%	dP0.2R6	0,2	5,8	3	17	DMSO	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%	P3R 2	3,0	2,3	68	154	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
283	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
284	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	55%
285	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP0. 6R3	0,6	3,0	12	35	DMS O	55%
286	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP0. 6R5	0,6	5,1	12	60	DMS O	55%
287	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP1 R3	1,0	3,0	22	66	DMS O	55%
288	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP1 R5	1,0	5,4	22	119	DMS O	55%
289	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP2 R1	2,0	1,3	45	58	DMS O	55%
290	4,0	8%	P3R 2	3,0	2,3	68	154	32%	dP2 R5	2,0	5,3	45	237	DMS O	55%
291	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP0. 2R2	0,2	2,2	3	7	DMS O	55%
292	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP0. 2R1 3	0,2	13,0	3	39	DMS O	55%
293	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP0. 4R2	0,4	2,0	7	14	DMS O	55%
294	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP0. 4R8	0,4	8,4	7	61	DMS O	55%
295	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP0. 6R3	0,6	3,0	12	35	DMS O	55%
296	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP0. 6R5	0,6	5,1	12	60	DMS O	55%
297	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP1 R3	1,0	3,0	22	66	DMS O	55%
298	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP1 R5	1,0	5,4	22	119	DMS O	55%
299	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP2 R1	2,0	1,3	45	58	DMS O	55%
300	4,0	8%	P6R 2	6,0	1,6	136	218	32%	dP2 R5	2,0	5,3	45	237	DMS O	55%
301	0,0	40%	P2R 3	2,0	3,5	45	157	0%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
302	0,05	38%	P2R 3	2,0	3,5	45	157	2%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
303	0,11	36%	P2R 3	2,0	3,5	45	157	4%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
304	0,25	32%	P2R 3	2,0	3,5	45	157	8%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
305	1,00	20%	P2R 3	2,0	3,5	45	157	20%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
306	4,0	8%	P2R 3	2,0	3,5	45	157	32%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
307	9,0	4%	P2R 3	2,0	3,5	45	157	36%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
308	19,0	2%	P2R 3	2,0	3,5	45	157	38%	dP0. 4R6	0,4	5,8	7	42	DMS O	55%
309	∞	0%	P2R 3	2,0	3,5	45	157	40%	dP0. 4R6	0,4	5,8	7	42	DMS O	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%	P2R5	2,0	4,8	45	216	2%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
339	0,11	36%	P2R5	2,0	4,8	45	216	4%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
340	0,25	32%	P2R5	2,0	4,8	45	216	8%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
341	1,00	20%	P2R5	2,0	4,8	45	216	20%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
342	4,0	8%	P2R5	2,0	4,8	45	216	32%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
343	9,0	4%	P2R5	2,0	4,8	45	216	36%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
344	19,0	2%	P2R5	2,0	4,8	45	216	38%	dP0.2R13	0,2	13,0	3	39	DMSO	55%
345	∞	0%	P2R5	2,0	4,8	45	216	40%	dP0.2R13	0,2	13,0	3	39	DMSO	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	% Solvent 1 (w /w)	Solvent 2	% Solvent 2 (w/w°)	Solubilisation 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	158,6	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 Poli1/Poli2	% 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	128	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:

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

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 or 2:3 or 4:1 or 2.3 to 4.1in said biodegradable drug composition; and (c) at least one pharmaceutically active principle, which is medroxyprogesterone acetate.

2. 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:

$$C_y\text{-}A_z$$

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 4.1in said

biodegradable drug composition; and (c) at least one pharmaceutically active principle, which is medroxyprogesterone acetate.

3. 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 or 2:3 or 4:1 or 2.3 to 4.1in said biodegradable drug composition and wherein the PEG in the diblock is end-capped; and (c) at least one pharmaceutically active principle, which is medroxyprogesterone acetate.

4. 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 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:

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, which is medroxyprogesterone acetate.

5. The biodegradable drug delivery composition according to any one of Claims 1 to 4, wherein said medroxyprogesterone is present in an amount of 1% to 20% (w%/w%) or 1% to 40% of the total composition or the at least one pharmaceutically active principle is present in an amount of 1 to 200 mg/ml.

6. The biodegradable drug delivery composition according to any one of Claims 1 to 4, wherein said medroxyprogesterone acetate is present in an amount of 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.

7. The biodegradable drug delivery compositions according to any one of Claims 1 to 6, 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.

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

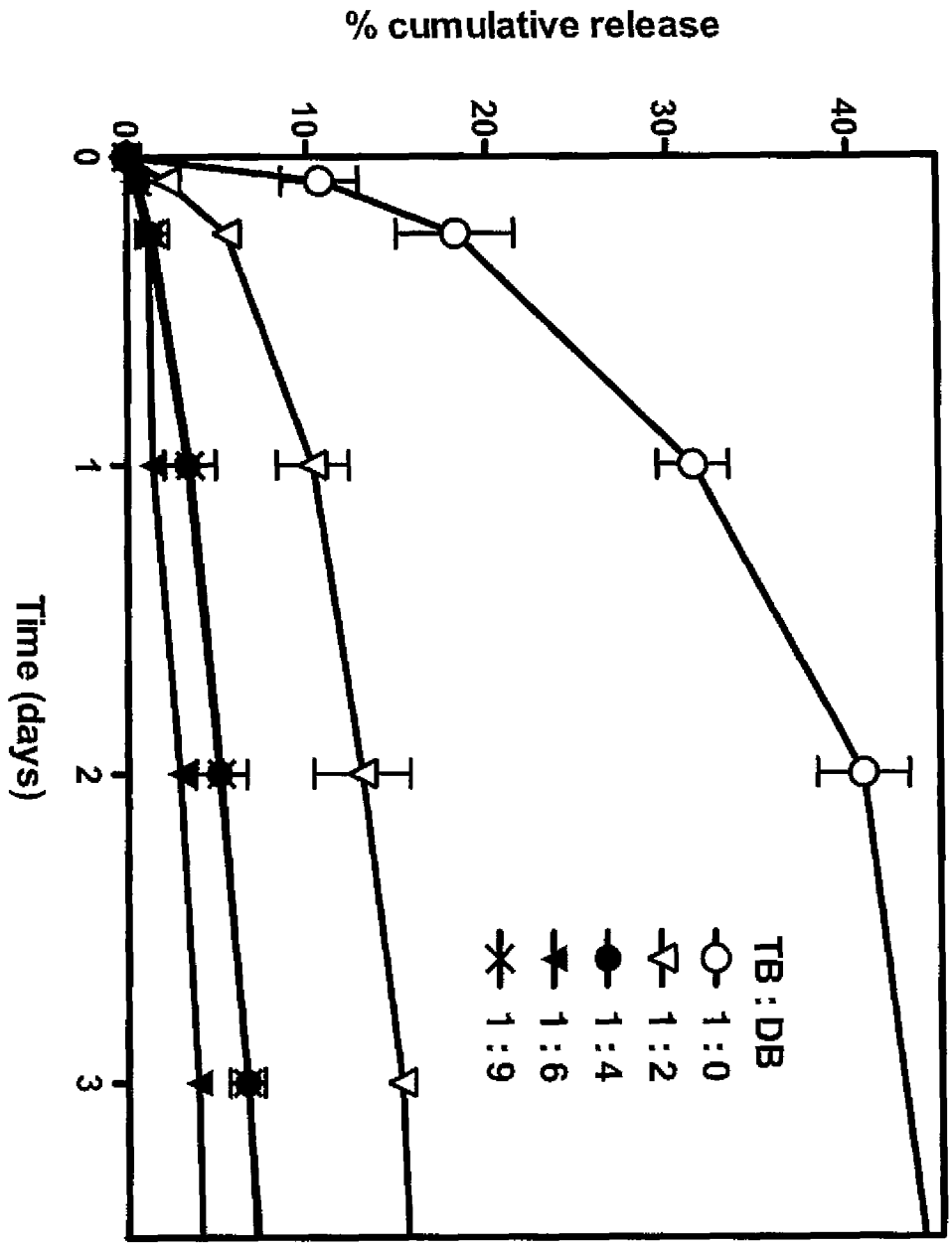
% cumulative release
0
10
20
30
40
Time (days)
0
1
2
3
TB : DB
1 : 0
1 : 2
1 : 4
1 : 6
1 : 9

FIGURE 1

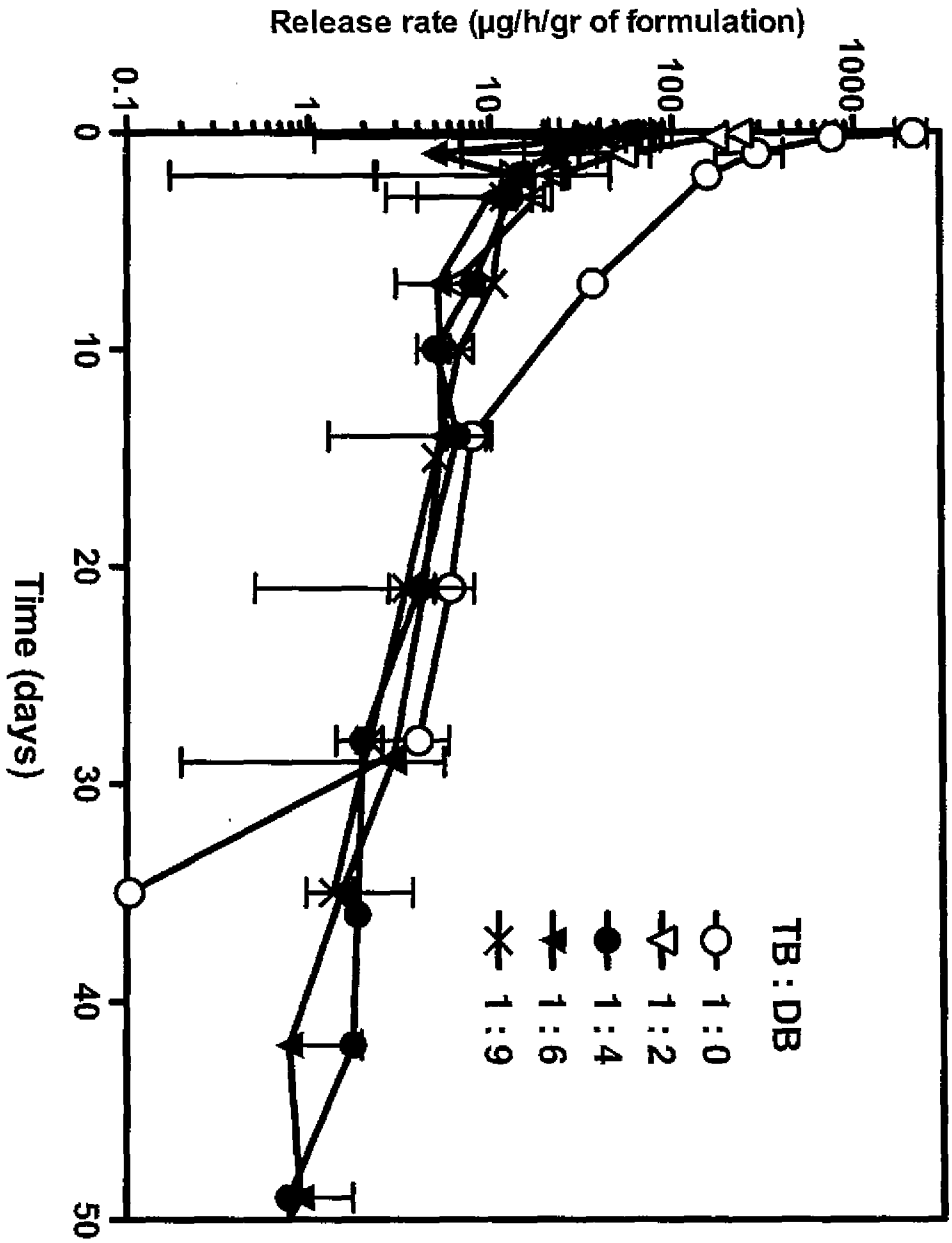
Release rate (µg/h/gr of formulation)
0.1
1
10
100
1000
Time (days)
0
10
20
30
40
50
TB : DB
1 : 0
1 : 2
1 : 4
1 : 6
1 : 9

FIGURE 2

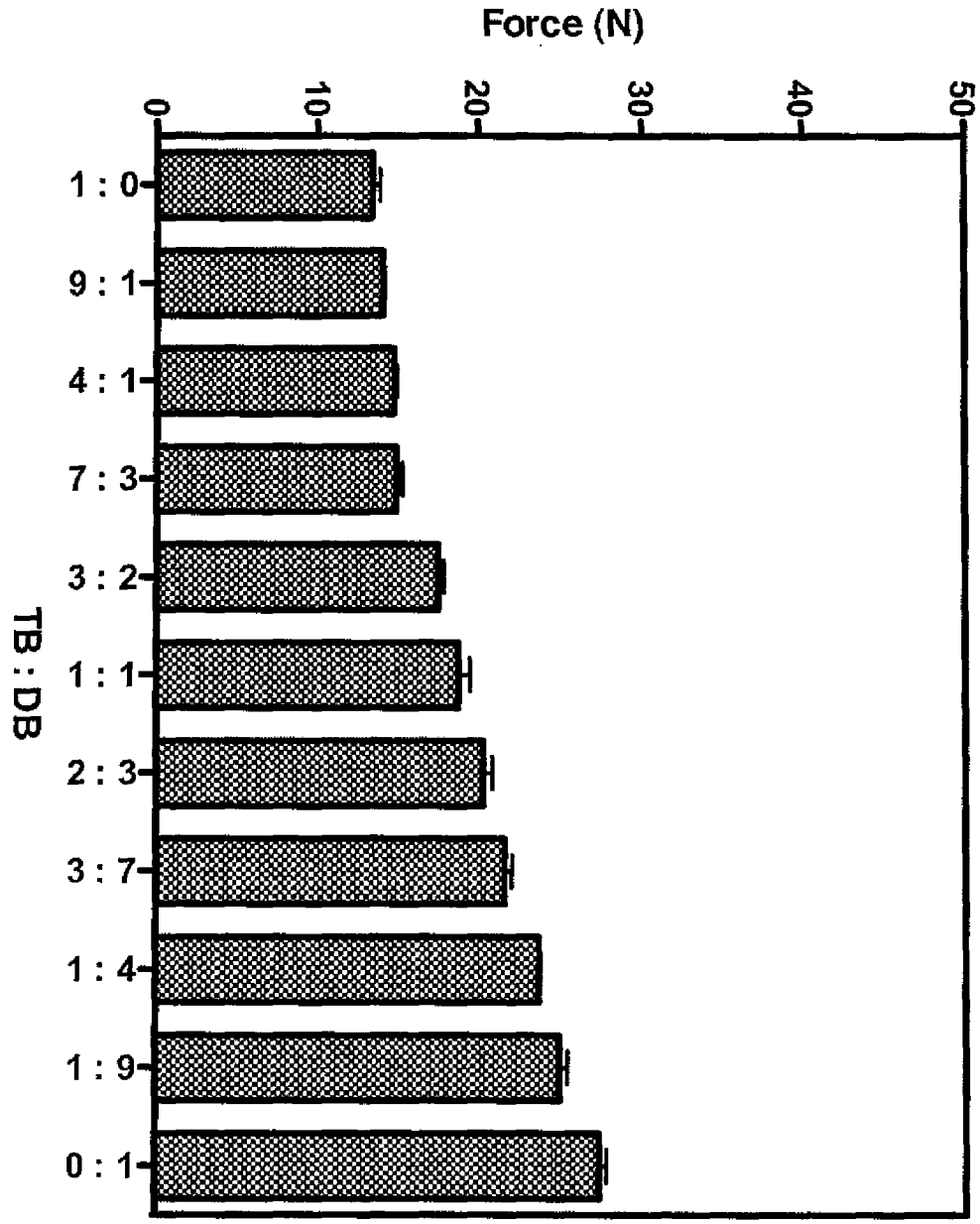

FIGURE 3

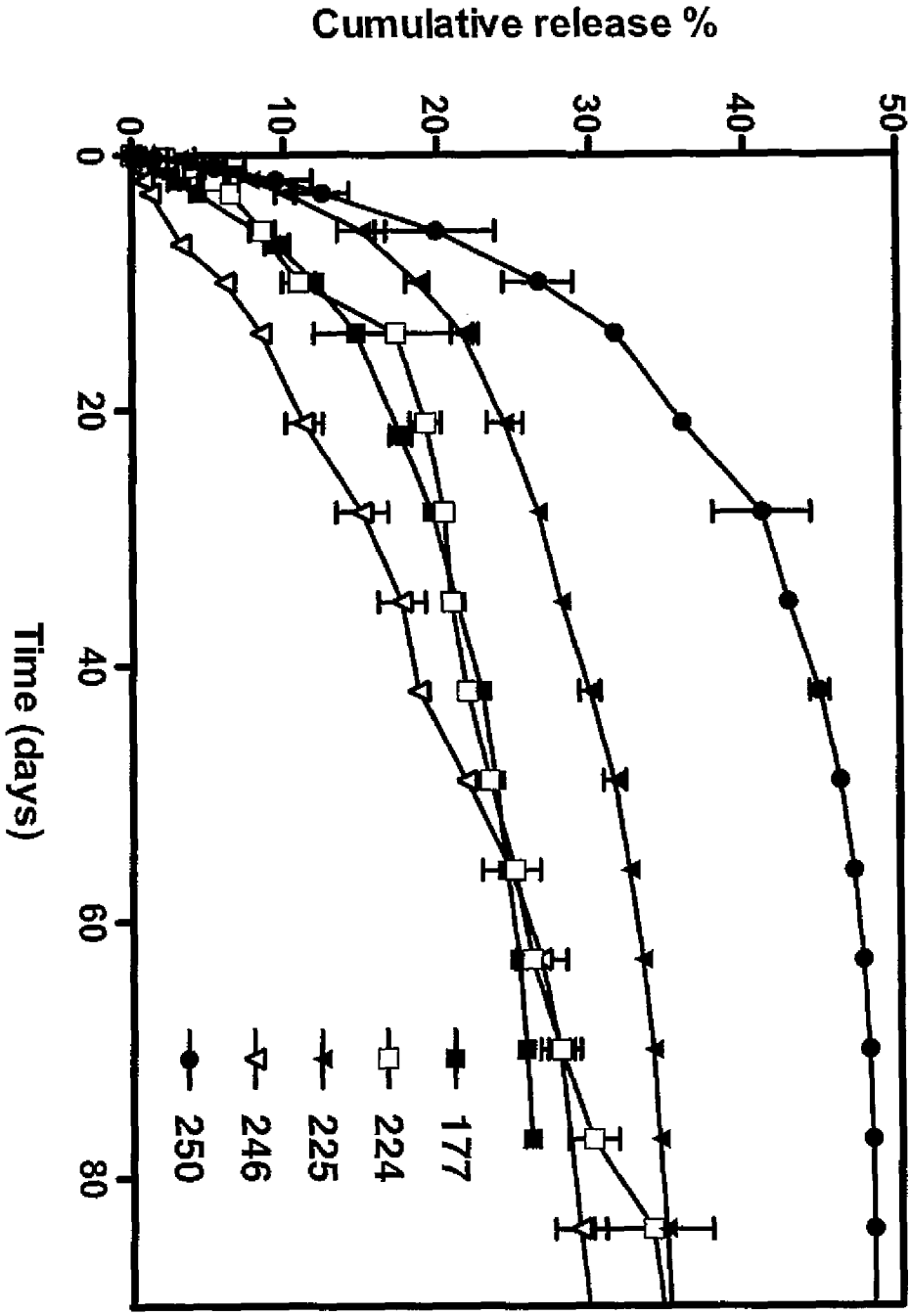
Cumulative release %
0
10
20
30
40
50
Time (days)
0
20
40
60
80
250
246
225
224
177

FIGURE 4

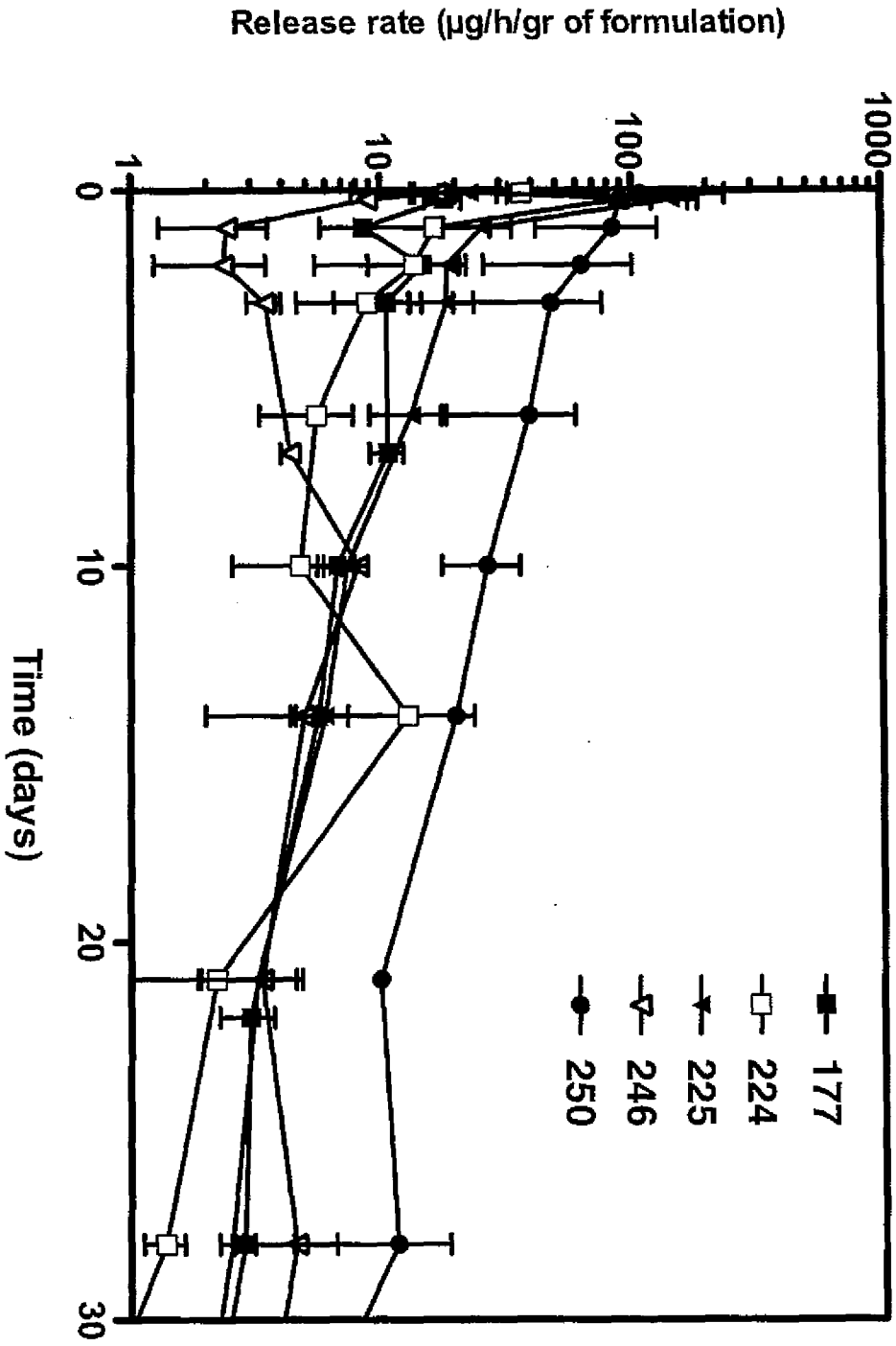
Release rate (µg/h/gr of formulation)
1
10
100
1000
0
10
20
30
Time (days)
177
224
225
246
250

FIGURE 5

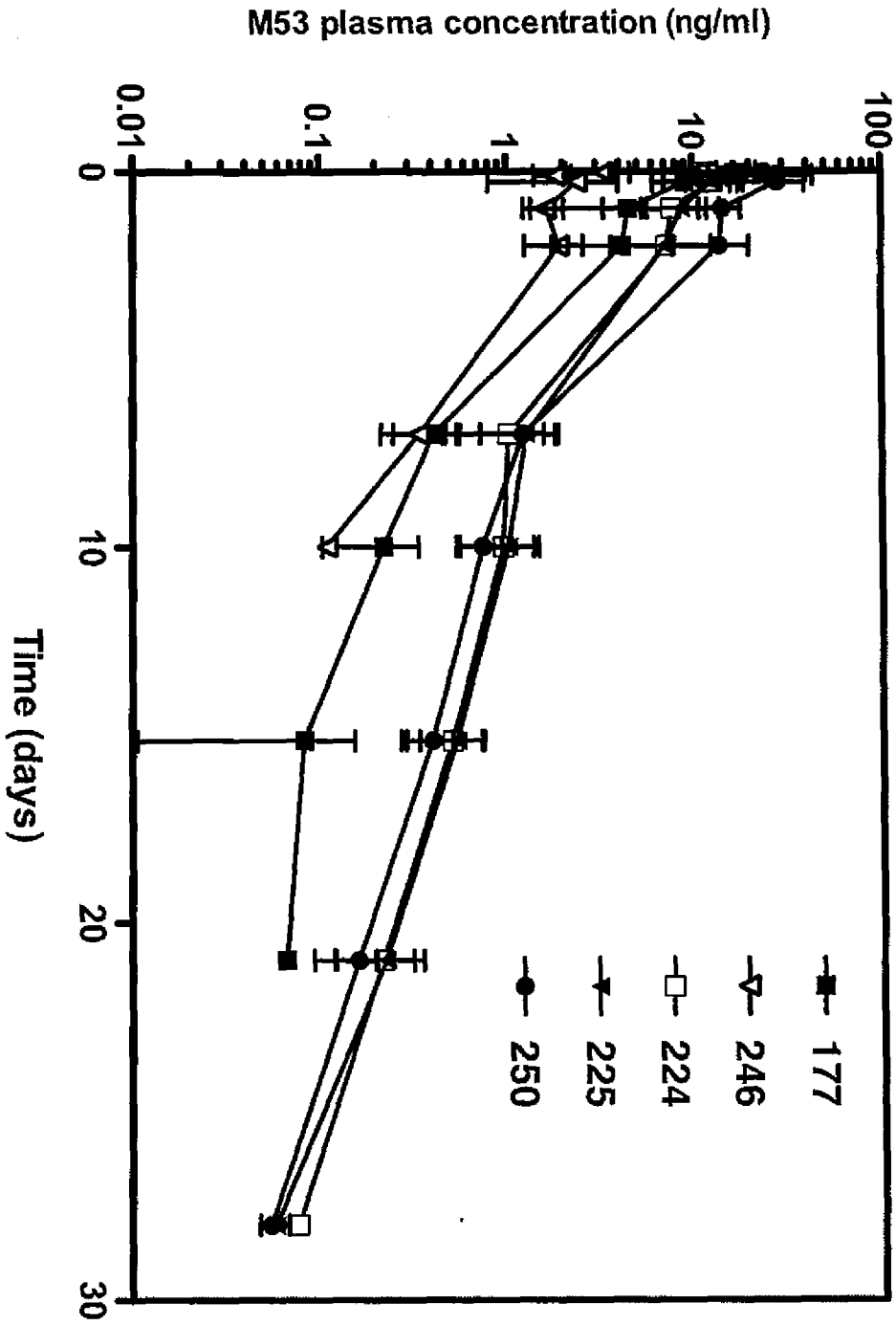
M53 plasma concentration (ng/ml)
0.01
0.1
1
10
100
0
10
20
30
Time (days)
177
246
224
225
250

FIGURE 6

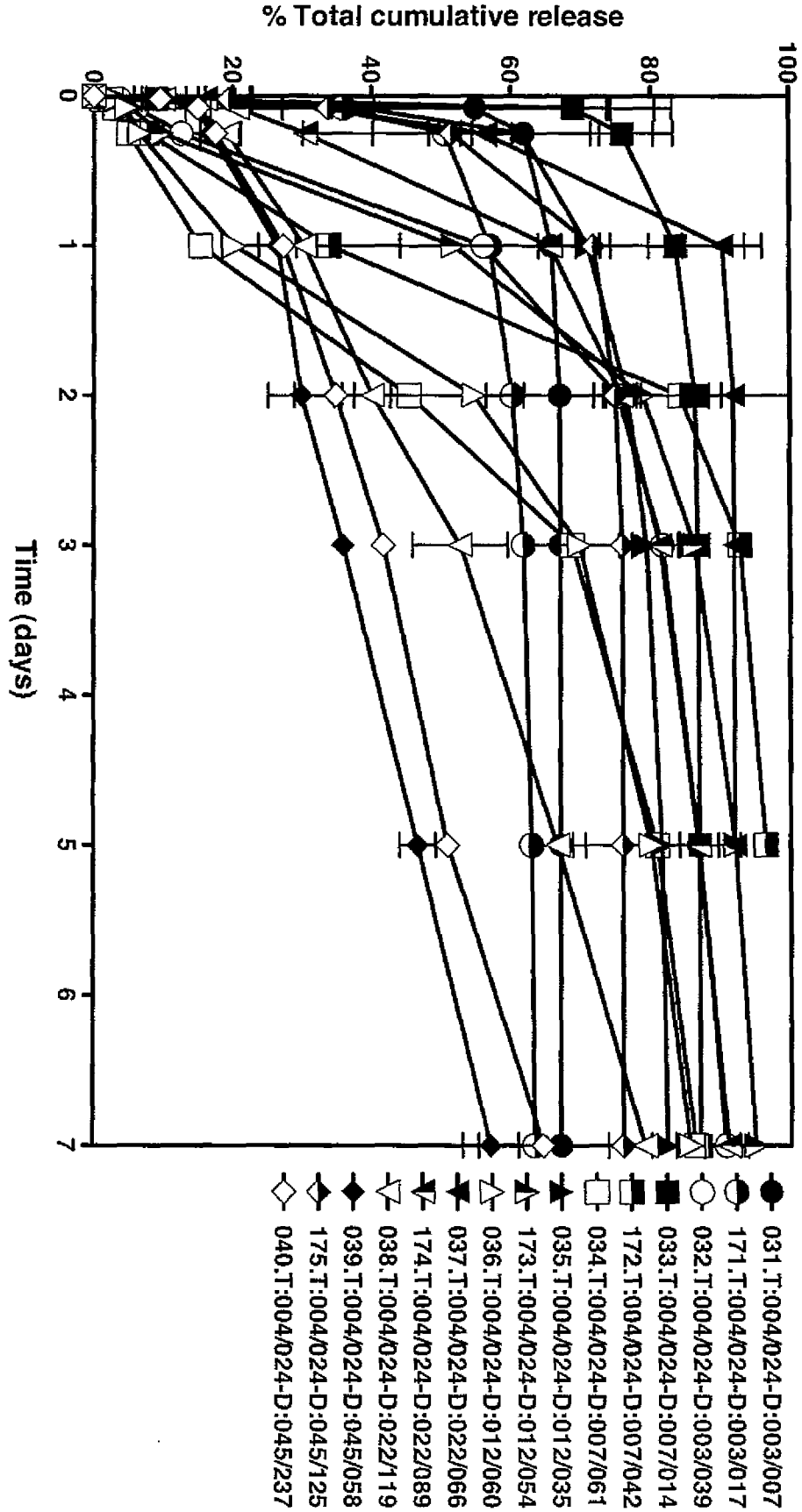
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
031.T:004/024-D:003/007
171.T:004/024-D:003/017
032.T:004/024-D:003/039
033.T:004/024-D:007/014
172.T:004/024-D:007/042
034.T:004/024-D:007/061
035.T:004/024-D:012/035
173.T:004/024-D:012/054
036.T:004/024-D:012/060
037.T:004/024-D:022/066
174.T:004/024-D:022/089
038.T:004/024-D:022/119
039.T:004/024-D:045/058
175.T:004/024-D:045/125
040.T:004/024-D:045/237

FIGURE 7

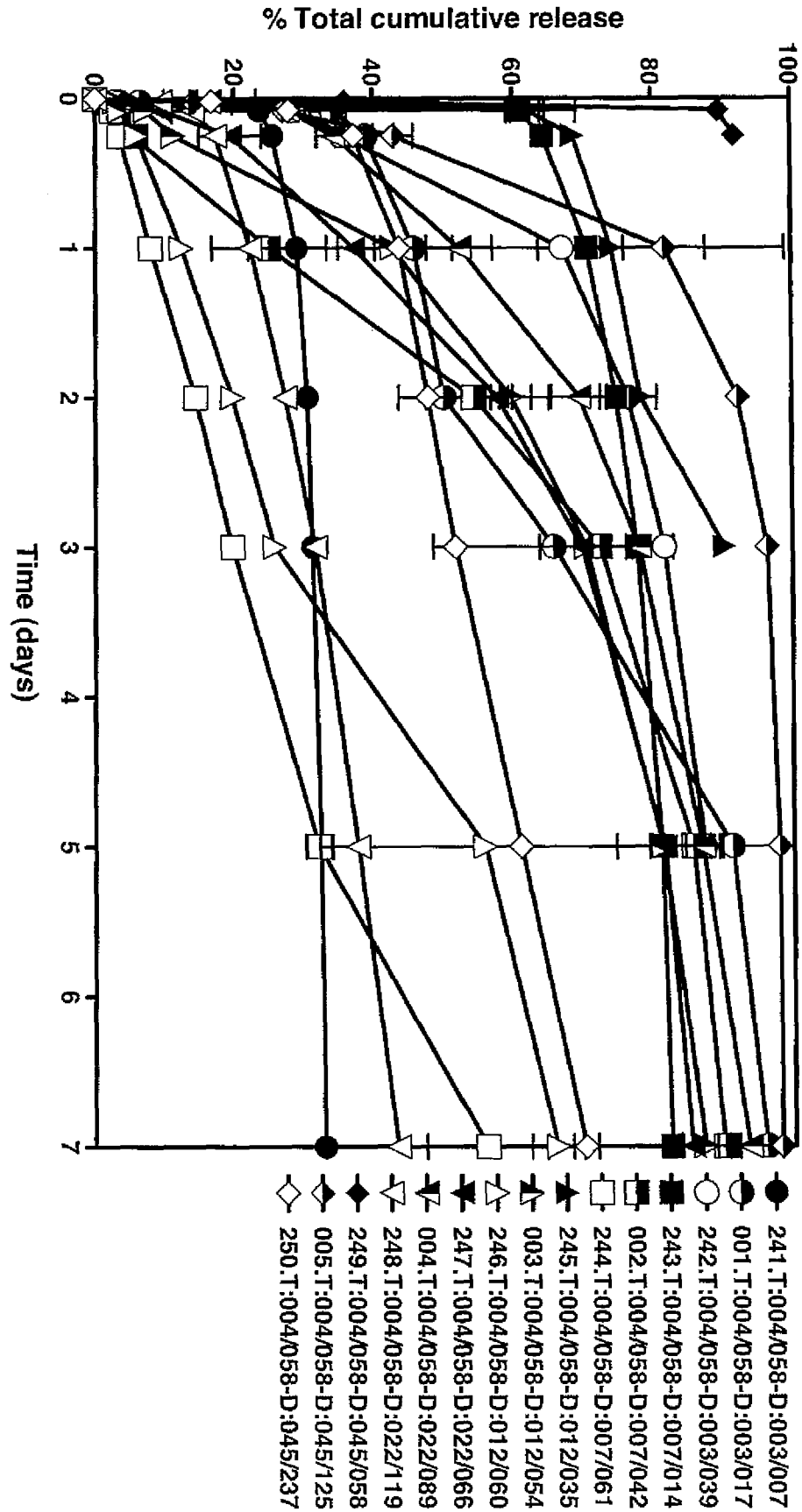
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
241.T:004/058-D:003/007
001.T:004/058-D:003/017
242.T:004/058-D:003/039
243.T:004/058-D:007/014
002.T:004/058-D:007/042
244.T:004/058-D:007/061
245.T:004/058-D:012/035
003.T:004/058-D:012/054
246.T:004/058-D:012/060
247.T:004/058-D:022/066
004.T:004/058-D:022/089
248.T:004/058-D:022/119
249.T:004/058-D:045/058
005.T:004/058-D:045/125
250.T:004/058-D:045/237

FIGURE 8

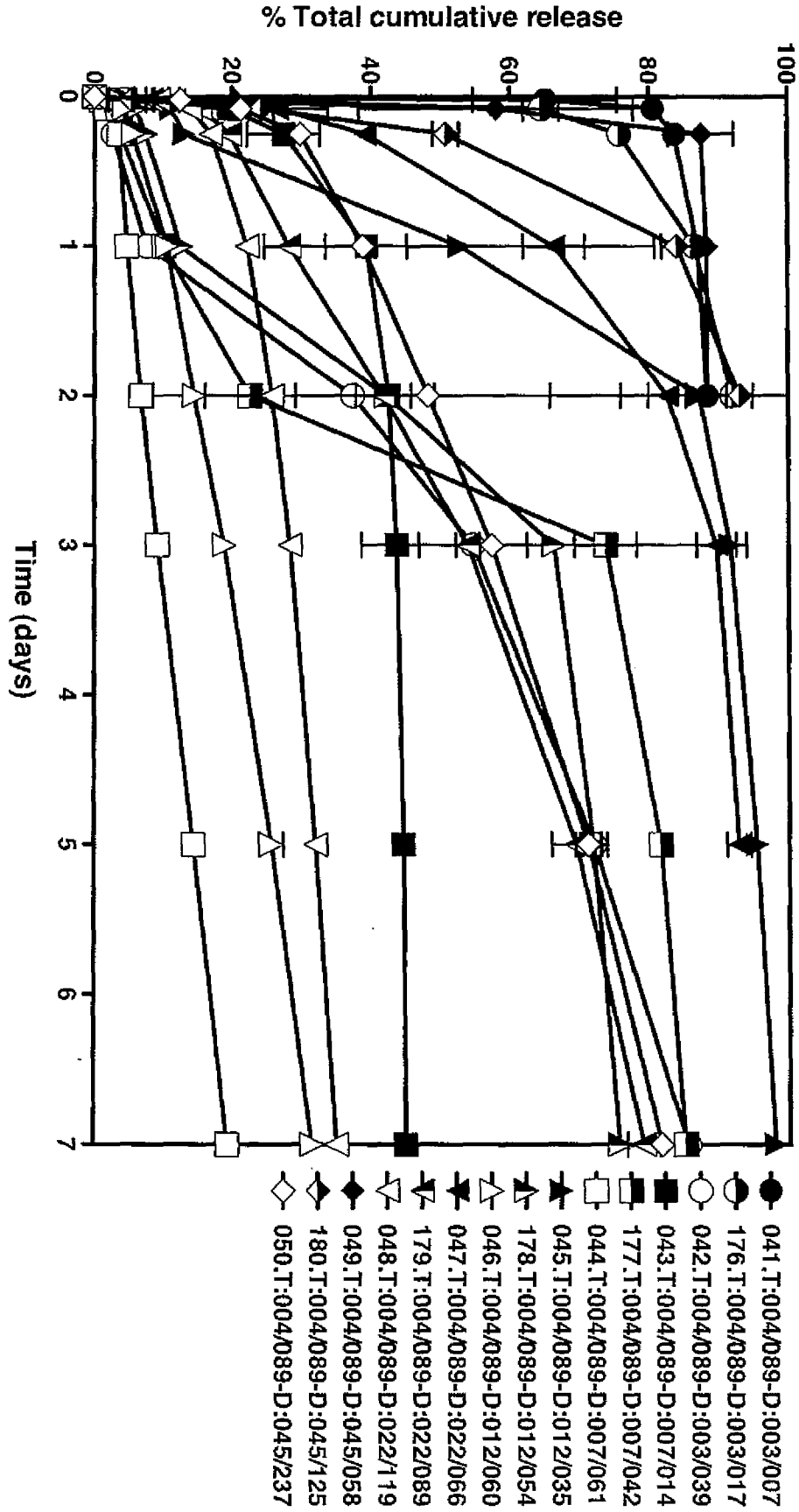
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
041.T:004/089-D:003/007
176.T:004/089-D:003/017
042.T:004/089-D:003/039
043.T:004/089-D:007/014
177.T:004/089-D:007/042
044.T:004/089-D:007/061
045.T:004/089-D:012/035
178.T:004/089-D:012/054
046.T:004/089-D:012/060
047.T:004/089-D:022/066
179.T:004/089-D:022/089
048.T:004/089-D:022/119
049.T:004/089-D:045/058
180.T:004/089-D:045/125
050.T:004/089-D:045/237

FIGURE 9

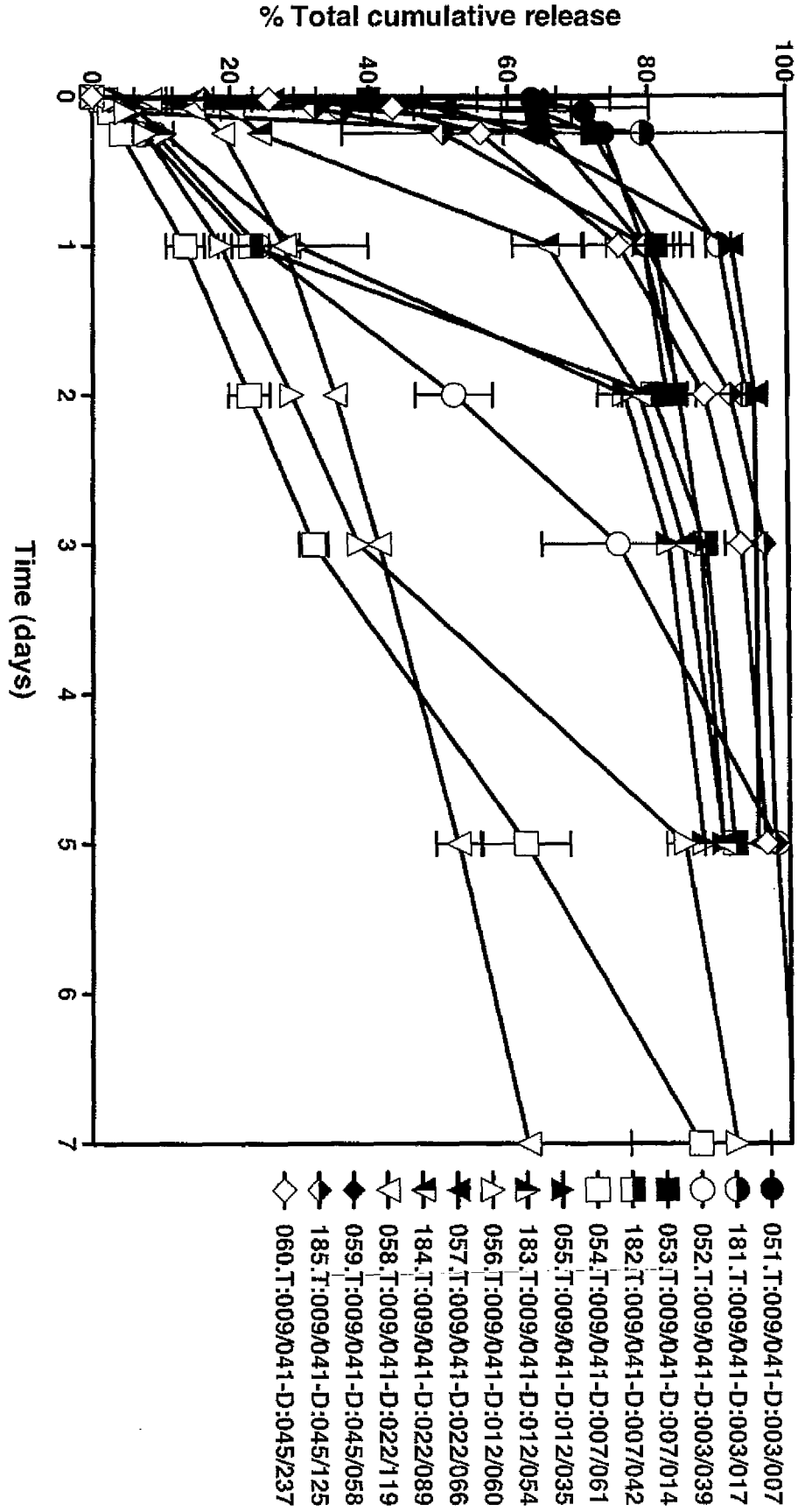
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
051.T:009/041-D:003/007
181.T:009/041-D:003/017
052.T:009/041-D:003/039
053.T:009/041-D:007/014
182.T:009/041-D:007/042
054.T:009/041-D:007/061
055.T:009/041-D:012/035
183.T:009/041-D:012/054
056.T:009/041-D:012/060
057.T:009/041-D:022/066
184.T:009/041-D:022/089
058.T:009/041-D:022/119
059.T:009/041-D:045/058
185.T:009/041-D:045/125
060.T:009/041-D:045/237

FIGURE 10

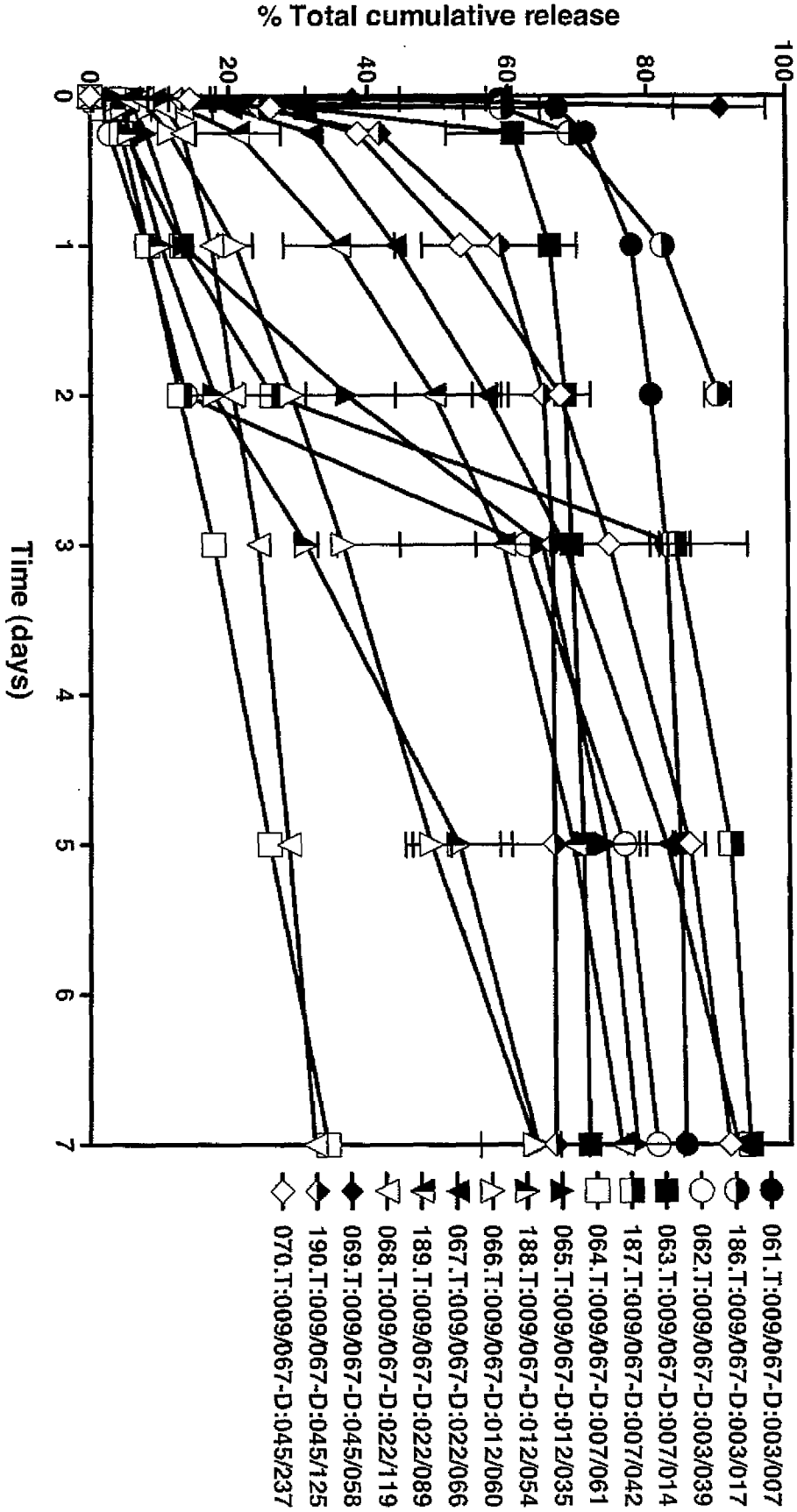
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
061.T:009/067-D:003/007
186.T:009/067-D:003/017
062.T:009/067-D:003/039
063.T:009/067-D:007/014
187.T:009/067-D:007/042
064.T:009/067-D:007/061
065.T:009/067-D:012/035
188.T:009/067-D:012/054
066.T:009/067-D:012/060
067.T:009/067-D:022/066
189.T:009/067-D:022/089
068.T:009/067-D:022/119
069.T:009/067-D:045/058
190.T:009/067-D:045/125
070.T:009/067-D:045/237

FIGURE 11

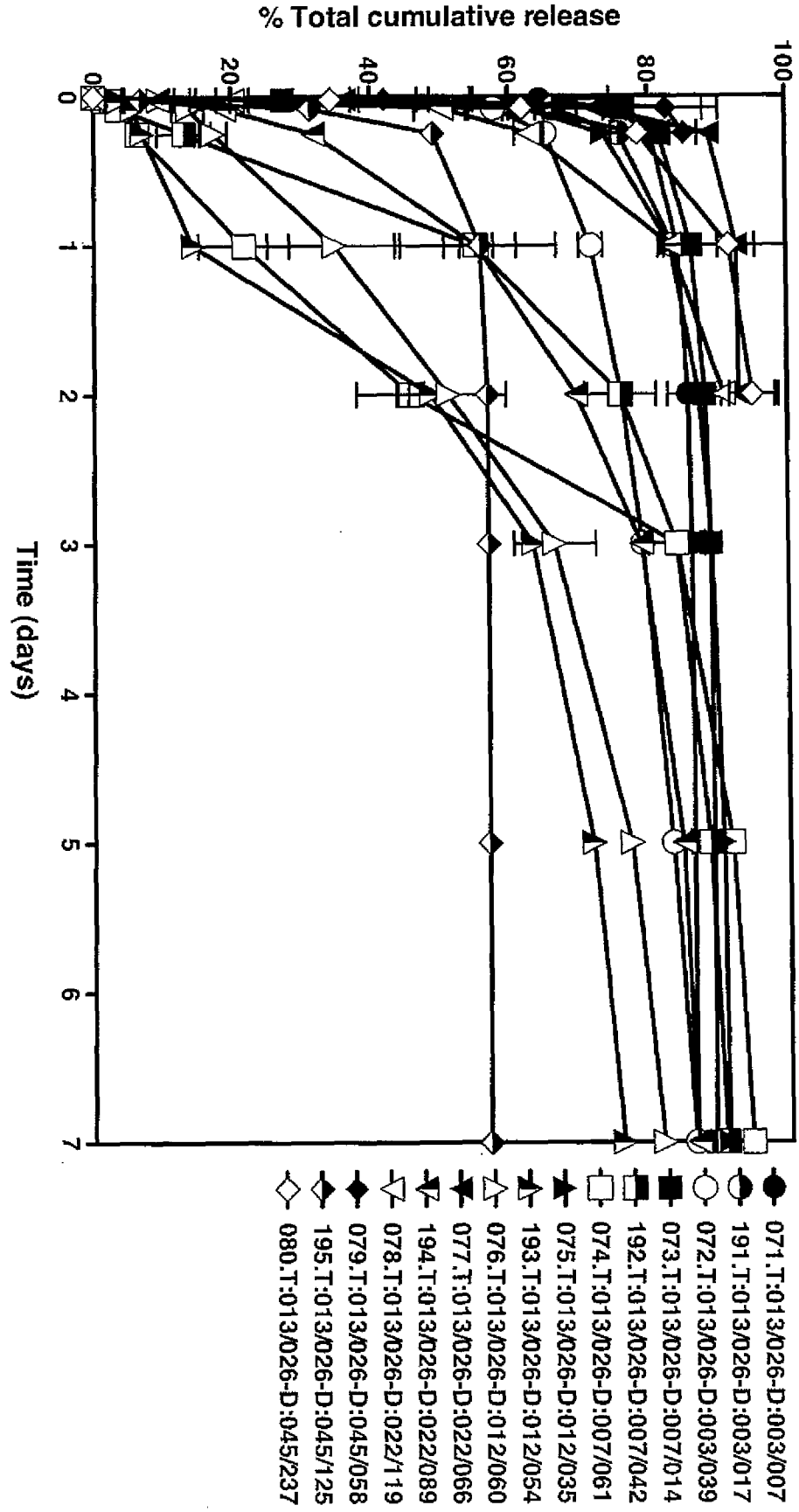
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
071.T:013/026-D:003/007
191.T:013/026-D:003/017
072.T:013/026-D:003/039
073.T:013/026-D:007/014
192.T:013/026-D:007/042
074.T:013/026-D:007/061
075.T:013/026-D:012/035
193.T:013/026-D:012/054
076.T:013/026-D:012/060
077.T:013/026-D:022/066
194.T:013/026-D:022/089
078.T:013/026-D:022/119
079.T:013/026-D:045/058
195.T:013/026-D:045/125
080.T:013/026-D:045/237

FIGURE 12

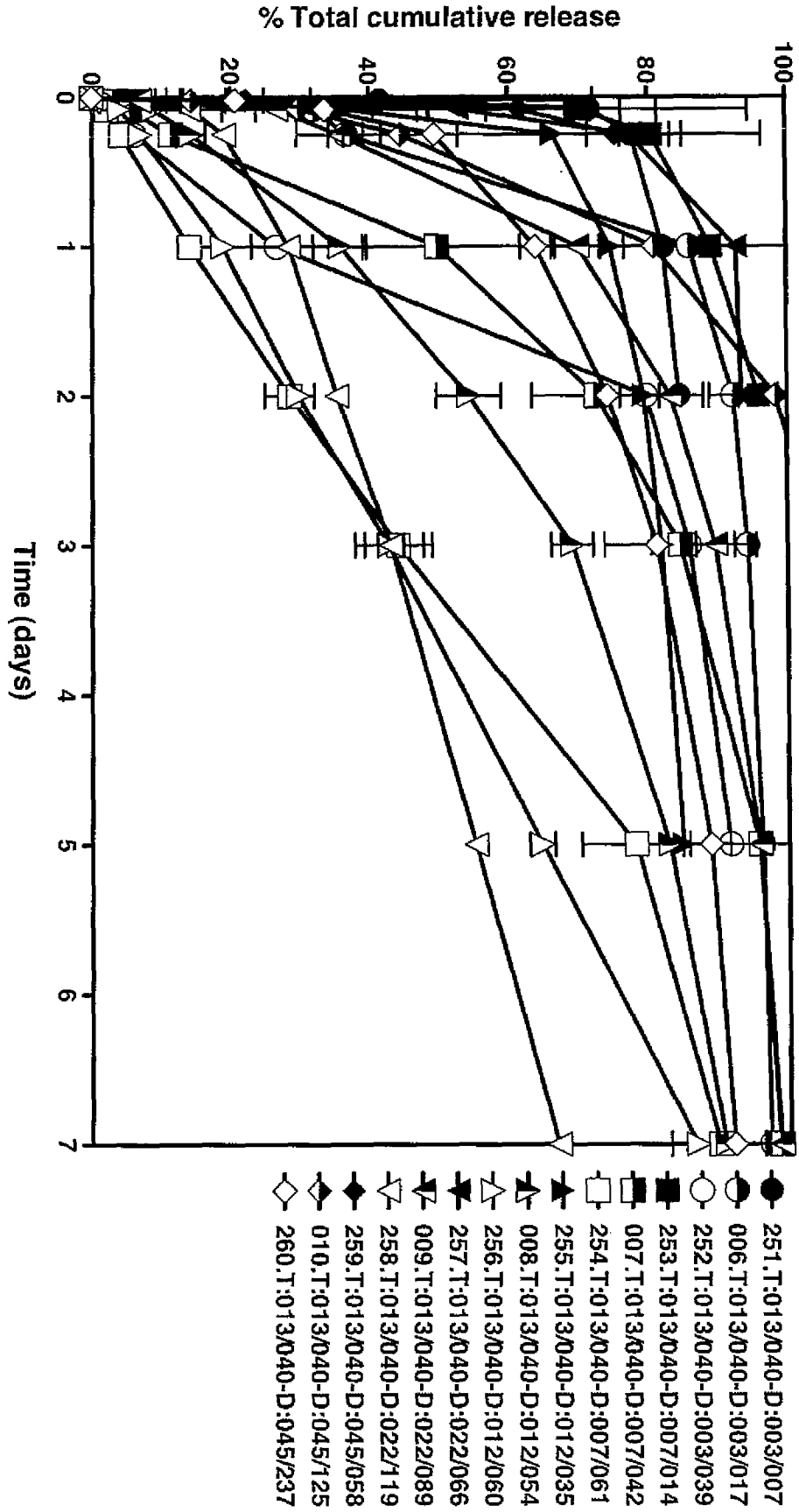
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
251.T:013/040-D:003/007
006.T:013/040-D:003/017
252.T:013/040-D:003/039
253.T:013/040-D:007/014
007.T:013/040-D:007/042
254.T:013/040-D:007/061
255.T:013/040-D:012/035
008.T:013/040-D:012/054
256.T:013/040-D:012/060
257.T:013/040-D:022/066
009.T:013/040-D:022/089
258.T:013/040-D:022/119
259.T:013/040-D:045/058
010.T:013/040-D:045/125
260.T:013/040-D:045/237

FIGURE 13

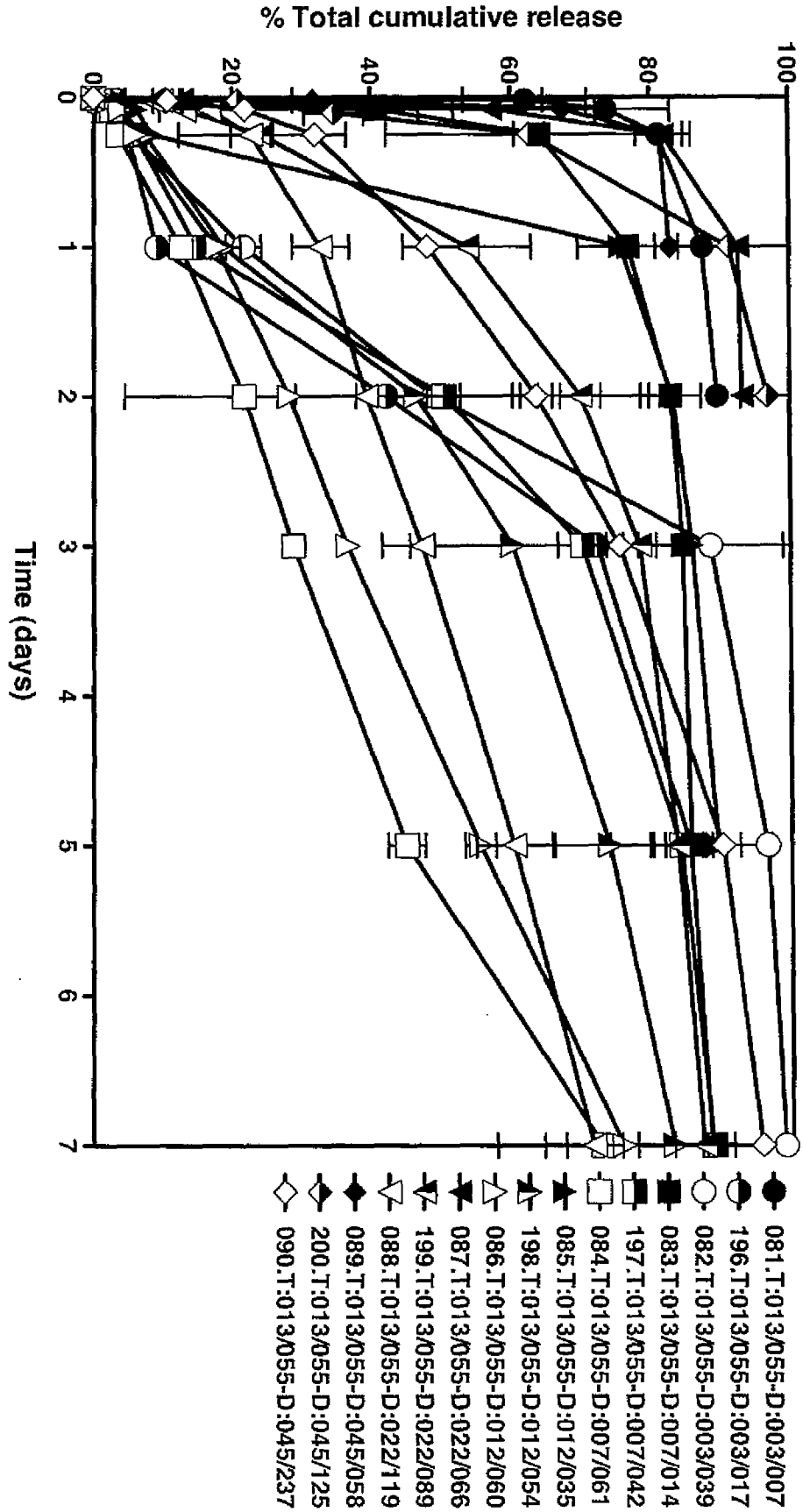
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
081.T:013/055-D:003/007
196.T:013/055-D:003/017
082.T:013/055-D:003/039
083.T:013/055-D:007/014
197.T:013/055-D:007/042
084.T:013/055-D:007/061
085.T:013/055-D:012/035
198.T:013/055-D:012/054
086.T:013/055-D:012/060
087.T:013/055-D:022/066
199.T:013/055-D:022/089
088.T:013/055-D:022/119
089.T:013/055-D:045/058
200.T:013/055-D:045/125
090.T:013/055-D:045/237

FIGURE 14

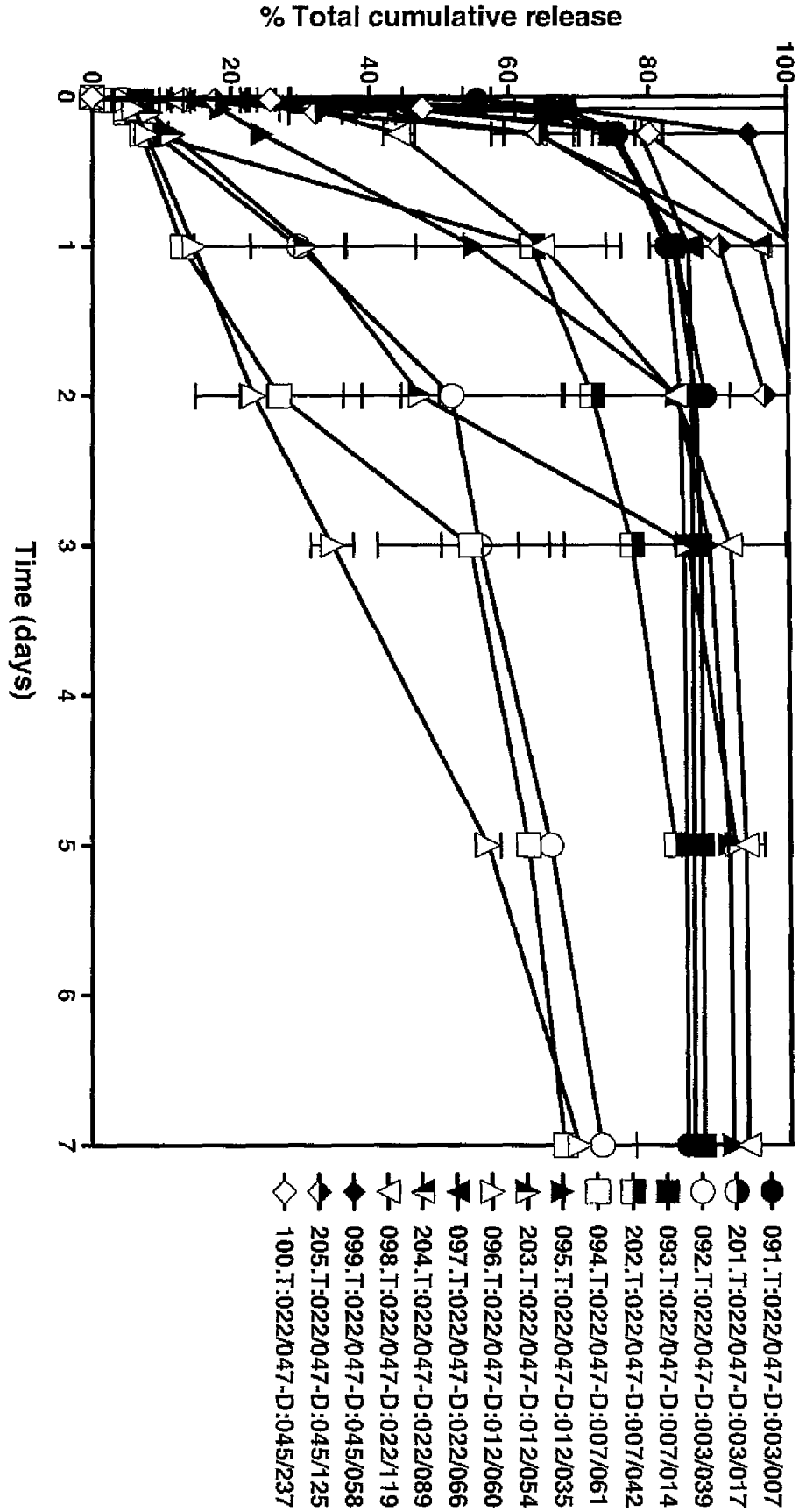
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
091.T:022/047-D:003/007
201.T:022/047-D:003/017
092.T:022/047-D:003/039
093.T:022/047-D:007/014
202.T:022/047-D:007/042
094.T:022/047-D:007/061
095.T:022/047-D:012/035
203.T:022/047-D:012/054
096.T:022/047-D:012/060
097.T:022/047-D:022/066
204.T:022/047-D:022/089
098.T:022/047-D:022/119
099.T:022/047-D:045/058
205.T:022/047-D:045/125
100.T:022/047-D:045/237

FIGURE 15

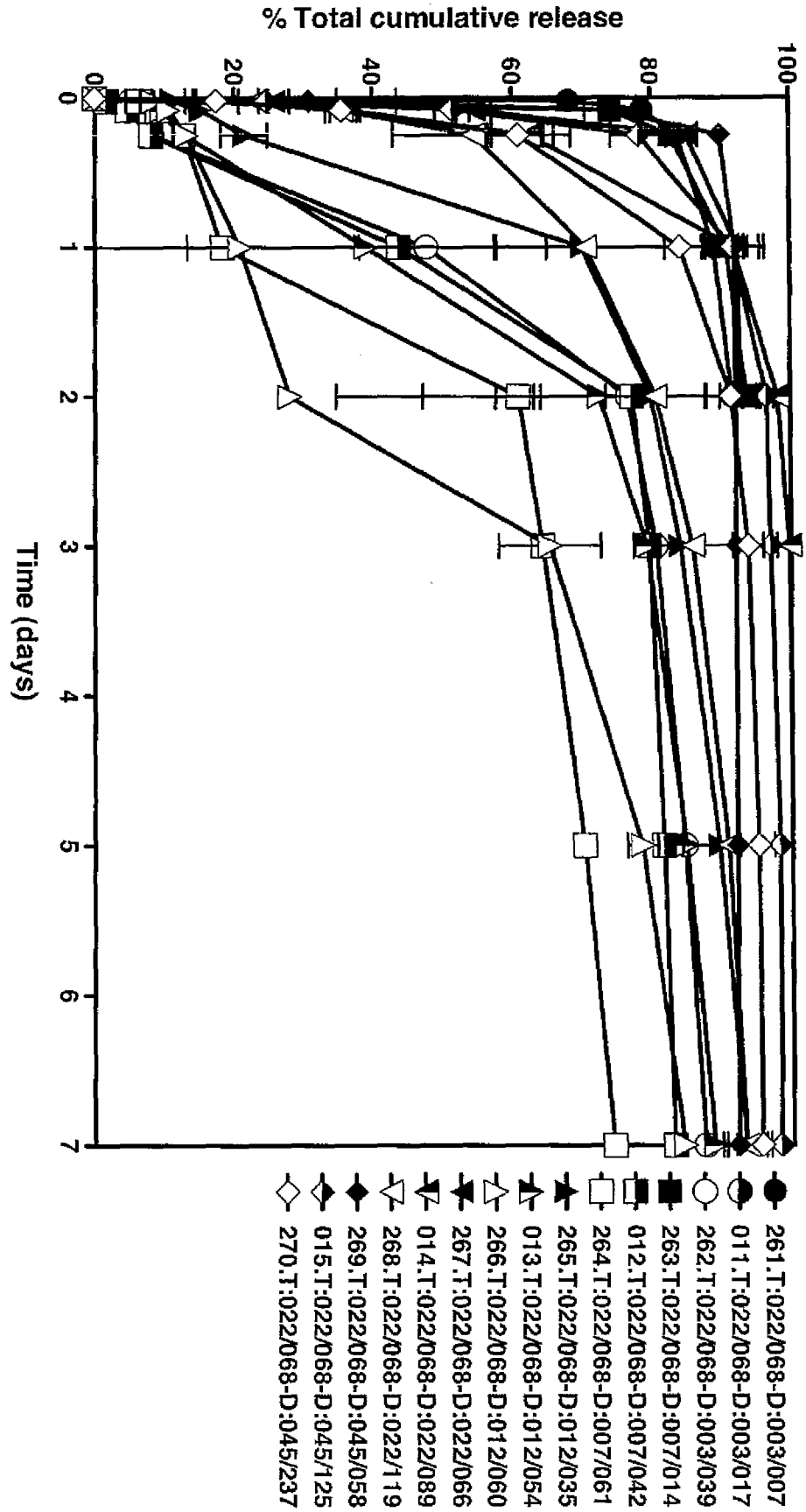
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
261.T:022/068-D:003/007
011.T:022/068-D:003/017
262.T:022/068-D:003/039
263.T:022/068-D:007/014
012.T:022/068-D:007/042
264.T:022/068-D:007/061
265.T:022/068-D:012/035
013.T:022/068-D:012/054
266.T:022/068-D:012/060
267.T:022/068-D:022/066
014.T:022/068-D:022/089
268.T:022/068-D:022/119
269.T:022/068-D:045/058
015.T:022/068-D:045/125
270.T:022/068-D:045/237

FIGURE 16

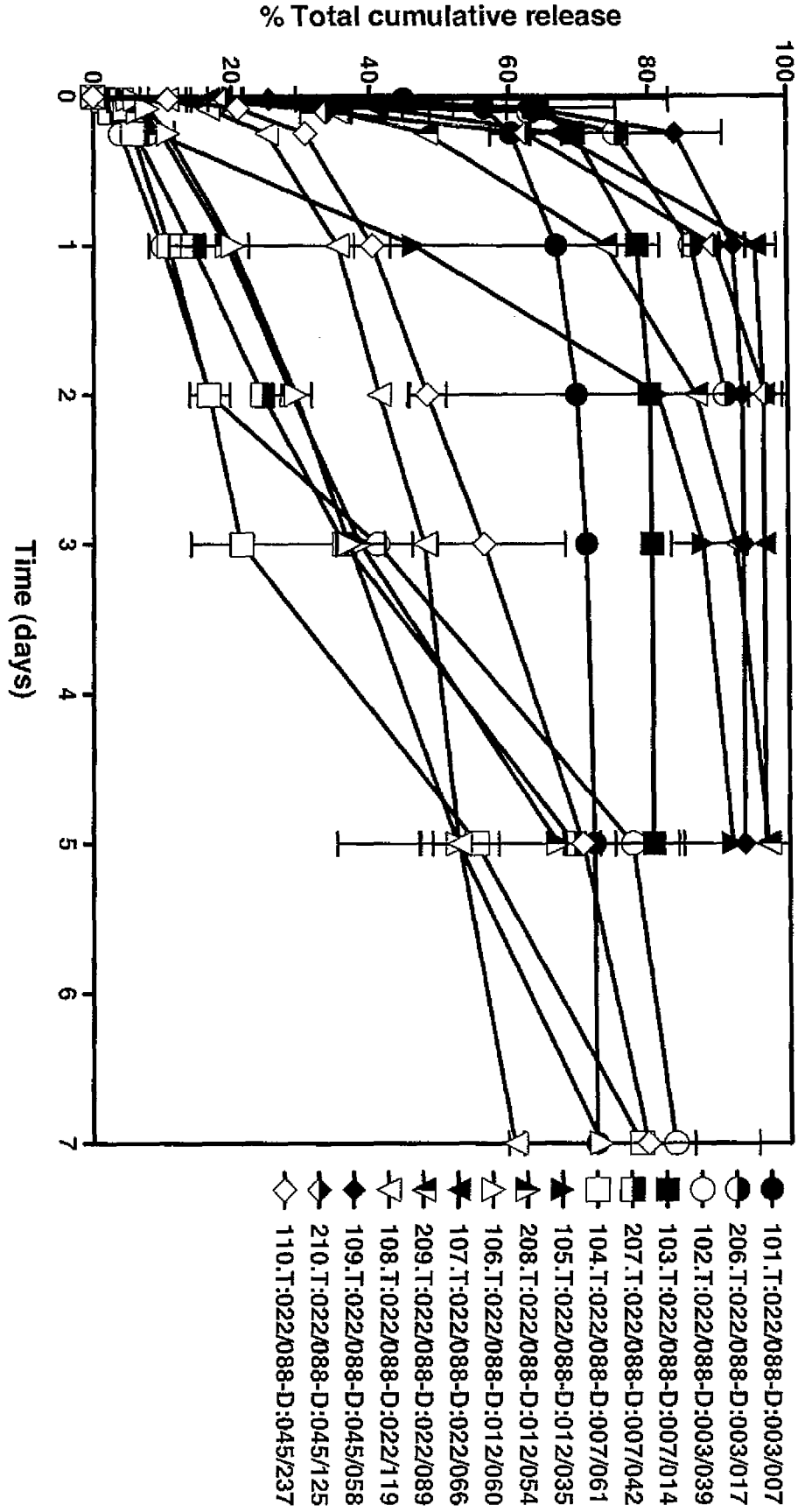
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
101.T:022/088-D:003/007
206.T:022/088-D:003/017
102.T:022/088-D:003/039
103.T:022/088-D:007/014
207.T:022/088-D:007/042
104.T:022/088-D:007/061
105.T:022/088-D:012/035
208.T:022/088-D:012/054
106.T:022/088-D:012/060
107.T:022/088-D:022/066
209.T:022/088-D:022/089
108.T:022/088-D:022/119
109.T:022/088-D:045/058
210.T:022/088-D:045/125
110.T:022/088-D:045/237

FIGURE 17

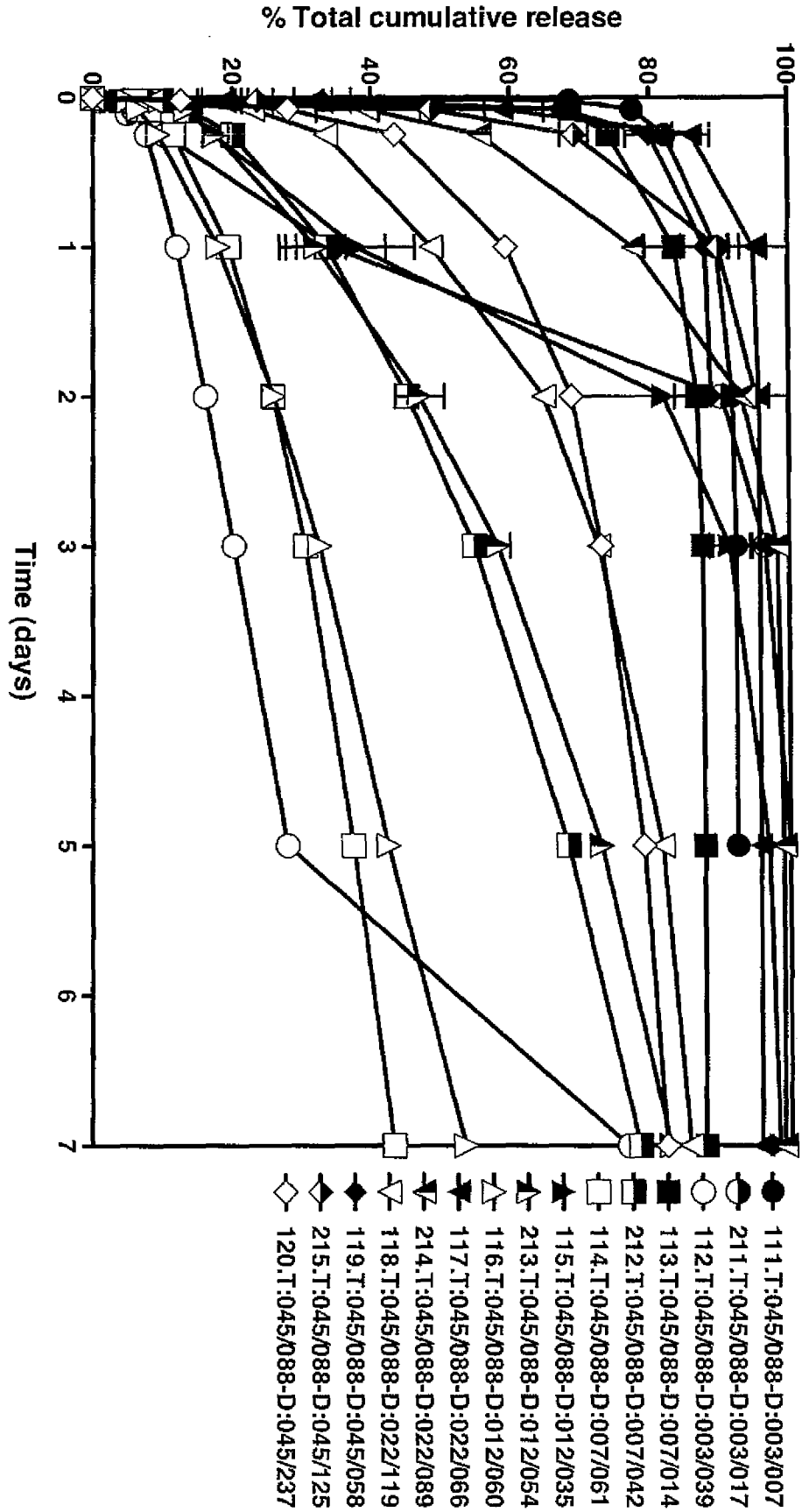
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
111.T:045/088-D:003/007
211.T:045/088-D:003/017
112.T:045/088-D:003/039
113.T:045/088-D:007/014
212.T:045/088-D:007/042
114.T:045/088-D:007/061
115.T:045/088-D:012/035
213.T:045/088-D:012/054
116.T:045/088-D:012/060
117.T:045/088-D:022/066
214.T:045/088-D:022/089
118.T:045/088-D:022/119
119.T:045/088-D:045/058
215.T:045/088-D:045/125
120.T:045/088-D:045/237

FIGURE 18

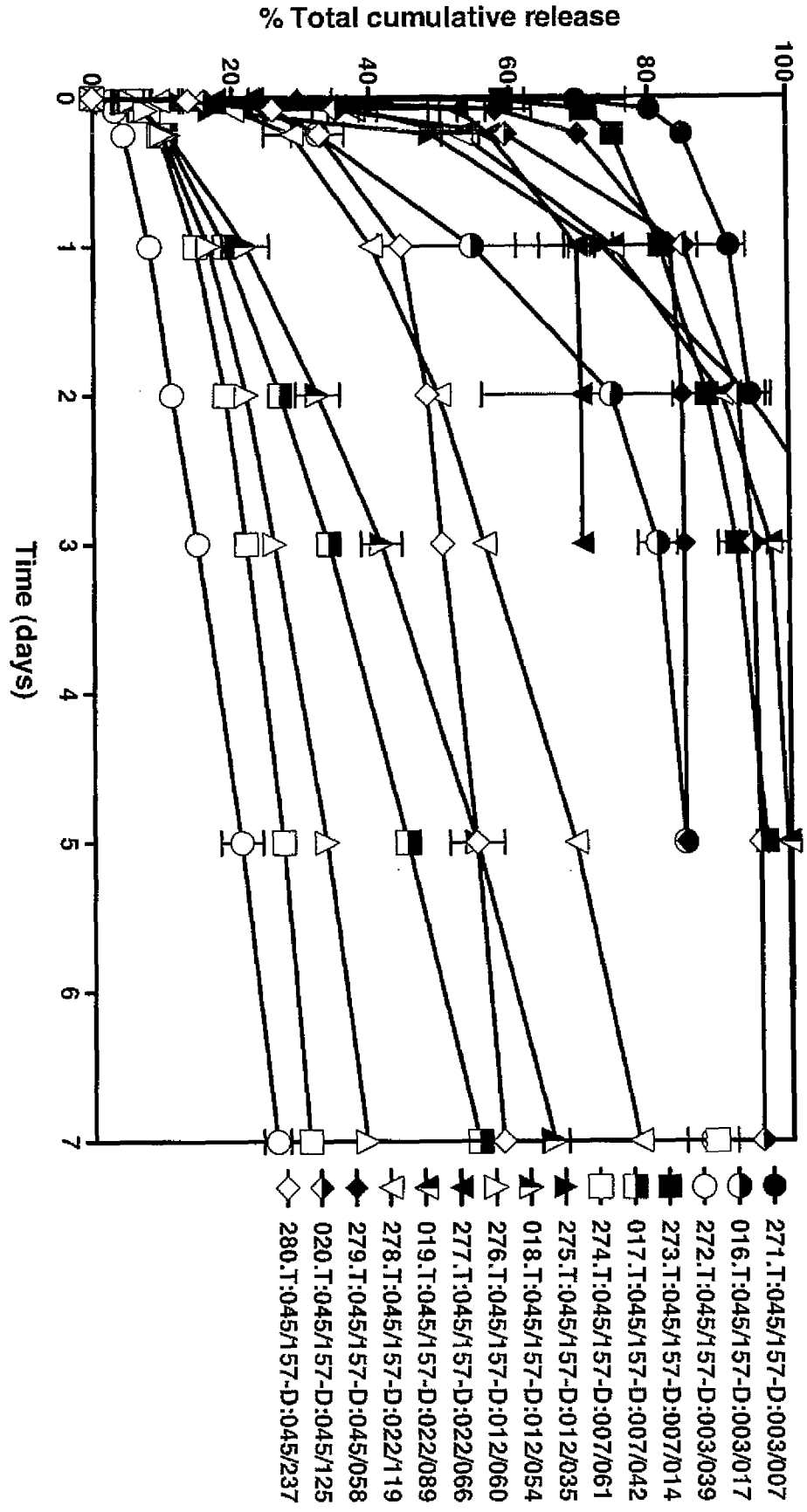
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
271.T:045/157-D:003/007
016.T:045/157-D:003/017
272.T:045/157-D:003/039
273.T:045/157-D:007/014
017.T:045/157-D:007/042
274.T:045/157-D:007/061
275.T:045/157-D:012/035
018.T:045/157-D:012/054
276.T:045/157-D:012/060
277.T:045/157-D:022/066
019.T:045/157-D:022/089
278.T:045/157-D:022/119
279.T:045/157-D:045/058
020.T:045/157-D:045/125
280.T:045/157-D:045/237

FIGURE 19

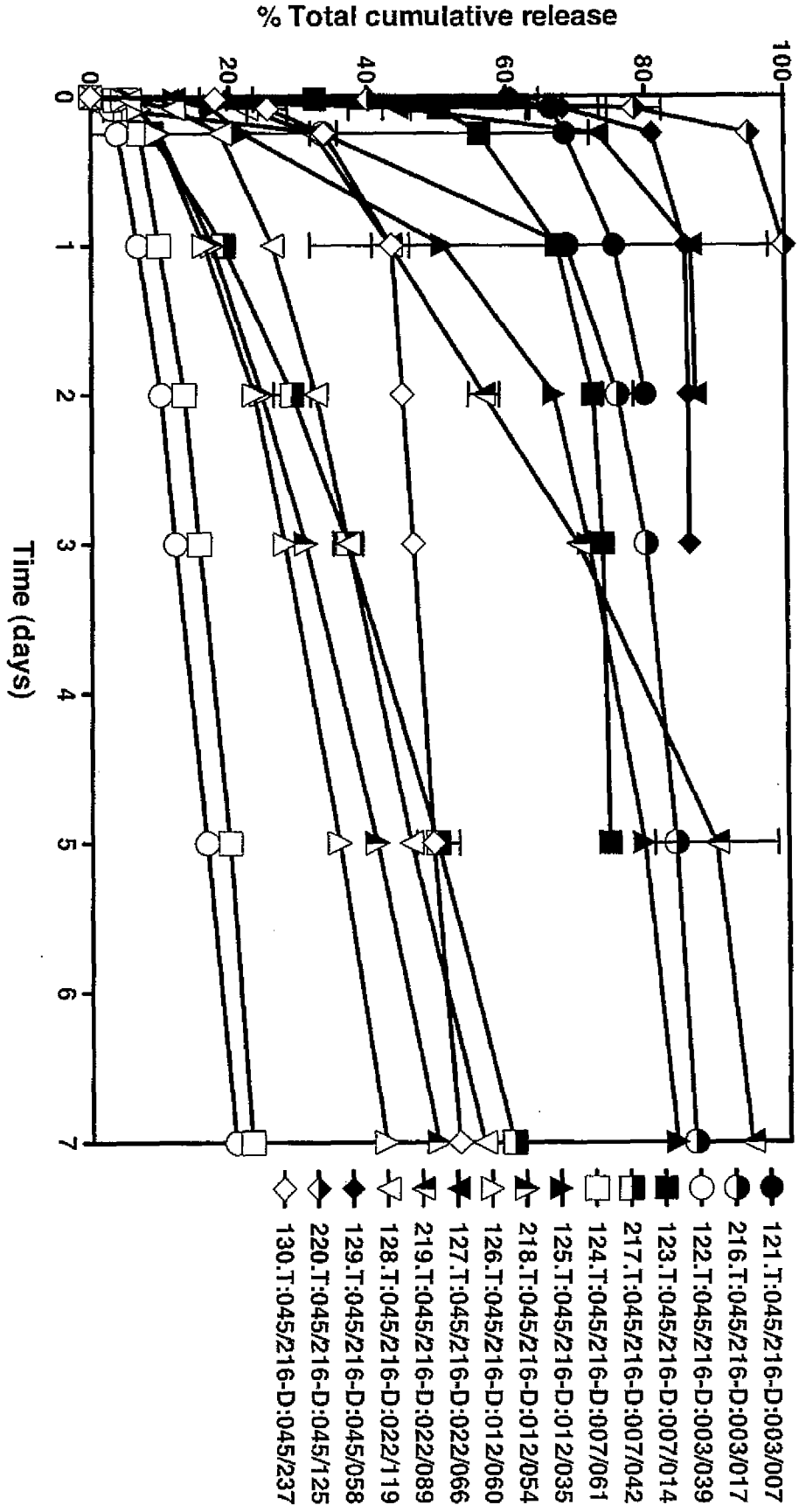
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
121.T:045/216-D:003/007
216.T:045/216-D:003/017
122.T:045/216-D:003/039
123.T:045/216-D:007/014
217.T:045/216-D:007/042
124.T:045/216-D:007/061
125.T:045/216-D:012/035
218.T:045/216-D:012/054
126.T:045/216-D:012/060
127.T:045/216-D:022/066
219.T:045/216-D:022/089
128.T:045/216-D:022/119
129.T:045/216-D:045/058
220.T:045/216-D:045/125
130.T:045/216-D:045/237

FIGURE 20

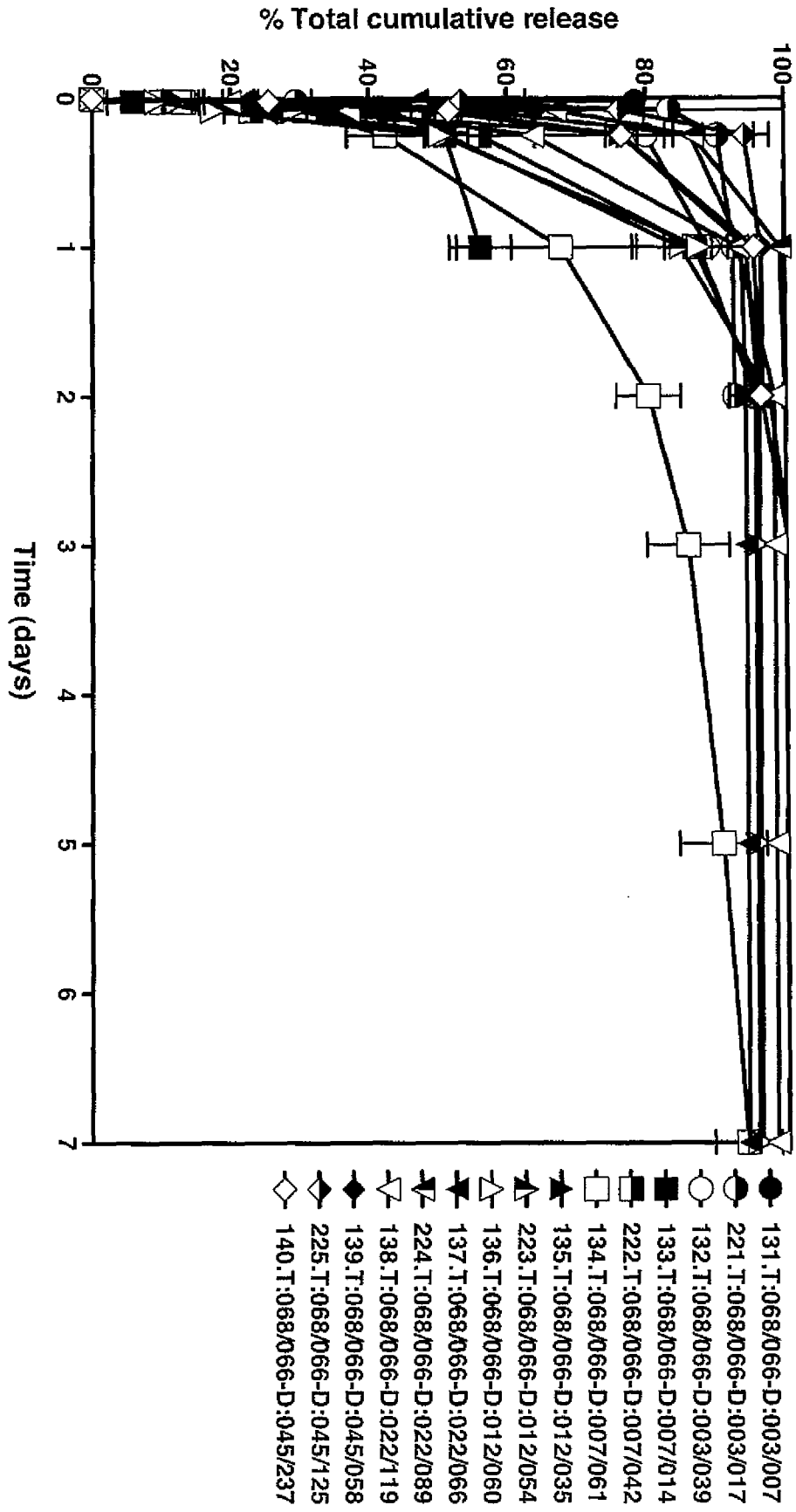
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
131.T:068/066-D:003/007
221.T:068/066-D:003/017
132.T:068/066-D:003/039
133.T:068/066-D:007/014
222.T:068/066-D:007/042
134.T:068/066-D:007/061
135.T:068/066-D:012/035
223.T:068/066-D:012/054
136.T:068/066-D:012/060
137.T:068/066-D:022/066
224.T:068/066-D:022/089
138.T:068/066-D:022/119
139.T:068/066-D:045/058
225.T:068/066-D:045/125
140.T:068/066-D:045/237

FIGURE 21

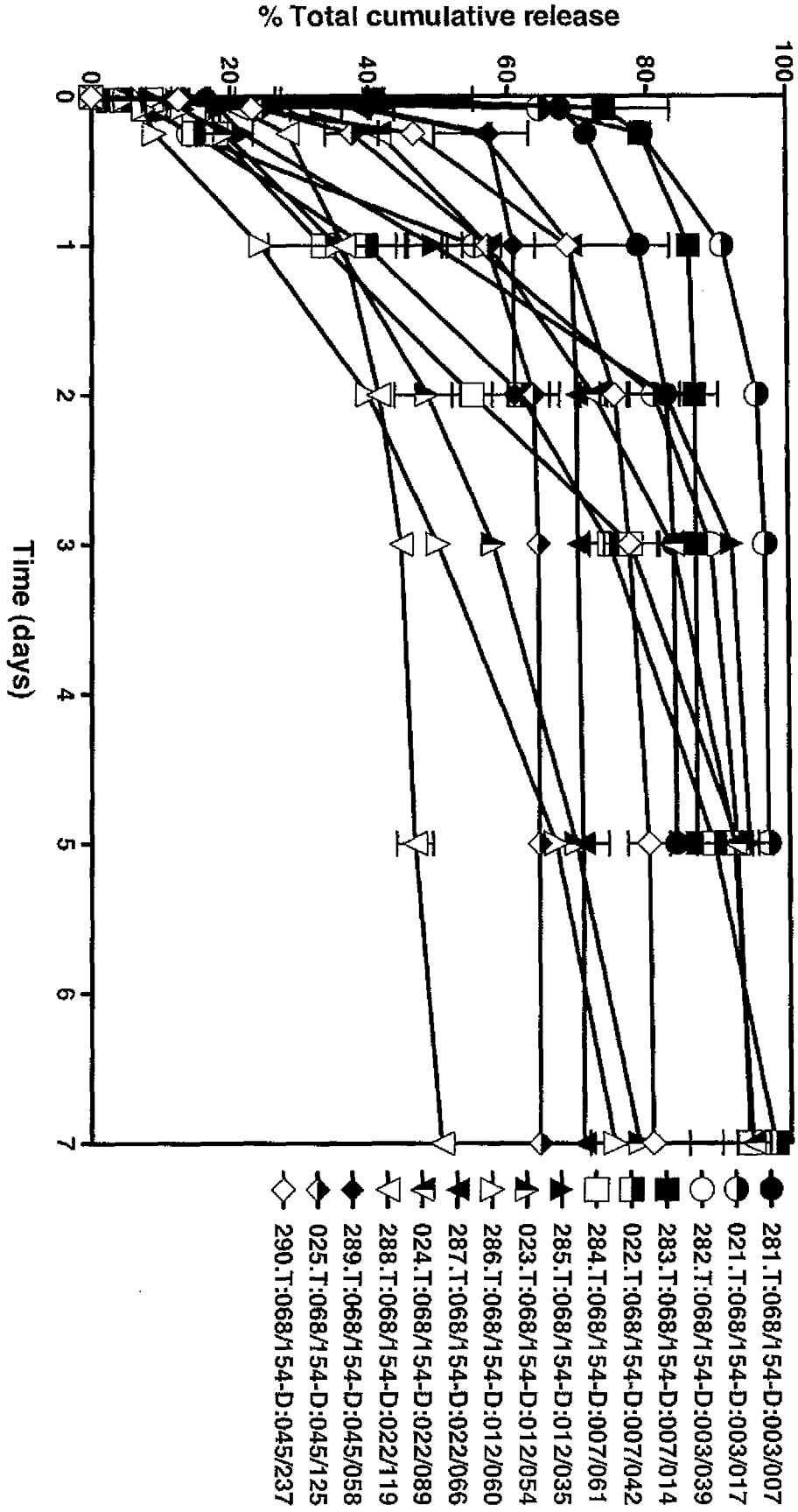
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
281.T:068/154-D:003/007
021.T:068/154-D:003/017
282.T:068/154-D:003/039
283.T:068/154-D:007/014
022.T:068/154-D:007/042
284.T:068/154-D:007/061
285.T:068/154-D:012/035
023.T:068/154-D:012/054
286.T:068/154-D:012/060
287.T:068/154-D:022/066
024.T:068/154-D:022/089
288.T:068/154-D:022/119
289.T:068/154-D:045/058
025.T:068/154-D:045/125
290.T:068/154-D:045/237

FIGURE 22

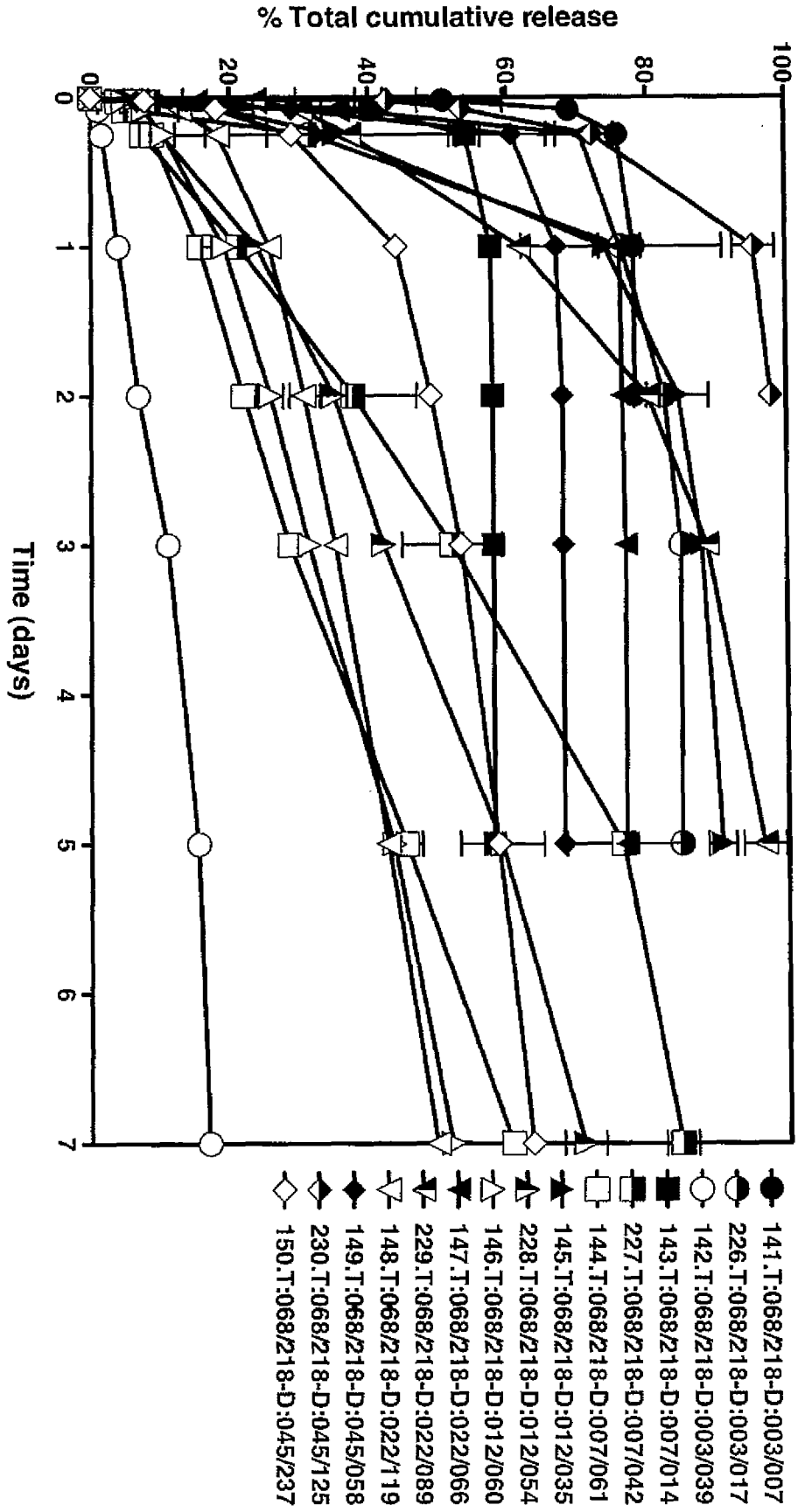
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
141.T:068/218-D:003/007
226.T:068/218-D:003/017
142.T:068/218-D:003/039
143.T:068/218-D:007/014
227.T:068/218-D:007/042
144.T:068/218-D:007/061
145.T:068/218-D:012/035
228.T:068/218-D:012/054
146.T:068/218-D:012/060
147.T:068/218-D:022/066
229.T:068/218-D:022/089
148.T:068/218-D:022/119
149.T:068/218-D:045/058
230.T:068/218-D:045/125
150.T:068/218-D:045/237

FIGURE 23

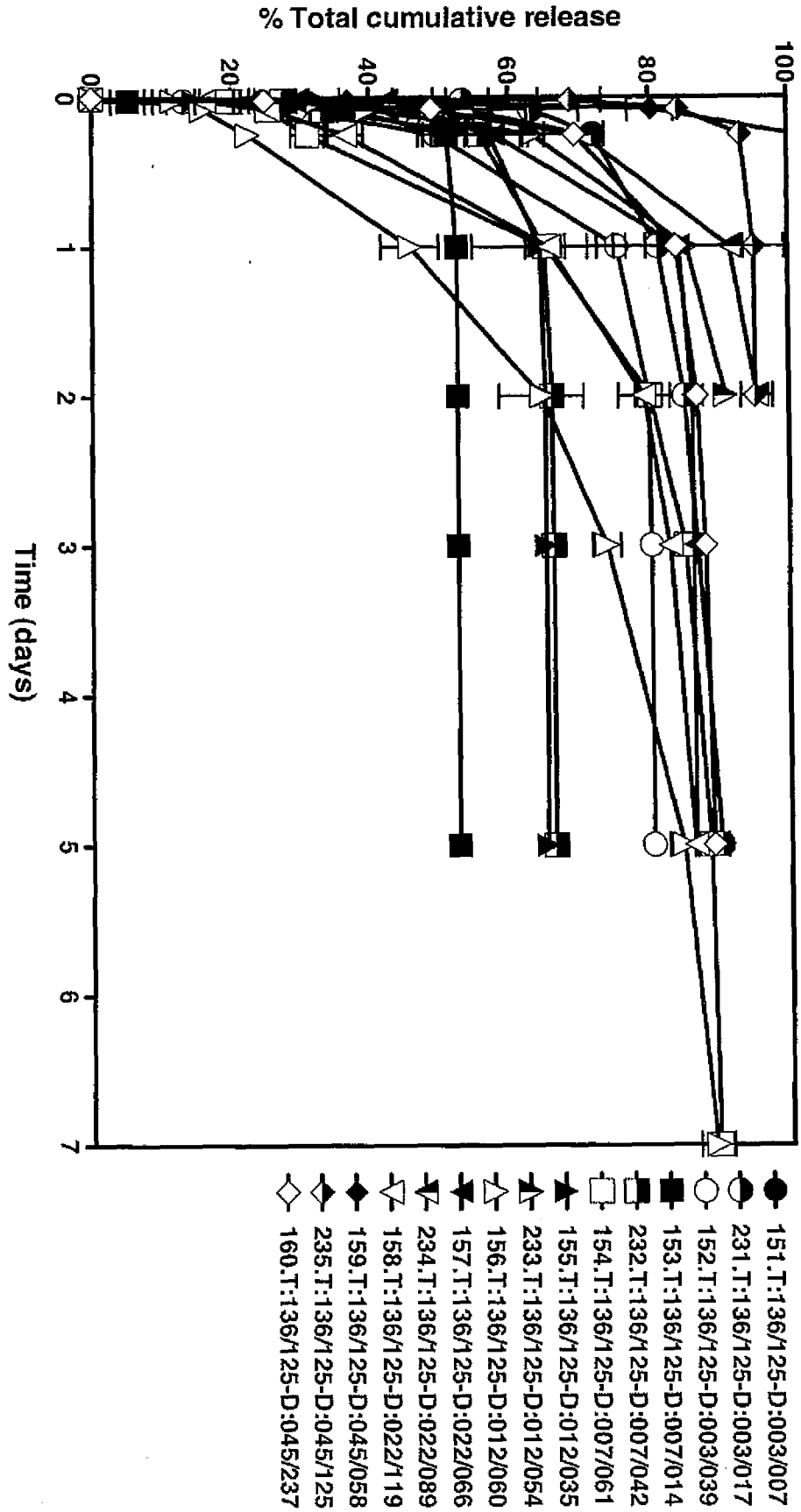
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
151.T:136/125-D:003/007
231.T:136/125-D:003/017
152.T:136/125-D:003/039
153.T:136/125-D:007/014
232.T:136/125-D:007/042
154.T:136/125-D:007/061
155.T:136/125-D:012/035
233.T:136/125-D:012/054
156.T:136/125-D:012/060
157.T:136/125-D:022/066
234.T:136/125-D:022/089
158.T:136/125-D:022/119
159.T:136/125-D:045/058
235.T:136/125-D:045/125
160.T:136/125-D:045/237

FIGURE 24

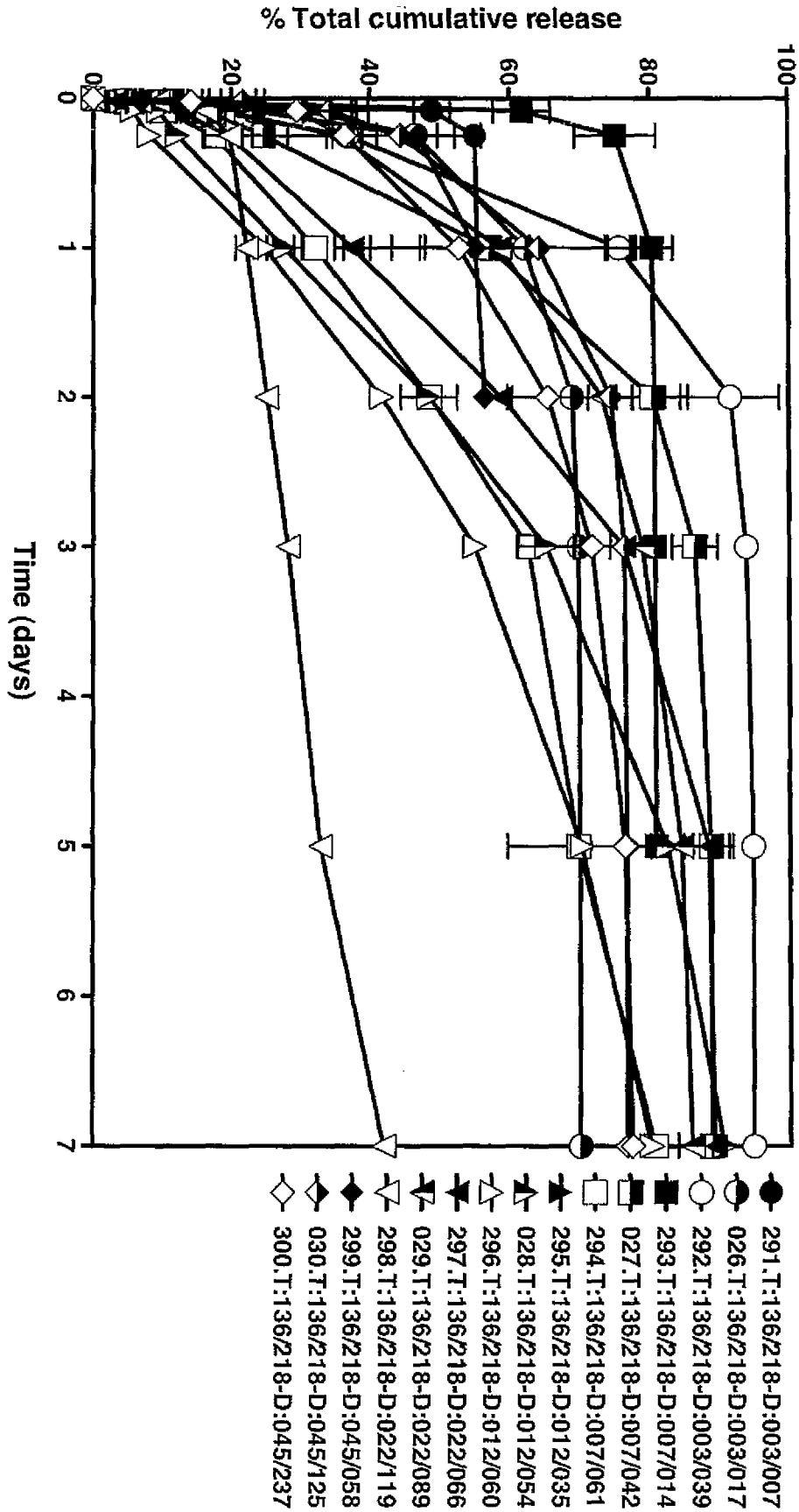
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
291.T:136/218-D:003/007
026.T:136/218-D:003/017
292.T:136/218-D:003/039
293.T:136/218-D:007/014
027.T:136/218-D:007/042
294.T:136/218-D:007/061
295.T:136/218-D:012/035
028.T:136/218-D:012/054
296.T:136/218-D:012/060
297.T:136/218-D:022/066
029.T:136/218-D:022/089
298.T:136/218-D:022/119
299.T:136/218-D:045/058
030.T:136/218-D:045/125
300.T:136/218-D:045/237

FIGURE 25

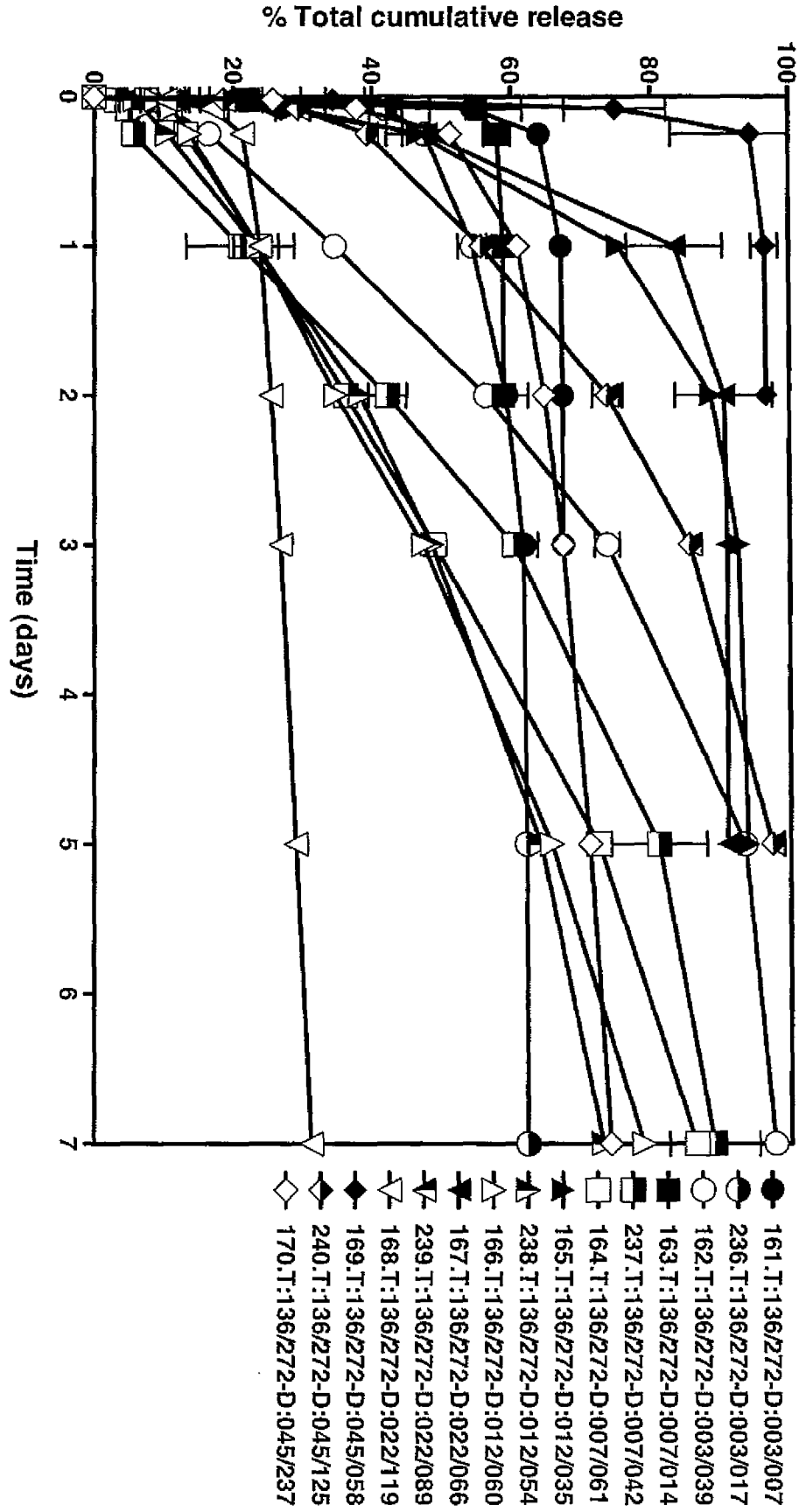
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
161.T:136/272-D:003/007
236.T:136/272-D:003/017
162.T:136/272-D:003/039
163.T:136/272-D:007/014
237.T:136/272-D:007/042
164.T:136/272-D:007/061
165.T:136/272-D:012/035
238.T:136/272-D:012/054
166.T:136/272-D:012/060
167.T:136/272-D:022/066
239.T:136/272-D:022/089
168.T:136/272-D:022/119
169.T:136/272-D:045/058
240.T:136/272-D:045/125
170.T:136/272-D:045/237

FIGURE 26

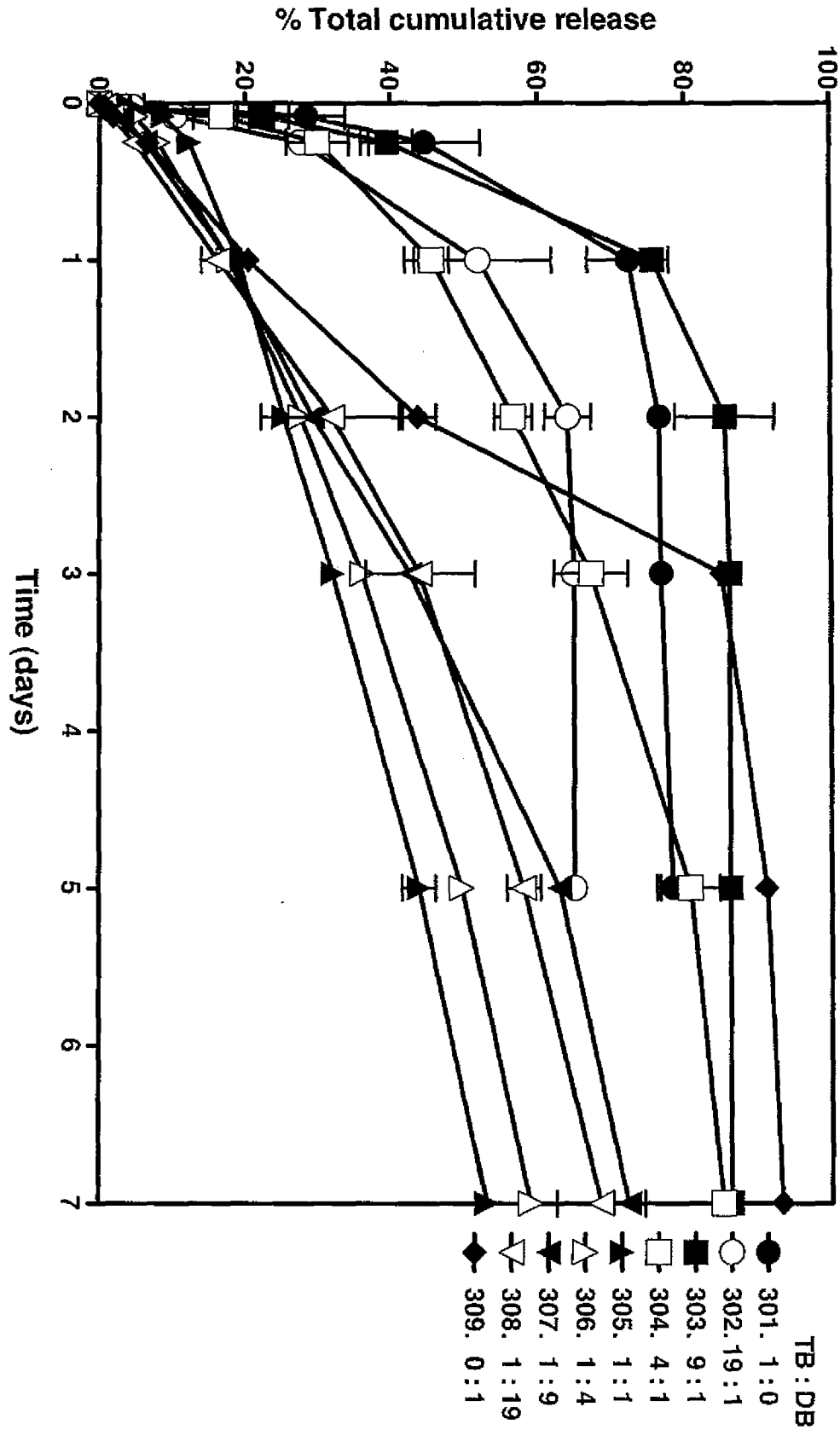
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
TB : DB
301. 1 : 0
302. 19 : 1
303. 9 : 1
304. 4 : 1
305. 1 : 1
306. 1 : 4
307. 1 : 9
308. 1 : 19
309. 0 : 1

FIGURE 27

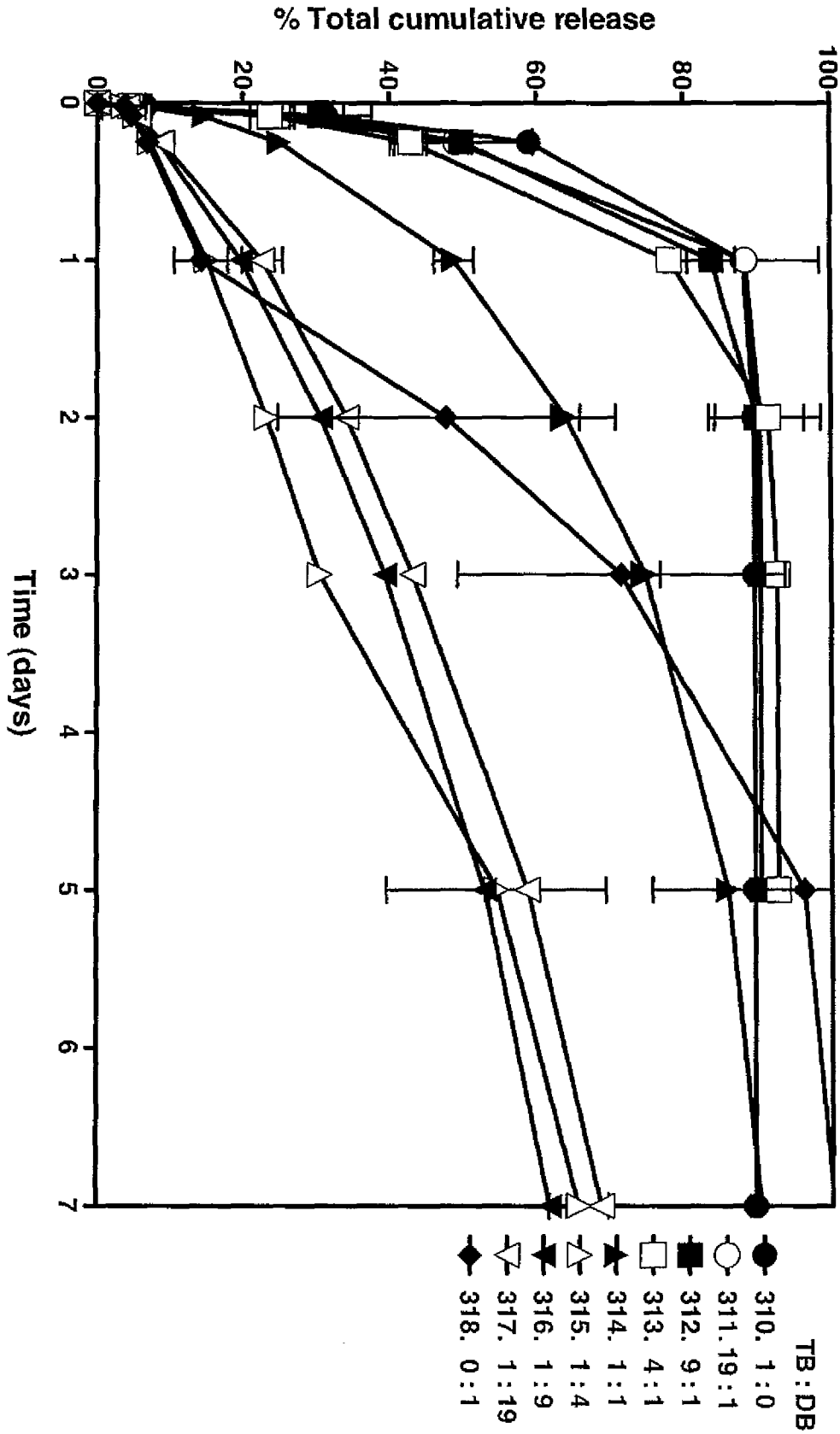
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
TB : DB
310. 1 : 0
311. 19 : 1
312. 9 : 1
313. 4 : 1
314. 1 : 1
315. 1 : 4
316. 1 : 9
317. 1 : 19
318. 0 : 1

FIGURE 28

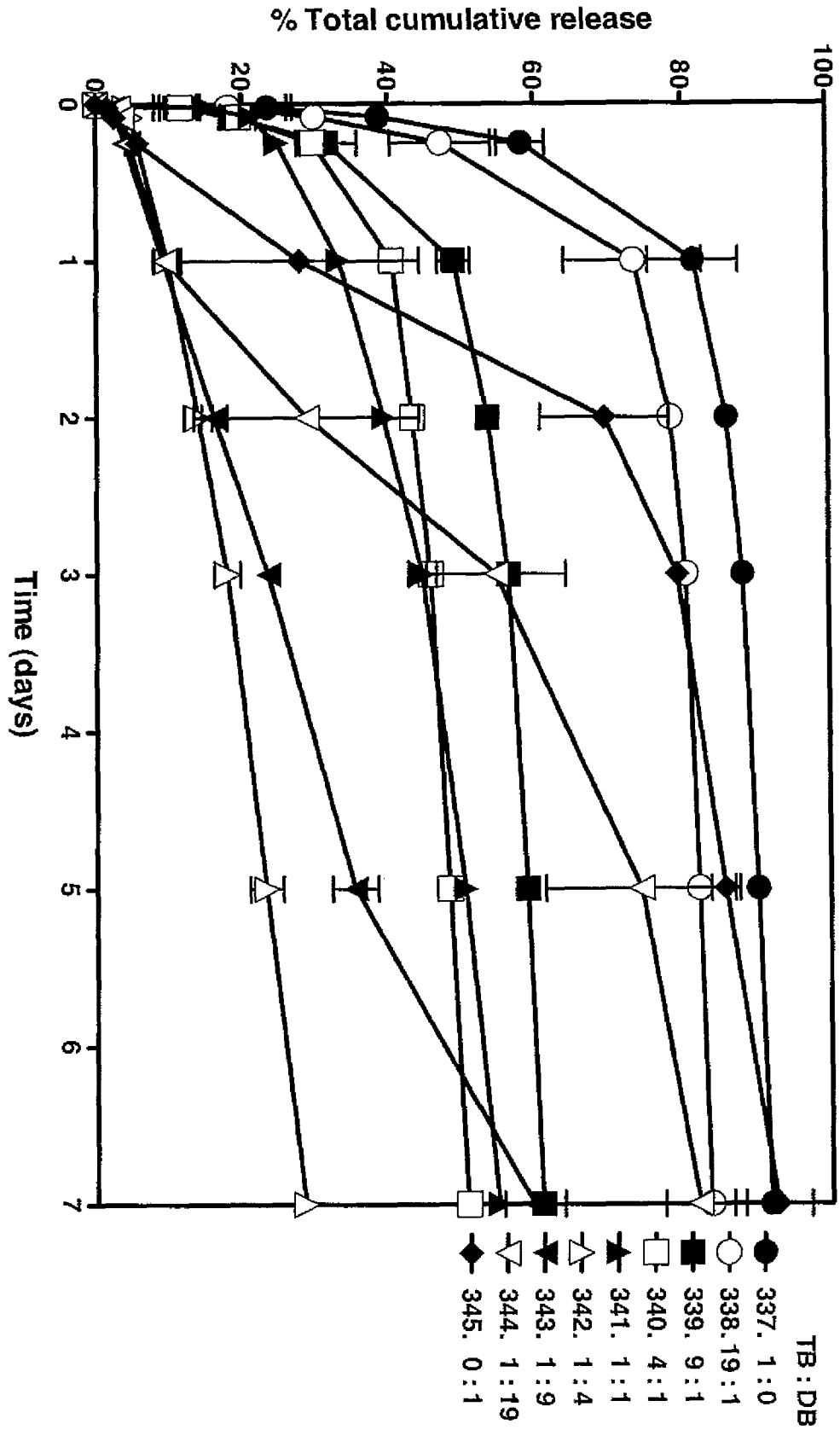
% Total cumulative release
0
20
40
60
80
100
Time (days)
0
1
2
3
4
5
6
7
TB : DB
337. 1 : 0
338. 19 : 1
339. 9 : 1
340. 4 : 1
341. 1 : 1
342. 1 : 4
343. 1 : 9
344. 1 : 19
345. 0 : 1

FIGURE 29

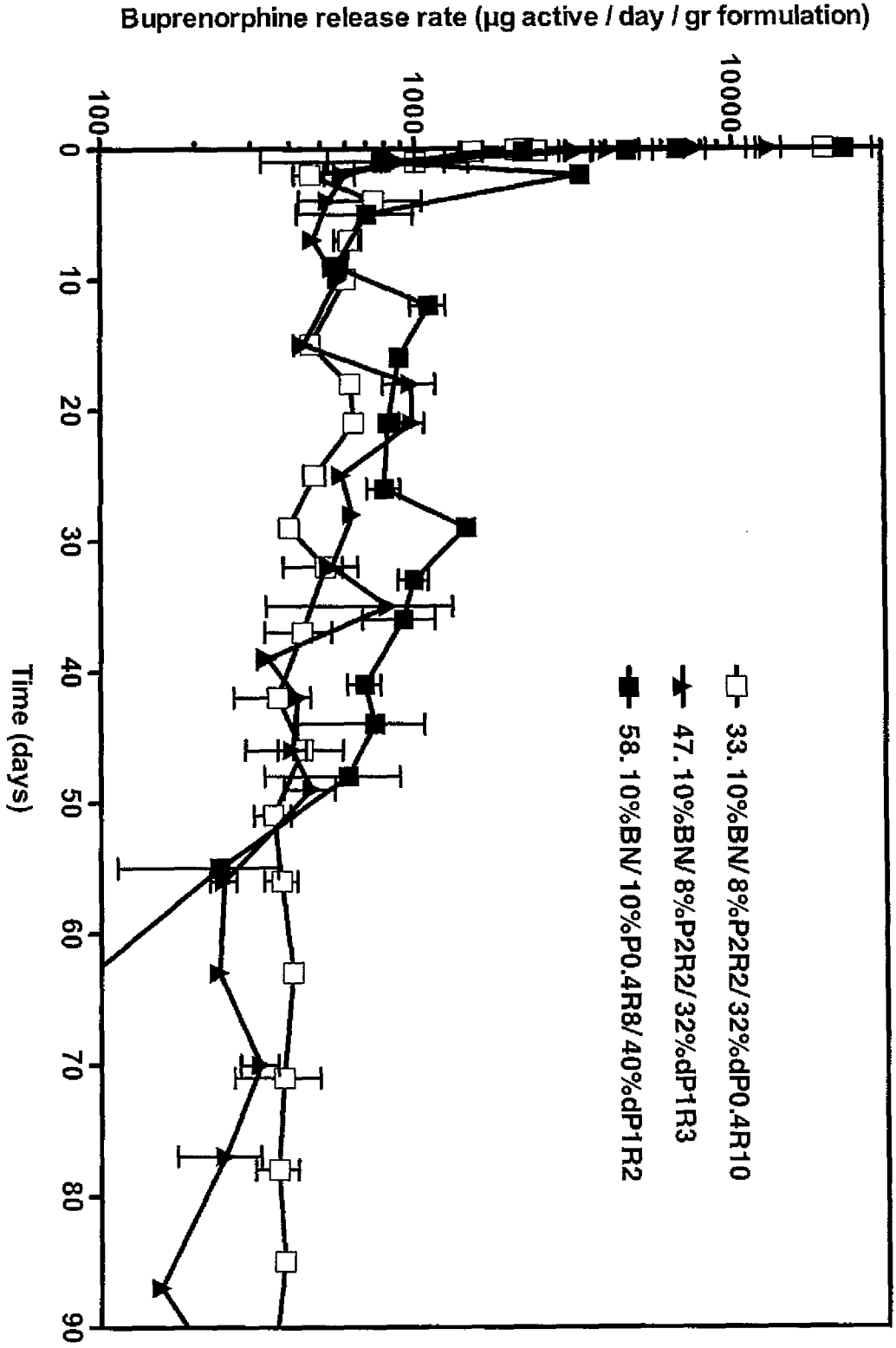
Buprenorphine release rate (µg active / day / gr formulation)
100
1000
10000
0
10
20
30
40
50
60
70
80
90
Time (days)
33.10%BN/8%P2R2/32%dP0.4R10
47.10%BN/8%P2R2/32%dP1R3
58.10%BN/10%P0.4R8/40%dP1R2

FIGURE 30

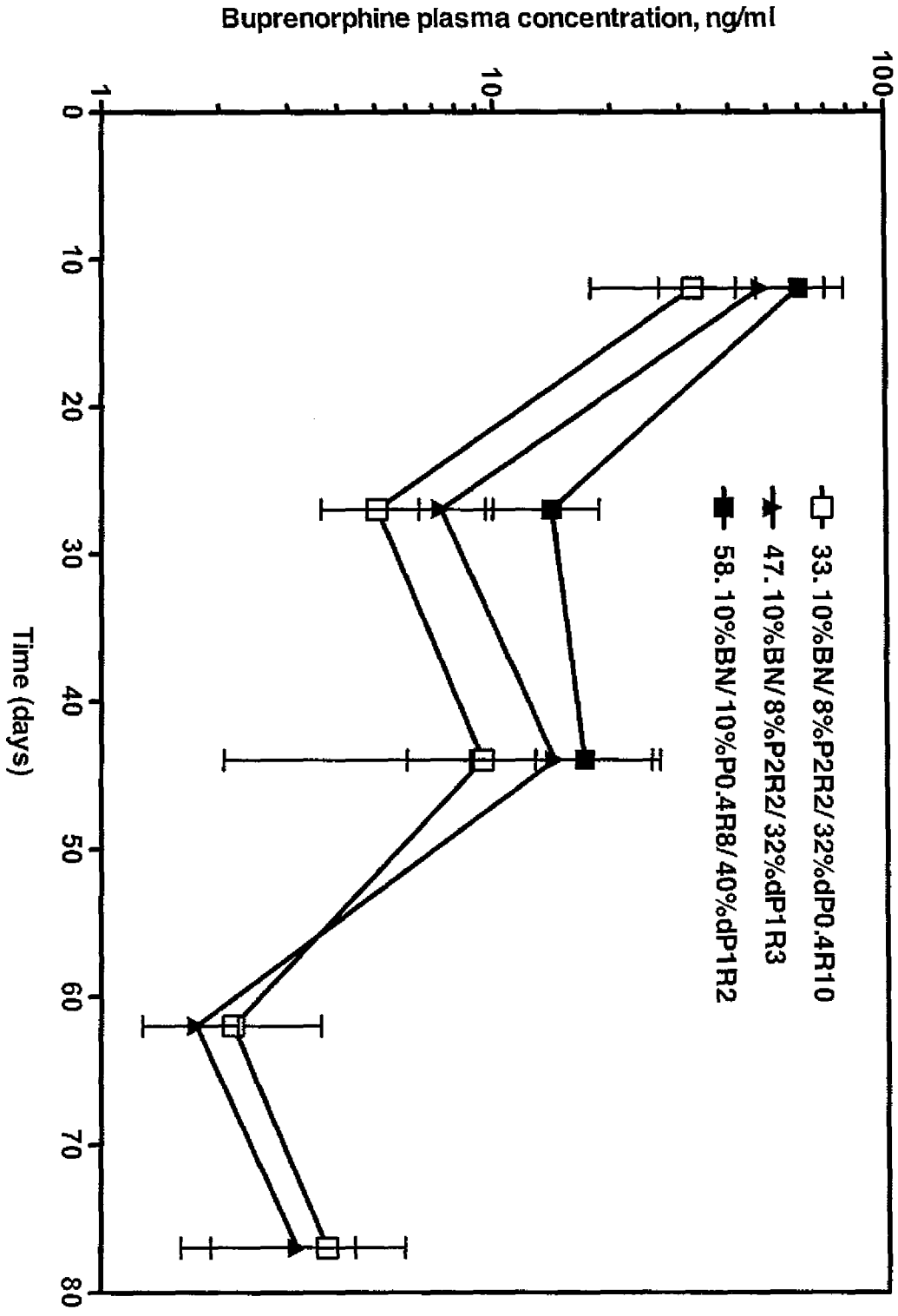
Buprenorphine plasma concentration, ng/ml
1
10
100
0
10
20
30
40
50
60
70
80
Time (days)
33.10%BN/8%P2R2/32%dP0.4R10
47.10%BN/8%P2R2/32%dP1R3
58.10%BN/10%P0.4R8/40%dP1R2

FIGURE 31

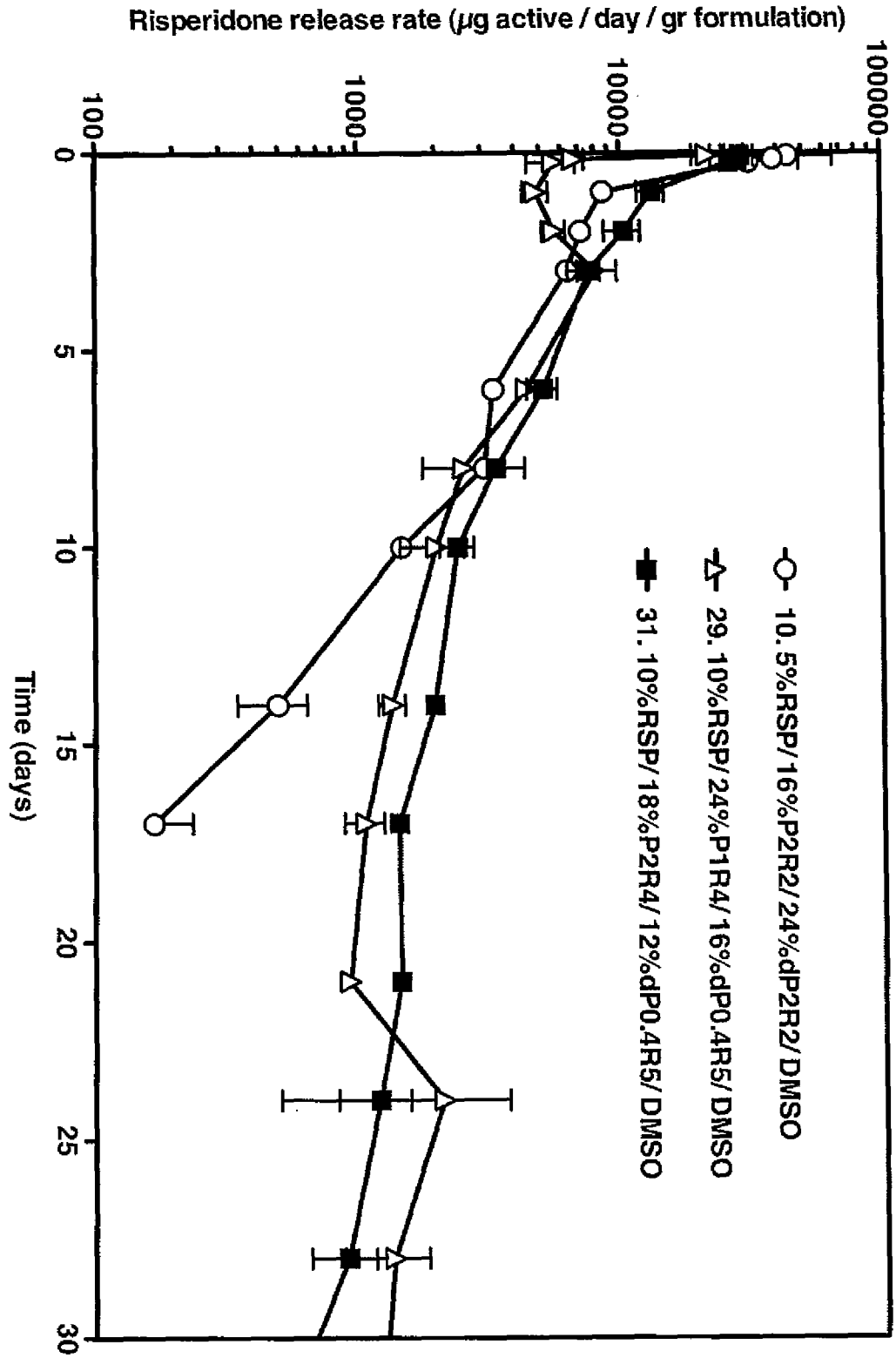
Risperidone release rate (µg active / day / gr formulation)
100
1000
10000
100000
0
5
10
15
20
25
30
Time (days)
10.5%RSP/16%P2R2/24%dP2R2/DMSO
29.10%RSP/24%P1R4/16%dP0.4R5/DMSO
31.10%RSP/18%P2R4/12%dP0.4R5/DMSO

FIGURE 32

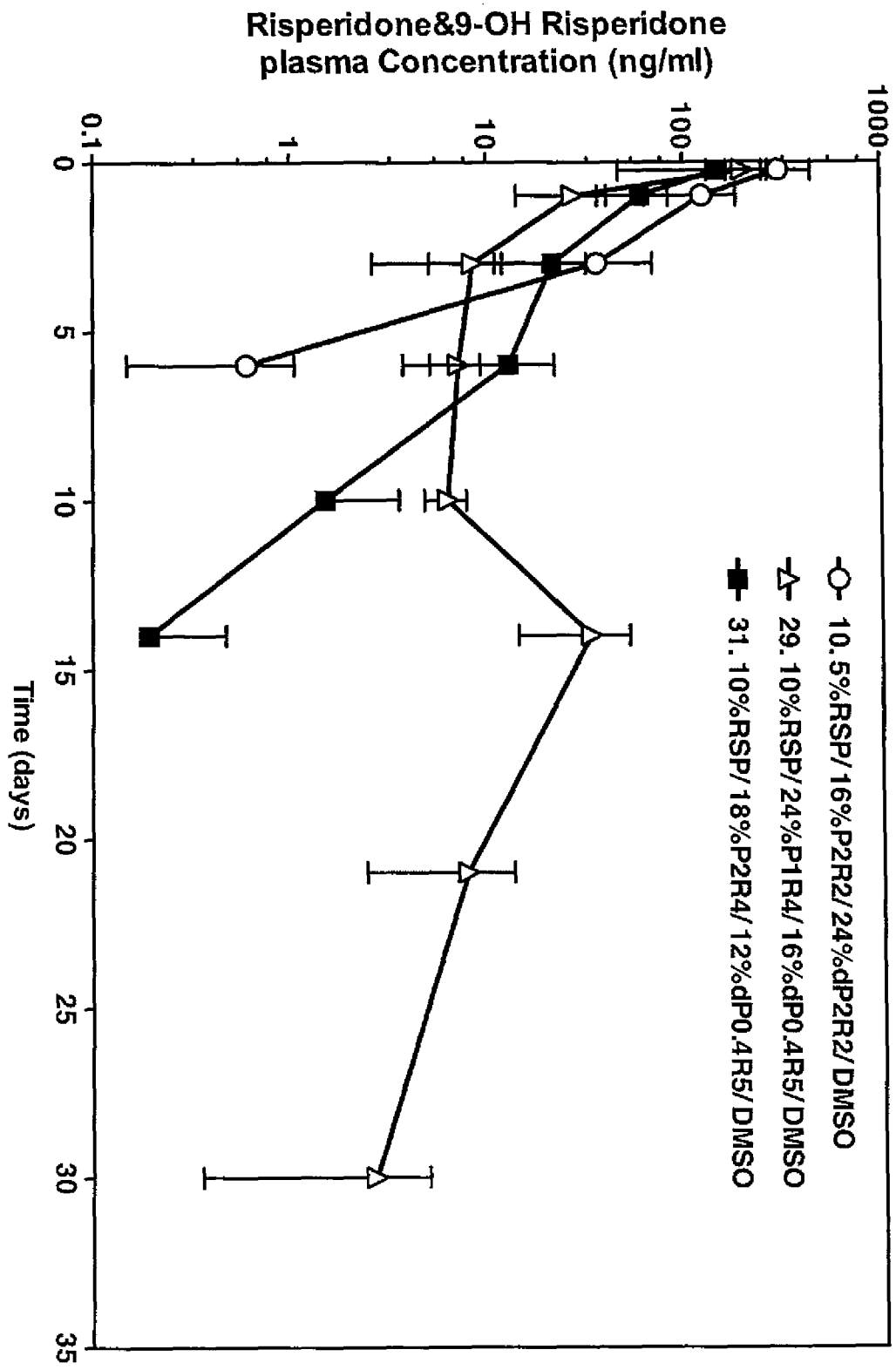
Risperidone&9-OH Risperidone
plasma Concentration (ng/ml)
0.1
1
10
100
1000
0
5
10
15
20
25
30
35
Time (days)
10.5%RSP/16%P2R2/24%dP2R2/DMSO
29.10%RSP/24%P1R4/16%dP0.4R5/DMSO
31.10%RSP/18%P2R4/12%dP0.4R5/DMSO

FIGURE 33

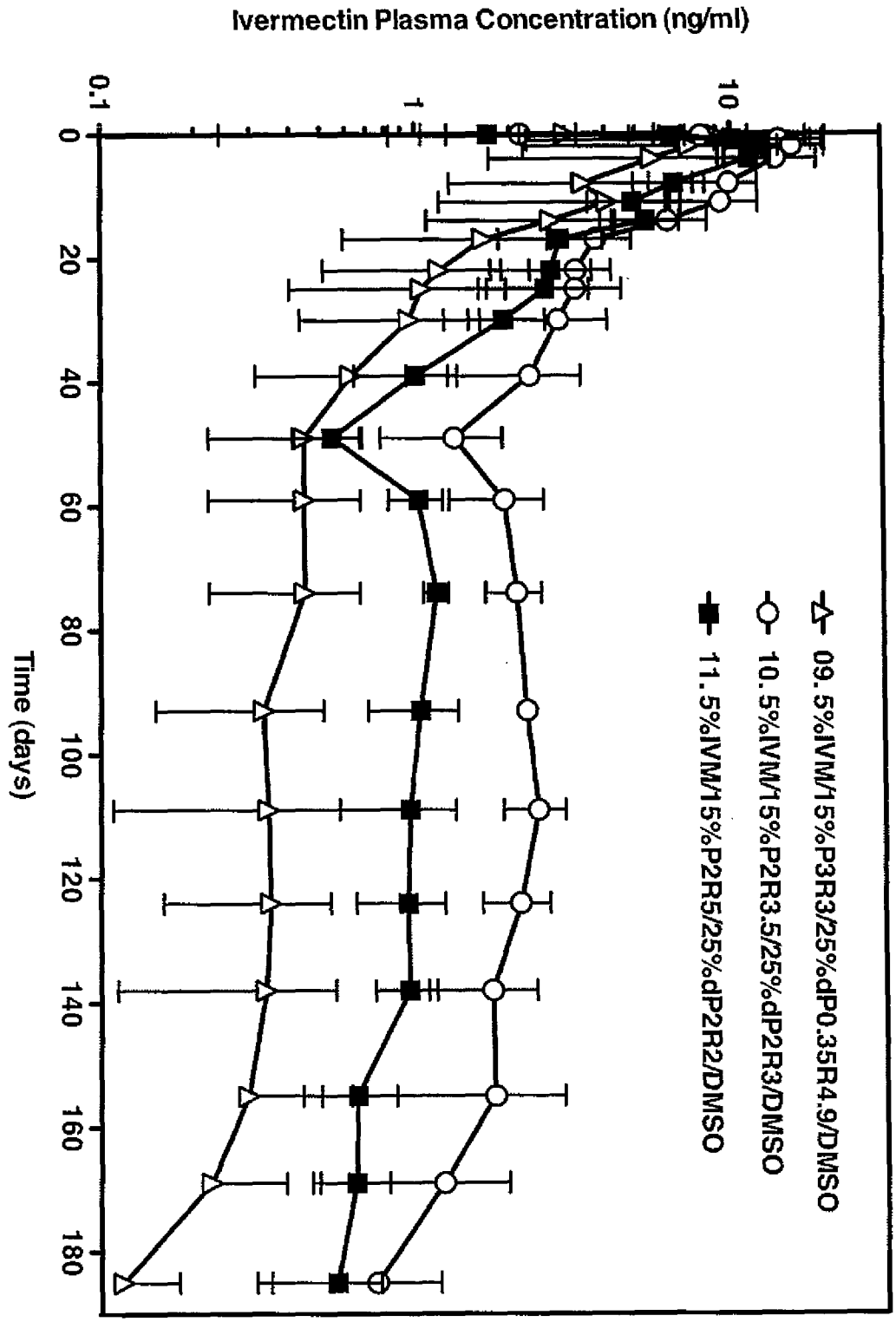
Ivermectin Plasma Concentration (ng/ml)
0.1
1
10
0
20
40
60
80
100
120
140
160
180
Time (days)
09.5%IVM/15%P3R3/25%dP0.35R4.9/DMSO
10.5%IVM/15%P2R3.5/25%dP2R3/DMSO
11.5%IVM/15%P2R5/25%dP2R2/DMSO

FIGURE 34

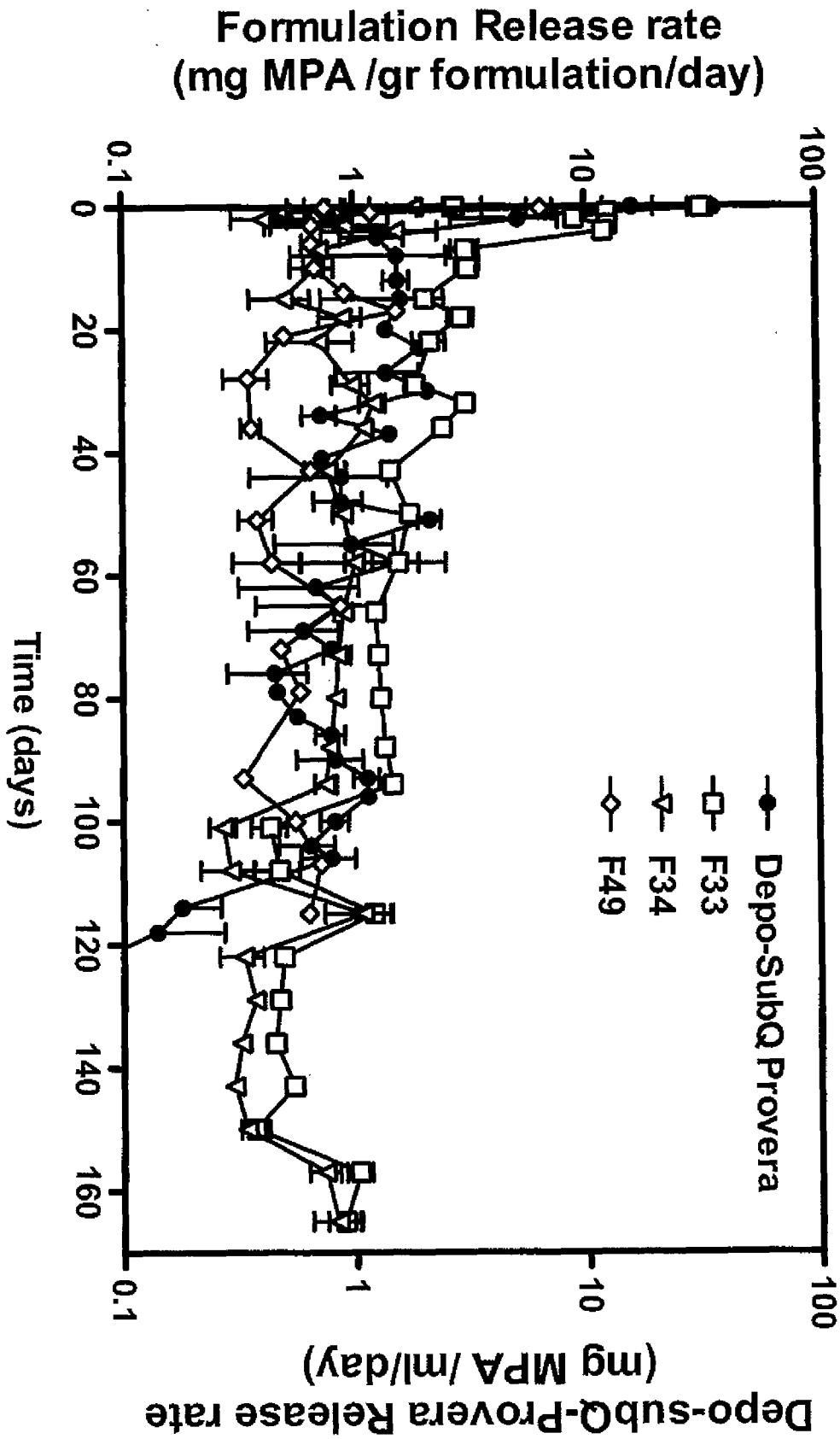
Formulation Release rate
(mg MPA /gr formulation/day)
0.1
1
10
100
0
20
40
60
80
100
120
140
160
Time (days)
Depo-SubQ Provera
F33
F34
F49
Depo-subQ-Provera Release rate
(mg MPA /ml/day)

FIGURE 35

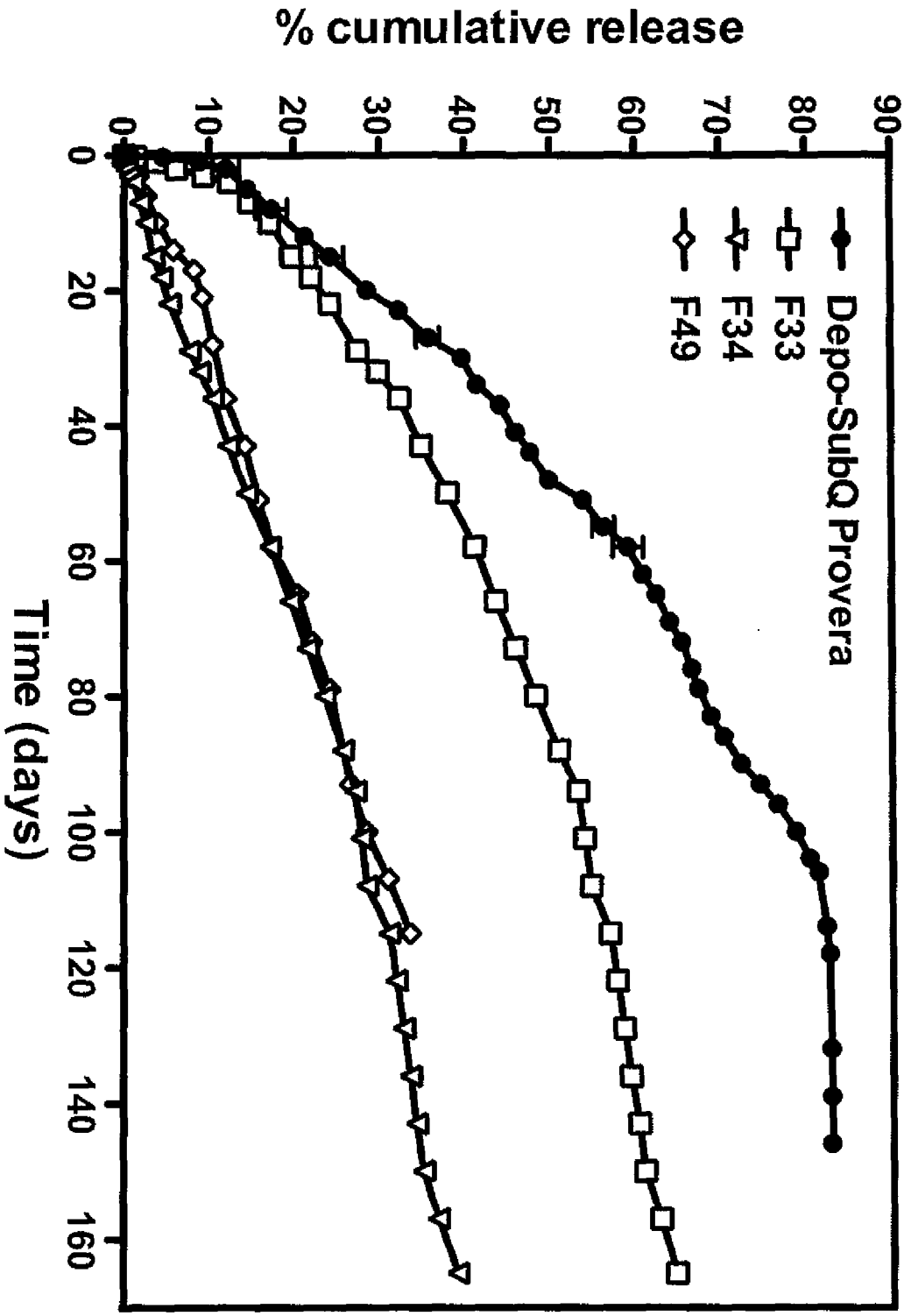
% cumulative release
0
10
20
30
40
50
60
70
80
90
Time (days)
0
20
40
60
80
100
120
140
160
Depo-SubQ Provera
F33
F34
F49

FIGURE 36

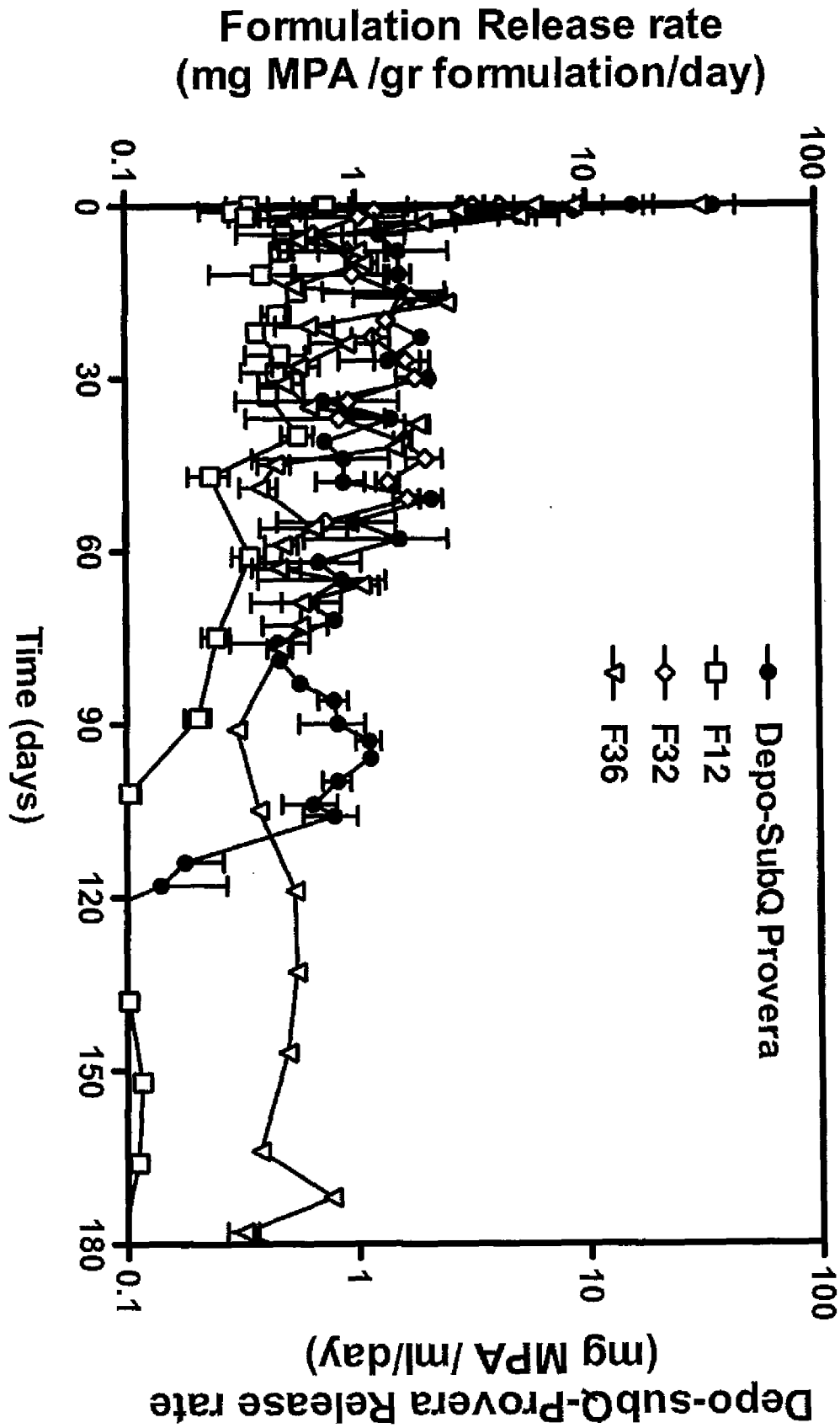
Formulation Release rate
(mg MPA /gr formulation/day)
Depo-subQ-Provera Release rate
(mg MPA /ml/day)
Time (days)
0.1
1
10
100
0
30
60
90
120
150
180
Depo-SubQ Provera
F12
F32
F36

FIGURE 37

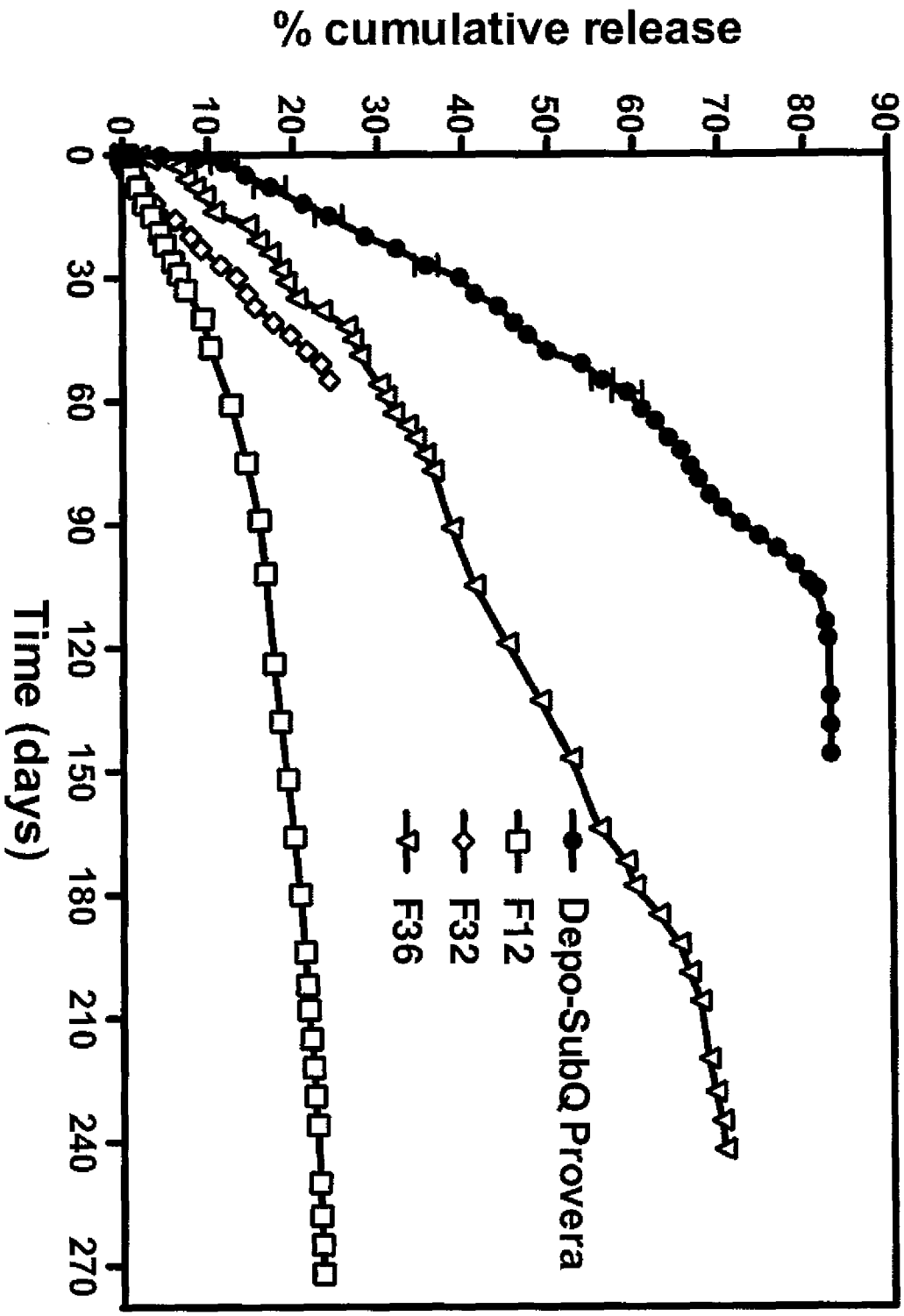
% cumulative release
0
10
20
30
40
50
60
70
80
90
Time (days)
0
30
60
90
120
150
180
210
240
270
Depo-SubQ Provera
F12
F32
F36

FIGURE 38

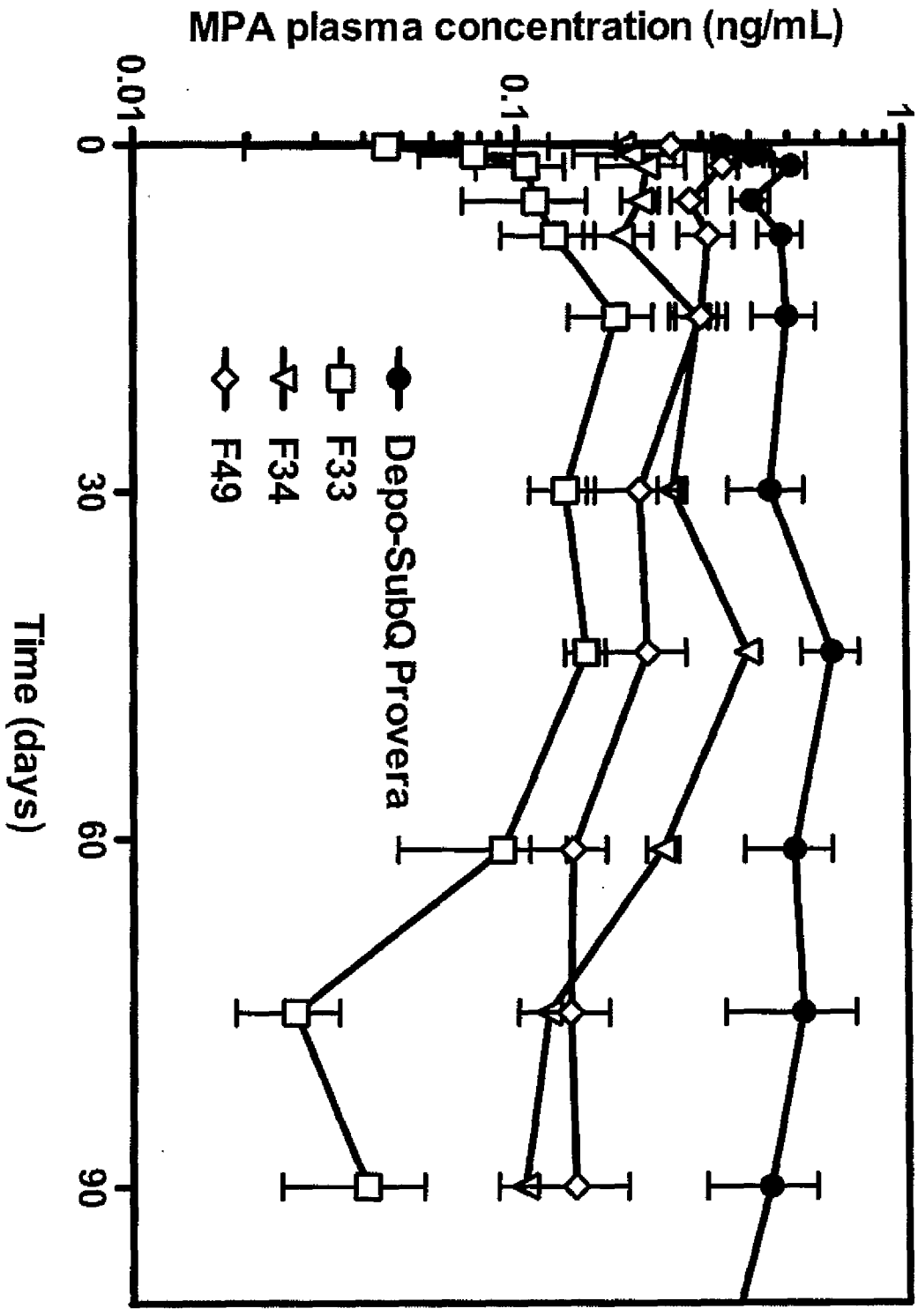
MPA plasma concentration (ng/mL)
0.01
0.1
1
0
30
60
90
Time (days)
F49
F34
F33
Depo-SubQ Provera

FIGURE 39

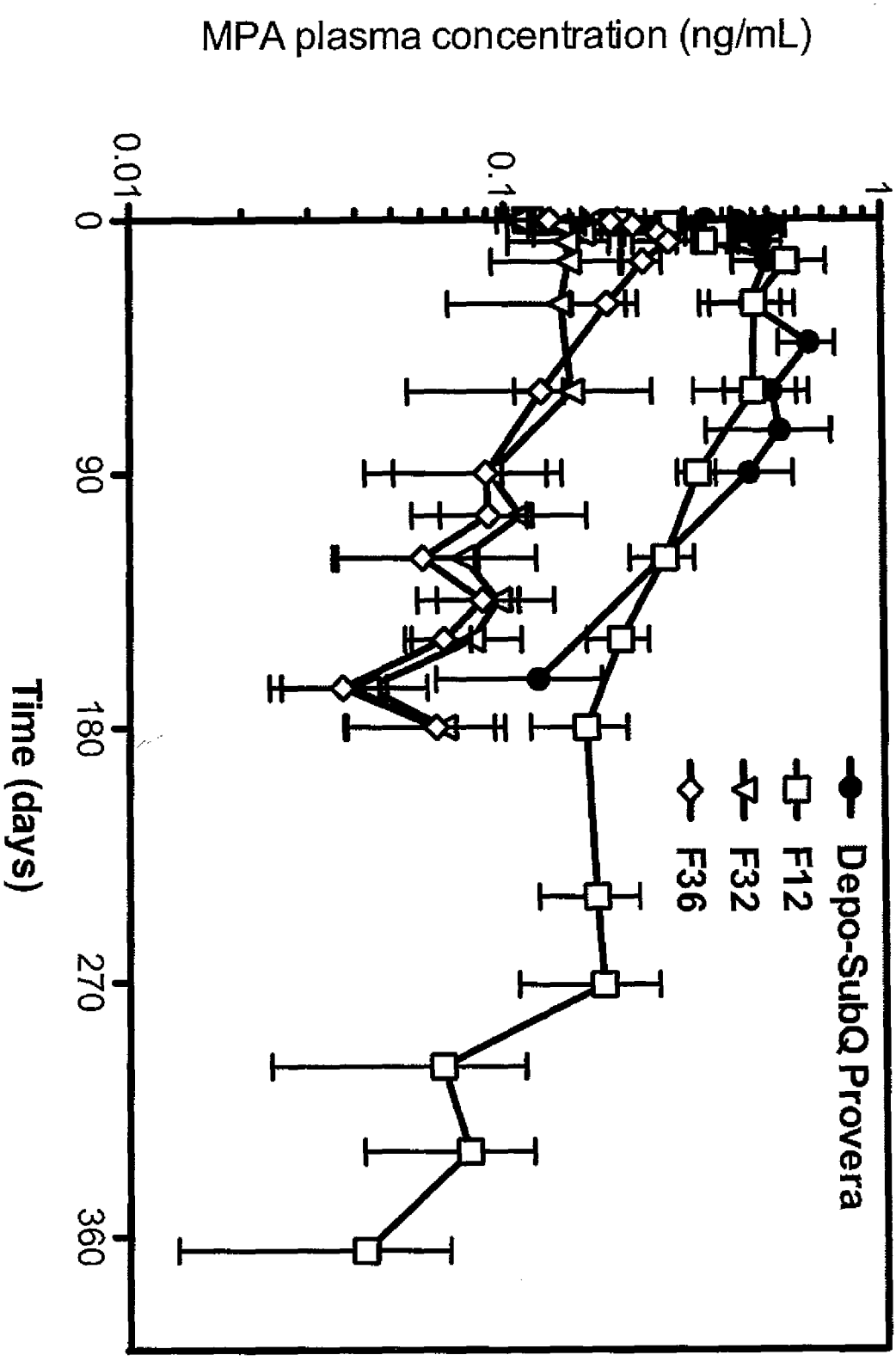
MPA plasma concentration (ng/mL)
0.01
0.1
1
0
90
180
270
360
Time (days)
Depo-SubQ Provera
F12
F32
F36

FIGURE 40

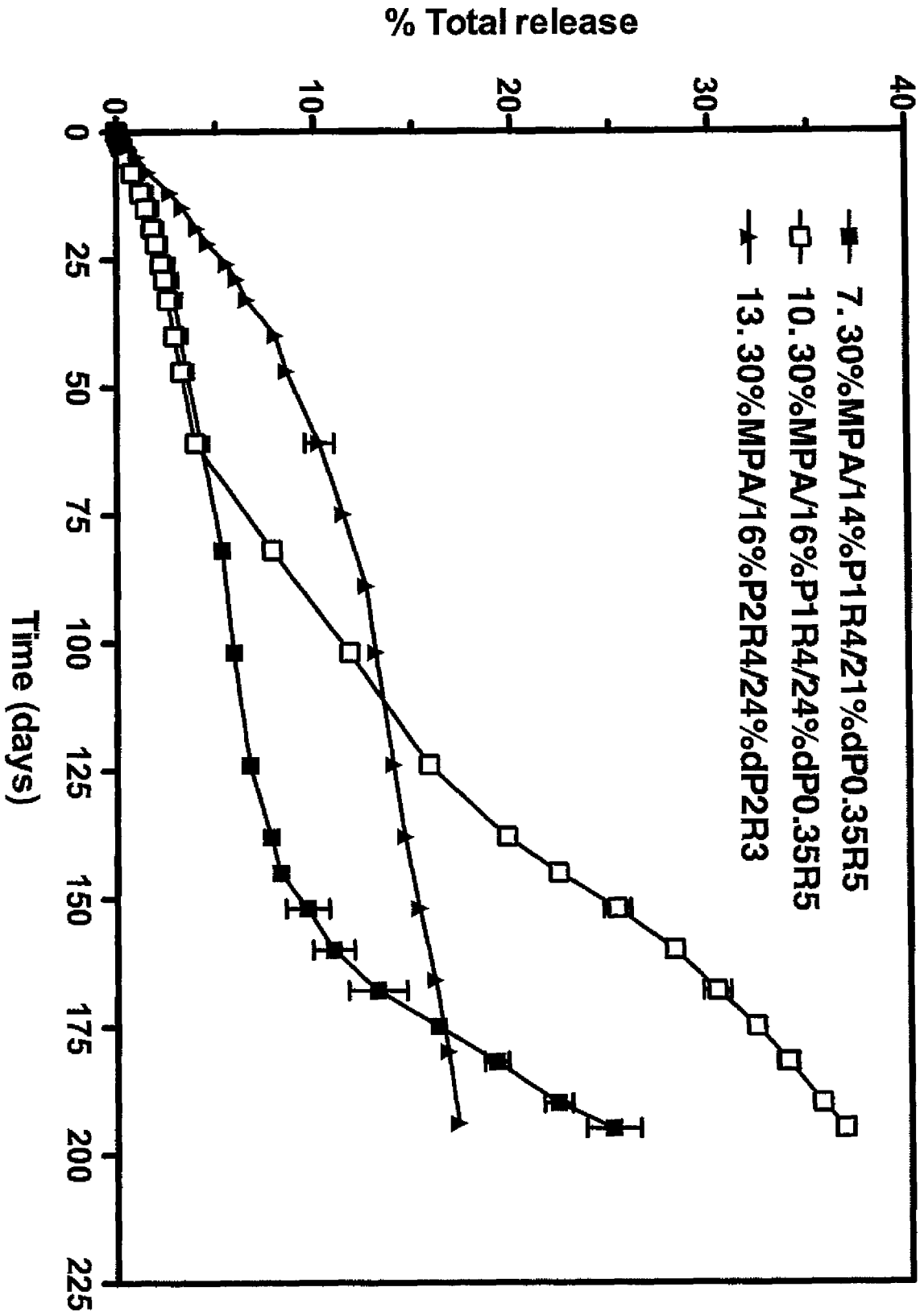
% Total release
0
10
20
30
40
Time (days)
0
25
50
75
100
125
150
175
200
225
7.30%MPA/14%P1R4/21%dP0.35R5
10.30%MPA/16%P1R4/24%dP0.35R5
13.30%MPA/16%P2R4/24%dP2R3

FIGURE 41

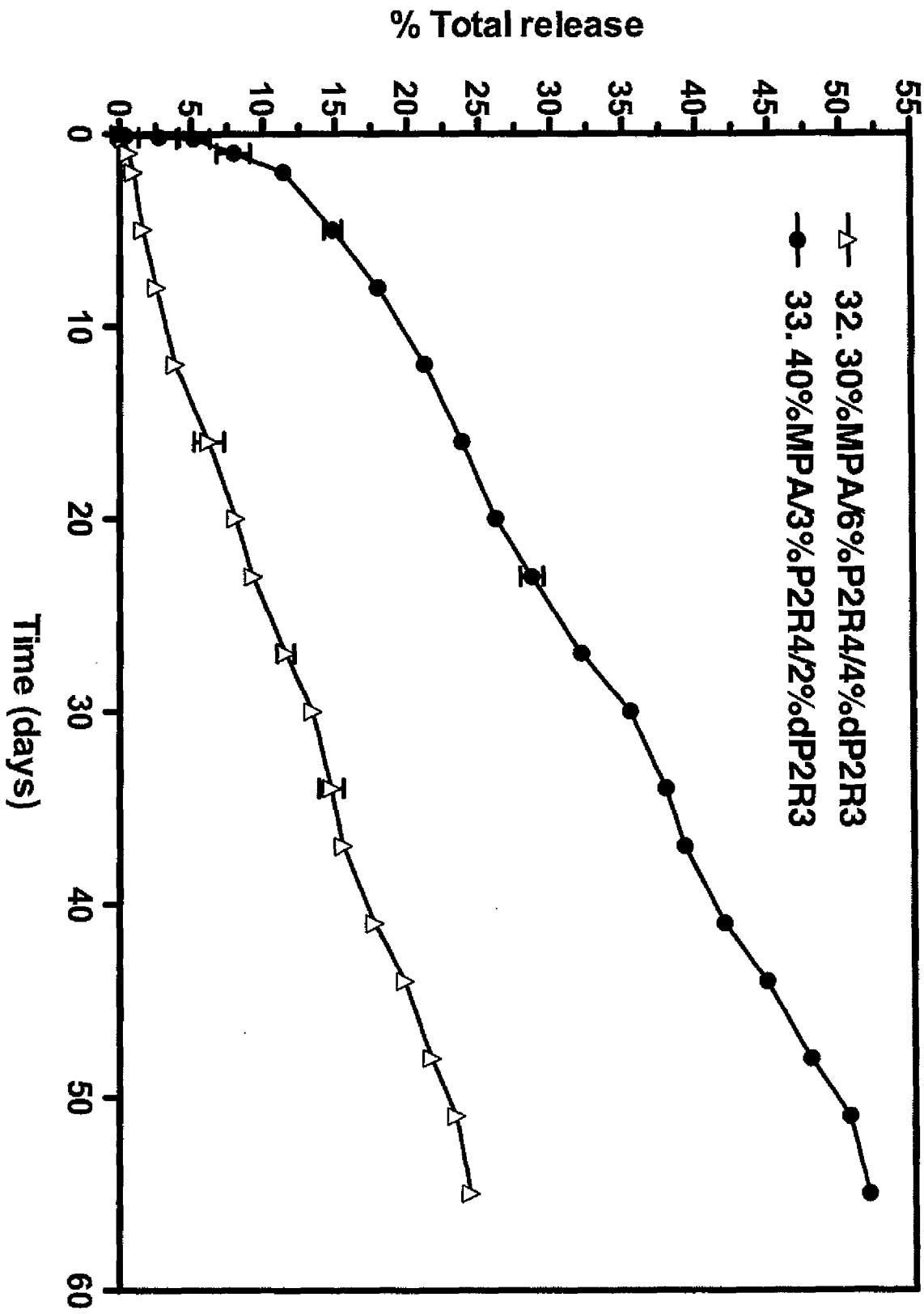
% Total release
0
5
10
15
20
25
30
35
40
45
50
55
Time (days)
0
10
20
30
40
50
60
32. 30%MPA/6%P2R4/4%dP2R3
33. 40%MPA/3%P2R4/2%dP2R3

FIGURE 42

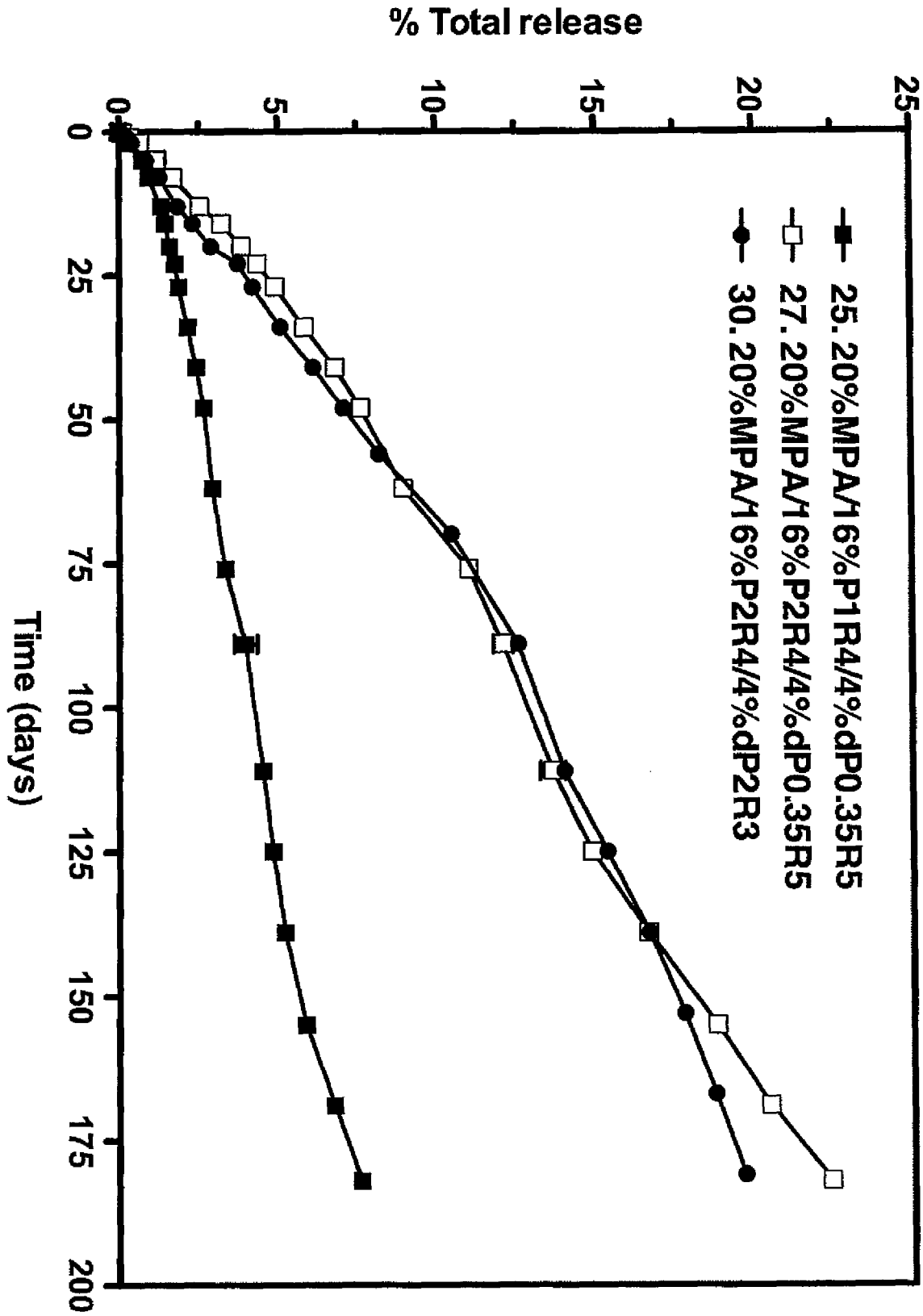
% Total release
0
5
10
15
20
25
Time (days)
0
25
50
75
100
125
150
175
200
25. 20%MPA/16%P1R4/4%dP0.35R5
27. 20%MPA/16%P2R4/4%dP0.35R5
30. 20%MPA/16%P2R4/4%dP2R3

FIGURE 43

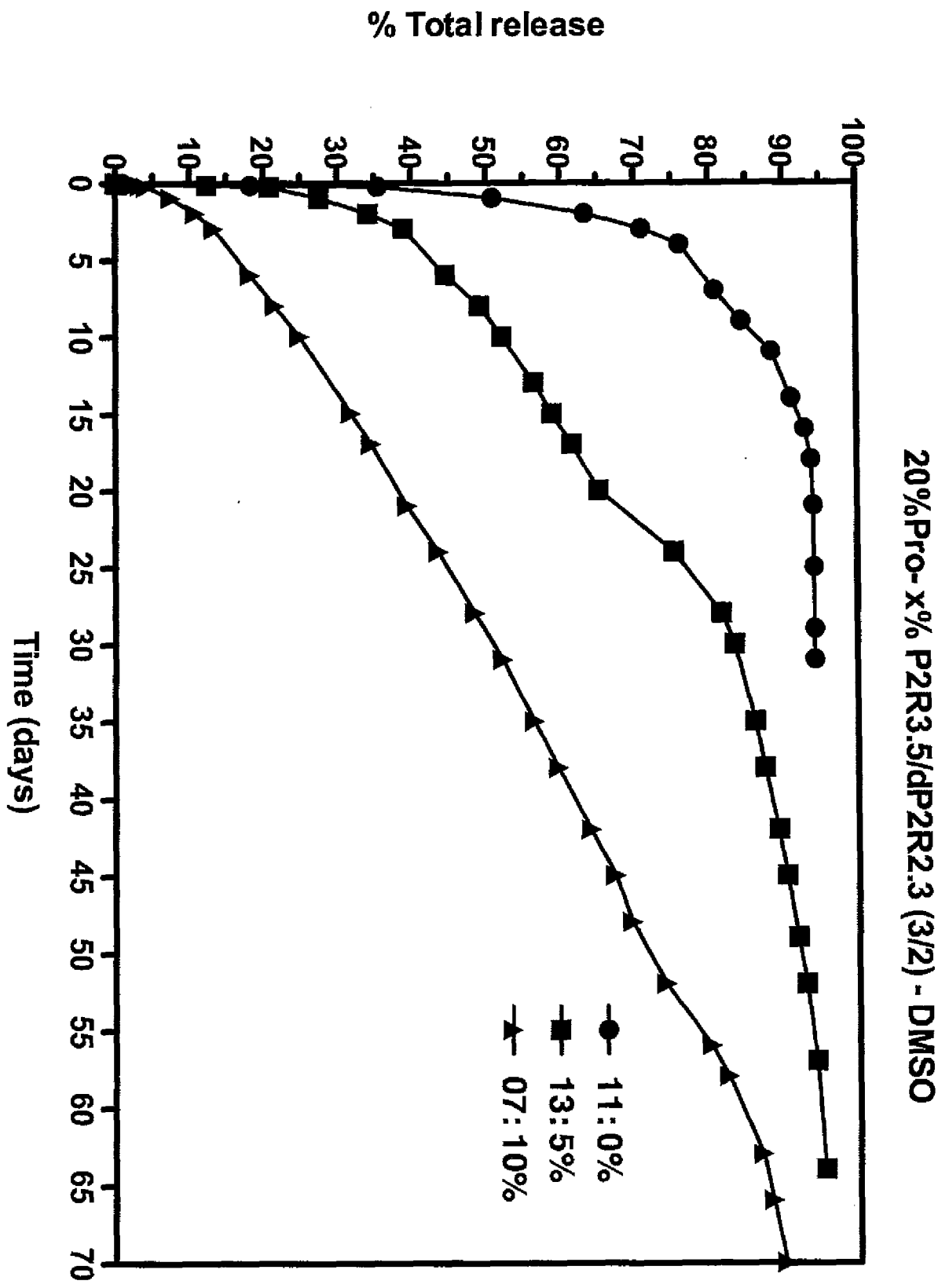
% Total release
0
10
20
30
40
50
60
70
80
90
100
Time (days)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
11:0%
13:5%
07:10%
20%Pro- x% P2R3.5/dP2R2.3 (3/2) - DMSO

FIGURE 44

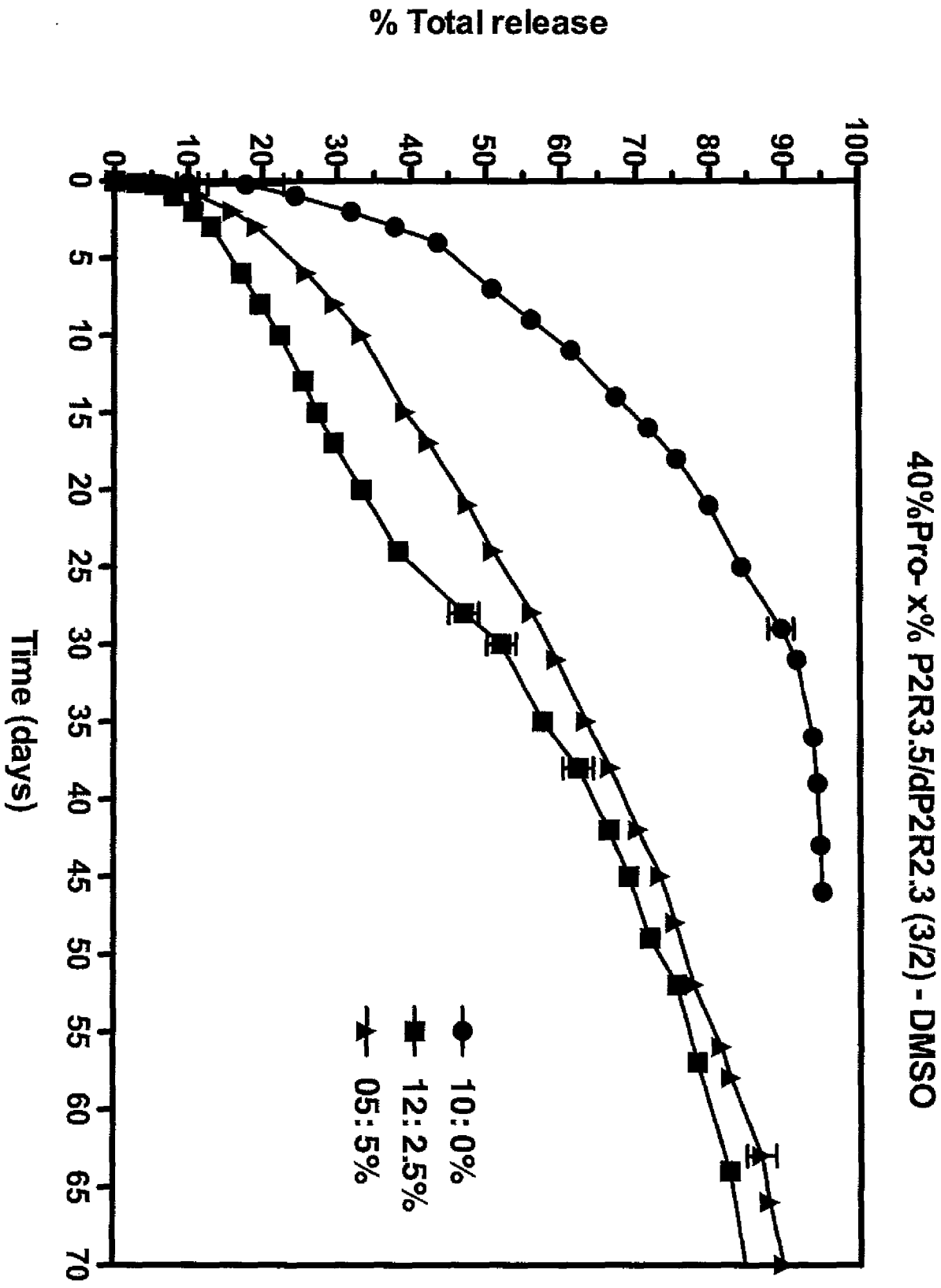
% Total release
0
10
20
30
40
50
60
70
80
90
100
Time (days)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
10: 0%
12: 2.5%
05: 5%
40%Pro- x% P2R3.5/dP2R2.3 (3/2) - DMSO

FIGURE 45

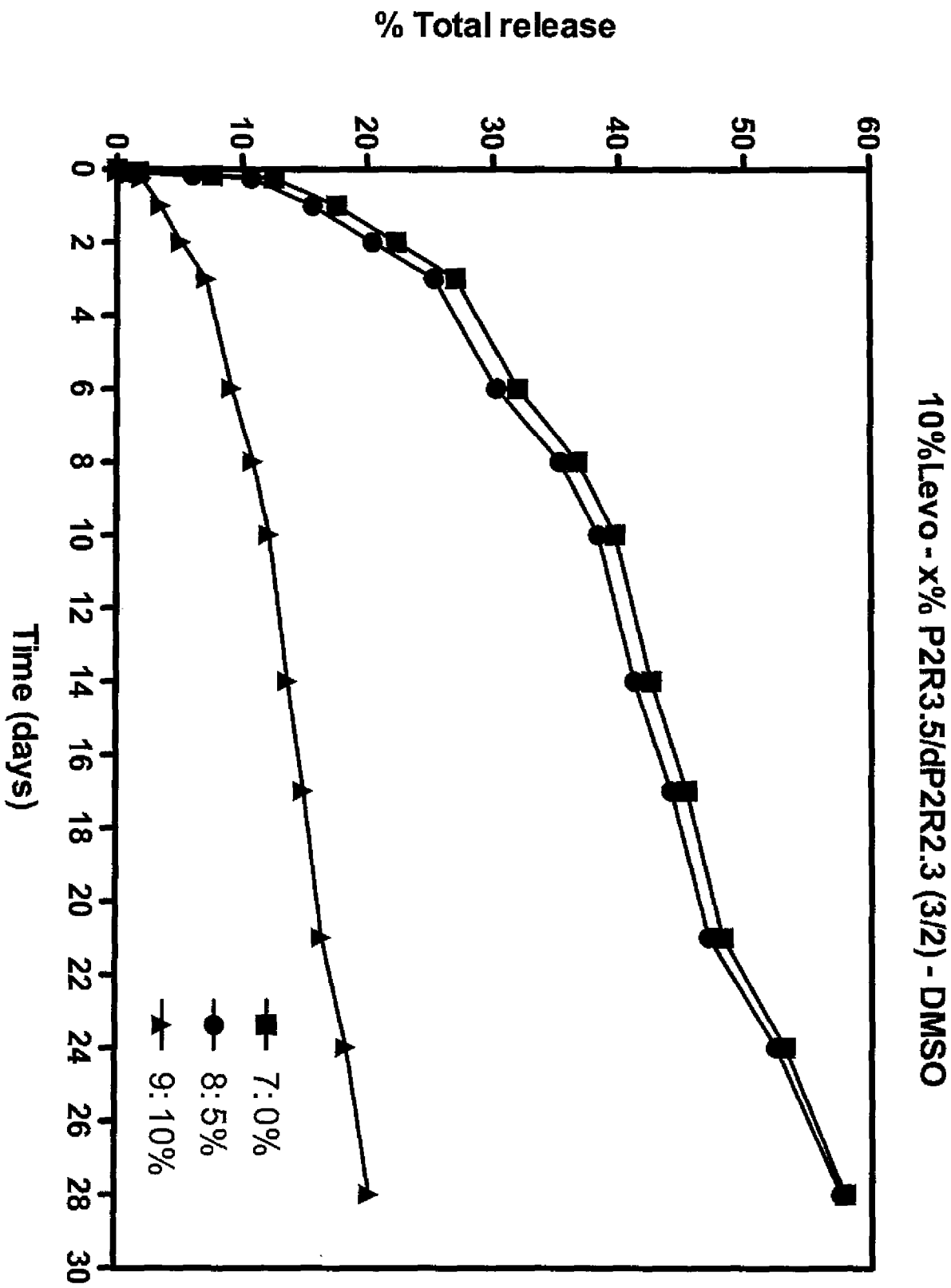
% Total release
0
10
20
30
40
50
60
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
Time (days)
7:0%
8:5%
9:10%
10%Levo - x% P2R3.5/dP2R2.3 (3/2) - DMSO

FIGURE 46

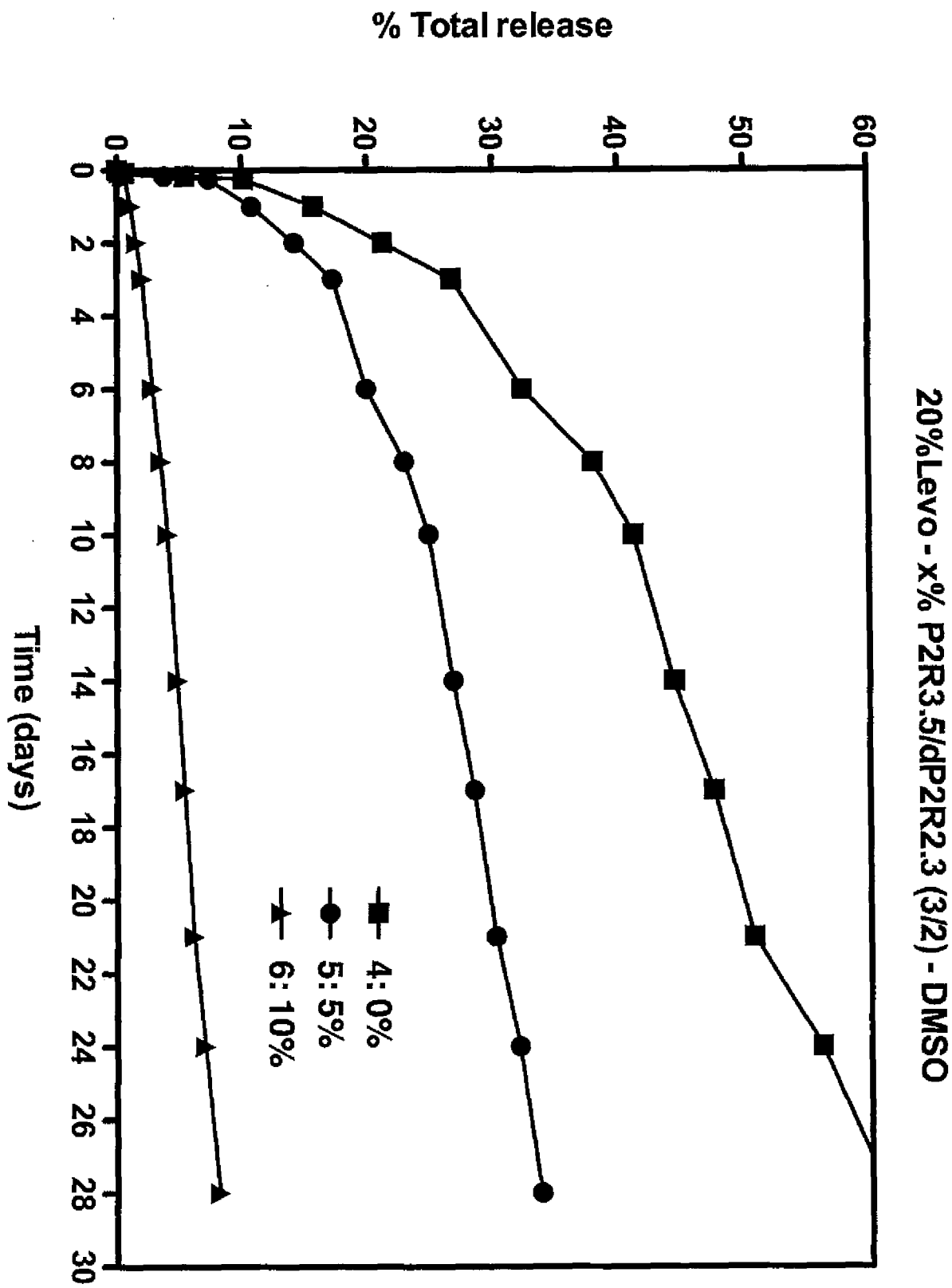
% Total release
0
10
20
30
40
50
60
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
Time (days)
4: 0%
5: 5%
6: 10%
20%Levo - x% P2R3.5/dP2R2.3 (3/2) - DMSO

FIGURE 47

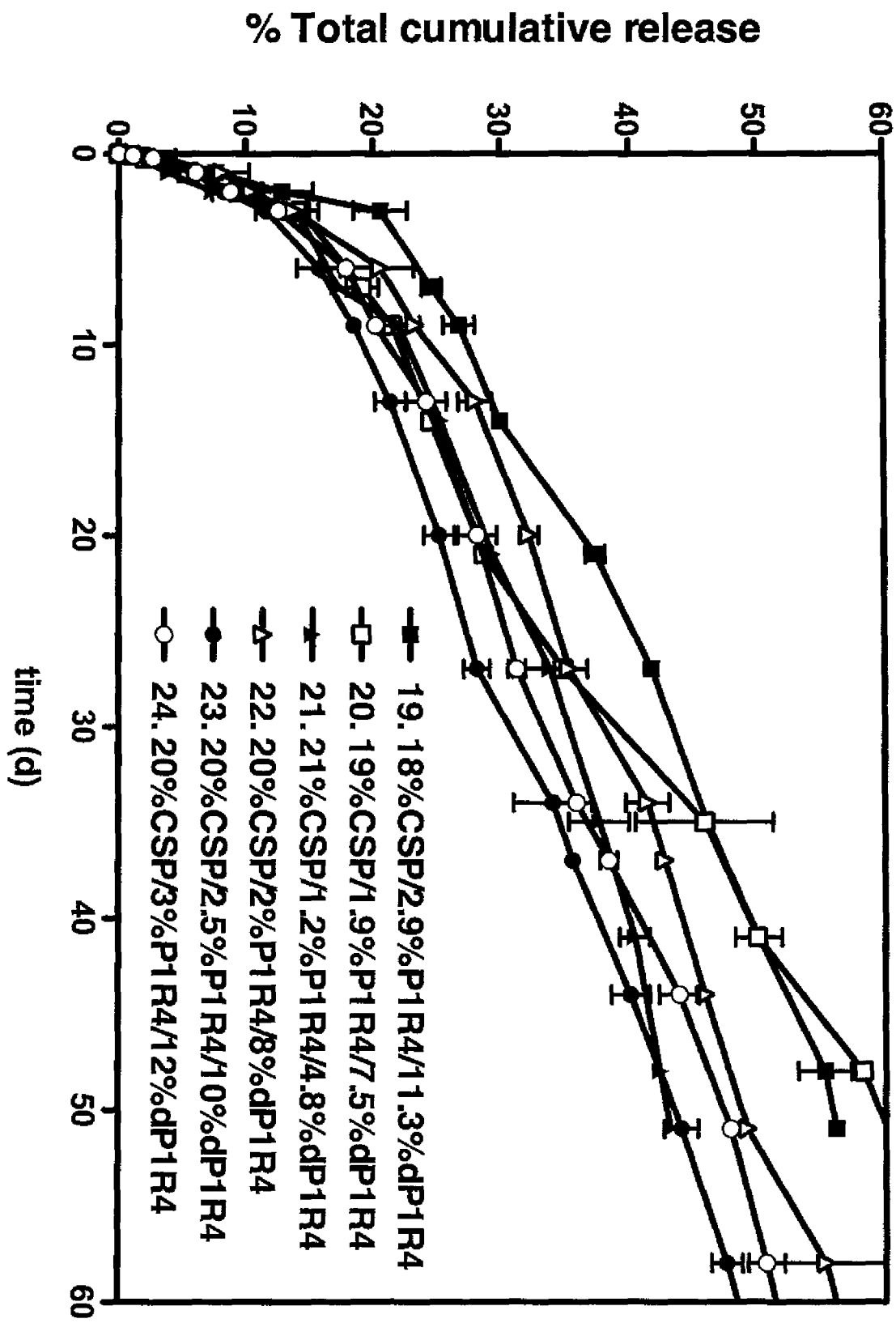
% Total cumulative release
0
10
20
30
40
50
60
time (d)
19. 18%CSP/2.9%P1R4/11.3%dP1R4
20. 19%CSP/1.9%P1R4/7.5%dP1R4
21. 21%CSP/1.2%P1R4/4.8%dP1R4
22. 20%CSP/2%P1R4/8%dP1R4
23. 20%CSP/2.5%P1R4/10%dP1R4
24. 20%CSP/3%P1R4/12%dP1R4

FIGURE 48

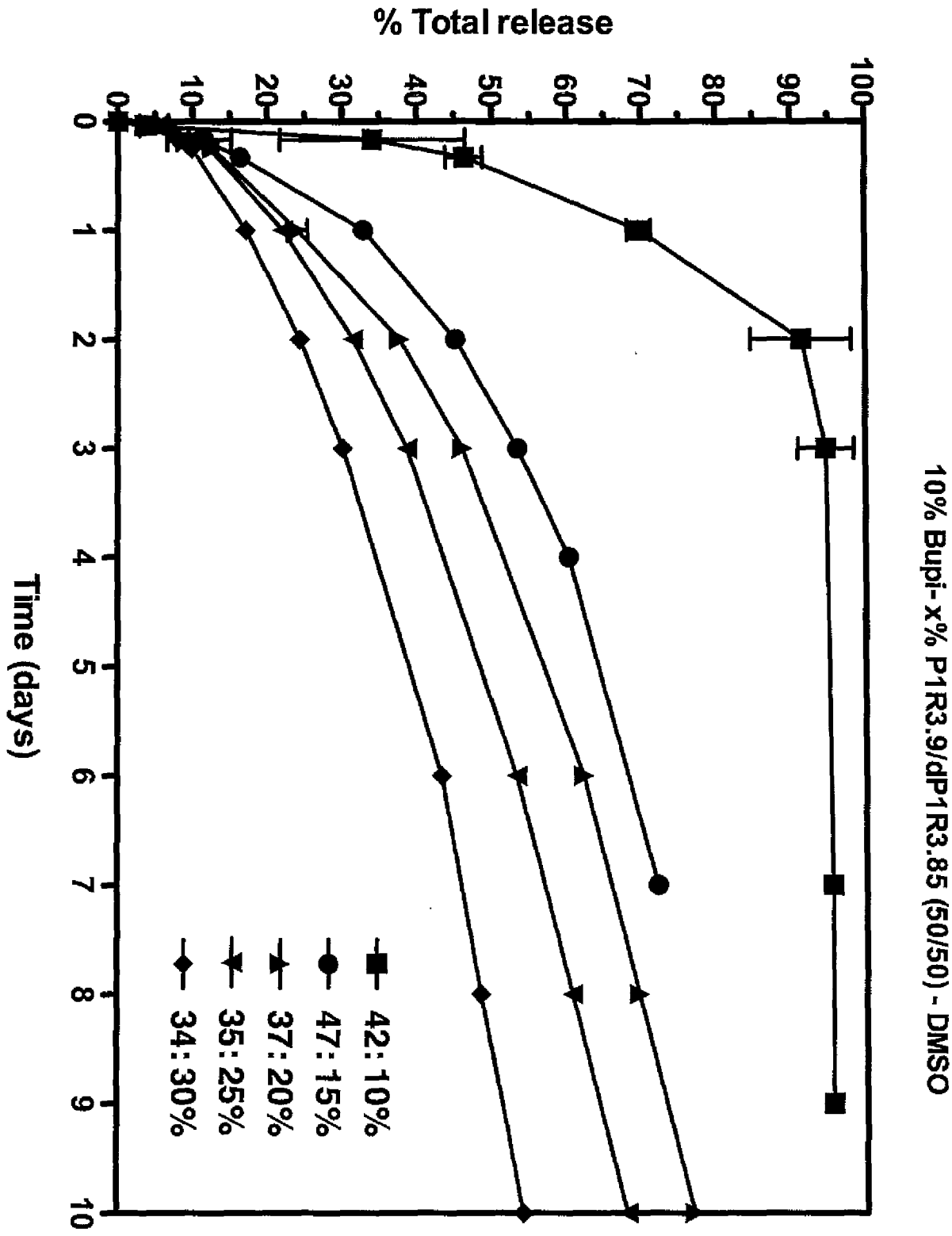
% Total release
0
10
20
30
40
50
60
70
80
90
100
Time (days)
0
1
2
3
4
5
6
7
8
9
10
42:10%
47:15%
37:20%
35:25%
34:30%
10% Bupi- x% P1R3.9/dP1R3.85 (50/50) - DMSO

FIGURE 49

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/001549

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/34 A61K31/57
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/112170 A1 (HOSSAINY SYED F [US] ET AL) 26 May 2005 (2005-05-26) page 1, paragraph 9 page 4, paragraph 46 - page 5, paragraph 52 page 5, paragraph 58-67 page 6, paragraphs 78,79 page 8 - page 9; examples 5-7 claims 1-36 -----	1-8
X	WO 93/24154 A1 (FUISZ TECHNOLOGIES LTD [US]; FUISZ RICHARD C [US]) 9 December 1993 (1993-12-09) page 7, lines 23-28 page 15, lines 7-27 page 18, line 12 - page 19, line 28 page 20, lines 29-35 claims 1-26 -----	1-8
	-/--	

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2013	02/12/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gómez Gallardo, S

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/000278 A1 (MEDIOLANUM PHARMACEUTICALS LTD [IE]) 6 January 2005 (2005-01-06) page 23 - page 26; examples 14-16	1-8
A	WO 93/00070 A1 (ENDORECHERCHE INC [CA]) 7 January 1993 (1993-01-07) page 1, paragraph 1 page 43, last paragraph - page 44, paragraph 1 page 47, paragraph 2 page 55 - page 57; examples 3,4	1-8
A	DATABASE WPI Section Ch, Week 200914 Thomson Scientific, London, GB; Class A96, AN 2009-B25806 XP002716235, KONG Q; WEI M: "Temperature controlled slow-release injection useful for treating primary cancer, caruncle or cancer caruncle of e.g. brain and kidney, comprises given range of anticancer drug, amphiphilic block copolymer, menstruum and regulator", -& CN 101 273 963 A ((SHAN-N) SHANDONG LANJIN BIOENGINEERING CO LTD) 1 October 2008 (2008-10-01) page 15 - page 20; examples 8-11 claims 1-10	1-8
A	WO 2007/019439 A2 (ANGIOTECH INT AG [CH]; ANGIOTECH PHARM INC [US]) 15 February 2007 (2007-02-15) page 4, line 10 - page 5, line 29 page 18, lines 8-28 page 19, line 19 - page 20, line 21 page 36, lines 5-28 page 44, line 24 - page 45, line 26	1-8
A	US 6 592 899 B2 (FOWERS KIRK DEE [US] ET AL) 15 July 2003 (2003-07-15) cited in the application column 3, line 27 - column 4, line 13 column 10, line 58 - column 11, line 13 column 11 - column 12; examples 1-3 column 13 - column 14; example 9 column 14, line 60 - column 15, line 16 claims 1-79	1-8
A	US 4 745 160 A (CHURCHILL JEFFREY R [GB] ET AL) 17 May 1988 (1988-05-17) the whole document	1-8

-/--

1

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/001549

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 350 812 B1 (VERT MICHEL [FR] ET AL) 26 February 2002 (2002-02-26) cited in the application the whole document	1-8
A	US 7 875 677 B2 (JACKSON JOHN K [CA] ET AL) 25 January 2011 (2011-01-25) cited in the application the whole document	1-8
X,P	WO 2012/090070 A2 (MEDINCELL [FR]) 5 July 2012 (2012-07-05) the whole document	1-8

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2013/001549

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005112170 A1	26-05-2005	AT 389423 T	15-04-2008
		DE 602004012597 T2	16-04-2009
		EP 1689462 A1	16-08-2006
		EP 1932551 A1	18-06-2008
		JP 2007512094 A	17-05-2007
		US 2005112170 A1	26-05-2005
		WO 2005051449 A1	09-06-2005
WO 9324154 A1	09-12-1993	AU 665844 B2	18-01-1996
		AU 4405893 A	30-12-1993
		CA 2137268 A1	09-12-1993
		DE 69332210 D1	19-09-2002
		DE 69332210 T2	24-04-2003
		EP 0746342 A1	11-12-1996
		JP 3941878 B2	04-07-2007
		JP H07507548 A	24-08-1995
		US 5518730 A	21-05-1996
		WO 9324154 A1	09-12-1993
WO 2005000278 A1	06-01-2005	AT 367803 T	15-08-2007
		AU 2004251457 A1	06-01-2005
		BR PI0411752 A	08-08-2006
		CA 2530120 A1	06-01-2005
		CN 1812771 A	02-08-2006
		CY 1106943 T1	26-09-2012
		DE 602004007802 T2	17-04-2008
		EP 1638535 A1	29-03-2006
		ES 2291893 T3	01-03-2008
		HK 1087031 A1	18-01-2008
		JP 2009513493 A	02-04-2009
		KR 20060027353 A	27-03-2006
		MX PA05013698 A	17-05-2006
		PT 1638535 E	08-11-2007
		US 2007116738 A1	24-05-2007
		WO 2005000278 A1	06-01-2005
WO 9300070 A1	07-01-1993	AT 161173 T	15-01-1998
		AU 672750 B2	17-10-1996
		AU 707401 B2	08-07-1999
		CA 2112393 A1	07-01-1993
		CZ 285972 B6	15-12-1999
		DE 69223620 D1	29-01-1998
		DE 69223620 T2	23-04-1998
		EP 0591311 A1	13-04-1994
		FI 935893 A	28-12-1993
		HU 222501 B1	28-07-2003
		IE 922123 A1	30-12-1992
		IL 102447 A	10-03-1998
		JP H06508624 A	29-09-1994
		MY 131099 A	31-07-2007
		NO 934742 A	21-12-1993
		NZ 243370 A	27-02-1996
		NZ 264279 A	28-05-1996
		NZ 272633 A	24-06-1997
		NZ 314568 A	29-09-2000
		RU 2142276 C1	10-12-1999
		SK 147893 A3	07-09-1994
		US 5434146 A	18-07-1995

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 5541172 A	30-07-1996
		US 5629303 A	13-05-1997
		US 5814340 A	29-09-1998
		US 5861387 A	19-01-1999
		WO 9300070 A1	07-01-1993
CN 101273963 A	01-10-2008	NONE	
WO 2007019439 A2	15-02-2007	AU 2006278328 A1	15-02-2007
		CA 2618404 A1	15-02-2007
		EP 1909774 A2	16-04-2008
		US 2008247987 A1	09-10-2008
		WO 2007019439 A2	15-02-2007
US 6592899 B2	15-07-2003	TW 592726 B	21-06-2004
		US 2003068377 A1	10-04-2003
		WO 03028589 A1	10-04-2003
US 4745160 A	17-05-1988	AU 587977 B2	07-09-1989
		AU 4315085 A	02-01-1986
		CA 1247271 A1	20-12-1988
		DE 3582088 D1	18-04-1991
		DK 287885 A	27-12-1985
		EP 0166596 A2	02-01-1986
		ES 8609374 A1	16-12-1986
		ES 8704726 A1	01-07-1987
		ES 8705221 A1	16-07-1987
		ES 8705222 A1	16-07-1987
		FI 852374 A	27-12-1985
		GR 851474 A1	25-11-1985
		HU 193994 B	28-12-1987
		HU 196301 B	28-11-1988
		IE 58678 B1	03-11-1993
		IL 75407 A	30-11-1988
		JP H0751517 B2	05-06-1995
		JP H0769929 A	14-03-1995
		JP H0769930 A	14-03-1995
		JP S6115846 A	23-01-1986
		JP H07106987 B2	15-11-1995
		JP H07106988 B2	15-11-1995
		NO 852547 A	27-12-1985
		NZ 212538 A	12-02-1988
		PT 80710 A	01-07-1985
		US 4745160 A	17-05-1988
		US 4877606 A	31-10-1989
		YU 106385 A	31-10-1988
		ZA 8504188 A	26-02-1986
US 6350812 B1	26-02-2002	AT 202373 T	15-07-2001
		DE 69613481 D1	26-07-2001
		DE 69613481 T2	25-04-2002
		DK 0863933 T3	24-09-2001
		EP 0863933 A1	16-09-1998
		ES 2159767 T3	16-10-2001
		FR 2741628 A1	30-05-1997
		GR 3036586 T3	31-12-2001
		JP 4521067 B2	11-08-2010
		JP 2000500803 A	25-01-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2013/001549

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		JP 2008056935 A	13-03-2008
		PT 863933 E	28-12-2001
		US 6350812 B1	26-02-2002
		WO 9719973 A1	05-06-1997
US 7875677 B2	25-01-2011	AT 363898 T	15-06-2007
		CA 2444529 A1	31-10-2002
		DE 60220519 T2	27-09-2007
		DK 1392254 T3	02-07-2007
		EP 1392254 A1	03-03-2004
		EP 1800670 A1	27-06-2007
		ES 2286244 T3	01-12-2007
		HK 1063742 A1	14-12-2007
		JP 2004532847 A	28-10-2004
		NZ 529647 A	31-05-2007
		PT 1392254 E	29-06-2007
		US 2004234472 A1	25-11-2004
		US 2006189785 A1	24-08-2006
		US 2009105351 A1	23-04-2009
		WO 02085337 A1	31-10-2002
WO 2012090070 A2	05-07-2012	AU 2011350898 A1	11-07-2013
		CA 2822854 A1	05-07-2012
		EP 2658525 A2	06-11-2013
		SG 191414 A1	30-08-2013
		US 2012172454 A1	05-07-2012
		WO 2012090070 A2	05-07-2012