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(57) **Abrégé/Abstract:**

An injectable depot formulation includes a biocompatible polymer, an organic solvent combined with the biocompatible polymer to form a viscous gel, and a small molecule drug incorporated in the viscous gel such that the formulation exhibits an in vivo release profile having C_{max} to C_{min} ratio less than 200 and lag time less than 0.2.

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(54) Title: SUSTAINED RELEASE SMALL MOLECULE DRUG FORMULATION

(57) Abstract: An injectable depot formulation includes a biocompatible polymer, an organic solvent combined with the biocompatible polymer to form a viscous gel, and a small molecule drug incorporated in the viscous gel such that the formulation exhibits an in vivo release profile having C_{max} to C_{min} ratio less than 200 and lag time less than 0.2.



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SUSTAINED RELEASE SMALL MOLECULE DRUG FORMULATION

BACKGROUND OF THE INVENTION

[0001] The invention relates generally to delivery of small molecule drugs.

[0002] The term "small molecule drug," as used herein, refers to beneficial agents having low molecular weight. The beneficial agents are usually synthesized by organic chemistry, but may also be isolated from natural sources such as plants, fungi, and microbes. The common routes for delivering small molecule drugs are oral, injection, pulmonary, and transdermal.

[0003] Many psychotherapeutic drugs are small molecule drugs and are usually provided as oral pills or bolus injections that can be administered one or more times daily. However, oral pills and bolus injections may not be optimal routes for administering small molecule psychotherapeutic drugs because of the peaks and troughs observed in plasma concentration after dosing. Adverse effects and loss of therapeutic effect have been associated with plasma concentration peaks and troughs, respectively.

[0004] From the foregoing, psychotherapy as well as other forms of therapy presently relying on small molecule drugs administered in the form of oral pills and bolus injections may benefit from a sustained release dosage form designed to minimize variations in plasma concentration following dosing. Administration of psychotherapeutic agents as sustained release formulations will also increase patient compliance.

BRIEF SUMMARY

[0005] In one aspect, this disclosure provides an injectable depot formulation which comprises a biocompatible polymer, an organic solvent combined with the biocompatible polymer to form a viscous gel, and a small molecule drug incorporated in the viscous gel such that the formulation exhibits an *in vivo* release profile having C_{\max} to C_{\min} ratio less than 200 and lag time less than 0.2.

[005A] In another aspect, this disclosure provides a method of administering a small molecule drug to a subject in a controlled manner which comprises implanting in the subject an effective amount of an injectable depot formulation comprising a biocompatible polymer, an organic solvent combined with the biocompatible polymer to form a viscous gel, and a small molecule drug incorporated in the viscous gel such that the formulation exhibits an *in vivo* release profile having C_{\max} to C_{\min} ratio less than 200 and lag time less than 0.2.

[0006] The claimed invention relates to an injectable depot formulation, comprising: a biocompatible polylactide which is a polymer based on lactic acid or a copolymer based on lactic acid and glycolic acid, wherein said copolymer has a monomer ratio of lactic acid to glycolic acid of from 100:0 to 15:85 and wherein the polylactide has a number average molecular weight of 1000 to 30,000; an organic solvent combined with the biocompatible polymer to form a viscous gel; and risperidone, in base or salt form, incorporated in the viscous gel. In some embodiments, the polylactide has a number average molecular weight of 5,000 to 30,000 and in other embodiments, 1,000 to 5,000. In some embodiments, the risperidone is present in an amount ranging from 5 wt% to 40 wt% and in other embodiments, from 5 wt% to 30 wt%, based on total weight of the formulation. In some embodiments, the risperidone is in the form of particles having an average particle size of 0.1 to 125 μm . In some embodiments, the particles are less than 38 μm in size. Thus, in some embodiments, the invention relates to a composition comprising: (i) a vehicle comprising: 5 wt% to 80 wt%, based on total weight of the vehicle, of a biocompatible polymer, the polymer comprising a copolymer having a monomer ratio of lactic acid to glycolic acid from 100:0 to 50:50, the polymer having a number average molecular weight from 1000 Daltons to 120,000 Daltons; and 20 wt% to 95 wt%, based on total weight of the vehicle, of a solvent selected from benzyl alcohol, benzyl benzoate, ethyl benzoate, ethyl hydroxide, N-methyl-2-pyrrolidone, and mixtures thereof; and (ii) 5 wt% to 30 wt%, based on total weight of the composition, of a drug selected from base and salt forms of risperidone.

[0007] Other features and advantages will be apparent from the following description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] FIG. 1 shows influence of drug salt form on *in vivo* release profile of formulations according to embodiments of the invention.

[0009] FIG. 2 shows influence of solvent type on *in vivo* release profile of formulations according to embodiments of the invention.

[0010] FIG. 3 shows influence of polymer type on *in vivo* release profile of formulations according to embodiments of the invention.

[0011] FIG. 4 shows formulations having near zero-order release profiles according to embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The invention will now be described in detail with reference to a few preferred embodiments, as illustrated in accompanying drawings. In the following description, numerous specific details are set forth in order to provide a thorough understanding of the invention. However, it will be apparent to one skilled in the art that the invention may be practiced without some or all of these specific details. In other instances, well-known features and/or process steps have not been described in detail in order to not unnecessarily obscure the invention. The features and advantages of the invention may be better understood with reference to the drawings and discussions that follow.

[0013] The invention is based in part on the discovery that incorporation of a sparingly soluble small molecule drug in a depot gel vehicle produces a small molecule drug formulation that has near zero-order release *in vivo*. The release profile shows minimal lag time and burst. For a depot formulation, this release profile is surprising because the prevailing thought in the art is that a low burst, near zero-order release is virtually impossible to attain unless special steps are taken, such as coatings for drugs and microencapsulation. Several small drug formulations have been identified in this invention with *in vivo* release profiles having a C_{\max} to C_{\min} ratio less than 200 and lag time, T_{lag} , less than 0.2.

[0014] The variable " C_{\min} " is the minimum drug concentration in plasma or serum. The variable " C_{\max} " is the maximum drug concentration in plasma or serum. The variable " T_{lag} " is the ratio of T_{valley} to T_{total} , where T_{valley} is less than T_{total} . The variable " T_{valley} " is the time to reach C_{valley} . The variable " C_{valley} " is the first trough of drug concentration in plasma or serum during release. The variable " T_{total} " is the total release duration.

[0015] Small molecule drug formulations according to embodiments of the invention can be prepared as depot injections. The environment of use is a fluid environment and may include a subcutaneous, intramuscular, intramyocardial, adventitial, intratumoral, or intracerebral portion, a wound site, or tight joint spaces or body cavity of a human or animal. Multiple or repeated injections may be administered to the subject, for example, when the therapeutic effect of the drug has subsided or the period of time for the drug to have a therapeutic effect has lapsed or when the subject requires further administration of the drug for any reason. The formulation serves as an implanted sustained release drug delivery system after injection into the subject. Such controlled release can be over a period of one week, more than one week, one month, or more than one month. Preferably, the controlled release is over at least a period of one week, more preferably over a period of at least one month.

[0016] A small molecule drug formulation according to an embodiment of the invention includes a depot gel vehicle. The depot gel vehicle includes a biocompatible polymer, i.e., a polymer that would not cause irritation or necrosis in the environment of use. Biocompatible polymers that may be useful in the invention may be bioerodible, i.e., gradually decompose, dissolve, hydrolyze and/or erode *in situ*. Examples of bioerodible

polymers include, but are not limited to, polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamines, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, succinates, poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, polysaccharides, chitin, chitosan, and copolymers, terpolymers and mixtures thereof. The polymer is typically present in the depot gel vehicle in an amount ranging from about 5 to 80% by weight, preferably from about 20 to 70%, often from about 40 to 60% by weight.

[0017] In one embodiment, the polymer is a polylactide. A polylactide polymer is a polymer based on lactic acid or a copolymer based on lactic acid and glycolic acid. The polylactide polymer can include small amounts of other comonomers that do not substantially affect the advantageous results that can be achieved in accordance with the invention. The term "lactic acid" includes the isomers L-lactic acid, D-lactic acid, DL-lactic acid, and lactide. The term "glycolic acid" includes glycolide. The polymer may have a lactic-acid to glycolic-acid monomer ratio of from about 100:0 to 15:85, preferably from about 60:40 to 75:25, often about 50:50. The polylactide polymer has a number average molecular weight ranging from about 1,000 to about 120,000, preferably from about 5,000 to about 30,000, as determined by gel permeation chromatography. Suitable polylactide polymers are available commercially.

[0018] The depot gel vehicle further includes a biocompatible solvent which when combined with the polymer forms a viscous gel, typically exhibiting viscosity in a range from 500 poise to 200,000 poise, preferably from about 1,000 poise to 50,000 poise. The solvent used in the depot gel vehicle is typically an organic solvent and may be a single solvent or a mixture of solvents. To limit water intake by the depot gel vehicle in the environment of use, the solvent, or at least one of the components of the solvent in the case of a multi-component solvent, preferably has limited miscibility with water, e.g., less than 7% by weight, preferably less than 5% by weight, more preferably less than 3% by weight miscibility with water. Examples of suitable solvents include, but are not limited to, benzyl benzoate (BB), benzyl alcohol (BA), ethyl benzoate (EB), triacetin, and N-methyl-2-pyrrolidone (NMP). The solvent is typically present in the depot gel vehicle in an amount ranging from about 20 to

95% by weight, preferably in an amount ranging from about 30 to 80% by weight, often in an amount ranging from about 40 to 60 % by weight.

[0019] A formulation according to an embodiment of the invention includes a small molecule drug dispersed or dissolved in a depot gel vehicle as described above. The term “dispersed or dissolved” is intended to encompass all means of establishing the presence of the small molecule drug in the viscous gel and includes dissolution, dispersion, suspension, and the like. Small molecule drugs used in formulations of the invention are sparingly soluble in water. In a preferred embodiment, small molecule drugs used in formulations of the invention have less than 1 mg/ml solubility in water. In one embodiment, small molecule drugs used in formulations of the invention have a molecular weight in a range from 200 to 2,000 Daltons. Small molecule drugs used in formulations of the invention may have a narrow or wide therapeutic window. However, the invention generally delivers salubrious results in terms of C_{max} and toxicity control for small molecule drugs having a narrow therapeutic window. The small molecule drug is typically present in the formulation in an amount ranging from about 1 to 50% by weight, more preferably in an amount ranging from about 5 to 40% by weight, often in an amount ranging from about 10 to 30% by weight.

[0020] In one embodiment, a small molecule drug formulation includes a small molecule psychotherapeutic drug, such as a small molecule antipsychotic, dopamine receptor agonist, dopamine receptor antagonist, serotonin receptor agonist, serotonin receptor antagonist, and serotonin uptake inhibitor drug. Table 1 below shows physiochemical properties of some small molecule psychotherapeutic drugs. R209130-base has the molecular formula $C_{19}H_{20}FNO$. R209130-mandelic acid salt (R209130) has the molecular formula $C_{19}H_{20}FNO.C_8H_8O_3$. R209130-tartaric acid salt (R167154) has the molecular formula $C_{19}H_{20}FNO.C_4H_6O_6$. R209130 and its analogs possess putative atypical antipsychotic properties and have demonstrated antianxiety, antidepressive, and socializing effects in animal models. These characteristics may be attributed to R209130 dual antagonism of central dopamine D_2 receptors, serotonin $5-HT_{2A}$ and $5-HT_{2C}$ receptors, and the inhibition norepinephrine uptake. Risperidone-base has the molecular formula $C_{23}H_{27}FN_4O_2$. Risperidone-pamoate has the molecular formula $C_{23}H_{27}FN_4O_2.C_{23}H_{16}O_6$. Risperidone is a combined serotonin ($5-HT_2$) and dopamine (D_2) receptor antagonist.

TABLE 1

Property	R209130	R167154	R209130 base	Risperidone base	Risperidone pamoate
pKa	9.2	9.2	9.2	8.2/3.1	8.2/3.1
Solubility in H ₂ O (mg/ml)	0.32 (pH 4.9)	41.84 (pH 3.4)	0.008 (pH 9.5)	0.09 (pH 8.8)	0.2 (pH 7.2)
Solubility at pH 7 (mg/ml)	0.35	6.1 (pH 6.5)	2	1	0.2 (pH 7.2)
Solubility in BB (µg/ml)	58.6 at 40°C	10.3 at 40°C	> 200,000	32,000	50
Solubility in BA (mg/ml)	7.3 at 40°C	41.3 at 40°C	> 200,000	407	2.97
Intrinsic dissolution rate (mg/cm ² .min)	0.054	3.7	0.7	0.0025	N/A
LogP (C ₈ OH/pH 7 buffer)	3.9	4.0	N/A	3.04	N/A
Molecular weight	449.5	447.5	297.4	410.5	798.5

[0021] A study was conducted to determine the PK profile of a small molecule drug delivered from a depot gel vehicle according to the invention and the influence of salt form of the drug, solvent type, polymer type, polymer molecular weight, polymer/solvent ratio, drug loading, and particle size on the PK profile.

[0022] The following examples are presented for illustration purposes and are not intended to limit the invention as otherwise described herein.

EXAMPLE 1

[0023] A depot gel vehicle was prepared as follows: A HDPE container was tared on a Mettler PJ3000 top loader balance. Poly D,L-lactide-co-glycolide (PLGA), (L/G ratio of 50/50), available as RESOMER® RG 502 (PLGA-502), was weighed into the container. The container containing PLGA-502 was tared, and the corresponding solvent was added to the PLGA-502. Amounts expressed as percentages for various combinations of PLGA-502 and

solvent are set forth below in Table 2. A hybrid mixer was used to mix the PLGA-502 and solvent mixture, resulting in a clear gel-like solution of the polymer in the solvent.

TABLE 2

Formulation	PLGA-502 (wt%, g)	Benzyl Benzoate (wt%, g)	Benzyl Alcohol (wt%, g)
A	50.067	50.044	
B	50.023	24.988	24.988
C	50.365	45.093	5.1780
D	50.139	37.553	12.560
E	50.350	45.193	

[0024] Additional depot gel vehicles were prepared with solvents, selected from benzyl benzoate (BB), benzyl alcohol (BA), ethyl benzoate (EB), ethyl hydroxide (EtOH), triacetin, and N-methyl-2-pyrrolidone (NMP), and mixtures thereof, and polymers, selected from Poly D,L-lactide, available as RESOMER® L 104, RESOMER® R 104, RESOMER® 202, RESOMER® 203, RESOMER® 206, RESOMER® 207, RESOMER® 208; PLGA, L/G ratio of 50/50, available as RESOMER® RG 502H; PLGA, L/G ratio of 50/50, available as RESOMER® RG 503; PLGA, L/G ratio of 50/50, available as RESOMER® RG 755; Poly L-lactide, molecular weight of 2000, available as RESOMER® L 206, RESOMER® L 207, RESOMER® L 209, RESOMER® L 214; Poly L-lactide-co-D,L-lactide, L/G ratio of 90/10, available as RESOMER® LR 209; PLGA, L/G ratio of 75/25, available as RESOMER® RG 752, RESOMER® RG 756, PLGA, L/G ratio of 85/15, available as RESOMER® RG 858; Poly L-lactide-co-trimethylene carbonate, L/G ratio of 70/30, available as RESOMER® LT 706, and Poly dioxanone, available as RESOMER® X210 (Boehringer Ingelheim Chemicals, Inc. Petersburg, VA); DL-lactide/glycolide (DL), L/G ratio of 100/0, available as MEDISORB® Polymer 100 DL High, MEDISORB® Polymer 100 DL Low; DL-lactide/glycolide (DL), L/G ratio of 85/15, available as MEDISORB® Polymer 8515 DL High, MEDISORB® Polymer 8515 DL Low; DL-lactide/glycolide (DL), L/G ratio of 75/25, available as MEDISORB® Polymer 7525 DL High, MEDISORB® Polymer 7525 DL Low; DL-lactide/glycolide (DL), L/G ratio of 65/35, available as MEDISORB® Polymer 6535 DL High, MEDISORB® Polymer 6535 DL Low;

DL-lactide/glycolide (DL), L/G ratio of 54/46, available as MEDISORB® Polymer 5050 DL High, MEDISORB® Polymer 5050 DL Low, MEDISORB® 5050 Polymer DL 2A(3), MEDISORB® 5050 Polymer DL 3A(3), MEDISORB® 5050 Polymer DL 4A(3) (Medisorb Technologies International L.P., Cincinnati, OH); and PLGA (L/G ratio of 50/50), PLGA (L/G ratio of 65/35), PLGA (L/G ratio of 75/25), PLGA (L/G ratio of 85/15), Poly D,L-lactide, Poly L-lactide, Poly glycolide, Poly ϵ -caprolactone, Poly D,L-lactide-co-caprolactone (L/C ratio of 25/75), and Poly D,L-lactide-co-caprolactone (L/C ratio of 75/25), available from Birmingham Polymers, Inc., Birmingham, AL. Polycaprolactone-glycolic acid-lactic acid copolymer (PCL-GA-LA) was also used either mixed with polyvinylpyrrolidone (PVP) or by itself. Typical molecular weights of these polymers are in the range of 6,000 to 20,000.

EXAMPLE 2

[0025] Drug particles were prepared as follows: R209130, R167154, risperidone base, or risperidone pamoate drug was passed through sieves of different sizes to obtain drug particles having a certain range of particle size distribution. Particles in the range of 20 to 63 μm , 63 to 125 μm , 75 to 125 μm , or less than 38 μm were obtained. Micronized particles received were also used as drug particles.

EXAMPLE 3

[0026] Depot formulations were prepared as follows: sieved drug particles prepared as described in Example 2 were added into the depot gel vehicles prepared as described in Example 1 in an amount of 0 to 50% by weight and blended manually until the drug particles were wetted completely. Then, the mixture of drug particles and depot gel was thoroughly blended by conventional mixing using a Caframo mechanical stirrer with an attached square-tip metal spatula. Final homogeneous gel formulations were transferred to 3, 10, or 30 cc disposable syringes for storage or dispensing.

EXAMPLE 4

[0027] A representative number of implantable gels were prepared in accordance with the foregoing procedures and tested *in vivo* in rats to determine release of the drug as determined by blood serum or plasma concentration of drug as a function of time.

[0028] In general, *in vivo* studies in rats were performed following an open protocol to determine plasma levels of the drug (e.g., R209130, R167154, risperidone base, risperidone pamoate) upon systemic administration of the drug via the implant systems of the invention. Depot gel formulations containing the drug, prepared as described in the Examples above, were loaded into 0.5 cc disposable syringes. Disposable needles (18 gauge) were attached to the syringes and heated to 37°C using a circulator bath. The depot gel formulations were injected into rats. Blood was drawn at specified time intervals and analyzed for drug content. All plasma samples were stored at 4°C prior to analysis.

EXAMPLE 5

[0029] This example investigates influence of drug salt form on *in vivo* release of small molecule drugs from depot gel vehicles.

[0030] Particles of R209130 and R167154, in appropriate size range, were incorporated in depot gel vehicles, as per procedure in Example 3. Resulting formulations are illustrated in Table 2 below. Final homogeneous depot formulations were transferred to 3, 10, or 30 cc disposable syringes for storage or dispensing. *In vivo* release of the drugs were analyzed, as per procedure in Example 4. *In vivo* release profiles of the formulations are shown in FIG. 1. C_{max} to C_{min} ratio and T_{lag} of the formulations are shown in Table 2. R167154 and R209130 are different salt forms of the same drug. Formulation 7 (R209130) has C_{max} to C_{min} ratio of 19.2 and T_{lag} of 0.61, while formulation 3 (R167154) has C_{max} to C_{min} ratio of 25.7 and T_{lag} of 0.33. This example shows that *in vivo* release is influenced by salt form of the formulation. Even though T_{lag} for formulation 7 (R209130) is higher than T_{lag} for formulation 3 (R167154), formulation 7 appears to have better release rate profile and duration of release in comparison to formulation 3.

TABLE 2

No.	PLGA (wt%)	BA (wt%)	BB (wt%)	Triacetin (wt%)	Drug (wt%)	C _{max} /C _{min}	T _{lag}
3 ^{2,a,II,α,A}	45	22.5	22.5	0	10	25.7	0.33
7 ^{1,a,II,α,B}	45	22.5	22.5	0	10	19.2	0.61

1 = R209130, 2 = R167154, 3 = risperidone base, 4 = risperidone pamoate; a = 50/50 PLGA-502 (MW = 16,000), b = 50/50 PLGA-502H (MW = 11,000), c = 50/50 PLGA (MW = 6400), d = 40/55/5 PCL-GA-LA (MW = ~13,500), e = 75/25 PLGA (MW = 14,300), f = 80/20 PCL-GA-LA/PVP, g = RG502:RG502H (1:1); α = P/S ratio of 50/50, β = P/S ratio of 40/60, χ = P/S ratio of 45/55, δ = P/S ratio of 60/40, ε = P/S ratio of 55/45; A = 63-125 μm, B = 20-63 μm, C = 75-125 μm, D = <38 μm, E = micronized, F = as is, G = not applicable; NV = no valley

EXAMPLE 6

[0031] This example investigates influence of solvent type on *in vivo* release of small molecule drugs from depot gel vehicles.

[0032] Depot gel vehicles were prepared with PLGA-502 and a solvent selected from BA, BB, EB, EtOH, NMP, and triacetin, and combinations thereof, as per procedure in Example 1. The depot gel vehicles were loaded with drug substance, in appropriate range, as per procedure in Example 3. Resulting formulations are illustrated in Table 3 below. Final homogeneous depot formulations were transferred to 3, 10 or 30 cc disposable syringes for storage or dispensing. *In vivo* release profiles of the formulations in Table 3 are shown in FIG. 2. C_{max} to C_{min} ratio and T_{lag} of the formulations are shown in Table 3.

TABLE 3

No.	Target content in formulation (% w/w)								C _{max} / C _{min}	T _{lag}
	PLGA	BA	BB	EtOH	NMP	Triacetin	EB	Drug		
2 ^{2,a,II,α,A}	45	0	45	0	0	0	0	10	59.86	NV
3 ^{2,a,II,α,A}	45	22.5	22.5	0	0	0	0	10	25.68	0.33
10 ^{1,a,III,α,C}	40	40	0	0	0	0	0	20	4.35	0.61
14 ^{1,a,III,α,C}	40	20	20	0	0	0	0	20	3.15	0.50
63 ^{3,a,VII,α,C}	43.3	0	0	0	0	43.3	0	13.4	1364.43	0.14

No.	Target content in formulation (% w/w)								C_{max}/C_{min}	T_{lag}
	PLGA	BA	BB	EtOH	NMP	Triacetin	EB	Drug		
73 ^{3,a,VII,α,G}	43.3	0	0	0	0	0	43.3	13.4	5.20	N/A

1 = R209130, 2 = R167154, 3 = risperidone base, 4 = risperidone pamoate, a = 50/50 PLGA-502 (MW = 16,000), b = 50/50 PLGA-502H (MW = 11,000), c = 50/50 PLGA (MW = 6400), d = 40/55/5 PCL-GA-LA (MW = ~13,500), e = 75/25 PLGA (MW = 14,300), f = 80/20 PCL-GA-LA/PVP, g = RG502:RG502H (1:1); α = P/S ratio of 50/50, β = P/S ratio of 40/60, χ = P/S ratio of 45/55, δ = P/S ratio of 60/40, ϵ = P/S ratio of 55/45; A = 63-125 μ m, B = 20-63 μ m, C = 75-125 μ m, D = <38 μ m, E = micronized, F = as is, G = not applicable; NV = no valley

[0033] In Table 3 above, formulation 63 (risperidone base/PLGA/triacetin depot) has a C_{max} to C_{min} ratio of 1364.64. On the other hand, formulation 73 (risperidone base/PLGA/EB depot) has a C_{max} to C_{min} ratio of 5.20, which is significantly lower than the C_{max} to C_{min} ratio for formulation 63. Formulation 2 (R167154/PLGA/BB depot) has a C_{max} to C_{min} ratio of 59.68. On the other hand, formulation 3 (R167154/PLGA/BA/BB) has a C_{max} to C_{min} ratio of 25.68, which is less than half the C_{max} to C_{min} ratio for formulation 2. This indicates that solvent type can influence *in vivo* release profile of the formulation.

EXAMPLE 7

[0034] This example investigates influence of polymer type on *in vivo* release of small molecule drugs from depot gel vehicles.

[0035] Depot gel vehicles were prepared with different polymers and loaded with R209130, in appropriate size range, as per procedure in Example 3. Resulting formulations are illustrated in Table 4 below. Final homogeneous depot formulations were transferred to 3, 10 or 30 cc disposable syringes for storage or dispensing. Table 4 shows C_{max} to C_{min} ratio and T_{lag} for *in vivo* release profiles of the formulations. FIG. 3 shows *in vivo* release profiles of formulations in Table 4.

TABLE 4

No.	Target content in formulation (% w/w)					C_{max}/C_{min}	T_{lag}
	Polymer	BA	BB	Drug			
22 ^{1,a,IV,α,C}	35	35	0	30		9.86	0.17
23 ^{1,a,IV,α,C}	35	0	35	30		6.83	0.17

No.	Target content in formulation (% w/w)					C_{max}/C_{min}	T_{lag}
	Polymer	BA	BB	Drug			
24 ^{1,a,IV,α,E}	35	0	35	30		44.0	NV
25 ^{1,c,IV,α,C}	35	0	35	30		29.49	0.45
32 ^{1,d,IV,α,C}	35	0	35	30		10.65	0.12
33 ^{1,f,IV,α,C}	35	0	35	30		6.35	0.14
34 ^{1,a,IV,α,C}	35	35	0	30		8.75	0.23
35 ^{1,c,IV,α,C}	35	0	35	30		44.21	NV
48 ^{1,c,IV,α,E}	35	0	35	30		163.12	NV
53 ^{1,e,IV,α,E}	35	0	35	30		31.16	0.25
59 ^{1,d,IV,α,C}	35	0	35	30		6.26	0.07

1 = R209130, 2 = R167154, 3 = risperidone base, 4 = risperidone pamoate, a = 50/50 PLGA-502 (MW = 16,000), b = 50/50 PLGA-502H (MW = 11,000), c = 50/50 PLGA (MW = 6400), d = 40/55/5 PCL-GA-LA (MW = ~13,500), e = 75/25 PLGA (MW = 14,300), f = 80/20 PCL-GA-LA/PVP, g = RG502:RG502H (1:1); α = P/S ratio of 50/50, β = P/S ratio of 40/60, χ = P/S ratio of 45/55, δ = P/S ratio of 60/40, ϵ = P/S ratio of 55/45; A = 63-125 μ m, B = 20-63 μ m, C = 75-125 μ m, D = <38 μ m, E = micronized, F = as is, G = not applicable; NV = no valley

EXAMPLE 8

[0036] This example investigates influence of molecular weight of polymers on *in vivo* release of small molecule drugs from depot gel vehicles.

[0037] Depot gel vehicles were prepared with polymers with different molecular weights and loaded with drug substance, in appropriate size range, as per procedure in Example 3. Resulting formulations are illustrated in Table 5 below. Final homogeneous depot formulations were transferred to 3, 10 or 30 cc disposable syringes for storage or dispensing. Table 5 shows C_{max} to C_{min} ratio and T_{lag} for *in vivo* release profiles of the formulations.

TABLE 5

No.	Target content in Formulation (% w/w)					C_{max}/C_{min}	T_{lag}
	PLGA	BA	BB	Triacetin	Drug		
10 ^{1,a,III,α,C}	40	40	0	0	20	4.35	0.61
11 ^{1,a,III,α,D}	40	40	0	0	20	12.06	0.61
12 ^{1,a,IV,α,C}	35	35	0	0	30	4.78	0.14

No.	Target content in Formulation (% w/w)					C_{max}/C_{min}	T_{lag}
	PLGA	BA	BB	Triacetin	Drug		
13 ^{1,a,IV,α,D}	35	35	0	0	30	5.29	0.36
21 ^{1,c,III,α,C}	40	40	0	0	20	48.55	No valley
25 ^{1,c,IV,α,C}	35	0	35	0	30	29.49	0.45
26 ^{1,c,IV,α,D}	35	0	35	0	30	41.67	No valley
48 ^{1,c,IV,α,E}	35	0	35	0	30	163.12	No valley
49 ^{1,c,IV,δ,E}	42	0	28	0	30	66.31	0.39
63 ^{3,a,VII,α,C}	43.3	0	0	43.3	13.4	1364.43	0.14
64 ^{4,c,VIII,α,C}	36.9	0	36.9	0	26.1	11.66	No valley
69 ^{4,a,VIII,α,E}	36.9	0	36.9	0	26.1	14.12	0.90
70 ^{4,c,VIII,α,C}	36.9	0	36.9	0	26.1	22.11	no valley
72 ^{3,a,VII,α,G}	43.3	0	43.3	0	13.4	24.48	N/A

1 = R209130, 2 = R167154, 3 = risperidone base, 4 = risperidone pamoate, a = 50/50 PLGA-502 (MW = 16,000), b = 50/50 PLGA-502H (MW = 11,000), c = 50/50 PLGA (MW = 6400), d = 40/55/5 PCL-GA-LA (MW = ~13,500), e = 75/25 PLGA (MW = 14,300), f = 80/20 PCL-GA-LA/PVP, g = RG502:RG502H (1:1); α = P/S ratio of 50/50, β = P/S ratio of 40/60, χ = P/S ratio of 45/55, δ = P/S ratio of 60/40, ϵ = P/S ratio of 55/45; A = 63-125 μ m, B = 20-63 μ m, C = 75-125 μ m, D = <38 μ m, E = micronized, F = as is, G = not applicable; NV = no valley

EXAMPLE 9

[0038] This example investigates influence of polymer/solvent ratios on *in vivo* release of small molecule drugs from depot gel vehicles.

[0039] Depot gel vehicles were prepared with different polymer/solvent ratios and loaded with drug substance, in appropriate size range, as per procedure in Example 3. Resulting formulations are illustrated in Table 6 below. Final homogeneous depot formulations were transferred to 3, 10 or 30 cc disposable syringes for storage or dispensing. Table 6 shows C_{max} to C_{min} ratio and T_{lag} for *in vivo* release profiles of the formulations.

TABLE 6

Target content in Formulation (% w/w)			
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No.	PLGA	BB	EtOH	Drug	C _{max} /C _{min}	T _{lag}
22 ^{1,a,IV,α,C}	35	0	0	30	9.86	0.17
23 ^{1,a,IV,α,C}	35	35	0	30	6.83	0.17
24 ^{1,a,IV,α,E}	35	35	0	30	44.00	NV
25 ^{1,c,IV,α,C}	35	35	0	30	29.49	0.45
26 ^{1,c,IV,α,D}	35	35	0	30	41.67	NV
27 ^{1,c,IV,β,C}	28	42	0	30	54.16	NV
28 ^{1,c,IV,β,D}	28	42	0	30	120.74	NV
29 ^{1,a,IV,χ,C}	31.5	34.65	3.85	30	1.93	NV
30 ^{1,a,IV,χ,D}	31.5	34.65	3.85	30	7.07	0.29
48 ^{1,c,IV,α,E}	35	35	0	30	163.12	NV
49 ^{1,c,IV,δ,E}	42	28	0	30	66.31	0.39
52 ^{1,e,IV,β,E}	28	42	0	30	47.86	NV
53 ^{1,e,IV,α,E}	35	35	0	30	31.16	0.25
56 ^{1,b,IV,ε,F}	38.5	31.5	0	30	17.10	NV
65 ^{4,c,VIII,α,E}	36.9	36.9	0	26.1	50.87	NV
66 ^{4,c,VIII,ε,G}	40.6	33.2	0	26.1	38.39	NV
67 ^{4,c,VIII,ε,G}	33.2	40.6	0	26.1	43.55	NV

1 = R209130, 2 = R167154, 3 = risperidone base, 4 = risperidone pamoate, a = 50/50 PLGA-502 (MW = 16,000), b = 50/50 PLGA-502H (MW = 11,000), c = 50/50 PLGA (MW = 6400), d = 40/55/5 PCL-GA-LA (MW = ~13,500), e = 75/25 PLGA (MW = 14,300), f = 80/20 PCL-GA-LA/PVP, g = RG502:RG502H (1:1); α = P/S ratio of 50/50, β = P/S ratio of 40/60, χ = P/S ratio of 45/55, δ = P/S ratio of 60/40, ε = P/S ratio of 55/45; A = 63-125 μm, B = 20-63 μm, C = 75-125 μm, D = <38 μm, E = micronized, F = as is, G = not applicable; NV = no valley

EXAMPLE 10

[0040] This example investigates influence of drug loading on *in vivo* release of small molecule drugs from depot gel vehicles

[0041] Depot gel vehicles were prepared with varying percentages of drug, in appropriate size range, as per procedure in Example 3. Resulting formulations are illustrated in Table 7 below. Final homogeneous depot formulations were transferred to 3, 10 or 30 cc disposable syringes for storage or dispensing. Table 7 shows C_{max} to C_{min} ratio and T_{lag} for *in vivo* release profiles of the formulations.

TABLE 7

Formulation No.	Target content in Formulation (% w/w)				C_{max}/C_{min}	T_{lag}
	PLGA	BA	BB	Drug		
4 ^{1,a,II,α,B}	45	45	0	10	4.37	0.50
5 ^{1,a,III,α,B}	40	20	20	20	10.66	0.61
7 ^{1,a,II,α,B}	45	22.5	22.5	10	19.17	0.61
10 ^{1,a,III,α,C}	40	40	0	20	4.35	0.61
11 ^{1,a,III,α,D}	40	40	0	20	12.06	0.61
12 ^{1,a,IV,α,C}	35	35	0	30	4.78	0.14
13 ^{1,a,IV,α,D}	35	35	0	30	5.29	0.36
14 ^{1,a,III,α,C}	40	20	20	20	3.15	0.50
15 ^{1,a,III,α,D}	40	20	20	20	9.60	0.61
16 ^{1,a,IV,α,C}	35	17.5	17.5	30	7.16	0.61
17 ^{1,a,IV,α,D}	35	17.5	17.5	30	17.35	0.36
18 ^{1,a,V,α,C}	30	30	0	40	3.54	0.39

1 = R209130, 2 = R167154, 3 = risperidone base, 4 = risperidone pamoate, a = 50/50 PLGA-502 (MW = 16,000), b = 50/50 PLGA-502H (MW = 11,000), c = 50/50 PLGA (MW = 6400), d = 40/55/5 PCL-GA-LA (MW = ~13,500), e = 75/25 PLGA (MW = 14,300), f = 80/20 PCL-GA-LA/PVP, g = RG502:RG502H (1:1); α = P/S ratio of 50/50, β = P/S ratio of 40/60, χ = P/S ratio of 45/55, δ = P/S ratio of 60/40, ϵ = P/S ratio of 55/45; A = 63-125 μ m, B = 20-63 μ m, C = 75-125 μ m, D = <38 μ m, E = micronized, F = as is, G = not applicable; NV = no valley

EXAMPLE 11

[0042] This example investigates influence of drug particle size on *in vivo* release of small molecule drugs from depot gel vehicles.

[0043] Depot gel vehicles were prepared and loaded with drug particles in appropriate size range, as per procedure in Example 3. Resulting formulations are illustrated in Table 8 below. Final homogeneous depot formulations were transferred to 3, 10 or 30 cc disposable syringes for storage or dispensing. Table 8 shows C_{max} to C_{min} ratio and T_{lag} for *in vivo* release profiles of the formulations.

TABLE 8

	Target content in Formulation (% w/w)		
--	---------------------------------------	--	--

Formulation No.	PLGA	BA	BB	Drug	C _{max} /C _{min}	T _{lag}
7 ^{1,a,II,α,B}	45	22.5	22.5	10	19.17	0.61
10 ^{1,a,III,α,C}	40	40	0	20	4.35	0.61
11 ^{1,a,III,α,D}	40	40	0	20	12.06	0.61
23 ^{1,a,IV,α,C}	35	0	35	30	6.83	0.17
24 ^{1,a,IV,α,E}	35	0	35	30	44.00	NV
25 ^{1,c,IV,α,C}	35	0	35	30	29.49	0.45
26 ^{1,c,IV,α,D}	35	0	35	30	41.67	NV
64 ^{4,c,VIII,α,C}	36.9	0	36.9	26.1	11.66	NV
65 ^{4,c,VIII,α,E}	36.9	0	36.9	26.1	50.87	NV
66 ^{4,c,VIII,ε,G}	40.6	0	33.2	26.1	38.39	NV
72 ^{3,a,VII,α,G}	43.3	0	43.3	13.4	24.48	N/A

1 = R209130, 2 = R167154, 3 = risperidone base, 4 = risperidone pamoate, a = 50/50 PLGA-502 (MW = 16,000), b = 50/50 PLGA-502H (MW = 11,000), c = 50/50 PLGA (MW = 6400), d = 40/55/5 PCL-GA-LA (MW = ~13,500), e = 75/25 PLGA (MW = 14,300), f = 80/20 PCL-GA-LA/PVP, g = RG502:RG502H (1:1); α = P/S ratio of 50/50, β = P/S ratio of 40/60, χ = P/S ratio of 45/55, δ = P/S ratio of 60/40, ε = P/S ratio of 55/45; A = 63-125 μm, B = 20-63 μm, C = 75-125 μm, D = <38 μm, E = micronized, F = as is, G = not applicable; NV = no valley

EXAMPLE 12

[0044] A formulation is described as near zero-order if the ratio of C_{max} to C_{min} is less than 200, preferably less than 50, more preferably less than 30. T_{lag} in release of formulation is preferably less than 0.2. Formulations that do not show C_{valley} do not exhibit lag. Table 9 shows a number of formulations that exhibited the characteristic near zero-order release. FIG. 4 shows *in vivo* release profiles of selected formulations in Table 9.

TABLE 9

Formulation No.	Target content in Formulation (% w/w)					C _{max} /C _{min}	T _{lag}
	Polymer	BA	BB	EtOH	Drug Particles		
12 ^{1,a,IV,α,C}	35	35	0	0	30	4.78	0.14
22 ^{1,a,IV,α,C}	35	35	0	0	30	9.86	0.17
23 ^{1,a,IV,α,C}	35	0	35	0	30	6.83	0.17
29 ^{1,a,IV,χ,C}	31.5	0	34.65	3.85	30	1.93	NV

Formulation No.	Target content in Formulation (% w/w)					C_{max}/C_{min}	T_{lag}
	Polymer	BA	BB	EtOH	Drug Particles		
32 ^{1,d,IV,α,C}	35	35	0	0	30	10.65	0.12
33 ^{1,f,IV,α,C}	35	0	35	0	30	6.35	0.14
35 ^{1,c,IV,α,C}	35	0	35	0	30	44.21	NV
55 ^{1,e,IV,α,C}	35	0	35	0	30	6.33	0.11
56 ^{1,b,IV,ϵ,F}	38.5	0	31.5	0	30	17.10	NV
60 ^{1,c,VI,α,C}	25	0	25	0	50	12.90	0.07
61 ^{1,c,IV,α,C}	35	0	35	0	30	26.53	0.11
64 ^{4,c,VIII,α,C}	36.9	0	36.9	0	26.1	11.66	NV
70 ^{4,c,VIII,α,C}	36.9	0	36.9	0	26.1	22.11	NV

1 = R209130, 2 = R167154, 3 = risperidone base, 4 = risperidone pamoate; a = 50/50 PLGA-502 (MW = 16,000), b = 50/50 PLGA-502H (MW = 11,000), c = 50/50 PLGA (MW = 6400), d = 40/55/5 PCL-GA-LA (MW = ~13,500), e = 75/25 PLGA (MW = 14,300), f = 80/20 PCL-GA-LA/PVP, g = RG502:RG502H (1:1); α = P/S ratio of 50/50, β = P/S ratio of 40/60, χ = P/S ratio of 45/55, δ = P/S ratio of 60/40, ϵ = P/S ratio of 55/45; A = 63-125 μ m, B = 20-63 μ m, C = 75-125 μ m, D = <38 μ m, E = micronized, F = as is, G = not applicable; NV = no valley

[0045] While the invention has been described with respect to a limited number of embodiments, those skilled in the art, having benefit of this disclosure, will appreciate that other embodiments can be devised which do not depart from the scope of the invention as disclosed herein.

CLAIMS

What is claimed is:

1. An injectable depot formulation, comprising:
a biocompatible polylactide which is a polymer based on lactic acid or a copolymer based on lactic acid and glycolic acid, wherein said copolymer has a monomer ratio of lactic acid to glycolic acid of from 100:0 to 15:85 and wherein the polylactide has a number average molecular weight of 1000 to 30,000;
an organic solvent combined with the biocompatible polymer to form a viscous gel; and
risperidone, in base or salt form, incorporated in the viscous gel.
2. The formulation of claim 1, wherein the polylactide has a number average molecular weight of 5000 to 30,000.
3. The formulation of claim 1, wherein the polylactide has a number average molecular weight of 1000 to 5000.
4. The formulation of claim 1, 2 or 3, wherein the organic solvent is selected from benzyl alcohol, benzyl benzoate, ethyl benzoate, ethyl hydroxide, triacetin, N-methyl-2-pyrrolidone, and mixtures thereof.
5. The formulation of any one of claims 1 to 4, wherein the organic solvent comprises N-methyl-2-pyrrolidone.
6. The formulation of any one of claims 1 to 5, wherein the polylactide is said copolymer and the monomer ratio of lactic acid to glycolic acid is from 100:0 to 50:50.
7. The formulation of any one of claims 1 to 5, wherein the polylactide is said copolymer and the monomer ratio of lactic acid to glycolic acid is from 100:0 to 60:40.

8. The formulation of any one of claims 1 to 7, wherein the risperidone is present in an amount ranging from 5 wt% to 40 wt%, based on total weight of the formulation.
9. The formulation of any one of claims 1 to 7, wherein the risperidone is present in an amount ranging from 5 wt% to 30 wt%, based on total weight of the formulation.
10. The formulation of any one of claims 1 to 9, wherein the risperidone is in the form of particles having an average particle size in a range from 0.1 to 125 μm .
11. The formulation of any one of claims 1 to 10, wherein the risperidone is in the form of particles less than 38 μm in particle size.
12. The formulation of any one of claims 1 to 11, wherein the risperidone is in base form.
13. The formulation of any one of claims 1 to 12, wherein the formulation exhibits an *in vivo* release profile having C_{max} to C_{min} ratio less than 200.
14. The formulation of any one of claims 1 to 12, wherein the formulation exhibits an *in vivo* release profile having C_{max} to C_{min} ratio less than 30.
15. The formulation of any one of claims 1 to 14, wherein the formulation exhibits a lag time less than 0.2.
16. An injectable depot formulation as defined in any one of claims 1 to 15, for use in administration of the risperidone to a subject in a controlled manner.
17. An injectable depot formulation as defined in any one of claims 1 to 15, for use in administration of the risperidone to a subject in a controlled manner over a release duration.
18. A formulation as defined in claim 17, wherein the release duration is at least one week.

19. A composition comprising:
- (i) a vehicle comprising:
 - 5 wt% to 80 wt%, based on total weight of the vehicle, of a biocompatible polymer, the polymer comprising a copolymer having a monomer ratio of lactic acid to glycolic acid from 100:0 to 50:50, the polymer having a number average molecular weight from 1000 Daltons to 120,000 Daltons; and
 - 20 wt% to 95 wt%, based on total weight of the vehicle, of a solvent selected from benzyl alcohol, benzyl benzoate, ethyl benzoate, ethyl hydroxide, N-methyl-2-pyrrolidone, and mixtures thereof; and
 - (ii) 5 wt% to 30 wt%, based on total weight of the composition, of a drug selected from base and salt forms of risperidone.
20. The composition of claim 19, wherein the solvent comprises N-methyl-2-pyrrolidone.
21. The composition of claim 19 or 20, wherein the drug is in the form of particles having an average particle size from 0.1 to 125 μm .
22. The composition of claim 19, 20 or 21, wherein the drug is in the form of particles less than 38 μm in particle size.
23. The composition of any one of claims 19 to 22, wherein the monomer ratio of lactic acid to glycolic acid is from 100:0 to 60:40.
24. The composition of any one of claims 19 to 23, wherein the drug is risperidone in base form.

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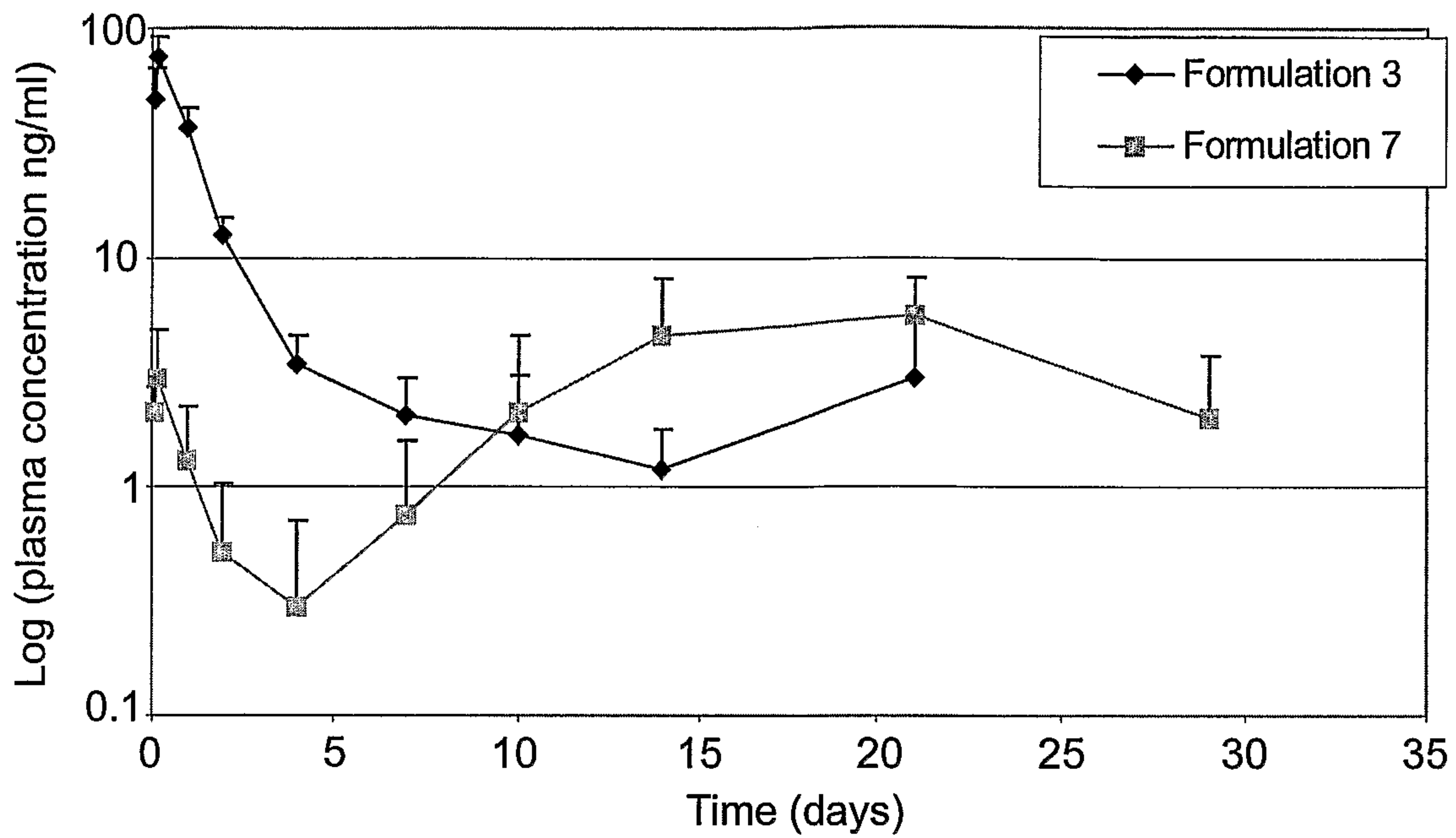


FIG. 1

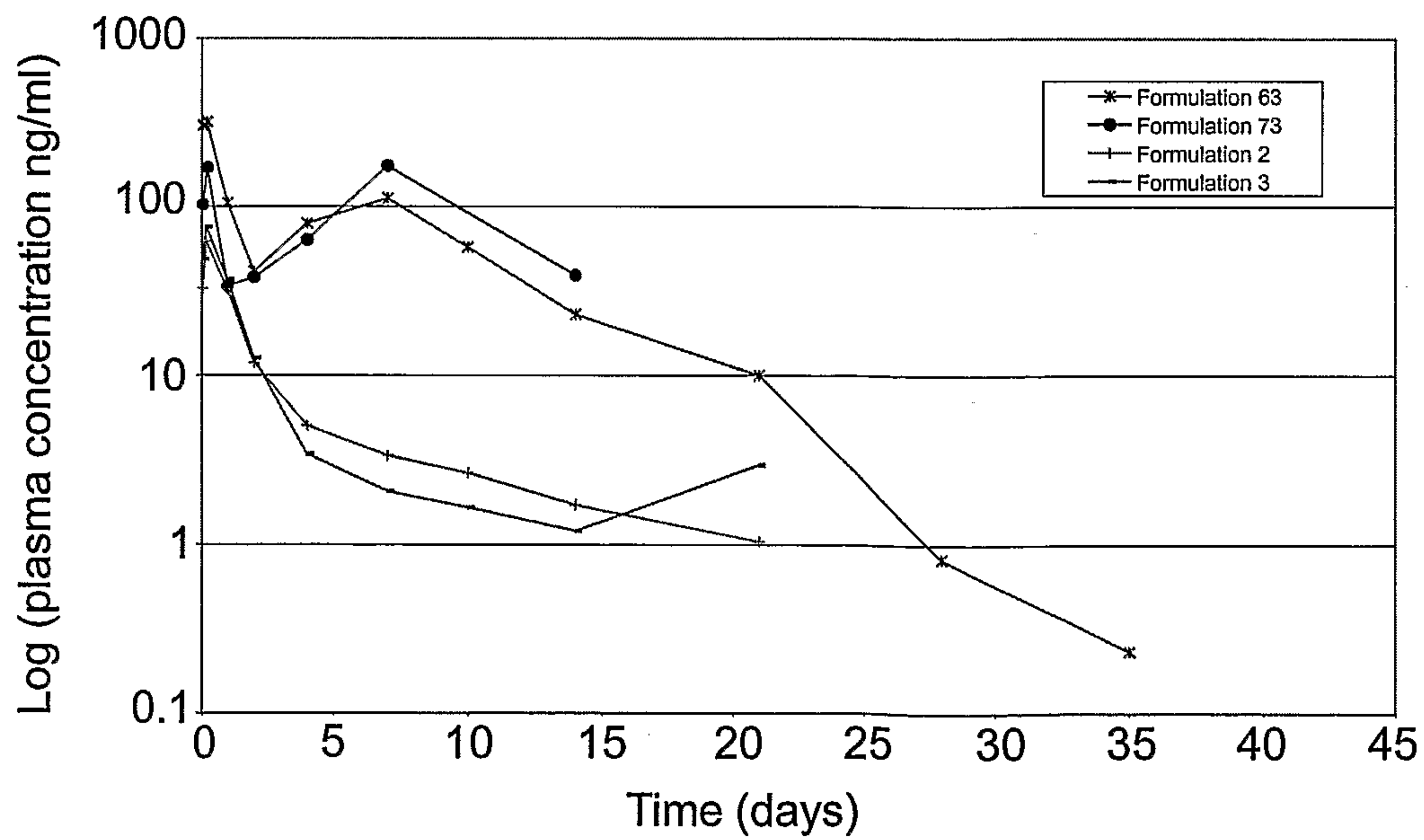


FIG. 2

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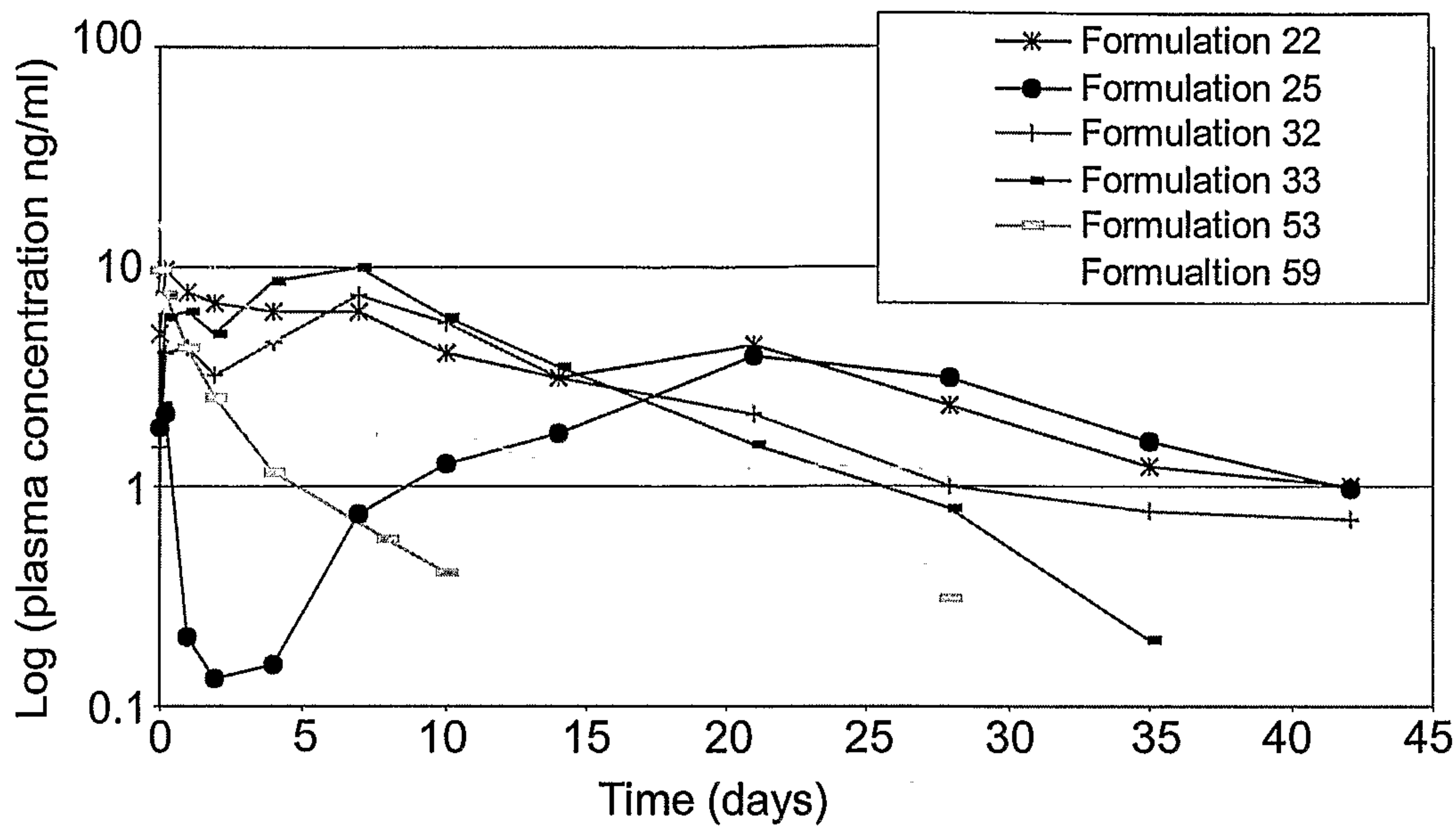


FIG. 3

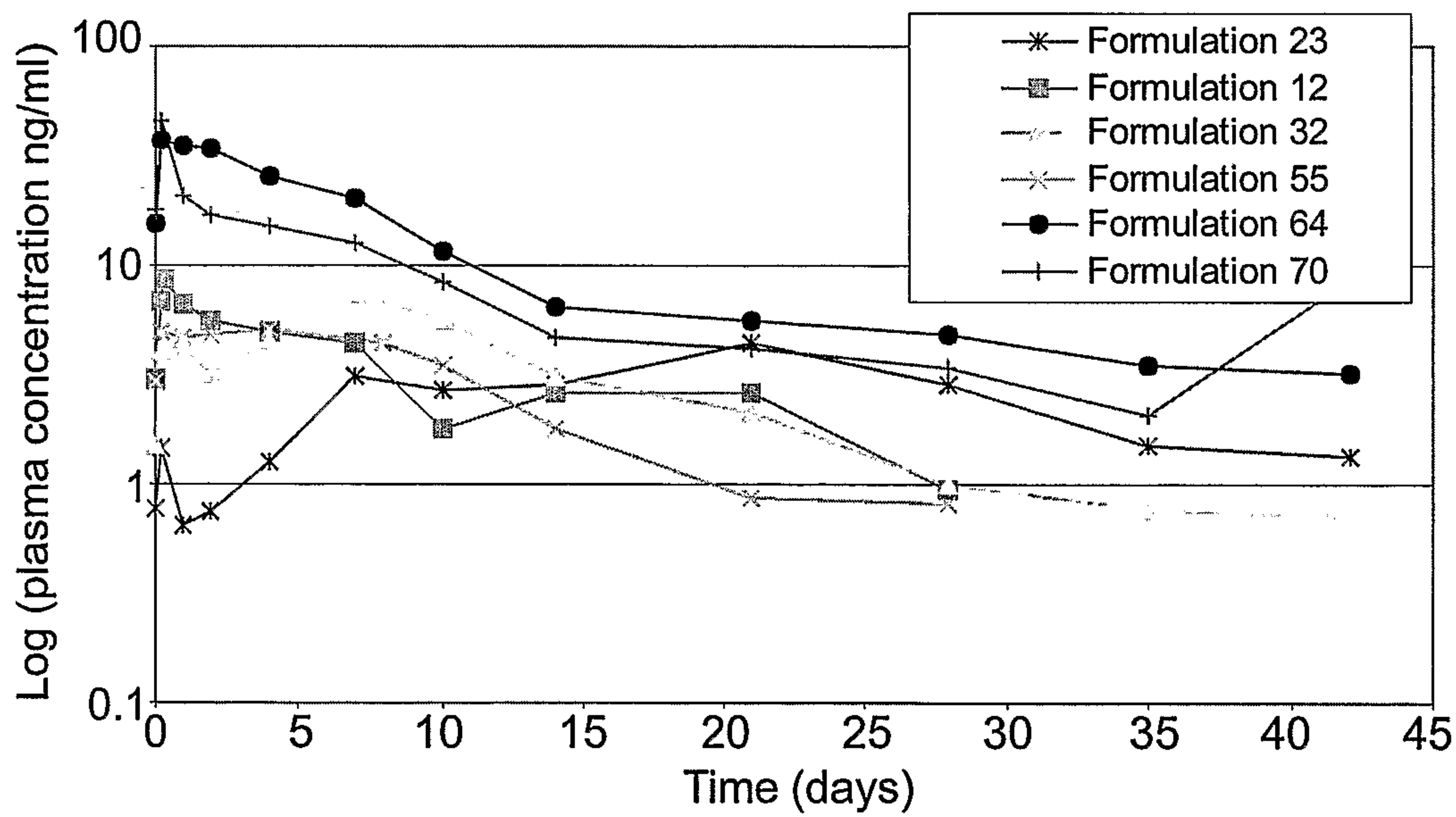


FIG. 4