

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 152 749 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:

12.04.2006 Bulletin 2006/15

(51) Int Cl.:

A61K 9/10 (2006.01)

(21) Application number: **00913350.5**

(86) International application number:

PCT/US2000/002772

(22) Date of filing: **02.02.2000**

(87) International publication number:

WO 2000/045790 (10.08.2000 Gazette 2000/32)

(54) **STABLE NON-AQUEOUS SINGLE PHASE VISCOUS VEHICLES AND FORMULATIONS UTILIZING SUCH VEHICLES**

STABILE NICHT WÄSSERIGE EINPHASIGE VISKÖSE VEHIKELN UND FORMULIERUNGEN DIE DIESE VEHIKELN VERWENDEN

EXCIPIENTS VISQUEUX A PHASE UNIQUE NON AQUEUX STABLES ET FORMULATIONS UTILISANT CES EXCIPIENTS

(84) Designated Contracting States:

**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**

• **DEHNAD, Houdin**

El Granada, CA 94018-1325 (US)

• **MUCHNIK, Anna**

Belmont, CA 94002 (US)

(30) Priority: **08.02.1999 US 119170 P**

(43) Date of publication of application:

14.11.2001 Bulletin 2001/46

(73) Proprietor: **ALZA CORPORATION**

Mountain View, CA 94039-7210 (US)

(74) Representative: **Suèr, Steven Johannes et al**

Ablett & Stebbing,

Caparo House,

101-103 Baker Street

London W1M 1FD (GB)

(72) Inventors:

• **BERRY, Stephen, A.**

Hollister, CA 95023 (US)

• **FEREIRA, Pamela, J.**

Redwood City, CA 94065 (US)

(56) References cited:

WO-A-96/39142

WO-A-98/27962

WO-A-98/27963

US-A- 4 734 284

US-A- 5 071 642

US-A- 5 385 738

US-A- 5 756 450

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 152 749 B1

DescriptionField of the invention

[0001] This invention relates to stable non-aqueous single phase biocompatible viscous vehicles capable of suspending beneficial agents and uniformly dispensing said agents at low flow rates and more particularly to stable uniformly mixed formulations of beneficial agents in stable non-aqueous single phase biocompatible viscous vehicles.

References

[0002] The following references are referred to by numbers in brackets ([]) at the relevant portion of the specification.

1. Wang, et al., *J. Parenteral Sci. Tech*, **42**: S4-S26 (1988).
2. Desai, et al., *J. Am. Chem. Soc.*, **116**: 9420-9422 (1994).
3. Chang, et al., *Pharm. Tech.*, 80-84 (Jan. 1996).
4. Manning, et al., *Pharm. Res.*, **6**: 903-918 (1989).
5. Hageman, *Drug Dev. Ind. Pharm*, **14**: 2047-2070 (1988).
6. Bell, et al., *Biopolymers*, **35**: 201-209 (1995).
7. Zhang, et al., *Pharm. Res.* **12**: 1447-1452 (1995).
8. PCT published application 98/00158
9. PCT published application 98/16250
10. Knepp, et al., *Pharm. Res.* **15** (7) 1090-1095 (1998).
11. PCT published application 98/00157
12. PCT published application 98/00152
13. U.S. Patent 5,540,912
14. U.S. Patent 5,571,525
15. U.S. Patent 5,512,293
16. PCT published application 96/40049
17. Yu, et al., *J. Pharm. Sci.*, **85**: 396-401 (1996).
18. Mitchell, U.S. Patent No. 5,411,951 (1995).
19. Brooks, et al., U.S. Patent No. 5,352,662 (1994)
20. Geller, L., U.S. Patent No. 3,869,549 (1975).
21. Larsen, et al., PCT Publication No. WO95/34285 (1995).
22. Knepp, et al., *J. Pharm. Sci. Tech*, **50**: 163-171 (1996).
23. U.S. Patent 5,614,221
24. U.S. Patent 4,594,108
25. U.S. Patent 5,300,302
26. U.S. Patent 4,588,614
27. U.S. Patent 4,310,516
28. U.S. Patent 5,635,213
29. EP 379,147

Background of the Invention

[0003] Peptides, polypeptides, proteins and other proteinaceous substances (e.g., viruses, antibodies) collectively referred to herein as proteins, have great utility as pharmaceuticals in the prevention, treatment and diagnosis of disease. Proteins are naturally active in aqueous environments, thus the preferred formulations of proteins have been in aqueous solutions. However, proteins are only marginally stable in aqueous solutions. Thus, protein pharmaceuticals often have short shelf-lives under ambient conditions or require refrigeration. Further, many proteins have only limited solubility in aqueous solutions. Even when they are soluble at high concentrations, they are prone to aggregation and precipitation.

[0004] Because proteins can easily degrade, the standard method for delivering such compounds has been daily injections. Proteins can degrade via a number of mechanisms, including deamidations of asparagine and glutamine; oxidation of methionine and, to a lesser degree, tryptophan, tyrosine and histidine; hydrolysis of peptide bonds; disulfide interchange; and racemization of chiral amino acid residues [1-7]. Water is a reactant in nearly all of these degradation pathways. Further, water acts as a plasticizer, which facilitates unfolding and irreversible aggregation of proteins. Since water is a participant in almost all protein degradation pathways, reduction of aqueous protein solution to a dry powder provides an alternative formulation methodology to enhance the stability of protein pharmaceuticals.

[0005] One approach to stabilizing proteins is to dry them using various techniques, including freeze-drying, spray-

drying, lyophilization, and desiccation. Dried proteins are stored as dry powders until their use is required.

[0006] A serious drawback to drying of proteins is that often one would like to use proteins in some sort of flowable form. Parenteral injection and the use of drug delivery devices for sustained delivery of drug are two examples of the applications where one would like to use proteins in a flowable form. For injection, dried proteins must be reconstituted, adding additional steps which are time-consuming and where contamination may occur, and exposing the protein to potentially destabilizing conditions [7]. For drug delivery devices the protein formulations must be stable for extended periods of time at body temperature and maintain their flowability for the expected life of the device.

[0007] Solution formulations of proteins/peptides in non-aqueous polar aprotic solvents such as DMSO and DMF have been shown to be stable at elevated temperatures for long periods of time [8]. However, such solvent based formulations will not be useable for all proteins since many proteins have low solubility in these solvents. The lower the solubility of the protein in the formulation, the more solvent would have to be used for delivery of a specific amount of protein. Low concentration solutions may be useful for injections, but may not be useful for long term delivery at low flow rates.

[0008] Proteins have been formulated for delivery using perfluorodecalin [9, 10], methoxyflurane [9], high concentrations in water [11], polyethylene glycol [12], PLGA [13, 14], ethylenevinylacetate/polyvinylpyrrolidone mixtures [15], PEG400/povidone [16]. However, these formulations were not shown to retain a uniform suspension of protein in viscous vehicle over long periods of time.

[0009] Many biologically active compounds degrade over time in aqueous solution. Carriers in which proteins do not dissolve but rather are suspended, can often offer improved chemical stability. Furthermore, it can be beneficial to suspend the beneficial agent in a carrier when the agent exhibits low solubility in the desired vehicle. However, suspensions can have poor physical stability due to settling and agglomeration of the suspended beneficial agent. The problems with non-aqueous carriers tend to be exacerbated as the concentration of the active compound is increased.

[0010] Dispersing powdered proteins or peptides in lipid vehicles to yield parenteral sustained release formulations has been investigated [17-21]. The vehicles used were either various vegetable (sesame, soy, peanut, etc.) or synthetic oils (e.g., Miglyol) gelled with aluminum fatty acid esters such as aluminum stearates (mono-, di- or tri-), or with a polyglycerol ester. Although theoretically these vehicles might preclude solution denaturation and protect the drug from aqueous chemical degradation, the vehicles themselves are unstable at higher temperatures. The storage of liquid vegetable oils at body temperatures results in the formation of reactive species such as free fatty acids and peroxides (a process which is accelerated by the presence of traces of various metal ions such as copper or iron which can leach from some implantable devices). These peroxides not only adversely affect protein stability [22] but would be toxic when delivered directly to, for example, the central nervous system of a human or animal.

[0011] The sustained delivery of drugs has many advantages. Use of implantable devices assures patient compliance, since the delivery device is tamper-proof. With one insertion of a device, rather than daily injections, there is reduced site irritation, fewer occupational hazards for practitioners improved cost effectiveness through decreased costs of equipment for repeated injections, reduced hazards of waste disposal, and enhanced efficacy through controlled release as compared with depot injection. The use of implantable devices for sustained delivery of a wide variety of drugs or other beneficial agents is well known in the art. Typical devices are described, for example, in U.S. Patents Nos. 5,034,229; 5,057,318; 5,110,596; and 5,782,396. The disclosure of each of these patents is incorporated herein by reference.

[0012] For drug delivering implants, dosing durations of up to one year are not unusual. Beneficial agents which have low therapeutic delivery rates are prime candidates for use in implants. When the device is implanted or stored, settling of the beneficial agent in a liquid formulation can occur. This heterogeneity can adversely affect the concentration of the beneficial agent dispensed. Compounding this problem is the size of the implanted beneficial agent reservoir. Implant reservoirs are generally on the order of 25-250 μ l, but can be up to 25 ml.

[0013] Viscous formulations have been prepared using two separate components to be mixed with drug at use [23], thickening agents added to aqueous compositions [24], gelling agents added to aqueous drug solutions [25], porous textile sheet material [26], thickening agents with oleaginous material [27], viscous aqueous carrier for limited solubility drug [28], and extrudable elastic gels [29]. However, these formulations are mixed at use, contain aqueous components, use sheet matrices, or are delivered topically, orally, or intraduodenally.

[0014] Stability of formulations can be enhanced by freeze-drying, lyophilizing or spray-drying the active ingredient. The process of drying the active ingredient includes further advantages such as compounds which are relatively unstable in aqueous solution can be processed and filled into dosage containers, dried without elevated temperatures, and then stored in the dry state in which there are relatively few stability problems.

[0015] Pharmaceutical formulations, particularly parenteral products, should be sterilized after being sealed in the final container and within as short a time as possible after the filling and sealing have been completed. (See, for example Remington, Pharmaceutical Sciences, 15th ed.(1975)). Examples of sterilization techniques include thermal or dry-heat, aseptic, and ionized radiation. Combinations of these sterilization procedures may also be used to produce a sterile product.

[0016] WO 98/27963 discloses formulations which may be used as injectable gels. The formulations include a beneficial agent dispersed or dissolved in a viscous gel, the gel being formed from a polymer and a solvent.

[0017] WO 98/27962 discloses injectable gel formulations which comprise a polymer, a solvent, a beneficial agent, and an emulsifying agent. In the formulations, the emulsifying agent forms a separate phase of droplets dispersed in within the viscous gel.

[0018] US 5,071,642 discloses dihydropyridine drug formulations in which the drug is dissolved within a polyethylene glycol solvent.

[0019] US 5,385,738 discloses formulations in which a powdered drug is suspended within a viscous solvent. The powdered drug comprises drug incorporated in a carrier material, the latter being chosen from biodegradable carriers such as collagen, gelatin, albumin, polysaccharides (such as chitins), and synthetic high molecular weight compounds, such as polyglycolic acid, polylactic acid, and polyglutamic acid. The solvent is the vehicle in which the powdered drug is suspended.

[0020] US 5,756,450 discloses formulations which are a combination of a pharmaceutically active compound and a water soluble monoester of a saturated or unsaturated fatty acid and a polyol. The formulations are solid solutions.

[0021] US 4,734,284 discloses etoposide compositions, in which the etoposide is dissolved in a water soluble cellulose ether derivative or polyvinylpyrrolidone.

[0022] WO 96/39142 discloses pharmaceutical compositions in which a proteinase inhibitor, salts or esters, is dissolved in a carrier which comprises a monoglyceride of a medium chain fatty acid, the monoglyceride being present in an amount which is sufficient to dissolve the proteinase inhibitor.

[0023] There is a need to be able to deliver protein compositions to the body which are stable at body temperatures over extended periods of time to enable long term delivery of the protein. There is a need to be able to deliver concentrations of proteins that are efficacious. There is a need for a novel non-aqueous formulation capable of homogeneously suspending proteins and dispensing such agents at body temperatures and low flow rates over extended periods of time.

Summary of the Invention

[0024] The present invention provides stable single phase non-aqueous biocompatible viscous vehicles capable of forming uniform suspensions with proteins. The components of the viscous vehicle comprise polymer, surfactant, and solvent. The ratios of the components will vary depending on the molecular weight of the components and the desired viscosity of the final vehicle. Presently preferred component ratios are: polymer, about 5% to about 60%; solvent, about 30% to about 50%; and surfactant, about 5% to about 20%.

[0025] The present invention also provides stable formulations in which beneficial agents are uniformly suspended in stable single phase non-aqueous biocompatible viscous vehicles. In particular, the beneficial agents are formulated in the viscous vehicles at concentrations of at least about 0.1%, depending upon the potency of the beneficial agent. These stable formulations may be stored at the temperature appropriate for the beneficial agent, ranging from cold, to body temperature (about 37°C) for long periods of time (1 month to 1 year or more). In a preferred embodiment the formulation comprises about 0.1 to 50% (w/w) of beneficial agent, depending on the potency of the beneficial agent, the duration of treatment, and the rate of release for the drug delivery system.

[0026] These formulations are especially useful in implantable delivery devices for long term delivery (e.g., 1 to 12 months or longer) of beneficial agent at body temperature, preferably about 37°C. Thus, the formulations of the present invention may deliver said proteins to the body over extended period of time to enable long term delivery of the protein at low flow rates of about 0.3 to 100 μ l/day, preferably about 0.3 to 4 μ l/day for about a 6 month delivery period and preferably 5 to 8 μ l/day for about a 3 month delivery period.

[0027] In another aspect, the invention provides methods for preparing stable non-aqueous biocompatible formulations of a beneficial agent in a single phase viscous vehicle. Preferred formulations comprise about 0.1 to 50% (w/w) beneficial agent depending on the potency of the beneficial agent, the duration of treatment, and the rate of release from the delivery system.

[0028] A further aspect of the invention is that non-aqueous single phase viscous vehicles containing beneficial agents are chemically and physically stable over a broad temperature range for long periods of time. The beneficial agents in the viscous vehicles are also chemically and physically stable over a broad temperature range for long periods of time. Thus, these formulations are advantageous in that they may be shipped and stored at temperatures below, at, or above room temperature for long period of time. They are also suitable for use in implantable delivery devices in which the formulation must be stable at body temperature for extended periods of time.

[0029] The formulations of the present invention also remain stable when delivered from implantable drug delivery systems. The beneficial agents have been shown to exhibit zero order release rates when delivered from implantable drug delivery systems at very low flow rates over extended periods of time.

Brief Description of the Drawings

[0030]

Figure 1 shows the stability of hGH formulations of the present invention as determined at 37°C by reverse phase HPLC.

Figure 2 shows the stability of hGH formulations of the present invention as determined at 37°C by size exclusion chromatography.

Figure 3 shows the average release rate ($\mu\text{l/day}$) of 10% (w/w) spray-dried lysozyme in formulations of the present invention.

Figure 4 shows the average release rate ($\mu\text{l/day}$) of 10% (w/w) spray-dried hGH in a glycerol monolaurate/lauryl lactate/polyvinylpyrrolidone vehicle.

Figure 5 shows the average release rate ($\mu\text{g/day}$) of 10% lysozyme in a lauryl alcohol/polyvinylpyrrolidone vehicle.

Figure 6 shows the average release rate ($\mu\text{g/day}$) of 25% lysozyme in a glycerol monolaurate/lauryl lactate/polyvinylpyrrolidone vehicle.

Figure 7 shows the average release rate ($\mu\text{g/day}$) of 33% lysozyme in a glycerol monolaurate/lauryl lactate/polyvinylpyrrolidone vehicle.

Figure 8 shows the average release rate ($\mu\text{g/day}$) of 45% lysozyme in a glycerol monolaurate/lauryl lactate/polyvinylpyrrolidone vehicle.

Detailed Description of the Invention

[0031] The present invention is drawn to the unexpected discovery that uniformly suspending beneficial agents in non-aqueous single phase biocompatible viscous vehicles results in stable formulations which can be delivered at body temperature over an extended period of time at low flow rates. Previously known formulations of beneficial agents which are buffered aqueous or non-aqueous solutions which may or may not contain excipients do not provide formulations which can be uniformly dispensed at body temperatures at low flow rates over an extended period or time without exhibiting unacceptable amounts of aggregation or degradation of the formulation. The presently claimed formulations stabilize beneficial agents and can be stored at the temperature appropriate for the beneficial agent. The temperatures can range from cold (not exceeding 8°C) to body temperature (about 37°C) for long periods of time. These formulations are especially useful in implantable delivery devices for long term delivery (e.g., 1 to 12 months or longer) of drug at low flow rates and at body temperature, preferably about 37°C.

[0032] Standard beneficial agent formulations consist of dilute aqueous or non-aqueous solutions or suspensions. Drug stability is usually achieved by varying one of more of the following: pH, buffer type, ionic strength, excipients (EDTA, ascorbic acid, etc.) For these formulations, degradation pathways requiring water (hydrolysis, deamidation, racemization) cannot be fully stabilized. In the present invention, beneficial agents formulated in non-aqueous biocompatible single phase viscous vehicles containing for example, polyvinylpyrrolidone, vinyl acetate, and/or polyoxyethylene-polyoxypropylene block copolymers were shown to be chemically and physically stable. The viscosity of the formulation will depend upon a number of criteria, including the beneficial agent potency and concentration, and the process by which the formulation is prepared. The viscosity of the formulation can be chosen so that the desired amount of beneficial agent is delivered over the desired period of time.

[0033] The invention provides non-aqueous single phase biocompatible viscous vehicles capable of uniformly suspending beneficial agents and formulations containing at least one beneficial agent uniformly suspended in said viscous vehicle. The invention also provides formulations containing at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle, which formulations are stable for an extended period of time at body temperatures, and capable of delivering said beneficial agents uniformly at low flow rates. The discovery consists of the realization that stable non-aqueous viscous vehicles improve the stability of beneficial agents in a wide range of formulation conditions including concentration, elevated temperatures and duration of stable formulation, thus making possible the delivery of beneficial agents in long term implantable devices that would not otherwise be feasible.

Definitions

[0034] As used herein, the following terms have the following meanings:

[0035] The term "chemical stability" means that an acceptable percentage of degradation products produced by chemical pathways such as oxidation, deamidation, or hydrolysis is formed. In particular, a formulation is considered chemically stable if no more than about 35% breakdown products are formed after 2 months at 37°C.

[0036] The term "physical stability" means that an acceptable percentage of aggregates (e.g., dimers, trimers and larger forms) are formed by the beneficial agent. For the formulation (viscous vehicle and beneficial agent) this term means that the formulation retains stability, flowability, and the ability to uniformly dispense the beneficial agent. In particular, a formulation is considered physically stable if no more than about 15% aggregates are formed after two months at 37°C.

[0037] The term "stable formulation" means that at least about 65% chemically and physically stable beneficial agent

remains after two months at 37°C (or equivalent conditions at an elevated temperature). Particularly preferred formulations are those which retain at least about 80% chemically and physically stable beneficial agent under these conditions. Especially preferred stable formulations are those which do not exhibit degradation after sterilizing irradiation (e.g., gamma, beta or electron beam).

[0038] The term "beneficial agent" means peptides, proteins, nucleotides, hormones, viruses, antibodies, etc. that comprise polymers of amino acid or nucleic acid residues. These beneficial agents are generally degradable in water and generally stable as a dry powder at elevated temperatures. Synthetically produced, naturally derived or recombinantly produced moieties are included in this term. The term also includes lipoproteins and post translationally modified forms, e.g., glycosylated proteins. Analogs, derivatives, agonists, antagonists and pharmaceutically acceptable salts of any of these are included in this term. The term also includes proteins and/or protein substances which have D-amino acids, modified, derivatized or non-naturally occurring amino acids in the D- or L- configuration and/or peptomimetic units as part of their structure. The term protein will be used in the present invention. The term also means that the beneficial agent is present in the solid state, e.g., powder or crystalline.

[0039] The term "excipient" means a more or less inert substance in a formulation that is added as a diluent or vehicle or to give form or consistency. Excipients are distinguished from solvents such as ETOH, which are used to dissolve drugs in formulations. Excipients include non-ionic surfactants such as polysorbates, which are used to solubilize drugs in formulations; preservatives such as benzyl alcohols or methyl or propyl parabens, which are used to prevent or inhibit microbial growth; chelating agents; flavoring agents; and other pharmaceutically acceptable formulation aides.

[0040] The term "viscous vehicle" means a vehicle with a viscosity in the range of about 1,000 to 10,000,000 poise. The term includes Newtonian and non-Newtonian materials. Preferred are vehicles with a viscosity of about 10,000 to 250,000 poise. The formulations of this invention can uniformly expel beneficial agents suspended in the viscous vehicle from implantable drug delivery devices. The formulations exhibit a shear rate at the exit of said devices of 1 to 1×10^{-7} reciprocal second. Preferably an exit shear rate of 1×10^{-2} to 1×10^{-5} reciprocal second.

[0041] The term "single phase" means a solid, semi-solid, or liquid homogeneous system that is both physically and chemically uniform throughout as determined by differential scanning calorimetry(DSC). The DSC scan should show one peak indicative of a single phase.

[0042] The term "biocompatible" means a property or characteristic of a viscous vehicle to disintegrate or break down, over a prolonged period of time, in response to the biological environment in the patient, by one or more physical or chemical degradative processes, for example by enzymatic action, oxidation or reduction, hydrolysis (proteolysis), displacement, e.g. ion exchange, or dissolution by solubilization, emulsion or micelle formation, and which material is then absorbed by the body and surrounding tissue, or otherwise dissipated thereby.

[0043] The term "polymer" includes polyesters such as PLA (polylactic acid) [having an inherent viscosity in the range of about 0.5 to 2.0 i.v.] and PLGA (polylacticpolyglycolic acid) [having an inherent viscosity in the range of about 0.5 to 2.0 i.v.], pyrrolidones such as polyvinylpyrrolidone (having a molecular weight range of about 2,000 to 1,000,000); esters or ethers of unsaturated alcohols such as vinyl acetate, and polyoxyethylenepolyoxypropylene block copolymers (exhibiting a high viscosity at 37°C) such as Pluronic 105. Currently preferred polymer is polyvinylpyrrolidone.

[0044] The term "solvent" includes lauryl alcohol and lauryl lactate.

[0045] The terms "surfactant" includes esters of polyhydric alcohols such as glycerol monolaurate, ethoxylated castor oil, polysorbates, esters or ethers of saturated alcohols such as myristyl lactate (Ceraphyl 50), and polyoxyethylenepolyoxypropylene block copolymers such as Pluronic. Currently preferred are glycerol monolaurate and polysorbates.

[0046] The term "antioxidant" means a pharmaceutically acceptable aid for stabilization of the beneficial agent against degradation such as oxidation. Antioxidants include, but are not limited to, tocopherol (vitamin E), ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate. A preferred antioxidant depends on solubility and the efficiency of the antioxidant for protecting against degradation or chemical change of the beneficial agent in the preferred vehicle. Currently preferred is ascorbyl palmitate.

Preparation of Formulations

[0047] The present invention is drawn to stable non-aqueous single phase biocompatible viscous vehicles capable of suspending beneficial agents and uniformly dispensing said beneficial agents at body temperatures at low flow rates over an extended period of time. The present invention is also directed to formulations containing beneficial agents uniformly suspended in said single phase biocompatible viscous vehicles which are stable for prolonged periods of time at body temperatures.

[0048] Examples of beneficial agents that may be formulated using the present invention include those peptides or proteins that have biological activity or that may be used to treat a disease or other pathological condition. They include, but are not limited to, adrenocorticotrophic hormone, angiotensin I and II, atrial natriuretic peptide, bombesin, bradykinin, calcitonin, cerebellin, dynorphin N, alpha and beta endorphin, endothelin, enkephalin, epidermal growth factor, fertirelin, follicular gonadotropin releasing peptide, galanin, glucagon, GLP-1, gonadorelin, gonadotropin, goserelin, growth hor-

mone releasing peptide, histrelin, human growth hormone, insulin, interferons, leuprolide, LHRH, motilin, nafarerlin, neurotensin, oxytocin, relaxin, somatostatin, substance P, tumor necrosis factor, triptorelin, vasopressin, growth hormone, nerve growth factor, blood clotting factors, ribozymes, and antisense oligonucleotides. Analogs, derivatives, antagonists agonists and pharmaceutically acceptable salts of the above may also be used.

[0049] The beneficial agents useful in the formulations and methods of the present invention can be used in the form of a salt, preferably a pharmaceutically acceptable salt. Useful salts are known to those of skill in the art and include salts with inorganic acids, organic acids, inorganic bases, or organic bases.

[0050] Beneficial agents that are not readily soluble in non-aqueous solvents are preferred for use in the present invention. One of skill in the art can easily determine which compounds will be useful on the basis of their solubility. The amount of beneficial agent may vary depending on the potency of the compound, the condition to be treated, the solubility of the compound, the expected dose and the duration of administration. (See, for example, Gilman, et. al, The Pharmacological Basis of Therapeutics, 7th ed. (1990) and Remington, Pharmacological Sciences, 18th ed. (1990).

[0051] It has been unexpectedly found that using a stable non-aqueous single phase biocompatible viscous vehicle increases the stability of the beneficial agent. For example, as seen in Figures 1 and 2, human growth hormone (hGH) was found to be stable at 37°C over 12 weeks in formulations of polyvinylpyrrolidone/PEG; Pluronic; and glycerol monolaurate/lauryl lactate/polyvinylpyrrolidone. Figure 1 shows stability results using reverse phase HPLC. Figure 2 shows stability results using size exclusion chromatography.

[0052] Generally, stable non-aqueous single phase biocompatible viscous vehicles may be prepared by combining the dry (low moisture content) ingredients in a dry box or under other dry conditions and blending them at elevated temperature, preferably about 40 to about 70°C, to allow them to liquify. The liquid vehicle is allowed to cool to room temperature. Differential scanning calorimetry was used to verify that the vehicle was single phase. The final moisture content of the viscous vehicle was <2%.

[0053] Generally, the stable formulations of the present invention may be prepared by combining the vehicle and beneficial agent under dry conditions and blending them under vacuum at elevated temperature, preferably about 40 to about 70°C, to disperse the beneficial agent uniformly throughout the vehicle. The formulation is allowed to cool to room temperature.

[0054] It has been found that drying the beneficial agent prior to formulation enhances the stability of the formulation.

[0055] It has also been found that adding antioxidants, such as tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate reduces the formation of degradation products (e.g., unstable chemical intermediates) during sterilization.

Methodology

[0056] We have found that stable non-aqueous beneficial agent formulations utilizing viscous vehicles may be prepared by combining the ingredients for the viscous vehicle under dry conditions and blending them at elevated temperature to allow them to liquify and form a single phase. Once a single phase viscous vehicle is formed, the vehicle is allowed to cool to room temperature. Beneficial agent is added with mixing at elevated temperature under vacuum to uniformly disperse it in the viscous vehicle.

[0057] We have tested these beneficial agent formulations, for example formulations of hGH, for stability by subjecting them to accelerated aging tests. Results show that these formulations remained stable over extended periods of time.

[0058] We have tested beneficial agent formulations, for example human growth hormone and lysozyme, for stability by suspending them in a variety of non-aqueous single phase viscous vehicles prepared according to the present invention, then subjecting them to accelerated aging at elevated temperatures. The stability of the formulations was measured. Results of these studies demonstrate that these formulations were stable at conditions that approximate or exceed storage for one year at 37°C.

[0059] We have also tested beneficial agent formulations prepared as described herein for stability after 2.5 megarads gamma irradiation. Results show that these formulations remained chemically and physically stable after such irradiation.

Methods

[0060] The following methods were used to perform the studies in the Examples that follow.

1. Preparing Protein powders

Human Growth Hormone (obtained for example, from BresaGen Limited, Adelaide, Australia)

[0061] The active agent was reconstituted in deionized water. The solution containing the active agent was buffer exchanged using an Amicon Diaflo® Ultrafiltration membrane (molecular weight cut-off 10,000).

[0062] The diafiltrated active agent solution was spray dried using a Yamato mini-spray dryer. Powder was collected in a collection vessel through a cyclone trap. All handling of the spray dried powder took place in a dry box evacuated with nitrogen. The generated powder was analyzed for particle size and distribution, moisture content, protein content and stability by size exclusion and reverse-phase chromatography.

[0063] It is known that the conformation of some proteins can be stabilized by the addition of a sugar (such as sucrose or mannitol) or a polyol (such as ethylene glycol, glycerol, glucose, and dextran.)

2. Preparation of Viscous Vehicles

[0064] We have found that stable single phase biocompatible viscous vehicles may be prepared by combining the ingredients and blending them at elevated temperatures to allow them to liquify and form a single phase. A differential scanning calorimetry scan showed one peak, indicative of a single phase.

The mixing was completed under vacuum to remove trapped air bubbles produced from the powders. The mixer was a dual helix blade mixer (D.I.T.) which runs at a speed around 40 rpm. Higher speeds can be used but are not required.

[0065] If a three component viscous vehicle is prepared, the solvent portion of the vehicle was added to the heated bowl of the mixer first, followed by the surfactant. The polymer was added last, and the ingredients were mixed until a solution (single phase) resulted. Vacuum was applied during mixing to remove air bubbles. The solution was dispensed from the bowl while at elevated temperature, and allowed to cool to room temperature. On cooling the vehicle exhibited increased viscosity. Two and single component gels were made using the same process.

3. Preparation of beneficial agent formulations

[0066] To prepare the formulation, the single phase viscous vehicle was heated and then blended under vacuum with a weighed amount of beneficial agent. The beneficial agent and the single phase viscous vehicle were blended in the same manner as the vehicle was prepared, using a dual helix blade mixer (or other similar mixer). Mixing speed was between 40 and 120 rpm for approximately 15 minutes or until a uniform dispersion was attained. The resulting mixture was removed from the mixer, sealed in a dry container, and allowed to cool to room temperature.

4. Preparation of reservoirs

[0067] The reservoirs of implantable drug delivery devices were filled with the appropriate hGH formulation. The formulation was filled into titanium reservoirs with a polymer plug blocking each end. The filled reservoir was then sealed in a polyfoil bag and placed in a stability testing oven. It should be noted that the formulations in the reservoirs of these devices are completely isolated from the outside environment.

5. Reverse Phase-HPLC (RP-HPLC)

[0068] All stability samples of hGH were assayed for protein content and chemical stability by reverse phase chromatography (RP-HPLC). Analyses were performed on a Hewlett Packard HP-1090 system with a refrigerated autosampler (4°C). The chromatographic conditions used are listed below.

TABLE 1 RP-HPLC Chromatographic Conditions

Description	Parameter		
Column	J.T. Baker-C18, 4.6x250 mm		
Flow Rate	1.0 mL/min		
Detection	214 nm		
Mobile Phase	A: 0.1 % TFA in water B: 0.1% TFA in acetonitrile		
Gradient	time	%A	%B
	0	65	35
	5	50	50
	45	35	65
	50	30	70
	55	65	35

[0069] An hGH reference standard solution was prepared and its protein content calculated from the absorbance measurement at 280 nm. Three dilutions of this solution, representing 80%, 100%, and 120% of the expected concentration of hGH in the samples were run in duplicate at the beginning and the end of each run and used to calculate total protein content of the samples.

6. Size Exclusion Chromatography (SEC)

[0070] All stability samples of hGH were assayed for protein content and high molecular weight degradation products by size exclusion chromatography. Analyses were performed on a Hewlett Packard HP-1090 system with a refrigerated autosampler (4°C). The chromatographic conditions used are listed below

TABLE 2 SEC Chromatographic Conditions

Description	Parameter
Column	TSK-2000SWXL
Flow Rate	0.5 ml/min
Detection	214 nm
Mobile Phase	25 mM sodium phosphate, 100 mM sodium chloride, pH 7.0

[0071] A hGH reference standard solution was prepared and its protein content calculated from the absorbance measurement at 280 nm. Three dilutions of this solution, representing 80%, 100%, and 120% of the expected concentration of hGH in the samples were run in duplicate at the beginning and the end of each run and used to calculate total protein content of the samples. The amount of high molecular weight degradation products was calculated by area normalization.

[0072] The following examples are offered to illustrate this invention and are not meant to be construed in any way as limiting the scope of this invention.

EXAMPLE 1

Preparation of Non-aqueous Single Phase Viscous Vehicles

[0073] The non-aqueous single phase viscous vehicles can be prepared as follows and shown in the below table

A. Glycerol monolaurate (Danisco Ingredients, New Century, Kansas) (25 g) was dissolved in lauryl lactate (ISP Van Dyk Inc., Belleville, NJ) (35 g) at 65°C. Polyvinylpyrrolidone C30 (BASF, Mount Olive, NJ) (40 g) was added and the mixture blended at about 40 rpm in a dual helix blade mixer (D.I.T.) until a single phase was achieved. Trapped air bubbles were removed by applying vacuum to the mixing chamber. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.

B. Glycerol monolaurate (Danisco Ingredients, New Century, Kansas) (25 g) was dissolved in lauryl lactate (ISP Van Dyk Inc., Belleville, NJ) (35 g) at 65°C. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (40 g) was added and the mixture blended at about 40 rpm in a dual helix blade mixer (D.I.T.) until a single phase was achieved. Trapped air bubbles were removed by applying vacuum to the mixing chamber. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.

C. Polyvinylpyrrolidone C30 (BASF, Mount Olive, NJ) (50 g) was dissolved in polyethylene glycol 400 (Union Carbide) (50 g) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.

D. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (50 g) was dissolved in polyethylene glycol 400 (Union Carbide) (50 g) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.

E. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (50 g) was dissolved in castor oil (Spectrum, Gardena, CA) (50 g) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.

F. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (50 g) was dissolved in octanoic acid (Spectrum, Gardena, CA) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.

G. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (50 g) was dissolved in oleic acid (Spectrum, Gardena, CA) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the

EP 1 152 749 B1

mixer, and allowed to cool to room temperature.

H. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (35%) was dissolved in glycerin (Baker, NJ) (65%) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.

I. Cremophor EL (ethoxylated castor oil) (BASF, Mount Olive, NJ) (5%) was dissolved in castor oil (Spectrum, Gardena, CA) (70%), and polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (25%) was added and dissolved by mixing at approximately 40 rpm to form a single phase vehicle. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.

J. Pluronic 105 (BASF, Mount Olive, NJ) was heated to approximately 65°C with mixing until melted. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.

Table 3 Component Ratios

Polymer	Component Surfactant	Solvent	Ratio	Viscosity at Low Shear Rate (Poise)
PVP	GML	LL	53:5:42	25,000
PVP	GML	LL	55:10:35	50,000
PVP	GML	LL	50:15:35	7,000
PVP	----	LA	60:40	
PVP	Ceraphyl 50	LA	60:10:30	
PVP	----	oleic acid	50:50	30,000
PVP	----	octanoic acid	55:45	7,000
PVP	polysorbate 80	----	50:50	
PVP	----	PEG 400	50:50	
PVP	castor oil	----	50:50	
----	Pluronic 105	----	100	1,000,000
PVP	----	glycerin	50:50	5,000

Wherein:

GML = glycerol monolaurate

LL = lauryl lactate

PVP = polyvinylpyrrolidone C30

LA = lauryl alcohol

PEG = polyethyleneglycol 400

EXAMPLE 2

Preparation of hGH

A. Preparation by spray drying

[0074] Lyophilized hGH (BresaGen Limited, Adelaide, Australia) was reconstituted in 150 ml of deionized water. This stock solution contained 1050 mg of hGH. Buffer exchange was accomplished using an Amicon Diaflo® Ultrafiltration membrane (molecular weight cut-off 10,000). The ultrafiltration cell was connected to an auxiliary reservoir containing 5mM phosphate buffer (pH 7). The cell's fluid volume, as well as the hGH concentration, remained constant as excipients were replaced by phosphate buffer.

[0075] The diafiltrated protein solution (protein concentration in the solution approximately 2%) was spray dried using a Yamato mini-spray dryer. Settings on the spray dryer were as follows: aspiration pressure constantly adjusted to 1.3 kgf/cm², inlet temperature 120°C, solution flow rate 2.5 (approximately 3 ml/min). Powder was collected in a collection vessel through a cyclone trap. All handling of the spray dried powder took place in a dry box evacuated with nitrogen (% RH: 1-4%). The water content of the suspending vehicles is shown in the below table.

TABLE 4 WATER CONTENT OF SUSPENDING VEHICLES

Vehicle	Water Content of Vehicle at T0 % w/w	Water Content of Vehicle in 12 wks. At 37°C % w/w
Pluronic 105	0.25	0.4

EP 1 152 749 B1

Table continued

Vehicle	Water Content of Vehicle at T0 % w/w	Water Content of Vehicle in 12 wks. At 37°C % w/w
GML/LL/PVP	1.5	1.3
PVP/PEG	2.0	2.0

Wherein:

GML = glycerol monolaurate

LL = lauryl lactate

PVP = polyvinylpyrrolidone C30

PEG = polyethyleneglycol 400

EXAMPLE 3

Preparation of hGH Formulation

[0076] A portion of the single phase viscous vehicle was weighed (9 g) and heated to 60°C. hGH (BresaGen Limited, Adelaide, Australia) (1 g) was added to the vehicle and mixed for 15 minutes. The mixing was completed under vacuum to remove air bubbles added from the powder.

[0077] Approximately 10 mg of the spray-dried hGH powder were weighed out (content of hGH in the powder was recalculated based on the determined water and salt content) and mixed with 100 µl of the vehicle at 55-65°C (3 samples per each vehicle). Special care was taken while mixing powder in the suspending vehicle to achieve maximum particle uniform dispersion in the vehicle. All steps were done in a dry box.

[0078] The resulting suspension was dissolved with 10 ml of release rate buffer and analyzed by size exclusion and reverse-phase chromatography. Spray dried hGH powder was used as a control.

TABLE 5 STABILITY OF hGH SUSPENSIONS AT 37°C AS MEASURED BY SIZE EXCLUSION CHROMATOGRAPHY

Time Weeks	Spray-dried Powder -80°C %LS	PVP/PEG 400 suspension %LS	GML/LL/PVP suspension %LS	Pluronic 105 suspension %LS
0	96±1	88±6	92±2	87±7
1	99±8	81±2	94±3	93±3
2	99±3	83±1	97±1	94±1
3	97±1	84±2	95±2	95±3
4	95±2	82±8	94±4	93±5
7	95±4	76±3	93±4	88±2
12	97±4	79±3	97±1	95±6

Each data point represents the mean ± relative standard deviation of three individual samples taken from three separate vials.

TABLE 6 STABILITY OF hGH SUSPENSIONS at 37°C AS MEASURED BY REVERSE PHASE CHROMATOGRAPHY

Time Weeks	spray-dried Powder -80°C %LS	PVP/PEG 400 suspension %LS	GML/LL/PVP suspension %LS	Pluronic 105 suspension %LS
0	104±1	99±3	99±2	89±7
1	104±8	78±2	98±3	96±6
2	104±4	73±3	95±1	96±1
3	104±2	78±4	97±3	97±4
4	100±2	74±10	93±4	96±4
7	108±5	72±4	96±2	94±2
9	102±3	66±3	92±3	93±2
12	101±2	66±1	89±2	92±5

Each data point represents the mean \pm relative standard deviation of three individual samples taken from three separate vials.

EXAMPLE 4

Preparation of Reservoirs Release Rate Profiles

[0079] Titanium reservoir systems of implantable drug delivery devices were each assembled with an osmotic engine, piston, and rate controlling membrane. The reservoirs were filled with the appropriate amount of viscous vehicle formulation and capped with a flow plug. The systems were placed in a water bath at 37°C, and allowed to release formulation for an extended period of time. Released material was sampled twice per week. Assays for released material were completed using reverse phase HPLC. The resulting concentrations of beneficial agent for each system were converted to released amount per day. The beneficial agent was found to have a zero order release from the implantable drug delivery device. As shown in Figures 3 through 8.

EXAMPLE 5

Stability of hGH in Non-aqueous Viscous Vehicle Formulations

[0080] Formulations of 10% w/w hGH in vehicle were prepared as described above and placed in vials. The formulations were subjected to accelerated aging by storing them at elevated temperatures and times shown in the below table in a controlled temperature oven.

TABLE 7

Vehicle	Time(hrs)	Temperature	%LS by SEC	%LS by RP-HPLC
Pluronic 105	0	50°C	98 \pm 3	101 \pm 3
Pluronic 105	1	50°C	98 \pm 3	101 \pm 4
Pluronic 105	2	50°C	100 \pm 1	102 \pm 3
Pluronic 105	4	50°C	101 \pm 3	105 \pm 3
GML/LL/PVP	0	65°C	99 \pm 3	101 \pm 3
GML/LL/PVP	1	65°C	93 \pm 6	97 \pm 6
GML/LL/PVP	2	65°C	91 \pm 5	95 \pm 5
GML/LL/PVP	4	65°C	95 \pm 3	98 \pm 3

Each data point represents the mean \pm relative standard deviation of three individual samples taken from three separate vials.

[0081] Results, presented in the following table, demonstrate that these formulations were able to maintain the stability of the hGH in each case. In each case, at least 70% hGH was retained.

TABLE 8 RECOVERY OF hGH FROM NONAQUEOUS SUSPENSIONS

Vehicle	%LS by RP-HPLC	%LS by Size-exclusion HPLC
PVP/PEG 400	99 \pm 3%	88 \pm 6%
GML/LL/PVP	99 \pm 2%	92 \pm 2%
Pluronic 105	89 \pm 7%	87 \pm 7%

Each data point represents the mean \pm relative standard deviation of three individual samples taken from three separate vials.

$$\%LS \text{ or } \% \text{ label strength} = (\text{measured protein content} + \text{theoretical protein content}) \times 100\%$$

[0082] Modification of the above-described modes of carrying out various embodiments of this invention will be apparent to those of skill in the art following the teachings of this invention as set forth herein. The examples described above are

not limiting, but are merely exemplary of this invention, the scope of which is defined by the following claims.

Claims

1. A beneficial agent formulation comprising at least one beneficial agent suspended within a non-aqueous single phase biocompatible viscous vehicle capable of suspending the beneficial agent and dispensing the beneficial agent over an extended period of time at body temperature, which vehicle comprises solvent, surfactant, and polymer, wherein the solvent, surfactant and polymer are not the same, the solvent is lauryl alcohol or lauryl lactate, the surfactant is selected from the group consisting of esters of polyhydric alcohols, ethoxylated castor oil, polysorbates, esters or ethers of saturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers, and the polymer is selected from the group consisting of polyesters, pyrrolidones, esters or ethers of unsaturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.
2. A beneficial agent formulation according to claim 1 wherein the vehicle is formulated to provide a beneficial agent formulation which is deliverable from a delivery system at an exit shear rate of between substantially 1 and 1×10^{-7} reciprocal second.
3. A formulation according to claim 1 or 2 wherein said formulation is stable at body temperature for extended periods of time.
4. A formulation according to claim 1, 2 or 3 which comprises at least substantially 0.1% (w/w) beneficial agent.
5. A formulation according to claim 4 which comprises at least substantially 10% (w/w) beneficial agent.
6. A formulation according to any one of claims 1 to 5 wherein said beneficial agent is selected from the group consisting of peptide, protein, nucleotide, hormone, virus, or antibody.
7. A formulation according to claim 6 wherein said beneficial agent is a protein.
8. A formulation according to any one of claims 1 to 7 which is stable at 65°C for at least substantially 2 months.
9. A formulation according to any one of claims 1 to 7 which is stable at 37°C for at least substantially 3 months.
10. A formulation according to claim 9 which is stable at 37°C for at least substantially one year.
11. A formulation according to any one of claims 1 to 10 which is adapted for use in an implantable drug delivery device.
12. A formulation according to any one of claims 1 to 11 wherein the beneficial agent has been dried to a low moisture content prior to incorporation in said formulation.
13. A formulation according to any one of claims 1 to 12 which is stable after sterilization.
14. A formulation according to any preceding claim wherein the viscosity of the vehicle is between substantially 1,000 and substantially 10,000,000 poise.
15. A formulation according to claim 14 wherein the viscosity of the vehicle is between substantially 10,000 and substantially 250,000,000 poise.
16. A formulation according to any preceding claim wherein the ratios of the components are in the range of substantially 30% to substantially 50% for solvent, substantially 5% to substantially 20% for surfactant, and substantially 5% to substantially 60% for polymer.
17. A formulation according to any preceding claim wherein the surfactant is selected from the group consisting of glycerol monolaurate and myristyl lactate.
18. A formulation according to any preceding claim wherein the polymer is selected from the group consisting of polylactic acid, polylacticpolyglycolic acid, polyvinylpyrrolidone and polyvinyl acetate.

19. A formulation according to any preceding claim wherein the polymer is polyvinylpyrrolidone and the surfactant is gml.
20. A formulation according to any preceding claim wherein the polymer is polyvinylpyrrolidone and the surfactant is polysorbate.
21. A formulation according to any preceding claim which comprises an antioxidant.
22. A formulation according to claim 21 wherein said antioxidant is selected from the group consisting of tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate.
23. A formulation according to any preceding claim wherein the beneficial agent is human growth hormone.
24. A method for preparing a formulation as defined by any preceding claim comprising combining the single phase viscous vehicle and beneficial agent under dry conditions and blending them under vacuum at elevated temperature to uniformly disperse the beneficial agent in the vehicle, and allowing the formulation to cool to room temperature.

Revendications

1. Formulation d'agent utile comprenant au moins un agent utile en suspension à l'intérieur d'un véhicule visqueux biocompatible à une seule phase, non-aqueux, capable de mettre en suspension l'agent utile et de distribuer l'agent utile sur une période de temps prolongée à la température corporelle, lequel véhicule comprend du solvant, de l'agent tensio-actif et du polymère, le solvant, l'agent tensio-actif et le polymère n'étant pas les mêmes, le solvant étant l'alcool laurylique ou le lactate de lauryle, l'agent tensio-actif étant choisi dans le groupe constitué par les esters d'alcools polyvalents, l'huile de ricin éthoxylée, les polysorbates, les esters ou éthers d'alcools saturés, et les copolymères à blocs polyoxyéthylène-polyoxypropylène, et le polymère étant choisi dans le groupe constitué par les polyesters, les pyrrolidones, les esters ou éthers d'alcools insaturés et les copolymères à blocs polyoxyéthylène-polyoxypropylène.
2. Formulation d'agent utile selon la revendication 1, dans laquelle le véhicule est formulé pour fournir une formulation d'agent utile qui est apte à être administrée à partir d'un système d'administration à un gradient de cisaillement de sortie d'entre sensiblement 1 et 1×10^{-7} seconde⁻¹.
3. Formulation selon l'une des revendications 1 ou 2, dans laquelle ladite formulation est stable à la température corporelle pendant des périodes de temps prolongées.
4. Formulation selon l'une des revendications 1, 2 ou 3, qui comprend au moins sensiblement 0,1% (p/p) d'agent utile.
5. Formulation selon la revendication 4, qui comprend au moins sensiblement 10% (p/p) d'agent utile.
6. Formulation selon l'une quelconque des revendications 1 à 5, dans laquelle ledit agent utile est choisi dans le groupe constitué par les peptides, les protéines, les nucléotides, les hormones, les virus ou les anticorps.
7. Formulation la revendication 6, dans laquelle ledit agent utile est une protéine.
8. Formulation selon l'une quelconque des revendications 1 à 7, qui est stable à 65°C pendant au moins sensiblement 2 mois.
9. Formulation selon l'une quelconque des revendications 1 à 7, qui est stable à 37°C pendant au moins sensiblement 3 mois.
10. Formulation selon la revendication 9, qui est stable à 37°C pendant au moins sensiblement une année.
11. Formulation selon l'une quelconque des revendications 1 à 10, qui est adaptée pour être utilisée dans un dispositif d'administration de médicament implantable.
12. Formulation selon l'une quelconque des revendications 1 à 11, dans laquelle l'agent utile a été séché jusqu'à une faible teneur en humidité avant l'incorporation dans ladite formulation.

13. Formulation selon l'une quelconque des revendications 1 à 12, qui est stable après stérilisation.
14. Formulation selon l'une quelconque des revendications précédentes, dans laquelle la viscosité du véhicule est entre sensiblement 1000 et sensiblement 10 000 000 poises.
15. Formulation selon la revendication 14, dans laquelle la viscosité du véhicule est entre sensiblement 10 000 et sensiblement 250 000 000 poises.
16. Formulation selon l'une quelconque des revendications précédentes, dans laquelle les rapports des composants se situent dans la plage de sensiblement 30% à sensiblement 50% pour le solvant, sensiblement 5% à sensiblement 20% l'agent tensio-actif, et sensiblement 5% à sensiblement 60% pour le polymère.
17. Formulation selon l'une quelconque des revendications précédentes, dans laquelle l'agent tensio-actif est choisi dans le groupe constitué par le monolaurate de glycérol et le lactate de myristyle.
18. Formulation selon l'une quelconque des revendications précédentes, dans laquelle le polymère est choisi dans le groupe constitué par l'acide polylactique, l'acide polylactiquepolyglycolique, la polyvinylpyrrolidone et le poly(acétate de vinyle).
19. Formulation selon l'une quelconque des revendications précédentes, dans laquelle le polymère est la polyvinylpyrrolidone et l'agent tensio-actif est le monolaurate de glycérol (gml).
20. Formulation selon l'une quelconque des revendications précédentes, dans laquelle le polymère est la polyvinylpyrrolidone et l'agent tensio-actif est un polysorbate.
21. Formulation selon l'une quelconque des revendications précédentes qui comprend un anti-oxydant.
22. Formulation selon la revendication 21, dans laquelle ledit anti-oxydant est choisi dans le groupe constitué par le tocophérol, l'acide ascorbique, le palmitate d'ascorbyle, l'hydroxyanisole butylé, l'hydroxytoluène butylé et le gallate de propyle.
23. Formulation selon l'une quelconque des revendications précédentes, dans laquelle l'agent utile est l'hormone de croissance humaine.
24. Procédé de préparation d'une formulation telle que définie par l'une quelconque des revendications précédentes, comprenant les opérations consistant à combiner le véhicule visqueux à une seule phase et l'agent utile dans des conditions sèches et mélanger ceux-ci sous vide à température élevée pour disperser uniformément l'agent utile dans le véhicule, et laisser la formulation refroidir jusqu'à la température ambiante.

Patentansprüche

1. Formulierung eines nützlichen Mittels, umfassend mindestens ein nützliches Mittel, das in einem blokompatiblen, viskosen Träger aus einer nicht-wässrigen, einzelnen Phase suspendiert ist, der in der Lage ist, das nützliche Mittel über einen verlängerten Zeitraum bei Körpertemperatur zu suspendieren oder zu dispergieren, wobei der Träger ein Lösungsmittel, ein Tensid und ein Polymer umfasst, und wobei das Lösungsmittel, Tensid und Polymer nicht gleich sind, das Lösungsmittel Laurylalkohol oder Lauryllactat ist, das Tensid aus der Gruppe ausgewählt ist, die aus Estern von mehrwertigen Alkoholen, ethoxyliertem Flizinusöl, Polysorbaten, Estern oder Ethern von gesättigten Alkoholen und Polyoxyethylen-Polyoxypropylen-Blockcopolymeren besteht, und das Polymer aus der Gruppe ausgewählt ist, die aus Polyestern, Pyrrolidonen, Estern oder Ethern von ungesättigten Alkoholen und Polyoxyethylen-Polyoxypropylen-Blockcopolymeren besteht.
2. Formulierung eines nützlichen Mittels nach Anspruch 1, worin der Träger zur Bereitstellung einer Formulierung eines nützlichen Mittels formuliert ist, die mit einer Ausgangsschergeschwindigkeit zwischen im wesentlichen 1 und 1×10^{-7} pro Sekunde aus einem Abgabesystem abgegeben werden kann.
3. Formulierung nach Anspruch 1 oder 2, worin die Formulierung bei Körpertemperatur über verlängerte Zeiträume stabil ist.

4. Formulierung nach den Ansprüchen 1, 2 oder 3, die im wesentlichen mindestens 0,1% (Gew./Gew.) nützliches Mittel enthält.
5. Formulierung nach Anspruch 4, die im wesentlichen mindestens 10% (Gew./Gew.) nützliches Mittel enthält.
- 5 6. Formulierung nach einem der Ansprüche 1 bis 5, worin das nützliche Mittel aus der Gruppe ausgewählt ist, die aus einem Peptid, Protein, Nucleotid, Hormon, Virus oder Antikörper besteht.
7. Formulierung nach Anspruch 6, worin das nützliche Mittel ein Protein ist.
- 10 8. Formulierung nach einem der Ansprüche 1 bis 7, die bei 65°C mindestens 2 Monate lang stabil ist.
9. Formulierung nach Anspruch 9, die bei 37°C mindestens 3 Monate lang stabil ist.
- 15 10. Formulierung nach einem der Ansprüche 1 bis 7, die bei 37°C mindestens ein Jahr lang stabil ist.
11. Formulierung nach einem der Ansprüche 1 bis 10, die zur Verwendung in einer Implantierbaren Medikamentenabgabevorrichtung geeignet ist.
- 20 12. Formulierung nach einem der Ansprüche 1 bis 11, worin das nützliche Mittel vor dem Einbringen in die Formulierung auf einen niedrigen Feuchtigkeitsgehalt getrocknet wurde.
13. Formulierung nach einem der Ansprüche 1 bis 12, die nach Sterilisieren stabil ist.
- 25 14. Formulierung nach einem der vorhergehenden Ansprüche, worin die Viskosität des Trägers im wesentlichen zwischen 1000 und 10 000 000 Poise liegt.
15. Formulierung nach Anspruch 14, worin die Viskosität des Trägers im wesentlichen zwischen 10 000 und 250 000 000 Poise liegt.
- 30 16. Formulierung nach einem der vorhergehenden Ansprüche, worin die Anteile der Komponenten im wesentlichen im Bereich von 30% bis 50% für das Lösungsmittel, 5% bis 20% für das Tensid und 5% bis 60% für das Polymer liegen.
17. Formulierung nach einem der vorhergehenden Ansprüche, worin das Tensid aus der Gruppe ausgewählt ist, die aus Glycerinmonolaurat und Myristyllactat besteht.
- 35 18. Formulierung nach einem der vorhergehenden Ansprüche, worin das Polymer aus der Gruppe ausgewählt ist, die aus Polymilchsäure, Polymilchsäure-Polyglycolsäure, Polyvinylpyrrolidon und Polyvinylacetat besteht.
- 40 19. Formulierung nach einem der vorhergehenden Ansprüche, worin das Polymer Polyvinylpyrrolidon und das Tensid Glycerinmonolaurat (gml) ist.
20. Formulierung nach einem der vorhergehenden Ansprüche, worin das Polymer Polyvinylpyrrolidon und das Tensid Polysorbat ist.
- 45 21. Formulierung nach einem der vorhergehenden Ansprüche, die ein Antioxidationsmittel umfasst.
22. Formulierung nach Anspruch 21, worin das Antioxidationsmittel aus der Gruppe ausgewählt ist, die aus Tocopherol, Ascorbinsäure, Ascorbylpalmitat, butyliertem Hydroxyanisol, butyliertem Hydroxytoluol und Propylgallat besteht.
- 50 23. Formulierung nach einem der vorhergehenden Ansprüche, worin das nützliche Mittel menschliches Wachstumshormon ist.
- 55 24. Verfahren zur Herstellung einer Formulierung nach einem der vorhergehenden Ansprüche, umfassend das Vereinigen des einphasigen viskosen Trägers und des nützlichen Mittels unter trockenen Bedingungen und deren Mischen unter Vakuum bei erhöhter Temperatur, um das nützliche Mittel gleichmäßig im Träger zu dispergieren, und Abkühlenlassen der Formulierung auf Raumtemperatur.

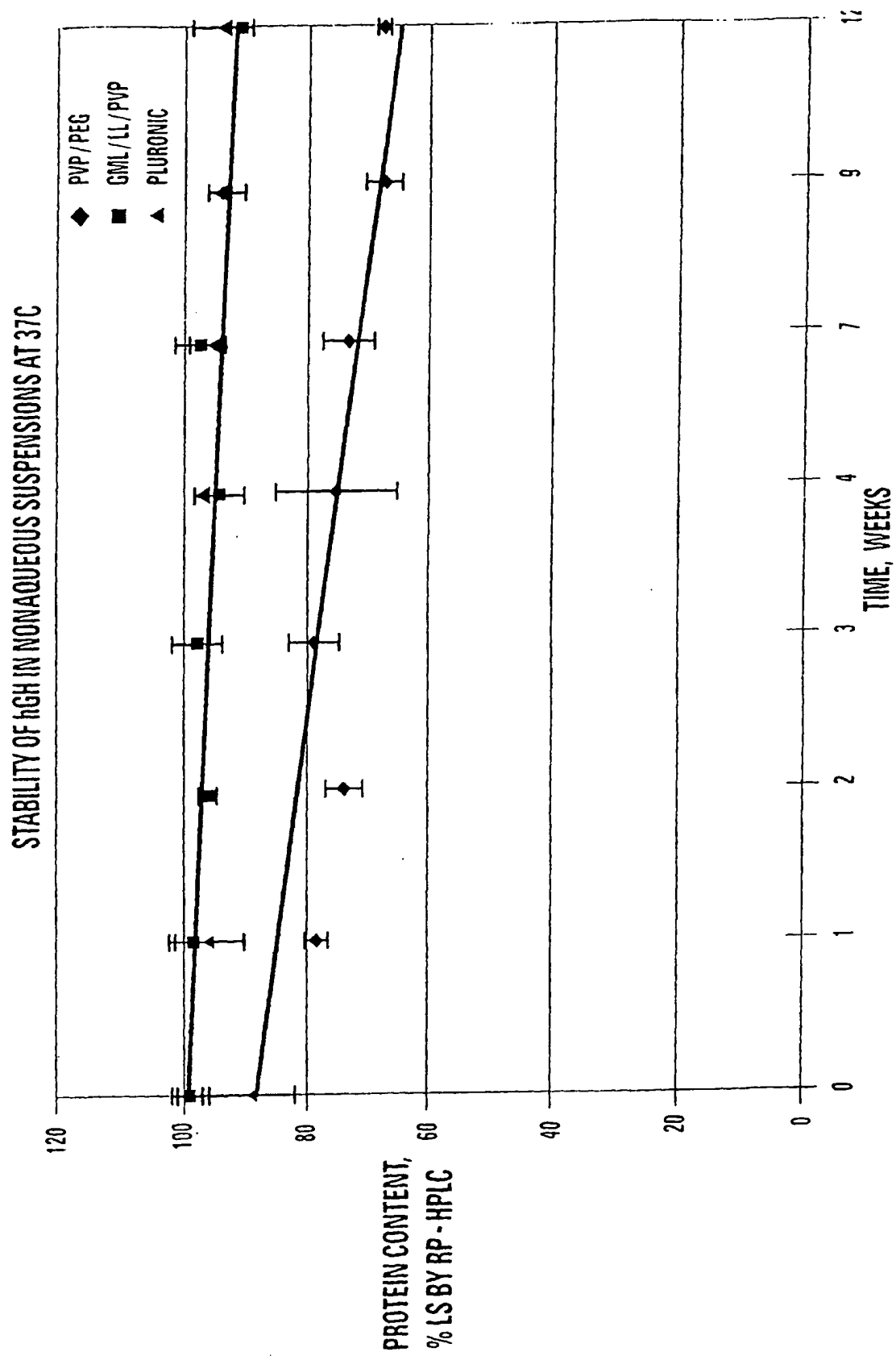


FIGURE 1

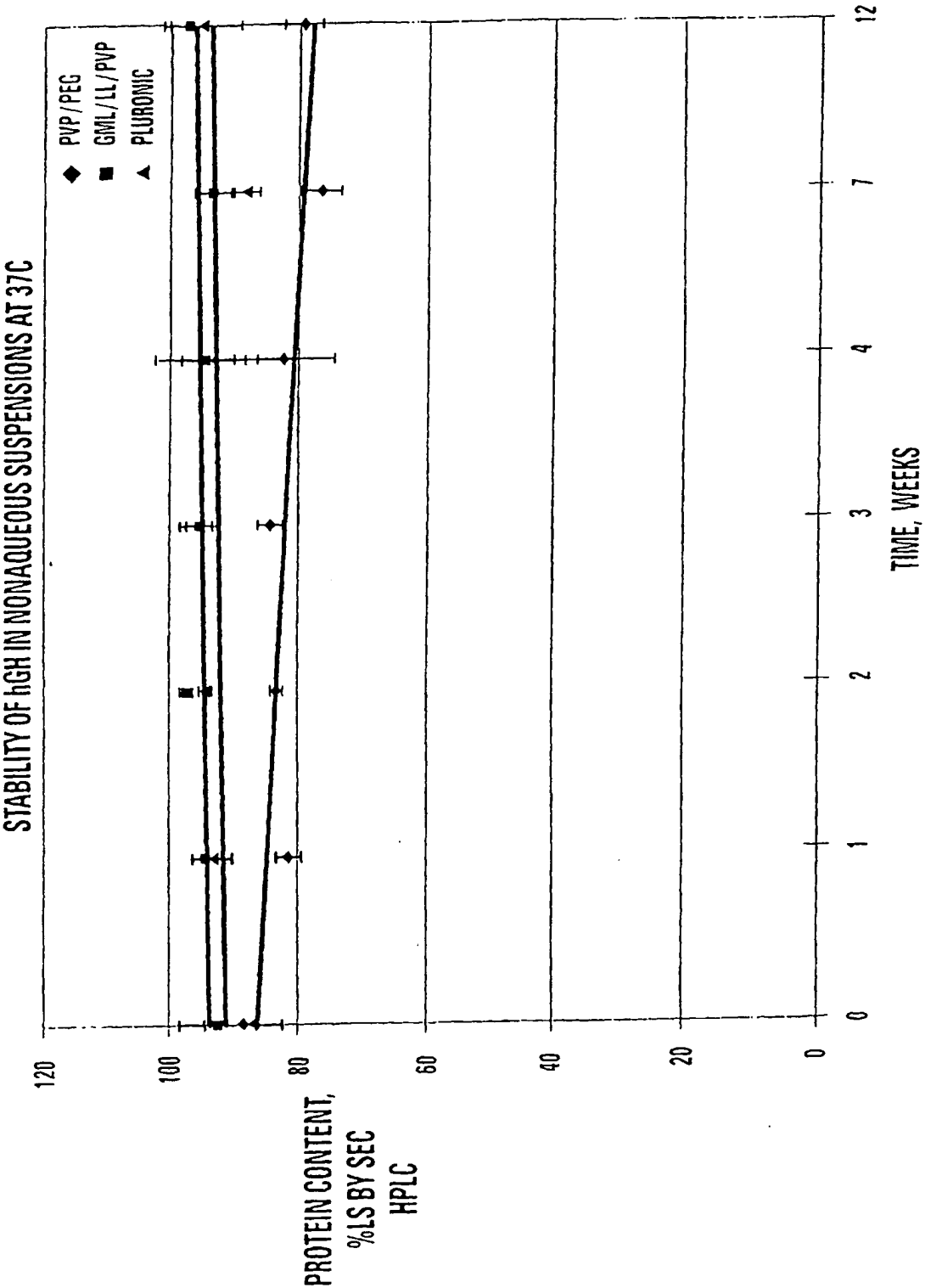
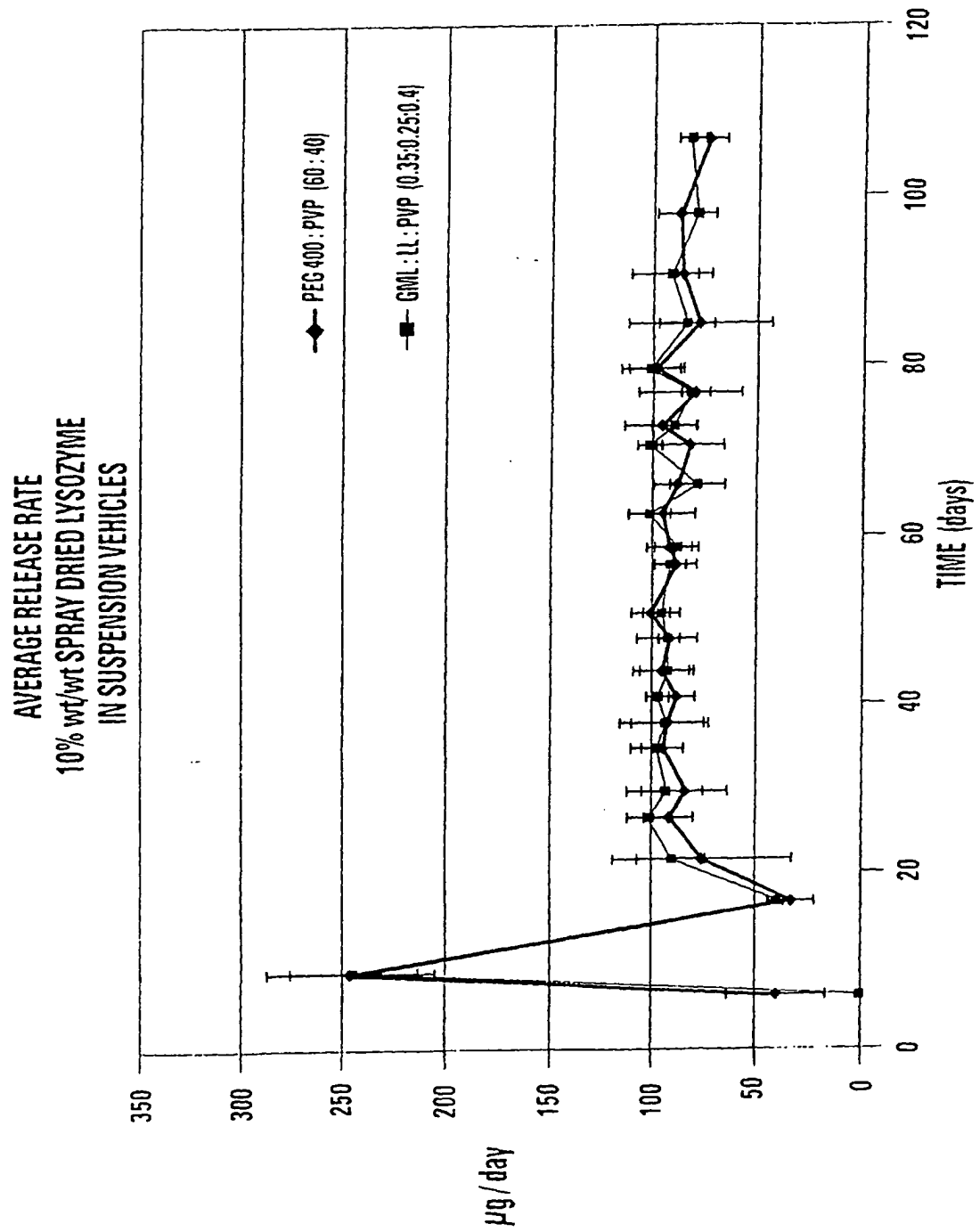


FIGURE 2

**FIGURE 3**

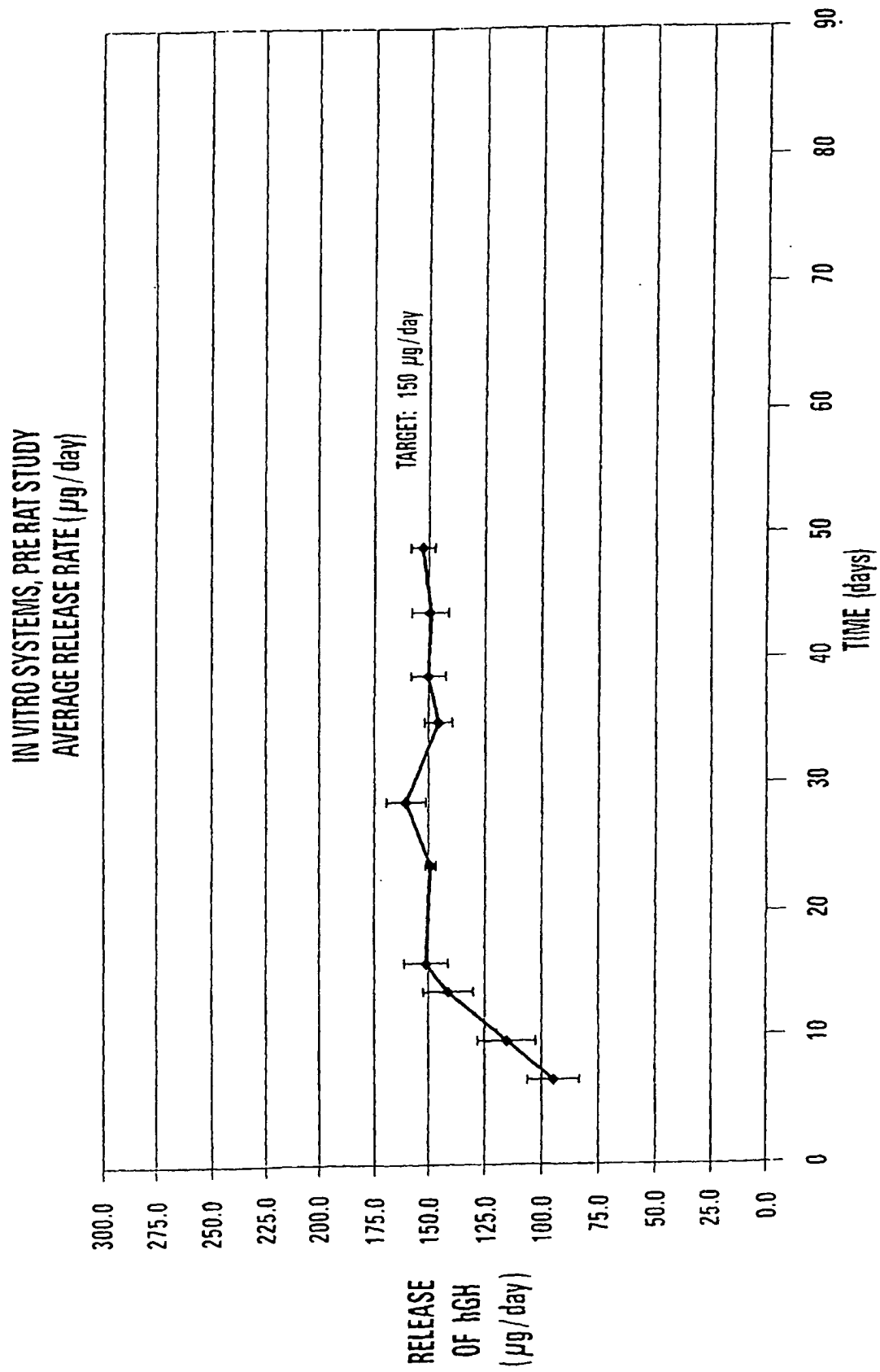


FIGURE 4

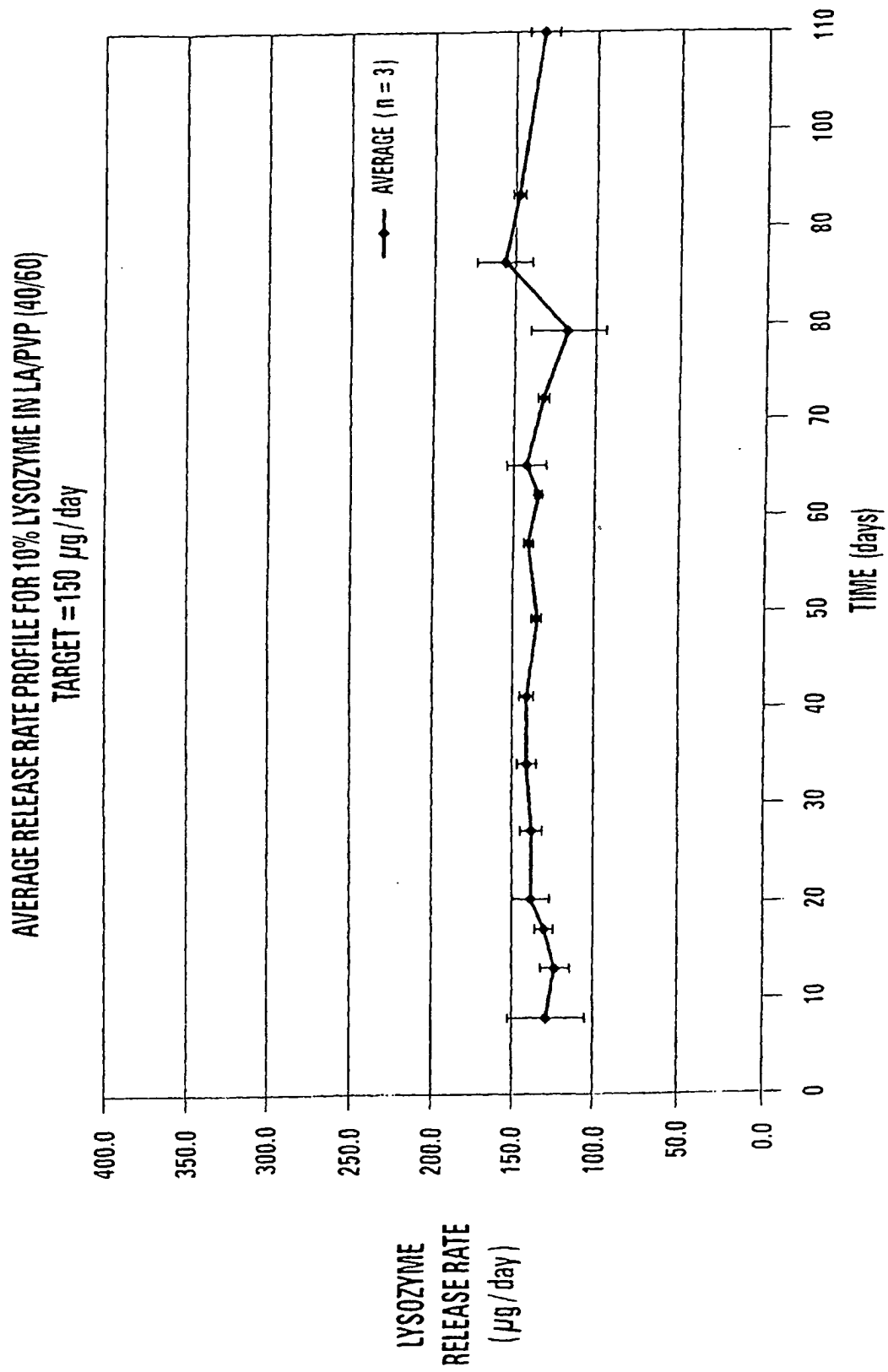


FIGURE 5

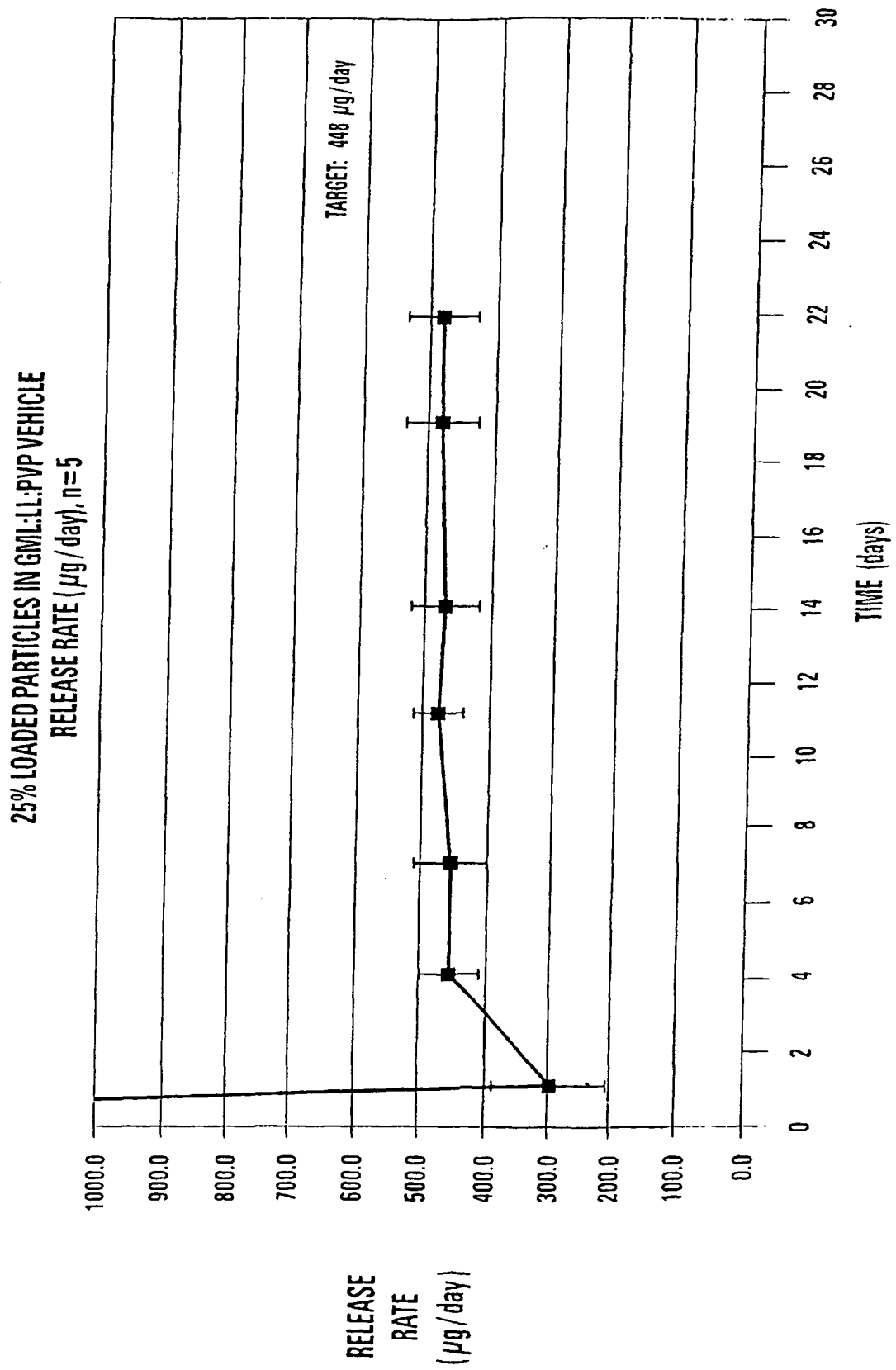


FIGURE 6

33% PARTICLES LOADED VEHICLE GML:LL:PVP
RELEASE RATE ($\mu\text{g/day}$), $n=4$

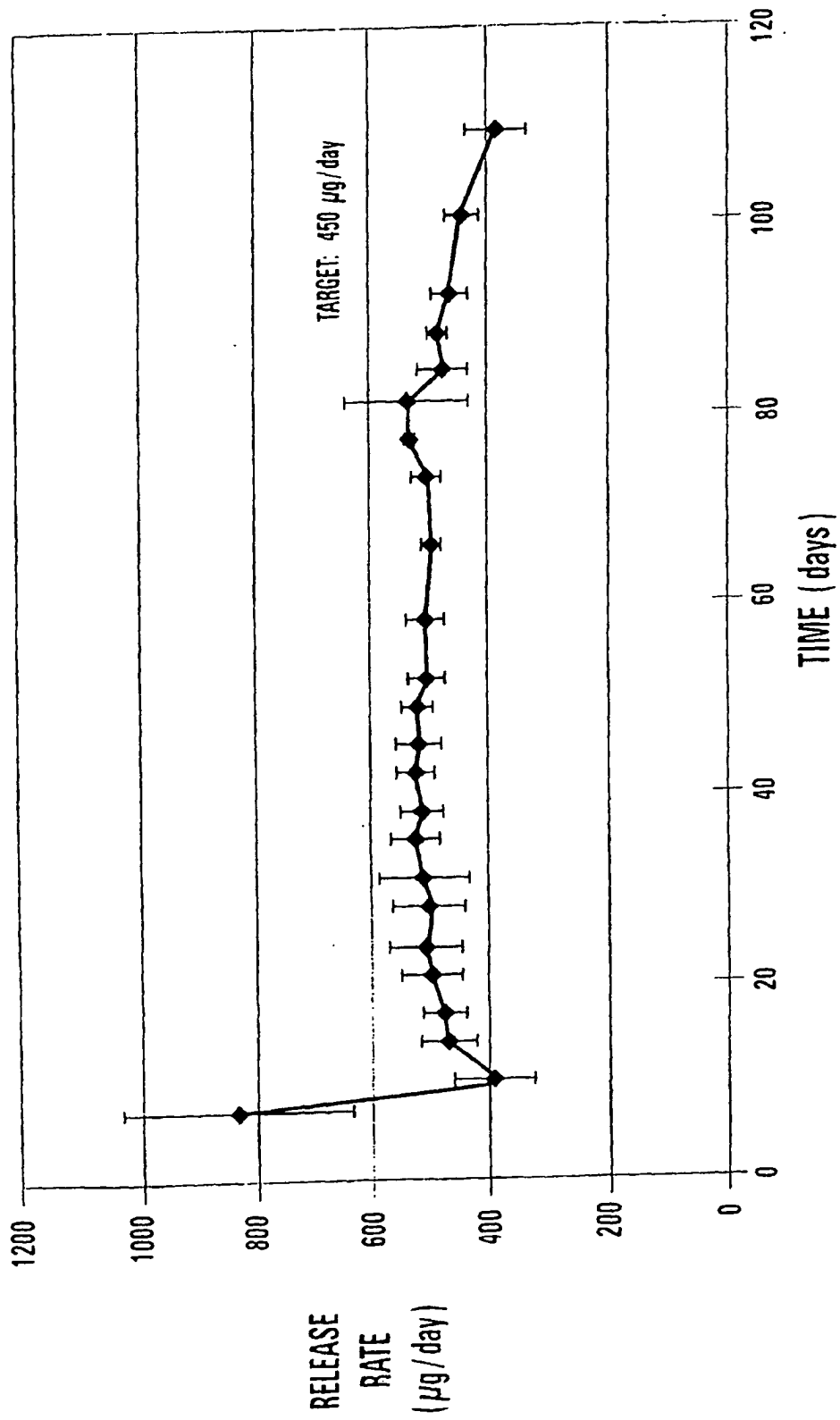


FIGURE 7

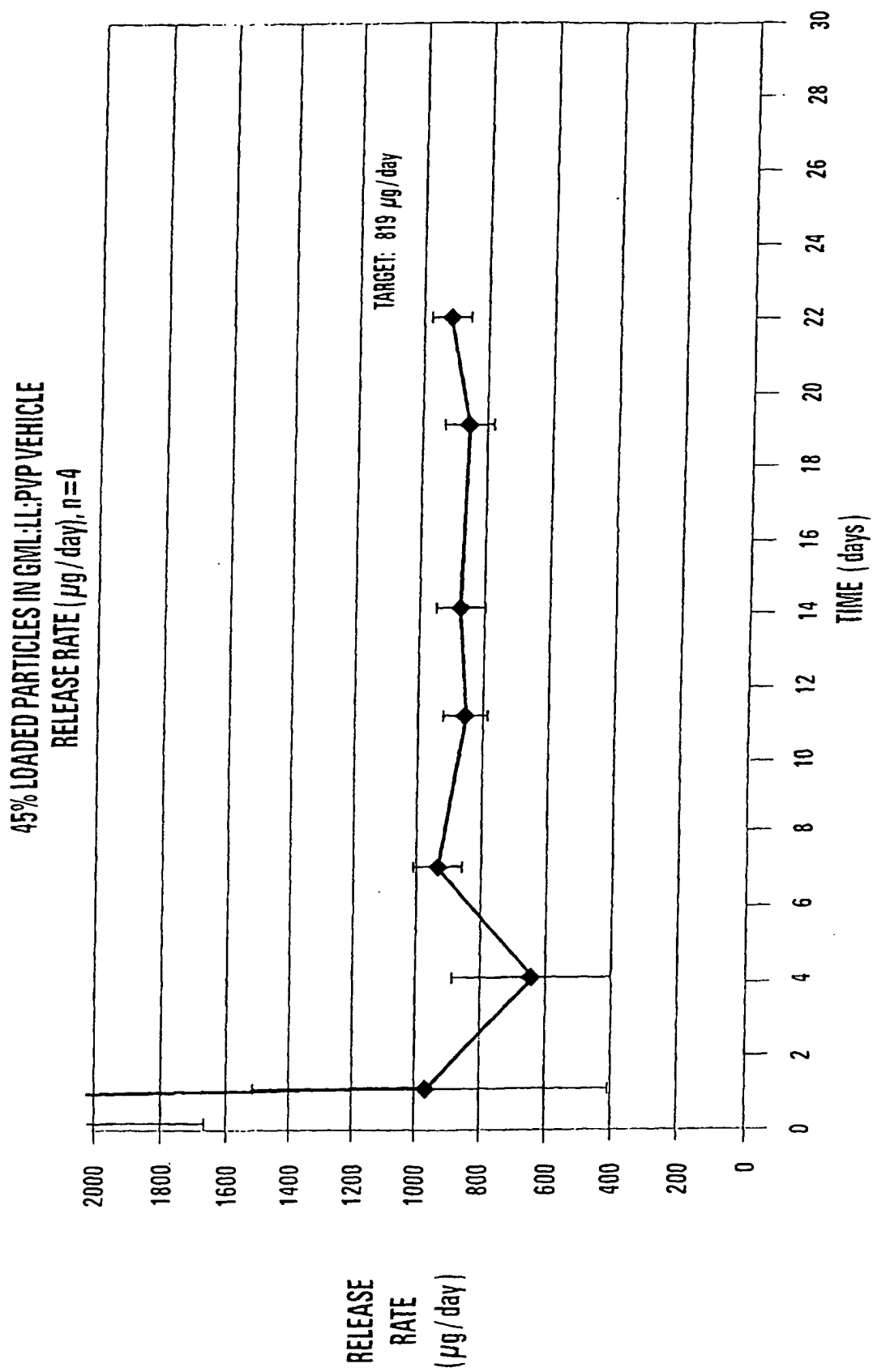


FIGURE 8