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(54) Title: POLYPHOSPHAZENE MATRIX EROSION AND DIFFUSION RELEASE SYSTEMS			
(57) Abstract <p>A biologically active substance, e.g. a therapeutic agent, is delivered from an inorganic polymeric system including a polyphosphazene polymer body, the active substance being physically entrapped by the polymer body. When the system is exposed to an aqueous fluid, e.g. when implanted in physiological fluid of a living mammal, the agent is released from the polymer body at a sustained and controlled rate.</p>			

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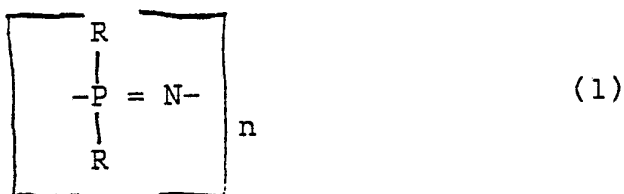
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POLYPHOSPHAZENE MATRIX EROSION
AND DIFFUSION RELEASE SYSTEMS

Background of the Invention

The invention relates to polyphosphazene
5 sustained and controlled release systems.

Polyphosphazenes are polymers with backbones
consisting of nitrogen and phosphorous separated by
alternating single and double bonds. Each phosphorous
atom generally is covalently bonded to two side chains
10 ("R"). The repeat unit in polyphosphazenes has the
general structure (1):



15

Grolleman et al., J. Controlled Release 3:143
(1986), and deVisser et al., Proceedings of the 10th
Internat. Sym. on Controlled Release of Bioactive Mater.
43 (1983), describe bioerodible drug delivery systems
20 consisting of a polyphosphazene polymer covalently
bonded to a therapeutic agent, i.e., the drug is part of
the class of systems called "pendant side chain" systems
in which the drug is covalently attached to the polymer
backbone.

25

Summary of the Invention

In general, one aspect of the invention
features an inorganic polymeric matrix system (as
distinguished from pendant side chain systems) for
delivering a biologically active substance to an aqueous
30 environment. The system includes a polyphosphazene
polymer matrix body which physically entraps the
biologically active substance to be released.

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Physically entrapped, as used herein, means that, until the body is introduced into the aqueous environment, the substance is physically retained within, but not covalently bonded to, the polyphosphazene polymer. The system components are designed and selected so that, when the system is exposed to an aqueous environment, the active substance is released to the environment at a sustained and controlled rate over a prolonged period. By "sustained release", we mean release over a period substantially longer than the period of biological activity achieved by administration in a single dose. By "controlled release", we mean release at rates that are predictable over time.

In preferred embodiments, the biologically active substance is a therapeutic agent, and the polymeric body provides controlled, sustained in vivo release of the therapeutic agent to a physiological fluid of a living organism (e.g. a mammal).

In one embodiment, the polymer is a bioerodible polyaminophosphazene that has side chains (e.g., imidazole groups or amino acid esters) that are capable of hydrolyzing when exposed to a physiological environment. The term bioerodible, as used herein, means a polymer that dissolves or degrades within a period that is acceptable in the desired application, (usually in vivo therapy), e.g. less than about five years and most preferably less than about one year, once exposed to an aqueous environment, e.g., a physiological solution of pH6-8 having a temperature of between about 25°C and 45°C. In another embodiment, the active molecule is released from the polymer substantially by diffusion when the system is exposed to an aqueous environment. Release by diffusion means release

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resulting from mechanisms other than erosion. A polymer is considered to release "substantially by diffusion" if its average release rate is no more than twice the rate achieved with a comparable non-eroding polymer.

5 A second aspect of the invention features reinforcing in vivo tissue by applying a bioerodible polyphosphazene to the tissue. The polymer is selected to erode as its structural support is no longer needed.

A third aspect of the invention features
10 treating a living organism to provide controlled sustained release of ammonia and phosphate at a desired location by implanting a bioerodible inorganic polymer body comprising a polyphosphazene at the location.

The polyphosphazene release system is
15 particularly advantageous because it has an inorganic backbone that is biocompatible overtime and (in the bioerodible embodiments) that degrades to harmless small-molecule products: ammonia, phosphate and water. The system can be made bioerodible to avoid surgical
20 removal of the polymer after use, and the bioerosion products are relatively benign in low concentrations. The system can accomodate a large variety of drugs including small drugs and macromolecules.

Other features and advantages of the invention
25 will be apparent from the following description of preferred embodiments thereof and from the claims.

Description of the Preferred Embodiment

I. Drawings

Figs. 1a and b are graphs depicting polymer
30 degradation over time.

Figs. 2-6 are graphs depicting release of various molecules over tissue.

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II. Structure

The preferred delivery system includes a bioerodible polyaminophosphazene polymer having side chains that hydrolyze in a physiological environment.

5 The hydrolysis results in the chemical breakdown and eventual erosion of the polymer. Mixed throughout and entrapped by the the polymer is a therapeutic agent that is released at a controlled and sustained rate when the system is placed in a physiological environment.

10 The preferred polyphosphazenes are those in which at least a portion (generally greater than 10% of the side chains (the R groups in formula 1) are capable of hydrolyzing in a physiological environment. Hydrolysis of the side chain results in hydrolysis of
15 the polymer backbone, and in erosion of the polymer. Examples of hydrolyzing side chains are unsubstituted and substituted imidizoles and amino acid esters in which the group is bonded to the phosphorous atom through an amino linkage (polyphosphazene polymers in
20 which both R groups are attached in this manner are known as polyaminophosphazenes). For polyimidizolephosphazenes, some of the "R" groups on the polyphosphazene backbone are imidizole rings, attached to phosphorous in the backbone through a ring nitrogen
25 atom. Other "R" groups can be organic residues that do not participate in hydrolysis, such as methyl phenoxy groups or other groups shown in Allcock et al. (1977) Macromolecule 10:824-830.

The R groups that are not capable of
30 hydrolyzing can be any alkyl, aralkyl, or aryl group having 20 carbon atoms or less (more preferably 12 carbon atoms or less); or a heteroalkyl, heteroaralkyl, or heteroaryl group having 20 or less carbons and

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heteroatoms (more preferably 12 or less carbon or heteroatoms). The groups can be bonded to the phosphorous atom through e.g., an oxygen, sulfur, nitrogen, or carbon atom.

5 The preferred polyphosphazenes are made by reacting poly(dichlorophosphazene) with the appropriate side chain nucleophiles, which displace the chlorines. Desired proportions of hydrolyzible to nonhydrolyzible side chains in the polymer can be achieved by adjusting
10 the quantity of the corresponding nucleophiles that are reacted with the poly(dichlorophosphazene).

 The preferred polyphosphazenes have a molecular weight of over 100,000. If the molecular weight is below 100,000, the polymer may lose some of its film
15 forming capability.

 The term therapeutic agent, as used herein, means any agent used to treat or prevent any disease or disorder of the body. Both low molecular weight (less than about 1000) agents and higher molecular weight
20 (greater than about 1000) agents (macromolecules) can be used in the delivery system. Representative agents include hormones (and hormone fragments and analogues), e.g., testosterone, progesterone, luteinizing hormone-releasing hormone (LHRH); diuretics, e.g.,
25 chlorothiazide; anti-inflammatories; pain killers, e.g., morphine; antibiotics, e.g., tetracycline; antipsychotic drugs, anticancer drugs, e.g., methotrexate, actinomycin D, vinblastine, and cytosine arabinoside; vaccines; and antiarthritic drugs, e.g., ibuprofen and flurbiprofen.

30 The delivery systems can be made in virtually any shape or size, depending upon the physiological environment of use. For example, the system can be shaped and sized for buccal, oral, vaginal,

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intrauterine, ocular, and anal insertion; for skin patches, e.g., to fit behind the ear; or for parenteral insertion or injection, e.g., through a syringe (in which case the delivery systems would be in the form of powder in which each particle is small enough to fit through a syringe tip). The bioerodible characteristic of the polymer is particularly important where the mode of administration of the delivery system is parenteral insertion or injection, as the fact that the polymer eventually dissipates makes it unnecessary to go into the body parenterally to remove the system once it is depleted of the agent.

The preferred delivery systems can contain up to 50% by weight (more preferably up to 30% by weight) of therapeutic agent. If too low a proportion of polymer is present, the mechanical properties of the delivery system may be adversely affected.

The therapeutic agent is physically entrapped by the polymer, preferably by casting a polymer/agent mixture.

When the delivery system is exposed to an aqueous physiological environment, a sustained and controlled release of the therapeutic agent occurs. Sustained release means that the agent is released continuously from the system over an appropriate prolonged period of time. As discussed below, the period of time over which the agent is released can be adjusted for a particular system by varying the size of the system and by varying the type side chains on the polyphosphazene. Controlled release means that the agent is released from the system within a desired dosage range for most of the sustained period. Towards the end of the sustained period, the amount of agent

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released may begin to decrease due to a depletion of the supply of agent. At the beginning of the sustained period (2-5 days), it is common to see a initial burst of agent released that is somewhat higher than the
5 long-term release rate.

The agent can be released from the delivery system by one or both of two general mechanisms. (1) The agent can be released as the polyphosphazene erodes; and (2) the agent can be released by diffusion of the
10 agent and aqueous fluid through the polymer and into the environment of use.

The mechanism by which the agent is released from the system can be selected by adjusting the proportion of hydrolyzable to non-hydrolyzible side
15 chains on the polyphosphazene. The greater the number of hydrolyzable side chains, the higher the proportion of agent that will be released through the erosion of the polymer. Vice versa, the lower the number of hydrolyzable side chains, the higher the proportion of
20 agent that will be released by diffusion. Where the matrix is implanted in a location accessible only by surgery, it is desirable to use an erodible matrix.

III. Methods

The synthesis and characterization of two
25 polyphosphazenes is described first.

A. Reagents:

Most experimental manipulations were performed under an atmosphere of dry nitrogen (Burdett). Tetrahydrofuran (THF) (MCB Omnisolve) was distilled
30 under nitrogen from sodium benzophenone ketyl. All other solvents used were reagent grade or better. p-Methylphenol (Aldrich) was sublimed before use.

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Imidazole (Aldrich) was recrystallized from absolute alcohol. Sodium spheres (Aldrich) were used as received.

B. Equipment:

¹H NMR spectra were recorded on a Bruker
5 WP-200 spectrometer operating at 200MHz in the Fourier
transform mode. All data are for samples in C₆D₆.
³¹P NMR spectra were recorded on a Varian CFT-20
spectrometer operating at 32 MHz in the Fourier
transform mode. All spectra were recorded for samples
10 in THF. Polymer molecular weights were determined by
gel permeation chromatography with the use of a Waters
Associates ALC-201 instrument, with two PL Gel Columns
(Polymer Laboratories) using THF as the eluting
solvent. Calibration of the columns was accomplished by
15 means of polystyrene standards obtained from Waters
Associates. Infrared spectra were recorded as thin
films on NaCl plates using a Perkin-Elmer 1420 IR
Spectrophotometer. Elemental analyses were performed by
Galbraith Laboratories, Knoxville, Tennessee. Samples
20 were dried for at least 72 hours over phosphorus
pentoxide in a vacuum desiccator before analyses.

C. Synthesis of 1.1:0.9 p-methylphenoxyl:
imidazole polyphosphazene

Hexachlorocyclotriphosphazene (Ethyl
25 Corporation) was purified by two recrystallizations from
hexane and by two sublimations at 50°C (6.7 Pa: 0.05
torr). Poly(dichlorophosphazene) was prepared by the
thermal polymerization of (NPCl₂)₃ at 250°C. An
average of 50%-60% conversion to the linear polymer was
30 obtained.

The sodium salt of p-methoxyphenol was prepared
as follows. A 500 ml, 3 neck round bottomed flask
containing a magnetic stir bar was equipped with a gas

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inlet, a water cooled condenser and an addition funnel. The flask was flame dried and allowed to cool while being flushed with a stream of nitrogen. The flask was flame dried and allowed to cool while being flushed with
5 a stream of dry nitrogen. The flask was charged with 300 ml freshly distilled THF followed by the addition of NaH (4.12g, 60% NaH in mineral oil). The flask was cooled by means of an ice bath and to the slurry was added dropwise through the addition funnel a solution of
10 p-methylphenol (13.2g, 0.122 mol.) in THF (75 ml). When addition was complete the ice bath was removed and the solution allowed to warm to room temperature. The solution was heated to 40°C by means of a heating mantle and heating was continued for 10 hours. A clear
15 colorless to pale yellow solution was obtained.

A solution was prepared of $[\text{NPCl}_2]_n$ (10g 0.086 mol in THF (900 ml)) in a 3000 ml 3 neck flask equipped with an overhead mechanical stirrer, a water cooled condenser (fitted with a gas inlet) and a fritted
20 addition funnel. Dissolution of the polymer took approximately 10 hours, care being taken to rigorously exclude water and oxygen during this time. The sodium salt prepared above was transferred to the addition funnel by means of a transfer tube, and was then added
25 dropwise to the polymer solution. The addition was at such a rate that precipitation or gelling of the polymer did not occur. A heavy white precipitate of NaCl slowly formed. Upon completion of sodium salt addition, the solution was heated to reflux for 24 hours.

30 The solution of partially substituted polymer was cooled to room temperature and a solution of imidazole (15g, 0.22 moles) dissolved in THF (100 ml) was added dropwise. The solution was heated to reflux

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and heating was continued for a further 48 hours. Upon cooling to room temperature, the solution was filtered to remove NaCl and the filter cake washed thoroughly with dry THF. The combined THF fractions were concentrated using a rotary evaporator to 400 ml and the now viscous solution was added to a vigorously stirred solution of heptane (previously dried over MgSO_4). The crude polymer precipitated and was recovered by filtration as a white fibrous material. The polymer was redissolved in the minimum amount of dry THF and the precipitation procedure was repeated three times. Soxhlet extraction using hot heptane followed by drying over P_2O_5 in vacuo yielded the final product in 55% yield.

15 D. Synthesis of 1.6:0.4 p-methylphenoxy:imidazole polyphosphazene

This polymer was prepared using the same methods and materials as with the copolymer above, with the exception that 8 grams (.069 moles) of $[\text{NPCl}_2]_n$ in 700 ml of THF was used.

E. Imidazole Substituted Polyphosphazene Matrices

2.0 grams of polymer were dissolved in THF to make a 20% solution. The solution was cast in a flat bottomed glass mold (Pyrex) that had been pre-cooled to -20°C , and allowed to dry at -20°C for 24 hours. The mold was allowed to dry at 0°C for 24 hours more, then circular disks 7.0 mm in diameter and .5 mm in thickness were formed using a cork borer. The disks were air dried until no detectable changes in weight were noted. The weight of these disks averaged $30. \pm 1$ mg.

F. 20% Imidazole Substituted Polyphosphazene Matrices

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Circular disks were prepared as above. The weight of these disks averaged $30. \pm .5$ mg.

G. Polymer Characteristics

Table 1 gives characterization data for the 5 polymers synthesized. The polymers were rubbery and translucent and possessed glass transition temperatures of 301 K (45% imidazole substituted polymer) and 307 K (20% imidazole polymer). No melting point temperature was detected, implying that the polymers were 10 essentially completely amorphous. The exact ratio of the two side chain substituents, imidazole and p-methylphenol, were determined by NMR from a comparison of peak intensities at 7.35 ppm and 1.94 ppm and confirmed by elemental analysis.

15 The polymers used readily dissolved in THF. 20% solutions of polymer in THF were found to be optimal in achieving liquids viscous enough to prevent settling of drug or protein during the casting process. In that same regard the casting solutions and molds were kept 20 cooled to below the polymers' glass transition temperatures. Use of low temperature casting procedures are quite important in achieving reproducible release kinetics from polymeric devices. The resulting polymer disks were firm but flexible and could be easily bored 25 to desired dimensions.

H. p-Nitroaniline/Polyphosphazene Matrices:

0.2% and 1% solutions of p-nitroaniline (Matheson, Coleman and Bell) were prepared in THF. 2.0 grams of 20% imidazole substituted polyphosphazene was 30 dissolved in appropriate volumes of each of these solutions to create 1% and 5% p-nitroaniline/polyphosphazene solutions. The solutions were cast on flat bottomed glass molds (Pyrex) that had been

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pre-cooled to -20°C , and allowed to dry at -20°C for 24 hours. The molds were allowed to dry at 0°C for 24 hours more, then circular disks of 7.0 mm in diameter, .5 mm thick were formed using a cork borer. The disks were air dried until no detectable changes in weight were noted. These disks average 25 ± 1 mg in weight.

I. Progesterone/Polyphosphazene Matrices:

^3H -progesterone (New England Nuclear) was mixed with unlabelled progesterone (Sigma) to produce radioactive progesterone with a specific activity of 25 microcuries/mg (5.5×10^7 dpm/mg). 1% and 5% solutions of progesterone were prepared in THF. 2.0 grams of 20% imidazole substituted polyphosphazene was dissolved in appropriate volumes of each of these solutions to create 5% and 10% tritiated progesterone/polyphosphazene solutions. The solutions were cast and dried as above. Circular disks of 7.0 mm in diameter and .4 mm in thickness were formed using a cork borer. These disks averaged 20 ± 1 mg in weight.

J. Bovine Serum Albumin/Polyphosphazene Matrices:

^{14}C -bovine serum albumin (BSA, New England Nuclear) was mixed with unlabelled BSA (Sigma) to produce radioactive BSA with a specific activity of .01 microcuries/mg (2.2×10^4 dpm/mg). 2 grams of 20% imidazole substituted polyphosphazene was dissolved in THF to make a 20% solution. BSA was then added to form a 2.5% BSA/polyphosphazene mixture. The solution was cast and dried as above. Circular disks of 7.0 mm in diameter and .2 mm in thickness were formed using a cork borer. These disks averaged 10 ± 1 mg in weight.

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K. Degradation Studies:

Degradation studies of 20% imidazole substituted polyphosphazene were carried out in .1M sodium phosphate buffer solutions at pH 7.4. Polymeric
5 slabs were placed in 20 ml scintillation vials (Kimble) with 10 ml of buffer. Percent degradation was determined by freeze drying samples at specific time intervals and measuring weight loss. Since the rate of degradation of the 20% imidazole substituted
10 polyphosphazene was low, and extinction coefficient for the first 10% of polymer degradation was formulated and percent degradation with time was determined spectrophotometrically, and confirmed by freeze drying samples periodically in a parallel study. The
15 degradation of 45% imidazole substituted polphosphazene was performed in deionized water at pH 5.5. All degradation studies were performed in quadruplicate.

Fig. 1 shows erosion profiles for both 20% and 45% imidazole containing polyphosphazenes. Degradation
20 of 20% imidazole substituted polyphosphazene was quite slow, with 4% of polymer degrading in 600 hours (Fig. 1a). This low rate of degradation would be expected since degradation is imidazole dependent. In contrast to the slow rate of degradation of the 20% imidazole
25 substituted polyphosphazene, 30% of the 45% imidazole substituted polyphosphazene degraded in approximately 300 hours (Fig. 1b), with a marked decrease in degradation rate after that point. With kinetics continuing at the decreased rate the polymer would be
30 expected to have a degradative lifetime of 3 years. Polyphosphazenes synthesized containing 80% imidazole and 20% methoxyphenoxy degraded on the order of hours in room humidity. Such variation in degradative

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characteristics provides the ability to formulate release systems based primarily on diffusion, erosion, or a mixture of erosion and diffusion.

L. Release Studies

- 5 20% imidazole substituted polyphosphazene matrices with drug or protein were placed in 20 ml scintillation vials with 10 ml .1M sodium phosphate buffer at pH 7.4. buffer was changed frequently using a 20 ml syringe fitted with a 1.5 inch 18 gauge needle
10 (Becton-Dickinson). Care was taken during the studies to insure that the concentration of drug or protein released was never greater than 10% of their respective solubilities in phosphate buffer. These studies were performed in triplicate.
- 15 In addition to in vitro work, in vivo studies were performed with ³H-progesterone/polyphosphazene matrices. Polymeric devices were implanted subcutaneously in 200-225 gm female Sprague-Dawley rats (Charles River Breeding Laboratories). After shaving an
20 animal's hair, and prepping with betadine and alcohol, a 2 cm incision was made on the dorsum of the rat at the midline. Sterile round-edged scissors were used to form a subcutaneous space 6 to 7 cm laterally from the incision site. The polymeric disk was placed into the
25 space using sterile forceps, and the incision site was closed using sterile wound clips (Autoclip Kit; Clay Adams).

- At different time points, rats were sacrificed by CO₂ asphyxiation, and the polymer disk was
30 removed. The disk was dissolved in THF, and progesterone present was determined as stated below.

To determine the rate of p-nitroaniline release, the collected buffer samples were read

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spectrophotometrically at a wavelength of 380 nm, the absorption maximum for p-nitroaniline. At this wavelength, neither the polymer nor its degradation products have been found to absorb. (The extinction coefficient for p-nitroaniline dissolved in the buffer used was 97.1 ml/mg-cm.) Absorbance measurements were made using a Perkin Elmer 553 U.V./Vis. Spectrophotometer.

To determine the rate of ^3H -progesterone and ^{14}C -bovine serum albumin release collected samples were dissolved in Quasol II (New England Nuclear) and counted on a Packard Tri-Carb 4530 Liquid Scintillation Counter. Dpms were determined through an external standards method.

15 M. Release Characteristics:

p-Nitroaniline was chosen as a model molecule for release since its absorbance maximum was outside the range of any polymer degradation products. Figure 2 shows release kinetics for 1% p-nitroaniline loaded 20% imidazole polyphosphazene devices. Release took place over 250 hours with the amount of dye released over time being quite reproducible. When plotted as a function of square root time (Fig. 3), release of 1% and 5% loaded p-nitroaniline appeared to follow $t^{1/2}$ diffusional release kinetics as theorized by Higuchi, 52 J. Pharm. Sci. 1145 (1963). At the loadings studied, release rates were not found to be very dependent upon loading.

Using progesterone, a study of in vitro and in vivo release was performed both to illustrate the possibility of this systems use for release of bioactive molecules and to compare release kinetics. Fig. 4 shows release of progesterone from 5% and 10% loaded 20% imidazole polyphosphazene matrices. Release took place

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over approximately 1000 hours in vitro. Release of 10% loaded progesterone/polyphosphazene devices in vivo (Fig. 5) demonstrates a lag period of approximately 80 hours followed by a period of almost constant release
5 for 900 hours more.

Polypeptide release was demonstrated using 2.5% loaded BSA. Release from these matrices consisted of a burst of almost 25% percent followed by release over 1000 hours in which a total of 55% of protein was
10 released (Fig. 6). In an attempt to remove the burst, 2.5% loaded BSA matrices were dipped in 20% solutions of 20% imidazole polyphosphazene in THF for 3 seconds. Referring to Fig. 6, the polymer coating step eliminates the burst effect, with 5% release occurring during the
15 first 4 hours. At 1000 hours 45% of the protein is released.

Other Embodiments

Other embodiments are within the following claims. For example, polyphosphazenes that are not
20 biodegradable can be used in the delivery system; in such systems, the therapeutic agent is released via diffusion exclusively. Examples of nonbiodegradable polyphosphazenes are described by Allcock et al., J. Inorg. Chem. 21:515 (1982). The system can be used to
25 release biologically active substances to aqueous fluids other than physiological fluids in animals. For example, pesticides and poisons can be released slowly to an infested site such as an agriculture site.

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Claims

1. A polymer system for sustained controlled release of a biologically active substance to an aqueous environment comprising
 - 5 a polyphosphazene polymer body, and
 - said biologically active substance physically entrapped by said polymer,
 - whereby, upon exposure of said system to said aqueous environment, said active substance is released
 - 10 from said system at a sustained and controlled rate.
2. The polymer system of claim 1 wherein the biologically active substance is a therapeutic agent for in vivo delivery to physiological fluid in an organism.
3. The polymeric system of claim 1 wherein
 - 15 said polymer body is not bioerodible.
4. The polymeric system of claim 1 wherein said polymer body is bioerodible.
5. The inorganic polymeric system of claim 4 wherein said polyphosphazene polymer comprises side
 - 20 chains that are capable of hydrolyzing when exposed to a physiological environment.
6. The polymeric system of claim 4 wherein said side chains comprise imidazole groups.
7. The polymeric system of claim 1 wherein
 - 25 said substance is released from said polymer substantially by diffusion when said system is exposed to a physiological environment.
8. The polymeric system of claim 1 wherein said polymer comprises a polyaminophosphazene.
9. A method of administering a biologically
 - 30 active substance at a controlled and sustained rate, said method comprising the steps of

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providing a polymer delivery system comprising said biologically active substance and a polyphosphazene polymer body, said biologically active substance being physically entrapped by said polymer body, said system
5 being characterized in that, when said delivery system is exposed to an aqueous environment, said active substance is released from said polymer body at a controlled and sustained rate, and

contacting said polymer delivery system with
10 said aqueous environment.

10. The method of claim 9 wherein said biologically active compound is a therapeutic agent, and said polymer system is placed in contact with a physiological fluid of a living organism.

15 11. The method of claim 10 wherein said polymer delivery system is implanted in tissue of a living mammal.

12. The method of claim 9 wherein said polymer is bioerodible.

20 13. The method of claim 12 wherein said side chains comprise imidazole groups.

14. The method of claim 9 wherein said polymer is a polydiaminophosphazene.

15. The method of claim 9 wherein said polymer
25 body is substantially non-erodible, and said agent is released from said polymer substantially by diffusion when said system is exposed to a physiological environment.

16. A method of temporarily reinforcing in
30 vivo tissue comprising applying a bioerodible inorganic polymer to said tissue, said polymer comprising a bioerodible polyphosphazene.

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17. A method of treating a living organism to provide controlled sustained release of ammonia or phosphate at a desired location, said method comprising implanting a bioerodible polymer body in said organism
5 in the location of release, said polymer body comprising of a bioerodible polyphosphazene.

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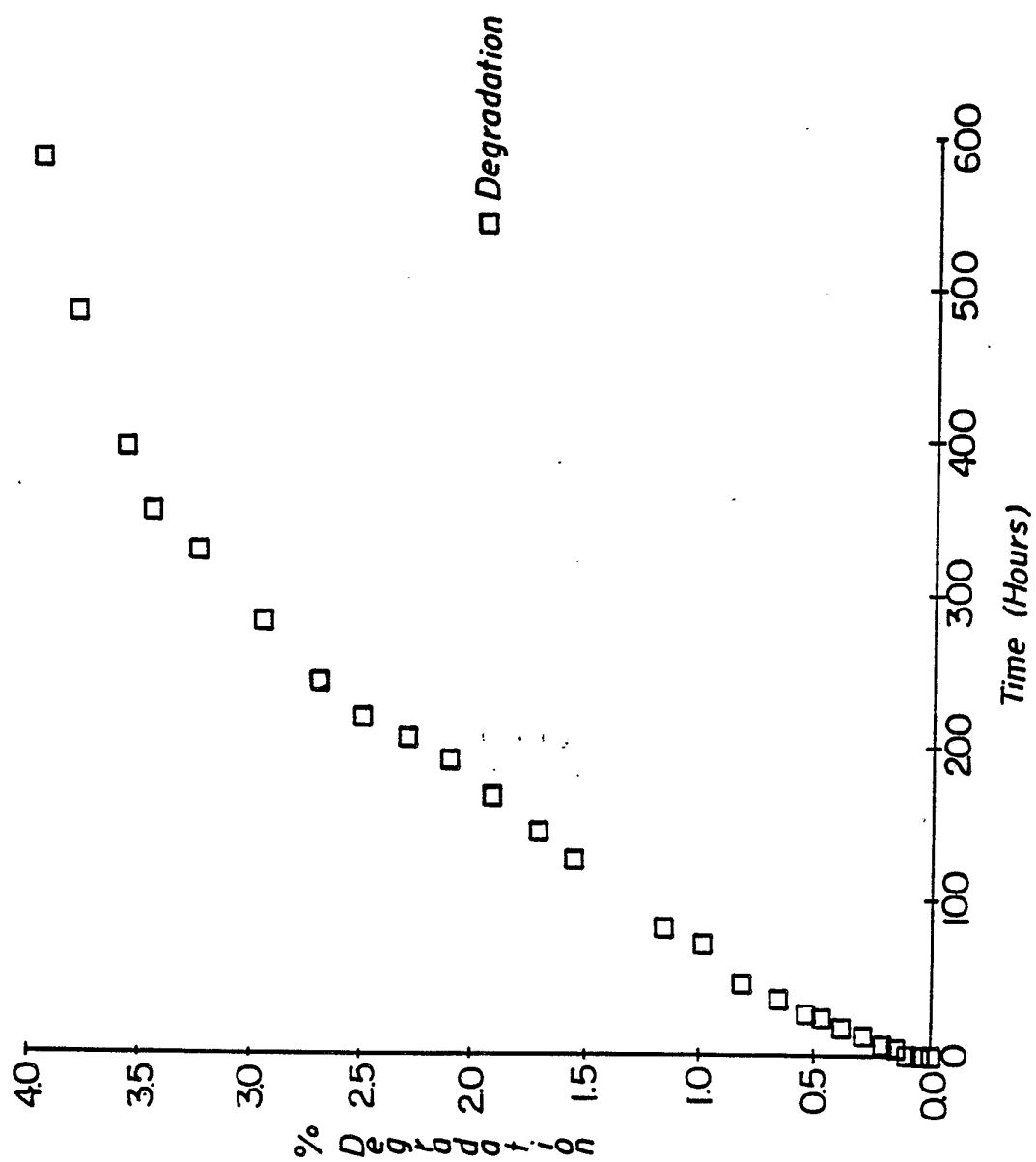


FIG. 1a

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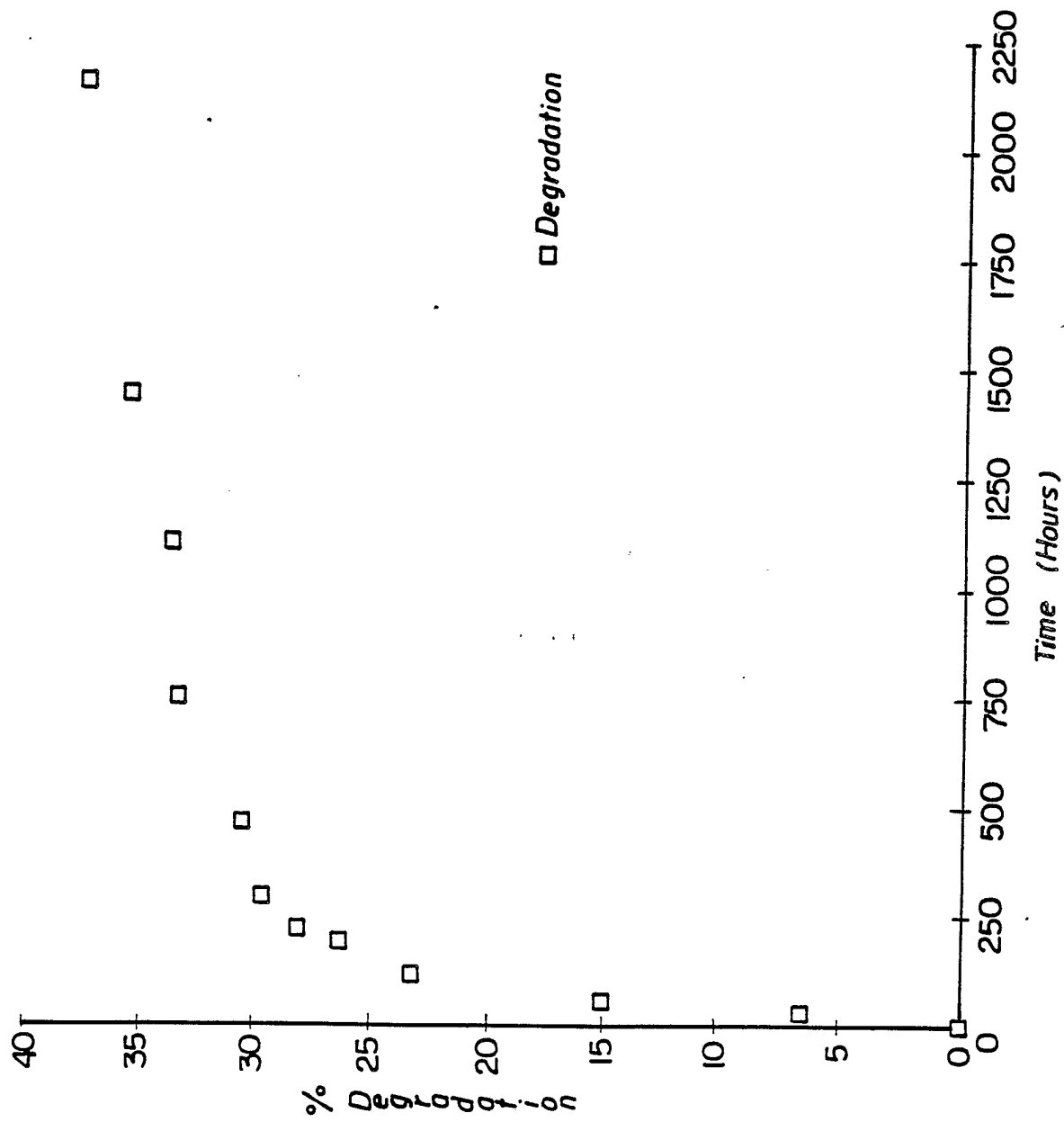


FIG. 1b

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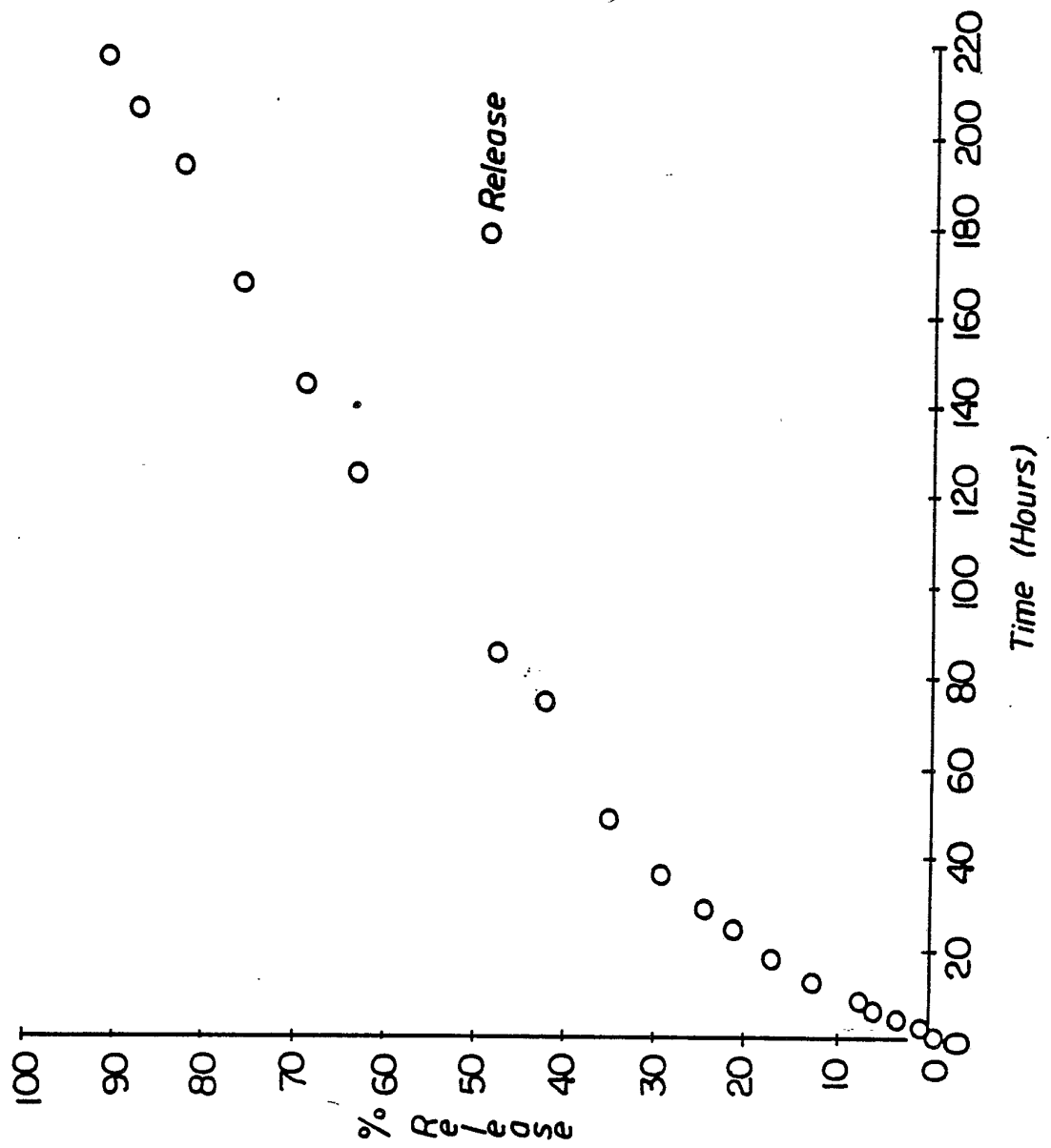


FIG. 2

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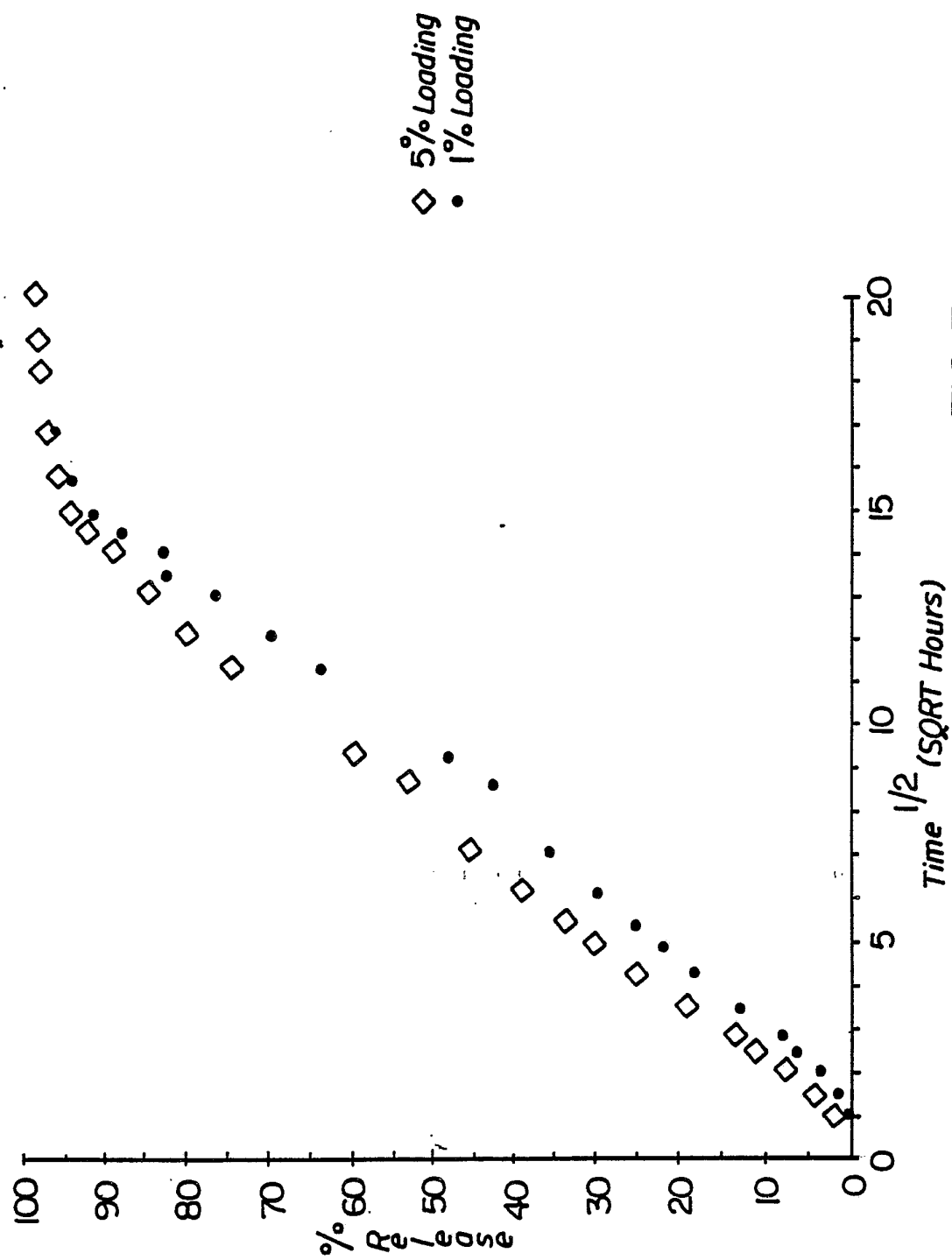


FIG.3

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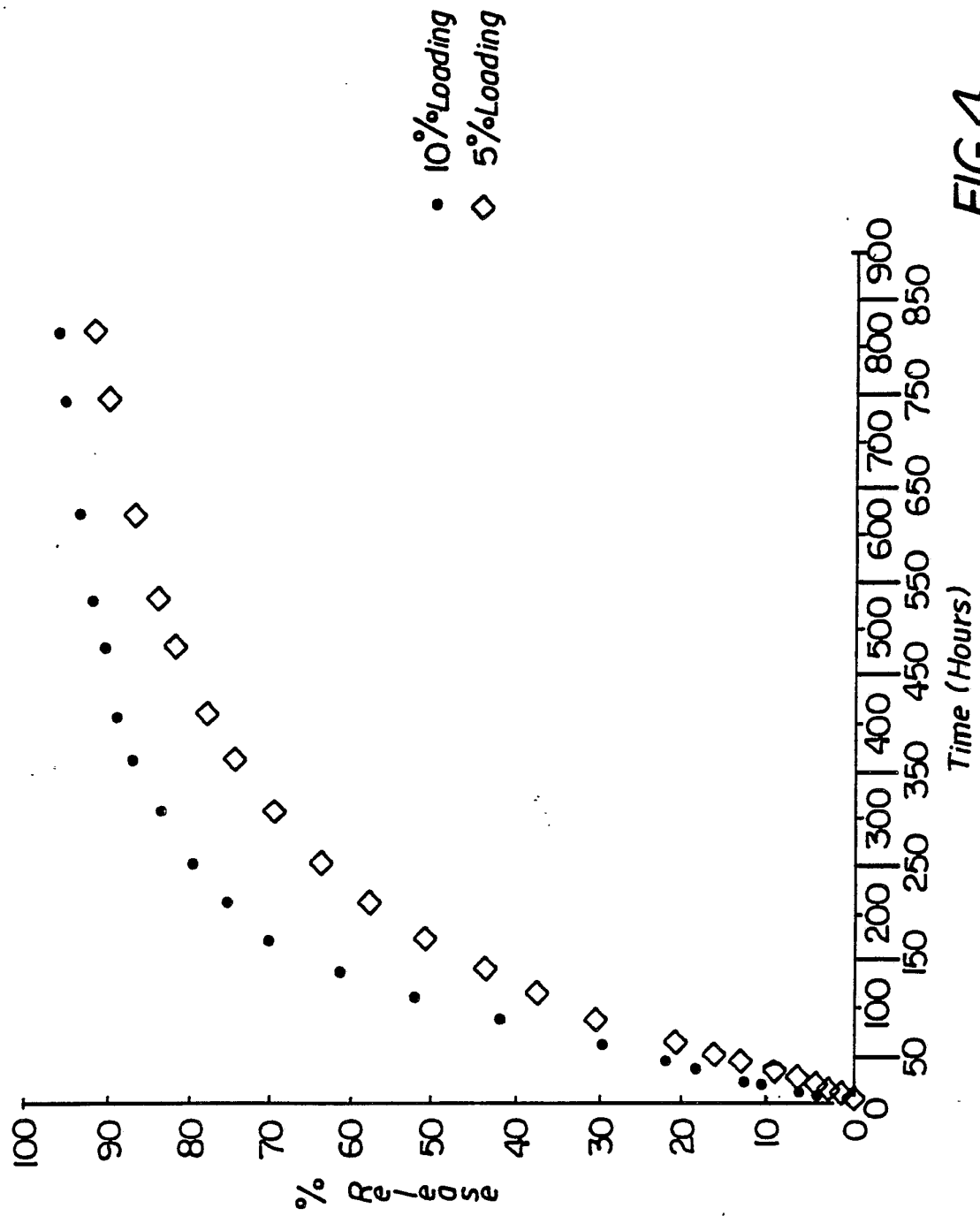
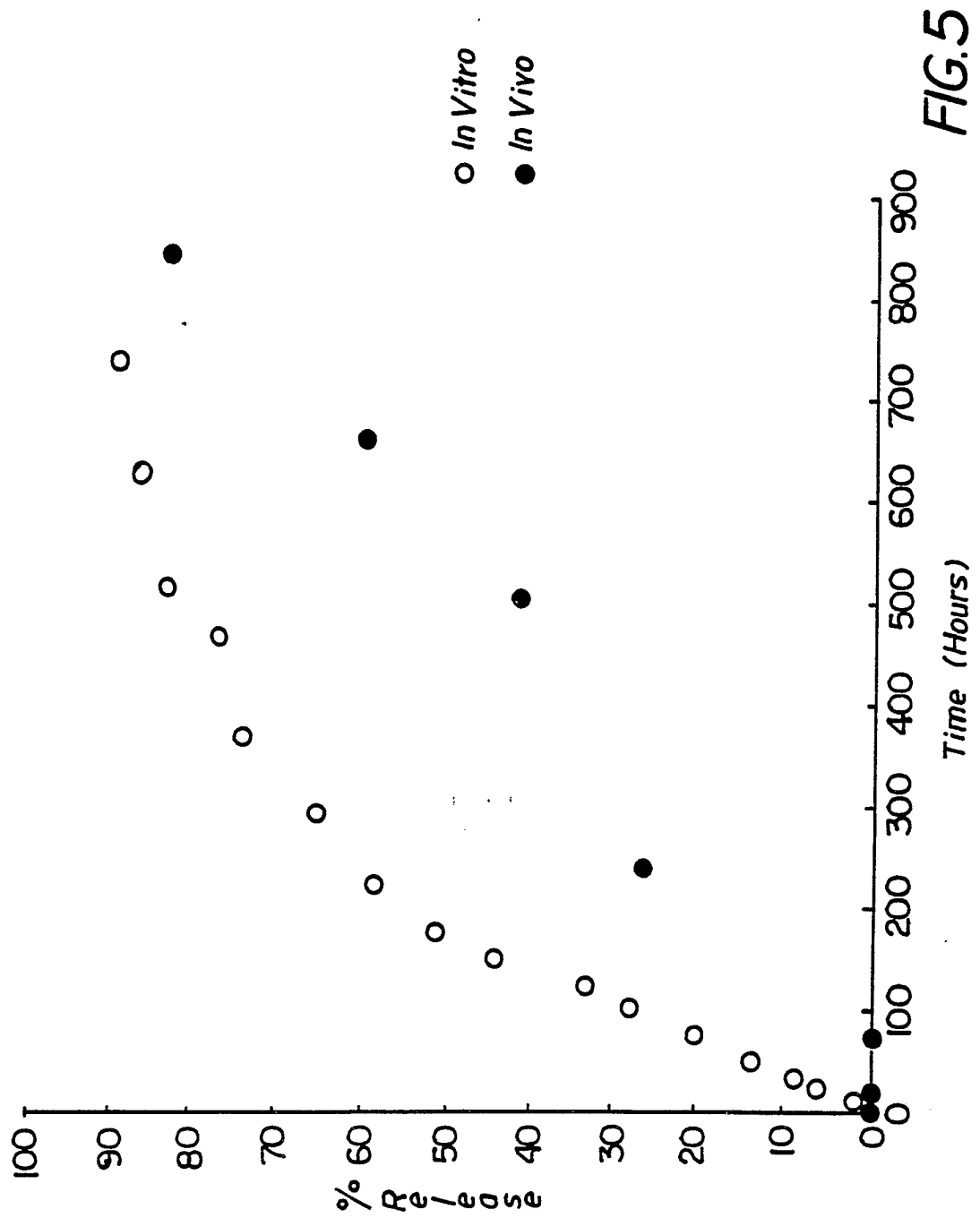


FIG. 4

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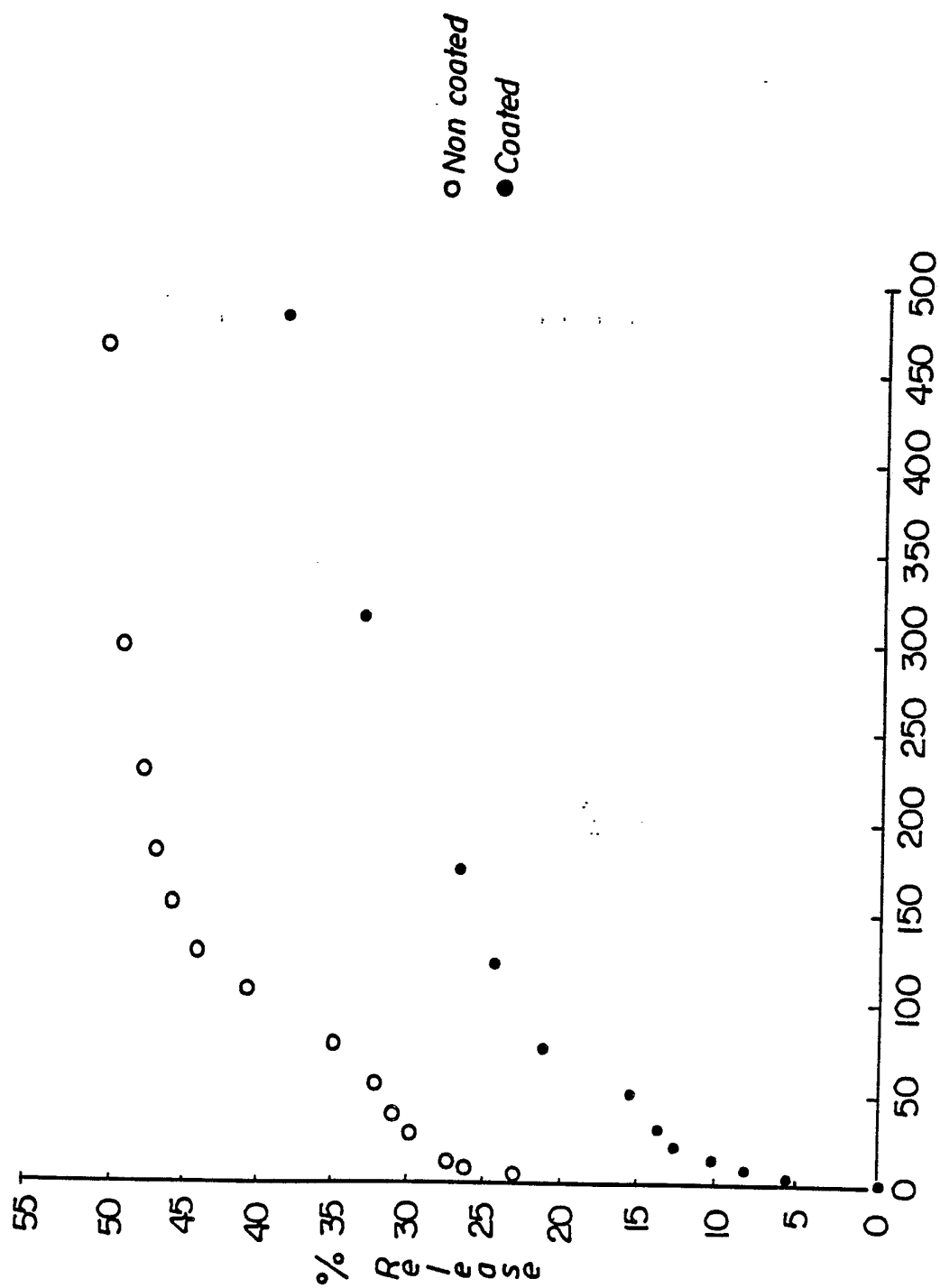
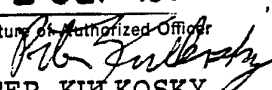


FIG. 6

INTERNATIONAL SEARCH REPORT

International Application No. **PCT/US88/01965**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
<div style="display: flex; justify-content: space-between;"> INT. CL4 A61K 31/74 </div> <div style="display: flex; justify-content: space-between;"> US. CL 424/78 424/468 </div>		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
U.S.	424/78, 428, 468	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	N CHEMICAL ABSTRACTS, VOL. 102, ENTRY 32116L (DEVISSER ET AL) JANUARY 1984	1-17
Y	N DISSERTATION ABSTRACTS NO. DA8409012 (AUSTIN) DECEMBER 1983. SEE ENTIRE DOCUMENT.	1-17
Y	US, A, 3,993,071 (HIGUCHI ET AL) NOVEMBER 1976, SEE COLS. 21-24.	1-17
Y	US, A, 4,440,921 (ALLCOCK ET AL) APRIL 1984, SEE COL. 7.	1-17
Y	US, A, 4,495,174 (ALLCOCK ET AL) JANUARY 1985, SEE COL. 11.	1-17
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
JULY 22, 1988	22 SEP 1988	
International Searching Authority	Signature of Authorized Officer	
ISA/US	 PETER KULKOSKY	