(54) Title: THERAPEUTIC AGENT DELIVERY SYSTEM

(57) Abstract

A therapeutic agent delivery system that includes a biodegradable polymer and a therapeutic agent, the delivery system being coated with a barrier substance that decreases the quantity of the agent released from the system, compared to the quantity of the agent released from a system not coated with the substance, in the forty-eight hours subsequent to the parenteral injection or implantation of the system into a living person or animal.

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Therapeutic Agent Delivery System
Background of the Invention

This invention relates to the release of
therapeutic agents from delivery systems.

5   Biodegradable polymers containing a therapeutic
agent are often used to administer the agent to a
patient. Generally the release results from the
dissolution of the polymer and from the diffusion of the
agent through pores and channels in the matrix.

10   Summary of the Invention

In general, the invention features, in one
aspect, a therapeutic agent delivery system that
includes a biodegradable polymer and a therapeutic
agent, the delivery system being coated with a barrier

15   substance that decreases the quantity of the agent
released from the system, compared to the quantity of
the agent released from a system not coated with the
substance, in the forty-eight hours subsequent to the
parenteral injection or implantation of the matrix into

20   a living person or animal.

In preferred embodiments, the barrier substance
is silicone oil that has a viscosity of between 10^2
centipoise (cp) and 10^4 cp.

In another aspect, the invention features a

25   method of providing a coated therapeutic agent delivery
system that includes a biodegradable polymer and a
therapeutic agent, the method including the steps of
coating the delivery system with a barrier substance,
and treating the delivery system to remove some but not

30   all of the barrier substance.

In some preferred embodiments, the barrier
substance is a silicone oil, and the treating includes

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washing the delivery system with a solvent that removes
some of the barrier substance.

Delivery systems consisting of a biodegradable
polymer and a therapeutic agent are made in a variety of
ways, e.g., solvent casting, coacervation procedures, or
dispersion. When the former procedure is used, the
agent is dispersed as small particles throughout the
system. The small particles are irregularly shaped
with small jagged edges; the edges may extend to the
surface of the system, or may cause cracks in the system
that extend to the surface. When such a system is
inserted into a patient, a dose of agent larger than the
desired dosage is released from the system through these
surface contacts.

Delivery systems prepared by coacervation
consist of an aggregate of agent surrounded by the
polymer. The large crystal may have jagged edges
extending to the surface, or may cause cracks that
extend to the surface. Accordingly, the initial burst
of agent problem is also present in these systems.

Coating the surface of th · delivery system with
a barrier substance limits the release of agent from the
delivery system for the initial one or two day period
following administration, thus decreasing the agent's
possible deleterious side effects that can result from
initial bursts of high agent release. In addition,
because the initial quantity of agent released is
limited, more agent remains in the system allowing for a
longer effective period of use for the matrix.

The delivery system is easy to use and
inexpensive to make. Moreover, because of the coating,
the delivery system has superior handling properties in
that it does not clump together when in powdered form.

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    Other features and advantages of the invention
will be apparent from the following description of the
preferred embodiment, and from the claims.

    Description of the Preferred Embodiment

5   We now describe the structure, method of
preparation, and use of the preferred embodiment.

Structure

    The delivery system employs a biodegradable
polymer containing a therapeutic agent. The system is
10 coated with a barrier substance; the barrier substance,
when the system is introduced into a vertebrate
(preferably a mammal such as a human or domestic animal
such as a dog or cow) decreases the initial burst of
therapeutic agent from the system.

15   A biodegradable polymer is a polymer which
slowly dissolves or degrades in a physiological
environment into low molecular weight molecules that are
then transported from the site. Types of biodegradable
polymers suitable for use in a delivery system include
20 polyanhydrides, partially crosslinked proteins,
polylactic acid, polyglycolic acid, polyorthoesters,
polysaccharides, polaxomers, hydroxypropylcellulose,
polyethyleneglycol, copolymers of lactide and glycolide,
and carboxymethylcellulose. Some representative
25 examples of poly(lactide/glycolide) biodegradable
polymers are described by Kitchell & Wise, 112 Methods
In Enzymology 436 (1985).

    The delivery sysytems of the invention
preferably are injected or implanted parenterally into
30 an animal or a human patient. Where the system is to be
injected, it should be small enough in diameter to fit
through the needle tip of the syringe. The preferred
delivery systems for injection have an average size of
500 microns or less (more preferably 250 microns or

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less, most prefereably 100 or 200 microns); rod shaped
systems of 1-10 mm diameter, which generally are long
and slender, may also be used.

5   The term therapeutic agent, as used herein,
means any agent used to treat or prevent any disease or
disorder of the body. Representative agents include
hormones (and hormone fragments and analogues), e.g.,
testosterone, luteinizing hormone-releasing hormone
(LHRH); diuretics, e.g., chlorothiazide;

10   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.

15   One of the roles of the barrier substance is to
limit the initial burst of therapeutic agent from the
delivery system. The substance should not affect the
long term sustained release of the agent, and therefore
should be a substance that dissolves or wears off the

20   surface of the system within a short period of time
after injection; preferably, the barrier substance
should dissipate within 5 days after injection, more
preferably within 2 days after injection. The substance
should be non-toxic, non-irritating, non-sensitizing,

25   and hydrophobic. Preferably the substance is on the
GRAS list or is USP approved.
        Examples of suitable barrier substances include
paraffins, beeswax, and, preferably, silicone oils.

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Silicone oils are organo-siloxane polymers based on a structure consisting of alterating silicon and oxygen atoms with organic groups (R) attached to the silicon atoms:

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$$
\begin{array}{ccc}
R & R & R \\
| & | & | \\
-SiO\!-\!Si\!-\!OSi\!- \\
| & | & | \\
R & R & R
\end{array}
$$
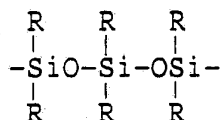
Typical silicone oils include those in which R is a lower alkyl group having six or less carbons, e.g., a
10   methyl group. Silicone oils have a viscosity of between 1 cp and 10^6 cp. The more preferred silicone oils have a viscosity of between 10^2 cp and 10^4 cp; most preferably the silicone oils have a viscosity of between 500 cp and 2000 cp. Representative examples of silicone
15   oils include Union Carbide dimethylpolysilicone #L-45 (viscosity 1000 cp), Dow Corning medical grade silicone oil #360, Aldrich silicone oil (catalogue no. 17,563-3), and Aldrich silicone oil (catalogue no. 14,615-3).
         The delivery system can comprise up to 70%
20   agent by weight. If a system comprises greater than 70% agent by weight, the mechanical properties of the system may be adversely affected.

Method of Preparation
         The uncoated delivery system can be prepared by
25   standard solvent casting techniques. In general, the polymer is dissolved in an organic solvent and the therapeutic agent added. The solution or suspension is then poured into a suitable mold and the solvent evaporated to yield a polymer-agent combination.
30   Alternatively, the agent can be dispersed with the polymer without solvent.
         The delivery systems can also be prepared by coacervation procedures, such as those described by

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Lapka et al., U.S. Pat. No. 4,622,244, which is hereby
incorporated by reference.

The uncoated delivery system of choice
(generally in the form of a powder) is placed in a flask
5   and covered with a silicone oil such as Union Carbide
dimethylpolysilicone #L-45. The thickness of the
coating can be adjusted by rinsing with hexane or other
organic solvent capable of dissolving silicone oil. The
thicker the coating, the more limited the initial burst
10   of release of agent from the system. The powder is
dried under a stream of nitrogen gas, and then under
vacuum for 24 hours.

Alternate methods of coating include spraying a
thin coat of silicone oil onto the powder; and mixing
15   the powder in a solvent in which the barrier substance
has been dissolved and then evaporating off the solvent.

Where the delivery system is a powder made up
of particles having an average size 100-200 microns,
following coating each particle should be 0.05%-10%
20   (more preferably 0.1%-2%) silicone oil by weight. The
amount of silicone oil present can be calculated by
first conducting an elemental analysis of the powder to
determine the amount of silicon present; knowing the
percentage of silicon in the oil, the amount of oil can
25   then be determined.

Use

The delivery systems containing the standard
dosage of the selected therapeutic agent and coated with
a barrier substance are injected, implanted, or
30   otherwise inserted parenterally into a patient. The
barrier substance limits the initial burst of the agent
from the polymer; over a short period of time, the
barrier substance wears off of the surface of the

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system, allowing the system to release the desired
dosage over a sustained period of time.

A comparison of the initial quantity of agent
released from the coated delivery system and an uncoated
5   delivery system can be made by (1) injecting or
implanting equal amounts (uncoated weight) of the
systems into different animals; and (2) either
determining the levels of agent in the animal's blood
after 48 hours, or measuring the biological effect that
10   the agent induces (e.g., for delivery systems that
release LHRH, the level of testosterone in serum is
measured, that level being directly correlated to the
amount of LHRH released). It is understood that,
although it is most preferred that the initial release
15   be limited to the desired dosage of the agent, the
advantages of the invention, such as reducing side
effects of large dosages of the agent, are achieved if
the initial release is reduced by as little as ten
percent (more preferably twenty percent).

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Claims

1. A therapeutic agent delivery system comprising a biodegradable polymer and a therapeutic agent, said delivery system being coated with a barrier substance that decreases the quantity of said agent released from said system, compared with the quantity of said agent released from a said system not coated with said substance, in the forty-eight hours subsequent to the parenteral injection or implantation of said system into a living person or animal.

2. The therapeutic agent delivery system of claim 1 wherein said barrier substance is a silicone oil.

3. The therapeutic agent release system of claim 2 wherein said silicone oil has a viscosity of between 10^2 centipoise and 10^4 centipoise.

4. The therapeutic agent release system of claim 3 wherein said silicone oil has a viscosity of between 500 centipoise and 2000 centipoise.

5. A method of administering a therapeutic agent to a vertebrate comprising the steps of

    providing a therapeutic agent delivery system comprising a biodegradable polymer and a therapeutic agent,

    coating said delivery system with a barrier substance, and

    injecting or implanting the coated delivery system into said vertebrate, said barrier substance limiting the initial release of said agent from said system in comparison with the initial release obtained when a said system is not coated with said substance.

6. The method of claim 5 wherein said barrier substance is a silicone oil.

      7. The method of claim 6 wherein said silicone oil has a viscosity of between 10^2 centipoise and 10^4 centipoise.

      8. The method of claim 7 wherein said silicone
5   oil has a viscosity of between 500 centipoise and 2000 centipoise.

      9. The method of claim 6 wherein said vertebrate is a human.

      10. A method of providing a coated therapeutic
10 agent delivery system comprising

      coating a therapeutic agent delivery system comprising a biodegradable polymer and a therapeutic agent with a barrier substance that decreases the quantity of said agent released from said system,
15 compared with the quantity of said agent released from a said system not coated with said substance, in the forty-eight hours subsequent to the parental injection or implantation of said system into a living person or animal; and
20   treating said delivery system to remove some but not all of said barrier substance.

      11. The method of claim 10 wherein said barrier substance is a silicone oil.

      12. The method of claim 10 wherein said
25 treating comprises washing said delivery system with a solvent.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/02546

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

IPC(4): A61F 2/00

U.S.CL: 424/422

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
U.S.	424/422, 423,424, 425, 426, 486

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
Y	US, A,3,279,996 (LONG, JR.) 18OCTOBER 1966 SEE ENTIRE DOCUMENT	1 12
Y	US, A 3,854,480 (ZAFFARONI) 17 DECEMBER 1974 SEE ENTIRE DOCUMENT	1-12
Y	US, A,3,944,064 (BASHAW) 16 MARCH 1976 SEE ENTIRE DOCUMENT	1-12
Y	US, A,4,159,322 (CLOYD) 26 JUNE 1979 SEE ENTIRE DOCUMENT	1-12
Y	US, A,4,230,686 (SCHOPFLIN) 28 OCTOBER 1980 SEE ENTIRE DOCUMENT	1-12
Y	US, A, 4,351,337 (SIDMAN) 28 SEPTEMBER 1982 SEE ENTIRE DOCUMENT	1-12
Y	US, A, 4,622,244 (LAPKA) 11 NOVEMBER 1986 SEE ENTIRE DOCUMENT	1-12

* Special categories of cited documents: 10

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

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

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

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

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

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

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

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 OCTOBER 1988	0 1 DEC 1988

International Searching Authority	Signature of Authorized Officer
ISA/US	T.K. PAGE

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