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(54) Title: CONTROLLED RELEASE DOPAMINE AND ITS USE TO STIMULATE NERVE FIBER GROWTH

(57) Abstract

The present invention relates to polymeric microspheres as injectable, drug-delivery systems for use do deliver bioactive agents to sites within the central nervous system, and for the stimulation of nerve fiber growth by implanting such microspheres within the central nervous system of a patient.

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CONTROLLED RELEASE DOPAMINE AND ITS USE TO STIMULATE NERVE FIBER GROWTH

It has long been recognized that delivering a drug to its therapeutic site of action within the central nervous system can be a very difficult task because of the numerous chemical and physical barriers which must be overcome in order for such delivery to be successful. A number of methods have been designed to overcome some of these barriers to central nervous system drug delivery as, for instance, the use of liposomes to surmount the blood-brain barrier. However, the disadvantages of a liposome delivery system, including low drug loadings, short duration of action, limited ways to manipulate the rate of drug release, poor storage stability, and problems with scale-up, have precluded the use of such a system. Another method to overcome some of the barriers to central nervous system drug delivery consists of chemically modifying the active drug to a form, called a prodrug, that is capable of crossing the blood-brain barrier, and once across this barrier the prodrug reverts to its active form. One example of such a prodrug delivery system consists of the neurotransmitter dopamine attached to a molecular mask derived from the fat-soluble vitamin niacin. The modified dopamine is taken up into the brain where it is then slowly stripped from its prodrug mask to yield free dopamine.

The most common method to surmount some of the physical barriers preventing drug delivery to the central nervous system

has been through the use of pumps. A variety of pumps have been designed to deliver drugs from an externally worn reservoir through a small tube into the central nervous system. Although such pump delivery systems can be externally controlled to a certain degree, the potential for infection directly within the central nervous system is great and the exact site of action of the drug within the central nervous system is largely beyond control.

To be successful, it does not suffice just to deliver the drug within the central nervous system. The drug must be delivered to the intended site of action, at the required rate of administration, and in the proper therapeutic dose. Commercially, the Alzet osmotic mini-pump has become an acceptable, very useful, and successful means of delivering drugs at a controlled rate and dose over extended periods within the central nervous system. However, adapting this device to deliver the desired drug to discrete brain nuclei presents vast difficulties such as implanting cannulas directly within the designated brain regions.

Still another technique that has been developed to deliver neuro-active agents, such as neurotransmitters, to the central nervous system is with the use of neural transplants. Viable neuronal tissue can be implanted directly within discrete brain nuclei. The duration of substance delivery from the transplanted tissue does not present a problem because implanted tissue may survive for a long time in the host's central nervous system. This technique surmounts a number of obstacles cited above, however,

despite claims that neuronal grafts from fetal dopamine cells exhibit some of the autoregulatory feedback proterties that are normally found in intact dopamine neuronal systems, the exact rate at which the neurotransmitters are delivered from neuronal transplants at their site of action can not be predetermined.

In 1817, James Parkinson described a disease which he termed "shaking palsy". This condition is presently known as Parkinson's disease and occurs in the middle-aged and ederly. While its onset is insidious, often beginning with tremor in one hand followed by increasing bradykinesia and rigidity, it is slowly progressive and may become incapaciting after several years. In idiopathic Parkinson's disease, there is usually a loss of cells in the substantia nigra, locus ceruleus and other pigmented neurons, and a decrease of dopamine content in axon terminals of cells projecting from the substantia nigra to the caudate nucleus and putamen commonly referred to as the nigrostriatal pathway.

Some symptoms of Parkinson's disease can be treated by the administration of L-3,4-dihydroxyphenylalanine (levodopa or L-dopa). L-dopa, the metabolic precursor of dopamine, is used for replacement therapy because dopamine itself does not cross the blood-brain barrier. However, it must be given in large doses of 3 to 15 grams per day because much of the drug is metabolized before it reaches the site of action in the brain. Alternatively, it is often given in combination with a dopa decarboxylase inhibitor, such as carbidopa, which prevents the metabolism of L-dopa until it crosses the blood-brain barrier. Its greatest effect is on

bradykinesic symptoms. After about five years of treatment, side effects develop and the treatment becomes less and less effective even with increasing doses of the drug. These problems have raised the question of whether or not it would be possible to replace the lost dopamine by other means which would deliver the drug to its therapeutic site of action within the central nervous system.

Even though these approaches are well documented for experimental animal models, their use as therapy for neurodegenerative disorders such as Parkinson's disease present a number of practical as well as ethical considerations. Not only is the use of human aborted fetal tissue a controversial issue, but this technique involves complicated surgical procedures. Furthermore, although clinical trials of adrenal and fetal tissue implants in Parkinsonian patients are being conducted, the mechanism and long-term efficacy of tissue transplants within the nervous system remain unclear and is still a matter of medical debate. The best theoretical approach for treatment of such central nervous system pathologies continues to be one which would deliver the biologically active agent directly to the damaged region of the central nervous system.

Although a number of different methods have been proposed and are presently being utilized for the delivery of pharmaceutically active compounds to the central nervous system, there are sufficient disadvantages to each method that the need for delivering biologically active substances to the

central nervous system still exists. The present invention addresses this need in a unique manner.

The discovery that a unilateral lesion of the nigrostriatal pathway with the neurotoxin 6-hydroxy-dopamine produced an asymmetry of movement and posture in the rat, provided an animal model for Parkinson's disease. This asymmetry of movement is employed in the rotometer model developed to measure rotational behavior induced by drugs that interfere with dopamine neurotransmission such as apomorphine. The characteristic apomorphine induced rotational behavior is only observed in animals with a 95% reduction of dopamine levels in the striatum, and replacement dopamine in this tissue either by transplants of fetal dopamine producing cells or adrenal medullary tissue results in significant decreases in apomorphine induced rotational behavior.

Broadly defined, the present invention relates, in part, to microspheres that have been developed as injectable, drug-delivery systems in which bioactive agents are contained within a compatible biodegradable polymer. As used with regard to the present invention, the term microsphere includes microcapsules, nanocapsules and nanospheres.

Microcapsules and microspheres are conventionally free flowing powders consisting of spherical particles of 2 millimeters or less in diameter, usually 500 microns or less in diameter. Particles less than 1 micron are conventionally referred to as nanocapsules or nanospheres. For the most part,

the difference between a microcapsule and a nanocapsule, or a microsphere and a nanosphere, is size; generally there is little, if any, difference between the internal structure of the two.

As used in the present invention, the microcapsule, or nanocapsule, has its encapsulated material (in the present invention this is a bioactive agent or drug) centrally located within a unique membrane. This membrane may be termed a wall-forming polymeric material. Because of their internal structure, permeable microcapsules designed for controlled-release applications release their agent at a constant rate (called a "zero order" rate of release). Thus, as used in the present invention, microcapsules include microparticles in general which comprise a central core surrounded by a polymeric membrane.

In addition, microspheres encompass "monolithic" and similar particles in which the bioactive agent is dispersed througout the particle; that is, the internal sturcutre is a matrix of the bioactive agent and a polymer excipient. Usually such particles release their bioactive agents at a declining rate (a "first order" rate of release), however such particles may be designed to release internal agents within the matrix at a near zero order rate. Thus, as used in the present invention, microspheres also include microparticles in general which have an internal structure comprising a matrix of bioactive agent and polymer excipient.

The specific polymer employed in the present invention, poly (lactide-co-glycolide), has a number of advantages which

render it unique to the method of the present invention. An advantage of this polymer is that it is similar to materials used in the manufacture of present-day resorable sutures. Another advantage is that this material is biocompatible with the tissues of the CNS. Still another advantage is that this material is biodegradable within the tissues of the central nervous system without producing any toxic byproducts of degradation. A still further advantage of this material is the ability to modify the duration of drug release by manipulating the polymer's biodegradation kinetics, i.e. by modifying the ratio of lactide and glycolide in the polymer; this is particularly important because of the ability to deliver neuro-active molecules to specific regions of the brain at a controlled rate over a predetermined period of time is a more effective and desirable therapy over current procedures for administration. Microspheres made with this polymer serve two functions: they protect drugs from degradation and they release drugs at a controlled rate over a predesired time. Although polymers have been previously reported for use in the microencapsulation of drugs, the physical, chemical and medical parameters of the microencapsulating polymer for neuro-active molecules to be used in central nervous system implantation technique according to the present invention are narrow; there is no general equivalency among polymers which allows a polymer previously used for encapsulation of drugs to be freely exchanged for the polymers used to encapsulate neuro-active molecules for drug delivery to the central nervous system according to the

present invention. This is especially true when the site of utilization is the central nervous system. Although the specifically named polymer according to the present invention meets the criteria necessary for implantation within the central nervous system, other biocompatible, biodegradable polymers and copolymers having advantages which are similar to those named advantages of poly(lactide-co-glycolide) may be substituted.

Results obtained from a number of studies indicate that implantation of these neuro-active agent containing microspheres provides a feasible method for prolonged release of the agent into the central nervous system. Moreover, the data obtained from studies involving dopamine as the encapsulated agent indicate that dopamine microsphere preparations have the potential of being employed as a source of transmitter replacement allowing diffusion of the microencapsulated dopamine directly into the central nervous system at a controlled rate for pre-determined periods of time assuring functional significance and at the same time remaining compatible with the central nervous system tissue. However, most surprisingly, the data indicate that microencapsulated dopamine injected into specific regions of the brain has the heretofore unreported ability to cause growth of nerve fibers. Thus, the method of placing the microencapsulated neuro-active agents, manufactured in accordance with one aspect of the present invention, has the potential of promoting the growth of those neural elements which are responsible for the production of endogenous dopamine within the central nervous

system. Once growth has taken place and the neural fiber elements have matured and stabilized within their environment, they will continue to produce and release dopamine within the central nervous system thereby providing for the first time a potential cure for Parkinson's disease.

Among the neuro-active molecules or agents which may be microencapsulated and used according to the present invention are neurotransmitters, neuropeptides, and neurotrophic factors including such agents as norepinephrine, epinephrine, serotonin, dopamine, substance P, somatostatin, nerve growth fa tor, angiotensin II, and gamma aminobutyric acid.

Among the neurological diseases which may be treated microencapsulated neuro-active molecules being placed directly within the tissues of the central nervous system are Parkinson's disease, Huntington's Chorea, Alzheimer's disease, Epilepsy, and Tardive dyskinesia. Depending upon the disease to be treated, it may be advantageous to provide more than one microencapsulated neurotransmitter, neuropeptide and neuronotrophic factor to the central nervous system. For example, as dopamine, cholecystokinin, and epidermal and basic fibroblast growth factors may all be involved in Parkinson's disease, ultimately it may be advantageous when presented with a patient having the disease to provide a mixture of microencapsules containing two, three, or all four neural-active molecules to the central nervous system.

In order to provide a more complete description and provide a greater understanding of the various aspects of the present invention, reference is made to the following examples.

EXAMPLE 1

Preparation Of Dopamine Microspheres

A weight % polymer solution was prepared by dissolving 2 g of 50:50 poly(DL-lactide-co-glycolide) ("DL-PLG") in 198 g of dichloromethane (The DL-PLG had an inherent viscosity of 1.27 dL/g.). Two grams of dopamine (3-hydroxytyramine hydrochloride) were suspended in the polymer solution by homogenization. The dopamine suspension was then poured into 300 mL resin kettle and stirred at 3500 rpm with a 1.5 inch Teflon impeller. Silicone oil (350 cs) was pumped into the resin kettle at a rate of 2 mL per min. After approximately 50 mL of oil was added, the contents of the resin kettle were poured into 3.5 L of heptane. The heptane was stirred at 900 rpm with a 2.5 inch stainless steel impeller. After 0.5 h of stirring, the dopamine microsphere suspension was poured through a stainless steel sieve with 45 μm openings to remove microspheres larger than 45 μm in diameter. Microshperes less than 45 μm in diameter were collected on a fritted glass filter funnel and dried at room temperature in a vacuum oven for 48 h. The dopamine microspheres were then collected in tared glass scintillation vials and stored under desiccant at 4°C.

Dopamine was encapsulated in two types of copolymer excipients made in accordance with Example 1. One copoylmer had a 50:50 mole ratio of lactide to glycolide and the other copolymer had a 65:35 mole ratio. In view of the higher lactide content of the 65:35 copolymer, this copolymer will take longer to biodegrade than the 50:50 copolymer. Thus, the delivery time of the 65:35 copolymer can be longer than the delivery time of the 50:50 copolymer. Additional variations of the actual proportions of lactide and glycolide in the copolymer and the copolymer morphology may be manufactured to more or less custom adjust the rate and amount of neuro-active molecule being released into the central nervous system

The final microspheres are free-flowing powders consisting of spherical particles approximately 5 to 45 μm in diameter. These microspheres can easily be suspended in aqueous vehicles and injected through conventional hypodermic needles. Although the amount of dopamine contained in each microsphere may vary, the microspheres manufactured and used in the following example consisted of about 40 % (by weight) dopamine and of about 60 % (by weight) of the poly(DL-lactide-co-glycolide). When used as a therapeutic, the microspheres may contain from about 10% to about 80% [by weight] dopamine). In vitro diffusion tests of these microspheres showed that most of the dopamine was released into deionized water within 30 minutes. Prior to injection, the microspheres are sterilized with, preferably, gamma radiation.

EXAMPLE 2

Administration Of Microspheres

Microencapsulated dopamine was formulated (15 mg of 50:50 microcapsulated dopamine in 50 µL saline or 30 mg of 65:35 microencapsulated dopamine in 50 µL of saline) for implantation into previously treated rat models.

Male Sprague Dawley rats were unilaterally lesioned in the ascending median forebrain bundle of monoamine neurons using the neurotoxin 6-hydroxy-dopamine. Two weeks later, the animals were challenged with apomorphine (0.1 mg/kg SC) and rotational responses were monitored in a computerized rotometer set-up. Only rats in which the dopamine denervation has been successful will display strong contralateral rotation to apomorphine challence. Therefore, animals responding to apomorphine with less than 400 contralateral rotations per 60 minutes during the first two weeks of testing were eliminated from the study. Testing of positive responders was then continued on a weekly basis using apomorphine.

Once the aminals reached a stable rotational baseline level to dopamine agonist challenge, they were stereotaxically injected under light ether anesthesia with a suspension of dopamine microspheres. Dopamine/50:50 DL-PLG microspheres (15 mg microspheres/50 µL saline) were injected in 3 µL implants into the striatum. Dopamine/65:35 DL-DPG microspheres were correspondingly implanted (30 mg microspheres/50 µL saline) in the striatum. Based upon experience, it was expected that the 65:35 DL-PLG microspheres would biodegrade completely in about 12 weeks, and the 50:50 DL-PLG microspheres would do so in about 6 weeks. Thus, to ensure similar doses of dopamine would be released per unit time, the amount of dopamine in the 50:50 DL-PLG microspheres was half that of the 65:35 DL-PLG microspheres. Control rats received similar implants with dopamine-free microspheres. Standard Hamilton syringes (50 µL) connected by polyethylene tubing to stainless steel injection cannulae were used for the injections. Upon completion of the injection, the cannula were left in situ for an additional 60 sec before being slowly retracted and the skin wound closed. Starting 1 to 3 days after implantation of the dopamine microspheres, the animals were repeatedly tested for dopamine agonist-induced rotation at various intervals over an 8 week period.

Thirty to forty minutes after intrastriatal implantation of the microencapsulated dopamine, those rats receiving the dopamine/50:50 DL-PLG microsphere implantation exhibited contralateral rotations with an amplitude similar to that of a previous test dose of apomorphine but with longer duration. Rats receiving the dopamine/65:35 DL-PLG microsphere implantation displayed a somewhat more protracted response to the implantation, however once begun, these animals have a peak rotation amplitude similar to that of those receiving the dopamine/50:50 DL-PLG microspheres. Rats receiving a control charge of empty microspheres did not display rotational behavior. Histological evaluations made upon sacrificed animals indicate that the injection of a suspension of microspheres according to the present invention into the rat brain is an acceptable means of delivering dopamine to the central nervous system; only minimal damage to the surrounding tissue and minimal glial reaction was noted following injection. Thus, there is little concern that a morphological barrier exists which would prevent the diffusion of dopamine into the targeted region.

Thus, we have confirmed our original belief that the specific polymeric microspheres according to the present invention provide a unique and acceptable means to introduce neuro-active molecules into the central nervous system.

The most outstanding result of delivering dopamine to the central nervous system utilizing the method and microspheres of the present invention is finding the presence of dopamine

immunoreactive fibers growing towards the dopamine microspheres. This is not seen in control (those not containing dopamine) microsphere implantation. The ability of implanted dopamine microspheres manufactured and implanted according to the present invention to elicit neuronal sprouting may provide not only a treatment for neurologically debilitating diseases such as Parkinson's disease, but a cure as well.

As part of ongoing research into the direct delivery of nuero-active molecules to the brain, an antibody to dopamine showing no cross reactivity with other neurotransmitter systems (such as norepinephrine, serotonin or gamma amino butyric acid) when utilized in ELISA test systems was developed. This antibody has been shown in both ELISA and immunocytochemical test systems to recognize dopamine and is a reliable means of demonstrating fiber outgrowth in the rat brain as depicted in the following example:

EXAMPLE 3

Fiber Formation

The immunogen complex to obtain antibodies against dopamine is prepared by coupling the hapten to glutaraldehyde (G) and bovine serum albumin (BSA). Rabbits are then immunized with this immunigen. Antibodies directed toward dopamine were detected 50 days following the immunization schedule of 4 injections at 10 day intervals. To eliminate antibodies that are produced against BSA-G, the dopamine antibody was adsorbed by affinity chromatography. In order to visualize dopamine within brain tissue, the rats were perfused with gluteraldehyde thereby fixing dopamine and tissue proteins. Thus, because the antibody is directed against dopamine-gluteraldehyde and a protein, the antibody will recoginize this complex within the brain. Rats were deeply anesthetized with sodium pentobarbital and perfused through the aorta with a mixture composed of 5% glutaraldehyde and an anti-oxidant to prevent the rapid release of dopamine from the brain tissue. After the rats were perfused with this mixture, the brains were removed and allowed to equilibrate overnight in 10% sucrose solution. The brains were then frozen, sectioned, and the sections incubated with anti-dopamine antiserum for 24 hours. The following day the sections were reacted with goat anti-rabbit biotin IgG which recognizes the antiserum produced in the rabbit. Following this, the sections were incubated with avidin biotin-peroxidase complex which recognizes the fixed

biotin molecules. The peroxidase was then reacted with a classical chromatogen for this type of reaction, 3,3 diaminobenzidine, and the reaction enhanced by the addition of ammonium nickel sulphate giving a purple stain to the antibody reaction. Therefore, the presence of dopamine in the brain tissue is visualized as a purple deposit in the tissue; if dopamine is not present in the tissue, the tissue remains unstained.

As noted previously, the implantation of control microspheres did not modify the apomorphine-induced rotational responses in the rat, indicating at least a 95% decrease of dopamine in the central nervous system. Microscopic observations of the tissues following staining in accordance with Example 3 confirmed that dopamine was absent in the striatum of the rats receiving the control microspheres, that is the brain tissue remained unstained. However, in animals that received the dopamine microspheres and displayed a continued decrease in apomorphine rotational behavior, microscopic observations indicated dopamine was present both in the microcapsules and the tissue. As noted previously, numerous fine fiber extensions were seen growing towards the implanted microspheres, and dopamine was present in these fibers. These findings indicate that dopamine nerve fibers were growing within the host animals' central nervous system, a phenomena heretofore unreported. The implanted dopamine containing microspheres apparently have the ability to elicit growth of nerve fibers from the base of the brain toward the microspheres. These fibers were present in all animals which displayed a continued decrease in the number of apomorphine induced rotations which appears to be due to a release of dopamine from the microspheres as well as the growing dopamine fibers within the host's central nervous system. Similar observations were noted for both the 50:50 DL-PLG and 65:35 DL-PLG dopamine microspheres.

The anatomical placement of the dopamine microspheres appears to be important for both fiber growth and functional recuperation. One rat striatum is about 3 mm in width and 4 mm in depth. Dopamine fibers growing from the base of the brain are mainly located in the more medially ventral portion of the striatum in comparison to the extreme lateral portion of this nucleus. Placing dopamine microspheres at the base of the brain stimulates growth of these particular fibers. It appears that the diffusion of dopamine from these microspheres placed in this location reaches these fibers and they grow towards the microspheres. The lateral placement of dopamine containing microspheres therefore appears too distant to allow dopamine diffused from the microspheres to influence these fibers.

Immunocytochemical investigations with an antibody to growth associated protein, a protein associated with systems undergoing fiber growth, indicated the growing fibers were reactive to this protein, an indication that the nerve fibers are undergoing a fiber growth. Injection of fluorogold within the denervated striatum 2 weeks after implantation of dopamine microspheres indicates retrograde labelling of neurons within the ventral tegmentum region, sugesting that the dopamine microspheres trigger the growth of dopamine fibers.

Another observation of growth of fibers has been made when the microspheres were implanted into the striatum of a genetic mouse model. The Weaver mouse strain carries an autosomal recessive mutation and provides investigators a means to

investigate fiber growth following dopamine microsphere implantation into a brain region where dopamine is "naturally" depleted. These genetically abberant mice are severely depleted of their brain dopamine. The abnormality is particularly marked in the nigrostriatal dopamine tract while the mesolimbic dopamine neurons appear less affected. Implanting dopamine microspheres within the striatum of this mouse model equally stimulates the growth of dopamine-induced fibers in the striatum probably emanating from the genetically unaffected dopamine system.

In addition to dopamine, we have recently implanted microspheres, made as above but containing norepinephrine in the denervated rat striatum. Although these studies are still preliminary, a 46% reduction in the contralateral rotational behavior has been observed for 4 weeks. This reduction is comparable to what is seen in rats implanted with microspheres containing dopamine. Although there are presently no histochemical observations available after implantation of the norepinephrine microspheres, it appears that the results may be caused because of the similar structures (dopamine being a precursor for norepinephrine) of the two compounds.

Thus, while we have illustrated and described the perferred embodiement of my invention, it is to be understood that this invention is capable of variation and modification, and we therefore do not wish or intend to be limited to the precise terms set forth, but desire and intend to avail ourselves of such changes

and modifications which may be made for adapting the present invention to various usages and conditions. Accordingly, such changes and modifications are properly intended to be within the full range of equivalents, and therefore within the purview of the following claims. The terms and expressions which have been employed in the foregoing specification are used as terms of description and not of limitation, and thus there is no intention, in the use of such terms and expressions, of excluding equivalents of the features shown and described, or portions thereof; the scope of the invention being defined and limited only by the claims which follow.

Having thus described our invention and the manner and process of making and using it in such full, clear, concise, and exact terms so as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same,

WE CLAIM:

1. A drug delivery system for administering a neuro-active molecule to the central nervous system of an animal which comprises a neuro-active molecule, other than dopamine, within a microsphere comprising a polymer, said polymer (1) being permeable to the neuro-active molecule, (2) being biocompatible with the tissues of the central nervous system, (3) being biodegradable within the tissues of the central nervous system without producing toxic byproducts of degradation, and (3) having biodegradation kinetics which may be manipulated to allow for the permeation of the neuro-active molecule through the polymer at a controlled rate and a predetermined period of time.

2. A drug delivery system for administering a neuro-active molecule to the central nervous system of an animal which comprises a neuro-active molecule, other than dopamine, encapsulated within a copolymer of poly(lactide-co-glycolide) or homopolymer of polylactide or polyglycolide.

3. A method for eliciting neural fiber growth within the central nervous system which comprises:

gaining access to the central nervous system of a patient;

providing a microsphere comprising a neuro-active molecule encapsulated within a polymer, said polymer (1) being permeable to the neuro-active molecule, (2) being

biocompatible with the tissues of the central nervous system, (3) being biodegradable within the tissues of the central nervous system without producing toxic byproducts of degradation, and (3) having biodegradation kinetics which may be manipulated to allow for the permeation of the neuro-active molecule through the polymer at a controlled rate and a predetermined period of time; and

implanting said microsphere into the central nervous system of the patient.

4. A method for eliciting neural fiber growth within the central nervous system which comprises implanting with the central nervous system a neuro-active molecule encapsulated within a copolymer of poly(lactide-co-glycolide) or homopolymer of polylactide or polyglycolide.

5. A method according to claim 4 wherein the neuro-active molucule is norepinephrine, dopamine or a norepinephrine or dopamine precursor.

6. A method according to claim 5 wherein implantation placement is within the medial ventral axis of the central nervous system.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/03356

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 47/30
U.S.CL: 424/422

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/422, 423, 424, 425, 426, 486, 487

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category [6]	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [19]
X	US, A, 4,883,666 (SABEL ET AL.) 28 NOVEMBER 1989. See the claims.	1-6

[6] Special categories of cited documents: [15]

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

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

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
09 July 1991	26 JUL 1991
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Carlos Azpuru