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SEÑORES
SUPERINTENDENCIA DE INDUSTRIA Y COMERC.
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Ref.: Expediente No. 07-058.649
Solicitud de Patente de Invención titulada: "IMPLANTE FORMADO IN SITU PARA ANIMALES"
Solicitante: NOVARTIS A.G.
Nuestra Ref.: P2007/000077

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 596

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado de la sociedad de la referencia, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el articulo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de $420.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 de 26 de diciembre 2007.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por $420.000 pesos

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-058649- -00003-0000

Fecha: 2008-12-04 16:39:41 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 93,865
FECHA : DICIEMBRE 2 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445211	02/12/2008	8,195,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL : $	420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-58649

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **596** DE

FECHA **30 DE SEPTIEMBRE DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **30 DE DICIEMBRE DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ___X___

US005702716A

United States Patent [19]

Dunn et al.

[11] Patent Number: 5,702,716

[45] Date of Patent: *Dec. 30, 1997

[54] **POLYMERIC COMPOSITIONS USEFUL AS CONTROLLED RELEASE IMPLANTS**

[75] Inventors: **Richard L. Dunn**; **Arthur J. Tipton**, both of Fort Collins, Colo.

[73] Assignee: **Atrix Laboratories, Inc.**, Fort Collins, Colo.

[*] Notice: The portion of the term of this patent subsequent to Jul. 3, 2007, has been disclaimed.

[21] Appl. No.: **70,498**

[22] Filed: **Jun. 2, 1993**

Related U.S. Application Data

[63] Continuation of Ser. No. 776,816, Oct. 15, 1991, abandoned.

[51] **Int. Cl.**[6] **A61K 9/20**

[52] **U.S. Cl.** **424/422**; 424/423; 424/424; 424/426; 424/427; 424/430; 424/434; 424/437; 523/105; 523/113

[58] **Field of Search** 424/484, 422, 424/423, 424, 426, 427, 430, 434, 437; 523/113, 105

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Primary Examiner—Raj Bawa, Ph.D.
Attorney, Agent, or Firm—Merchant, Gould, Smith, Edell, Welter & Schmidt

[57] **ABSTRACT**

The invention is directed to an improved system for controlled release of biologically active materials and to a liquid composition for its formation. The liquid composition is composed of a thermoplastic polymer, rate modifying agent, bioactive material and organic solvent. The liquid composition is capable of forming a biodegradable and/or bioerodible microporous, solid polymer matrix. The matrix is useful as an implant in patients (humans and animals) for delivery of biologically active substances to tissues or organs.

8 Claims, No Drawings

space into which the composition is placed. When the polymer system is formed outside the body it can be molded or adapted into substantially the appropriate shape of the cavity or other space of the body into which it is being fitted.

Pursuant to the parameters and conditions of the invention, the polymer system can control the sustained release of biologically active materials in vivo. In particular, the rate and extent of release of the biologically active material from the polymer system of the invention are controlled over a range of speeds and amounts. This control is accomplished by variation of: (a) the polymer type and molecular weight, (b) the rate modifying agent, (c) the concentration of the polymer, (d) concentration of the biologically active material, (e) the form of the biologically active material, and (f) the concentration and kinds of other additives present, if any, within the polymer system. Preferably, the rate and extent of release of bioactive material from the polymer system according to the invention can be controlled by varying: (1) the type and molecular weight of the polymer or polymers, (2) the concentration of a suitable rate modifying agent, or a mixture of rate modifying agents and/or (3) the concentration of the polymer. More preferably, the control is accomplished by varying the molecular weight of the polymer and/or the concentration of the rate modifying agent present. Most preferably, the control is accomplished by varying both the molecular weight of the polymer and the concentration of the rate modifying agent. In preferred embodiments, the rate of release increases as polymer molecular weight increases, and independent of the polymer molecular weight, the rate of release increases as the concentration of the rate modifying agent decreases.

The method of the invention is based upon the therapeutic effect of the in situ controlled release of the bioactive material from the polymer system. The implantation of the liquid composition or implantation of the polymer system preformed as described above can generally occur anywhere within the body of a patient in need of therapeutic treatment. Examples include soft tissue such as muscle or fat; hard tissue such as bone; or a cavity or pocket such as the periodontal, oral, vaginal, rectal, nasal, or the cul-de-sac of the eye. The composition can be administered to the implant site by any suitable method for applying a liquid, as for example, by means of a syringe, needle, cannula or catheter. The polymer system preformed as an implant can be inserted by known surgical techniques.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a polymer system for the controlled delivery of bioactive materials, a liquid composition for producing such a system, and a method for use of such a system in therapeutic treatment. The polymer system of the present invention is advantageous in that it can be manipulated to control the amount of bioactive material released and the rate at which it is released in vivo.

The polymer system is prepared by combining the liquid composition and an aqueous medium to coagulate the composition into a solid, microporous polymeric matrix. The liquid composition contains a thermoplastic polymer or copolymer in combination with a suitable solvent and rate modifying agent. The polymers or copolymers, which form the body of the matrix, are substantially insoluble, preferably essentially completely insoluble, in water and body fluids. The insolubility of the matrix body enables it to function as a single site for the controlled release of bioactive material. The polymers or copolymers also are biocompatible and biodegradable and/or bioerodible within the body of an animal, e.g., mammal. The biodegradation enables the patient to metabolize the polymer matrix so that it can be excreted by the patient without the need for further surgery to remove it. Because the liquid composition and polymer system are biocompatible, the insertion process and the presence of the polymer system within the body do not cause substantial tissue irritation or necrosis at the implant site.

The liquid composition can be administered as a liquid directly into body tissues or cavities wherein an implant of the polymer system is formed in situ. Alternatively, the liquid composition can be externally combined with an aqueous medium to form an implantable polymer system. The implantable polymer system is then inserted surgically into the body.

Thermoplastic Polymer

Suitable thermoplastic polymers for incorporation as the solid matrix of the controlled release polymer system are solids, pharmaceutically compatible and biodegradable by cellular action and/or by the action of body fluids. Examples of appropriate thermoplastic polymers include polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid) polymers, polymaleic anhydrides, poly(methylvinyl) ethers, poly(amino acids), chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures of the above materials.

Preferred materials are the polylactides, polyglycolides, polycaprolactones, and copolymers thereof. These polymers can be used to advantage in the polymer system in part because they show excellent biocompatibility. They produce little, if any, tissue irritation, inflammation, necrosis, or toxicity. In the presence of water, these polymers produce lactic, glycolic, and hydroxycaproic acid, respectively, which are readily metabolized by the body. The polylactides and polycaprolactones can also incorporate glycolide monomer to enhance the resulting polymer's degradation.

Depending on the desired softness and flexibility of the implant rate and extent of bioactive material release, rate of degradation, and the like, the amount and type of polymer can be varied to produce the desired result. For example, for a relatively soft and flexible polymer system, copolymers with a low Tg can be used, primarily the lactide/caprolactone copolymers. The ratio of glycolide to lactide or to caprolactone can also be varied to effect water diffusibility, which increases with an increasing amount of the more hydrophilic monomer. The hydrophilic character of these monomers increases in the series as caprolactone <lactide<glycolide.

The solubility or miscibility of a thermoplastic polymer in the organic solvent of the composition will vary according to factors such as crystallinity, hydrophilicity, capacity for hydrogen bonding and molecular weight of the polymer. Consequently, the molecular weight and the concentration of the polymer in the solvent are adjusted to achieve desired miscibility, as well as a desired release rate for the incorporated bioactive material. Highly preferred thermoplastic polymers are those having solubility parameters such as a low degree of crystallization, a low degree of hydrogen bonding, low solubility in water, and high solubility in organic solvents.

According to the practice of the invention, the liquid composition of thermoplastic polymer, solvent, rate modifying agent and bioactive material is a stable liquid substance. Depending on the bioactive material and solvent chosen, either a homogenous solution of the bioactive material in organic solvent, or a suspension or dispersion of the bioactive material in the solvent results. In either case, the thermoplastic polymer is substantially soluble in the organic solvent. Upon placement of the liquid composition into the aqueous medium inside or outside the body, the solvent will dissipate and the polymer will solidify to form the polymer system having the bioactive material within a solid polymeric matrix.

Organic Solvents

The solvents used in the thermoplastic compositions of the present invention are preferably pharmaceutically acceptable, water-miscible, and biocompatible. Preferably, they cause relatively little, if any, tissue irritation or necrosis at the site of the injection and implantation. The solvent is water-miscible so that it will quickly disperse from the polymeric composition into the aqueous medium such as body fluids. Concomitant with the dispersion of solvent the thermoplastic polymer coagulates into the solid polymer system. As the thermoplastic polymer coagulates, the solvent dispersion causes pore formation within the polymer system. As a result, the liquid composition containing thermoplastic polymer, solvent, rate modifying agent and bioactive substance alone will form a porous solid polymer system.

Suitable solvents include those liquid organic compounds meeting the foregoing criteria. Examples include, but are not limited to, N-methyl-2-pyrrolidone (NMP); 2-pyrrolidone (2-pyrol); C_2–C_6 alkanols; 2-ethoryethanol; alkyl esters such as 2-ethoxyethyl acetate, methyl acetate, ethyl acetate, propylene carbonate, ethyl lactate; ethylene glycol dimethyl ether; propylene glycol; alkyl ketones such as acetone, methyl ethyl ketone; dimethylformamide; dimethyl sulfoxide; dimethyl sulfone; tetrahydrofuran; cyclic alkyl amides such as caprolactam; decylmethyl sulfoxide; oleic acid; N,N-dimethyl-m-toluamide; and 1-dodecylazacycloheptan-2-one. The preferred solvents are, N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, propylene carbonate and ethyl lactate due, at least in part, to their solvating ability and their biocompatibility.

The solvents for the thermoplastic polymer liquid compositions of the present invention are chosen for compatibility and appropriate solubility of the polymer and solvent. Lower molecular weight thermoplastic polymers will normally dissolve more readily in the solvents than high molecular weight polymers. As a result, the concentration of a thermoplastic polymer dissolved in the various solvents differs depending upon type of polymer and its molecular weight. Conversely, the higher molecular weight thermoplastic polymers will tend to coagulate or solidify faster than the very low molecular weight thermoplastic polymers. Moreover, the higher molecular weight polymers tend to give higher solution viscosities than the low molecular weight materials. Thus, for advantageous injection efficiency, in addition to advantageous release rate, the molecular weight and the concentration of the polymer in the solvent are controlled.

A solvent mixture can be used to increase the coagulation rate of thermoplastic polymers that exhibit a slow coagulation or setting rate. In such a system one component of the mixture is typically a good solvent for the thermoplastic polymer, and the other component is a poorer solvent or a nonsolvent. The two liquids are mixed at a ratio such that the thermoplastic polymer is still soluble, but precipitates with the slightest increase in the amount of nonsolvent, such as water in a physiological environment. By necessity, the solvent system must be miscible with both the thermoplastic polymer and water. An example of such binary solvent system is the use of NMP and ethanol for low molecular weight DL-PLA. The addition of ethanol to the NMP/polymer solution increases its coagulation rate significantly.

Polymer Molecular Weight

It has been discovered that the molecular weight of the polymer used in the present invention distinctly affects the rate of bioactive material release as long as the liquid composition has been used as an intermediate. Under these conditions, as the molecular weight of the polymer increases, the rate of bioactive material release from the system decreases, passes through a minimum, and then increases again. This phenomenon can be advantageously used in the formulation of systems for the controlled release of various bioactive materials. For relatively quick release of a bioactive material, polymer molecular weight on either side of the minimum for that particular polymer can be chosen to provide the desired release rate. For release of a bioactive material over a relatively long period of time, a polymer molecular weight in the vicinity of the minimum for the particular polymer can be chosen.

Prior to the present invention, it was known that for most, if not all, polymers, the higher the molecular weight of a polymeric composition, the slower the rate of bioactive material release. This was believed to be a result of chain entanglements in the higher molecular weight polymer, which were believed to slow down the diffusion of drug molecules through the polymer matrix. In contrast, it has been surprisingly discovered that for polymer matrices formed through intermediacy of the liquid composition of the invention, the release rate of a bioactive substance follows a "U" shaped curve as the molecular weight of the polymer increases. Accordingly, a polymer system can be produced with an optimum polymer molecular weight range for the release of bioactive substances over a selected length of time.

For the polymer system of the present invention, the typical minimum rate of release of the incorporated bioactive material occurs at an inherent viscosity (I.V. in deciliters/gm) of about 0.2 but can vary depending on the particular components of the composition. For most systems it is preferred to adjust the molecular weight of the polymer to at least about 0.2 I.V. (15,000 molecular weight as determined by gel permeation chromatography in comparison to polystyrene) for a more sustained release of the bioactive material. Typically, acceptable sustained release rates are obtained if the molecular weight is below about 0.8 I.V. (100,000 molecular weight). More preferably, the molecular weight is adjusted to be within a range of about 0.2–0.5 I.V., for effective sustained release. For a poly(DL-lactide) or a lactide-co-glycolide system, as discussed below, the desired molecular weight range is about 0.2–0.5 I.V. If a molecular weight of a specific polymer is chosen from these parameters and the release of the bioactive substance is too slow or too fast, the rate can be varied simply by determining a few experimental points along the U curve for that polymer and adjusting the molecular weight accordingly.

The molecular weight of a polymer can be varied by any of a variety of methods. The choice of method is typically determined by the type of polymer composition. For

example, if a thermoplastic polymer is used that is biodegradable by hydrolysis, the molecular weight can be varied by controlled hydrolysis, such as in a steam autoclave. Typically, the degree of polymerization can be controlled, for example, by varying the number and type of reactive groups and the reaction times.

Rate Modifying Agents

It has been discovered that under the conditions of the invention, rate modifying agents provide significantly improved control to the sustained release character of the polymer system of the present invention. The combination of a rate modifying agent and matrix polymer as influenced by the interaction of the liquid composition with an aqueous medium according to the present invention has the surprising effect of retarding the release of the bioactive material. This effect contrasts with the knowledge and belief in the art. Under typical, known circumstances, which do not result from the interaction of the liquid composition and an aqueous medium, use of a rate modifying agent within a sustained release matrix will only increase the rate of release of the pharmaceutical compound within the matrix. Thus, under most known circumstances, it is difficult, if not impossible, to slow down or retard the release of a medicament from an implant.

As practiced according to the present invention, the use of a rate modifying agent in the polymer system of the present invention can be adapted to cause a decrease in the range of multiple orders of magnitude (e.g., 1 to 10 to 100), preferably up to a ten-fold decrease, in the release rate of the bioactive material relative to that of the same polymer matrix without the rate modifying agent. For example, naltrexone and doxycycline are substantially completely released from a polymer matrix of poly(DL-lactide) within about two to three days in vitro. With the addition of a rate modifying agent (e.g., ethyl heptanoate) and formation of the polymer system through interaction of the liquid composition and an aqueous medium, the release rate can be slowed to produce substantially complete release of the drug within about seven days. With the use of a greater amount of rate modifying agent according to the invention, the period of time can be increased to about fourteen days. By appropriate choice of the polymer molecular weight in optional combination (i.e., from none to significant proportions) with the rate modifying agent, the rate and extent of bioactive material release from the polymer system can be varied from very fast to very slow.

Rate modifying agents useful in the invention are typically miscible with the polymer. That is, the rate modifying agent and polymer are chosen for a particular composition such that the intermolecular forces of each are similar. Rate modifying agents can be either water-soluble or water-insoluble. Preferably, they are water-insoluble, i.e., immiscible. The specific rate modifying agent chosen for a polymer system is preferably more hydrophobic than the organic solvent of choice for that polymer system. It is also preferably a high boiling liquid.

Although it is not intended to be a limitation of the invention, it is believed the rate modifying agent affects the release rate of the polymer system of the present invention by causing the formation of a heretofore unknown distinctive macromolecular structure within the skin and core of the implant as the implant is formed. The distinctive structure is believed to slow down the cross-diffusion of bioactive material and body fluid. It is believed to be absent from implants formed without rate modifying agent or those containing rate modifying agent but which are not prepared through the intermediacy of the liquid composition. Irrespective of the mechanism of action, the effect controls the release characteristics of the polymer system of the invention.

The rate modifying agent chosen typically imparts to an implant a glass transition temperature (Tg) of less than about 55° C., preferably less than about 50° C., and more preferably less than about 37° C. such that the implant is soft, resilient, and flexible in the body.

The rate modifying agents used in the present invention are pharmaceutically acceptable. Typically, the rate modifiers are organic compounds that substitute as the complementary molecules for secondary valence bonding that typically occurs between polymer molecules. Such compounds increase the flexibility and ability of the polymer molecules to slide past each other. The chemical formulas of such compounds will exhibit hydrophobic and hydrophilic regions so as to effect secondary valence bonding. Such organic compounds are often characterized as "plasticizers". However, typical "plasticizers" are not the only compounds that function as rate modifying agents in the polymer system of the present invention to control the rate of release of a bioactive material. Other useful rate modifying agents include fatty acids, triglycerides, other hydrophobic compounds and some organic solvents.

Specific examples of rate modifying agents include, but are not limited to esters of mono-, di-, and tricarboxylic acids, such as 2-ethoxyethyl acetate, methyl acetate, ethyl acetate, diethyl phthalate, dimethyl phthalate, dibutyl phthalate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, glycerol triacetate, di(n-butyl) sebecate, and the like; polyhydroxy alcohols, such as propylene glycol, polyethylene glycol, glycerin, sorbitol, and the like; fatty acids; triesters of glycerol, such as triglycerides, epoxidized soybean oil, and other epoxidized vegetable oils; sterols, such as cholesterol; alcohols, such as C_6–C_{12} alkanols, 2-ethoxyethanol, and the like. Mixtures of rate modifying agents, such as glycerin/propylene glycol, sorbitol/glycerine, ethylene oxide/propylene oxide, and butylene glycol/adipic acid, can also be used in the polymer systems of the invention.

The choice of rate modifying agent employed depends on the mixture of polymers and the solvent in the thermoplastic system. Preferred rate modifying agents include dimethyl citrate, triethyl citrate, ethyl heptanoate, glycerin, and hexanediol.

The quantity of rate modifying agent in the system will vary depending on the release rate of the medicament desired. Typically, the rate modifying agent is present in an amount up to about 15%, preferably up to about 10%, based upon the total weight of the system.

Polymer Concentration

The concentration of the polymer in the system can also be varied to adjust the release rate of the incorporated bioactive material. It has been discovered that the more dilute the polymer concentration, the more readily the bioactive material will be released. For example, in a system containing 5 percent flurbiprofen and a polymer concentration of 55 percent poly(DL-lactide), a cumulative release of approximately 11.4 percent at day 1 and 23 percent at day 7 is seen. With a polymer concentration of 45 percent, the cumulative percent release at day 1 is 23 percent and about 40 percent at day 7.

This effect can be used in combination with other methods to more effectively control the release of the incorporated

medicament as desired. For example, by adjusting the concentration of the polymer, and bioactive material if desired, along with the control of the molecular weight and the amount of rate modifying agent, a wide range of release rates can be obtained.

Pore-Forming Agents

Other additives can be used to advantage in further controlling the desired release rate of a bioactive material for a particular treatment protocol. For example, if the thermoplastic polymer liquid composition is too impervious to water, a pore-forming agent can be added to generate additional pores in the matrix. Any biocompatible water-soluble material can be used as the pore-forming agent. These agents can be either soluble in the liquid composition or simply dispersed within it. They are capable of dissolving, diffusing or dispersing out of both the coagulating polymer matrix and the formed polymer system whereupon pores and microporous channels are generated in the matrix and system. The amount of pore-forming agent (and size of dispersed particles of such pore-forming agent, if appropriate) within the composition will directly affect the size and number of the pores in the polymer system.

Other factors can also influence the size and/or diameter of the pores formed in the polymer system. For example, the amount of organic solvent, and the rate at which the polymer system solidifies, can all affect the porosity of the polymer system. Although a generally microporous matrix without a resolved core and skin can be produced according to the invention, typically, without an additional pore-forming agent a polymer system formed from the liquid composition is composed of a surface skin and inner core. The surface skin is typically less porous, and even relatively nonporous, when compared to the inner core. The inner core can contain pores with a diameter of about 10–1000 um. With additional pore-forming agent, the pore sizes of the core and skin become substantially uniform such that they both have pores in the range of 10 to 1000

The concentration of pore-forming agent relative to thermoplastic polymer in the composition will vary according to the degree of pore-formation desired. Generally, this concentration will range from about 0.01 to 1 gram of pore-forming agent per gram of polymer. If the agent is soluble in the liquid composition, then the mixing or distribution of the agent in the liquid composition and the aggregation when the thermoplastic coagulates will determine the size of the resultant pores as the agent dissolves out of the polymer matrix.

Pore-forming agents include, any pharmaceutically acceptable organic or inorganic substance that is substantially miscible in water and body fluids and will dissipate from the forming and formed matrix into aqueous medium or body fluids or water-immiscible substances that rapidly degrade to water-soluble substances. The pore-forming agent may be soluble or insoluble in the polymer liquid composition of the invention. In the liquid composition of the invention, it is further preferred that the pore-forming agent is miscible or dispersible in the organic solvent to form a uniform mixture. Suitable pore-forming agents include, for example, sugars such as sucrose and dextrose, salts such as sodium chloride and sodium carbonate, and polymers such as hydroxylpropylcellulose, carboxymethylcellulose, polyethylene glycol, and polyvinylpyrrolidone. The size and extent of the pores can be varied over a wide range by changing the molecular weight and percentage of pore-forming agent incorporated into the polymer system.

Bioactive Materials

The terms "drug," "medicament," or "bioactive material" (i.e., biologically active material) as used herein include, biologically, physiologically, or pharmacologically active substances that act locally or systemically in the human or animal body. Various forms of the medicaments or biologically active materials can be used which are capable of being released from the polymer matrix into adjacent tissues or fluids. The medicaments are at least very slightly water-soluble, preferably moderately water-soluble, and are diffusible through the polymeric composition. They can be acidic, basic, or salts. They can be neutral molecules, polar molecules, or molecular complexes capable of hydrogen bonding. They can be in the form of ethers, esters, amides and the like, which are biologically activated when injected into the human or animal body.

Generally, any drugs or bioactive materials that can be dissolved or dispersed in an aqueous environment can be utilized in the liquid composition and polymer system of the present invention. For example, the bioactive material can be a penicillin or cephalosporin antibiotic, a hormone such as ACTH, estrogen or testosterone, a protein such as a monoclonal antibody or an essential human or animal enzyme, insulin or an insulin precursor, a vaccine or serum substance useful in the treatment of viral diseases, an activator or inhibitor of a specific enzyme, a releasing factor for a physiologically active substance, or any other suitable substance.

Representative drugs or bioactive materials that can be used in the injectable sustained release compositions of the present invention include, but are not limited to, peptide drugs, protein drugs, such as enzymes, insulin, interleukin, platelet anticoagulating agent, hormones, calcitonin, vasopressin, desensitizing agents, bronchodilating agents, anti-infective agents, antibiotics, antimicrobial agents, anti-allergenics, androgenic steroids, decongestants, hypnotics, steroidal and nonsteroidal anti-inflammatory agents, anticholinergics, sympathomimetics, sedatives, miotics, steroids, corticosteroids, regulatory agents, nephritic agents, psychic energizers, tranquilizers, vaccines, estrogens, progestational agents, humoral agents, prostaglandins, analgesics, antispasmodics, antimalarials, antihistamines, cardioactive agents, male and female birth control agents, tissue growth factors, antiparkinsonian agents, antihypertensive agents, α-adrenergic blocking agents, nutritional agents, and alkaloid pharmaceutical agents.

The bioactive material may also be a substance, or metabolic precursor thereof, which is capable of promoting growth and survival of cells and tissues, or augmenting the activity of functioning cells, as for example, blood cells, neurons, muscle, bone marrow, bone cells and tissues, and the like. For example, the bioactive material may be a nerve growth promoting substance, as for example, a ganglioside, phosphatidylserine, a nerve growth factor, brain-derived neurotrophic factor, a fibroblast growth factor, and the like. In particular, the in situ implants are capable of enhancing regeneration of the periodontium by providing an outer surface having a porosity which serves as a physical barrier between an exposed root surface and encroaching epithelial cells to promote guided tissue regeneration.

To promote tissue growth, the biologically active material may be a tissue growth factor substance. Suitable tissue growth promoting agents include, for example, fibronectin (FN), endothelial cell growth factor (ECGF), cementum attachment extracts (CAE), human growth hormone (HGH), a periodontal ligament cell growth factor, animal growth

and a pharmaceutically acceptable organic solvent in which the thermoplastic polymer, biologically active agent and rate-retarding agent are dissolved or dispersed, the organic solvent being miscible to dispersible in aqueous medium or human or animal body fluids;

the combining step or administering step resulting in diffusion of the organic solvent into the aqueous medium or body fluid and resulting in coagulation of the thermoplastic polymer to form the solid microporous matrix;

the thermoplastic polymer being selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyothoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), and copolymers, terpolymers and any combination thereof, and the thermoplastic polymer having a molecular weight up to about 0.8 inherent viscosity; and,

the rate-retarding agent being selected from the group consisting of an ester of a mono, di or tricarboxylic acid, a polyhydroxy alcohol, a fatty acid, a fatty acid ester, an epoxidized oil, a sterol, a higher alkyl alcohol, and any mixture thereof.

2. A system according to claim 1 wherein the rate-retarding agent is less water-soluble than the organic solvent.

3. A system according to claim 1 wherein the solvent is selected form the group consisting of N-methyl-2-pyrrolidone, 2-pyrrolidone, ethanol, propylene glycol, acetone, acetic acid, ethyl acetate, ethyl lactate, methyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, dimethyl sulfone, tetrahydrofuran, propylene carbonate, caprolactam, decylmethylsulfoxide, oleic acid, N,N-diethyl-m-toluamide, and t-dodecylazacycloheptan-2-one, and any combination thereof.

4. A system according to claim 1 wherein the rate-retarding agent is selected from the group consisting of ethyl heptanoate, glycerin, diethyl citrate, and triethyl citrate.

5. A system according to claim 1 further comprising a pore forming agent.

6. A system according to claim 1 wherein the matrix comprises a core and skin, the core being microporous and the skin having pores of substantially smaller size than the core.

7. A system according to claim 1 wherein the thermoplastic polymer is polylactide, polyglycolide, polycaprolactone or a copolymer of any combination of lactide, glycolide and caprolactone monomer.

8. A composition suitable for formation of a controlled release implant for use in a patient, comprising:

a) a pharmaceutically acceptable, biodegradable thermoplastic polymer that is insoluble in aqueous medium or human or animal body fluid;

b) a biocompatible organic solvent that is miscible to dispersible in water or human or animal body fluids;

c) a biologically active compound;

d) up to about 15% by weight of a pharmaceutically acceptable, water-insoluble, rate-retarding agent which remains in the implant after the formation of the implant from the composition, which imparts a Tg to the implant of less than about 55° C., and which retards the rate of release of the biologically active compound from the implant up to 100 fold relative to the rate of release of the biologically active compound from the same implant without the rate-retarding agent when the implant is made externally or in situ respectively by combining the composition and the aqueous medium or by administering the composition directly to a body tissue or cavity having the human or animal body fluids, the weight being relative to the sum of the weights of the thermoplastic polymer, the biologically active agent and the rate retarding-agent:

the combining step or administering step resulting in diffusion of the organic solvent into the aqueous medium or body fluid and resulting in coagulation of the thermoplastic polymer to form the solid microporous matrix:

the thermoplastic polymer being selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyothoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), and copolymers, terpolymers and any combination thereof and the thermoplastic polymer having a molecular weight up to about 0.8 inherent viscosity; and,

the rate-retarding agent being selected from the group consisting of an ester of a mono, di or tricarboxylic acid, a polyhydroxy alcohol, a fatty acid, a fatty, acid ester, an epoxidized oil, a sterol, a higher alkyl alcohol, and any mixture thereof.

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 539 751 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **92116802.7**

(22) Date of filing: **01.10.92**

(51) Int. Cl.5: **A61K 9/00**, A61K 9/16, A61K 47/34, A61L 27/00

(30) Priority: **28.10.91 US 783512**

(43) Date of publication of application: **05.05.93 Bulletin 93/18**

(84) Designated Contracting States: **AT BE CH DE DK ES FR GB IE IT LI LU NL SE**

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(54) Biodegradable polymer composition.

(57) The invention is directed to a composition composed of a thermoplastic or thermosetting polymer which is capable of forming a biodegradable and/or bioerodible microporous, solid or gelatinous polymer matrix. The matrix is useful as an implant in animals for enhancing regeneration of cells and tissue, such as bone and nerve cells, or for delivery of biologically-active substances to tissue or organs. The composition is administered to an implant site as a liquid. The invention also includes a method of preventing and treating disorders and diseases, such as bone or nerve growth disorders, or of altering body functions such as birth control, using the compositions and implants of the invention.

EP 0 539 751 A1

(19) OFICINA ESPAÑOLA DE PATENTES Y MARCAS

ESPAÑA

(11) Número de publicación: **2 284 211**

(51) Int. Cl.:
A61K 9/00 (2006.01)
A61K 9/20 (2006.01)

(12) TRADUCCIÓN DE PATENTE EUROPEA T3

(86) Número de solicitud europea: **98936136 .5**
(86) Fecha de presentación : **05.06.1998**
(87) Número de publicación de la solicitud: **0996426**
(87) Fecha de publicación de la solicitud: **03.05.2000**

(54) Título: **Sistema multifásico.**

(30) Prioridad: **05.06.1997 DE 197 24 784**
13.03.1998 DE 198 11 951

(45) Fecha de publicación de la mención BOPI:
01.11.2007

(45) Fecha de la publicación del folleto de la patente:
01.11.2007

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ES 2 284 211 T3

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Advanced Drug Delivery Reviews 56 (2004) 1453–1466

Advanced
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Biodegradable polymers and their potential use in parenteral veterinary drug delivery systems

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Received 22 July 2003; accepted 18 February 2004

Abstract

Biodegradable polymers have been extensively studied for numerous drug delivery systems for human health purposes. The ever-increasing value of animals to human society allows the application of pharmaceutical developments in the veterinary field from those developed in human medicine. Although many similarities between the human and animal health industries exist there are also notable differences. This paper provides an insight into the animal health market with regard to the challenges and special considerations associated with veterinary drug delivery. It also gives an overview of biodegradable polymers that are used or have been tested in the veterinary field. The purpose of this paper is to highlight some recent developments in this area and to investigate the directions in which veterinary pharmaceutics is heading. In particular, examples of existing biodegradable veterinary drug delivery systems are presented together with applications including intravaginal devices, injectables and implantable systems.

Keywords: Biodegradable polymers; Veterinary drug delivery; Therapeutic applications

Contents

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0169-409X/$ - see front matter
doi:10.1016/j.addr.2004.02.008

In recent years biodegradable veterinary drug delivery systems such as microspheres, implants and in-situ forming implants have been tested in the area of estrus control [7], growth promotion [5], control of ectoparasites [8] and vaccine delivery [9].

Biodegradable polymers, which allow delivery of a range of bioactive materials with high bioavailability, have demonstrated their potential for veterinary application. However, presently only a few biodegradable drug delivery systems are commercially available for veterinary use. Among other reasons, the final price of the device, followed by regulatory considerations and challenges in formulation stability, have limited the development of such delivery devices.

It is the intention of this chapter to give an overview of biodegradable polymers, which are used or have been tested in the veterinary field. The paper will highlight some recent developments in this area and will look into the future to examine the directions in which veterinary pharmaceutics is heading. Examples of currently available and future biodegradable veterinary drug delivery systems will be presented and explained including intravaginal devices, injectables and implantable systems.

2. Biodegradable polymers for veterinary applications

The most attractive and commonly used biodegradable polymers are polyesters such as poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA) and poly(ε-caprolactone (PCL) (Table 1). These materials are commercially available in different compositions and molecular weights which allow control of degradation of the polymer [10,11].

The term degradation designates the process of polymer chain cleavage which leads to a loss in molecular weight. Degradation induces the subsequent erosion of the material which is defined as mass loss of material due to the process of polymer chain cleavage [12].

For degradable polymers two different erosion mechanisms have been proposed: homogeneous or bulk erosion, and heterogeneous or surface erosion [13]. The difference is illustrated in Fig. 1. Bulk-eroding polymers degrade all over their cross-section because the penetration of water into the polymer bulk is faster than degradation of polymer. In surface-eroding polymers, in contrast, degradation is faster than the penetration of water into the bulk. In consequence these polymers erode mainly from their surface. However, for most polymers, erosion has features of both mechanisms. The erosion mechanism has consequences for the mechanism of drug release which has been classified into diffusion-, swelling- and erosion-controlled.

A biodegradable polymer device might release the drug by all three mechanisms and the fastest mechanism dominates (Fig. 2). In the case of biodegradable polyesters, which consist of monomers connected to each other by ester bonds, degradation starts after penetration of water into the device. The breakage of ester bonds occurs randomly via hydrolytic ester cleavage and leads to the subsequent erosion of the device. The hydrolysis rate is influenced by molecular weight, copolymer ratio, polydispersity and crystallinity, and all these factors can be used to control drug release. For example, poly(ε-caprolactone), which is a highly hydrophobic and crystalline polyester, degrades very slowly compared to amorphous less hydrophobic PLGA. Depending on these variables the degradation time varies from several weeks up to years and allows the release of drugs over this time period. However, the achievement of controlled drug release from polyester-based delivery systems is difficult because these polymers undergo bulk erosion which changes the polymer matrix and influences drug release. As a consequence, drug release is controlled by swelling, drug diffusion and polymer erosion, which is not straight forward to predict [10,14,15].

The above-mentioned polyesters have one characteristic in common: the hydrolytic sensitive groups are located in the polymer backbone. This feature stimulated the development of a new class of biodegradable polymers based on tartaric acid which, in addition to ester bonds in the backbone, has ketal bonds in the polymer side chains [16] (Table 1). These so-called "polytartrates" seem to be promising due to the modification in the polymer structure. Early experiments demonstrated the suitability of described polytartrates for controlled release applications [17]. However, until now these polytartrates have not received commercial status and little information is available about this polymer class [18].

the application of gonadotropin-releasing hormone (GnRH) analogs. PLGA is the most frequently studied polymer in this field and microparticles [33], extruded implants [34,35] or in-situ formed implants [36,37] prepared from various types of these polymers containing GnRH analogs were successfully used for chemical castration in dogs for 1–6 months.

Other polymers that were investigated for reproduction control in veterinary field are polyanhydrides. To induce ovulation and spermiation in fish p(FAD-SA) microspheres containing a gonadotropin-releasing hormone (GnRH) analog (D-Ala^6, Pro^{9}NEt-GnRH) were prepared by a double emulsion technique [38]. Two commercially important fish, the striped bass and the Atlantic salmon, were treated. All female fish ovulated either within 11 days (Striped bass) or 15 days (Atlantic salmon) after microsphere administration and were also effective in enhancing sperm production in male fish.

However, scaling up commercial microsphere production to meet the demands of the animal market is a very complex process which requires costly facilities, water systems and equipment [5].

More cost effective delivery systems compared to microspheres are implants formed in-situ. The technology is based on the fact that biodegradable polymers like PLGA spontaneously form solid depots when a solution of the polymer is injected into water. First, the polymer is dissolved in a pharmaceutically acceptable solvent such as *N*-methyl-2-pyrrolidone (NMP) or benzoyl benzoate. Thereafter the solution is mixed with the active pharmaceutical ingredient and the resulting solution or suspension can be easily injected either subcutaneously or intramuscularly using a small gauge needle [7,39].

After injection displacement of the carrier with water in the tissue fluids causes the polymer to precipitate to form a solid film or implant (Atrigel technology™). The drug encapsulated within the implant is then released in a controlled manner as the polymer matrix biodegrades with time. The timeframe of the release can be adjusted using different formulation variables, chiefly by altering the polymer composition and molecular weight [40]. The Atrigel technology™ was recently investigated for the controlled release of leuprolide in rats and dogs [36,37]. Serum testosterone and leuprolide levels showed no significant difference in the pharmacologic efficacy compared to marketed leuprolide-containing microspheres (Lupron Depot™). Due to the simple manufacturing technique this technology is more cost effective than marketed microspheres and implant products and appears promising for product development. However, NMP which is often used as solvent for PLGA causes pain reactions during the application and therefore alternative solvents would be beneficial for veterinary use [7].

Viscous poly(ortho esters) allow subcutaneous injection and avoid the need for organic solvents. Recently, a low molecular weight POE, containing 30% of lactic acid units in the polymer backbone (POE70LA30) was used for estrus synchronization in sheep [41]. Fluorogestone acetate (FGA), a potent synthetic progestagen, which is used in several non-degradable intravaginal inserts or sponges, was added to POE70LA30 (1.5 and 3% w/w) by mixing. The addition of 20% poly(ethylene glycol) increased the syringeability of the formulation and the cumulative release. Nevertheless, FGA was released slowly and almost constantly and only 29% of incorporated FGA was released in vitro after 14 days. In vivo testing in sheep is currently in progress to determine the efficacy of the POE-based formulation.

3.2. Biodegradable delivery systems for the control of ectoparasites

The control of ectoparasites such as fleas, flies, ticks and mites is of great importance in the animal health market. In livestock animals infection with ectoparasites leads to animal suffering and hence to weight loss and reduced milk production which ultimately affects the productivity. In companion animals ectoparasites cause skin diseases which affect the well-being of the animals. The research and development costs for the discovery of new chemical entities to control parasites in both livestock and companion animals have increased significantly. In parallel, advances have been made in the development of biodegradable drug delivery systems [42]. For such delivery systems drug substances which are highly efficient at extremely low dosages are ideal candidates such as ivermectin, a semi-synthetic macrocyclic lactone [43].

Ivermectin containing microspheres were obtained by a solvent evaporation technique using PLGA,

status and has been launched in New Zealand (SmartShot™) [80]. The formulation continuously releases the vitamin over a period of more than 20 days.

Other interesting polymers for veterinary application are injectable semi-solid poly(ortho esters). A paper has recently reviewed their potential in human as well as animal health [22] and one possible application for companion animals is the treatment of gastrointestinal disorder (GD) in dogs.

Metoclopramide is a useful agent in treating and preventing various types of vomiting, which is one characteristic of GD. Due to the short biological half-life it is usually administered up to four times daily orally in order to maintain therapeutic concentration over the whole day [81]. To prevent fluctuation of plasma levels, which produces adverse reactions especially in long-term therapy, as well as to improve the compliance, a slow release formulation for 3–5 days would be beneficial. This was achieved using a viscous POE to which the drug was added by simple mixing. Preliminary pharmacokinetic results in dogs showed sustained plasma concentration for up to 30 h. Further development is necessary to prolong the period of drug release.

4. Conclusion and perspectives of biodegradable polymers for veterinary application

Biodegradable polymers have proven their potential for the development of new, advanced and efficient drug delivery systems. They are capable of delivering a wide range of bioactive materials for a broad range of veterinary applications.

Suitable therapeutic agents for such biodegradable drug delivery systems are generally those that need to be administered over a long period of time, which are highly active or have a short biological half life such as peptides and proteins.

In the last two decades technological advances have made the production of biodegradable delivery systems more practical and economical. However, until now only a few biodegradable delivery systems have entered the market in both the human and veterinary areas.

The reasons are obvious. At first many drugs such as peptides and proteins are sensitive to heat, shear forces or organic solvents. Such conditions are required for most of the manufacturing processes of classical biodegradable delivery systems such as microspheres or implants. Thus solvent free and gentle methods are of significant interest to avoid stability problems during manufacture. Furthermore polymers which allow the incorporation of sensitive and/or instable drugs by simple mixing, without the use of heat or solvents such as viscous poly(ortho esters) are promising. Secondly, several factors such as moisture, acidification or interactions between the polymer and drug lead to stability problems during storage and release. Last but not least the often desired zero-order release profile cannot be achieved due to the combination of diffusion and erosion processes. As a consequence, the drug release rate varies over time, especially in the case of long-term applications. Thus, a prediction of the in vivo release based on in vitro data is very difficult and a matter of concern due to the time and cost associated with the intensive experiments that are necessary to develop suitable in vitro test systems.

The most important step to overcome this problem is to fully understand the degradation mechanism of the polymer in order to allow adjustment of the release profile. Although systematic degradation studies have been performed especially with aliphatic polyesters the degradation mechanism of these polymers is still not completely understood and demands further investigations.

Nevertheless, in the future many new therapeutic agents will require parenteral application and might benefit from the advantages of biodegradable polymers. Currently promising biodegradable applications are under investigation for veterinary applications such as guided tissue regeneration, ocular diseases, single-shot vaccination, osteoarthritis and fertility control.

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Abogado: CARLOS REINALDO OLARTE

ASUNTO:

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Trámite	002
Evento	001
Actuación	430
Oficio	
Folios	

Patente de Invención ☒

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap.I ☒ Cap. II ☐

No. Solicitud Internacional PCT/EP2005/013377
Fecha de Presentación Internacional 2005-12-13

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Documentos estudiados:

Descripción: Folios 40 a 57 como se radicó inicialmente.
Reivindicaciones: Folios 58 a 61 como se radicó inicialmente.

Prioridad: EP200404029498 (2004-12-14)

Objeto de la Invención

Titulo de la invención: Implante formado IN SITU para animales

Problema Técnico Planteado: Necesidad de una composición adecuada para implantes in situ que pueda tener liberación sostenida en animales o humanos.

Solución: Composición, que comprende un polímero termoplástico, un agente modificador de velocidad y un agente biológicamente activo, útil como un implante de administración de medicamento de liberación retardada en el cuerpo de un humano o animal, que puede administrarse en forma líquida en el cuerpo.

IPC: A61K9/08

Excepciones a la Patentabilidad (Art 20 D 486 literales (a) – (d))

La reivindicación 20 establece una composición para uso en un método de implantar la composición en un cuerpo humano o animal, caracterizada en que la composición es inyectada lo cual incumple con el artículo 20 D486 en cuanto a que los métodos de tratamiento para animales o humanos no son patentables.

Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 reivindica una composición para formar un implante que comprende: un polímero, biodegradable, termoplástico; un solvente orgánico, un adyuvante biocompatible y un agente activo biológicamente.
Debido a que las denominaciones de los componentes de esta reivindicación son muy generales en cuanto a que se encuentran dentro del estado del arte muchos y diferentes tipos de polímeros, solventes, adyuvantes y agentes activos farmacéuticamente aceptables es necesario que el solicitante restrinja el objeto de la composición de acuerdo a los componentes específicos que la componen.

De igual manera la reivindicación 1 establece en su último párrafo: "...un agente activo biológicamente, caracterizado en que la cantidad en peso del solvente es más alta que la del polímero termoplástico y en que el adyuvante es seleccionado del grupo que consiste de etanol, glicerol y glicerol formal" para dicha reivindicación no se ve si "la cantidad en peso del solvente" y posteriores se refieren a la composición en general o al agente activo biológicamente, por lo tanto se sugiere se establezca mejor la redacción de la reivindicación.

Las reivindicaciones 2, 3 contienen el término "aproximadamente", dicho término no se acepta pues es impreciso, la reivindicación deja de ser clara y no permite una comparación con el estado de la técnica.

La reivindicación 10 establece una composición caracterizada porque el agente activo biológicamente es un "medicamento animal". A partir de lo anterior y teniendo en cuenta que la definición de medicamento en el ámbito farmacéutico es la combinación de 1 ó varios principios activos con excipientes para conformación de una forma farmacéutica definida mediante la utilización de tecnología farmacéutica, esta reivindicación es inexacta y debe ser modificada pues uno de los componentes de composición no puede ser un medicamento.

La reivindicación 12 establece una composición caracterizada por la presencia de un agente activo biológicamente de la fórmula (I), y describe que debe ser en una proporción 1:4; esta reivindicación no es clara en cuanto a no se especifica si esta proporción corresponde a dos compuestos ó a la proporción con respecto a los otros componentes de la composición; de igual manera, se debe establecer las proporciones de los componentes dentro de la composición.

Las reivindicaciones 15 y 17 son equivalentes por lo cual debe retirarse una de ellas del capitulo reivindicatorio.

Las reivindicaciones 18 y 19 establecen una composición caracterizada en que el implante es formado in situ dentro del cuerpo, lo cual corresponde a un resultado a alcanzar que no es una característica técnica de la invención, por lo cual se deben eliminar del capitulo reivindicatorio.

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de solicitud prioritaria 2004-12-14 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	US5702716	*Polymeric compositions useful as controlled release implants*	1997-12-30
D2	Advanced Drug Delivery Reviews 56 (2004) 1453–1466	Biodegradable polymers and their potential use in parenteral veterinary drug delivery systems	2004-02-18

D1- Composición integrada por un polímero termoplástico o termoendurecible que sea capaz de formar una matriz microporosa, sólida o gelatinosa biodegradable del polímero. La matriz es útil como implante en los animales para realzar la regeneración de células y del tejido, tal como hueso y células nerviosas, o para la entrega de sustancias biológicamente activas al tejido o a los órganos. La composición se administra a un sitio del implante como líquido.

D2- Descripción de los polímeros biodegradables que se utilizan o se han probado en el campo veterinario. Descripcion de sistemas de entrega biodegradables existentes de la de sustancias activas veterinariaas junto con usos incluyendo los dispositivos intravaginales, los injectables y los sistemas implantables

Análisis de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

Respecto a la solicitud en estudio la reivindicación 1 dice: "Composición para formar un implante sólido in situ dentro de un cuerpo por exposición a fluidos corporales, convenientes para una liberación controlada de material bioactivo, que comprende:

- un **polímero**, biodegradable, termoplástico, farmacéuticamente aceptable, el cual es insoluble en un medio acuoso o fluidos corporales humano o animal,
- **solvente orgánico** ligeramente soluble en agua o insoluble en agua, biodegradable, farmacéuticamente aceptable,
- un **adyuvante biocompatible** y soluble en agua farmacéuticamente aceptable y,
- un **agente activo** biológicamente, caracterizado en que la cantidad en peso del solvente es más alta que la del polímero termoplástico y en que el adyuvante es seleccionado del grupo que consiste de etanol, glicerol y glicerol formal".

Respecto al estado de la Técnica:

D1 da a conocer una composición líquida de útil como implante in situ para humanos y animales para la entrega controlada de sustancias activas que comprende:

- un **polímero o copolímero termoplástico**, biodegradable y biocompatible (columna 3 línea 60, 61; columna 4 línea 1,2, 21,22) de tipo poliláctido (columna 4, línea 23, reivindicación 1).
- un **solvente orgánico** y un **modificador de liberación (adyuvante)** biocompatible y farmacéuticamente aceptable (columna 5, línea a 4, 15 a 18) entre los que se encuentran C2-C6-alcanoles (etanol), alcoholes polihidroxi (glicerol), triesteres de glicerol (triacetato de glicerol), entre otros (columna 5, línea 30 a 45; columna 8 línea 26 a 46); dichos solventes y adyuvantes se encuentran en una proporción mayor a la del polímero termoplástico (columna 8, línea 57 a 59; ejemplo 5).
- Un **material bioactivo** que puede incluir un agente biológica, fisiológicamente ó farmacológicamente activo para la administración tópica o sistémica de un animal o humano (columna 10, línea 3 a 7).

D1 contiene las características técnicas esenciales de la reivindicación independiente 1 y sus reivindicaciones dependientes 2 a 9; por lo cual el objeto a reivindicar **NO ES NUEVO**

Nivel Inventivo (Art18 D486)

La **reivindicación 10** dice: "Composición de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado en que el agente activo biológicamente es un medicamento animal"

Estado de la Técnica más cercano es **D1** debido a que da a conocer una composición líquida de útil como implante in situ para humanos y animales para la entrega controlada de sustancias activas que comprende un **polímero o copolímero termoplástico**, biodegradable, un **solvente orgánico** y un **modificador de liberación (adyuvante)** biocompatible y farmacéuticamente aceptable y un **material bioactivo** que puede incluir un agente biológica, fisiológicamente ó farmacológicamente activo para la administración tópica o sistémica de un animal o humano.

La solicitud se diferencia de D1 en que dicha composición contiene como agente activo un medicamento específicamente un **acaricida-insecticida** de uso animal.

El Efecto Técnico que logra la diferencia es la utilización de implantes de formación in situ con liberación controlada para animales que contienen como agente activo un acaricida-insecticida.

El Problema Técnico Objetivo de esta solicitud es la necesidad de obtener implantes de formación in situ con liberación retardada para animales que contengan como agente activo un acaricida – insecticida.

D2 describe el uso de composiciones poliméricas tipo ímplate de uso parenteral de formación in situ para la administración de diferentes tipos de sustancias activas para animales y que requieren de liberación controlada; dichas composiciones que involucran **polímeros de acido poliláctico** (Folio 103, numeral 2; folio 104, numeral 3.2) y **agentes activos como la ivermectina (acaricida)** (Folio 104, numeral 3.2) en combinación con otros componentes, pueden ser utilizadas para el control de parásitos ó insectos, vacunas, anticonceptivos entre otros y son una alternativa actual para el manejo de enfermedades animales.

Es así que el estado de la técnica disponible da una indicación para que experto medio en la materia llegue al objeto de la solicitud ya que para obtener una composición de liberación controlada tipo implante in situ sería evidente combinar la solución propuesta en D1 (polímero o copolímero termoplástico, biodegradable, un solvente orgánico y un modificador de liberación (adyuvante) biocompatible y farmacéuticamente aceptable) con el agente activo indicado en D4, llegando de esta manera al contenido de las reivindicaciones 1 a 17, circunstancia que **compromete el nivel inventivo de la solicitud.**

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US5702716	1-9	Novedad
D2	Advanced Drug Delivery Reviews 56 (2004) 1453– 1466	10-17	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 12 NOV. 2008

CONCEPTO TECNICO NUMERO: 3433	EXAMINADOR TÉCNICO Código:202093