611085

FORM 1

REGULATION 9

AUSTRALIAN
10 JUN 1987
PATENT OFFICE

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

We, WARNER-LAMBERT COMPANY, a Corporation organised under the laws of the State of Delaware, United States of America, of 201 Tabor Road, Morris Plains, New Jersey, United States of America, hereby apply for the grant of a Standard Patent for an invention entitled:-

"SUSTAINED RELEASE PHARMACEUTICAL PREPARATIONS"

which is described in the accompanying Complete Specification.

Details of basic application:-

Number: 875,146

Country: U.S.A.

Date: 17th June, 1986

LODGED AT SUB-OFFICE
12 JUN 1987
Sydney

Our address for service is: SHELSTON WATERS
55 Clarence Street
SYDNEY, N.S.W. 2000.

DATED this 12th day of June, 1987

WARNER-LAMBERT COMPANY

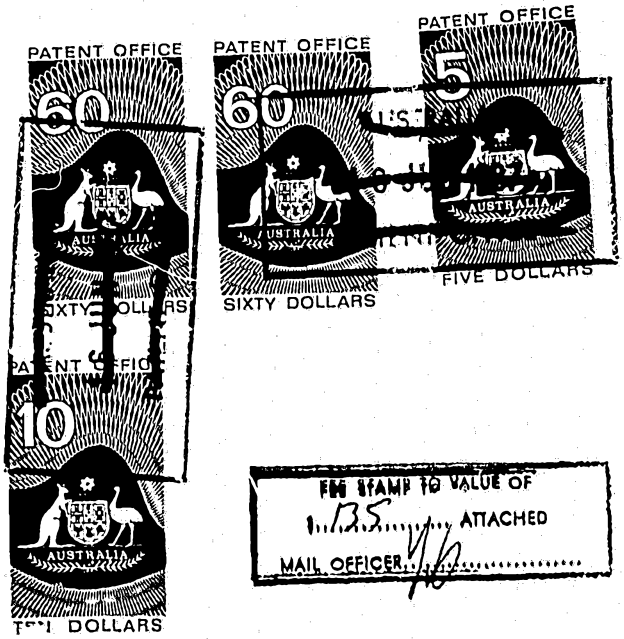
by Robert F. Shelston

Fellow Institute of Patent Attorneys of Australia
of SHELSTON WATERS

To: The Commissioner of Patents
WODEN A.C.T. 2606

File: D.B.59D

Fee: $135.00



FEE STAMP TO VALUE OF
$135 ATTACHED
MAIL OFFICER

PK-3346-11-2NP

(CONVENTION - Company)

FORM 8 - REGULATION 12 (2)

COMMONWEALTH OF AUSTRALIA
Patents Act, 1952-1973

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application No. made by WARNER-LAMBERT COMPANY, a corporation organized under the laws of the State of Delaware, United States of America

(hereinafter referred to as "Applicant") for a patent for an invention entitled:

"SUSTAINED RELEASE PHARMACEUTICAL PREPARATIONS"

I, Stephen Raines

of 201 Tabor Road, Morris Plains, New Jersey 07950, United States of America

do solemnly and sincerely declare as follows:

1. I am authorised by Applicant to make this declaration on its behalf.

2. The basic Application(s) as defined by section 141 of the Act was/were made in the United States of America on June 17, 1986

by Issac Ghebre Sellassie, Russell Nesbitt, Jr., Uma Iyer, Mahdi B. Fawzi

3 Issac Ghebre Sellassie, of 559 Dell Place, Stanhope, New Jersey 07874 USA; Russell Nesbitt, Jr., of 292 Miller Avenue, Somerville, New Jersey 08876 USA; Uma Iyer, of 7 Florie Farm Road, Mendham, New Jersey 07945 USA; Mahdi B. Fawzi of 11 Timberline Drive, Flanders, New Jersey 07836 USA

is/are the actual Inventor(s) of the invention and the facts upon which Applicant is entitled to make the Application are as follows:
Applicant is the Assignee of the said Inventor(s).

4. The basic Application(s) referred to in paragraph 2 of this Declaration was/were the first Application(s) made in a Convention country in respect of the invention, the subject of the Application.

DECLARED at Morris Plains, N.J., U.S.A. 07950

this 26th day of May 1987.

WARNER-LAMBERT COMPANY

Stephen Raines
Assistant Secretary

TO THE COMMISSIONER OF PATENTS.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-74196/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 611085

(54) Title
ADSORPTION OF PHARMACEUTICALS ON IONICALLY NEUTRAL POLYMERS TO GIVE SUSTAINED RELEASE PREPARATIONS

(51)[4] International Patent Classification(s)
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(71) Applicant(s)

WARNER LAMBERT COMPANY

(72) Inventor(s)

ISSAC GHEBRE SELLASSIE; RUSSELL NESBITT JR.; UMA IYER; MAHDI B. FAWZI

(74) Attorney or Agent
SHELSTON WATERS, 55 Clarence Street, SYDNEY NSW 2000

(56) Prior Art Documents
EP 177000
US 4221778

(57) Claim

1. A process for treating a biologically active substance to prepare the substance for constant rate sustained release comprising:-

(a) adsorbing active ingredient onto either an ionic particulate substrate or silicious material;

(b) mixing the product thus formed with a neutral polymeric binder to form a suspension;

(c) layering the suspension on solid inert material to form a product; and

(d) encapsulating the product formed with a neutral polymeric resin.

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FORM 10

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COMPLETE SPECIFICATION

FOR OFFICE USE:

Class Int.Class

Application Number:
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Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

Name of Applicant: WARNER-LAMBERT COMPANY

Address of Applicant: 201 TABOR ROAD,
MORRIS PLAINS, NEW JERSEY 07950
U.S.A.

Actual Inventor: ISSAC GHEBRE SELLASSIE,
RUSSELL NESBITT, JR.,
UMA IYER AND MAHDI B. FAWZI

Address for Service: SHELSTON WATERS, 55 Clarence Street, Sydney

Complete Specification for the Invention entitled:

"SUSTAINED RELEASE PHARMACEUTICAL PREPARATIONS"

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

Background

The treatment or coating of active substances, such as drugs, vitamins, minerals, and the like, has resulted in a variety of orally-administrable dosage forms. One principal goal in the formulation of such dosage forms is often the slow and sustained release of the active ingredient over a relatively long period of time, e.g., several hours. Such sustained release profiles generally afford such benefits as maximum dosage delivery with minimal compliance problems since, in the case of drugs, the patient need not take repeated dosages in order to ensure long-term drug release.

The Invention

It has been discovered that solid preparations for the administration of pharmaceuticals and other active substances can be produced having sustained release properties when the drug or other active ingredient is treated in accordance with a process which comprises:

(1) contacting at least one active substance with at least one ionically neutral polymer and at least one ionic particulate material or adsorbent;

(2) producing a composite of particulate material and active substance in which ion pairs bond the active substance to the particulate material, or the active is adsorbed on the particulate material and neutral polymers form binders;

(3) coating the composite produced with a neutral polymer; and

(4) recovering the product of step (3).

The present invention consists in a process for treating a biologically active substance to prepare the substance for constant rate sustained release comprising:-

(a) adsorbing active ingredient onto either an ionic particulate substrate or silicious material;

(b) mixing the product thus formed with a neutral polymeric binder to form a suspension;

(c) layering the suspension on solid inert material;

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to form a product

d) encapsulating the product formed with a neutral polymeric resin.

The composite product made in accordance with the process of the invention is believed to be a result of adsorption and/or ionic bonding between the surfaces of the active substance, e.g., drug, and the particulate ionic material. The bonding is believed to be more electrostatic than chemical in nature, that is electro-chemical, since the chemical nature of one of the components has been shown to be altered.

Advantages

The process of the invention has several advantages over prior art methods of treating active substances. First, the products have beneficial release profiles. That is, drugs or other active ingredients are released into the system of the patient/consumer gradually over a period of up to several hours at a constant rate.

In addition, the permeability characteristics of the polymer-containing membranes can be modified by suitable adjustment of the ratio of the coating levels of the neutral polymer.

Other advantages and aspects of the invention will be made apparent by the following description.

Description of the Invention

The invention comprises the process as summarized above. In general, it can be said to reside in a method which calls for:

(1) adsorbing one or more drugs or other active substances onto a particulate material which has ionic and/or adsorbent character,

(2) mixing the product of the interaction of step 1 with a neutral polymer that acts as a binder,

(3) layering the suspension on solid inert material; to form a product

(4) encapsulating the product formed with a neutral polymeric resin which forms a membrane that partially

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controls the rate of release of the active component after ingestion; and

optionally recovering the product of steps (b)-(d).

Drug release is believed to be controlled by desorption from the adsorbent or disassociation of the ion pair and the encasing membrane (i.e. the film coating).

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Active Substances

The active component or ingredient to be treated in accordance with the invention is a biologically active substance. A wide variety of active materials are contemplated. Chief among them are drugs or pharmaceuticals, vitamins, minerals and other psychological substances which have beneficial biological effects after ingestion.

The following is merely a sampling of the types of active substances which can be employed. Such substances include: acetylcholine, noradrenalin, serotonin, callicretin, gastrin, secretin, adrenalin, insulin, glucagon, ACTH, growth hormone, genadotropic hormone, oxytocin, vasopressin, thyroxin, testicular hormone (testosterone), ovarian hormone (estradiol), corpus luteum hormone, luteal hormone (progesterone), adrenocortical hormone, prostagladin, various antihistaminic agents, antihypertensives, vasodilators, vasoprotectors, stomachics and digestives, anti-diarrheals and intestinal absorbers, contraceptives, antiphlogistic, acetysalicylic acid, ibuprofen, phenacetin, mefenamic acid, maproxen, tiaramide, indomethacin, vitamins, various enzymes, antitumor agents (bleomycin, sarcomycin, actinomycin D, cyclophosphamide, nitrogen mustard, triethylene thiophosphoramide, mercaptopurine, metho- trexate, thorouracil, mitomycin C, carsinophilin, chromomycin A, 1-2(2-tetrahydro-furyl)-5-fluorouracil etc.), radiopharmaceuticals, antibiotics (streptomycins, chloramphenicols, tetracyclines, erythromycins, trichomycins, bacitracins, colistins, polymixins, gramicidins, penicillins, griseofulvins, etc.), sulfanilamide and its derivatives, antituberculosis drugs (TB preparations), antisyphilitics, antilep, various biological preparations (vaccines, antiserums, toxins and antitoxins, etc.) amebicides, anthelmintics, ataraxocs, (anticataract agents, antiglaucoma agents, etc.), various fish drugs, agricultural drugs, interferon, auxin, gibberelline, cytokinin, absinthic acid, other phytohormones, sex pheromone, aggregatien pheromone, alarm

pheromone, trail pheromone, cast pheromone, other pheromones, and the like. Mixtures can be used.

The active ingredient will generally comprise about 0.001 to about 50 wt %, preferably about 0.001 to about 40 wt %, of the final dosage form, based on total weight.

Neutral Polymeric Materials

The binder or matrix portion of the composite made in accordance with the instant process is a polymeric material having no ionizable groups in its backbone or elsewhere in its structure. By "ionizable groups" is meant groups which, when present in appropriate vehicle(s), dissociate to furnish positively and negative charged species. One typical ionically neutral polymer is hydroxypropyl cellulose.

The coating polymers are derived from acrylic esters, cellulosics and polyvinyl esters and ethers and/or other functionally equivalent monomers. Preferably, the polymer is supplied as an aqueous dispersion containing a copolymer derived from monomers selected from acrylic esters, methacrylic esters and mixtures thereof. While the final polymers are essentially neutral, the presence of acid, salt or other moieties which do not significantly effect the ionic neutrality of the polymers is permissible.

Useful coating polymers are usually supplied as aqueous dispersions. They can also be solvent-based coating systems. The presence of one or more co-diluents is contemplated. However, dispersions containing water as the only diluent are preferred for safety reasons.

In the final dosage form, the polymeric material will comprise about 10 to about 50 wt %, preferably about 10 to about 40 wt %, based on total weight.

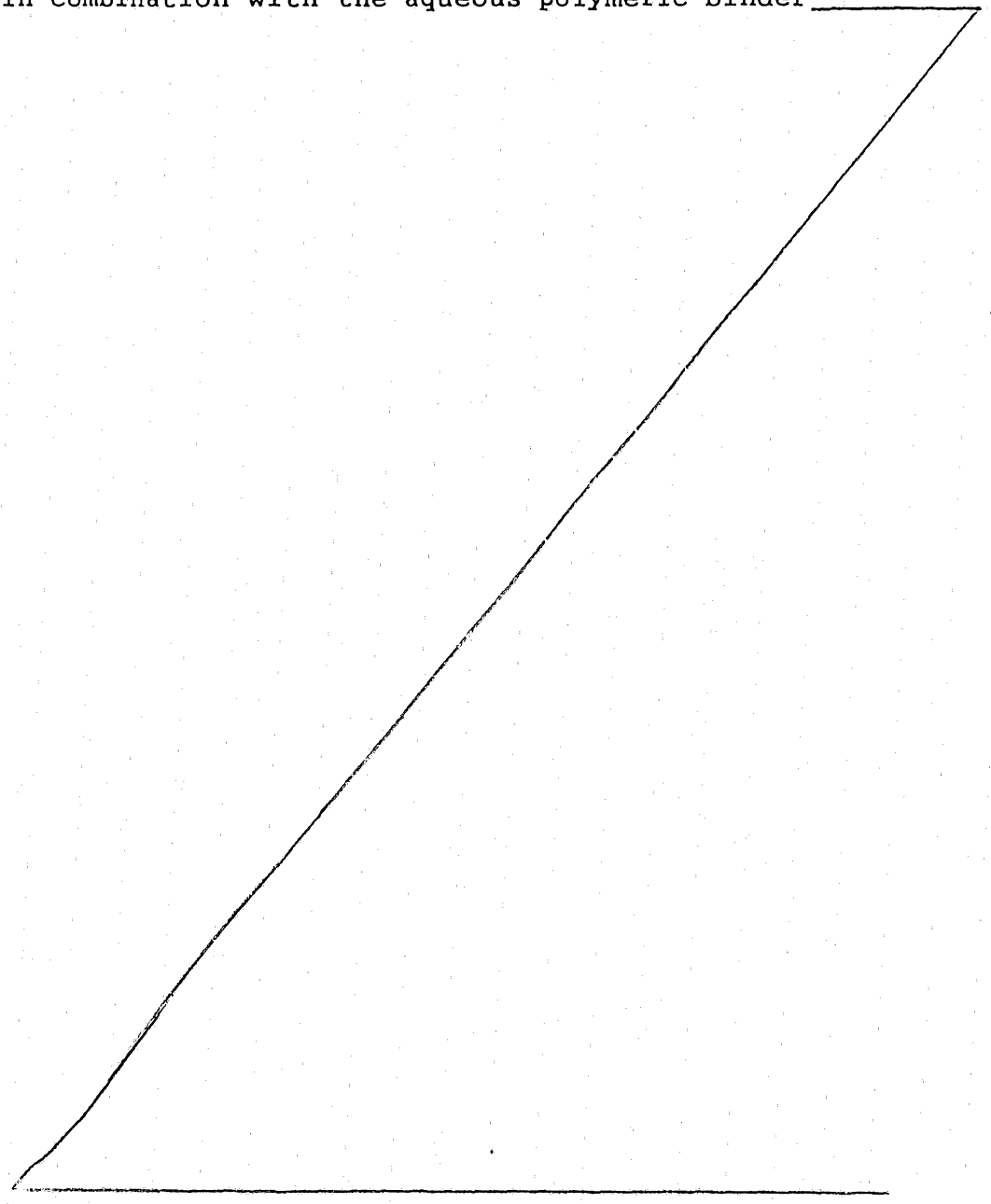
The Particulate Ionic Material

Useful particulate materials are those whose ionic character make them candidates for participation in the ion pair bonds or adsorption to be formed between the

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surface of the active substance and the surface of the ionic particulate.

While particle size is not critical, it is generally advisable to employ particles whose rheological properties in combination with the aqueous polymeric binder



component render them suitable as components of slow-release cores for ingestible substances. Typically, the particulate materials used herein will have particle sizes of about 325 mesh or less, preferably about 400 mesh or less based on U.S. standard sieve.

The ionic particles used are generally either inorganic, e.g., minerals and clays, or organic, e.g., ion exchange resins, modified neutral polymers. Mixtures of any of these types are operable. Two or more of the same type can be used.

The particles are preferably either silicious materials, e.g., kaolin, kaolin clay, silica, mineral silicates, etc., or ionic organic materials, such as styrene copolymers bearing functional ionic groups, and the like. Examples of such ionic copolymers are the styrenedivinyl benzene copolymers bearing sulfonate, carboxylate, quaternary ammonium and/or amine substituents.

The ionic character of minerals and other useful silicious particles is generally associated with their pKa values in aqueous media. In general, kaolin and other clays or clay-like materials having a significant surface charge density will be operable.

While not desiring to be bound by any particular theory, Applicants believe that an electro-chemical bonding akin to, and possibly involving, adsorption occurs between the active ingredients and the ionic particulates.

In general, the quantities of ionic particulate materials to be employed will be such that the final dosage form will contain from about 20 to about 90 wt % and preferably about 30 to about 80 wt % of this ingredient.

Other excipients and ingredients conventionally employed in the oral formulations for the administration of biologically beneficial active substances can also be employed in the instant formulations.

Dosage Forms

The method described herein is suitable for producing a variety of solid dosage/administration forms. Powders, pellets, granules, and tablets which contain one or more active ingredients and the requisite coating or membrane of particulate and polymer can be produced.

While solid products are preferred, semisolids and liquids can also be treated in accordance herewith.

Processing Techniques

In general, any apparatus reasonably suited for handling materials and substances of the types described above can be used in carrying out the invention.

Typical Scheme

A typical process for the suspension layering of sugar seeds is demonstrated by the following:

Non pareil sugar seeds in the range of 14-16# were coated with a suspension of drug, kaolin and binder to produce extremely smooth spherical drug pellets. These pellets were subsequently coated with a polymer dispersion.

The procedure employed was:

Kaolin was suspended in water. Diphenhydramine HCl was adsorbed onto the kaolin of mixing with the kaolin suspension. To the drug/kaolin mixture, an aqueous binder solution of hydroxypropyl cellulose in water was added. The resultant suspension was sprayed at a rate of---------

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1 ml/min onto a fluidizing bed of nonpareil sugar seeds to yield pellets.

The pellets were then coated with an aqueous polymeric dispersion of ethylcellulose (Aquacoat®) and dried overnight at 40°C.

The release of drugs from the coated pellets was studied and found to follow zero order up to 90% drug depletion.

Drawing

The figure shows the release profile of the pellets discussed in the Example. The upper curve shows the profile for pellets without kaolin. The lower shows the profile for pellets with kaolin.

Example

100 g of kaolin was mixed thoroughly with 500 g of deionized water. 50g of diphenhydramine HCl was dissolved in the suspension and stirred. 35 g of Klucel® (hydroxy propyl cellulose) was dissolved in 165 g of deionized water and mixed with the suspension.

The mixture was sprayed onto 150 g 14-16 mesh nonpareil seeds. The drug layered pellets were coated with Aquacoat® to a coating level of about 7%. The drug release from the water-layered pellets was compared with that from similarly coated diphenhydramine HCl pellets.

Time HR	Percent Drug Released	
	Layered pellets	Regular Pellets
0.5	--	28.8
1	4.2	45.1
2	17.8	61.7
4	43.9	77.4
6	67.1	86.4
8	84.8	92.9
10	95.9	97.1
12	100.0	100.0

Reasonable variations, such as those which would occur to a skilled artisan, can be made herein without departing from the scope of the invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A process for treating a biologically active substance to prepare the substance for constant rate sustained release comprising:-

(a) adsorbing active ingredient onto either an ionic particulate substrate or silicious material;

(b) mixing the product thus formed with a neutral polymeric binder to form a suspension;

(c) layering the suspension on solid inert material to form a product; and

(d) encapsulating the product formed with a neutral polymeric resin.

2. The process of Claim 1 wherein the particulate material is of acidic or basic character prior to step (a).

3. The process of Claim 2 wherein the particulate material is selected from the group consisting of: kaolin, non-kaolin clay, ion exchange resins having acidic or basic character and mixtures thereof.

4. The process of Claim 1 wherein the particulate material is kaolin.

5. The process of any one of the preceding Claims wherein the neutral polymeric binder is selected from the group consisting of hydroxy propyl cellulose.

6. The process of any one of the claims 1 to 4 wherein the neutral polymer is a water insoluble aqueous polymer selected from the group consisting of acrylic esters, cellulosics, and polyvinyl esters.

7. The process of Claim 6 wherein the polymer is supplied as an aqueous dispersion containing a copolymer derived from monomers selected from acrylic esters, methacrylic esters, and mixtures thereof.

8. The process of Claim 1 wherein the particulate material is an ion-exchange resin having acidic or basic character.

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9. The process of Claim 8 wherein the ion exchange resin contains at least one ionic group selected from the group consisting of sulfonates, carboxylates, quaternary ammonium groups, amine groups, and mixtures thereof.

10. The process of Claim 9 wherein the ion exchange resin is strongly acidic.

DATED this 2nd day of May, 1990
WARNER-LAMBERT COMPANY

Attorney: IAN T. ERNST
Fellow Institute of Patent Attorneys of Australia
of SHELSTON WATERS