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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: **EXPEDIENTE 03-112-111**

TÍTULO SOLICITADO: **"FORMA DE LIBERACIÓN SOSTENIDA INCLUYENDO UNA PLURALIDAD DE MINI-IMPLANTES O COMPRIMIDOS DE LIBERACIÓN SOSTENIDA QUE INCLUYE UN ACTIVO ANTIPARASITARIO"**

PUBLICACIÓN: **GACETA 555 DE 31-08-2005, NÚMERO DE PUBLICACIÓN 461, PÁGINA 448.**

PRIORIDAD: **AU-PR 6105 (04/07/2001)**

SOLICITANTE: **SMART DRUG SYSTEMS INC.**

APODERADO: **RAMIRO CASTRO DUQUE**

TRÁMITE: **SUSTENTACIÓN DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, identificado como aparece al pie de mi firma, reconocido apoderado del opositor en el trámite de la referencia, estando dentro de los términos de la prórroga solicitada, por medio del presente escrito ratifico mi petición en el sentido de que se niegue el beneficio patentario a la solicitud contenida en el expediente **03-112-111,** por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

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I. COMPLEMENTO DE INFORMACIÓN

La solicitud en trámite revela el uso de un agente antiparasitario en una forma de liberación sostenida que incluye una pluralidad de mini-implantes o comprimidos de liberación sostenida y los cuales a su vez incluyen una capa interna que contiene el activo y una capa externa impermeable al agua en el tratamiento de infecciones ectoparasitarias. De igual manera pretende beneficio patentario sobre un método para el tratamiento terapéutico o profiláctico de una condición parasitaria.

1.1. El uso del agente antiparasitario y el método para el tratamiento terapéutico o profiláctico de una condición parasitaria animal no son patentables

Es ampliamente conocido por el Despacho que "los **métodos** terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicado a los seres humanos o a animales" no son patentables, de conformidad con lo dispuesto por el artículo 20 literal d de la Decisión 486.

De igual manera, me permito resaltar que el capítulo reivindicatorio de la solicitud colombiana en curso, dirigida al **uso** de un agente antiparasitario en una forma de liberación sostenida, es inaceptable a la luz de la Decisión 486. En efecto, a la luz de la normativa subregional resulta inaceptable pretender atribuirse exclusiva sobre un "Uso", categoría no incluida en el concepto de "Productos o Procedimientos" que establece la Decisión 486 de 2000. Lo anterior, además, en consonancia con la reiterada interpretación de la SIC sobre este punto.

Sin perjuicio de lo anterior me permito hacer notar que aún si los usos o métodos terapéuticos fueran permitidos en nuestro medio, éstos deberían cumplir necesariamente con los requisitos materiales de patentabilidad, novedad, nivel inventivo y aplicación industrial, circunstancia que no ocurre en el caso que nos ocupa.

Aunque a la ausencia de los dos primeros nos referiremos más adelante, cabe desde ahora anotar que el último resulta de imposible cumplimiento, en tanto la *reproducción industrial* del **uso** separado, combinado o secuencial de

medicamentos para tratar ciertas patologías, y del **método** de tratamiento, son del resorte de la profesión médica y no de las actividades industriales.

1.2. <u>La forma de liberación sostenida incluyendo una pluralidad de mini-implantes o comprimidos de liberación sostenida que incluyen un activo antiparasitario y que se revela en la solicitud colombiana en trámite, carece de novedad y nivel inventivo.</u>

Como adición a lo expuesto en el punto precedente, ruego al Despacho se sirva tener en cuenta de igual manera lo consignado a continuación:

A. La patente europea EP 0 990 450 A2 de título "PHARMACEUTICAL IMPLANT", publicada el **5 de abril de 2000** revela, un método para proporcionar control inmediato y a largo plazo de la infestación de parásitos en un animal, que comprende un sistema parasiticida multicomponente de pellets que proporciona un sistema pellet para liberación tanto inmediata como sostenida de un parasiticida para matar parásitos internos y externos presentes en un animal y que además incluye un aparato implantador para inyectar pellets subcutáneamente. La combinación de los pellets son empacados y almacenados en orden secuencial para liberación simultánea de una dosis inmediata y una dosis extendida como parte de una sola inyección.

Además se refiere a que dicho método comprende:

a) Proveer un aparato implantador para implantar pellets parasiticidas en un animal a través de un agujero de una aguja hipodérmica el cual está operablemente unido al almacén de pellet;

b) Cargar el almacén de pellet con una dosis de pellets de liberación inmediata del agente parasiticida (seleccionado del grupo que consiste de Avermectina, milbencina, ivermectina, fenbendazol y Lufeneron) y una dosis de pellets de liberación sostenida del dicho agente;

c) Insertar la aguja hipodérmica bajo la piel del animal e inyectar la dosis de liberación inmediata y la extendida dentro del animal, y

d) Retirar la aguja hipodérmica de debajo de la piel del animal para dejar las dosis mencionadas debajo de la piel.

También describe que el implante descrito anteriormente incluye una pluralidad de pellets de tamaños y formas y que además, cada pellet de liberación inmediata incluye un agente de desintegración y cada pellet de liberación extendida incluye una matriz bioerosionable.

Para mayor claridad, tenemos:

CO 03-112.111	EP 0 990 450 A2
Uso de agente antiparasitario en forma de liberación sostenida.	Uso de agente parasiticida en forma de liberación inmediata o extendida.
Tratamiento de infecciones ectoparasitarias	Control de infestación de parásitos tanto internos como externos en un animal
El agente antiparasitario se provee en un aparato de liberación sostenida que incluye una pluralidad de mini-implantes o comprimidos	El agente parasiticida se provee en un aparato implantador de una pluralidad de discretos pellets dosificados con parasiticida.
El agente antiparasitario incluye una lactona macrocíclica seleccionada del grupo conformado por Ivermectina, Moxidectina, Eprinomectina y Doramectina.	El agente parasiticida se selecciona del grupo que consiste de Avermectina, Milbemicina, Ivermectina, Fenbendazol y Lufeneron.
El aparato transportador de liberación sostenida que contiene una pluralidad de mini-implantes o comprimidos se administra mediante inyección subcutánea o intramuscular	El sistema de pellets incluye un aparato implantador para inyectar subcutáneamente los pellets en un animal a través del agujero de una aguja hipodérmica.
Cada mini-implante o comprimido contiene una capa interna que contiene el activo antiparasitario y una capa externa impermeable al agua	Cada pellet de liberación inmediata del agente incluye un agente desintegrante, y cada pellet de liberación extendida del agente incluye una matriz bioerosionable.

Como se observa, y luego de una sencilla comparación podemos afirmar que, tanto el uso en el tratamiento de infecciones parasiticidas, el principio activo parasiticida (Ivermectina), la forma de liberación del mismo, el aparato transportador así como la administración de dicha composición, que se

pretende patentar en la solicitud colombiana en trámite, ya fueron claramente revelados en la patente europea EP 0 990 450 A2, lo que permite desvirtuar la novedad y el nivel inventivo de las reivindicaciones de la solicitud en curso.

B. La aplicación internacional PCT WO01/37811 A1 titulada "COMPOSITION ALLOWING PREDEFINED AND CONTROLLED RELEASE OF ACTIVE INGREDIENT, PREPARATION THEREOF AND USE" y publicada el 31 de mayo de 2001, revela una composición especialmente diseñada para combatir la parasitosis externa e interna, que contiene como principio activo un agente endectocida como una avermectina o una milbemicina, en particular Ivermectina y el cual está en la forma de un implante subcutáneo constituido por uno o más pellets que liberan el ingrediente activo de manera predeterminada y controlada y que a su vez estos implantes se encuentran empacados en cartuchos plásticos.

De igual manera, nos permitimos presentar un cuadro comparativo para efectos de claridad:

CO 03-112111	WO 01/37811 A1
Uso de agente antiparasitario en forma de liberación sostenida.	Uso de agente antiparasitario, preferiblemente un endectocida en forma de liberación controlada.
Tratamiento de infecciones ectoparasitarias	Combatir la parasitosis externa e interna.
El agente antiparasitario se provee en un aparato de liberación sostenida que incluye una pluralidad de mini-implantes o comprimidos	El agente endectocida se provee en cartuchos plásticos que contienen implantes constituidos por uno o más pellets.
El agente antiparasitario incluye una lactona macrocíclica seleccionada del grupo de Ivermectina, Moxidectina, Eprinomectina y Doramectina.	El agente endectocida preferido es una Avermectina como Ivermectina y/o Abamectina o puede ser una Milbemicina.
El aparato transportador de liberación sostenida que contiene una pluralidad de mini-implantes o comprimidos se administra mediante inyección	La composición está en la forma de implante subcutáneo constituido por un o más pellets que liberan el principio activo de manera controlada.

CO 03-112-111	WO 01/37811 A1
subcutánea o intramuscular	
Cada mini-implante o comprimido contiene una capa interna que contiene el activo antiparasitario y una capa externa impermeable al agua	Cada pellet contiene a) al menos un ingrediente activo en forma de sólido dispersado, al menos un agente gelificante, opcionalmente al menos un agente de relleno y al menos un adyuvante embebidos en una matriz y b) un agente formador de poro "pore-forming" y al menos un adyuvante.

Una vez más podemos afirmar que, tanto el uso en el tratamiento de infecciones parasiticidas, el principio activo parasiticida (Ivermectina), la forma de liberación del mismo así como la administración de dicha composición, que se pretende patentar en la solicitud colombiana en trámite, fueron contemplados en la solicitud Internacional WO 01/37811, lo que permite desvirtuar nuevamente la novedad y el nivel inventivo de las reivindicaciones de la solicitud en curso.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

II. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho de esta oposición el Título II, Capítulo I y el artículo 42 de la Decisión 486 de 2000.

III. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, las siguientes:

- Copia de la portada, de las páginas 2 a 6 de la patente europea EP 0 990 450 A2.

- Copia de la portada, de las páginas 3, 6 y 7 y del capítulo reivindicatorio de la publicación internacional WO01/37811.

IV. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A. las recibirá en sus oficinas localizadas en la Calle 23 No. 7-39 de Cali.

Señor Superintendente,

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T.P.A. 44.655 de C.S.J.

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(54) Pharmaceutical Implants

(57) A pharmaceutical pellet system (10), which delivers both immediate nad long term control of parasite infestation in an animal as part of a single implant procedure, includes an implanter apparatus (12) for subcutaneously implanting parasiticidal pellets (14, 16) in an animal through the bore of a hypodermic needle (22) which is operably coupled to a pellet magazine (18), and a plurality of pellets (14, 16) sized to be implanted through the needle and positioned in the magazine for selective alignment of a pellet with a needle. The pellets include at least one immediate release parasiticidal agent first dose pellet and at least one extended release parasiticidal agent dose second pellet. The combined pellets are packaged in the magazine in sequential order for simultaneous delivery of an immediate dose and an extended dose as part of a single injection.

EP 0 990 450 A2

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Description

[0001] The present invention is broadly concerned with a pellet implant system and in particular one that simultaneously administers both an immediate parasiticidal dosage first component and a long term release parasiticidal dosage of a second component placed in subcutaneous pellets in order to control internal and external parasites in domesticated and wild animals. More particularly, it is concerned with an implanter having a pellet magazine containing parasiticidal pellets with an associated injection needle, as well as structure permitting injection of the pellets from the magazine through the needle for implantation under the skin of a animal. The pellets are formulated to deliver two separate doses simultaneously. The first dose is a parasiticidal dose which is immediately available for absorption. The second dose is a parasiticidal dose which is available for sustained absorption through bioerosion and diffusion over an extended period of time.

[0002] The importance of parasite control in animals used for meat and other agriculture production, recreation and companionship is well recognized. Meat, milk and fiber producing animals, such as suckling, growing, grazing and feed lot cattle, domesticated swine, sheep, goats, poultry and companion animals such as horses, dogs and cats all serve as hosts for a large number of internal and external parasites. The presence of such parasites is known to reduce overall production in animals producing meat and other agricultural products. In the case of companion and recreational animals, the presence of parasites can lead to discomfort, impaired health and performance, and even death.

[0003] Wild animal populations infested with parasites may experience substantial harmful effects as well as reduced reproductive efficiency. Such harmful effects are of particular concern in populations of endangered species, since it may impair attempts to reintroduce the species into an environment or to build the species population up to a level which can be easily sustained by natural growth. Endangered mammalian species which are maintained or managed in limited area preserves such as game preserves, animal parks, national parks or wildlife areas as well as zoo animals which are maintained in confined areas, are particularly susceptible to parasite infestation since they inhabit areas substantially smaller than their natural habitats, with denser populations of both parasites and their animal hosts.

[0004] Implant technology, that is to say, subcutaneous implant of pharmaceuticals and medical devices, is now well accepted and widespread in the fields of animal health and production enhancement and human health. Many types of biologically active compounds, including hormones, vitamins, antibiotics, antiinflammatory agents, vaccines and biocides are administered as solid compressed pellets which are injected by an implanter equipped with a hypodermic needle. The needle is used to make a small self-sealing and noncoring implant-receiving puncture beneath the skin at a suitable location on the body of the animal. Small pellets of the bioactive compound are forced through the needle and left under the skin as the needle is removed. The ears are a preferred site for pellet implantation in livestock such as cows, pigs and sheep. Implanted ears are commonly discarded in slaughtering, so that no unabsorbed pellet residue will end up in food products intended for consumption by humans or domestic animals.

[0005] The pellets are normally implanted in farm animals while the animal is confined in a chute. An ear is grasped in one hand, and an implanter device having a large hypodermic needle is used to puncture the hide and subcutaneously inject a pellet dose into an implant-receiving puncture. Implantation must be done carefully to ensure that the pellets are properly placed and that no portion of the pellet remains extending from the puncture outside the hide. The procedure must also be carried out quickly since the animals are not entirely cooperative and may shake their heads to free the held ear.

[0006] U.S. Patent No. 5,522,797 (hereinafter "the '797 patent"), and entitled Slide Action Veterinary Implanter, which patent is hereby incorporated by reference, discloses an implanter which employs a slide action mechanism to retract an impeller, store an impeller driving force in a spring in cooperation with a latch mechanism, reset a trigger, and advance a pellet magazine, all by a single trigger actuated reciprocation of the slide mechanism. Operation of the trigger also forces the pellets from the magazine through the needle and under the skin of the animal.

[0007] Efficient implanters such as that taught in the '797 patent permit rapid sequential injection of many animals in a single session and make implant technology particularly well-suited for administration of parasiticides while the animals are confined for ear tagging, branding, veterinary procedures or the like. Even where only a single animal is to be treated, implantation offers a particularly safe method for administering certain biocides, so as to allow a user to avoid biocides that could be toxic if ingested by the animal, for example by licking off residue left on its own hide or fur or on that of another animal following treatment by dipping, spraying or dusting.

[0008] A number of effective compounds are available for internal and external parasite control, including the polylactide avermectins, the milbemycins and milbemycin oximes, fenbendazole and lufeneron. The most commonly used avermectins are ivermectin, doramectin, moxidectin, eprinomectin and abamectin. However, such parasiticidal compounds have not previously been available in implantable pellet formulations which provide for immediate as well as extended release of the parasiticide.

[0009] Previous avermectin and milbemycin implants such as disclosed by Hepler in PCT application WO 9625852 and by Wallace in U.S. Patent No. 4,847,243 do not provide prolonged controlled release of the par-

asiticide dose. Consequently, additional parasiticidal pellets must be periodically implanted in host animals to treat parasites in the immediate environment of the host animal.

[0010] This requirement for periodic readministration is not only cumbersome and inefficient, it increases the likelihood that a dose will be delayed or missed altogether and that parasites endemic to the environment will reinfest the host animal. Moreover, each such procedure subjects the animal to stress and risk of infection at the injection site.

[0011] A variety of techniques are currently employed to obtain sustained release of parasiticides. Oral boluses are formulated in double walled cylinders, with layers of racemates of active ingredients, with outer and inner layers having polymer coatings, with wax and fat to retard dissolution, and with a heat responsive carriers.

[0012] While such measures provide for sustained release of parasiticides over many hours, they do not obviate the need for periodic redosing. Effective parasite control requires prolonged sustained release for periods of up to several months in order to interrupt the parasite life cycle in the environment of the host animal.

[0013] Accordingly, there is a need for a system which delivers subcutaneously pellet implants of varying controlled release parasiticidal dosages to provide immediate as well as sustained release of the parasiticide for a period of up to several months, and which does so without requiring periodic redosing.

[0014] The present invention resolves the problems previously outlined and provides a greatly improved parasiticidal pellet system which delivers separate doses of both immediate and long term control of parasite infestation in an animal as part of a single implant procedure wherein the immediate dose is sufficient to kill pests already present in the animal and the long term dose is sufficient to prevent reinfestation.

[0015] Broadly speaking, the pellet system includes an implanter apparatus for subcutaneously implanting parasiticidal pellets in an animal through the bore of a hypodermic needle which is operably coupled to a pellet magazine, and a plurality of pellets sized to be implanted through the needle and positioned in the magazine for selective alignment of a pellet with the needle. The pellets include at least one immediate release parasiticidal agent first dose pellet and at least one extended release parasiticidal agent dose second pellet. The combined pellets are packaged in the magazine in an individual dosing chamber for simultaneous delivery of an immediate dose and an extended dose as part of a single injection.

Advantageously, the system permits both immediate and sustained release of an effective dose of the parasiticidal agent, in order to control present parasite infestation and release sufficient agent over time to prevent reinfestation for a period of up to about 150 days. The immediate and sustained release agents may be the same or different parasiticidal agents with the principal difference between the agents being that the immediate agent is formulated to completely release into the system of the animal very quickly after implanting to provide a sufficient systemic amount of the immediate agent to kill pests that are currently in the animal and the sustained agent is formulated in a slow release matrix that slowly releases the sustained agent over a comparatively long time, for example about 150 days, in a sufficient amount to systemically prevent reinfestation of the animal.

[0016] The principal objects and advantages of the present invention include: providing a multicomponent parasiticidal pellet system; providing a pellet system for immediate as well as sustained delivery of a parasiticide in order to kill both internal and external parasites present on an animal and which may reinfest the animal in the future; providing a pellet system which includes an implanter apparatus for subcutaneously injecting pellets in an animal through the bore of a hypodermic needle which is operably coupled to a pellet magazine and simultaneously introduces separate immediate and extended release parasiticidal pellet doses; providing such a system and method which permits injection of predetermined doses of each of a parasiticide for immediate release and a parasiticide for extended release in a single injection; providing such a system and method which permits subcutaneous injection of both an immediate release parasiticidal dose and an extended release parasiticidal dose; providing such a system and method which permits an operator to selectively inject an extended release parasiticidal dose into the needle; providing such a system and method which permits serial injection of large numbers of animals in a single session; providing such a system and method which may employ a wide range of parasiticidal agents for use in control of infestation; providing such a system and method which is simple and efficient and economical to manufacture, which effectively prevents reinfestation of the animal for a period of up to about 150 days and which is particularly well-adapted for its intended purpose.

[0017] Other objects and advantages of this invention will become apparent from the following description taken in conjunction with the accompanying drawings wherein are set forth, by way of illustration and example, certain embodiments of this invention.

[0018] The drawings constitute a part of this specification and include exemplary embodiments of the present invention and illustrate various objects and features thereof.

[0019] Figure 1 is a fragmentary perspective view of a cow, an implanter apparatus in accordance with the present invention, and an apparatus operator.

[0020] Fig. 2 is an enlarged, fragmentary cross-sectional view, taken along line 2-2 of Fig. 1, illustrating a hypodermic needle with pellets inside the needle being inserted into an ear of the cow.

[0021] Fig. 3 is an enlarged, fragmentary cross sectional view similar to Fig. 2, illustrating subcutaneous

of injection. The extended release pellets 16 are formulated to release active parasiticide into the animal's blood system slowly and continuously over a period of many days, for example about 150 days, in order to sustain sufficient parasiticide systemically in the animal being treated to prevent reinfestation by undesirable pests.

[0032] The compressed pellets 14, 16 can be produced inexpensively and in large quantities by a variety of conventional manufacturing equipment.

[0033] In the illustrated embodiment, one pellet 14 incorporates an immediate release parasiticidal dose and the other five pellets 16 incorporate an extended release parasiticidal dose. It is foreseen that the number of pellets within an individual dosing chamber 40 within a magazine 18 for each release formulation within may vary, depending on the desired dose of parasiticide to be delivered. As an example, the extended release pellets 16 may number one or many, such as the illustrated five.

[0034] Each magazine chamber 40 is prefilled with a preferred number of discrete pellets 14 and 16, each containing a parasiticidal dose in a compressed pellet formulation designed respectively for immediate and extended release, the chamber 40 containing at least one immediate release pellet 14 and one extended release pellet 16. The magazine strip 18 is preferably loaded onto implanter housing 30 in an orientation so that the immediate release parasiticidal pellet 14 will be delivered first, followed by the extended release parasiticidal pellets 16.

[0035] In use, an operator grasps the implanter 12 by the grip 32 and urges the needle 22 into the hide 42 and under the skin of the target animal 20 to make the implant receiving puncture 28. The puncture 28 shown in Fig. 2, is approximately half complete and is complete in Fig. 2. The operator 24 depresses the trigger member 34, thereby propelling a pin 48 of the impeller member 36 forwardly through an aligned magazine chamber 40, forcing the pellets 14 and 16 through the needle bore 38 and into the implant receiving puncture 28. The operator 24 then withdraws the needle 22, leaving the pellets 14 and 16 in the implant receiving puncture 28.

[0036] The bioerodible excipient disintegration aids included in the formulation of immediate release pellet 14 allows the pellet 14 to immediately make available for systemic absorption an effective dose of a parasiticidal compound, such as ivermectin. The long circulatory half-lives of such compounds ensures protection of the animal against parasites for up to 30 days. The binders included in the extended release pellets 16 cause delayed bioerosion of the pellets and diffusion of the effective dose of the parasiticidal compound for absorption into the bloodstream of the animal over an additional period of up to 120 days. This multicomponent formulation lengthens the pellet delivery period for the parasiticidal compound dose so that effective blood levels of the parasiticidal compound are maintained for periods of up to 150 days. In this manner, the internal and external parasites of the host animal are eliminated, and the animal is protected from reinfestation until the parasite life cycle in the environment has been interrupted and persistency, that is to say, repeated reinfestation of the animal with parasites endemic to the environment is eliminated.

[0037] Advantageously, the magazine strip 18 may be loaded for selective injection of any number of immediate release pellets 14 or extended release pellets 16 in order to obtain delivery of a selected dosage by each formulation tailored to the species, weight, age or sex in a wide variety of animals. Where a number of pellets of each formulation of pellets 14 and 16 are to be delivered, the pellets may be alternated. In other embodiments, both immediate and delayed release antiparasitic pellets 14 and 16 may be alternated in a stack of pellets of other pharmaceuticals, for delivery through the implant receiving puncture 28.

[0038] The pellet system 10 of the present invention may be employed efficaciously with cows, sheep, swine, goats, poultry, horses, dogs, cats or any other suitable animal, including wild animals and humans.

[0039] The following example is provided for the purpose of illustrating the invention and is not intended to be limiting upon the scope of the claims.

EXAMPLE 1

[0040] A quick release pellet is produced including 100 milligrams of ivermectin in a quick release matrix of lactose and microcrystalline cellulose as a disintegration aid. A set of five sustained released pellets is formulated and formed containing a total of 125 milligrams of ivermectin in a controlled and sustained release matrix of polyethylene glycol. Thereafter, all six pellets are implanted under the skin in the ear of a cow.

[0041] It is to be understood that while certain forms of the present invention have been illustrated and described herein, it is not to be limited to the specific forms or arrangement of parts described and shown.

Claims

1. A method for providing immediate and long term control of parasite infestation in an animal; said method compising:

   (a) providing an implanter apparatus for implanting parasiticidal pellets in an animal through the bore of a hypodermic needle which is operably coupled to a pellet magazine;
   (b) loading the pellet magazine with an immediate release parasiticidal agent pellet dose and an extended release parasiticidal agent pellet dose;
   (c) inserting the hypodermic needle under the skin of the animal and injecting the immediate

release pellet dose and the extended release pellet dose into the animal; and
(d) withdrawing the hypodermic needle from under the skin of the animal so as to leave the immediate release pellet dose and extended release pellet dose beneath the skin.

2. The method according to claim 1 including providing a plurality of discrete pellet doses.

3. The method according to claim 2 including providing at least one discrete immediate release dose in a first pellet and at lease one discrete extended release dose in a second pellet.

4. The method according to claim 1 including:

(a) inserting the hypodermic needle under the skin of the animal and injecting an immediate release pellet dose; and while
(b) maintaining the hypodermic needle in place under the skin of the animal, sequentially injecting an extended release pellet dose.

5. In a method of administering a subcutaneous implant to an animal, the improvement comprising:
(a) injecting an implant for retention under the skin of the animal including an immediate release parasiticidal agent dose and an extended release parasiticidal agent dose in a single injection.

6. A method for providing immediate and sustained parasiticide release in an animal, comprising:

(a) providing an implanter apparatus for implanting pharmaceutical pellets in an animal through the bore of a hypodermic needle which is operably coupled to a pellet magazine;
(b) loading the pellet magazine with an immediate release parasiticidal agent pellet dose and an extended release parasiticidal agent pellet dose;
(c) inserting the hypodermic needle under the skin of an animal and selectively injecting the immediate release pellet dose;
(d) maintaining the hypodermic needle in place under the skin of the animal and also selectively injecting extended release parasiticidal agent pellet dose;
(e) withdrawing the hypodermic needle from under the skin of the animal while leaving said pellets beneath the skin of the animal.

7. In an implant adapted for subcutaneous implantation in an animal by an implanter apparatus (12) through the bore of a hypodermic needle (22) which is coupled to a pellet magazine (18), the improvement comprising:

(a) said implant including a plurality of pellets (14, 16) sized and shaped to be implanted through the needle and positioned in the magazine for selective alignment of the implant with the needle; and
(b) the pellets including an immediate release parasiticidal agent pellet dose and an extended release parasiticidal agent pellet dose.

8. The implant according to Claim 7 wherein:
(a) the pellets (14, 16) are packaged in the magazine (18) in sequential order for delivery of an immediate release parasiticidal agent dose in at least one discrete pellet followed by an extended release parasiticidal agent dose in at least one pellet for subcutaneous placement in a single injection.

9. The implant according to Claim 8 wherein the parasiticidal agent dose pellets comprise compositions selected form the group consisting of avermectin, milbemycin, fenbendazole and lufeneron and mixtures thereof.

10. The implant according to Claim 9 wherein the parasiticidal agent comprises ivermectin.

11. The implant according to Claim 8 wherein:

a) each immediate release agent pellet includes a disintegration agent; and
b) each extended release agent pellet includes a bioerodible matrix.

12. An implant for subcutaneous implantation in an animal comprising:

(a) at least one discrete immediate release parasiticidal agent pellet dose; and
(b) at least one discrete extended release parasiticidal agent pellet dose; all of said pellets being combined in a single unit for implantation side by side into the same site.

13. The implant according to Claim 12 including:
(a) an excipient and each of said parasiticidal agent pellets comprises a composition selected from the group consisting of the avermectin, milbemycin, fenbendazole, lufeneron and mixtures thereof.

14. The implant according to Claim 13 wherein the parasiticidal agent comprises ivermectin.

15. The implant according to Claim 12 wherein:

a) each immediate release parasiticidal agent pellet includes a disintegration agent; and
b) each extended release parasiticidal agent

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(54) Title: COMPOSITION ALLOWING PREDEFINED AND CONTROLLED RELEASE OF ACTIVE INGREDIENT, PREPARATION THEREOF AND USE

(57) Abstract: A new composition is disclosed which is especially designed for combating external and internal parasitoses. In one embodiment this composition contains, as an active ingredient, an endectocide, the form of a subcutaneous implant constituted by one or more pellets that release the active ingredient in a predetermined and controlled way. In specific embodiments the endectocide is an avermectin or a milbemicin, in particular ivermectin.

effects following the administration to the organism. Thus there is a continued need for improved subcutaneous implant and an improved production method for such a formulation.

Whereas the compositions of this invention can become administered to any kind of organism, such as humans and animals, preferably mammals, the invention will be described in more detail via the treatment of animals with pharmaceutically active substances, especially antiparasitics.

One indication, which is economically important in agriculture, is the use of pre-defined and controlled release of pharmaceutically active ingredients in the control of parasites in livestock ruminants (e.g. cattle, sheep and goat).

Parasites can be classified into Endoparasites and Ectoparasites. Endoparasites, for example worms (*nematodes*), cestodes and trematodes are hosted inside (*e.g. gastrointestinal tract*, respiratory tract) the organism (human or animal). Ectoparasites, for example fleas, mites, ticks and lice are hosted on (on or in the skin) the organism (human or animal).

Active ingredients are known that control Endoparasites (Endoparasitica, e.g. Fenbendazol, Pyrantel, Praziquantel) or Ectoparasities (Ectoparasitica, e.g. Deltamethrin, Fipronil, Lufenuron) and active ingredients that control both Endoparasites and Ectoparasites (Endectoparasitics, e.g. Abamectin, Ivermectin, Milbemycin, Cydectin).

These active ingredients can be adminstered in various formulation, e.g. as powder, spray, pour-on, bath, dip, injection, tablets, bolus or suspension.

For an effective control of the parasite in or on the animal the following facts are especially important; species and stage of the parasite as well as species, age, breed and sex, body weight and condition of the host animal. Therefore it is for an effective control of parasites important to have a formulation available that allows an individual dosage of the active ingredient.

On the other hand the administration of antiparasitics to animals, especially ruminante is a very labour intensive work and causes stress and loss of body weight of the animals. It woud be

Examples of biologically active substances are antibiotics, antiparasitics, hormones, growth promotors, anti-cancer drugs, vitamines and vaccines.

More specific examples of pharmaceutically active substances are BST, trenbolone, zeranol, ivermectin, abamectin, doramectin, moxidectin, selamectin and other systemical compounds.

More than one active ingredient can be used, for example a synergistic combination of two pharmaceutically active ingredients.

Thus, a composition according to the present invention can also additionally contain other biologically active agents used in human or veterinary medicine such as, for example, vaccines, antibiotics, growth promoters, agents that potentialize the antiparasite effect of the active ingredient or that improve or avoid its side effects.

Preferably the active ingredient is an endectocide, especially preferred an avermectin or a milbemicin and most especially preferred ivermectin and abamectin.

When administering an endectocide to an animal, effective treatment and control of the different species of pulmonary and gastrointestinal round worms, ticks, myiases (known as "bicheiras"), larvae of Dermatobia hominis, lice, mites of mange and of the fly known as "mosca-dos-chifres" is possible.

The active ingredient is solid and is applied in dispersed form, for example in the form of powder or preferred in the form of granules. Solid shall mean solid at 25°C.

The gelling agent b) can be of any kind as long as this agent is physiologically acceptable and forms together a gel or a shapable mass with component a), with optional components c) and d) and with a liquid, for example water or body fluids.

Examples of gelling agents are organic or inorganic gelling agents, such as modified cellulose, modified starch, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylates, polymethacrylates, or

dispersed silica. Preferred is modified cellulose, preferably alkylated cellulose, most preferred ethylcellulose.

The filler c) can be of any kind as long as this is a pharmacologically inactive substance. Examples of filler c) are carbohydrates and silica, preferably a disaccharide, and most preferred lactose.

The matrix material B) embedding shaped particles from components a), b), optionally c) and optionally d) is a pore-forming agent. This agent is soluble in body fluids and after being administered to the organism this agent dissolves thereby forming pores in the matrix. Thus the body fluids become access to the combination A) comprising components a), b) and optionally c) and d) and the active ingredient is released in a predetermined and controlled manner. Examples of pore-forming agents are polyalkylene ethers, polyvinyl alcohol, sugar and sugar alcohols. Examples for sugars are lactose, glucose and preferred saccarose. Examples for sugar alcohols are mannitol and sorbitol.

Preferred as pore-forming agents are polyalkylene ethers or polyvinyl alcohol. Said polyalkylene ethers or polyvinylalcohols are available in different aggregate forms, depending on their molecular weight, as liquids or solids at 25°C. For use in the instant invention the polyalkylene ethers and the polyvinylalcohols should be matrix-forming and shapable via compression methods. The molecular weight of the pore-forming agent should be selected adequately to allow pore-forming effects in contact with body fluids.

Examples of polyalkylene ethers are polybutylene ethers, polypropylene ethers or especially polyethylene ethers. Preferably a nonionic polymer of polyethylene oxide, a polyethylene glycol, a polyethyleneglycol alkyl ether or combinations thereof are used. Said matrix material B) in addition can contain one or more adjuvants d).

Most preferred as a material forming matrix B) is a a nonionic polymer of polyethylene oxide possessing a molecular weight (weight average) between 3M and 10 M, whereby M stands for a million.

Polyox 303:	57.5 g
Lactose:	3.3 g
Talc:	4.0 g
Magnesium stearate:	1.9 g
Ethylcellulose 200:	1.9 g
To result in a total of:	199.1 g

Example 17

Pellets containing 14.64 mg of ivermectin/pellet and 30% of Polyox 303:

Ivermectin:	83.17 g
Polyox 303:	47.3 g
Lactose:	22.1 g
Talc:	6.2 g
Magnesium stearate:	1.6 g
Ethylcellulose 200:	1.2 g
To result in a total of:	161.3 g

Example 18

Pellets containing 10,40 mg of ivermectin/pellet and 30% of Polyox 303:

Ivermectin:	57.46 g
Polyox 303:	47.5 g
Lactose:	46.9 g
Talc:	6.2 g
Magnesium stearate:	1.6 g
Ethylcellulose 200:	0,8 g
To result in a total of:	160.5 g

CLAIMS

1 A composition allowing a predefined and controlled release of an active ingredient to an organism when administered to said organism, which composition comprises a combination A) of at least two components

a) at least one active ingredient in dispersed solid form,

b) at least one gelling agent,

c) optionally at least one filler, and

d) optionally at least one adjuvant

which combination A) is in the form of discrete particles and is embedded into a matrix B) which is formed by a pore-forming agent and optionally at least one adjuvant.

2. A composition according to claim 1 wherein the active ingredient is a pharmaceutically active substance.

3. A composition according to claim 1 wherein the active ingredient is selected from the group consisting of antibiotics, antiparasitics, hormons, growth promoters, anti-cancer drugs, vitamines and vaccines.

4. A composition according to claim 2 wherein the pharmaceutically active substance is an antiparasitics, preferably an endectocide, and most preferably an avermectin or a milbemicin.

5. A composition according to claim 3 or 4 wherein the avermectin is ivermectin and/or abamectin.

6. A composition for combatting external and internal parasitoses according to claim 1, which contains an endectocide as an active ingredient and which is in the form of a subcutaneous implant constituted by one or more pellets that release the active ingredient in a controlled and prolonged way.

7. A composition according to claim 1 wherein the gelling agent is selcted from the group consisting of modified cellulose, modified starch, pectin, polyvinyl alcohol, polyvinyl pyrrolidone and dispersed silica or combinations thereof

8. A composition according to claim 7 wherein the modified cellulose is an alkylated cellulose, preferably ethylcellulose.

9. A composition according to claim 1 wherein the filler is selected from the group consisting of carbohydrates and silica or combinations thereof.

10. A composition according to claim 9 wherein the carbohydrate is a disaccharide, preferably lactose

11. A composition according to claim 1 wherein the pore-forming agent forming matrix B) is selected from the group consisting of polyethylene ether, polyvinyl alcohol, sugar, sugar alcohol or combinations thereof.

12. A composition according to claim 1 wherein the polyethylene ether is a nonionic polymer of polyethylene oxide, a polyethylene glycol or a polyethyleneglycol alkyl ether

13. A composition according to claim 1 wherein the composition is in the form of a pellet.

14. A composition according to claim 13 wherein an implant is constituted by a plurality of such pellets.

15. A composition according to claim 14 wherein said implants are packed in plastic cartridges.

16. A process of manufacturing the composition of claim 1 said process encompassing the measures:

i) combining components a), b), optionally c) and optionally d) according to claim 1 *in a mixing equipment*,

ii) mixing said components together with a liquid to form a shapable mass A)

iii) shaping said mass A) into a plurality of small pieces by applying a first shaping means to said mass A) and separating said mass A) into a plurality of small pieces;

iv) combining said small pieces of mass A) with pore-forming agent B) and optionally with at least one adjuvant d);

v) mixing said combination of components A) and B) to form a shapable composition; and

vi) shaping said composition to a desired shape by means of a second shaping means.

17. A process according to claim 16 wherein said second shaping means is a tablet press.

18. A method of treating an organism with an active ingredient in a predetermined and controlled manner said method comprises administering to said organism a composition according to claim 1.

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Bogotá, D.C.,

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Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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 Nº 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 31 MAR. 2006.

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