Industria y Comercio

SUPERINTENDENCIA

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. EXPEDIENTE Nº 03-61096

54. TÍTULO FORMULACIONES DE ANTIBIOTICOS DE IONOFORO

51. CLASIFICACIÓN INTERNACIONAL 51 A61K31/19, A61K9/00

71. SOLICITANTE ELI LILLY AND COMPANY

DOMICILIO INDIANAPOLIS, IN 46285, ESTADOS UNIDOS DE AMERICA

74. APODERADO ALVARO CORREA ORDOÑEZ

22. BOGOTÁ, D. C. 18 DE JULIO DE 2003

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(FORMA P 10)

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 03081096 00000000 Folios: 205
Fecha (MM): 2003-07-18 16:44:37 dicación
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

[X]	Patente de Invención	[ ]	Patente de Modelo de Utilidad
[ ]	Capítulo I.	[X]	Capítulo II.

(2) SOLICITANTE (71)

Nombre: ELI LILLY AND COMPANY.
Dirección: Indianapolis, IN 46285 Estados Unidos de América.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Indianapolis, Estados Unidos de América.
Teléfono: Fax:
E-Mail

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número

(3) REPRESENTANTE O APODERADO

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Teléfono: 6341500 Fax: 3762211
E-Mail: patents.bogota@bakernet.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.143.366 TP 20.281

(4) INVENTOR (ES) (72)

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Nacionalidad o Domicilio: New Zealand, New Zealand; New Zealand; New Zealand

(5) PCT (85)

Solicitud Internacional No. PCT/NZ01/00290 Fecha Diciembre 18, 2001
Publicación Internacional No. WO 02/49609 Fecha Junio 27, 2002

(6) Título (54) FORMULACIONES DE ANTIBIÓTICOS DE IONÓFORO

(7) Clasificación Internacional (51) A61K 9/100 A61K31/19.

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
NZ	Diciembre 19, 2000	NZ509092
NZ	Septiembre 13, 2001	NZ514183

(9) Comprobante de pago No. 33.815 **Fecha** MAYO 15, 2003

(10) ANEXOS

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [X] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [X] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [ ] Otros:

(11) FIGURA CARATERISTICA

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 T.P. 20.281

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SUPERINTENDENCIA Y COMERCIO
Radicacion : 03061096 00000000 Folios: 205
Fecha (AMD): 2003-07-16 16:44:37
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 33,015
FECHA : MAYO 15 DE 2003

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JORGE LUIS GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	13227941	15/05/2003	25,300,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN		400,000.00
		TOTAL :	9	400,000.

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

4 f

SECRETARÍA DE ESTADO
ESTADO DE INDIANA

APOSTILLA
(Convención de la Haya del 5 de octubre de 1961)

1. País: ESTADOS UNIDOS DE AMERICA

2. Este documento público ha sido suscrito por: Julie A. Worland

3. en calidad de Notario Público para el Condado de Morgan

4. y lleva el sello de Notario Público del Estado de Indiana

Certificó

5. en la ciudad de Indianápolis, Indiana

6. el ocho de enero de 2003,

7. por el Secretario del Estado de Indiana

8. No. A2002-31613

9. Sello: Sello del Estado de Indiana - 1816

10. Firma: (Todd Rokita)
Todd Rokita
Secretario del Estado de Indiana

ROBERTO M. OLARTE GARCIA
Traductor e Intérprete Oficial
Resolución No. 0041
Minijusticia 1995

NOTARIA ONCE (E) DE ESTE
CERTIFICO HAGO CONSTAR QUE ESTA
FOTOCOPIA COINCIDE CON EL
ORIGINAL QUE HE TENIDO A LA VISTA
18 JUL 2003
BOGOTA, D.C. - COLOMBIA
VERONICA PALMA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.

POD-02236

SECRETARY OF STATE
STATE OF INDIANA

Todd Rokita
Secretary of State

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. **Country: United States of America**
2. **This public document has been signed by** *Julie A. Worland*
3. **acting in the capacity of Notary Public in & for** *Morgan* **County**
4. **and bears the seal/stamp of notary public in & for the State of Indiana**

Certified

5. **at Indianapolis, Indiana**
6. **this** *Eighth* **day of** *January, 2003*
7. **by Secretary of State of Indiana**
8. **No. A2002-** *31613*

COMO NOTARIA ONCE (E) DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
18 JUL 2003
BOGOTA, D.C. - COLOMBIA
MONICA ZULMA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.

9. **Seal/Stamp:**

10. **Signature:**

Todd Rokita
Indiana Secretary of State

The State House, Indianapolis, Indiana 46204, (317) 232-6531, FAX (317) 233-3283

PODER Y CERTIFICACIÓN NOTARIAL

(nota traductor: Han sido diligenciados y suscritos en la columna izquierda (inglés) que corresponde a la columna derecha en español)

(nota traductor: punto 6- Acta del Directorio con fecha 29 de agosto de 1986 y Certificado de Constitución con fecha 17 de enero de 1901.)

EN TESTIMONIO DE LO CUAL, este Poder ha sido suscrito por Robert A. Armitage, Vicepresidente Ejecutivo y Asesor Jurídico, el 7 de enero de 2003 en Indianápolis, Indiana, Estados Unidos de América.

SUSCRITO Y JURAMENTADO ante mí el 7 de enero de 2003.

(firmado: Julie Ann Worland)
NOTARIO PUBLICO

JULIE ANN WORLAND
CONDADO MORGAN
MI COMISION VENCE:
20 DE JULIO DE 2008

ROBERTO M. OLARTE GARCIA
Traductor e Intérprete Oficial
Resolución No. 0041
Minijusticia 1996

NOTARIA ONCE (E) DE ESTE
CULO HAGO CONSTAR QUE ESTA
FOTOCOPIA COINCIDE CON EL
ORIGINAL QUE HE TENIDO A LA VISTA
8 JUL 2003
BOGOTA, D.C. - COLOMBIA
ONICA ZULMA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.

RABBECK, LARA, RODRIGUEZ & RUEDA
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POWER OF ATTORNEY

The undersigned,

(name of the company) Eli Lilly and Company

located in *(full street address)* Lilly Corporate Center

(city, state) Indianapolis, Indiana U.S.A.

declares that it hereby grants to

CARLOS REINALDO OLARTE AND/OR

ALVARO CORREA ORDOÑEZ

a full and sufficient power of attorney to apply to the proper national officers and authorities for the issue of:

Patents of Invention, Patents for Utility Models, Industrial Design Registrations, mergers, changes of name, assignments, filing and prosecution of oppositions, changes of address.

to which end it empowers them to take all steps necessary before said authorities for the objects stated, to file petitions, prepare descriptions, make protests, declarations, appeals and objections, pay imposts, apply for certifications, receive documents and securities, abandon applications and collect refunds. To the said mandatories sufficient power is granted hereby to receive notifications for and on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the patents, and to do everything that may be required, before administrative or judicial officers of any class giving them likewise power to substitute these presents and revoke such substitutions if necessary.

Done and subscribed in

Indianapolis, Indiana U.S.A.

On the *(day)* 17th day of *(month)* January

2003

(signature)

Robert A. Armitage
Senior Vice President
and General Counsel

PODER

La abajo firmada,

domiciliada en _____

declara por el presente otorgar a

CARLOS REINALDO OLARTE Y/O

ALVARO CORREA ORDOÑEZ

poder especial amplio y bastante para recabar de las oficinas y autoridades nacionales que correspondan, la obtención de :
Patentes de Invención, Patentes de Modelo de Utilidad, Registro de Diseños Industriales, fusiones, cambios de nombre, cesiones, presentación y trámite de oposiciones, cambios de dirección.

a cuyo efecto los faculta para dar ante dichas autoridades, todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, protestas, declaraciones, apelaciones y reclamos, oblar impuestos, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede a los expresados mandatarios poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de las pátentes se presentaren y hacer cuanto fuere necesario, ante las autoridades administrativas o judiciales de cualquier orden, dándoles asimismo facultad para sustituir el presente y en caso necesario revocar dichas sustituciones.

Dado y firmado en

_____

A los ____ días del mes de _____

2002

ESTADO NOTARIA ONCE (E) DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
18 JUL 2003
BOGOTA, D.C. - COLOMBIA
MONICA ZULMA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.

RANSEEK, LARA, RODRIGUEZ & RUEDA
MEMBERS OF THE FIRM
BAKER & McKENZIE
ATTORNEYS AT LAW

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NOTARIAL CERTIFICATION

This (day) 7th day of (month) January 2003 the undersigned Notary Julie Ann Worland (name of the notary)

CERTIFIES

1. That (name of the officer) Robert A. Armitage of legal age and domiciled in (city, state) Indianapolis, Indiana set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as (officer's title/position) Senior Vice President and General Counsel of the juridical person Eli Lilly and Company (name of the company)

4. That the juridical person Eli Lilly and Company (name of the company) having its home office in (full street address) Lilly Corporate Center, Indianapolis, Indiana 46285 U.S.A. is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source: (provide name of documents and their dates) Board Meeting Minutes dated August 29, 1986 and Certificate of Incorporation dated January 17, 1901.

Notary Public

CERTIFICACION NOTARIAL

A los _____ días del mes de _____ de 2003, el suscrito Notario

DA FE

1. Que _____ mayor y domiciliado en _____ suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3. Que el otorgante ha suscrito el referido documento en su condición de _____ de la persona jurídica

4. Que la persona jurídica _____ con sede en _____ está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se ha otorgado el poder está comprendido entre los que constituyen su objeto social.

5. Que el otorgante tiene efectivamente la representación que ostenta, y que esta es legítima.

6. Que ha tenido las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia: _____

El Notario Público

ESTE ES COPIA DEL ORIGINAL QUE REPOSA EN LA NOTARIA ONCE (11) DE BOGOTA, D.C. - COLOMBIA
ANGELICA ZULMA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.

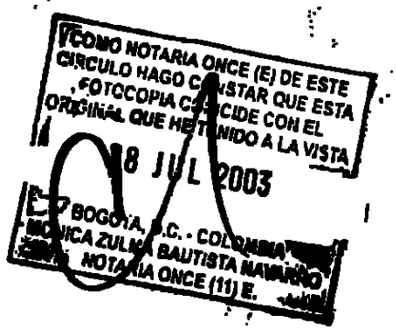
ESTE ES COPIA DEL ORIGINAL QUE REPOSA EN LA NOTARIA ONCE (E) DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
18 JUL 2003

IN WITNESS WHEREOF, this Power of Attorney has been signed by Robert A. Armitage, Senior Vice President and General Counsel this 7th day of January, 2003 at Indianapolis, Indiana USA.

SUBSCRIBED AND SWORN to be before me this 7th day of January, 2003.

Julie Ann Worland
NOTARY PUBLIC

JULIE ANN WORLAND
MORGAN COUNTY
MY COMMISSION EXPIRES:
JULY 20, 2008



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 June 2002 (27.06.2002)

PCT

(10) International Publication Number
WO 02/49609 A1

(51) International Patent Classification[7]: A61K 9/00, 47/34, 47/36, 47/10, 9/14

(21) International Application Number: PCT/NZ01/00290

(22) International Filing Date:
18 December 2001 (18.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
509092 19 December 2000 (19.12.2000) NZ
514183 13 September 2001 (13.09.2001) NZ

(71) Applicant *(for all designated States except US)*: ELI LILLY & COMPANY (NZ) LIMITED [NZ/NZ]; 9 Gladding Place, Manukau City, Auckland (NZ).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: AGNEW, Kim, Ewing, Melville [NZ/NZ]; 12 Revell Court, Pukekohe, Auckland (NZ). HEWITT, William, Austin [NZ/NZ]; 5 Ealing Crescent, Beachlands, Auckland (NZ). HANHAM, Craig; Richard [NZ/NZ]; 21 Wright Road, St Chevalier, Auckland (NZ). PURDY, Kevin, Grant [NZ/NZ]; 36 Sefton Ave, Grey Lynn, Auckland (NZ).

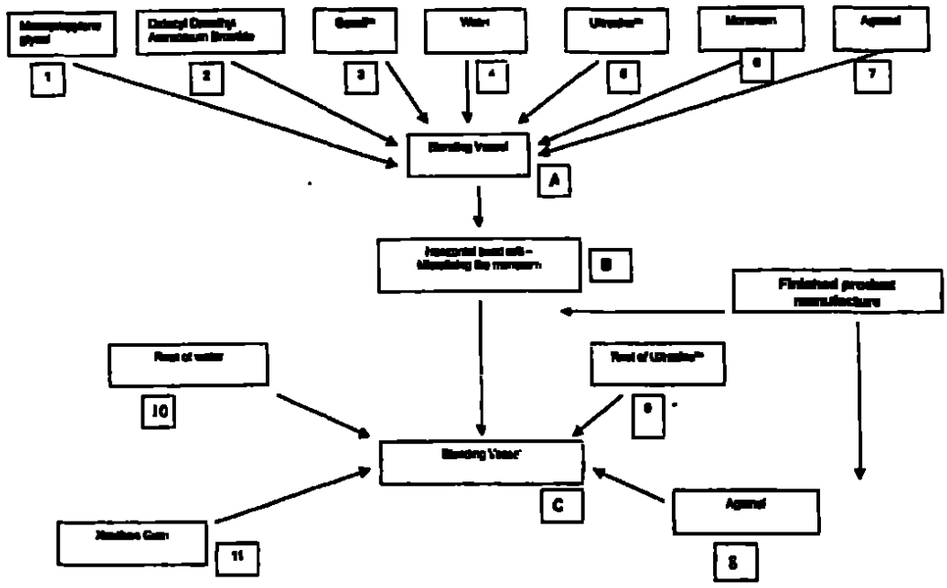
(74) Agents: CALHOUN, Douglas C et al.; A J Park, 6th Floor Huddart Parker Building, 1 Post Office Square, PO Box 949, Wellington (NZ).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: IONOPHORE ANTIBIOTIC FORMULATIONS



(57) Abstract: The invention relates to an ionophore antibiotic composition capable of dilution with water to a substantially stable dispersed form in all water then present, said composition comprising or including: - at least one ionophore antibiotic (preferably monensin) of a mean particle size of less than 20 microns. - and at least one dispersing agent. A method of preparing the ionophore antibiotic composition is also disclosed.

WO 02/49609 A1

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

"IONOPHORE ANTIBIOTIC FORMULATIONS"

The present invention relates to ionophore antibiotic compositions and particularly, but not solely, to ionophore antibiotic compositions capable of dilution with water, suitable for inclusion directly or via a holding tank in the drinking water of an animal to have administered and/or self administered an ionophore antibiotic or ionophore antibiotics.

BACKGROUND

Administration of ionophore antibiotics such as monensin to animals (preferably ruminants) is known to achieve in appropriate dosages advantages for a number of different purposes. These include the treatment or prevention of ketosis and/or bloat, the enhancement of milk production, enhancement of milk protein content in milk, enhancement of mineral uptake, enhancement of weight gain, and/or enhancement of feed conversion efficiency (in ruminants), desirable reproduction advantages and as a milk replacement. See US Patent 3,829,557.

In this respect we refer to European Patent Specification 0,139,595 A2 of KOFFOLK (1949) LTD which relates to a liquid ionophore antibiotic composition for ruminants and poultry where the antibiotic is dissolved in a non-toxic water-soluble organic solvent rather than a water soluble organic solvent, and in use the resulting solution is admixed with a liquid feed, a liquid vitamin concentrate or drinking water. There are claims for stability on standing.

The composition of EP 0,139,595 indicates that because monensin and its sodium salt is only slightly soluble in water that it is generally administered in a dry form in an animal feed and/or in dry liquid milk replacer compositions. The same is also indicated as being true for another ionophore antibiotic lasalocid which in US Patent 3,715,372 is reported to be completely insoluble in water.

The composition of EP 0,139,595 uses as an organic solvent for the ionophore antibiotic a solvent selected from the group comprising propylene glycol, glycerol, ethanol and isopropanol and mixtures thereof.

Example 1 of EP 0,139,595 indicates that 250 g of a mycelium containing 10% monensin was mixed at room temperature with 1250 cc propylene glycol for 2 hours by exposing the mixture to ultrasound. There is an indication that 50% of the monensin was found in solution in the propylene glycol.

Monensin is usually available commercially as the sodium salt of the acid. Monensin sodium is available in two forms, namely, a crystalline form or a mycelial form. The mycelial form has only about a 20% activity while the crystalline form has greater than 90% active monensin sodium.

Reference herein to "monensin" where the context allows encompasses all forms thereof including monensin, alkali metal salts of monensin and monensin esters and includes mixtures. Likewise for the other ionophore antibiotics.

In our New Zealand Patent Specification 272574/272940 (equivalent to PCT/NZ96/00068 WO 97/03650) we disclose an aqueous base suspension concentrate of an ionophore antibiotic or ionophore antibiotics such as monensin.

In one aspect in NZ 272574/272940 that invention is defined as **an aqueous base suspension concentrate of an ionophore antibiotic or ionophore antibiotics** capable of aqueous dilution (if desired) and capable (with or without such aqueous dilution) of being orally administered to an animal by an active dosing regime (eg; by drenching), said concentrate comprising or including

(I) at least one ionophore antibiotic in

(II) an aqueous system containing

(i) a wetting and/or surfactant agent, (preferably alkyl polyglycoside)

(ii) an antifreeze agent or agents in which the ionophore antibiotic or

antibiotics is or are no more than sparingly soluble,

(iii) a suspension agent (eg gum(s)),

(iv) optionally, an antifoam agent or system,

(v) optionally, a preservative,

(vi) optionally, a de-bittering agent,

(vii) optionally, a pH buffering system, and

(viii) water.

The preferred ionophore antibiotic of NZ 272574/272940 is sodium monensin. Preferably an antifreeze agent or agents in which the ionophore antibiotic(s) is no more than sparingly soluble (such as a glycol or polyglycol) is present. Additional, preferably an antifoam agent is present (e.g. simethicone and a particulate carrier such as silicon dioxide therefor).

NZ 272574/272940 also discloses a method of drenching an animal with such an ionophore antibiotic which involves administering orally to such an animal a diluted form of the compositions, such dilution being with water.

We have found monopropylene glycol to be a poor solvent of monensin. While we have in NZ 272574/272940 referred to monopropylene glycol as being an antifreeze agent in which the ionophore antibiotic is sparingly soluble, we do appreciate that solubility to the extent referred to in Example 1 of EP 0,139,595 may be achieved when induced with ultrasound or heating.

The form of crystalline monensin used for the examples in NZ272574/272940 has a mean particle size of the order of about 40 microns and in order to hold such large particles in suspension an aggressive supporting system for that purpose has been required.

Thus despite the advances represented by the invention disclosed in NZ272574/272940 (providing compositions useful for an active system of administering ionophore

antibiotics to ruminants), and despite assertions of EP139595, there continues to be a substantial need for compositions containing ionophore antibiotics which are inherently poorly soluble or insoluble in aqueous based systems, suitable for passive system administrations to ruminants. Such compositions must, to avoid under-dosing or toxic dosing, remain substantially homogeneous for extended periods of time.

The present invention investigates alternatives to such aggressive systems and targets a dosable composition capable of dispersion stability as a suspension in highly dilute drinking water for animals.

The present invention relies upon both a preferred smaller mean particle size of the ionophore antibiotic and an associated regime including related methods of manufacture, uses etc.

The present invention also recognises *inter alia* the therapeutic, energy and productivity benefits were monensin or any other suitable ionophore antibiotic (see the listing in our aforementioned patent specification, and below) to be used as a trough treatment.

Trough Treatment Systems

Currently three types of trough treatment system for animal drinking water and not hitherto used with an ionophore antibiotic are known.

Three types are in use:

1. Proportional feed systems e.g. that branded DOSATRON™
   delivers a %mix in proportion to demand (from 0.2-2% for dosatron).
   Aim is to spread delivery of the complete batch over 24 hours
2. Dump systems
   Continually delivers drench into lines regardless of demand. Tends to be all used up within 5 hours.
3. Individual trough systems e.g. PETA™ dispenser
   Delivers concentrated drench in relation to demand but pay out is skewed early on.

The present invention includes an ionophore antibiotic base composition capable of aqueous dilution which may be useful in such a trough treatment system. The object of the present invention is to provide such a composition and/or to provide drinking water for an animal to allow administration of an ionophore antibiotic to the animal.

We have determined that a microfine form of an ionophore antibiotic with its smaller mass to surface area ratio is a significant advantage over less fine (eg; 40 micron mean particle size) ionophore antibiotic inclusions in an aqueous composition and more so when it is to be used in such a way where it is subjected to unsupervised dilution, eg; to provide an infeed (directly or indirectly) into a dilution quantity of trough make up water. Such advantages to uniform suspendability we believe to be equally applicable to the more preferred crystalline forms as well as the less preferred mycellial forms of the ionophore(s).

We have also determined that a suitable glycol such as monopropylene glycol can be used in such a way to pre-prepare an ionophore antibiotic for subsequent suspension as a aqueous concentrate and thereafter to carry at least an antifreeze advantage over to its subsequent use (eg; as an infeed aqueous concentrate for a dose-certain water system) without leading to crashing out of the ionophore antibiotic. Glycols (such as monopropylene glycol) unless agressively treated provide no significant uptake of the stably suspended ionophore antibiotic (such as monensin) from an aqueous system. This we consider desirable since an organic uptake can lead to crashing out on dilution. For example, an organic solvent, such as methanol, allows monensin to crash out of solution if any water is added.

In the preferred forms of the present invention the ionophore antibiotic of choice is monensin in any of its appropriate forms (eg; sodium monensin). Other ionophore antibiotics however fall within the scope of the present invention and these include

Lonomycin, Ionomycin, Laidlomycin, Nigericin, Grisorixin, Dianemycin, Lenoremycin, Salinomycin, Narasin, Antibiotic X206, Alborixin, Septamycin, Antibiotic A204, Maduramicin and Semduramicin, Compound 47224, Lasalocid (also including factors A, B, C, D and E), Mutalomycin, Isolasalocid A, Lysocellin, Tetronasin, Echeromycin, Antibiotic X-14766a, Antibiotic A23187, Antibiotic A32887, Compound 51532 and K41.

STATEMENTS OF THE INVENTION

In a first aspect the present invention consists in **a method of forming an aqueous suspension** capable of subsequent dilution, said method including prior to any substantial presence of water and/or a suspension agent (such as a suitable gum), milling the ionophore antibiotic or ionophore antibiotics (preferably in a crystalline form) with at least a suitable glycol.

Preferably said milling is to a mean particle size very much less than 40 microns.

Preferably the mean particle size is less than 20 microns, more preferably less than 5 microns and most preferably into a mean particle size of from 0.1 to 1.0 microns.

Preferably said milling includes the presence of a suitable lignosulfonate and/or a suitable polyglycoside.

Preferably said milling includes the presence of an antifoam agent.

Preferably said milling includes at least some water.

Preferably no suspension agent (eg; a gum typified by xanthan gum or guar gum) is present at said milling.

Preferably said method is performed substantially as hereinafter described with reference to the accompanying drawing.

Preferably the product includes as its suitable glycol monopropylene glycol.

Preferably the aqueous suspension is of a kind hereinafter described which includes monopropylene glycol, an additional wetting agent (eg; a lignosulfonate or polyglycoside or both) and a suspension agent.

Preferably the ionophore antibiotic is monensin and preferably that monensin is in a crystalline form.

In a further aspect the present invention consists in a method of forming an aqueous suspension of at least one ionophore antibiotic capable of subsequent dilution, said method including milling the ionophore antibiotic or ionophore antibiotics (preferably in a crystalline form) with at least a suitable polyglycoside or a suitable lignosulfonate.

Preferably said method performs part of a method as previously defined.

In yet a further aspect the present invention consists in a method of forming an aqueous suspension of at least one ionophore antibiotic capable of subsequent dilution, said method comprising or including

milling an ionophore antibiotic or ionophore antibiotics (preferably in a crystalline form) with at least (i) a suitable glycol and (ii) at least one of a suitable lignosulfonate and a suitable polyglycoside, and

subsequently formulating the suspension with at least water or, optionally, additional water.

Preferably said subsequent formulation involves the addition of a suitable dispersion agent.

Preferably said suitable dispersion agent is a suitable gum typified by xanthan gum and guar gum.

Other suitable dispersion agents include hydroxy-ethyl cellulose, bentonite clay, montmorillinite clay and fumed silica.

Preferably said ionophore antibiotic is of sufficient purity as to minimise any requirement for an anti foaming agent but if an anti foaming agent is necessary, preferably said anti foaming agent is a GENSIL™ system, i.e. of simethicone/silicon dioxide support for the simethicone.

Preferably said suspension includes a buffer system.
Preferably said suspension includes a preservative.

Where reference is made to a suitable glycol preferably said glycol is a liquid and preferably said glycol assumes an anti freezing role in the resultant aqueous suspension.

Example of a suitable glycol is monopropylene glycol but other examples include ethylene glycol, diethylene glycol and dipropylene glycol.

Preferably the ionophore antibiotic or ionophore antibiotics is at least primarily of a crystalline form but in other forms it can in part be of the mycelial form. For example, if as is preferred, the ionophore antibiotic is monensin (e.g. present for example as sodium monensin), preferably the ionophore antibiotic is substantially free of the mycelial form. Were the mycelial formed to be utilised however, preferably there are commensurate changes in the inclusions to reflect the lesser activity of that form or an additional input to any dilution system to achieve appropriate activities.
Preferably said milling is in liquid supported conditions (preferably as a result of a liquid glycol inclusion), preferably with a minimum of water necessary for the purpose (if any), and preferably is such as to reduce the antibiotic to a microfine form.

In a preferred form of the present invention, irrespective of whether or not the milling is dry or in a liquid environment, preferably the ionophore antibiotic is reduced to a mean particle size less than 50 microns.
Preferably said mean particle size is reduced to less than 20 microns.
Most preferably the microfine condition of the ionophore antibiotic is to a mean particle size less than 5 microns.
Most preferably the mean particle size resulting from the milling procedure or procedures (can be a single or multiple milling procedures) is such as to provide a mean particle size of the preferably crystalline ionophore antibiotic (e.g. monensin) in a range of from 0.1 to 1.0 microns.

Preferably the milling stage or stages involves milling with a suitable polyglycoside or lignosulfonate, or both. One such polyglycoside is alkyl polyglycoside. One possible lignosulfonate compound is ULTRAZINE NA™ or BORRESPERSE NA™ [of Borregaard Industries Ltd of Norway] (most preferably ULTRAZINE NA™).
Optionally GENSIL™ or another suitable antifoam agent is also milled with the crystalline monensin or other antibiotic.
Preferably the milling of all coating agents is simultaneous although it can be in part or totally serially.

In a preferred mix the ionophore antibiotic is milled simultaneously with liquid monopropylene glycol and a suitable polyglycoside and/or lignosulfonate compound (more preferably a lignosulfonate) having a "wetting" function and (optionally) an antifoam agent and/or some water.

In a further aspect the present invention consists in **an aqueous suspension** formed by one or more of the methods of the present invention.

In still a further aspect the present invention consists in **an aqueous ionophore antibiotic suspension** capable of further dilution without any substantial crashing out of the ionophore inclusion, said aqueous concentrate comprising or including

an ionophore antibiotic,
monoproplyene glycol (or other suitable glycol),
optionally a further material having a wetting characteristic,
a suspension agent,
optionally an antifoam agent, and
water,

wherein at least the monopropylene glycol and the ionophore antibiotic have been milled together prior to mixing with the water or at least any substantial amount of the water.

Preferably the further material having a wetting characteristic is a suitable polyglycoside or lignosulfonate.

Preferably said suitable polyglycoside is alkyl polyglycoside although more preferably the additional wetting agent is a lignosulfonate typified by ULTRAZINE NA™ or BORRESPERSE NA™ (more preferably ULTRAZINE NA™).

Preferably the ionophore antibiotic is a crystalline form rather than a mycellial form.

Preferably the ionophore antibiotic is monensin or a monensin.

Preferably the ionophore antibiotic at least post milling has a particle size less than 5 microns and more preferably below 2 microns.

Preferably the particle size range of the antibiotic is from 0.1 microns to 1.0 microns.

Preferably the aqueous ionophore antibiotic suspension remains substantially homogeneous for a period longer than 7 days; more preferably for a period longer than 24 days.

It does not matter whether or not the milling reduces the ionophore antibiotic to the requisite mean particle size or whether or not it is already milled almost to that size. What is important is to have resultant particles of that size appropriately coated with the "wetting" agents which includes preferably a multifunctional glycol (eg; monopropylene glycol) and preferably an additional wetting agent.

In a further aspect the present invention consists in an **aqueous ionophore antibiotic suspension** comprising or including

0 to20% w/v of a microfine (i.e. less than 40 micron mean particle size) crystalline ionophore antibiotic,

2 to 20% w/v of monopropylene glycol,

0 to 10% w/v of a wetting agent,

0.1 to 5% w/v suspension agent, and

water.

Preferably the aqueous ionophore antibiotic suspension remains substantially homogeneous for a period longer than 7 days; more preferably for a period longer than 24 days.

Preferably the formulation is substantially as described in any one of Examples 1 to 5.

In another aspect the present invention is directed to **a composition suitable for providing a direct in feed and/or indirect in feed (e.g. via a make up tank) into a water system from which target animal can drink,**

said composition being an aqueous composition of (at least)

(a) microfine ionophore antibiotic or microfine ionophore antibiotics,

(b) a glycol in which the ionophore antibiotic(s) is or are no more than sparingly soluble,

(c) a wetting agent,

(d) a suspension agent, and

(e) water, and

optionally any one or more of

- an antifoam agent or system,
- a preservative,
- a debittering agent, and
- a pH buffering system.

Preferably the aqueous ionophore antibiotic suspension remains substantially homogeneous for a period longer than 7 days; more preferably for a period longer than 24 days.

Preferably said suspension agent is xanthan gum.

Preferably said wetting and/or surfactant agent (c) is a lignosulphonate (e.g. ULTRAZINE NA™) or a polyglycoside (preferably alkyl polyglycoside).

Preferably said ionophore antibiotic is in either a crystalline or mycellial form or both.

Preferably a crystalline form is utilised.

Preferably said ionophore antibiotic is monensin (e.g. sodium monensin).

Preferably said microfine ionophore antibiotic is of a particle size less than 5 microns (preferably less than 2 microns) and preferably has a mean particle size in the range of from 0.1 to 1.0 microns.

Preferably xanthan gum is present and in a quantity greater than 0.16 w/v% and preferably about 0.4 w/v% (ie, the amount required being more for the more concentrated aqueous concentrate, eg; will unlimited dilute none may be required).

Preferably the mode of mixing and formulation is substantially as disclosed herein with a preferred composition being substantially as follows (wherein preferably the mean sodium monensin particle size is substantially 5 microns)–

Ingredient (common /chemical name)	Quantity (%w/w)	Function
Sodium Monensin	6.33%(about 6%monensin) w/v	Ionophore antibiotic
Monopropylene glycol	10% w/v	Antifreeze/
Alkyl Polyglycoside or	0.5% w/v	Surfactant/Wetting agent
ULTRAZINE NA™	4-5% w/v	
Disodium Phosphate Anhydrous	0.355% w/v	Buffer
MonoPotassium phosphate Dihydrate	0.04% w/v	Buffer
Dialkyl dimethyl ammonium bromide	.0064% w/v	Preservative
Xanthan Gum	0.4% w/v	Suspension agent
Simethicone	0.333% w/v)	(e.g. GENSIL™
Silicon Dioxide	0.167% w/v)	Antifoam system)
Water	to 100%	

An alternative preferred formulation is (wherein preferably the mean sodium monensin particle size is substantially 5 microns):

Ingredient name (common or chemical)	Quantity (%w/w)	Function
Sodium Monensin QA 166H	6.747%	Active
Monopropylene glycol	10%	Antifreeze
Didecyl dimethyl Ammonium Bromide	0.1%	Preservative
Xanthan Gum	0.5%	Suspension agent
Sodium lignosulphonate	4.1%	Wetting agent
Alkyl Polyglycoside	3.8%	Wetting agent

Simethicone	0.333%	Antifoam
Silicon Dioxide	0.167%	Antifoam
Water balance q.v	74.47%	diluent

In other aspect the present invention is a pre mill mix or post mill mix of the present invention as hereinafter described.

In yet a further aspect the present invention consists in a composition for inclusion in a water trough fed in system being a composition as previously defined which without dilution is adapted to be in feed into the water supply.

In still a further aspect the present invention consists in a drinking water supply for an animal (preferably a ruminant animal) which has an in feed therein of a composition as previously defined.

In yet a further aspect the present invention consists in a method of providing an ionophore antibiotic to a target mammal which comprises providing to the animal drinking water with a dispersed ionophore antibiotic, said ionophore antibiotic having been included in the water supply by an intake from a composition as previously defined.

According to a further aspect of the invention there is provided an ionophore antibiotic composition capable of dilution with water to a substantially stable dispersed form in all water then present, said composition comprising or including:

- at least one ionophore antibiotic of a mean particle size of less than 20 microns,
- and at least one dispersing agent.

Preferably the mean particle size of at least one ionophore antibiotic is substantially 5 microns.

Preferably the dispensed form in water remains substantially homogeneous for at least 24 days.

Preferably the at least one dispersing agent is selected from one or more of the following:

i) a compatible polyglycoside capable of acting as a dispersing agent,
ii) a compatible lignosulfonate capable of acting as a dispersing agent, and
iii) a compatible and suitable glycol in a form capable of acting as a dispersing agent.

Preferably a liquid vehicle is or is also present which preferably is or includes water.
Preferably or alternatively said liquid vehicle is or includes one compatible liquid organic compound, preferably selected from mineral and vegetable oils.
Preferably the ionophore antibiotic(s) has been milled in the presence of at least one of :

i) a compatible polyglycoside capable of acting as a dispersing agent,
ii) a compatible lignosulfonate capable of acting as a dispersing agent, and
iii) a compatible and suitable glycol in a form capable of acting as a dispersing agent.

Preferably the milling is in the absence of any suspension agent, or alternatively a suspension agent selected from the gums as previously described is present; preferably the suspension agent is one or more of xanthan gum, guar gum, acacia gum and a cellulose gum.
Preferably a liquid vehicle(s) was present at the time of milling of the ionophore antibiotic sufficient to reduce the consistency of the mill mix to a millable consistency.

According to a further aspect of the invention there is provided **animal drinking water** having at least one particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic is stably suspended.
Preferably the ionophore antibiotic remains stably suspended for at least 24 days.
Preferably particles of the ionophore antibiotic(s) are of a mean particle size of less than 10 microns; more preferably they are of a mean particle size of substantially 5 microns.
Preferably the drinking water is made by a proportioned mix dispensing there into of a more concentrated aqueous suspension of the ionophore antibiotic and dispersing agents present in that more concentrated aqueous suspension provides the substantially uniform dispersion of the ionophore antibiotic(s) in the drinking water.

Preferably the more concentrated aqueous suspension contains ore or more suspension agents.

According to a further aspect of the invention there is provided animal drinking water having at least one particulate ionophore antibiotic substantially uniformly suspended therein, wherein the particles of the ionophore antibiotics are of a mean particle size less than 10 microns; more preferably the particle size of the ionophore antibiotics are of a mean particle size of substantially 5 microns.
Preferably the ionophore antibiotic remains stably suspended for at least 24 days.

According to a further aspect of the invention there is provided trough water accessible to an animal to drink, the water having a particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic is stably suspended.
Preferably the ionophore antibiotic remains stably suspended for at least 24 days.
Preferably the particles of the ionophore antibiotic(s) is of a mean particle size of less than 10 microns; more preferably the particles of the ionophore antibiotic(s) is of a mean particle size of substantially 5 microns.
Preferably the trough water is made by a proportioned mix dispensing there into of a more concentrated aqueous suspension of the ionophore antibiotic and dispersing agents present in that more concentrated form provides the substantially uniform dispersion of the ionophore antibiotic(s) in the drinking water.
Preferably the more concentrated aqueous suspension contains ore or more suspension agents.

According to a further aspect of the invention there is provided trough water accessible to an animal to drink the water having a particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic remains stably suspended for at least 24 days.
Preferably the particle size of the ionophore antibiotics are substantially 5 microns.
Preferably the ionophore antibiotic remains stably suspended for at least 24 days.

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According to a further aspect of the invention there is provided a method of dispensing a particulate ionophore antibiotic into a body of drinking water which comprises or includes the steps of :

- taking a composition comprising or including at least one ionophore antibiotic of mean particle size of less than 20 microns and at least one dispersing agent:
- forming an aqueous suspension of the composition that has the ionophore antibiotic(s) substantially uniformly dispersed therein and which aqueous suspension is available for dispensing into animal drinking water, and
- dispensing at a rate (continuously or continually), that aqueous suspension into the drinking water or a makeup supply of water thereto so as to provide the body of drinking water with a uniform dispersion of the ionophore antibiotic(s) therein which is within an acceptable imbibing concentration range for the animal or animals having access thereto.

Preferably the mean particle size of the at least one ionophore antibiotic is substantially 5 microns.

Preferably said composition is in the form of a stable aqueous suspension prior to the forming of an aqueous suspension and the subsequent dispensing thereof into the drinking water or a make up supply of water.

Preferably said composition includes one or more dispersing agent selected from one or more of the following:

i) a compatible polyglycoside capable of acting as a dispersing agent,
ii) a compatible lignosulfonate capable of acting as a dispersing agent, and
iii) a compatible and suitable glycol in a form capable of acting as a dispersing agent.

Preferably a suspension agent selected from gums (as previously described) is present.

Preferably the ionophore antibiotic(s) remains stably suspended for at least 24 days.

According to a further aspect of the invention there is provided a body of drinking water having a particulate ionophore suspended therein prepared by the method as previously described.

According to a further aspect of the invention there is provided a **method of forming a suspendable composition of at least one ionophore antibiotic** and which suspendable composition is capable of subsequent dilution, said method including, prior to any optional presence of water and optional presence of a suspension agent, milling the ionophore antibiotic(s) with a suitable glycol.

Preferably said milling takes place in the presence of at least some liquid, which preferably includes water.

Preferably no gum is present.

Preferably said milling is to a mean particle size very much less than 20 microns; more preferably the mean particle size is of about 5 microns.

Preferably the milling takes place in the presence of a suitable lignosulfonate.

Preferably said milling takes place in the presence of a suitable Polyglycoside.

Preferably said milling takes place in the presence of a suitable antifoam agent.

According to a further aspect of the invention there is provided a suspendable composition of at least one ionophore antibiotic prepared according to the method as previously described.

According to a further aspect of the invention there is provided a **method of forming a suspendable composition of at least one ionophore antibiotic** and which suspendable composition is capable of subsequent dilution, said method including, prior to any optional presence of water and optional presence of a suspension agent, milling the ionophore antibiotic(s) with a suitable dispersion agent.

Preferably the milling takes place in the presence of a suitable lignosulfonate.

Preferably or alternatively said milling takes place in the presence of a suitable polyglycoside.

Preferably said suitable dispersion agent is selected from the group consisting of a suitable lignosulfonate and a suitable polyglycoside.

Preferably the mean particle size is less than 20 microns; more preferably less than 10 microns; even more preferably the mean particle size is substantially 5 microns.

Preferably said milling takes place in the presence of a suitable antifoam agent.
Preferably said milling takes place in the presence of at least some liquid..
Preferably a suitable glycol is present.
Preferably no gum is present.

According to a further aspect of the invention there is provided a dose dispensable ionophore antibiotic composition comprising or including:

- at least one ionophore antibiotic,
- at least one dispersing agent,
- at least one suspension agent, and
- water,

wherein the ionophore antibiotic(s) and at least one dispersing agent have been milled together in the presence of a liquid (which may be water or may include water but not necessarily so) and where the dispersing agent has been added post-milling in the presence of water.

Preferably the ionophore antibiotic is of a mean particle size of less than 50 microns; more preferably a mean particle size of less than 20 microns.
Preferably at least one suspension agent is or includes a gum and no such gum was present at the milling procedure.
Preferably some water was present at the milling procedure.
Preferably a polyglycoside was present as a dispersing agent at the milling stage.
Preferably a lignosulfonate was present as a dispersing agent at the milling stage.
Preferably a glycol was present as a dispersing agent at the milling stage.
Preferably an alkyl polyglycoside, a lignosulfonate and a propylene glycol are present at the milling stage.
Preferably any one or more of an antifoam agent or system, a preservative, a debittering agent and a pH buffering system is present.

According to a further aspect of the invention there is provided a milled product useful in providing an aqueous suspension of at least one ionophore antibiotic, said product being the milled outcome of a mill mix of at least

- at least one ionophore antibiotic, and
- at least one dispersing agent,

wherein the mill mix has been substantially free of suspension agents selected from the gums previously described and the mill mix has included at least one liquid component (which optionally can be the or one of the dispersing agent(s) or an additional material),

and wherein, in the product, the process of milling has resulted in some physical association of the or at least one dispersing agent on the ionophore antibiotic particles,

and wherein, in the product, the mean particle size of the ionophore antibiotic(s) is less than 20 microns.

Preferably the mean particle size is substantially 5 microns.

According to a further aspect of the invention there is provide a suspendable composition for substantial dilution by water, said method comprising or including:

(I) milling at least one ionophore antibiotic and at least one dispersing agent so as to provide some physical association of the or at least one dispersing agent on ionophore antibiotic particles of a mean particle size of less than 20 microns, and

(II) blending the post mill ionophore antibiotic(s)/dispersing agent(s) milled outcome with at least a suspension agent.

This invention may also be said broadly to consist in the parts, elements and features referred to or indicated in the specification of the application, individually or collectively, and any or all combinations of any two or more of said parts, elements or features, and where specific integers are mentioned herein which have known equivalents in the art to which this invention relates, such known equivalents are deemed to be incorporated herein as if individually set forth.

The invention consists in the foregoing and also envisages constructions of which the following gives examples.

DEFINITIONS

Wherein the specification the following terms are used there are a number of possible alternatives, examples of which follow:

Surfactants / Dispersants:

- sorbitan esters
- ethoxylated sorbitan esters
- castor oil ethoxylates
- ethoxylated fatty acids
- ethoxylated alcohols
- polyethylene glycol fatty acids
- condensed napthalene sulphonic acid
- glycerol esters
- phosphate esters
- sodium lauryl sulphate
- sodium polyacrylate
- ammonium polyacrylate
- octyl phenyl ethoxylates
- nonyl phenyl ethoxylates
- quaternary ammonium compounds
- sulphosuccinates
- soya lecithin

Suspending aids, including gums:

- aluminium stearate
- silicon dioxide
- modified clay including Smectite, Monmorillonite, Hectorite, Bentonite
- dehydrogenated castor oil
- titanium chelates
- alkali soluble acrylic polymers
- nonionic diurethanes
- polyvinyl pyrollidone
- polyvinyl alcohol
- guar gum
- gum arabic
- hydroxy propyl methyl cellulose

- hydroxy ethyl cellulose
- sodium carboxy methyl cellulose
- hydrophobically modified hydroxy ethyl cellulose

Defoamers / Antifoams
- polymethyl siloxane
- unsaturated hydrocarbon oil
- mineral oil
- silica in oil type

Preservatives:
- oxazolidines
- benzothiazoles
- benzalkonium chloride
- substituted triazines
- isothiazolones
- hemiacetals
- substituted benzoates
- zinc pyridinethiol oxide
- sodium pyridinethiol oxide

Buffering agents:
- potassium tetroxalate
- potassium hydrogen tartrate
- potassium hydrogen phthalate
- borax

DETAILED DESCRIPTION OF THE INVENTION

Preferred forms of the present invention will now be described with reference to the accompanying drawings in which

Figure 1: shows one mixing procedure utilised in accordance with the invention,

Figure 2: shows a second mixing procedure utilised in accordance with the invention, and

Figures 3A – 3C: illustrate a DOSTATRON™ trough treatment system in three different modes of operation.

Shown in figures 3A to 3C are three installations of a DOSATRON™ type installation used for dosing materials into drinking water. The DOSATRON™ apparatus is recommended as being usable in line (figure 3A), on a bypass line (figure 3B) and in parallel (figure 3C). In this respect see the publicity materials available from the New Zealand distributor Mark Bell-Booth Ltd.

The DOSATRON™ apparatus itself employees a dosing piston driven by a volumetric hydraulic piston motor. The spread rhythm of the motor is proportional to the flow of water passing through the system and thus the rate of injection will likewise remain proportional in its reciprocating motion.

The apparatus has the capability of a wide range of daily dose settings and the parallel arrangement shown in figure 3 allows these to be doubled owing to the use of two DOSATRON™ dispensing units.

Preferred forms will now be described with reference to the following examples of which the mixing procedures utilised is preferably as depicted and sequenced in one of Figures 1 or 2.

The present invention recognises that having evolved a suitable stable aqueous suspension of microfine monensin a predictable in feed thereof to animals is possible simply by providing to the animal drinking water which includes the microfine ionophore antibiotic dispersed therein, said ionophore antibiotic having been included in the water supply by an intake directly or indirectly from a composition as previously defined. The less dilute the concentrate the more suspension agent we have found to be desirable.

Preferably the composition is for use in one or more of the trough treatment systems available.

Example 1

Sodium Monensin	6.33%(about 6%monensin) w/v
Monopropylene glycol	10% w/v
ULTRAZINE NA™	4-5% w/v
Disodium Phosphate Anhydrous	0.355% w/v
MonoPotassium phosphate Dihydrate	0.04% w/v
Dialkyl dimethyl ammonium bromide	.0064% w/v
Xanthan Gum	
0.4% w/v	
Simethicone	] GENSIL™
0.333% w/v	
Silicon Dioxide] Antifoam	0.167% w/v
Water to 100%	

Milling has resulted in a mean particle size for sodium monensin of 5 microns.

Example 2

Sodium Monensin	6.33%(about 6%monensin) w/v
Monopropylene glycol	10% w/v
Alkyl Polyglycoside	0.5% w/v
Disodium Phosphate Anhydrous	0.355% w/v
MonoPotassium phosphate Dihydrate	0.04% w/v
Dialkyl dimethyl ammonium bromide	.0064% w/v
Xanthan Gum	0.4% w/v
Simethicone] GENSIL™	0.333% w/v
Silicon Dioxide] Antifoam	0.167% w/v
Water to 100%	

Milling has resulted in a mean particle size for sodium monensin of 5 microns.

Example 3

Sodium Monensin	6.33%(about 6%monensin) w/v
Monopropylene glycol	10% w/v
ULTRAZINE NA™	4-5% w/v
Disodium Phosphate Anhydrous	0.355% w/v
MonoPotassium phosphate Dihydrate	0.04% w/v
Dialkyl dimethyl ammonium bromide	.0064% w/v
Xanthan Gum	0.4% w/v
Simethicone] GENSIL™	0.333% w/v
Silicon Dioxide] Antifoam	0.167% w/v
Sorbitol as a Debittering agent	3.5% w/v
Water to 100%	

Milling has resulted in a mean particle size for sodium monensin of 5 microns.

Example 4

Sodium Monensin	6.33%(about 6%monensin) w/v
Monopropylene glycol	10% w/v
Alkyl Polyglycoside	0.5% w/v
Disodium Phosphate Anhydrous	0.355% w/v
MonoPotassium phosphate Dihydrate	0.04% w/v
Dialkyl dimethyl ammonium bromide	.0064% w/v
Xanthan Gum	0.4% w/v
Simethicone] GENSIL™	0.333% w/v
Silicon Dioxide] Antifoam	0.167% w/v
Sorbitol as a Debittering agent	3.5% w/v
Water to 100%	

Milling has resulted in a mean particle size for sodium monensin of 5 microns.

Example 5

Ingredient name (common or chemical)	CAS number	Quantity (%w/w)	Function
Sodium Monensin QA 166H	17090-79-8	6.747%	Active

Monopropylene glycol	57-55-6	10%	Antifreeze
Didecyl dimethyl Ammonium Bromide	2390-68-3	0.1%	Preservative
Xanthan Gum	11138-66-2	0.5%	Suspension agent
Sodium lignosulphonate	8061-51-6	4.1%	Wetting agent
Alkyl Polyglycoside	68515-73-1	3.8%	Wetting agent
Simethicone	8050-81-5	0.333%	Antifoam
Silicon Dioxide	7631-86-9	0.167%	Antifoam
Water balance q.v	7732-18-5	74.47%	diluent

Milling has resulted in a mean particle size for sodium monensin of 5 microns.

Simethicone and Silicon dioxide together make up the proprietary brand "Gensil".

1. Preparation Procedure

The formulations of each of Examples 1 to 4 can be prepared by the procedure shown in Figure 1. The formulation of Example 5 is prepared by the procedure shown in Figure 2. The preferred method of preparing a formulation such as Example 1 is as follows.

As can been seen from Figures 1 and 2 a blending vessel (A) which can, if desired, be the horizontal bead mill (B) but is preferably not, and a blending vessel (C) are utilised as the apparatus.

Most preferably however there is a three stage equipment base for the process viz. blending vessel (A), horizontal bead mill (B) for microfining the ionophore antibiotic and a blending vessel (C).

As can be seen from Figure 1 ingredients 1 through 6 are blended in the reference number sequence in the blending vessel (A) prior to passage into the horizontal bead mill (B). These pre-blended materials include :

- monopropylene glycol,

- dialkyl dimethyl ammonium bromide,
- GENSIL™ antifoam,
- some water,
- ULTRAZINE NA™ wetting agent, and
- monensin.

After the milling that premill mix, the product can be taken away either as an intermediate product (eg; post mill product) for subsequent use elsewhere for blending. Preferably however the output milled mix passes to blending vessel (C) where it is blended with the rest of the water (7), the remainder of the ULTRAZINE NA™ wetting agent (8) and the xanthan gum or other dispersion agent (9).

With a formulation whether to the formula of Example 1 or Example 3 or another (Figures 1 and 2 do not refer to the buffering system nor to a debittering agent) very good suspensibility is obtained both of the concentrate and of a subsequent diluted form (eg; in a trough usage where the dilution is, for example, to about 3 to 6 ppm monensin).

The numerals 1 - 9 (Figure 1) or 1- 11 (Figure 2) indicate the preferred sequence of ingredient addition. With reference to Figure 1, a pre-mill non sequenced mix of components 1 through 6 in the blending vessel (A) will still lead to a good mill mix yet is detrimental to the best suspensibility of the diluted form.

A preferred formulation as in Example 1 made by a procedure as in Figure 1 has a capability of being added as an aqueous concentrate into a large volume of water such as might be experienced in providing an infeed into a water system.

It is important to note the following processing issues:

- the order of addition of the components to the grind base premix is not critical
- the appropriate particle size induced by the grinding operation is critical
- the order of addition of the components in the makeup tank is critical.

2. The Mill Mix

The mill mix is an important factor in the invention. It is the pre-mix of components which are added into the bead mill. The composition (identity and amount) is important in determining the ultimate particle size and the coatings on the particles which result. The relative quantities (eg of MPG : monensin) are important in this respect.

3. Stability Data

a) shelf life stability

The following shelf file stability data indicates the 6% concentrate exhibits stability, at differing temperatures for at least 3 months (the length of time of the trials).

Trough Treatment 6% Concentrate Shelf Life Study

Batch number: 1183				
25°C Sample:				
	Time 0	**1 months**	**2 months**	**3 months**
Appearance	Normal	Normal	Normal	Normal
Coliforms	<1	<1	<1	<1
Monensin Biopotency	5.7	5.5	5.4	5.6
PH	8.11	8.00	7.77	7.51
Yeasts and Moulds	<1	<1	<1	<1
APC	<10	<10	<10	<10
42°C Sample:				
	Time 0	**1 months**	**2 months**	**3 months**
Appearance	Normal	Normal	Normal	Normal
Coliforms	<1	<1	<1	<1
Monensin Biopotency	5.7	5.6	5.4	5.4
PH	8.11	7.60	7.39	7.28
Yeasts and Moulds	<1	<1	<1	<1
APC	<10	<10	<10	<10

* Appearance- normal means light brown gelatinous liquid with brown specks present.

b) Positional Stability

The following experiments detail the positional stability of the trough treatment of the invention (TT).

Positional stability studies were conducted with a DOSATRON™ trough treatment system. This is a proportional feed system which delivers a % mix in proportion to demand. Such an administration system is able to spread delivery of a complete batch over 24 hours.

Figure 3 illustrates a dosation system used in obtaining the positional stability data.

Example 1

Trough treatment (TT) (600ppm) in a 200L plastic solution tank with a functioning Dosatron 8000.

Method:

100 litres water were added to the solution tank connected to a Dosatron 8000.
2 litres TT were mixed well with 2 litres water.
This mix was added to the half-full solution tank, filled to the 200 litre level, mixed thoroughly.
The Dosatron was set at 2 % and the water flow at 400 litres/hour to ensure the solution tank is completely used within 24 hours.
The draw off tube from the Dosatron was set at a height 10 cm from the bottom of the tank.

Sampling

Samples for assay were taken from the draw-off taps. Before sampling, a 50 ml sample was drawn off and discarded. 1 x 100 ml samples are taken from each of the 4 taps set at

either the top, middle or bottom of the tank. Samples will be taken at the specified time intervals.

Each sample taken was individually identified and 50 ml from each sample taken and to a pooled sample (total Vol 200 ml).

This sample was that assayed and the other samples retained.

Samples were also taken from the four-tap set, here positioned in the plastic tank at a level 10 cm from the bottom of the tank.

Samples were taken 0, 12, 24 hours after mixing.

After 24 hours a further 4 x 100 ml samples were taken from the bottom of the tank. Each sample taken was individually identified and 50 ml from each sample taken and pooled (total Vol 200 ml). This sample was assayed and the other samples retained. In this case the drench gun tube attached to the rod was used.

Example 2

Measurement of the positional stability of the TT (3000ppm) in a static 200 L plastic solution tank over a 4 day period

Method

Before filling the tank, the bottom tap hoses were bent so the end was 5 cm from the bottom of the tank.

100 litres of water was added to the solution tank.

10 litres of TT was mixed well with 10 litres water.

This mix was added to the half-full solution tank, filled to the 200 litre level and mixed.

Sampling

Samples for assay were taken from the draw-off taps. Before sampling, a 50 ml sample was drawn off and discarded. Each sample taken was individually identified and 50 ml from each sample taken and pooled (total Vol 200 ml). This sample was that assayed and the other samples retained.

Samples were taken from the top, middle and bottom of the tank at the intervals of 0, 12hrs, 24 hrs, 2 days and 4 days after mixing.

Example 3

Measurement of the positional stability of TT (6 ppm) in a concrete trough over a 24 day period.

Method

50 litres of water was added to the solution tank connected to the Dosatron 8000.
1 litre of TT was mixed well with 1 litre water.
This mix was added to the half-full solution tank, filled to the 100 litre level and mixed.
Set the Dosatron at 1 % to ensure a trough concentration of 6 ppm.
The trough was connected to the solution tank containing the Dosatron and TT.
The new concrete trough was scrubbed clean and the water in the trough pH tested before use.
A neutral pH (7-8) is acceptable.
The water was discarded before filling from the Dosatron 8000

Activation of the ball-cock filled the trough with TT (6 ppm).
After filling the trough herd drinking was simulated by siphoning water from the top of the trough to activate the ball-cock. 5000 litres was siphoned from the trough over a 24 hour period

Sampling

The draw-off tube from the drench gun was attached to a rigid pole. The end of the draw off tube was set to sample the trough from 3 levels – top, middle and bottom.
4 x 100 ml samples was taken from each position.
Each sample taken was individually identified and 50 ml from each sample taken and pooled (total Vol 200 ml).
This sample was that assayed and the other samples retained.

Sampling of the trough at the intervals of 0, 6 hrs,12hrs, 24 hrs, 5 days, 10 days and 24 days after mixing.

Example 4

Measurement of the amount of Monensin settling in the drum after mixing TT at 3000 ppm and leaving for 4 days undisturbed.

Methods

100 litres water was added to the solution tank connected to the Dosatron 8000.
10 litres of TT was mixed with 10 litres of water.
This mix was added to the half-full solution tank, filled to the 200 litre level and mixed.

Sampling

Samples for assay were taken from the bottom of the tank.
Before sampling, opened all middle taps and bottom taps to provide a slow release of tank mix. The rate of removal of the fluid was slow enough so the bottom of the tank was not disturbed.
After the level of water fell below the bottom taps, mixed the bottom of the tank thoroughly and drew off 4 x 100 ml samples taken at different locations.
Each sample taken was individually identified and 50 ml from each of the samples taken and pooled (total Vol 200 ml).
The sample was that assayed and the other samples retained.

N.B Please calculate the volume of water left in the drum before taking the samples.
This will be to calculate the total amount of monensin settling in the bottom of the tank after 4 days

Positional stability results and discussion

The test had the following accuracy parameters:

Repeatability: The difference between results of duplicate portions of the same sample tested in the same run should not exceed 10% of the mean result. Recent results indicate that duplicate results are not exceeding 5.4% of the mean result.

Reproducibility: The difference between results of portions of the same sample tested at different times by different analysts should not exceed 15% of the mean result.

The repeatability and reproducibility data affords us quantifiable parameters for substantial homogeneity, indicating a substantially uniform suspension over time.

Table 1: Example 1 Results (600 ppm)

Time	Bottom Sample Result
0 hours	556 ppm
12 hours	504 ppm
24 hours	439 ppm

Table 2: Example 1 Repeated Trial Results (600 ppm)

Time	Bottom Sample Result
0 hours	580 ppm
12 hours	470 ppm
24 hours	420 ppm

Table 3: Example 2 Results (3000 ppm)

Time	Top Sample (ppm)	Middle Sample (ppm)	Bottom Sample (ppm)
0 hours	2970	2900	3030
12 hours	2680	2720	2760
24 hours	2930	2970	3060
2 days	2960	2950	3030
4 days	2190	2930	3050

Table 4: Example 3 Results (6 ppm)

Time	Top Sample (ppm)	Middle Sample (ppm)	Bottom Sample (ppm)
0 hours	5.0	5.5	5.1
6 hours	4.9	4.6	5.2
12 hours	4.7	4.9	5.0
24 hours	5.6	5.2	5.0
4 days	5.1	5.3	4.3
10 days	5.5	5.1	5.8
24 days	5.0	5.0	5.3

CLAIMS:

1. An ionophore antibiotic composition capable of dilution with water to a substantially stable dispersed form in all water then present, said composition comprising or including:
   - at least one ionophore antibiotic of a mean particle size of less than 20 microns,
   - and at least one dispersing agent.
2. A composition as claimed in claim 1 wherein the mean particle size of at least one ionophore antibiotic is substantially 5 microns.
3. A composition as claimed in claim 1 or 2 wherein the dispensed form in water remains substantially homogeneous for at least 24 days.
4. A composition as claimed in any one of claims 1 to 3 wherein said at least one dispersing agent is selected from one or more of the following:
   iv) a compatible polyglycoside capable of acting as a dispersing agent,
   v) a compatible lignosulfonate capable of acting as a dispersing agent, and
   vi) a compatible and suitable glycol in a form capable of acting as a dispersing agent.
5. A composition as claimed in claim 3 or 4 wherein a liquid vehicle is or is also present.
6. A composition as claimed in claim 5 wherein said liquid vehicle is or includes water.
7. A composition as claimed in claim 5 or 6 wherein said liquid vehicle is or includes one compatible liquid organic compound.
8. A composition as claimed in claim 7 wherein said organic compound is selected from mineral and vegetable oils.
9. A composition as claimed in any one of claims 1 to 8 wherein said ionophore antibiotic(s) has been milled in the presence of at least one of :
   iv) a compatible polyglycoside capable of acting as a dispersing agent,
   v) a compatible lignosulfonate capable of acting as a dispersing agent, and
   vi) a compatible and suitable glycol in a form capable of acting as a dispersing agent.
10. A composition as claimed in claim 9 wherein the milling is in the absence of any suspension agent.

11. A composition as claimed in claim 9 wherein a suspension agent selected from the gums as previously described is present.
12. A composition as claimed in claim 11 wherein the suspension agent is one or more of xanthan gum, guar gum, acacia gum and a cellulose gum.
13. A composition as claimed in any one of claims 9 to 11 wherein a liquid vehicle(s) was present at the time of milling of the ionophore antibiotic sufficient to reduce the consistency of the mill mix to a millable consistency.
14. **Animal drinking water** having at least one particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic is stably suspended.
15. Drinking water as claimed in claim 14 wherein the ionophore antibiotic remains stably suspended for at least 24 days.
16. Drinking water as claimed in claim 14 or 15 wherein the particles of the ionophore antibiotic(s) are of a mean particle size of less than 10 microns.
17. Drinking water as claimed in claim 16 wherein the particles of the ionophore antibiotic(s) are of a mean particle size of substantially 5 microns.
18. Drinking water as claimed in 17 it being made by a proportioned mix dispensing there into of a more concentrated aqueous suspension of the ionophore antibiotic and dispersing agents present in that more concentrated aqueous suspension provides the substantially uniform dispersion of the ionophore antibiotic(s) in the drinking water.
19. Drinking water as claimed in claim 18 which the more concentrated aqueous suspension contains ore or more suspension agents.
20. **Animal drinking water** having at least one particulate ionophore antibiotic substantially uniformly suspended therein, wherein the particles of the ionophore antibiotics are of a mean particle size less than 10 microns.
21. Animal drinking water as claimed in claim 20 wherein the particle size of the ionophore antibiotics are of a mean particle size of substantially 5 microns.
22. Animal drinking water as claimed in claim 21 wherein the ionophore antibiotic remains stably suspended for at least 24 days.

23. **Trough water accessible to an animal to drink,** the water having a particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic is stably suspended.
24. Trough water as claimed in claim 23 wherein the ionophore antibiotic remains stably suspended for at least 24 days.
25. Trough water as claimed in claim 24 wherein the particles of the ionophore antibiotic(s) is of a mean particle size of less than 10 microns.
26. Trough water as claimed in claim 25 wherein the particles of the ionophore antibiotic(s) is of a mean particle size of substantially 5 microns.
27. Trough water as claimed in 26 it is being made by a proportioned mix dispensing there into of a more concentrated aqueous suspension of the ionophore antibiotic and dispersing agents present in that more concentrated form provides the substantially uniform dispersion of the ionophore antibiotic(s) in the drinking water.
28. Drinking water as claimed in claim 27 which the more concentrated aqueous suspension contains ore or more suspension agents.
29. **Trough water accessible to an animal to drink** the water having a particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic remains stably suspended for at least 24 days.
30. Animal drinking water as claimed in claim 29 wherein the particle size of the ionophore antibiotics are substantially 5 microns.
31. Animal drinking water as claimed in claim 30 wherein the ionophore antibiotic remains stably suspended for at least 24 days.
32. **A method of dispensing a particulate ionophore antibiotic into a body of drinking water** which comprises or includes the steps of :
    - taking a composition comprising or including at least one ionophore antibiotic of mean particle size of less than 20 microns and at least one dispersing agent:
    - forming an aqueous suspension of the composition that has the ionophore antibiotic(s) substantially uniformly dispersed therein and which aqueous suspension is available for dispensing into animal drinking water, and
    - dispensing at a rate (continuously or continually), that aqueous suspension into the drinking water or a makeup supply of water thereto so as to provide the body

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of drinking water with a uniform dispersion of the ionophore antibiotic(s) therein which is within an acceptable imbibing concentration range for the animal or animals having access thereto.

33. A method as claimed in claim 32 wherein the mean particle size of the at least one ionophore antibiotic is substantially 5 microns.
34. A method of claim 32 or 33 wherein said composition is in the form of a stable aqueous suspension prior to the forming of an aqueous suspension and the subsequent dispensing thereof into the drinking water or a make up supply of water.
35. A method of claim 34 wherein said composition includes one or more dispersing agent selected from one or more of the following:
    i) a compatible polyglycoside capable of acting as a dispersing agent,
    iv) a compatible lignosulfonate capable of acting as a dispersing agent, and
    v) a compatible and suitable glycol in a form capable of acting as a dispersing agent.
36. A method as claimed in claim 35 wherein a suspension agent selected from gums (as previously described) is present.
37. A method as claimed in any one of claims 32 to 36 wherein the ionophore antibiotic(s) remains stably suspended for at least 24 days.
38. A body of drinking water having a particulate ionophore suspended therein prepared by the method of anyone of claims 32 to 37.
39. A method of forming a suspendable composition of at least one ionophore antibiotic and which suspendable composition is capable of subsequent dilution, said method including, prior to any optional presence of water and optional presence of a suspension agent, milling the ionophore antibiotic(s) with a suitable glycol.
40. A method as claimed in claim 39 wherein said milling takes place in the presence of at least some liquid.
41. A method as claimed in claim 40 wherein said at least some liquid includes water.
42. A method as claimed in claim 41 wherein no gum is present.
43. A method as claimed in 41 or 42 wherein said milling is to a mean particle size very much less than 20 microns.
44. A method of 43 wherein the mean particle size is of about 5 microns.

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45. A method of 44 wherein the milling takes place in the presence of a suitable lignosulfonate.
46. A method of 45 wherein said milling takes place in the presence of a suitable Polyglycoside.
47. A method of 46 wherein said milling takes place in the presence of a suitable antifoam agent.
48. A suspendable composition of at least one ionophore antibiotic prepared according to the method of any one of claims 39 to 47.
49. **A method of forming a suspendable composition of at least one ionophore antibiotic** and which suspendable composition is capable of subsequent dilution, said method including, prior to any optional presence of water and optional presence of a suspension agent, milling the ionophore antibiotic(s) with a suitable dispersion agent.
50. A method of 49 wherein the milling takes place in the presence of a suitable lignosulfonate.
51. A method of 50 wherein said milling takes place in the presence of a suitable polyglycoside.
52. A method as claimed in 51 wherein said suitable dispersion agent is selected from the group consisting of a suitable lignosulfonate and a suitable polyglycoside.
53. A method as claimed in 52 wherein the mean particle size is less than 20 microns.
54. A method of 53 wherein the mean particle size is less than 10 microns.
55. A method of 54 wherein the mean particle size is substantially 5 microns.
56. A method of 55 wherein said milling takes place in the presence of a suitable antifoam agent.
57. A method of 56 wherein said milling takes place in the presence of at least some liquid.
58. A method as claimed in claim 57 wherein a suitable glycol is present.
59. A method as claimed in claim 58 wherein no gum is present.
60. **A dose dispensable ionophore antibiotic composition** comprising or including:
    - at least one ionophore antibiotic,
    - at least one dispersing agent,

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- at least one suspension agent, and
- water,

wherein the ionophore antibiotic(s) and at least one dispersing agent have been milled together in the presence of a liquid (which may be water or may include water but not necessarily so) and where the dispersing agent has been added post-milling in the presence of water.

61. A composition of claim 60 wherein the ionophore antibiotic is of a mean particle size of less than 50 microns
62. A composition of claim 61 wherein said ionophore antibiotic(s) is present at a mean particle size of less than 20 microns.
63. A composition of claim 62 wherein said at least one suspension agent is or includes a gum and no such gum was present at the milling procedure.
64. A composition as claimed in claim 63 wherein some water was present at the milling procedure.
65. A composition as claimed in claim 64 wherein a polyglycoside was present as a dispersing agent at the milling stage.
66. A composition as claimed in claim 64 wherein a lignosulfonate was present as a dispersing agent at the milling stage.
67. A composition as claimed in claim 64 wherein a glycol was present as a dispersing agent at the milling stage.
68. A composition as claimed in claim 64 wherein an alkyl polyglycoside, a lignosulfonate and a propylene glycol are present at the milling stage.
69. A composition as claimed in any one of claims 64-68 wherein any one or more of an antifoam agent or system, a preservative, a debittering agent and a pH buffering system is present.
70. A milled product useful in providing an aqueous suspension of at least one ionophore antibiotic, said product being the milled outcome of a mill mix of at least
    - at least one ionophore antibiotic, and
    - at least one dispersing agent,

    wherein the mill mix has been substantially free of suspension agents selected from the gums previously described and the mill mix has included at

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least one liquid component (which optionally can be the or one of the dispersing agent(s) or an additional material),

and wherein, in the product, the process of milling has resulted in some physical association of the or at least one dispersing agent on the ionophore antibiotic particles,

and wherein, in the product, the mean particle size of the ionophore antibiotic(s) is less than 20 microns.

71. A milled product as claimed in claim 70 wherein the mean particle size is substantially 5 microns.

72. **A method of preparing a suspendable composition for substantial dilution by water, said method comprising or including:**

(I) milling at least one ionophore antibiotic and at least one dispersing agent so as to provide some physical association of the or at least one dispersing agent on ionophore antibiotic particles of a mean particle size of less than 20 microns, and

(III) blending the post mill ionophore antibiotic(s)/dispersing agent(s) milled outcome with at least a suspension agent.

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PCT/NZ01/00290

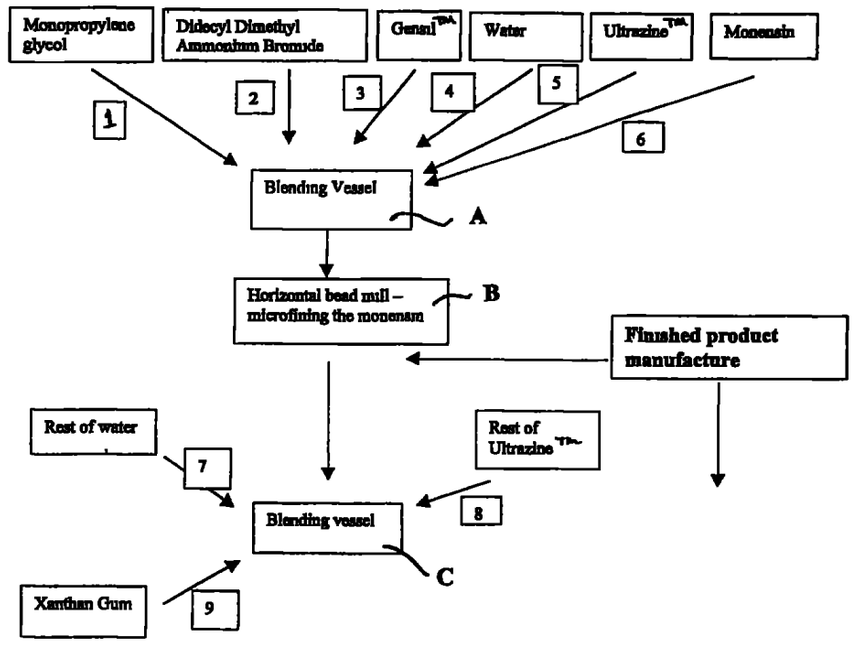

FIGURE 1

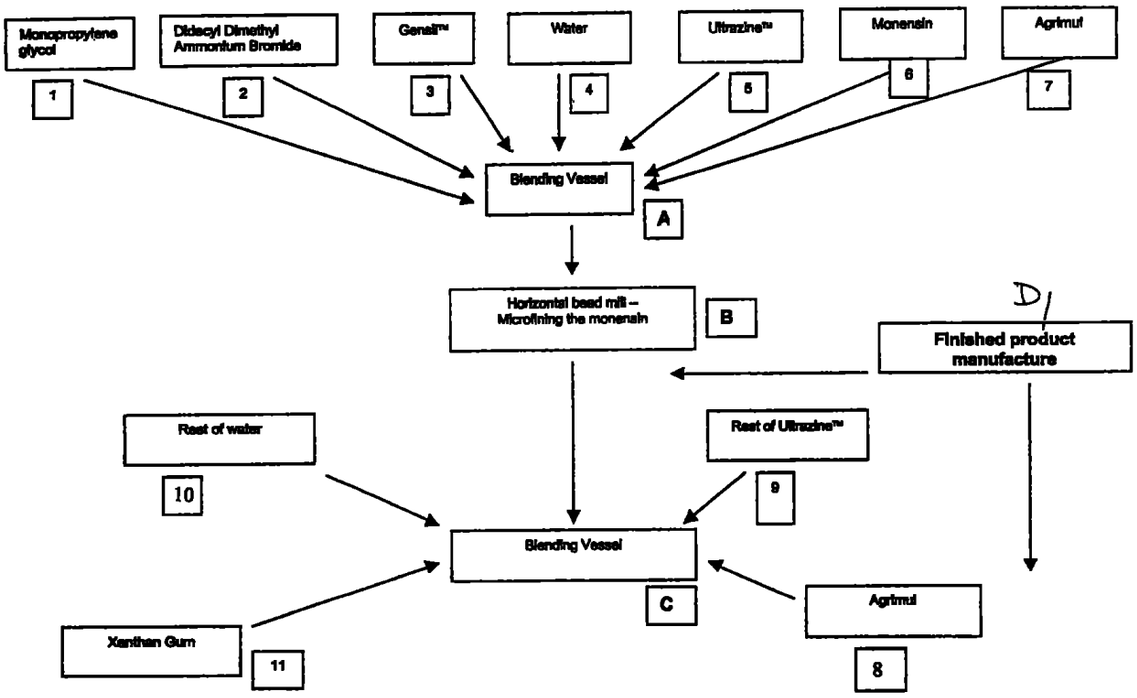
Monopropylene glycol
1
Didecyl Dimethyl Ammonium Bromide
2
Genasil™
3
Water
4
Ultrazine™
5
Monensin
6
Agrimul
7
Blending Vessel
A
Horizontal bead mill – Microfining the monensin
B
Finished product manufacture
D
Rest of water
10
Rest of Ultrazine™
9
Blending Vessel
C
Xanthan Gum
11
Agrimul
8

FIGURE 2

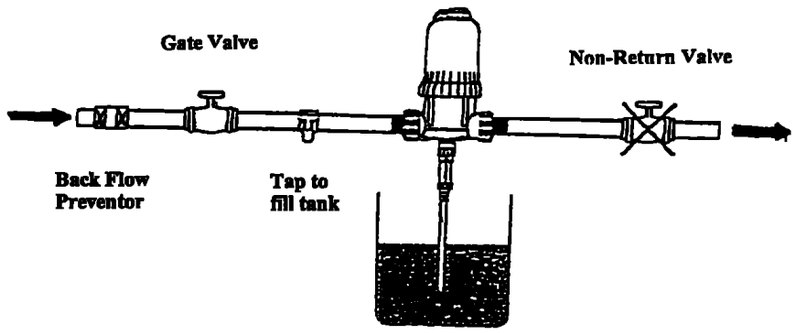
Gate Valve
Non-Return Valve
Back Flow Preventor
Tap to fill tank

FIGURE 3A

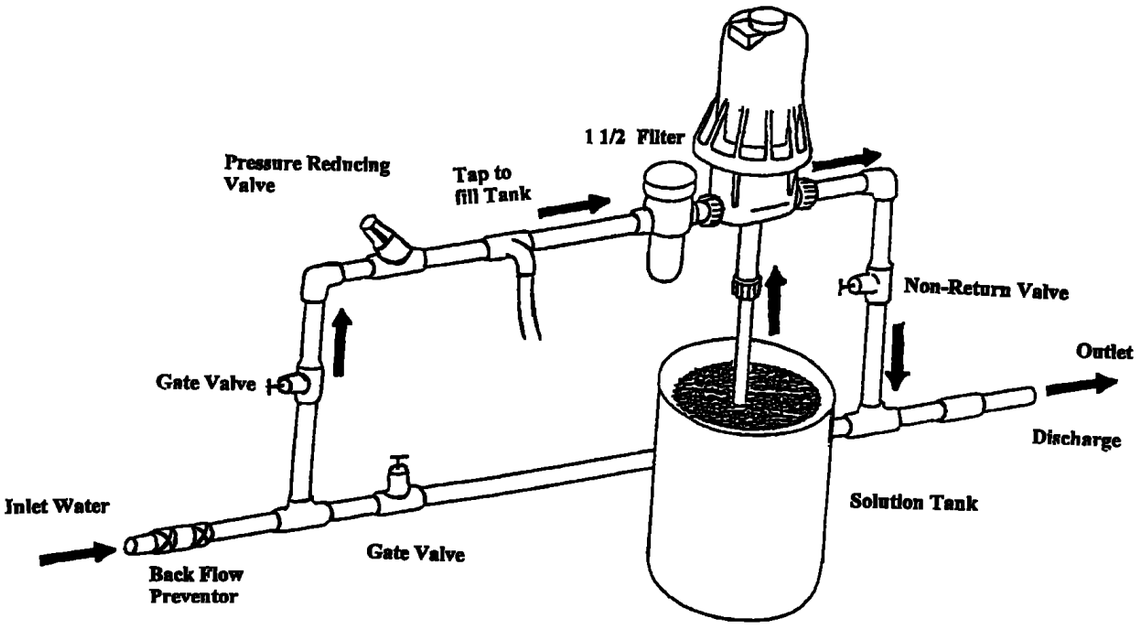
1 1/2 Filter
Pressure Reducing Valve
Tap to fill Tank
Non-Return Valve
Outlet
Gate Valve
Discharge
Inlet Water
Solution Tank
Gate Valve
Back Flow Preventor

FIGURE 3B

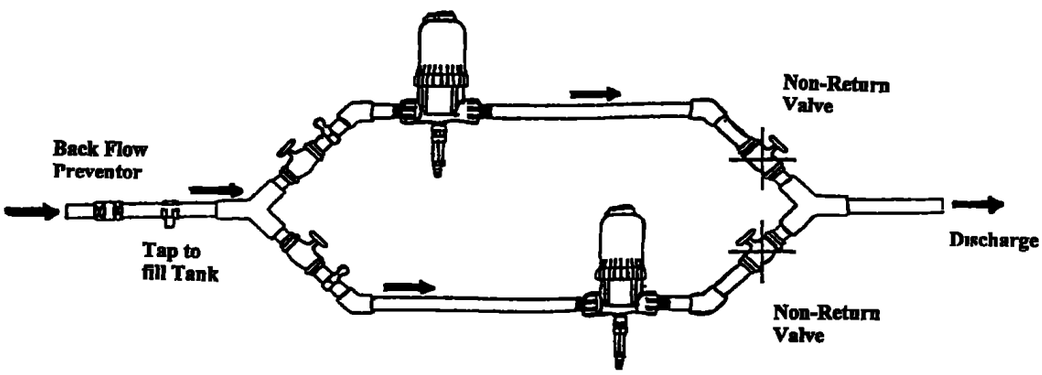
Non-Return
Valve
Back Flow
Preventor
Discharge
Tap to
fill Tank
Non-Return
Valve

FIGURE 3C

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/NZ 01/00290

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57

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K47/34 A61K47/36 A61K47/10 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 16663 A (ELI LILLY) 23 April 1998 (1998-04-23)	1-3
Y	claims 1,4,9 page 6, line 6 - line 19	4-8, 14-38, 70,71
Y	WO 97 03650 A (ELI LILLY) 6 February 1997 (1997-02-06) cited in the application claims 1-41	4-8, 14-38, 70,71

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 May 2002	28/05/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

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(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

(19) ORGANIZACIÓN MUNDIAL DE LA PROPIEDAD INTELECTUAL
Oficina Internacional

PCT

(43) Fecha de Publicación Internacional:
27 de Junio de 2002 (27.06.2002)

(10) Número de Publicación Internacional:
WO 02/49609 A1

(51) Clasificación Internacional de Patentes [7]: A61K 9/00, 47/34, 47/36, 47/10, 9/14

(21) Número de Solicitud Internacional: PCT/NZ 01/00290

(22) Fecha de Presentación Internacional:
18 de Diciembre de 2001 (18.12.2001)

(25) Lenguaje Presentado: Inglés

(26) Lenguaje de Publicación: Inglés

(30) Fecha de Prioridad:
509092 19 de Diciembre de 2000 (19.12.2000) NZ
514183 13 de Septiembre de 2001 (13.09.2001) NZ

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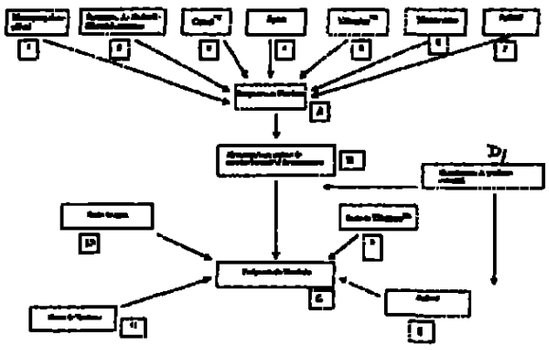
(81) Estados Designados: (nacional): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Estados Designados: (regional): patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), patente Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), patent OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Publicada:
Con el informe de búsqueda internacional
Antes de la expiración, el tiempo límite para enmendar as reivindicaciones y para ser vueltas a publicar en el caso de la recepción de las enmiendas

Para códigos de dos letras y otras abreviaciones, referirse a "Notas de Guía de Códigos y Abreviaturas" que aparece al comienzo de cada emisión regular de la Gaceta del PCT.

(54) Título: **FORMULACIONES DE ANTIBIÓTICOS DE IONÓFORO**



(57) Resumen: La invención se refiere a una composición de antibiótico de ionóforo capaz de la dilución con agua a una forma dispersada sustancialmente estable en toda el agua entonces presente, la composición que comprende o que incluye: al menos un antibiótico de ionóforo (de manera preferente, monensina) de un tamaño promedio de partícula de menos de 20 micras; y al menos un agente de dispersión. También se describe un método para preparar la composición de antibiótico de ionóforo.

WO 02/49609 A1

FORMULACIONES DE ANTIBIÓTICO DE IONÓFORO

La presente invención se refiere a composiciones de antibiótico de ionóforo y de manera particular, pero sin limitación, a composiciones de antibiótico de ionóforo capaces de la dilución con agua, adecuadas para la inclusión directa o vía un tanque de retención en el agua para beber de un animal para administrar y/o auto-administrar un antibiótico de ionóforo o antibióticos de ionóforo.

Antecedentes de la Invención

Se conoce la administración a animales (de manera preferente, rumiantes) de antibióticos de ionóforo tal como monensina para lograr en dosis apropiadas, ventajas para varios propósitos diferentes. Estos incluyen el tratamiento o prevención de la cetosis y/o hinchazón, el incremento de la producción de leche, el incremento del contenido de proteína láctea en la leche, el incremento de la captación de minerales, el incremento de la ganancia de peso, y/o el incremento de la eficiencia de conversión de alimento (en rumiantes), las ventajas deseables de reproducción y como un reemplazo de leche. Ver patente de los Estados Unidos No. 3,829,557.

A este respecto, se hace referencia a la especificación de patente europea No. 0,139,595 A2 de

KOFFOLK (1949) LTD que se refiere a una composición líquida de antibiótico de ionóforo para rumiantes y aves de corral, donde el antibiótico se disuelve en un solvente orgánico, no tóxico, soluble en agua en lugar de un solvente orgánico soluble en agua, y en el uso, la solución resultante se mezcla con una alimentación líquida, un concentrado líquido de vitaminas o el agua para beber. Hay reivindicaciones para la estabilidad en el reposo.

La composición de la EP 0,139,595 indica que debido a que la monensina y su sal de sodio es sólo ligeramente soluble en agua, que se administra en general en una forma seca en la alimentación de un animal y/o en composiciones secas de reemplazo de leche líquida. Lo mismo también se indica como cierto para otro antibiótico de ionóforo, lasalocid, que en la patente de los Estados Unidos No. 3,715,372 se informa que es completamente insoluble en agua.

La composición de la EP 0,139,595 usa como un solvente orgánico para el antibiótico de ionóforo, un solvente seleccionado del grupo que comprende propilenglicol, glicerol, etanol e isopropanol y mezclas de los mismos.

El Ejemplo 1 de la EP 0,139,595 indica que se mezclaron 250 g de un micelio que contiene 10 % de monensina a temperatura ambiente con 1250 centímetros cúbicos de propilenglicol durante 2 horas al exponer la mezcla a

ultrasonido. Existe una indicación que 50 % de la monensina se encontró en solución en el propilenglicol.

La monensina está usualmente disponible de manera comercial como la sal sódica del ácido. La monensina sódica está disponible en dos formas, específicamente, una forma cristalina o una forma micelial. La forma micelial tiene sólo aproximadamente 20 % de actividad en tanto que la forma cristalina tiene monensina sódica más de 90 % activa.

La referencia en la presente a "monensina" donde el contexto permite abarcar todas las formas de la misma, incluyendo monensina, sales de metales alcalinos de monensina y ésteres de monensina e incluye mezclas. Igualmente, para los otros antibióticos de ionóforo.

En la especificación de patente de Nueva Zelanda 272574/272940 (equivalente a la PCT/NZ96/00068) se describe un concentrado en suspensión de base acuosa de un antibiótico de ionóforo o antibióticos de ionóforo tal como monensina.

En un aspecto en la NZ 272574/272940, la invención se define como un concentrado en suspensión de base acuosa de un antibiótico de ionóforo o antibióticos de ionóforo capaces de dilución acuosa (si se desea) y capaces (con o sin esta dilución acuosa) de ser administrados de manera oral a un animal por un régimen de dosis activa (por ejemplo; por administración por la boca), el concentrado comprende o incluye:

(I) al menos un antibiótico de ionóforo, en

(II) un sistema acuoso que contiene

(i) un agente humectante y/o agente tensioactivo (de manera preferente, alquil-poliglicósido);

(ii) un agente anticongelante o agentes en los cuales el antibiótico de ionóforo o antibióticos, están o son no más que escasamente solubles;

(iii) un agente de suspensión (por ejemplo, goma(s)),

(iv) opcionalmente, un agente o sistema antiespuma,

(v) opcionalmente, un conservador,

(vi) opcionalmente, un agente de amargador,

(vii) opcionalmente, un sistema de amortiguamiento del pH,

(viii) agua.

El antibiótico de ionóforo preferido de la NZ 272574/272940 es monensina sódica. De manera preferente, un agente anticongelante o agentes en los cuales el(los) antibiótico(s) de ionóforo no es más que escasamente soluble (tal como glicol o poliglicol) está presente. Adicionalmente está presente de forma preferente un agente antiespuma (por ejemplo, simeticona y un portador en forma de partícula tal como dióxido de silicio para el mismo).

La NZ 272574/272940 también describe un método para administrar por la boca a un animal, un antibiótico de

ionóforo que comprende administrar oralmente a este animal una forma diluida de las composiciones, esta dilución que es con agua.

Se ha encontrado que el monopropilenglicol es un solvente pobre de la monensina. En tanto que en la NZ 272574/272940 se hace referencia a monopropilenglicol como que es un agente anticongelante en el cual es escasamente soluble el antibiótico de ionóforo, se aprecia que la solubilidad al grado referido en el Ejemplo 1 de EP 0,149,595 se puede lograr cuando se induce con ultrasonido o calentamiento.

La forma de la monensina cristalina usada para los ejemplos en la NZ272574/272940 tiene un tamaño promedio de partícula del orden de aproximadamente 40 micras a fin de retener estas partículas grandes en suspensión, se ha requerido un sistema de soporte, agresivo, para este propósito.

De esta manera, a pesar de los avances representados por la invención descrita en la NZ272574/272940 (que proporciona composiciones útiles para un sistema activo para administrar antibióticos de ionóforo a rumiantes), y a pesar de las argumentaciones de la EP139595, continúa una necesidad sustancial por composiciones que contengan antibióticos de ionóforo que sean inherentemente, solubles de manera pobre o insolubles en sistemas de base acuosa, y que

sean adecuados para las administraciones de sistemas pasivos a rumiantes. Estas composiciones deben permanecer, para evitar la sub-dosificación o la dosificación tóxica, sustancialmente homogéneas durante periodos prolongados de tiempo.

La presente invención investiga alternativas a sistemas agresivos y tiene como objetivo una composición dosificable capaz de la estabilidad de la dispersión como una suspensión en agua para bebida altamente diluible para animales.

La presente invención depende tanto de un tamaño de partícula promedio, pequeño, preferido del antibiótico de ionóforo como de un régimen asociado que incluye métodos relacionados de manufactura, usos, etc.

La presente invención también reconoce inter alia los beneficios terapéuticos, energéticos y de productividad de que la monensina o cualquier otro antibiótico adecuado de ionóforo (ver listado en la especificación de patente mencionada con anterioridad, y posteriores) que se usen como un tratamiento de pesebre.

Sistemas de tratamiento en Pesebre

Actualmente, se conocen tres tipos de sistemas de tratamiento en pesebre para el agua para beber para animales y no se usan hasta la fecha con un antibiótico de ionóforo.

Los tres tipos en uso son:

1. Sistemas de alimentación proporcional, por ejemplo, se distribuye DOSATRON[MR] de marca a un % de mezcla en proporción a demanda (desde 0.2-2 % de Dosatron). La finalidad es la distribución propagada del lote completo durante 24 horas.

2. Sistemas de descarga:

Distribuyen continuamente el pesebre en las líneas a pesar de la demanda. Tienden a ser usados hasta durante 5 horas.

3. Sistemas de pesebre individual, por ejemplo, distribuidor PETA[MR]:

Distribuye una administración concentrada con relación a la demanda pero se falsea pronto el desembolso.

La presente invención incluye una composición con base en antibiótico de ionóforo capaz de la dilución acuosa, la cual puede ser útil en un sistema de tratamiento en pesebre. El objeto de la presente invención es proporcionar esta composición y/o proporcionar agua para beber para un animal para permitir la administración de un antibiótico de ionóforo al animal.

Se ha determinado que una forma microfina de un antibiótico de ionóforo con su relación más pequeña de masa a área superficial es una ventaja significativa con respecto a inclusiones de antibiótico de ionóforo, menos fina (por

ejemplo; tamaño promedio de partícula de 40 micras) en una composición acuosa y más, de modo que cuando se va a usar de esta manera donde se somete a una dilución no supervisada, por ejemplo, para proporcionar una alimentación (directa o indirectamente) en una cantidad de dilución de agua que constituye el pesebre. Estas ventajas para uniformizar la capacidad de suspensión se cree que son igualmente aplicables a formas cristalinas más preferidas así como a las formas miceliales menos preferidas del(los) ionóforo(s).

También se ha determinado que un glicol adecuado tal como monopropilenglicol se puede usar de esta manera para pre-preparar un antibiótico de ionóforo para la suspensión subsiguiente como un concentrado acuoso y posteriormente para portar al menos un anticongelante, ventaja con respecto a su uso subsiguiente (por ejemplo; como un concentrado acuoso de alimentación para un sistema acuoso de cierta dosis) sin conducir al colapso del antibiótico de ionóforo. Los glicoles (tal como monopropilenglicol), a menos que se traten de forma agresiva, no proporcionan captación significante del antibiótico de ionóforo, establemente suspendido o dispersado (tal como monensina) de un sistema acuoso. Esto se considera deseable puesto que una captación orgánica puede conducir al colapso en la dilución. Por ejemplo, un solvente orgánico, tal como metanol, permite que la monensina colapse de la solución si se adiciona agua.

En las formas preferidas de la presente invención, el antibiótico de ionóforo de elección es monensina en cualquiera de sus formas apropiadas (por ejemplo; monensina sódica). Sin embargo, otros antibióticos de ionóforo, caen dentro del alcance de la presente invención y estos incluyen Lonomicina, lonomicina, Laidlomicina, Nigericina, Grisorixina, Dianemicina, Lenoremicina, Salinomicina, Narasina, Antibiótico X206, Alborixina, Septamicina, Antibiótico A204, Maduramicina y Semduramicina, Compuesto 47224, Lasalocid (también incluye factores A, B, C, D y E), Mutalomicina, Isolasalocid A, Lisocelina, Tetronasina, Echeromicina, Antibiótico X-14766a, Antibiótico A23187, Antibiótico A32887, Compuesto 51532 y K41.

Descripción de la Invención

En un aspecto, la presente invención es una composición de antibiótico de ionóforo, concentrada, en suspensión acuosa, la composición que comprende:

- al menos un antibiótico de ionóforo de un tamaño promedio de partícula de menos de 20 micras;

- al menos un agente dispersante seleccionado de uno o más de un poliglicósido compatible, un lignosulfonato compatible, y un glicol compatible y adecuado; y

un agente de suspensión seleccionado de goma.

En donde, que comprende, es capaz de dilución con

agua a una composición sustancialmente estable y diluida, dispersada; y

en donde la forma diluida en agua permanece sustancialmente homogénea durante al menos 24 días.

De manera preferente, el tamaño promedio de partícula de al menos un antibiótico de ionóforo es sustancialmente 5 micras.

De manera preferente, el agente de suspensión es uno o más de goma de xantano, goma de guar, goma de acacia o una goma de celulosa.

La composición puede comprender además un vehículo líquido que es un compuesto orgánico, líquido, compatible.

De manera preferente, el compuesto orgánico se selecciona de aceites mineral y vegetal.

De manera preferente, el antibiótico de ionóforo se ha molido en la presencia de al menos un agente dispersante seleccionado de uno o más de un poliglicósido compatible, un lignosulfonato compatible, y un glicol compatible y adecuado.

En otro aspecto, la invención es una composición de agua para beber para un animal; que comprende:

- al menos un antibiótico de ionóforo, en forma de partículas, suspendido de manera sustancialmente uniforme en el mismo, en donde el antibiótico de ionóforo se suspende de manera estable y en donde el tamaño de partículas del antibiótico de ionóforo es de un tamaño promedio de partícula

de menos de 10 micras;

- al menos un agente dispersante seleccionado de uno o más de un poliglicósido compatible, un lignosulfonato compatible, y un glicol compatible y adecuado, y

- uno o más agentes de suspensión,

en donde el antibiótico de ionóforo permanece sustancialmente suspendido durante al menos 24 días.

De manera preferente, el tamaño de partículas del antibiótico de ionóforo es de un tamaño promedio de partícula de sustancialmente 5 micras.

En aun otro aspecto de la invención, la invención es un método para dispersar un antibiótico de ionóforo en forma de partículas en un cuerpo de agua para beber, que comprende:

- formar una suspensión acuosa de una composición que comprende:

- al menos un antibiótico de ionóforo de tamaño promedio de partícula de menos de 20 micras;

- al menos un agente dispersante seleccionado de uno o más de un poliglicósido compatible, un lignosulfonato compatible, y un glicol compatible y adecuado; y

- un agente de suspensión seleccionado de gomas;

en donde el antibiótico de ionóforo se dispersa de manera sustancialmente uniforme en el mismo;

- en donde la suspensión acuosa es adecuada para la

disminución en el agua para beber de animales, y es capaz de la dilución adicional para producir un cuerpo de agua para beber con una dispersión uniforme del antibiótico de ionóforo en el mismo que esta dentro de un intervalo aceptable de concentración de inhibición para el animal o animales que tienen acceso al mismo, y

en donde el antibiótico de ionóforo permanece suspendido de manera estable durante al menos 24 días.

De manera preferente, el tamaño de partícula de los antibióticos de ionóforo es de un tamaño promedio de partícula de sustancialmente cinco micras.

El método puede comprender además:

- distribuir la suspensión acuosa en el agua para beber al mismo, para proporcionar el cuerpo del agua para beber con una dispersión uniforme del antibiótico de ionóforo en la misma que está dentro de un intervalo aceptable de concentración de inhibición para el animal o animales que tienen acceso a la misma.

En otro aspecto, la invención es un método para formar una composición concentrada, suspendible de al menos un antibiótico de ionóforo, en donde la composición concentrada, suspendible es capaz de la dilución subsiguiente, el método comprende.

- moler el antibiótico de ionóforo con un agente adecuado de dispersión seleccionado de uno o más de un

poliglicósido compatible, un lignosulfonato compatible y un glicol compatible y adecuado,

en donde la molienda es aun tamaño promedio de partícula de menos 20 micras.

De manera preferente, la molienda toma lugar en la presencia de agua y un agente de suspensión.

De manera preferente, la molienda va a ser a un tamaño promedio de partícula de aproximadamente 5 micras.

De manera preferente, la molienda tomar lugar en la presencia de al menos algún líquido no acuoso.

De manera preferente, la molienda toma lugar en la presencia de un agente antiespuma adecuado.

En otro aspecto, la invención es una composición suspendida de al menos un antibiótico de ionóforo preparado de acuerdo al método de la presente invención.

En aun otro aspecto, la invención es una composición de antibiótico de ionóforo, dispersable en dosis, que comprende:

- al menos un antibiótico de ionóforo en donde el tamaño de partícula del antibiótico de ionóforo es de un tamaño promedio de partícula de al menos de 50 micras;

- al menos un agente de dispersión seleccionado de uno o más de un poliglicósido compatible, un lignosulfonato compatible, y un glicol compatible y adecuado;

- al menos un agente de suspensión; y

- agua,

en donde el antibiótico de ionóforo y al menos un agente de dispersión se han molido conjuntamente en la presencia de un líquido no acuoso y donde al menos se adicionan después de la molienda una alícuota adicional de al menos un agente de dispersión y agua.

De manera preferente, el antibiótico de ionóforo está presente a un tamaño promedio de partícula de menos de 20 micras.

De manera preferente, se presenta algo de agua en el procedimiento de molienda.

De manera preferente, está presente en la tapa de molienda un alquil-poliglicósido, un lignosulfonato y un propilenglicol.

De manera preferente, está presente uno o más de un agente o sistema antiespuma, un conservador, un agente desamargador y un sistema de amortiguamiento del pH.

En otro aspecto, la presente invención consiste de un método para formar una suspensión acuosa capaz de la dilución subsiguiente, el método que incluye antes de cualquier presencia sustancial de agua y/o un agente de suspensión (tal como una goma adecuada), moler el antibiótico de ionóforo o antibióticos de ionóforo (de manera preferente en una forma cristalina) con al menos un glicol adecuado.

De manera preferente, la molienda es a un tamaño

promedio de partícula mucho menor de 40 micras.

De manera preferente, el tamaño promedio de partículas es menos de 20 micras, de manera más preferente menos de cinco micras y de manera más preferente en un tamaño promedio de partículas de 0.1 a 1.0 micras.

De manera preferente, la molienda incluye la presencia de un lignosulfonato adecuado y/o un poliglicósido adecuado.

De manera preferente, la molienda incluye la presencia de un agente antiespuma.

De manera preferente, la molienda incluye al menos algo de agua.

De manera preferente, no está presente ningún agente de suspensión en la molienda (por ejemplo, una goma tipificada por goma de xantano o goma de guar).

De manera preferente, el método se realiza sustancialmente como se describe posteriormente en la presente con referencia al dibujo anexo.

De manera preferente, el producto incluye como su glicol adecuado, monopropilenglicol.

De manera preferente, la suspensión acuosa es de una clase descrita posteriormente en la presente, que incluye monopropilenglicol, un agente adicional de humectación (por ejemplo; un lignosulfonato o poliglicosido o ambos) y un agente de suspensión.

De manera preferente, el antibiótico de ionóforo es monensina y de manera preferente esa monensina está en una forma cristalina.

En un aspecto adicional, la presente invención consiste de un método para formar una suspensión acuosa de al menos un antibiótico de ionóforo capaz de la dilución subsiguiente, el método que incluye moler el antibiótico de ionóforo o antibióticos de ionóforo (de manera preferente, en una forma cristalina) con al menos un poliglicósido adecuado o un lignosulfonato adecuado.

De manera preferente, el método forma parte de un método como se define previamente.

En aun un aspecto adicional, la presente invención consiste de un método para formar una suspensión acuosa de al menos un antibiótico de ionóforo capaz de la dilución subsiguiente, el método que comprende o que incluye:

moler un antibiótico de ionóforo o antibióticos de ionóforo (de manera preferente en una forma cristalina) con al menos (i) un glicol adecuado y (ii) al menos uno de un lignosulfonato adecuado y un poliglicosido adecuado; y

formular de manera subsiguiente la suspensión con al menos agua u opcionalmente, agua adicional.

De manera preferente, la formulación subsiguiente comprende la adición de un agente adecuado de dispersión.

De manera preferente, el agente adecuado de

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dispersión es una goma adecuada tipificada por goma de xantano y goma de guar.

Otros agentes adecuados de dispersión incluyen hidroxietilcelulosa, arcilla de bentonita, arcilla de montmorillinita y sílice ahumada.

De manera preferente, el antibiótico de ionóforo es de pureza suficiente para reducir al mínimo cualquier requerimiento de un agente antiespuma pero si es necesario un agente antiespuma, de manera preferente, el agente antiespuma es un sistema GENSIL^{MR}, es decir, de simeticona/dióxido de silicio, soporte para la simeticona.

De manera preferente, la suspensión incluye un sistema amortiguador.

De manera preferente, la suspensión incluye un conservador.

Cuando se hace referencia a un glicol adecuado, de manera preferente el glicol es un líquido y de manera preferente el glicol asume un papel de anticongelante en la suspensión acuosa resultante.

El ejemplo de un glicol adecuado es monopropilenglicol pero otros ejemplos incluyen etilenglicol, dietilenglicol y dipropilenglicol.

De manera preferente, el antibiótico de ionóforo o antibióticos de ionóforo es al menos principalmente de una forma cristalina pero en otras formas puede ser en parte de

forma micelial. Por ejemplo, si es como se prefiere, el antibiótico de ionóforo es monensina (por ejemplo, presente por ejemplo como monensina sódica), de manera preferente, el antibiótico de ionóforo está sustancialmente libre de la forma micelial. Las ondas miceliales formadas que se van a utilizar, sin embargo, de manera preferente, son cambios proporcionales en las inclusiones para reflejar la primera actividad de esta forma o una entrada adicional a cualquier sistema de dilución para lograr actividades apropiadas.

De manera preferente, la molienda es en condiciones soportadas en líquido (de manera preferente, como resultado de la inclusión de glicol líquidos), de manera preferente con un mínimo de agua necesario para el propósito (si lo hay), de manera preferente es tal, como para reducir el antibiótico a una forma microfina.

En una forma preferida de la presente invención, a pesar de si o no la molienda se realice en un ambiente seco o líquido, de manera preferente, el antibiótico de ionóforo se reduce a un tamaño promedio de partícula de menos de 50 micras.

De manera preferente, el tamaño promedio de partículas se reduce al menos a 20 micras.

De manera más preferente, la condición microfina del antibiótico de ionóforo es a un tamaño promedio de partícula de menos 5 micras.

De manera más preferente, el tamaño promedio de partícula que resulta del procedimiento de molienda o los procedimientos de molienda (pueden ser un procedimiento individual o múltiple de molienda) están para proporcionar un tamaño promedio de partícula del antibiótico de ionóforo preferentemente cristalino (por ejemplo, monensina) en un intervalo de 0.1 a 1.0 micras.

De manera preferente, la etapa o etapas de molienda comprenden una molienda con un poliglicósido o lignosulfonato adecuado, o ambos. Este poliglicósido es alquil-poliglicósido. Un compuesto de lignosulfonato posible es ULTRAZINE NA^{MR} o BORRESPERSE NA^{MR} [de Borregaard Industries Ltd de Noruega] (de manera más preferente, ULTRAZINE NA^{MR}).

Finalmente, también se muele GENSIL^{MR} u otro agente antiespuma adecuado con la monensina cristalina u otro antibiótico.

De manera preferente, la molienda de todos los agentes de revestimiento es simultánea aunque puede ser en parte o totalmente en serie.

En una mezcla preferida, el antibiótico de ionóforo se muele de manera simultánea con el monopropilenglicol líquido y un poliglicósido adecuado y/o compuesto de lignosulfonato (de manera más preferente un lignosulfonato) que tiene una función de "humectación" y (opcionalmente) un agente antiespuma y/o algo de agua.

En un aspecto adicional, la presente invención consiste de una suspensión acuosa formada por uno o más de los métodos de la presente invención.

En aun un aspecto adicional, la presente invención consiste de una suspensión acuosa de antibiótico de ionóforo capaz de la dilución adicional sin ningún colapso sustancial de la inclusión de ionóforo, el concentrado acuoso que comprende o incluye:

- un antibiótico de ionóforo,
- monopropilenglicol (u otro glicol adecuado),
- opcionalmente, un material adicional que tiene una característica de humectación,
- un agente de suspensión,
- opcionalmente, un agente antiespuma; y
- agua,

en donde al menos el monopropilenglicol y el antibiótico de ionóforo se han molido conjuntamente antes del mezclado con agua o al menos cualquier cantidad sustancial de agua.

De manera preferente, el material adicional que tiene una característica de humectación es un poliglicósido o lignosulfonato adecuado.

De manera preferente, el poliglicósido adecuado es alquil-poliglicósido aunque de manera más preferente el agente humectante adicional es un lignosulfonato tipificado

por ULTRAZINE NA[MR] o BORRESPERSE NA[MR] (de manera más preferente ULTRAZINE NA[MR]).

De manera preferente, el antibiótico de ionóforo esta en una forma cristalina en lugar de una forma micelial.

De manera preferente, el antibiótico de ionóforo es monensina o una monensina.

De manera preferente, el antibiótico de ionóforo al menos después de la molienda tiene un tamaño de partícula de al menos 5 micras de manera más preferente por debajo de 2 micras.

De manera preferente, el intervalo de tamaño de partícula del antibiótico es de 0.1 micras a 1.0 micras.

De manera preferente, la suspensión acuosa de antibiótico de ionóforo permanece sustancialmente homogénea durante un periodo no mayor de 7 días; de manera más preferente, durante un periodo mayor de 24 días.

No importa si o no la molienda reduzca el antibiótico de ionóforo a el tamaño promedio de partícula necesario o si o no este molido casi a ese tamaño. Lo que es importante es tener las partículas resultantes de ese tamaño apropiadamente revestidas con los agentes "humectantes" se incluyen de manera preferente un glicol multifuncional (por ejemplo; monopropilenglicol) y de manera preferente un agente humectante adicional.

En un aspecto adicional, la presente invención

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consiste de una suspensión acuosa de antibiótico de ionóforo que comprende o que incluye:

De 0 a 20 % p/v de un antibiótico de ionóforo, cristalino, microfino (es decir, menos de 40 micras de su tamaño promedio de partículas),

de 2 a 20 % p/v de monopropilenglicol,

de 0 a 10 % p/v de un agente humectante,

de 0.1 a 5 % p/v de agente de suspensión, y

agua.

De manera preferente, la suspensión acuosa del antibiótico de ionóforo permanece sustancialmente homogénea durante un periodo mayor de 7 días; de manera más preferente durante un periodo mayor de 24 días.

De manera preferente, la formulación es sustancialmente como se describe en cualquiera de los ejemplos 1 a 5.

En otro aspecto, la presente invención se refiere a una composición adecuada para proporcionar una alimentación directa o indirecta (por ejemplo vía un tanque de composición) en un sistema acuoso del cual puede beber el animal objetivo,

la composición que es una composición acuosa de (al menos)

(a) un antibiótico de ionóforo microfino o antibióticos de ionóforo, microfinos;

(b) un glicol en el cual el(los) antibiótico(s) de ionóforo es o son no más que escasamente solubles;

(c) un agente restante;

(d) un agente de suspensión; y

(e) agua, y

opcionalmente cualquiera de uno o más de:

- un sistema o agente antiespuma,
- un conservador;
- un agente desamargador;
- un sistema de amortiguamiento de pH.

De manera preferente, la suspensión acuosa de antibiótico de ionóforo permanece sustancialmente homogénea durante un periodo no mayor de 7 días; de manera más preferente durante un periodo no mayor de 24 días.

De manera preferente, el agente de suspensión es goma de xantano.

De manera preferente, el agente humectante y/o tensioactivo (c) es un lignosulfonato (Por ejemplo, ULTRAZINE NA^{MR}) o un poliglicósido).

De manera preferente, el antibiótico de ionóforo está en una forma ya sea cristalina o micelial o ambas.

De manera preferente, se utiliza una forma cristalina.

De manera preferente, el antibiótico de ionóforo es monensina (por ejemplo, monensina sódica).

De manera preferente, el antibiótico de ionóforo microfino es de un tamaño de partícula de menos de 5 micras (de manera preferente menos de 2 micras) y de manera preferente tiene un tamaño promedio de partículas en el intervalo de 0.1 a 1.0 micras.

De manera preferente, la goma de xantano está presente en una cantidad de más de 0.16 % p/v y de manera preferente cerca de 0.4 % p/v (es decir, la cantidad requerida que es más para el concentrado acuoso más concentrado; por ejemplo; puede ser requerido que ninguno sea diluido de manera ilimitada).

De manera preferente, el modo de mezclado y formulación es como se describe sustancialmente en la presente con una composición preferida que es sustancialmente como sigue (en donde, de manera preferente, el tamaño promedio de partícula de monensina sódica es sustancialmente 5 micras.

Ingrediente (nombre común/químico)	cantidad (% p/p)	Función
Monensina Sódica	6.33 % (aproximadamente 6 % de monensina) p/v	Antibiótico de Ionóforo
Monopropilenglicol	10 % p/v	Anticongelante
Alquil-poliglicósido, o	0.5% p/v	Agente tensioactivo/Agente Humectante
ULTRAZINE NA[MR]	4-5 % p/v	
Fosfato disódico anhidro	0.355 % p/v	Amortiguador
Fosfato monopotásico dihidratado.	0.04 % p/v	Amortiguador
Bromuro de dialquildimetil-amonio	.0064 % p/v	Conservador
Goma de xantano	0.4 % p/v	Agente de suspensión
Simeticona	0.333 % p/v)	(Por ejemplo GENSIL[MR]
Dióxido de Silicio	0.167 % p/v)	Sistema antiespuma)
Agua	A 100 %	

Una formulación preferida alternativa es (en donde de manera preferente, el tamaño promedio de partícula de monensina sódica es sustancialmente 5 micras):

Nombre del ingrediente (común o químico)	cantidad (% p/p)	Función
Monensina Sódica QA 166H	6.747 %	Compuesto Activo
Monopropilenglicol	10 %	Anticongelante
Bromuro de didecil-dimetil-amonio	0.1 %	Conservador
Goma de Xantano	0.5 %	Agente de suspensión
Lignosulfonato de sodio	4.1 %	Agente humectante
Alquil-Poliglicósido	3.8 %	Agente humectante
Simeticona	0.333 %	Antiespuma
Dióxido de silicio	0.167 %	Antiespuma
Agua resto cs	74.47 %	Diluyente

En otro aspecto, la presente invención es una mezcla de pre-molienda o una mezcla de post-molienda de la presente invención como se describe posteriormente en la presente.

En aun un aspecto adicional, la presente invención consiste de una composición para la inclusión en una

alimentación de pesebre para agua en sistema que es una composición como se define en forma previa que sin dilución se adapta para estar en el alimento en el suministro de agua.

En aun un aspecto adicional, la presente invención consiste de un suministro de agua para beber para un animal (de manera preferente, un animal rumiante) que tiene una alimentación en el mismo y una composición como se define en forma previa.

En aun un aspecto adicional, la presente invención consiste de un método para proporcionar un antibiótico de ionóforo a un mamífero objetivo que comprende proporcionar al animal, agua para beber con un antibiótico de ionóforo dispersado, el antibiótico de ionóforo que se ha incluido en el suministro de agua por una toma de una composición como se define de forma previa.

De acuerdo a un aspecto adicional de la invención, se proporciona una composición de antibiótico de ionóforo capaz de la dilución con agua a una forma dispersada sustancialmente estable en toda el agua cuando está presente, la composición que comprende o que incluye:

- al menos un antibiótico de ionóforo de un tamaño promedio de partícula de menos de 20 micras,

- y al menos un agente dispersante.

De manera preferente, el tamaño promedio de partícula de al menos un antibiótico de ionóforo es

sustancialmente 5 micras.

De manera preferente, la forma dispersada en agua permanece sustancialmente homogénea durante al menos 24 días.

De manera preferente, en al menos un agente dispersante se selecciona de uno o más de lo siguiente:

i) un poliglicósido compatible capaz de actuar como un agente dispersante;

ii) un lignosulfonato compatible capaz de actuar como un agente dispersante; y

iii) un glicol compatible y adecuado en una forma capaz de actuar como un agente dispersante.

De manera preferente, un vehículo líquido esta o también está presente, que de manera preferente es o incluye agua.

De manera preferente o de manera alternativa, el vehículo líquido es o incluye un compuesto organolíquido, compatible, seleccionado de manera preferente de aceites minerales y vegetales.

De manera preferente, el(los) antibiótico(s) de ionóforo se ha molido en la presencia de al menos uno de:

i) un poliglicósido compatible capaz actuar como un agente de dispersión;

ii) un lignosulfonato compatible capaz de actuar como un agente de dispersión; y

iii) un glicol compatible y adecuado en una forma

capaz de actuar como un agente dispersante.

De manera preferente, la molienda es en la ausencia de cualquier agente de suspensión, o de manera alternativa está presente un agente de suspensión seleccionado de las gomas como se describe previamente; de manera preferente el agente de suspensión es uno o más de goma de xantano, goma de guar, de acacia y una goma de celulosa.

De manera preferente, un(unos) vehículo(s) líquido(s) estuvo presente en el momento de la molienda del antibiótico de ionóforo suficiente para reducir la consistencia de la mezcla de molienda a una consistencia molible.

De acuerdo a un aspecto adicional de la invención, se proporciona agua para beber para animal que tiene al menos un antibiótico de ionóforo en forma de partículas, suspendido de manera sustancialmente en el mismo, en donde el antibiótico de ionóforo está suspendido de forma estable.

De manera preferente el antibiótico de ionóforo permanece suspendido de manera estable durante al menos 24 días.

De manera preferente, las partículas del(los) antibiótico(s) de ionóforo son de un tamaño promedio de partícula de menos de aproximadamente 10 micras, de manera más preferente, son de un tamaño promedio de partícula de sustancialmente 5 micras.

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De manera preferente, el agua para beber se elabora por una mezcla proporcionada que distribuye una suspensión acuosa más concentrada del antibiótico de ionóforo y agentes de dispersión presentes ya que la suspensión acuosa más concentrada proporciona la dispersión sustancialmente uniforme del(los) antibiótico(s) de ionóforo en el agua para beber.

De manera preferente, la suspensión acuosa más concentrada contiene uno o más agentes de suspensión.

De acuerdo a un aspecto adicional de la invención, se proporciona agua para beber para animal que tiene al menos un antibiótico de ionóforo en forma de partículas, suspendido de manera sustancialmente uniforme en el mismo, en donde las partículas de los antibióticos de ionóforo son de un tamaño promedio de partícula menor de 10 micras; de manera más preferente, el tamaño de partícula de los antibióticos de ionóforo son de un amaño promedio de partícula de sustancialmente 5 micras.

De manera preferente, el antibiótico de ionóforo permanece establemente suspendido durante al menos 24 días.

De acuerdo a un aspecto adicional de la invención, se proporciona agua para beber para animal que tiene al menos un antibiótico de ionóforo, en forma de partículas, sustancialmente dispersado de manera uniforme en el mismo, en donde las partículas de los antibióticos de ionóforo son de

un tamaño promedio de partícula de menos de 10 micras; de manera más preferente, el tamaño de partícula de los antibióticos de ionóforo son de un tamaño promedio de partícula de sustancialmente 5 micras.

De manera preferente, el antibiótico de ionóforo permanece establemente suspendido durante al menos 24 días.

De acuerdo a un aspecto adicional de la invención, se proporciona agua de pesebre accesible a un animal para beber, en donde el agua tiene un antibiótico de ionóforo, en forma de partículas, suspendido de manera sustancialmente uniforme en la misma, en donde el antibiótico de ionóforo está suspendido dispersable de manera estable.

De manera preferente, el antibiótico de ionóforo permanece suspendido de forma estable durante al menos 24 días.

De manera preferente, las partículas del(los) antibiótico(s) de ionóforo es de un tamaño promedio de partículas de menos de 10 micras; de manera más preferente, las partículas del(los) antibiótico(s) de ionóforo es de un tamaño promedio de partícula de sustancialmente 5 micras.

De manera preferente, el agua de pesebre se elabora por una mezcla proporcionada que distribuye en la misma una suspensión acuosa más concentrada del antibiótico de ionóforo y los agentes de dispersión presentes en esa forma más concentrada, proporcionan la suspensión sustancialmente

uniforme del(los) antibiótico(s) de ionóforo en el agua para beber.

De manera preferente, la suspensión acuosa más concentrada contiene uno o más agentes de suspensión.

De acuerdo a un aspecto adicional de la invención, se proporciona agua de pesebre accesible a un animal para beber, el agua tiene un antibiótico de ionóforo en forma de partículas sustancialmente suspendido de manera uniforme en la misma, en donde el antibiótico de ionóforo permanece establemente suspendido durante al menos 24 días.

De manera preferente, el tamaño de partícula de los antibióticos de ionóforo son sustancialmente de 5 micras.

De manera preferente, el antibiótico de ionóforo permanece establemente suspendido durante al menos 24 días.

De acuerdo a un aspecto adicional de la invención, se proporciona un método para dispersar un antibiótico de ionóforo en forma de partículas en un cuerpo de agua para beber, que comprende o incluye los pasos de:

- tomar una composición que comprende o que incluye al menos un antibiótico de ionóforo de un tamaño promedio de partícula de menos de 20 micras y al menos un agente de dispersión;

- formar una composición acuosa de la composición que tiene el(los) antibiótico(s) de ionóforo sustancialmente dispersados de manera uniforme en la misma y suspensión

acuosa que está disponible para la distribución en el agua para beber del animal; y

- distribuir a una velocidad (de manera continua o continuamente), esa suspensión acuosa en el agua para beber o en un suministro de composición de agua a la misma, para proporcionar el cuerpo de agua para beber con una dispersión uniforme del(los) antibiótico(s) de ionóforo en el mismo que esta dentro de un intervalo aceptable de concentración de imbibición para el animal o animales que tienen acceso a la misma.

De manera preferente, el tamaño promedio de partícula de al menos un antibiótico de ionóforo es sustancialmente de 5 micras.

De manera preferente, la composición está en la forma de una suspensión acuosa estable antes de la formación de una suspensión acuosa y la distribución subsiguiente de la misma en el agua para beber o un suministro de composición en el agua.

De manera preferente, la composición incluye uno o más agentes de dispersión seleccionados de uno o más de los siguientes:

i) un poliglicósido compatible capaz de actuar como un agente de dispersión;

ii) un lignosulfonato compatible capaz de actuar como un agente de dispersión; y

iii) un glicol compatible y adecuado en una forma capaz de actuar como un agente de dispersión.

De manera preferente, está presente un agente de suspensión seleccionado de gomas, (como se describe de manera previa). De manera preferente, el(los) antibiótico(s) de ionóforo permanece suspendido de manera estable durante al menos 24 días.

De acuerdo a un aspecto adicional de la invención, se proporciona un cuerpo de agua para beber que tiene un ionóforo en forma de partícula suspendido en el mismo, preparado por el método como se describe de forma previa.

De acuerdo a un aspecto adicional de la invención, se proporciona un método para formar una composición dispersable de al menos un antibiótico de ionóforo y la composición dispersable que es capaz de la dilución subsiguiente, el método incluye, antes de cualquier presencia opcional de agua y cualquier presencia opcional de un agente de suspensión, la molienda del(los) antibiótico(s) de ionóforo con un glicol adecuado.

De manera preferente, la molienda toma lugar en la presencia de al menos un líquido, que incluye de manera preferente agua.

De manera preferente, no está presente ninguna goma.

De manera preferente, la molienda es a un tamaño

promedio de partícula mucho menor de 20 micras; de manera más preferente el tamaño promedio de partícula es de aproximadamente 5 micras.

De manera preferente, la molienda toma lugar en la presencia de un lignosulfonato adecuado.

De manera preferente, la molienda toma lugar en la presencia de un poliglicósido adecuado.

De manera preferente, la molienda toma lugar en la presencia de un agente adecuado antiespuma.

De acuerdo a un aspecto adicional de la invención, se proporciona una composición dispersable de al menos un antibiótico de ionóforo preparado de acuerdo al método como se describe de forma previa.

De acuerdo a un aspecto adicional de la invención, se proporciona un método para formar una composición dispersable de al menos un antibiótico de ionóforo y composición dispersable que es capaz de la dilución subsiguiente; el método incluye, antes de cualquier presencia opcional de agua y de cualquier presencia opcional de un agente de suspensión, la molienda de(los) antibiótico(s) de ionóforo con un agente adecuado de dispersión.

De manera preferente, la molienda toma lugar en la presencia de un lignosulfonato adecuado.

De manera preferente o de manera alternativa, la molienda toma lugar en la presencia de un glicósido adecuado.

De manera preferente, el agente adecuado de dispersión se selecciona del grupo que consiste de un lignosulfonato adecuado y un poliglicósido adecuado.

De manera preferente, el tamaño promedio de partícula es de menos de 20 micras; de manera más preferente menos de 10 micras; de manera aun más preferente el tamaño promedio de partícula es de sustancialmente 5 micras.

De manera preferente, la molienda toma lugar en la presencia de un agente adecuado antiespuma.

De manera preferente, la molienda toma lugar en la presencia de al menos algún líquido.

De manera preferente, está presente un glicol adecuado.

De manera preferente, no está presente ninguna goma.

De acuerdo a un aspecto adicional de la invención, se proporciona una composición de antibiótico de ionóforo, distribuible por dosis, que comprende o que incluye:

- al menos un antibiótico de ionóforo;
- al menos un agente de dispersión;
- al menos un agente de suspensión; y
- agua

en donde el(los) antibiótico(s) de ionóforo y al menos un agente de dispersión se han molido conjuntamente en la presencia de un líquido (que puede ser agua o puede

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incluir agua pero no necesariamente así) y donde el agente de dispersión sea adicionado después de la molienda en la presencia de agua.

De manera preferente, el antibiótico de ionóforo es de un tamaño promedio de partícula de menos de 50 micras; de manera más preferente un tamaño promedio de partícula de menos de 20 micras.

De manera preferente, al menos un agente de suspensión es o incluye una goma y no estuvo presente ninguna goma en el procedimiento de molienda.

De manera preferente, estuvo presente algo de agua en el procedimiento de molienda.

De manera preferente, estuvo presente un poliglicósido como un agente de dispersión en la etapa de molienda.

De manera preferente, estuvo presente un lignosulfonato como un agente de dispersión en la etapa de molienda.

De manera preferente, estuvo presente un glicol como un agente de dispersión en la etapa de molienda.

De manera preferente, están presentes en la etapa de molienda un alquil-poliglicósido, un lignosulfonato y un propilenglicol.

De manera preferente, está presente cualquiera o más de un agente o sistema antiespuma, un conservador, un

agente desamargador y un sistema de amortiguamiento del pH.

De acuerdo a un aspecto adicional de la invención, se proporciona un producto molido útil en la provisión de una suspensión acuosa de al menos un antibiótico de ionóforo; el producto que es el resultado molido de una mezcla de molienda de al menos:

- al menos un antibiótico de ionóforo; y
- al menos un agente de dispersión;

en donde la mezcla de molienda ha estado sustancialmente libre de agente de suspensión seleccionado de las gomas previamente descritas y la mezcla de molienda ha incluido al menos un componente líquido (que opcionalmente puede ser uno o uno del(los) agente(s) de dispersión o un material adicional);

en donde, en el producto, el proceso de molienda ha dado por resultado alguna asociación física de al menos un agente de dispersión en las partículas del antibiótico de ionóforo; y

en donde, en el producto, el tamaño promedio de partícula de(los) antibiótico(s) de ionóforo es menos de 20 micras.

De manera preferente, el tamaño promedio de partículas es sustancialmente 5 micras.

De acuerdo a un aspecto adicional de la invención, se proporciona una composición dispersable para la dilución sustancial por agua, el método que comprende o incluye:

(I) moler al menos un antibiótico de ionóforo y al

menos un agente de dispersión para proporcionar alguna asociación física de al menos un agente de dispersión en las partículas de antibiótico de ionóforo de un tamaño promedio de partícula de menos de 20 micras; y

(II) mezclar el resultado molido del(los) antibiótico(s) de ionóforo/agente(s) de dispersión después de la molienda, en al menos un agente de suspensión.

Esta invención también puede ser ampliamente que consista en las partes, elementos y características referidas o indicadas en la especificación de la solicitud, de manera individual o colectiva, y cualquiera o todas las combinaciones de cualquiera de dos o más de las partes, elementos o características y donde se mencionan números enteros específicos en la presente que tienen equivalentes conocidos en la técnica a los cuales se refiere esta invención, estos equivalentes conocidos parecen ser incorporados en la presente como si se expusieran de manera individual.

La invención consiste en lo anterior y también contempla, construcciones de las cuales lo siguiente da ejemplos.

Definiciones

En donde, en la especificación se usan los siguientes términos, existen varias alternativas posibles, los ejemplos de las cuales son como sigue:

Agentes Tensioactivos/Dispersantes:

- ésteres de sorbitan
- ésteres de sorbitan etoxilados
- etoxilado de aceite de ricino
- ácidos grasos etoxilados;
- alcoholes etoxilados;
- ácidos grasos de polietilenglicol;
- ácido naftaleno-sulfónico condensado;
- ésteres de glicerol;
- ésteres de fosfato;
- laurilsulfato de sodio;
- poliacrilato de sodio;
- poliacrilato de amonio;
- octil-fenil-etoxilatos;
- nonil-fenil-etoxilatos;
- compuestos de amonio cuaternario;
- sulfosuccinatos;
- lecitina de soya;

Auxiliares de suspensión, incluyendo gomas:

- estearato de aluminio;
- dióxido de silicio;
- arcilla modificada, incluyendo Smectita, Monmorillonita, Hectorita, Bentonita;
- aceite de ricino deshidrogenado;
- quelato de titanio;

- polímeros acrílicos solubles en álcali;
- diuretanos no iónicos;
- polivinil-pirolidona;
- alcohol polivinílico;
- goma de guar;
- goma arábiga;
- hidroxi-propil-metil-celulosa;
- hidroxi-etil-celulosa;
- carboximetilcelulosa sódica;
- hidroxi-etil-celulosa hidrófobamente modificada

Desespumadores/Antiespuma:

- polimetil-siloxano;
- aceite de hidrocarburo insaturado;
- aceite mineral;
- sílice en tipo aceite

Conservadores:

- oxazolidinas;
- benzotiazoles;
- cloruro de benzalconio;
- triazinas sustituidas;
- isotiazolonas;
- hemiacetales;
- benzoatos sustituidos;
- piridina-óxido de zinc;

- piridinatiol-óxido de sodio;

Agentes de Amortiguamiento:

- tetroxolato de potasio;
- tartrato ácido de potasio;
- ftalato ácido de potasio;
- bórax.

Descripción Detallada de la Invención

Ahora se describirán formas preferidas de la presente invención con referencia a los dibujos anexos, en los cuales:

La Figura 1 muestra un procedimiento de mezclado utilizado de acuerdo con la presente invención;

La Figura 2 muestra un segundo procedimiento de mezclado utilizado de acuerdo con la invención; y

Las Figuras 3A-3C ilustran un sistema de tratamiento en pesebre DOSTATRON^{MR} en tres diferentes modos de operación.

Mostradas en las Figuras 3A a 3C están tres instalaciones de una instalación tipo DOSATRON^{MR} usada para dosificar materiales en el agua para beber. El aparato DOSATRON^{MR} se recomienda puesto que es útil en línea (Figura 3A), en una línea de derivación (Figura 3B) y en paralelo (Figura 3C). A este respecto, ver los materiales de publicidad disponible del distribuidor de Nueva Zelanda Mark Bell-Booth Ltd.

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El aparato DOSATRON^MR emplea por sí mismo un pistón de dosificación impulsado por un motor de pistón hidráulico volumétrico. El ritmo de propagación del motor es proporcionar al flujo del agua que pasa a través de un sistema y de esta manera la velocidad de inyección permanecerá igualmente proporcional en su movimiento de vaivén.

El aparato tiene la capacidad de un amplio intervalo de ajuste de dosificación diaria y el arreglo paralelo mostrado en la Figura 3 permite que estos se dupliquen debido al uso de dos unidades de distribución DOSATRON^MR.

Ahora se describirán formas preferidas con referencia a los siguientes ejemplos de los cuales los procedimientos de mezclado utilizados son como se representan y secuencian de manera preferente en una de las Figuras 1 ó 2.

La presente invención reconoce que habiendo desarrollado una suspensión acuosa, estable, adecuada de monensina microfina, una alimentación previsible de la misma a animales, es posible simplemente al proporcionar al animal agua para beber la cual incluye el antibiótico de ionóforo microfino dispersado en la misma, el antibiótico de ionóforo que se ha incluido en el suministro de agua por una incisión directa o indirecta de una composición como se define de

forma previa. Entre menos diluida este el concentrado, se va a encontrar más deseable el agente de suspensión.

De manera preferente, la composición es para el uso en uno o más de los sistemas de tratamiento en pesebre, disponibles.

Ejemplo 1

Monensina Sódica	6.33 % (aproximadamente 6 % de monensina) p/v
Monopropilenglicol	10 % p/v
ULTRAZINE NA[MR]	4.5 % p/v
Fosfato Disódico Anhidro	0.355 % p/v
Fosfato Monopotásico Dihidratado	0.04 % p/v
Bromuro de Dialquil-Dimetil-Amonio	.0064 % p/v
Goma de Xantano	
0.4 % p/v	
Simeticona	GENSIN[MR]
0.333 % p/v	
Dióxido de Silicio, Antiespuma	0.167 % p/v
Agua a 100 %	

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La molienda ha dado por resultado un tamaño promedio de partícula para monensina sódica de 5 micras.

Ejemplo 2

Monensina Sódica	6.33 % (aproximadamente 5 % de monensina) p/v
Monopropilenglicol	10 % p/v
Alquil-Poliglicósido	0.5 % p/v
Fosfato Disódico Anhidro	0.355 % p/v
Fosfato Monopotásico Dihidratado	0.04 % p/v
Bromuro de Dialquil-dimetil-amonio	.0064 % p/v
Goma de Xantano	0.4 % p/v
Simeticona GENSIL^{MR}	0.333 % p/v
Dióxido de Silicio, Antiespuma	0.167 % p/v
Agua a 100 %	

La molienda da por resultado un tamaño promedio de partícula para monensina sódica de 5 micras.

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Ejemplo 3

Monensina Sódica	6.33 % (aproximadamente 6 % de monensina) p/v
Monopropilenglicol	10 % p/v
ULTRAZINE NA[MR]	4.5 % p/v
Fosfato Disódico Anhidro	0.355 % p/v
Fosfato Monopotásico Dihidratado	0.04 % p/v
Bromuro de dialquil-dimetil-amonio	.0064 % p/v
Goma de Xantano	0.4 % p/v
Simeticona GENSIL[MR]	0.333 % p/v
Dióxido de Silicio Antiespuma	0.167 % p/v
Sorbitol como un agente Desamargador	3.5 % p/v
Agua	

La molienda ha dado por resultado un tamaño promedio de partícula para monensina sódica de 5 micras.

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Ejemplo 4

Monensina Sódica	6.33 % (aproximadamente 6 % de monensina) p/v .
Monopropilenglicol	10 % p/v
Alquil-poliglicósido	0.5 % p/v
Fosfato Disódico Anhidro	0.355 % p/v
Fosfato Monopotásico Dihidratado	0.04 % p/v
Bromuro de dialquil-dimetil-amonio	.0064 % p/v
Goma de Xantano	0.4 % p/v
Simeticona GENSIL^{MR}	0.333 % p/v
Dióxido de Silicio; Antiespuma	0.167 % p/v
Sorbitol como un agente Desamargador	3.5 % p/v
Agua a 100 %	

La molienda ha dado por resultado un tamaño promedio de partícula para monensina sódica de 5 micras.

Ejemplo 5

Nombre de ingrediente (común o químico)	Número CAS	Cantidad (% p/p)	Función
Monensina Sódica QA 166H	17090-79-8	6.747 %	Sustancia activa
Monopropilenglicol	57.55-6	10 %	Anticongelante
Bromuro de didecil-dimetil-Amonio	2390-68-3	0.1	Conservador
Goma de Xantano	11138-66-2	0.5 %	Agente de Suspensión
Lignosulfonato de Sodio	8061-51-6	4.1 %	Agente humectante
Alquil-poliglicósido	68515-73-1	3.8	Agente humectante
Simeticona	8050-81-5	0.333 %	Antiespuma
Dióxido de Silicio	7631-89-9	0.167 %	Antiespuma
Agua c.s.	7732-18-5	74.47 %	Diluyente

La molienda ha dado por resultado un tamaño promedio de partícula para monensina sódica de 5 micras.

La simeticona y dióxido de silicio conjuntamente constituyen la marca de patente "Gensil".

1. Procedimiento de Preparación

Las formulaciones de cada uno de los Ejemplos 1 a 4 se pueden preparar por el procedimiento mostrado en la Figura 1. La formulación del Ejemplo 5 se prepara por el procedimiento mostrado en la Figura 2. El método preferido para preparar una formulación tal como Ejemplo 1 es como sigue.

Como se puede ver de las Figuras 1 y 2, un recipiente de mezclado (A) que puede ser, si se desea, el molino (B) de cuentas, horizontal pero de manera preferente no lo es, y se utiliza en un recipiente de mezclado (C) como el aparato.

Sin embargo, de manera más preferente, existe un equipo de tres etapas basado en el proceso, tal como el recipiente de mezclado (A), el molino (B) de cuentas, horizontal, para volver microfino el antibiótico de ionóforo y un recipiente de mezclado (C).

Como se puede ver de la Figura 1, se mezclan los ingredientes 1 hasta 6 en la secuencia de los números de secuencia en los recipientes de mezclado (A) antes del paso en el molino (B) de cuentas, horizontal. Estos materiales pre-mezclados incluyen:

- monopropilenglicol;
- bromuro de dialquil-dimetil-amonio;
- antiespuma GENSIL^{MR}

- algo de agua;
- agente humectante ULTRAZINE NA^{MR}, y
- monensina.

Después de la molienda de la mezcla de pre-molienda, el producto se puede quitar ya sea como un producto intermedio (por ejemplo; producto de post-molienda) para el uso subsiguiente, en otro sitio para el mezclado. Sin embargo, y de manera preferente, la mezcla molida de salida pasa al recipiente de mezclado (C) donde se mezcla con el resto del agua (7), el resto del agente humectante ULTRAZINE NA^{MR} (8) y la goma de xantano u otro agente de dispersión (9).

Con una formulación ya sea de la fórmula del Ejemplo 1 ó el Ejemplo 3 u otra (Figuras 1 y 2 no se refieren al sistema de amortiguamiento ni a un sistema desamargador) se obtiene una muy buena suspendibilidad tanto del concentrado como de la forma diluida, subsiguiente (por ejemplo; en un uso en pesebre donde la dilución es por ejemplo a aproximadamente 3 a 6 ppm de monensina).

Los números 1-9 (Figura 1) ó 1-11 (Figura 2) indican las secuencias preferidas de la adición de los ingredientes. Con referencia a la Figura 1, una mezcla de pre-molienda sin secuencia de los componentes 1 hasta 6 en el recipiente de mezclado (A) conducirá aun a una buena mezcla de molienda, que es perjudicial a la mejor susceptibilidad de la forma diluida.

Una formulación preferida como en el Ejemplo 1 hecha por el procedimiento como en la Figura 1 tiene una capacidad de ser adicionada con un concentrado acuoso en un gran volumen de agua tal como se puede experimentar al proporcionar una alimentación en un sistema acuoso.

Es importante señalar las siguientes cuestiones de procesamiento:

- el orden de adición de los componentes a la premezcla a base de molienda no es crítico;
- el tamaño apropiado de partícula inducido por la operación de molienda es crítico;
- es crítico el orden de adición de los componentes en el tanque de composición.

2. La Mezcla de Molienda

La mezcla de molienda es un factor importante en la invención. Es la premezcla de los componentes que se adicionan en el molino de cuentas. La composición (identidad y cantidad) es importante al determinar el tamaño final de partícula y los revestimientos de las partículas que resultan. Las cantidades relativas (por ejemplo de MPG: monensina) son importantes a este respecto.

3. Datos de Estabilidad

a) Estabilidad de vida en anaquel

Los siguientes datos de estabilidad de vida en anaquel indican que el concentrado de 6 % exhibe estabilidad, a diferentes temperaturas durante al menos 3 meses (la duración de tiempo de los ensayos).

Estudio de Vida en Anaquel de Concentrado de 6 % en Tratamiento en Pesebre

Número de lote: 1183				
Muestra 25°C:				
	Tiempo 0	1 Mes	2 Meses	3 Meses
Apariencia	Normal	Normal	Normal	Normal
Coliformes	<1	<1	<1	<1
Biopotencia de Monensina	5.7	5.5	5.4	5.6
pH	8.11	8.00	7.77	7.51
Levaduras y Mohos	<1	<1	<1	<1
APC	<10	<10	<10	<10

Muestra a 42°C:				
	Tiempo 0	1 mes	2 meses	3 meses
Apariencia	Normal	Normal	Normal	Normal
Coliformes	<1	<1	<1	<1
Biopotencia de Monensina	5.7	5.6	5.4	5.4
pH	8.11	7.60	7.39	7.28
Levaduras y Mohos	<1	<1	<1	<1
APC	<10	<10	<10	<10

*Apariencia normal significa líquidos gelatinoso café claro con motas café presentes.

b) Estabilidad en reposo

Los siguientes experimentos detallan la estabilidad en reposo del tratamiento en pesebre de la invención (TT).

Se llevaron a cabo estudios de estabilidad en reposo con un sistema de tratamiento en pesebre DOSATRON^{MR}. Este es un sistema de alimentación proporcional que distribuye un % de mezcla en proporción a la demanda. Este sistema de administración es capaz de la distribución propagada de un lote completo durante 24 horas.

La Figura 3 ilustra un sistema de dosificación usado en la obtención de los datos de la estabilidad en reposo.

Ejemplo 1

Tratamiento en pesebre (TT) (600ppm) en un tanque de solución de plástico de 200L con un Dosatron 8000 funcionando.

Método

Se adicionaron 100 litros de agua al tanque de solución conectado a un Dosatron 8000.

Se mezclaron 2 litros de TT con 2 litros de agua.

Esta mezcla se adicionó al tanque de solución medio lleno, relleno al nivel de 200 litros, y se mezcló completamente.

El Dosatron se ajustó a 2 % y el flujo de agua a 400 litros/hora para asegurar que el tanque de solución se use de manera completa en el espacio de 24 horas.

El tubo de extracción de Dosatron se ajustó a una altura de 10 cm. desde el fondo del tanque.

Muestreo

Se tomaron muestras para el ensayo de las derivaciones de extracción. Antes del muestreo, se extrajo y

descartó una muestra de 50 ml. Se toman muestras de una porción de 1 x 100 ml de cada una de las cuatro derivaciones colocadas ya sea en la parte superior, parte intermedia o fondo del tanque. Se tomarán muestras a intervalos específicos de tiempo.

Cada muestra tomada se identificó de manera individual y se tomaron 50 ml de cada muestra y se adicionaron a una muestra mezclada (volumen total de 200 ml).

Esta muestra fue aquella analizada y las otras muestras se retuvieron.

También se tomaron muestras del ajuste de la tercera derivación, colocada aquí en el tanque de plástico a un nivel de 10 cm desde el fondo del tanque.

Las muestras se toman a 0, 12, 24 horas después del mezclado.

Después de 24 horas, se toman muestras adicionales de 4 x 100 ml del fondo del tanque. Cada muestra tomada se identificó de manera individual y se toman 50 ml de cada muestra y se mezclan (un volumen total de 200 ml). Esta muestra se analizó y las otras muestras se retienen. En este caso, se usó el tubo de pistola de administración unido a la varilla.

Ejemplo 2

Medición de la estabilidad en reposo del TT (3000ppm) en un tanque de solución de plástico de 200 L,

estático durante un periodo de 4 días.

Método

Antes del relleno del tanque, las mangueras de derivación del fondo se doblan de modo que el extremo estuvo a 5 cm del fondo del tanque.

Se adicionaron 100 litros de agua al tanque de solución.

Se mezclaron 10 litros de TT con 10 litros de agua.

Esta mezcla se adicionó al tanque de solución medio lleno, relleno al nivel de 200 litros y se mezcló.

Muestreo

Los muestreos del ensayo se tomaron de las derivaciones de extracción. Antes del muestreo, se extrajo y descartó una muestra de 50 ml. Cada muestra tomada se identificó de manera individual y se tomaron y mezclaron 50 ml de cada muestra (volumen total de 200 ml). Esta muestra fue la que se analizó y las otras muestras se retuvieron.

Se tomaron muestras de la parte superior, parte intermedia y fondo del tanque a intervalos de 0, 12 horas, 24 horas, 2 días y 4 días después del mezclado.

Ejemplo 3

Medición de la estabilidad en reposo de TT (6 ppm) en un pesebre concentrado durante un periodo de 24 días.

Método

Se adicionaron 50 litros de agua al tanque de solución conectado al Dosatron 8000.

Se mezcló 1 litro de TT con un litro de agua.

Esta mezcla se adicionó al tanque de solución medio lleno, se rellenó al nivel de 100 litros y se mezcló. Se ajustó el Dosatron a 1 % para asegurar una concentración de pesebre de 6 ppm.

El pesebre se conectó al tanque de solución que contiene el Dosatron y TT.

Se lavó el pesebre nuevo de concreto y el agua al pH de pesebre probado antes del uso.

Es aceptable un pH neutral (7-8).

El agua se descartó antes del relleno del Dosatron 8000.

La activación de la llave de bola rellenó el pesebre con TT (6 ppm).

Después del relleno del pesebre se simuló la bebida al someter a sifón al agua desde la parte superior del pesebre para activar la llave de bola. Se sometieron a sifón 5000 litros del pesebre durante un periodo de 24 horas.

Muestreo

El tubo de extracción de la pistola de administración se unió a un poste rígido. El extremo del tubo de extracción se ajustó para muestrear el pesebre desde 3 niveles, parte superior, parte intermedia y fondo, se tomaron

muestras de 4 x 100 ml de cada posición.

Cada muestra tomada se identificó de manera individual y se tomaron y mezclaron 50 ml de cada muestra (volumen total 200 ml).

Esta muestra fue la que se analizó y las otras muestras se retuvieron.

Se muestreo el pesebre a intervalos de 0, 6 horas, 12 horas, 24 horas,. 5 días, 10 días y 24 días después del mezclado.

Ejemplo 4

Medición de la cantidad de asentamiento de Monensina en el tambor después de mezclar TT a 3000 ppm y dejar durante 4 días sin perturbar.

Métodos

Se adicionaron 100 litros de agua al tanque de solución conectado al Dosatron 8000.

Se mezclaron 10 litros de TT con 10 litros de agua.

Esta mezcla se adicionó al tanque de solución medio lleno, se relleno al nivel de 200 litros y se mezcló.

Muestreo

Las muestras para el ensayo se toman del fondo del tanque.

Antes del muestreo, se abrieron todas las

derivaciones intermedias y las derivaciones del fondo para proporcionar una liberación lenta de la mezcla del tanque. La velocidad de remoción del fluido fue lenta de forma suficiente de modo que no se perturbó el fondo del tanque.

Después de que el nivel de agua calló por debajo de las derivaciones del fondo, se mezcló el fondo del tanque completamente y se extrajeron muestras 4 x 100 ml tomadas en diferentes ubicaciones.

Cada muestra tomada se identificó de manera individual y se toman y mezclan 50 ml de cada una de las muestras (volumen total 200 ml).

La muestra fue la que se analizó y las otras muestras se retuvieron.

N.B. Calcular el volumen del agua dejada en el tambor antes de tomar las muestras.

Esto será calcular la cantidad total de asentamiento de monensina en el fondo del tanque después de 4 días.

Resultados y análisis de la estabilidad en reposo

La prueba tiene los siguientes parámetros de exactitud.

Repetitibilidad: La diferencia entre los resultados

de las porciones duplicadas de la misma muestra probada en la misma corrida no debe exceder 10 % del resultado promedio. Los resultados recientes indican que los resultados duplicados no exceden 5.4 % del resultado promedio.

Reproducibilidad: La diferencia entre los resultados de las porciones de la misma muestra probada a diferentes tiempos por diferentes analistas no debe exceder 15 % del resultado promedio.

Los datos de repetitibilidad y reproducibilidad dan parámetros cuantificables para la homogeneidad sustancial, indicando una suspensión sustancialmente uniforme durante el tiempo.

Tabla 1: Ejemplo 1 Resultados (600 ppm)

Tiempo	Resultados de Muestra del Fondo
0 horas	556 ppm
12 horas	504 ppm
24 horas	439 ppm

Tabla 2: Ejemplo 1 Resultados de Ensayo Repetido (600 ppm)

Tiempo	Resultados de Muestra del Fondo
0 horas	580 ppm
12 horas	470 ppm
24 horas	420 ppm

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Tabla 3: Ejemplo 2 Resultados (3000 ppm)

Tiempo	Muestra de Parte Superior (ppm)	Muestra de Parte Intermedia (ppm)	Muestra de Fondo (ppm)
0 horas	2970	2900	3030
12 horas	2680	2720	2760
24 horas	2930	2970	3060
2 días	2960	2950	3030
4 días	2190	2930	3050

Tabla 4: Ejemplo 3 Resultados (6 ppm)

Tiempo	Muestra de Parte Superior (ppm)	Muestra de Parte Intermedia (ppm)	Muestra de Fondo (ppm)
0 horas	5.0	5.5	5.1
6 horas	4.9	4.6	5.2
12 horas	4.7	4.9	5.0
24 horas	5.6	5.2	5.0
4 días	5.1	5.3	4.3
10 días	5.5	5.1	5.8
24 días	5.0	5.0	5.3

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REIVINDICACIONES

1. Una composición de antibiótico de ionóforo, concentrada, en suspensión acuosa; la composición comprende:

- al menos un antibiótico de ionóforo de un tamaño promedio de partícula de menos de 20 micras;

- al menos un agente de dispersión seleccionado de uno o más de un poliglicósido compatible, un lignosulfonato compatible y un glicol compatible y adecuado; y

- un agente de suspensión seleccionado de gomas;

en donde la composición es capaz de la dilución con agua a una composición sustancialmente estable y a una composición diluida, sustancialmente estable y dispersada; y

en donde la forma diluida en agua permanece sustancialmente homogénea durante al menos 24 días.

2. Una composición de conformidad con la reivindicación 1, donde el tamaño promedio de partícula de al menos un antibiótico ionóforo es sustancialmente 5 micras.

3. Una composición de conformidad con la reivindicación 1 o 2, donde el agente de suspensión es uno o más de goma de xantano, goma de guar, goma de acacia, o goma de celulosa.

4. Una composición de conformidad con la reivindicación 3, que además comprende un vehículo líquido que es un compuesto orgánico, líquido, compatible.

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5. Una composición de conformidad con la reivindicación 4, donde el compuesto orgánico se selecciona de aceites minerales y vegetales.

6. Una composición de conformidad con cualquiera de las reivindicaciones 3 a 5, donde el antibiótico de ionóforo se ha molido en la presencia de al menos un agente de dispersión seleccionado de uno o más de un poliglicósido compatible, lignosulfonato compatible y un glicol compatible y adecuado.

7. Una composición de agua para beber para animal que comprende:

- al menos un antibiótico de ionóforo en forma de partículas, sustancialmente dispersado o suspendido de manera uniforme en el mismo, en donde el antibiótico de ionóforo está suspendido o dispersado de manera estable y en donde el tamaño de partícula del antibiótico de ionóforo es de un tamaño promedio de partícula de menos de 10 micras;

- al menos un agente de dispersión seleccionado de uno o más de un poliglicósido compatible, un lignosulfonato compatible y un glicol compatible y adecuado; y

- uno o más agentes de suspensión;

en donde el antibiótico de ionóforo permanece establemente suspendido durante al menos 24 días.

8. La composición de agua para beber para animal de conformidad con la reivindicación 7, donde el tamaño de

partículas del antibiótico de ionóforo es de un tamaño promedio de partícula de sustancialmente 5 micras.

9. Un método para distribuir un antibiótico de ionóforo en forma de partículas en un cuerpo de agua para beber, que comprende:

- formar una suspensión acuosa de una composición que comprende:

- al menos un antibiótico de ionóforo de un tamaño promedio de partícula de menos de 20 micras;

- al menos un agente de dispersión seleccionado de uno o más de un poliglicósido compatible; un lignosulfonato compatible y un glicol compatible y adecuado; y

- un agente de suspensión seleccionado de gomas;

en donde el antibiótico de ionóforo está sustancialmente dispersado de manera uniforme en el mismo;

en donde la suspensión acuosa es adecuada para la distribución en el agua para beber para animal, y es capaz de la dilución adicional para producir un cuerpo de agua para beber con una dispersión uniforme del antibiótico de ionóforo en el mismo que está dentro de un intervalo aceptable de concentración de imbibición para el animal o animales que tienen acceso a la misma; y

en donde el antibiótico de ionóforo permanece suspendido de manera estable durante al menos 24 días.

10. El método de conformidad con la reivindicación

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9, donde el tamaño de partículas de los antibióticos de ionóforo son de un tamaño promedio de partícula de sustancialmente 5 micras.

11. El método de conformidad con la reivindicación 9 o 10, que además comprende:

- distribuir la suspensión acuosa en el agua para beber para la misma, para proporcionar el cuerpo de agua para beber con una dispersión uniforme del antibiótico de ionóforo en la misma que está dentro de un intervalo aceptable de concentración de imbibición para el animal o animales que tienen acceso a la misma.

12. Un método para formar una composición concentrada, dispersable de al menos un antibiótico de ionóforo, en donde la composición concentrada, dispersable es capaz de la dilución subsiguiente; el método comprende:

- moler el antibiótico de ionóforo con un agente adecuado de dispersión seleccionado de uno o más de un poliglicósido compatible, un lignosulfonato compatible, y un glicol compatible inadecuado;

en donde la molienda es a un tamaño promedio de partícula de menos de 20 micras.

13. El método de conformidad con la reivindicación 12, donde la molienda toma lugar en la presencia de agua y un agente de suspensión.

14. El método de conformidad con la reivindicación

12 o 13, donde la molienda es a un tamaño promedio de partícula de aproximadamente 5 micras.

15. El método de conformidad con cualquiera de las reivindicaciones 12 a 14, donde la molienda toma lugar en la presencia de al menos algún líquido no acuoso.

16. El método de conformidad con la reivindicación 15, donde la molienda toma lugar en la presencia de un agente antiespuma, adecuado.

17. Una composición suspendida o dispersada que comprende un antibiótico de ionóforo preparado de acuerdo al método de cualquiera de las reivindicaciones 12 a 16.

18. Una composición de antibiótico de ionóforo, diluible en dosis, que comprende:

- al menos un antibiótico de ionóforo en donde el tamaño de partícula del antibiótico de ionóforo es de un tamaño promedio de partículas de menos de 50 micras;

- al menos un agente de dispersión seleccionado de uno o más de un poliglicósido compatible, un lignosulfonato compatible y un glicol compatible y adecuado; y

- al menos un agente de suspensión; y

- agua;

en donde el antibiótico de ionóforo y al menos un agente de dispersión se han molido conjuntamente en la presencia de un líquido no acuoso y en donde al menos una alícuota adicional de al menos un agente de dispersión y agua

se adicionan después de la molienda.

19. La composición de conformidad con la reivindicación 18, donde el antibiótico de ionóforo está presente a un tamaño promedio de partícula de menos de 20 micras.

20. La composición de conformidad con la reivindicación 18 o 19, donde algo de agua está presente en el procedimiento de molienda.

21. Una composición de conformidad con la reivindicación 20, donde están presentes en la etapa de molienda alquil-poliglicósido, un lignosulfonato y un propilenglicol.

22. La composición de conformidad con la reivindicación 20 o 21, donde está presente uno o más de un agente o sistema antiespuma y un conservador, un agente de desamargador, y un sistema de amortiguamiento del pH.

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RESUMEN DE LA INVENCIÓN

La invención es un dispositivo de recolección de energía accionado neumáticamente. El dispositivo incluye un soporte el cual tiene un recolector de energía en el mismo. Se une deslizablemente un obturador al soporte y se puede mover entre una primera posición "cerrada" y una segunda posición "abierta". En su primera posición, el obturador cubre al recolector, y en su segunda posición, el obturador descubre al recolector. El obturador está desviado a una de las posiciones. Se coloca una cámara adyacente al obturador de manera que cuando se presuriza la cámara, se vence la desviación del obturador y el obturador se mueve entre la primera posición y la segunda posición.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P451785 DJJ/jif	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/NZ01/00290	International Filing Date *(day/month/year)* 18 December 2001	Priority Date *(day/month/year)* 19 December 2000
International Patent Classification (IPC) or national classification and IPC Int. Cl. [7] A61K 9/00, 9/14, 47/34, 47/36, 47/10		
Applicant ELI LILLY AND COMPANY (NZ) LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

This REPORT consists of a total of 3 sheets, including this cover sheet.

[X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 40 sheet(s).

3. This report contains indications relating to the following items:

- I [X] Basis of the report
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of the report
12 June 2002	15 April 2003
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer ANDREW ACHILLEOS Telephone No. (02) 6283 2280

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/NZ01/00290

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I. Basis of the report

1. With regard to the elements of the international application:*

- [ ] the international application as originally filed.
- [X] the description, pages , as originally filed,
  pages , filed with the demand,
  pages 1-36, received on 19 March 2003 with the letter of 18 March 2003
- [X] the claims, pages , as originally filed,
  pages , as amended (together with any statement) under Article 19,
  pages , filed with the demand,
  pages 37-40, received on 19 March 2003 with the letter of 18 March 2003
- [ ] the drawings, pages , as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- [ ] contained in the international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [X] the claims, Nos. 23-72
   - [ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/NZ01/00290

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-22	YES
	Claims	NO
Inventive step (IS)	Claims 1-22	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-22	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

Novelty

The prior art documents WO 97/03650 (D1) and WO 98/16663 (D2), both belonging to the applicant, do not disclose the invention defined in your amended claims 1-22. D2 does not disclose the use of the specific surfactants defined in your application or the use of suspending agents. D1 does not disclose the antibiotic particle size distribution or the milling process of production defined in your application.

Inventive Step

Your amended claims 1-22 involve an inventive step as it would not have been obvious to a person skilled in the art to use the particle size distribution or milling process defined in your application.

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"IONOPHORE ANTIBIOTIC FORMULATIONS"

The present invention relates to ionophore antibiotic compositions and particularly, but not solely, to ionophore antibiotic compositions capable of dilution with water, suitable for inclusion directly or via a holding tank in the drinking water of an animal to have administered and/or self administered an ionophore antibiotic or ionophore antibiotics.

BACKGROUND

Administration of ionophore antibiotics such as monensin to animals (preferably ruminants) is known to achieve in appropriate dosages advantages for a number of different purposes. These include the treatment or prevention of ketosis and/or bloat, the enhancement of milk production, enhancement of milk protein content in milk, enhancement of mineral uptake, enhancement of weight gain, and/or enhancement of feed conversion efficiency (in ruminants), desirable reproduction advantages and as a milk replacement. See US Patent 3,829,557.

In this respect we refer to European Patent Specification 0,139,595 A2 of KOFFOLK (1949) LTD which relates to a liquid ionophore antibiotic composition for ruminants and poultry where the antibiotic is dissolved in a non-toxic water-soluble organic solvent rather than a water soluble organic solvent, and in use the resulting solution is admixed with a liquid feed, a liquid vitamin concentrate or drinking water. There are claims for stability on standing.

The composition of EP 0,139,595 indicates that because monensin and its sodium salt is only slightly soluble in water that it is generally administered in a dry form in an animal feed and/or in dry liquid milk replacer compositions. The same is also indicated as being true for another ionophore antibiotic lasalocid which in US Patent 3,715,372 is reported to be completely insoluble in water.

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The composition of EP 0,139,595 uses as an organic solvent for the ionophore antibiotic a solvent selected from the group comprising propylene glycol, glycerol, ethanol and isopropanol and mixtures thereof.

Example 1 of EP 0,139,595 indicates that 250 g of a mycelium containing 10% monensin was mixed at room temperature with 1250 cc propylene glycol for 2 hours by exposing the mixture to ultrasound. There is an indication that 50% of the monensin was found in solution in the propylene glycol.

Monensin is usually available commercially as the sodium salt of the acid. Monensin sodium is available in two forms, namely, a crystalline form or a mycelial form. The mycelial form has only about a 20% activity while the crystalline form has greater than 90% active monensin sodium.

Reference herein to "monensin" where the context allows encompasses all forms thereof including monensin, alkali metal salts of monensin and monensin esters and includes mixtures. Likewise for the other ionophore antibiotics.

In our New Zealand Patent Specification 272574/272940 (equivalent to PCT/NZ96/00068 WO 97/03650) we disclose an aqueous base suspension concentrate of an ionophore antibiotic or ionophore antibiotics such as monensin.

In one aspect in NZ 272574/272940 that invention is defined as an aqueous base suspension concentrate of an ionophore antibiotic or ionophore antibiotics capable of aqueous dilution (if desired) and capable (with or without such aqueous dilution) of being orally administered to an animal by an active dosing regime (eg; by drenching), said concentrate comprising or including

(I) at least one ionophore antibiotic in

(II) an aqueous system containing

(i) a wetting and/or surfactant agent, (preferably alkyl polyglycoside)

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(ii) an antifreeze agent or agents in which the ionophore antibiotic or antibiotics is or are no more than sparingly soluble,

(iii) a suspension agent (eg. gum(s)),

(iv) optionally, an antifoam agent or system,

(v) optionally, a preservative,

(vi) optionally, a de-bittering agent,

(vii) optionally, a pH buffering system, and

(viii) water.

The preferred ionophore antibiotic of NZ 272574/272940 is sodium monensin. Preferably an antifreeze agent or agents in which the ionophore antibiotic(s) is no more than sparingly soluble (such as a glycol or polyglycol) is present. Additional, preferably an antifoam agent is present (e.g. simethicone and a particulate carrier such as silicon dioxide therefor).

NZ 272574/272940 also discloses a method of drenching an animal with such an ionophore antibiotic which involves administering orally to such an animal a diluted form of the compositions, such dilution being with water.

We have found monopropylene glycol to be a poor solvent of monensin. While we have in NZ 272574/272940 referred to monopropylene glycol as being an antifreeze agent in which the ionophore antibiotic is sparingly soluble, we do appreciate that solubility to the extent referred to in Example 1 of EP 0,139,595 may be achieved when induced with ultrasound or heating.

The form of crystalline monensin used for the examples in NZ272574/272940 has a mean particle size of the order of about 40 microns and in order to hold such large particles in suspension an aggressive supporting system for that purpose has been required.

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Thus despite the advances represented by the invention disclosed in NZ272574/272940 (providing compositions useful for an active system of administering ionophore antibiotics to ruminants), and despite assertions of EP139595, there continues to be a substantial need for compositions containing ionophore antibiotics which are inherently poorly soluble or insoluble in aqueous based systems, suitable for passive system administrations to ruminants. Such compositions must, to avoid under-dosing or toxic dosing, remain substantially homogeneous for extended periods of time.

The present invention investigates alternatives to such aggressive systems and targets a dosable composition capable of dispersion stability as a suspension in highly dilute drinking water for animals.

The present invention relies upon both a preferred smaller mean particle size of the ionophore antibiotic and an associated regime including related methods of manufacture, uses etc.

The present invention also recognises *inter alia* the therapeutic, energy and productivity benefits were monensin or any other suitable ionophore antibiotic (see the listing in our aforementioned patent specification, and below) to be used as a trough treatment.

Trough Treatment Systems

Currently three types of trough treatment system for animal drinking water and not hitherto used with an ionophore antibiotic are known.

Three types are in use:

1. Proportional feed systems e.g. that branded DOSATRON™
   delivers a %mix in proportion to demand (from 0.2-2% for dosatron).
   Aim is to spread delivery of the complete batch over 24 hours
2. Dump systems
   Continually delivers drench into lines regardless of demand. Tends to be all used up within 5 hours.
3. Individual trough systems e.g. PETA™ dispenser

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Delivers concentrated drench in relation to demand but pay out is skewed early on.

The present invention includes an ionophore antibiotic base composition capable of aqueous dilution which may be useful in such a trough treatment system. The object of the present invention is to provide such a composition and/or to provide drinking water for an animal to allow administration of an ionophore antibiotic to the animal.

We have determined that a microfine form of an ionophore antibiotic with its smaller mass to surface area ratio is a significant advantage over less fine (eg; 40 micron mean particle size) ionophore antibiotic inclusions in an aqueous composition and more so when it is to be used in such a way where it is subjected to unsupervised dilution, eg; to provide an infeed (directly or indirectly) into a dilution quantity of trough make up water. Such advantages to uniform suspendability we believe to be equally applicable to the more preferred crystalline forms as well as the less preferred mycellial forms of the ionophore(s).

We have also determined that a suitable glycol such as monopropylene glycol can be used in such a way to pre-prepare an ionophore antibiotic for subsequent suspension as a aqueous concentrate and thereafter to carry at least an antifreeze advantage over to its subsequent use (eg; as an infeed aqueous concentrate for a dose-certain water system) without leading to crashing out of the ionophore antibiotic. Glycols (such as monopropylene glycol) unless aggressively treated provide no significant uptake of the stably suspended ionophore antibiotic (such as monensin) from an aqueous system. This we consider desirable since an organic uptake can lead to crashing out on dilution. For example, an organic solvent, such as methanol, allows monensin to crash out of solution if any water is added.

In the preferred forms of the present invention the ionophore antibiotic of choice is monensin in any of its appropriate forms (eg; sodium monensin). Other ionophore

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antibiotics however fall within the scope of the present invention and these include Lonomycin, Ionomycin, Laidlomycin, Nigericin, Grisorixin, Dianemycin, Lenoremycin, Salinomycin, Narasin, Antibiotic X206, Alborixin, Septamycin, Antibiotic A204, Maduramicin and Semduramicin, Compound 47224, Lasalocid (also including factors A, B, C, D and E), Mutalomycin, Isolasalocid A, Lysocellin, Tetronasin, Echeromycin, Antibiotic X-14766a, Antibiotic A23187, Antibiotic A32887, Compound 51532 and K41.

STATEMENTS OF THE INVENTION

In one aspect the present invention is an aqueous suspension concentrate ionophore antibiotic composition, said composition comprising:

- at least one ionophore antibiotic of a mean particle size of less than 20 microns,
- at least one dispersing agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol, and
- a suspension agent selected from gums,

wherein said comprising is capable of dilution with water to a substantially stable and dispersed dilute composition, and

wherein the dilute form in water remains substantially homogeneous for at least 24 days.

Preferably the mean particle size of at least one ionophore antibiotic is substantially 5 microns.

Preferably the suspension agent is one or more of xanthan gum, guar gum, acacia gum or a cellulose gum.

The composition may further comprise a liquid vehicle which is a compatible liquid organic compound.

Preferably said organic compound is selected from mineral and vegetable oils.

Preferably said ionophore antibiotic has been milled in the present of at least one dispensing agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol.

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In another aspect the invention is an animal drinking water composition comprising:

- at least one particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic is stably suspended and wherein the particle size of the ionophore antibiotic is of a mean particle size less than 10 microns;
- at least one dispersing agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol,

and

- one or more suspension agent,

wherein the ionophore antibiotic remains stably suspended for at least 24 days.

Preferably the particle size of the ionophore antibiotic is of a mean particle size of substantially 5 microns.

In still another aspect the invention is a method of dispensing a particulate ionophore antibiotic into a body of drinking water which comprises:

- forming an aqueous suspension of a composition comprising:
  - at least one ionophore antibiotic of mean particle size of less than 20 microns,
  - at least one dispersing agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol, and
  - a suspension agent selected from gums,

wherein said ionophore antibiotic is substantially uniformly dispersed therein, wherein said aqueous suspension is suitable for dispensing into animal drinking water, and is capable of further dilution to produce a body of drinking water with a uniform dispersion of the ionophore antibiotic therein which is within an acceptable imbibing concentration range for the animal or animals having access thereto, and

wherein the ionophore antibiotic remains stably suspended for at least 24 days.

Preferably the particle size of the ionophore antibiotics are of a mean particle size of substantially 5 microns.

The method may further comprise:

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- dispensing said aqueous suspension into the drinking water thereto so as to provide the body of drinking water with a uniform dispersion of the ionophore antibiotic therein which is within an acceptable imbibing concentration range for the animal or animals having access thereto.

In another aspect the invention is a method forming a suspendable concentrate composition of at least one ionophore antibiotic, wherein said suspendable concentrate composition is capable of subsequent dilution, said method comprising:

- milling the ionophore antibiotic with a suitable dispersion agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol,

wherein said milling is to a mean particle size less than 20 microns.

Preferably said milling takes place in the presence of water and a suspension agent.

Preferably said milling is to a mean particle size of about 5 microns.

Preferably said milling takes place in the presence of at least some non-aqueous liquid.

Preferably said milling takes place in the presence of a suitable antifoam agent.

In another aspect the invention is a suspended composition of at least one ionophore antibiotic prepared according to the method of the present invention.

In yet another aspect the invention is a dose dispensable ionophore antibiotic composition comprising:

- at least one ionophore antibiotic wherein the particle size of the ionophore antibiotic is of a mean particle size less than 50 microns,
- at least one dispersing agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol,
- at least one suspension agent, and
- water,

wherein the ionophore antibiotic and at least one dispersing agent have been milled together in the presence of a non-aqueous liquid and where at least one additional aliquot of at least one dispensing agent and water is added post-milling.

Preferably said ionophore antibiotic is present at a mean particle size of less than 20 microns.

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Preferably some water was present at the milling procedure.

Preferably an alkyl polyglycoside, a lignosulfonate, and a propylene glycol are present at the milling stage.

Preferably one or more of an antifoam agent or system, a preservative, a debittering agent, and a pH buffering system is present.

In another aspect the present invention consists in a method of forming an aqueous suspension capable of subsequent dilution, said method including prior to any substantial presence of water and/or a suspension agent (such as a suitable gum), milling the ionophore antibiotic or ionophore antibiotics (preferably in a crystalline form) with at least a suitable glycol.

Preferably said milling is to a mean particle size very much less than 40 microns.

Preferably the mean particle size is less than 20 microns, more preferably less than 5 microns and most preferably into a mean particle size of from 0.1 to 1.0 microns.

Preferably said milling includes the presence of a suitable lignosulfonate and/or a suitable polyglycoside.

Preferably said milling includes the presence of an antifoam agent.

Preferably said milling includes at least some water.

Preferably no suspension agent (eg; a gum typified by xanthan gum or guar gum) is present at said milling.

Preferably said method is performed substantially as hereinafter described with reference to the accompanying drawing.

Preferably the product includes as its suitable glycol monopropylene glycol.

Preferably the aqueous suspension is of a kind hereinafter described which includes monopropylene glycol, an additional wetting agent (eg; a lignosulfonate or polyglycoside or both) and a suspension agent.

Preferably the ionophore antibiotic is monensin and preferably that monensin is in a crystalline form.

In a further aspect the present invention consists in a method of forming an aqueous suspension of at least one ionophore antibiotic capable of subsequent dilution, said

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method including milling the ionophore antibiotic or ionophore antibiotics (preferably in a crystalline form) with at least a suitable polyglycoside or a suitable lignosulfonate.

Preferably said method performs part of a method as previously defined.

In yet a further aspect the present invention consists in a method of forming an aqueous suspension of at least one ionophore antibiotic capable of subsequent dilution, said method comprising or including

milling an ionophore antibiotic or ionophore antibiotics (preferably in a crystalline form) with at least (i) a suitable glycol and (ii) at least one of a suitable lignosulfonate and a suitable polyglycoside, and

subsequently formulating the suspension with at least water or, optionally, additional water.

Preferably said subsequent formulation involves the addition of a suitable dispersion agent.

Preferably said suitable dispersion agent is a suitable gum typified by xanthan gum and guar gum.

Other suitable dispersion agents include hydroxy-ethyl cellulose, bentonite clay, montmorillinite clay and fumed silica.

Preferably said ionophore antibiotic is of sufficient purity as to minimise any requirement for an anti foaming agent but if an anti foaming agent is necessary, preferably said anti foaming agent is a GENSIL™ system, i.e. of simethicone/silicon dioxide support for the simethicone.

Preferably said suspension includes a buffer system.

Preferably said suspension includes a preservative.

Where reference is made to a suitable glycol preferably said glycol is a liquid and preferably said glycol assumes an anti freezing role in the resultant aqueous suspension.

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Example of a suitable glycol is monopropylene glycol but other examples include ethylene glycol, diethylene glycol and dipropylene glycol.

Preferably the ionophore antibiotic or ionophore antibiotics is at least primarily of a crystalline form but in other forms it can in part be of the mycelial form. For example, if as is preferred, the ionophore antibiotic is monensin (e.g. present for example as sodium monensin), preferably the ionophore antibiotic is substantially free of the mycelial form. Were the mycelial formed to be utilised however, preferably there are commensurate changes in the inclusions to reflect the lesser activity of that form or an additional input to any dilution system to achieve appropriate activities.

Preferably said milling is in liquid supported conditions (preferably as a result of a liquid glycol inclusion), preferably with a minimum of water necessary for the purpose (if any), and preferably is such as to reduce the antibiotic to a microfine form.

In a preferred form of the present invention, irrespective of whether or not the milling is dry or in a liquid environment, preferably the ionophore antibiotic is reduced to a mean particle size less than 50 microns.

Preferably said mean particle size is reduced to less than 20 microns.

Most preferably the microfine condition of the ionophore antibiotic is to a mean particle size less than 5 microns.

Most preferably the mean particle size resulting from the milling procedure or procedures (can be a single or multiple milling procedures) is such as to provide a mean particle size of the preferably crystalline ionophore antibiotic (e.g. monensin) in a range of from 0.1 to 1.0 microns.

Preferably the milling stage or stages involves milling with a suitable polyglycoside or lignosulfonate, or both. One such polyglycoside is alkyl polyglycoside. One possible lignosulfonate compound is ULTRAZINE NA™ or BORRESPERSE NA™ [of Borregaard Industries Ltd of Norway] (most preferably ULTRAZINE NA™).

Optionally GENSIL™ or another suitable antifoam agent is also milled with the crystalline monensin or other antibiotic.

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Preferably the milling of all coating agents is simultaneous although it can be in part or totally serially.

In a preferred mix the ionophore antibiotic is milled simultaneously with liquid monopropylene glycol and a suitable polyglycoside and/or lignosulfonate compound (more preferably a lignosulfonate) having a "wetting" function and (optionally) an antifoam agent and/or some water.

In a further aspect the present invention consists in an aqueous suspension formed by one or more of the methods of the present invention.

In still a further aspect the present invention consists in an aqueous ionophore antibiotic suspension capable of further dilution without any substantial crashing out of the ionophore inclusion, said aqueous concentrate comprising or including

an ionophore antibiotic,
monopropylyene glycol (or other suitable glycol),
optionally a further material having a wetting characteristic,
a suspension agent,
optionally an antifoam agent, and
water,

wherein at least the monopropylene glycol and the ionophore antibiotic have been milled together prior to mixing with the water or at least any substantial amount of the water.

Preferably the further material having a wetting characteristic is a suitable polyglycoside or lignosulfonate.
Preferably said suitable polyglycoside is alkyl polyglycoside although more preferably the additional wetting agent is a lignosulfonate typified by ULTRAZINE NA™ or BORRESPERSE NA™ (more preferably ULTRAZINE NA™).
Preferably the ionophore antibiotic is a crystalline form rather than a mycellial form.
Preferably the ionophore antibiotic is monensin or a monensin.

Preferably the ionophore antibiotic at least post milling has a particle size less than 5 microns and more preferably below 2 microns.
Preferably the particle size range of the antibiotic is from 0.1 microns to 1.0 microns.

Preferably the aqueous ionophore antibiotic suspension remains substantially homogeneous for a period longer than 7 days; more preferably for a period longer than 24 days.

It does not matter whether or not the milling reduces the ionophore antibiotic to the requisite mean particle size or whether or not it is already milled almost to that size. What is important is to have resultant particles of that size appropriately coated with the "wetting" agents which includes preferably a multifunctional glycol (eg; monopropylene glycol) and preferably an additional wetting agent.

In a further aspect the present invention consists in an aqueous ionophore antibiotic suspension comprising or including

0 to20% w/v of a microfine (i.e. less than 40 micron mean particle size) crystalline ionophore antibiotic,

2 to 20% w/v of monopropylene glycol,

0 to 10% w/v of a wetting agent,

0.1 to 5% w/v suspension agent, and

water.

Preferably the aqueous ionophore antibiotic suspension remains substantially homogeneous for a period longer than 7 days; more preferably for a period longer than 24 days.
Preferably the formulation is substantially as described in any one of Examples 1 to 5.

In another aspect the present invention is directed to a composition suitable for providing a direct in feed and/or indirect in feed (e.g. via a make up tank) into a water system from which target animal can drink,

said composition being an aqueous composition of (at least)

(a) microfine ionophore antibiotic or microfine ionophore antibiotics,

(b) a glycol in which the ionophore antibiotic(s) is or are no more than sparingly soluble,

(c) a wetting agent,

(d) a suspension agent, and

(e) water, and

optionally any one or more of

- an antifoam agent or system,
- a preservative,
- a debittering agent, and
- a pH buffering system.

Preferably the aqueous ionophore antibiotic suspension remains substantially homogeneous for a period longer than 7 days; more preferably for a period longer than 24 days.

Preferably said suspension agent is xanthan gum.

Preferably said wetting and/or surfactant agent (c) is a lignosulphonate (e.g. ULTRAZINE NA™) or a polyglycoside (preferably alkyl polyglycoside).

Preferably said ionophore antibiotic is in either a crystalline or mycellial form or both. Preferably a crystalline form is utilised.

Preferably said ionophore antibiotic is monensin (e.g. sodium monensin).

Preferably said microfine ionophore antibiotic is of a particle size less than 5 microns (preferably less than 2 microns) and preferably has a mean particle size in the range of from 0.1 to 1.0 microns.

Preferably xanthan gum is present and in a quantity greater than 0.16 w/v% and preferably about 0.4 w/v% (ie, the amount required being more for the more concentrated aqueous concentrate, eg; will unlimited dilute none may be required).

Preferably the mode of mixing and formulation is substantially as disclosed herein with a preferred composition being substantially as follows (wherein preferably the mean sodium monensin particle size is substantially 5 microns)–

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Ingredient (common /chemical name)	Quantity (%w/w)	Function
Sodium Monensin	6.33%(about 6%monensin) w/v	Ionophore antibiotic
Monopropylene glycol	10% w/v	Antifreeze/
Alkyl Polyglycoside or	0.5% w/v	Surfactant/Wetting agent
ULTRAZINE NA™	4-5% w/v	
Disodium Phosphate Ankydrous	0.355% w/v	Buffer
MonoPotassium phosphate Dihydrate	0.04% w/v	Buffer
Dialkyl dimethyl ammonium bromide	.0064% w/v	Preservative
Xanthan Gum	0.4% w/v	Suspension agent
Simethicone	0.333% w/v)	(e.g. GENSIL™
Silicon Dioxide	0.167% w/v)	Antifoam system)
Water	to 100%	

An alternative preferred formulation is (wherein preferably the mean sodium monensin particle size is substantially 5 microns):

Ingredient name (common or chemical)	Quantity (%w/w)	Function
Sodium Monensin QA 166H	6.747%	Active
Monopropylene glycol	10%	Antifreeze
Didecyl dimethyl Ammonium Bromide	0.1%	Preservative
Xanthan Gum	0.5%	Suspension agent
Sodium lignosulphonate	4.1%	Wetting agent
Alkyl Polyglycoside	3.8%	Wetting agent
Simethicone	0.333%	Antifoam
Silicon Dioxide	0.167%	Antifoam
Water balance q.v	74.47%	diluent

In other aspect the present invention is a pre mill mix or post mill mix of the present invention as hereinafter described.

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In yet a further aspect the present invention consists in a composition for inclusion in a water trough fed in system being a composition as previously defined which without dilution is adapted to be in feed into the water supply.

In still a further aspect the present invention consists in a drinking water supply for an animal (preferably a ruminant animal) which has an in feed therein of a composition as previously defined.

In yet a further aspect the present invention consists in a method of providing an ionophore antibiotic to a target mammal which comprises providing to the animal drinking water with a dispersed ionophore antibiotic, said ionophore antibiotic having been included in the water supply by an intake from a composition as previoualy defined.

According to a further aspect of the invention there is provided an ionophore antibiotic composition capable of dilution with water to a substantially stable dispersed form in all water then present, said composition comprising or including:

- at least one ionophore antibiotic of a mean particle size of less than 20 microns,
- and at least one dispersing agent.

Preferably the mean particle size of at least one ionophore antibiotic is substantially 5 microns.

Preferably the dispensed form in water remains substantially homogeneous for at least 24 days.

Preferably the at least one dispersing agent is selected from one or more of the following:

i) a compatible polyglycoside capable of acting as a dispersing agent,
ii) a compatible lignosulfonate capable of acting as a dispersing agent, and
iii) a compatible and suitable glycol in a form capable of acting as a dispersing agent.

Preferably a liquid vehicle is or is also present which preferably is or includes water.

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Preferably or alternatively said liquid vehicle is or includes one compatible liquid organic compound, preferably selected from mineral and vegetable oils.

Preferably the ionophore antibiotic(s) has been milled in the presence of at least one of:

i) a compatible polyglycoside capable of acting as a dispersing agent,

ii) a compatible lignosulfonate capable of acting as a dispersing agent, and

iii) a compatible and suitable glycol in a form capable of acting as a dispersing agent.

Preferably the milling is in the absence of any suspension agent, or alternatively a suspension agent selected from the gums as previously described is present; preferably the suspension agent is one or more of xanthan gum, guar gum, acacia gum and a cellulose gum.

Preferably a liquid vehicle(s) was present at the time of milling of the ionophore antibiotic sufficient to reduce the consistency of the mill mix to a millable consistency.

According to a further aspect of the invention there is provided animal drinking water having at least one particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic is stably suspended.

Preferably the ionophore antibiotic remains stably suspended for at least 24 days.

Preferably particles of the ionophore antibiotic(s) are of a mean particle size of less than 10 microns; more preferably they are of a mean particle size of substantially 5 microns.

Preferably the drinking water is made by a proportioned mix dispensing there into of a more concentrated aqueous suspension of the ionophore antibiotic and dispersing agents present in that more concentrated aqueous suspension provides the substantially uniform dispersion of the ionophore antibiotic(s) in the drinking water.

Preferably the more concentrated aqueous suspension contains ore or more suspension agents.

According to a further aspect of the invention there is provided animal drinking water having at least one particulate ionophore antibiotic substantially uniformly suspended therein, wherein the particles of the ionophore antibiotics are of a mean particle size less

than 10 microns; more preferably the particle size of the ionophore antibiotics are of a mean particle size of substantially 5 microns.
Preferably the ionophore antibiotic remains stably suspended for at least 24 days.

According to a further aspect of the invention there is provided trough water accessible to an animal to drink, the water having a particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic is stably suspended.
Preferably the ionophore antibiotic remains stably suspended for at least 24 days.
Preferably the particles of the ionophore antibiotic(s) is of a mean particle size of less than 10 microns; more preferably the particles of the ionophore antibiotic(s) is of a mean particle size of substantially 5 microns.
Preferably the trough water is made by a proportioned mix dispensing there into of a more concentrated aqueous suspension of the ionophore antibiotic and dispersing agents present in that more concentrated form provides the substantially uniform dispersion of the ionophore antibiotic(s) in the drinking water.
Preferably the more concentrated aqueous suspension contains ore or more suspension agents.

According to a further aspect of the invention there is provided trough water accessible to an animal to drink the water having a particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic remains stably suspended for at least 24 days.
Preferably the particle size of the ionophore antibiotics are substantially 5 microns.
Preferably the ionophore antibiotic remains stably suspended for at least 24 days.

According to a further aspect of the invention there is provided a method of dispensing a particulate ionophore antibiotic into a body of drinking water which comprises or includes the steps of:

- taking a composition comprising or including at least one ionophore antibiotic of mean particle size of less than 20 microns and at least one dispersing agent:

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- forming an aqueous suspension of the composition that has the ionophore antibiotic(s) substantially uniformly dispersed therein and which aqueous suspension is available for dispensing into animal drinking water, and
- dispensing at a rate (continuously or continually), that aqueous suspension into the drinking water or a makeup supply of water thereto so as to provide the body of drinking water with a uniform dispersion of the ionophore antibiotic(s) therein which is within an acceptable imbibing concentration range for the animal or animals having access thereto.

Preferably the mean particle size of the at least one ionophore antibiotic is substantially 5 microns.

Preferably said composition is in the form of a stable aqueous suspension prior to the forming of an aqueous suspension and the subsequent dispensing thereof into the drinking water or a make up supply of water.

Preferably said composition includes one or more dispersing agent selected from one or more of the following:

i) a compatible polyglycoside capable of acting as a dispersing agent,
ii) a compatible lignosulfonate capable of acting as a dispersing agent, and
iii) a compatible and suitable glycol in a form capable of acting as a dispersing agent.

Preferably a suspension agent selected from gums (as previously described) is present.

Preferably the ionophore antibiotic(s) remains stably suspended for at least 24 days.

According to a further aspect of the invention there is provided a body of drinking water having a particulate ionophore suspended therein prepared by the method as previously described.

According to a further aspect of the invention there is provided a method of forming a suspendable composition of at least one ionophore antibiotic and which suspendable composition is capable of subsequent dilution, said method including, prior to any optional presence of water and optional presence of a suspension agent, milling the ionophore antibiotic(s) with a suitable glycol.

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Preferably said milling takes place in the presence of at least some liquid, which preferably includes water.

Preferably no gum is present.

Preferably said milling is to a mean particle size very much less than 20 microns; more preferably the mean particle size is of about 5 microns.

Preferably the milling takes place in the presence of a suitable lignosulfonate.

Preferably said milling takes place in the presence of a suitable Polyglycoside.

Preferably said milling takes place in the presence of a suitable antifoam agent.

According to a further aspect of the invention there is provided a suspendable composition of at least one ionophore antibiotic prepared according to the method as previously described.

According to a further aspect of the invention there is provided a method of forming a suspendable composition of at least one ionophore antibiotic and which suspendable composition is capable of subsequent dilution, said method including, prior to any optional presence of water and optional presence of a suspension agent, milling the ionophore antibiotic(s) with a suitable dispersion agent.

Preferably the milling takes place in the presence of a suitable lignosulfonate.

Preferably or alternatively said milling takes place in the presence of a suitable polyglycoside.

Preferably said suitable dispersion agent is selected from the group consisting of a suitable lignosulfonate and a suitable polyglycoside.

Preferably the mean particle size is less than 20 microns; more preferably less than 10 microns; even more preferably the mean particle size is substantially 5 microns.

Preferably said milling takes place in the presence of a suitable antifoam agent.

Preferably said milling takes place in the presence of at least some liquid.

Preferably a suitable glycol is present.

Preferably no gum is present.

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According to a further aspect of the invention there is provided a dose dispensable ionophore antibiotic composition comprising or including:

- at least one ionophore antibiotic,
- at least one dispersing agent,
- at least one suspension agent, and
- water,

wherein the ionophore antibiotic(s) and at least one dispersing agent have been milled together in the presence of a liquid (which may be water or may include water but not necessarily so) and where the dispersing agent has been added post-milling in the presence of water.

Preferably the ionophore antibiotic is of a mean particle size of less than 50 microns; more preferably a mean particle size of less than 20 microns.

Preferably at least one suspension agent is or includes a gum and no such gum was present at the milling procedure.

Preferably some water was present at the milling procedure.

Preferably a polyglycoside was present as a dispersing agent at the milling stage.

Preferably a lignosulfonate was present as a dispersing agent at the milling stage.

Preferably a glycol was present as a dispersing agent at the milling stage.

Preferably an alkyl polyglycoside, a lignosulfonate and a propylene glycol are present at the milling stage.

Preferably any one or more of an antifoam agent or system, a preservative, a debittering agent and a pH buffering system is present.

According to a further aspect of the invention there is provided a milled product useful in providing an aqueous suspension of at least one ionophore antibiotic, said product being the milled outcome of a mill mix of at least

- at least one ionophore antibiotic, and
- at least one dispersing agent,

wherein the mill mix has been substantially free of suspension agents selected from the gums previously described and the mill mix has included at

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least one liquid component (which optionally can be the or one of the dispersing agent(s) or an additional material),

and wherein, in the product, the process of milling has resulted in some physical association of the or at least one dispersing agent on the ionophore antibiotic particles,

and wherein, in the product, the mean particle size of the ionophore antibiotic(s) is less than 20 microns.

Preferably the mean particle size is substantially 5 microns.

According to a further aspect of the invention there is provided a suspendable composition for substantial dilution by water, said method comprising or including:

(I) milling at least one ionophore antibiotic and at least one dispersing agent so as to provide some physical association of the or at least one dispersing agent on ionophore antibiotic particles of a mean particle size of less than 20 microns, and

(II) blending the post mill ionophore antibiotic(s)/dispersing agent(s) milled outcome with at least a suspension agent.

This invention may also be said broadly to consist in the parts, elements and features referred to or indicated in the specification of the application, individually or collectively, and any or all combinations of any two or more of said parts, elements or features, and where specific integers are mentioned herein which have known equivalents in the art to which this invention relates, such known equivalents are deemed to be incorporated herein as if individually set forth.

The invention consists in the foregoing and also envisages constructions of which the following gives examples.

DEFINITIONS

Wherein the specification the following terms are used there are a number of possible alternatives, examples of which follow:

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Surfactants / Dispersants:

- sorbitan esters
- ethoxylated sorbitan esters
- castor oil ethoxylates
- ethoxylated fatty acids
- ethoxylated alcohols
- polyethylene glycol fatty acids
- condensed napthalene sulphonic acid
- glycerol esters
- phosphate esters
- sodium lauryl sulphate
- sodium polyacrylate
- ammonium polyacrylate
- octyl phenyl ethoxylates
- nonyl phenyl ethoxylates
- quaternary ammonium compounds
- sulphosuccinates
- soya lecithin

Suspending aids, including gums:

- aluminium stearate
- silicon dioxide
- modified clay including Smectite, Monmorillonite, Hectorite, Bentonite
- dehydrogenated castor oil
- titanium chelates
- alkali soluble acrylic polymers
- nonionic diurethanes
- polyvinyl pyrollidone
- polyvinyl alcohol
- guar gum
- gum arabic
- hydroxy propyl methyl cellulose
- hydroxy ethyl cellulose
- sodium carboxy methyl cellulose
- hydrophobically modified hydroxy ethyl cellulose

Defoamers / Antifoams

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- polymethyl siloxane
- unsaturated hydrocarbon oil
- mineral oil
- silica in oil type

Preservatives:

- oxazolidines
- benzothiazoles
- benzalkonium chloride
- substituted triazines
- isothiazolones
- hemiacetals
- substituted benzoates
- zinc pyridinethiol oxide
- sodium pyridinethiol oxide

Buffering agents:

- potassium tetroxalate
- potassium hydrogen tartrate
- potassium hydrogen phthalate
- borax

DETAILED DESCRIPTION OF THE INVENTION

Preferred forms of the present invention will now be described with reference to the accompanying drawings in which

Figure 1:	shows one mixing procedure utilised in accordance with the invention,
Figure 2:	shows a second mixing procedure utilised in accordance with the invention, and
Figures 3A – 3C:	illustrate a DOSTATRON™ trough treatment system in three different modes of operation.

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Shown in figures 3A to 3C are three installations of a DOSATRON™ type installation used for dosing materials into drinking water. The DOSATRON™ apparatus is recommended as being usable in line (figure 3A), on a bypass line (figure 3B) and in parallel (figure 3C). In this respect see the publicity materials available from the New Zealand distributor Mark Bell-Booth Ltd.

The DOSATRON™ apparatus itself employees a dosing piston driven by a volumetric hydraulic piston motor. The spread rhythm of the motor is proportional to the flow of water passing through the system and thus the rate of injection will likewise remain proportional in its reciprocating motion.

The apparatus has the capability of a wide range of daily dose settings and the parallel arrangement shown in figure 3 allows these to be doubled owing to the use of two DOSATRON™ dispensing units.

Preferred forms will now be described with reference to the following examples of which the mixing procedures utilised is preferably as depicted and sequenced in one of Figures 1 or 2.

The present invention recognises that having evolved a suitable stable aqueous suspension of microfine monensin a predictable in feed thereof to animals is possible simply by providing to the animal drinking water which includes the microfine ionophore antibiotic dispersed therein, said ionophore antibiotic having been included in the water supply by an intake directly or indirectly from a composition as previously defined. The less dilute the concentrate the more suspension agent we have found to be desirable.

Preferably the composition is for use in one or more of the trough treatment systems available.

Example 1

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Sodium Monensin	6.33%(about 6%monensin) w/v
Monopropylene glycol	10% w/v
ULTRAZINE NA™	4-5% w/v
Disodium Phosphate Anhydrous	0.355% w/v
MonoPotassium phosphate Dihydrate	0.04% w/v
Dialkyl dimethyl ammonium bromide	.0064% w/v
Xanthan Gum	
0.4% w/v	
Simethicone	] GENSIL™
0.333% w/v	
Silicon Dioxide] Antifoam	0.167% w/v
Water to 100%	

Milling has resulted in a mean particle size for sodium monensin of 5 microns.

Example 2

Sodium Monensin	6.33%(about 6%monensin) w/v
Monopropylene glycol	10% w/v
Alkyl Polyglycoside	0.5% w/v
Disodium Phosphate Anhydrous	0.355% w/v
MonoPotassium phosphate Dihydrate	0.04% w/v
Dialkyl dimethyl ammonium bromide	.0064% w/v
Xanthan Gum	0.4% w/v
Simethicone] GENSIL™	0.333% w/v
Silicon Dioxide] Antifoam	0.167% w/v
Water to 100%	

Milling has resulted in a mean particle size for sodium monensin of 5 microns.

Example 3

Sodium Monensin	6.33%(about 6%monensin) w/v
Monopropylene glycol	10% w/v
ULTRAZINE NA™	4-5% w/v
Disodium Phosphate Anhydrous	0.355% w/v
MonoPotassium phosphate Dihydrate	0.04% w/v

Dialkyl dimethyl ammonium bromide	.0064% w/v
Xanthan Gum	0.4% w/v
Simethicone] GENSIL™	0.333% w/v
Silicon Dioxide] Antifoam	0.167% w/v
Sorbitol as a Debittering agent	3.5% w/v
Water to 100%	

Milling has resulted in a mean particle size for sodium monensin of 5 microns.

Example 4

Sodium Monensin	6.33%(about 6%monensin) w/v
Monopropylene glycol	10% w/v
Alkyl Polyglycoside	0.5% w/v
Disodium Phosphate Anhydrous	0.355% w/v
MonoPotassium phosphate Dihydrate	0.04% w/v
Dialkyl dimethyl ammonium bromide	.0064% w/v
Xanthan Gum	0.4% w/v
Simethicone] GENSIL™	0.333% w/v
Silicon Dioxide] Antifoam	0.167% w/v
Sorbitol as a Debittering agent	3.5% w/v
Water to 100%	

Milling has resulted in a mean particle size for sodium monensin of 5 microns.

Example 5

Ingredient name (common or chemical)	CAS number	Quantity (%w/w)	Function
Sodium Monensin QA 166H	17090-79-8	6.747%	Active
Monopropylene glycol	57-55-6	10%	Antifreeze
Didecyl dimethyl Ammonium Bromide	2390-68-3	0.1%	Preservative
Xanthan Gum	11138-66-2	0.5%	Suspension agent

Sodium lignosulphonate	8061-51-6	4.1%	Wetting agent
Alkyl Polyglycoside	68515-73-1	3.8%	Wetting agent
Simethicone	8050-81-5	0.333%	Antifoam
Silicon Dioxide	7631-86-9	0.167%	Antifoam
Water balance q.v	7732-18-5	74.47%	diluent

Milling has resulted in a mean particle size for sodium monensin of 5 microns.

Simethicone and Silicon dioxide together make up the proprietary brand "Gensil".

1. Preparation Procedure

The formulations of each of Examples 1 to 4 can be prepared by the procedure shown in Figure 1. The formulation of Example 5 is prepared by the procedure shown in Figure 2. The preferred method of preparing a formulation such as Example 1 is as follows.

As can been seen from Figures 1 and 2 a blending vessel (A) which can, if desired, be the horizontal bead mill (B) but is preferably not, and a blending vessel (C) are utilised as the apparatus.

Most preferably however there is a three stage equipment base for the process viz. blending vessel (A), horizontal bead mill (B) for microfining the ionophore antibiotic and a blending vessel (C).

As can be seen from Figure 1 ingredients 1 through 6 are blended in the reference number sequence in the blending vessel (A) prior to passage into the horizontal bead mill (B). These pre-blended materials include:

- monopropylene glycol,
- dialkyl dimethyl ammonium bromide,
- GENSIL™ antifoam,
- some water,
- ULTRAZINE NA™ wetting agent, and

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monensin.

After the milling that premill mix, the product can be taken away either as an intermediate product (eg; post mill product) for subsequent use elsewhere for blending. Preferably however the output milled mix passes to blending vessel (C) where it is blended with the rest of the water (7), the remainder of the ULTRAZINE NA™ wetting agent (8) and the xanthan gum or other dispersion agent (9).

With a formulation whether to the formula of Example 1 or Example 3 or another (Figures 1 and 2 do not refer to the buffering system nor to a debittering agent) very good suspensibility is obtained both of the concentrate and of a subsequent diluted form (eg; in a trough usage where the dilution is, for example, to about 3 to 6 ppm monensin).

The numerals 1 - 9 (Figure 1) or 1- 11 (Figure 2) indicate the preferred sequence of ingredient addition. With reference to Figure 1, a pre-mill non sequenced mix of components 1 through 6 in the blending vessel (A) will still lead to a good mill mix yet is detrimental to the best suspensibility of the diluted form.

A preferred formulation as in Example 1 made by a procedure as in Figure 1 has a capability of being added as an aqueous concentrate into a large volume of water such as might be experienced in providing an infeed into a water system.

It is important to note the following processing issues:

- the order of addition of the components to the grind base premix is not critical
- the appropriate particle size induced by the grinding operation is critical
- the order of addition of the components in the makeup tank is critical.

2. The Mill Mix

The mill mix is an important factor in the invention. It is the pre-mix of components which are added into the bead mill. The composition (identity and amount) is important

in determining the ultimate particle size and the coatings on the particles which result. The relative quantities (eg of MPG : monensin) are important in this respect.

3. Stability Data

a) shelf life stability

The following shelf file stability data indicates the 6% concentrate exhibits stability, at differing temperatures for at least 3 months (the length of time of the trials).

Trough Treatment 6% Concentrate Shelf Life Study

Batch number: 1183				
25°C Sample:				
	Time 0	1 months	2 months	3 months
Appearance	Normal	Normal	Normal	Normal
Coliforms	<1	<1	<1	<1
Monensin Biopotency	5.7	5.5	5.4	5.6
PH	8.11	8.00	7.77	7.51
Yeasts and Moulds	<1	<1	<1	<1
APC	<10	<10	<10	<10
42°C Sample:				
	Time 0	1 months	2 months	3 months
Appearance	Normal	Normal	Normal	Normal
Coliforms	<1	<1	<1	<1
Monensin Biopotency	5.7	5.6	5.4	5.4
PH	8.11	7.60	7.39	7.28
Yeasts and Moulds	<1	<1	<1	<1
APC	<10	<10	<10	<10

* Appearance- normal means light brown gelatinous liquid with brown specks present.

b) Positional Stability

The following experiments detail the positional stability of the trough treatment of the invention (TT).

Positional stability studies were conducted with a DOSATRON™ trough treatment system. This is a proportional feed system which delivers a % mix in proportion to demand. Such an administration system is able to spread delivery of a complete batch over 24 hours.

Figure 3 illustrates a dosation system used in obtaining the positional stability data.

Example 1

Trough treatment (TT) (600ppm) in a 200L plastic solution tank with a functioning Dosatron 8000.

Method:

100 litres water were added to the solution tank connected to a Dosatron 8000.
2 litres TT were mixed well with 2 litres water.
This mix was added to the half-full solution tank, filled to the 200 litre level, mixed thoroughly.
The Dosatron was set at 2 % and the water flow at 400 litres/hour to ensure the solution tank is completely used within 24 hours.
The draw off tube from the Dosatron was set at a height 10 cm from the bottom of the tank.

Sampling

Samples for assay were taken from the draw-off taps. Before sampling, a 50 ml sample was drawn off and discarded. 1 x 100 ml samples are taken from each of the 4 taps set at either the top, middle or bottom of the tank. Samples will be taken at the specified time intervals.
Each sample taken was individually identified and 50 ml from each sample taken and to a pooled sample (total Vol 200 ml).
This sample was that assayed and the other samples retained.

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Samples were also taken from the four-tap set, here positioned in the plastic tank at a level 10 cm from the bottom of the tank.
Samples were taken 0, 12, 24 hours after mixing.

After 24 hours a further 4 x 100 ml samples were taken from the bottom of the tank. Each sample taken was individually identified and 50 ml from each sample taken and pooled (total Vol 200 ml). This sample was assayed and the other samples retained. In this case the drench gun tube attached to the rod was used.

Example 2

Measurement of the positional stability of the TT (3000ppm) in a static 200 L plastic solution tank over a 4 day period

Method

Before filling the tank, the bottom tap hoses were bent so the end was 5 cm from the bottom of the tank.
100 litres of water was added to the solution tank.
10 litres of TT was mixed well with 10 litres water.
This mix was added to the half-full solution tank, filled to the 200 litre level and mixed.

Sampling

Samples for assay were taken from the draw-off taps. Before sampling, a 50 ml sample was drawn off and discarded. Each sample taken was individually identified and 50 ml from each sample taken and pooled (total Vol 200 ml). This sample was that assayed and the other samples retained.

Samples were taken from the top, middle and bottom of the tank at the intervals of 0, 12hrs, 24 hrs, 2 days and 4 days after mixing.

Example 3

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Measurement of the positional stability of TT (6 ppm) in a concrete trough over a 24 day period.

Method

50 litres of water was added to the solution tank connected to the Dosatron 8000.
1 litre of TT was mixed well with 1 litre water.
This mix was added to the half-full solution tank, filled to the 100 litre level and mixed.
Set the Dosatron at 1 % to ensure a trough concentration of 6 ppm.
The trough was connected to the solution tank containing the Dosatron and TT.
The new concrete trough was scrubbed clean and the water in the trough pH tested before use.
A neutral pH (7-8) is acceptable.
The water was discarded before filling from the Dosatron 8000

Activation of the ball-cock filled the trough with TT (6 ppm).
After filling the trough herd drinking was simulated by siphoning water from the top of the trough to activate the ball-cock. 5000 litres was siphoned from the trough over a 24 hour period

Sampling

The draw-off tube from the drench gun was attached to a rigid pole. The end of the draw off tube was set to sample the trough from 3 levels – top, middle and bottom.
4 x 100 ml samples was taken from each position.
Each sample taken was individually identified and 50 ml from each sample taken and pooled (total Vol 200 ml).
This sample was that assayed and the other samples retained.
Sampling of the trough at the intervals of 0, 6 hrs,12hrs, 24 hrs, 5 days, 10 days and 24 days after mixing.

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Example 4

Measurement of the amount of Monensin settling in the drum after mixing TT at 3000 ppm and leaving for 4 days undisturbed.

Methods

100 litres water was added to the solution tank connected to the Dosatron 8000.

10 litres of TT was mixed with 10 litres of water.

This mix was added to the half-full solution tank, filled to the 200 litre level and mixed.

Sampling

Samples for assay were taken from the bottom of the tank.

Before sampling, opened all middle taps and bottom taps to provide a slow release of tank mix. The rate of removal of the fluid was slow enough so the bottom of the tank was not disturbed.

After the level of water fell below the bottom taps, mixed the bottom of the tank thoroughly and drew off 4 x 100 ml samples taken at different locations.

Each sample taken was individually identified and 50 ml from each of the samples taken and pooled (total Vol 200 ml).

The sample was that assayed and the other samples retained.

N.B Please calculate the volume of water left in the drum before taking the samples.

This will be to calculate the total amount of monensin settling in the bottom of the tank after 4 days

Positional stability results and discussion

The test had the following accuracy parameters:

Repeatability: The difference between results of duplicate portions of the same sample tested in the same run should not exceed 10% of the mean result. Recent results indicate that duplicate results are not exceeding 5.4% of the mean result.

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Reproducibility: The difference between results of portions of the same sample tested at different times by different analysts should not exceed 15% of the mean result.

The repeatability and reproducibility data affords us quantifiable parameters for substantial homogeneity, indicating a substantially uniform suspension over time.

Table 1: Example 1 Results (600 ppm)

Time	Bottom Sample Result
0 hours	556 ppm
12 hours	504 ppm
24 hours	439 ppm

Table 2: Example 1 Repeated Trial Results (600 ppm)

Time	Bottom Sample Result
0 hours	580 ppm
12 hours	470 ppm
24 hours	420 ppm

Table 3: Example 2 Results (3000 ppm)

Time	Top Sample (ppm)	Middle Sample (ppm)	Bottom Sample (ppm)
0 hours	2970	2900	3030
12 hours	2680	2720	2760
24 hours	2930	2970	3060
2 days	2960	2950	3030
4 days	2190	2930	3050

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Table 4: Example 3 Results (6 ppm)

Time	Top Sample (ppm)	Middle Sample (ppm)	Bottom Sample (ppm)
0 hours	5.0	5.5	5.1
6 hours	4.9	4.6	5.2
12 hours	4.7	4.9	5.0
24 hours	5.6	5.2	5.0
4 days	5.1	5.3	4.3
10 days	5.5	5.1	5.8
24 days	5.0	5.0	5.3

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CLAIMS:

1. An aqueous suspension concentrate ionophore antibiotic composition, said composition comprising:

- at least one ionophore antibiotic of a mean particle size of less than 20 microns,
- at least one dispersing agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol, and
- a suspension agent selected from gums,

wherein said comprising is capable of dilution with water to a substantially stable and dispersed dilute composition, and

wherein the dilute form in water remains substantially homogeneous for at least 24 days.

2. A composition as claimed in claim 1 wherein the mean particle size of at least one ionophore antibiotic is substantially 5 microns.

3. A composition as claimed in claim 1 or 2 wherein the suspension agent is one or more of xanthan gum, guar gum, acacia gum, or a cellulose gum.

4. A composition as claimed in claim 3 further comprising a liquid vehicle which is a compatible liquid organic compound.

5. A composition as claimed in claim 4 wherein said organic compound is selected from mineral and vegetable oils.

6. A composition as claimed in any one of claims 3 to 5 wherein said ionophore antibiotic has been milled in the presence of at least one dispersing agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol.

7. Animal drinking water composition comprising:

- at least one particulate ionophore antibiotic substantially uniformly suspended therein, wherein the ionophore antibiotic is stably suspended and wherein the particle size of the ionophore antibiotic is of a mean particle size less than 10 microns;

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- at least one dispersing agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol,
  and
- one or more suspension agent,

wherein the ionophore antibiotic remains stably suspended for at least 24 days.

8. Animal drinking water composition as claimed in claim 7 wherein the particle size of the ionophore antibiotic is of a mean particle size of substantially 5 microns.

9. A method of dispensing a particulate ionophore antibiotic into a body of drinking water which comprises:

- forming an aqueous suspension of a composition comprising:
  - o at least one ionophore antibiotic of mean particle size of less than 20 microns,
  - o at least one dispersing agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol, and
  - o a suspension agent selected from gums,

wherein said ionophore antibiotic is substantially uniformly dispersed therein, wherein said aqueous suspension is suitable for dispensing into animal drinking water, and is capable of further dilution to produce a body of drinking water with a uniform dispersion of the ionophore antibiotic therein which is within an acceptable imbibing concentration range for the animal or animals having access thereto, and wherein the ionophore antibiotic remains stably suspended for at least 24 days.

10. The method of claim 9 wherein the particle size of the ionophore antibiotics are of a mean particle size of substantially 5 microns.

11. The method of claim 9 or 10 further comprising:

- dispensing said aqueous suspension into the drinking water thereto so as to provide the body of drinking water with a uniform dispersion of the ionophore antibiotic therein which is within an acceptable imbibing concentration range for the animal or animals having access thereto.

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12. A method forming a suspendable concentrate composition of at least one ionophore antibiotic, wherein said suspendable concentrate composition is capable of subsequent dilution, said method comprising:

- milling the ionophore antibiotic with a suitable dispersion agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol,

wherein said milling is to a mean particle size less than 20 microns.

13. The method of claim 12 wherein said milling takes place in the presence of water and a suspension agent.

14. The method of claim 12 or 13 wherein said milling is to a mean particle size of about 5 microns.

15. The method of any one of claims 12 to 14 wherein said milling takes place in the presence of at least some non-aqueous liquid.

16. The method of claim 15 wherein said milling takes place in the presence of a suitable antifoam agent.

17. A suspended composition of at least one ionophore antibiotic prepared according to the method of any one of claims 12 to 16.

18. A dose dispensable ionophore antibiotic composition comprising:

- at least one ionophore antibiotic wherein the particle size of the ionophore antibiotic is of a mean particle size less than 50 microns,
- at least one dispersing agent selected from one or more of a compatible polyglycoside, a compatible lignosulfonate, and a compatible and suitable glycol,
- at least one suspension agent, and
- water,

wherein the ionophore antibiotic and at least one dispersing agent have been milled together in the presence of a non-aqueous liquid and where at least one additional aliquot of at least one dispensing agent and water is added post-milling.

19. The composition of claim 18 wherein said ionophore antibiotic is present at a mean particle size of less than 20 microns.

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20. The composition of claim 18 or 19 wherein some water was present at the milling procedure.

21. A composition of claim 20 wheein an alkyl polyglycoside, a lignosulfonate, and a propylene glycol are present at the milling stage.

22. The composition of claim 20 or 21 wherein one or more of an antifoam agent or system, a preservative, a debittering agent, and a pH buffering system is present.

ABSTRACT

The invention relates to an ionophore antibiotic composition capable of dilution with water to a substantially stable dispersed form in all water then present, said composition comprising or including:

- **at least one ionophore antibiotic (preferably monensin) of a mean particle size of less than 20 microns,**
- **and at least one dispersing agent.**

A method of preparing the ionophore antibiotic composition is also disclosed.

PA 478

TRATADO DE COOPERACION EN MATERIA DE PATENTES

P C T

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 del PCT)

Referencia de registro del Solicitante o del Agente	PARA TOMAR ACCION ADICIONAL	Véase la Notificación de la Transmisión del Informe de Examen Preliminar Internacional (Forma PCT/IPEA/416)
P451785 DJJ/jif		
Solicitud Internacional No.	**Fecha de Presentación Internacional**	**Fecha de Prioridad**
PCT/NZ 01/00290	*18 de Diciembre de 2001*	*19 de Diciembre de 2000*

Clasificación de Patente Internacional (IPC) o Clasificación nacional e IPC
Int Cl.[7] A61K 9/00, 9/14, 47/34, 47/36, 47/10

Solicitante
ELI LILLY AND COMPANY (NZ) LIMITED et al

1. Este informe de examen preliminar internacional ha sido preparado por esta Autoridad de Examen Preliminar Internacional y es transmitido al solicitante de acuerdo con el Artículo 36.

2. Este INFORME consiste de 3 hojas, incluyendo esta hoja de cubierta

☒ Este informe también está acompañado por ANEXOS, es decir, hojas de la descripción, las reivindicaciones y/o los dibujos, los cuales han sido enmendados y son la base para este informe y/o las hojas que contienen las rectificaciones hechas antes de esta Autoridad. (Véase la Regla 70.16 y la Sección 607 de las Instrucciones Administrativa bajo el PCT).

Estos anexos consisten de un total de 40 Hojas.

3. Este informe contiene las indicaciones que están relacionadas con los siguientes puntos:

I ☒ Base del informe

II ☐ Prioridad

III ☐ Ningún establecimiento del informe con respecto a la novedad, paso inventivo, o aplicabilidad industrial

IV ☐ Carencia de unidad de la invención

V ☒ Declaración razonada bajo el Artículo 35(2) con respecto a la novedad, paso inventivo o aplicabilidad industrial; las citas y explicaciones que soportan tal declaración

VI ☐ Ciertos documentos citados

VII ☐ Ciertos defectos en la solicitud internacional

VIII ☐ Ciertas observaciones en la solicitud internacional.

Fecha de presentación de la solicitud	Fecha de terminación de este informe
12 de Junio de 2002	*15 de Abril de 2003*
Nombre y dirección de envío de la IPEA/AU OFICINA DE PATENTES AUSTRALIANAS PO Box 200, WODEN ACT 2606, AUSTRALIA Correo electrónico pct@ipaustralia.gov.au No. Fax. (02) 6285 3929	Oficial Autorizado ANDREW ACHILLEOS Teléfono No. (02) 6283 2280

Forma PCT/IPEA/409 (hoja de cubierta) (Julio de 1998)

INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/NZ 01/00290

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1. bases del informe

1. Con respecto a los elementos de la solicitud internacional *
   - ☐ la solicitud internacional como se presentó originalmente.
   - ☒ las descripción, páginas, como se presentó originalmente.
     páginas, presentadas con la solicitud.
     Páginas 1-36, recibido el 19 de Marzo de 2003 con la carta de 18 de Marzo de 2003
   - ☒ las reivindicaciones, páginas, como se presentó originalmente.
     Páginas, como se enmendó bajo el Artículo 19
     Páginas, presentadas con la demanda
     Páginas 37-40 recibido el 19 de Marzo de 2003 con la carta de 18 de Marzo de 2003
   - ☐ los dibujos, páginas, como se presentaron originalmente.
     Páginas, como se presentaron originalmente
     páginas, presentadas con la demanda
     páginas, presentadas con la carta de _____.
   - ☐ el listado de secuencias de la descripción
     páginas, como se presentaron originalmente
     páginas, presentadas con la demanda
     páginas, presentadas con la carta de _____.

2. Con respecto al idioma, todos los elementos marcados con anterioridad estaban disponibles o se presentaron a esta autoridad en el idioma en el cual se presentó la Solicitud Internacional, a menos que se indique de otro modo en este punto.

   Estos elementos estaban disponibles o se presentaron a esta utilidad en el siguiente idioma que es:
   - ☐ idioma de una traducción presentada para el propósito de búsqueda internacional (de acuerdo con Regla 23.1(b)).
   - ☐ el idioma de publicación de la solicitud internacional de acuerdo con la Regla 48.3 (b)).
   - ☐ el idioma de la traducción presentada para el propósito del examen preliminar internacional (de acuerdo con las reglas 55.2 y/o 55.3).

3. Con respecto a cualquier secuencia de nucleótidos y/o aminoácidos descrita en la solicitud internacional, el examen preliminar internacional se llevó a cabo en base al estado de secuencia:

   - ☐ contenido en la solicitud internacional en forma escrita
   - ☐ presentado junto con la solicitud internacional en una forma libre por computadora
   - ☐ presentado subsecuentemente a esta autoridad en forma escrita.
   - ☐ presentado subsecuentemente a esta autoridad en una forma libre por computadora.
   - ☐ se ha proporcionado la declaración que el estado de secuencias escrito subsecuentemente presentado no va más allá de la descripción en la solicitud internacional como se presentó.
   - ☐ se ha proporcionado a la declaración que la información registrada en la forma libre por computadora es idéntica al estado de secuencia descrito.

4. ☐ Las enmiendas han dado por resultado la cancelación de:
   - ☐ la descripción, páginas
   - ☒ las reivindicaciones, Números 23-72
   - ☐ los dibujos, hojas/figuras

5. ☐ Este informe se ha establecido como si (alguna de) las enmiendas no se hayan hecho, puesto que se han considerado que van más allá de la descripción como se presentó como se indica en el recuadro complementario (Regla 70.2 (c)):**

* Las hojas de reemplazo que se han suministrado a la oficina receptora en respuesta a una invitación de acuerdo al artículo 14 se refieren en este informe como "originalmente presentadas" y no se anexan a este informe puesto que no contienen enmiendas (Regla 70.16).

***Cualquier hoja de reemplazo que contenga estas enmiendas se debe referir bajo este punto 1 y anexar a este informe.*

EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/NZ 01/00290

V. Declaración razonada bajo el Artículo 35(2) con respecto a la novedad, el paso inventivo o la aplicabilidad industrial; en las citaciones y explicaciones que soportan tal declaración

1. DECLARACION.

Novedad (N)	Reivindicaciones	1-22	SI
	Reivindicaciones		NO
Paso Inventivo (PI)	Reivindicaciones	1-22	SI
	Reivindicaciones		NO
Aplicabilidad Industrial (AI)	Reivindicaciones	1-22	SI
	Reivindicaciones		NO

2. Citas y explicaciones (Regla 70.7)

Novedad

Los documentos de la técnica anterior WO 97/03650 (D1) y WO 98/16663 (D2), que corresponden ambos al solicitante, no describe la invención definida en las reivindicaciones enmendadas 1-22. D2 no describe el uso de los agentes tensioactivos específicos definidos en la presente solicitud por el uso de agentes de suspensión. D1 no describe la distribución del tamaño de partícula de antibiótico o el proceso de molienda de la producción definida en la presente solicitud.

Actividad Inventiva

Las resientes reivindicaciones enmendadas 1-22 comprenden una actividad inventiva como habría sido obvio por un experto en la técnica para usar la distribución de tamaño de partícula o proceso de molienda definido en la presente solicitud.

1x5 182

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Original (para SUMISIÓN) impreso el 18.12.2001 04:02:18 PM

0 0-1	Para uso de la Oficina receptora Solamente Solicitud Internacional No.	
0-2	Fecha de Presentación Internacional	
0-3	Nombre de la oficina receptora y "Solicitud Internacional de PCT	
0-4 0-4-1	Forma – PCT/RO/101 PCT Petitorio Preparado usando	PCT-EASY Versión 2.92 (actualizada 01.03.2001)
0-5	Petición El abajo firmante solicita que la presente solicitud internacional sea procesada de acuerdo al Tratado de Cooperación en Materia de Patentes	
0-6	Oficina Receptora (especificada por el solicitante)	Propiedad Intelectual de la Oficina de Nueva Zelanda (RO/NZ)
0-7	Referencia de archivo del solicitante o mandatario	P451785
I	Título de la invención	FORMULACIONES DE ANTIBIÓTICOS DE IONÓFORO
II II-1 II-2 II-4 II-5 II-6 II-7 II-8 II-9	Solicitante Esta persona es: Solicitante para: Nombre Dirección: Estado de nacionalidad Estado de Residencia No. de Teléfono No. de facsímile	 solamente solicitante Todos los estados designados excepto US ELI LILLY & COMPANY (NZ) LIMITED 9 Gladding Place Manukau City Auckland Nueva Zelanda NZ NZ +64 9 262-1370 +64 9 262-1408
III-1 III-1-1 III-1-2 III-1-4 III-1-5 II-1-6 II-1-7	Solicitante y/o Inventor Esta persona es: Solicitante para Nombre (ÚLTIMO, primero) Dirección: Estado de nacionalidad Estado de Residencia	 solamente inventor solo US AGNEW, Kim, Ewing, Melville 12 Revell Court Pukekohe Auckland Nueva Zelanda NZ NZ

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III-2	Solicitante y/o Inventor	
III-2-1	Esta persona es:	solamente inventor
III-2-2	Solicitante para	solo US
III-2-4	Nombre (ÚLTIMO, primero)	HEWITT, William, Austin
III-2-5	Dirección:	5 Ealing Cresent Beachlands Auckland Nueva Zelanda
II-2-6	Estado de nacionalidad	NZ
II-2-7	Estado de Residencia	NZ
III-3	Solicitante y/o Inventor	
III-3-1	Esta persona es:	solamente inventor
III-3-2	Solicitante para	solo US
III-3-4	Nombre (ÚLTIMO, primero)	HANHAM, Craig, Richard
III-3-5	Dirección:	21 Wright Road Pt Chevalier Auckland Nueva Zelanda
II-3-6	Estado de nacionalidad	NZ
II-3-7	Estado de Residencia	NZ
III-4	Solicitante y/o Inventor	
III-4-1	Esta persona es:	solamente inventor
III-4-2	Solicitante para	solo US
III-4-4	Nombre (ÚLTIMO, primero)	PURDY, Kevin, Grant
III-4-5	Dirección:	36 Sefton Ave Grey Lynn Auckland Nueva Zelanda
II-4-6	Estado de nacionalidad	NZ
II-4-7	Estado de Residencia	NZ
IV-1	Agente o representante común; o dirección para correspondencia La persona identificada a continuación se/ha sido nombrada al acto en representación del (los) solicitante(s) antes de la Autoridad Internacional Competente como:	Agente
IV-1-1	Nombre (APELLIDO, Nombre)	CALHOUN, Douglas C
IV-1-2	Dirección:	A J Park 6th Floor Huddart Parker Building 1 Post Office Square PO Box 949 Wellington
IV-1-3	No. de Teléfono	Nueva Zelanda
IV-1-4	No. de Facsímile	+64 9 356 6996
IV-1-5	e-mail	+64 9 356 6990 akl@ajpark.com

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Original (para SUMISIÓN) impreso el 18.12.2001 04:02:18 PM

IV-2		agente(s) adicional(es) con la misma dirección como el primer agente nombrado
IV-2-1	Nombre(s)	GRIFFITHS, Teresa V; HACKETT, John Bruno; JONES, David John; MOON, Kenneth Reginald; SYDDALL, Thomas H; THOMPSON, Bryan Lindsay; WEST-WALKER, Greg J
V	Designación de Estados	
V-1	Patente Regional (si cualquier otra clase de protección o tratamiento, se especifica entre paréntesis después de la(s) designación(es) concernida(s)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW y cualquier otro estado que sea un Estado Contratante de la Convención de Patentes Europeas y del PCT EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro estado que sea un Estado Contratante de la Convención de Patentes Europeas y del PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR y cualquier otro estado que sea un Estado Contratante de la Convención de Patentes Europeas y del PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG y cualquier otro estado que sea un Estado Contratante de la Convención de Patentes Europeas y del PCT
V-2	Patente Regional (si cualquier otra clase de protección o tratamiento, se especifica entre paréntesis después de la(s) designación(es) concernida(s)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW.
V-3	Patente Nacional (Estados los cuales se han convertido en parte del PCT después de la emisión de esta versión de EASY)	OM ZM TN
V-5	Declaración de Designación Preventiva Además de las designaciones hechas bajo los puntos V-1, V-2 y V-3, el solicitante también se marca bajo la Regla 4.9(b) todas las designaciones las cuales deben ser permitidas bajo el PCT, excepto cualquier designación(es) de los estado(s) indicado(s) bajo el punto V-6 posterior. El solicitante afirma que aquellas designaciones adicionales se argumentan para confirmación y que cualquier designación la cual no se haya confirmado antes de la expiración de 15 meses a partir de la fecha de prioridad no será apreciadas como apartadas por el solicitante a la expiración del tiempo límite.	

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V-6	Exclusión(es) a partir de las designaciones preventivas	NINGUNO	
VI-1	Reivindicación de prioridad de la solicitud nacional anterior		
VI-1-1	Fecha de Presentación	19 de Diciembre de 2000 (19.12.2000)	
VI-1-2	Número	509092	
VI-1-3	País	NZ	
VI-2	Reivindicación de prioridad de la solicitud nacional anterior		
VI-2-1	Fecha de Presentación	13 de Septiembre de 2001 (13.09.2001)	
VI-2-2	Número	514183	
VI-2-3	País	NZ	
VI-2	Petición de documentos de prioridad Se pide a la Oficina receptora preparar y transmitir a la Oficina Internacional una copia certificada de la(s) solicitud(es) anterior(es) identificadas anteriormente como punto(s):	VI-1, VI-2	
VII-1	Elección de la Autoridad de Búsqueda Internacional	Oficina Europea de Patentes (EPO) (ISA/EP)	
VIII	Lista de verificación	Nombre de declaraciones	
VIII-1	Declaración en cuanto la identidad del inventor	-	
VIII-2	Declaración en cuanto al título del solicitante, como en la fecha de presentación internacional, para solicitud y otorgación de una patente.	-	
VIII-3	Declaración en cuanto al título del solicitante, como en la fecha de presentación internacional, para reclamar de la solicitud más anterior.	-	
VIII-4	Declaración de inventividad (sólo para los propósitos de la designación de los Estados Unidos de América.	-	
VIII-5	Declaración en cuanto a las descripciones no perjudiciales a excepciones para carecer de novedad.	-	
IX	Lista de verificación	Número de Hojas	Archivo(s) electrónico(s) anexos
IX-1	Petitorio (incluyendo hoja de declaración) .	5	-
IX-2	Descripción	33	-
IX-3	Reivindicaciones	7	-
IX-4	Resumen	1	EZABST00.TXT
IX-5	Dibujos	5	-
IX-7	TOTAL	51	
	Puntos que acompañan	Documento(s) anexo(s)	Archivo(s) electrónico(s) anexos
IX-8	Hoja de cálculos de tasas	✓	-
IX-17	Disquete PCT-FÁCIL	-	Disquete
VIII-19	Figura de los dibujos que debe adjuntarse al resumen:	2	
VIII-20	Idioma de presentación de la solicitud internacional:	Inglés	

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IX-1	Firma del Solicitante o agente	
IX-1-1	Nombre	THOMPSON, Bryan Lindsay

PARA USO DE LA OFICINA RECEPTORA UNICAMENTE

10-1	Fecha del recibo real de la solicitud internacional alegada:	
10-2 10-2-1 10-2-2	Dibujos Recibida No Recibida	
10-3	Fecha corregida del vencimiento del recibo real a los documentos o dibujos recibidos posteriormente pero a tiempo que complementan la solicitud internacional alegada:	
10-4	Fecha de recepción puntual de las correcciones requeridas bajo el Articulo 11(2) del PCT	
10-5	Autoridad de Búsqueda Internacional	ISA/EP
10-6	Transmisión de copia de búsqueda retrasada hasta que la tasa de búsqueda se pague	

PARA USO DE LA OFICINA INTERNACIONAL ÚNICAMENTE

11-1	Fecha de la recepción de la copia de registro por la Oficina Internacional	

PCT REQUEST

P451785

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0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.03.2001)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	Intellectual Property Office of New Zealand (RO/NZ)
0-7	Applicant's or agent's file reference	P451785
I	Title of invention	IONOPHORE ANTIBIOTIC FORMULATIONS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	ELI LILLY & COMPANY (NZ) LIMITED
II-5	Address:	9 Gladding Place Manukau City Auckland New Zealand
II-6	State of nationality	NZ
II-7	State of residence	NZ
II-8	Telephone No.	+ 64 9 262-1370
II-9	Facsimile No.	+ 64 9 262-1408
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	AGNEW, Kim, Ewing, Melville
III-1-5	Address:	12 Revell Court Pukekohe Auckland New Zealand
III-1-6	State of nationality	NZ
III-1-7	State of residence	NZ

PCT REQUEST

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III-2	Applicant and/or Inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	HEWITT, William, Austin
III-2-5	Address:	5 Ealing Cresent Beachlands Auckland New Zealand
III-2-6	State of nationality	NZ
III-2-7	State of residence	NZ
III-3	Applicant and/or Inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	HANHAM, Craig, Richard
III-3-5	Address:	21 Wright Road Pt Chevalier Auckland New Zealand
III-3-6	State of nationality	NZ
III-3-7	State of residence	NZ
III-4	Applicant and/or Inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	PURDY, Kevin, Grant
III-4-5	Address:	36 Sefton Ave Grey Lynn Auckland New Zealand
III-4-6	State of nationality	NZ
III-4-7	State of residence	NZ
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	CALHOUN, Douglas C
IV-1-2	Address:	A J Park 6th Floor Huddart Parker Building 1 Post Office Square PO Box 949 Wellington New Zealand
IV-1-3	Telephone No.	+64 9 356 6996
IV-1-4	Facsimile No.	+64 9 356 6990
IV-1-5	e-mail	akl@ajpark.com

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IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	GRIFFITHS, Teresa V; HACKETT, John Bruno; JONES, David John; MOON, Kenneth Reginald; SYDDALL, Thomas H; THOMPSON, Bryan Lindsay; WEST-WALKER, Greg J
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
V-3	National Patent (States which have become party to the PCT after the issuance of this version of EASY)	OM ZM TN
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	

PCT REQUEST

P451785

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V-8	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	19 December 2000 (19.12.2000)	
VI-1-2	Number	509092	
VI-1-3	Country	NZ	
VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	13 September 2001 (13.09.2001)	
VI-2-2	Number	514183	
VI-2-3	Country	NZ	
VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	33	-
IX-3	Claims	7	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	5	-
IX-7	TOTAL	51	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract	2	
IX-20	Language of filing of the international application	English	

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PCT REQUEST P451785

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X-1	Signature of applicant, agent or common representative	
X-1-1	Name (LAST, First)	THOMPSON, Bryan Lindsay

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

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PCT (ANNEX - FEE CALCULATION SHEET) P451785

Original (for SUBMISSION) - printed on 18.12.2001 04:02:18 PM

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	

0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet				
0-4-1	Prepared using		PCT-EASY Version 2.92 (updated 01.03.2001)		
0-9	Applicant's or agent's file reference		P451785		
2	Applicant		ELI LILLY & COMPANY (NZ) LIMITED, et al.		
12	Calculation of prescribed fees		fee amount/multiplier	total amounts (NZD)	
12-1	Transmittal fee	T	⇨	180	
12-2	Search fee	S	⇨	2,000	
12-3	International fee				
	Basic fee				
	(first 30 sheets)	b1	923		
12-4	Remaining sheets		21		
12-5	Additional amount	(X)	21		
12-6	Total additional amount	b2	441		
12-7	b1 + b2 =	B	1,364		
12-8	Designation fees				
	Number of designations contained in international application		93		
12-9	Number of designation fees payable (maximum 6)		6		
12-10	Amount of designation fee	(X)	199		
12-11	Total designation fees	D	1,194		
12-12	PCT-EASY fee reduction	R	-284		
12-13	Total international fee (B+D-R)	I	⇨	2,274	
12-14	Fee for priority document				
	Number of priority documents requested		2		
12-15	Fee per document	(X)	0		
12-16	Total priority document fee	P	⇨	0	
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	4,454	
12-19	Mode of payment		cheque		

VALIDATION LOG AND REMARKS

13-2-2	Validation messages States	Yellow! Additional national designation added: Obtain updated maintenance tables rather than using this field.

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PCT (ANNEX - FEE CALCULATI N SHEET) P451785

Original (for SUBMISSION) - printed on 18.12.2001 04:02:18 PM

13-3-3	Validation messages Names	
		Yellow Applicant 1.:Postal code missing
		Yellow Applicant 2.:Postal code missing
		Yellow Applicant 3.:Postal code missing
		Yellow Applicant 4.:Postal code missing
		Yellow Applicant 5.:Postal code missing
		Green? Agent 1.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Yellow Agent 1.:Postal code missing
		Green? Agent 2.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 3.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 4.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 5.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 6.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.

PCT (ANNEX - FEE CALCULATION SHEET) P451785

Original (for SUBMISSION) - printed on 18.12.2001 04:02:18 PM

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		Green? Agent 7.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 8.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
13-2-7	Validation messages Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
13-2-8	Validation messages Fees	Green? Please confirm that fee schedule utilized is the latest available

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PCT

P451785

Original (for SUBMISSION) - printed on 18.12.2001 04:02:18 PM

PCT-EASY INFORMATION SHEET

(For applicant use only, DO NOT submit this sheet with the international application)

VALIDATION LOG

	States
Yellow!	Additional national designation added: Obtain updated maintenance tables rather than using this field.
	Names
Yellow	Applicant 1.:Postal code missing
Yellow	Applicant 2.:Postal code missing
Yellow	Applicant 3.:Postal code missing
Yellow	Applicant 4.:Postal code missing
Yellow	Applicant 5.:Postal code missing
Green?	Agent 1.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
Yellow	Agent 1.:Postal code missing
Green?	Agent 2.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
Green?	Agent 3.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
Green?	Agent 4.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
Green?	Agent 5.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
Green?	Agent 6.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
Green?	Agent 7.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
Green?	Agent 8.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
	Contents
Yellow!	The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
	Fees
Green?	Please confirm that fee schedule utilized is the latest available

Before submitting the International Application, please carefully verify that:

-the information contained on printed Request form is correct;
-Box X of the Request form has been signed;
-all elements of the international application as indicated in Boxes VIII and IX of the Request form have been attached; and,
-the diskette containing the PCT-EASY zip file of the International Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION

DO NOT modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.

The invention relates to an ionophore antibiotic composition capable of dilution with water to a substantially stable dispersed form in all water then present, said composition comprising or including:

- at least one ionophore antibiotic (preferably monensin) of a mean particle size of less than 20 microns,
- and at least one dispersing agent.

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A method of preparing the ionophore antibiotic composition is also disclosed.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/_____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference P451785 KJR/ghb
International application No. PCT/NZ01/00290	International filing date *(day/month/year)* 18/12/2001	(Earliest) Priority date *(day/month/year)* 19/12/2000
Title of invention IONOPHORE ANTIBIOTIC FORMULATIONS		

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No. +64 9 262-1370
ELI LILLY & COMPANY (NZ) LIMITED 9 Gladding Place Manukau City Auckland	Facsimile No. +64 9 262-1408
	Teleprinter No.
	Applicant's registration No. with the Office

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
New Zealand	New Zealand

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
AGNEW, Kim Ewing Melville
12 Revell Court
Pukekohe
Auckland

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
New Zealand	New Zealand

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
HEWITT, William Austin
5 Ealing Cresent
Beachlands
Auckland

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
New Zealand	New Zealand

☒ Further applicants are indicated on a continuation sheet.

International application No.
PCT/NZ01/00290

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
HANHAM, Craig Richard
21 Wright Road
Pt Chevalier
Auckland

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
New Zealand	New Zealand

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
PURDY, Kevin Grant
36 Sefton Ave
Grey Lynn
Auckland

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

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Sheet No. ..3

International application No.
PCT/NZ01/00290

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

A J FARK; CALHOUN, Douglas, C; GRIFFITHS, Teresa, V; HACKETT, John B; SYDDALL, Thomas H; THOMSON, Keith, C; THOMPSON, Bryan L; MOON, Kenneth, R; and JONES, David, J.

all Intellectual Property Lawyers & Patent Attorneys of Huddart Parker Building, 1 Post Office Square, Wellington, New Zealand

Telephone No.
+64 9 356 6998

Facsimile No.
+64 9 356 6990

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☒ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

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Sheet No. 4.

International application No.
PCT/NZ01/00290

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

DAVID JOHN JONES
AGENT FOR THE APPLICANT

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 80.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

20+

CHAPTER II 19

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/NZ01/00280	For International Preliminary Examining Authority use only
Applicant's or agent's file reference P451785	Date stamp of the IPEA

Applicant

ELI LILLY & COMPANY (NZ) LIMITED

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	AU$450.00	P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	AU$297.00	H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	AU$747.00		
	TOTAL		

MODE OF PAYMENT

- ☐ authorization to charge deposit account with the IPEA (see below)
- ☒ cheque
- ☐ postal money order
- ☐ bank draft
- ☐ cash
- ☐ revenue stamps
- ☐ coupons
- ☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ _____

☐ Authorization to charge the total fees indicated above.

☐ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: _____

Date: _____

Name: _____

Signature: _____

PATENT COOPERATION TREATY

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From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

A J PARK & SON
PO Box 949
WELLINGTON 6001
New Zealand

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	19 NOV 2002
Applicant's or agent's file reference: P451785 KJR/ghb	REPLY DUE within TWO MONTHS from the above date of mailing

International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/NZ01/00290	18 December 2001	19 December 2000

International Patent Classification (IPC) or both national classification and IPC
Int. Cl.[7] A61K 9/00, 9/14, 47/34, 47/36, 47/10

Applicant
ELI LILLY AND COMPANY (NZ) LIMITED et al

1. This written opinion is the **first** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

3. The FINAL DATE by which the international preliminary examination report must be established according to Rule 69.2 is:
19 April 2003

4. The applicant is hereby invited to reply to this opinion.

When? See the Reply Due date indicated above. However, the Australian Patent Office will not establish the Report before the earlier of (i) a response being filed, or (ii) one month before the Final Date by which the international preliminary examination report must be established. The Report will take into account any response (including amendments) filed before the Report is established.
If no response is filed by 1 month before the Final Date, the international preliminary examination report will be established on the basis of this opinion.
Applicants wishing to have the benefit of a further opinion (if needed) before the report is established should ensure that a response is filed at least 3 months before the Final Date by which the international preliminary examination report must be established.

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3.
For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	ANDREW ACHILLEOS Telephone No. (02) 6283 2280

WRITTEN OPINION

International application No.
PCT/NZ01/00290

I. Basis of the opinion

1. With regard to the elements of the international application:*

   [X] the international application as originally filed.

   [ ] the description, pages , as originally filed,
   pages , filed with the demand,
   pages , received on with the letter of

   [ ] the claims, pages , as originally filed,
   pages , as amended under Article 19,
   pages , filed with the demand,
   pages , received on with the letter of

   [ ] the drawings, pages , as originally filed,
   pages , filed with the demand,
   pages , received on with the letter of

   [ ] the sequence listing part of the description:
   pages , as originally filed
   pages , filed with the demand
   pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
   These elements were available or furnished to this Authority in the following language which is:

   [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

   [ ] the language of publication of the international application (under Rule 48.3(b)).

   [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

   [ ] contained in the international application in printed form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readable form.

   [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

   [ ] the description, pages

   [ ] the claims, Nos.

   [ ] the drawings, sheets/fig.

5. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

WRITTEN OPINION

International application No.
PCT/NZ01/00290

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 4,7-13,19,28,34-36,39-72	YES
	Claims 1-3,5,6,14-18,20-27,29-33,37,38	NO
Inventive step (IS)	Claims	YES
	Claims 1-72	NO
Industrial applicability (IA)	Claims 1-72	YES
	Claims	NO

2. Citations and explanations

WO 97/03650 = document 1 (D1)

WO 98/16663 = document 2 (D2)

NOVELTY

Claims 14,15,23,24,29

D1 at page 3 para.2 to page 4 para.1 discloses an aqueous suspension of an ionophore antibiotic that includes a surfactant, a suspension agent and an antifreeze agent. Page 11 para.4 of D1 directs the skilled addressee to treat an animal with said aqueous suspension or a water diluted version thereof. Page 14 para.3 describes how crystalline monensin (an ionophore antibiotic) can be prepared. Page 21 final para. Describes the preparation of a drench.

The diluted form of the aqueous suspension of D1 anticipates claim 14. Defining claim 14 as "Animal drinking water" places no limitation on the claim other than that the composition defined in the claim be suitable for the purpose. The composition of D1 would be suitable for animals to drink as it is used as a drench. Claim 15 is not novel because with enough surfactant or suspending agent the suspension would be stable for 24 days. A similar objection applies to claims 23 24 and 29, for example, the term "trough water accessible to an animal to drink" places no real limitation on claims 23 and 29.

Claims 1-3,5,6,14-18,20-27,29-33,37 and 38

D2 discloses a composition for treating animal hides with a composition that anticipates the above claims. Page 3 line 10 to page 4 line 16 of D2 discloses a composition of an antibiotic (monensin, page 6 line 9) of a particle size less than 25 microns, preferably 7-10 microns and a surfactant effective to uniformly disperse the antibiotic in aqueous suspension (0.1-10 g/l). Examples of the surfactants are given at page 7 lines 14-26. Page 8 lines 5-22 discloses the proportional relationship between particle size and surfactant concentration. Page 9 lines 2-11 discloses that milling is used to get the desired particle size and that the surfactant is mixed in after milling has occurred; example 1 at page 10 exemplifies this process.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claim 11 is not clear because the term "as previously described" does not refer to any place in particular. For example, "as hereinbefore described" or "as described in the body of the specification" would refer the skilled addressee to the description, the term "as previously described" is indefinite. A similar objection applies to claims 36 and 70.
2. Claim 18 is not clear, the claim appears to be to the product of a method of preparing the suspension however I cannot clearly determine what the method steps are. A similar objection applies to claim 27.
3. Claims 14,15,20-26,29-31,39-42,49-52,60 and 61 are not supported by the description. These claims lack essential features of your invention. At page 3 para. 3, page 4 para. 3 and page 5 para. 2 of your specification the feature of a mean particle size of less than about 40 microns is described as essential. At page 4 para. 2 the feature of the ability to form a stable dispersion is described as being essential. Page 10 para. 3 describes the feature of the particles of ionophore antibiotic being coated by "wetting" agents as being essential. Claims 14,15,23,24,29,39-42, 49-52,60 and 61 do not have the essential feature of particle size being less than about 40 microns. Claims 20-26, 29,30 and 31 do not have the essential feature of a "wetting" agent or dispersing agent.
4. Claim 60 is not clear because it defines the milling together of the antibiotic and a "dispersing agent" and then defines that the addition of the "dispersing agent" should be after milling (post-milling addition).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of BOX V

NOVELTY(cont.)

Your claims 1-3 are anticipated by the disclosure of D2 because 7 microns may be regarded as being substantially 5 microns and as the compositions are similar then you would expect the suspensions of D2 to be stable for 24 days. Your claims 5 and 6 are anticipated by the aqueous suspension of D2.

Your claims 14-18 are anticipated by D2. Defining claim 14 as "Animal drinking water" places no limitation on the claim other than that the composition defined in the claim be suitable for the purpose. The composition of D2 would be suitable for animals to drink as it is in a suitable concentration; 0.1-10 g/l. A similar objection applies to claims 20-27 and 29-31.

Your claims 32-34 and 37,38 are not novel as they define the serial dilution of the composition of D2 and the product of this dilution.

INVENTIVE STEP

Claims 1-72

Claims 1-3,5,6,14-18,20-27,29-33,37 and 38

Your claims 1-3,5,6,14-18,20-27,29-33,37 and 38, as well as being not novel, do not involve an inventive step.

Claims 4,7-13,19,28,35 and 36

Your claims 4, 9 and 35 define the use of surfactants that have not been specifically exemplified in D2, however, they are merely alternative surfactants that are technically equivalent to those exemplified in D2. Your claims 7 and 8 define the addition of an organic liquid, however, there does not appear to be anything inventive about its addition disclosed in your specification. From claim 13 the organic liquid is to act as a lubricant in the milling process, this use would be within the common general knowledge (CGK) of the skilled addressee. Claims 10-12,19,28 and 36 define the addition of a suspension agent, it would be within the CGK of the skilled addressee to uses a suspension agent to help stabilise a dispersion.

Claims 32-72

Example 1 at page 10 of D2 discloses the milling of an ionophore antibiotic to the required particle size followed by the addition of surfactant. Your claims 32-72 define a process where the ionophore antibiotic is milled with the surfactant. At page 10 para.3 you disclose that it is essential to have the antibiotic particles appropriately coated with the "wetting agents", your milling of the antibiotic together with the surfactants would ensure appropriate coating. However, it appears from D2 (example 1, page 10) that appropriate coating of the antibiotic particles is achieved by the post-milling addition of surfactant. Example 2 and table 1 at pages 12 and 13 disclose that stable suspensions can be prepared from the product of example 1, concentrations vary from 0.1-10 g/l. Therefore, there is no inventive step involved in milling the antibiotic with the surfactant.

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.		( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		( )
- Descripción de la invención.		( )
- Dibujos de ser estos pertinentes.		( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable: ANDREA ROSSE

Fecha:

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
ALVARO CORREA ORDOÑEZ
Apoderado
ELI LILLY AND COMPANY

Oficio N° 09709

ASUNTO:	Radicación N°	03-61096
	Solicitud internacional	PCT/NZ01/00290
	Fecha inicio fase nacional	19-07-2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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 CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

07 NOV. 2003

El anterior requerimiento fue notificado por fijación en lista de fecha_____.

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