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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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*

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(54) Title: ANTIBIOTIC PRODUCT FORMULATION

(57) Abstract: This invention discloses an antibiotic formulation in an immediate release antibiotic dosage form, comprising an antibiotic, colloidal silicon dioxide, povidone, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate and a coating, said formulation having a release profile wherein the Cmax is reached in less than five hours.

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ANTIBIOTIC PRODUCT FORMULATION

BACKGROUND OF THE INVENTION

This invention relates to an antibiotic product formulation.

A wide variety of antibiotics have been used, and will be used, in order to combat bacterial infection. In general, such antibiotics can be administered by a repeated dosing of immediate release dosage forms. The composition of the dosage form can impact the bioavailability of the antibiotic.

This invention provides a formulation that consistently produces an antibiotic product that meets predetermined specifications and quality attributes.

BRIEF SUMMARY OF THE INVENTION

In accordance with an aspect of this invention there is provided an antibiotic dosage formulation comprising an antibiotic, colloidal silicon dioxide, povidone, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate and optionally a coating, the formulation having a release profile wherein the C_{max} is reached in less than five hours.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING

Figure 1 is a graph of the dissolution of several antibiotic product formulations containing ethionamide as the active ingredient. The x-axis is the time in days. The y-axis is the % dissolution. The dissolution profiles of the formulations do not meet the dissolution specification desired.

Figure 2 - Figure 5 contain tables of dissolution profiles of the antibiotic product formulation of this invention containing ethionamide as the active ingredient.

Figure 6 is a graph of the C_{max} for the antibiotic product formulation of Figure 1 (reference) and Figure 2 (test). The x-axis is the time in hours. The y-axis is the concentration in picograms/mL.

DETAILED DESCRIPTION OF THE INVENTION

The following experimental details are set forth to aid in an understanding of the invention, and are not intended, and should not be construed, to limit in any way the invention set forth in the claims that follow thereafter.

In accordance with an aspect of this invention there is provided an antibiotic formulation in an immediate release antibiotic dosage form, comprising an antibiotic, colloidal silicon dioxide, povidone, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate and a coating, the formulation having a release profile wherein the C_{max} is reached in less than five hours

The formulation will be especially useful in reaching a C_{max} in less than 5 hours. The following are examples of antibiotics that may be used in the formulation of this invention: cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cephacelor, cephprozil, cephadrine, cefamandole, cefonicid, ceforanide, cefuroxime, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftaxidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, cefinetazole, cefotetan, cefoxitin, loracarbef, imipenem, erythromycin and salts thereof, azithromycin, clarithromycin, dirithromycin, troleanomycin, penicillin V penicillin salts and complexes, methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, bacampicillin, carbenicillin indanyl sodium, salts of carbenicillin, mezlocillin, piperacillin, tazobactam, ticarcillin, ticarcillin and clavulanate potassium, clindamycin, vancomycin, novobiocin, aminosalicyclic acid, capreomycin, cycloserine, ethambutol HCl and other salts, ethionamide, isoniazid, ciprofloxacin, levofloxacin, lomefloxacin, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, sulfacytine, sulfamerazine, sulfamethazine, sulfamethixole, sulfasalazine, sulfisoxazole, sulfapyrizine, sulfadiazine, sulfinethoxazole, sulfapyridine, metronidazole, methenamine, fosfomycin, nitrofurantoin, trimethoprim, clofazimine, co-triamoxazole, pentamidine, and trimetrexate.

An oral dosage form may comprise an antibiotic, e.g., ethionamide, in combination with one or more of a pharmaceutically acceptable lubricant, binder, and carrier. The oral dosage form is a tablet

C_{max} was determined from the graph in Figure 6 and is the highest concentration at any given dose appearing on the graph.

In an embodiment of this invention the antibiotic comprises up to about 42.0 % w/w of the uncoated tablet. Other examples include from about 40 to about 45% (w/w) of antibiotic such as ethionamide.

In one embodiment colloidal silicon dioxide comprises up to about 0.5 % w/w of the uncoated tablet. Examples include from 0.4 to about 0.6% (w/w) colloidal silicon dioxide.

In other embodiments povidone is up to about 5.0 % w/w of the uncoated tablet. For example povidone comprises from about 3 to about 7 % w/w of the uncoated tablet.

In further embodiments silicified microcrystalline cellulose comprises up to about 47.0 % w/w of the uncoated tablet. For example silicified microcrystalline cellulose comprises from about 42 to about 50% w/w of the uncoated tablet.

Croscarmellose sodium may be included up to 5.0 % w/w of the uncoated tablet. For example croscarmellose sodium comprises from about 3 to about 7 % w/w of the uncoated tablet.

In yet further embodiments magnesium stearate comprises up to about 0.5 % w/w of the uncoated tablet, e.g., from about 0.3 to about 0.7% w/w of the uncoated tablet.

The coating may for example be applied to give an increase in weight of about 4%(w/w) of the core or uncoated tablet.

The formulation is administered to a host in an amount effective for treating a bacterial infection. Any bacteria that is not considered normal flora in the host may cause the bacterial infection. An example of a bacterial infection includes, but is not limited to, tuberculosis.

The antibiotic formulation of the present invention may be initially produced and then coated to produce a form to give the desired C_{max}.

The coating is any coating that will produce a form to give the desired C_{max}. Opadry II Orange is an example of a coating that may be used.

Example Formulation

Ingredient	Amount per Tablet (mg)	% (w/w)	Quantity per Batch (90,000) (kg)
Ethionamide USP	250.0	42.0	22.5
Colloidal Silicon Dioxide	3.0	0.5	0.27
Povidone USP K 29/32	30.0	5.0	2.70
Silicified Microcrystalline Cellulose NF	284.0	47.0	25.56
Croscarmellose Sodium NF	30.0	5.0	2.70
Magnesium Stearate NF	3.0	0.5	0.27
Total Core Weight	600.0	100	54.00
Opadry II Orange 85F13774	24.0		10.80*
Sterile Water for Irrigation, USP	removed		8.64
Total	624.0		

*Represents a 20 % solids dispersion in water

The ingredients found in the table above were screened in the following order to delump the ingredients: one half of the silicified microcrystalline cellulose, povidone, croscarmellose sodium, ethionamide, colloidal silicon dioxide, and the remainder of the silicified microcrystalline cellulose through a 20-mesh screen. The

screened ingredients were transferred into a 5 cubic foot cross-flow V-blender and mixed for 20 minutes.

The magnesium stearate was passed through a NF through a 40-mesh screen and added through one blender charging port to the mixed powders. The powders were blended for 3 minutes. The blends were compressed into tablets. The tablets were acceptable if the target weight of 570 –630 mg ± 5 %, the dissolution of not less than 90 % in 45 minutes, and the friability of less than 0.5%, were met.

Opadry Orange 85F13774 in sterile water for irrigation, USP, was dispensed and the above tablets were color coated using a Vector HCT-60 (24"/60 cm pan) at an inlet air temperature of 65° C ± 10° C and an outlet air temperature of 48° C ± 5° C.

WHAT IS CLAIMED IS:

1. An antibiotic formulation comprising an antibiotic, colloidal silicon dioxide, povidone, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate and a coating, said formulation having a release profile wherein the C_{max} is reached in less than five hours.

2. The formulation of claim 1 wherein the antibiotic is cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cephacelor, cephprozil, cephadrine, cefamandole, cefonicid, ceforanide, cefuroxime, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftaxidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, cefinetazole, cefotetan, cefoxitin, loracarbef, imipenem, erythromycin and salts thereof, azithromycin, clarithromycin, dirithromycin, troleanomycin, penicillin V penicillin salts and complexes, methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, bacampicillin, carbenicillin indanyl sodium, salts of carbenicillin, mezlocillin, piperacillin, tazobactam, ticarcillin, ticarcillin and clavulanate potassium, clindamycin, vancomycin, novobiocin, aminosalicyclic acid, capreomycin, cycloserine, ethambutol HCl and other salts, ethionamide, isoniazid, ciprofloxacin, levofloxacin, lomefloxacin, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, sulfacytine, sulfamerazine, sulfamethazine, sulfamethixole, sulfasalazine, sulfisoxazole, sulfapyrizine, sulfadiazine, sulfinethoxazole, sulfapyridine, metronidazole, methenamine, fosfomycin, nitrofurantoin, trimethoprim, clofazimine, co-triamoxazole, pentamidine, and trimetrexate.

3. The formulation of claim 1 wherein the antibiotic is ethionamide.

4. The formulation of any one of claims 1 to 3 wherein said formulation is in an oral dosage form.

5. The formulation of claim 4 wherein said formulation is a tablet.

6. The formulation of claim 5 wherein the tablet coating is Opadry II Orange.

7. The formulation of claim 5 or claim 6 wherein the tablet has a dissolution of ≥ 90% in 45 minutes.

8. The formulation of any one of claims 5 to 7 wherein the tablet has a friability of < 0.5%.

9. The formulation of any one of claims 5 to 8 wherein the uncoated tablet has a target weight of 570 – 630 mg ± 5 %.

10. The formulation of any one of claims 1 to 9 wherein the antibiotic is up to 42.0 % w/w of the uncoated tablet.

11. The formulation of any one of claims 1 to 10 wherein the colloidal silicon dioxide is up to 0.5 % w/w of the uncoated tablet.

12. The formulation of any one of claims 1 to 11 wherein the povidone is up to 5.0 % w/w of the uncoated tablet.

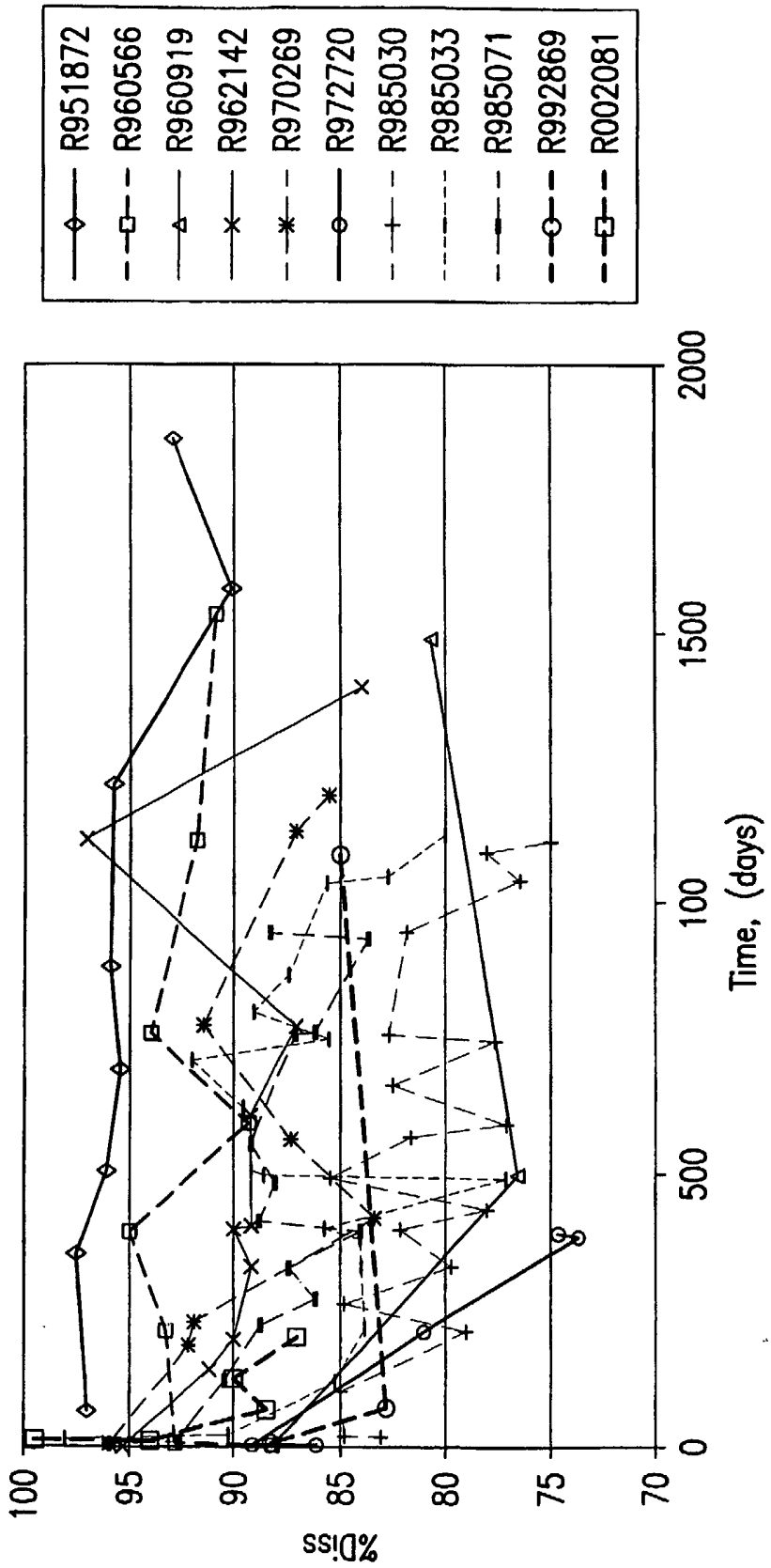
13. The formulation of any one of claims 1 to 12 wherein the silicified microcrystalline cellulose is up to 47.0 % w/w of the uncoated tablet.

14. The formulation of any one of claims 1 to 13 wherein the croscarmellose sodium is up to 5.0 % w/w of the uncoated tablet.

15. The formulation of any one of claims 1 to 14 wherein the magnesium stearate is up to 0.5 % w/w of the uncoated tablet.

16. A method for treating a bacterial infection in a host comprising administering to the host the antibiotic formulation of any one of claims 1 to 15.

17. The method of claim 16 wherein the bacterial infection is tuberculosis.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100
95
90
85
80
75
70
%Diss
0
500
100
1500
2000
Time, (days)

FIG. 1

Time (min)	Vessel	% Label Release						
		Initial	1-Month @25/60	1-Month @40/75	2-Months @25/60	2-Months @40/75	3-Months @25/60	3-Months @40/75
15	1	100	97	101	101	101	98	97
	2	99	99	100	102	101	96	98
	3	100	99	100	101	99	100	97
	4	100	100	100	100	100	100	99
	5	101	100	100	101	100	98	100
	6	101	99	100	100	102	101	98
	Mean	100	99	100	101	100	99	98
30	1	100	101	101	101	101	99	98
	2	99	102	100	102	100	99	98
	3	100	100	100	101	99	100	97
	4	100	100	100	100	100	100	100
	5	101	100	100	101	100	98	100
	6	100	100	100	100	102	101	98
	Mean	100	100	100	101	100	99	99
45	1	100	100	101	101	101	99	98
	2	99	101	101	102	101	98	97
	3	100	100	101	101	99	99	97
	4	100	100	100	100	100	100	100
	5	101	100	100	101	100	98	100
	6	100	100	101	100	102	101	98
	Mean	100	100	101	101	100	99	98
60	1	100	100	101	101	101	98	98
	2	99	102	101	102	101	98	98
	3	100	99	100	101	99	99	97
	4	100	100	101	100	100	99	100
	5	102	101	99	101	100	98	100
	6	100	100	101	100	102	100	98
	Mean	100	100	101	101	101	99	99

FIG.2

Time (min)	Vessel	% Label Release						
		Initial	1-Month @25/60	1-Month @40/75	2-Months @25/60	2-Months @40/75	3-Months @25/60	3-Months @40/75
15	1	100	101	99	95	99	52	97
	2	99	100	99	98	102	57	100
	3	100	100	97	99	100	77	97
	4	100	100	102	100	101	59	99
	5	101	100	100	95	102	71	100
	6	101	95	98	104	100	84	99
	Mean	100	100	99	99	101	67	99
30	1	100	101	100	99	100	72	98
	2	99	101	99	100	102	76	100
	3	100	100	99	99	100	90	97
	4	100	100	102	101	101	81	99
	5	101	101	100	99	102	81	100
	6	100	99	99	104	101	94	99
	Mean	100	100	100	100	101	82	99
45	1	100	100	100	100	100	86	98
	2	99	99	99	100	102	85	100
	3	100	100	100	99	100	95	97
	4	100	100	102	101	101	93	99
	5	101	100	100	99	102	87	100
	6	100	99	99	103	101	97	99
	Mean	100	100	100	100	101	91	99
60	1	100	101	100	100	100	96	97
	2	99	100	99	100	102	98	100
	3	100	100	100	99	100	100	97
	4	100	100	102	101	101	100	99
	5	102	101	100	99	102	96	100
	6	100	100	99	105	101	99	99
	Mean	100	100	100	101	101	98	99

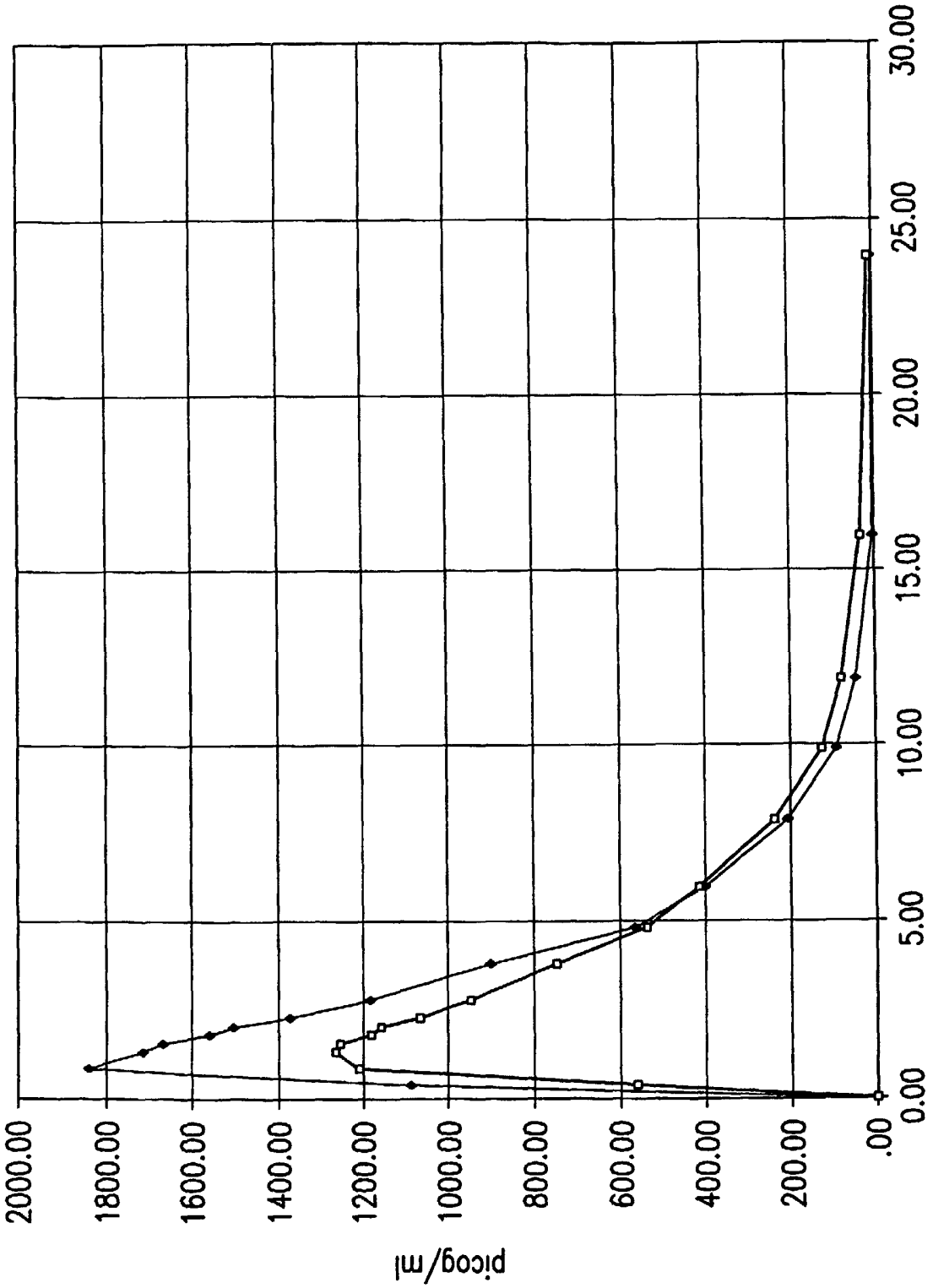
FIG.3

Time (min)	Vessel	% Label Release						
		Initial	1-Month @25/60	1-Month @40/75	2-Months @25/60	2-Months @40/75	3-Months @25/60	3-Months @40/75
15	1	101	100	97	101	94	100	100
	2	97	98	99	90	98	95	97
	3	100	96	100	101	99	102	101
	4	101	101	102	102	98	103	100
	5	102	100	98	100	95	100	102
	6	101	98	94	100	93	100	88
	Mean	100	99	99	99	96	100	98
30	1	101	103	101	101	99	100	101
	2	102	102	102	99	99	99	100
	3	100	102	103	102	99	102	100
	4	102	101	103	102	99	102	100
	5	103	101	100	101	98	100	102
	6	102	103	101	102	93	101	100
	Mean	102	102	102	101	98	101	101
45	1	102	103	101	101	99	100	101
	2	102	102	103	100	99	98	100
	3	101	102	103	102	99	102	101
	4	102	101	103	102	99	103	100
	5	103	101	101	101	98	100	102
	6	102	103	101	102	93	101	101
	Mean	102	102	102	101	98	101	101
60	1	102	102	102	101	99	100	101
	2	102	102	103	100	99	99	100
	3	101	102	103	102	99	101	101
	4	102	101	103	101	99	102	100
	5	103	101	101	101	98	100	102
	6	102	103	102	101	93	101	101
	Mean	102	102	102	101	98	101	101

FIG.4

Time (min)	Vessel	% Label Release						
		Initial	1-Month @25/60	1-Month @40/75	2-Months @25/60	2-Months @40/75	3-Months @25/60	3-Months @40/75
15	1	101	91	98	99	95	85	97
	2	97	101	102	100	100	102	95
	3	100	102	101	100	98	101	101
	4	101	94	101	98	100	97	101
	5	102	95	98	98	94	99	101
	6	101	90	100	92	97	99	102
	Mean	100	96	100	98	97	97	100
30	1	101	101	101	100	100	99	101
	2	102	102	102	100	100	102	101
	3	100	104	101	100	98	101	101
	4	102	99	102	100	100	101	101
	5	103	100	101	100	101	100	101
	6	102	99	102	99	99	100	102
	Mean	102	101	102	100	100	100	101
45	1	102	101	101	100	100	100	101
	2	102	102	102	100	99	102	101
	3	101	104	101	100	98	101	101
	4	102	99	102	100	100	101	101
	5	103	101	101	100	101	100	101
	6	102	100	103	100	100	100	102
	Mean	102	101	102	100	100	101	101
60	1	102	101	101	100	100	100	101
	2	102	103	103	100	100	102	101
	3	101	103	101	100	98	100	101
	4	102	99	102	100	100	101	101
	5	103	101	101	100	101	100	101
	6	102	100	103	100	100	100	102
	Mean	102	101	102	100	100	100	101

FIG.5


2000.00
1800.00
1600.00
1400.00
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600.00
400.00
200.00
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picog/ml
0.00
5.00
10.00
15.00
20.00
25.00
30.00
Time (hours)

FIG.6

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/037705

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/28 A61K31/44 A61P31/04

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)
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)
EPO-Internal, PAJ, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/63970 A (PHARMACIA & UPJOHN COMPANY; MARTINO, ALICE, C; BATES, ASHLEY, H; MOROZ) 16 December 1999 (1999-12-16)	1,2,4,5, 7-17
Y	page 3, line 1 - page 6, line 3 claims 1-32	1-17
Y	US 4 897 270 A (DEUTSCH ET AL) 30 January 1990 (1990-01-30) examples 1-4 claims 1-8	1-17
Y	EP 0 890 359 A (FUJISAWA PHARMACEUTICAL CO., LTD) 13 January 1999 (1999-01-13) claims 1-7 page 4, line 5 - page 4, line 57 table 8	1-17

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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
7 March 2006	16/03/2006

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	Schifferer, H

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/037705

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/59500 A (ZAMBON GROUP S.P.A; CASTEGINI, FRANCO; GRASSANO, ALESSANDRO; BARINA, R) 12 October 2000 (2000-10-12) claims 1-13 page 2, line 5 - page 3, line 8	1-17
A	EP 0 290 168 A (MCNEILAB, INC) 9 November 1988 (1988-11-09) claims 1-3 page 7, line 10 - page 7, line 11	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/03 7705

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16, 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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