

REYES & REYES

A B O G A D O S

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 329 CTOINFORMACION Folios: 3

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

Ref.

Expediente 07-094.220

Solicitud de patente de invención

Título solicitado:

**"TERAPIA DE COMBINACIÓN PARENTERAL PARA
ENFERMEDADES INFECCIOSAS CAUSADAS POR
UNA BACTERIA RESISTENTE A MEDICAMENTOS"**

Solicitante:

VENUS REMEDIES LIMITED

Apoderado:

JOSE LUIS REYES VILLAMIZAR

Trámite:

SOLICITUD DE EXAMEN DE PATENTABILIDAD

JOSE LUIS REYES VILLAMIZAR, reconocido apoderado del solicitante en el trámite de la referencia, estando dentro de los términos establecidos por el artículo 44 de la Decisión 486 de 2000, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la solicitud en cuestión.

Para el efecto, me permito acompañar copia del recibo No. 07-73.890 de fecha septiembre 12 de 2007, expedido por esa Superintendencia, que acredita el pago de las tasas establecidas por la realización de este trámite, el cual fue radicado con la solicitud de registro. Igualmente anexo copia del excedente que cubre el valor del examen de patentabilidad, por incremento de tasas del 2007 al 2008 por valor de \$8.000.00.

Recibo No. 08-79,478 de fecha Diciembre de 2008 (23).

Señor Superintendente,

JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P.A. 44655 del C.S.J.

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NIT : 800176089-2

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SEPTIEMBRE 12 DE 2007

***** CONSIGNACION *****

Origen	Tipo Pago	Banco	Cuenta	No. Pago	Fecha Pago	Vr. Pago
1899-00131-10 REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	68218700	12/09/2007	\$19,000.00

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

FECHA	CONCEPTO	TOTAL CONCEPTO
30005-01-01	SOLICITUDES	
	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	202,000.00
	TOTAL :	\$ 202,000.00
DOSCIENTOS DOS MIL PESOS		

3-3-21-27 CABLE :

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Examien Patentabilidad

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 99,478
FECHA : DICIEMBRE 23 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	10540810	22/12/2008	16,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS
			TOTAL : \$ 8,000.00

SON: OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-94220

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 596 DE

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

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

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

Fractional Maximal Effect Method for In Vitro Synergy between Amoxicillin and Ceftriaxone and between Vancomycin and Ceftriaxone against Enterococcus faecalis and Penicillin-Resistant Streptococcus pneumoniae

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In the present study we assessed the use of a new in vitro testing method and graphical representation of the results to investigate the potential effectiveness of combinations of amoxicillin (AMZ) plus ceftriaxone (CRO) and of CRO plus vancomycin (VAN) against strains of *Streptococcus pneumoniae* highly resistant to penicillin and cephalosporins (PRP strains). We used the fractional maximal effect (FME) method of time-kill curves to calculate adequate concentrations of the drugs to be tested rather than relying on arbitrary choices. The concentrations obtained, each of which corresponded to a fraction of the maximal effect, were tested alone and in combination with the bacterial strains in a broth medium. Synergy was defined as a ratio of observed effect/theoretical effect, called FME, of greater than 1, additivity was defined as an FME equal to 1, and antagonism was defined as an observed effect lower than the best effect of one of the antibiotics used alone. The area between antagonism and additivity is the indifference zone. The well-known synergy between amoxicillin and gentamicin against a reference strain of *Enterococcus faecalis* was confirmed, with a best FME equal to 1.07. Two strains of PRP, strains PRP-1 and PRP-2, were studied. The MICs for PRP-1 and PRP-2 were as follows: penicillin, 4 and 16 µg/ml, respectively; AMZ, 2 and 8 µg/ml, respectively; CRO, 1 and 4 µg/ml, respectively; and VAN, 0.5 and 0.25 µg/ml, respectively. For PRP-1 the best FME for the combination AMZ-CRO was 1.22 with drug concentrations of 1.68 mg/liter for AMZ and 0.17 mg/liter for CRO; the best FME for the combination VAN-CRO was 1.75 with VAN at 0.57 mg/liter and CRO at 0.17 mg/liter. For PRP-2 the best FME obtained for the combination AMZ-CRO was 1.05 with drug concentrations of 11.28 mg/liter for AMZ and 0.64 mg/liter for CRO; the best FME obtained for the combination VAN-CRO was 1.35 with VAN at 0.25 mg/liter and CRO at 1.49 mg/liter. These results demonstrated the synergy of both combinations, AMZ-CRO and VAN-CRO, against PRP strains at drug concentrations achievable in humans. Consequently, either of the combinations can be proposed for use for the treatment of PRP infections.

The emergence of strains of *Streptococcus pneumoniae* highly resistant to penicillin and cephalosporins (PRP strains) (5, 10) and, often, to other classes of antimicrobial agents (33) complicates empirical treatment of pneumococcal infections. Therefore, all potential modalities for the treatment of these infections must be considered (6). Ceftriaxone or vancomycin is often one of the drugs recommended for the treatment of severe infections due to PRP such as meningitis. However, a combination of amoxicillin and ceftriaxone could also be a candidate for the treatment of such infections.

In this context, our purpose was, first, to investigate the in vitro interaction between amoxicillin and ceftriaxone and between vancomycin and ceftriaxone against PRP and, second, to identify the range of concentrations that are of clinical interest.

The traditional methods used to test the in vitro interactions between drugs are not very satisfactory, with difficulties in the interpretation of the results (16). All these methods come from two original models: the Loewe additivity model (24), illustrated by isobolograms, and the Bliss independence model (4), illustrated by dose-effect curves. The checkerboard method,

with fractional inhibitory concentration indices and isobolograms, and the killing-curve method are used. Both methods have their advantages and drawbacks (7, 8, 32, 36, 37).

There is also a great disparity in the definitions used to characterize the interactions between drugs. For example, the limit value of fractional inhibitory concentration indices used to define antagonism varies from 1 to 8 according to previous studies. This disparity also appears in the duration of the times of killing, which can vary from 4 to 24 h and even longer (2).

The lack of standard definitions causes major problems, as it is impossible to compare the results of different studies.

Several investigators have looked further into the interpretation of the interactions between drugs (3) or the graphical representation of bacterial killing (34) or have proposed the use of the area under the curve (AUC) of bacterial killing as a criterion (1). Thus, additivity, synergy, antagonism, and autonomy or indifference have been defined (17, 21, 35).

Methods based on mathematical models have been used as a general approach to study the interactions between drugs (15). By these methods, the characterization of the dose-effect curve of each agent alone is critical; for this, the better-adapted structural model is the Hill model applied to a Michaelis-Menten curve.

According to these principles, the use of the AUC obtained

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from killing curves seems to be one of the better ways to evaluate in vitro the interactions of drugs used together in comparison with the theoretical AUC (26).

A further study has been carried out by using the fractional maximal effect (FME) method (23). The main characteristic of this method is that it tests calculated and not arbitrarily chosen concentrations of drugs. As a result, a maximal effect (E_{max}) can be determined for each drug.

The theoretical effect of the combination is calculated by adding the effects of each antibiotic used alone at the concentration tested in the combination. This theoretical effect is then compared with the effect obtained during the experiment.

The different interaction areas are defined as follows: additivity is an observed effect equal to the theoretical effect, and the ratio between them is equal to 1; synergy is an observed effect higher than the theoretical effect, and the ratio between them is more than 1; antagonism is an observed effect lower than the theoretical effect, and the ratio between them is less than 1.

For the graphical representation, Li et al. chose the isobologram method (23).

In the present study, we used the isobologram method with two modifications: first, as proposed previously (17, 35), we introduced indifference as a fourth zone of interaction; second, the graphical representation of the concentration-effect curve in two dimensions was preferred, as it allows a global illustration of the effects of each drug alone, drug-drug interactions, and theoretical addition.

MATERIALS AND METHODS

Drugs. Ceftriaxone was obtained from Roche (Nutley, N.J.), vancomycin was obtained from Lilly Laboratories (Indianapolis, Ind.), and amoxicillin was obtained from SmithKline Beecham (Brentford, United Kingdom). The drugs were reconstituted as recommended by the manufacturers.

Strains. Two strains of PRP (strains PRP-1 and PRP-2) isolated from a clinical specimen were used. The penicillin MICs for strains PRP-1 and PRP-2 were 4 and 16 mg/liter, respectively. Strains were identified by common tests and were stored at -70°C in brain heart infusion (BHI) with 15% glycerol. *Enterococcus faecalis* CIP 76117 was used as a reference strain and was provided by the Institut Pasteur (Paris, France).

In vitro testing. (i) MIC. MICs were determined by the agar dilution method described by the National Committee for Clinical Laboratory Standards (31).

(ii) Killing curves. The organisms were grown in BHI for 4 h at 37°C and were then adjusted by dilution in BHI to obtain a final inoculum of 5.5×10^6 organisms per ml. The antibiotics were diluted in BHI to obtain the different concentrations tested. To obtain a 1.9-ml final volume in 5-ml sterile hemolysis tubes, 0.1 ml of the bacterial inoculum was finally added to the tubes. They were then placed in an incubator at 37°C . A 100- μl volume was then removed; and cultures were performed after serial dilutions at 0, 3, 6, and 12 h for PRP strains and 24 h for *E. faecalis* on Mueller-Hinton agar plates supplemented with sheep blood at 37°C and in 5% CO_2 for *S. pneumoniae*. These counts were then expressed as log number of CFU per milliliter and were used to calculate the AUC by using the trapezoidal method.

This protocol was used with the concentrations of antibiotics in each tube required to achieve bactericidal activity, as well as with the antibiotics alone and in combination, to create the killing curves.

Criterion to achieve concentrations tested and calculations. We derived a method from the FME method of time-kill curves in which the concentrations of the drugs to be tested are calculated from the bactericidal activity curves and are chosen rather arbitrarily. The AUC was the criterion chosen to construct the bactericidal activity curves in triplicate for each antibiotic; the effect (E) is equal to the ratio $1/\text{AUC}$. A nonlinear regression (the formula used was $E = E_{max} \times C^n / (EC_{50}^n + C^n)$), performed with SPSS software (SPSS Inc., Chicago, Ill.), was applied to each curve (for each concentration C) to determine the following constants: E_{max} (maximal effect), EC_{50} (the concentration that produces one-half of the E_{max}), and n (Hill's coefficient).

The FME is defined by the ratio observed effect/theoretical effect.

Next, the two antibiotics (antibiotics A and B) are combined so that the sum of FME is always equal to 1. The following pairs were tested: $0.1\text{FME}_A + 0.9\text{FME}_B$, $0.3\text{FME}_A + 0.7\text{FME}_B$, $0.5\text{FME}_A + 0.5\text{FME}_B$, $0.7\text{FME}_A + 0.3\text{FME}_B$, and $0.9\text{FME}_A + 0.1\text{FME}_B$.

The corresponding concentrations (C) to be tested alone and in combination were calculated by using the appropriate formula: $C = (\text{FME} \times EC_{50}) / (1 - \text{FME})$.

Because the relation between the two antibiotics is not linear, the theoretical effect of the combination had to be calculated by using the following formula (M. Katzper, personal communication):

$$E_{A+B} = [(E_{maxA} \times C_A^n / EC_{50A}^n) + (E_{maxB} \times C_B^n / EC_{50B}^n)] / [1 + (C_A^n / EC_{50A}^n) + (C_B^n / EC_{50B}^n)]$$

These results (the FME for each test) were then plotted versus the concentrations (antibiotics alone and in combination). In this way, different areas of interaction were defined as follows: additivity was defined as an effect equal to the theoretical sum of the effects of each antibiotic tested alone and was expressed as an FME equal to 1; synergy was defined as an effect superior to additivity and was expressed as an FME of greater than 1; antagonism was defined as an observed effect lower than the best effect of an antibiotic used alone and was expressed as an FME lower than the best FME of the antibiotics tested alone; and the area between antagonism and additivity was the indifference zone and was expressed as an FME for the antibiotic combination between the FME values for antagonism and additivity.

These theoretical interactions are represented graphically in Fig. 1.

RESULTS

MIC. The MICs of the antibiotics tested are presented in Table 1. Both pneumococcal strains were resistant to penicillin, while PRP-2 was also resistant to ceftriaxone.

E. faecalis. Killing curve studies were done over 24 h in triplicate at multiples of the MICs of amoxicillin and gentamicin alone. The AUC was calculated for each concentration tested, and the effect was defined as the inverse of the AUC. The criteria for the nonlinear regression obtained from the killing curve studies of each antibiotic are shown in Table 2. Figure 2A illustrates the FME for each antibiotic concentration tested and the FMEs for the antibiotic combinations tested. Synergy was observed when the concentration of amoxicillin was above 0.3 mg/liter. Below this concentration, the effect of the combination was indifferent.

S. pneumoniae. For both PRP strains, the criteria for the nonlinear regression obtained from the killing curve studies with the range of antibiotic concentrations tested are shown in Table 2. The FMEs of each antibiotic tested alone and the FMEs of the different combinations are shown in Fig. 2B to E.

For strain PRP-1 and the combination amoxicillin-ceftriaxone, synergy was observed with a concentration of amoxicillin of 0.3 mg/liter and relatively low concentrations of ceftriaxone (Fig. 2B). For this strain and the combination of vancomycin and ceftriaxone, synergy was obtained with any concentration of each antibiotic (Fig. 2C).

For strain PRP-2, the combination amoxicillin-ceftriaxone was found to be synergistic for only one pair of concentrations. With the other pair of concentrations, the results were in the indifference area (Fig. 2D). A synergistic effect was obtained for the vancomycin-ceftriaxone combination, but it did not exist for the lowest concentration of ceftriaxone tested (Fig. 2E).

DISCUSSION

By the method used in the present study, we used the logarithmic transformation of CFU to construct AUCs. Previous

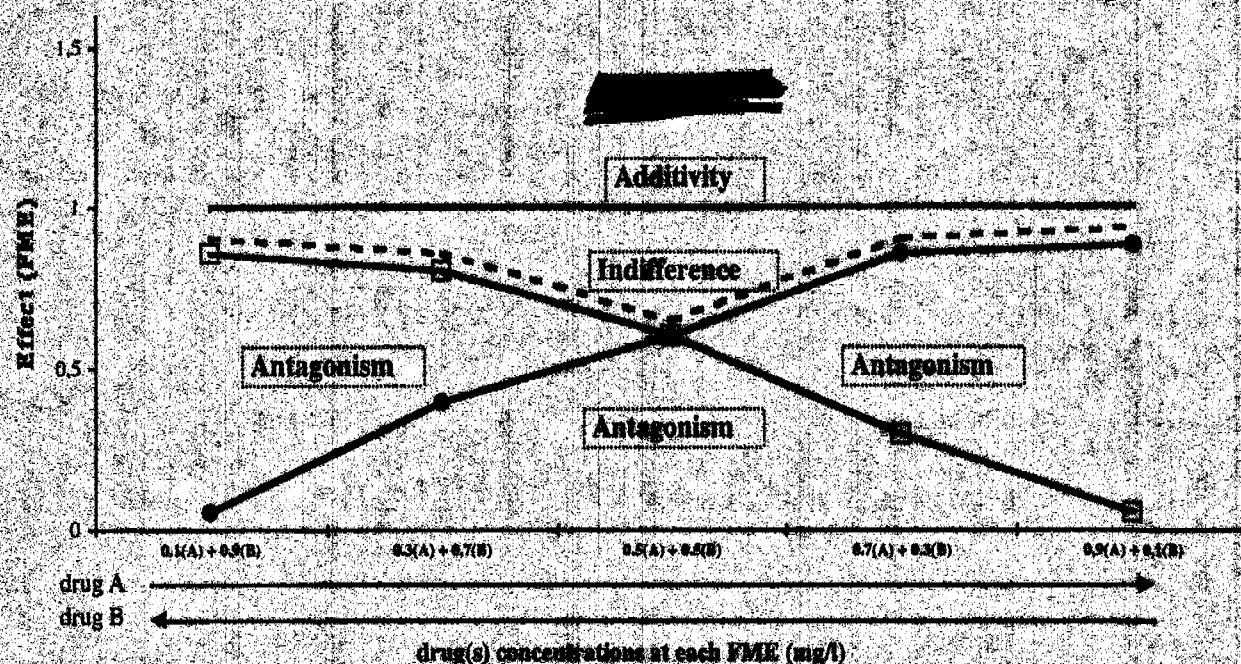


FIG. 1. Theoretical graphical representation of the different interactions between two antibiotics, antibiotics A and B. The y axis represents the FME of each antibiotic alone (A, B) and the antibiotic pair (A + B). The x axis represents the concentration of either antibiotic A (increasing concentrations from the left) or antibiotic B (increasing concentrations from the right). The concentrations tested are those corresponding to each fraction of maximal effect. $\square$, effect of antibiotic A; this effect is expressed as the FME of antibiotic A; $\bullet$, effect of antibiotic B; this effect is expressed as the FME of antibiotic B; $\cdots$, the best effect of either antibiotic A or B ("best alone" line); additivity line, theoretical addition of the effects of A and B; this sum is always equal to 1; Synergy, area of synergy above the additivity line; Indifference, indifference zone between the additivity line and the best alone line; antagonism, area of antagonism below the best alone line.

experiments were performed with the metric results of CFU (data not shown), which allows one to cope with very large variations in bacterial contents that range from 0 to 10^{11} but with no advantages for the graphical representation. Therefore, the method used to count the bacterial concentration in the present work is commonly used and is easier to perform. This logarithmic transformation of CFU probably minimizes the contrasts by smoothing the graphical representation and so leads to a more cautious interpretation.

Our findings demonstrated synergy for amoxicillin and gentamicin against *E. faecalis* (FME > 1) and thus confirmed conclusions drawn from previous studies performed by different methods (18, 19, 27, 30). The concentrations tested were very high for gentamicin because the MIC was also very high; therefore, high concentrations were needed to obtain the E_{max} . Despite this, synergy was observed at concentrations achievable in humans. More precisely, synergy appears when the amoxicillin concentration is at least at 0.29 mg/liter, which is about the MIC of this antibiotic for this strain. This is in

accordance with previous data (25), in which synergy was achieved if the penicillin concentration was at least equal to the MIC for the strain, even for very resistant bacteria. Taken together, these findings are in accordance with the known mechanism of the interaction between beta-lactams and aminoglycosides (29).

For penicillin-resistant (PRP-1) and broad-spectrum cephalosporin-resistant pneumococci (PRP-2), the effect obtained with both combinations (amoxicillin-ceftriaxone and vancomycin-ceftriaxone) was not constant with the concentrations tested because this method was very dynamic. However, in all cases there was always a section of the curve that was in the

TABLE 1. MICs for the strains tested

Strain	MIC (μ g/ml)			
	Amoxicillin	Ceftriaxone	Vancomycin	Gentamicin
<i>E. faecalis</i>	0.38	ND ^a	ND	12.00
PRP-1	2.00	1.00	0.50	ND
PRP-2	8.00	4.00	0.25	ND

^a ND, not determined.

TABLE 2. E_{max} concentrations that produce EC_{50} and Hill's coefficients deduced from in vitro killing curves^a

Strain	Antibiotic	E_{max}	EC_{50} (multiple of MIC)	Hill's coefficient	r^2
<i>E. faecalis</i>	Amoxicillin	0.018	0.76	0.96	0.87
	Gentamicin	0.032	4.5	0.88	0.97
PRP-1	Amoxicillin	0.030	0.36	1.29	0.49
	Ceftriaxone	0.027	0.39	0.61	0.53
	Vancomycin	0.038	0.49	1.83	0.74
PRP-2	Amoxicillin	0.060	1.41	1.11	0.7
	Ceftriaxone	0.026	0.16	0.57	0.58
	Vancomycin	0.072	2.33	0.63	0.74

^a See Materials and Methods.

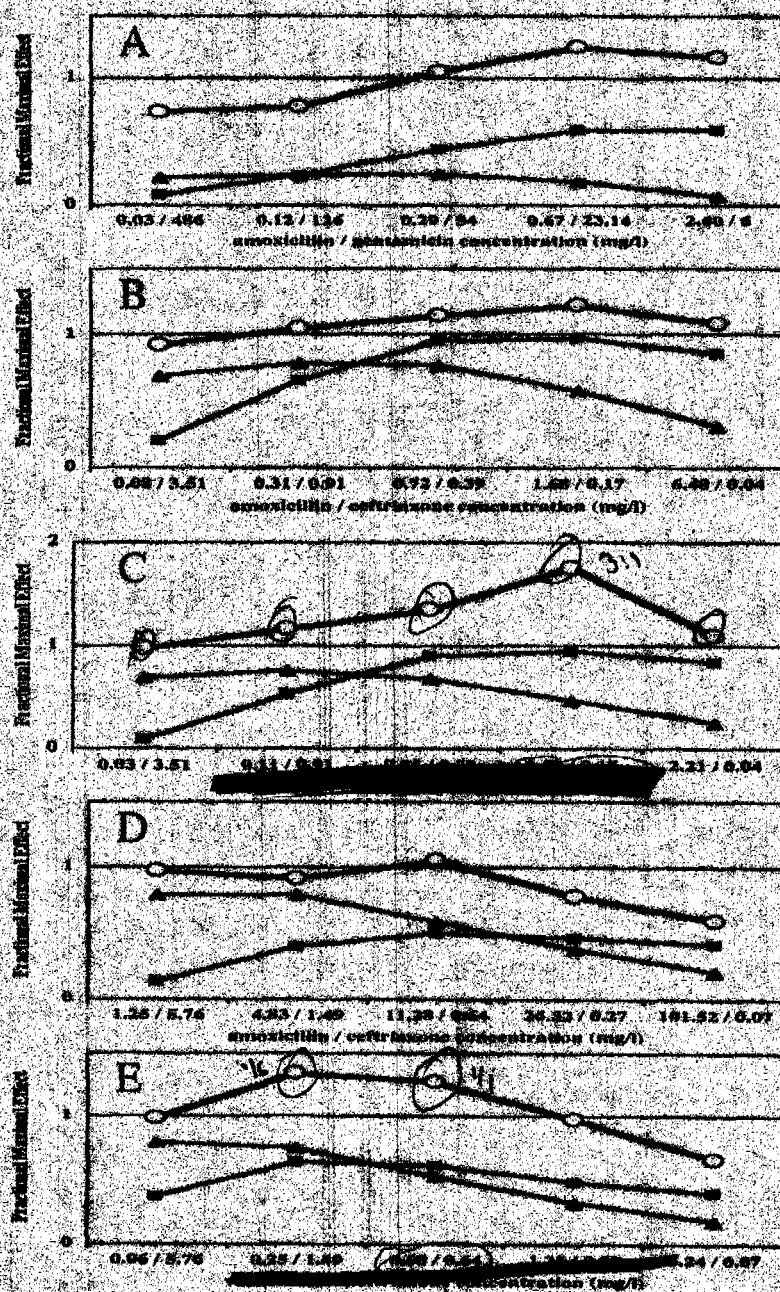


FIG. 2. In vitro FMEs of amoxicillin, gentamicin, ceftriaxone, and vancomycin against a reference strain of *E. faecalis* and two penicillin-resistant pneumococcal strains (strains PRP-1 and PRP-2). (A) FME of the combination (open circle), amoxicillin (increasing concentrations from the left; ■), or gentamicin (increasing concentration from the right; ▲) against *E. faecalis*. (B) FME of the combination (open circle), amoxicillin (increasing concentrations from the left; ■), or ceftriaxone (increasing concentration from the right; ▲) against strain PRP-1. (C) FME of the combination (open circle), vancomycin (increasing concentrations from the left; ■), or ceftriaxone (increasing concentration from the right; ▲) against strain PRP-1. (D) FME of the combination (open circle), amoxicillin (increasing concentrations from the left; ■), or ceftriaxone (increasing concentration from the right; ▲) against strain PRP-2. (E) FME of the combination (open circle), vancomycin (increasing concentrations from the left; ■), or ceftriaxone (increasing concentration from the right; ▲) against strain PRP-2.

area for synergism; the worst values were always in the indifference zone, and antagonism was never found.

A closer analysis reveals that the vancomycin-ceftriaxone combination seems to be slightly more effective than the amoxicillin-ceftriaxone combination, as it has higher FME values (the highest FMEs, 1.73 versus 1.21, respectively) and

more extensive areas of synergy (the part of the curve above the additivity line). For both combinations, the synergy seems to be greater for strain PRP-1, which is the least resistant strain, than for strain PRP-2, which is also reflected by higher FME values (the highest FMEs for the two strains were 1.73 and 1.34, respectively) and more extensive areas of synergy.

However, the results that we obtained with the amoxicillin-ceftriaxone combination are in accordance with those previously obtained with the same strains (9). In the previous study, we demonstrated by two different *in vitro* methods (the checkerboard method and classical time-kill curve studies) that this antibiotic combination has an improved antibacterial effect, but there were interpretation difficulties; this improvement was also observed in an *in vivo* model of pneumococcal infection. The method described here allows a simple interpretation of results; notably, it provides a clearly defined distinction between the different interaction areas and the range of concentrations of interest.

Our results are also concordant with those of other studies that used different *in vivo* or *in vitro* methods. When studying the interactions between a broad-spectrum cephalosporin and amoxicillin against 25 PRP strains, Johnson and Jones (20) have always observed favorable interactions: synergy, partial synergy, additivity, or indifference. Friedland et al. (13, 14) have shown at least an additive or a synergistic interaction between ceftriaxone and vancomycin against four PRP strains *in vivo* and *in vitro*. Marton and Major (28) have also demonstrated the superiority of the vancomycin-broad-spectrum cephalosporin combination over cephalosporins alone against two PRP strains. Other investigators (22) have studied the bacterial activities of drug combinations against cephalosporin-resistant *S. pneumoniae* in the cerebrospinal fluid (CSF) of children with acute bacterial meningitis. Their results showed that a combination of ceftriaxone and vancomycin or a combination of ceftriaxone and rifampin had higher levels of antibacterial activity in CSF than ceftriaxone alone.

Similarly, a French group (11) has shown that the cefotaxime-vancomycin combination was at least additive against a broad-spectrum cephalosporin-intermediate pneumococcal strain by measuring bactericidal activity in the CSF of children with acute bacterial meningitis. They also reported the results of *in vitro* studies of different drug combinations against PRP strains that had various levels of susceptibility to broad-spectrum cephalosporins. The activities of trovafloxacin-vancomycin and beta-lactam-vancomycin combinations were found to be additive or indifferent even against broad-spectrum cephalosporin-resistant strains (12).

Conclusion. The new method for the testing of drug-drug interactions described here permits a simple graphical representation of the interaction and then an approach that uses the range of concentrations of interest.

Our results confirm the results of previous *in vitro* and *in vivo* studies in which amoxicillin-ceftriaxone and vancomycin-ceftriaxone combinations appeared to be synergistic at some concentrations against penicillin- and/or broad-spectrum cephalosporin-resistant pneumococcal strains. Moreover, this synergy is present at drug concentrations achievable in humans. Therefore, the clinical interest in these combinations for the treatment of PRP infections seems to be confirmed.

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LYOPHILIZED PREPARATION OF VANCOMYCIN

CLAIMS

[Claim(s)]

[Claim 1] ~~Vancomycin lyophilized products containing a vancomycin, or its salt permitted pharmacologically and amino acid.~~

[Claim 2] ~~The pharmaceutical preparation according to claim 1 which is one sort or two sorts or more of mixtures in which amino acid is chosen from arginine, an alanine, aspartic acid, histidine, and a glycine.~~

[Claim 3] ~~The pharmaceutical preparation according to claim 1 or 2 characterized by amino acid being eight to 100 weight section to a vancomycin or its salt 100 weight section permitted pharmacologically.~~

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[The technical field to which invention belongs] This invention relates to the lyophilized products of the stable vancomycin in detail about the lyophilized products of a vancomycin.

[0002]

[Description of the Prior Art] A vancomycin is a glycopeptide system antibiotic of streptomyces cage ene TARISU (Streptomyces orientalis) origin, and is mainly effective in gram negative bacteria. In using a vancomycin as injections, the mineral acid salt is used as powder pharmaceutical preparation or lyophilized products, and before prescribing this for the patient, it dissolves and uses it in many cases. However, if the mothball of the mineral acid salt of a vancomycin is carried out, chemical splitting will advance and coloring and an antibacterial fall will take place. Therefore, the method of replacing conventionally the inside of the vial which encloses a vancomycin with inactive gas, such as nitrogen, or making storage temperature as low as possible, etc. were taken. The effect was not enough although stabilization was tried by blending sugar, sugar-alcohol, a water soluble polysaccharide, etc. at JP,3-193735,A.

[0003]

[Problem to be solved by the invention] ~~It waited eagerly for development of the good pharmaceutical preparation of the stability of a vancomycin from the above thing. The purpose of this invention controls the chemical splitting of a vancomycin, and there is in providing stable lyophilized products.~~

[0004]

[Means for solving problem] This invention persons looked for the compound which has an effect which controls the chemical splitting of a vancomycin. As a result, as a result of finding out that amino acid has a stabilization effect of a vancomycin also unexpectedly and examining it wholeheartedly, it came to complete this invention.

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[0005] That is, this invention consists of the following composition.

(1) Vancomycin lyophilized products containing a vancomycin, or its salt permitted pharmacologically and amino acid.

(2) Pharmaceutical preparation given in (1) which is one sort or two sorts or more of mixtures in which amino acid is chosen from arginine, an alanine, aspartic acid, histidine, and a glycine.

(3) Pharmaceutical preparation (1) or given in (2) characterized by amino acid being eight to 100 weight section to a vancomycin or its salt 100 weight section permitted pharmacologically.

[0006]

[Mode for carrying out the invention] The vancomycin used for this invention can be manufactured, for example by a method given in US, 3067099, B. The bulk drug of a commercial drugs grade can also be used. Since the free base of a vancomycin is refractory in water, after it changes the free base into water soluble salt, it is supplied as a bulk drug for injection undesirably as a bulk drug for injection as it is. Therefore, as a salt with which the vancomycin used for this invention is permitted pharmacologically, although water soluble salt, such as a hydrochloride and sulfate, is raised, a hydrochloride is especially preferred.

[0007] Arginine, an alanine, aspartic acid, histidine, and a glycine are raised, and the amino acid used in this invention has especially preferred arginine. These amino acid may be independent, or it may combine and it may be used. 16 or more weight sections of loadings of amino acid are eight or more weight sections usually 32 or more weight sections more preferably to vancomycin 100 weight section. Sufficient stabilization effect is not acquired as the loadings of amino acid are less than eight weight sections. Although a stabilization effect also increases according to the increase in the loadings of amino acid, stability sufficient by combination to 100 weight sections is obtained, and even if it blends more, increase of a stabilization effect is not accepted.

[0008] Various additives can also be added, in order to raise the solubility of lyophilized products, or in order to adjust pH and the osmotic pressure as injections. As long as these additives are the substance and an addition by which normal use is carried out as an additive of pharmaceutical preparation, there is no restriction in particular, for example, the following additives may be added if needed.

[0009] In order to raise the solubility of lyophilized products, or in order to gather a dissolution rate, A polyethylene glycol, glycerin, etc. as a surface-active agent as a solubilizing agent Polysorbate, Sorbitan sesquioleate, a polyoxyethylene polyoxypropylene glycol, Polyoxyethylene hydrogenated castor oil etc. are grape sugar, mannitol, xylitol, sorbitol, sucrose, etc. as a pH adjuster as chloride, phosphoric acid, citrate, malic acid, tartaric acid, succinic acid or those salts, and an osmotic adjustment agent.

[0010] As the method of preparation of the lyophilized products of this invention, various additives, such as a pH adjuster, are dissolved in an aqueous medium a vancomycin or its salt permitted pharmacologically, amino acid, and if needed, and it filtrates aseptically using a membrane filter etc. Next, a sterile solution is poured distributively on a vial, a tray, etc. and is prepared with the usual freeze drying method.

[0011] these lyophilized products -- business -- preparation at the time is able to ** as what is called simple kit pharmaceutical preparation for a drop by drop titration.

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Namely, the kit pharmaceutical preparation of the types (for example, JP,6-254136,A etc.) which combine the vial containing a freeze-drying constituent with a solution, and dissolve at the time of use, enclosing with the 1st room of a multi-chamber vessel that has a partition which can open a freeze-drying constituent for free passage, and enclosing a solution with the 2nd room -- business -- it is made sometimes open for free passage, and the kit pharmaceutical preparation etc. of the types (for example, JP,4-364851,A etc.) which dissolve and use this freeze-drying constituent are raised.

[0012]

[Working example] Although an embodiment is shown below and this invention is explained to it in detail, this invention is not limited to these.

[0013] 500 mg of L-arginine was dissolved as per 5 ml of embodiment 1 distilled water for injection, 500 mg of vancomycin hydrochloride, and a stabilizing agent, and 50 ml of liquid which added chloride and adjusted pH to four was prepared. This solution was filtrated aseptically with the membrane filter (0.22 micrometer), and it filled up the vial with a content volume of about 15 ml with 5 ml of solutions at a time. After cooling and freezing this to -40 ** in accordance with the usual freeze drying method and holding for 2 hours, under the vacuum of 100 or less mTorr, it dried at 10 more ** for 8 hours, the sealed tube of the vacuum was canceled and carried out with nitrogen gas, and it was considered as lyophilized products for -25 ** 15 hours-10 ** 12 hours.

[0014] 180 mg of L-arginine was dissolved as per 5 ml of embodiment 2 distilled water for injection, 500 mg of vancomycin hydrochloride, and a stabilizing agent, and 50 ml of liquid which added chloride and adjusted pH to four was prepared. This solution was filtrated aseptically with a membrane filter (0.22 micrometer), and it filled up a vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0015] 90 mg of L-arginine was dissolved as per 5 ml of embodiment 3 distilled water for injection, 500 mg of vancomycin hydrochloride, and a stabilizing agent, and 50 ml of liquid which added chloride and adjusted pH to four was prepared. This solution was filtrated aseptically with a membrane filter (0.22 micrometer), and it filled up a vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0016] 40 mg was dissolved for 90 mg of L-arginine, and polyethylene-glycol #400 as per 5 ml of embodiment 4 distilled water for injection, 500 mg of vancomycin hydrochloride, and a stabilizing agent, and 50 ml of liquid which added chloride and adjusted pH to four was prepared. This solution was filtrated aseptically with a membrane filter (0.22 micrometer), and it filled up a vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0017] 180 mg of L-arginine and 30 mg of glycerin were dissolved as per 5 ml of embodiment 5 distilled water for injection, 500 mg of vancomycin hydrochloride, and a stabilizing agent, and 50 ml of liquid which added chloride and adjusted pH to four was prepared. This solution was filtrated aseptically with the membrane filter (0.22 micrometer), and it filled up the vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0018] 180 mg of L-arginine and 100 mg of mannitol were dissolved as per 5 ml of

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embodiment 6 distilled water for injection, 500 mg of vancomycin hydrochloride, and a stabilizing agent, and 50 ml of liquid which added chloride and adjusted pH to four was prepared. This solution was filtrated aseptically with the membrane filter (0.22 micrometer), and it filled up the vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0019]Per 5 ml of embodiment 7 distilled water for injection, 500 mg of vancomycin hydrochloride, and 50 ml of solutions that 160 mg of L-alanine added as a stabilizing agent were prepared. This solution was filtrated aseptically with the membrane filter (0.22 micrometer), and it filled up the vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0020]Per 5 ml of embodiment 8 distilled water for injection, 500 mg of vancomycin hydrochloride, and 50 ml of solutions that 80 mg of L-alanine added as a stabilizing agent were prepared. This solution was filtrated aseptically with a membrane filter (0.22 micrometer), and it filled up a vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0021]50 ml of solutions which added 40 mg of L-alanine as per 5 ml of embodiment 9 distilled water for injection, 500 mg of vancomycin hydrochloride, and a stabilizing agent, and added polyethylene-glycol #400 [40-mg] as a solubilizing agent were prepared. This solution was filtrated aseptically with a membrane filter (0.22 micrometer), and it filled up a vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0022]Per 5 ml of embodiment 10 distilled water for injection, 500 mg of vancomycin hydrochloride, and 50 ml of solutions that 180 mg of L-arginine and 40 mg of L-alanine added as a stabilizing agent were prepared. This solution was filtrated aseptically with a membrane filter (0.22 micrometer), and it filled up a vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0023]Per 5 ml of embodiment 11 distilled water for injection, 500 mg of vancomycin hydrochloride, and 50 ml of solutions that 300 mg of L-histidine added as a stabilizing agent were prepared. This solution was filtrated aseptically with a membrane filter (0.22 micrometer), and it filled up a vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0024]Per 5 ml of embodiment 12 distilled water for injection, 500 mg of vancomycin hydrochloride, and 50 ml of solutions that 250 mg of glycines added as a stabilizing agent were prepared. This solution was filtrated aseptically with the membrane filter (0.22 micrometer), and it filled up the vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0025]50 ml of solutions which melted per 5 ml of example of contrast 1 distilled water for injection and 500 mg of vancomycin hydrochloride were prepared. This solution was filtrated aseptically with the membrane filter (0.22 micrometer), and it filled up the

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vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0026] Per 5 ml of example of contrast 2 distilled water for injection, 500 mg of vancomycin hydrochloride, and 50 ml of solutions that 100 mg of L-mannitol added as a stabilizing agent were prepared. This solution was filtrated aseptically with the membrane filter (0.22 micrometer), and it filled up the vial with a content volume of about 15 ml with 5 ml of solutions at a time. Lyophilized products were obtained for this by the same operation as Embodiment 1.

[0027] The lyophilized products and the examples 1 and 2 of contrast of this invention obtained in example embodiments 1-12 of an examination were saved for 10 and 20 or 30 days under a 60 ** acceleration condition, respectively. By the high-performance-chromatography (HPLC) method by the following conditions, the vancomycin B peak area ratio showing the purity of a vancomycin was calculated, and it was considered as the vancomycin B content (%).

[0028]

High voltage pump system : Shimadzu LC-10AT type . Detector : [Shimadzu SPD-10A type] Detection wave length : 280 nm Data processing equipment . : Shimadzu C-R7A type Column used : GL science Inertsil ODS-3 4.6x250 mm of 5 micrometer mobile phase presentation : A liquid; triethylamine buffer solution / acetonitrile / tetrahydrofuran ** Liquid (93:6:1)

B liquid; triethylamine buffer solution / acetonitrile / tetrahydrofuran ** Liquid (70:29:1)

Triethylamine buffer solution; 2000 ml of water is added to 4 ml of triethylamine. ***** is carried out and pH is adjusted to 3.2 using phosphoric acid.

Liquid sending of A liquid and B liquid is performed according to the program of the next table 1 by the gradient method.

[0029]

[Table 1]

	開始時	12分	20分	22分	23分	30分
移動相A	100%	100%	0%	0%	100%	100%
移動相B	0%	0%	100%	100%	0%	0%

[0030]

Flow : it is retention time by about 2-ml/. : Medium presentation of about 9-minute test liquid : Mobile phase A liquid Triethylamine buffer solution / acetonitrile / tetrahydrofuran mixture (93:6:1)

[0031] Next, the survival rate of the vancomycin B was searched for with the following formula. A result is shown in Table 2.

[Mathematical formula 1]

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$$\text{バンコマイシンBのピーク面積} \\ \text{バンコマイシンB含量 (\%)} = \frac{\text{バンコマイシンBのピーク面積}}{\text{全ピーク面積}} \times 100$$

$$\text{残存率 (\%)} = \frac{\text{経時後のバンコマイシンB含量 (\%)}}{\text{製造直後のバンコマイシンB含量 (\%)}} \times 100$$

(製造直後に対するバンコマイシンB残存率)

[0032]

[Table 2]

60℃保存におけるバンコマイシンB残存率 (%)

実施例	製造直後	10日	20日	30日
対照例1	100.0	95.1	92.5	90.5
対照例2	100.0	98.0	97.2	95.8
実施例1	100.0	100.0	99.4	99.4
実施例2	100.0	99.8	99.7	99.6
実施例3	100.0	98.8	98.1	97.8
実施例4	100.0	99.1	98.8	98.5
実施例5	100.0	99.8	99.4	99.3
実施例6	100.0	99.7	99.5	99.4
実施例7	100.0	99.9	99.2	98.8
実施例8	100.0	98.5	97.4	96.8
実施例9	100.0	98.2	97.2	97.5
実施例10	100.0	100.2	100.5	100.4
実施例11	100.0	99.9	100.4	100.2
実施例12	100.0	99.5	99.8	99.5

[0033]As compared with the pharmaceutical preparation which does not contain the example of contrast, i.e., stabilizer, and the pharmaceutical preparation which added conventional mannitol, it has checked that the pharmaceutical preparation which blended the amino acid of this invention had a remarkably high survival rate.

[0034]

[Effect of the Invention]According to this invention, ~~complicated combination and a preparing method can be unnecessary~~, the chemical splitting of a vancomycin can be controlled to the grade in which it could not succeed conventionally, and stable lyophilized products can be provided.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
JOSE LUIS REYES VILLAMIZAR

ASUNTO

Radicación 07-94220
Trámite 011
Evento 378
Actuación 411
Oficio **0 2780**
Folios 018

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/IN2006/000044
Fecha de Presentación Interna. 08/02/2006

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

1. Documentos estudiados

Descripción: Folios 4-26 como se radicó inicialmente
Reivindicaciones: Folios 36-41 como se radicó inicialmente
Prioridad: Folio 1 IN, 308/DEL/2005, 14-02-2005

2. Objeto de la invención

Título de la solicitud: TERAPIA DE COMBINACIÓN PARENTERAL PARA ENFERMEDADES INFECCIOSAS CAUSADAS POR UNA BACTERIA RESISTENTE A MEDICAMENTOS (folio 1).

El problema técnico planteado en esta solicitud está relacionado con la necesidad de proporcionar una composición farmacéutica de una mezcla de antibióticos en forma de polvo seco para reconstituir, que permita una solución reconstituida estable con reducción de la precipitación o material particulado, útil para administración parenteral (folio 11-12; pág. 8-9).

Para solucionar este problema técnico la solicitud en estudio ofrece una composición farmacéutica de antibióticos para inyección parenteral de una mezcla en polvo seco para reconstituir, que contiene a) por lo menos dos agentes antibacterianos en relación de 1:5 a 5:1 y b) un agente estabilizante/agente de compatibilidad; composición que puede ser reconstituida en un solvente farmacéuticamente adecuado como cloruro de sodio 0,9% estéril o dextrosa al 5% estéril.

El objeto de la solicitud se relaciona con la clasificación A61K31/545, A61K38/14, A61P31/04, de acuerdo con la Clasificación Internacional de Patentes (IPC).

3. De la solicitud de Patente

3.1 Reivindicaciones (artículo 30 D 486)

- Se solicita en las reivindicaciones 1-7, una composición farmacéutica de antibióticos para inyección parenteral de una mezcla en polvo seco para reconstituir, que contiene:

- a) por lo menos dos agentes antibacterianos en relación de 1:5 a 5:1
- b) un agente estabilizante/agente de compatibilidad
- c) un vehículo disolvente acuoso que contiene un agente estabilizante y un inhibidor de formación de partículas.

No obstante, se encuentra que existe falta de claridad, concisión y soporte en tal materia reclamada, puesto que:

- Términos imprecisos como "en combinación sinérgica, además, alrededor, preferiblemente, mas preferiblemente" no permiten dar un alcance definido a la materia reclamada; por tal razón, tales términos deben ser eliminados.
- Dado que la composición en polvo seco para reconstituir es un producto y el vehículo disolvente es otro producto diferente que se utiliza al momento de uso de la composición para reconstituirla, se aclara que el vehículo disolvente (c) no es un elemento que haga parte de la composición farmacéutica en polvo seco para reconstituir reclamada, por lo que debe eliminarse como un elemento de la misma. En consecuencia, se aclara que para la evaluación sólo se tendrán en cuenta los elementos a) y b) que conforman la composición en polvo seco para reconstituir reclamada.
- Las expresiones generales y ambiguas: "por lo menos dos agentes antibacteriales" y "un agente estabilizante/agente de compatibilidad", no son claras ni concisas y no permiten dar un alcance definido a la materia reclamada, puesto que no permiten definir cuántos y cuáles son los agentes antibacteriales y cuál es agente estabilizante o de compatibilidad en la composición; por ende, tales expresiones deben ser definidas de manera concreta y acorde con las composiciones específicas que ejemplifican y soportan la invención.

Asimismo, aunque se define como característica un rango de relación de 1:5 a 5:1 entre dos agentes antibacteriales, no existe soporte de composiciones específicas que permitan reconocer tal característica en la composición reclamada.

Del mismo modo, se señala que la amplia materia reclamada bajo la composición farmacéutica definida no tiene soporte en la descripción como una invención real (desarrollada); puesto que, sólo se señala una composición con ceftriaxona y vancomicina (tabla 2, folio 25; pág. 22) sin que además exista información de cuál es la relación y cantidad de estos antibacteriales, ni de cuál es el agente estabilizante utilizado en la misma.

- En la reivindicación 7 no es adecuada la caracterización de una composición farmacéutica por estar "envasa y sellada en un recipiente estéril, donde el recipiente es uno mas frasquitos,..."; puesto que una composición farmacéutica sólo debe caracterizarse por los elementos que la comprenden, como son agentes activos, excipientes y proporciones si es necesario.
- Se solicita en la reivindicación 9, un proceso para preparar un vehículo disolvente adecuado para la composición de la reivindicación 1.

Se aclara primero que, no existe soporte para el proceso de preparar un vehículo adecuado (con diversos excipientes) como se reclama, dado que en la única composición de antibióticos en polvo seco de ceftriaxona y vancomicina (tabla 2, folio 25; pág. 22) no se divulga cuál es el vehículo disolvente de reconstitución de la misma.

Además, acorde con la descripción, el vehículo disolvente adecuado puede ser cloruro de sodio 0,9% estéril o dextrosa al 5% estéril (disolventes que se preparan comúnmente en este campo; folios 17, pág. 14); por tanto, el vehículo disolvente y su proceso de preparación no es una característica esencial de la invención. De manera tal, que se recomienda eliminarlo de la materia reclamada.

Por lo anterior, el capítulo reivindicatorio no cumple con el requisito de tener claridad, concisión y sustento de acuerdo con las exigencias de los artículos 30 de la Decisión 486.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente es 14-02-2005, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a ésta.

Nº	Documento	Título	Fecha de Publicación
D1	Bibliografía 1	Fractional Maximal Effect Method for In Vitro Synergy between Amoxicillin and Ceftriaxone and between Vancomycin and Ceftriaxone against <i>Enterococcus faecalis</i> and Penicillin-Resistant <i>Streptococcus pneumoniae</i> .	12-2001
D2	JP11-080022	Lyophilized preparation of vancomycin	23-03-1999

Anterioridad D1 en folios 111-116 y D2 en folios 117-122.

Bibliografía 1: NORBERT DESBIOLLES; "Fractional Maximal Effect Method for In Vitro Synergy between Amoxicillin and Ceftriaxone and between Vancomycin and Ceftriaxone against *Enterococcus faecalis* and Penicillin-Resistant *Streptococcus pneumoniae*"; Antimicrobial Agents and Chemotherapy; vol. 4, No. 12; Dec. 2001; p. 3328-3333.

D1 se refiere a un estudio que revela efectos sinérgicos entre combinaciones de amoxicilina y ceftriaxona, así como entre vancomicina y ceftriaxona, contra cepas de *Streptococcus pneumoniae* altamente resistentes a penicilinas y cefalosporinas; siendo estas combinaciones útiles en el tratamiento de infecciones resistentes a penicilinas y cefalosporinas (folio 111; pág. 3328).

D2 se refiere a un producto farmacéutico inyectable de vancomicina estabilizada por medio de uno o mas aminoácidos seleccionados de arginina, alanina, histidina y glicina (folio 117; pág. 1).

5. Análisis de patentabilidad (artículo 14 D486)

5.1 Nivel inventivo (artículo 18 D486)

- Se solicita en las reivindicaciones 1-7, una composición farmacéutica de antibióticos para inyección parenteral de una mezcla en polvo seco para reconstituir, que contiene a) por lo menos dos agentes antibacterianos en relación de 1:5 a 5:1 y b) un agente estabilizante/agente de compatibilidad

SOLICITUD	D1	D2
Composición farmacéutica en polvo seco para reconstituir que contiene:	Combinación sinérgica entre composiciones farmacéutica de:	Composición farmacéutica para reconstituir estable de:
a) por lo menos dos agentes antibacterianos en relación de 1:5 a 5:1	SI dos agentes antibacterianos vancomicina y ceftriaxona (folio 111; pág. 3328)	NO vancomicina
b) un agente estabilizante/agente de compatibilidad	NO ---	SI agente estabilizante: uno o más aminoácidos seleccionados de arginina, alanina, histidina y glicina (folios 121; pág. 1)

El estado de la técnica más cercano es D1 que señala que ceftriaxona o vancomicina son frecuentemente uno de los fármacos recomendados para el tratamiento de infecciones severas, tal como meningitis, debidas a cepas de *Streptococcus pneumoniae* altamente resistentes a penicilinas y cefalosporinas; y que divulga un efecto sinérgico con la combinación de vancomicina y ceftriaxona, la cual puede ser utilizada para el tratamiento de tales infecciones (folio 111; pág. 3328).

La solicitud se diferencia de D1 en que señala específicamente un agente estabilizante (seleccionado de arginina, lisina y histidina, según reivindicación 4) en una composición en polvo para reconstituir que contiene vancomicina y ceftriaxona.

Y el efecto técnico que logra tal diferencia, es que al reconstituirse tal composición en polvo se logra una reducida formación de partículas en la solución, haciéndola estable luego de la reconstitución (folio 16, 20; pág. 13, 17).

De forma que, el problema técnico objetivo de la solicitud es cómo lograr una composición estable en solución de una composición en polvo para reconstituir que contenga vancomicina y ceftriaxona.

Sin embargo, se encuentra que D2 enseña que uno o más aminoácidos seleccionados de arginina, alanina, histidina y glicina son adecuados para estabilizar soluciones inyectables de vancomicina (folios 121; pág. 1).

Por consiguiente, para un experto en la materia teniendo en cuenta la información divulgada por D1 (combinación de vancomicina y ceftriaxona) y D2 (uno o más aminoácidos seleccionados de arginina, alanina, histidina y glicina para estabilizar soluciones inyectables de vancomicina), la composición reivindicada no tiene nivel inventivo.

- Se solicita un proceso de preparar la composición en polvo seco para reconstituir de la reivindicación 1, que consiste en envasar/mezclar estérilmente los antibióticos con el agente estabilizante, continuar el envasado mezcla por 1 a 4 horas, distribuir en porciones el envasado/mezcla estéril y sellar escépticamente con pre-pos gasificación con gas inerte.

No obstante, dado que D1 divulga una combinación de antibióticos (vancomicina y ceftriaxona) y D2 divulga agentes estabilizantes (uno o más aminoácidos seleccionados de arginina, alanina, histidina y glicina) para estabilizar composiciones de vancomicina.

Y teniendo en cuenta que para un experto en la materia, son comúnmente conocidos los pasos de envasar/mezclar estérilmente agentes activos y excipientes (como un agente estabilizante), continuar tal operación por un tiempo dado (dependiente del tamaño del lote a preparar), envasar la mezcla estéril en porciones dadas y sellar escépticamente con gasificación de un gas inerte, para obtener una composición farmacéutica, envasada, en polvo seco de agentes activos con excipientes farmacéuticamente aceptables; el proceso reclamado no tiene nivel inventivo.

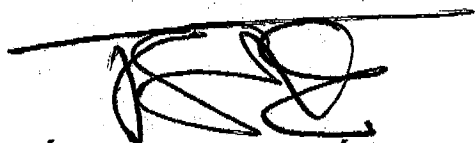
6. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones Afectadas	Requisito que Afecta
D1	Bibliografía 1	1-9	Nivel inventivo
D2	JP11-080022	1-9	Nivel inventivo

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

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
19 FEB. 2011

CONCEPTO TECNICO No. 239	EXAMINADOR TECNICO Código No. 202079
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