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Fecha: 2007-10-12 14:57:17 Dep. 2020 NUECREACIONES
Tra. 11 PATENTE Y Lve. 379 PASL NACIONAL
Act. 538 PLIICION Folios: 2

Señores.

Superintendencia de Industria y Comercio

División de Nuevas Creaciones

E. S. D.

Ref: Expediente No. 05059213

Solicitud de Patente de Invención – Capítulo I PCT
denominada **COMPOSICIONES FARMACÉUTICAS
MEJORADAS DE TOXINA BOTULINICA**

**Solicitante: BOTULINUM TOXIN RESEARCH
ASSOCIATES, INC.**

Darío Cárdenas Navas, identificado como aparece al pie de mi firma y obrando en mi condición de apoderado de la sociedad **BOTULINUM TOXIN RESEARCH ASSOCIATES, INC.** solicitante de la patente de invención mencionada en la referencia, solicito al Despacho se sirva proceder con el examen de patentabilidad de esta patente.

Para tal fin adjunto el Recibo oficial No 07-82,440.

Atentamente,

Darío Cardenas Navas
C.C 17.066.629 de Bogotá
T.P. 1.250 C.S.J. *CH*
Fol No P-334

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-059213- -00005-0000

Fecha: 2007-10-12 14:57:17 Dep. 2020 NUECREACIONE
Pag. 11 PATENTEIYII Eje. 379 FASENACIONALI
Act. 508 RELICION Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 82,440
FECHA : OCTUBRE 8 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARDENAS Y CARDENAS P.I.	CONSIGNACION	BANCO POPULAR	050-00110-6	59809106	08/10/2007	6,946,200.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		B5 EXAMEN DE PATENTABILIDAD DE INVEN	404,000.00
		TOTAL :	\$ 404,000.00

SON: CUATROCIENTOS CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

7

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-59213

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **576** DE

FECHA **31 DE MAYO DE 2007** EL TERMINO HABIL SEÑALADO POR LA LEY

EXPIRA EL **31 DE AGOSTO DE 2007**

NOTA: Dentro del plazo de los tres (3) 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 y en concordancia con el artículo 85 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _ _ _ _ _

NO **_ X _** _ _ _



US005512547A

United States Patent [19][11] **Patent Number:** **5,512,547****Johnson et al.**[45] **Date of Patent:** **Apr. 30, 1996**

[54] **PHARMACEUTICAL COMPOSITION OF
BOTULINUM NEUROTOXIN AND METHOD
OF PREPARATION**

[75] Inventors: **Eric A. Johnson; Michael C.
Goodnough**, both of Madison, Wis.

[73] Assignee: **Wisconsin Alumni Research
Foundation**, Madison, Wis.

[21] Appl. No.: **322,624**

[22] Filed: **Oct. 13, 1994**

[51] Int. Cl.⁶ **A61K 38/00; C07K 1/00**

[52] U.S. Cl. **514/21; 514/2; 530/350;
530/363; 530/364; 530/825**

[58] Field of Search **514/21.2; 530/350,
530/363, 364, 825**

[56] **References Cited
PUBLICATIONS**

Goodnough et al, *Applied and Environmental Microbiology*,
vol. 58, No. 10, pp. 3426-3428, Oct. 1992.
Schantz, E. J. and Scott, A. B., *Biomedical Aspects of*

Botulism, Academic Press, Inc., pp.143-150 (1981).

Schantz, E. J., and Kautter, D. A., *Journal of the Association
of Official Analytical Chemists*, vol. 61, pp. 96-99 (1978).

Melling et al., "Clostridium Botulinum Toxins: Nature and
Preparation for Clinical Use." *Eye*, vol. 2, 1988, pp.-16-23.

Hambleton et al. "Production, Purification and Toxoiding of
Clostridium Botulinum Type A Toxin", *Biomedical Aspects
of Botulism*, Academic Press, Inc., (1981) pp. 247-260.

Primary Examiner—Christina Y. Chan

Assistant Examiner—Abdel A. Mohamed

Attorney, Agent, or Firm—Quarles & Brady

[57] **ABSTRACT**

Pharmaceutical compositions of botulinum neurotoxin con-
taining higher specific toxicity and increased stability at
higher temperatures than currently available preparations.

3 Claims, No Drawings

PHARMACEUTICAL COMPOSITION OF BOTULINUM NEUROTOXIN AND METHOD OF PREPARATION

FIELD OF THE INVENTION

The present invention relates to botulinum toxin. More particularly, it relates to novel pharmaceutical compositions containing botulinum toxin and a method for preparing the compositions.

BACKGROUND OF THE INVENTION

The most serious form of bacterial food poisoning is botulism which is caused by neurotoxins produced by *Clostridium botulinum*. The toxins are usually preformed by the causative organism in foods and subsequently absorbed through the intestinal tract and transported via the circulatory system to motor nerve synapses where their action blocks normal neural transmissions. Various serotypes of *C. botulinum* produce neurotoxins with similar toxic activity but which differ antigenically. Serotype A toxin is the predominant cause of botulism in the United States while type B toxin is the most prevalent in Europe.

Crystalline type A botulinum toxin complex was prepared in 1979 by E. J. Schantz of the Food Research Institute/ Department of Food Microbiology and Toxicology at the University of Wisconsin-Madison. It has been used medically to treat hyperactive muscle disorders such as strabismus, blepharospasm, and spasmodic torticollis. Treatment involves injection of nanogram quantities of the toxin directly into the hyperactive muscles. The toxin inhibits the release of acetylcholine across the synaptic junction causing a decrease in the activity of the injected muscles.

Type A neurotoxin produced by *C. botulinum* is present as part of a complex of at least seven different noncovalently bound proteins. High quality type A toxin complex has a specific toxicity of 3×10^7 mouse intraperitoneal 50% lethal doses (LD_{50}) per mg. The purified neurotoxin, that is the neurotoxin that has been chromatographically separated from the other proteins of the toxin complex, has a specific toxicity of 9×10^7 to 1×10^8 LD_{50} per mg. In the medical field, a unit (U) is considered to be 1 LD_{50} . Toxin titers are determined in female, white mice, 18-22g in weight according to the method of Schantz and Kautter as described in Association of Official and Analytical Chemistry, vol. 61, p. 96, (1978).

A major drawback to the use of botulinum toxin in treatment of hyperactive muscle disorders is development of antibodies or other types of immunity by patients. The toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective. One way to reduce the number of patients developing neutralizing antibodies would be to develop a more shelf-stable product with a higher specific activity following lyophilization. Such a formulation would result in a product that is not as antigenic as the currently available product and lesser quantities of toxin would be required for treatment.

Botulinal toxin is very susceptible to denaturation due to surface denaturation, heat, and alkaline conditions. Lyophilization or freeze-drying of botulinal toxin is the most economically sound and practical method of distributing the product in a form that is stable and readily used by the clinician. The current commercial type A botulinal toxin

product is made by combining up to 500 ng/ml of type A toxin complex in 5.0 mg/ml human serum albumin (HSA) with 9.0 mg/ml sodium chloride at a pH of 7.3. After dissolution, 0.1 ml is dried to obtain 100 ± 30 active U of toxin, 0.5 mg of HSA, and 0.9 mg of sodium chloride per vial. This product has a saline concentration of 0.9% when reconstituted in 1.0 ml of dH_2O . The current commercial formulation which employs the toxin complex has a specific toxicity of about 2.5 U/ng after drying BOTOX®, crystalline botulinum toxin complex, Allergon, Inc. of Irvine, Calif. The considerable loss (up to 90%) of activity during drying causes the formation of inactive toxin that serves as a toxoid inciting antibody formation.

A rabbit model in which repetitive injections of various type A toxin preparations have been given to simulate the treatment of a focal dystonia has been used to assess the immunogenicity of various toxin preparations. The model consists of injecting albino rabbits with sublethal doses of the toxin over a period of time and assaying the serum of the animals for the ability to neutralize a small but carefully quantitated amount of purified type A toxin. Our results show that the product presently available in the United States which has the lowest specific toxicity of all preparations tested is the most antigenic of all the preparations tested to date. These results indicate that high specific activity preparations reduce the probability of patients developing neutralizing antibodies. It obviously would be desirable to have higher specific activity preparations than those currently available.

The current commercial product must be stored at a temperature of -10° C. or less to maintain the labelled potency for the one year shelf life. It also would be advantageous to have a product that could be stored at higher temperatures (i.e. room temperature). This would facilitate more practical shipping and storage of the toxin.

BRIEF SUMMARY OF THE INVENTION

We have discovered that pharmaceutical compositions made from a liquid formulation containing essentially pure botulinum type A neurotoxin, human serum albumin (HSA), and trehalose provides for the improved recovery of active toxin following lyophilization (>80%). The use of the pure neurotoxin instead of the toxin complex, which is used commercially, reduces the amount of toxin required to obtain the necessary number of active U per vial as mandated by the U.S. Food and Drug Administration. This improvement also reduces the amount of inactive toxin (toxoid) in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients.

We also have discovered that the compositions obtained by adding trehalose to the pre-lyophilization formula increases the glass transition temperature of the dried material and thereby increases the usable storage temperature. The addition of the trehalose surprisingly enhances the temperature stability of the dried toxin and lessens both the risk of loss in potency with corresponding degradation during storage and shipment with a consequent increase in antigenic potential due to temperature abuse. In addition to trehalose, we have discovered that the polyhydroxy compound maltotriose and possibly other polyols can be used.

DESCRIPTION OF PREFERRED EMBODIMENT

The preferred pharmaceutical compositions of the present invention have the following composition:

TABLE 1-continued

Effect of excipients on recovery of toxicity of <i>Clostridium botulinum</i> type A toxin complex after lyophilization of 0.1 ml of each solution.			
Excipients	Starting Toxin concentration ^a	pH	% recovery ^b
human serum albumin ^c	100, 1,000	6.4-6.8	>90, >90
alpha-lactalbumin ^d	1,800	6.1	>78
lysozyme ^e	1,800	5.3	>78
gelatin ^f	1,800	6.3	>78
bovine serum albumin/trehalose ^g	500	5.7	>90
bovine serum albumin/sucrose ^h	325	6.6	65
bovine serum albumin/maltotriose ⁱ	250	7.0	>80

^aType A mouse lethal doses/vial before lyophilization;

^b% recovery = (number mouse lethal doses after lyophilization/number mouse lethal doses prior to lyophilization) × 100;

^c50 mM sodium phosphate;

^dbovine serum albumin (5.0 mg/ml), sodium chloride (9.0 mg/ml);

^ebovine serum albumin (9.0 mg/ml);

^fbovine serum albumin (9.0 mg/ml), 50 mM sodium citrate;

^gbovine serum albumin (9.0 mg/ml), 50 mM sodium phosphate;

^hbovine serum albumin (9.0 mg/ml), 50 mM potassium phosphate;

ⁱhuman serum albumin (9.0 mg/ml);

^jconcentration = 9.0 mg/ml;

^k9.0 mg/ml bovine serum albumin, 100 mg/ml trehalose;

^l9.0 mg/ml bovine serum albumin, 250 mg/ml sucrose;

^m9.0 mg/ml bovine serum albumin, 100 mg/ml maltotriose. (adapted from Goodnough and Johnson, 1992).

TABLE 2

Recovery of activity following lyophilization of purified <i>Clostridium botulinum</i> type A neurotoxin.			
Excipient combination	Starting Toxin concentration ^b	pH	% recovery ^c
bovine serum albumin	200	6.4	90
human serum albumin	1,000	6.4	90
bovine serum albumin, trehalose	500	5.7	>90
bovine serum albumin, sucrose	325	6.6	50
bovine serum albumin, maltotriose	250	7.0	>80

^abovine and human serum albumin concentration was 9.0 mg/ml, carbohydrate concentration was 100 mg/ml in all cases except sucrose which was 250 mg/ml;

^bmouse intraperitoneal lethal doses/vial;

^c(number of mouse lethal doses/vial after lyophilization, number of mouse lethal doses before lyophilization) × 100.

It was found that the formulations used for lyophilization had a marked effect on the recovery of toxin. The most critical factor was the absence of sodium chloride in the solution in combination with a pH less than 7.0. In the best cases, recovery of active toxin was >90% following lyophilization.

The addition of trehalose in particular, allowed the recovery of active type A neurotoxin following lyophilization and storage at temperatures in excess of those required for storage of the commercially available type A toxin complex (37° C. versus -10° C.).

The antigenicity of various toxin preparations (containing low or high specific toxicities) was evaluated in rabbits by repetitive injection of sublethal doses of toxin simulating treatment of a focal dystonia with botulinum toxin. The samples were standardized to contain the same number of active lethal doses in order that the immune response from the rabbits could be compared. The samples with the highest specific activity were those consisting of purified type A neurotoxin (96 U/ng) while the lowest were the commercially available BOTOX®, crystalline botulinum toxin complex, samples (4.3 U/ng).

Total toxin concentration for each preparation (i.e. both active and inactive) was determined using an enzyme-linked immunosorbent assay (ELISA) specific for type A botulinum toxin. The ELISA assays performed on BOTOX®, crystalline botulinum toxin complex, and ASB indicated that BOTOX®, crystalline botulinum toxin complex, had an average specific toxicity of 4.3 U/ng and ASB had an average specific toxicity of 17.3 U/ng after reconstitution. Type A toxin complex used in these assays had a specific activity of 18 U/ng.

Serum samples were drawn on the days shown in Table 3 and titrated for the ability to neutralize 5.6 U of essentially pure type A neurotoxin. Total toxin concentration (active+inactive) in each preparation was determined by ELISA following reconstitution except in the cases of A neurotoxin and A complex which were not lyophilized.

(19) World Intellectual Property Organization
International Bureau



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47/36, 47/42, 47/22

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(22) International Filing Date: 5 February 2001 (05.02.2001)

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(72) Inventor; and

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(74) Agents: **DONOVAN, Stephen et al.**; Allergan Sales, Inc.,
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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, 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,
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(84) Designated States (*regional*): ARIPO patent (GH, GM,
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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, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report

*For two letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: **BOTULINUM TOXIN PHARMACEUTICAL COMPOSITIONS**

(57) Abstract: A botulinum toxin pharmaceutical composition free of blood derived albumin, comprising a botulinum toxin, sodium chloride or water and a polysaccharide such as a hydroxyethyl starch and/or an amino acid, the pharmaceutical composition being suitable for therapeutic administration to a human patient. Alternately, the polysaccharide and amino acid can be replaced by recombinant albumin.

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Botulinum toxin type A is the most lethal natural biological agent known to man. About 50 picograms of botulinum toxin (purified neurotoxin complex) type A is a LD₅₀ in mice. Interestingly, on a molar basis, botulinum toxin type A is 1.8 billion times more lethal than diphtheria, 600 million times more lethal than sodium cyanide, 30 million times more lethal than cobrotoxin and 12 million times more lethal than cholera. Singh, *Critical Aspects of Bacterial Protein Toxins*, pages 63-84 (chapter 4) of *Natural Toxins II*, edited by B.R. Singh et al., Plenum Press, New York (1976) (where the stated LD₅₀ of botulinum toxin type A of 0.3 ng equals 1 U is corrected for the fact that about 0.05 ng of BOTOX® equals 1 unit). One unit (U) of botulinum toxin is defined as the LD₅₀ upon intraperitoneal injection into female Swiss Webster mice weighing 18-20 grams each. Seven immunologically distinct botulinum neurotoxins have been characterized, these being respectively botulinum neurotoxin serotypes A, B, C₁, D, E, F and G each of which is distinguished by neutralization with type-specific antibodies. The different serotypes of botulinum toxin vary in the animal species that they affect and in the severity and duration of the paralysis they evoke. For example, it has been determined that botulinum toxin type A is 500 times more potent, as measured by the rate of paralysis produced in the rat, than is botulinum toxin type B. Additionally, botulinum toxin type B has been determined to be non-toxic in primates at a dose of 480 U/kg which is about 12 times the primate LD₅₀ for botulinum toxin type A. The botulinum toxins apparently bind with high affinity to cholinergic motor neurons, are translocated into the neuron and block the presynaptic release of acetylcholine.

Botulinum toxins have been used in clinical settings for the treatment of neuromuscular disorders characterized by hyperactive skeletal muscles. Botulinum toxin type A was approved by the U.S. Food and Drug Administration in 1989 for the treatment of essential blepharospasm, strabismus and hemifacial spasm in patients over the

(such as glucose or a polymer of glucose) or carbohydrates because proteins and glucose are known to interact together and to undergo the well-described Maillard reaction, due, i.e. to the reducing nature of glucose and glucose polymers. Much work has been dedicated to mostly unsuccessful attempts at preventing this protein-saccharide reaction by, for example, reduction of moisture or use of non-reducing sugars. Significantly, the degradative pathway of the Maillard reaction can result in a therapeutic insufficiency of the protein active ingredient. A pharmaceutical formulation comprising protein and a reducing saccharide, carbohydrate or sugar, such as a glucose polymer, is therefore inherently unstable and cannot be stored for a long period of time without significant loss of the active ingredient protein's desired biological activity.

Notably, one of the reasons human serum albumin can function effectively as a stabilizer of a protein active ingredient in a pharmaceutical composition is because, albumin, being a protein, does not undergo the Maillard reaction with the protein active ingredient in a pharmaceutical composition. Hence, one would expect to find and to look for a substitute for albumin amongst other proteins.

Finding an appropriate substitute for albumin as a stabilizer of the botulinum toxin present in a pharmaceutical composition is difficult and problematic because albumin is believed to function in a pharmaceutical composition as more than a mere bulking agent. Thus, albumin apparently can interact with botulinum toxin so as to increase the potency of the neurotoxin. For example, it is known that bovine serum albumin can act as more than a mere stabilizing excipient for botulinum toxin type A, since bovine serum albumin apparently also accelerates the rate of catalysis of synthetic peptide substrates, which substrates resemble the SNAP-25 intraneuronal substrate for botulinum toxin type A Schmidt, et al., *Endoproteinase Activity of Type A Botulinum Neurotoxin Substrate Requirements and Activation by*

As noted, hydroxyethyl starch, can participate to at least some extent, in Maillard reactions. Thus, and as set forth above, a polysaccharide alone may not be sufficient to provide optimal stabilization of the toxin. Thus, I discovered the advantages of inclusion of an amino acid to act as a competitive inhibitor. Without wishing to be bound by theory, the hypothesis is that by providing another amine source, in high concentrations compared to the toxin, the probability of the Maillard reaction occurring with the toxin is reduced, thereby stabilizing the toxin. Any amino acid can be used however lysine being highly reactive and is a preferred amino acid.

My invention also encompasses addition of a zinc ion source to a botulinum toxin containing pharmaceutical formulation. Metals, especially divalent cations, are reported to greatly influence the success of a freeze-dried formulation due to various cryo-properties including the lattice structures of formed ices. Extraneous metals such as copper and iron species lend themselves to radical oxidations and are generally to be avoided. More specifically Botulinum Type-A toxin is dependent upon bound zinc for activity. Many of the proposed excipients or reaction products of the excipients will chelate metals. This could lead to formation of unstable ices and/or inactivated toxin. By supplying ample zinc in the formulation the presence of desirable divalent cations is assured, the likelihood of zinc loss by the toxin is reduced, and stability enhanced. This can be accomplished by the addition of $ZnSO_4$ to a botulinum toxin pharmaceutical composition.

Is it known to make recombinant human serum albumin (rHSA) production using an expression strain of the methylotrophic yeast *Pichia pastoris* with high productivity. Botulinum toxin containing pharmaceutical formulations can be prepared containing stabilizing rHSA. rHSA expressed by genetically altered yeast host cells, while having the same primary amino acid sequence, differ in other respects from plasma derived HSA. Thus, while eukaryotic, yeast, lacking many

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
DARÍO CARDENAS NAVAS

ASUNTO	Radicación	05-59213
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	Nº 1 5 0 1 8
	Folios	12

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/IB2003/006145
Fecha de Presentación Internal. 22-12-2003

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

- 1.1. Descripción: Folios: 38 a 65 (como se radicó inicialmente)
- 1.2. Reivindicaciones: Folios 66 a 73 (como se radicó inicialmente)
- 1.3. Prioridad: Folio: 1
Fecha: 20-12-2002; país y número: US60/435,901.

2. Objeto de la invención

Título de la solicitud: "COMPOSICIONES FARMACÉTICAS MEJORADAS DE TOXINA BOTULÍNICA"

El objeto de la presente solicitud de patente de invención consiste en una composición que comprende toxina botulínica y un agente secuestrante.

Reivindicaciones 1– 32 y 59-60: Una composición de toxina botulínica.
Reivindicaciones 33-55: Un método de denervación localizada en un individuo.
Reivindicaciones 56-58 Un método para producir la composición.

El problema planteado en esta solicitud es la necesidad de composiciones de toxina botulínica que mejoren la efectividad clínica y reduzcan los efectos colaterales debidos a la difusión de la toxina.

Para solucionar este problema técnico la solicitud en estudio proporciona una composición que contiene toxina botulínica y un agente secuestrante como la albúmina.

La invención se catalogó según la Clasificación Internacional de Patentes (IPC.) como: A61K 38/00, A61K 38/16.

3. De la solicitud de Patente

3.1. Descripción (artículo 28 D. 486)

La solicitud presenta los ejemplos 1 a 9, en los cuales se divulga la utilidad de la combinación de albúmina y toxina tipo A o B para el tratamiento de blefaroespasma esencial y crónico y del espasmo hemi-facial, utilizando albúmina en 12750µg a 25500µg. Por lo tanto, no es posible para el experto en la materia establecer la ventaja de utilizar composiciones en las cuales el contenido de albúmina sea superior a las cantidades presentadas en los ejemplos, y si estas mezclas también son ventajosas al utilizar otros subtipos de toxina botulínica ya que la solicitud sólo presenta ejemplos con el subtipo A y B y tampoco evalúa el uso de proteínas quiméricas.

La descripción no cumple con el requisito de divulgación completa lo que haría difícil su comprensión y ejecución de acuerdo al art. 28 de la Decisión 486 o art. 22 del Tratado PCT.)

3.2. Reivindicaciones (artículo 30 D 486)

El término “agente secuestrante”, es ambiguo y da lugar a un indeterminado número de composiciones diferentes que no se encuentran soportadas en la descripción.

Las composiciones reclamadas en las reivindicaciones 1, 7, 15 y 59 carecen de soporte suficiente por la descripción debido a que los ejemplos presentados solo enseñan combinaciones de toxina tipo A y B con albúmina en una cantidad que va de 2750µg a 25500µg. Por lo tanto no es claro a partir de la información contenida en la descripción cuál es la ventaja de utilizar mayores cantidades de albúmina como las reclamadas y si el resultado es igual con otros subtipos de neurotoxina.

Las reivindicaciones 11 y 12 establecen que se utiliza una mezcla híbrido, formas traslocadas y formas quiméricas de toxina botulínica. La solicitud no discute la

estructura de estas cadenas ni la preparación de composiciones o bioensayos con cadenas modificadas de la proteína o formas quiméricas como las aquí reclamadas.

Las reivindicaciones 13 y 17 caracterizan una composición por un resultado a alcanzar como lo es la actividad específica y el tipo de enlace que se produce entre la toxina y el agente secuestrante.

La expresión “uno o mas agentes secuestrantes adicionales”, de la reivindicación 28, le resta concisión a la solicitud. Adicionalmente el soporte descriptivo es insuficiente para el número de mezclas que pueden generarse a partir de esta definición.

Las reivindicaciones 57 y 58 establecen métodos para obtener las composiciones que comprenden secar por congelación o flash la mezcla o la liofilización de la mezcla. Sin embargo ninguno de los ejemplos 10 a 13 establece la preparación de la mezcla mediante alguno de los procesos reclamados.

Las reivindicaciones mencionadas no cumplen con el requisito de concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. Excepción a la patentabilidad (artículo 20 D486 literal a)-d)

Las reivindicaciones 33 a 55 reclaman un método para tratar un padecimiento mediante la administración de una composición que contiene toxina botulínica. Los métodos para tratamiento no son patentables

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 20-12-2002

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación
D1	US5512547	PHARMACEUTICAL COMPOSITION OF BOTULINUM HEUROXIN AND METHOD OF PREPARATION	30-04-1996
D2	WO0158472	BOTULINUM TOXIN PHARMACEUTICAL COMPOSITIONS	16-08-2001

6. Análisis de patentabilidad (artículo 14 D486)

6.2 Nivel inventivo (artículo 18 D486)

El documento del Estado de la Técnica más próximo es D1 que enseña composiciones que comprenden neurotoxina botulínica tipo A y albúmina en altas concentraciones (Ver columna 2 párrafo 40 y columna 5 tabla 1), con lo que se mejora la actividad de la toxina botulínica.

La única diferencia con D1 es que esta solicitud menciona el uso de albúmina recombinante. Pero esta diferencia no parece conceder un efecto técnico inesperado porque estas composiciones siguen siendo más estables mediante la adición de elevadas concentraciones de albumina como se ve en D1 en la tabla 1, excipiente 8 en donde se utilizan 9mg/ml de albumina para 100 o 1000 unidades LD50 de toxina botulínica.

El problema técnico planteado en esta solicitud consiste en la necesidad de composiciones de toxina botulínica que mejoren la efectividad clínica y reduzcan los efectos colaterales debidos a la difusión de la toxina. Este problema se había resuelto previamente mediante el mismo tipo de composiciones divulgadas en D1, ya que esta referencia demuestra la elevada recuperación de la neurotoxina al utilizar albúmina en altas proporciones (columna 5, tabla 1). Por esta razón se considera que la sustitución de albúmina humana por albúmina recombinante es algo evidente a la luz de D2 en donde se divulgan composiciones de toxina botulínica tipos A, B, C, D, E, F, y G (página 5 párrafo 15) combinados con albumina recombinante lo cual la hace libre de efectos adversos de la albúmina proveniente de sangre (página 32), así es sencillo para el experto en la materia utilizar albúmina recombinante de D2 en concentraciones mayores de 550µg por 100 unidades LD50 de toxina como las de D1 y obtener los efectos secuestrantes esperados sin la contaminación que se deriva del uso de albúmina proveniente de sangre humana o animal. Por lo anterior, las reivindicaciones 1 a 32, y 56 a 60 no poseen Nivel Inventivo.

7. Conclusión:

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

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	US5512547	1 a 32 y 56 a 60	Nivel Inventivo
D2	WO0158472	1 a 32 y 56 a 60	Nivel Inventivo

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8. Respuesta a los argumentos del solicitante:

Dar respuesta al pronunciamiento del solicitante respecto del concepto técnico de art. 45 y argumentar el motivo por el cual no se aceptan dichos argumentos

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 numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
28 NOV. 2008

CONCEPTO TÉCNICO No.2798	EXAMINADOR TÉCNICO Código No. 202073
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