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SUPERINDUSTRIA Y COMERCIO
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Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Re.: Expediente No. 01.022.123

Solicitud del examen de patentabilidad correspondiente a la Patente de Invención para:

**"COMPOSICIÓN DE SOMATOTROPINA CON MEJORIAS PARA ADMINISTRACIÓN
POR JERINGA"**

Solicitante: LG CHEMICAL LTD.

SOLICITUD EXAMEN DE PATENTABILIDAD

Yo, **MARGARITA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pie de mi firma, obrando en mi calidad de apoderada de la sociedad solicitante, atentamente me permito solicitar a Ud. que se realice el examen de patentabilidad de la invención arriba citada, para lo cual anexo el comprobante de pago No. 03 - 61.579 de Agosto 29 de 2003, correspondiente a la tasa establecida para dicha solicitud.

En consecuencia, atentamente solicito a Ud. se anexe este memorial junto con el comprobante de pago al expediente correspondiente a esta solicitud de Patente de Invención, y se continúe con su tramitación.

Señor Jefe,


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MCA/gcb/4812

2003

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SUPERINDUSTRIA Y COMERCIO

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NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 61,579
FECHA : AGOSTO 29 DE 2003

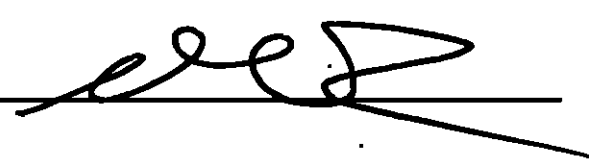
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
TERESA ESPINOSA	CONSIGNACION	BANCO POPULAR	050-00110-6	9931985	27/08/2003	5,717,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	05 EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
	TOTAL :	\$ 335,000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 01-22123

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 526, DE
FECHA 31 DE MARZO DE 2003, EL TERMINO HABIL SEÑALADO POR LA LEY
EXPIRA EL 01 DE JULIO DE 2003.

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**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/27, 31/59, 31/595, 31/355		A1	(11) International Publication Number: WO 99/43342 (43) International Publication Date: 2 September 1999 (02.09.99)
(21) International Application Number: PCT/KR98/00153 (22) International Filing Date: 11 June 1998 (11.06.98) (30) Priority Data: 1998/6601 28 February 1998 (28.02.98) KR (71) Applicant (for all designated States except US): LG CHEMICAL LTD. [KR/KR]; 20, Yoido-dong, Youngdeungpo-ku, Seoul 150-010 (KR). (72) Inventors; and (73) Inventors/Applicants (for US only): KIM, Nam, Joong [KR/KR]; #603-301, Hansin Kookwha Apt., Samcheon-dong, Seo-ku, Taejeon-si 302-222 (KR). RYOO, Ja, Phil [KR/KR]; #9-202, Lucky Apt., Doryong-dong, Yusong-ku, Taejeon-si 305-340 (KR). CHANG, Byoung, Sun [KR/KR]; #9-501, Lucky Apt., 381-42, Doryong-dong, Yusong-ku, Taejeon-si 305-340 (KR). KIM, Doo [KR/KR]; #2-201, Keumho Village, 866, Hoopyoung-dong, Chooncheon-si, Kangwon-do 200-160 (KR). (74) Agent: LEE, Won-Hae; Suite 805, Sung-Ji Heights II, 642-16, Yoksam-dong, Kangnam-ku, Seoul 135-080 (KR).		(81) Designated States: AU, BR, CA, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.	
(54) Title: SOMATOTROPIN COMPOSITIONS MIXED WITH VITAMINS (57) Abstract The present invention relates to a pharmaceutical composition which comprises bioactive somatotropin and at least two kinds of lipid-soluble vitamins, and more particularly to a parenterally administered pharmaceutical composition which can solve inconvenience of administering somatotropin and lipid-soluble vitamins respectively and which shows the sustained effect of somatotropin and the synergic effect of somatotropin and lipid-soluble vitamins.			

What is claimed is :

1. A pharmaceutical composition comprising somatotropin and at least two kinds of lipid-soluble vitamins.
- 5 2. The pharmaceutical composition according to Claim 1, wherein somatotropin is bovine somatotropin or porcine somatotropin.
- 10 3. The pharmaceutical composition according to Claim 1, wherein somatotropin is bovine somatotropin produced by recombinant DNA technology.
4. The pharmaceutical composition according to Claim 1,
15 wherein somatotropin is contained in the range of 10 - 40 wt%.
5. The pharmaceutical composition according to Claim 1, wherein at least two kinds of lipid-soluble vitamins are
20 selected in the group consisted of vitamin A, vitamin D and vitamin E.
6. The pharmaceutical composition according to Claim 5, wherein vitamin A is mixed in the range of 500,000 -
25 5,000,000 units per 1 g of somatotropin.

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7. The pharmaceutical composition according to Claim 5, wherein vitamin D is mixed in the range of 100,000 - 700,000 units per 1 g of somatotropin.
- 5 8. The pharmaceutical composition according to Claim 5, wherein vitamin E is mixed in the range of 500 - 4,000 units per 1 g of somatotropin.
9. A method of preparing the pharmaceutical composition as set forth in Claim 1 which comprises;
- 10 (a) adding lipid-soluble vitamins to a powdered somatotropin,
- (b) and then homogenizing them
- 15 10. The method according to Claim 9, wherein a powdered somatotropin is prepared by lyophilizing only the somatotropin.
11. The method according to Claim 9, wherein a powdered
- 20 somatotropin is prepared by lyophilizing microparticles prepared by mixing delaying agent and the somatotropin solution.
12. The method according to Claim 9, wherein a powdered
- 25 somatotropin is prepared by lyophilizing the mixture of

stabilizing agent and the somatotropin solution.

13. The method according to Claim 11, wherein the delaying agent is lecithin.

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14. The method according to Claim 12, wherein the stabilizing agent is selected from a group consisted of sucrose, mannitol and trehalose.

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US005520927A

United States Patent [19]

Kim et al.

[11] Patent Number: 5,520,927

[45] Date of Patent: May 28, 1996

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461[54] METHOD FOR THE PREPARATION OF
SUSTAINED RELEASE SOMATOTROPIN
AND PRODUCT PRODUCED THEREBY[75] Inventors: Nam J. Kim; Byung G. Rhee; Heung
S. Cho, all of Daejeon-Si, Rep. of
Korea

[73] Assignee: Lucky, Ltd., Seoul, Rep. of Korea

[21] Appl. No.: 275,329

[22] Filed: Jul. 14, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 944,754, Sep. 14, 1992, abandoned,
which is a continuation of Ser. No. 634,025, Feb. 12, 1991,
abandoned.

[30] Foreign Application Priority Data

Feb. 12, 1990 [KR] Rep. of Korea 90-1689
Dec. 31, 1990 [KR] Rep. of Korea 90-23104[51] Int. Cl.⁶ A61K 9/127

[52] U.S. Cl. 434/450; 530/399

[58] Field of Search 434/450, 400;
530/399

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Primary Examiner—Thurman K. Page

Assistant Examiner—S. Howard

Attorney, Agent, or Firm—Birch, Stewart, Kolisch & Birch

[57] ABSTRACT

A parenterally administered, slow releasing bioactive phar-
macological composition comprises at least one bioactive
polypeptide, at least one tocopherol compound, and a release
delaying agent.

14 Claims, 11 Drawing Sheets

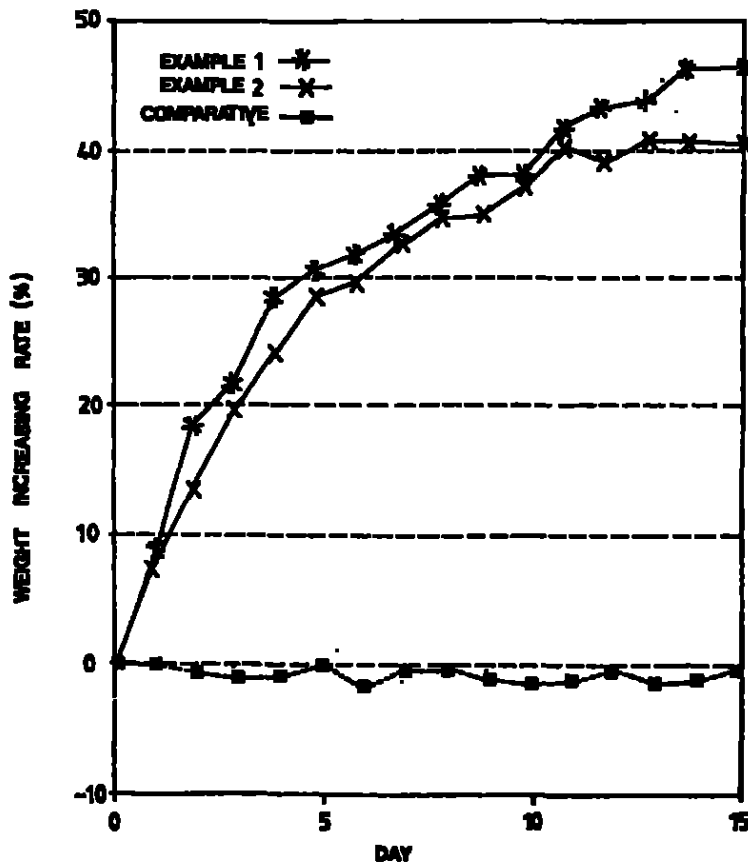


TABLE 3-continued

The increase rate of body weight affected from the injection of the bovine somatotropin compositions, %				
Day	Example 6	Example 7	Example 8	Control
12	27.2	33.5	11.8	-0.5
13	28.7	33.2	12.5	-1.3
14	30.5	37.1	13.7	-1.2
15	30.4	35.6	12.1	-0.3

Example 9

The composition was prepared according to the same procedure as Example 1, except that 400 ml of bovine somatotropin (23 mg/ml) and 3.102 g of L- α -phosphatidyl choline were mixed. 13.3 mg of lyophilized mixture bovine somatotropin content 10 mg was added to 1 ml of tocopherol acetate. The compositions were tested by the same method as Example 1 and the results are shown in Table 4 and FIG. 4.

Example 10

The composition was prepared according to the same procedure as Example 9, except that 66.5 mg of lyophilized mixture (bovine somatotropin content 50 mg) was added to 1 ml of tocopheryl acetate. The compositions were tested by the same method as Example 1 and the results are shown in Table 4 and FIG. 4.

Example 11

The composition was prepared according to the same procedure as Example 1, except that 100 mg of lyophilized bovine somatotropin without L- α -phosphatidyl choline was mixed with 1 ml of tocopheryl acetate. The compositions were tested by the same method as Example 1 and the results are shown in Table 4 and FIG. 4.

Example 12

Example 1, except that 1 ml of tocopherol acetate and 20 mg of aluminum monostearate were heated to 150° C. for 5 minutes and then cooled to room temperature 100 mg of bovine somatotropin without L- α -phosphatidyl choline was suspended in this mixture. The compositions were tested by the same method as Example 1 and the results are shown in Table 4 and FIG. 4.

Example 13

The composition was prepared according to the same procedure as Example 12, except that bovine somatotropin bound to Zn was used. The compositions were tested by the same method as Example 1 and the results are shown in Table 4 and FIG. 4.

TABLE 4

The increase rate of body weight affected from the injection of the bovine somatotropin composition, %						
Day	Example 9	Example 10	Example 11	Example 12	Example 13	Control
1	8.7	8.8	7.3	7.9	5.5	-0.2
2	12.2	13.9	8.8	15.5	9.9	-0.8
3	13.9	16.1	9.6	22.4	12.4	-1.2
4	15.2	20.9	8.9	24.0	15.5	-1.0

TABLE 4-continued

The increase rate of body weight affected from the injection of the bovine somatotropin composition, %						
Day	Example 9	Example 10	Example 11	Example 12	Example 13	Control
5	16.3	24.2	10.5	28.0	17.2	0.0
6	17.2	27.8	10.8	30.0	19.8	-1.6
7	16.9	25.5	12.6	31.7	22.5	-0.4
8	18.1	28.0	14.1	31.3	22.8	-0.5
9	18.9	30.6	14.1	32.2	23.8	-1.2
10	17.1	30.2	14.8	34.1	25.9	-1.5
11	19.2	33.5	17.2	36.1	29.3	-1.2
12	19.6	34.4	16.4	36.7	28.2	-0.5
13	20.2	35.2	18.2	40.6	29.4	-1.3
14	20.4	32.9	19.2	46.5	31.3	-1.2
15	21.9	36.1	18.1	45.4	29.1	-0.3

Example 14

The composition was prepared according to the same procedure as Example 1, except that 1 ml of tocopheryl acetate and 20 mg of polyethylene glycol-75 lanolin (PEG-75 Lanolin or Solan E) were mixed in a homomixer and hereto 100 mg of bovine somatotropin bound to Zn was added. The compositions were tested by the same method as in Example 1 and the results are shown in Table 5 and FIG. 5.

Example 15

The composition was prepared according to the same procedure as Example 14, except that 1 ml of tocopherol acetate and 33 mg of ARLACEL 165 (a complex of glyceryl monostearate and PEG-100 stearate) instead of PEG-75 lanolin was used. The compositions were tested by the same method as Example 1 and the results are shown in Table 5 and FIG. 5.

Example 16

The composition was prepared according to the same procedure as Example 12, except that the spray-dried bovine somatotropin instead of the lyophilized bovine somatotropin was used. The compositions were tested by the same method as Example 1 and the results are shown in Table 5 and FIG. 5.

Example 17

The composition was prepared according to the same procedure as Example 12, except that 10 mg of aluminum monostearate and 10 mg of cholesterol were used. The compositions were tested by the same method as Example 1 and the results are shown in Table 5 and FIG. 5.

TABLE 5

The increase rate of body weight affected from the injection of the bovine somatotropin compositions, %					
Day	Example 14	Example 15	Example 16	Example 17	Control
1	6.9	4.1	8.5	6.7	-0.2
2	10.9	10.3	11.7	9.9	-0.8
3	13.7	13.3	16.1	10.2	-1.2
4	16.7	16.6	16.1	11.0	-1.0
5	17.2	18.1	16.3	12.5	0.0
6	19.2	19.6	16.9	11.8	-1.6

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ml of tocopheryl acetate. The mixture was homogenized in a homomixer for 5 minutes.

Thus obtained somatotropin compositions were injected to animals and tested for the effect on the body weight.

The test was carried out using female SD rats weighing about 80 to 100 g. The rats were subjected to a peripharyngeal method to eliminate their pituitaries. After 2 weeks, their body weights were measured at regular time everyday for 1 week. The rats whose body weights were not changed were selected, and subjected to as follows;

Bovine somatotropin compositions were injected to three hypophysectomized rats subcutaneously into their abdominal region by an amount of 0.1 ml per head. As a control group, only tocopheryl acetate was injected. Their body weights were measured at regular time everyday, the increase rate of the body weight to one before injection was calculated. The results are shown in Table 1 and FIG. 1.

Example 2

The composition was prepared according to the same procedure as in Example 1, except that L- α -phosphatidyl choline was not passed through a microfluidizer. The compositions were tested by the same method as Example 1 and the results are shown in Table 1 and FIG. 1.

TABLE 1

The rate of body weight affected from the injection of the bovine somatotropin compositions, %			
Day	Example 1	Example 2	Control
1	8.1	7.5	-0.2
2	18.4	13.5	-0.8
3	21.4	19.8	-1.3
4	28.2	24.2	-1.0
5	30.3	28.6	0.0
6	31.5	29.5	-1.6
7	33.4	32.6	-0.4
8	35.8	34.9	-0.5
9	38.0	35.1	-1.2
10	38.0	37.3	-1.5
11	41.9	40.5	-1.2
12	43.6	39.1	-0.5
13	44.5	40.8	-1.3
14	47.2	40.7	-1.2
15	47.3	40.5	-0.3

Example 3

The composition was prepared according to the same procedure as in Example 1, except that 200 ml of porcine somatotropin (24 mg/ml) and 1.58 g of L- α -phosphatidyl choline were used. Thus obtained compositions were tested by the same method as Example 1 and the results are shown in Table 2 and FIG. 2.

Example 4

The composition was prepared according to the same procedure as Example 3, except that 0.5 ml of tocopherol acetate and 0.5 ml of sesame oil were used. The compositions were tested by the same method as Example 1 and the results are shown in Table 2 and FIG. 2.

Example 5

The composition was prepared according to the same procedure as Example 4, except that peanut oil instead of sesame oil was used. The compositions were tested by the

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same method as Example 1 and the results are shown in Table 2 and FIG. 2.

TABLE 2

The increase rate of body weight affected from the injection of the porcine somatotropin compositions, %				
Day	Example 3	Example 4	Example 5	Control
1	6.6	4.6	8.1	-0.2
2	13.6	2.5	13.4	-0.8
3	19.7	13.0	12.4	-1.3
4	22.6	14.3	13.9	-1.0
5	25.5	14.9	15.4	0.0
6	29.0	15.7	16.4	-1.6
7	31.8	16.1	16.9	-0.4
8	33.5	16.3	18.7	-0.5
9	36.3	17.5	21.1	-1.2
10	35.2	17.02	2.0	-1.5
11	37.6	19.2	23.2	-1.2
12	41.1	19.9	26.4	-0.5
13	43.7	21.2	27.5	-1.5
14	45.5	18.5	28.2	1.2
15	47.7	20.4	30.2	0.3
16	48.5	20.0	31.4	0.0
17	50.5	20.5	32.6	-1.2
18	50.9	22.6	32.4	-0.1
19	51.8	22.6	33.0	-0.4
20	53.0	22.7	34.0	0.0

Example 6

The composition was prepared according to the same procedure as Example 1, except that 1 ml of tocopheryl acetate and 33 mg of L- α -phosphatidyl choline were mixed in a homomixer and hereto the 100 mg of lyophilized porcine somatotropin was added. The compositions were tested by the same method as Example 1 and the results are shown in Table 3 and FIG. 3.

Example 7

The composition was prepared according to the same procedure as Example 3, except that 2 ml of tocopheryl acetate was used. The compositions were tested by the same method as Example 1 and the results are shown in Table 3 and FIG. 3.

Example 8

The composition was prepared according to the same procedure as Example 3, except that peanut oil instead of tocopheryl acetate was used. The compositions were tested by the same method as Example 1 and the results are shown in Table 3 and FIG. 3.

TABLE 3

The increase rate of body weight affected from the injection of the porcine somatotropin compositions, %				
Day	Example 6	Example 7	Example 8	Control
1	6.2	8.0	4.7	-0.2
2	14.1	14.8	10.1	-0.8
3	19.7	20.7	10.0	-1.3
4	23.4	22.1	10.4	-1.0
5	23.3	23.3	11.1	0.0
6	23.4	24.9	11.9	-1.6
7	23.1	26.2	12.9	-0.4
8	26.3	24.3	4.9	-0.5
9	26.6	28.3	10.8	-1.3
10	23.9	31.5	9.9	-1.5
11	24.7	32.3	9.6	-1.2

FIG. 9 is a graph showing the polypeptide concentration in milk when the composition of the present invention is injected;

FIG. 10 is a graph showing the effect on the milk production when the composition of the present invention is injected;

FIG. 11 is a graph showing the polypeptide concentration in serum when the composition of the present invention is injected;

FIG. 12 is a graph showing the polypeptide concentration in milk when the composition of the present invention is injected;

FIG. 13 is a graph showing the effect on the milk production when the composition of the present invention is injected; and

FIG. 14 is a graph showing the polypeptide concentration in serum when the composition of the present invention is injected.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now in detail to the drawings for the purpose of illustration and the preferred embodiments of the present invention, the slowly releasing composition of bioactive polypeptides as shown in FIGS. 1 to 14, comprises at least one bioactive polypeptide, at least one tocopherol compound, and a lecithin. The tocopherol compound is selected from the group consisting of tocopherol, tocopherol acetate, tocopherol derivatives, and tocopheryl acetate derivative.

The bioactive polypeptide according to the present invention includes all the known bioactive polypeptides, for examples, growth hormones, insulin, interferon, interleukin II, tumor necrosis factor, colony stimulating factor and derivatives thereof.

Of the bioactive polypeptides, somatotropin is very suitable for the present invention due to its short half-life thereof in vivo. Examples for somatotropins include animal somatotropins such as bovine somatotropin, porcine somatotropin, goat or sheep somatotropin, salmon growth hormone, calf growth hormone and human growth hormone.

The somatotropin can be obtained from a pituitary gland of animal. Alternatively, the somatotropin may be obtained by recombinant DNA-technology.

The polypeptide may be used in the form bound or unbound to metal in the present invention. However, the bound form is not necessary, because the composition has the sufficient durability although the polypeptide is not bound with metal or any materials conventionally used for decreasing the solubility of the polypeptide in an aqueous solution in this field.

Tocopheryl acetate, tocopherol, and derivatives thereof used in the composition of the present invention have pharmacological activities as well as its function in delaying the release of the polypeptides. For examples, tocopherol compound helps the normal reproduction in a rat, a mouse, a guinea pig, a pig, or fowls, prevent the defects of muscle development in a young sheep, a calf or a dog, prevent softening of brain, irregularity of muscle movement, hardening of muscle, underexercise and tetanus in a chicken, and prevent steatitis in a milk, a pig, or a cat.

The composition of the present invention contains an assistant release delaying agent as well as tocopherol compound for the purpose of more excellent durability. Various assistant delaying agents are known. Particularly, choline

derivatives, aluminum monostearate, calcium stearate, wax, carnauba wax, and paraffine are preferable to other known assistant delaying agents. As an assistant delaying agent of the present invention, one or more compounds selected from a group consisting of compounds listed above are used.

Especially, choline derivatives are preferred. Examples of choline derivatives include phosphatidyl choline, lysophospholipid, plasmalogen, sphingomyelin etc. Phosphatidyl choline can be extracted from soybean, bovine liver, bovine heart or egg yolk.

The amount of the bioactive polypeptides used in the composition is wide. The lower limit is a minimum amount of polypeptide required to exert its effect in the body. The upper limit is a maximum amount of polypeptide capable of being contained in the tocopherol component used. Without any special purpose, it is not necessary to use the polypeptide in an excess amount.

When the total of the tocopherol component and the assistant delaying agent is 100% by weight, the assistant delaying agent is conventionally 2 to 10% by weight, preferably 2 to 7% by weight, more preferably 2 to 5% by weight, and the tocopherol component is the rest.

The composition of the present invention may be prepared by mixing at least one tocopherol component and an assistant delaying agent and then combining at least one bioactive polypeptide thereto. Alternative method comprises dispersing at least one bioactive polypeptide in an assistant delaying agent and then combining the dispersion with tocopherol component. The tocopherol component and an assistant delaying agent are added to a beaker.

The beaker is placed in an oil bath at a temperature between about 130° C. and 160° C., preferably 140° C. and 150° C, for about 10 to 40 minutes, preferably 20 to 30 minutes.

In prior art, the polypeptide must be used in the form bound to metal or transition metal to decrease the solubility and it is used in an excess amount to make up for the loss resulted from the initial burst effect. But, the composition of the present invention has an excellent durability without any binding of the polypeptide to the metal. The present invention has no problems such as side-effects occurred from metal bound to the polypeptide. The tocopherol component used in the present invention has a pharmacological functions such as the prevention or alleviation of the sensitive responses against foreign materials in vivo. Furthermore, according to the present invention, the initial releasing of the effective component is reasonable and the bioavailability is increased. Both of the preparation and the administration of the composition become simple and convenient.

The present invention will now be described in more detail in connection with the following examples which should be considered as being exemplary and not limiting the present invention.

Example 1

500 ml of bovine somatotropin (18 mg/ml produced by Lucky Ltd.) and 3 g of L- α -phosphatidyl choline (L- α -lecithin) extracted from soybeans were mixed in a homomixer for 10 minutes and operated in a microfluidizer at 40° C. for 5 minutes. This emulsion was put into a bottle, rapidly cooled to -70° C. using dry ice and acetone and then lyophilized.

The lyophilized mixture was ground and 161.8 mg (bovine somatotropin content 100 mg) was suspended in 1

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(lecithina)

TABLE 5-continued

The increase rate of body weight affected from the injection of the bovine somatotropin compositions, %					
Day	Example 14	Example 15	Example 16	Example 17	Control
7	21.6	20.3	18.7	12.5	-0.4
8	23.4	19.1	20.0	12.5	-0.5
9	22.6	20.4	19.6	12.3	-1.2
10	22.8	20.5	21.2	13.2	-1.3
11	23.9	20.6	21.0	12.4	-1.2
12	23.1	21.6	20.6	15.1	-0.5
13	23.9	21.5	19.9	11.9	-1.3
14	24.6	21.6	22.0	14.1	-1.2
15	24.0	19.8	21.9	11.3	-0.3

Example 18

The composition was prepared according to the same procedure as Example 12, except that Zn-bound bovine somatotropin was used. The compositions were tested by the same method as Example 1 and the results are shown in Table 6 and FIG. 6.

Example 19

The composition was prepared according to the same procedure as Example 12, except that Zn-bound porcine somatotropin instead of bovine somatotropin was used. The compositions were tested by the same method as Example 1 and the results are shown in Table 6 and FIG. 6.

TABLE 6

The increase rate of body weight affected from the injection of the bovine somatotropin compositions, %			
Day	Example 18	Example 19	Control
1	8.0	5.9	-0.2
2	13.6	10.4	-0.8
3	17.9	12.3	-1.2
4	14.8	14.4	-1.0
5	13.5	14.7	0.0
6	17.3	14.1	-1.6
7	21.0	14.6	-0.4
8	22.8	17.3	-0.5
9	16.7	16.0	-1.2
10	24.6	14.5	-1.5
11	26.4	17.6	-1.2
12	28.2	17.1	-0.5
13	27.9	18.4	-1.3
14	30.3	15.3	-1.2
15	30.5	17.5	-0.3

Example 20

30 ml of tocopherol acetate and 600 mg of aluminum monostearate were put into a 50 ml-beaker. Separately, a beaker containing 150 ml of tocopheryl acetate was heated at 150° C. on a temperature-controlled hot plate stirrer. The content of the former beaker was added to the latter and the mixture was heated in an oil bath with stirring bar for 20 minutes to dissolve aluminum monostearate. The mixture was removed from the bath, kept under vacuum and allowed to cool to 25° C. On cooling, the solution converted to a thick gel. 3 g of bovine somatotropin produced by Lucky LTD. was added to the gel and heated to 40° C. After stirring for 2 hours, 10 ml of composition was filled in a 20 ml-syringe having a 15 gauge needle.

The compositions were injected into two Holstein cows in the second trimester of their second lactation. The compositions were injected subcutaneously in the suprascapular region. Two cows were used as a control group without any injection. The daily milk production was accumulated. The increase rate of the increase rate in an injected group to one in a control group was calculated as following;

$$\text{Increase rate (\%)} = \frac{\frac{\text{the increase rate of the milk production in an injected group}}{\text{the increase rate of the milk production in a control group}}}{\text{the increase rate of the milk production in an injected group}} \times 100$$

The results are shown in Table 7 and FIG. 7.

TABLE 7

Cumulative average daily milk production, kg/day			
Day	Injected group	Control group	Increase rate (%)
-5-0	24.5	27.9	—
-7	27.6	27.5	14.3
-14	27.8	27.7	13.9
-21	27.3	27.8	11.7
-30	26.6	27.8	8.7

Blood samples were analyzed for bovine somatotropin. Representative analyses by radioimmunoassay are shown in Table 8 and FIG. 8 where the concentrations of bovine somatotropin in blood serum are expressed in nanograms per milliliter.

TABLE 8

The average concentration of bovine somatotropin in serum, ng/ml		
Day	Injected group	Control group
-3	9.2	16.9
0	187.7	48.2
1	75.1	22.7
3	61.3	13.3
5	38.4	41.3
7	60.0	31.5
9	69.3	26.6
11	54.9	21.1
13	33.4	11.3
15	24.9	16.0
17	24.4	13.3
19	43.5	28.9
21	35.7	29.3
23	34.2	22.2
30	34.2	23.7

Milk samples were analyzed for bovine somatotropin. Representative analyses by radioimmunoassay are shown in Table 9 and FIG. 9.

TABLE 9

The average concentration of bovine somatotropin in milk, ng/ml		
Day	Injected group	Control group
5	0.3310	0.3204
12	0.3184	0.3337
20	0.3337	0.3677
28	0.3237	0.3812
35	0.3096	0.3043

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Before the injection and everyweek after the injection, their body weights was measured at regular time. The average daily gain (ADG, kg/day) was calculated. The feed efficiency (FE) was calculated as follows;

$$FE = \frac{\text{The amount of feed intake}}{\text{The amount of increased body weight}}$$

(* Lower FE value represents higher efficiency).

The back fat thickness (FT) was measured and the decrease ratio of FT was calculated. The results are shown in Table 15.

TABLE 15

Average daily weight gain and feed efficiency from the injection of porcine somatotropin			
	Control group	Injected group 1	Injected group 2
<u>1st week:</u>			
ADG	1.00	0.97	1.08
FE	3.05	3.26	2.75
<u>2nd week:</u>			
ADG	0.96	0.77	0.87
FE	3.36	4.48	4.16
<u>3rd week:</u>			
ADG	1.07	0.98	1.00
FE	3.14	2.95	3.45
<u>4th week:</u>			
ADG	0.90	1.05	1.09
FE	4.35	3.57	3.13
<u>5th week:</u>			
ADG	0.84	0.81	1.04
FE	5.85	4.57	3.65
<u>6th week:</u>			
ADG	1.09	1.14	1.08
FE	4.91	4.04	4.30
<u>1st-6th weeks:</u>			
ADG	0.98	0.96	1.02
FE	3.85	3.50	3.46
Increase rate of FE (%)	—	4.1	5.26
<u>1st-6th weeks:</u>			
Decrease rate of FT (%)	—	6%	9%

Example 24

The porcine somatotropin compositions prepared as in Example 19 were injected by an amount of 0.9 ml per head every three weeks to 5 hogs, by an amount of 1.8 ml per head every three weeks to other 5 hogs [Injected group 2], and by an amount of 6 mg per head everyday to other 5 hogs (daily injected group). The other 5 hogs were used as control group without any injection. Their body weights were measured every 2 weeks. ADG, FE, the increase rate of FE and the decrease rate of FE were determined as in Example 23 and the results are shown in Table 16.

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TABLE 16

Average daily gain and feed efficiency from the injection of porcine somatotropin				
	Control group	Daily injected group	Injected group 1	Injected group 2
<u>1st-3rd weeks:</u>				
ADG	1.01	0.85	1.06	1.02
FE	2.92	2.60	2.79	2.70
<u>3rd-6th weeks:</u>				
ADG	0.91	1.04	1.09	1.04
FE	3.87	2.68	2.98	3.09
<u>5th-6th weeks:</u>				
ADG	0.88	0.98	0.64	1.01
FE	3.67	3.14	5.86	3.65
<u>1st-6th weeks:</u>				
ADG	0.93	0.95	0.93	1.02
FE	3.45	2.79	3.37	3.16
Increase rate of FE (%)	—	19.1%	2.3%	8.4%
<u>1st-6th weeks:</u>				
Decrease rate of FT (%)	—	39%	24%	11%

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention, and all such modifications as would be obvious to one skilled in the art are intended to be included in the scope of the following claims.

What is claimed is:

1. A method of producing a sustained release formulation of a somatotropin which comprises:

(a) forming an aqueous solution of a lecithin and a somatotropin to form liposomal somatotropin;

(b) lyophilizing said liposomal somatotropin;

(c) suspending said lyophilized liposomal somatotropin in an α -tocopheryl acetate to form a mixture wherein said α -tocopheryl acetate is present in an amount of from 90 to 98% by weight based on the total weight of said α -tocopheryl acetate and said lecithin and said lecithin is present in an amount of from 2 to 10% by weight based on the total weight of said α -tocopheryl acetate and said lecithin; and

(d) homogenizing said mixture to produce said sustained release formulation of somatotropin, wherein said somatotropin is present in an amount of from 1% to 10% by weight of said sustained release formulation.

2. The method according to claim 1, wherein said somatotropin is selected from the group consisting of bovine somatotropin, porcine somatotropin, and ovine somatotropin.

3. The method according to claim 2, wherein said somatotropin is recombinantly prepared bovine somatotropin.

4. The method according to claim 2, wherein said somatotropin is recombinantly prepared porcine somatotropin.

5. The method according to claim 1, wherein said lecithin is extracted from soy bean or egg yolk.

6. The sustained release somatotropin formulation produced according to the method of claim 1.

7. A slow release parenteral composition produced by the process of

providing a lyophilized mixture comprising somatotropin and a release delaying agent,

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suspending said lyophilized mixture in a tocopherol compound to form a suspension wherein said tocopherol compound is selected from the group consisting of tocopherol and tocopheryl acetate, and is present in an amount of from 90 to 98% by weight based on the total weight of said tocopherol compound and said release delaying agent, and said release delaying agent is present in an amount of from 2 to 10% by weight based on the total weight of said tocopherol compound and said release delaying agent, and

homogenizing said suspension wherein said somatotropin is present in an amount of from 1% to 10% by weight of said slow release parenteral composition.

8. The composition according to claim 7, wherein said release delaying agent is a choline compound.

9. The composition according to claim 8, wherein said release delaying agent is a choline compound consisting of phosphatidyl choline.

10. The composition according to claim 8, wherein said release delaying agent is a choline compound comprising an extract of egg yolk.

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11. The composition according to claim 11, wherein said somatotropin is an animal somatotropin.

12. The composition according to claim 11, wherein said somatotropin is an animal somatotropin selected from the group consisting of bovine somatotropin, and porcine somatotropin.

13. The composition according to claim 12, wherein said animal somatotropin is obtained from a recombinantly prepared microorganism.

14. The composition according to claim 7, wherein said tocopherol compound is present in an amount of from 95 to 98% by weight based on the total weight of said tocopherol compound and said release delaying agent, and said release delaying agent is present in an amount of from 2 to 5% by weight based on the total weight of said tocopherol compound and said release delaying agent.

* * * * *

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

Doctor(a)
Margarita Castellanos Abondano
Apoderado(a)
LG CHEMICAL LTD.

Oficio N° 13159

REFERENCIA	Radicación	01 22123
	Trámite	002
	Evento	001
	Actuación	430
	Folios	004

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 01 22123, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

1. DOCUMENTOS ESTUDIADOS:

- La copia de la solicitud original mediante la cual se reivindica prioridad de Corea KO2000-0015091 de 24/03/2000 en los folios 15 a 42, junto con su traducción correspondiente en los folios 46 a 48.
- El resumen y el capítulo descriptivo de la solicitud en los folios 80 y 50 a 63 respectivamente.
- Los ejemplos que ilustran la invención en los folios 64 a 76.
- Las cláusulas 1 a 14 relacionadas en el capítulo reivindicatorio de la solicitud que se encuentran en los folios 77 a 79.
- El primer examen de forma realizado a la solicitud de oficio No. 1346, que se encuentra en el folio 83.
- La respuesta al primer examen de forma, allegada mediante memorial de fecha 06/06/2001 que se encuentra en los folios 85 a 93.
- El memorial de fecha 23/07/2001 mediante el cual se complementa la información correspondiente a la traducción del documento de prioridad, documento que se encuentra en los folios 94 a 151.
- La solicitud de examen de patentabilidad junto con el pago de la tasa correspondiente, allegada mediante memorial de fecha 01/09/2003, que se encuentra en los folios 154 y 155.

2. OBJETO DE LA INVENCION:

La solicitud hace referencia a una ***“Composición de somatotropina con mejoras para administración por jeringa”***

• **Reivindicaciones 1 a 14:**

Se reivindica una composición que contiene somatotropina, por lo menos una vitamina liposoluble como la vitamina A o E y sus derivados y por lo menos un lubricante liposoluble como alcohol o uno de sus derivados, éster o ácido graso y alcohol, ácido graso insaturado, éster de ácido y alcohol aromático u otro material que pueda mezclarse con vitaminas liposolubles, en particular: alcohol bencílico, alcohol etílico, alcohol isopropílico, alcohol butílico o similar, etil oleato, isopropil miristato, isopropil laurato, isopropil lanolato, isopropil palmitato, ácido oléico, ácido linoléico, benzoato de bencilo, polioxietilen alquil éster, glicofurol o un derivado de polietilenglicol, glicerina o similar.

En particular se reivindica la composición de somatotropina que es producida por tecnología de ADN recombinante y está presente en una cantidad que varía entre 10 y 50% en peso basándose en el peso total de la composición. Y la composición en la cual la vitamina A está presente en una cantidad entre 100.000 a 5.000.000 de unidades por cada gramo de somatotropina. O en el caso de la vitamina E que está presente en cantidades que van desde 500 hasta 12.000 unidades por cada gramo de somatotropina. Y en el caso del lubricante se encuentra presente en una cantidad de 0.5 a 25% en peso basándose en el peso total de la composición.

Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³⁸/27 // C 07 K¹⁴/61** de la Clasificación Internacional de Patentes.

3. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la solicitud en estudio - 24.03.2000- y relacionados con la materia técnica reivindicada:

Nº	Documento	Título	Fecha de Publicación
D1	WO9943342	"Somatotropin compositions mixed with vitamins"	02/09/1999
D2	US5520927	"Method for the preparation of sustained release somatotropin and product produced thereby"	28/05/1996

Anterioridades D1 y D2 en los folios 157 a 167.

4. EVALUACIÓN DE LOS REQUISITOS DE PATENTABILIDAD:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

4.1 Evaluación del NIVEL INVENTIVO :

El artículo 18 de la decisión 486 dispone "Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica".

La anterioridad D1 comprende composiciones de somatotropina, producida mediante tecnología de DNA recombinante, con dos clases de vitaminas liposolubles como A, D o E.

La vitamina A se encuentra en un rango entre 500.000 y 5.000.000 unidades por gramo de somatotropina. La vitamina D se mezcla en un rango entre 100.000 a 700.000 unidades por gramo de somatotropina y la vitamina E se mezcla en un rango entre 500 a 4.000 unidades por gramo de somatotropina.

Además la anterioridad D1 revela un método para fabricar las composiciones que comprende adicionar las vitaminas liposolubles a los polvos de somatotropina y luego homogenizar la mezcla. Y en particular enfatiza en la adición de un agente estabilizante como sucrosa, manitol o tetralosa y la adición de un agente que retarda la descomposición de la fórmula como lecitina.

La anterioridad D2 por su parte, señala formulaciones para inyección que contienen somatotropina. En particular en su ejemplo 20 profundiza en el hecho de la administración de las composiciones veterinarias en vacas Holstein que se encuentran en el segundo trimestre de su segunda lactancia, las cuales recibieron la composición dosificada que contenía acetato de tocoferol, monoestearato de aluminio y somatotropina.

En consecuencia, al comparar la fórmula reclamada con las señaladas por los documentos en mención, se encuentra que existe evidencia suficiente en las anterioridades D1 y D2 que podría inducir a una persona versada en la materia técnica a desarrollar formulaciones como las propuestas por la solicitud, tan sólo con la revisión de los auxiliares y excipientes más comúnmente utilizados para la formulación de hormonas en medios hidrofóbicos.

Fórmula reivindicada	Anterioridad D1	Anterioridad D2
Somatotropina	Somatotropina	Somatotropina
Vitamina liposoluble: A o E	Vitaminas liposolubles: A, D y E	Alfa-tocoferol
Agente lubricante que se selecciona entre: alcohol o uno de sus derivados, éster o ácido graso y alcohol, ácido graso insaturado, éster de ácido y alcohol aromático u otro material que pueda mezclarse con vitaminas liposolubles, en particular: alcohol bencílico, alcohol etílico, alcohol isopropílico, alcohol butílico o similar, etil oleato, isopropil miristato, isopropil laurato, isopropil lanolato, isopropil palmitato, ácido oléico, ácido linoléico, benzoato de bencilo, polioxietilen alquil éster, glicofuroil o un derivado de polietilenglicol, glicerina o similar.	Agente estabilizante: lecitina Agente conservante: Sucrosa, manitol y tetralosa	Auxiliar de formulación: Monoestearato de aluminio

Así las cosas y al tenor de las cláusulas 1 a 14 se considera que la afectación ejercida por las anterioridades D1 y D2 no permite evidenciar un verdadero salto cualitativo en la regla técnica que permita otorgar el privilegio de patente a la materia objeto de estudio, lo anterior dada la obviedad de la solución propuesta, la forma tan

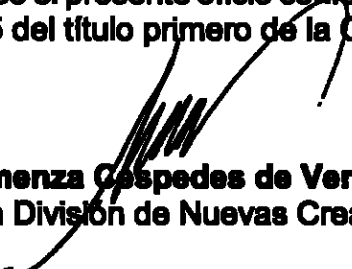
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general como se reivindican las composiciones y la derivación evidente del estado de la técnica.

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO9943342	1 a 14	Nivel Inventivo
D2	US5520927	1 a 14	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 la 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 5 del título primero de la Circular Única N° 10 de 2001.


Álix Carmenza Gaspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 16 NOV. 2006

CONCEPTO TÉCNICO Número 01752	EXAMINADOR TÉCNICO Código 202044
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