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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 379
Actuación : 444

Referencia : Expediente No. 05074968
Asunto : Solicitud de patente para: **FORMULACIONES
FARMACÉUTICAS LÍQUIDAS DE PALONOSETRON**
Solicitante : HELSINN HEALTHCARE SA
Clase : A61K 031/4747, A61P 001/008
Fecha solicitud: 29 de julio de 2005

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado me refiero al oficio No. 4502 notificado por fijación en lista del 14 de abril de 2009.

2. Mediante memorial radicado el día 15 de julio de 2009 solicité plazo de treinta (30) días para atender el oficio No. 4502.

3. Mediante oficio No. 4502 se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

3.1 De la solicitud de de patente

3.1.1 Descripción

Señala el Examinador que la solicitud carece de sustento por cuanto dentro de los ejemplos anexados en la solicitud únicamente de encuentra una composición que corresponde a palonosetron (o una sal farmacéuticamente aceptable) con Manitol Buffer citrato y un agente quelante (EDTA).

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3.1.2 Reivindicaciones

De acuerdo con el Examinador, el pliego reivindicatorio carece de concisión ya que distingue dos tipos de formulaciones diferentes. Asimismo señala que se presentan varias reivindicaciones independientes que no son consideradas necesarias para definir la invención.

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3.2 Análisis de patentabilidad

3.2.1 Novedad

El Examinador considera que el documento D1: US 5202333 afecta la novedad de la presente solicitud, afirmando que el elemento característico de la composición de las reivindicaciones 32 a 36, 42 a 46 y 51 a 52 era conocido en D1, es decir, una solución que comprende palonosetron y un portador farmacéuticamente aceptable.

3.2.2 Nivel inventivo

Para este requisito se han citado los documentos D2: "PHARMACEUTICAL PREFORMULATION AND FORMULATION", D3: "STRAUSS' FEDERAL DRUG LAWS AND EXAMINATION REVIEW" y D3: "REMINGTON FARMACIA 17ª EDICIÓN", considerando que los mismos afectan el nivel inventivo de la solicitud.

Por una parte se afirma que la combinación de los documentos D1 y D2 afecta el nivel inventivo de las reivindicaciones 1 a 31, 37 a 41, 47 a 50 y 53 a 56, toda vez que sería obvio para una persona medianamente versada en la materia obtener una solución que comprende palonosetron, un portador farmacéuticamente aceptable seleccionado de manitol, buffer citrato o EDTA a partir de las enseñanzas dichos documentos. Lo mismo se afirma para la reivindicación 57, ya que el Examinador considera que el documento D3 afecta su nivel inventivo (almacenamiento de un producto) y para la reivindicación 58, afectada por el documento D4 y relacionado con las etapas para llenar un recipiente.

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4. Con el fin de superar las objeciones expuestas se presentan las siguientes modificaciones, aclaraciones y argumentos:

4.1 Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 6 reivindicaciones. Las modificaciones realizadas sobre el pliego reivindicatorio son las siguientes:

- Teniendo en cuenta las observaciones del Examinador, se ha limitado el pliego reivindicatorio únicamente a composiciones que comprenden palonosetron, un portador farmacéuticamente aceptable, buffer citrato y un agente quelante, de manera que la solución se encuentra debidamente sustentada en la descripción
- De acuerdo con lo anterior, la reivindicación principal introduce los componentes y las reivindicaciones dependientes están dirigidas a limitar el rango de concentración de cada uno de ellos, de acuerdo con las modalidades preferidas de la invención
- De la misma manera se han eliminado las reivindicaciones que podrían generar confusión, con el fin de presentar la materia de forma clara y concisa
- Se han eliminado las reivindicaciones relacionadas con el almacenamiento del producto y llenado del recipiente para superar las objeciones relacionadas con éstas

De este modo, con las modificaciones introducidas, se presenta un pliego reivindicatorio claro conciso y debidamente sustentado en la descripción. Solicitamos atentamente tener en cuenta este pliego reivindicatorio que cumple con las disposiciones de la Decisión 486.

4.2 Análisis de patentabilidad

4.2.1 Novedad

El artículo 16 de la Decisión 486 establece:

Artículo 16.- Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Con base en este artículo y teniendo en cuenta los argumentos expuestos por el Examinador, solicitamos atentamente tener en cuenta las modificaciones realizadas sobre el pliego reivindicatorio. De esta manera ya no se presentan reivindicaciones dirigidas a una composición que comprende únicamente palonosetron y un portador farmacéuticamente aceptable, por lo que el documento D1 ya no afecta la novedad de la presente solicitud.

En efecto, la reivindicación principal modificada hace referencia a los siguientes componentes: 0,03 a 0,2 mg/ml de palonosetron, un portador farmacéuticamente aceptable, buffer citrato y un agente quelante a un pH de 4 a 6. Teniendo en cuenta que el documento D1 no revela todos los elementos esenciales de esta reivindicación, no puede ser considerado un documento válido capaz de afectar la novedad de la presente solicitud. Por lo tanto, consideramos que la objeción a este respecto se debe tener por superada.

4.2.2 Nivel inventivo

De acuerdo con el artículo 18 de la Decisión 486:

Artículo 18.- 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.

En primer lugar deseamos poner de presente que al eliminarse las reivindicaciones 57 y 58 del pliego reivindicatorio, la objeción de nivel inventivo con respecto a los documentos D3 y D4 ha sido superada.

Ahora bien con respecto a los documentos D1 y D2 deseamos expresar nuestro desacuerdo con los argumentos del Examinador, toda vez que la combinación de las enseñanzas de dichos documentos no permiten a un técnico versado en la materia obtener de manera obvia la presente invención.

A este respecto, consideramos que un documento o una combinación de éstos sólo deben ser considerados válidos para la afectación de este requisito, cuando una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras sobre la manera como se resuelve el problema técnico, es decir, sobre la invención tal como se encuentra reivindicada.

Para los anteriores efectos, el método problema solución enseña que el primer paso en el estudio del nivel inventivo de una invención es determinar cuál es el estado del arte más próximo a la invención frente al cual ésta última debe ser comparada.

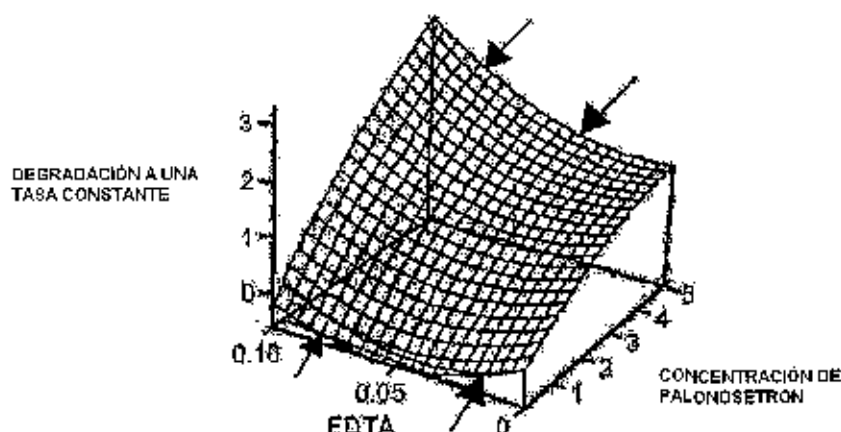
Dicho estado del arte más próximo es, de acuerdo con el Manual Andino de Patentes, aquel que resuelve el mismo problema técnico que pretende resolver la invención bajo estudio. Lo anterior, por cuanto esta sería la información a la cual normalmente accedería quien pretende resolver dicho problema técnico.

Con el fin de demostrar el nivel inventivo de la solución reivindicada se presentan junto con este memorial, dos declaraciones del Dr. Daniele Bonadeo en las que se establece el salto cualitativo y el efecto técnico del empleo de un agente quelante con bajas concentraciones de palonosetron.

El estado de la técnica más cercano para este caso es el ejemplo 13 de D1. Dicho ejemplo describe una formulación que contiene de 10 a 100 mg/ml de palonosetron, pero no EDTA. Sin embargo, si la concentración de palonosetron es muy alta, el EDTA desestabilizará la formulación, tal como se demuestra en la siguiente tabla 4 de la declaración del Dr. Bonadeo en la fecha 02/09/09:

Concentración EDTA (%)	Concentración citrato (mM)	Concentración palonosetron (mg/ml)	Degradación
0,0	10	0,4	0,71% (6 mo.)
0,1	10	0,4	0,1% (3 mo.)
0,3	10	5	2,86% (6 mo.)
0,1	10	5	13,87% (3 mo.)

Estos datos muestran que el EDTA desestabiliza el palonosetron cuando es añadido en las concentraciones próximas al arte previo (Ver la declaración del Dr. Bonadeo). La siguiente figura ha sido reproducida con el objeto de hacer aún más claro este punto:



Tal como puede ser establecido, el EDTA hace menos estable el palonosetron cuando las concentraciones se aproximan a las del arte previo. En contraste, cuando el EDTA es añadido al palonosetron en bajas concentraciones, por ejemplo 0,03 a 0,02 mg/ml, como se describe en las reivindicaciones, el EDTA hace más estable el palonosetron. Éste es un resultado superior inesperado, basado en la comparación directa del arte previo más cercano, el cual demuestra plenamente la patentabilidad de la presente invención.

Los agentes quelantes son añadidos a los metales quelatos y a otras especies oxidantes. Una persona medianamente versada en la materia no se vería motivada a añadir un quelante a formulaciones líquidas de palonosetron, dado que al parecer, los metales estabilizan el medicamento bajo ciertas condiciones, cuando son comparados con los resultados de muestras sin la presencia de metales: (Ver declaración del Dr. Bonadeo):

	Temperatura ambiente	40°C	60°C	80°C
% remanente en el punto de tiempo final (palonosetron <u>con</u> metales)	100	75	68	99
% remanente en el punto de tiempo final (palonosetron <u>sin</u> metales)	86,5	22,5	22	60

*10 mg/ml de palonosetron; promedio de las dos pruebas

Tal como puede observarse, el palonosetron parece volverse más estable bajo la presencia de metales y ciertas condiciones de prueba. Esto es inconsistente con un producto que es sometido a una auto-oxidación catalizada por metales.

El palonosetron también exhibe otros comportamientos que son inconsistentes con un producto que es sometido a una auto-oxidación catalizada por metales, tal como explica el Dr. Bonadeo en el párrafo 16 de su declaración:

16. El hecho de que el EDTA mejore la estabilidad del palonosetron es del todo sorprendente, dado nuestro trabajo anterior con la molécula, en la cual el palonosetron demostró una estabilidad comparable a 5°C tal como lo hizo a 60-100°C. Si la molécula estuviera sometida a una auto-oxidación (la razón típica para añadir un agente quelante), uno esperaría una mayor temperatura para producir más radicales iniciadores y una reacción y degradación más rápidas.

La obviedad exige una expectativa razonable de éxito. En el presente caso una persona medianamente versada en la materia no tendría una expectativa razonable con respecto a la estabilidad del palonosetron junto con un agente quelante bajo las circunstancias que se describen en la invención.

Por lo tanto, teniendo en cuenta que ninguno de los dos documentos citados por el Examinador enseña o sugiere este efecto técnico, consideramos que la objeción de nivel inventivo debe tenerse por superada.

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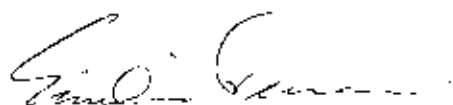
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5. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

6. ANEXOS

- Nuevo pliego reivindicatorio conformado por 6 reivindicaciones
- Formulario de modificaciones correspondiente
- Copia de la declaración del Dr. Bonadeo.

Señora Jefe,



EMILIO FERRERO

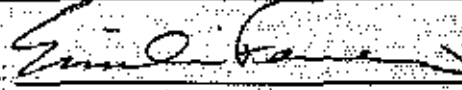
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No. M-2009-156767\JMS

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: HELSINN HEALTHCARE SA Sociedad constituida y existente bajo las leyes de Suiza. Dirección: P. O. Box 357, CH-8915 Pambio-Noranco, Suiza. Domicilio: Pambio-Noranco, Suiza. Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 438.019 TP 31 929
4	Número de expediente: <u>05.074.968</u>	
5	Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 6 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.	
6	Comprobante de pago No. _____ Fecha: _____	
7	Anexos ☐ Comprobante de pago de la tasa por \$111.000, por concepto de modificaciones. ☐ Comprobante de pago por reivindicaciones adicionales después de la decimoquinta reivindicación por ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO FIRMA:  C.C. 438 019 de Usaquén T.P.A. 31 929	

REIVINDICACIONES

1. Una solución farmacéuticamente estable para prevenir o reducir la náusea, caracterizada porque comprende:

a) de 0,03 a 0,2 mg/ml de palonosetron o una sal farmacéuticamente aceptable de éste; y

b) un portador farmacéuticamente aceptable que comprende manitol, un amortiguador de citrato y un agente quelante, a un pH de 4 a 6.

2. La solución de la reivindicación 1, caracterizada porque comprende de 0,005 a 1,0 mg/ml de EDTA.

3. La solución de la reivindicación 1, caracterizada porque comprende de 10 a 80 mg/ml de manitol.

4. La solución de la reivindicación 1 caracterizada porque comprende de 10 a 100 milimoles de un amortiguador de citrato.

5. La solución de la reivindicación 1, caracterizada porque comprende de 0,005 a 1,0 mg/ml de EDTA, de 10 a 80 mg/ml de manitol y de 10 a 100 milimoles de un amortiguador de citrato.

6. La solución de la reivindicación 1, caracterizada porque comprende aproximadamente 0,05 de palonosetron como clorhidrato de palonosetrón.

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IN THE UNITED STATES PATENT OFFICE

In re Application of:)
)
Calderari, et al.)
)
Serial No.: 11/186,311)
)
Filing Date: July 21, 2005)
)
Title: **LIQUID PHARMACEUTICAL**)
 FORMULATIONS OF)
 PALONOSETRON)

DECLARATION OF DANIELE BONADEO, M. Chem. Pharm.
37 C.F.R. § 1.132

I, Daniele Bonadeo, hereby give this declaration.

- 1) My name is Daniele Bonadeo.
- 2) I am an inventor for this application.
- 3) I am also Director, Head of Corporate Technical Affairs, Manufacturing Operations, for Helsinn Healthcare SA ("Helsinn"), the assignee of the above-referenced patent application.
- 4) One of my job responsibilities at Helsinn is to ensure that Helsinn's drug products are stable, and that adequate testing is performed to ensure such stability.
- 5) One of Helsinn's main products is palonosetron hydrochloride, which is marketed in the United States as Aloxi®. The product is marketed in injectable form and marketing authorization has been obtained for gel-cap dosage form for the treatment of nausea and vomiting from chemotherapy, radiotherapy and general surgery.
- 6) Numerous stability studies have been performed on the injectable formulation of palonosetron over the years to evaluate how changes to the formulation and manufacturing process would impact stability. These studies were performed by Helsinn, our contract manufacturers, and the owner of palonosetron before we acquired the drug.

- 7) All of our studies, regardless of the formulation parameter which was varied, show that the stability of palonosetron generally improves as the concentration of palonosetron is reduced, and that concentration is the most important determinant of product stability.
- 8) Table 1 contains the results of one of our stability studies, conducted in a phosphate-buffered, saline solution at pH 7.4.

TABLE 1. Palonosetron HCl Concentration-Stability Study (pH 7.4, 40 °C)

Palonosetron HCl Conc. (mg/ml, as free base)	% Palonosetron HCl Remaining at			
	1 week	2 weeks	5 weeks	8 weeks
0.01				100 ✓
0.1	100	100		101 ✓
1.0		101		99 ✓
10	99	93	57	23 ✓
50	102	73		49 ✓

- 9) As can be seen, the stability of the molecule improves in this formulation as its concentration decreased, with greatest stability seen below 0.1 mg/ml. We made this same observation in other studies, as discussed in greater detail below.
- 10) We also performed a pH-stability study to determine the best pH at which to formulate the molecule. The study was conducted with 60 mcg/ml palonosetron aqueous solutions, buffered at pH 2.0, 5.0, 7.4 and 10.0. No ingredients were present other than the pH adjusting agent, pH buffer, and palonosetron. The results are reported in Table 2.

TABLE 2. Palonosetron HCl 80 °C pH-Stability Study

pH at Room Temp.	pH at Reaction Temp.	Buffer	T ₉₀ (days)
2.0	2.0	0.01 M HCl	76
5.0	5.0	Acetate	Not determined. 99.2% remaining at 252 days
7.4	7.3	Phosphate	180
10	9.4	Carbonate	270

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- 11) The results demonstrate that the molecule is extremely stable at a pH of 5.0, when maintained at a low palonosetron concentration such 60 mcg/ml, and that stabilizers and the like are unnecessary to maintain that stability.
- 12) We also conducted additional studies to evaluate the impact of various excipients on stability, and improve the stability even further.
- 13) After settling on mannitol and a citrate buffer for the formulation for practical reasons, we studied the effect of palonosetron and EDTA concentration on stability, maintaining the pH constant at approximately 5.0, and keeping the same tonicifying agent (mannitol) and buffering agent (trisodium citrate). Stability was measured based on the percentage of palonosetron that remained undegraded at 1, 2, 3 and 6 months, under standard conditions of accelerated stability testing (i.e. 40 °C).
- 14) The results are reported below in Table 3.

TABLE 3. Formulation Optimization Study

Formulation (1)			Potency (% Label Strength)						Degradation Products (Total % Label Strength)					
Palo, Conc.	Buff er Con c.	EDTA Conc.	Storage Time (mo.) at 40C					Rate Const.	Storage Time (mo.) at 40 C					Rate Const.
(2)	(3)	(% w/v)	0	1	2	3	6	(4)	0	1	2	3	6	(4)
0.10	20	0.000	10	103	99	101	100	-0.29	0	0.30	0.68	0.61	0.97	0.15
0.10	40	0.000	10	106	103	106	104	-0.61	0	0.24	0.49	0.46	0.70	0.11
0.40	60	0.000	99	99	98	100	95	-0.75	0	0.07	0.14	0.46	1.92	0.33
0.40	10	0.000	99	98	97	97	95	-0.59	0	0.13	0.09	0.22	0.71	0.12
0.40	35	0.050	10	103	103	103	102	-0.15	0	0.07	0.06	0.21	0.16	0.03
0.40	10	0.100	10	102	101	101	100	-0.29	0	0.13	0.17	0.06	0.10	0.01
0.40	60	0.100	10	99	99	100	99	-0.27	0	0.00	0.00	0.02	0.13	0.02
1.00	20	0.050	10	102	102	100	99	-0.35	0	0.21	0.08	0.28	0.37	0.06
1.00	20	0.050	99	100	99	99	98	-0.31	0	0.15	0.07	0.20	0.22	0.03
1.20	40	0.000	97	99	96	97	88	-1.73	0	0.36	1.00	1.59	8.77	1.49
1.20	20	0.000	98	99	97	98	95	-0.55	0	0.03	0.37	0.61	1.73	0.30
2.50	80	0.000	10		93	91		-3.25	0		4.04	7.81		2.52
2.50	40	0.000	10		97	94		-1.75	0		2.77	4.39		1.45
2.50	20	0.000	10		97	95		-1.50	0		2.65	4.04		1.34
2.50	80	0.050	10		99	97		-1.11	0		0.79	1.07		0.36
2.70	35	0.000	10	100	102	99	91	-1.58	0	1.22	2.72	2.76	7.21	1.17
2.70	10	0.050	99	98	99	100	96	-0.48	0	1.40	1.22	1.17	3.03	0.43
5.00	60	0.000	10	100	98	97		-1.16	0	2.25	2.90	5.56		
5.00	10	0.000	10	102	100	99		-0.75	0	1.24	2.02	2.86		
5.00	0	0.000	99	99	98	93		-1.92	0	1.93	3.95	7.83		
5.00	60	0.050	10	99	98	94		-2.41	0	3.10	3.56	8.14		
5.00	60	0.050	10	101	97	96		-1.66	0	2.86	4.19	7.10		
5.00	60	0.100	99	98	93	91		-2.82	0	2.65	4.29	7.55		
5.00	10	0.100	98	98	95	85		-4.37	0	2.19	4.23	13.87		

1. Lots are sorted by Palonosetron HCl concentration, EDTA concentration and buffer concentration. All lots contain mannitol as the tonicifying agent.
2. Palonosetron concentrations are in mg/mL free base equivalents.
3. Citrate buffer concentrations are millimolar. All formulations are pH 5.0.
4. Rate constants are calculated with degradation product concentrations in two significant digits.

15) One notable observation from these results is that the presence of EDTA improves stability at low palonosetron concentrations, but actually decreases stability at high palonosetron HCl concentrations.

- 16) The fact that EDTA improves the stability of palonosetron at all is somewhat surprising, given our earliest work with the molecule, in which palonosetron demonstrated comparable stability at 5 °C as it did at 60-100 °C. If the molecule were undergoing auto-oxidation (the typical reason for adding a chelating agent), one would expect the higher temperature to produce more radical initiators and a faster reaction and degradation.
- 17) The fact that the chelating agent consistently improves the molecule's stability only at lower concentrations is also an intriguing discovery.
- 18) Based on the results in Table 3, we prepared several graphs to inform our analysis, including the response surface plot depicted below as Figure 1. This graph plots degradation rate constant as a function of EDTA concentration and palonosetron HCl concentration, holding the buffer strength constant at 20 mM. A lower degradation rate constant indicates a more stable formulation.

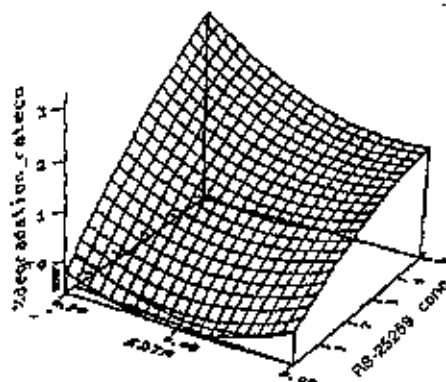


FIGURE 1

- 19) As can be seen, the stability of palonosetron improved as its concentration was reduced across the entire range of conditions studied. This same result can be seen when the buffer strength is varied, as shown below in Table 4. These results are consistent with the results reported above in Table 1, and reinforce our opinion that palonosetron concentration is a critical factor for the stability of palonosetron formulations.

TABLE 4

EDTA Conc. (%w/w)	Citrate Conc. (mM)	palonosetron Conc. (mg/ml)	% Degradation at 6 mo.
0	10	0.4	0.71%
0	10	5	2.86%
0	20	0.1	0.97%
0	20	1.2	1.73%
0	20	2.5	4.04% (3 mo.)
0	40	0.1	0.7%
0	40	1.2	8.77%
0	40	2.5	4.39% (3 mo.)
0.1	10	0.4	0.1%
0.1	10	5	13.87 (3 mo.)
0.1	60	0.4	0.13%
0.1	60	5	7.55% (3 mo.)

- 20) We also prepared a contour plot of potency rate constant as a function of buffer and EDTA concentrations based on the data reported in Figure 3, at a low palonosetron concentration (0.4 mg/ml). This plot is depicted below in Figure 2:

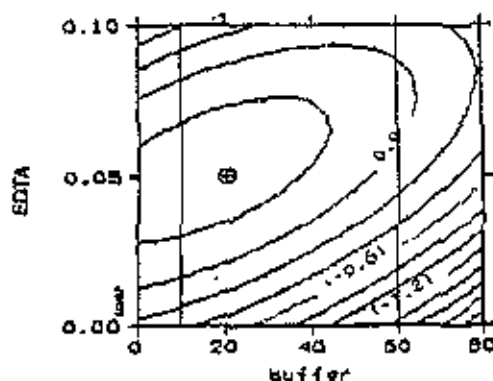


FIGURE 2

- 21) As can be seen from this figure, at the low palonosetron concentration depicted, there is a region of no apparent degradation with EDTA from 0.025 to 0.075 % w/v and buffer from 10 to 40 mM. This region is marked by the $\oplus$ symbol.

- 22) The foregoing results should be contrasted with the stability of the intravenous formulation reported in example 13 of the Berger 5,202,333 patent ("Berger '333").
- 23) The Berger '333 formulation used a higher palonosetron concentration than we eventually settled upon (10-100 mg/ml for the Berger '333 formulation vs. 0.05 mg/ml for the optimum formulation in the present invention), and a lower pH (3.7 for the Berger '333 formulation vs. 5.0 for the optimum formulation in the present invention).
- 24) The following Table 5 compares the formulations described in Berger '333 example 13 and example 4 of the current application, and their relative stability:

TABLE 5

	Berger '333 Example 13 Intravenous Formulation	Example 4 of Present Application
Palonosetron Hydrochloride	10-100 mg *	0.05 mg
pH	3.7	5.0
Dextrose monohydrate tonicifying agent	q.s. to render isotonic	--
Mannitol tonicifying agent	--	41.5 mg/ml
Citric acid monohydrate	1.05 mg	1.56 mg
Sodium hydroxide**	0.18 mg	q.s. to pH 5.0 ± 0.5
EDTA	--	0.5 mg
Trisodium citrate	--	3.7 mg
Water for injection	q.s. to 1.0 ml	q.s. to 1.0 ml
1-2 Year Stability?	NO	YES

*Assuming compound of formula I in Example 13 is palonosetron

**Assumes formulation requires pH increase

- 25) This comparison shows, once again, that palonosetron concentration and pH have the most significant impact on the stability of the formulation.

- 26) The formulations differ in terms of tonicifying agent, but I am unaware of any literature that would suggest that changing the tonicifying agent from dextrose to mannitol in a system such as this can have a bearing on the stability of the formulation. A study we performed comparing mannitol and saline, summarized below in table 6, supports this opinion.

TABLE 6. Chemical Stability Summary of Palonosetron HCl Injection Citrate Formulations

Lot #	Formulation (1)		Potency (% Label Strength)		Degradation Products (Total % Label Strength)	
	Tonicifier	Buffer Conc.(2)	At 0 mo. 40 °C	At 1 mo. 40 °C	At 0 mo. 40 °C	At 1 mo. 40 °C
18635-DML-045-05	Mannitol	20	96	95	0.46	1.85
18635-DML-045-04	Mannitol	40	94	93	1.41	4.32
18635-DML-045-06	Mannitol	80	95	94	1.20	3.80
18635-DML-045-08	Saline	20	98	96	0.46	2.18
18635-DML-045-07	Saline	40	98	94	0.44	4.54
18635-DML-045-09	Saline	80	98	96	1.50	3.10

1. Palonosetron concentration is 10 mg/mL as free base equivalents. Lots do not contain EDTA.
2. Citrate buffer concentrations are millimolar. All formulations are pH 5.0.

- 27) The formulations also differ in terms of the buffering mechanism (Berger '333 uses citric acid as a buffering agent while Example 4 uses citric acid and sodium citrate). However, the buffering agent is incorporated to maintain the solution at the prescribed pH, and would not be expected to significantly influence the stability of the formulation except through its pH maintenance capacity.

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132 Declaration of Daniele Bonadeo
U.S.S.N. 11/186,311
Page 9 of 9

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code. I declare under penalty of perjury that the foregoing is true and correct.

Dated: February 9th, 2009

Daniele Bonadeo
Daniele Bonadeo

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:	)	
	)	
Calderari, et al.	)	Examiner: Shirley V. Gembeth
	)	
Serial No. 11/388,270	)	Art Unit: 1614
	)	
Filed: March 24, 2006	)	
	)	
For: Liquid Pharmaceutical	)	
Formulations of Palonosetron	)	

SUPPLEMENTAL DECLARATION OF DANIELE BONADEO
37 C.F.R. 1.132

I, Daniele Bonadeo, hereby give this declaration.

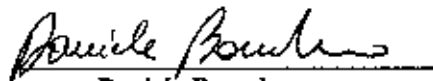
- 1) My name is Daniele Bonadeo.
- 2) I previously gave a declaration in this application on February 9, 2009.
- 3) In that declaration I reported the results of two sets of stability experiments with palonosetron that are inconsistent with an auto-oxidation pathway of degradation, or a degradation pathway catalyzed by ionic species.
- 4) In particular, I made reference to earlier work with the molecule in which we observed that the stability of palonosetron improved as its concentration in water decreased. See par. 7.
- 5) I also made reference to earlier work with palonosetron in which we observed that, as the temperature was raised above 60 °C, the stability improves such that at 100 °C the percent drug remaining was the same as that at 5 °C. See par. 16. A summary of this stability data is reproduced in Exhibit 1 hereto.
- 6) The effect of metal ions (1 ppm each of iron, chromium, and copper ions) on palonosetron stability has also been studied, and is reported in Exhibit 2 hereto.
- 7) Surprisingly, metals do not consistently catalyze the degradation of palonosetron. In fact, the metals actually appeared to stabilize the drug under some conditions, as compared to the data for samples without metals. See Exhibit 3. This was most obvious for the 10 mg/ml sample at the 8 week time point for the room temperature, 40 °C and 60 °C data.

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- 8) All of this data points away from an auto-oxidation pathway, which is the usual reason for adding a chelating agent such as EDTA in the first place.
- 9) While the EDTA that we add to our palonosetron formulations could be improving the stability by chelating metal ions, we actually postulate a different mechanism, based on the ability of the EDTA to break up micelles that destabilize the molecule.
- 10) In particular, we postulate that the results we have observed are due to the formation of drug micelles at a molecular level, and that these micelles facilitate a radical chain oxidation mechanism by reducing the distance between drug molecules thereby allowing hydrogen abstraction to occur efficiently.
- 11) Under this theory, the chelating agent stabilizes the formulation by breaking up the micelles, and dissociating the drug into a more stable monomeric form.
- 12) This theory could explain the unusual concentration effect that we have observed for this molecule, since the molecules would be more likely to form micelles at higher concentrations of palonosetron. This theory could also explain the unusual temperature effect, since the higher temperatures would likely break down the micelles and promote a more stable molecule. This theory could even explain the metal ion effect, since the binding of metals to the drug in a specific geometry could disrupt the aggregated micellar form of the drug, resulting in monomers of greater stability.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: June 8, 2009


Daniele Bonadeo

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Serial No. 11/388,270
Supplemental Declaration of Daniele Bonadco
June 8, 2009
Page 3 of 5

EXHIBIT 1

The Chemical Stability of Palonosetron at pH 7.4 Under Air as a Function of Drug Concentration and Temperature.^{a,b}

Percent Drug Remaining at:

<u>Temperature^h</u>	<u>1 week</u>	<u>2 weeks</u>	<u>3 weeks</u>	<u>8 weeks</u>
5°C	- -	- -	- -	97, 96
RT	- -	100	89-	87, 86
40°C	99	93	51, 62	23 ^d , 22 ^d
60°C	88	55, 54	22 ^c , 23 ^c , 24 ^c	23 ^e , 21 ^e
80°C	94	71 ^d , 71 ^d	50, 77	48 ^e , 72
100°C	100	98, 98	95, 96	94 ^e , 94 ^e

^a 10 mg/ml palonosetron solutions were 0.01 M phosphate buffer with the ionic strength adjusted to 0.15 M with KCl. Solutions were flame sealed in Type I colorless ampules and protected from light.

^b Solutions were colorless except where noted.

^c Pale yellow solution.

^d Pale brown solution.

^e Yellow solution.

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EXHIBIT 2

The Chemical Stability of Palonosetron at pH 7.4 Under Air as a Function of Temperature in the Presence of EDTA and Metals.^{a,b}

Drug Conc.		Percent Drug Remaining at:			
Temperature ^b	1 week	2 weeks	5 weeks	8 weeks	
<u>0.1 mg/ml with Metalsⁱ</u>					
5°C	- -	- -	- -	- -	
RT	- -	- -	- -	99, 101	
40°C	99	100	- -	99, 99	
60°C	- -	99, 100	- -	98, 98	
80°C	98	97, 98	- -	94, 94	
100°C	96	82, 82	- -	24, 24	
<u>10 mg/ml with Metals^j</u>					
5°C	- -	- -	- -	92, 101	
RT	- -	- -	- -	100, 100	
40°C	101	100	- -	50 ^d , 100	
60°C	- -	20 ^d , 101	- -	16 ^e , 100	
80°C	100	100	- -	99 ^d , 99 ^d	
100°C	99 ^e	95 ^e	- -	82 ^e	
<u>10 mg/ml with 0.1 % EDTA</u>					
5°C	- -	- -	- -	- -	
RT	- -	99, 100	99	- -	
40°C	- -	97, 98	86, 91	- -	
60°C	- -	82, 82	60 ^f , 60 ^f	- -	
80°C	- -	74 ^g , 74 ^g	70 ^f , 71 ^f	- -	
100°C	- -	68 ^f , 71 ^f	63 ^h , 63 ^h	- -	

^a Solutions were 0.01 M phosphate buffer with the ionic strength adjusted to 0.15 M with KCl. Solutions were flamed sealed in Type I colorless ampules and protected from light.

^b Solutions were colorless except where noted. ^c Pale yellow solution. ^d Pale brown solution. ^e Yellow solution. ^f Dark yellow solution. ^g Dark brown solution.

^h RT is 23°C ± 1.5°C.

ⁱ The reaction with metals used 1 ppm each of iron, chromium, and copper ions.

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EXHIBIT 3

The Chemical Stability of Palonosetron at pH 7.4 Under Air as a Function of Drug Concentration and Temperature,^{a,b}

Drug Conc. Temperature	1 week	Percent Drug Remaining at:		
		2 weeks	5 weeks	8 weeks
<u>0.01 mg/ml</u>				
5°C	- -	- -	- -	- -
RT	- -	- -	- -	100, 101
40°C	- -	- -	- -	100, 99
60°C	- -	101	- -	100, 101
80°C	- -	99	- -	98, 97
100°C	- -	96	- -	92, 92
<u>0.1 mg/ml</u>				
5°C	- -	- -	- -	100, 100
RT	- -	- -	- -	101, 101
40°C	100	100	- -	100, 101
60°C	- -	100, 100	- -	100, 100
80°C	100	100, 99	- -	100, 99
100°C	99	98, 98	- -	96, 98
<u>1.0 mg/ml</u>				
5°C	- -	- -	- -	100, 100
RT	- -	- -	- -	100, 100
40°C	- -	101	- -	99, 99
60°C	- -	101	- -	100, 100
80°C	- -	100	- -	100, 100
100°C	- -	100, 99	- -	99, 96
<u>10 mg/ml</u>				
5°C	- -	- -	- -	97, 96
RT	- -	100	89-	87, 86
40°C	99	93	51, 62	23d, 22d
60°C	88	55, 54	22 ^c , 23 ^c , 24 ^c	23 ^c , 21 ^b
80°C	94	71 ^d , 71 ^c	50, 77	48 ^c , 72
100°C	100	98, 98	95, 96	94 ^c , 94 ^c
<u>50 mg/ml</u>				
5°C	- -	- -	- -	80, 83
RT	- -	90 ^c , 100	- -	46
40°C	102	73	- -	46 ^c , 52 ^c
60°C	- -	- -	- -	- -
80°C	50	50 ^f , 97 ^d	- -	54 ^f
100°C	- -	96 ^c	- -	- -

^a Solutions were 0.01 M phosphate buffer with the ionic strength adjusted to 0.15 M with KCl. Solutions were flame sealed in Type I colorless ampules and protected from light.

^b Solutions were colorless except where noted. ^c Pale yellow solution. ^d Pale brown solution. ^e Yellow solution. ^f Dark yellow solution.

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lies, and, possibly, to decrease pain on injection. A modified drug that converts back to the active structure is defined as a prodrug. This conversion usually occurs within the body system or, for drugs that are formulated as dry powders, occurs on reconstitution. The preparation of prodrugs is becoming a common practice with many types of drugs. Examples of antibiotic prodrugs include benzathine penicillin, procaine penicillin, metronidazole phosphate, and chloramphenicol sodium succinate. Prodrugs are also common for injectable steroids such as prednisolone (formulated as methylprednisolone sodium succinate) and hydrocortisone (formulated as hydrocortisone sodium succinate).

Preparation of salts of organic compounds is the most important tool available to the formulator. Compounds for both IM and IV solutions require high solubility in order for the drug to be injected into acceptable volumes for bolus administration (see Table 1). Sodium and potassium salts of acids and hydrochloride and sulfate salts of bases are widely used in parenterals requiring soluble compounds, based on their overall use and history of clinical acceptance.

The solubility of a drug is to be reduced to ensure stability or to prepare a suspension, the formulator may prepare water-insoluble salts. A classic example is procaine penicillin G, the decreased solubility (7 mg/mL) of which, when compared with the highly soluble penicillin G potassium, is utilized to prepare parenteral suspensions. Another alternative for an insoluble drug is to use the parent or basic drug and to buffer the pH of the solution in the range of minimum solubility.

Polymorphism

This section lists numerous examples of polymorphism, the existence of several crystal forms of a given material that exhibit different physical properties [7]. Conversion of one polymorph to another may cause significant changes in the physical properties of the drug, critical quality attributes of drug products. Studies of polymorphs in recent years have pointed out effects of polymorphism on solubility and, more importantly, on dissolution rates. The aspect of polymorphism that is of particular concern to the parenteral formulator is physical stability of the product [8]. Substantial form polymorphs must be evaluated so that the form used is stable in a particular solvent system. It stresses that occur during suspension manufacture may also give rise to changes in crystal form [9].

pH and pK

Profiles of pH versus solubility and pH versus stability are needed for solution and suspension formulations to help assure physical and chemical stability as well as to maximize or minimize solubility. This information is also valuable for predicting the compatibility of drugs with various infusion fluids.

In summary, the physical and chemical data that should be obtained on the drug substance include the following:

- Molecular structure and weight
- Melting point
- Thermal profile
- Particle size and shape
- Hydrophobicity potential
- Ionization constant
- Light stability
- Optical activity
- pH solubility profile
- pH stability profile
- Polymorphism potential
- Solvate formation

B. Added Substances (Excipients) in Parenteral Formulations

To provide efficacious and safe parenteral dosage forms, added substances must frequently be incorporated into the formula to maintain pharmaceutical stability, control product attributes, ensure sterility, or aid in parenteral administration. These substances include antioxidants, antimicrobial agents, buffers, bulking materials, chelating agents, inert gases, solubilizing agents, and protectants. In parenteral product development work, any additive to a formulation must be justified by a clear purpose and function. In addition, every attempt should be made to choose added substances that are accepted by regulatory agencies throughout the world, since most pharmaceutical development is international in scope. Because of the extensive pharmacological and toxicological data required to obtain approval for any new additive, most formulators continue to depend on materials already used in marketed parenteral products.

Some of the most commonly used added substances are listed in Table 2. Pharmacists involved in IV admixture programs must be aware of the types of additives that may be present in the products being combined, since the source of incompatibility between different drugs mixed in solution may be the excipients present. For example, drug formulations containing

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Table 2. Classes and Examples of Parenteral Additives

Additive class	Examples	Usual concentration (%)
Antimicrobials	Benzalkonium chloride	0.01
	Benzyl alcohol	1-2
	Chlorobutanol	0.25-0.5
	Metacresol	0.1-0.3
	Butyl <i>p</i> -hydroxybenzoate	0.015
	Methyl <i>p</i> -hydroxybenzoate	0.1-0.2
	Propyl <i>p</i> -hydroxybenzoate	0.2
	Phenol	0.25-0.3
	Thimerosal	0.01
	Ascorbic acid	0.01-0.05
Antioxidants	Cysteine	0.1-0.5
	Monosialoglycerol	0.1-1.0
	Sodium bisulfite	0.1-1.0
	Sodium metabisulfite	0.1-1.0
	Tocopherols	0.05-0.5
	Acetate	1-3
Buffers	Citrate	1-5
	Phosphate	0.8-2.0
Bulkling Agents	Lactose	1-8
	Mannitol	1-10
	Sorbitol	1-10
	Glycerol	1-2
Chelating Agents	Salts of ethylenediaminetetraacetic acid	0.01-0.05
Protectants	Sucrose	2-5
	Glucose	2-5
	Lactose	2-5
	Maltose	2-5
	Trehalose	2-5
	Human serum albumin	0.1-1.0
Solubilizing Agents	Ethyl alcohol	1-50
	Glycerin	1-50
	Polyethylene glycol	1-50
	Propylene glycol	1-50
	Lecithin	0.5-2.0
Surfactants	Polyoxyethylene	0.1-0.5
	Sorbitan monooleate	0.05-0.25
Tonicity-adjusting agents	Dextrose	4-5
	Sodium chloride	0.3-0.9

the preservative benzalkonium chloride, which is positively charged, are commonly incompatible with products containing anionic drugs and excipients.

Antioxidants

Salts of sulfur dioxide, including bisulfite, metabisulfite, and sulfite, are the most common antioxidants used in aqueous parenterals. These antioxidants maintain product stability by being preferentially oxidized and

gradually consumed over the shelf life of the product. Irrespective of which salt is added to the solution, the antioxidant moiety depends on the final concentration of the thio compound and the final pH of the formulation [10]. While undergoing oxidation reactions, sulfites may be converted to sulfates and other species. Sulfites can also react with certain drug molecules (e.g., epinephrine).

Sulfite levels are determined by the reactivity of the drug, the type of container, single- or multiple-dose use,

lner headspace, use of inert gas purge, and the expiration period to be employed. Upper limits for levels are specified in most pharmacopoeias. Advice on upper limits are made for concentrated that are diluted extensively before use. Allergies have been reported to cause allergic reaction in some asthmatics. If possible, alternative antiseptics should be considered or the product should be manufactured and packaged in a manner such as to use or minimize the concentration of benzalkonium. Deoxygenation of the makeup water, maintaining the solution under a nitrogen atmosphere throughout the manufacturing process, and purging filled vials with an inert gas may significantly reduce the amount of antioxidant required.

Microbial Agents

A suitable preservative system is required in all multiple-dose parenteral products to inhibit the growth of organisms accidentally introduced during withdrawal of individual doses. Preservatives may be added to single-dose parenteral products that are not terminally sterilized as a sterility assurance measure; i.e., to prevent growth of any microorganisms that could be introduced during filling operations. However, the inclusion of a preservative in single-dose parenteral products must be weighed against the need to develop formulations that are acceptable to regulatory bodies worldwide. Inclusion of a preservative can be a difficult task, given the wide range of viewpoints concerning which preservatives are acceptable and when it is appropriate to include them in a formulation. Partly because of this, there is a trend in parenteral product development to eliminate preservatives wherever it is possible to do so. This may require added measures in manufacturing to improve sterility assurance, such as barrier technology to provide positive separation of personnel from product during aseptic filling and/or stops.

The formulation scientist must be aware of interactions between preservatives and other components of the formulation that could compromise the efficacy of the preservative. For example, proteins can bind thimerosal, reducing preservative efficacy. Partitioning of the preservative into a micellar phase or an oil phase (in an emulsion) can also reduce the effective concentration of preservative available for bactericidal or bacteriostatic action. Preservative efficacy testing should be performed on the proposed formulation to assure an effective preservative concentration.

Several investigators have published research on incompatibilities of preservatives with rubber closures and other packaging components, particularly polymeric materials [11]. Again, challenging the product with selected microorganisms to measure bacteriostatic or bactericidal activity is necessary, including evaluation of efficacy as a function of time throughout the anticipated shelf life of the product.

More subtle effects of preservatives on injectable formulations are possible. Formulation of insulin is an illustrative case study. Insulin is usually formulated as a multiple-dose vial, since individual dosage varies among patients. Preservation of zinc insulin with phenol causes physical instability of the suspension, whereas methylparaben does not. However, the presence of phenol is required for obtaining protamine insulin crystals [9].

Buffers

Many drugs require a certain pH range to maintain product stability. As discussed previously, drug solubility may also be strongly dependent on the pH of the solution. An important aid to the formulator is the information contained in a graph of the solubility profile of the drug as a function of pH (Fig. 2). The

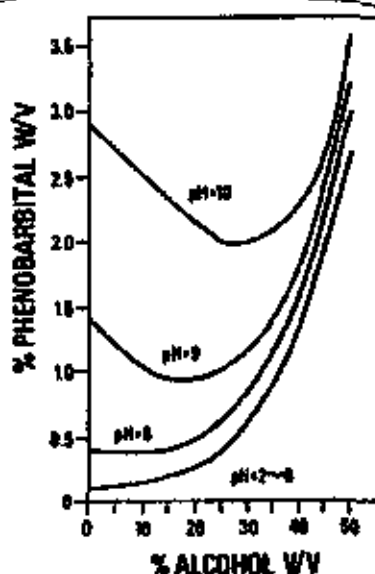


Fig. 2 Solubility of phenobarbital as a function of pH and alcohol concentration. (From Ref. 5).

product can then be buffered to approach maximum or minimum solubility, whichever is desired.

Parenteral products should be formulated to possess sufficient buffer capacity to maintain proper product pH. Factors that influence pH include product degradation, container and stopper effects, diffusion of gases through the closure, and the effect of gases in the product or in the headspace. However, the buffer capacity of a formulation must be readily overcome by the biological fluids; thus, the concentration and ratios of buffer ingredients must be carefully selected.

Buffer systems for parenterals consist of either a weak base and the salt of a weak base or a weak acid and the salt of a weak acid. Buffer systems commonly used for injectable products are acetates, citrates, and phosphates (see Table 2). Amino acids are being increasingly used as buffers, especially for parenteral injectables.

Chelating Agents

Chelating agents are added to complex and, thereby, inactivate metals such as copper, iron, and zinc that generally catalyze oxidative degradation of drug molecules. Sources of metal contamination include raw material impurities, solvents, such as water, rubber stoppers, and containers; and equipment employed in the manufacturing process [12]. The most widely used chelating agents are edotate disodium derivatives and salts. Citric and tartaric acids are also employed as chelating agents.

Inert Gases

Another means of enhancing the product integrity of oxygen-sensitive medicaments is by displacing the air in the solution with nitrogen or argon. This technique may be made more effective by first purging with nitrogen or boiling the water to reduce dissolved oxygen. The container is also purged with nitrogen or argon before filling and may also be topped off with the gas before sealing.

Glass-seal ampoules provide the most impervious barrier for gas transmission. A butyl rubber stock is used with rubber-stoppered products that are sensitive to oxygen because it provides better resistance to gas permeation than other rubber stocks.

Solubilizing Agents and Surfactants

Drug solubility can be increased by the use of solubilizing agents, such as those listed in Table 2, and by nonaqueous solvents or mixed solvent systems, to be

discussed shortly. When using solubilizing agents, the formulator must consider their effect on the safety and stability of the drug.

A surfactant is a surface-active agent that is used to disperse a water-insoluble drug as a colloidal dispersion. Surfactants are used for wetting and to prevent crystal growth in a suspension. Surfactants are used quite extensively in parenteral suspensions for wetting powders and to provide acceptable syringability. They are also used in emulsions and for solubilizing steroids and fat-soluble vitamins.

Tonicity Adjustment Agents

It is important that injectable solutions that are to be given intravenously are isotonic or nearly so, because of osmotic pressure changes and the resultant exchange of ionic species across red blood cell membranes. Nonisotonic solutions, particularly if given in quantities larger than 100 mL, can cause hemolysis or crenation of red blood cells (owing to hypotonic or hypertonic solutions, respectively). Dextrose, sodium chloride, or potassium chloride is commonly used to achieve isotonicity in a parenteral formula.

Protectants

A protectant is a substance that is added to a formulation to protect against loss of activity caused by some stress that is introduced by the manufacturing process or to prevent loss of active ingredients by adsorption to process equipment or to primary packaging materials. Protectants are used primarily in protein formulations, liposomal formulations, and vaccines. For example, cryoprotectants and lyoprotectants are used to inhibit loss of integrity of the active substance resulting from freezing and drying, respectively. Compounds that provide cryoprotection are not necessarily the same as those that provide lyoprotection. Polyethylene glycol protects lactate dehydrogenase and phosphofructokinase from damage by freezing, but does not protect either protein from damage by freeze-drying. Compounds such as sucrose and trehalose are effective lyoprotectants for both proteins [13]. Effective cryo- and lyoprotectants must be determined on a case-by-case basis, but sugars and polyhydroxy compounds are usually the best candidate compounds. These same types of compounds also tend to markedly improve the stability of proteins against inactivation by thermal denaturation.

Another type of protectant is used to prevent loss of active substance—again, usually a protein and usually present at a very low concentration—by adsorption to

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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2020
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Patente de Invención



Patente de Modelo de Utilidad



Vía Nacional



Vía PCT (fase nacional)



Cap. I



Cap. II



No. Sol. Internacional

PCT/EP2004000888

Fecha de Presentación Internal.

30-01-2004

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:

Documentos estudiados

Descripción:

Folios: 91 a 113 (como se radicó inicialmente)

Reivindicaciones:

Folios: 114 a 127 (como se radicó inicialmente)

Folios: 141 a 151 Primera Modificación.

Folio: 193. Segunda Modificación.

Prioridad:

Folio 1 (30-01-2003, US60/444,351).

Respuesta del solicitante

Folios: 184 a 191 y Folios 194 a 207.

Se acepta para estudio el capítulo reivindicatorio del folio 193.

Objeto de la invención

Título de la solicitud: Formulaciones Farmacéuticas Líquidas de Palonosetron.

El objeto de la presente solicitud consiste en:

Suministrar una formulación de clorhidrato de palonosetrón con estabilidad farmacéutica creciente.