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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **06.019.211**
Solicitud de patente a nombre de **The Procter & Gamble Company**

Yo, DILIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como obrando como apoderada de la sociedad **The Procter & Gamble Company**, domiciliada en Cincinnati, Ohio, Estados Unidos de América, solicitante de la patente de la referencia, en respuesta al oficio No. 0635 notificado por fijación en lista el 14 de enero de 2011, relacionado con el concepto técnico de fondo No. 4463, me permito manifestar:

1. Nivel Inventivo

El examinador objeta el nivel inventivo de la presente solicitud, a la luz de lo divulgado por la anterioridad US 2002002282 (en adelante D1). En su examen técnico, el examinador asevera lo siguiente:

> *"[...] D1 enseña de manera directa un procedimiento para obtener hemipentahidrato de risendronato, en donde se usa agua, isopropanol a una temperatura entre 50-70°C y ajustando el pH a un valor entre 4,7-5,0, además dice que la temperatura de nucleación y la rata de cristalización son variables críticas para formar el hidrato que se desea, controlándose mediante la proporción de agua, la temperatura y la proporción de solvente [...]"*

En primer lugar, el solicitante quisiera anotar que la anterioridad D1 en el párrafo [0012] dice que la temperatura de nucleación se puede controlar ajustando la proporción de agua a soluto, la temperatura o la proporción de solvente orgánico a agua. En ningún momento hasta este punto se establece que el orden de adición del solvente orgánico respecto al agua sea un factor determinante al momento de controlar la proporción de los hidratos formados. Esto es reforzado en el párrafo [0021] de dicha anterioridad.

De hecho, como se puede observar en el párrafo [0025] de D1, el proceso allí divulgado comprende los siguientes pasos:

- Suspender Risendronato en agua a 60°C;
- Ajustar el pH de 4,7-5.0 con NaOH;
- Agregar isopropanol a la solución resultante;
- Enfriar la solución; y
- Recuperar el sólido suspendido.

En contraste, el proceso de la presente solicitud se lleva a cabo de la siguiente forma:

- Disolver Risendronato en una **solución de agua e isopropanol**;
- Ajustar el **pH a 6**;
- Calentar la solución a una **temperatura entre 50 y 60°C**;
- **Filtrar** la solución caliente:
- Ajustar nuevamente el pH a entre 4,7 y 5;
- **enfriar** la solución a entre 20 y 40°C;
- agregar nuevamente **isopropanol y un ácido inorgánico** para obtener un pH de entre 4,7 y 5,2; y
- Aislar la forma hemipentahidratada de Risendronato.

Como se puede observar, la presente solicitud reclama un proceso muy diferente respecto a lo divulgado en D1. En primer lugar, la anterioridad citada no enseña ni sugiere empezar con una solución de agua e isopropanol principalmente porque, como se establece en los párrafos [0012] y [0021], la proporción de agua a solvente es una de las variables que determina el tipo de cristal que se forma y en D1 esta proporción se controla agregando el isopropanol al agua una vez se ha disuelto el Risendronato.

Segundo, la presente solicitud eleva el pH hasta 6, cosa que no se menciona en ninguna parte en D1. De hecho, un pH de 6 se encuentra muy por encima del rango de 4,7-5,0 establecido en el proceso de D1. Para ningún técnico con habilidad ordinaria en la materia sería obvio o evidente elevar el pH por encima de los valores establecidos en el arte previo, especialmente cuando dicho arte previo no enseña ni sugiere que llevar el pH por encima de 5,0 represente u ofrezca alguna ventaja técnica, y menos que tal ajuste de pH deba realizarse luego de disolver el Ridendronato en la mezcla de agua a isopropanol.

Tercero, la anterioridad D1 agrega el Risendronato al agua caliente a una temperatura de 60°C en tanto que la presente solicitud agrega el Risendronato a una solución fría **y luego eleva la temperatura** hasta 60°C. Si bien D1 enseña que la temperatura es una condición importante para regular el tipo de hidrato que se obtiene o la proporción de los hidratos obtenidos, nada en dicha anterioridad enseña o sugiere que exista una ventaja al **disolver el Risendronato en una solución fría y luego subir la temperatura de la misma**.

Cuarto, el pH de la solución se ajusta a entre 4,7 y 5,0, condición que se diferencia de D1 ya que en la presente solicitud el pH inicial de la solución es 6,0, lo cual implica la adición de una solución que reduzca el pH de la solución. El paso de **reducir el pH de la solución** no es enseñado ni sugerido por la anterioridad D1. Nada en la anterioridad D1 enseña o sugiere que el ajuste del pH sea una variable importante al momento de establecer cual forma cristalina se obtiene. De hecho, nada en el arte previo o en el conocimiento del experto medio en la materia enseña o sugiere que el pH de la solución sea un factor que afecte la formación selectiva de una forma cristalina sobre otra. Por lo tanto, este ajuste del pH de 6,0 a entre 4,5 y 5,0 no es obvio ni evidente a partir de D1.

Quinto, la presente solicitud enfría la solución hasta entre 20 y 40°C y agrega una solución de isopropanol y un ácido orgánico para ajustar nuevamente el pH a un valor entre 4,7 y 5,2. Como se puede apreciar, **la adición de más solvente junto con un ácido inorgánico no se enseña ni sugiere en D1**. Es evidente que para el solicitante la clave para lograr la formación selectiva de la forma hemipentahidratada de Risendronato gira en base al ajuste del pH y el orden en que se adicionan los solventes, más que la proporción de agua a isopropanol, la temperatura o la proporción de agua a soluto como se establece en D1.

Contrario a lo establecido por el examinador, los pasos adicionales de la presente solicitud van más allá de un simple ajuste de las variables del proceso. Un técnico que quisiera mejorar las características del proceso de D1 realizaría cambios alrededor de las condiciones establecidas en dicha anterioridad, no tendría ninguna razón particular para agregar etapas, elevar el pH, modificar la curva de enfriamiento y adicionar nuevas sustancias al proceso cuando claramente dicha anterioridad no enseña ni sugiere que llevar a cabo tales modificaciones pueda resultar en un efecto benéfico y menos aún en un proceso que forma de manera selectiva el hemipentahidrato de Risendronato.

Como se puede apreciar en D1, la materia allí divulgada se enfoca básicamente en incrementar la presencia de una u otra forma, hemipentahidrato o monohidrato, en el producto resultante. En ningún momento dicha anterioridad enseña o sugiere que sea posible obtener de manera selectiva una u otra forma. De hecho, el técnico con habilidad ordinaria en la materia puede concluir de D1 que lo que allí se busca es incrementar la proporción de una u otra forma cristalina, no como obtener de manera selectiva y específica el hemipentahidrato o el monohidrato.

El examinador dice que la presente solicitud no presenta evidencia de un efecto mejorado o sorprendente. Si el hecho que el proceso reclamado logre obtener de manera selectiva la forma hemipentahidratada del Risendronato no resulta un efecto mejorado o sorprendente por sobre un documento que solo logra

incrementar la presencia de una forma sin eliminar la otra, entonces el solicitante no sabe exactamente que es lo que el examinador considera un efecto mejorado o sorprendente, particularmente cuando se consideran las ventajas terapéuticas que se logran del empleo exclusivo de la forma hemipentahidratada por sobre la forma monohidratada.

Finalmente y aún cuando el solicitante es consciente del contenido del Artículo 4bis del Convenio de París el cual establece la independencia de las patentes obtenidas para la misma invención en diferentes países, consideramos importante señalar que la novedad y el nivel inventivo de la presente solicitud han sido reconocidos en Estados Unidos y en la Oficina de Patentes Europea, toda vez que se ha otorgado la patente a esta invención bajo los números US 7.002.014 y EP 1.651.656. En prueba de este hecho, adjuntamos la primera página y las reivindicaciones de dichas patentes.

En resumen, me permito decir que gracias a los argumentos anteriormente mencionados, la presente solicitud cumple cabalmente con los requisitos de nivel inventivo respecto al proceso expuesto en el capítulo reivindicatorio adjunto. Por lo tanto, solicito comedidamente a ese despacho se sirva reconocer estos requisitos y conceder el privilegio de patente de invención a la solicitud en estudio.

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(54) **PROCESS FOR CONTROLLING CRYSTAL STRUCTURE OF RISEDRONATE**

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(57) **ABSTRACT**

The present invention relates to a process for controlling the crystal form of 3-pyridyl-1-hydroxy-ethylidene-1,1-bisphosphonic acid salt (Risedronate). The process employs a pH adjustment step to induce the proper hydrate form and thereby avoiding inadvertent nucleation of undesired hydrate forms.

embodiment, cooling to a range of from 20° C. to 30° C. is used to ensure a thorough ripening of the desired crystal form.

[0042] The present invention makes use of the fact that the saturated nucleation solution can be re-heated or held at a temperature between the temperature of Step (b) and the final desired temperature of Step (e) if unwanted monohydrate crystals are present, thereby providing the following optional Steps (c) (i) and (c) (ii), said steps comprising:

[0043] c) (i) holding said nucleating slurry to a temperature from about 20° C. to about 30° C. and holding said slurry at said temperature until said monohydrate form is converted to said hemipentahydrate form;

[0044] c) (ii) repeating step (c).

[0045] Because these optional steps may be necessary due to unforeseen circumstances which cause the undesirable formation of monohydrate crystals, the formulator may also modify one or more of the conditions of Step (c), inter alia, the rate of cooling or the final temperature.

[0046] Step (f):

[0047] Step (f) of the present invention relates to adding to said nucleating slurry obtained in Step (e), isopropyl alcohol and sufficient inorganic acid to provide a pH of from 4.7 to 5.2 to form a ripened slurry of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt in the hemipentahydrate crystal form. The ripened slurry comprises the bulk of the Risedronate which was charged to the process in Step (a).

[0048] The isopropyl alcohol is added to the nucleating slurry prior to adjusting the pH to the desired range. In one embodiment, isopropyl alcohol in an amount 0.25 times the weight of water present is added with full agitation followed by stirring for 30 minutes.

[0049] Non-limiting examples of inorganic acids which can be used to adjust the pH range once the final aliquot of isopropyl alcohol is added, include HCl, H_2SO_4, and H_3PO_4. Once the desired amount of acid is added the formulator can continue stirring unit crystallization is complete.

[0050] In the event the pH range of the final nucleating slurry is lower than the desired final range, an inorganic base can be used to adjust the pH to the desired range. Suitable inorganic bases include those described herein above for Step (a).

[0051] There are several iterations by which Step (f) can be conducted. For Example, in a first iteration the isopropyl alcohol and inorganic acid used to form said ripened slurry is added as an admixture. This admixture can be added above or below the level of liquid in the nucleating slurry. Alternatively, the isopropyl alcohol can be added separately from said and inorganic acid either completely or in an alternating manner.

[0052] Step (g):

[0053] Step (g) of the present invention relates to isolating 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt hemipentahydrate. This step can be accomplished in any manner which is compatible with the equipment used in the steps herein above.

[0054] One means for isolating the Risedronate crystals is by filtration, either via gravity or via vacuum. However, the formulator may instead desire to decant the filtrate to provide the final product.

[0055] The process of the present invention relates to controlling nucleation and crystal form by adjusting the pH of the solute saturated solution and, therefore, addition of isopropyl alcohol must be done in a manner which does not shock the stabilized system and cause the undesired formation of monohydrate crystals. In addition, controlled cooling below the temperature utilized in Step (b) will ensure controlled growth of the desired hemipentahydrate crystals.

[0056] One embodiment of the present invention comprises the steps of:

[0057] a) dissolving in an admixture of isopropyl alcohol and water, 3-pyridyl-1-hydroxy-ethylidene-1,1-bisphosphonic acid and NaOH in sufficient amount to provide a pH of 6, to form a solution;

[0058] b) heating the solution to 55° C. to form a heated solution;

[0059] c) filtering said heated solution to form a filtered solution, while maintaining a temperature of 55° C.;

[0060] d) adjusting the pH of said filtered solution with HCl to a pH range of from 4.7 to 5, while maintaining a temperature of 55° C., to form a neutralized solution;

[0061] e) cooling the neutralized solution to 25° C. to form nucleating slurry of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt; and

[0062] f) adding to said slurry isopropyl alcohol and sufficient HCl to provide a pH of from 4.7 to 5.2 to form a ripened slurry of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt in the hemipentahydrate crystal form The following is a non-limiting example of the process of the present invention.

[0063] a) To a first vessel is charged water (1640 mL) and isopropyl alcohol (246 g). The solution is stirred and 3-pyridyl-1-hydroxy-ethylidene-1,1-bisphosphonic acid (Risedronate) (200 g) is added. With stirring, a 16.7% aqueous solution of NaOH (318.1 g, 2.0 eq, 1.328 mol) is added.

[0064] b) The solution is then heated to 55° C. and held at a temperature of 55±5° C. until all of the solute has dissolved.

[0065] c) The solution is then filtered and transferred to a second vessel which is pre-heated to a temperature of 55±5° C. The filter is washed with water (80 g).

[0066] d) While maintaining the temperature at about 55° C., 12 N HCl (38.7 mL, 0.7 eq., 0.465 mol) is added to provide a pH of from 4.7 to 5.0. The solution is stirred for 30 minutes.

[0067] e) The solution is then slowly cooled to 25° C. over a period of 2.5 hours and a nucleating slurry of Risedronate forms.

[0068] f) Isopropyl alcohol (410 g) is added to the nucleating slurry and the contents stirred for 30 minutes after which sufficient HCl is added to provide a pH of from 4.7 to 5.2.

[0069] g) After stirring for an additional hour the crystals of Risedronate which have formed are collected by filtration.

[0070] A further embodiment of the present invention relates to a process wherein lower yields with higher purity are obtained, said embodiment comprising the steps of:

[0071] a) dissolving in an admixture of isopropyl alcohol and water, 3-pyridyl-1-hydroxy-ethylidene-1,1-bisphosphonic acid and an inorganic base in sufficient amount to provide a pH of 6, to form a solution;

[0072] b) heating the solution from about 50° C. to about 60° C. to form a heated solution;

[0073] c) filtering said heated solution to form a filtered solution;

[0074] d) adjusting the pH of said filtered solution with an inorganic acid to a pH range of from 4.7 to 5 while maintaining the temperature at the level obtained in step (b) to form a neutralized solution;

[0075] e) cooling the neutralized solution to a temperature of about 20° C. to about 40° C. to form a nucleating slurry of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt; and

[0076] f) isolating 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt hemipentahydrate.

[0077] All documents cited in the Detailed Description of the Invention are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

[0078] While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

What is claimed is:

1. A process for preparing 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt in the hemipentahydrate crystal form, said process comprising the steps of:

a) dissolving in an admixture of isopropyl alcohol and water, 3-pyridyl-1-hydroxy-ethylidene-1,1-bisphosphonic acid and an inorganic base in sufficient amount to provide a pH of 6, to form a solution;

b) heating the solution from about 50° C. to about 60° C. to form a heated solution;

c) filtering said heated solution to form a filtered solution;

d) adjusting the pH of said filtered solution with an inorganic acid to a pH range of from 4.7 to 5 while maintaining the temperature at the level obtained in step (b) to form a neutralized solution;

e) cooling the neutralized solution to a temperature of about 20° C. to about 40° C. to form a nucleating slurry of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt;

f) adding to said slurry isopropyl alcohol and sufficient inorganic acid to provide a pH of from 4.7 to 5.2 to form a ripened slurry of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt in the hemipentahydrate crystal form; and

g) isolating 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt hemipentahydrate.

2. A process according to claim 1 wherein the percentage of isopropyl alcohol to water in step (a) is from 0% to 30%.

3. A process according to claim 1 wherein the ratio of isopropyl alcohol to water in step (a) is 1:6.7.

4. A process according to claim 1 wherein the ratio of isopropyl alcohol to water in step (a) is from 1:5.9 to 1:9.1.

5. A process according to claim 1 wherein said inorganic base is step (a) is selected from the group consisting of NaOH, $NaOCH_3$, and $NaOC(O)CH_3$.

6. A process according to claim 5 wherein said inorganic base is NaOH.

7. A process according to claim 1 wherein said temperature in step (b) is from 52° C. to 58° C.

8. A process according to claim 7 wherein said temperature is 55° C.

9. A process according to claim 1 wherein said filtered solution formed in step (c) has the same temperature as the heated solution formed in step (b).

10. A process according to claim 1 wherein said inorganic acid in step (d) is selected from the group consisting of HCl, H_2SO_4, and H_3PO_4.

11. A process according to claim 10 wherein said inorganic acid is HCl.

12. A process according to claim 1 wherein said temperature in step (e) is from 20° C. to 40° C.

13. A process according to claim 12 wherein said temperature is from 20° C. to 30° C.

14. A process according to claim 13 wherein said temperature is 25° C.

15. A process according to claim 1 wherein said inorganic acid in step (f) is selected from the group consisting of HCl, H_2SO_4, and H_3PO_4.

16. A process according to claim 15 wherein said inorganic acid is HCl.

17. A process according to claim 1 wherein said isopropyl alcohol and inorganic acid used to form said ripened slurry in step (f) is added as an admixture.

18. A process according to claim 1 wherein said isopropyl alcohol added in step (f) is added separately from said and inorganic acid.

19. A process according to claim 18 wherein said isopropyl alcohol and said inorganic acid are added separately but concurrently.

20. A process according to claim 18 wherein said isopropyl alcohol and said inorganic acid are added in alternating portions.

21. A process according to claim 1 wherein said product isolated in step (g) is isolated by filtration.

22. A process according to claim 1 wherein said product isolated in step (g) is isolated by decanting the solvent.

23. A process according to claim 1 wherein said product isolated in step (g) is isolated by centrifugation.

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(54) **PROCESS FOR CONTROLLING CRYSTAL STRUCTURE OF RISEDRONATE**

VERFAHREN ZUR STEUERUNG DER KRISTALLSTRUKTUR VON RISEDRONAT

PROCEDE POUR CONTROLLER LA STRUCTURE CRISTALLINE DU RISEDRONATE

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1,1-bisphosphonic acid salt in the hemipentahydrate crystal form

[0039] The following is a non-limiting example of the process of the present invention.

a) To a first vessel is charged water (1640 mL) and isopropyl alcohol (246 g). The solution is stirred and 3-pyridyl-1-hydroxy-ethylidene-1,1-bisphosphonic acid (Risedronate) (200 g) is added. With stirring, a 16.7% aqueous solution of NaOH (318.1 g, 2.0 eq, 1.328mol) is added.
b) The solution is then heated to 55 °C and held at a temperature of 55 ± 5 °C until all of the solute has dissolved.
c) The solution is then filtered and transferred to a second vessel which is pro-heated to a temperature of 55 ± 5 °C. The filter is washed with water (80 g).
d) While maintaining the temperature at about 55 °C, 12 N HCl (38.7 mL, 0.7 eq., 0.465 mol) is added to provide a pH of from 4.7 to 5.0. The solution is stirred for 30 minutes.
e) The solution is then slowly cooled to 25 °C over a period of 2.5 hours and a nucleating slurry of Risedronate forms.
f) Isopropyl alcohol (410 g) is added to the nucleating slurry and the contents stirred for 30 minutes after which sufficient HCl is added to provide a pH of from 4.7 to 5.2.
g) After stirring for an additional hour the crystals of Risedronate which have formed are collected by filtration.

[0040] A further embodiment of the present invention relates to a process wherein lower yields with higher purity are obtained, said embodiment comprising the steps of:

a) dissolving in an admixture of isopropyl alcohol and water, 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid and an inorganic base in sufficient amount to provide a pH of 6, to form a solution;
b) heating the solution to a temperature of from 50 °C to 60 °C to form a heated solution;
c) filtering said heated solution to form a filtered solution;
d) adjusting the pH of said filtered solution with an inorganic acid to a pH range of from 4.7 to 5 while maintaining the temperature at the level obtained in step (b) to form a neutralized solution;
e) cooling the neutralized solution to a temperature of from 20 °C to 40 °C to form a nucleating slurry of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt; and
f) isolating 3-pyridyl-1-hydroxyethylideno-1,1-bisphosphonic acid salt hemipentahydrate.

Claims

1. A process for preparing 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt in the hemipentahydrate crystal form, said process comprising the steps of:

   a) dissolving in an admixture of isopropyl alcohol and water, 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid and an inorganic base in sufficient amount to provide a pH of 6, to form a solution;
   b) heating the solution to a temperature of from 50°C to 60°C to form a heated solution;
   c) filtering said heated solution to form a filtered solution;
   d) adjusting the pH of said filtered solution with an inorganic acid to a pH of from 4.7 to 5 while maintaining the temperature at the level obtained in step (b) to form a neutralized solution;
   e) cooling the neutralized solution to a temperature of from 20°C to 40°C to form a nucleating slurry of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt;
   f) optionally, adding to said slurry isopropyl alcohol and sufficient inorganic acid to provide a pH of from 4.7 to 5.2 to form a ripened slurry of 3- pyridyl- 1- hydroxyethylidene- 1,1- bisphosphonic acid salt in the hemipentahydrate crystal form; and
   g) isolating 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt hemipentahydrate.

2. A process according to Claim 1 wherein step (f) is performed.

3. A process according to Claim 1 or Claim 2 wherein, in step (a), the ratio of isopropyl alcohol to water is less than or equal to 30%, preferably from 1:5.9 to 1:9.1.

4. A process according to any of Claims 1 to 3 wherein said inorganic base in step (a) is selected from NaOH, $NaOCH_3$, and $NaOC(O)CH_3$; and is preferably NaOH.

5. A process according to any of Claims 1 to 4 wherein said temperature in step (b) is from 52°C to 58°C, preferably wherein said temperature is 55°C.

6. A process according to any of Claims 1 to 5 wherein said filtered solution formed in step (c) has the same temperature as the heated solution formed in step (b).

7. A process according to any of Claims 1 to 6 wherein said inorganic acid in step (d) is selected from HCl, H_2SO_4, and H_3PO_4; and preferably is HCl.

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8. A process according to any of Claims 1 to 7 wherein said temperature in step (e) is from 20°C to 40°C, preferably from 20°C to 30°C, more preferably wherein said temperature is 25°C.

9. A process according to any of Claims 2 to 8 wherein said inorganic acid in step (f) is selected from HCl, H_2SO_4, and H_3PO_4; and is preferably HCl.

10. A process according to any of Claims 2 to 9 wherein said isopropyl alcohol and said inorganic acid used to form said ripened slurry in step (f) is added as an admixture.

11. A process according to any of Claims 2 to 9 wherein said isopropyl alcohol added in step (f) is added separately from said inorganic acid.

12. A process according to Claim 11 wherein said isopropyl alcohol and said inorganic acid are added concurrently.

13. A process according to Claim 11 wherein said isopropyl alcohol and said inorganic acid are added in alternating portions.

14. A process according to any of Claims 1 to 13 wherein said product isolated in step (g) is isolated by filtration.

15. A process according to any of Claims 1 to 13 wherein said product isolated in step (g) is isolated by decanting the solvent.

16. A process according to any of Claims 1 to 13 wherein said product isolated in step (g) is isolated by centrifugation.

17. A process according to any of Claims 1 to 16 having an optional step (c) (i), said step comprising:

    c) (i) adding to said filtered solution 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid salt hemipentahydrate seed crystals.

18. A process according to any of Claims 2 to 17 wherein said product formed in step (f) is in the platelet crystal form.

19. A process according to any of Claims 1 to 16 wherein when said nucleating slurry formed in step (e) comprises an admixture of monohydrate and hemipentahydrate crystal forms, said process further comprises the steps of:

    e) (i) holding said nucleating slurry to a temperature from 20°C to 30°C and holding said slurry at said temperature until said monohydrate form is converted to said hemipentahydrate form;
    e) (ii) repeating step (e).

20. A process according to Claim 2 wherein:

    a) in step (a) the inorganic base is NaOH;
    b) in step (b) the solution is heated to 55°C;
    c) during step (c) a temperature of 55°C is maintained;
    d) in step (d) the inorganic acid is HCl and the temperature is maintained at 55°C;
    e) in step (e) the neutralized solution is cooled to 25°C; and
    f) in step (f) the inorganic acid is HCl.

Patentansprüche

1. Verfahren zum Herstellen von 3-Pyridyl-1-hydroxyethyliden-1,1-bisphosphonsäuresalz in der Hemipentahydrat-Kristallform, wobei das Verfahren die folgenden Schritte umfasst:

    a) Auflösen in einer Beimischung aus Isopropylalkohol und Wasser, 3-Pyridyl-1-hydroxy-ethyliden-1,1-bisphosphonsäure und einer anorganischen Base in ausreichender Menge zur Bereitstellung eines pH von 6, zum Bilden einer Lösung;
    b) Erhitzen der Lösung auf eine Temperatur von 50 °C bis 60 °C zum Bilden einer erhitzten Lösung;
    c) Filtrieren der erhitzten Lösung zum Bilden einer filtrierten Lösung;
    d) Einstellen des pH der filtrierten Lösung mit einer anorganischen Säure auf einen pH von 4,7 bis 5, während die Temperatur bei der in Schritt (b) erhaltenen Höhe zum Bilden einer neutralisierten Lösung aufrechterhalten wird;
    e) Abkühlen der neutralisierten Lösung auf eine Temperatur von 20 °C bis 40 °C zum Bilden einer keimbildenden Aufschlämmung von 3-Pyridyl-1-hydroxyethyliden-1,1-bisphosphonsäuresalz;
    f) optional Zufügen von Isopropylalkohol und ausreichend anorganischer Säure zur Aufschlämmung, um einen pH von 4,7 bis 5,2 zum Bilden einer gereiften Aufschlämmung von 3-Pyridyl-1-hydroxy-ethyliden-1,1-bisphosphonsäuresalz in der Hemipentahydrat-Kristallform bereitzustellen; und
    g) Isolieren von 3-Pyridyl-1-hydroxyethyliden-1,1-bisphosphonsäuresalz-Hemipentahydrat.

2. Verfahren nach Anspruch 1, worin Schritt (f) durchgeführt wird.

3. Verfahren nach Anspruch 1 oder 2, worin in Schritt

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