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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 02102450 00000003 Folios: 2
Fecha (ARD): 2005-04-20 09:26:54
Tramite : 011 PCT-PATENT 379 FASE NACI 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref: Expediente No.02.102.450

Solicitud de patente de invención titulada:

"PROCESO PARA LA PURIFICACIÓN DE UNA SAL DEL ÁCIDO CLAVULÁNICO".

Solicitante: SMITHKLINE BEECHAM P.L.C.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTICULO 44 DE LA DECISION 486, GACETA No. 546

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Dando cumplimiento a lo establecido en el articulo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de \$186.000 pesos para cubrir la tasa correspondiente, según la Resolución 31980 del año 2004.

Atentamente,



CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$186.000 pesos

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SUPERINDUSTRIA Y COMERCIO
 Radicacion : 02102450 00000003 Folios: 2
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 27,861
 FECHA : ABRIL 18 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
JOSE SANTOS	CONSIGNACION	BANCO POPULAR	050-00110-6	27054702	14/04/2005	6,954,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD
			186,000.00
		TOTAL :	186,000.00

SON: CIENTO OCHENTA Y SEIS MIL PESOS

RESPONSABLE : _____

[Handwritten signature]

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 02-102450

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION -
PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 546,
DE FECHA 30 DE NOVIEMBRE DE 2004, EL TERMINO HABIL SEÑALADO
POR LA LEY EXPIRA EL 24 DE FEBRERO DE 2005.**

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 ☒ _____

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12P 17/18, C07D 503/00	A1	(11) International Publication Number: WO 98/42858 (43) International Publication Date: 1 October 1998 (01.10.98)
(21) International Application Number: PCT/EP98/01637 (22) International Filing Date: 20 March 1998 (20.03.98) (30) Priority Data: 97104947.3 24 March 1997 (24.03.97) EP (34) Countries for which the regional or international application was filed: PT et al. (71) Applicant (for all designated States except US): CIPAN-COMPANHIA INDUSTRIAL PRODUTORA DE ANTIBIÓTICOS, S.A. [PT/PT]; Vala do Carregado, Apartado 60, P-2600 Castanheira do Ribatejo (PT). (72) Inventor; and (75) Inventor/Applicant (for US only): CARDOSO, Joaquim, P. [PT/PT]; Cipan-Companhia Industrial Produtora de Antibióticos, S.A., Vala do Carregado, Apartado 60, P-2600 Castanheira do Ribatejo (PT). (74) Agent: GODEMEYER, Thomas; Hauptstrasse 58, D-51491 Overath (DE).		(81) Designated States: AU, JP, NZ, US. Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PROCESS FOR THE ISOLATION OF A PHARMACEUTICALLY ACCEPTABLE ALKALI METAL SALT OF CLAVULANIC ACID		
(57) Abstract The invention relates to the process for the isolation of a pharmaceutically acceptable alkali metal salt of clavulanic acid from a fermentation broth containing impure clavulanic acid comprising the steps of filtration of the fermented broth, extraction of the clavulanic acid to a water immiscible or partly water immiscible solvent at pH from 1.2 - 2, precipitation of an alkali metal salt A of clavulanic acid by addition of a solution of an alkali metal alkylalkanoate, characterized by the following steps: before the filtration the fermented broth containing clavulanic acid is diluted with water, a flocculating agent is added and the pH is adjusted to 3 - 5, for further purification the alkali metal salt A of clavulanic acid is converted to clavulanic acid by addition of an inorganic acid and is extracted into a water immiscible or partly water immiscible solvent; a solution of a different alkali metal B alkyl alkanoate is added and the alkali metal salt B of clavulanic acid is precipitated.		

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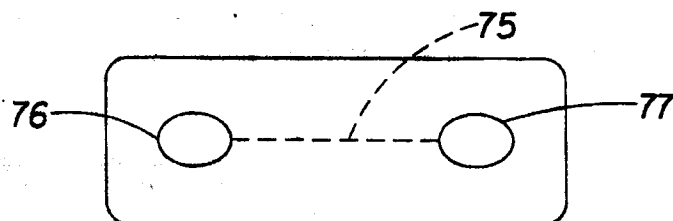


Fig. 7

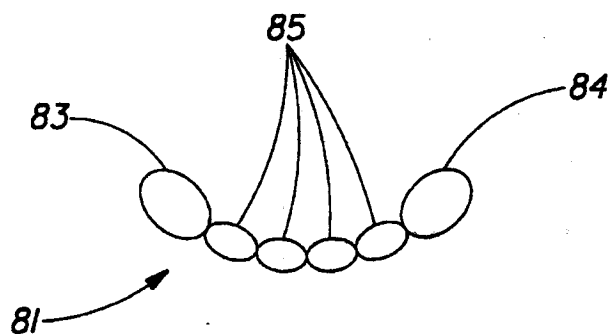


Fig. 8A

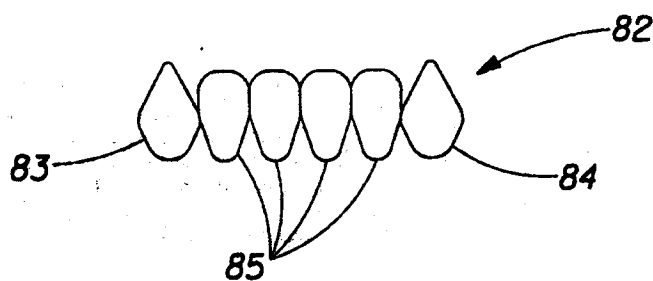


Fig. 8B

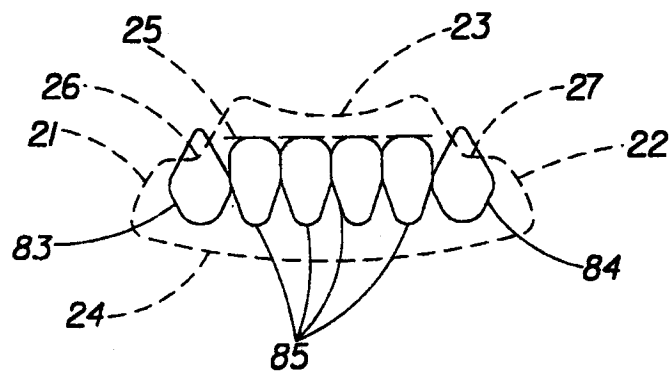


Fig. 9

Process for the isolation of a pharmaceutically acceptable
alkali metal salt of clavulanic acid

5 The present invention relates to a novel process for the isolation of the pharmaceutically acceptable alkali metal salt of clavulanic acid from a fermentation broth containing impure clavulanic acid comprising the steps of filtration of the fermented broth, extraction of clavulanic acid to a water im-
10 miscible or partly water immiscible solvent at a pH from 1.2 to 2, precipitation of the alkali metal salt A of clavulanic acid by addition of a solution of an alkali metal alkylalkanoate.

15 Clavulanic acid and its alkali metal salts and esters are used in pharmaceutical preparation to prevent the deactivation of β -lactam antibiotics. Commercial preparations of clavulanic acid contain potassium clavulanate in combination with amoxycillin trihydrate. Clavulanic acid is an unstable hygro-
20 scopic oil. Potassium clavulanate is more stable than the free acid or other salts, and is therefore most frequently used for commercial preparations.

Clavulanic acid and its derivatives are inhibitors of the β -
25 lactamases. The resistance of β -lactam antibiotics is associated with inactivation of β -lactam structure due to the opening of β -lactam ring by β -lactamase produced by bacteria. Thus the inactivating enzymes are commonly called as β -lactamase, they are divided into penicillinase and cephalos-
30 porinase.

Furthermore clavulanic acid itself is believed to have an antibacterial activity.

Clavulanic acid is produced from various strains of microorganism by a fermentation process. For this process for example strains belonging to the genus Streptomyces such as S. clavuligerus NRRL 3585 (USA Patent 4,110,165), S. jumonjinensis NRRL 5741 (British Patent 1,563,103), S. katsurahamanus IFO 13716 (Japanese Patent 83,009,579), and Streptomyces sp. P6621 FERM 2804 (Japanese Patent 55,162,993) are used. For the preparation of clavulanic acid by a fermentation process the microorganism Streptomyces clavuligerus is preferred.

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In the state of art different processes for the preparation and purification of the clavulanic acid containing fermentation broth are described.

15 GB 1 508 977 discloses preparation of clavulanic acid and its salts by filtration of the fermentation broth by passage through an anionic exchange resin.

GB 1 543 563 discloses a fermentation process wherein the pH
20 value of the medium is maintained in the range of 6.3 to 6.7. A pharmaceutically acceptable salt such as potassium clavulanate is prepared by ion exchange process from lithium clavulanate. However lithium clavulanate is not a pharmaceutically acceptable salt. Therefore it is necessary to add an
25 ion exchange process as a further step for preparing a pharmaceutically acceptable form of the compound. Furthermore, the remaining salt lithium chloride is soluble in organic solvents and therefore it is difficult to separate the lithium chloride in the aqueous phase during the extraction
30 process.

Further documents of the state of the art like EP-0 647 229 describe the use of amine salts of clavulanic acid as intermediate compounds for the preparation and purification of

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clavulanic acid and its alkali metal salts. EP-0 647 229 for example describes a process for the preparation of a purified clavulanic acid or a salt or ester thereof by preparing a diamine salt of clavulanic acid and converting this intermediate compound into clavulanic acid or a pharmaceutically acceptable salt or ester. The conversion is made by adding for example potassium 2-ethylhexanoate and precipitating potassium clavulanate. Many of such amines are either unsuitable for the production of a salt of clavulanic acid or they give rise to amine salts of clavulanic acid which are either hygroscopic or toxic or both and, therefore, are unsuitable for use as intermediates for the preparation of a pharmaceutically acceptable compound.

Other purification processes of the state of the arts are performed without any amine compounds. For example WO 95/34194 A2 describes a process for manufacturing an alkali metal salt of clavulanic acid wherein impure clavulanic acid in aqueous solution is extracted by a solvent mixture of ketone and alkyl acetate under acidic condition. The solution is then treated in a conventional manner and the solution of an alkali metal salt of alkanolic acid dissolved in ketone or alkanol solvent is added to obtain pure alkali metal salt of clavulanic acid. Thus the process according to this state of the art omits the step of formation of amine salts. This process has the advantage that the use of mostly toxic amines is no longer necessary. In a preferred embodiment as alkali metal salt of alkanolic acid sodium or potassium salts are used, especially potassium 2-ethylhexanoate.

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A similar process is also described in WO 96/28452 A1. This process comprises the steps of removing solids from a clavulanic acid containing fermentation broth by microfiltration, acidifying the filtrate to a pH between 1 and 3, extracting

the acidified filtrate with a water immiscible solvent and separating the clavulanic acid containing extract. This extract is mixed with a metal donor and at least one additional solvent. From the solution the metal clavulanate salt is separated.

As metal donor compounds organic salts, carbonates, bicarbonates or hydroxides of potassium, sodium, lithium or magnesium can be used. The use of carboxylic acid salt is preferred. Further preferred metal donors include potassium 2-ethylhexanoate, potassium acetate, lithium 2-ethylhexanoate and lithium acetate.

EP-0 182 522 B1 also describes a process for the preparation of clavulanic acid and its salts and esters. In this process the fermentation broth is worked up as follows. The solids are removed by filtration or centrifugation. The broth is acidified to a pH of 1 to 3 and clavulanic acid is extracted by adding a water immiscible solvent with two phases being separated for example by centrifugation. This gives the clavulanic acid in the water immiscible phase. The solution is purified by mixing it with the dissolved lithium 2-ethylhexanoate solution isolating lithium clavulanate and optionally converting the lithium salt to other salts or an ester. The conversion of the lithium salt to other salts is carried out by ion exchange procedures using ion exchange resins in the form of the desired cation preferably sodium or potassium.

The processes of the state of the art referred above have the disadvantage, that the alkali metal salts prepared by direct precipitation are not pure enough for a pharmaceutical use. Therefore, further purification steps like recrystallization, purification over a column etc. are necessary.

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The object of the invention therefore is to prepare clavulanic acid and its pharmaceutically acceptable alkali metal salts such as potassium clavulanate in a new and simple manner wherein the desired substance is obtained in a very high yield without any additional purification steps and of high purity avoiding the use of toxic amines or lithium compounds.

This technical problem is solved by a process which is characterized by the following steps:

- 10 - before the filtration of the fermentation broth, the fermentation broth containing clavulanic acid is diluted with water, a flocculating agent is added and the pH is adjusted to pH 3 to 5,
- for further purification the alkali metal salt A of clavulanic acid is converted to clavulanic acid by addition
15 of an inorganic acid and is extracted into a water immiscible or partly water immiscible solvent,
- and to the solution of clavulanic acid a solution of a different alkali metal alkylalkanoate B is added and the
20 alkali metal salt B of clavulanic acid is precipitated.

Suitable salts according to the present invention are pharmaceutically acceptable alkali metal salts and alkaline earth metal salts like sodium, potassium, calcium and magnesium
25 salts.

Of these compounds potassium clavulanate is the most stable compound which is normally used for pharmaceutical preparations. The clavulanic acid itself is an unstable hygroscopic
30 oil which is not used for the preparation of pharmaceutical compounds.

In a preferred embodiment the alkylalkanoate is an alkylhexanoate, especially 2-ethylhexanoate. The alkali metal A is sodium and the alkali metal B is potassium.

- 5 In a further preferred embodiment the filtered broth containing clavulanic acid is purified after the filtration step by adsorption on an anion exchange resin containing column and eluted with an aqueous solution of an alkali metal salt. As anionic exchange resin for example DIAION[®] SA-11A is used.
- 10 After the elution step clavulanic acid is extracted into a water immiscible solvent or a partly water immiscible solvent and sodium clavulanate is precipitated by the addition of sodium 2-ethylhexanoate solution in an appropriate solvent after dehydration with anhydrous sodium or magnesium sulphates
- 15 and purification with activated carbon.

As an alternative process step it is also possible to carry out the direct extraction of the clavulanic acid contained in the filtered broth to a water immiscible or partly water im-

20 miscible solvent at an adequate pH between 1.2 - 2.0 without using a column. Preferably 3 to 4 volumes of solvent in relation to the filtered broth are used in this step. The clavulanic acid is extracted from the above solvent to an aqueous solution using an organic base, preferably triethylamine or

25 diethylamine. In this operation, a concentration of about 10 to 15 times is obtained. The exhaust solvent can be re-used in the process without a purification step. The clavulanic acid is back extracted to a water immiscible or partly water immiscible solvent. From the solvent sodium clavulanate is

30 precipitated by addition of the sodium 2-ethylhexanoate solution in an appropriate solvent after dehydration.

Clavulanic acid is a hygroscopic oil and is not very stable in aqueous solution. Therefore, this solution of clavulanic

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Claims

1. Process for the isolation of a pharmaceutically acceptable alkali metal salt of clavulanic acid from a fermentation broth containing impure clavulanic acid comprising the steps of filtration of the fermented broth, extraction of the clavulanic acid to a water immiscible ~~partly water immiscible solvent~~ precipitation of an alkali metal salt A of clavulanic acid by addition of a solution of an alkali metal alkylalkanoate, characterized by the following steps:
- before the filtration the fermented broth containing clavulanic acid is diluted with water, a flocculating agent is added and the pH is adjusted to 3 - 5
 - for further purification the alkali metal salt A of clavulanic acid is converted to clavulanic acid by addition of an inorganic acid and is extracted into a water immiscible or partly water immiscible solvent
 - a solution of a different alkali metal B alkyl alkanoate is added and the alkali metal salt B of clavulanic acid is precipitated.
2. Process according to claim 1 wherein the alkylalkanoate is an alkylhexanoate, especially 2-ethylhexanoate.
3. Process according to claim 1 or 2 wherein the alkali metal A is sodium and the alkali metal B is potassium.
4. Process according to claims 1 to 3 wherein after the filtration step the clavulanic acid containing filtered

broth is purified by adsorption on an anion exchange resin containing column and eluted with an aqueous solution of an alkali metal salt.

- 5 5. Process according to claims 1 to 4 wherein the solution of clavulanic acid in the water immiscible or partly water immiscible solvent is dehydrated by addition of anhydrous sodium or magnesium sulphates and further purified by addition of activated carbon.
- 10 6. Process according to claim 1 to 5 wherein 3 to 4 volumes of water immiscible or partly water immiscible solvent are used in relation to the solution of the filtered broth containing the clavulanic acid.
- 15 7. Process according to claim 1 to 6 wherein the solvent is ethyl acetate, butyl acetate, methyl isobutyl ketone and mixtures thereof.
- 20 8. Process according to claim 1 to 7 wherein as flocculating agent a quaternary ammonium salt is used.
- 25 9. Process according to claims 1 to 8 wherein after the filtration step the clavulanic acid is extracted without using a column to a water immiscible or partly water immiscible solvent at a pH from 1.2 to 2.0.
- 30 10. Process according to claims 1 to 9 wherein 3 to 4 volumes of solvent in relation to the filtered broth are used.
11. Process according to claims 1 to 10 wherein clavulanic acid is extracted from the water immiscible or partly water immiscible solvent to an aqueous solution using an

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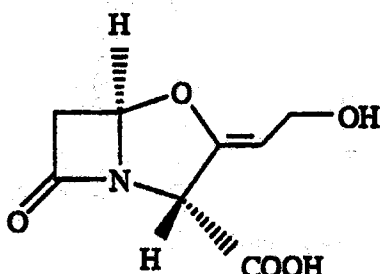
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 503/02	A1	(11) International Publication Number: WO 96/23622 (43) International Publication Date: 4 June 1996 (04.06.96)
(21) International Application Number: PCT/EP97/06578 (22) International Filing Date: 25 November 1997 (25.11.97) (30) Priority Data: A 2062/96 27 November 1996 (27.11.96) AT (71) Applicant (for all designated States except US): BIOCHEMIE GESELLSCHAFT MBH [AT/AT]; A-6250 Kundl (AT). (72) Inventors; and (75) Inventors/Applicants (for US only): SUMMER, Harald [AT/AT]; Winklweg 8, A-6300 Woergl (AT). RENZL, Alois [AT/AT]; A-6233 Kramsach 208 (AT). WAGNER, Helmut [AT/AT]; A-6233 Kramsach (AT). (74) Agents: WYMANN, Gérard et al.; Novartis AG, Patent & Trademark Dept., Lichtstrasse 35, CH-4002 Basle (CH).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PURIFICATION OF FERMENTED CLAVULANIC ACID (57) Abstract A process for the production of clavulanic acid and pharmaceutically acceptable salts thereof by: a) fermentation of a micro-organism which is capable to produce clavulanic acid, b) isolation of clavulanic acid from the fermentation broth, c) purification of clavulanic acid, e.g. via a salt thereof, d) conversion of the purified clavulanic acid of step c), e.g. of a salt thereof into a pharmaceutically acceptable salt of clavulanic acid, wherein the fermentation broth is extracted with a solvent prior to isolation of clavulanic acid.		

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PURIFICATION OF FERMENTED CLAVULANIC ACID

- 5 The present invention relates to a process for the purification of fermented products, *i.e.* in the production of pharmaceutically acceptable salts of clavulanic acid of formula



- 10 *e.g.* potassium clavulanate.

Pharmaceutically acceptable salts of clavulanic acid are known and various production processes, for example *via*

- 15 a) fermentation of a micro-organism which is capable to produce clavulanic acid
b) isolation of clavulanic acid from the fermentation broth
c) purification of clavulanic acid, *e.g.* *via* a salt thereof
d) conversion of the purified clavulanic acid of step c), *e.g.* of a salt thereof into a pharmaceutically acceptable salt of clavulanic acid
are disclosed.

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- It has now been found that the production of a pharmaceutically acceptable salt of clavulanic acid, *e.g.* such as the potassium salt may surprisingly be improved, if the aqueous fermentation broth is extracted with a solvent before clavulanic acid is isolated. Due to such an extraction prior to isolation, clavulanic acid, *e.g.* in form of a pharmaceutically acceptable salt, may be
25 obtained in surprising pure form and surprising high yields from the fermentation broth.

In one aspect the present invention provides a process for the production of clavulanic acid and pharmaceutically acceptable salts thereof by

- 30 a) fermentation of a micro-organism which is capable to produce clavulanic acid
b) isolation of clavulanic acid from the fermentation broth
c) purification of clavulanic acid, *e.g.* *via* a salt thereof

d) conversion of the purified clavulanic acid of step c), *e.g.* of a salt thereof into a pharmaceutically acceptable salt of clavulanic acid, *e.g.* potassium clavulanate, characterized in that the fermentation broth is extracted with a solvent, *e.g.* selected from an ether, a ketone, an ester or an alcohol, prior to isolation of clavulanic acid.

5

Fermentation step a) may be carried out as usual, for example, as generally described *e.g.* in GB 1508977 and WO 93/25557. A particular fermentation process, is disclosed, *e.g.* in EP 182 522 by continuously or intermittently feeding a carbon source during fermentation; *e.g.* in WO 96/18743 by keeping low levels of ammonium and urea; *e.g.* in WO 97/19187 by strict control of the soluble phosphate content in the fermentation medium; *e.g.* in EP 349 121; WO 95/03416; CA 2108113; WO 94/18326; WO 94/12654; and WO 96/10084; by production of clavulanic acid from a host transformed with a vector comprising a DNA or a DNA fragment that is encoding at least one enzyme involved in clavulanic acid production. An appropriate micro-organism may be for example a micro-organism of the genus *Streptomyces*, such as *S. clavuligerus*, *i.e.* strain NRRL 3585, or *Streptomyces sp.* P6621 FERM 2804 (Japanese patent 55,162,993) or other mutants. Fermentation under appropriate conditions is in more detail known from various publications, *e.g.* from references cited herein under step a) and under steps b), c) and d) below, the content of which, including prior art citations therein, is incorporated herein by reference.

20

According to the present invention the fermentation broth is extracted prior to isolation of clavulanic acid. Extraction of an aqueous fermentation broth may *e.g.* be carried out as follows: Extraction may be carried out as usual, *e.g.* according to any method disclosed in any of the references cited under step a) above, or step b), c) and d) below.

25

The entire unfiltered fermentation broth, or, a fermentation broth from which at least part of the suspended solids have been removed, for example by flocculation, *e.g.* by pH adjustment or addition of flocculation agent(s); by filtration, *e.g.* by precoat filtration on a rotary vacuum filter, *e.g.* assisted by a filtering aid, for example based on mineral or cellulose; by crossflow filtration with or without prior sieving of coarse particles; by microfiltration; or by centrifugation may be extracted with a solvent, *e.g.* an organic solvent, which is able to form a liquid/liquid phase system in contact with an aqueous fermentation broth, *e.g.* which is immiscible with the broth.

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The aqueous, clavulanic acid containing liquid may be pre-concentrated prior to extraction, to achieve specific concentration ranges, *e.g.* by anion exchange or osmotic methods to a

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concentration of clavulanic acid of 20 to 80 g/kg, such as 10 to 50 g/kg, *e.g.* 10 to 40 g/kg, for example 10 to 30 g/kg.

In another aspect the present invention provides a process as defined above, characterized in that
5 at least part of the solids suspended in the fermentation broth are removed before extraction;
and a process as defined above, characterized in that the fermentation broth is concentrated prior
to extraction.

A solvent for extraction includes, *e.g.* an organic solvent, which is able to form a liquid/liquid
10 phase system in contact with an aqueous fermentation broth, such as ethers, ketones, *e.g.* methyl
isobutyl ketone, diethylketone, methylethyl ketone; esters, *e.g.* ethyl acetate, a propylacetate; or
alcohols, such as a butanol, for example *n*-butanol or iso-butanol, preferably ethyl acetate,
diethylketone, methyl isobutylketone, such as ethyl acetate; wherein clavulanic acid should be
preferably not or only to a small extent soluble under the extraction conditions, *e.g.* depending
15 on the pH of the fermentation broth. Mixtures of individual solvents, *e.g.* as described above
may be used.

The ratio, *e.g.* volume ration, of the solvent and the fermentation broth is not critical; *e.g.* a ratio
of 0.5:1 to 3:1 may be used. One or several extractions may be carried out. An amount of solvent
may be used which is sufficient that two liquid phases in contact with the fermentation broth are
20 formed.

Extraction may be carried out at and around a native pH, *e.g.* at a pH of 5.5 to 7.5.

Phase separation of the aqueous and the organic phase may be facilitated, for example by
centrifugation methods, *e.g.* centrifugal separators or centrifugal decanters.

Removal of impurities, such as dyes or other, *e.g.* biomass residues, of the clavulanic acid
25 containing liquid may be carried out, either prior or subsequent to extraction, *e.g.* as usual, *e.g.*
by adsorption, *e.g.* by use of activated carbon in powder form, *e.g.* in a quantity of ca. 0.5% to
5% (based on the weight of a clavulanic acid containing liquid); or by use of activated carbon in
granulated form, which when filled into a column may purify an, *e.g.* preconcentrated clavulanic
acid containing liquid, percolating through; or by use of adsorber or ion exchange resins, which,
30 *e.g.* may be suitable for selectively removing dyes and other impurities from solvents, *e.g.* by use
of such resins in a batch process or column-percolation process; or *e.g.* by other methods, such as
a crossflow method, *e.g.* permeation of the clavulanic acid containing liquid through, *e.g.* a
membrane of *e.g.* small pore size, such as a pore size of *e.g.* 1 to 3 kD.

35 Isolation step b) may be carried out, for example,

by adjusting the pH of a fermentation broth, *e.g.* to an pH at which clavulanic acid is present in free acid form, *e.g.* a pH of ca. 1.5 to 2.5, such as 1.5 to 2.5; after the extraction according to the present invention; and

- 5 extraction of an pH adjusted, *e.g.* acidified fermentation broth with a solvent in which clavulanic acid is soluble under the extraction conditions, and which is able to form a liquid/liquid phase system in contact with an aqueous fermentation broth, *e.g.* by direct extraction of an *e.g.* acidified fermentation broth, or after removing at least part of the solids suspended in an *e.g.* acidified fermentation broth, *e.g.* according to an extraction method as usual, *e.g.* as described above.

- 10 Solids may be removed, for example by flocculation, filtration, *e.g.* by microfiltration, or by centrifugation.

A water-miscible solvent may be added to a fermentation broth in order to improve filterability of the fermentation broth prior to solid removal.

- 15 An extraction solvent includes a solvent wherein clavulanic acid is soluble under the extraction conditions, *e.g.* ketones, such as methyl-iso-butyl ketone, diethylketone; esters, such as ethyl acetate, a propyl or a butyl acetate or alcohols, such as a butanol, for example n-butanol or isobutanol, preferably ethyl acetate. Mixtures of individual solvents, *e.g.* as described above may be used. Preferably the same solvent may be used which was used for extraction of the fermentation broth prior to isolation of clavulanic acid (*e.g.* at or around a native pH).

- 20 An amount of solvent may be used which is sufficient that two liquid phases in contact with the fermentation broth are formed. Per part of the fermentation broth, *e.g.* 1:1 to 5:1 parts of the solvent may be used.

One or several extractions of the *e.g.* acidified fermentation broth may be carried out.

- 25 In another aspect the present invention provides process as defined above, characterized in that isolation step c) is effected *via* extraction from an aqueous solution of clavulanic acid; and a process as defined above, characterized in that as a solvent for the extraction of clavulanic acid from an aqueous solution thereof the same solvent is used which was used for extraction of the fermentation broth prior to isolation of clavulanic acid thereof.

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An aqueous, clavulanic acid containing liquid may be pre-concentrated, conveniently prior to acidification and clavulanic acid extraction, to achieve specific clavulanic acid concentration ranges by a method as usual, such as by fine vacuum evaporation; or an osmotic method such as crossflow reversed osmosis, crossflow nanofiltration, anion exchange, to obtain a concentration of *e.g.* 20 g to 80 g clavulanic acid per kg in the concentrate, such as 10 to 50 g/kg, *e.g.* 10 to 40 g/kg, for example 10 to 30 g/kg.

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R₁₅, R₁₆, R₁₇ and R₁₈ jointly independently denotes a cyclic alkylene ring having 3 to 6 methylene groups, one of these groups being optionally substituted by an oxygen or a sulphur atom or by an amino group; and

R₁₉ denotes a hydrogen atom or a methyl group; and

5 p denotes an integer from 1 to 3.

Particularly useful amines may be *e.g.* tert.butylamine, tert.octylamine, diisopropyl-ethylen-diamine, N,N,N',N'-tetramethyl-ethylendiamine, 1,3-bis(dimethylamino)-2-propanol and bis(2-dimethylaminoethyl)ether, such as such as tert.butylamine, tert.octylamine, diisopropyl-ethylen-diamine, N,N,N',N'-tetramethyl-ethylendiamine and bis(2-dimethylaminoethyl)ether, *e.g.*

10 tert.butylamine, tert.octylamine.

In another aspect the present invention provides a process as defined above, characterized in that purification of clavulanic acid is effected *via* a salt of clavulanic acid with tert.butylamine, tert.octylamine, diisopropyl-ethylen-diamine, N,N,N',N'-tetramethyl-ethylendiamine, 1,3-

15 bis(dimethylamino)-2-propanol or bis(2-dimethylaminoethyl)ether.

Purification under appropriate conditions is in more detail known from various publications, *e.g.* from references cited under step a), b) and c), and under step d) below, the content of which, including prior art citations therein, is incorporated herein by reference.

20

For salt formation the amine may be contacted with clavulanic acid in solution, in an organic solvent or solvent system. Conveniently the same solvent may be used which was used for extraction of clavulanic acid from the aqueous phase, for example of the optionally extracted and optionally pre-treated fermentation broth, *e.g.* ethyl acetate.

25 Prior to contacting the clavulanic acid containing organic solution with an amine the solution may be pre-concentrated, *e.g.* as described above.

Contacting clavulanic acid with the amine may be carried out by any appropriate method, for example the amine may be added to a solution of clavulanic acid in an organic solvent, for example by simple addition to the solution of clavulanic acid in a solvent, or, *e.g.* by mixing an amine into a stream of a solution of clavulanic acid in a solvent.

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The desired salt of clavulanic acid with an amine may be isolated from the organic solvent as usual, for example by filtration or centrifugation, *e.g.* if the salt forms a solid, for examples if the salt crystallises.

A further solvent may be added to the mixture, *e.g.* a mixture containing clavulanic acid, a solvent and an amine, *e.g.* before, simultaneously or after addition of the amine to a mixture of clavulanic acid and a solvent, that may cause precipitation of the amine salt of clavulanic acid.

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The amine salt of clavulanic acid may be obtained in form of a solvate, for example of the acetone solvate. Recrystallisation of the amine salt of clavulanic acid may be effected. If the solvent is wholly or partly immiscible with water, the amine salt of clavulanic acid may also be extracted into water to form an aqueous solution of the salt, which may be very concentrated, as
5 *e.g.* is described in WO 95/21173. Conditions such as reaction conditions, specific reaction conditions, reagents, amount ranges of reagents, concentration ranges, temperatures, etc. for purification and/or isolation of a salt of clavulanic acid, for example an amine salt, are known from, for example, references cited under points a), b) and c) and d) below, the content of which, including prior art citations therein, is incorporated herein by reference.

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Conversion step d) may be carried out according to known methods.

In a process according to step d) clavulanic acid may be converted as such; or in form of a labile derivative thereof, for example a salt thereof, for example a lithium salt or a sodium salt thereof; or in form of an amine salt thereof.

15 A pharmaceutically acceptable salt of clavulanic acid may be, for example, a salt of clavulanic acid with pharmaceutically acceptable alkali or alkaline earth metals, preferably a potassium salt. Generally, clavulanic acid, or a salt thereof, for example an amine salt thereof, conveniently in solution, may be contacted with a cation source which is able to form a pharmaceutically acceptable salt of clavulanic acid. Suitable cation sources are described, for example in references
20 cited above. A preferred cation source may be an alkali or earth alkali salt of a carboxylic acid, for example 2-ethylhexanoic acid, for example the potassium salt thereof, and *e.g.* an acetate, optionally in combination with acetic acid. In WO 97/18216, published 22.05.1997, a process for the production of a pharmaceutically acceptable salt of clavulanic acid by conversion of clavulanic acid into a pharmaceutically acceptable salt of clavulanic acid in *n*-butanol or iso-
25 butanol (2-methyl-1-propanol) as a solvent is disclosed.

Conditions such as reaction conditions, specific reaction conditions, reagents, amount ranges of reagents, concentration ranges, temperatures, etc. for purification and/or isolation of a salt of clavulanic acid, for example an amine salt, are known from, for example, references cited under points a), b) c) and d), the content of which, including prior art citations therein, is incorporated
30 herein by reference.

In one aspect a process according to the present invention may, for example be carried out as follows:

A fermentation broth containing clavulanic acid, having a pH of 5.5 to 7.5, *e.g.* obtained after
35 fermentation with a clavulanic acid-producing micro-organism, may be extracted in a ratio by volume of 1 part fermentation broth to 0.5 to 3.0 parts, preferably 1.0 to 1.5 parts, of an, *e.g.*

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organic, solvent which is able to form a liquid/liquid phase system with an aqueous fermentation broth. An appropriate solvent includes *e.g.* ethers, ketones, such as methyl isobutyl ketone, methyl ethyl ketone, diethyl ketone; esters, such as ethyl acetate, propyl acetate; and alcohols, such as n-butanol or i-butanol. Mixtures of individual solvents, *e.g.* as described above may be used. A solvent which subsequently may be used for extraction of the clavulanic acid from the aqueous, clavulanic acid containing mixture, *e.g.* after acidification, such as a ketone, ester and alcohol, *e.g.* ethyl acetate, methyl isobutyl ketone or diethyl ketone, *e.g.* ethyl acetate may preferably be used.

The clavulanic acid containing mixture may be adjusted, *e.g.* by use of an acidic agent, such as an acid to obtain a pH of 1.0 to 3.0 in that mixture, preferably 1.5 to 2.5, and the pH adjusted mixture may be extracted, *e.g.* with a solvent which forms a liquid/liquid phase system with that mixture, such as a ketone, ester and alcohol. Extraction may be also carried out simultaneously with acidification.

Clavulanic acid may be extracted into the organic phase. The organic phase containing clavulanic acid may *e.g.* be concentrated, purified, *e.g.* by use of activated carbon, *e.g.* as described above, mixed with a cosolvent, *e.g.* from the group acetone, methyl isobutyl ketone or diethyl ketone, *e.g.* acetone, and an amine salt of clavulanic acid may be precipitated. An amine salt of clavulanic acid may be isolated and converted into a pharmaceutically acceptable salt of clavulanic acid, *e.g.* the potassium salt, *e.g.* as described above.

Appropriate methods for such steps are described above and, *e.g.* described in references cited under point a) to d) above, the content of which is incorporated herein by reference including prior art citations therein.

In a further aspect a process according to the present invention may be carried out as follows:

At least some of the solids in a fermentation broth containing clavulanic acid, *e.g.* obtained after fermentation with a clavulanic acid-producing micro-organism, may be removed, *e.g.* by filtration, such as precoat filtration and crossflow filtration. The filtrate obtained may be concentrated to a concentration of *e.g.* 10 g to 40 g clavulanic acid per kg, and may be treated with activated carbon, *e.g.* powdery, in a quantity of *e.g.* 0.5% to 5% of the whole mass. An aqueous concentrate of clavulanic acid obtained may be extracted at pH 5.5 to 7.5 in a ratio by volume of 1 part fermentation broth to 0.5 to 3.0 parts, preferably 1.0 to 1.5 parts, with an organic solvent which is able to form a liquid/liquid phase system with that concentrate, *e.g.* an extraction solvent as described above. Further processing of the clavulanic acid containing concentrate to obtain a pharmaceutically acceptable salt of clavulanic acid may take place according to a method as described above.

Appropriate methods for such steps are described above and, *e.g.* described in references cited under point a) to d) above, the content of which is incorporated herein by reference including prior art citations therein.

- 5 In general, filtration, extraction, removal of impurities and concentration may be carried out at any appropriate stage of the process according to the present invention, *e.g.* according to any method described or referred to above. Centrifugal separators or centrifugal decanters for any phase separation in a process according to the present invention may be used, *e.g.*, particularly if the process is carried out on technical scale. Multi-staged countercurrent methods may be used.
- 10 Appropriate flocculation agents or wetting agents may be added to the clavulanic acid containing mixture, *e.g.* as usual, *e.g.* in amounts of 0.001 to 1% w/w, if desired. A wetting agent includes *e.g.* Armogard D-5411[®], cetyl trimethylammonium bromide, Dodigen[®], Demulso[®] and a flocculation agent includes *e.g.* Bozefloc[®], Ferrocryl[®], Locron[®]. For crossflow filtration, *e.g.* for separating off the biomass from the fermentation broth, there are a variety of commercial
- 15 modular designs, *e.g.* plate, tubular or spiral moduli; the membrane materials may be *e.g.* polymeric or ceramic material. The separation ability of the membranes may vary from ca. 10 to 300 kD or 0.005 to 0.1 μm (UF range) up to ca. 0.1 to 2 μm (MF range). A normal crossflow pump speed may be 2 to 7 m/s, preferably 4 to 6 m/s.
- 20 For thermal concentration of *e.g.* an aqueous, clavulanic acid containing liquid, special vacuum evaporators may be used, *e.g.* operating at very low pressures and with short retention time. Appropriate special vacuum evaporators include thin-layer evaporators. An alternative may be a membrane process, such as reversed osmosis or nanofiltration. Appropriate membrane materials including *e.g.* polymers and ceramics and appropriate modular designs including *e.g.* spirals,
- 25 tubes, plates are known. An additional purification of *e.g.* a concentrate *e.g.* obtained by reversed osmosis or nanofiltration of high molecular compounds may take place effectively through, *e.g.* narrow ultrafiltration membranes, which are available commercially *e.g.* as spiral moduli having a separation ability of 1 to 3 kD.
- 30 Impurities may be removed at any stage of the process of the present invention. Appropriate methods for removing impurities are described above and, *e.g.* described in references cited under point a) to d) above, the content of which is incorporated herein by reference including prior art citations therein.
- 35 In another aspect the present invention provides a process for the production of clavulanic acid and its alkali salts by extraction of clavulanic acid from the culture broth obtained by microbial

fermentation, reaction with an amine to form an amine salt of clavulanic acid and reaction to form clavulanic acid alkali salts, characterised in that

- 5 a) the entire unfiltered fermentation broth obtained after fermentation with a microorganism which produces clavulanic acid is extracted, at a native pH (5.5 - 7.5), with a solvent which is immiscible with water, selected from ethers, ketones, esters or alcohols; or
- 10 b) the fermentation broth obtained after fermentation with a micro-organism which produces clavulanic acid is filtrated by use of usual filtration processes; after optional pre-treatment by addition of flocculation agents; the culture filtrate is concentrated and optionally purified, and afterwards extracted at a pH of 5.5 - 7.5 with a solvent which is immiscible with water, selected from ethers, ketones, esters or alcohols,
- the active ingredient is subsequently extracted in several stages at an acidic pH of 1.5 to 2.5 into a solvent which is immiscible with water selected from ketones, esters or alcohols, and reacted by known methods to obtain an amine salt of clavulanic acid, and an amine salt obtained is converted by known methods into a pharmaceutically acceptable salt of clavulanic acid.

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A solvent which is immiscible with water is regarded herein to be a solvent which is able to form a liquid/liquid phase system in contact with an aqueous mixture, *e.g.* an aqueous fermentation broth.

- 20 Owing to its inhibiting activity on β -lactamases, clavulanic acid, a compound of formula I, *i.e.* (2R,5R,Z)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-aza-bicyclo-[3,2,0]-heptane-2-carboxylic acid, *e.g.* in form of a salt, *e.g.* in form of a potassium salt is useful as an additive for β -lactam antibiotic formulations, *e.g.* in combination with amoxicillin, *e.g.* in form of a trihydrate; and a process according to the present invention is useful for the provision of clavulanic acid.
- 25 The present invention may be viewed as an alternative to other commercially useful processes for producing clavulanic acid and/or pharmaceutically acceptable salts thereof. It may be viewed as an unobvious improvement to processes as described in processes of prior art, including processes of references cited above under points a) to d).
- 30 The following examples illustrate the invention without limiting its scope. All temperatures are given in degrees Celsius.

Example 1

105 kg of a fermentation broth containing clavulanic acid are treated using crossflow-ultra/diafiltration for the removal of biomass. 200 kg of a permeate are obtained which is concentrated to obtain a clavulanic acid content of about 15 g/kg by use of reversed osmosis under cooling. 34 kg of the concentrate obtained are extracted at neutral pH, whilst cooling, with three times the amount of ethyl acetate. The extracted concentrate obtained is extracted at pH 2 under cooling, in several stages, with ethyl acetate. A clavulanic acid extraction yield of 80%, determined by HPLC is obtained. The clavulanic acid containing extract is concentrated by evaporation *in vacuo* to give a concentrate containing ca. 8 g clavulanic acid per kg and the concentrate obtained is dried over anhydrous sodium sulphate. Activated carbon is added to the mixture containing clavulanic acid, ethyl acetate and sodium sulphate, and the mixture obtained is clear-filtrated. The filtrate is evaporated to give a concentrate containing about 30 g clavulanic acid per kg and the concentrate is diluted with acetone in a ratio of about 1:1. A 15% solution of tert.butylamine in acetone at about 20° is added until a pH of ca. 6.1 is adjusted. Crystallisation occurs and the precipitate is isolated, washed with acetone and dried. An acetone solvate of a tert.butylamine salt of clavulanic acid is obtained. Content of clavulanic acid tert.butylamine salt (HPLC): 95% on a solvent-free basis

Example 2

900 kg of a clavulanic acid containing fermentation broth (pH 7.0) are filtrated by crossflow ultrafiltration. De-ionised water is added and the mixture is diafiltrated. 2700 kg of a filtrate containing clavulanic acid are obtained. 1200 kg of a filtrate obtained are concentrated by use of reversed osmosis/nanofiltration at 4° to give a concentrate containing 9 g of clavulanic acid per kg. The concentrate is ultrafiltrated through a membrane (2 to 3 kD). 62 kg of the permeate obtained are extracted at neutral pH with three times the quantity of ethyl acetate. The aqueous solution is extracted continuously with four times the amount of ethyl acetate under cooling, at pH 2.0, using a two-stage counter-current extraction apparatus (2 centrifugal separators). 320 kg of ethyl acetate are concentrated by evaporation in an agitator vessel evaporator to obtain a concentrate containing ca. 80 g clavulanic acid per kg. 1.9 kg of the concentrate obtained are treated with 0.3 times the quantity of activated carbon based on the clavulanic acid mass and the mixture is clear-filtrated. The carbon is washed with ethyl acetate until the concentration in the filtrate is 30 g clavulanic acid per kg. The same quantity of acetone is added to the filtrate. 1.2 equivalents of a 25% solution of tert.octylamine in acetone at 20° are added and a pH of 6.3 is adjusted. After cooling to 4°, a tert.octylamine salt of clavulanic acid is obtained in crystalline form, isolated, washed with acetone and dried. Content of clavulanic acid tert. octylamine salt (HPLC): 98% (absolutely dry).

Patent Claims:

1. A process for the production of clavulanic acid and pharmaceutically acceptable salts thereof
by
5 a) fermentation of a micro-organism which is capable to produce clavulanic acid
b) isolation of clavulanic acid from the fermentation broth
c) purification of clavulanic acid, *e.g. via* a salt thereof
d) conversion of the purified clavulanic acid of step c), *e.g.* of a salt thereof into a
10 pharmaceutically acceptable salt of clavulanic acid,
characterised in that the fermentation broth is extracted with a solvent prior to isolation of
clavulanic acid.
2. A process according to claim 1, characterized in that the solvent is selected from an ether, a
ketone, an ester or an alcohol.
- 15 3. A process according to anyone of claims 1 to 2, characterized in that at least part of the
solids suspended in the fermentation broth are removed prior to extraction.
4. A process according to claim 3, characterized in that the fermentation broth is concentrated
20 prior to extraction.
5. A process according to any one of claims 1 to 4, characterized in that isolation step c) is
effected *via* extraction from an aqueous solution of clavulanic acid.
- 25 6. A process according to claim 5, characterized in that as a solvent for the extraction of
clavulanic acid from an aqueous solution thereof the same solvent is used which was used
for extraction of the fermentation broth prior to isolation of clavulanic acid thereof.
7. A process according to claim 6, characterized in that a clavulanic acid containing solvent is
30 concentrated prior to purification step d).
8. A process according to anyone of claims 1 to 7, characterized in that purification of
clavulanic acid is effected *via* a salt of clavulanic acid with tert.butylamine, tert.octylamine,
diisopropyl-ethylen-diamine, N,N,N',N'-tetramethyl-ethylendiamine, 1,3-
35 bis(dimethylamino)-2-propanol or bis(2-dimethylaminoethyl)ether.

9. A process according to anyone of claims 1 to 8, characterized in that a pharmaceutically acceptable salt of clavulanic acid is a potassium salt of clavulanic acid.
10. A process for the production of clavulanic acid and its alkali salts by extraction of clavulanic acid from the culture broth obtained by microbial fermentation, reaction with an amine to form an amine salt of clavulanic acid and reaction to form clavulanic acid alkali salts, characterised in that
- 5 a) the entire unfiltered fermentation broth obtained after fermentation with a microorganism which produces clavulanic acid is extracted, at a native pH (5.5 - 7.5), with a solvent which is immiscible with water, selected from ethers, ketones, esters or alcohols; or
- 10 b) the fermentation broth obtained after fermentation with a micro-organism which produces clavulanic acid is filtrated by use of usual filtration processes; after optional pre-treatment by addition of flocculation agents; the culture filtrate is concentrated and optionally purified, and
- 15 afterwards extracted at a pH of 5.5 - 7.5 with a solvent which is immiscible with water, selected from ethers, ketones, esters or alcohols,
- the active ingredient is subsequently extracted in several stages at an acidic pH of 1.5 to 2.5 into a solvent which is immiscible with water selected from ketones, esters or alcohols, and reacted by known methods to obtain an amine salt of clavulanic acid, and an amine salt
- 20 obtained is converted by known methods into a pharmaceutically acceptable salt of clavulanic acid.

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

2020
Bogotá, D.C.,

Abogado:
CARLOS R OLARTE

ASUNTO:	Radicación No.	02 10 2450
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	
	Folios	12536

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 comunica:

Documentos estudiados:

Descripción: Folios 18 a 38 como se radicó inicialmente.
Reivindicaciones: Folios 39 a 44 modificadas en fase nacional.
Prioridad: GB 0011521.2 13.05.2000; GB 0011519.6 13.05.2000

Objeto de la Invención

Título de la invención: "Proceso para la purificación de una sal de ácido clavulánico"

Problema Técnico Planteado: "Necesidad de obtener la sal farmacológicamente aceptable del producto final del ácido clavulánico con pocas impurezas"

Solución: "Proveer un proceso de purificación en el cual una sal de ácido clavulánico, contaminada con tirosina de N-succinilo es sometida a condiciones las cuales son seleccionadas para retirar la tirosina de N-succinilo."

IPC: C07D 498/04; A61K 31/407

Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Concisión: La reivindicación 1 reclama un proceso y específicamente se refiere a medio líquido a un pH menor a 6.5. La forma de redacción hace que el alcance de esta reivindicación sea demasiado general ya que abarca un rango amplio de pH. Se sugiere reclamar el rango que ha sido objeto de investigación.

Las reivindicaciones de proceso deben reclamar una secuencia lógica de pasos de manera que describan clara y concisa los pasos a seguir para obtener el producto. La reivindicación 1 no presenta los pasos esenciales que hacen parte de la

obtención del ácido clavulánico, sino que solo reclama su exposición a un rango amplio de pH.

Por otro lado, la reivindicación 23 reclama dicho proceso involucrando una secuencia ordenada de diferentes pasos, sin embargo, no establece cuales solventes orgánicos preferiblemente son empleados, por lo cual se considera que carece de suficiente sustento en la descripción.

La reivindicación 24 y 25 se refiere a una sal de la amina del producto del ácido clavulánico, y clavulanato de potasio como productos de un proceso según las reivindicaciones anteriores. Se anota que la molécula ya era conocida en el estado del arte por lo cual no es posible otorgar protección sobre dicha entidad química.

Le reivindicación 27 se refiere a un proceso de purificación en el cual una sal del ácido clavulánico que contiene n-succinilo es sometida a condiciones en las cuales se remueve la tirosina N-succnilo. Esta reivindicación carece de claridad ya que permite a la persona versada en la materia proponer cualquier condición y no llegaría al mismo resultado de la invención ya que estas no han sido definidas.

Las reivindicaciones 28 y 29 reclaman un proceso en el cual la n-succinil es destruida por medio de un reactivo líquido, sin embargo no define cual es dicho reactivo ni tampoco las condiciones en que este debe estar adicionado o incluido en el medio de reacción.

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación 2000.05.13 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO9842858	<i>Process for the isolation of a pharmaceutically acceptable alkali metal salt of clavulanic acid</i>	01/10/98
D2	WO9823622	<i>Purification of fermented clavulanic acid</i>	04/06/98

Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 dice: "Un proceso que comprende la exposición de una sal del ácido clavulánico a un medio líquido con un pH menor a 6.5"

D1 divulga un proceso para el aislamiento de una sal metálica aceptable del ácido clavulánico de un caldo de cultivo que contiene ácido clavulánico impuro y comprende pasos de filtrado, extracción a una mezcla de solvente -agua inmiscible a un pH de 1,2 a 2, y precipitación de la sal de metal de ácido clavulánico por adición de una solución de un alcanato en donde antes del filtrado el caldo fermentado que contiene ácido clavulánico es diluido con agua, un agente floculante es adicionado y el pH es ajustado de 3 – 5 para purificación de las sal del álcali metálica de ácido clavulánico (portada).

La solicitud se diferencia de D1 en que la sal del ácido clavulánico es expuesta a un medio líquido con un pH menor a 6.5.

El Efecto Técnico que logra la diferencia es purificar el ácido clavulánico por medio de una dilución de su sal.

El Problema Técnico Objetivo de esta solicitud es proporcionar un método para purificar la sal de ácido clavulánico.

D2 describe un proceso para la purificación de productos fermentados en la producción de ácido clavulánico (página 1). Además, presenta como un solvente posible para la extracción un solvente orgánico el cual esta disponible en la forma de un sistema de fase líquida/líquida, y afirma que la extracción puede realizarse cerca a pH de 5.5 a pH 7.5 (página 3). Adicionalmente, esta anterioridad sugiere que el paso de aislamiento puede ser efectuado por vía de extracción desde la solución acuosa del ácido clavulánico.

La persona versada en la materia, habría sido motivada por D2 a incluir pH un poco más elevados en el proceso que D1 enseña.

Adicionalmente, la persona versada habría sido motivada por las sugerencias de D1 y D2 a realizar un paso adicional de purificación de la sal en donde el pH se ajustaría en un rango menor a 6.5, como lo revela la presente solicitud. Las demás reivindicaciones no presentan materia que hagan inventiva a la solicitud.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO9842858	1-32	Nivel inventivo
D2	WO9823622	1-32	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 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

13 NOV. 2009

CONCEPTO TECNICO NUMERO: 3631	EXAMINADOR TÉCNICO Código:202092
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