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(54) Title: A NOVEL PROCESS OF LIBERATION OF ERYTHROMYCIN AND PREPARATION OF ITS SALTS

(57) Abstract: The present invention relates to a novel process for the liberation of Erythromycin from Erythromycin salts such as Erythromycin thiocyanate using water as a solvent in presence of a base. Erythromycin obtained by process of the present invention has purity of more than 95%. The present invention further relates to a novel process for the preparation of Erythromycin Stearate by reacting Erythromycin or its salts with stearic acid in presence of water.

A Novel Process of Liberation of Erythromycin And Preparation of its Salts

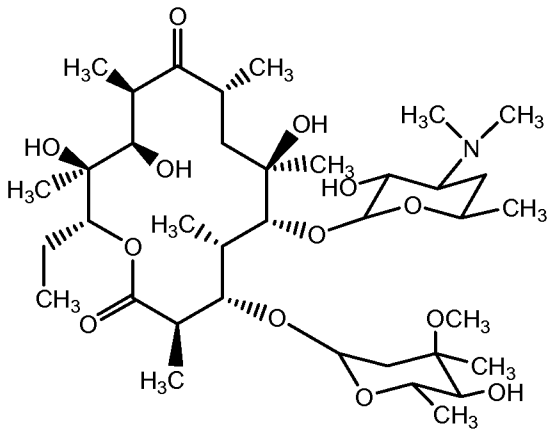
FIELD OF INVENTION

The present invention relates to a novel process for the liberation of Erythromycin from Erythromycin salts. More particularly, the present invention relates to a novel process for the liberation of Erythromycin from Erythromycin thiocyanate in presence of a base and using water as a solvent.

The present invention further relates to a novel process for the preparation of Erythromycin salts like Erythromycin Stearate from Erythromycin or its salts using water as a solvent.

BACKGROUND OF INVENTION

Erythromycin of formula I is the most important member of the macrolide antibiotics of microbial origin. It is effective against many Gram-positive and Gram-negative bacteria and is often used for people who have an allergy to penicillin.



Formula I

Being bitter in taste Erythromycin has limitations when administered orally. Hence orally it is administered as Erythromycin Stearate in the form of a tablet. Erythromycin Stearate is not only palatable but also has an anti bacterial property. It is relatively stable and has high erythromycin potency.

Erythromycin was first disclosed in U.S. patent 2,653,899 in 1952. Various prior art discloses different processes for preparation of Erythromycin.

497/MUM/2005 discloses preparation of Erythromycin base from Erythromycin thiocyanate in presence of halogenated solvents and ammonia. The process involves use of 6 volumes of chlorinated solvent such as dichloromethane for liberating Erythromycin from Erythromycin thiocyanate.

627/MUM/2005 discloses preparation of 6,9 imino ether from Erythromycin thiocyanate. As stated in this patent application, the process comprises dissolving Erythromycin thiocyanate in methylene chloride and adding liquid ammonia as a base, separating organic layer, distilling solvent from organic layer to obtain residue of Erythromycin base which further converted to the title compound.

Other patent applications e.g. 626/MUM/2005, WO2007029266 and WO2009023191, also describe preparation of Erythromycin from Erythromycin thiocyanate in dichloromethane using aqueous ammonia.

Polish patent PL83707 describes preparation of low melting Erythromycin base by treating Erythromycin thiocyanate with of 20% aqueous ethanol and 5% NaOH at 40-50°C followed by filtering and treating the precipitate with water and alkali till suspension shows no reaction of SCN ions and pH becomes constant to obtain erythromycin base.

Therefore, the processes reported in literature for the liberation of Erythromycin from Erythromycin thiocyanate employ organic solvents, primarily halogenated solvents which have bad impact on environment when one is dealing with industrial scale. During the recovery of chlorinated solvents, there is particular loss of solvent which can not be accounted, thus causing environment pollution and also considerable economical loss.

Erythromycin Stearate was first disclosed in US2862921 in 1958. The said patent discloses Erythromycin esters as novel compounds and process for their preparation. The process as described comprises reaction of Erythromycin with stearoyl chloride in an inert solvent such as methylene chloride in presence of base such as 1-ethyl piperidine. The reaction mass was kept overnight.

US 2881 163 describes the process for preparation of Erythromycin acid addition salts from its salt such as Erythromycin acetate in presence of water miscible organic solvent. The process involves mixing of aqueous solution of Erythromycin acetate with acetone, 10% sodium hydroxide, sodium chloride. The mixture was heated at 45°C followed by separation of acetone phase which was reacted with steric acid. After steric acid was dissolved completely the solution was filtered and water was added at same temperature. The solution was allowed to crystallize at 18°C. Crystals are filtered, washed and dried to obtain Erythromycin Stearate.

Thus, there are very few prior art references which disclose preparation of Erythromycin Stearate. All the reported processes are carried out in presence of organic solvents. The processes are lengthy and involve extended work up process which makes them costly and difficult to handle on large scale and environment unfriendly.

The inventors of the present invention have surprisingly found a novel process for the liberation of Erythromycin from Erythromycin thiocyanate using only water as a solvent in presence of a base, which has not been previously reported in any prior art as Erythromycin thiocyanate is insoluble in water. It is a common practice to obtain the product from its salt that use a solvent in which salt is soluble and product is insoluble.

But process of the present invention uses water as a solvent in which Erythromycin thiocyanate is insoluble. The inventors of the present invention further found out a novel process for the preparation of Erythromycin Stearate from Erythromycin or its salts by reacting it with stearic acid in presence of water as a solvent by avoiding use of any organic solvent. Thus, the inventors of the present invention have found out a novel process wherein both Erythromycin and stearic acid are insoluble in water, however reacts to form an insoluble salt.

Thus, the processes of the present invention are cost effective, operationally simple, industrially feasible and environment friendly.

OBJECT OF INVENTION

i) An object of the present invention is to provide a novel process for the liberation of Erythromycin from Erythromycin salts. More particularly, the present invention provides a novel process for the liberation of Erythromycin from Erythromycin thiocyanate in water in presence of a base.

ii) Another object of the present invention is to provide a novel process for the preparation of Erythromycin with more than 95% purity and good yield.

iii) Another object of the present invention is to obtain Erythromycin substantially free of impurities by avoiding any purification process.

iv) Another object of the present invention is to provide a novel process for the preparation of Erythromycin salts like Erythromycin Stearate from Erythromycin using only water as a solvent. Thus, process of the present invention avoids the use of any organic solvent.

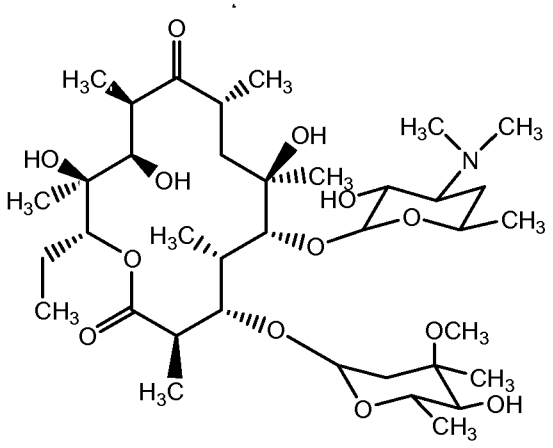
v) Yet another object of the present invention is to provide a novel process for the preparation of Erythromycin Stearate from Erythromycin salts such as Erythromycin thiocyanate via liberation of Erythromycin. Entire process is carried out in presence of only water without using any organic solvent.

vi) Yet another object of the present invention is to provide simple, economic, environment friendly and industrially viable processes for liberation of Erythromycin and preparation of its salts like Erythromycin Stearate from liberated Erythromycin or via liberation of Erythromycin.

vii) Yet another object of the present invention is to provide a novel process wherein both Erythromycin and stearic acid are insoluble in water, however reacts to form an insoluble salt.

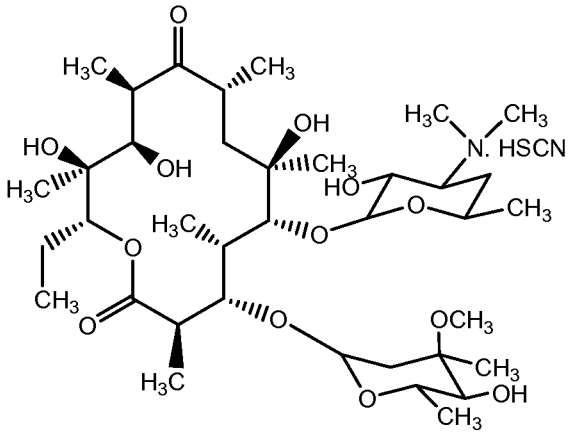
SUMMARY OF INVENTION

In first aspect of the present invention, there is provided a novel process for the liberation of Erythromycin of Formula I from Erythromycin salts such as Erythromycin thiocyanate



Formula I

by treating Erythromycin thiocyanate of Formula II



Formula II

with a base in presence of water as a solvent.

Another aspect of the present invention is to provide Erythromycin with more than 95% purity without any further purification process.

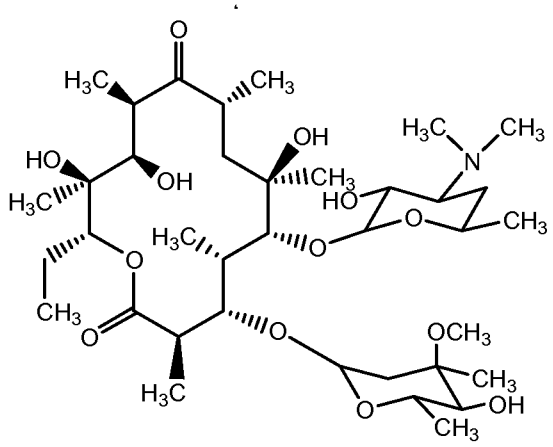
In second aspect of the present invention, there is provided a novel process for the preparation of Erythromycin Stearate from Erythromycin by reacting it with stearic acid in presence of water as a solvent.

In third aspect of the present invention, there is provided a novel process for the preparation of Erythromycin Stearate from Erythromycin salts such as Erythromycin thiocyanate via liberation of Erythromycin comprising i) reacting Erythromycin thiocyanate of formula II with base in presence of water at 30 to 80 °C to liberate Erythromycin of formula I ii) treating Erythromycin of step i) with stearic acid in presence of water to obtain Erythromycin Stearate.

Thus, the processes of the present invention are simple and avoid the use of any organic solvent.

DETAILED DESCRIPTION OF INVENTION

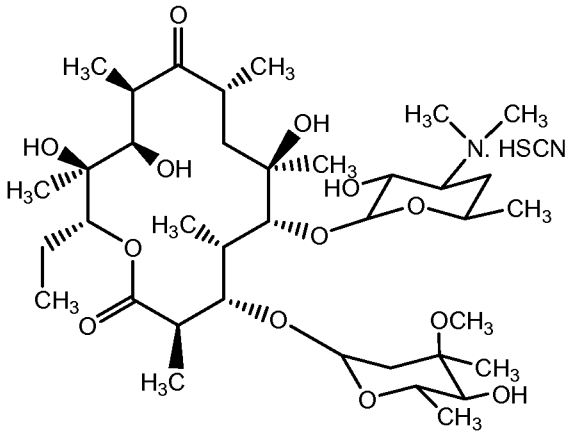
The present invention provides a novel process for the liberation of Erythromycin of Formula I from Erythromycin salts.



Formula I

The present invention further relates to a novel process for the preparation of Erythromycin Stearate from Erythromycin or its salts using water as the only solvent.

In one aspect, the present invention relates to a novel process for the liberation of Erythromycin of Formula I from Erythromycin thiocyanate of Formula II



Formula II

by treating Erythromycin thiocyanate of Formula II with a base in presence of water as a solvent.

In another aspect, the process of the present invention further comprises isolation of obtained Erythromycin by optional cooling, filtering and washing the product with water till it is free from thiocyanate and further drying it to get Erythromycin.

In an embodiment of the present invention, the base used is selected from organic or inorganic base, wherein organic base is selected from dimethylamine, diethylamine or triethylamine and inorganic base is selected from ammonia, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide or potassium hydroxide. Preferably, ammonia is used.

In another embodiment of the present invention, ammonia used can be in the form of aqueous ammonia or ammonia gas or combination thereof.

It has been observed by inventors of the present invention that ammonia as a base works most effectively in terms of completion of liberation of Erythromycin, yield and purity of the obtained Erythromycin than the other bases e.g. above-mentioned inorganic bases such as sodium hydroxide, sodium carbonate, sodium bicarbonate etc. Further, aqueous ammonia does not work efficiently at low temperature and same is the case with other bases.

Thus, inventors of the present invention provide a novel process for liberation of Erythromycin in presence of base and water as a solvent. None of the prior art teaches use of water as a solvent. For the person skilled in art it is common to get the product like Erythromycin base by liberating it from salt like Erythromycin thiocyanate in a solvent like chlorinated solvent in which the salt is soluble and the product is insoluble. However, in the process of the present invention solvent used is water in which both salt Erythromycin thiocyanate and product Erythromycin is insoluble.

In another embodiment of the present invention, the range of suitable stoichiometries of base with respect to Erythromycin thiocyanate is between 1-10 equivalents and range of suitable stoichiometries of water solvent with respect to Erythromycin thiocyanate is between 1-5 equivalents, preferably 1.

In another embodiment of the present invention, the process of liberation of Erythromycin is carried out at temperature ranging from 30 °C to 80 °C.

In yet another embodiment, process of the present invention provides Erythromycin base with more than 95% purity without further purification process. Thus, Erythromycin base obtained by the process of the present invention is substantially free of impurities.

In second aspect of the present invention, there is provided a novel process for the preparation of Erythromycin Stearate from Erythromycin of formula I, by reacting it with stearic acid in presence of water.

Erythromycin of formula I used is obtained by its process of liberation as discussed above. Erythromycin of formula I, available by commercial source also can be used. The scope of the present invention also covers the use of Erythromycin of formula I that is obtained by commercial source as described in Ex.9 and 10. Thus, according to process of the present invention Erythromycin Stearate can be prepared by reacting Erythromycin, obtained by the process of liberation as discussed herein above or obtained by commercial source with stearic acid in presence of water.

In third aspect of the present invention, there is provided a process for preparation of Erythromycin Stearate from Erythromycin thiocyanate of formula II via liberation of Erythromycin comprising steps of

i) reacting Erythromycin thiocyanate of formula II with a base in presence of water at 30 to 80 °C to liberate Erythromycin of formula I

ii) treating Erythromycin obtained in step i) with stearic acid in presence of water

iii) filtering the reaction mass obtained in step ii) followed by drying the product to obtain desired Erythromycin Stearate

Base used in the step i) is selected from organic or inorganic base, wherein organic base is selected from dimethylamine, diethylamine or triethylamine and inorganic base is selected from ammonia, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide or potassium hydroxide. Preferably, ammonia is used.

Erythromycin obtained in step i) is isolated by optional cooling, filtering and washing the product with water till it is free from thiocyanate. The wet cake obtained is used as such for step ii) reaction.

Erythromycin of formula I, as liberated is reacted with stearic acid at temperature ranging from 30 to 70°C.

According to another embodiment of the present invention, the molar ratio of stearic acid to Erythromycin used is 1.1 to 1.35, preferably ratio is 1.2 to 1.35.

Thus, process of the present invention for preparation of Erythromycin Stearate avoids the use of any organic solvent. Also it avoids the extended isolation and crystallization process. Hence, it is cost-effective, environmental friendly and industrially viable process.

The detail of the invention provided in the following example is given by the way of illustration only and should not be construed to limit the scope of the present invention.

EXAMPLES AND COMPARATIVE EXAMPLES

Comparative Example 1

For comparison purposes. Erythromycin base was prepared by process as known in the art

100 g active Erythromycin thiocyanate was suspended in dichloromethane (560 ml). To it, a solution of NaOH (8.8 g in 154 ml water) was added and the mass was refluxed for 1 hour. Cooled to room temperature and separated the aqueous and organic phases. The organic phase was washed with water (5 xlOO ml). Then it was concentrated partially to dehydrate, chilled to 0 to 5°C, stirred for 1 hour and filtered. Washed the cake with chilled MDC (50 ml). Wet cake was then dried at 50 to 55°C.

Dry weight: 92 to 94 g (Moisture: 5%).

HPLC purity:

Erythromycin thiocyanate HPLC analysis: Erythromycin A: 84.61%, Erythromycin B: 1.37%, Erythromycin C: 1.46%

Erythromycin base HPLC analysis: Erythromycin A: 96.28%, Erythromycin B: 0.17%, Erythromycin C: 0.71%

Experimental Example 1

Preparation of Erythromycin according to present invention.

Erythromycin thiocyanate (243 g) was suspended in water (200 ml). The slurry was heated up to 35°C and liquor Ammonia (200 ml) was added in half an hour. The mass was heated further up to 70°C and stirred for 1 hour. The suspension was cooled to ambient temperature and filtered. The residue was washed with water till free from ammonium thiocyanate (test with $FeCl_3$ solution). The product was dried at 55 to 60°C.

Yield: 212 g (moisture: 5%)

Erythromycin thiocyanate HPLC analysis: Erythromycin A: 84.61%, Erythromycin B: 1.37%, Erythromycin C: 1.46%

Erythromycin base HPLC analysis: Erythromycin A: 96.34%, Erythromycin B: 0.68%, Erythromycin C: 1.15%

Experimental Example 2

Preparation of Erythromycin according to present invention.

Erythromycin thiocyanate (121.5 g) was suspended in water (100 ml). The slurry was heated up to 35°C and liquor Ammonia (100 ml) was added in half an hour. The mass was heated further up to 70°C and stirred for 1 hour. The suspension was cooled to 50°C temperature and filtered. The residue was washed with water till free from ammonium thiocyanate (test with FeC¾ solution). The product was dried at 55 to 60°C.

Yield: 106 g

Erythromycin thiocyanate HPLC analysis: Erythromycin A: 84.61%, Erythromycin B: 1.37%, Erythromycin C: 1.46%

Erythromycin base HPLC analysis: Erythromycin A: 96.58%, Erythromycin B: 0.69%, Erythromycin C: 1.03%

Experimental Example 3

Preparation of Erythromycin according to present invention.

To a suspended solution of Erythromcyin thiocyanate (32 g) in water (100 ml) was charged 19 ml Dimethyl amine (40%) and the mass was heated at 70°C for 3 hours. The suspension was cooled to 50°C , filtered and washed with water till free from dimethyl ammonium thiocyanate (test with FeC13 solution). The product was dried at 55 to 60°C.

Yield: 24.6 g (moisture :5.92%)

Erythromycin thiocyanate HPLC analysis: Erythromycin A: 76.63%, Erythromycin B **:3.02%,** Erythromycin C:0.77%

Erythromycin base HPLC analysis: Erythromycin A: 81.37%, Erythromycin B: 4.85%, Erythromycin C: 1.01%

Experimental Example 4

Preparation of Erythromycin according to present invention.

To a suspended solution of Erythromcyin thiocyanate (32 g) in water(80 ml) was charged Diethyl amine (9.2 g) and the mass was heated at 70°C for 2 hours. The suspension was cooled to 50°C ,filtered and washed with water till free from diethyl ammonium thiocyanate (test with FeC13 solution). The product was dried at 55 to 60°C.

Yield : 19.1 g (moisture :5.45%)

Erythromycin thiocyanate HPLC analysis: Erythromycin A: 84.61%, Erythromycin B :1.37%, Erythromycin C:1.46%

Erythromycin base HPLC analysis: Erythromycin A: 95.28%, Erythromycin B: 1.15%, Erythromycin C: 0.98%

Example 5

Preparation of Erythromycin Stearate from Erythromycin obtained by the process of liberation of the present invention

Erythromycin base taken as a dry cake (25 g), stearic acid (12.5 g) and water (175 ml) were charged to a round-bottom flask. The reaction mass was heated to 35 to 40°C and stirred for 2 hours. The product was then filtered and dried at 60°C.

Yield: 36.4 g

Moisture: 2.60% (complies limit of NMT 4%)

HPLC (Erythromycin A + B + C) (on anhydrous basis): 65.6% (complies limit of NLT 60.5%)

Free Stearic acid: 6.94% (complies limit of NMT 14%)

Total impurities: 3.38% (complies limit of NMT 6%)

Example 6

Preparation of Erythromycin Stearate from Erythromycin obtained by the process of liberation of the present invention

Erythromycin base taken as a dry cake (25 g), stearic acid (12 g) and water (100 ml) were charged to a round-bottom flask. The reaction mass was heated to 35 to 40°C and stirred for 2 hours, The product was then filtered and dried at 60°C.

Yield: 35.2 g

Moisture 2.72%

HPLC (Erythromycin A + B + C) (on anhydrous basis): 68.6%

Free Stearic acid: 4.52%

Total impurities: 2.698%

Example 7

Preparation of Erythromycin Stearate from Erythromycin obtained by the process of liberation of the present invention

Erythromycin base (25 g), Stearic acid (13 g) and water (175 ml) were charged to a round-bottom flask. The reaction mass was heated up to 35 to 40°C and stirred for 2 hours. The product was filtered and dried at 60°C.

Yield: 36.2 g

Moisture: 2.42%

HPLC (Erythromycin A + B + C) (on anhydrous basis): 65.2%

Free Stearic acid: 5.21%

Total impurities: 2%

Example 8

Preparation of Erythromycin Stearate from Erythromycin thiocyanate via liberation of Erythromycin

Erythromycin thiocyanate (121 g) and water (300 ml) were charged to a round-bottom flask. The suspension was heated to 35°C and liquor Ammonia (100 ml) was added in about half an hour. The reaction mass was further heated up to 70°C, stirred at 70°C for 1 hour, cooled to 50°C and filtered. The wet cake of Erythromycin is then treated with stearic acid (55.12 g) and water (125 ml). The reaction mass was heated to 35 to 40°C and stirred for 2 hours. The product was filtered and dried at 60°C.

Yield: 159 g

Moisture: 2.64%

HPLC (Erythromycin A + B + C) (on anhydrous basis): 66.32%

Free Stearic acid: 6.97%

Total impurities: 3.5%

Example 9

Preparation of Erythromycin Stearate from commercially available Erythromycin

Erythromycin base (25 g), Stearic acid (13 g) and water (175 ml) were charged to a round-bottom flask. The reaction mass was heated up to 50 to 55°C and stirred for 2 hours. The product was filtered and dried at 60°C.

Yield: 36.2 g

Moisture: 2.54%

HPLC (Erythromycin A + B + C) (on anhydrous basis): 60.64%

Free Stearic acid: 6.03%

Total impurities: 4.91%

Example 10

Preparation of Erythromycin Stearate from commercially available Erythromycin

Erythromycin base (25 g), Stearic acid (13 g) and water (175 ml) were charged to a round-bottom flask. The reaction mass was heated to 60 to 65°C and stirred for 2 hours, The product was filtered and dried at 60°C.

Yield: 36.2 g

Moisture: 2.60%

HPLC (Erythromycin A + B + C) (on anhydrous basis): 60.75%

Free Stearic acid: 10.9%

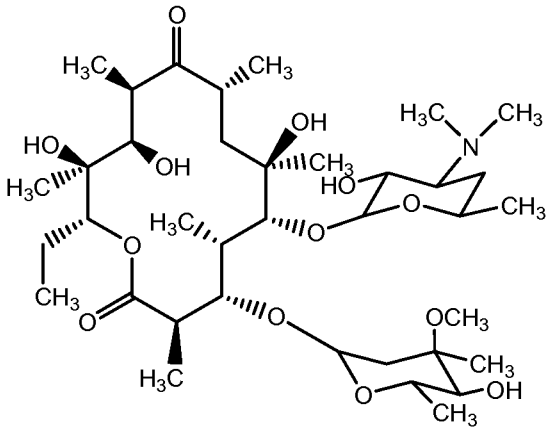
Total impurities: 5.16%

Advantages of the novel processes of the present invention for the preparation of Erythromycin and Erythromycin Stearate are

1. The processes of the present invention are carried out in water as a solvent. Thus, present invention avoids use of any organic solvent especially chlorinated solvents.
2. The processes of the present invention are thus environmentally friendly.
3. The processes of the present invention avoid tedious steps such as separation of organic solvent, concentration of solvent etc during isolation of Erythromycin base and Erythromycin Stearate.
4. The processes of the present invention are thus economically and industrially viable.
5. The process of the present invention provides Erythromycin base with more than 95% purity by avoiding further purification process.

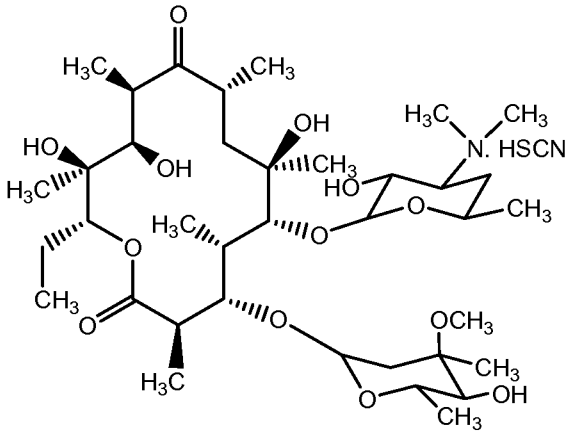
We claim

1. A novel process for the liberation of Erythromycin of Formula I



Formula I

from Erythromycin thiocyanate of Formula II



Formula II

by treating Erythromycin thiocyanate of Formula II with a base in presence of water as a solvent

2. The process for liberation of Erythromycin as claimed in claim 1, further comprises isolation of obtained Erythromycin by optional cooling, filtering and washing the product with water

3. The process for liberation of Erythromycin as claimed in claim 1, wherein the base used is selected from organic or inorganic base, wherein organic base is selected from dimethylamine, diethylamine or triethylamine and inorganic base is selected from ammonia, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide or potassium hydroxide, preferably ammonia is used

4. The process for liberation of Erythromycin as claimed in claim 3, wherein ammonia used can be in the form of aqueous ammonia or ammonia gas or combination thereof

5. The process for liberation of Erythromycin as claimed in claim 1 or 3, wherein the range of suitable stoichiometries of the base with respect to the Erythromycin thiocyanate is between 1 to 10 equivalents

6. The process for liberation of Erythromycin as claimed in claim 1, wherein the said process is carried out at temperature ranging from 30 °C to 80 °C

7. The process for liberation of Erythromycin as claimed in claim 1, wherein the range of suitable stoichiometries of water solvent with respect to Erythromycin thiocyanate is between 1 to 5 equivalents, preferably 1

8. A novel process for the preparation of Erythromycin Stearate by reacting Erythromycin with stearic acid in presence of water

9. A novel process for the preparation of Erythromycin Stearate from Erythromycin thiocyanate comprising steps of

i) reacting Erythromycin thiocyanate with a base in presence of water at 30 to 80 °C to liberate Erythromycin

ii) treating Erythromycin obtained in step i) with stearic acid in presence of water

iii) filtering the reaction mass obtained in step ii) followed by drying the product to obtain desired Erythromycin Stearate

10. The process as claimed in claim 8 or 9, wherein Erythromycin is reacted with stearic acid at temperature ranging from 30 to 70°C

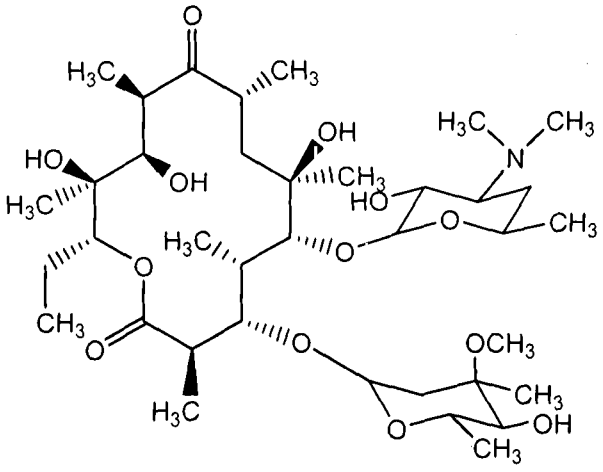
11. The process as claimed in claim 8 or 9, wherein the molar ratio of stearic acid to Erythromycin used is 1.1 to 1.35, preferably ration is 1.2 to 1.35

12. The process as claimed in claim 9, wherein base used in the step i) is selected from organic or inorganic base, wherein organic base is selected from dimethylamine, diethylamine or triethylamine and inorganic base is selected from ammonia, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide or potassium hydroxide. Preferably, ammonia is used.

AMENDED CLAIMS
received by the International Bureau on 04.12.2013

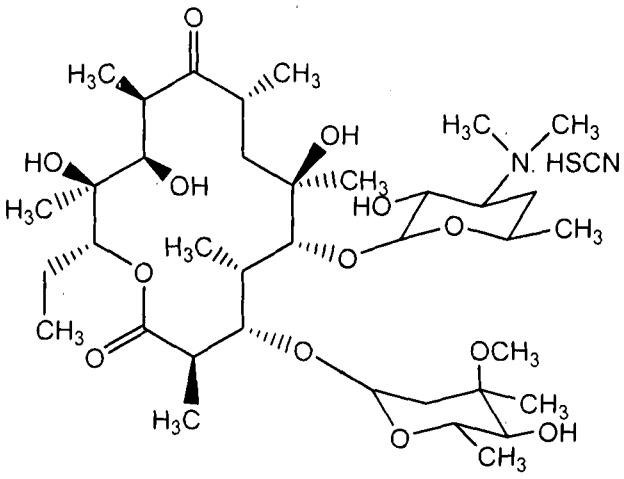
We claim

1. A novel process for the liberation of Erythromycin of Formula I



Formula I

from Erythromycin thiocyanate of Formula II



Formula II

by treating Erythromycin thiocyanate of Formula II with a base such as ammonia in presence of water as the liquid medium

2. The process for liberation of Erythromycin as claimed in claim 1, further comprises isolation of obtained Erythromycin by optional cooling, filtering and washing the product with water

3. The process for liberation of Erythromycin as claimed in claim 1, wherein ammonia used can be in the form of aqueous ammonia or ammonia gas or combination thereof

4. The process for liberation of Erythromycin as claimed in claim 1, wherein the range of suitable stoichiometrics of the base ammonia with respect to the Erythromycin thiocyanate is between 1 to 10 equivalents

5. The process for liberation of Erythromycin as claimed in claim 1, wherein the said process is carried out at temperature 30 to 80 °C

6. The process for liberation of Erythromycin as claimed in claim 1, wherein the range of suitable stoichiometrics of water solvent with respect to Erythromycin thiocyanate is between 1 to 5 equivalents, preferably 1

7. A novel process for the preparation of Erythromycin Stearate by reacting Erythromycin with stearic acid in presence of water

8. A novel process for the preparation of Erythromycin Stearate from Erythromycin thiocyanate comprising steps of

i) reacting Erythromycin thiocyanate with a base such as ammonia in presence of water at 30 to 80 °C to liberate Erythromycin

ii) treating Erythromycin obtained in step i) with stearic acid in presence of water

iii) filtering the reaction mass obtained in step ii) followed by drying the product to obtain desired Erythromycin Stearate

9. The process as claimed in claim 7 or 8, wherein Erythromycin is reacted with stearic acid at temperature ranging from 30 to 70°C

10. The process as claimed in claim 7 or 8. wherein the molar ratio of stearic acid to Erythromycin used is 1.1 to 1.35, preferably ration is 1.2 to 1.35.

STATEMENT UNDER ARTICLE 19

The present invention is based on principle wherein solid erythromycin thiocyanate without getting into solution does reacts in a solid state to give the desired insoluble product wherein water acts as a liquid medium. Also in the present invention base ammonia penetrates thiocyanate in solid state and takes away thiocyanate part as ammonium thiocyanate.

Present invention further teaches use of ammonia specifically for liberation of erythromycin from erythromycin thiocyanate which can not be anticipated from EP0853087. EP0853087 reports the liberation of erythromycin using sodium hydroxide as a base. However, it has been observed by inventors of the present invention that ammonia as a base works most effectively in terms of completion of liberation of erythromycin, yield and purity of the obtained erythromycin than the other bases. In the present invention, ammonia penetrates thiocyanate in solid state and takes away thiocyanate part as ammonium thiocyanate.

Therefore, we amended claim 1 and claim 8 wherein base is restricted to ammonia since it works most effectively in liberation of erythromycin base.

Thus, in one aspect, present invention generates erythromycin base by reacting erythromycin thiocyanate with ammonia in presence of water as a liquid medium which is a novel process and can not be anticipated by EP0853087. while in the other aspect present invention generates erythromycin stearate from erythromycin base and stearic acid in presence of water acting as the liquid medium.

In present invention preparation of erythromycin stearate is based on the principle wherein "both erythromycin and stearic acid are insoluble in water, however reacts to form an insoluble salts". It is a common practice to obtain the product from its salt that use a solvent in which salt is soluble and product is insoluble as described in US2881 163. Unlike US288163 present invention involves preparation of erythromycin stearate from erythromycin or its salts by reacting it with stearic acid in presence of water as a liquid medium by avoiding use of any organic solvent and other regents such as salting out agent. It is also seen in prior art that erythromycin thiocyanate solid state had to be broken and taken into solution and then free base is liberated in the usual way.

Thus, the process of the present invention is a novel process wherein both erythromycin and stearic acid are insoluble in water, however reacts to form an insoluble salt and is not motivated by the cited documents alone or in combination.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 13/53860

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/70; C07H 17/08 (2013.01)
USPC - 514/29; 536/7.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8)- A61K 31/70; C07H 17/08 (2013.01)
USPC-514/29; 536/7.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/7.5

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST, PatBase, FreePatentsOnline (US Pat, PgPub, EPO, JPO, WIPO, NPL), GoogleScholar (PL, NPL); search terms: Erythromycin stearate thiocyanate process water acid addition salt free base alkali aqueous

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	EP 0 853 087 A1 **(Diago et al.)** 15 July 1998 (15.07.1998) **pg** 2, ln 10-30; **pg** 3, ln 39-51; **pg** 4, ln 23-26	1-7 --- 9, (10-11)/9 and 12
X --- Y	US 2,881,163 A (Walasek) 7 April 1959 (07.04.1959) col 2, **ln** 18-30, col 4, **ln** 1-15, col 5, **ln** 42-52	8 and (10-11)/8 --- 9, (10-11)/9 and 12
A	US 2,862,921 A (Booth et al.) 2 December 1958 (02.12.1958) col 3, **ln** 12-18, col 4, ln 5-9, ln 21-26, **ln** 30-32	1-12
A	US 6,140,479 A (Asaka et al.) 31 October 2000 (31.10.2000) col 2, **ln** 33-46, col 3, **ln** 64 to col 4, ln 5	1-12
A	US 4,599,326 A (Marvola et al.) 08 July 1986 (08.07.1986) col 1, ln 57 to col 2, ln 7, col 4, **ln** 41-62	1-12

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"V" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 October 2013 (04.10.2013)	21 OCT 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)