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(54) Title: PROCESSES FOR THE PREPARATION OF GLATIRAMER ACETATE

(57) Abstract: Methods for preparing glatiramer acetate comprising polymerising amino acids L-alanine, L-glutamic acid, L-tyrosine and L-lysine, optionally treating an acidic resin or trimethylsilyl chloride/sodium iodide, treatment with base, followed by adjusting pH and isolating glatiramer acetate. The amino acids are polymerised as their N-carboxyanhydride derivatives, wherein L-glutamic acid and L-lysine are protected. Preferable bases include benzyl trialkyl ammonium hydroxides.



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“PROCESSES FOR THE PREPARATION OF GLATIRAMER ACETATE”**TECHNICAL FIELD**

The present disclosure provides for processes for preparation of Glatiramer acetate. The present disclosure also relates to preparation process of peptide based polymer mixtures, where each polymer is arranged in a random manner comprising the amino acids: L-Glutamic acid, L-Alanine, L-Tyrosine, and L- Lysine. This mixture of random polymers is used to treat multiple sclerosis as glatiramer in a pharmaceutically acceptable salt form.

BACKGROUND AND PRIOR ART OF THE DISCLOSURE

Glatiramer is a peptide based polymer composed of four amino acids: L-Glutamaic acid, L-Alanine, L-Tyrosine, and L-Lysine. It's pharmaceutically acceptable salt Glatiramer acetate is approved by FDA and marketed as Copaxone® for the treatment of multiple sclerosis. Copaxone is also known as copolymer-1 and cop-1. Multiple sclerosis is an autoimmune disease affects the brain and central nervous system due to the damage to the myelin sheath of the nerve cells, which results as demyelination of axons. Glatiramer acetate is a synthetic polypeptide analogue of myelin basic protein (MBP). Pharmacologically, Copaxone is a non-interferon and non-steroidal immunomodulator, which arrests the multiple sclerosis aggression. Glatiramer acetate is administrated by subcutaneous injections.

Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate salt. Its structural formula is:



Average molecular weight of glatiramer acetate is 5,000-11,000 daltons and the average molar fractions of the respective amino acids are: 0.141, 0.427, 0.095, and 0.338.

U.S.Pat. No. 3,849,550 describes the observation of MBP arrest in experimental allergic encephalomyelitis (a disease similar to multiple sclerosis) by immunotherapy agents. With continuous endeavours, glatiramer acetate is resulted as an advanced analogue for the treatment of multiple sclerosis with improved safety and efficacy.

U.S.Pat. Nos. 5,800,808; 5,981,589; 6,048,898 describes the process preparation of glatiramer acetate employing the N-carboxyanhydrides (NCAs) derived from alanine, -benzyl

glutamate, N-trifluoroacetyl lysine, and tyrosine. Following the steps: polymerization, sequential cleavage of the -benzyl ester of glutamate and N-trifluoroacetyl of lysine, acetate salt formation and final purification. U.S.Pat. No. 6,620,847 describes a process for the preparation of glatiramer acetate using the aqueous piperidine for trifluoroacetyl cleavage of lysine. U.S.Pat. No. 7,049,399 describes the process for preparation of polypeptide-1 using the catalytic transfer hydrogenation for the cleavage of -benzyl ester of glutamate. E.P. Pat. No. 1,807,467 describes the processes for preparation of glatiramer using NCAs of alanine, tyrosine, N-*t*-butoxycarbonyl L-Lysine, and protected glutamic acid, where in the protecting group is selected from -methoxybenzyl and -benzyl. U.S.Pat. No. 7,495,072 describes the process for the preparation of mixtures of polypeptides using purified hydrobromic acid. The main drawback of all these processes is the generation of impurities and multiple steps of purification which is not only time consuming but also affects the yield of the final product.

The instant disclosure is circumventing these shortcomings and yields the much purer end product which requires fewer numbers of purification steps.

The new process for the preparation of glatiramer acetate was developed with minimum possible steps using eco-friendly solvent (water) and non-hazardous reagents for the cleavage of protecting groups at ambient temperatures. This process is also adequate to produce glatiramer acetate in large quantities.

STATEMENT OF THE DISCLOSURE

Accordingly, the present disclosure relates to a process for isolating glatiramer acetate said process comprising acts of a) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine, b) optionally treating with acidic resin in a suitable solvent or trimethylsilyl chloride/sodium iodide or any combination thereof, c) treating with suitable base in suitable solvent d) adjusting pH and e) isolating the glatiramer acetate; a process for isolating glatiramer acetate, said process comprising acts of a) preparing N-carboxyanhydride derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine, b) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine, c) optionally treating with acidic resin in a suitable solvent or trimethylsilyl chloride/sodium iodide or any combination thereof, d) treating with suitable base in a suitable solvent, e) adjusting pH and f) isolating the glatiramer acetate; a

process for isolating glatiramer acetate, said process comprising acts of a) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine, b) treating with benzyl trialkyl ammonium hydroxide (BTAAH) in suitable solvent, c) adjusting pH and d) isolating the glatiramer acetate; a process for isolating glatiramer acetate, said process comprising acts of a) preparing N-carboxyanhydride derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine, b) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine, c) treating with benzyl trialkyl ammonium hydroxide (BTAAH) in suitable solvent, d) adjusting pH and e) isolating the glatiramer acetate; a process for isolating glatiramer acetate, said process comprising acts of, a) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine, b) treating with resin in suitable solvent, c) adjusting pH and d) isolating the glatiramer acetate; a process for isolating glatiramer acetate, said process comprising acts of: a) preparing N-carboxyanhydride derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine, b) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine, c) treating with resin in suitable solvent, d) adjusting pH and e) isolating the glatiramer acetate; and Glatiramer acetate isolated by the processes as claimed above, wherein said glatiramer acetate is used for treating multiple sclerosis.

BRIEF DESCRIPTION OF THE ACCOMPANYING FIGURES

Figure 1: Scheme 1- A process for isolating Glatiramer acetate

Figure 2: Scheme 2- A process for isolating Glatiramer acetate

SUMMARY OF THE DISCLOSURE

The present disclosure describes the robust processes for the preparation of glatiramer acetate. The instant disclosure demonstrates the process which discloses the deprotection of protected polymer by employing resins and Benzyl trialkyl ammonium hydroxide (BTAAH) independently. In an embodiment of the present disclosure, Benzyl trialkyl ammonium hydroxide (BTAAH) includes Benzyl triethyl ammonium hydroxide (BTEAH) and Benzyl trimethyl ammonium hydroxide (BTMAH) or mixture thereof. In one of the embodiments, after the polymerization of NCAs of alanine, tyrosine, N-*t*-butoxycarbonyl L-Lysine, and

protected glutamic acid, the deprotection of protected L-glutamate moiety and protected l-lysine separately by employing acid resin followed by a suitable base.

In an embodiment, after the polymerization of NCAs of alanine, tyrosine, N-*t*-butoxycarbonyl L-Lysine, and protected glutamic acid, the deprotection of protected L-glutamate moiety and protected l-lysine is done in a single step by employing Benzyl trialkyl ammonium hydroxide (BTAAH).

In another embodiment, after the deprotection, in both the cases process was proceeded to make acetate salt followed by optional purification.

In an embodiment, the disclosed processes are better in ease of handling, operations, and isolations in large scales. The acidic resins employed for the deprotection in the instant disclosure are less hazardous, easy to handle and provides better separation from the reaction mixture compared to any other reagents like HBr, H₂SO₄ for cleavage of the protected groups.

In another embodiment, use of benzyl trialkyl ammonium hydroxide (BTAAH) reduced the number operations and solvents by cleaving all the protecting groups in single step in an aqueous media. Further, this method results in isolating much purer intermediate.

DETAILED DESCRIPTION OF THE DISCLOSURE

The present disclosure relates to a process for isolating glatiramer acetate, said process comprising acts of:

- a) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine;
- b) optionally treating with acidic resin in a suitable solvent or trimethylsilyl chloride/sodium iodide or any combination thereof;
- c) treating with suitable base in suitable solvent;
- d) adjusting pH; and
- e) isolating the glatiramer acetate.

The present disclosure also relates to a process for isolating glatiramer acetate, said process comprising acts of:

- a) preparing N-carboxyanhydride derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine;
- b) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine;
- 5 c) optionally treating with acidic resin in a suitable solvent or trimethylsilyl chloride/sodium iodide or any combination thereof;
- d) treating with suitable base in a suitable solvent;
- e) adjusting pH; and
- f) isolating the glatiramer acetate.

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In an embodiment of the present disclosure, the protected L-glutamate NCA derivative is -alkyl ester of L-glutamic acid.

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In another embodiment of the present disclosure, the -alkyl ester is selected from a group comprising esters of optionally protected -methyl, -ethyl, -propyl and -butyl, or any combination thereof.

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In yet another embodiment of the present disclosure, the optionally protected -methyl is -benzyl.

In still another embodiment of the present disclosure, the optionally protected tyrosine is selected from a group comprising L-tyrosine and acetyl-L-tyrosine, or combination thereof.

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In still another embodiment of the present disclosure, the protected L-lysine is selected from N-t-butoxycarbonyl L-Lysine or trifluoro acetyl L-lysine.

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In still another embodiment of the present disclosure, the base is selected from a group comprising benzyl trialkyl ammonium hydroxide (BTAAH), piperadine, piperazine, hydrazine hydrate and basic resin, or any combination thereof.

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In still another embodiment of the present disclosure, the suitable solvent is selected from a group comprising water, dioxane, tetrahydrofuran, and acetonitrile or any combination thereof.

In still another embodiment of the present disclosure, the treatment is carried out at temperature ranging from about -20°C to about 75°C.

In still another embodiment of the present disclosure, the treatment is carried out for time duration ranging from about 2h to about 72h.

The present disclosure also relates to process for isolating glatiramer acetate, said process comprising acts of:

- a) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine;
- b) treating with benzyl trialkyl ammonium hydroxide (BTAAH) in suitable solvent;
- c) adjusting pH; and
- d) isolating the glatiramer acetate.

The present disclosure also relates to a process for isolating glatiramer acetate, said process comprising acts of:

- a) preparing N-carboxyanhydride derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine;
- b) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine;
- c) treating with benzyl trialkyl ammonium hydroxide (BTAAH) in suitable solvent;
- d) adjusting pH; and
- e) isolating the glatiramer acetate.

In an embodiment of the present disclosure, the protected L-glutamate NCA derivative is -alkyl ester.

In another embodiment of the present disclosure, the -alkyl ester is selected from a group comprising esters of optionally protected -methyl, -ethyl, -propyl and -butyl, or any combination thereof.

In yet another embodiment of the present disclosure, the optionally protected alkyl ester is -benzyl ester.

In still another embodiment of the present disclosure, the optionally protected tyrosine is selected from a group comprising L-tyrosine and acetyl-L-tyrosine, or combination thereof.

In still another embodiment of the present disclosure, the protected L-lysine is selected from N-t-butoxycarbonyl L-Lysine or trifluoro acetyl L-lysine.

- 5 In still another embodiment of the present disclosure, the suitable solvent is selected from a group comprising water, dioxane, tetrahydrofuran and acetonitrile, or any combination thereof.

10 In still another embodiment of the present disclosure, the treatment is carried out at temperature ranging from about -20°C to about 75°C.

In still another embodiment of the present disclosure, the treatment is carried out for time duration ranging from about 2h to about 72h.

- 15 In still another embodiment of the present disclosure, the benzyl trialkyl ammonium hydroxide (BTAH) is selected from a group comprising benzyl triethyl ammonium hydroxide (BTEAH) and benzyl trimethyl ammonium hydroxide (BTMAH) or a combination thereof.

20 The present disclosure also relates to a process for isolating glatiramer acetate, said process comprising acts of:

- a) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine;
b) treating with resin in suitable solvent;
25 c) adjusting pH; and
d) isolating the glatiramer acetate.

The present disclosure also relates to a process for isolating glatiramer acetate, said process comprising acts of:

- 30 a) preparing N-carboxyanhydride derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine;
b) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine;
c) treating with resin in suitable solvent;
35 d) adjusting pH; and

e) isolating the glatiramer acetate.

In an embodiment of the present disclosure, the protected L-glutamate NCA derivative is -alkyl ester.

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In another embodiment of the present disclosure, the -alkyl ester is selected from a group comprising esters of optionally protected -methyl, -ethyl, -propyl and -butyl, or any combination thereof.

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In yet another embodiment of the present disclosure, the optionally protected alkyl ester is – benzyl ester.

In still another embodiment of the present disclosure, the optionally protected tyrosine is selected from a group comprising L-tyrosine and acetyl-L-tyrosine, or combination thereof.

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In still another embodiment of the present disclosure, the protected L-lysine is selected from N-t-butoxycarbonyl L-Lysine or trifluoro acetyl L-lysine.

In still another embodiment of the present disclosure, the resin is selected from the group of
20 acidic resins and basic resins.

In still another embodiment of the present disclosure, the suitable solvent is selected from a group comprising water, dioxane, tetrahydrofuran, and acetonitrile or any combination thereof.

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In still another embodiment of the present disclosure, the treatment is carried out at temperature ranging from about 20°C to about 85°C.

In still another embodiment of the present disclosure, the treatment is carried out for time
30 duration ranging from about 12 hours to about 48 hours.

The present disclosure also relates to Glatiramer acetate isolated by the processes as above, wherein said glatiramer acetate is used for treating multiple sclerosis.

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In an embodiment, the NCA derivatives of protected L-Glutamate, L-alanine, L-Tyrosine, and protected L-Lysine are prepared by following the known procedure. Upon the

polymerization, these derivatives produce the corresponding protected copolymer. Deprotection of protecting groups with suitable reagents yields crude glatiramer, further treated with glacial acetic acid and purification leads to get the pure glatiramer acetate.

- 5 In one embodiment of the disclosure, the protected polymer 1 was treated with solid acidic resin with and work up procedures to produce corresponding protected polymer 2 by cleaving the acid labile groups. The reaction proceeded smoothly in short time even in large scales, followed by simple workup and isolation steps. The reaction workup procedure for these resins mediated reactions was very simple when compared to another literature known acids.

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In another embodiment of the present disclosure the basic resin is selected from a group comprising Lewatit MP 62, Lewatit MP M500-OH, PA 408-Dianion and HPA 75-Dianion, or any combination thereof.

- 15 Protected polymer 1 was produced using NCA derivative of -benzyl glutamate as one of the components in the polymer, which upon treatment with acidic resin selected from Lewatit K 2629, Diaion UBK 550, Diaion SK 110, Amberlyst-15, or mixture thereof produced the corresponding protected copolymer 2. Interestingly, the same protected polymer 2 was produced by replacing the resin with aluminium chloride, NaI/TMSCl in suitable solvents at
20 appropriate conditions. The solvent was selected from dioxane, THF, acetonitrile, water or mixture thereof. In the next step, base labile protecting groups were cleaved using suitable reagent selected from benzyl trialkyl ammonium hydroxide (BTAAH), piperadine, piperazine, hydrazine hydrate, or mixture thereof (Figure 1). Followed by adjusting pH to 6 with acetic acid and finally purified to obtain glatiramer acetate.

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In another embodiment, protected polymer 3 was produced using the NCA derivatives of alkyl glutamate, L-alanine, acetyl-L-tyrosine, and N-*t*-butoxycarbonyl L-Lysine (Figure 2). Alkyl group in alkyl glutamate is selected from C1 to C4 alkanes and optionally substituted with a phenyl group. Cleavage of all the protecting groups of the protected polymer 3 was
30 achieved using benzyl trialkyl ammonium hydroxide (BTAAH) in suitable solvents. Further, the pH was adjusted to 6 using glacial acetic acid followed by purification to obtain glatiramer acetate. Benzyl trialkyl ammonium hydroxide (BTAAH) was turned out as the best reagent for the preparation of glatiramer by cleaving all the protecting groups of the polymer in a single step. Easily available very cheap BTEAH reagent was obtained as 40%

solution in water. Water was used as the single solvent for this crucial step and the resulting glatiramer acetate with minimum impurities was isolated by filtration.

In another embodiment of this disclosure, protected polymer 3 was treated with the piperidine solution and then with BETAH to produce the glatiramer crude. The resulted in product was adjusted with pH to 6 using glacial acetic acid and purification of the crude mass to obtain glatiramer acetate.

A more complete understanding can be obtained by reference to the following specific examples, which are provided for purposes of illustration only and are not intended to limit the scope of the disclosure.

EXAMPLES:

Example 1: Preparation of Glatiramer acetate using benzyl triethyl ammonium hydroxide:

100 ml of benzyl triethyl ammonium hydroxide (40% solution in methanol) was added to the suspension of protected polymer 3 (10 g) in water (100 ml) and stirred at room temperature for 20 h. pH was adjusted to 6 after the completion of reaction with glacial acetic acid and purified to obtain glatiramer acetate as solid (50 g).

Example 2A: Preparation of glatiramer acetate using resin:

Lewatit K 2629 resin (10 g) was added to a suspension of protected polymer 1 (10 g) in THF (150 ml) and stirred at 65 °C for 24 h. The reaction mixture was filtered to separate resin residue and washed with THF (50 ml). Water was added to the filtrate to precipitate out the solid. Filtered the solids and dried under vacuum for 24 h at 40-45°C to obtain protected polymer 2 (6 g).

The resulted protected polymer 2 was suspended in water (60 ml), added 60 mL of 40% solution of benzyl triethyl ammonium hydroxide in water and stirred for 20h at room temperature. The pH of the reaction mass was adjusted to 6 using glacial acetic acid to obtain glatiramer acetate (4 g).

Example 2B: Preparation of glatiramer acetate using resin:

Lewatit K 2629 resin (2 gm) was added to the protected polymer 1 (1 gm) in a mixture of THF(8 ml) and water (2ml) later, stirred at 65°C for 24 h. The resin was filtered and washed

with THF(5 ml).The reaction mass was distilled to 3-4 volume stage and water was added and the precipitated product was filtered and dried in VTD for 24h at 40-45°C to get protected copolymer 2.

Protected copolymer 2 (1 gm) was charged with 20 ml of benzyl trimethyl ammonium hydroxide (40% aq.solution) and stirred for 20 h at 25-30°C.The reaction mass was adjusted to pH 6 using glacial acetic acid. The crude Glatiramer acetate was purified by Gel Permeation Chromatography.

Example 3: Preparation of glatiramer acetate using TMSCl/NaI followed by benzyl triethyl ammonium hydroxide:

Protected polymer 1 (20 g) was charged in THF (200 ml) under nitrogen atmosphere, added sodium iodide-NaI (1 g) was added followed by trimethylsilyl chloride-TMSCl (20 ml) at room temperature and stirred for 3h. The reaction mass was quenched after the completion of reaction with water (20 ml). The solids were filtered, washed with water (100 ml) and dried under high vacuum to obtain protected copolymer 2 (10 g).

The resulted protected polymer 2 was suspended in water (100 ml), 40% solution of benzyl triethyl ammonium hydroxide in water (100 ml) was added and stirred at room temperature for 5 h. pH was adjusted after the completion of the reaction to 6 with glacial acetic acid, and the mass was purified to obtain glatiramer acetate (6 g).

Example 4: Preparation of glatiramer acetate from protected polymer 3: 40% Solution of benzyl triethyl ammonium hydroxide in water (10 ml) was added to protected copolymer 3 (1 g) in water (10 ml) at room temperature and stirred for 5 h. pH was adjusted to 6 after completion of the reaction with glacial acetic acid. The resulted in mass was purified to obtain glatiramer acetate (0.6 g).

Example 5: Preparation of glatiramer acetate using piperadine followed by benzyl triethyl ammonium hydroxide:

Piperidine (500 ml) was added to protected polymer 3 (250 g) in water (5 L) at room temperature and stirred for 20 h. After completion of the reaction, benzyl triethyl ammonium hydroxide was added (500 ml) and continued the stir for 5h, filtered the reaction mass and washed twice with water (100 ml). Suspended the resulted solid in water (1 L), adjusted the pH to 6 using glacial acetic acid and purified to obtain glatiramer acetate (110 g).

Example 6: Procedure for the purification of glatiramer acetate:

- Gel permeable chromatography column preparation:

A column for gel filtration, FRACTOGEL® TSK HW55 (600 x 26mm) was prepared in a Superformance® 26. The column was equilibrated with water and acetone solution was
5 injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH 5.0.

- Crude glatiramer acetate from above processes was purified by following gel permeable chromatography technique: Copolymer-1 samples (20mg/ml, in 0.2M ammonium acetate pH 5.0) were loaded on the column and fractions were collected
10 every 10 minutes. Fractions having an average molecular weight of 5-11 k Da were isolated between 120-130 minutes and pooled. All the pooled fractions were lyophilized to obtain pure glatiramer acetate as solid.

We claim:

1. A process for isolating glatiramer acetate, said process comprising acts of:
 - f) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine;
 - 5 g) optionally treating with acidic resin in a suitable solvent or trimethylsilyl chloride/sodium iodide or any combination thereof;
 - h) treating with suitable base in suitable solvent;
 - i) adjusting pH; and
 - j) isolating the glatiramer acetate.
- 10 2. A process for isolating glatiramer acetate, said process comprising acts of:
 - g) preparing N-carboxyanhydride derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine;
 - h) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine;
 - 15 i) optionally treating with acidic resin in a suitable solvent or trimethylsilyl chloride/sodium iodide or any combination thereof;
 - j) treating with suitable base in a suitable solvent;
 - k) adjusting pH; and
 - l) isolating the glatiramer acetate.
- 20 3. The process as claimed in claims 1 and 2, wherein the protected L-glutamate NCA derivative is -alkyl ester of L-glutamic acid.
4. The process as claimed in claim 3, wherein the -alkyl ester is selected from a group comprising esters of optionally protected -methyl, -ethyl, -propyl and -butyl, or any combination thereof.
- 25 5. The process as claimed in claim 4, wherein the optionally protected -methyl is – benzyl.
6. The process as claimed in claims 1 and 2, wherein the optionally protected tyrosine is selected from a group comprising L-tyrosine and acetyl-L-tyrosine, or combination thereof.
- 30 7. The process as claimed in claims 1 and 2, wherein the protected L-lysine is selected from N-t-butoxycarbonyl L-Lysine or trifluoro acetyl L-lysine .

8. The process as claimed in claims 1 and 2, wherein the base is selected from a group comprising benzyl trialkyl ammonium hydroxide (BTAAH), piperadine, piperazine, hydrazine hydrate and basic resin, or any combination thereof.
9. The process as claimed in claims 1 and 2, wherein the suitable solvent is selected
5 from a group comprising water, dioxane, tetrahydrofuran, and acetonitrile or any combination thereof.
10. The process as claimed in claims 1 and 2, wherein the treatment is carried out at temperature ranging from about -20°C to about 75°C.
11. The process as claimed in claims 1 and 2, wherein the treatment is carried out for time
10 duration ranging from about 2h to about 72h.
12. A process for isolating glatiramer acetate, said process comprising acts of:
 - e) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine;
 - f) treating with benzyl trialkyl ammonium hydroxide (BTAAH) in suitable
15 solvent;
 - g) adjusting pH; and
 - h) isolating the glatiramer acetate.
13. A process for isolating glatiramer acetate, said process comprising acts of:
 - f) preparing N-carboxyanhydride derivatives of protected L-Glutamate, L-
20 Alanine, optionally protected Tyrosine, and protected Lysine;
 - g) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine;
 - h) treating with benzyl trialkyl ammonium hydroxide (BTAAH) in suitable solvent;
 - 25 i) adjusting pH; and
 - j) isolating the glatiramer acetate.
14. The process as claimed in claims 12 and 13, wherein the protected L-glutamate NCA derivative is -alkyl ester.
15. The process as claimed in claim 14, wherein the -alkyl ester is selected from a group
30 comprising esters of optionally protected -methyl, -ethyl, -propyl and -butyl, or any combination thereof.
16. The process as claimed in claim 15, wherein the optionally protected alkyl ester is – benzyl ester.

17. The process as claimed in claims 12 and 13, wherein the optionally protected tyrosine is selected from a group comprising L-tyrosine and acetyl-L-tyrosine, or combination thereof.
18. The process as claimed in claims 12 and 13, wherein the protected L-lysine is selected from N-t-butoxycarbonyl L-Lysine or trifluoro acetyl L-lysine.
19. The process as claimed in claims 12 and 13, wherein the suitable solvent is selected from a group comprising water, dioxane, tetrahydrofuran and acetonitrile, or any combination thereof.
20. The process as claimed in claims 12 and 13, wherein the treatment is carried out at temperature ranging from about -20°C to about 75°C.
21. The process as claimed in claims 12 and 13, wherein the treatment is carried out for time duration ranging from about 2h to about 72h.
22. The processes as claimed in claims 8, 12 and 13, wherein the benzyl trialkyl ammonium hydroxide (BTAAH) is selected from a group comprising benzyl triethyl ammonium hydroxide (BTEAH) and benzyl trimethyl ammonium hydroxide (BTMAH) or a combination thereof.
23. A process for isolating glatiramer acetate, said process comprising acts of:
- e) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine;
 - f) treating with resin in suitable solvent;
 - g) adjusting pH; and
 - h) isolating the glatiramer acetate.
24. A process for isolating glatiramer acetate, said process comprising acts of:
- f) preparing N-carboxyanhydride derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected Lysine;
 - g) polymerizing N-carboxyanhydride (NCA) derivatives of protected L-Glutamate, L-Alanine, optionally protected Tyrosine, and protected L-Lysine;
 - h) treating with resin in suitable solvent;
 - i) adjusting pH; and
 - j) isolating the glatiramer acetate.
25. The process as claimed in claims 23 and 24, wherein the protected L-glutamate NCA derivative is -alkyl ester.

26. The process as claimed in claim 25, wherein the -alkyl ester is selected from a group comprising esters of optionally protected -methyl, -ethyl, -propyl and -butyl, or any combination thereof.
27. The process as claimed in claim 26, wherein the optionally protected alkyl ester is –
5 benzyl ester.
28. The process as claimed in claims 23 and 24, wherein the optionally protected tyrosine is selected from a group comprising L-tyrosine and acetyl-L-tyrosine, or combination thereof.
29. The process as claimed in claims 23 and 24, wherein the protected L-lysine is selected
10 from N-t-butoxycarbonyl L-Lysine or trifluoro acetyl L-lysine.
30. The process as claimed in claims 23 and 24, wherein the resin is selected from the group of acidic resins and basic resins.
31. The process as claimed in claims 23 and 24, wherein the suitable solvent is selected from a group comprising water, dioxane, tetrahydrofuran, and acetonitrile or any
15 combination thereof.
32. The process as claimed in claims 23 and 24, wherein the treatment is carried out at temperature ranging from about 20°C to about 85°C.
33. The process as claimed in claims 23 and 24, wherein the treatment is carried out for time duration ranging from about 12 hours to about 48 hours.
- 20 34. Glatiramer acetate isolated by the processes as claimed in claims 1, 2, 12, 13, 23 or 24, wherein said glatiramer acetate is used for treating multiple sclerosis.

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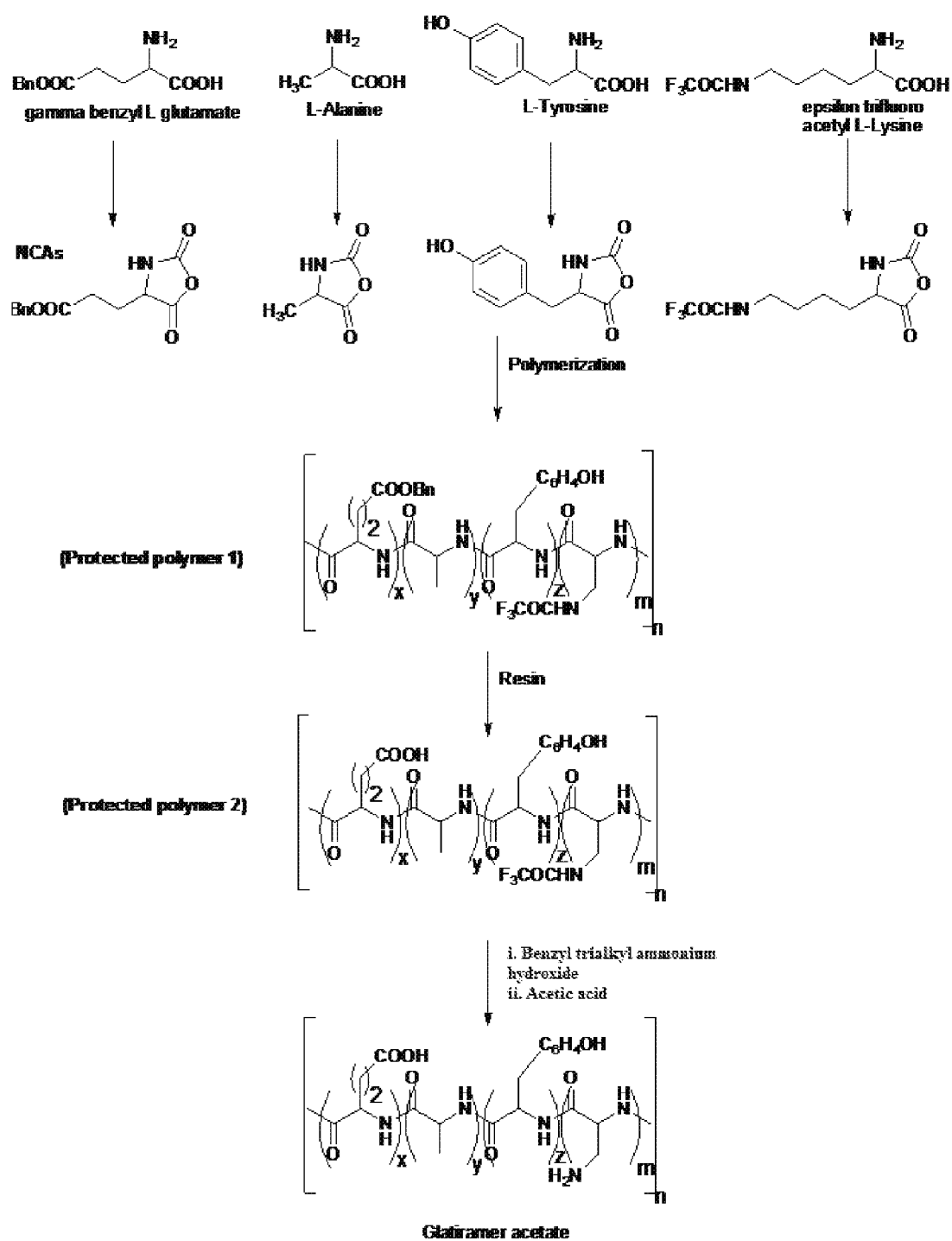


Figure 1

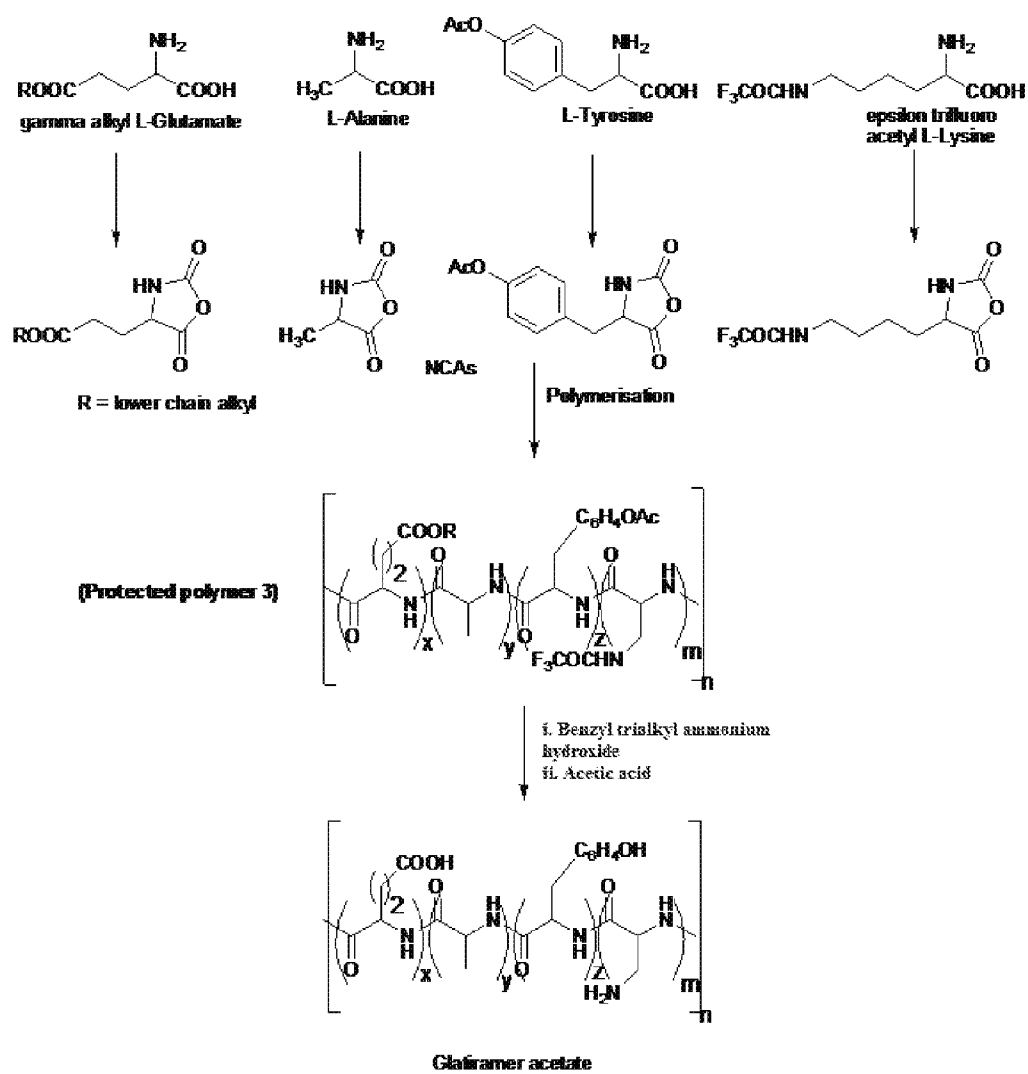


Figure 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2011/055172

A. CLASSIFICATION OF SUBJECT MATTER		
Int. Cl.		
C07K 1/02 (2006.01) C07K 2/00 (2006.01) C07K 1/06 (2006.01)		
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)		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN: files REG, CAPLUS, MEDLINE, WPIDS, searched based on CAS RN for glatiramer acetate and preparation role in CAPLUS, keywords in CAPLUS, MEDLINE, WPIDS based on glatiramer acetate and synonyms, preparation, synthesis, resin, ammonium hydroxide and related terms and truncations thereof.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/050122 A1 (SANDOZ AG) 11 May 2006 See examples, especially 19, 22, 23 on pages 27 and 28	1, 3-7, 9-11, 34
X	WO 2010/017292 A1 (SCINOPHARM TAIWAN, LTD.) 11 February 2010 See examples, especially 1 and 3 on pages 8 and 9	1, 3-7, 9-11, 34
X	IN 01082/MUM/2009 A (USV LIMITED) 05 November 2010 See examples, especially 1 to 8 from page 19 onwards, 25 on page 27 and also examples 14 to 17, see also pages 2 and 17	1-22, 34
X	IN 00599/DEL/2008 A (COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH) 01 January 2010 See examples, especially 1 to 5 on pages 10 to 12	1-11, 34
☐ Further documents are listed in the continuation of Box C ☒ See patent family annex		
* 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 "T" 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 04 February 2012		Date of mailing of the international search report 21 February 2012
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. +61 2 6283 7999		Authorized officer CHETAN MAKANI AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6283 2896

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IB2011/055172

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report			Patent Family Member				
WO	2006050122	AR	052321	AU	2005302500	CA	2583589
		CN	101044188	EP	1807467	JP	2008518930
		US	2006154862	US	2008021200	US	2010174048
		US	2010234272	US	2010234566		
WO	2010017292	AR	072974	AU	2009279636	CA	2733500
		CN	102112485	EP	2326657	JP	2011530523
		KR	20110059606	US	2010036092		
IN	01082MUM2009	NONE					
IN	00599DEL2008	NONE					

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX