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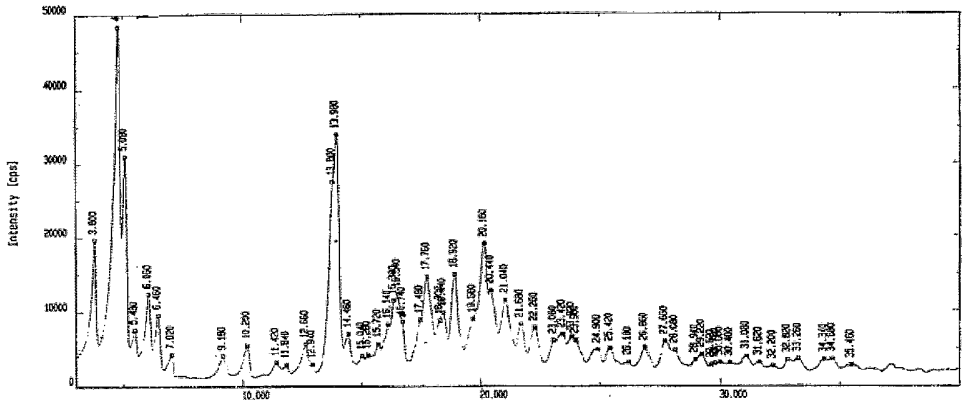
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(54) Title: PREPARATIONS OF STABLE PHARMACEUTICAL COMPOSITIONS OF NATEGLINIDE AND PROCESSES FOR THEIR PREPARATION



(57) Abstract: The present invention relates to preparations of stable pharmaceutical compositions of nateglinide and processes for their preparation. The processes for preparing the stable pharmaceutical composition of nateglinide Form B includes a step of granulating with isopropyl alcohol.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PREPARATIONS OF STABLE PHARMACEUTICAL COMPOSITIONS OF NATEGLINIDE AND PROCESSES FOR THEIR PREPARATION

Field of the Invention

The present invention relates to preparations of stable pharmaceutical compositions comprising nateglinide Form B, and processes for their preparation.

Background of the Invention

Nateglinide is an amino acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. It is widely indicated as monotherapy to lower blood glucose in patients with Type 2 diabetes. It is also indicated for use in combination with metformin. Presently nateglinide oral tablets are available in 60 mg or 120 mg strengths and are marketed by Novartis under the trade name STARLIX®.

Nateglinide is disclosed in Japanese Patent Application Laid Open No. 63-54321 (equivalent to EP-A-196222 and US 4,816,484) and in J. Med. Chem. 32, 1436. The Japanese application describes how the compound may be crystallized from aqueous methanol to yield crystals having a melting point of 129°C to 130°C. These crystals are in a crystalline form known as "B-type" crystals. The known B-type crystals suffer from problems of instability, especially when subjected to pulverization. The instability results in conversion of the B-type crystals into other forms. US 5,463,116 discloses a method of producing a crystalline form of nateglinide having improved stability (H Type) to pulverization, and is thus said to be more suitable for use in dosage forms than those of the B-type.

US 6,559,188 describes compositions of nateglinide, or a pharmaceutically acceptable salt thereof, which are capable of being granulated without the need for pulverization after the granulation step. The process of granulation as described in this patent is carried out in the presence of water, i.e., aqueous granulation.

We have found that pharmaceutical compositions of nateglinide form B when prepared by dry granulation or direct compression show low dissolution profiles, in addition to the known processing issues such as poor flow, poor compressibility, etc.

Similarly, in wet granulation with water or ethanol as a granulating fluid, nateglinide Form B converts to other polymorphic forms.

In the present invention we have discovered that pharmaceutical compositions comprising nateglinide Form B, when prepared by granulation with isopropyl alcohol, are stable even after pulverization, i.e., there is no conversion of Form B to any other polymorphic form even when stored at accelerated aging conditions of temperature. Moreover these preparations showed a dissolution profile comparable with STARLIX®.

Summary of the Invention

In one general aspect there is provided a process for preparing a stable pharmaceutical composition of nateglinide Form B. The process includes a step of granulating with isopropyl alcohol.

Embodiments of the process may include one or more of the following features. For example, the process may further include blending nateglinide with one or more of filler, surfactant and disintegrant to form a blend; granulating the blend with a solution of binder in isopropyl alcohol to form a granulation; and drying, pulverizing; lubricating, and compressed the granulation into tablets. The process also may further include mixing the nateglinide with one or more of filler, surfactant, disintegrant and binder to form a blend; granulating the blend with isopropyl alcohol to form a granulation; and drying, pulverizing, lubricating and compressing the granulation into tablets. In theses processes there may be no conversion of Form B of nateglinide to any other polymorphic form during processing of the Form B of nateglinide.

The nateglinide Form B may include a premix of nateglinide Form B with premix filler(s). The premix filler may include one or more of mannitol, starch, lactose, mannitol, microcrystalline cellulose, starch or a combination thereof. In particular, the premix filler may include a mixture of starch and mannitol. The ratio of nateglinide, mannitol and starch in the premix may be about 2:1:1.

The process may further include blending the nateglinide premix with filler, surfactant and disintegrant to form a blend; granulating the blend with a solution of binder

in isopropyl alcohol to form a granulation; and drying, pulverizing, lubricating, and compressing the granulation into tablets. The process instead may further include blending the nateglinide premix with filler, surfactant, disintegrant and binder to form a blend; granulating the blend with isopropyl alcohol to form a granulation; and drying, pulverizing, lubricating, and compressing the granulation into tablets. In these processes, there may be no conversion of Form B of nateglinide to any other polymorphic form during process of the Form B of nateglinide.

The composition may further include one or more pharmaceutically acceptable excipients including filler, binder, disintegrant, surfactant, lubricant, coloring and flavoring agent. The filler may be one or more of corn starch, lactose, mannitol, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, sorbitol, starch, starch pregelatinized, sucrose, and mixtures thereof.

The binder may be one or more of polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and mixtures thereof. The disintegrant may be one or more of crospovidone, sodium starch glycolate, croscarmellose sodium, starch and mixtures thereof. The surfactant may be one or more of sodium lauryl sulphate, poloxamer, Polysorbate 80 and mixtures thereof. The lubricant may be one or more of magnesium stearate, stearic acid, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and mixtures thereof.

In another general aspect there is provided a medicament for the prevention, delay of progression or treatment of metabolic disorders, type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus. The medicament includes nateglinide Form B and the medicament is formed by a process that includes a step of granulation with isopropyl alcohol. The medicament may include any one or more of the features described above.

In another general aspect there is provided a medicament for the prevention, delay of progression or treatment of metabolic disorders, type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus. The medicament includes a premix of nateglinide form B with fillers and the medicament is formed by a process comprising a step of granulation with isopropyl alcohol. The medicament may include any one or more of the features described above.

In another general aspect there is provided a premix of nateglinide Form B, one or more fillers, and isopropyl alcohol. Embodiments may include one or more of the following features or those described above. For example, the premix may be incorporated into a medicament. The medicament may contain a pharmaceutically acceptable residual amount of isopropyl alcohol being present at an amount that is less than 50 mg and/or 5,000 ppm.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description, figures, and claims.

Detailed Description of the Drawings

Figure 1 is an XRD profile of nateglinide Form B.

Figure 2 is an XRD profile of a nateglinide premix.

Figures 3 and 4 are XRD profiles of nateglinide tablet of Examples 1 and 2.

Figures 5 and 6 are XRD of the placebo tablet for Example 1 and 2, respectively.

Detailed Description of the Invention

Hence in one aspect there is provided a process for preparing stable pharmaceutical compositions that comprise nateglinide Form B, the process comprising a step of granulation with isopropyl alcohol.

In one of the embodiments nateglinide tablets may be prepared by blending nateglinide with other excipients such as filler(s), surfactant(s), and disintegrant(s);

granulating the blend with a solution of binder(s) in isopropyl alcohol; drying the granules; pulverizing; lubricating; and compressing the lubricated granules.

In another embodiment nateglinide tablets may be prepared by blending nateglinide with other excipients such as filler(s), surfactant(s), disintegrant(s) and binder(s); granulating the blend with isopropyl alcohol; drying the granules; pulverizing; lubricating; and compressing the lubricated granules.

In another embodiment nateglinide tablets may be prepared by blending nateglinide with other excipients such as fillers and disintegrant; mixing the blend with a solution of surfactant in a half quantity of the isopropyl alcohol; granulating the mixture with a solution of binder in the remaining quantity of isopropyl alcohol; drying the granules; pulverizing; lubricating; and compressing the lubricated granules.

Nateglinide may be mixed as such with other excipients to make the blend, or used as a premix that can be prepared with filler(s) and then this premix is mixed with other excipients to prepare a blend, which is granulated with isopropyl alcohol and compressed to form tablet.

Therefore in another aspect the present invention provides a process for preparing stable pharmaceutical compositions that include a premix of nateglinide Form B with fillers, wherein the process includes a step of granulation with isopropyl alcohol.

The fillers may be selected from lactose, mannitol, microcrystalline cellulose, starch and the likes thereof.

A premix of nateglinide can be made with mannitol and starch wherein these three components can be used in ratio of, for example, 2:1:1.

Hence in another aspect the present invention provides a process of preparation of stable pharmaceutical composition comprising a premix of nateglinide Form B with mannitol and starch in the ratio of 2:1:1, wherein the process comprises a step of granulation with isopropyl alcohol.

In all the above embodiments, nateglinide can be used alone or in combination with other antidiabetic agents.

The present invention also provides a process for preparing stable pharmaceutical compositions of nateglinide Form B or a premix of nateglinide Form B in combination with mannitol and starch, wherein the composition is used for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus and the process comprises a step of granulation with isopropyl alcohol.

The pharmaceutical compositions as described herein may include other pharmaceutically acceptable excipients in addition to nateglinide or its premix.

The term 'nateglinide' as used herein includes nateglinide in a free or pharmaceutically acceptable salt form such as an acid addition salt, for example, as a sodium salt or as a maleate. In particular, the composition comprises the B type crystal modification of nateglinide. Nateglinide or a pharmaceutically acceptable salt thereof may also be used in the form of a hydrate or include other solvents used for crystallization. Nateglinide may be present either substantially in the form of one optically pure enantiomer or as a mixture, racemic or otherwise, of enantiomers. Nateglinide may be present in an amount of about 5% to about 70% (w/w), and most preferably about 15% to about 40% (w/w), based on the total weight of the pharmaceutical composition.

The term 'Premix' refers to a combination of nateglinide form B with fillers, particularly mannitol and starch in the ratio of 2:1:1.

The term 'pharmaceutically acceptable excipients' refers to ingredients of the composition, but excludes the active drug substance. Examples of other pharmaceutically acceptable excipients as used herein include fillers, binders, disintegrants, lubricants, surfactants, glidants, colors and the like.

The fillers can be selected from one or more of corn starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline

cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, starch pregelatinized, sucrose, and the like. In particular lactose, microcrystalline cellulose or mannitol can be used.

Examples of binders include one or more of methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Examples of disintegrants include one or more of starch, croscarmellose sodium, crospovidone, sodium starch glycolate and the like.

Examples of lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and the like.

Examples of surfactants include one or more of sodium lauryl sulphate, poloxamer, Polysorbate 80 and the like.

The coloring agents of the present invention may be selected from any FDA approved colors for oral use.

The premix can be prepared by simple physical mixing at controlled temperature and pressure wither with or without the presence of organic solvents.

The stable pharmaceutical composition can be prepared by wet granulation and may be in the form of tablet or capsule. After granulation pulverization can be carried out in conventional milling instruments such as an air jet mill, multi mill, ball mill or by any other method of particle attrition.

The tablets prepared by the present invention may be coated with one or more additional layers comprising film forming agents and/or pharmaceutically acceptable excipients.

The coating layers over the tablet may be applied as a solution/dispersion of coating ingredients using any conventional technique known in the art such as spray coating in a conventional coating pan or fluidized bed processor, dip coating, and the like.

Examples of solvents used for preparing a solution/dispersion of the coating ingredients include methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and the like and mixtures thereof.

Examples of film forming agents include ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate; waxes such as polyethylene glycol; methacrylic acid polymers such as Eudragit ® RL and RS; and the like and mixture thereof. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry® may also be used for coating.

The following examples are illustrative of the invention, and are not to be construed as limiting the invention.

EXAMPLE 1

Ingredient	**Example 1 (wt/tablet) mg**
Intragranular ingredients	
Nateglinide premix (nateglinide : mannitol : starch) (2:1:1)	240
Lactose monohydrate	100
Polyvinylpyrrolidone	12
Microcrystalline cellulose*	60
Sodium lauryl sulphate	24
Colloidal silicon dioxide	15
Sodium starch glycolate	76
Isopropyl alcohol	q.s
Extragranular ingredients	
Lactose monohydrate	60
Microcrystalline cellulose	30
Crospovidone	56
Colloidal silicon dioxide	15
Magnesium stearate	12

* Concentration may be adjusted to maintain constant tablet weight based on the quantity of premix.

PROCEDURE:

1. Nateglinide premix, lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide and sodium starch glycolate are mixed in a high shear blender to give a uniform dry mixture.

2. Sodium lauryl sulphate is dispersed in about 50% of the total quantity of isopropyl alcohol and is added slowly to the dry mixture of Step 1 under fast mixing in a rapid mixer granulator (RMG).

3. Polyvinylpyrrolidone is dissolved in the remaining quantity of isopropyl alcohol till a clear solution is formed, and this solution is added slowly to the mixture of Step 2 and the bulk is then granulated.

4. The wet granules are dried in a fluid bed drier, passed through a screen and then

subjected to a pulverization step to mill the retentions.

5. The extragranular colloidal silicon dioxide, microcrystalline cellulose, lactose monohydrate and crospovidone are mixed, passed through a screen and blended with the granules of step 4.

6. The magnesium stearate is passed through a screen, blended with the blend of step 5 and the total mixture is compressed into tablets.

EXAMPLE 2

Ingredient	**Example 2 (wt/tablet) mg**
Intragranular ingredients	
Nateglinide premix (nateglinide : mannitol : starch) (2:1:1)	240
Lactose monohydrate	150
Polyvinylpyrrolidone	12
Microcrystalline cellulose	43
Sodium lauryl sulphate	20
Colloidal silicon dioxide	8
Sodium starch glycolate	55
Isopropyl alcohol	q.s
Extragranular ingredients	
Mannitol	119
Crospovidone	35
Colloidal silicon dioxide	6
Magnesium stearate	12

PROCEDURE:

1. Nateglinide premix, lactose monohydrate, colloidal silicon dioxide, microcrystalline cellulose and sodium starch glycolate are mixed in a high shear blender to give a uniform dry mixture.

2. Sodium lauryl sulphate is dissolved in about 50% of the isopropyl alcohol and is added slowly to the dry mixture of Step 1 under fast mixing in a rapid mixer granulator (RMG).

3. Polyvinylpyrrolidone is dissolved in the remaining quantity of the isopropyl alcohol till a clear solution is formed, and this solution is added slowly to the premixture of Step 2 and the bulk is then granulated.

4. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to a pulverization step.

5. The extragranular colloidal silicon dioxide, mannitol and crospovidone are mixed, passed through a screen and blended with the granules of step 4.

6. The magnesium stearate is passed through a screen, blended with the blend of step 5 and the total mixture is compressed into tablets.

Comparative *In vitro* dissolution study

The *in vitro* release of nateglinide from tablets as per the compositions of Examples 1 and 2 was studied in 1000 ml, 0.01 N HCl, with 0.5% SLS, using USP apparatus – II, at 50 rpm. The results are listed in Table 1.

Table 1: In vitro release of nateglinide from tablets

Time	Cumulative percentage (%) release of nateglinide from tablets		
	STARLIX*	Example 1	Example 2
10	74	61	54
20	86	82	74
30	94	87	84

Table 1 clearly indicates that pharmaceutical compositions of present invention show a comparable dissolution profile to that of STARLIX.

Stability data

Figure 1 shows the XRD profile of Nateglinide Form B which indicates characteristic peaks at 2θ 3.8, 4.9, 5.1, 6.1, 6.5, 14.0, 17.8, 18.9 and 20.2. Figure 2 shows the XRD profile of nateglinide premix. Figures 3 and 4 show the XRD profiles of the nateglinide tablet prepared as per the details given in Example 1 and 2. Figures 5 and 6

show the XRD of the placebo tablet for Examples 1 and 2, respectively. From the above given XRD data it is clear that pharmaceutical compositions of nateglinide when granulated with isopropyl alcohol remain stable, and there is no conversion of Form B to other forms on granulation.

Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative limitation. For example, it is expected that upon granulation with isopropyl alcohol, the resulting dosage form made from either the premix process or other processes disclosed herein, will contain residual amounts of isopropyl alcohol present within pharmaceutically acceptable limits (e.g., FDA, ICH guidelines) as measured by conventional analytical means (e.g., LCMS and/or gas chromatography). In particular, FDA limits for isopropyl alcohol, a class 3 solvent, are a permitted daily exposure of 50 mg or 5,000 ppm. These values are found in FDA guidance documents: Guidance for Industry – Q3C Impurities: Residual Solvents (December 1997) and Guidance for Industry: Q3C – Tables and List (November 2003). Accordingly, it is not intended that the invention be limited, except as by the appended claims.

We Claim:

1. A process for preparing a stable pharmaceutical composition of nateglinide Form B, the process comprising a step of granulating with isopropyl alcohol.

2. The process of claim 1, wherein the nateglinide Form B comprises a premix of nateglinide Form B with premix filler(s).

3. The process of claim 2, wherein the premix filler comprises one or more of mannitol, starch, lactose, mannitol, microcrystalline cellulose, starch or a combination thereof.

4. The process of claim 3, wherein the premix filler comprises a mixture of starch and mannitol.

5. The process of claim 4, wherein the ratio of nateglinide, mannitol and starch in the premix comprises about 2:1:1.

6. The process of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients comprising filler, binder, disintegrant, surfactant, lubricant, coloring and flavoring agent.

7. The process of claim 6, wherein the filler comprises one or more of corn starch, lactose, mannitol, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, sorbitol, starch, starch pregelatinized, sucrose, and mixtures thereof.

8. The process of claim 6, wherein the binder comprises one or more of polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and mixtures thereof.

9. The process of claim 6, wherein disintegrant comprises one or more of crospovidone, sodium starch glycolate, croscarmellose sodium, starch and mixtures thereof.

10. The process of claim 6, wherein surfactant comprises one or more of sodium lauryl sulphate, poloxamer, Polysorbate 80 and mixtures thereof.

11. The process of claim 6, wherein the lubricant comprises one or more of magnesium stearate, stearic acid, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and mixtures thereof.

12. The process of claim 1, further comprising:

blending nateglinide with one or more of filler, surfactant and disintegrant to form a blend;

granulating the blend with a solution of binder in isopropyl alcohol to form a granulation; and

drying, pulverizing; lubricating, and compressed the granulation into tablets.

13. The process of claim 1, further comprising

mixing the nateglinide with one or more of filler, surfactant, disintegrant and binder to form a blend;

granulating the blend with isopropyl alcohol to form a granulation; and

drying, pulverizing, lubricating and compressing the granulation into tablets.

14. The process of claim 1, wherein there is no conversion of Form B of nateglinide to any other polymorphic form during processing of the Form B of nateglinide.

15. The process of claim 2, further comprising:

blending the nateglinide premix with filler, surfactant and disintegrant to form a blend;

granulating the blend with a solution of binder in isopropyl alcohol to form a granulation; and

drying, pulverizing, lubricating, and compressing the granulation into tablets.

16. The process of claim 2, further comprising:

blending the nateglinide premix with filler, surfactant, disintegrant and binder to form a blend;

granulating the blend with isopropyl alcohol to form a granulation; and

drying, pulverizing, lubricating, and compressing the granulation into tablets.

17. The process of claim 2, wherein there is no conversion of Form B of nateglinide to any other polymorphic form during process of the Form B of nateglinide.

18. A medicament for the prevention, delay of progression or treatment of metabolic disorders, type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus, the medicament comprising nateglinide Form B wherein the medicament is formed by a process comprising a step of granulation with isopropyl alcohol.

19. A medicament for the prevention, delay of progression or treatment of metabolic disorders, type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus, the medicament comprising a premix of nateglinide form B with fillers wherein the medicament is formed by a process comprising a step of granulation with isopropyl alcohol.

20. A premix comprising nateglinide Form B, one or more fillers, and isopropyl alcohol.

21. The premix of claim 20, wherein the premix is incorporated into a medicament.

22. The premix of claim 21, wherein the medicament contains a pharmaceutically acceptable residual amount of isopropyl alcohol being present at an amount that is less than 50 mg and/or 5,000 ppm.

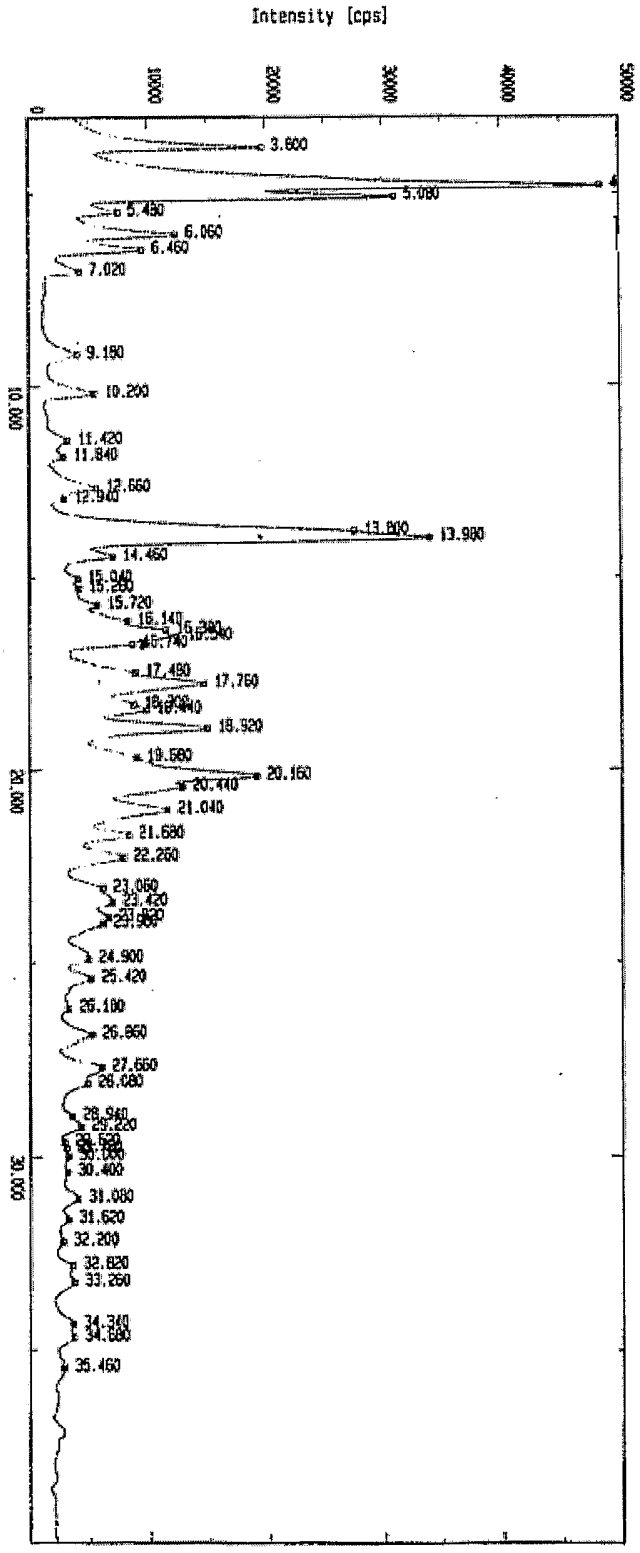

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FIGURE 1/6

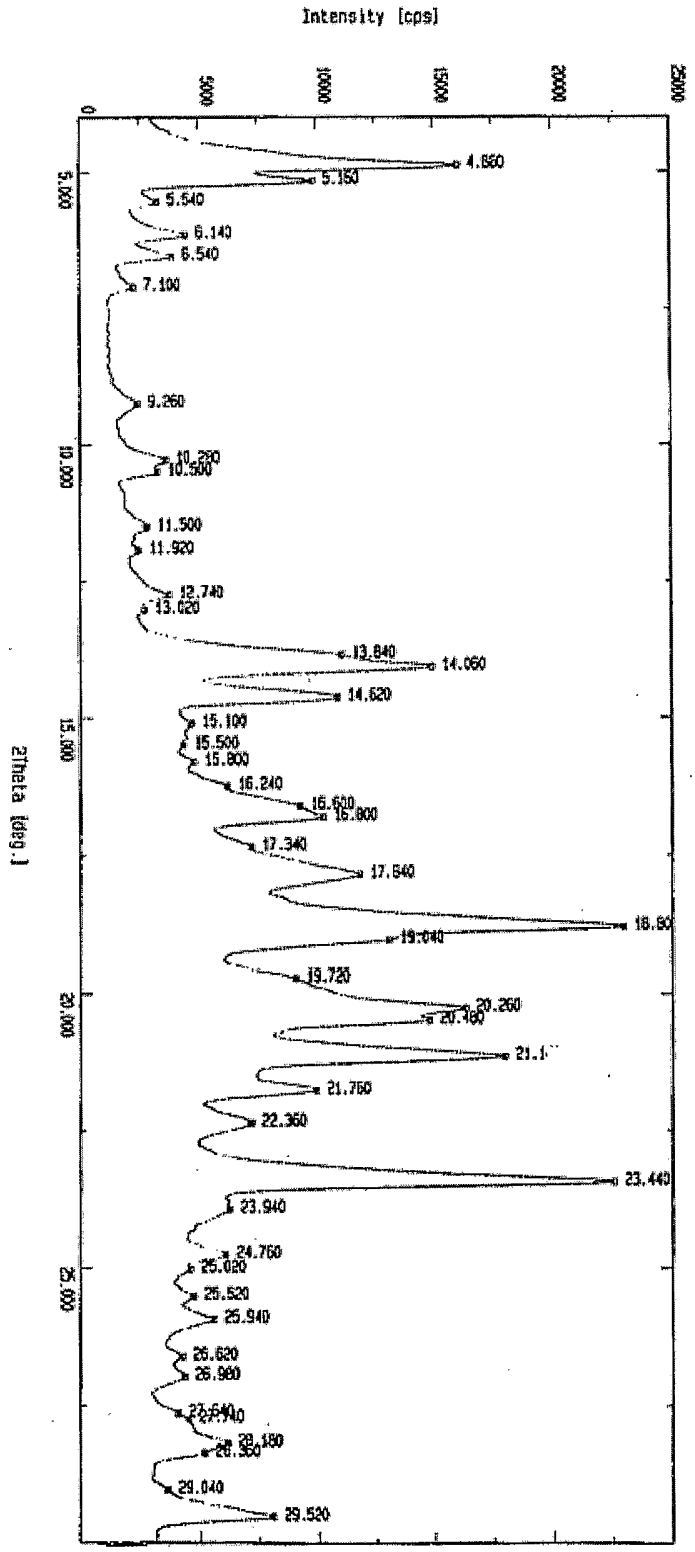

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FIGURE 2/6

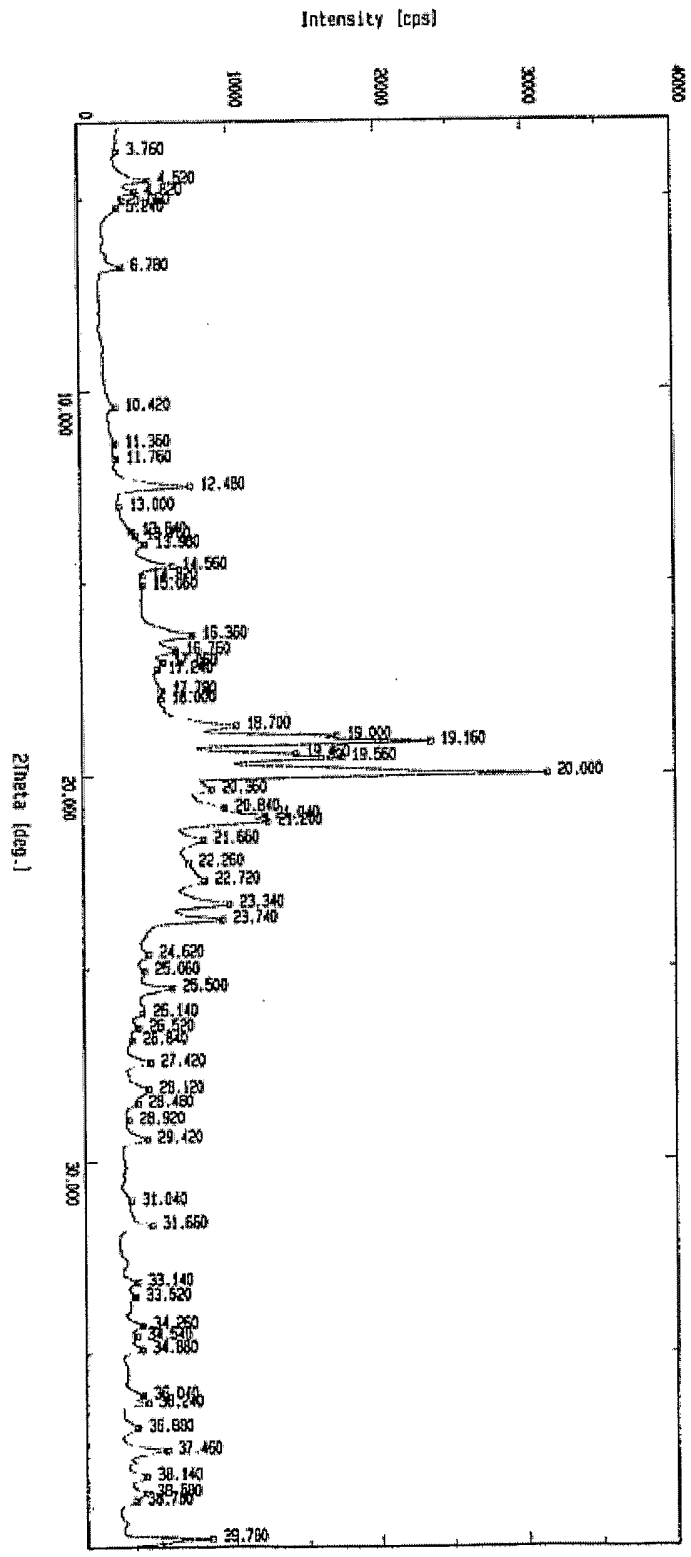

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30000
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6.780
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14.560
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19.000
19.160
19.560
20.000
20.360
21.660
22.260
22.720
23.340
23.740
24.620
25.060
25.500
26.140
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28.920
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34.260
34.880
36.880
37.460
38.140
29.780

FIGURE 3/6

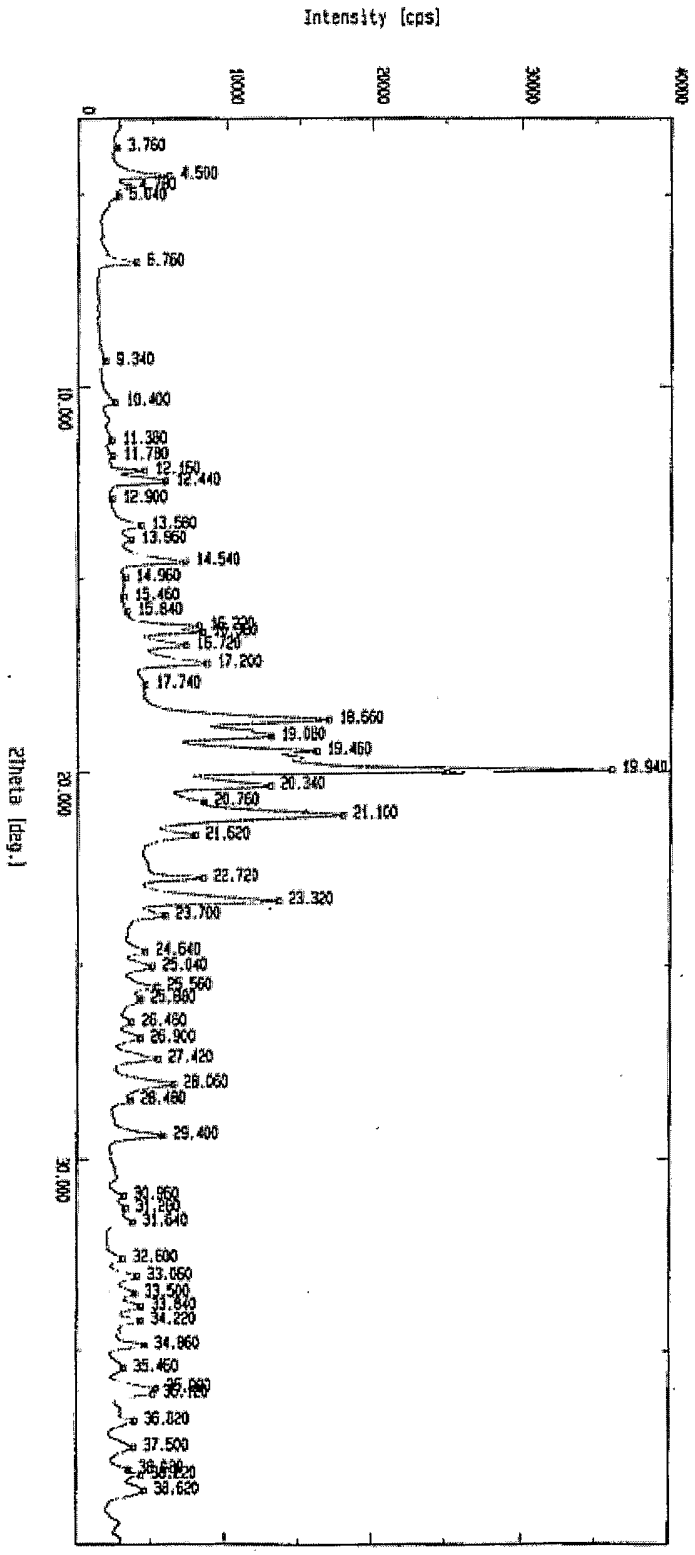

Intensity [cps]
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12.440
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13.560
13.960
14.540
14.960
15.460
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17.200
17.740
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19.940
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21.620
22.720
23.320
23.700
24.640
25.040
25.880
26.460
26.900
27.420
28.060
28.480
29.400
31.040
32.600
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36.020
37.500
38.620

FIGURE 4/6

FIGURE 5/6

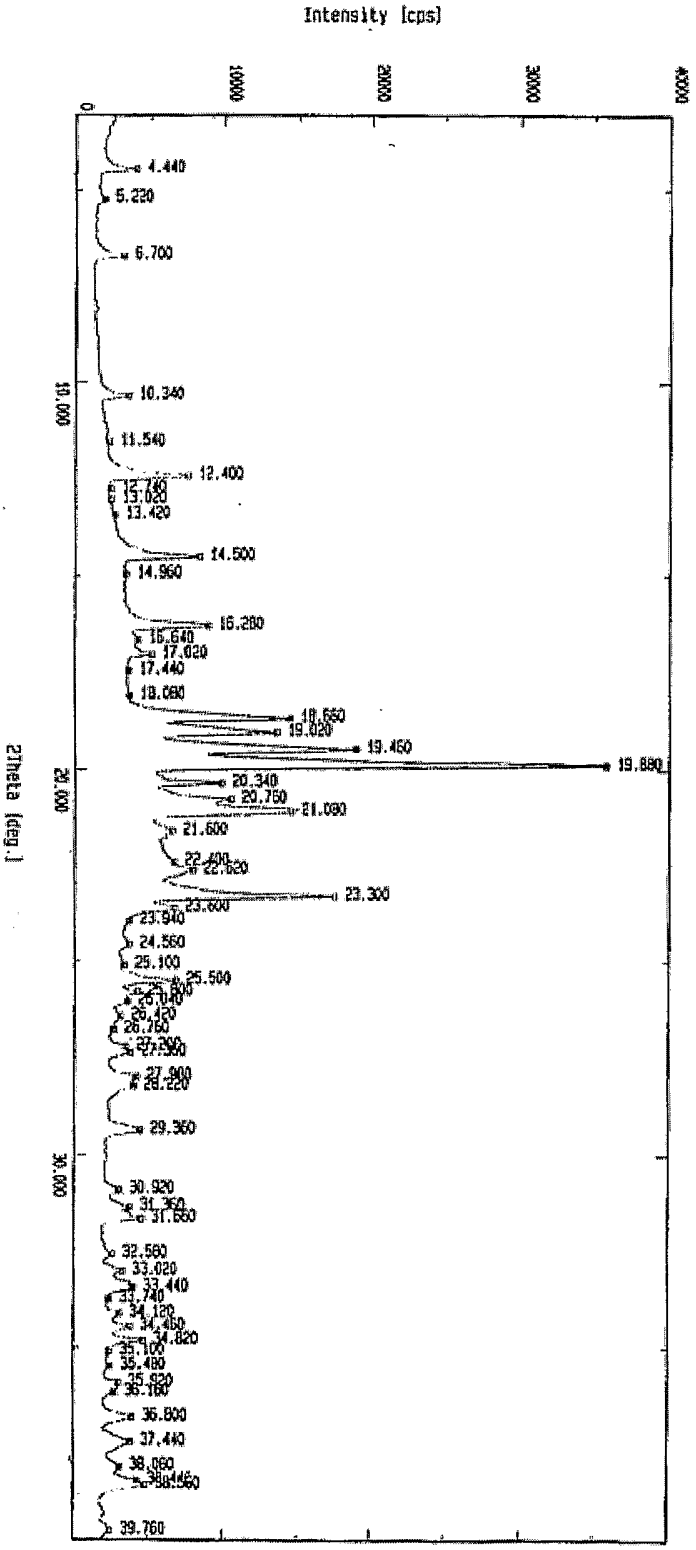
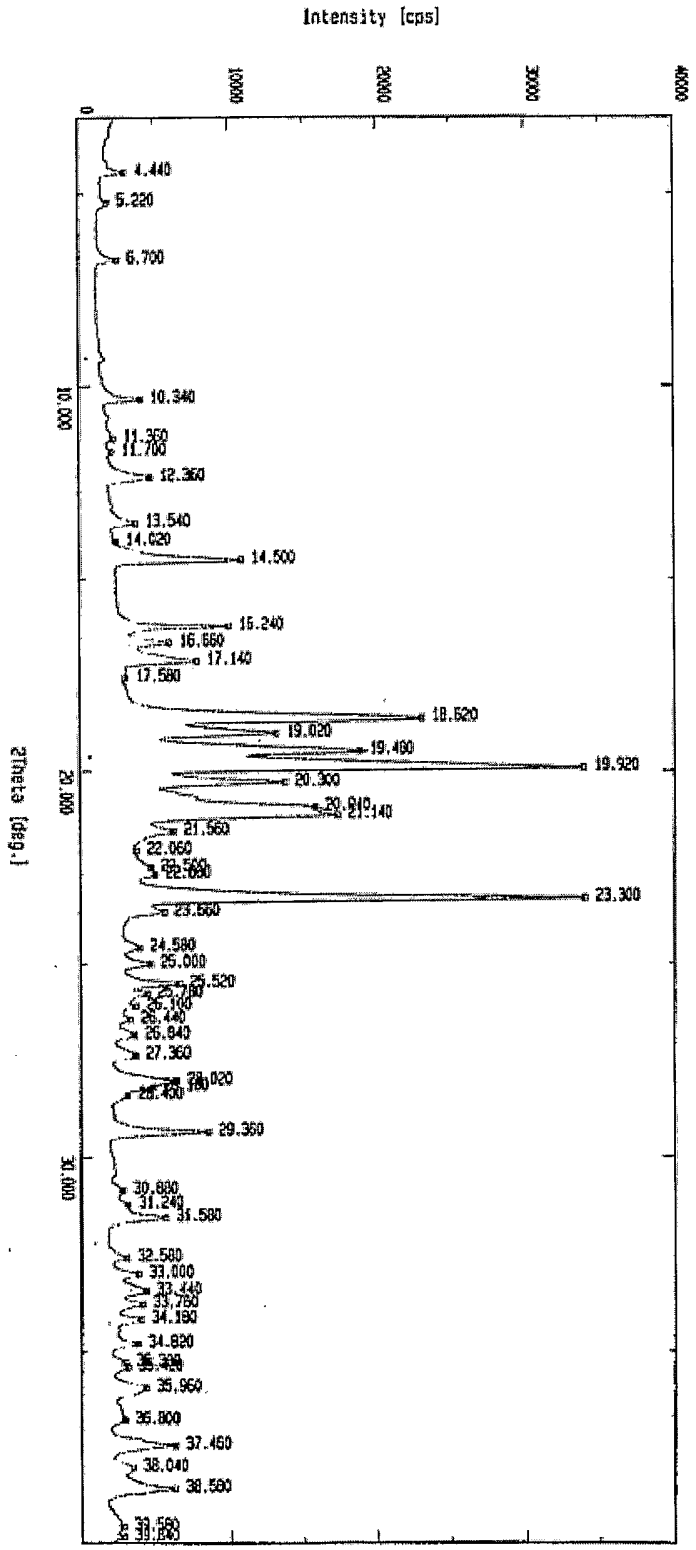

Intensity [cps]
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30000
40000
2Theta [deg.]
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20.000
30.000
4.440
5.220
6.700
10.340
11.540
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13.420
14.500
14.960
16.280
16.640
17.020
17.440
18.080
18.660
19.020
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25.500
26.420
26.760
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30.920
31.660
32.560
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36.800
37.440
38.060
39.760

FIGURE 6/6


Intensity [cps]
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100000
200000
300000
400000
10.000
20.000
30.000
2theta [deg.]
4.440
5.220
6.700
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11.360
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26.940
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INTERNATIONAL SEARCH REPORT

'ional Application No
'IB2005/002245

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/198 A61K9/16 A61K9/20 A61K47/10 A61P3/10

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)
A61K A61P

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 practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 143 323 A (YABUKI ET AL) 7 November 2000 (2000-11-07) column 3, lines 24-31; claims	1-22
P,X	WO 2005/016315 A (RANBAXY LABORATORIES LIMITED; SINGH, ROMI, BARAT; SHILPA, ANU; NAGAPRA) 24 February 2005 (2005-02-24) claim 26	1-22
P,X	WO 2005/051360 A (RANBAXY LABORATORIES LIMITED; SINGH, ROMI, BARAT; SHILPA, ANU; PRASAD,) 9 June 2005 (2005-06-09) claim 37	1-22

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

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2006	17/01/2006

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

ıational Application No
T/IB2005/002245

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