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(54) Title: AMORPHOUS Hmg-CoA REDUCTASE INHIBITORS OF DESIRED PARTICLE SIZE

(57) Abrégé/Abstract:
A process for the preparation of amorphous HMG-CoA reductase inhibitor and its hydrates thereof of desired particle size, which comprises: (a) dissolving the HMG-CoA reductase inhibitor in a hydroxylic solvent; (b) removing the solvent by freeze-drying.

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(54) Title: AMORPHOUS Hmg-CoA REDUCTASE INHIBITORS OF DESIRED PARTICLE SIZE

(57) Abstract: A process for the preparation of amorphous HMG-CoA reductase inhibitor and its hydrates thereof of desired particle size, which comprises: (a) dissolving the HMG-CoA reductase inhibitor in a hydroxylic solvent; (b) removing the solvent by freeze-drying.

TITLE OF THE INVENTION

'AMORPHOUS HMG-CoA REDUCTASE INHIBITORS OF DESIRED PARTICLE SIZE'

FIELD OF THE INVENTION

The present invention relates to a process for the production of amorphous HMG-CoA reductase inhibitors of desired particle size.

BACKGROUND OF THE INVENTION

Lovastatin, pravastatin, simvastatin, mevastatin, atorvastatin, fluvastatin and cervastatin and derivatives and analogs thereof are known as HMG-CoA reductase inhibitors and are used as antihypercholesterolemic agents. The majority of them are produced by fermentation using microorganisms of different species identified as species belonging to *Aspergillus*, *Monascus*, *Nocardia*, *Amycolatopsis*, *Mucor* or *Penicillium* genus, some are obtained by treating the fermentation products using the methods of chemical synthesis or they are the products.

The present invention relates to amorphous form HMG-CoA reductase inhibitors, which are useful as a pharmaceutical substance, to the method for its production and isolation HMG-CoA reductase inhibitors, are used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease.

United States Patent 5,273,995, describes that R-form of the ring opened acid form inhibits the biosynthesis of cholesterol. Atorvastatin in its calcium salt form, i.e. amorphous [R-(R*,R*)]-

2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (2: 1) is discussed in literature.

Various United States patents like, 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,248,793; 5,280,126; 5,342,952, which are herein incorporated by reference, describe various processes and key intermediates for preparing atorvastatin calcium.

The process mentioned in the above patents does not produce atorvastatin calcium in its amorphous form consistently. Often a mixture of crystalline and amorphous form is obtained which is not suitable for filtration and drying and therefore not a desirable process for large-scale production.

PCT application, WO 97/03959, discloses novel crystalline forms of atorvastatin calcium designated as Form I, Form II, and Form IV and method for their preparation. PCT application WO 97/03960 describes a procedure for converting the crystalline form of atorvastatin to the amorphous form.

The process described in the above mentioned patent involves dissolving the crystalline atorvastatin (form-I) in a non hydroxylic solvent like tetrahydrofuran or mixtures of tetrahydrofuran and toluene, followed by removal of the solvents under high temperature (about 90°C) and high vacuum (about 5mm). This process may not suitable on a large scale as the conditions used for drying may lead to degradation of the product.

PCT application WO 00/71116 claims a process for the preparation of amorphous atorvastatin calcium where the crystalline form is dissolved in a non-hydroxilic solvent is treated with a non-polar hydrocarbon anti-solvent followed by the removal of the solvent to result in the amorphous form.

Pravastatin, which was first reported as a metabolite of compactin in US4,346,227. WO01/43723 describes certain novel forms of pravastatin which are characterized by X-Ray patterns.

SUMMARY OF THE INVENTION

It is desirable to have a process, which provides amorphous HMG-CoA reductase inhibitor using a procedure, which can be readily scaled up to a commercial scale. The present invention describes a process, which is ideal for large scale production of amorphous HMG-CoA reductase inhibitor.

The present invention provides a process for the preparation of amorphous HMG-CoA reductase inhibitor and hydrates thereof of desired particle size, which comprises:

(i) dissolving the heterogeneous mixture of HMG-CoA reductase inhibitor in a hydroxylic solvent and

(ii) removing the solvent to obtain amorphous HMG-CoA reductase inhibitor.

The process further comprises

(iii) subjecting the amorphous HMG-CoA reductase inhibitor to milling.

The solvent is removed by freeze drying or spray drying.

The amorphous HMG-CoA reductase inhibitor has a particle size of 1 to 150 microns.

The hydroxylic solvent solvent in step (i) is methanol.

The HMG-CoA reductase inhibitor is a statin, preferably, atorvastatin or pravastatin having a particle size of 1 to 150 microns.

Major advantages of the present invention compared to the prior art processes are:

i. Produces amorphous HMG-CoA reductase inhibitor consistently.
ii. Results in the final product of desired particle size.
iii. Avoids the necessity to remove solvents.
iv. Simpler and faster filtration.
v. Easy to operate on large-scale.
vi. Avoids the use of hydrocarbons.

The present invention thus provides a simple and novel process for the preparation of amorphous atorvastatin calcium and hydrates thereof. The starting material used in the instant invention comprises of a mixture of both amorphous and crystalline forms – henceforth referred to as heterogeneous mixture.

BRIEF DESCRIPTION OF THE ACCOMPANYING FIGURES

Figure 1 is the diffractogram of amorphous atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure 2 is the diffractogram of amorphous pravastatin. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

The present invention is illustrated by the following examples, which an intended to limit the effective scope of the claims.

DETAILED DESCRIPTION OF THE INVENTION

Major advantages of the present invention compared to the prior art processes are:

i. Produces amorphous HMG-CoA reductase inhibitor consistently.
ii. Results in the final product of desired particle size.
iii. Avoids the necessity to remove solvents.
iv. Simpler and faster filtration.
v. Easy to operate on large-scale.
vi. Avoids the use of hydrocarbons.

The present invention thus provides a simple and novel process for the preparation of amorphous atorvastatin calcium and hydrates thereof. The starting material used in the instant invention comprises of a mixture of both amorphous and

crystalline forms – henceforth referred to as heterogeneous mixture.

The present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Amorphous Atorvasatin calcium).

A heterogenous mixture of atorvastatin (5g) was added to methanol (100ml) and the resulting reaction mixture was freeze dried to afford amorphous atorvastatin.

The particle size as measured by malvern particle size analyser gave the following pattern:

D_{10}	3 microns
D_{50}	9 microns
D_{90}	16 microns

Example 2

[1S-([1α(β*,δ*)2α,6α,8B(R*),8aα]]-1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthalene heptanoic acid sodium salt (Amorphous Pravastatin)

A heterogenous mixture of pravastatin sodium (5g) was added to methanol (100ml) and the resulting reaction mixture was spray dried to afford amorphous pravastatin sodium. The amorphous pravastatin sodium so obtained was milled using an air jet mill

The particle size as measured by malvern particle size analyser gave the following pattern:

D10	3 micron
D50	11 micron
D90	19 micron

Example 3

[1S-([1α(β*,δ*)2α,6α,8B(R*),8aα]]-1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthalene heptanoic acid sodium salt (Amorphous Pravastatin)

A heterogenous mixture of pravastatin sodium (5g) was added to water (100ml) and the resulting reaction mixture was spray dried to afford amorphous pravastatin sodium. The amorphous pravastatin sodium so obtained was milled using an air jet mill. The particle size as measured by malvern particle size analyser gave the following pattern:

D10	2 micron
D50	4 micron
D90	10 micron

Example - 4

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Amorphous Atorvasatin calcium).

A heterogenous mixture of atorvastatin (5g) was added to methanol (100ml) and the resulting reaction mixture was spray dried to afford amorphous atorvastatin.

The particle size as measured by malvern particle size analyser gave the following pattern:

D_{10}	1 microns
D_{50}	6 microns
D_{90}	11 microns

Example 5

[1S-([1α(β*,δ*)2α,6α,8B(R*),8aα]]-1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthalene heptanoic acid sodium salt (Amorphous Pravastatin)

A heterogenous mixture of pravastatin sodium (5g) was added to methanol (100ml) and the resulting reaction mixture was freeze dried to afford amorphous pravastatin sodium. The amorphous pravastatin sodium so obtained was milled using an air jet mill

The particle size as measured by malvern particle size analyser gave the following pattern:

D10	2 micron

D50	8 micron
D90	16 micron

X-ray powder diffraction pattern (Figure 1 and 2 as shown in the accompanied drawings) demonstrates the amorphous nature of the product.

WE CLAIM:

1. A process for the preparation of amorphous HMG-CoA reductase inhibitor and hydrates thereof of desired particle size, which comprises:
(i) dissolving the heterogeneous mixture of HMG-CoA reductase inhibitor in a hydroxylic solvent and
(ii) removing the solvent to obtain amorphous HMG-CoA reductase inhibitor by freeze drying

2. The process of claim 1, further comprising
(iii) subjecting the amorphous HMG-CoA reductase inhibitor to milling.

3. The process of claim 1 wherein the solvent is removed by spray drying instead of freeze drying.

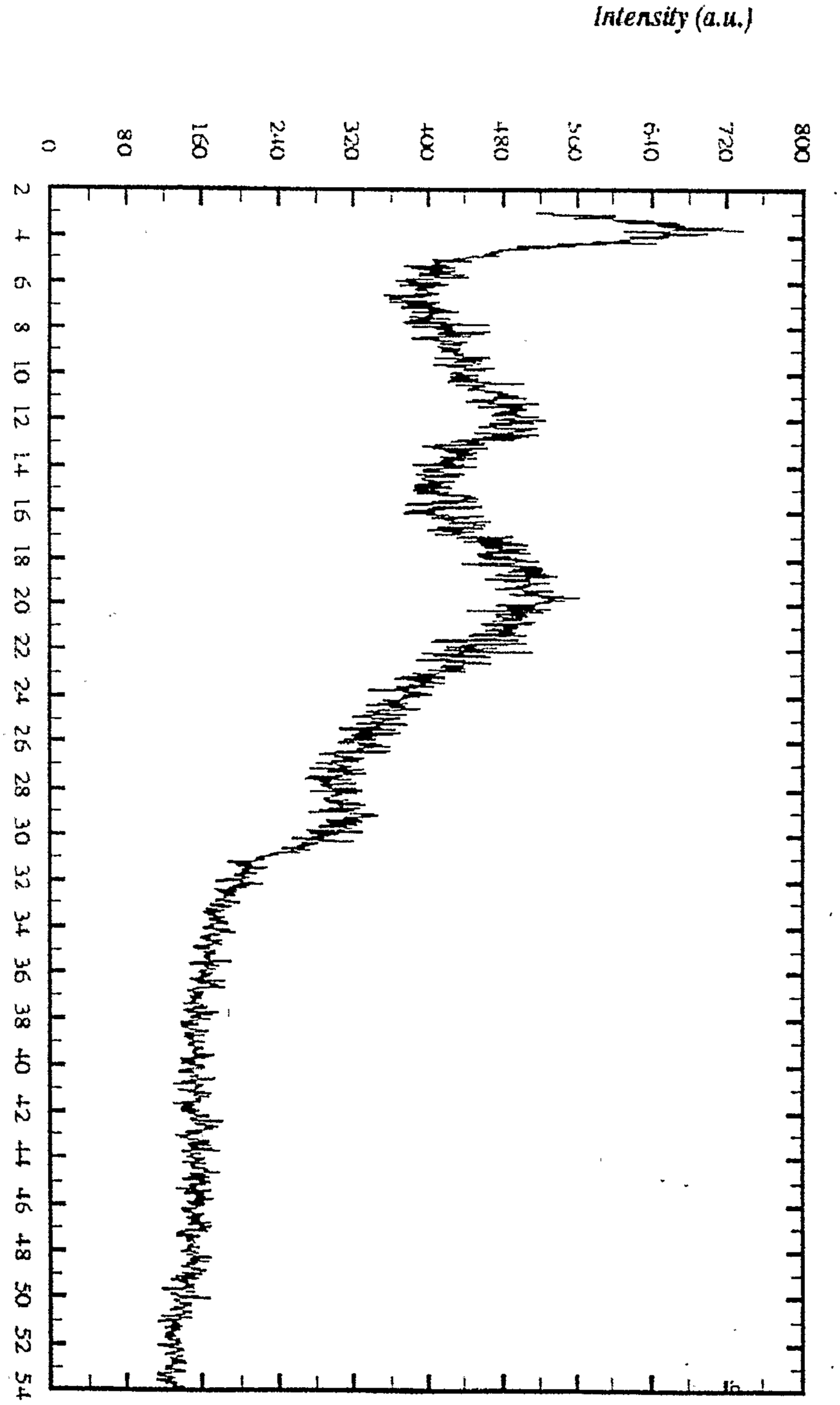
4. The process of claim 1, wherein the amorphous HMG-CoA reductase inhibitor has a particle size of 1 to 150 microns.

5. The process of claim 1, wherein the hydroxylic solvent solvent in step (i) is methanol.

6. The process of claim 1, wherein the HMG-CoA reductase inhibitor is a statin.

7. The process of claim 6, wherein the HMG-CoA reductase inhibitor is atorvastatin or pravastatin.

8. HMG-CoA reductase inhibitor of particle size 1 to 150 microns.


ATORVASTATIN CALCIUM
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0
80
160
240
320
400
480
560
640
720
800
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54
2 θ (°)

FIGURE 1

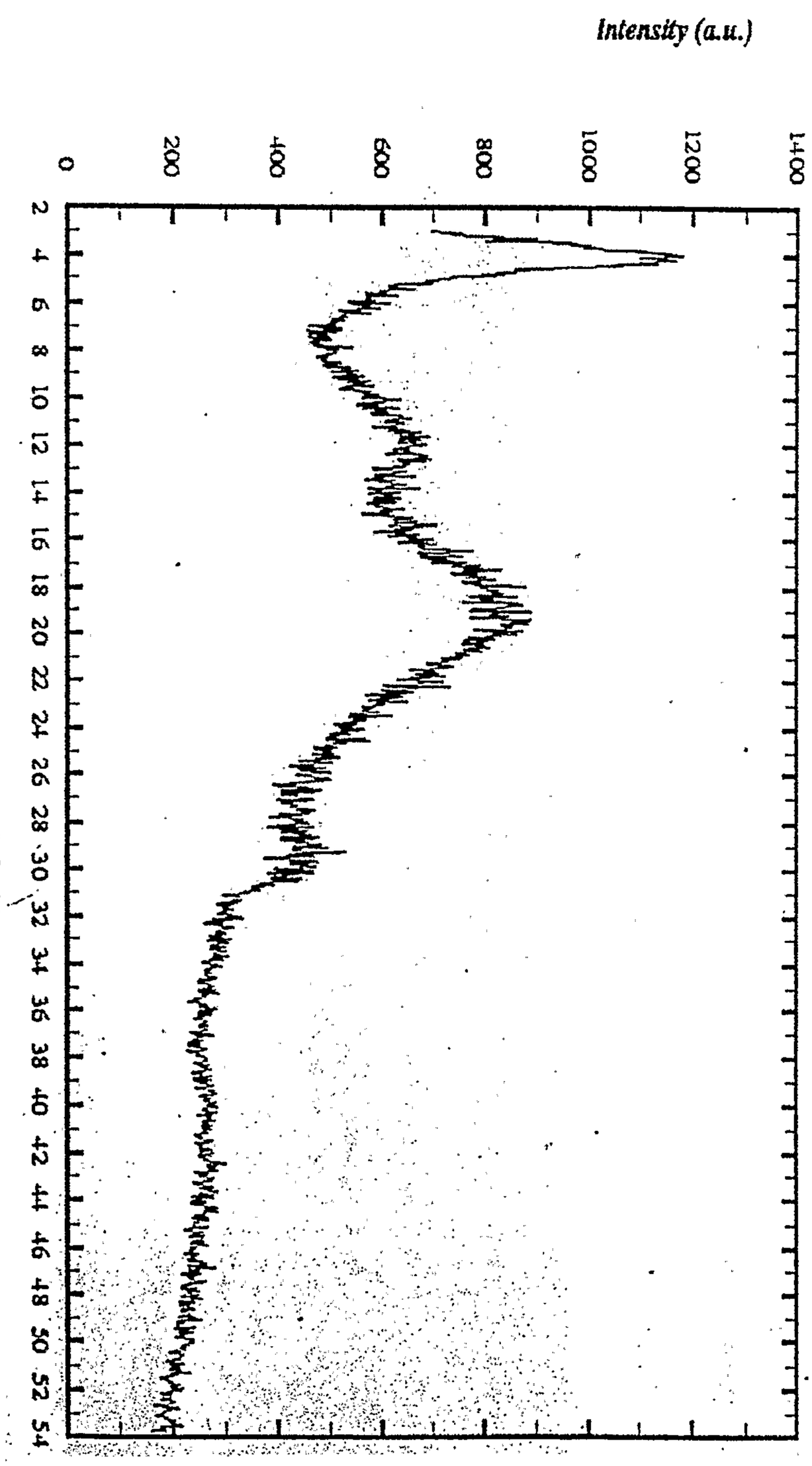
PRAVASTATIN SODIUM
Intensity (a.u.)
0
200
400
600
800
1000
1200
1400
2 θ (°)
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54

FIGURE 2