

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 September 2006 (14.09.2006)

PCT

(10) International Publication Number
WO 2006/096709 A2

(51) International Patent Classification:
C07D 403/02 (2006.01)

(21) International Application Number:
PCT/US2006/008064

(22) International Filing Date: 7 March 2006 (07.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
227/CHE/2005 8 March 2005 (08.03.2005) IN
60/673,142 20 April 2005 (20.04.2005) US
1543/CHE/2005 25 October 2005 (25.10.2005) IN

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

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.

(54) Title: PROCESS FOR PREPARING AMORPHOUS SALTS

(57) Abstract: Amorphous solid omeprazole magnesium or esomeprazole magnesium is prepared by subjecting a solution of omeprazole magnesium or esomeprazole magnesium to flash evaporation, such as by using an agitated thin film drier-vertical.



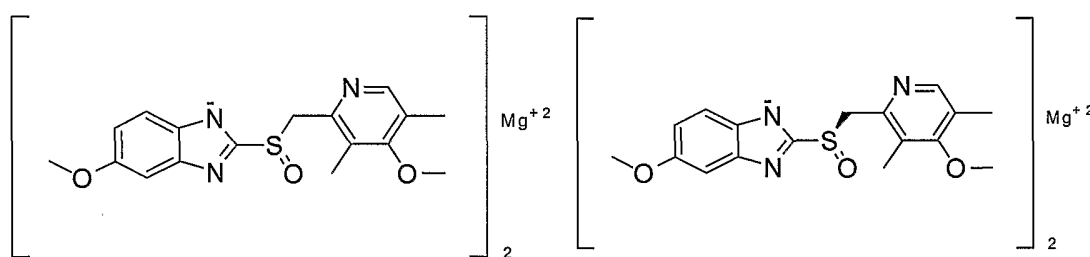
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PROCESS FOR PREPARING AMORPHOUS SALTS

INTRODUCTION TO THE INVENTION

The present invention relates to a process for the preparation of amorphous magnesium salts of omeprazole and its (S)-enantiomer.

Chemically, omeprazole is named 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole and the magnesium salt of omeprazole has the structural formula as shown in Formula I. The (S)-enantiomer is chemically named 5-Methoxy-2-[(S)-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-yl and has the adopted name "esomeprazole," the magnesium salt of esomeprazole being represented by Formula II.



Formula I

Formula II

Omeprazole is available commercially in products sold as ZEGERID™ powder for oral suspension, and omeprazole magnesium is available over the counter in the form of delayed release tablets under the brand name PRILOSEC OTC™. Esomeprazole magnesium is commercially available in delayed release capsules sold as NEXIUM™. The products are indicated for the treatment of gastric ulcers, gastroesophageal reflux disease, and for short-term treatment of active duodenal ulcers.

Omeprazole is a chiral compound, wherein the sulphur atom is the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the (R)- and (S)-enantiomers of omeprazole, herein referred to as R-omeprazole, and S-omeprazole (also known as esomeprazole). The (+)-enantiomer in the non-salt form and the (-)-enantiomer in the non-salt form are

found to have (R)- and (S)-configurations respectively and the (+)-enantiomer of the magnesium salt and the (-)-enantiomer of the magnesium salt are also found to have (R)- and (S)-configurations, respectively.

The preferred enantiomer of omeprazole referred to as the (-)-enantiomer of omeprazole or a pharmaceutical salt thereof, is said to be an improved alternative to omeprazole in the treatment of gastric acid related diseases which provides higher dose efficiencies and less inter-individual variation in plasma levels, both between rapid and slow metabolizers and within the group of rapid metabolizers, as is taught in U.S. Patent No. 5,877,192.

U.S. Patent No. 6,369,085 discloses three different types of crystalline esomeprazole magnesium viz. dihydrate Form A, dihydrate Form B and the trihydrate form.

U.S. Patent No. 5,900,424 also discloses omeprazole magnesium having a degree of crystallinity higher than 70%, a particle size less than 30 μm , a bulk density between 1.33 and 1.35 g/cm^3 , a water content between 5 and 10%, and a residual methanol content less than 500 ppm.

PCT Application Publication No. WO 2001/87831 A2 and U.S. Application Publication No. 2003/0212274 describe the amorphous form of omeprazole and its salts and a process for their preparation by spray drying.

PCT Application Publication No. WO 2001/36409, and U.S. Patent No. 6,894,066 describe flash evaporation using spray drying for the preparation of omeprazole and (R)- and (S)-omeprazole having a degree of crystallinity below 25%, and having a residual methanol content less than 1%.

U.S. Application Publication No. 2004/0235903 describes a spray drying process for the preparation of amorphous esomeprazole magnesium.

All of the documents discussed above utilize spray drying for obtaining the amorphous product. The product is further dried at elevated temperatures of about 60 to 65° C. The residual solvent content in the product even after further drying at elevated temperatures is more than the permitted limits as per ICH guidelines (International Conference for Harmonization). The permitted level for methanol according to ICH guidelines is 3000 ppm. The entire process requires the exposure of omeprazole or esomeprazole to elevated temperatures for extended periods of time. Also the yields obtained from a spray drier are low.

Therefore there exists a need for a process which provides amorphous magnesium salts of omeprazole and esomeprazole having a low solvent content. A process which is rapid and does not require exposure of omeprazole or esomeprazole salts to elevated temperatures for prolonged periods of time, and gives better yields would be helpful in the synthesis of these compounds.

The present invention provides a process for the preparation of amorphous form of omeprazole and esomeprazole magnesium on commercial scale using a process which is simple, cost effective and provides an amorphous product with a residual solvent content within the limits given in ICH guidelines.

SUMMARY OF THE INVENTION

The invention provides a process for preparing solid amorphous omeprazole magnesium or esomeprazole magnesium.

In an embodiment, a method for preparing amorphous esomeprazole magnesium comprises rapidly removing solvent from a solution of esomeprazole magnesium and recovering solid amorphous esomeprazole magnesium. Solvent removal can be accomplished using a flash evaporation technique, such as agitated thin film drying-vertical. Residual solvent content can be decreased by drying the amorphous product.

In another embodiment, a method for preparing amorphous omeprazole magnesium, comprising rapidly removing solvent from a solution of omeprazole magnesium and recovering solid amorphous omeprazole magnesium.

In yet another embodiment, a method for preparing amorphous omeprazole magnesium or esomeprazole magnesium comprises:

- a) providing a solution of omeprazole magnesium or esomeprazole magnesium;
- b) optionally, removing any undissolved particles by filtration;
- c) evaporating solvent from the solution of step a) or a filtrate obtained from step b) to produce an amorphous solid; and
- d) optionally drying the solid of step c) to afford amorphous omeprazole magnesium or esomeprazole magnesium.

A solution of omeprazole magnesium or esomeprazole magnesium can be provided by reacting a magnesium alkoxide slurry with omeprazole or esomeprazole.

5 BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an X-ray power diffraction ("XRPD") pattern of amorphous omeprazole magnesium prepared in Example 2.

10 Fig. 2 is a differential scanning calorimetric ("DSC") curve of amorphous omeprazole magnesium prepared in Example 2.

Fig. 3 is an infrared ("IR") absorption spectrum of amorphous omeprazole magnesium prepared in Example 2.

Fig. 4 is an XRPD pattern of amorphous esomeprazole magnesium prepared in Example 3.

15 Fig. 5 is a DSC curve of amorphous esomeprazole magnesium prepared in Example 3.

Fig. 6 is an IR absorption spectrum of amorphous esomeprazole magnesium prepared in Example 3.

20 DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the invention provides a process for the preparation of amorphous magnesium salts of omeprazole and esomeprazole.

25 An embodiment of a process for the preparation of amorphous magnesium salts of omeprazole or esomeprazole comprises the steps of:

- a) providing a solution of omeprazole magnesium or esomeprazole magnesium;
- b) optionally, removing any undissolved particles by filtration;
- c) evaporating solvent from the solution of step a) or the filtrate
- 30 obtained from step b) to produce a solid; and
- d) optionally, drying the solid of step c) to afford amorphous omeprazole magnesium or esomeprazole magnesium.

Step a) involves providing a solution of the magnesium salts of omeprazole or esomeprazole.

The solution of the magnesium salts of omeprazole or esomeprazole may be obtained by dissolving the appropriate salt in a suitable solvent, or such a solution may be obtained directly from a reaction in which omeprazole magnesium or esomeprazole magnesium is formed.

5 When the solution is prepared by dissolving the magnesium salt of omeprazole or esomeprazole in a suitable solvent, any form of omeprazole or esomeprazole such as the crystalline or amorphous form, including any salts, solvates and hydrates may be utilized for preparing the solution.

Suitable solvents which can be used for dissolving the magnesium salts of
10 omeprazole or esomeprazole include but are not limited to: alcoholic solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, and the like; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate,
15 n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; ethers such as diethyl ether, dimethyl ether, di-isopropyl ether, 1,4-dioxane and the like; hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the like; nitriles such as acetonitrile, propionitrile and the like; or mixtures thereof or their combinations with water in various proportions.

20 Alternatively, the solution may be obtained by reacting magnesium in a suitable solvent in the presence of a small amount of chlorinated hydrocarbon to get a magnesium alkoxide slurry followed by addition of omeprazole or esomeprazole to the slurry.

The magnesium source can be an organic or an inorganic magnesium salt,
25 such as magnesium acetate, magnesium nitrate, magnesium sulfate, magnesium carbonate, magnesium chloride and the like, or pure magnesium particles can be used.

Useful solvents for preparing the magnesium alkoxide slurry include,
without limitation, lower alcohols, ketones, esters, and mixtures thereof. The lower
30 alcohols may include one or more of primary, secondary, and tertiary alcohols having from one to six carbon atoms. The lower alcohols may include methanol, ethanol, denatured spirit, n-propanol, isopropanol, n-butanol, isobutanol, and t-butanol. The ketones may include one or more of acetone, 2-butanone, and 4-methyl-pentane-2-one. The esters may include ethyl acetate and n-butyl acetate.

Suitable chlorinated hydrocarbon solvents which can be used include but are not limited to chloroform, dichloromethane, carbon tetrachloride and the like or mixtures thereof.

These solvents are merely representative of those that can be used, and the lists are not intended to be exhaustive.

The order of charging the different materials is not critical for the product obtained. A specific order may be preferred with respect to the equipment actually used and will be easily determined by a person skilled in the art.

Suitable temperatures for preparing the solution of the magnesium salt of omeprazole or esomeprazole may range from about 30 to 80° C, or about 30 to 40° C.

The concentration of the solution can be about 0.1 g/ml of the solvent to 20 g/ml of the solvent or more. Any other concentration may be used as long as a clear solution is obtained.

Step b) involves removing the undissolved particles, and this step is optional if pure compounds are used and they dissolve completely.

The undissolved particles can be removed suitably by filtration, centrifugation, decantation, and other techniques. The solution can be filtered by passing through paper, glass fiber, or other membrane material, or a clarifying agent such as celite. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature crystallization.

Step c) involves evaporating the solvent from the solution of a) or the filtrate obtained in step b) using a suitable technique. The evaporation must proceed sufficiently rapidly to form the desired solid amorphous product.

Omeprazole is a temperature sensitive molecule due to the presence of the sulfur atom in the molecule and demonstrates a darkening of color upon exposure to elevated temperatures for a prolonged time. This temperature sensitivity of the product requires the evaporation technique to be rapid to provide a minimum exposure of the compound to elevated temperatures for limited periods of time.

Suitable techniques which can be used for the evaporation of the solvent involve equipment that provides flash evaporation including, but not limited to,

agitated thin film evaporators ("ATFD"), suppressed boiling type evaporators, and others.

These techniques are applicable to both aqueous and organic solutions of magnesium salts of omeprazole and esomeprazole. However, solutions using the more volatile organic solvents are preferred. In brief, the process involves drying of a solution of a magnesium salt of omeprazole or esomeprazole on a heated, constantly moving surface under vacuum.

Other techniques, such as Buchi Rotavapor drying and drying under vacuum, may be suitable for laboratory scale processes such as for quantities less than about 100 g. The processes of the present invention allow for preparing amorphous magnesium salts of omeprazole and esomeprazole on an industrial scale with a batch size of at least about 500 g, or about 1 kg, or greater.

An embodiment of the invention involves the evaporation of the solvent using an agitated thin film drying-vertical ("ATFD-V") technique.

The ATFD-V technique uses high vacuum along with elevated temperatures which allows operation at lower temperatures. This allows for a short residence time for the product in the drier, which is an important feature for heat sensitive products. The required evaporation can be achieved in a single pass, avoiding product recirculation and possible degradation. It is suitable for viscous products, and the operating pressures are from atmospheric down to 1 mbar. The equipment can be operated at a wide range of temperatures, such as 25 to 350° C or more.

The concentration, solvent type, temperature, vacuum, and feeding rate are set to combinations where the omeprazole or esomeprazole magnesium salt coming from the inlet precipitates essentially instantly. Otherwise, crystalline material can also form.

The process frequently is carried out at lower temperatures of about 35° C to about 50° C under reduced pressures of about 600 to about 700 mm Hg. These dryers are indirectly heated and therefore air does not come in contact with the product.

The solution of omeprazole magnesium or esomeprazole magnesium may be added drop-wise or continuously to the drying chamber. The speed of the addition of the solution will depend on the solvent used, the viscosity of the

mixture, and the height of the chamber. The rate of flow may range from 10 to 50 cm³/hour/inlet. These and other parameters are well known to a person skilled in the art of drying using ATFD.

The drop of solution evaporates almost instantaneously in the chamber.

- 5 The solidification is spontaneous and does not require further action such as stirring. This instant evaporation allows for obtaining a phase change (solidification) before the solution contacts the bottom of an industrial sized chamber when fed from the top.

10 ATFD-V helps in evaporating solvents by using heat transfer across the walls and prevents the growth of crystals and particles that can trap the solvent at higher levels. The resulting omeprazole magnesium or esomeprazole magnesium is a solid amorphous form having a solvent content lower than for the compound obtained from other techniques of evaporation like the Buchi Rotavapor or spray drier.

- 15 The yields obtained using this technique are superior to those obtained using other techniques.

Step d) involves drying of the isolated product of step c) to afford the amorphous magnesium salts of omeprazole or esomeprazole.

20 Drying can be carried out under reduced pressure until the residual solvent content reduces to an amount that is within the limits given by the ICH guidelines. The solvent level depends on the type of solvent but is not more than about 5000 ppm, or about 4000 ppm, or about 3000 ppm.

The drying can be carried out at reduced pressures, such as below 200 mm Hg or below 50 mm Hg, at temperatures of about 35° C to about 70° C. The
25 drying can be carried out for any desired time periods, times about 1 to 20 hours being suitable for preparing some products.

Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, or using a fluidized bed drier, spin flash dryer, flash dryer and the like.

30 An additional aspect of the invention involves the drying of the compounds in a fluidized bed drier.

In this technique, the feed of wet materials is dried by intimate contact with a heated atmosphere, such as air or an inert gas, when the material is in a fluidized state. A vibrating mechanism can be attached to give a forward motion

cum agitation to the product at a controlled rate. A fluidized dryer is a versatile piece of process equipment for uniform and efficient drying of products with minimum handling and is more hygienic.

The wet crystals of magnesium salts of omeprazole or esomeprazole can be dried while exposed to a moisture-containing atmosphere having a relative humidity, typically less than about 80%, when it is desired to form a hydrous product. The relative humidity level is not a critical aspect of the invention, and can be more or less than 80 percent. The time of exposure varies, and depends on the amount of material to be dried, as can be determined by simple experimentation.

The drying can advantageously be conducted at temperatures, which are slowly and gradually increased starting, for example, from an ambient temperature or about 25° C. The product is exposed to programmed stepwise increases in temperature. The product is usually maintained at each temperature range for different time intervals.

In an embodiment, the temperature for drying is varied by 5° C, starting from about 25° C, to 55° C. At each temperature condition, the product is maintained for about 1 to 4 hours. This gradual increase of temperature avoids the continuous exposure of the product to elevated temperatures. The whole drying process of this embodiment can take from 4 hours to 10 hours. Of course, the elapsed time can increase as the quantity of material to be dried increases, or if the residual solvent content is particularly high.

The programmed stepwise rise in temperature with appropriate holding times chosen at each temperature may be, as an example, 25 to 30° C for 1 to 4 hours, 30 to 35° C for 1 to 4 hours, 35 to 45° C for 1 to 4 hours, and then 45 to 55° C for 1 to 4 hours. Higher ultimate temperatures may be required, depending upon the boiling points of the solvents that are to be removed.

The programmed temperature increase provides the advantage of drying of the compound at lower temperatures. The compound need not be exposed constantly to an elevated temperature for extended periods of time. The material is exposed to elevated temperatures for a very short period of time. This drying technique also lowers the solvent content to amounts less than the maximum

limits set by ICH guidelines. The drying process is easily scalable for industrial purposes and the results obtained are reproducible.

The dried product can optionally be milled to get the required particle size. Milling or micronization can be performed prior to drying, or after the completion of
5 drying of the product. The milling operation reduces the size of particles and increases surface area of particles by colliding particles with each other at high velocities.

Drying is more efficient when the particle size of the material is smaller and the surface area is higher, hence milling can be performed prior to the drying
10 operation.

Milling can be done suitably using jet milling equipment like an air jet mill, or using other conventional milling equipment.

Amorphous magnesium salts of omeprazole and esomeprazole obtained using the above process are characterized by any of their X-ray powder diffraction
15 ("XRPD") patterns, infrared absorption ("IR") spectra, and differential scanning calorimetry ("DSC") curves.

Omeprazole magnesium is characterized by its XRPD pattern. All XRPD data reported herein were obtained using Cu K α radiation, having the wavelength 1.541 Å, and were obtained using a Bruker Axe, D8 Advance Powder X-ray
20 Diffractometer.

Amorphous omeprazole magnesium and esomeprazole magnesium are characterized by their XRPD patterns showing a plain halo with no peaks, which is highly characteristic of an amorphous solid, substantially in accordance with Fig. 1 and Fig. 4 respectively.

25 The amorphous omeprazole magnesium is also characterized by an infrared absorption spectrum in potassium bromide comprising peaks at about 770, 808, 837, 956, 999, 1076, 1115, 1154, 1199, 1271, 1301, 1361, 1409, 1477, 1570, 1589, 1612, and 2947, ± 5 cm⁻¹, substantially in accordance with the spectrum of Fig. 3.

30 The amorphous esomeprazole magnesium is also characterized by an infrared absorption spectrum in potassium bromide comprising peaks at about 632, 807, 836, 1077, 1155, 1271, 1409, 1478, 1570, 1614, 2831, 2947, 2995, and 3068, ± 5 cm⁻¹, substantially in accordance with the spectrum of Fig. 6.

The amorphous omeprazole magnesium is also characterized by a differential scanning calorimetry curve substantially in accordance with Fig. 2, having an exotherm at about 184°C.

5 The amorphous esomeprazole magnesium is also characterized by a differential scanning calorimetry curve substantially in accordance with the curve of Fig. 5, having an exotherm at about 200°C.

Yet another aspect of the invention provides magnesium salts of omeprazole and esomeprazole having low amounts of residual organic solvent.

10 Magnesium salts of omeprazole and esomeprazole obtained in this invention contain less than about 5000 ppm, or less than about 3000 ppm, or less than about 1000 ppm of methanol, and less than about 200 ppm, or less than about 100 ppm of dichloromethane.

The present invention provides magnesium salts of omeprazole and esomeprazole having a moisture content of about 5% to about 10% by weight.

15 The moisture content can be determined by Karl-Fischer analysis.

Still another aspect of the invention provides amorphous omeprazole and esomeprazole magnesium salts having a maximum particle size of less than about 50 μm , and a bulk density of about 0.3 to 0.5 g/ml.

20 The D_{10} , D_{50} and D_{90} values are useful ways for indicating a particle size distribution. D_{90} refers to the value for the particle size for which at least 90 volume percent of the particles have a size smaller than the said value. Likewise D_{50} and D_{10} refer to the values for the particle size for which 50 volume percent, and 10 volume percent of the particles have a size smaller than the said value. A D_{50} value can be considered as being the mean particle size of a powder.

25 Methods for determining D_{10} , D_{50} and D_{90} include laser diffraction using Malvern equipment.

Amorphous omeprazole and esomeprazole magnesium according to the invention have a D_{10} less than 10 μm or less than 5 μm , D_{50} less than 10 μm or less than 5 μm , and D_{90} less than 50 μm or less than 10 μm . There is no specific
30 lower limit for any of the D values.

The amorphous omeprazole and esomeprazole magnesium according to this invention have a bulk density of less than 0.5 g/ml or less than 0.3 g/ml before tapping, and bulk density of less than 0.6 g/ml, or less than 0.3 g/ml after tapping.

The bulk densities are determined using Test 616 "Bulk Density and Tapped Density," United States Pharmacopeia 24, pages 1913-4 (United States Pharmacopeial Convention, Inc., Rockville, Maryland, 1999).

5 These and other aspects and embodiments of this invention are described in further detail by the examples below, which examples are not intended to limit the scope of the appended claims in any manner. In the examples, moisture content was determined by Karl Fischer method and residual solvent content was determined by a gas chromatographic method.

10 COMPARATIVE EXAMPLE

EXPERIMENT TO ILLUSTRATE THE HEAT SENSITIVITY OF OMEPRAZOLE MAGNESIUM:

15 Amorphous omeprazole magnesium (prepared by following a process similar to that described in Example 1), containing residual methanol at 19544 ppm, was taken into a Buchi Rotavapor flask and then exposed to a temperature of 50° C and a vacuum of 300 mm Hg for 39 hours. The color of the product turned to light brown due to exposure to elevated temperatures for a prolonged period of time. The methanol content of the final product after drying for 39 hours
20 was 5536 ppm.

The above result shows that drying in a Buchi Rotavapor does not reduce the residual methanol content to the required levels, and also the color of the product turns to light brown when exposed to elevated temperatures for a prolonged period of time.

25

EXAMPLE 1

PREPARATION OF AMORPHOUS OMEPRAZOLE MAGNESIUM:

30 3.6 liters of methanol was taken into a round bottom flask and 72 g of magnesium turnings were added. 128 ml of dichloromethane was added to the above mixture. The temperature of the reaction mass was raised to 56° C. The mixture was maintained at 56° C for one hour, and then was cooled to 30° C. 50 liters of methanol was added to the reactor followed by 2 kg of omeprazole base.

The mixture was then cooled to 15° C and maintained under a nitrogen atmosphere for 1 hour. The reaction mass was then filtered through a sparkler filter followed by a 0.45 micron candy filter. The filtrate was then subjected to drying in an ATFD-V apparatus at a temperature of 45° C, and pressure of 640 mm/Hg. The feed rate was adjusted to 7 liters per hour. The powder obtained from the ATFD was milled using an air jet mill to yield 1.55 kg of the material of the desired particle size.

Residual methanol content: Before milling: 62,906; after milling: 49,502.

The particle size data for the product before and after milling was as follows:

D Value	Particle size before milling	Particle size after milling.
D ₁₀	460 µm	1.2 µm
D ₅₀	19.6 µm	7.6 µm
D ₉₀	114.5 µm	34.3 µm

EXAMPLE 2

15 PREPARATION OF AMORPHOUS OMEPRAZOLE MAGNESIUM:

18 liters of methanol was taken into a first reactor and 0.36 kg of magnesium turnings were added. The mixture was stirred for 10 minutes. 0.64 liters of dichloromethane was added to the above mixture. The mixture was agitated for 20 minutes and then the temperature was raised to 57° C. The mixture was maintained at 57° C for one hour, was cooled to 30° C, and then was added to 140 liters of methanol having a temperature of 5° C under a nitrogen atmosphere, in a second reactor. The first reactor was rinsed with 100 liters of methanol twice and the methanol was added to the second reactor and stirred for 10 minutes. The mixture was then cooled to 5° C and maintained under a nitrogen atmosphere. 10 kg of omeprazole was added to the above reaction mass at the same temperature. The reaction mass was maintained at 28° C for 1 hour, 15 minutes. The reaction mass was then filtered through a sparkler cartridge filter having a pore size of 15 microns at 5° C under a nitrogen atmosphere. The filter was washed with 20 liters of methanol. The combined filtrate was then transferred into the feeding tank of the ATFD-V equipment manufactured by Techno Force Solutions (India) Private Limited, Mumbai, India, Model No. ASME SEC. VIII DIV. I

ED-2001+A03. The equipment was maintained at a temperature of 45° C and a pressure of 675 mm Hg. The feed rate of the reaction mass into the reactor was adjusted to 35 to 40 liters per hour. The temperature of the reaction mass being fed into the reactor was maintained at 5° C. The material was stored in clean
5 polyethylene bags, and then sifted through a 40 mesh sieve. The sifted material was then subjected to drying in a fluidized bed drier (manufactured by Alliance Engineering Company of Mumbai, India, Model No. GM15 (S)) for 7 hours with a programmed temperature variation from 25 to 35° C for 3 hours and to 50 to 55° C for 4 hours. Atmospheric air was used to fluidize the particle bed, having an
10 estimated relative humidity about 30-40 percent. The seal air pressure was 1.75 kg/cm² and the blower discharge pressure was maintained at 110 mm Hg. Yield of the title compound was 8.0 kg. Finally the material was micronized in an air jet mill to yield 7.6 kg of the title compound.

Methanol content: 1636 ppm; dichloromethane content: less than 40 ppm.

15 Particle size distribution: D₁₀: 1 µm; D₅₀: 3 µm; D₉₀: 7 µm.

Bulk Density before tapping: 0.3 g/ml ; After tapping: 0.5 g/ml using tapping Method I of the USP 24 bulk density test.

Moisture content: 8.1% w/w.

20 Figs. 1, 2 and 3 are the XRPD, DSC and IR results for the compound prepared in this example. Fig. 1 has a vertical axis in intensity units and a horizontal axis of the 2θ angle, in degrees. Fig. 2 has a vertical axis of heat flow, in watts/gram, and a horizontal axis in degrees Celsius. Fig. 3 has a vertical axis of percent transmission and a horizontal axis of wavenumbers (cm⁻¹).

25 EXAMPLE 3

COMPARISON OF EVAPORATION TECHNIQUES FOR OMEPRAZOLE MAGNESIUM:

30 Omeprazole magnesium solution in methanol, as obtained by a process similar to that given in Example 1, was dried either by rotational evaporation or ATFD.

In Experiment (a), evaporation was carried out in a Buchi Rotavapor under a vacuum of 300 mm/Hg, and a temperature of 28° C, and the product was further dried in a vacuum oven at a temperature of 40° C and a vacuum of 150 mm/Hg.

In Experiment (b), evaporation was carried out in ATFD-V equipment and further drying was carried out in a fluidized bed drier as described in Example 2.

The results are given below in Table 1.

Table 1

Experiment	Batch Size	Evaporation Conditions	Drying Conditions	Time Required	Residual Solvent
(a)	25 g	28° C/300 mm Hg	40° C/150 mm Hg	Evaporation: 3 hours Drying: 11 hours	Methanol: 16456 ppm Dichloromethane: 154 ppm
(b)	10 kg	45° C/690 mm Hg	30° C/100 mm Hg	Evaporation: 10 hours Drying: 7 hours	Methanol: 1636 ppm, Dichloromethane: less than 40 ppm

This example demonstrates the enhanced capability of ATFD-V combined with fluidized bed drying in reducing residual solvent levels on a manufacturing scale when compared with the drying in a Buchi Rotavapor.

EXAMPLE 4

PREPARATION OF AMORPHOUS ESOMEPRAZOLE MAGNESIUM:

100 g of crude esomeprazole magnesium and 500 ml of methanol were taken into a round bottom flask and 30 ml of water was added. The mixture was stirred for 30 minutes, then was filtered through a celite bed and the bed was washed with 100 ml of methanol. The combined filtrate was subjected to evaporation in an ATFD-V apparatus with a feed rate of 5 liters/hour, under a reduced pressure of about 5 mm Hg, and a jacket temperature of 35° C. The material obtained was further dried at 34° C under a reduced pressure of 50 mm Hg for 24 hours to get 25 g of the title compound.

Moisture content: 7.68%.

Figs. 4, 5 and 6 are the XRD, DSC, and IR results for the compound prepared in this example. The axes in these drawings are as described above for the respective related Figs. 1, 2, and 3.

CLAIMS:

1. A method for preparing amorphous esomeprazole magnesium, comprising rapidly removing solvent from a solution of esomeprazole magnesium and recovering solid amorphous esomeprazole magnesium.
2. The method of claim 1, wherein solvent is removed using a flash evaporation technique.
3. The method of claim 1, wherein solvent is removed using an agitated thin film drier-vertical.
4. The method of claim 1, wherein recovered solid amorphous esomeprazole magnesium is dried to reduce a residual solvent concentration.
5. The method of claim 1, wherein recovered solid amorphous esomeprazole magnesium is dried in a moisture-containing atmosphere to reduce a residual solvent concentration.
6. The method of claim 5, wherein solid amorphous esomeprazole magnesium contains about 5 percent to about 10 percent by weight of water.
7. The method of either of claims 4 or 5, wherein solid amorphous esomeprazole magnesium contains not more than about 5000 ppm of residual solvent.
8. The method of either of claims 4 or 5, wherein solid amorphous esomeprazole magnesium contains not more than about 3000 ppm of a residual solvent.
9. The method of either of claims 4 or 5, wherein drying comprises a stepwise temperature increase.

10. The method of claim 1, wherein amorphous esomeprazole magnesium is subjected to particle size reduction, to produce particles having D_{90} less than about 50 μm .
11. A method for preparing amorphous omeprazole magnesium, comprising rapidly removing solvent from a solution of omeprazole magnesium and recovering solid amorphous omeprazole magnesium.
12. The method of claim 11, wherein solvent is removed using a flash evaporation technique.
13. The method of claim 11, wherein solvent is removed using an agitated thin film drier-vertical.
14. The method of claim 11, wherein recovered solid amorphous omeprazole magnesium is dried to reduce a residual solvent concentration.
15. The method of claim 14, wherein drying comprises a stepwise temperature increase.
16. A method for preparing amorphous omeprazole magnesium or esomeprazole magnesium, comprising:
 - a) providing a solution of omeprazole magnesium or esomeprazole magnesium;
 - b) optionally, removing any undissolved particles by filtration;
 - c) evaporating solvent from the solution of step a) or a filtrate obtained from step b) to produce an amorphous solid; and
 - d) optionally drying the solid of step c) to afford amorphous omeprazole magnesium or esomeprazole magnesium.
17. The method of claim 16, wherein a solution of esomeprazole magnesium is provided by reacting a magnesium alkoxide slurry with esomeprazole.

18. The method of claim 16, wherein a solution of omeprazole magnesium is provided by reacting a magnesium alkoxide slurry with omeprazole.
19. The method of claim 16, wherein solvent is removed using a flash evaporation technique.
20. The method of claim 16, wherein solvent is removed using an agitated thin film drier-vertical.

Fig 1

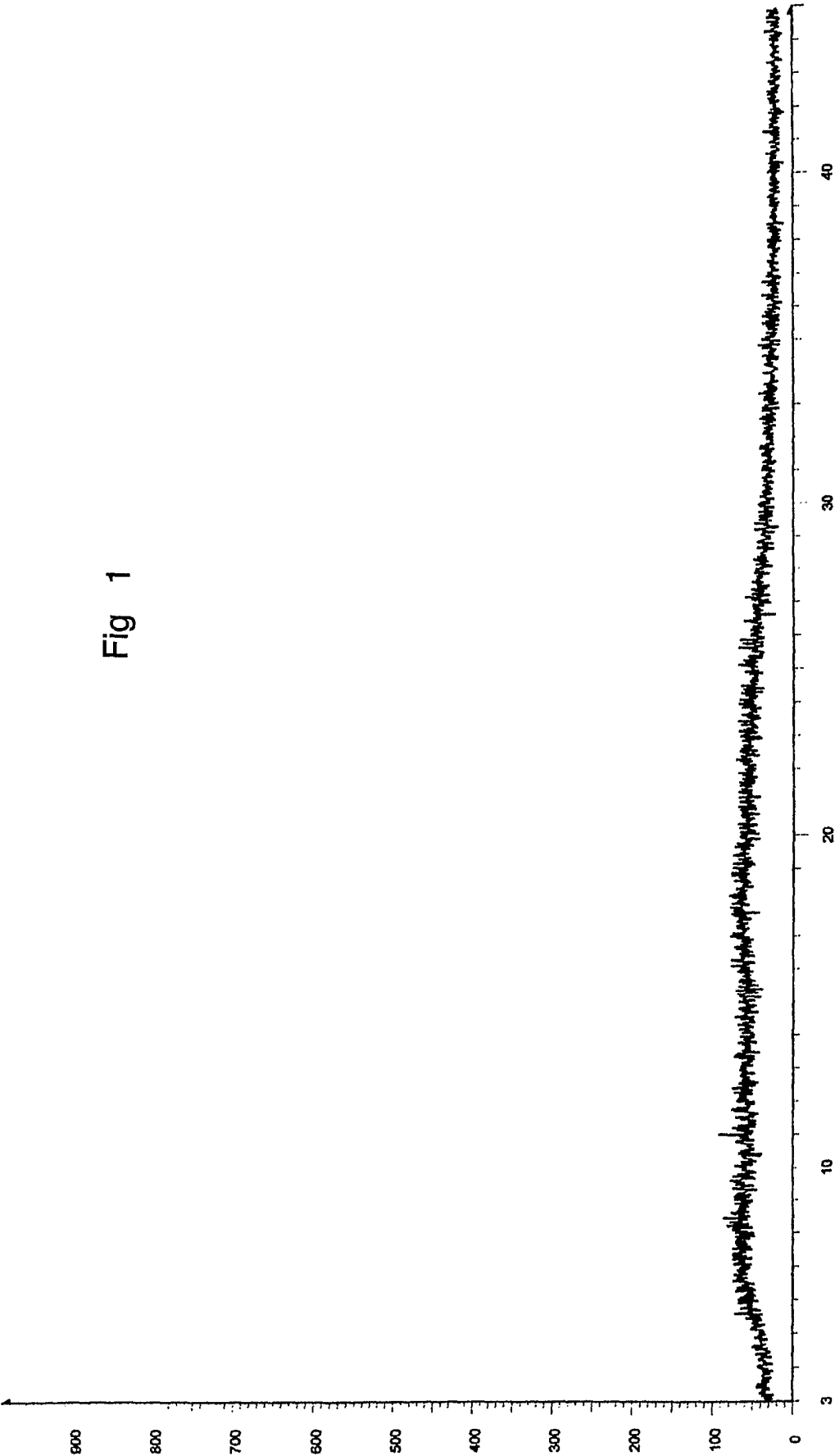


Fig 2

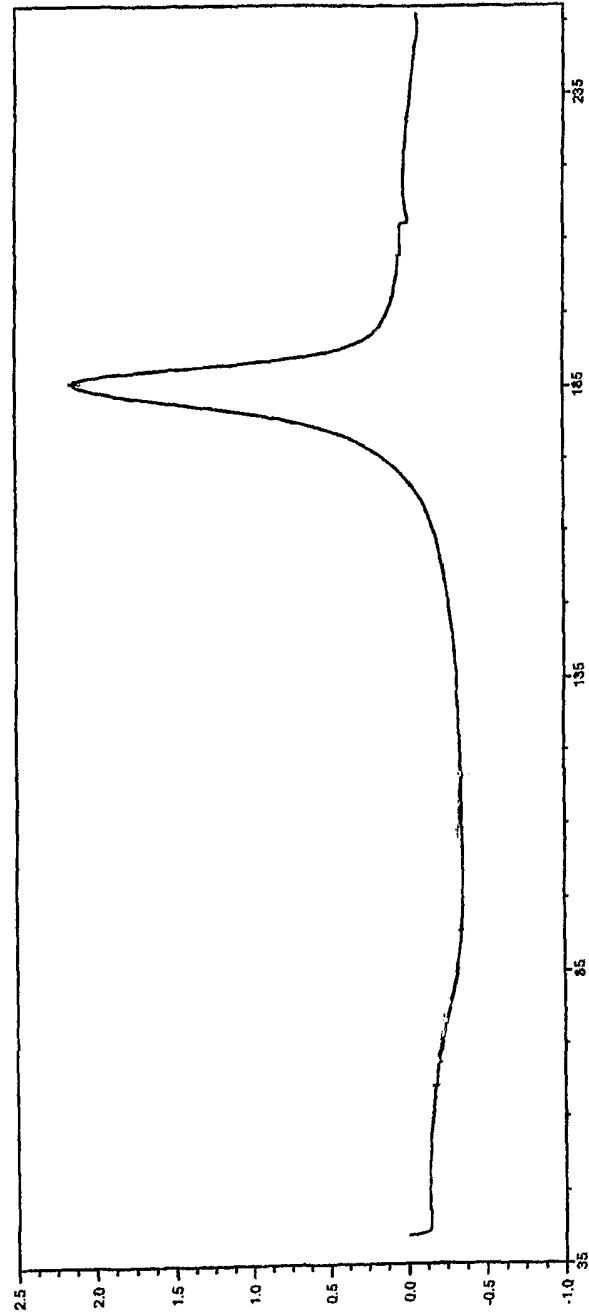
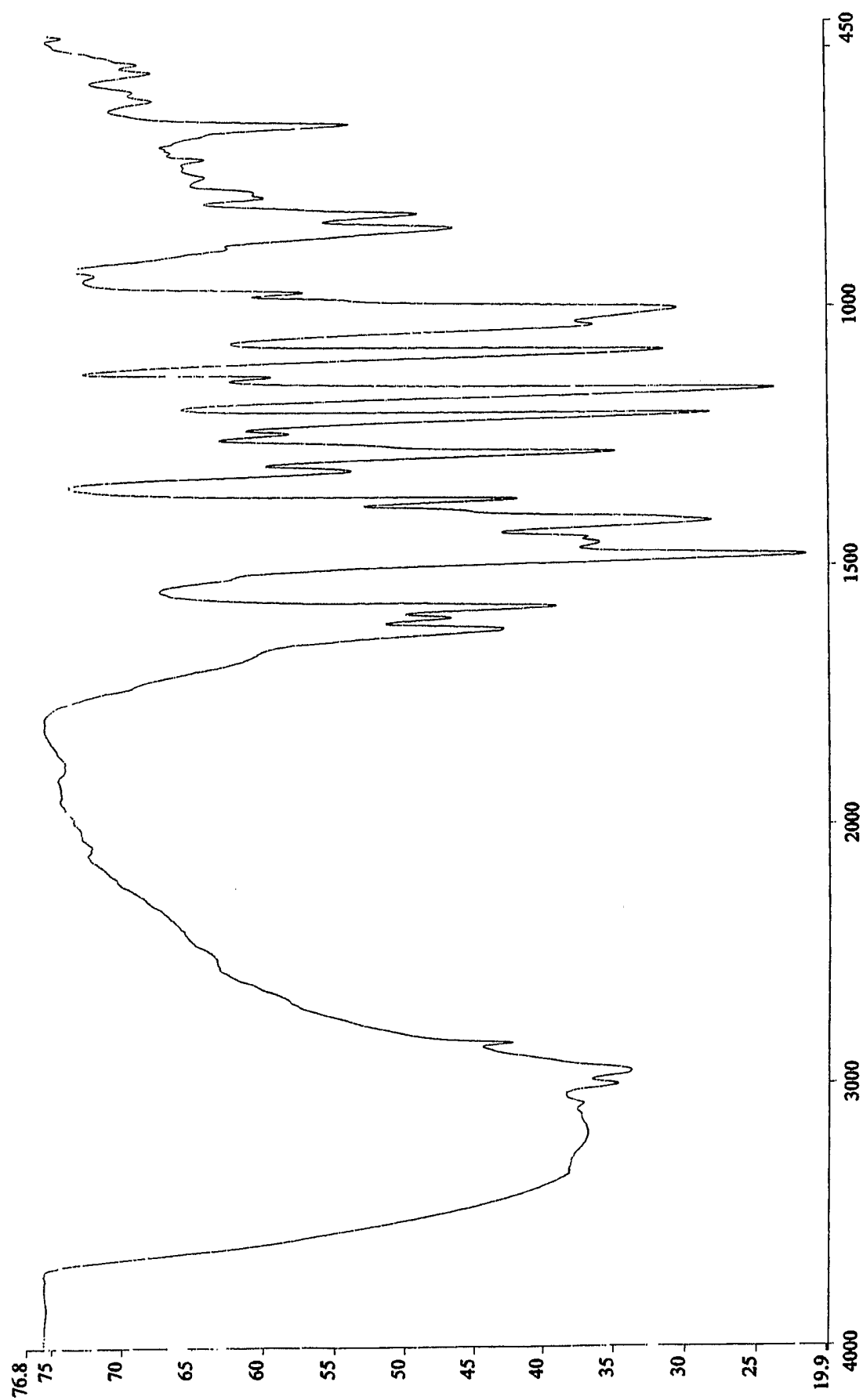


Fig. 3



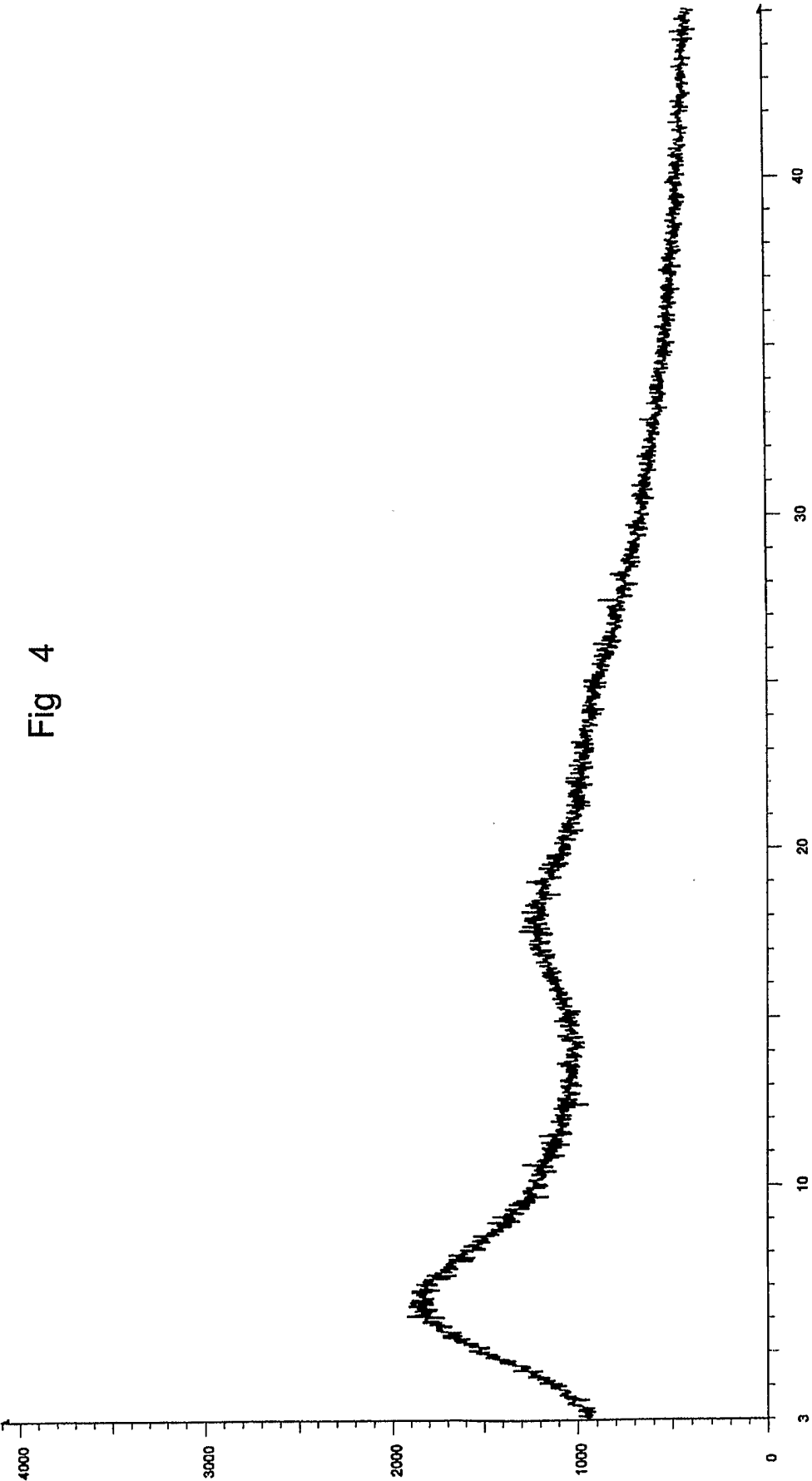


Fig 5

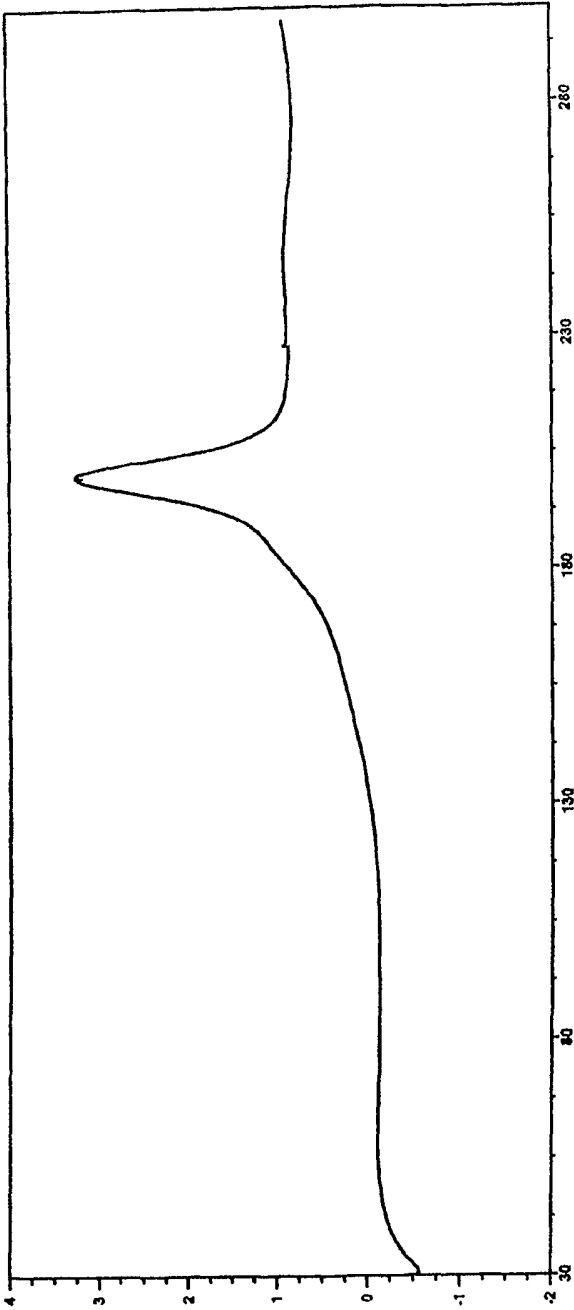


Fig 6

