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THIAZOLIDINONE NITRATE SALT

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of example 30 of EP 0,306,228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter also referred to as "Compound (I)").

International Patent Application, Publication Number WO94/05659 discloses certain salts of the compounds of EP 0,306,228. The preferred salt of WO94/05659 is the maleic acid salt.

It has now been discovered that Compound (I) forms a novel nitrate salt (hereinafter also referred to as the "Nitrate") that is particularly stable and hence is suitable for bulk preparation and handling.

The Nitrate also shows particularly good aqueous solubility and possesses good bulk flow properties. The Nitrate is therefore surprisingly amenable to large scale pharmaceutical processing and formulation. The novel salt can be prepared by an efficient, economic and reproducible process particularly suited to large-scale preparation

The novel Nitrate also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate salt or a solvate thereof.

In one favoured aspect, the Nitrate provides an infrared spectrum substantially in accordance with Figure 1.

In one favoured aspect, the Nitrate provides a Raman spectrum substantially in accordance with Figure 2.

In one favoured aspect, the Nitrate provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3.

In one favoured aspect, the Nitrate provides a solid state ^{13}C NMR spectrum substantially in accordance with Figure 4.

In a preferred aspect, the invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate salt, characterised in that it provides:

(i) an infrared spectrum substantially in accordance with Figure 1; and

(ii) a Raman spectrum substantially in accordance with Figure 2; and

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(iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3; and

(iv) a solid state ^{13}C NMR spectrum substantially in accordance with Figure 4.

The present invention encompasses the Nitrate or a solvate thereof isolated in pure form or when admixed with other materials.

Thus in one aspect there is provided the Nitrate or a solvate thereof in isolated form.

In a further aspect there is provided the Nitrate or solvate thereof in a purified form.

In yet a further aspect there is provided the Nitrate or solvate thereof in crystalline form.

Also, the invention provides the Nitrate or solvate thereof in a solid pharmaceutically acceptable form, such as a solid dosage form, especially when adapted for oral administration.

Moreover, the invention also provides the Nitrate or solvate thereof in a pharmaceutically acceptable form, especially in bulk form.

Furthermore, the invention provides the Nitrate or solvate thereof in a pharmaceutically acceptable form, especially in bulk form, such form having good flow properties, especially good bulk flow properties

A suitable solvate is a hydrate.

The invention also provides a process for preparing the Nitrate or a solvate thereof, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound (I)) or a salt thereof, preferably dispersed or dissolved in a suitable solvent, is reacted with a source of nitrate ion and thereafter, if required, a solvate of the resulting Nitrate is prepared; and the Nitrate or a solvate thereof is recovered.

Suitably, Compound (I) is used in the reaction, especially in a protonated form.

Suitably, a salt of Compound (I) is used in the reaction..

Compound (I) is preferably present in a protonated form.

A suitable reaction solvent is a ketone, such as acetone, an ester, such as ethyl acetate, an alkanol, for example propan-2-ol, or a hydrocarbon, such as toluene, an ether such as tetrahydrofuran, a nitrile such as acetonitrile, or a halogenated hydrocarbon such as dichloromethane or water, or an organic acid such as acetic acid; or a mixture thereof.

Conveniently, the source of Nitrate ion is nitric acid, for example concentrated nitric acid. An alternative source of nitrate ion for a salt of Compound (I) is a nitrate salt of a type which provides a double decomposition reaction resulting in the required nitrate in solution. An alternative source of Nitrate ion is provided by a base salt of nitric acid

for example ammonium nitrate, or the nitric acid salt of an amine, for example ethylamine or diethylamine.

The concentration of Compound (I) is preferably in the range 2 to 25% weight/volume, more preferably in the range 5 to 20%. The concentration of nitric acid solutions are preferably in the range of 5 to 100% weight/volume.

The reaction is usually carried out at ambient temperature or at an elevated temperature, for example at the reflux temperature of the solvent, although any convenient temperature that provides the required product may be employed.

Solvates, such as hydrates, of the Nitrate are prepared according to conventional procedures.

Recovery of the required compound generally comprises crystallisation from an appropriate solvent, conveniently the reaction solvent, usually assisted by cooling. For example, the Nitrate may be crystallised from an ester such as ethyl acetate or a ketone such as acetone. An improved yield of the salt can be obtained by evaporation of some or all of the solvent or by crystallisation at elevated temperature followed by controlled cooling, preferably in stages. Careful control of precipitation temperature and seeding may be used to improve the reproducibility of the product form.

Crystallisation can also be initiated by seeding with crystals of the Nitrate or a solvate thereof but this is not essential.

Compound (I) is prepared according to known procedures, such as those disclosed in EP 0,306,228 and WO94/05659. The disclosures of EP 0,306,228 and WO94/05659 are incorporated herein by reference.

When used herein in respect of certain compounds the term "good flow properties" is suitably characterised by the said compound having a Hausner ratio of less than or equal to 1.5, especially of less than or equal to 1.25.

"Hausner ratio" is an art accepted term.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

Diabetes mellitus preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly provides the Nitrate or a solvate thereof for use as an active therapeutic substance.

More particularly, the present invention provides the Nitrate or a solvate thereof for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

The Nitrate or a solvate thereof may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. Suitable methods for formulating the Nitrate or a solvate thereof are generally those disclosed for Compound (I) in the above mentioned publications.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Nitrate or a solvate thereof and a pharmaceutically acceptable carrier therefor.

The Nitrate or a solvate thereof is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium

stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

The compositions are formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Complete Drug Reference (London, The Pharmaceutical Press) and Harry's Cosmeticology (Leonard Hill Books).As used herein the term 'pharmaceutically

acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Nitrate or a solvate thereof to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In a further aspect the present invention provides the use of Nitrate or a solvate thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Nitrate or a solvate thereof may be taken in amounts so as to provide Compound (I) in suitable doses, such as those disclosed in EP 0,306,228, WO94/05659 or WO98/55122.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following examples illustrate the invention but do not limit it in any way.

EXAMPLES

Example 1 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate

A mixture of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (4.9 g) and ethyl acetate (200 ml) was stirred and heated to reflux to give a clear solution. Concentrated nitric acid (0.86 ml) was added to the mixture which was then cooled to 65°C. The mixture was sonicated for 5 minutes, cooled to 21°C and maintained at this temperature until crystallisation was complete. The product was collected by filtration and dried under vacuum at 21°C for 3 hours to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate (5.0 g) as a white crystalline solid.

Example 2 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate

A mixture of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (4.0 g) and acetone (90 ml) was stirred and heated to reflux to give a clear solution. Concentrated nitric acid (0.71 ml) was added slowly and the reaction mixture stirred at reflux for 10 minutes. The mixture was cooled to 21°C and maintained at this temperature until crystallisation was complete. The solvent was decanted and the product washed with acetone (20 ml) and dried under vacuum to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate (4.1 g) as a white crystalline solid.

1H-NMR (d6-DMSO): consistent with 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate containing acetone 0.2% by wt.

Example 3 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate

A mixture of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (3.0 g) and acetone (60 ml) was stirred and heated to reflux for 15 minutes. Concentrated nitric acid (0.53 ml) was added slowly and the reaction mixture stirred for 10 minutes at reflux, then cooled to 21°C over a period of approximately 1 hour and maintained at 21°C for 1.5 hours. The product was collected by filtration and dried under vacuum over phosphorus pentoxide for 18 hours, to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate (2.95 g) as a white crystalline solid.

Example 4 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitate

A mixture of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (10.0 g) and acetone (200 ml) was stirred and heated to reflux for a period of 10 minutes at which point a clear solution was observed. Concentrated nitric acid (1.77 ml) was added to the stirred reaction mixture which was then cooled to 21°C over a period of approximately 1 hour. Stirring was continued for 18 hour at 21°C and the product was collected by filtration and washed with acetone (50 ml) to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate (10.6 g) as a white crystalline solid.

Characterising data recorded for the product of Example 2:

The infrared absorption spectrum of a mineral oil dispersion of the product was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm^{-1} resolution (Figure 1). Data were digitised at 1 cm^{-1} intervals. Bands were observed at:
2922, 2853, 1746, 1698, 1642, 1615, 1545, 1513, 1457, 1378, 1311, 1287, 1255, 1222, 1200, 1184, 1146, 1074, 1051, 1017, 987, 907, 826, 802, 772, 737, 711, 660, 619, 603, 587, 557, 536, 521, 503, 468 cm^{-1}.

The infrared spectrum of the solid product was recorded using a Perkin-Elmer Spectrum One FT-IR spectrometer fitted with a universal ATR accessory. Bands were observed at: 2925, 2771, 1746, 1695, 1641, 1613, 1545, 1513, 1407, 1358, 1309, 1286, 1253, 1235, 1221, 1200, 1184, 1146, 1073, 1050, 1015, 987, 907, 871, 825, 801, 769, 737, 709, 658 cm^{-1}.

The Raman spectrum of the product (figure 2) was recorded with the sample in an NMR tube using a Nicolet 960 E.S.P. FT-Raman spectrometer, at 4 cm^{-1} resolution with excitation from a Nd:V04 laser (1064 nm) with a power output of 400 mW. Bands were observed at:
3108, 3068, 2925, 1748, 1611, 1587, 1545, 1444, 1385, 1317, 1289, 1273, 1233, 1207,1184, 1148, 1074, 1050, 1016, 989, 915, 827, 769, 740, 721, 661, 637, 621, 604, 505, 470, 431, 401, 335, 304, 95 cm^{-1}.

The X-Ray Powder Diffractogram pattern of the product (Figure 3) was recorded using the following acquisition conditions: Tube anode: Cu, Generator tension: 40 kV, Generator current: 40 mA, Start angle: 2.0 °2θ, End angle: 35.0 °2θ, Step size: 0.02 °2θ , Time per step: 2.5 seconds. Characteristic XRPD angles and relative intensities are recorded in Table 1.

Table 1

Angle	Intensity

2-Theta °	%
6.4	1.4
9.7	3.2
11.5	5
11.7	8.1
13.0	5.7
13.3	10.7
13.8	5.5
14.1	3.9
14.9	10.6
15.5	9.9
16.2	100
16.9	25.7
17.5	28.1
17.8	47.7
18.6	4.8
19.5	24.5
19.9	10.8
20.2	4
21.1	12.2
21.4	16
21.9	60
22.3	60.4
22.6	54
23.1	34
23.5	92.4
23.9	33.1
24.3	54.9
25.3	12.1
25.6	22.1
26.4	25.6
26.6	20.4
26.9	11.9
27.4	13.7
27.9	40.1
28.8	7.9
30.1	45.6
30.8	13.2
31.3	8.9
31.6	9.4
31.9	8.6

32.6	15
33.1	6.7
33.9	12.5
34.3	18.5

The solid-state NMR spectrum of the product (Figure 4) was recorded on a Bruker AMX36(instrument operating at 90.55 MHz: The solid was packed into a 4 mm zirconia MAS rotor fitted with a Kel-F cap and rotor spun at ca.10 kHz. The ^{13}C MAS spectrum was acquired by cross-polarisation from Hartmann-Hahn matched protons (CP contact time 3 ms, repetition time 15 s) and protons were decoupled during acquisition using a two-pulse phase modulated (TPPM) composite sequence. Chemical shifts were externally referenced to the carboxylate signal of glycine at 176.4 ppm relative to TMS and were observed at: 37.3, 38.9 50.8, 55.8, 65.7, 111.3, 113.8, 118.9, 130.3, 137.9, 145.1, 152.5, 158.7, 170.9, 176.3, 178.2 ppm.

Properties of the Nitrate

Solid State Stability of the Nitrate, recorded for the product of Example 4

The solid state stability of the drug substance was determined by storing approximately 1.0 g of the material in a glass bottle at a) 40°C / 75% Relative Humidity (RH), open exposure, for 1 month and b) at 50°C, closed, for 1 month. The material was assayed by HPLC for final content and degradation products in both cases.

a) 40°C / 75% RH: No significant degradation observed (HPLC assay 99% initial).

b) 50°C: No significant degradation observed (HPLC assay 99% initial).

Solubility of the Nitrate

The solubility of the material was determined by adding water in aliquots from 1 to 1000 ml to approximately 100 mg of drug substance until the powder had dissolved. The visual solubility was confirmed by an HPLC assay of a saturated solution. Solubility: 6 mg/ml.

CLAIMS:

1. A compound 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, nitrate salt or a solvate thereof.

2. A compound according to claim 1, characterised in that it provides:
(i) an infrared spectrum substantially in accordance with Figure 1; and
(ii) a Raman spectrum substantially in accordance with Figure 2; and
(iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3; and
(iv) a solid state ^{13}C NMR spectrum substantially in accordance with Figure 4.

3. A compound according to claim 1, characterised in that it provides two or more of:
(i) an infrared spectrum substantially in accordance with Figure 1; and
(ii) a Raman spectrum substantially in accordance with Figure 2; and
(iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3; and
(iv) a solid state ^{13}C NMR spectrum substantially in accordance with Figure 4.

4. A compound according to any one of claims 1 to 3, in purified form.

5. A compound according to any one of claims 1 to 3, in a solid dosage form.

6. A compound according to any one of claims 1 to 3, in a pharmaceutically acceptable form capable of being milled or in milled form

7. A compound according to any one of claims 1 to 3, in a pharmaceutically acceptable form and having good flow properties.

8. A process for preparing the nitrate or a solvate thereof, characterised in that characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound (I)) or a salt thereof, preferably dispersed or dissolved in a suitable solvent, is reacted with a source of nitrate ion and thereafter, if required, a solvate of the resulting Nitrate is prepared; and the Nitrate or a solvate thereof is recovered.

9. A pharmaceutical composition comprising 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate or a solvate thereof. and a pharmaceutically acceptable carrier therefor.

10. A compound 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate or a solvate thereof for use as an active therapeutic substance.

11. A use of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione nitrate or a solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.