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(71) Applicants *(for all designated States except US):* **GENERICS [UK] LIMITED** [GB/GB]; Albany Gate, Darkes Lane, Potters Bar, Hertfordshire EN6 IAG (GB). **GENERICS UK LIMITED** [GB/GB]; Albany Gate, Darkes Lane, Potters Bar, Hertfordshire EN6 IAG (GB). **MYLAN INDIA PRIVATE LIMITED** [IN/IN]; Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410 208 **(IN).**

(72) Inventors; and
(75) Inventors/Applicants *(for US only):* **GORE, Vinayak Govind** [IN/IN]; Mylan India Private Limited, Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410 208 **(IN). GADAKAR, Maheshkumar** [IN/IN]; Mylan India Private Limited, Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410 208 (IN). BHOSLE, **Priyanka** [IN/IN]; Mylan India Private Limited, Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410208 (IN). SHINDE, **Suresh** [IN/IN]; Mylan India Private Limited, Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410 208 **(IN).** YADAV, **Prashant** [IN/IN]; Mylan India Private Limited, Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410 208 (IN).

(74) Agents: ELEND, **Almut** et al; Venner Shipley LLP, Byron House, Cambridge Business Park, Cowley Road, Cambridge Cambridgeshire CB4 OWZ (GB).

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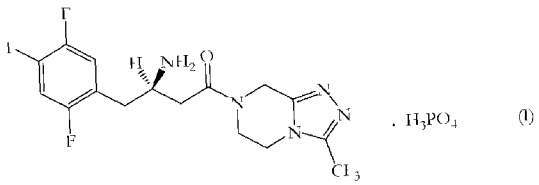
(54) Title: NOVEL CRYSTALLINE POLYMORPH OF SITAGLIPTIN DIHYDROGEN PHOSPHATE



(I)

(57) Abstract: The present invention relates to a novel anhydrous crystalline form of sitagliptin dihydrogenphosphate (I), to processes for its preparation and to its use in pharmaceutical compositions.

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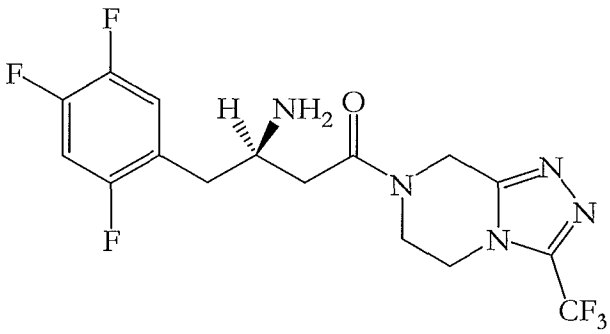
NOVEL CRYSTALLINE POLYMORPH OF SITAGLIPTIN DIHYDROGEN PHOSPHATE

Field **of the invention**

The present invention relates to a novel anhydrous crystalline form of sitagliptin dihydrogenphosphate (I), to processes for its preparation and to its use in pharmaceutical compositions.



. H_3PO_4 (I)

Background of **the** invention

The manufacturing process for many pharmaceuticals is hindered by the fact that the organic compound, which is the active pharmaceutical ingredient (API), has handling difficulties during the manufacturing process and may impart undesirable properties to the final drug or dosage form. In addition it can be difficult to control the polymorphic form of the API throughout the manufacturing process.

For pharmaceuticals in which the API can exist in more than one polymorphic form, it is particularly important to ensure that the manufacturing process for the API affords a single, pure polymorph with a consistent level of polymorphic purity. If the manufacturing process leads to a polymorph with varying degrees of polymorphic purity and/ or where the process does not control polymorphic interconversion, serious problems in dissolution and/or bioavailability can result in the finished pharmaceutical composition comprising the API.

Sitagliptin dihydrogenphosphate, represented by structural formula (I), is chemically named as (2R)-4-oxo-4-[3-(tofluoromethyl)-5,6-dihydro[l,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-l-(2,4,5-trifluorophenyl)butan-2-amine dihydrogenphosphate.

Sitagliptin is an oral antiliyperglycemic of the dipeptidyl peptidase-IV (DPP-IV) inhibitor class. Inhibition of dipeptidyl peptidase-IV, an enzyme that inactivates both glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-I), represents a recent approach to the treatment and prevention of type-2 diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM).

Therefore the novel crystalline form of the present invention can be used for the preparation of pharmaceutical compositions for the treatment and prevention of diseases and conditions for which an inhibitor of dipeptidyl peptidase-IV is indicated, in particular type-2 diabetes, hyperglycemia, insulin resistance, obesity, and high blood pressure. The novel crystalline form of the present invention can be used in combination with one or more other active ingredients if necessary.

Various structural analogues and salts of sitagliptin are disclosed in patent US 6,699,871, but no polymorphic data is given.

Solvate forms and three anhydrate polymorphs of sitagliptin dihydrogenphosphate (forms I, II and III) are disclosed in patent application US 2006/0287528. However, desolvated form II converts spontaneously to form I or III or a mixture thereof.

A process for the preparation of sitagliptin dihydrogenphosphate is disclosed in patent application US 2005/0032804 wherein the salt is prepared in isopropyl alcohol and water to afford sitagliptin dihydrogenphosphate monohydrate. However, this monohydrate form converts to an unstable dehydrated form at temperatures above 40^0C.

In addition, crystalline anhydrate form IV is disclosed in patent application US 2007/0021430, which is prepared from the sitagliptin dihydrogenphosphate monohydrate by heating at 120°C for 2 hours. However, form IV is metastable and converts into the

ciystalline monohydrate slowly undeï ambient conditions or rapidly under high relative humidity.

An amorphous form of sitagliptin dihydrogenphosphate salt is disclosed in patent application US 2007/0281941. However amorphous forms are not ideally suited for commercial production and crystalline forms are generally preferred.

As discussed above, the six polymorphic forms of sitagliptin dihydrogenphosphate disclosed in the prior art suffer from several disadvantages which do not make them ideal forms for pharmaceutical development. In particular, the disadvantages associated with the prior art forms can include discolouration, polymorphic impurities and instability. The processes to prepare the respective prior art polymorphs suffer from the disadvantages of being inconsistent and difficult to reproduce. Consequently, the prior art processes can often produce polymorphically impure products. In addition, the prior art processes are particularly inconvenient for large scale production.

If crystalline and amorphous forms are made with polymorphic impurities, this causes instability and it can accelerate significant interconversion to another polymorphic form. Therefore, for commercial production, it is crucial to produce forms, particularly crystalline forms, with very high polymorphic purity to avoid or minimize this interconversion.

In view of the importance acquired by sitagliptin for the treatment of diabetes, there is a great need for developing an alternative, relatively simple, economical and commercially feasible process for the synthesis of sitagliptin crystalline forms with commercially acceptable yield, high polymorphic purity and polymorphic stability.

Object of the invention

Therefore an object of the invention is to provide a new polymorphic form of sitagliptin dihydrogenphosphate, which is convenient to manufacture and has improved properties suitable for a marketed pharmaceutical composition.

Summary of **the** invention

The term "sitagliptin" as used herein throughout the description and claims means sitagliptin and/ or any salt, hydrate, solvate or tautomer thereof unless specified otherwise.

A first aspect of the present invention provides sitagliptin dihydrogenphosphate form M, characterised by an XRPD spectrum comprising the following degrees 2θ peaks: 5.0, 14.3, 18.6, 24.0 ± 0.2 degrees 2θ. Preferably sitagliptin dihydrogenphosphate form M is characterised by an XRPD spectrum comprising four or more (preferably five or more, preferably six or more, preferably seven or more, preferably eight or more, preferably nine or more, preferably ten or more, preferably eleven or more, preferably twelve or more, preferably thirteen or more, preferably fourteen or more, preferably fifteen) of the following degrees 2θ peaks: 5.0, 9.7, 13.7, 14.3, 15.4, 18.6, 19.5, 19.7, 20.3, 22.4, 24.0, 24.5, 25.7, 27.0, 27.3 ± 0.2 degrees 2θ.

Preferably, the first aspect of the present invention provides sitagliptin dihydrogenphosphate form M, characterised by an XRPD spectrum substantially comprising the following degrees 2θ peaks (± 0.2 degrees 2θ):

2θ values	d-values	Intensity %
5.0	17.68	100.0
9.7	9.13	17.8
13.7	6.41	25.9
14.3	6.16	56.7
15.4	5.72	40.8
18.6	4.75	84.2
19.5	4.53	46.7
19.7	4.49	40.4
20.3	4.35	31.6
22.4	3.95	41.0
24.0	3.70	67.3
24.5	3.61	49.3
25.7	3.45	44.0
27.0	3.29	43.6
27.3	3.25	44.3

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