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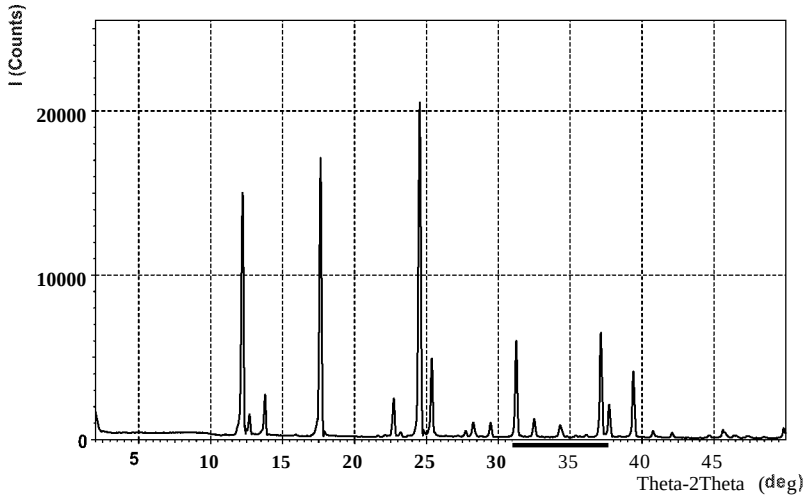
(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF HIGH PURE METFORMINE

Figure: 1 depicts X-ray diffraction pattern of crystalline Metformin hydrochloride as per example-1.



(57) Abstract: The present invention provided an improved process for the preparation of Metformin compound of formula I or its pharmaceutically acceptable salts 5 thereof, by employing an alcoholic solvent throughout the process

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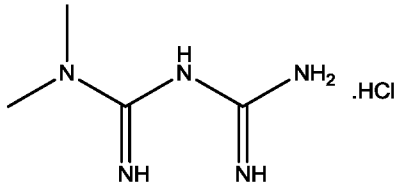
FIELD OF INVENTION

The present invention relates to an improved process for the preparation of Metformin compound of formula-I or its pharmaceutically acceptable salts thereof.

BACKGROUND OF THE INVENTION

Metformin hydrochloride is described chemically as N,N-Dimethylimidodicarbonimidic diamide hydrochloride (CAS# 1115-70-4). The empirical formula of Metformin hydrochloride is $C_4H_{11}N_5$.HCI and its molecular weight is 165.62 g/mol. The molecular structure of Metformin hydrochloride is represented by Formula I.



Formula I

Metformin, also known by other name like 1,1-dimethylbiguanide, it is first described in the scientific literature in J. Chem, Soc, 1922, 121, 1790. It is the only one available biguanide, most widely prescribed orally administered anti-diabetic drug for the treatment of type 2-diabetes. It is also used for the treatment of polycystic ovary syndrome

The advantages of Metformin hydrochloride are a very low risk of hypoglycaemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality.

In US patent no. 2,448,448 discloses use of 1,1-dimethylbiguanide in dyeing of textile fibers, wherein 1,1-dimetylbiguanide is prepared by reacting dicyandiamide with dimethylamine.

In US patent no 3,174,901 discloses composition containing 1,1-dimethylbiguanide in the form of hydrochloride salt used for treating diabetes by oral administration.

In DE patent no. 1023757 discloses preparation of Metformin hydrochloride by reacting dicyandiamide with dimethylamine hydrochloride in xylene at reflux temperature and crystallization with water to obtain Metformin hydrochloride with 47% yield.

In FR patent no 2322860 discloses preparation of Metformin hydrochloride by reacting equimolar amounts of dimethylamine and dicyandiamide in xylene followed by treating with HC1 gas to obtain crude Metformin hydrochloride is further purified by methanol.

In US patent application no 201 1/021634 discloses preparation of Metformin hydrochloride substantially free from dimethylamine wherein an aqueous solution of Metformin hydrochloride is concentrated to remove water and the obtained residue is treated with C1-C4 alcohols to obtain pure Metformin hydrochloride.

In an Indian patent 189077 discloses a preparation of Metformin hydrochloride in absence of solvents followed by purification to obtain pure Metformin hydrochloride crystals.

In CN patent no 100391939 discloses a preparation of Metformin hydrochloride by treating 40% aqueous dimethylamine solution with 31% hydrochloric acid followed by dicyandiamide in ethanol to get crude compound, followed by

recrystallization with ethanol to obtain Metformin hydrochloride with 75-80 % yield.

In IN patent application No. 1350/MUM/2007 discloses preparation of highly pure Metformin hydrochloride substantially free from melamine and cyanoguanidine impurities by condensation of dimethylamine hydrochloride with dicyandiamide in xylene; extracting the product into water followed by distillation of water under vacuum at 65-72°C and crystallizing Metformin hydrochloride from methanol or a mixture of water and methanol.

In IN patent application No. 1346/MUM/2008 discloses a one-pot process for preparation of highly pure Metformin hydrochloride substantially free from melamine and cyanoguanidine impurities by reacting dimethylamine hydrochloride solution prepared insitu with cyanoguanidine in xylene, extracting metformin hydrochloride in to water, and distillation of around 50% of water followed by isolation.

In PCT publication no. 2010146604 discloses a preparation of Metformin hydrochloride using hydrocarbon solvents, followed by treating with water and alcoholic solvents to get Metformin hydrochloride as a product.

In PCT publication no. 2014041566 discloses a preparation of Metformin hydrochloride by removing solvents from the Metformin hydrochloride solution using agitated thin film dryer technique.

In Pharmaceutical Chemistry Journal, 1987, 21 (12), 892-894 discloses a preparation of Metformin hydrochloride by using n-butanol, followed by purification with isopropanol to obtain Metformin Hydrochloride as a final product with 65% yield.

Above mentioned prior art processes for the preparation of Metformin hydrochloride suffers from several disadvantages like decrease in yield of final compound, difficult in removal of the solvents during process, formation of several impurities during process, which are not economic at commercial scale. Further prior art processes involves non food grade solvent which will impact the final compound.

Substantially these factors affect the commercial viability of manufacturing process of Metformin hydrochloride. Therefore, there is a need to develop an improved process for the preparation of Metformin hydrochloride which can be practiced on large scale to produce Metformin hydrochloride in a cost efficient manner.

OBJECTIVE OF THE INVENTION

The main object of the present invention is to provide an improved process for the preparation of highly pure Metformin hydrochloride compound of Formula I.

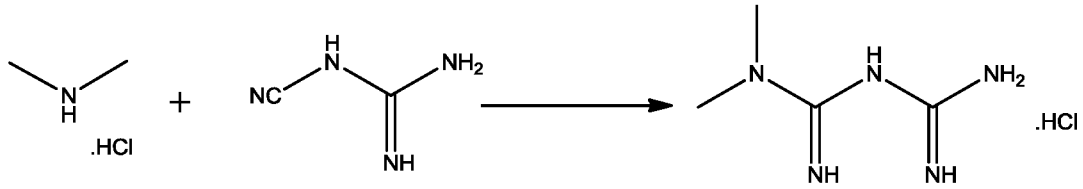
Another object of the present invention is use of single organic solvent for the preparation of highly pure Metformin hydrochloride compound of Formula I.

Yet another object of the present invention is use of single alcoholic solvent for the preparation of pure Metformin hydrochloride compound of Formula I.

Yet another object of the present invention is use of n-butanol (is also a food grade material use in the industries) alcoholic solvent for the preparation of pure Metformin hydrochloride compound of Formula I.

SUMMARY OF THE INVENTION

In an embodiment, the present invention provides an improved process for the preparation of Metformin hydrochloride compound of formula I, which comprises the steps of



i) treating dimethyl amine in the form of hydrochloride (DMA HCl) with 2-cyanoguanidine (DCDA) in presence of alcoholic solvent at ambient to reflux temperature.

ii) isolation of Metformin by filtration.

iii) With or without washing step (ii) with alcoholic solvent and drying to get compound of formula- 1 as a pure product.

According to present invention the term alcohol includes primary, secondary and tertiary alcohols, preferably primary alcohols; more preferably n-butanol.

In the first aspect of invention is use of minimum amount of n-butanol for the preparation of Metformin Hydrochloride.

In the second aspect of invention is use of 0.4 to 4.0 kg of n-butanol for 1 kg of 2-cyanoguanidine.

In the third aspect of invention is preparation of Metformin hydrochloride having purity > 99.9 %

In the fourth aspect of the invention is preparation of high yield of Metformin hydrochloride is about >92 to 98 %.

In the fifth aspect of invention is preparation of highly pure Metformin hydrochloride, with residual quantity of Dimethyl amine is less than 5 ppm.

Unlike prior art the present invention involves the use of n-butanol , which is also a food grade material use in the industries, will minimize the multiple residual solvents and improves the quality and purity of the API which leads to consumption of finished formulations at patient end for safe use.

BRIEF DESCRIPTION OF DRAWINGS

Figure: 1 depicts X-ray diffraction pattern of crystalline Metformin hydrochloride as per example- 1.

Figure: 2 depicts X-ray diffraction pattern of crystalline Metformin hydrochloride as per example-2.

Figure: 3 depicts X-ray diffraction pattern of crystalline Metformin hydrochloride as per example-3.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an improved process for the preparation of highly pure metformin hydrochloride crystal by using single alcoholic solvent. The simple process offers high yield and low level of impurities makes the process more convenient and economical, particularly on commercial scale.

In an embodiment, the invention provides a process for preparation of Metformin hydrochloride, which comprises the steps of:

i) treating dimethyl amine in the form of hydrochloride (DMA HC1) with 2-cyanoguanidine (DCDA) in presence of alcoholic solvent at ambient to reflux temperature.

ii) isolation of Metformin by filtration.

iii) With or without washing step (ii) with alcoholic solvent and drying to get compound of formula- 1 as a pure product.

2-cyanoguanidine and dimethyl amine hydrochloride were added to alcoholic solvent to form the reaction mixture. The reaction mixture is condensed using the cooling water condenser for 16-28 hr. The resulting reaction mass is cooled to ambient temperature, preferably 10-1 10°C. The reaction mass is filtered to receive the wet mass. The wet mass can be washed with n-butanol and dried to get pure Metformin hydrochloride. The reaction mass is filtered and dried using standard techniques that have been widely used in industry.

The alcohols that are selected include primary, secondary and tertiary alcohols, preferably primary alcohols; more preferably n-butanol.

According to another aspect of invention, the Metformin hydrochloride prepared by this method have purity >99.9%.

In another aspect of the invention is preparation of high yield of Metformin hydrochloride is about >92 to 98%.

In yet another aspect of invention is preparation of highly pure Metformin hydrochloride, with residual quantity of Dimethyl amine is less than 5 ppm. The final product has low level of other impurities wherein melamine and 2-cyanoguanidine (DCDA) is less than 0.02%, more preferably 0.01%.

EXAMPLES

In the following examples, the preferred embodiment of the present invention is described only by way of illustrating the processes of the invention. However, these are not intended to limit the scope of the invention in any way.

Example: 1 Preparation of Metformin hydrochloride (Formula 1)

84.07 g of 2-cyanoguanidine and 81.54 g of Dimethyl amine hydrochloride were added to 100 g of n-butanol in a 500 mL glass flask. The flask was equipped with cooling water condenser and the flask was allowed to reflux for 16 h. The resulting reaction mass was cooled to ambient temperature, preferably 10-1 10°C and filtered. The obtained wet solid was washed with 50g of n-butanol and dried to get Pure Metformin hydrochloride (160g).

EXAMPLE 2: Preparation of Metformin hydrochloride (Formula 1)

100 g of 2-cyanoguanidine and 108 g of Dimethyl amine hydrochloride were added to 400 g of n-butanol in a 1000 mL glass flask. The flask was equipped with cooling water condenser and the flask was allowed to reflux for 28 h. The resulting reaction mass was cooled to ambient temperature, preferably 10-1 10°C and filtered. Dried the obtained solid at 50°¯75°C, to get Pure Metformin hydrochloride (188 g)

EXAMPLE 3: Preparation of metformin hydrochloride (Formula 1)

1 Kg of 2-cyanoguanidine and 1.15 Kg of Dimethyl amine hydrochloride were added to 2 Kg of n-butanol in a 5 L glass flask. The flask was equipped with cooling water condenser and the flask was allowed to reflux for 22 h. The resulting reaction mass was cooled to ambient temperature, preferably 10-1 10°C and filtered. Dried the obtained solid at 50°¯75°C, to get Pure Metformin hydrochloride (1.9 Kg)

Above obtained Metformin Hydrochloride samples were analyzed for related substances by HPLC as per the European Pharmacopoeia monograph (Ph.Eur) 8.0

Examples	Single Maximum Unknown Impurity	Total impurities	Metformin Hydrochloride purity
1	**0.02%**	**0.03%**	**99.97%**
2	**0.02%**	**0.05%**	**99.95%**
3	**0.01%**	**0.04%**	**99.96%**

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Content of related impurity- A, Impurity-F and Melamine is as follows:

Examples	Related compound A	Impurity-F content	Melamine content
1	0.01%	2 ppm	Not detected
2	0.01%	3 ppm	Not detected
3	0.01%	2 ppm	Not detected
Related compound- A is 2-cyanoguamdine Impurity - F is Dimethylaniine			

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CLAIMS:

1) An improved process for the preparation of Metformin or its pharmaceutically acceptable salts, comprising the steps of

i) treating dimethyl amine in the form of salt with 2-cyanoguanidine (DCDA) in presence of minimum amount of alcoholic solvent.

ii) isolation of Metformin by filtration without washing with alocoholic solvent and drying to get compound of formula-I as a pure product or

iii) Washing step (ii) with alcoholic solvent and drying to get compound of formula- 1 as a pure product.

2) The process according to claim 1, wherein pharmaceutically acceptable salts are organic or inorganic salts thereof.

3) The process according to claim 1, wherein alcoholic solvent selected from primary, secondary or tertiary alcohols, preferably primary alcohols, more preferably n-butanol.

4) The process according to claim 1, wherein the reaction temperature is selected from ambient to reflux temperature.

5) An improved process for the preparation of Metformin hydrochloride, comprising the steps of

i) treating dimethyl amine hydrochloride (DMA HC1) with 2-cyanoguanidine (DCDA) in presence of n-butanol

ii) isolation of Metformin hydrochloride by filtration without washing with alocoholic solvent and drying to get compound of formula-I as a pure product or

iii) washing wet compound from step (ii) with n-butanol and drying to get pure Metformin hydrochloride as a product.

6) The process according to claim 5, step (i) is carried out at ambient to reflux temperature and step (ii) or step (iii) is carried out at a temperature 10°C to 110°C.

7) The process according to claim 5, yield and purity of Metformin hydrochloride is not less than 92 % and not less than 99.5 % respectively.

8) The process according to claim 5, isolated Metformin hydrochloride contains dimethyl amine content less than 5ppm.

9) The process according to claim 5, the content of melamine and 2-cyanoguanidine (DCDA) is less than 0.02%, more preferably 0.01%.

10) The process according to claim 5, wherein process provides therapeutically effective amount of Metformin Hydrochloride substantially free from dimethyl amine and related impurities.

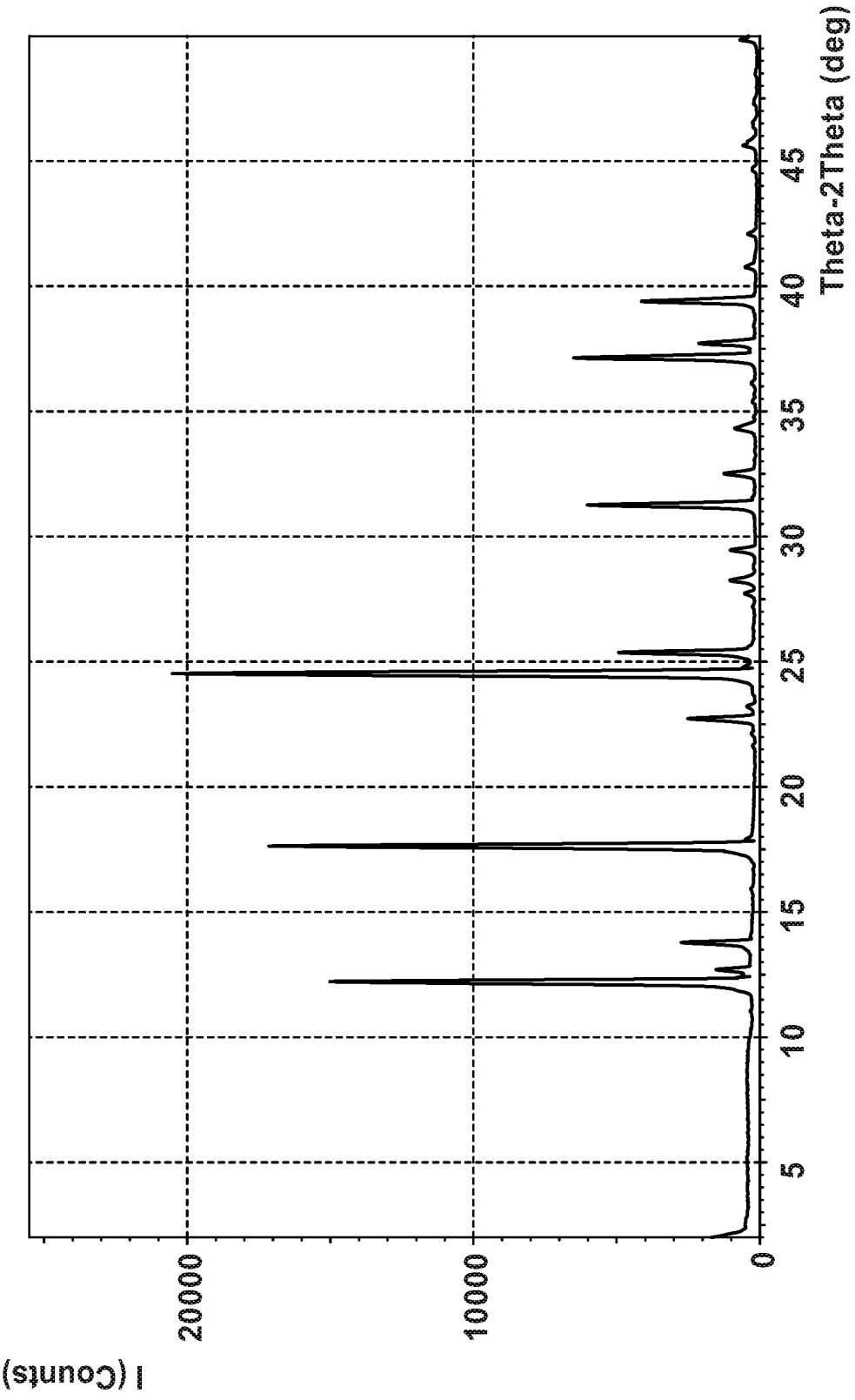

Figure: 1 depicts X-ray diffraction pattern of crystalline Metformin hydrochloride as per example-1.

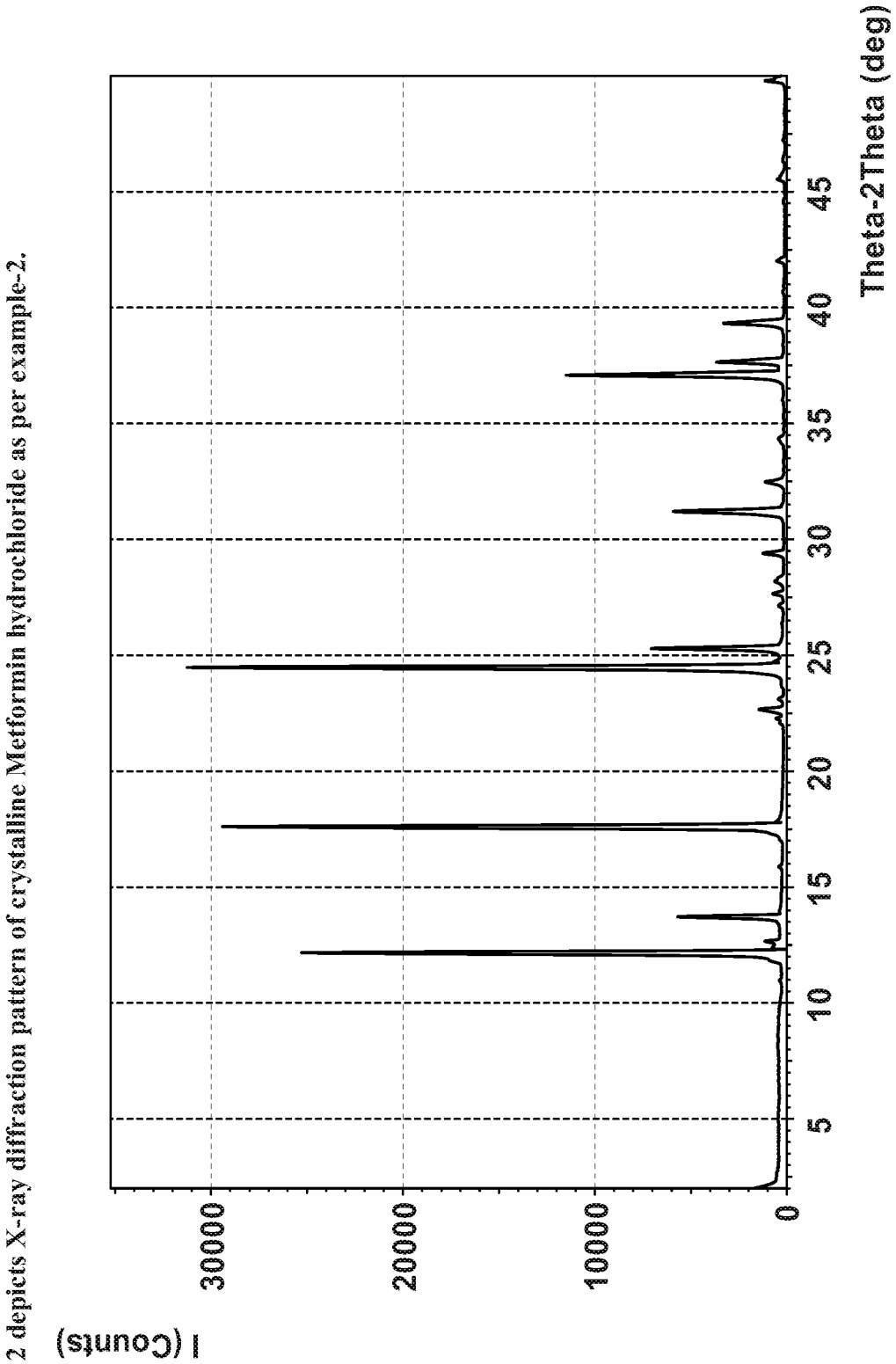

Figure: 2 depicts X-ray diffraction pattern of crystalline Metformin hydrochloride as per example-2.

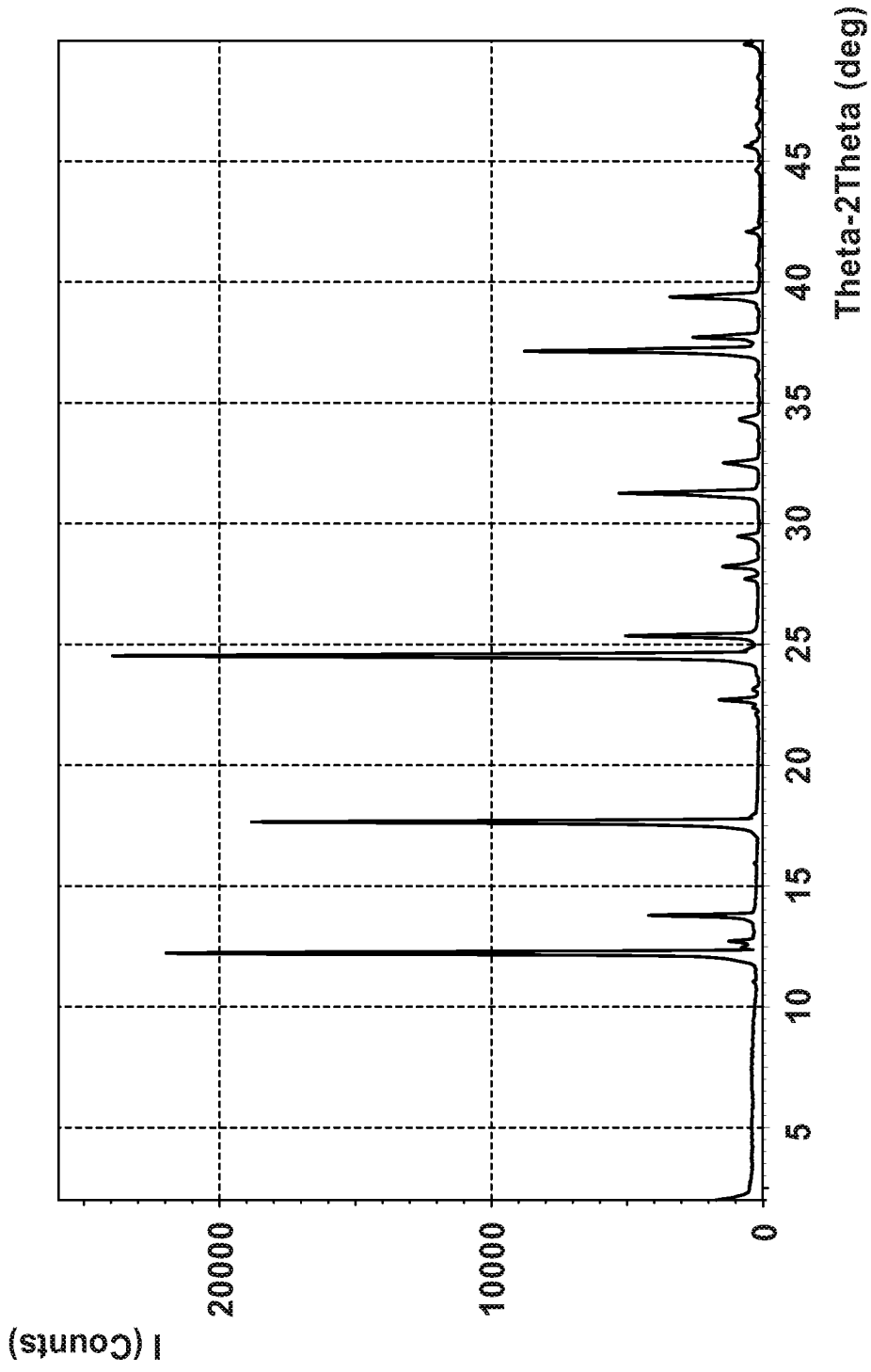

Figure: 3 depicts X-ray diffraction pattern of crystalline Metformin hydrochloride as per example-3.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/057575

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C279/26 C07C277/Q8
ADD.

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)
C07C

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 practicable, search terms used)
EPO-Internal , WPI Data, 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	FR 2 696 740 Al (DOSPHARMA SA [FR]) 15 Apri l 1994 (1994-04-15) abstract page 4, l ast paragraph page 8, l i ne 12 - page 9, l ine 20 cl aim 10 -----	1-10
X	FR 1 324 295 A (PROD DE CHIMI E 0RGANIQUE DE LA) 19 Apri l 1963 (1963-04-19) page 1, r i ght-hand col umn , paragraph 1 exampl e 1 cl aims 1-2 -----	1-10
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
26 November 2015	08/12/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dunet, Gui l l aume

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/057575

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NI KHI L SACHDEVA ET AL: 'Regi osel ecti ve synthesi s of pyrimi do[l,2-a] [l ,3,5] tri azin-6-ones via reacti on of 1- (6-oxo- 1,6-di hydropyri mi din -2-yl)guanidi nes wi t h tri ethyl orthoacetate: observation of an unexpected rearrangement" , ORGANIC & BIOMOLECULAR CHEMISTRY, vol . 10, no. 23, January 2012 (2012-01) , page 4586, XP55226481 , GB ISSN : 1477-0520, D0I : 10. 1039/c2ob25195g * scheme 1, method B" ; page 4587 * penul timate paragraph" ; page 4592 , r i ght-hand col umn	1-10
X	CN 1 844 093 A (ZHAI SHUJUN [CN]) 11 October 2006 (2006-10-11) ci ted i n the appl i cati on abstract exampl es 1-2 cl aims 1-8	1-10
X	CN 101 450 920 A (SHANDONG FANGXING SCI ENCE AND [CN]) 10 June 2009 (2009-06-10) abstract exampl es 1-3 cl aims 1-5	1-10
X	CN 101 450 919 A (SHANDONG FANGXING SCI ENCE AND [CN]) 10 June 2009 (2009-06-10) abstract exampl es 1-3 cl aims 1-5	1-10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/057575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2696740 A1	15-04-1994	NONE	
FR 1324295 A	19-04-1963	NONE	
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CN 101450920 A	10-06-2009	NONE	
CN 101450919 A	10-06-2009	NONE	