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PATENT STUDY FOR THE PROCESS OF SYNTHESIS OF GLICLAZIDE AND COMPOSITIONS WITH MODIFIED RELEASE CONTAINING THE SAME ACTIVE SUBSTANCE

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ABSTRACT

Background: Sulfonylurea drugs are widely used for treatment of diabetes mellitus type 2 and from this group Gliclazide is mainly prescribed. The study aimed to summarize the available in ESPACENET database information for applications and granted patents which concerned process of synthesis/preparation of the active substance as well as for compositions with modified-release containing it. **Methods:** Patent status study was conducted for the period from 2000 to January 2018. The EPO database and especially the ESPACENET database was used. Documents found were divided into two main groups, namely for process of synthesis of active substance and for compositions with modified-release which contain gliclazide. Each group was subdivided into granted patents and applications of patent by using the International Patent Documentation (INPADOC) information. **Results:** Seven documents were found for process of synthesis of active substance - 3 granted patents and 4 applications for patent. For compositions with modified-release containing gliclazide were found 30 documents in the database – 14 granted patents and 16 patent applications. Seven of the applications found were at phase of substantive examination and four-PCT applications have not entered in European phase. Mainly the protection claimed in above mentioned documents was for composition (30) and technological approach (25). There were also claims for application of drug product, dissolution profile, particle size of the active substance, related substances, and equipment. Patent families were found for 4 granted patents and 6

applications for patent. **Conclusion:** In conclusion the period was characterized with relatively low activity of issuing of patents and submission of applications for patents for the process of gliclazide synthesis and compositions with modified-release of the active substance.

KEYWORD: Gliclazide, process of synthesis, active substance, modified-release composition, patent application, granted patent.

INTRODUCTION

Diabetes mellitus is a metabolic disease, characterized with chronic hyperglycemia, disturbance of carbohydrate, fat and protein metabolism, which is due to defect in insulin secretion, insulin action or both of them.[1]

Four types of diabetes mellitus exist – type 1, type 2, gestational and other specific types of diabetes mellitus.[2]

Characteristics of the pathophysiology of diabetes mellitus type 2 are peripheral insulin resistance, impaired regulation of hepatic glucose production, worsening in the function of β-cells which could lead to lack of β-cells.[3] According to the conducted by Paolisso et al. study another risk marker for diabetes mellitus type 2 is the high levels of non-esterified fatty acids (NEFA).[4] Absence of early insulin secretion as a response to hyperglycemia is typical of type 2 diabetes.[5]

Frequency of type 2 appearance varies in different ethnical groups. People from Polynesian, Micronesian, South Asian, African, Arabian and American origin have greater predisposition in development of this disease than that from European origin.[6]

The risk of development of diabetes increases in obesity and overweight people[7] and those leading sedentary lifestyles. Increase in total activities and vigorous exercises (swimming, running, tennis) could prevent the appearance of type 2 diabetes mellitus – the number of cases decreases with increase in energy expenditure from less than 500 kcal to 3500 kcal.[8]

Sulfonylurea products are applied for treatment of diabetes mellitus type 2. They are divided into two generations – first (Tolbutamide, Chlorpropamide) and second (Glibenclamide, Glipizide, Gliclazide, Glimepiride). The most common adverse reaction of sulfonylurea therapy is hypoglycemia.[9]

Gliclazide is as efficient as Glibenclamide in regard to potency, but possesses lower frequency of secondary failure and hypoglycemia, which determines it as a drug of first choice for treatment.[10] Gliclazide decreases the level of plasma glucose in absence of food, the postprandial levels of blood glucose and the levels of glycosolated hemoglobin[11] Gliclazide protects beta-cells from apoptosis, which is probably due to the antioxidant properties of the molecule.[12]

The aim of the present study is to analyze and summarize the available in ESPACENET database information for applications and granted patents for the active substance gliclazide with respect to synthesis/preparation of it and compositions with modified-release that contain the same substance.

MATERIALS AND METHODS

Patent status study for active substance gliclazide was conducted using the EPO database and more precisely the ESPACENET database. The covered period was from 2000 to January 2018. The keyword used during the search was the INN of the active substance. The keyword was mentioned in 132 documents, part of which were excluded from the study because they concerned the preparation of intermediates during the gliclazide synthesis, combination drug products and compositions with immediate release of the active substance. The remaining documents were divided into two main groups – documents concerning the process of synthesis/preparation of the active substance and those related to compositions with modified release of gliclazide. By using the International Patent Documentation (INPADOC) information, which refers to the legal status, the documents found for each group were subdivided into applications for patent and granted patents.

RESULTS AND DISCUSSION

Patent status for process of synthesis/preparation of active substance – Gliclazide

For process of synthesis of active substance seven documents were found in ESPACENET database. By using INPADOC legal status database they were divided into two groups, namely granted patents (3) and patent applications (4).

Table 1: Granted patents for process of synthesis/preparation of active substance.

Number	Title	Date of granting the patent
CN102050778[13]	Method for synthesizing gliclazide and intermediate thereof	05.09.2012
CN102584677[14]	Method for preparing gliclazide	08.01.2014
CN102993080[15]	Synthetic method of gliclazide	16.12.2015

Table 2: Patent applications for process of synthesis/preparation of active substance.

Number	Title
US2007255056[16]	Method for manufacture of compounds related to the class of substituted sulfonylurea anti-diabetics
CN106588746[17]	Preparation method of gliclazide side chain and preparation method of gliclazide
CN106831536[18]	Preparation method of gliclazide in green synthesis technology
CN106892856[19]	Preparation method of gliclazide crude product recrystal

Two of the above mentioned applications were subject to substantive examination - CN106588746[17] (from 24.05.2017) and CN106831536[18] (from 07.07.2017).

According to the international patent classification all of them are classified in C07 – chemistry and metallurgy and more precisely organic chemistry. Patent application US 2007255056[16] and granted patent CN102050778[13] fell into classes C07C (acyclic or carbocyclic compounds) and C07D (heterocyclic compounds), while patent applications (CN106588746[17], CN106831536[18], CN106892856[19]) and granted patents (CN102584677[14] and CN102993080[15]) were classified only in class C07D.

Patent status of compositions, containing gliclazide, with modified-release

In ESPACENET database were found 30 documents. By using INPADOC legal status database they were divided into two groups, namely granted patents (14) and patent applications (16).

Seven of the applications found were at phase of substantive examination and 4-PCT applications were not in European phase.

Table 3: Granted patents of compositions with modified-release of the active substance - gliclazide

Number	Title	Date of granting the patent
EA003751 [20]	Solid thermoformable controlled-release pharmaceutical composition	28.08.2003
WO0018373 [21]	Core tablet for controlled release of gliclazide after oral administration	4.12.2003
RU2273482 [22]	Pharmaceutical composition with sustained-release of gliclazide	10.04.2006
CN1483401 [23]	Slow-released preparation	17.05.2006
UA81040 [24]	Prolonged release matrix tablet of Gliclazide and process for the preparation thereof	26.11.2007
CN101647785 [25]	Gliclazide sustained-release tablet and preparation	07.12.2011

	method thereof	
CN101721392[26]	Method for preparing gliclazide slow-release capsule and special equipment thereof	08.02.2012
CA2629670[27]	Scored dosage form allowing modified release of the active ingredient	17.04.2012
CN102058563[28]	Double-controlled release gliclazide sustained-release capsules and preparation method thereof	24.04.2013
CN102440972[29]	Gliclazide tablet and preparation method thereof	01.05.2013
CN103191077[30]	Gliclazide tablet and preparation method thereof	20.08.2014
EP3027177[31]	A modified-release oral pharmaceutical formulation containin gliclazide	12.07.2017
CN 104940940[32]	Montmorillonite compound slow-release preparation, gliclazide sustained release tablet and preparation method and application thereof	02.01.2018
CN105168183[33]	Gliclazide sustained-release capsule and preparation method and application thereof	26.01.2018

Table 4: Patent applications of compositions with modified-release of the active substance – gliclazide.

Number	Title
WO2006061697[34]	Sulfonylurea compositions and a process for its preparation
TR200708938[35]	Extended release Gliclazide tablet
IS8660[36]	Modified release dosage form of Sulfonylurea compound
ITFI20080016[37]	Oral pharmaceutical formulations containing Gliclazide
WO2014128116[38]	A production process for gliclazide formulations

Table 5: Patent applications of compositions with modified-release of the active substance subject to substantive examination.

Number	Title	Date on which the application became subject to a substantive examination
CN104784130[39]	Gliclazide tablet composition	19.08.2015
CN104784050[40]	Preparation method for gliclazide tablet composition	19.08.2015
CN105193758[41]	Gliclazide sustained release tablets and preparation method thereof	27.01.2016
CN105560200[42]	Insoluble medicine controlled-release tablets and preparation method thereof	08.06.2016
CN106074424[43]	Gliclazide sustained-release tablet and preparation method thereof	07.12.2016
CN106902089[44]	Gliclazide sustained-release tablet and preparation method thereof	25.07.2017
CN104546778[45]	Medical composition of Gliclazide sustained release preparation and preparation method of medical composition	14.11.2017

Table 6: PCT - applications of compositions with modified-release of the active substance

Number	Title	Date on which the application has not entered European phase
WO2006123213[46]	Modified release formulations of Gliclazide	09.07.2008
WO2008062470[47]	Stabilized controlled release dosage form of Gliclazide	18.11.2009
WO2013124832[48]	Stabilized controlled release pharmaceutical composition comprising gliclazide	18.03.2015
WO2016042568[49]	Extended release formulation of Gliclazide	11.10.2017

According to the international patent classification the applications and granted patents found were classified in class A61 – medical or veterinary science and hygiene. Basically they fell into class A61K – preparations for medical, dental or toilet purposes and class A61P – specific therapeutic activity of chemical compounds or medicinal preparations. An exception was PCT-application WO2013124832[48] which was classified not only in class A61K, but also in class B29C (shaping or joining of plastics, shaping of material in a plastic state and after-treatment of the shaped products) and class B29K which was connected to classes B29B, B29C, B29D and was related to moulding of materials.

Application CN104784050[40] and granted patent CN101721392[26] fell into classes A61 K and A61J. Class A61J concerned containers specially adapted for medical or pharmaceutical purposes, devices or methods specially adapted for bringing pharmaceutical products into particular physical or administering forms. Application CN106074424[43] was also an exception. It was classified in classes A61K, A61P and B01F. Class B01F was related to the apparatus in which the process of mixing (dissolving, emulsifying, dispersing) took place.

Table 7: The applications and granted patents found were divided according to the international patent classification as follows:

A61K and A61P	A61K	A61K, B29C and B29K	A61K, A61P and A61J	A61K and A61J	A61K, A61P and B01F
EA003751	CN101647785	WO2013124832	CN104784050	CN101721392	CN106074424
WO0018373	WO2006061697				
CN1483401	TR200708938				
UA81040	IS8660				
CA2629670	ITFI20080016				
CN102058563	CN105560200				
CN102440972	WO2006123213				
CN103191077	WO2008062470				
EP3027177	WO2016042568				
CN104940940					
CN105168183					
RU2273482					
WO2014128116					
CN104784130					
CN105193758					
CN106902089					
CN104546778					
17	**9**	**1**	**1**	**1**	**1**

According to the type of protection, claimed in the title, abstract or in the claims, the applications and granted patents were divided into seven groups. One application or granted patent was included in more than one type of protection due to the fact that simultaneous protection was claimed.

Table 8: Type of protection

Type of protection						
Composition	**Technological approach**	**Particle size of the active substance**	**Dissolution profile**	**Related substances**	**Applica-tion of drug product**	**Equip-ment**
EA003751	EA003751	WO2006061697	WO0018373	WO2014128116	WO 0018373	CN101721392
WO0018373	WO0018373	WO2014128116	CA2629670		CA 2629670	CN106074424
RU2273482	CN1483401	CN104784050	EP3027177			
CN1483401	UA81040	CN106902089	WO2006061697		CN 104940940	
UA81040	CN101647785	WO2006123213	TR200708938		CN 105168183	
CN101647785	CN101721392		WO2008062470		WO2014128116	
CN101721392	CA2629670					
CA2629670	CN102058563				WO2006123213	
CN102058563	CN102440972					

CN102440972	CN103191077					
CN103191077	EP3027177					
EP3027177	CN104940940					
CN104940940	CN105168183					
CN105168183	WO2006061697					
WO2006 061697	ITFI20080016					
TR200708938	WO2014128116					
IS8660	CN104784050					
ITFI20080016	CN105193758					
WO2014 128116	CN105560200					
CN104784130	CN106074424					
CN104784050	CN106902089					
CN105193758	CN104546778					
CN105560200	WO2006123213					
CN106074424	WO2008062470					
CN106902089	WO2013124832					
CN104546778	WO2016042568					
WO2006 123213						
WO2008 062470						
WO2013 124832						
WO2016 042568						
30	**26**	**5**	**6**	**1**	**6**	**2**

The largest number of applications and granted patents protected composition (30) and technological approach (26).

Patent families were found for 4 granted patents and 6 applications. They were as follows:

EA003751[20] - patent family with 23 members with priority date 28.06.1999;

WO0018373[21] – patent family with 36 members with priority date 01.02.1999;

CA2629670[27] - patent family with 39 members with priority date 21.03.2008;

EP3027177[31] - patent family with 7 members with priority date 01.08.2013;

WO2006061697[34] - patent family with 2 members with priority date 06.12.2004;

TR200708938[35] - patent family with 3 members with priority date 26.12.2007

IS8660[36] - patent family with 2 members with priority date 02.07.2007

ITFI20080016[37] - patent family with 3 members with priority date 05.02.2008;

WO2014128116[38] - patent family with 2 members with priority date 19.02.2013;

WO2013124832[48] - patent family with 4 members with priority date 24.02.2012

CONCLUSIONS

Submission of patent applications for the process of synthesis of gliclazide indicated increase during the last but one year covered by the study. Three out of four applications were submitted in 2017. Approximately the same trend was observed for the granted patents. Patents were issued during the period 2012-2015.

The tendency in granting patents for compositions with modified-release, containing gliclazide, could be characterized with relatively low activity because only one patent was issued per year as well as there were periods without a patent (2000-2002, 2004-2005, 2008-2010, 2015-2016). Two patents were granted only in 2003, 2006, 2012, 2013 and 2018.

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