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Combination Therapy Including Metformin hydrochloride for the Treatment of Diabetes and Related Comorbidity: A Patent Filed Survey

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Abstract

Diabetes is a group of metabolic dysfunctions/disorders and specifically type 2 diabetes (T2D) constitutes ~90-95% of all diabetic patients. For its treatment, Metformin hydrochloride is the most preferred anti-hyperglycemic oral agent. Due to the complexity of T2D, the use of Metformin hydrochloride alone (monotherapy) as the first-line drug has resulted to be inadequate and the addition of a second or multiple agents is necessary. Thus, in the last years there has been an enormous interest in the development of new therapeutic agents, leading to a large number of inventions (patents) regarding alternative therapies involving the use of Metformin hydrochloride in the presence of a second or more agents for the treatment and care of T2D.

Thus, this revision deals with the chronological appearance of patents filed related with combination therapy for the treatment of diabetes or any other related comorbidity with special emphasis in the utilization of Metformin hydrochloride or any related Metformin salt (used equally as first-line or as a second-line of choice), administered simultaneously, separately or sequentially with one or more agents (e.g. drugs, natural products, hormones, peptides, proteins, etc.). In addition, this work highlights some important issues related with combination therapeutic regimes, such as: proposed terminology, the importance of gaining knowledge about the potential mechanisms by which these treatments operate as well as adverse effects observed and so on.

Keywords: Diabetes; Combination therapy; Metformin hydrochloride; Patent; Monotherapy; Fixed dose tablets/pills; Metabolic syndrome

Abbreviations: ADA: American Diabetes Association; AMPK: AMP-Activated Protein Kinase; CVD: Cardiovascular Disease; DDIs: Drug Drug Interaction; DNA: Deoxyribonucleic Acid; FDA: Food and Drug Administration; GIP: Glucose Dependent Insulin tropic Peptide; GLP-1: Glucagon-Like Peptide-1; GMD: Gestational Diabetes Mellitus; HIV/AIDS: Human Immunodeficiency Virus Infection/Acquired Immune Deficiency Syndrome; IDDM: Insulin Dependent Diabetes Mellitus; mRNA: Messenger Ribonucleic Acid; NIDDM: Non-Insulin Dependent Diabetes Mellitus; NPH: Insulin Isophane; PhRMA: Pharmaceutical Research and Manufacturers of America; RNA: Ribonucleic Acid; SPIDDM: Slowly Progressive Insulin-Dependent Diabetes Mellitus; SU: Sulfonylurea; TZD: Thiazolidinediones; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes

Introduction

The worldwide impact in our society related with diabetes mellitus is an alarming issue. According with a recent study, the prevalence of diabetic patients around the world (aged 20-79 years) was estimated in 2010 as 285 million adults affected and this number is expected to increase to almost double in 2030 (439 million of diabetic persons) [1]. The predictions indicate there will be an increase of 69% of diabetic adults in developing countries (over-populated most of them) and 20% of incidence in developed countries [1]. Thus, the development of new, more effective, easily available and cheap pharmaceutical agents for the treatment of this illness becomes a priority.

Definition of Diabetes And Their Clinical Profiles

The American Diabetes Association (ADA), defines diabetes as a chronic condition that requires continuous pharmacologic and non-pharmacologic treatment [2]. Diabetes is a complex and chronic condition associated with a group of metabolic dysfunctions mainly due to hyperglycemia disorders associated with insulin secretion, insulin action or both. Long-term episodes

of hyperglycemia in diabetic patients derived in different cardiovascular damages and dysfunctions in multiple organs, e.g. eyes, kidneys, nerves, heart and blood vessels [2c].

According with the ADA "Standards of Medical Care in Diabetes-2012", diabetes has been classified in four groups: gestational diabetes mellitus (GDM), other types of diabetes due to other causes, type 1 diabetes (T1D) and type 2 diabetes (T2D) [2b]. Although, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus in 2003 formerly had considered ill nutrition-related diabetes as the fifth clinical profile in this classification[2a]. In 1980[2a], the World Health Organization (WHO) Expert Committee on Diabetes and later the WHO Study Group on Diabetes Mellitus, recognized diabetes in only two main groups and termed as: insulin dependent diabetes mellitus (IDDM, nowadays known as T1D) and non–insulin dependent diabetes mellitus (NIDDM, known today as T2D). Both terms have been eliminated to avoid confusions [2a].

Gestational Diabetes Mellitus (GMD)

Gestational diabetes mellitus (GMD) is a condition detected during pregnancy, and is characterized as glucose intolerance [3] having an incidence in the USA of 3-5% of cases per year (about the 135,000 pregnancies reported) [4,5]. During pregnancy, insulin resistance episodes can occur naturally often triggering diabetes, another common scenario occurs when the insulin secretory capacity is compromised due to impaired insulin action and secretion thus resulting in developing of T2D. In this regard, women with a GMD history are more likely to develop T2D at some point of their life [6] even when the glucose levels, after delivery, are restored to normal. Thus, the incidence to develop T2D in the future is still possible, but the risk to develop T1D is less likely [5].

Diabetes Due to Other Causes (e.g. Genetic Factors or Induced by Medication)

Although lifestyle and excess nutrient intake are considered the principal triggers for the development of T2D, genetic factors (heredity) can also play a fundamental role. Thus, families with a diabetes history exhibit a 2 to 4 fold increased probability to develop T2D during their lifetime. And, 15-25% of first-degree relatives of T2D patients are prone to develop impaired glucose tolerance or diabetes [7]. Thus, lifetime risk (at age 80 years) for T2D has been calculated to be 38% when one parent had T2D, and this probability increases to almost double when both parents had diabetes, estimating the prevalence of T2D in the offspring to approach to 60% by the age of 60 years [7].

The genetic etiology of T1D and T2D is very complex and no conclusive data have determined their origins, however predisposition and environmental factors are considered to be associated with these conditions [8]. For example, very low incidence of T1D is seen in several Asian countries [9], but Finland shows the highest rates (35 cases per 100,000) [10]. In contrast, only one third of incidence is observed in the Baltic population [11](e.g. Estonia) [12] despite the ethnical similarity with Finland´s population, this being indicative of environmental factors playing an important role [8]. However, T2D is more manifest in certain specific ethnicities and significant disparities are observed. For instance, among the diverse ethnic groups in American population the risk to develop T2D is less prone in non-Hispanic white adults compared with Asian Americans (9%), Hispanics (12.8 %) and non-Hispanic blacks (13.2 %) exhibit a higher incidence [13].

On the other hand, different chemical agents or medications, such as: pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, beta-adrenergic agonists, thiazides or Alfa- interferon can induce the development of diabetes [14]. Whilst conditions such as pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, fibro calculus and pancreatopathy, can also trigger diabetes [14].

T1D

Beta-cell destruction usually leads to absolute insulin deficiency. T1D is a condition associated by the endogenous insufficiency of insulin in the body, and this defect is due to autoimmune destruction of the beta-cells of the endocrine pancreas, as a consequence patients with T1D must receive insulin injections permanently [15].

Since the beta-cells destruction is quite rapid in infants and children, the prevalence of T1D in children and young compared with adults is greater [16]. Besides, after several years it tends to be a very common episode for patients diagnosed with T2D to be re-diagnosed with T1D due to gradual exhaustion of insulin secretion [17]. This process is known as slowly progressive insulin-dependent diabetes mellitus (SPIDDM), condition that is different from typical T2D patients that frequently are obese and insulin resistant [17]. T1D represents 5-10% of diabetic patients [2c].

T2D

T2D is a chronic condition that manifests by disorders of insulin action and/or insulin secretion [18]. This clinical profile accounts for ~90-95% of diabetic patients, and the patients are characterized to have insulin resistance and usually have relative (rather than absolute) insulin deficiency [2b]. Surprisingly, from the people who suffer T2D, at least half, have never been diagnosed, and thus this population have no knowledge of their condition [18]. As mentioned above, T2D is related with family history, age, ethnicity, previous history of gestational diabetes and physical inactivity. According with the WHO, evidence indicates that sedentary lifestyle (lack of physical activity, obesity or overweigh), tobacco and alcohol abuse, family diabetes history and unhealthy dietary regimen contribute to the development of T2D in young adults, children or adolescents [18,19]. Hence, T2D can be prevented encouraging people to make lifestyle changes on diet and promoting the practice of physical exercise. However these actions do not seem to be enough to attack the problem

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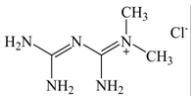
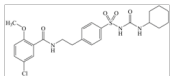
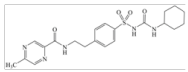
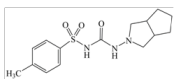
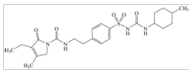
mainly due to people's apathy. Thus, T2D prevention is the key and may save money, for instance Mexico in 2006 spent about US $ 1,164.8 million dollars on the treatment of diabetic patients, situation that can become unsustainable given the accelerated rates of cases [20].

In addition, cardiovascular diseases (CVD), such as myocardial infarction or stroke are the major causes of death in patients with T2D [21]. Hence, a combination of a balanced diet, moderate physical activity and the use of an appropriate pharmacological and/or non-pharmacological agent reduce substantially the risk to develop this and other long-term conditions: retinopathy, nephropathy, CVD, etc [2a]. In addition, recent discoveries indicate that agents such as, hormones, drugs, natural products, etc. may activate physiologically or pharmacology AMP-activated protein kinase (AMPK) considered the therapeutic target for the treatment of T2D [22]. In this sense, the most common pharmacological agents used for the treatment of hyperglycemia in T2D are: biguanides, sulfonylurea's (SUs, 2nd generation), meglitinides, thiazolidinediones (TZDs), Alfa-glucosidase inhibitors, GLP-1 receptor agonists (incretin mimetics), DPP-4 inhibitors (incretin enhancers), bile acid sequestrants and dopamine-2 agonists [2b] (Table 1).

Table 1: Properties, effectiveness, mechanisms of glucose-lowering medications.

Class	Compound(s)	Mechanism	Action(s)	Advantages	Disadvantages	Cost
Biguanides [2b]	Metformin  hydrochloride	"Activates AMP-kinase"[2b]	"- Hepatic glucose production ↓ - Intestinal glucose absorption ↓ - Insulin action ↑"[2b]	"- No weight gain - No hypoglycemia - Reduction in cardiovascular events and mortality (UKPDS f/u)"[2b]	"- Gastrointestinal side effects (diarrhea, abdominal cramping) - Lactic acidosis (rare) - Vitamin B12 deficiency - Contraindications: reduced kidney function"[2b]	"Low"[2b]
Sulfonylureas SUs (2nd generation) [2b]	- Glibenclamide/ Glyburide  -Glipizide  - Gliclazide  -Glimepiride 	"Closes KATP channels on beta-cell plasma membranes" [2b]	"- Insulin secretion ↑" [2b]	"- Generally well tolerated - Reduction in cardiovascular events and mortality (UKPDS f/u)"[2b]	"- Generally well tolerated - Reduction in cardiovascular events and mortality (UKPDS f/u)"[2b]	"Low"[2b]

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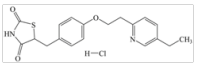
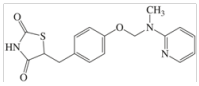
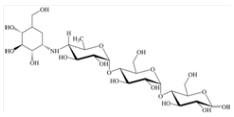
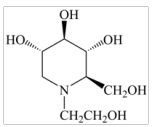
Thiazolidinediones (Glitazones) [2b]	-Pioglitazone hydrochloride  - Rosiglitazone 	"Activates the nuclear anscription factor PPAR-gamma"[2b] "As above" [2b]	"- Peripheral insulin sensitivity↑" [2b] As above [2b]	"- No hypoglycemia - HDL cholesterol ↑ - Triglycerides ↓" [2b] "- No hypoglycemia" [2b]	"- Weight gain - Edema - Heart failure - Bone fractures - LDL cholesterol↑" [2b] "- Weight gain - Edema - Heart failure - Bone fractures - Increased cardiovascular events (mixed evidence) - FDA warnings on cardiovascular safety - Contraindicated in patients with heart disease"[2b]	"High" [2b]
alfa-Glucosidase inhibitors [2b]	-Acarbose  - Miglitol 	"Inhibits intestinal alfa-glucosidase" [2b]	"Intestinal carbohydrate digestion (and, consecutively, absorption) slowed" [2b]	"- Nonsystemic medication - Postprandial glucose ↓" [2b]	"- Gastrointestinal side effects (gas, flatulence, diarrhea) - Dosing frequency" [2b]	"Medium" [2b]

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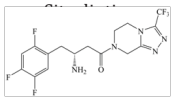
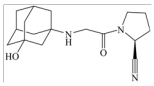
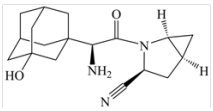
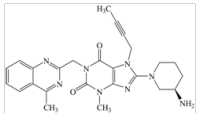
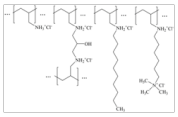
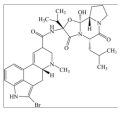
GLP-1 receptor agonists (incretin mimetics) [2b]	-Exenatide H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 - Liraglutide	"Activates GLP-1 receptors (beta-cells/ endocrine pancreas; brain/autonomous nervous system)" [2b]	"- Insulin secretion ↑ (glucose-dependent) - Glucagon secretion ↓ (glucose-dependent) - Slows gastric emptying - Satiety ↑" [2b]	"- Weight reduction - Potential for improved beta-cell mass/function" [2b]	"- Gastrointestinal side effects (nausea, vomiting, diarrhea) - Cases of acute pancreatitis observed - C-cell hyperplasia/ medullary thyroid tumors in animals (liraglutide) - Injectable - Long-term safety unknown" [2b]	"High" [2b]
DPP-4 inhibitors (incretin enhancers) [2b]	 - Vildagliptin  - Saxagliptin  -Linagliptin 	"Inhibits DPP-4 activity, prolongs survival of endogenously released incretin hormones" [2b]	"- Active GLP-1 concentration ↑ - Active GIP concentration ↑ - Insulin secretion ↑ - Glucagon secretion ↓" [2b]	"- No hypoglycemia - Weight (neutrality)" [2b]	"- Occasional reports of urticaria/ angioedema - Cases of pancreatitis observed - Long-term safety unknown" [2b]	"High" [2b]
Bile acid sequestrants [2b]	- Colesevelam® 	"Binds bile acids/ cholesterol" [2b]	"Unknown" [2b]	"- No hypoglycemia - LDL cholesterol ↓" [2b]	"- Constipation - Triglycerides ↑ - May interfere with absorption of other medications" [2b]	"High" [2b]
Dopamine-2 agonists [2b]	- Bromocriptine 	"Activates dopaminergic receptors" [2b]	"- Alters hypothalamic regulation of metabolism - Insulin sensitivity ↑" [2b]	"- No hypoglycemia" [2b]	"-Dizziness/ syncope - Nausea - Fatigue - Rhinitis - Long-term safety unknown" [2b]	"Medium" [2b]

Adapted from: [2b] Position Statement. Standards of Medical Care in Diabetes-2012. Diabetes Care 2012; 35(1): S11-S63.

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There is a wide dossier of drugs or chemical agents, depending on the clinical profile of the patient, for the treatment and management of T2D. However, most of these medications have some disadvantages, e.g: elevated cost, limited pharmacological action, after prolonged use some patients develop progressive detrimental pharmacological effectiveness until obsolescence (e.g. SUs) [23] and the appearance of other long-term risk factors (e.g. reduced kidney function, CVD). Due to the nature and complexity of T2D, at this moment there is no efficient pharmacotherapy for the control of hyperglycemia and the efficiency of new drugs is continuously evaluated. As a matter of fact, before 1995 management of diabetes was limited to the use of SUs, isophane (also known as NPH), insulin and regular insulin's were the most prescribed anti-diabetic agents [24]. Since then, in the last 15 years lots of pharmacotherapy options have appeared in an attempt to improve the effectiveness and safety for the management of diabetes [24]. The patients diagnosed with diabetes, only 14% are co-administrated simultaneously with insulin and other medication and 58% only consume oral medications [25].

Thus, the problem is, that due to the complexity in the treatment of T2D, monotherapy does not seem to be the most appropriate strategy in the glycemic control, since the use of a single pharmaceutical agent is likely to target only a single defect, causing in a long-term lapse, the appearance of other inconveniences (vide supra). Hence, today Metformin hydrochloride represents the first choice drug for glycemic control, since: it is cheap compared to other related drugs, their toxicological profile is more innocuous (during monotherapeutic administration less adverse effects where observed) and Metformin hydrochloride is better adapted to the lifestyle even in overweighed patients [25].

Sadly, it is likely that Metformin hydrochloride-glycemic controlled T2D patients, will eventually require the administration of a second drug, being this the main problem in the treatment of T2D and motif for the present review, that comprehensively accounts and describes the chronological appearance of the so far known, inventions/patents filed involving the use of Metformin hydrochloride or any Metformin analogue in the presence of a second or more agents for the efficient treatment of T2D patients. This paper also reviews, important aspects related with combination therapeutic regimes, such as: proposed terminology, clinical in vitro and in vivo studies in an attempt to elucidate the potential mechanisms related with drug-drug interactions (DDIs), etc., to hopefully reach, in time, not a proper and efficient treatment but a real cure for this pandemic illness.

Combination Therapeutics Regime

Due to the complexity of many diseases such as diabetes, cancer, HIV/AIDS, etc., administration of a single drug regimen (monotherapy) to target a single defect, is no longer the most appropriate treatment, due to the fact that prolonged exposure results in the development of other complications [26,27]. Alternatively to monotherapy, administration of multiple agents is therapeutic option, based on the premise that combination of the agents can be more effective than the sum of the effectiveness of the individual agents [27].

Combination drug therapeutics (also known as multi-component therapeutics) might lead to new medication strategies showing mutually interdependent activities required to improve clinical efficacy and understanding the side effects and toxicity involved during the treatment [28]. In fact, the action of a single drug activates/modulates multiple proteins rather than single targets and this may limit its therapeutic effect [28,29]. The combination of multiple drugs may target, multiple subpopulations, or multiple diseases simultaneously, since every drug can work through different mechanisms or modes of action improving efficacy of the therapeutic effect, lowering the dose administration but increasing or maintaining the same efficacy, minimizing or slowing down the development of drug resistance, and giving different types of synergism (additive or antagonist effect; potentiate or reduce effect) [30].

For instance, when patients with severe hyperglycemia are prescribed with one pharmacological agent and glycemic levels are not controlled, is mandatory the administration of another agent to control the hyperglycemia [31]. Some years ago combination drug regimens were prescribed as separated tablets, but today fixed-dose single tablet combinations are available, based on the bio-equivalence of the separate tablets and giving similar efficacy, reducing the pill burden and simplifying the administration regimen of the patient [31]. Fixed-dose single tablets/pills is also a current tendency embraced by the Pharmaceutical companies since may have some important implications in the drug commercialization (cost/effectiveness), lowering the price in the treatment of some diseases by using combination drug therapies rather than single drug treatment and helping the duration of the treatment to be shortened [32].

In 2013 the Food and Drug Administration (FDA) established some recommendations for the combination of two or more drugs as therapeutic regime [33].

i. "The combination is intended to treat a serious disease or condition".

ii. "There is a strong biological rationale for the use of the combination (e.g., the agents inhibit distinct targets in the same molecular pathway or steps in disease pathogenesis, provide inhibition of both a primary and compensatory pathway, or inhibit the same target at different binding sites to decrease resistance or allow use of lower doses to minimize toxicity)".

iii. "A full non-clinical characterization of the activity of both the combination and the individual new investigational drugs, or a short-term clinical study on an established

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biomarker, suggests that the combination may provide a significant therapeutic advance over available therapy and is superior to the individual agents. A non-clinical model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response (e.g., delayed resistance), or a better toxicity profile than the individual agents".

iv. "There is a compelling reason why the new investigational drugs cannot be developed independently (e.g., monotherapy for the disease of interest leads to resistance, one or both of the agents would be expected to have very limited activity when used as monotherapy)".

In this regard, some pharmaceutical companies, such as Glaxo-Smith-Kline (Advair for the treatment of asthma and Combivir for HIV) and Kos Pharmaceuticals (Advicor for hypercholesterolemia) have combined the above-mentioned drugs with other pharmaceutical agents on the basis of clinical rationale (comprising two or more drugs), showing therapeutic success [28].

Proposed Terminology and Types of Combination Drug Therapeutics

The syncretism given by the combination of two drugs may arise a fundamental question: what is the expected effect of the combination? In the spirit to give an answer for the meaning and relevance of this, we must reformulated the question as: these combinations are syncretic or congruous? [28,30]. In this case an appropriate terminology is proposed by Stockwell et al. [28] to differentiate the kind of combination.

Syncretic combination drug

"It is used to denote a drug that is composed of two or more active ingredients, at least one of which is not used individually to treat the target disease indication".

Congruous combination drug

"A drug that is composed of two or more active ingredients, each of which has been individually used to treat the target disease indication".

Multicomponent therapeutic

"An optimized combination and formulation of multiple active ingredients. This category includes both syncretic and congruous drugs". Based on this, in attempt to categorize what type of cooperation is observed in these combinations, depending the synergism presented can be classified as is indicated by several authors as: Chou, Tallarida, Jia, etcetera [30,34,35].

Additive or antagonist effect

"Is when the combination is pharmacodynamically additive or antagonist if the effect is greater than, equal to, or less than the summed effects of the partner drugs."

Potentiative or reductive effect

"Is when the therapeutic effect of one drug is augmented or reduced and this can be modulated or regulated by the action of another drug."

Coalistic combination

"This is when the activity of all the drugs involved is inactive separately but is active in combination."

In this sense, extensive and rigorous analyses must be done to decipher the mechanisms circumscribed behind the combination, contrasting the type of cooperation involved (additive, antagonistic and reductive synergism). And, to determine what type of cooperation is observed, experimental data can reveal valuable information. Many of these analyses are: "checkerboard, combination index, fractional effect analysis, isobolographic analysis, interaction index, median drug effect analysis, and response surface approaches" [35].

Knowledge-Gained In the Mechanisms (Signaling Pathways) of Combinations Drugs

The manifestation and origins of different diseases are determined by different potential factors: environmental factors, tissue type, hormone levels, aging, etc. Thus, in order to gain knowledge in the dynamics and on how different constituents within the cell are integrated and interconnected (e.g. proteins, DNA, RNA and small molecules) in a complex signaling network, it is important to correlate diverse interactions (metabolic, regulatory, spatial, etc) [36]. Thus, a great number of studies including: genomics, proteomics and phosphoproteomics have been carried out in order to discover gene expressions signatures and protein signaling pathways associated with a particular disease [37].

Chemicals agents, hormones, protein receptors, ligands, enzymes, transcription factors, ions or DNA/RNA are responsible to modulate biochemical reactions, electrical signals, mRNA transcription and protein translation in a complex machinery of signaling network [37]. Gaining knowledge at the molecular level of how this complicated network of signals is functioning and/or how is perturbed, is fundamental for the development of drugs. In this regard, systematic studies have been done using a rationale combination of drugs exploring the connectivity of biological pathways, entailing how these small molecules activate or perturb cellular signaling networks in a desired fashion [28-29,35-36,38-43].

Most of the molecular targets of specific drugs have been elucidated or identified serendipitously after studying the mechanisms of action by naive mechanistic assumptions [39]. In fact, many of the US FDA-approved drugs for the treatment of specific diseases are used by clinicians without a previous knowledge of the molecular mechanisms of action [44].

The way of how a drug interacts with a specific target

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interfering or perturbing the cellular signaling networks is a complicated job, because most of the drugs interact with more than one target and in most cases this assumption is not linearly deducible from single effects [42]. Therefore, one of the largest problems to solve is: once is identified and validated a disease-specific target or once is identified a drug like molecule that can modify this target, how this could be correlated in a way that makes therapeutic sense? This represents a major challenge to confront [45].

The complexity is greater trying to determine the perturbation in the signaling network when combination drug therapy is used, due to the fact that mechanisms of drug-drug interactions (DDIs) must be considered, since therapeutic response and effectiveness of combination pharmacotherapy depends of the pharmacodynamics interaction between the drugs involved, and in addition to that, the potential synergism concerted is strongly influenced with the dose and concentration of the pharmaceutical agents involved, and most of the time these assertions are based on trial and error [46,47].

Adverse Effects Observed In Some Combination Drug Therapies

Adverse episodes related with DDIs are considered the major cause of morbidity worldwide and several medicaments have been withdrawn of the market after fatal events were reported after their administration for a period of time [47], for instance the case of cerivastatin-gemfibrozil syncretism can be mentioned [48]. These adverse events may occur when the drugs shared metabolic and pharmacological pathways provoking diminution in effectiveness and safety profile [46].

Currently, before a drug can be entered in the marketplace extensive in vitro and in vivo pharmacokinetic DDIs studies must be carried out, emphasizing that combination drug toxicity is null or minimal [47]. An excellent compendium prepared by the Pharmaceutical Research and Manufacturers of America (PhRMA) can be taken as guidance where the best practice for the design of in vitro and in vivo DDIs studies is outlined [49]. Nowadays some of the endeavors currently used for the establishment of DDIs are based on in Silico Approaches (e.g. molecular fingerprints), which have produced uplifting and expeditious results [47,50].

Combination of Metformin Hydrochloride With Other Agents For the Treatment of Diabetes

Diabetes is a conjunction of systemic diseases and specifically T2D constitutes ~90-95% of diabetic patients [18] and its treatment usually requires the utilization of multiple oral agents (mainly drugs) since monotherapy for maintaining glycemic control may be overcame in some patients affording this approach inadequate. Thus, when monotherapy is no longer efficient, to improve the glycemic control in the patient can be achieved administrating the combination of diverse drugs with different mechanisms of action, [51] despite of some reports stating that long-termed combination therapy co-administrating oral pharmaceutical agents may result obsolete and the co-administration of incretin hormones (e.g. glucagon-like peptide-1 GLP1, glucose dependent insulin tropic peptide GIP, etc) stimulate insulin synthesis and secretion in a glucose-dependent manner and do not produce hyperglycemia [52].

Metformin hydrochloride has been established as the drug of choice for the first-line treatment of T2D [53]. Metformin hydrochloride is considered as one of the safest oral hypoglycemic agents [53], characterized by insulin resistance in overweighed patients and is the only anti-diabetic drug that have conclusively shown prevention in CVD and provide beneficial effects on dyslipidemia and hypofibrinolysis [25]. Besides, its low cost compared with other pharmaceutical agents makes it even more attractive. In specific, it has been pointed out that Metformin hydrochloride is a very efficacious medication used in monotherapy compared with another medications [25].

In practice, Metformin hydrochloride can be combined with any other medication (unless contraindications exist) [31], for instance combination of Metformin hydrochloride with some pharmacological agents may trigger hypoglycemia (e.g. TDZs and SUs) [25], although is pointed out that combination with SUs is associated with 6 times more risk for hypoglycemia than with TDZs [25]. Nevertheless, in the case of the fixed-dose single tablet of Metformin hydrochloride/glyburide shows similar bioequivalence compared with combined therapy of the components, and this tablet allows to have a better glycemic control with lower dosage [54]. On the other hand, Metformin hydrochloride and any other TZDs, can be combined on the treatment of T2D due to their different cellular mechanisms, showing additive syncretism and improving anti-hyperglycemic efficacy [31]. Also, Metformin hydrochloride may be combined with an insulin secretagogue, for instance a dipeptidylpeptidase-4 (DPP-4) inhibitor or an injectable GLP-1 agonist, and this syncretism exhibit reducing insulin resistance [31]. In addition, when Metformin hydrochloride monotherapy fails, the use of SUs, TZDs, insulin, alfa-glucosidase agents must be considered as adjuvants in combination therapy [25,31,55]. Nevertheless, their choice as hypoglycemic adjuvants is dependent on the profile of the patient [25, 31,55].

Moreover, recently it has been published that canagliflozin-metformin (Invokament®) approved by the FDA in 2014 as fixed-dose combination is a promising option for the treatment of T2D [56]. The first fixed-dose combination approved for the treatment of diabetes by the FDA was Glucovance® in 2000 combining glyburide and Metformin [57]. The combination of canagliflozin-metformin at this moment seems to be safe and effective as an option when Metformin hydrochloride monotherapy is no longer effective [56]. However this combination must be cautioned in patients with history in genital mycotic infections, hypotension and poor renal function [56].

In this review a survey was made to circumscribe inventions

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(patents) which claim the development of diverse formulations/compositions where the presence of Metformin hydrochloride or any Metformin salt is included combined or co-administrated with other agents (e.g. drug/nutraceutical or molecule with anti-diabetic activity, hormone, natural product, peptide, protein, etc.), for the treatment, prevention or amelioration of TD2 and in some cases T1D and/or any related complication considered within the metabolic syndrome, for instance: lipid disorders, hypertriglyceridemia, hyperinsulinemia and insulin resistance or any other related CVD, or any comorbidity associated.

Methods

The survey was made using Scifinder® (in addition with Espacenet® and Google Patent Search® for the reviewing of the original documents) under the restriction search ("Metformin Diabetes") retrieving only patents. The survey was made for the period of November 29th, 2015 to January 25th, 2016. From the total number of hits found and after a careful and thorough revision, only patents that covered combination therapy using Metformin hydrochloride or any related Metformin salt in the presence of one or more agents in a single composition or separately being administrated by different routes were considered. These combinations include simultaneously, separately or sequentially administration of Metformin hydrochloride or any other Metformin salt in addition to any other agent.

Inventions that include the administration of Metformin hydrochloride or any other Metformin analogues and one or more agents in a fixed-dose as a single pill/tablet were also selected. The inventions related with combination therapy including Metformin hydrochloride or any other Metformin analogues and one or more agents for the exclusively treatment of obesity were excluded. The inventions related with formulations/compositions where Metformin or any related Metformin salt that is not used as the main therapeutic agent or is optionally suggested as an adjuvant are also included. Patents where is suggested the utilization of Metformin hydrochloride or any Metformin salt as a conjugate with another agent also were included. Patents where the original language was other than English were excluded; unless the translated document was found in English language. Table 2 shows these results.

Chronological Apperarence of Patents Filed

Table 2: Chronological survey of patents claiming the development of combined therapy using metformin hydrochloride or any related metformin salt.

Patent/Country or Location	Inventors	Title	Year of invention
JP 47032644 B4/Japan	Kitano, Shichi; Naka, Kenji	Hypoglycemic tolbutamide-metformin salt	1972
WO 9203148 A1/International Patent	Cooper, Garth J. S.; Moore, Candace Xavierie	Method and compounds for treating type 2 diabetes mellitus	1992
WO 9717975 A1/International Patent	Barelli, Giulio; De, Regis Massimo	A glibenclamide-metformin combination for the treatment of diabetes mellitus type II.	1997
WO 9811435 A1/International Patent	Rademacher, Thomas William; McLean, Patricia	Materials and methods using P- and A-type inositolphosphoglycans and their antagonists for the diagnosis and treatment of diabetes and associated obesity	1998
WO 9815266 A1/International Patent	Khandwala, Atul S.; Luo, Jian	Use of bisphenolic compounds to treat type II diabetes	1998
US 5830434 A/United States	Taylor, Ian L.; Gettys, Thomas	Methods of treating non-insulin dependent diabetes mellitus with pancreatic polypeptide	1998
WO 9857634 A1/International Patent	Smith, Stephen Alistair	Treatment of diabetes with thiazolidinedione and metformin	1998
WO 9903477 A1/International Patent	Buckingham, Robin Edwin; Smith, Stephen Alistair	Treatment of diabetes with a thiazolidinedione, an insulin secretagogue, and a biguanide	1999
WO 9929314 A1/International Patent	Timmins, Peter; Winter, William J.; Srivastava, Sushil K.; Bretnall, Alison; Wei, Chenkou; Powers, Gerald L.	Novel salts of metformin and method	1999
WO 9936396 A1/International Patent	Ruggiero, Daniel; Wiernsperger, Nicolas; Patereau, Gerard; Moinet, Gerard	Preparation of triazepinones for treatment of diabetes and diabetic complications	1999

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WO 9940904 A2/International Patent	Bonhomme, Yves; Briet, Philippe	Pharmaceutical composition comprising a combination of metformin and fibrate, and its use for the preparation of medicines intended to reduce hyperglycemia	1999
WO 9943708 A1/International Patent	Knudsen, Liselotte Bjerre; Huusfeldt, Per Olaf; Nielsen, Per Franklin; Madsen, Kjeld	GLP-1 derivatives of GLP-1 and exendin with a protracted profile of action	1999
US 6011049 A/United States	Whitcomb, Randall Wayne	Combinations of glitazones, biguanides, and optional sulfonylureas for treatment of diabetes	2000
WO 2000027434 A1/International Patent	Arch, Jonathan Robert Sanders	Combinations comprising a β-agonist and a further antidiabetic agent for the treatment of diabetes mellitus and conditions assocd. with diabetes	2000
WO 0040233A1/International Patent	Struengmann, Thomas	New pharmaceutical composition for treatment of type II diabetes mellitus	2000
DE 19860699 A1/Germany	Struengmann, Thomas; Spaeth, Wolfgang	Pharmaceutical composition for treatment of diabetes mellitus	2000
WO 2000045818 A1/International Patent	Cameron, Norman Eugene; Cotter, Mary Anne	Use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for the manufacture of a medicament for the treatment of diabetic neuropathy	2000
WO 2000053171 A1 / International Patent	Mannucci, Edoardo; Rotella, Carlo Maria; Ognibene, Agostino	Use of metformin in the preparation of pharmaceutical compositions capable of inhibiting the enzyme dipeptidyl peptidase IV	2000
WO 2000059506 A1 / International Patent	Robl, Jeffrey A.; Sulsky, Richard B.; Magnin, David R.	Heterocyclylbiphenyl aP2 inhibitors	2000
WO 2001021159 A2/International Patent	Gatlin, Marjorie Regan; Pongowski, Michele; Mannion, Richard Owen; Karnachi, Anees Abdulquadar; Guitard, Christiane; Allison, Malcolm	Pharmaceuticals containing nateglinide or repaglinide for treating diabetes or conditions assocd. with diabetes	2001
WO 2001032157 A2/International Patent	Piper, Beth Anne	Method using metformin-glyburide combination for treating diabetes	2001
WO 2001032158 A2 / International Patent	Piper, Beth Anne	Antidiabetic formulation containing metformin and sulfonylurea	2001
WO 2001035941 A2/International Patent	Lilliott, Nicola Jayne; MacKenzie, Donald Colin	Antidiabetics containing thiazolidinedione derivatives and metformin	2001
WO 2001060807 A1/International Patent	Liu, Kun; Xu, Libo; Jones, A. Brian	Preparation of 1,2-benzoxazolyloxyacetic acids and analogs as PPAR agonists for treatment of diabetes and lipid disorders	2001
WO 2001068603 A2/International Patent	Robl, Jeffrey A.; Sulsky, Richard B.; Augeri, David J.; Magnin, David R.; Hamann, Lawrence G.; Betebenner, David A.	Preparation of fused cyclopropylpyrrolidine-based inhibitors of dipeptidyl peptidase IV	2001
WO 2001082916 A2/International Patent	Jaen, Juan C.; Chen, Jin-Long	Combination therapeutic compositions and methods of use	2001
WO 2001097808 A1/International Patent	Arch, Jonathan Robert Sanders; Lenhard, James Martin	Combinations of depeptidyl peptidase IV inhibitors and other antidiabetic agents for the treatment of diabetes mellitus	2001
WO 2002011721 A1/International Patent	Moinet, Gerard; Botton, Gerard; Mesangeau, Didier	Pharmaceutical composition comprising metformin and a 5-phenoxyalkyl-2,4-thiazolidinedione-type derivative	2002
WO 2002012177 A1 / International Patent	Pomytkin, Igor Anatolievich; Kolesova, Olga Evgenievna; Ukhanova, Tatyana Jurievna; Verteletsky, Pavel Vasilievich; Nenajdenko, Valentin Georgievich	Composition of metformin with succinic acid or salts thereof and method for treating diabetes	2002

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WO 2002030914 A1/International Patent	Reddy, Gaddam Om; Chandrasekhar, Batchu; Sarma, Mamillapalli Ramabhadra; Prasad, Addanki Siva Rama	Salts of benzothiazine and benzoxazine derivatives and pharmaceutical compositions containing them	2002
WO 2002040448 A1/International Patent	Sulsky, Richard; Robl, Jeffrey A.	Preparation of pyridone derivatives as aP2 inhibitors for treatment of Type II diabetes	2002
WO 2002064210 A2/International Patent	Connor, Gregory S.	Combination therapy for type II diabetes and syndrome X using antidiabetic and anticonvulsant agents	2002
WO 2002065120 A1/International Patent	Carter, W. Hans, Jr.; Gennings, Chris; Chinchilli, Vernon M.; Shih, Margaret	Multi-drug titration and evaluation	2002
US 6440931 B1/United States	Remmereit, Jan; Wadstein, Jan; Klaveness, Jo	Conjugated linoleic acid in treatment and prophylaxis of diabetes	2002
WO 2002083066 A2/International Patent	Gougoutas, Jack Z.	Amino acid complexes of C-aryl glucosides for treatment of diabetes	2002
WO 2002094285 A1/International Patent	Castan, Catherine; Soula, Gerard; Meyrueix, Remi	Single-daily-dose antidiabetic oral pharmaceutical form comprising a biguanide and at least another active principle	2002
US 20020183345 A1/United States	Piper, Beth Anne	Method for treating type 2 diabetes with low-dose combination of metformin and glyburide	2002
WO 2002098409 A1 / International Patent	Gwynne, John Tomas; Vitou, Philippe John Robert; Randazzo, Bruce Paul	Combination therapy for type II diabetes or Syndrome X	2002
EP 1275384 A1 /Europe	Mannucci, Edoardo; Angeli, Roberto; Bonifacio, Marco	Pharmaceutical compositions for oral use, containing, in combination, metformin and glyclazide	2003
WO 2003005991 A1 / International Patent	Adjei, Akwete L.; Zhu, Yaping; Cutie, Anthony J.	A core formulation comprising pioglitazone hydrochloride and a biguanide	2003
WO 2003006023 A1/ International Patent	Sulsky, Richard; Robl, Jeffrey A.	Preparation of pyrazinone inhibitors of fatty acid binding protein for treatment of diabetes and related diseases	2003
WO 2003026637 A2/ Intenational Patent	Tyebji, Ziauddin Z.; Reddy, Harivardhan L.	Dosage form containing a biguanide for treatment of diabetes mellitus	2003
WO 2003026653 A1/ International Patent	Biro, Katalin; Kuerthy, Maria; Jednakovits, Andrea; Mogyorosi, Tamas; Matyas, Istvan; Ueroegdi, Laszlo; Jegesne, Csakai Zita; Racz, Timea	Pharmaceutical composition comprising metformin and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride	2003
US 20030077335 A1/United States Patent	Richardson, Kenneth T.; Pearson, Don C.	Formulations for the prevention and treatment of insulin resistance and type 2 diabetes mellitus	2003
US 20030078269 A1/United States	Pearson, Don C.; Richardson, Kenneth T.	Biguanide and sulfonylurea formulations for the prevention and treatment of insulin resistance and type 2 diabetes mellitus	2003
FR 2832633 A1/ France	Moinet, Gerard; Marais, Dominique	Pharmaceutical composition containing metformin and a 4-oxobutanoic acid for the treatment of diabetes	2003
WO 2003045355 A1/International Patent	Tosetti, Alessandro; Guiducci, Mauro; Viti, Giovanni	Pharmaceutical compositions comprising metformin and glibenclamide for the treatment of type-II diabetes mellitus	2003
WO 2003051293 A2/ International Patent	Li, Danping; Phusanti, Lawan; Desai, Divyakant S.	Antidiabetic formulation containing metformin and glipizide	2003
WO 2003077949 A2/International Patent	Vasavada, Haren	Methods of treating diabetes using PDE11a inhibitors	2003
WO 2003099277 A1 / International Patent	Aruoma, Okezie I.	Method of reducing incidence diabetic embryopathy with L-ergothioneine	2003

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WO 2004018455 A1/ International Patent	Desai, Manoj; Ni, Zhi-Jie; Ng, Simon; Pfister, Keith B.; Ramurthy, Savithri; Subramanian, Sharadha; Wagman, Allan S.	Pyrrole based inhibitors of glycogen synthase kinase 3	2004
GB 2399015 A/ United Kingdom	Gidwani, Suresh Kumar; Singnurkar, Purushottam Sharshikant	Process for the preparation of oral dosage forms comprising metformin and glyburide	2004
WO 2004091612 A1/ International Patent	Egri, Janos	A synergistic pharmaceutical combination comprising cicletanine for the prevention or treatment of diabetes	2004
US 20040214811 A1/United States	Davis, Harry R.; Kosoglou, Teddy; Picard, Gilles J.; Ress, Rudyard J.; Strony, John T.; Veltri, Enrico P.	Methods and therapeutic combinations for the treatment of diabetes using sterol absorption inhibitors	2004
EP 1510208 A1/ Europe	Junien, Jean-Louis; Edgar, Alan	Pharmaceutical composition comprising a combination of metformin and statin	2005
WO 2005021039 A1/International Patent	Fong, Benson M.; Cornett, Glenn V.	Combination of cicletanine and an oral antidiabetic and/or blood lipid-lowering agent for treating diabetes and metabolic syndrome	2005
US 20050054731 A1/ United States	Folli, Franco; Manfredi, Paolo; Gonzales, Gilbert	Multi-system therapy for diabetes, the metabolic syndrome and obesity	2005
WO 2005023766 A1/ International Patent	Ganesh, Sambasivam; Das, Goutam; Atignal, Shankara Rao Arvind; Mazumdar-Shaw, Kiran	Salt of atorvastatin with metformin for treatment of hyperlipidemia and hyperglycemia	2005
WO 2005039626 A2/ International Patent	Bellini, Francesco; Vezeau, Claude; Ribes, Gerard; Chapal, Nicolas; Prentki, Marc	Methods and compositions using hydroxylated amino acids and additional antidiabetic agents for use in the treatment of diabetes	2005
WO 2005044192 A2/ International Patent	Cardozo, Mario G.; Powers, Jay P.; Goto, Hiroyuki; Harada, Kazuhito; Imamura, Katsuaki; Kakutani, Makoto; Matsuda, Isamu; Ohe, Yasuhiro; Yata, Shinji	Triazole compounds and uses related thereto	2005
US 20050137125 A1/United States Patent	Chan, Bill Piu; Po, Wong Gary Kwan; Xu, Jinxian; Chi, Francis	Compositions and methods for treating diabetes	2005
WO 2005065663 A1/International Patent	Boehm, Garth; Dundon, Josephine	Rosiglitazone and metformin formulations	2005
CN 1559394 A/China	Zeng, Zhaojun; Liu, Zheng; Deng, Yihui	Manufacture and application of composite medicine for lowering blood sugar	2005
WO 2005092293 A1/International Patent	Chawla, Manish; Raghuvanshi, Rajeev Singh; Rampal, Ashok	Formulations of metformin	2005
CN 1562034 A/China	Liang, Guodong; Zhang, Zhongqing; Liu, Quanguo; Yin, Sanfu; Chen, Zhijin	Manufacture of enteric tablets and capsules containing glipizide and metformin hydrochloride, and method for measuring dissolution rate	2005
WO 2005095350 A1/International Patent	Goto, Hiroyuki; Kakutani, Makoto; Nishiu, Jun; Ohe, Yasuhiro; Powers, Jay P.; Yata, Shinji	Preparation of pyrazole compounds as 11β-hydroxysteroid dehydrogenase 1 (HSD1) inhibitors	2005
WO 2005099760 A1/International Patent	Koike, Masahiko; Koyama, Hiroyoshi; Hamaguchi, Naoru	Solid pharmaceutical preparations for the treatment of diabetes	2005
WO 2005102290 A1/International Patent	Kesarwani, Amit Kumar; Chawla, Manish; Raghuvanshi, Rajeev Singh; Rampal, Ashok	Oral controlled release composition containing combination of a biguanide and a sulfonylurea for treatment of diabetes	2005
US 20050272814 A1/United States	Inoue, Keisuke; Tamaki, Tarou	Medicine for prevention or treatment of diabetes comprising 2,2-dichloro-12-(4-chlorophenyl)-dodecanoic acid and metformin	2005
CN 1582928 A/China	Wang, Xinglin; Xu, Weiyu; Zhang, Zongpeng; Chen, Xuemin; Zheng, Jiatong; Tian, Yihong	Pharmaceutical composition containing pioglitazone and dimethyl biguanide for treating diabetes	2005

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WO 2005117861 A1/International Patent	Hughes, Thomas Edward	Use of metformin in combination with a DPP-IV inhibitor to control glucose levels	2005
CN 1682737 A/China	Ouyang, Defang; Pan, Weisan	Compound metformin/glipizide controlled-release tablets	2005
CN 1628658 A/China	Liang, Guodong; Yang, Dongyun; Guo, Hailin; Yang, Ping; Zheng, Song	Manufacture of compound hypoglycemic drug containing mitiglinide and metformin hydrochloride	2005
CN 1634008 A/International Patent	Cui, Xiaoting	Manufacture of composite oral medicine containing metformin hydrochloride and xylitol for treating non-insulin dependent diabetes mellitus	2005
CN 1602960 A/China	Liang, Guodong; Guo, Hailin	Preparation of medical composition for treating cardio-cerebral vascular disease and diabetes	2005
WO 2006017541 A2/International Patent	Arbit, Ehud; Goldberg, Michael M.; Dinh, Steven	Antidiabetic oral insulin-biguanide combination	2006
US 20060034831 A1/United States	Tobin, James F.	Combination therapy for diabetes, obesity and cardiovascular diseases using growth differentiation factor 8 (GDF-8) inhibitors	2006
WO 2006009886 A1/International Patent	Biftu, Tesfaye; Feng, Danqing Dennis; Gao, Ying-Duo; Singh, Suresh; Weber, Ann E.	Preparation of heterocyclic aminocyclohexanes as dipeptidyl peptidase-IV inhibitors for the treatment or prevention of diabetes	2006
US 20060063722 A1/United States	Washburn, William; Meng, Wei	C-aryl glucoside SGLT2 inhibitors and method for the treatment of diabetes and related diseases	2006
WO 2006039325 A2/International Patent	Cox, Jason M.; Edmondson, Scott D.; Harper, Bart; Weber, Ann E.	Preparation of aminopiperidines as dipeptidyl peptidase IV inhibitors for the treatment or prevention of diabetes	2006
CN 1726912 A/China	Wang, Xinglin; Zhang, Junwei; Chen, Zhihua; Yang, Zhiqiang	Compound metformin-pioglitazone sustained-release capsules	2006
WO 2006042002 A2/International Patent	Clinton, Gail M.; Roberts, Charles T., Jr.	Herstatin modulation of the insulin receptor and its use in the treatment of diabetes and related disorders	2006
WO 2006044531 A2/International Patent	Bhanot, Sanjay; Monia, Brett P.; Geary, Richard S.; Kjems, Lise Lunt	Antisense oligonucleotides inhibiting protein phosphotyrosine phosphatase 1B mRNA and their use in treatment of diabetes, obesity and other metabolic disorders	2006
WO 2006047248 A1/International Patent	Burkey, Bryan; Hughes, Thomas Edward	Combination of DPP-IV inhibitor, PPAR antidiabetic and metformin	2006
WO 2006059163 A1 / International Patent	Thomas, Gerard Hugh; Thomsen, Mikael	Treatment of diabetes and diabetes-related conditions with glycogen phosphorylase inhibitors	2006
CN 1785188 A/China	Zhang, Zhiting; Guo, Zonghua; Lei, Lei	Compound dimethyldiguanide and glipizide formulation for treating type II diabetes and its preparation	2006
WO 2006064744 A1/International Patent	Yoshida, Taishi; Okuno, Akira	Medicinal compositions containing FBPase inhibitor for treating diabetes	2006
WO 2006086727 A2/International Patent	Polidori, David; Siler, Scott	Treating diabetes with glucagon-like peptide-1 secretagogues and DPP-IV inhibitors	2006
WO 2006087481 A1/International Patent	Hanotin, Corinne; Rosenzweig, Pierre	Use of rimonabant for the preparation of medicaments that can be used in the prevention and treatment of type 2 diabetes	2006
WO 2006092711 A2/International Patent	Kesarwani, Amit Kumar; Chawla, Manish; Raghuvanshi, Rajeev Singh; Rampal, Ashok Kumar	Extended-release tablets of metformin and glipizide	2006

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WO 2006094933 A1/International Patent	Kley, Hans-Peter; Hanauer, Guido; Hauser, Daniela; Schmidt, Beate; Bredenbroeker, Dirk; Wurst, Wilhelm; Kemkowski, Joerg	Roflumilast for the treatment of diabetes mellitus and accompanying disorders, and combinations with other agents	2006
WO 2006094942 A1/International Patent	Kley, Hans-Peter; Hanauer, Guido; Hauser, Daniela; Schmidt, Beate; Bredenbroeker, Dirk; Wurst, Wilhelm; Kemkowski, Joerg	Roflumilast for the treatment of diabetes mellitus	2006
WO 2006017541 A2/International Patent	Arbit, Ehud; Goldberg, Michael M.; Dinh, Steven	Antidiabetic oral insulin-biguanide combination	2006
WO 2006104349 A1/ International Patent	Choi, Yong-Moon; Shin, Hunwoo; Ilankumaran, Palanichamy	Substituted carboxylic acid derivatives for the treatment of diabetes and lipid disorders, their preparation and use	2006
KR 2006006469 A/Korea	Won, Kwon Yeon; Kim, Dong Wook; Lee, Yil Seob	Oral antidiabetic composition comprising pharmaceutically acceptable carrier, metformin and glimepiride and method for preparing thereof	2006
US 20060258621 A1/United States	Devasthale, Pratik; Wang, Wei; Hamann, Lawrence G.; O'Connor, Stephen P.; Fevig, John M.	Pyrrolopyridine- based inhibitors of dipeptidyl peptidase IV and their preparation, pharmaceutical compositions and use for treatment of diabetes and related diseases	2006
US 20060264457 A1/United States	Devasthale, Pratik; Wang, Wei; Hamann, Lawrence G.; O'Connor, Stephen P.; Fevig, John M.	Pyrrolopyridine-based inhibitors of dipeptidyl peptidase IV and methods	2006
WO 2006127948 A2/International Patent	Ewing, William R.; Mapelli, Claudio; Riexinger, Douglas James; Lee, Ving G.; Sulsky, Richard B.; Zhu, Yeheng	Preparation of N-terminally modified GLP-1 receptor modulators and their use in the treatment of diabetes and related conditions	2006
US 20060275249 A1/United States Patent	Jones, Michael R.	Biguanide-bile acid sequestrant co-therapy for diabetic conditions	2006
US 20060276410 A1/United States Patent	Campbell, David Alan; Winn, David T.; Betancort, Juan Manuel	Nitrogen-containing heterocyclic ketones as inhibitors of dipeptidyl peptidase-IV for the treatment of diabetes	2006
CN 1879753 A/China	Liu, Haitao; Feng, Guangbin; Ye, Chengyu	Compound medical formulation for treating diabetes mellitus with kidney-spleen deficiency and blood stasis syndromes	2006
CN 1879793 A/ China	Liu, Haitao; Feng, Guangbin; Ye, Chengyu	Chinese medicine preparation for treating internal-heat type Diabetes mellitus	2006
WO 2007007757 A1/International Patent	Okuno, Akira; Yoshida, Taishi; Ogawa, Junko	Pharmaceutical compositions containing PPARγ agonist for decreasing blood lactic acid content	2007
US 20070025953 A1/United States Patent	Jones, Michael R.	Co-therapy for diabetic conditions	2007
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WO 2011060256 A2/International Patent	Abebe, Admassu; Martin, Kyle; Patel, Jatin M.; Desai, Divyakant; Timmins, Peter	Bilayer tablet formulations containing metformin and SGLT2 inhibitor	2011
WO 2011060290 A2 / International Patent	Hallgren, Agneta; Swenson, Ralf Magnus Werner	Immediate release tablet formulations comprising SGLT2 inhibitor and metformin, and pharmaceutical combination comprising the same with other active agent	2011
CA 2685638 A1/Canada	Silvestre, Louise; Souhami, Elisabeth; Wei, Xiaodan	Method of treatment of diabetes type 2 comprising add-on therapy to insulin glargine and metformin	2011
CA 2685636 A1/Canada	Silvestre, Louise; Sert-Langeron, Caroline; Zhou, Tianyue	Method of treatment of diabetes type 2 comprising add-on therapy to metformin	2011
US 20110118178 A1/United States	Silvestre, Louise; Souhami, Elisabeth; Wei, Xiaodan	Method of treatment of diabetes type 2 comprising add-on therapy to insulin glargin and metformin	2011
US 20110118180 A1/United States	Silvestre, Louise; Zhou, Tianyue; Sert-Langeron, Caroline	Method of treatment of diabetes type 2 comprising add-on therapy to metformin	2011
KR 2011052990/Korea	Silvestre, Louise; Souhami, Elisabeth; Wei, Xiaodan	Combined therapy for type 2 diabetes	2011
EP 2324853 A1/Europe	Silvestre, Louise; Sert-Langeron, Caroline; Zhou, Tianyue	Lixisenatide as add-on to metformin in the treatment of diabetes type 2	2011
WO 2011064352 A1/International Patent	Dugi, Klaus; Graefe-Mody, Eva Ulrike; Mark, Michael; Woerle, Hans-Juergen; Zimdahl-Gelling, Heike	Treatment of genotyped diabetic patients with DPP-IV inhibitors such as linagliptin	2011
IN 2009MU01684 A/India	Ratilal, Vavia Pradeep; Majed, Khan Mohammed; Sheshrao, Chavan Sandip	Pharmaceutical formulations comprising a combination of metformin and acarbose	2011
CN 102093261 A/China	Sun, Hongbin; Zhang, Yingxia; Hong, Hao	Metformin salicylate and its preparation method and medical application	2011
GB 2476384 A/Great Britain	Gedulin, Bronislava; Greene, Howard E.	Labile bile acid sequestrant for use in the treatment of obesity or diabetes	2011
US 20110171142 A1/United States	Lara Ochoa, Jose Manuel Francisco	Metformin glycinate salt for blood glucose control	2011
WO 2011089203 A1/International Patent	Sommerfeld, Mark; Schaefer, Hans-Ludwig; Boscheinen, Oliver; Habermann, Paul; Rao, Ercole; Dreyer, Matthias	Pharmaceutical composition comprising fibroblast growth factor 21, glucagon-like peptide-1 receptor agonist, anti-diabetic drug and/or dipeptidyl peptidase-4 inhibitor for the treatment of metabolic syndrome and atherosclerosis	2011
CN 201906228 U/China	Wang, Yang; Pan, Xihai; Sun, Yanhua; Liu, Huailin	Pharmaceutical composition structure containing metformin hydrochloride and glimepiride for treating type II diabetes	2011
CN 102133402 A/China	Yang, Jinkui; Lv, Xiaohong; Wang, Lei; Yu, Mei	Application of thiazolidinone derivatives as cystic fibrosis transmembrane conductance regulator inhibitor for treating diabetes mellitus	2011
WO 2011098483 A1/International Patent	Smrdel, Polona; Stanic Ljubin, Tijana; Peternel, Luka; Klancar, Uros	Pharmaceutical compositions comprising combination of metformin and sitagliptin	2011

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WO 2011103256 A1/International Patent	Wilkening, Robert R.; Apgar, James M.; Biftu, Tesfaye; Feng, Danqing; Qian, Xiaoxia; Wei, Lan	Aminotetrahydrothiopyran derivatives as dipeptidyl peptidase-IV inhibitors and their preparation and use for the treatment of diabetes	2011
EP 2359843 A1/Europe	Sommerfeld, Mark; Schaefer, Hans-Ludwig; Boscheinen, Oliver; Habermann, Paul; Ercole, Rao; Dreyer, Matthias	Pharmaceutical composition of fibroblast growth factor 21, glucagon-like peptide-1 receptor agonist, dipeptidyl peptidase-4 inhibitors and antidiabetics for the treatment of metabolic syndrome and atherosclerosis	2011
RU 2428181 C1/Russia	Shcherbakova, E. I.; Batishcheva, G. A.; Chernov, Yu. N.; Korotkova, S. B.; Fetisova, N. G.	Method for reducing of hyperglycemia and insulin-resistance in patients with type 2 diabetes mellitus	2011
WO 2011113947 A1/International Patent	Eickelmann, Peter; Luippold, Gerd; Mark, Michael; Thomas, Leo	Combination of a GPR119 agonist and the DPP-IV inhibitor linagliptin for use in the treatment of diabetes and related conditions	2011
CN 102188429 A/China	Wu, Siqing; Tang, Jun; Ge, Haitao	Medical composition containing bromocriptine and metformin hydrochloride for treating diabetes mellitus, and its formulation	2011
WO 2011128782 A2/International Patent	Rosado, Jorge Luis; Duarte-Vazquez, Miguel Angel	Combination of pharmaceutical compositions for treatment of type II diabetes and related disorders	2011
WO 2011140638 A1/International Patent	Merzouki, Abderrazzak; Buschmann, Michael D.	Gene therapy for diabetes with chitosan-delivered plasmid encoding glucagon-like peptide 1	2011
KR 2011123908 A/Korea	Hong, Sun Seon; Hong, Sang Won; Jung, Gyeong Hui; Park, Byeong Hui; Son, Mi Gwon	Composition containing melatonin and metformin for treating or preventing diabetes mellitus	2011
WO 2011149337 A1/International Patent	Kooy, Adriaan	New combination treatment for type 2 diabetes and other disorders related to insulin resistance	2011
WO 2011149945 A1/International Patent	Mjalli, Adnan M. M.; Valcarce-Lopez, Maria Carmen	The use of metformin in combination with a glucokinase activator for antidiabetic pharmaceutical compositions	2011
CN 102266388 A/China	Wang, Weiping; Li, Xiao; Wang, Hongxia; Li, Hualin	Metformin hydrochloride and Cinnamomum cassia extract-containing medicinal composition for preventing and treating type 2 diabetes and its complication	2011
CN 102266325 A/China	Ma, Yingjun; Wang, Xiaoshu; Zhong, Zhengming; Luo, Tao	Metformin crystal and saxagliptin composition, and its preparation	2011
WO 2011159824 A1/International Patent	Oefelein, Michael G.	Composition comprising trospium and metformin and method for treating overactive bladder and/or diabetes	2011
WO 2011161521 A1/International Patent	Kulkarni, Shirishkumar; Dalal, Satish Kumar; Jahagirdar, Harshal Anil; Konda, Kishore Kumar	Compositions comprising metformin and rosiglitazone	2011
WO 2011161030 A1/International Patent	Keil, Stefanie; Defossa, Elisabeth; Dietrich, Viktoria; Stengelin, Siegfried; Herling, Andreas; Haschke, Guido; Klabunde, Thomas	Heterocyclic-substituted methoxyphenyl derivatives having an oxo group, method for producing same, and use thereof as GPR40 receptor modulators	2011
US 20120004167 A1/United States	Defossa, Elisabeth; Keil, Stefanie; Dietrich, Viktoria; Stengelin, Siegfried; Herling, Andreas; Haschke, Guido; Klabunde, Thomas	[(Aryloxyacetylamino)phenyl]propionic acid derivatives as GPR40 activators useful in prevention and treatment of hyperglycemia and diabetes	2012

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US 20120004166 A1/United States	Keil, Stefanie; Defossa, Elisabeth; Dietrich, Viktoria; Stengelin, Siegfried; Herling, Andreas; Haschke, Guido; Klabunde, Thomas	(Alkoxyphenyl)hexynoic acid derivatives as GPR40 receptor activators and their preparation and use for prevention and treatment of diabetes	2012
US 20120004187 A1/United States	Keil, Stefanie; Defossa, Elisabeth; Dietrich, Viktoria; Stengelin, Siegfried; Herling, Andreas; Haschke, Guido; Klabunde, Thomas	1,3-Propanediol ether derivatives and their preparation and use for treatment and prevention of hyperglycemia and diabetes	2012
WO 2012006298 A2/International Patent	Delaet, Urbain Alfons Clementina; Faure, Anne; Heyns, Philip Erna Hortentia Gilbert; Jans, Eugeen Maria Jozef; Railkar, Aniruddha	Formulation for co-therapy treatment of diabetes comprising metformin and glucopyranosyl (fluorophenyl-thienylmethyl) benzene compound	2012
CN 102349905 A/China	Wang, Xiaoshu; Zhong, Zhengming; Luo, Tao; Ma, Yingjun	Medicinal composition containing metformin crystal and pioglitazone, and its preparation	2012
WO 2012027555 A2/International Patent	Halperin, Jose A.; Chorev, Michael	Preparation of glycated Amadori products of human CD59 and antibodies or fragments for diagnosis and prognosis of pre-diabetes and diabetes	2012
CN 102366497 A/China	Nie, Wenhui; Liu, Jun; Zheng, Yongxi; Han, Chunyong; Wei, Fusheng; Wang, Yibo	Compounded medical preparation for treating diabetes mellitus and preparation method thereof	2012
CN 102391160 A/China	Yan, Shenhe; Li, Bo	Metformin 2,5-dihydroxybenzenesulfonate and its composition used for treating hyperglycemia, diabetic retinopathy and diabetic renal disease	2012
US 20120093878 A1/United States	Singh, Romi Barat; Ramaraju, Kalaiselvan; Vats, Sandeep Kumar; Mondal, Balaram	Pharmaceutical compositions containing a biguanide and a thiazolidinedione for treating diabetes	2012
CN 102423313 A/China	Yin, Shijie; Ding, Juping; Zhang, Renyan; Yu, Qiang	Composite sustained-release preparation containing rosiglitazone and metformin for treating diabetes	2012
WO 2012068274 A1/International Patent	Jin, Shengkan	Treatment of type II diabetes and diabetes-associated diseases with safe chemical mitochondrial uncoupling agents	2012
RU 2451506 C1/Russia	Leshkov, S. Yu.; Vikhrieva, N. S.; Krechetov, S. P.	Combination for treatment of diabetes and complications thereof	2012
WO 2012090225 A2/International Patent	Reddy, Jaggavarapu Satyanarayana; Dandela, Rambabu; Viswanadha, Ganesh Saraswatula; Nagalapalli, Ravikumar; Solomon, Anand Kamalakaran; Javed, Iqbal; Kruthiventi, Anil Kumar	Novel cocrystals/molecular salts of metformin with oleoylethanolamide as an effective antidiabetic and antiobesity agent	2012
WO 2012097144 A1/International Patent	Mylari, Banavara L.; Sciavolino, Frank C.	Lipid-lowering antidiabetic agent	2012
US 20120178813 A1/United States	Mylari, Banavara L.; Sciavolino, Frank C.	Lipid-lowering antidiabetic agent	2012
US 8236281 B1/United States	Sung, Hsing-Wen; Sonaje, Kiran; Tu, Hosheng	Nanoparticles comprising chitosan and charged compounds for treating diabetes	2012
WO 2012120040 A1/United States	Ito, Masanori; Egusa, Kenji; Messerschmid, Roman; Schneider, Peter	Pharmaceutical compositions comprising metformin and a DPP-4 inhibitor or a SGLT-2 inhibitor	2012
WO 2012125830 A2/International Patent	Helson, Lawrence	Curcumin combination with anti-type 2 diabetic drugs for prevention and treatment of disease sequelae, drug-related adverse reactions, and improved glycemic control	2012

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US 20120237590 A1/United States	Helson, Lawrence	Curcumin combination with anti-type 2 diabetic drugs for prevention and treatment of disease sequelae, drug-related adverse reactions, and improved glycemic control	2012
IN 2011MU00830 A/India	Jasvantbhai, Shah Mayank	A pharmaceutical composition comprising antidiabetic agent and methylcobalamin	2012
WO 2012130955 A1/International Patent	Boka, Gabor; Silvestre, Louise; Miossec, Patrick	Prevention of hypoglycaemia in diabetes mellitus type 2 patients with lixisenatide as add-on treatment to sulfonylurea with or without metformin	2012
WO 2012138776 A1/International Patent	Bartberger, Michael D.; Croghan, Michael D.; Fotsch, Christopher H.; Norman, Mark H.; Pennington, Lewis D.; Reichelt, Andreas; St. Jean, David J., Jr.; Tegley, Christopher M.	Preparation of benzodioxepine and benzodioxine compounds that interact with glucokinase regulatory protein for the treatment of diabetes	2012
CN 102727459 A/China	Xu, Jian; Lv, Aifeng; Liu, Ren; Shi, Xiaolei; Tu, Yanjun; Yuan, Tingting	Pharmaceutical antidiabetic controlled-release tablet containing metformin and pioglitazone	2012
CN 102743540/China	Huang, Peiguang	Chinese medicine-containing blood sugar-reducing formulation for combination therapy of diabetes mellitus and its complications	2012
US 20120289485 A1/United States	Mylari, Banavara L.	Metformin salts of salicylic acid and its congeners	2012
WO 2012154392 A1/International Patent	Mylari, Banavara L.	Metformin salts of salicylic acid and its congeners	2012
WO 2012156298 A1/International Patent	Ruus, Peter; Silvestre, Louise; Miossec, Patrick; Pinquier, Jean-Louis; Hincelin-Mery, Agnes	Lixisenatide and metformin for treatment of diabetes type 2	2012
WO 2012156296 A1/International Patent	Silvestre, Louise; Boka, Gabor; Miossec, Patrick	Pharmaceutical combination for use in inducing weight loss in diabetes type 2 patients or/and for preventing weight gain in diabetes type 2 patients comprising lixisenatide and metformin	2012
WO 2012156299 A1/International Patent	Niemoeller, Elisabeth; Silvestre, Louise; Boka, Gabor; Miossec, Patrick	Lixisenatide as add-on therapy to basal insulin in type 2 diabetes	2012
WO 2012156312 A1/International Patent	Silvestre, Louise; Boka, Gabor; Miossec, Patrick	Pharmaceutical combination comprising lixisenatide and metformin for use in the treatment of diabetes type 2	2012
IN 2010DE03159 A/India	Reddy, Jaggavarapu Satyanarayana; Dandela, Rambabu; Viswanadha, Ganesh Saraswatula; Nagalapalli, Ravikumar; Solomon, Anand Kamalakaran; Javed, Iqbal; Kruthiventi, Anil Kumar	Novel cocrystals/molecular salts of metformin with oleoylethanolamide as an effective antidiabetic and antiobesity agent	2012
CN 102813840 A/China	Liu, Juyan; Wu, Changhai; Zhou, Fengjiao; Zhou, Jie; Deng, Huimin; Yang, Wei; Xiao, Baiquan; Lai, Xiaoming; Lu, Suhong; Xiang, Lei	Application of medical composition to prepare the drug for preventing and treating diabetic cardiomyopathy	2012
CN 102813652 A/China	Qi, Yan; Xu, Zhuoye	Tablet of repaglinide and metformin hydrochloride	2012
WO 2013006526 A2/International Patent	Wu, Wen-Lian	Tricyclic heterocycles useful as dipeptidyl peptidase IV inhibitors and their preparation	2013
CN 102908349 A/China	Wang, Liuyi; Wang, Jincan; Wu, Hanfeng; Li, Biao	Medical composition containing metformin hydrochloride	2013
WO 2013025073 A2/International Patent	Chung, Bong Hyun; Kim, Moon Il; Yi, So Yeon; Lee, Ui Jin	Quamoclit pennata extracts for preventing and treating diabetic complications	2013

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WO 2013024968 A1/International Patent	Chung, Bong Hyun; Yi, So Yoen; Lee, Ui Jin	Novel compound isolated from Quamoclit extracts for preventing and treating diabetes and diabetic complications	2013
KR 2013017859 A/Korea	Myung, Hyeon Gun	Pinitol and antidiabetic drug combination for the treatment of diabetes	2013
EP 2561866 A1/Europe	Lammert, Eckhard; Marquard, Jan; Meissner, Thomas	Morphinan-derivatives for treating diabetes and related disorders	2013
WO 2013029762 A1/International Patent	Lammert, Eckhard; Marquard, Jan; Meissner, Thomas	Morphinan-derivatives for treating diabetes and related disorders	2013
IN 2010CH02038 A/India	Ramanan, Ezhil Arasan	Synergistic combination of biguanide and vitamin derivatives for treating diabetes	2013
WO 2013054338 A1/International Patent	Agarwal, Sameer; Jain, Mukul R.; Patel, Pankaj R.	Preparation of 2-thio-imidazole derivatives as TGR5 modulators for treating diabetes	2013
US 20130095140 A1/United States	Baron, Alain D.; Fineman, Mark S.; Beeley, Nigel R. A.	Biguanide compositions and methods of treating metabolic disorders including diabetes and obesity	2013
CN 103054856 A/China	Li, Jinshun	Solid oral preparation containing metformin hydrochloride and atorvastatin calcium, and its manufacture method	2013
WO 2013060850 A1/International Patent	Silvestre, Louise; Souhami, Elisabeth; Wei, Xiaodan	Treatment protocol of diabetes type 2 comprising lixisenatide in combination with insulin glargine and metformin	2013
WO 2013066277 A1 / International Patent	Bilgic, Mahmut	Synergic compositions comprising nateglinide and metformin hydrochloride for the treatment of type-2 diabetes	2013
WO 2013064913 A2/International Patent	Kouji, Hiroyuki	Method for treating type I and type II diabetes using alpha-helix mimetic structures that inhibit β-catenin	2013
GB 2496687 A/Great Britain	Cawthorne, Michael; Stott, Colin; Wright, Stephen	Tetrahydrocannabivarin for use in the protection of pancreatic islet cells	2013
WO 2013074049 A1/International Patent	Bilgic, Mahmut	Micronized metformin	2013
WO 2013076471 A1/International Patent	Cawthorne, Michael; Stott, Colin; Wright, Stephen	Tetrahydrocannabivarin for use in the protection of pancreatic islet cells	2013
WO 2013077821 A1/International Patent	Bilgic, Mahmut	Pharmaceutical composition comprising metformin for the treatment of type 2 diabetes	2013
WO 2013077824 A1/International Patent	Bilgic, Mahmut	Preparation process for a formulation comprising metformin	2013
WO 2013077822 A1/international Patent	Bilgic, Mahmut	Effervescent formulations comprising metformin for treatment of diabetes	2013
WO 2013077825 A1/International Patent	Bilgic, Mahmut	Preparation of formulations comprising metformin	2013
WO 2013077820 A1/International Patent	Bilgic, Mahmut	Package composed of dosage forms comprising nateglinide and metformin for treatment of diabetes	2013
WO 2013095316 A1/International Patent	Bilgic, Mahmut	Synergic combination comprising anti-diabetic agent	2013
US 20130172248 A1/United States	Defossa, Elisabeth; Dietrich, Viktoria; Klabunde, Thomas; Keil, Stefanie; Stengelin, Siegfried; Haschke, Guido; Herling, Andreas; Kuhlmann-Gottke, Johanna; Bartoschek, Stefan; Gessler, Simon; et al	3-[4-(Phenylaminooxalylamino)phenyl]hex-4-yonic acids useful in treatment of diabetes and their preparation	2013

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WO 2013102929 A1/International Patent	Agarwal, Sameer; Desai, Ranjit C.	Preparation of imidazole compounds for treatment of diabetes, obesity or related disorders	2013
WO 2013102921 A2 / International Patent	Prasad, Kompella Venkata Subramanya; Soman, Jay Laxman	Newer treatment modality for type 2 diabetes mellitus and associated co-morbid conditions comprising human chorionic gonadotropin either alone or in combination with another antidiabetic	2013
WO 2013106547 A1/International Patent	Annes, Justin P.; Melton, Douglas A.; Rubin, Lee L.	Phosphodiesterase inhibitors as Beta-cell replication promoting compounds and methods of their use for treating disorders such as diabetes	2013
WO 2013115745 A1/International Patent	Bilgic, Mahmut	A process for production of pharmaceutical effervescent composition comprising α-glucosidase inhibitor for treatment of type 2 diabetes	2013
WO 2013115741 A1/International Patent	Bilgic, Mahmut	Pharmaceutical compositions comprising α-glucosidase inhibitor for treatment of type 2 diabetes	2013
WO 2013115738 A1/International Patent	Bilgic, Mahmut	Micronized acarbose compositions for treatment of diabetes	2013
WO 2013115744 A1/International Patent	Bilgic, Mahmut	A process for production of pharmaceutical effervescent composition comprising alpha-glucosidase inhibitor such as voglibose and metformin	2013
WO 2013115746 A1/International Patent	Bilgic, Mahmut	A production method for (effervescent) pharmaceutical compositions comprising an alpha-glucosidase inhibitor (Miglitol) and metformin	2013
CN 103251593 A/China	Shen, Rujie; Li, Yuedong; Tang, Jianfei; He, Haizhen; Yao, Chenge; Zhao, Fubin; Liu, Yuyan; Liu, Qiumin; Ma, Wenxia	High-safety medicinal composition comprising repaglinide and metformin hydrochloride as active ingredients with high bioavailability and preparation method thereof	2013
CN 103251594 A /China	Shen, Rujie; Li, Yuedong; Tang, Jianfei; He, Haizhen; Yao, Chenge; Zhao, Fubin; Liu, Yuyan; Liu, Qiumin; Ma, Wenxia	Compound tablet comprising repaglinide and metformin hydrochloride capable of realizing synchronous release of medicinal materials, good in vitro dissolution and high bioavailability, and its preparation method	2013
CN 103263405 A/China	Chen, Qi; Li, Fei; Li, Kexue; Yang, Qing; Bai, Hui	Medicine composition comprising glycine and metformin hydrochloride for treating diabetes mellitus and application thereof	2013
CN 103263419 A/China	Zhang, Lei; Chen, Guangliang; Xu, Xiping; Xu, Xin; Tian, Minqing; Qin, Xianhui	New application of medicinal composition of metformin and 5-methyl tetrahydrofolic acid	2013
CN 103271907 A/China	Ji, Yong; Zhou, Kai; Su, Xianying; Zhou, Lianbo; Guo, Lang; Wang, Yaqian	Berberine and metformin-containing oral pharmaceutical composition for reducing blood lipid and glucose and its manufacture method	2013
CN 103285398 A/China	Zhu, Shaoliang; Zhang, Xingyue; Liang, Xiaoyu; Liu, Xiaohua; Hu, Jie	Compound preparations containing dipeptidyl peptidase IV (DPP-IV) inhibitor and type II diabetes drug and its production method	2013
EP 2638898 A1/Europe	Cifter, Uemit; Tuerkyilmaz, Ali; Mutlu, Onur	Metformin and pioglitazone formulation with different release profiles	2013
CN 103316017 A/China	Gao, Lihui; Li, Ling; Shen, Zhufang; Liu, Weiping; Shen, Xizhu; Li, Linyi; Li, Yunwei	Vanadyl di(α-furoate) composition used in preparing drugs for treating diabetes	2013
WO 2013142314 A1/International Patent	Dias, Marie Charmaine	Oral tablet formulation consisting of immediate release rosuvastatin and extended release metformin	2013

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IN 2011DE02868 A/India	Bhaskar, Radhika; Bhaskar, Rahul	Multilayered tablet containing three antidiabetic drugs with different mechanisms of action for severely diabetic patients	2013
CN 103356661 A/China	Wu, Guangyan	Tablet capsule comprising metformin hydrochloride solid preparation and glipizide solid preparation	2013
CN 103371981 A/China	Wang, Xinglin; Yin, Dongdong; Zhang, Junwei; Yang, Zhiqiang	Repaglinide and metformin hydrochloride containing immediate-release solid compound preparation and its preparation method and uses	2013
WO 2013159190 A1/International Patent	Gahler, Roland Jacques; Lyon, Michael Robert; Wood, Simon	Dietary fiber compositions for the treatment of metabolic disease	2013
WO 2013164838 A1/International Patent	Agarwal, Sameer; Desai, Ranjit C.	Preparation of thio-1,2,4-triazole compounds as TGR5 agonist for use in treatment of diabetes, obesity, and metabolic disorders	2013
WO 2013169007 A1/International Patent	Auh, Jin; Jeong, Hyeon Gun; Lee, Jong-Kwon; Youn, Ju Yong; Shin, Je Yong	Sustained-release complex preparations for treating diabetes with improved drug compliance and method for preparing same	2013
WO 2013167554 A1/International Patent	Rauch, Thomas; Hamilton, Bradford S.; Tsutsumi, Manami	Pharmaceutical combinations of a hydroxysteroid dehydrogenase inhibitor and another agent for the treatment of metabolic disorders	2013
WO 2013173417 A2/International Patent	Valcarce Lopez, Maria Carmen; Fong, Tung	Glucokinase activator compositions for the treatment of diabetes and related disorders	2013
KR 2013126253 A/Korea	Eo, Jin; Han, Chang Gyun; Jung, Hyeon Geun; Lee, Jong Gwon; Lee, Eun Hui; Yoon, Ju Yong	Sustained-release preparations for treating diabetes mellitus	2013
WO 2013173858 A1/International Patent	Walder, Ken; Krippner, Guy; Nicholson, Geoff	Method of weight reduction with use of methazolamide	2013
KR 1336499 B1/Korea	Kim, Eun Ji; Park, Hye Jeong; Yoon, Sang Jun; Park, Hyo Ju; Hong, Min Ju; Pyo, Hyo Ju; Jung, Yun A.; Park, Hyeon Uk; Kim, Yun Jeong; Song, Geun Seok et al	Antidiabetic compositions containing voglibose and metformin	2013
CN 103462903 A/China	Cui, Xingang; Wang, Yingying; Liang, Yanchun; Gao, Chunfang	Pioglitazone hydrochloride sustained-release pellet formulation and preparation method thereof	2013
KR 2013141273 A/Korea	Kim, Hak Hyeong; Shin, Jong Man; Lee, Gye Won	Oral preparations for treating diabetes containing metformin and sulfonylurea drugs	2013
WO 2014008374 A2/International Patent	Mylari, Banavara L.; Sciavolino, Frank C.	Combination therapies comprising metformin salts and antihyperglycemia agents or antihyperlipidemia agents	2014
CN 103505466 A/China	Zhang, Junwei; Song, Liming; Wang, Xinglin; Yang, Zhiqiang; Yin, Dongdong	Solid compound preparation containing metformin hydrochloride and glimepiride, and manufacture method and application thereof	2014
US 20140018419 A1/United States	Mylari, Banavara L.; Sciavolino, Frank C.	Preparation of tri-salt forms of metformin for treatment of Diabetes mellitus	2014
WO 2014011814 A1/International Patent	Mylari, Banavara L.; Sciavolino, Frank C.	Preparation of tri-salt forms of metformin for treatment of Diabetes mellitus	2014
WO 2014014530 A1/International Patent	Mylari, Banavara L.; Fleming, G. Alexander	Ursolic acid salts for treating diabetes and obesity	2014
US 20140024708 A1/United States	Mylari, Banavara L.; Fleming, G. Alexander	Ursolic acid salts for treating diabetes and obesity	2014

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WO 2014017833 A1/International Patent	Kim, Jin Cheul; Jeong, Ki Woo; Kim, Jae Ho; Kim, Yong Il; Park, Jae Hyun; Woo, Jong Soo	Composite formulation for oral administration comprising metformin and rosuvastatin	2014
WO 2014017787 A1/International Patent	Kim, Dae Joong; Jung, Nan Young	Pharmaceutical composition having antidiabetic and antiobesity activities	2014
WO 2014036528 A2/International Patent	Cortopassi, Gino; Tomilov, Alexey	Screening methods for identifying compounds useful for treating obesity, diabetes and related disorders	2014
KR 1373097 B1/Korea	Kang, Seok Bong; Son, Ho Sang; Byun, Jun Seok; Son, Gi Cheol; Ku, Se Gwang	Composition comprising Yukmijihwangtang extract for treatment of diabetes mellitus	2014
WO 2014049144 A1/International Patent	Banerjee, Shanta M.	Composition for use as a medicine or dietetic food in the prevention and/or treatment of diabetes and diabetes-associated diseases	2014
US 20140099333 A1/United States	Schwink, Lothar; Bossart, Martin; Glombik, Heiner; Gossel, Matthias; Kadereit, Dieter; Klabunde, Thomas; Maier, Thomas; Stengelin, Siegfried	Pyrrolidinone derivatives as GPR119 modulators for the treatment of diabetes, obesity, dyslipidemia and related disorders	2014
WO 2014058188 A1/International Patent	Kim, Geun Tae; Yun, Duck Il; Park, Ki Sook	Combination drug comprising gemigliptin and metformin, and method for the preparation thereof	2014
CN 103735544 A/China	Bao, Jinyuan; Xu, Rui; Jiang, Yuwei; Zhang, Xiaoqing	Preparation process of tablet of vildagliptin/ metformin	2014
WO 2014080307 A2/International Patent	Kandula, Mahesh	Compositions and methods for the treatment of diabetes and pre-diabetes	2014
CN 103845326 A/China	Chen, Qingcai; Zhao, Jun; Zhao, Xiaowei; Huang, Haiqin; Jin, Xuefeng	Compound tablet of vildagliptin and metformin and preparation method thereof	2014
FR 2999427 A1/France	Moinet, Gerard; Baverel, Gabriel	Preparation of piperazine derivatives and composition and kit including them and metformin for use in the treatment of diabetes	2014
CN 103877533 A/China	Meng, Xiaofei	Pharmaceutical composition comprising metformin for treating diabetes and its preparation method	2014
CN 103877445 A/China	Tan, Qilong	Formula and method for preparing blood sugar lowering capsule	2014
WO 2014095929 A1/International Patent	Moinet, Gerard; Baverel, Gabriel	Preparation of piperazine derivatives and composition and kit including them and metformin for use in the treatment of diabetes	2014
US 20140186321 A1/United States	Lines, Thomas Christian	Method for treating metabolic syndrome and diabetes using quercetin and Bauhinia forficata extract	2014
WO 2014109587 A1/International Patent	Kim, Jin Sook; Kim, Jung Hyun; Kim, Chan Sik; Kim, Young Sook; Shon, Eun Jin; Lee, Yun Mi; Jung, Dong Ho; Lee, Ik Soo; Jo, Gyu Hyeong; Kim, Joo Hwan	Pharmaceutical natural extracts for preventing and treating diabetic complications or angioedema	2014
WO 2014113357 A1/International Patent	Mjalli, Adnan M. M.; Clark, Bradley Alan; Polisetti, Dharma Rao; Quada, James C., Jr.; Valcarce Lopez, Maria Carmen; Andrews, Robert Carl; Davis, Stephen Thomas; Yokum, Thomas Scott	Combinations of a GLP1R agonist and metformin for the treatment of type 2 diabetes and other disorders	2014

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CN 103933031 A /China	Yin, Lifang; Zhu, Chunli; Zhao, Zhongyuan; Wang, Guangji; Sun, Hongbin; Wu, Zhannan; Zhou, Fang; Zhou, Chunyan; Wang, Wei; Cao, Lin	Compound preparation containing dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin hydrochloride for treating non-insulin-dependent diabetes mellitus, and its preparation method by penetration pump technology and coating	2014
US 20140221467 A1/United States	Mylari, Banavara L.	Metformin derivatives for treating diabetes and diabetes complications	2014
WO 2014124141 A1/International Patent	Mylari, Banavara L.	Metformin derivatives for treating diabetes	2014
US 20140228319 A1/United States	Mylari, Banavara L.	Water soluble salts of aldose reductase inhibitors for treatment of diabetic complications	2014
WO 2014126885 A1/International Patent	Mylari, Banavara L.	Water soluble salts of aldose reductase inhibitors for treatment of diabetic complications	2014
WO 2014137090 A1/International Patent	Kim, Eun Ji; Park, Hye Jung; Youn, Sang Jun; Park, Hyo Ju; Hong, Min Ju; Pyo, Hyo Ju; Jung, Yun Ah; Park, Hyun Wook; Kim, Yun Jung; Song, Geun Seog et al	Pharmaceutical combination of voglibose and metformin for prevention or treatment of diabetes	2014
WO 2014161837 A1/International Patent	Muehlen-Bartmer, Isabel; Ziemen, Monika	Treatment of diabetes mellitus by long-acting formulations of insulins	2014
WO 2014164404 A1/International Patent	Gerszten, Robert; Wang, Thomas; Clish, Clary	2-Aminoadipic acid (2-AAA) as a biomarker and therapeutic agent for diabetes	2014
WO 2014161918 A1 / International Patent	Broedl, Uli Christian; Cherney, David; Daiber, Andreas; Von Eynatten, Maximilian; Johansen, Odd-Erik; Kim, Gabriel Woojai; Mayoux, Eric Williams; Muenzel, Thomas; Perkins, Bruce A.; Salsali, Afshin; et al	Therapeutic uses of empagliflozin for treating oxidative stress and cardiovascular disease in patients with diabetes	2014
WO 2014165297 A1/International Patent	Housey, Gerard M.; Balash, Monica Elizabeth	Plant extracts with anti-diabetic and other useful activities	2014
RU 2530628 C1/Russia	Kornev, P. V.	Pharmaceutical combination and kit for treating and/or preventing obesity-related disorders, and method for treating and/or preventing obesity-related disorders	2014
WO 2014167437 A1/International Patents	Jain, Girish Kumar; Naidu, Venkataramana; Patil, Atul	Solid oral pharmaceutical compositions comprising fixed dose combination of metformin and sitagliptin or salts thereof	2014
WO 2014170383 A1/International Patent	Broedl, Uli Christian; Cherney, David; Von Eynatten, Maximilian; Johansen, Odd-Erik; Mayoux, Eric Williams; Perkins, Bruce A.; Soleymanlou, Nima; Woerle, Hans-Juergen	Pharmaceutical composition comprising SGLT-2 inhibitors for treating or preventing chronic kidney disease	2014
WO 2014174469 A1/International Patent	Tiwari, Ravindra; Tiwari, Kirpa Shankar; Kochhar, Ravi	Pharmaceutical compositions comprising a combination of sitagliptin and metformin	2014
WO 2014184376 A1/International Patent	Klein, Thomas; Mark, Michael	Combination of a DPP-4 inhibitor and an alpha-glucosidase inhibitor	2014
WO 2007033266 A2/International Patent	Christopher, Ronald J.; Covington, Paul	Administration of dipeptidyl peptidase inhibitors for treatment of diseases such as diabetes	2014
US 20140357680 A1/United States	Kandula, Mahesh	Preparation of compounds containing metformins and polyunsaturated fatty acid conjugates for treatment of diabetes and pre-diabetes	2014

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WO 2014195810 A2/International Patent	Kandula, Mahesh	Compositions and methods for the treatment of diabetes and pre-diabetes	2014
IN 2013CH00173 A/India	Senthilkumar, C.; Agarwal, Ankur	Composition for treating type-II diabetes and methods for preparation thereof	2014
WO 2014203059 A1/International Patent	Guthrie, Najla	Compositions comprising at least one polymethoxyflavone, flavonoid, liminoid, and/or tocotrienol useful in combination therapies for treating diabetes	2014
WO 2014205449 A2/International Patent	Crooke, Rosanne M.; Alexander, Veronica J.	Compounds and methods for modulating apolipoprotein C-III expression for improving a diabetic profile	2014
US 20140378374 A1/United States	Stewart, Murray Willis; Yang, Yonghong F.	GLP-1 receptor agonist for treatment of type 2 diabetes	2014
WO 2015001358 A1/International Patent	Richardson, Peter; Campbell, Bruce	Drug combination for therapy of obesity and type II diabetes	2015
WO 2015002818 A1/International Patent	Sands, Jeff M.; Blount, Mitsi A.; Klein, Janet D.	Methods for treating or preventing nephrogenic diabetes insipidus by administering AMPK kinase activators	2015
WO 2015012633 A1/International Patent	Kang, Kwi Man; Park, Young Joon; Park, Jun Hong; Lee, Ji Eun; Yoon, Seok Kee; Kim, Yu Jeong; Oh, Tack Oon; Cho, Tae Keun	Controlled-release complex formulation containing sustained release metformin and immediate release HMG-coA reductase inhibitor	2015
CN 104324033 A/China	Ma, Yuguo	Sustained-release tablet containing sitagliptin and metformin, and its preparation method	2015
WO 2015015403 A2/International	Kandula, Mahesh	Compositions and methods for the treatment of diabetes and pre-diabetes	2015
KR 2015012619 A/Korea	Kang, Gwi Man; Park, Yeong Jun; Park, Jun Hong; Lee, Ji Eun; Yoon, Seok Gi; Kim, Yu Jeong; Oh, Taek Un; Cho, Tae Geun	Controlled-release complex formulation containing sustained release metformin and immediate release HMG-coA reductase inhibitor	2015
CN 104337811 A/China	Qin, Yinlin; Shi, Shanwen	Repaglinide-metformin hydrochloride tablet and preparation method thereof	2015
WO 2015022420 A1/International Patent	Bednarek, Maria; Collinson, Andie; Hornigold, David; O'Brien, Siobhan; Papworth, Monika; Ravn, Peter; Sermadiras, Isabelle	GIP and GLP-1 receptor dual-agonists for the treatment of diabetes	2015
WO 2015022613 A1/International Patent	Kandula, Mahesh	Preparation of metformin salt compositions and methods for treatment of diabetes and pre-diabetes	2015
US 20150056297 A1/United States	Liu, Charles H.	Nutraceutical combination for prevention and treatment of type 2 diabetes mellitus	2015
US 20150064223 A1/United States	Baron, Alain D.; Fineman, Mark S.; Beeley, Nigel R. A.	Biguanide compositions and methods of treating metabolic disorders	2015
EP 2845590 A1 /Europe	Szewczyk, Jerzy Ryszard	Composition for treatment of diabetes	2015
WO 2015035419 A1/International Patent	Schmitt, Christophe; Hauptman, Jonathan; Jadidi, Shirin	Dosages of gastric inhibitory peptide/glucagon-like peptide-1 co-agonist peptides for human administration for treatment of diabetes or obesity	2015
WO 2015042495 A2/International Patent	Goel, Om P.	Metformin salts to treat type 2 diabetes	2015
CN 104473920 A/China	Anonymous	Compound pharmaceutical preparation containing ipragliflozin and metformin hydrochloride for treating type 2 diabetes, and its preparation method	2015

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KR 1512386 B1/Korea	Han, Jin U.; Lee, Seok; Kim, Yeong Hun	Method for producing mitiglinide and metformin complex formulation	2015
US 20150110881 A1/United States	Tibbs, Kenneth John; Tibbs, Dawn Ann	Pharmaceutical preparation and method for treatment of diabetes	2015
WO 2015055801 A1/International Patent	Riber, Ditte; Tolborg, Jakob Lind; Hamprecht, Dieter Wolfgang; Rist, Wolfgang	Acylated glucagon analogs and their use in treatment of obesity, diabetes and associated metabolic disorders	2015
WO 2015055802 A2/International Patent	Riber, Ditte; Tolborg, Jakob Lind; Hamprecht, Dieter Wolfgang	Glucagon analogs and their use in treatment of excess body weight, diabetes and other assocd. metabolic disorders	2015
CN 104586834 A/China	Sun, Zhongguo	Pharmaceutical composition containing empagliflozin and metformin and its preparation method	2015
WO 2015063140 A1/International Patent	Cohen, Daniel; Chumakov, Ilya; Nabirochkin, Serguei; Hajj, Rodolphe	Compositions, methods and uses for the treatment of diabetes and related conditions by controlling blood glucose level	2015
WO 2015074103 A1/International Patent	Lichti, Gottfried; Lichti, Christopher Walter	Regimen and method for treatment of type 2 diabetes	2015
KR 1526825 B1 /Korea	Hong, Eon Pyo; Kim, Dong Uk; Hong, Hye Suk; Bae, Jin Geon	Pharmaceutical composition containing metformin and DPP-IV inhibitor and used for treatment of diabetes	2015
KR 2015068730 A/Korea	Kim, Jin Cheol; Cho, Jeong Hyeon; Kim, Jae Ho; Kim, Yong Il; Park, Jae Hyeon; Woo, Jong Su	Bi-layered tablets comprising metformin and losartan	2015
EP 2891654 A1/Europe	Wu, Frank	Optically pure benzyl-4-chlorophenyl-C-glucoside derivatives as SGLT inhibitors (diabetes mellitus)	2015
CN 104771403 A/China	Liu, Jun; Zhang, Luyong; Wang, Xue; Sun, Hongbin	The pharmaceutical compositions containing oleanolic acid and its use in the treatment of diabetes	2015
US 20150197475 A1/United States	Mylari, Banavara L.; Sciavolino, Frank C.	Tri-salt form of metformin	2015
CN 104825446 A/China	Zhang, Pengwei; Yang, Xuefeng; Kuang, Shaoyi; Zhang, Li	A pharmaceutical composition containing vildagliptin and metformin hydrochloride for treating non-insulin dependent diabetes mellitus	2015
CN 104840480 A/China	Xu, Xiping; Zhang, Lei; Chen, Guangliang; Wang, Binyan	New application of pharmaceutical composition containing metformin, folic acid and vitamin B12 in the preparation of medicines for treating non-insulin-dependent diabetes mellitus and preventing or alleviating hyperhomocystinemia	2015
CN 104840960 A/China	Huang, Qibiao; Zhan, Zhenku; Zhao, Feng	Anti-diabetic pharmaceutical composition and its preparation method	2015
US 20150231123 A1/United States	Cohen, Daniel; Chumakov, Ilya; Nabirochkin, Serguei; Hajj, Rodolphe	Compositions, methods and uses for the treatment of diabetes and related conditions by controlling blood glucose level	2015
WO 2015134357 A1/International Patent	Ye, Keqiang	Modulators of insulin receptor	2015
CN 104906114 A/China	Xia, Zhengmei	A kind of compound sustained release capsules of metformin gliquidone and preparation method.	2015
WO 2015138916 A1/International Patent	Nicolau, Yves Claude; Greferath, Ruth; Lehn, Jean-Marie	Myo-inositol trispyrophoshate as an anti-diabetic agent	2015
US 20150258056 A1/United States	Woods, Thomas Cooper	Use of mir-221 and 222 lowering agents to prevent cardiovascular disease in diabetic subjects	2015

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CN 104958290 A/China	Ge, Depei; Wu, Qihua; Liu, Tao	Tofogliflozin and metformin compound preparation and its preparation method	2015
WO 2015150564 A1/International Patent	Schwink, Lothar; Buning, Christian; Glombik, Heiner; Gossel, Matthias; Kadereit, Dieter; Halland, Nis; Lohmann, Matthias; Poeverlein, Christoph; Ritter, Kurt	Preparation of fused heterocycles as GPR119 modulators for the treatment of diabetes, obesity, dyslipidemia and related disorders	2015
WO 2015150565 A1/International Patent	Schwink, Lothar; Buning, Christian; Glombik, Heiner; Gossel, Matthias; Kadereit, Dieter; Halland, Nis; Lohmann, Matthias; Poeverlein, Christoph; Ritter, Kurt	Preparation of isoindolinone compounds as GPR119 modulators for the treatment of diabetes, obesity, dyslipidemia and related disorders	2015
WO 2015150563 A1/International Patent	Schwink, Lothar; Buning, Christian; Glombik, Heiner; Gossel, Matthias; Kadereit, Dieter; Halland, Nis; Lohmann, Matthias; Poeverlein, Christoph; Ritter, Kurt	Preparation of oxoindanylpyrrolidinone derivatives as GPR119 modulators for the treatment of diabetes, obesity, dyslipidemia and related disorders	2015
WO 2015155303 A2/International Patent	Li, Jin; Kubicek, Stefan	Medical use of artemisinin compounds and gephyrin agonists	2015
EP 2929881 A1/Europe	Li, Jin; Kubicek, Stefan	Medical use of artemisinin compounds and gephyrin agonists	2015
US 20150297516 A1/United States	Lin, Hsin-Yung	Inhalation-type pharmaceutical composition for the treatment of diabetes and preparation method thereof	2015
WO 2015166472 A1/International Patent	Kumar, Ashish; Shear, Rajesh Srikrishan; Jain, Satish Kumar; Singh, Romi Barat; Jain, Paras P.	Extended release liquid compositions of metformin	2015
CN 105030793 A/China	Zhao, Yushan; Huang, Jingshan; Li, Wei; Yang, Jincheng; Shao, Wei	Preparation of metformin hydrochloride-glibenclamide capsule with high dissolution for diabetes treatment	2015
WO 2015180736 A1/International Patent	Gregersen, Soeren; Jeppesen, Per Bendix; Hermansen, Kjeld; Mellbye, Fredrik Brustad	Cafestol for treating diabetes	2015
WO 2015183794 A1/International Patent	Yu, Donna; Figarola, James Lester; David, Donald	TGR5 agonist complexes for treating diabetes and cancer	2015
CN 105125969 A/China	Xue, Haichuan	Compound Chinese-western medicine preparation for treatment of diabetes	2015
WO 2015188423 A1/International Patent	Jiang, Hulin; Wang, Fengzhen; Xing, Lei	Guanidine hypoglycemic drug-polysaccharide conjugate, prepn. method therefor and use thereof	2015
WO 2015200842 A1/International Patent	Heiman, Mark L.; Orndorff, Steve A.; Pfost, Dale R.	Pharmaceutical composition comprising metformin and a microbiome modulator	2015
WO 2015157476 A2/International Patent	Yang, Wen-Chin; Chang, Lee-Tian; Huang, Shou-Hsien	Pdia4 protein as a target for diagnosis, monitoring and treatment of diabetes	2015

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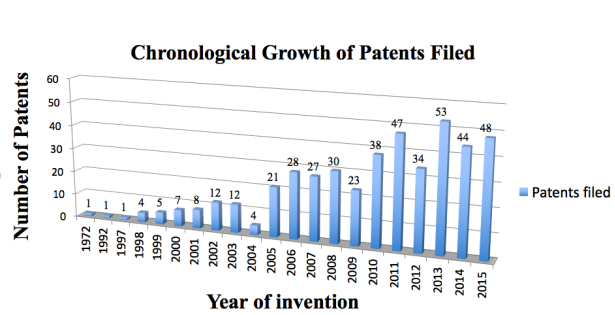

Figure 1: Chronological appearance of patents filed related with combination therapy for the treatment of diabetes using Metformin hydrochloride or any related Metformin salt.

The chronological survey made (Table 2) reflects an exponential growth (Figure 1) from the first patent claimed in 1972 (JP 47032644 B4, Hypoglycemic tolbutamide-metformin salt). It is noteworthy that it took twenty years for the appearance of a second patent in 1992 (WO 9203148 A1, Method and compounds for treating type 2 diabetes mellitus) after the first patent was filed. This absence and sudden outbreak is apparently related with the approval and distribution of Metformin hydrochloride in USA in 1994, despite the fact that Metformin hydrochloride was first introduced in France in 1968 [58]. Moreover, from the period from 1992 to 1997 there were no patent related, however from 1997 a large number of patents have appeared, marking the beginning of an exponential growth in the register of inventions related to Metformin hydrochloride.

Current & Future Developments

Diabetes is a very complex condition consisting in a group of metabolic dysregulations with no effective treatment up to date. As a consequence of its worldwide incidence an astonishing number of patents have appeared in the recent years claiming the development of new formulations/compositions where Metformin hydrochloride or Metformin analogues is included in the presence of two or more agents for the treatment, prevention or amelioration of diabetes, and this number is still increasing rapidly.

Despite the appearance of new drugs and therapies for the treatment of diabetes specifically T2D, Metformin hydrochloride remains as the agent of choice, [58] due to the multiple benefits provided (low cost, is one of the most efficacious hypoglycemic agents showing prevention in CVD and provide beneficial effects on Dyslipidemia and hypofibrinolysis) [25]. However, it has been pointed out that its utilization in monotherapy after prolonged exposure, results in the development of other complications and the administration of Metformin hydrochloride in the presence of one or multiple agents (e.g. drugs, natural products, hormones, peptides, etc.) becomes necessary, resulting this procedure the treatment of choice. This phenomenon being clearly exemplified in Figure 1, where the trend observed proves the incessant appearance of patents related with combination therapy in recent years.

Conclusion

Thus, these paper overviews the chronological appearance of patents related with combination therapy including Metformin hydrochloride or any Metformin analogue in the presence of one of more agents for the treatment of T2D. Due to its importance, Metformin hydrochloride is the preferred drug in the management of glycemic levels in T2D patients, and thus a considerable number of patents have been claimed in the last six years (2010-2015, with an average of 44 patents filed per year) demonstrating the importance of administration of Metformin hydrochloride for the treatment of diabetes, mainly in T2D.

Although the number of filed patents cannot be directly related to the growing number of patients with this condition, the statistics are not very promising and the number of patients is expected to increase in the years to come. However, the efforts devoted to the design and synthesis of new drugs based on combination therapy may lead to improving the glycemic controland thus the standard of life of those having T2D. The further understanding of the mechanisms through which thesedrugs work, may shed further light in the design of more efficient therapies ultimately leading not only to a proper control of the illness but to a potential cure of it.

Conflicts of Interests

The authors declare that they have no competing interests or conflict in the financial contribution.

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