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CLINICAL SAFETY AND RECENT PATENTS ON FIXED-DOSE COMBINATIONS OF DPP-4 INHIBITORS: AN UPDATED REVIEW

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Abstract

Type 2 diabetes mellitus (T2DM) is the epidemic metabolic disorder with rising globally incidence. The dipeptidyl peptidase-4 inhibitor (DPP-4I) is a newer class of anti-diabetic drugs showing a conceptual alteration in management of glycemic control by treating fundamental pathophysiological processes instead of a gluco-centric approach. DPP-4I reduced risk of hypoglycemia and weight gain in T2DM patient. Clinical studies revealed that DPP-4Is are safe and effective in T2DM patient and did not increase cardiovascular risk. This review focuses on recent patents (2015-2019) in DPP-4I containing pharmaceutical formulation. Various inventor and companies were pursued in developing fixed-dose combination (FDC) of DPP-4I with metformin or HMG Co-A reductase inhibitors. The present review also describes patented technology for chewable and effervescent dosage form of DPP-4I.

Key words: DPP-4 inhibitor, T2DM, Patent, Cardiovascular Risk, Glycemic control.

Introduction

Diabetes mellitus has been selected by world health organization as one of four main concerns non-communicable disease (NCDs) subjected for action by world leaders. USFDA defines diabetes mellitus, as a chronic diseases characterized by hyperglycemia resulted by imperfect insulin secretion (pancreatic β cell dysfunction) and insulin resistance in tissues (liver, muscles, kidney and fat) (Barnett, 2006; Wang *et al*., 2018; Zhong *et al*., 2015). Over 425 million adults (20-79 years) had diabetes mellitus and 352 million people were at pre-diabetes stage globally in 2017. The number of diabetic patient is projected to increase to 629 million by 2045. Majority (90%) of diabetes mellitus patient have type 2 diabetes mellitus (T2DM). The main causes of the pandemic of T2DM are high-energy diet, obesity and aging population and reduce physical activity (Ginter and Simko, 2013; Marín-Peñalver *et al*., 2016; Simó *et al*., 2002; Zheng *et al*., 2018). Dipeptidyl peptidase 4 (DPP4) inhibitors which have been widely used as superb blood glucose-dependent antidiabetic agents in T2DM patients show great promise. DPP4 is a membrane glycoprotein which is extensively expressed in several organs, such as the spleen, kidney, pancreas, lungs *and* prostate. It is articulated on endothelial cells as well as some immune cells including lymphocytes, macrophages and dendritic cells at high levels. DPP4 exists in plasma as a soluble material that either originates from a proteinase-driven shedding mechanism or vesicles including ectosomes, exosomes and apoptotic bodies release DPP into blood circulation (Barnett, 2006; Deacon, 2019; Schirra *et al*., 2002; Smushkin and Vella, 2009; Wang *et al*., 2018; Waugh *et al*., 2017; Zhong *et al*., 2015). DPP4 is well known for their catalytic incretin degradation. The incretin peptides like glucagon-like peptide (GLP-1) and gastric inhibitory polypeptide (GIP) are accountable for post-prandial glucose levels regulation through the stimulation of insulin secretion from pancreatic β-cells and through glucagonostatic activity. DPP4 promptly inactivates GLP-1 and GIP, resulting in their short half-life (Mentlein, 2009). Mechanism of action and examples of DPP4-inhibitors (DPP-4I) which has nowadays emerged as new medication for T2DM has been depicted in fig. 1 and 2, respectively (Barnett, 2006). The clinical investigations and randomized controlled trials (RCTs) prove that DPP4I are safe, efficacious and well-tolerated (Cai *et al*., 2018; Deacon and Holst, 2013; Holst *et al*., 1996; Kim *et al*., 2015; Kjems *et al*., 2003; Gallwitz, 2019; Ross *et al*., 2016; Scheen, 2018; Sesti *et al*., 2019; Soe *et al*., 2011;

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Table 1: Safety and efficacy of DPP-4I: summary of clinical studies.

Observation time(week)	Intervention	Primary endpoint	Outcome	Reference
104	Alogliptin 12.5 mg; Alogliptin 25 mg; Glipizide >5mg	Least square mean change from baseline in HbA1c level	Alogliptin efficacy was sustained over 2 years in patients with inadequate glycaemic control on metformin alone	Del Prato *et al*., 2014
104	linagliptin 5 mg; Glimepiride > 4 mg	Least square mean change from baseline in HbA1c level	Linagliptin was found non inferior to glimepride, with fewer cardiovascular events	Gallwitz *et al*., 2012
104	Saxagliptin 5 mg; Glipizide > 20 mg	Long-term safety, tolerability and efficacy of saxagliptin *vs.* glipizide	Saxagliptin was well tolerated, similar safety profile to glipizide, lower risk of hypo-glycaemia and no weight gain	Göke *et al*., 2013
104	Sitagliptin 100 mg q.d Glipizide > 20 mg	Change in HbA1C from baseline	Sitagliptin improved glycemic control similar to glipizide but with lesser risk of hypoglycaemia and weight gain	Seck *et al*., 2010
52	Vildagliptin 50 mg b.d; Gliclazide> 320 mg	Change in HbA1C from baseline	Vildagliptin provided similar glycemic control comparable to glicazide	Filozof *et al*., 2010
16	Teneligliptin 20 mg placebo	Reduction in HbA1C level after 16 week	FDC of tenligliptin/ metformin was well tolerated and effective in T2DM	Kim *et al*., 2015
24	FDC of linagliptin o.d (5 mg), metformin b.d (> 2000 mg)	Change in HbA1c from baseline after 24 weeks	Combination of linagliptin and metformin provided better glycemic control compare to linagliptin monotherapy	Ross *et al*., 2016
24	Gemigliptin 50 mg o.d placebo	Change in HbA1c from baseline to 24 weeks	Gemigliptin add on to metformin and sulfonylurea significantly improved glycemic control	Ahn *et al*., 2017
24	Sitagliptin 100 mg o.d; Placebo; Add on to metformin and sulfonylurea	Change from baseline in HbA1c after 24 weeks	Sitagliptin add on to metformin and sulfonylurea significantly improved glycemic control	Ba *et al*., 2017
24	Linagliptin 5 mg o.d; Placebo; Add on to metformin and pioglitazone therapy	Change in HbA1c from baseline to 24 weeks	Addition of linagliptin significantly improved glycemic control	Bajaj *et al*., 2014
52	Saxagliptin o.d (5 mg); Placebo; Add on to metformin and dapagliflozin	Change in baseline to 52 week in Hb1Ac	Sustained improvement in glycemic control without weight gain	Matthaei *et al*., 2016
78	Alogliptin < 25 mg o.d; Placebo; with standard care	Composite of first incidence of cardiovascular death, non fatal myocardial infarction and non fatal stroke	Cardiovascular risks were not increased with alogliptin compare to placebo	White *et al*., 2018
156	Sitagliptin 100 mg; Placebo	CV death, MI, stroke, or hospitalization for unstable angina	There was no increase in cardiovascular risk with saxagliptin *vs.* placebo	Green *et al*., 2015
114	Linagliptin 5 mg; Placebo	MACE-3 (major adverse cardiovascular endpoint)	No significant difference in occurrence of cardiovascular risk with linagliptin compare to placebo	Rosenstock *et al*., 2019

Table 2 *Continue...*

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110	Saxagliptin 5 mg; Placebo	Cardiovascular death, ischemic stroke or myocardial infarction	Saxagliptin not altered the speed of ischemic accidents but increase the rate of hospitalization for heart failure	Scirica *et al*., 2013
432	Linagliptin 5 mg o.d; Glimipride < 4 mg o.d	First 3-point Major Adverse Cardiovascular Events (3P-MACE)	Linagliptin was found non-inferior to glimipride for cardiovascular safety	Rosenstock *et al*., 2019
16	FDC (saxagliptin 5 mg + Metformin 2000 mg); Saxagliptin 5 mg; Metformin 2000 mg	Change of Hb1Ac from baseline to 16 week	FDC was found non-inferior to separate tablets	Elkind-Hirsch *et al*., 2017
2	Zemimet SR (Gemigliptin/Metformin SR 25/500 mg)	Pharmacodynamic and pharmacokinetic parameter	FDC tablet was found as suitable option for T2DM patient	Sang-In Park *et al*.

Vardarli *et al*., 2014). Table 1, presents an outline of phase III clinical studies on the safety and efficacy of DPP4I.

The TROICA study assessed efficacy of DPP-4I as add on therapy to sulfonylurea and metformin in T2DM patient not reaching Hb1Ac <7% with combination treatment of metformin and sulfonylurea. This study compared once daily 50 mg dose of gemigliptin with placebo in T2DM patients poorly managed with metformin hydrochloride and glimepiride. After 24 weeks, gemigliptin addition to metformin and glimepiride therapy reduced *hemoglobin A1c* (HbA1C) significantly more compared with placebo (-0.88% *versus* -0.01%; 95% confidence interval [CI] -1.09% to -0.64%, p<0.001 (Ahn *et al*., 2017). Jianming Ba *et al*., also reported improvement in glycemic control by adding sitagliptin to metformin and sulfonylurea in adequately controlled T2DM patient (Ba *et al*., 2017). Similar efficacies of DPP-4I as add on to pioglitazone and metformin therapy in T2DM patient adequately managed by metformin and pioglitazone (Bajaj *et al*., 2014).

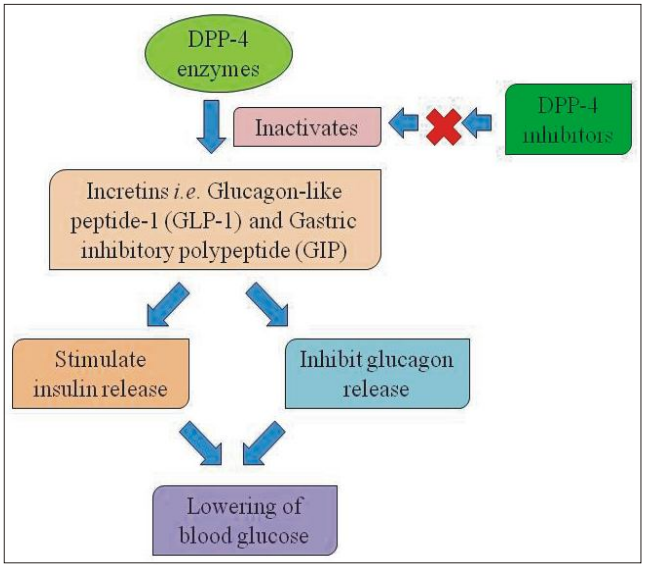

Fig. 1: Mechanism of action of DPP-4I.

Matthaei and his colleagues reported greater reduction in Hb1Ac with saxagliptin in comparison to placebo in T2DM patient having insufficient glycemic control with FDC of dapagliflozin (SGLT-2 inhibitor) and metformin. Study outcome illustrated that addition of DPP-4I to dapagliflozin and metformin has lesser risk of hypoglycaemia and loss of body weight in comparison to single/double therapy with dapagliflozin (Matthaei *et al*., 2016).

In 2008, the American Food and Drug Agency (FDA) agreed that marketing approval for all new anti-diabetic products will be mandatory on showing that they are not linked to increased cardiovascular (CV) risk. This resulted in massive randomized CV safety outcome studies being carried out by producers of new drugs intended for sale in the US (Deacon, 2018). Four DPP-4I CV safety studies have been completed and published up to this point: The EXAMINE study (alogliptin *vs*. standard of care) (White *et al*., 2011), the TECOS study (sitagliptin *vs*. placebo) (Green *et al*., 2013; Green *et al*., 2015), CARMELINA study (linagliptin *vs*. placebo (Rosenstock *et al*., 2019), SAVOR-TIMI 53 study (saxagliptin *vs*. placebo) (Mosenzon *et al*., 2013; Scirica *et al*., 2013)

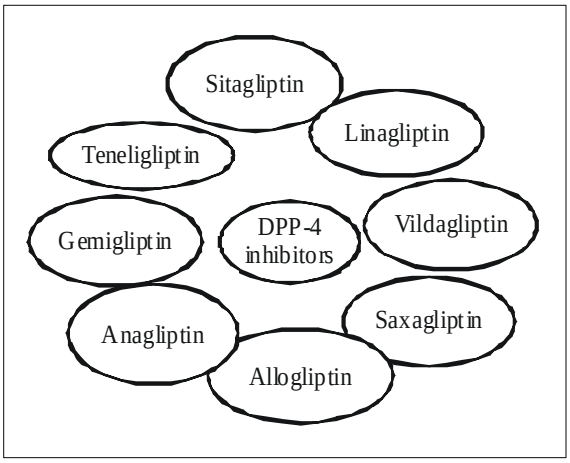

Fig. 2: Examples of DPP-4I.

Table 2: DPP-4I formulation approved by USFDA and EMA till Aug 2019 (https://www.accessdata.fda.gov/scripts/cder/daf/ ;https://www.ema.europa.eu/en/medicines).

Brand	Composition	Regulatory body	Date of approval
Janumet	Metformin hydrochloride; Sitagliptin phosphate	USFDA	March 30, 2007
Janumet xr	Sitagliptin/Metformin hydrochloride extended release	USFDA	February 2, 2012
Januvia	Sitagliptin phosphate	USFDA	October 16, 2006
Juvisync	Simvastatin; Sitagliptin phosphate	USFDA	October 7, 2011
Steglujan	Ertugliflozin; sitagliptin phosphate	USFDA	December 19, 2017
Kombiglyze xr	Saxagliptin/metformin hydrochloride extended-release	USFDA	November 5, 2010
Onglyza	Saxagliptin hydrochloride	USFDA	July 31, 2019
Qtern	Dapagliflozin; Saxagliptin hydrochloride	USFDA	February 27, 2017
Qternmet xr	Dapagliflozin, saxagliptin, and metformin hydrochloride extended release tablets	USFDA	May 2, 2019
Kazano	Alogliptin and metformin hydrochloride	USFDA	January 25, 2013
Nesina	Alogliptin benzoate	USFDA	January 25, 2013
Oseni	Alogliptin and pioglitazone	USFDA	January 25, 2013
Glyxambi	Empagliflozin and linagliptin	USFDA	January 30, 2015
Jentadueto	Linagliptin; metformin	USFDA	January 30, 2012
Jentadueto xr	Linagliptin; metformin hydrochloride extended release	USFDA	May 27, 2016
Tradjenta	Linagliptin	USFDA	February 5, 2011
Incresync	Alogliptin and pioglitazone	EMA	September 19, 2013
Vipdomet	Alogliptin and metformin	EMA	September 19, 2013
Vipidea	Alogliptin	EMA	September 18, 2013
Kombiglyze	Saxagliptin and metformin hydrochloride	EMA	November 14, 2011

and CAROLINA study (linagliptin *vs*. glimipride) (Marx *et al*., 2015). All these studies demonstrated safety at CV for the various DPP-4I. The studies found a quite homogenous outcome if compared with the effect on the primary endpoint. As for the secondary end point hospitalization because of heart failure, the results of the study are heterogeneous. Now a day's FDCs of DPP-4I and metformin extended release tablets are available in market. Fewer randomized double blind clinical trials have revealed safety and efficacy of these said FDCs. Such studies have shown that the DPP-4I FDC tablet and the controlled release of metformin can be a convenient therapeutic choice in T2DM patients needing a combination approach (Elkind-Hirsch*et al*., 2017; Takahashi *et al*., 2019).

Recent Patents on DPP-4I formulations

In the last ten years, DPP-4I have been investigated for their use in treatment of T2DM and it has been observed that DPP-4I adequately control glycemic index with reduce with fewer adverse effects. Table 2, shows different DPP-4I containing formulation approved by regulatory bodies. Various FDC of metformin hydrochloride and DPP-4I were approved by USFDA and EMA. Combination of DPP-4I with pioglitazone was approved by both USFDA and EMA. The USFDA approved JUVISYNC (sitagliptin and simvastatin), indicated when both DPP-4I and HMG Co-A reductase inhibitor is appropriate. Three FDCs of DPP-4I and SGLT-2 inhibitor were approved by USFDA: STEGLUJAN, QTERN and GLYXAMBI. QTERNMET XR, triple combination SGLT-2 inhibitor, DPP-4I and metformin was approved by USFDA as an adjunct to diet and exercise to control Hb1Ac in T2DM patient already taking metformin.

Various patents have been granted over DPP-4I formulations. Table 3, demonstrates an overview of these patents. The patent WO2019132833A1 is related to pharmaceutical product containing linagliptin and modified release metformin. Further this patent describes method for the preparation of formulation. The pharmaceutical tablet formulation comprises of two layers: core containing metformin and sustained release agent; first layer containing coating agent and second layer containing coating agent and linagliptin.

US patent US20190099367A1 is related to a pharmaceutical chewable dosage form of metformin hydrochloride and sitagliptin to a mammalian patient. The patent discloses that matrix comprises sitagliptin, metformin hydrochloride, a fully or partially pregelatinized starch, a polyethylene glycol, a lubricant, an emulsifier, a flavouring agent and a sweetener.

The patent US20180235911A1 is related to pharmaceutical tablet comprising FDC of alogliptin with metformin hydrochloride and method for formulation. It

Table 3: Recent patent (2015-2019) on DPP-4I dosage form.

Patent/application number (publication year)	Patent description	Reference
WO2019132833A1 (July 4, 2019)	This work describes composition and preparation of FDC oral tablet of metformin and linagliptin	Türkyilmaz *et al*., 2019
United States Patent Application No. 20190099368 (April 4, 2019)	This work relates to chewable tablet containing sitagliptin and metformin	Omwancha and Burlage, 2019
WO2017033115A1 (March 2, 2017)	The work illustrates process for formulation of FDC of alogliptin and metformin hydrochloride	Khapra *et al*., 2017
Publication No. WO 2018/185669 Al (October 11, 2018)	This work was directed towards effervescent composition of saxagliptin alone or in combination with metformin hydrochloride	Bobba *et al*., 2018
Publication No. WO2018/033808 Al (February 22, 2018)	This work presents composition of coated tablet comprising the combination of teneligliptin and metformin	Fiore, 2018
WO2017029609A1 (February 23, 2017)	This research discloses composition containing combination of alogliptin and metformin	Abraham *et al*., 2018
WO2017093419A1 (June 8, 2017)	This investigation elaborates composition of layered tablet comprising linagliptin and extended release metformin layer.	Boeck *et al*., 2017
WO 2016/059378 A1 (April 21, 2016)	This work discloses composition and methods for saxagliptin hydrochloride formulation.	Engstrom *et al*., 2016
WO2017/088812 A1 (June 1, 2016)	This patent relates to composition and process for preparation of eutectic mixture of saxagliptin and metformin with molar ratio 1:1	Chen *et al*., 2017
WO2015071889A1 (May 21, 2015)	This patent describes composition and process for oral dosage form of saxagliptin alone and further relates to combination of saxagliptin with other antidiabetic agents.	Agarwal *et al*., 2015

was observed that the FDC of alogliptin/metformin was not chemically stable as primary and tertiary amino group of alogliptin shown incompatibilities with the excipients such as lactose and other reducing sugars (Khapra *et al*., 2018). The US patent US20110206766 disclosed that in attempts to prepare pharmaceutical compositions of selected DPP-4I it has been noticed, that the DPP-4I with a primary or secondary amino group show incompatibilities, with a number of customary excipients such as microcrystalline cellulose, sodium starch glycolate, cross-carmellose sodium, tartaric acid, citric acid, glucose, fructose, saccharose, lactose, maltodextrins (Friedl *et al*., 2011). The patent US8900638 is related to a more stable solid pharmaceutical preparation containing metformin hydrochloride and alogliptin, which are separated therein from each other (Yamamoto and Koyama, 2014). The US20110206766A1 is also disclosed that use of nucleophilic and/or basic agent within pharmaceutical preparations comprising DPP-4I in combination with metformin hydrochloride can overcome incompatibility issue (Friedl *et al*., 2011).

The patent WO2018/185669 A1 is related to effervescent composition containing saxagliptin and process of preparation for same. The invention is disclosed that effervescent composition containing acidic agent, basic agent and optionally metformin hydrochloride. The work is disclosed that choice and ratio of acidic and basic agent affects the quality of effervescent composition of saxagliptin. The ratio may range from 1:3 to 3:1 in present invention (Bobba *et al*., 2018). The patent US 20190099367A1 described material and preparation method of chewable dosage form containing sitagliptin and metformin hydrochloride (Omwancha and Burlage, 2019).

The patent WO2018/033808 Al is related to pharmaceutical composition in the form of a coated oral tablet containing teneligliptin or metformin alone or their salts thereof, for T2DM treatment. The pharmaceutical composition is obtained by means of wet granulation, using metformin ground to a fine powder and a low load of excipients consisting of a binder, in this case povidone and magnesium stearate as a lubricant during compression. The use of ground metformin considerably improves the compressibility of same, allowing operative conditions to be optimised. Compared with the two active ingredients separately and vehiculised in the form of coated tablets, the improved pharmaceutical composition comprising the combination of teneligliptin and metformin show no differences *in-vitro* release (solution) and, moreover, improved the compressibility of the powder and the friability of the tablets (Fiore, 2018). The patent WO2017029609A1 relates to a stable pharmaceutical formulation consisting of an intimate combination of alogliptin with metformin and an effective pharmaceutically suitable excipient/s; where metformin

is contained in almost 3.3 parts or greater by weight compared to 100 parts by weight of the overall weight of the alogliptin component. Invention also encompasses different development procedures (Abraham *et al*., 2018). The patent WO2017093419A1 is related to pharmaceutical compositions comprising a FDC of the three active pharmaceutical ingredients linagliptin, empagliflozin and metformin hydrochloride wherein metformin hydrochloride is in extended release form (metformin XR); procedures for its formulation and its application in the treatment of many of these disorders (Boeck *et al*., 2017).

Conclusion

Clinical studies and DPP-4I patents demonstrated their safety and effectiveness in patients with T2DM without increasing cardiovascular risk. It was concluded, therefore, that the development of fixed-dose combinations of DPP-4I with other hypoglycaemic agents could be used effectively in diabetes control.

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Conflict of Interest

The authors report no conflicts of interest in this work.

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