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AN REVIEW ON ANTI DIABETIC BI-LAYERED MODIFIED RELEASE TABLETS

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Abstract:
The aim of the current study work was to formulate and assess a fixed dose mixture tablet of instant release oral solid dosage form comprising two anti-diabetic drugs (linagliptin and metformin hydrochloride) for managing of diabetes mellitus type 2.The innovator drug product (Jentadueto Tablet) was evaluated for the various evaluation parameters, which have been taken into consideration during the drug product development. Pre-formulation evaluation was accomplished to safeguard better parameters of formulated drug product. On the result of pre-formulation evaluation and innovator drug product characterization, the model drug product was recognized in various steps. The established formulation was augmented for different excipients. The instant release film covered tablet of linagliptin and metformin HCl was expressed and augmented at laboratory scale. The individual steps (procedures) were improved for the same and the scale-up contemplation have been engaged into account certify the product performance at pilot plant-up to commercial scale-up. Keywords: anti-diabetic, linagliptin, metformin.

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INTRODUCTION:

Major causes of death during last decade are coronary heart disease (cardiac problem), stroke, chronic pulmonary obstructive disease (COPD), diabetes mellitus and lower respirational infections. The diabetes instigated 1600000 (2.8%) deaths in 2015, up from 1000000 (1.8%) demises in 2000 1,2. As per report of International Diabetes Federation, the projected number of diabetic patients (age group 20–79 years) in global prevalence are 463.0 million, 578.4 million and 700.2 million in 2019, 2030 and 2045, respectively.

Thus, in global prevalence, the diabetic patients are increase day-by-day; as number of patients are increased yearly in top diabetic countries. From these data, it seems that all countries are playing a game (diabetes disease) and competes to become a winner player (first position in number of diabetic patients). Surprisingly, from the present data analysis, the number of diabetic patients in Pakistan would be higher than USA in 2045. Diabetes is one of the most common non-communicable disease globally and it is two types: Diabetes mellitus – metabolic disorder characterized with elevated level of blood sugar. Diabetes insipidus – metabolic disorder of salt and water metabolism characterized by strong thirst and heavy urination. As per World Health Organization (WHO), "diabetes mellitus is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves".

The FDC has been well advocated by Halimi S. et. al and Gohel N. et.al by effectively described single tablet of vildagliptin and metformin for the management of type II, that has proved better control of glycaemic control and enhanced patient compliance 3-4. Similarly, Blonde L. et. al has been encouraged for the FDC as therapy for type 2 diabetes mellitus by giving numerous examples of the same 5. In the same way, bilayer tablet of vildagliptin and metformin was articulated in the form of matrix tablet as instant release of vildagliptin and prolonged release of metformin over the 12 hours. The crospovidone (superdisintegrant, 10%) and gaur gum (controlled release polymers, 30%) were used for the immediate release and sustained release layer, respectively 6. Kupsal K et. al has been also summarized the dose of metformin with all the antidiabetic classes for the management of glycaemic control in diabetic patients 7. Fenugreek mucilage was used for bioadhesive agent to prepare sustained release layer of the metformin consisting Carbopol 934P (rheology modifier), sodium alginate (binding agent), both grade of hydroxypropyl methylcellulose (HPMC K4M and HPMC K 100M). As similar with other reports, vildagliptin was also compressed with super-disintegrating agent to prepare immediate release layer of bilayer tablet to treat patients with type II diabetes 8.

A combination therapy of metformin hydrochloride (MET) and linagliptin (LINA) achieves a perfect glycemic control in person with diabetes. Present work is focusing towards formulation of immediate release formulations of metformin hydrochloride and immediate release linagliptin in a single layer. Object of the current research work is to formulate and develop a tablet of fixed dose of quick release oral solid dosage form containing anti-diabetic drugs (linagliptin – DPP-inhibitor and metformin - biguanide) for management of type-II diabetes. Thus, the aim of current research was to articulate static dose amalgamation of two anti-diabetic medicines (linagliptin and metformin hydrochloride) in which they are envisioned for instantaneous drug action.

Place of DPP-4/Metformin Combination Therapy in T2DM Guidelines

Currently available treatment guidelines from the American Diabetes Association (ADA)/European Association for the Study of Diabetes,2 the American Association of Clinical Endocrinologists (AACE),3 the International Diabetes Federation (IDF),12 and the United Kingdom's National Institute for Clinical Excellence (NICE),13 recognize metformin as a first-line therapy because of its efficacy, low risk of hypoglycemia, and weight loss. Recommendations regarding the agents to be added when treatment needs to be intensified are less specific. The IDF and NICE guidelines mention sulfonylureas (SU) ahead of DPP-4 inhibitors. The ADA does not prioritize second-line agents, but stresses individualization of therapy.2 The AACE algorithm lists glucagon-like peptide (GLP)-1 agonists and DPP-4 ahead of thiazolidinediones (TZD) and SUs.3 Moreover, some guidelines call for initial combination therapy for patients with levels of glycated hemoglobin (HbA1c) 7.5%3 or 9.0%.2,3 SPCs are not specifically recommended because guidelines do not highlight.

Mechanism of Action, Metabolism, and Pharmacokinetic Profile of Linagliptin and Metformin Linagliptin and metformin exert their glucose-lowering effects through complementary mechanisms. Linagliptin inhibits the DPP-4 enzyme, thus prolonging the half-life of the intestinal incretins,

GLP-1 and gastric inhibitory polypeptide. This results in enhanced glucose-dependent insulin secretion and decreased glucagon production, leading to an overall improvement in glucose homeostasis both in the fasting and post-prandial state.14 In addition, preclinical data have shown that linagliptin, via its incretin-enhancing effects, can slow disease progression by preserving pancreatic β-cell mass and function.15,16 The mechanism of action of metformin is independent of insulin secretion and occurs mainly through inhibition of hepatic gluconeogenesis17,18 and improved peripheral insulin sensitivity.19 Its glucose-lowering effects can be observed in the fasting state after overnight inhibition of gluconeogenesis.12,13 Moreover, metformin increases GLP-1 production in obese patients with and without T2DM, and a recent study confirmed that metformin monotherapy increases GLP-1 levels postprandially independent of DPP-4 activity.20 Thus, the use of the linagliptin/metformin SPC may lead toa further increase in GLP-1 levels, potentially resulting in additive or synergistic glucose-lowering effects.

Pharmacokinetic/Pharmacodynamic Studies on Linagliptin and Metformin Alone and in Combination

Several studies have assessed the pharmacokinetic and pharmacodynamic properties of linagliptin and metformin alone and in combination.21 In a randomized crossover study of 16 male subjects, linagliptin 10 mg once daily (QD) and metformin 850 mg three times daily were each given alone and in combination. Coadministration of both agents had no clinically relevant effects on the pharmacokinetics and pharmacodynamics of either agent.22 Because linagliptin monotherapy is administered once daily, whereas metformin is administered twice daily, assessment of the pharmacodynamics and pharmacokinetics of linagliptin administered twice daily was required to facilitate development of the SPC. A 7-day crossover study in 16 healthy subjects showed bioequivalent exposure and similar DPP-4 inhibition with linagliptin 2.5 mg twice daily (BID) when compared with linagliptin 5 mg QD.23 Furthermore, the bioequivalence of three linagliptin/metformin SPC strengths and the corresponding combination of loose pills (linagliptin 2.5 mg plus metformin 500 mg, 850 mg, or 1000 mg) was evaluated in three separate prospective, randomized, open-label, single-dose, two-way crossover studies in healthy volunteers (n = 287).24 The 90% confidence intervals (CI) of the adjusted geometric mean ratios of the maximum plasma concentration and the area under the plasma concentration–time curve were within bioequivalence acceptance limits of 80% to 125%. The authors concluded that SPCs of linagliptin plus metformin are bioequivalent to the individual tablets.24 Another study showed that food does not have a clinically relevant effect on the administration of linagliptin/metformin SPCs.

Clinical Evaluation of Linagliptin/Metformin LPC

Findings from clinical trials of linagliptin and metformin administered as LPCs show significant improvements in HbA1c and fasting plasma glucose (FPG) compared with metformin alone. The safety profile of the LPC was similar to that of placebo and metformin, with a low risk of hypoglycemia and weight neutrality. These trials include patients across a wide spectrum of hyperglycemia, with baseline HbA1c levels ranging from □7.0% to □12.0%. Linagliptin as add-on to metformin compared with placebo. The addition of linagliptin to metformin in patients with T2DM whose glycemia is not well controlled on monotherapy has been assessed in several clinical studies.4,6,7 In a dose-ranging study, 333 patients were randomized in a double-blinded fashion to linagliptin (1, 5, or 10 mg QD), placebo, or open-label glimepiride (1–3 mg QD) for 12 weeks. Placebo-corrected HbA1c levels were -0.73% and -0.67% for 5 and 10 mg of linagliptin, respectively, compared with -0.9% for glimepiride. The only hypoglycemic events reported occurred in glimepiride patients (n = 3).4 In a 24-week, randomized, placebo-controlled study of patients inadequately controlled on metformin (□1500 mg/day), addition of linagliptin 5 mg resulted in clinically and statistically significant placebo-corrected reductions in HbA1c (-0.64%), FPG (-1.2 mmol), and 2-hour postprandial glucose (-3.7 mmol/L). Hypoglycemia was rare, occurring in three patients receiving linagliptin and five patients receiving placebo; the authors attribute this difference to the glucose-dependent actions of linagliptin. Body weight of these patients did not change significantly from baseline.

In addition to the studies of once-daily add-on linagliptin, Ross et al6 evaluated if linagliptin 2.5 mg BID provided comparable efficacy and safety to linagliptin 5 mg QD when added to metformin BID (maximum dose 1500 mg/day) in 491 patients with T2DM and inadequate glycemic control. After 12 weeks, mean placebo-adjusted reductions in HbA1c were -0.74% for linagliptin 2.5 mg BID and -0.80% for linagliptin 5 mg QD, with a treatment difference of 0.06. Thus, linagliptin 2.5 mg BID had non-inferior HbA1c-lowering effects when compared with linagliptin 5 mg QD, with comparable safety and tolerability. The incidence of hypoglycemia was low.

Linagliptin as add-on to metformin compared with SU. In a 2-year, parallel-group, non-inferiority study, patients with T2DM receiving metformin background therapy were randomized to either linagliptin 5 mg (n = 777) or glimepiride (1–4 mg; n = 775) QD.5 Reductions in adjusted HbA1c levels were similar in both groups (linagliptin, -0.16%; glimepiride, -0.36%) and met the non-inferiority criterion. The incidences of hypoglycemia (58 of 776 [7%] vs 280 of 775 [36%] patients, P 0.0001) and cardiovascular (CV) events (12 vs 26 patients; relative risk 0.46, 95% CI 0.23–0.91) were significantly lower in the linagliptin group than those in the glimepiride group. The currently ongoing Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA®) trial is the largest headto-head CV outcome trial, to date, that directly compares an SU (glimepiride) with a DPP-4 inhibitor (linagliptin). This study will provide a unique perspective with respect to CV outcomes with these two commonly used agents.

Initial combination of linagliptin and metformin. Initial combination therapy may be advantageous in treating T2DM, as it targets the numerous pathophysiologic defects early.11 In a 24-week study, 791 patients were randomized to one of the six treatment regimens: (1) linagliptin 2.5 mg plus metformin 500 mg BID, (2) linagliptin 2.5 mg BID plus metformin 1000 mg BID, (3) metformin 1000 mg BID, (4) metformin 500 mg BID, (5) linagliptin 5 mg QD, or (6) placebo.8 Mean placebo-corrected reductions in HbA1c were -1.7% (linagliptin + high-dose metformin), -1.3% (linagliptin + low-dose metformin), -1.2% (high-dose metformin), -0.8% (low-dose metformin), and -0.6% (linagliptin). Thus, initial combination therapy with linagliptin plus metformin was superior to metformin or linagliptin monotherapy with respect to efficacy and had a comparable safety profile. Sub group analyses of placebo-corrected HbA1c change by baseline HbA1c indicated that the efficacy response to initial combination therapy was greater in randomized patients with higher baseline HbA1c levels (8.5% HbA1c 11.0%) than with moderate HbA1c levels (HbA1c 8.5%). These findings were strongly corroborated by the large HbA1c reduction of -3.7% in the open-label cohort (baseline HbA1c 11.0%).8 In a 1-year extension of this study, patients previously in treatment groups 1 to 3 continued their regimen (non-switched, n = 333), whereas patients in treatment groups 4 to 6 were rerandomized to one of the three continuing regimens (switched, n = 233). Patients in the non-switched group maintained HbA1c reductions over the 1.5-year period (-1.63%, –1.32%, and -1.25%, respectively) for treatment groups 1, 2, and 3. Patients in the switched groups showed additional HbA1c reductions.9 Subgroup analyses of unadjusted HbA1c change by baseline for the non-switched group indicated that the efficacy response was greatest in patients with higher baseline HbA1c levels (9%) compared with those with moderate levels (HbA1c 8.0% to 9.0%). Notably, only 14 of 31 patients with baseline HbA1c levels 9% remained in the metformin monotherapy group at the end of the extension trial (Table 2).9 A recent 24-week study was conducted in adults newly diagnosed with T2DM who were randomized to linagliptin 5 mg QD (n = 157) or linagliptin 5 mg QD plus metformin BID (uptitrated to a maximum of 2000 mg/day; n = 159}.

Formulation development

Pre-formulation studies viz. solubility, particle size distribution, compressibility index, drug-drug interaction, drug-alkalizing agent interaction were performed to ensure better parameters of developed product. On the basis of preformulation study and reference product characterization, the prototype formulation was developed in different steps vis. excipient selection, feasibility trial, dissolution test. The developed formula was optimized by dissolution studies.

Pre-formulation study

The pre-formulation parameters viz. solubility of APIs (linagliptin and metformin HCl), particle size distribution, compressibility index of the powder, tapped and bulk density of the powders of the APIs, powder microscopy of APIs and drug-drug interaction study would enlighten the track of the product development of proposed study.

Solubility –

Linagliptin was found to exhibit pH-dependent solubility in aqueous media, where solubility was found to be high in acidic media and decreased with an increase in the pH of the media Thus, it has been concluded that the linagliptin is highly soluble over a pH range of 1.2-7.4 as per BCS (Biopharmaceutics classification system).In the similar fashion, the solubility of metformin hydrochloride was also performed in different buffers including water. It was observed in between 266.24 - 324.59 mg/mL, which is indication of the freely soluble drug in water its different buffers.

Compressibility index-

For linagliptin, it was found to be 28.54 %, which was determined from the tapped density (0.701 mg/mL) and bulk density (0.501 mg/mL) of the linagliptin

powder. This compressibility index (28.54%) has poor flow property but the dose of linagliptin (2.5 mg) was very low compare to total weight of the tablet or powder to be tablet. Similarly, the compressibility index of metformin HCl was found to be 31.22 %, which was determined from the tapped density (0.771 mg/mL) and bulk density (0.530 mg/mL) of the metformin HCl powder. The poor compressibility index (31.22%) of metformin was observed which leads to capping during tableting .

Drug-drug interaction & stabilizer –

Metformin hydrochloride in the presence of water (moisture) is less likely to interact with linagliptin and may results in the formation of N-acetyl derivative. Therefore, due to decreased level of total impurities related to linagliptin with meglumine, meglumine was best stabilizer for the proposed combined fixed dosage form of linagliptin and metformin HCl and it was selected for the further optimization of other excipients.

Prototype Formulation Development

The major difference between the innovator product (Jentadueto) and proposed FDC product that the Jentadueto consists of L-arginine as stabilizer in the core tablet, whereas meglumine was included in the proposed product. Both proposed formulation and the RLD comprise standard excipients consistent with the design of immediate release solid oral dosage form. On the basis of pre-formulation studies and innovator product (Jentadueto) characterization, the unit formulas for immediate release tablets of linagliptin and metformin hydrochloride in all the strengths (2.5 mg/1000 mg; 2.5 mg/850 mg; 2.5 mg/500 mg) were finalized.

The preliminary risk valuation of influence of study variables on product critical quality attributes (CQAs) was analyzed to ensure optimized formulation. The key factor of formulated dosage form was dissolution profile of product, which was governed by medium risk factors (quantity of corn starch and co-povidone). Similarly, quantity of meglumine was evaluated as medium risk for the related substances. In this context, the quantity of corn starch, co-povidone, stabilizer (meglumine), colloidal silicon dioxide and Opadry to ensure the low risk factor.

Uniformity and assay of dosage form –

The % assay of linagliptin and metformin HCl in both strengths were found within the limit as 101.2 % and 100.4 % (middle strength) and 100.0 % and 100.6 % (lower strength), respectively (Fig. 1). Similarly, the uniformity of dosage form for linagliptin was performed as low dose content (linagliptin) in tablet was very important than higher dose content (metformin HCl). It was observed for middle and lower strength tablets in between 100.9-103.3% and 98.6-99.9%, respectively.

Dissolution profile –

The dissolution profile middle and lower strengths of the test formulations were about 10-25 % faster than the reference product strengths. As per bioequivalence study; it has been observed that difference of 10-15% in the dissolution no significant impact on the therapeutic effect of the dosage form. It was proposed that the 10-25% difference observed between the three strengths was unlikely to have an impact on the in-vivo performance of the test product and was therefore considered to be acceptable. More than 90% drug content (linagliptin and metformin HCl) from all the strengths (higher, middle and lower) was released within 15-20 min .

CONCLUSION:

The immediate release layer tablet of linagliptin and metformin HCl was formulated and characterized at laboratory scale by using meglumine as alkalizing agent (stabilizer). The stabilizer prevents drug-drug interaction between both APIs of the formulated dosage form. It is recommended that in-vitro-in-vivo correlation (IVIVC) of the formulated drug product can be performed to ensure the optimization of the articulated dosage form.

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