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Safety, Efficacy, and Bioavailability of Fixed-Dose Combinations in Type 2 Diabetes Mellitus: A Systematic Updated Review

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ABSTRACT

Purpose: Type 2 diabetes mellitus (T2DM) is a multifactorial disease characterized by insulin resistance. As time progresses, monotherapy often does not provide effective glycemic control, generating the need for an add-on therapy. Hence, multiple oral hypoglycemic agents formulated as a single-dose form called fixed-dose combinations (FDCs) play an essential role in glycemic control. The purpose of this systematic review is to appraise the recently published evidence on the safety, efficacy, and bioavailability of FDCs.
Methods: A comprehensive literature search of PUBMED, Scopus, ScienceDirect.com, ProQuest, SpringerLink, clintrials.gov, Embase, and EBSCO using the key words FDCs, combination therapy, T2DM management, and add-on therapy was conducted. Studies on the safety profile/tolerability, efficacy, and bioavailability of various FDCs of oral hypoglycemic agents were preferred.
Findings: The systematic review of all the publications suggests that FDCs of oral hypoglycemic agents (OHAs) significantly reduce HbA_{1c} and fasting plasma glucose values, thereby efficiently reducing hyperglycemia in patients in whom monotherapy fails. FDCs are the bioequivalent of the concomitant drugs administered as individual components. Improved adherence to FDCs and the absence of serious adverse drug reactions compared with dual therapy play an important role in decreasing the incidence of hyperglycemia in patients with T2DM.
Implications: From this updated review, it was found that metformin was the most widely used component of FDCs with other OHAs. Studies on the safety and efficacy of newly approved OHAs such as sodium glucose cotransporter inhibitors were limited. An increasing number of randomized trials on the safety and efficacy of newly emerging FDCs suggests that they would be better treatment options for T2DM patients.

Type 2 diabetes mellitus (T2DM) is a multifactorial disease affecting multiple organ systems.[1,2] It is characterized by the resistance of cells to insulin, thereby causing hyperglycemia.[3] It is associated with microvascular and macrovascular complications that in the long run can lead to morbidity and mortality.[4,5]

Lifestyle modifications and monotherapy with oral hypoglycemic agents are generally considered first-line intervention for glycemic control.[5,6] As the disease progresses, β cells continue to deteriorate in T2DM patients who require effective glycemic control.[7] Most often, the efficacy of monotherapy decreases after a few years of treatment, resulting in ineffective glycemic control, and does not prevent the progression of disease, which requires an additional agent for effective glycemic control.[8] For the successful management of both insulin resistance and β-cell dysfunction, there arises a need for combination therapy with agents having complementary mechanisms of action formulated in a single-dose form called fixed-dose combinations (FDCs).[9] Sulfonylurea with biguanide and biguanide with thiazolidinedione are the most commonly used fixed-dose combinations.[1] A list of approved combination products available in the global market is presented in Table I.[3,5,8,10–27] The health care professionals should be aware of the role of these products, including their advantages and disadvantages.

Advantages of FDCs

- FDCs help in formulating 2 drugs into a single-dose form, thereby minimizing the medication burden to the patient.
- The relative adherence rates of T2DM patients can be improved.

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Table I
Available FDCs of various oral hypoglycemic agents.

FDCs	Available Doses	Mechanism of Action
Acarbose + metformin[5]	50 mg/500 mg	Acarbose: intestinal carbohydrate digestion is slowed down Metformin: reduces hepatic gluconeogenesis
Rosiglitazone + metformin[10,11]	4 mg/2 g 4 mg/2 g	Rosiglitazone: increases insulin sensitivity
Sitagliptin + metformin[12,13]	100 mg/1000 mg 100 mg/2000 mg	Sitagliptin: stimulates postprandial insulin and suppresses glucagon secretion
Glimepiride + metformin[14,15]	1 mg/500 mg 2 mg/500 mg	Glimepiride: increases insulin secretion from pancreatic β cells
Glibenclamide + metformin[14]	5 mg/500 mg	Glibenclamide: increases insulin secretion from pancreatic β cells
Glyburide + metformin[16,17]	2.5 mg/500 mg 5 mg/500 mg	Glyburide: increases insulin secretion from pancreatic β cells
Vildagliptin + metformin[3,18]	50 mg/500 mg 50 mg/850 mg 50 mg/1000 mg	Vildagliptin: stimulates postprandial insulin and suppresses glucagon secretion
Pioglitazone + metformin[8,19]	30 mg/50 mg	Pioglitazone: increases insulin sensitivity
Repaglinide + metformin[20,21]	1 mg/500 mg 2 mg/500 mg	Repaglinide: increases insulin secretion
Mitiglinide + metformin[22]	10 mg/500 mg	Mitiglinide: increases insulin secretion
Empagliflozin + linagliptin[23]	10 mg/5 mg 25 mg/5 mg	Empagliflozin: reduces renal glucose reabsorption Linagliptin: stimulates postprandial insulin and suppresses glucagon secretion
Glipizide + metformin[24]	2.5 mg/250 mg 2.5 mg/500 mg 5 mg/500 mg	Glipizide: increases insulin secretion from pancreatic β cells
Rosiglitazone + glimepiride[25]	4 mg/1 mg 4 mg/2 mg 4 mg/4 mg 8 mg/2 mg 8 mg/4 mg	Rosiglitazone: increases insulin sensitivity Glimepiride: increases insulin secretion from pancreatic β cells
Pioglitazone + glimepiride[26]	30 mg/2 mg 30 mg/4 mg	Pioglitazone: increases insulin sensitivity Glimepiride: increases insulin secretion from pancreatic β cells
Saxagliptin + metformin[27]	5 mg/500 mg 2.5 mg/1000 mg 5 mg/1000 mg	Saxagliptin: stimulates postprandial insulin and suppresses glucagon secretion

FDCs = fixed-dose combinations.

- FDCs improve glycemic control, showing better efficacy.[5]
- Medical expenditures due to hospitalization can be reduced.[28]
- It decreases the frequency of drug administration in patients with T2DM.[29]
- It prevents polypharmacy.[18]

Disadvantages of FDCs

- Dose titration will be difficult.
- A patient who is satisfied taking separate medications may not switch to FDCs.
- There may be an increase in the number of adverse drug reactions (ADRs).[28]
- The combination may affect the bioavailability of agents.[22]

The objective of this review was to analyze the use of FDCs in glycemic control and their efficacy, safety, and bioavailability in patients with T2DM.

Material and Methods

A comprehensive literature search of PUBMED, Scopus, ScienceDirect.com, ProQuest, SpringerLink, clintrials.gov, Embase, and EBSCO using the key words FDCs, combination therapy, T2DM management, and add-on therapy was conducted. The search resulted in the collection of 128 articles. The search was narrowed down to original research articles on FDCs in T2DM. Editorial letters, reviews, case report studies that included < 30 patients in the study, and articles related to studies in the special population (patients with comorbidities, pregnancy, and lactation) were excluded. The search was restricted to the articles published in English. The search on FDC therapies was concentrated on their efficacy, safety, tolerability, bioequivalence, adherence, and compliance. Of the 58 appropriate articles collected, 36 were included based on the criteria that the studies were conducted in patients with newly diagnosed T2DM and known cases of T2DM with increased fasting plasma glucose (FPG) levels, increased glycosylated hemoglobin (HbA_{1c}) levels, and increased post-prandial blood sugar levels in the age group of 18 to 80 years. The articles were included irrespective of the sex and race in which the studies were conducted. The various methods used in the studies include open-label, prospective, retrospective, randomized, nonrandomized, double-blind, parallel, placebo-controlled, noninterventional, and crossover studies.

The study characteristics such as author, year of publication, type of study, population size, baseline HbA_{1c}, FPG values, and outcomes such as efficacy and safety of FDCs were noted and checked. The systematic review protocol is represented in Figure 1.

Results and Discussion

The effect of FDCs in the treatment of T2DM was addressed by 9 studies, 2 of which were prospective, 1 was observational, and 7 were randomized, double-blind, parallel studies. The outcomes monitored were HbA_{1c}, FPG, and ADRs. An open-label, prospective, multicenter observational study conducted by Ved et al[3] in 2012 on 300 patients with T2DM treated with vildagliptin and metformin FDC showed a highly significant decrease in FBG, postprandial glucose (PPG), and HbA_{1c} values from the baseline at the end of 3 months. The study results showed that FDC of vildagliptin and metformin was effective in reducing the daily dose of insulin in patients with T2DM[3] and no data regarding the ADRs was reported.