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Review

Fixed-Dose Combination-Orally Disintegrating Tablet (FDC-ODT) Studies for the Treatment of Type 2 Diabetes or Cardiovascular Diseases -A Mini Review

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ABSTRACT:
The orally disintegrating tablet (ODT) is a dosage form that stands out for its organoleptic elegancy, better patient compliance, rapid disintegration, and rapid onset of action in geriatric, psychiatric, pediatric, paralyzed, and bedridden patients. Drug combination therapy refers to the concomitant use of two or more drugs used separately or the use of two or more active pharmaceutical ingredients (APIs) in fixed-dose combinations (FDCs) in a single dosage form. FDC drug products have been developed to target a single disease or multiple diseases/conditions. There have been studies showing that taking FDC drug products may be more effective than using dosage forms containing individual APIs. However, the safety, efficacy, and rationality of many FDCs still remain questionable. Furthermore, FDC-ODTs combine the advantages such as better compliance and efficacy of both FDC and ODTs, especially in dysphagic patients and the patients on multiple drug therapy. FDC-ODTs have been prepared for the treatment of different diseases such as Type 2 diabetes, epilepsy, cardiovascular disease, Parkinson's disease. In this mini-review, I aimed to provide an overview with some studies on FDC-ODTs prepared for cardiovascular diseases and Type 2 diabetes treatments in the literature.

Keywords*:* Cardiovascular diseases, fixed-dose combination, orally disintegrating tablet, type 2 diabetes

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1. INTRODUCTION

The ODT is a dosage form that stands out for its organoleptic elegancy, better patient compliance than conventional tablets and capsules, rapid disintegration, and rapid onset of action in geriatric, psychiatric, pediatric, paralyzed and bedridden patients [1–3]. ODT is also called as fast/rapid-dissolving, orodispersible, mouth-dissolving, or fast-disintegrating tablet. Pharmacopeias and Center for Drug Evaluation and Research (CDER) at Food and Drug Administration (FDA) have made some definitions for ODT. The following definition, developed by CDER for ODT, is given in the "Guidance for Industry Orally Disintegrating Tablets": "A solid dosage form containing medicinal

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substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [4]. Besides, European Pharmacopoeia defines ODT as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed. ODTs disintegrate within 3 min" [2,5]. Japanese Pharmacopoeia also defines ODT as follows: "Orally Disintegrating Tablets are tablets which are quickly dissolved or disintegrated in the oral cavity. ODTs show an appropriate disintegration" [6]. ODTs have the advantages of both liquid dosage forms and conventional tablets [2]. APIs with relatively higher doses are difficult to formulate as ODTs. However, some technologies such as Orasolv® technology, and Flashdose technology allow high API loading. APIs' bioavailability can be increased with the use of ODT because some APIs are absorbed from the mouth, pharynx, and esophagus and go down to the stomach in a dissolved form. Also, first-pass metabolism, the dose and side effects of APIs can be reduced. Besides these advantages, there are some limitations for ODTs. For example, ODTs have low mechanical strength compared to conventional tablets, so they need special packaging. Also, it is not easy to formulate bitter APIs as ODTs, so taste masking excipients must be used to develop ODT formulations of such APIs. Again, some excipients, such as surfactants, are needed to formulate poorly water-soluble APIs as ODTs [1,3,7,8].

Drug combination therapy refers to the concomitant use of two or more drugs used separately or the use of two or more APIs in FDCs in a single dosage form [9]. Drug combination therapy can be beneficial for lowering the concentrations of individual APIs, reducing their undesirable side effects, improving patient compliance, increasing therapeutic efficacy, and overcoming drug resistance compared to the use of a single pharmacological agent [10–12]. This approach has become a promising strategy for the treatment of various complex diseases such as diabetes, cancer, and bacterial infections [9,11]. The pharmaceutical industry has been studying the potential to improve the currently used medicinal products, including increasing the efficacy and safety of medicinal products or reducing the side effects of treatment. In this direction, studies aiming to increase patients' access to modern treatments and improve patient compliance have been carried out [13]. The FDA's "combination rule" (21CFR 300.50) states that "(1) each component must make a contribution to the claimed effects; and (2) the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for the intended patient population" [14]. FDC drug products have been developed to target a single disease or multiple diseases/conditions [9]. There have been studies showing that taking FDC drug products may be more effective than using dosage forms containing individual APIs. The importance of FDCs is increasing due to the synergistic effect, lower doses of individual APIs, reduction of side effects, simple treatment plan/reduction in drug (tablet, capsule, etc.) burden, reduced cost and increased patient compliance [13]. On the other hand, there are some concerns about the use of the FDC drug product. These: 1.

Limiting the ability of clinicians to customize dosing regimens (less dosage flexibility), 2. There are difficulties in developing FDC formulations (compatibility issues among APIs and excipients, solubility, etc.), 3. If an adverse reaction occurs, it may be hard to identify the API causing the reaction 4. May cause significant problems in patients using FDC drug products containing broad-spectrum antibiotics, such as antibiotic-associated diarrhea and increased risk of developing resistance to antibiotic/s [9,13]. Despite the positive aspects associated with prescribing FDCs [15], the safety, efficacy, and rationality of many FDCs still remain questionable [15,16]. Various FDCs were even banned due to reasons such as potential safety concern, lack of efficacy, and pharmacodynamic and pharmacokinetic mismatch [13,16–18].

The pharmaceutical industry prepared different dosage forms of FDC, such as tablets [e.g., Synjardy® tablet contains a combination of empagliflozin and metformin hydrochloride (MET)], extended-release tablets (e.g., Synjardy® XR tablet contains a combination of empagliflozin and MET), delayed-release tablets (e.g., Diclegis® delayed-release tablet contains a combination of doxylamine succinate and pyridoxine hydrochloride), ODTs (e.g., Carbidopa and Levodopa ODT contains a combination of carbidopa and levodopa), and capsules (e.g., Lotrel® capsule contains a combination of amlodipine besylate and benazepril hydrochloride), extended-release capsules (e.g., Adderall® XR capsule contains a combination of dextroamphetamine and amphetamine salts) and delayed-release capsules (e.g., Talicia® delayed-release capsule contains a combination of omeprazole magnesium, amoxicillin and rifabutin) [13,19].

FDC-ODTs (two or more APIs-containing ODTs) combine the advantages such as better compliance and efficacy of both FDC and ODTs, especially in dysphagic patients [20] and the patients on multiple drug therapy [2]. However, in the Orange Book ("Approved Drug Products with Therapeutic Equivalence Evaluations"), only FDC-ODTs containing carbidopa and levodopa (strength: 10 mg+100 mg or 25 mg+100 mg or 25 mg+250 mg) for the treatment of the symptoms of Parkinson's disease appear to have been approved by the FDA [19]. FDC-ODT is a suitable dosage form to help patients with Parkinson's who have difficulty taking their medications for various reasons (forgetting to take the drugs, leaving home without the drugs, etc.) overcome these difficulties and facilitate drug use. Poor medication adherence causes inadequate symptom control and undesirable side effects in Parkinson's patients. It has been reported that FDC-ODTs containing carbidopa and levodopa may provide improved patient compliance, ease of use, and rapid access to medication for patients with Parkinson's [21]. Furthermore, in the literature, FDC-ODTs have been prepared for the treatment of different diseases such as Type 2 diabetes [22–24], cardiovascular diseases [25,26], epilepsy [27], Parkinson's disease [21], and Tuberculosis [28].

Therefore, in this mini-review, I aimed to provide an overview with some studies on FDC-ODTs prepared for cardiovascular diseases and Type 2 diabetes treatments in the literature.

2. THE STUDIES ON FDC-ODTS PREPARED FOR THE TREATMENT OF CARDIOVASCULAR DISEASES AND TYPE 2 DIABETES IN THE LITERATURE

Cardiovascular diseases (coronary heart disease, peripheral arterial disease, rheumatic heart disease, cerebrovascular disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism) refers to a group of disorders/diseases of blood vessels and the heart [29]. The incidence of cardiovascular diseases, the leading cause of disability in humans and premature death, is increasing globally [26]. These diseases cause a heavy burden on the economies of low- and middle-income countries, where more than three-quarters of cardiovascular disease deaths occur. Hypertension, hyperlipidemia, obesity, diabetes, unhealthy diet, physical inactivity, and smoking are the risk factors leading to the onset of cardiovascular diseases. Primary approaches for the prevention and treatment of cardiovascular disease include lifestyle modifications (such as improvement in diet, increase in physical activity, and smoking cessation), use of antihypertensives, anticoagulants, lipid-lowering drugs, and antiplatelet therapy. Despite their effectiveness, new treatment approaches are still needed for cardiovascular diseases [26].

In a study on the preparation of FDC-ODTs for the treatment of cardiovascular diseases, optimum ODT formulations containing amlodipine besylate (AB) and/or atorvastatin calcium (AC) [in single (AB-containing formulation=AB-ODT and AC-containing formulation=AC-ODT) or FDC formulations (AB and AC-containing formulation=FDC-ODT; 6.95 mg AB and/or 10.85 mg of AC per 500 mg ODT)] was prepared using Pearlitol® Flash (mannitol-starch copolymer) as a direct compression agent with diluent and disintegrant properties, Avicel PH-102 (microcrystalline cellulose) as a binder and disintegrant, and sodium stearyl fumarate as a lubricant. The hardness and friability values were approximately 108 N and 0.71% for AB-ODT, about 114 N and 1.02% for AC-ODT, and about 118 N and 0.73% for FDC-ODT, respectively. The disintegration time of AB-ODT, AC-ODT, or FCD-ODT formulations was 25.33 sec, 24 sec, and 21.67 sec, respectively. In vitro dissolution studies performed in dissolution media [fasted-state simulated intestinal fluid (FaSSIF) and fed-state simulated intestinal fluid (FeSSIF)] for single or FDC-ODT formulations showed that there was no difference in AB or AC dissolution between single formulation (AB-ODT or AC-ODT) and FDC-ODT formulation (except for AB dissolution from single and FDC formulations in FeSSIF medium). Besides, Papp values for amlodipine and atorvastatin alone and in combination across Caco-2 monolayers were determined. Physiologically based pharmacokinetic (PBPK) modeling, which is a tool for prediction of API absorption through integration of information such as physicochemical and cell-based

permeability data, makes it possible to simulate clinical trials. The researchers found that there was no difference in bioavailability based on pharmacokinetic parameters between FDC and single doses of AB or AC in simulated clinical trials [25].

Statins are widely used to treat hypercholesterolemia and dyslipidemia and prevent the risk of cardiovascular disease development. One of the side effects of statin therapy is myopathy. A study was conducted in the literature to develop an FDC-ODT formulation containing pitavastatin calcium (PC) and lornoxicam (LX), and determine the pharmacokinetic parameters of PC and LX in FDC-ODT (PC+LX-FDC-ODT) by pharmacokinetic study in male Wistar rats [30]. In the PC+LX-FDC-ODTs, PC, which belongs to the statin drug class, was used for the management and treatment of hyperlipidemia, while LX, a non-steroidal anti-inflammatory drug, was used to help in the management of statin-induced myopathy. In that study, PC+LX-FDC-ODTs was prepared by direct compression method. The mean weight, friability, and in vitro disintegration time of PC+LX-FDC-ODTs were found to be as 98.66 mg, 0.84%, and 7.33 sec, respectively. In-vitro dissolution study for PC+LX-FDC-ODTs and the marketed products [Lipidalon® tablets containing PC (1 mg); Lornoxicam® tablets containing LX (4 mg)] was performed in simulated saliva fluid pH 6.8. The amounts of dissolved PC and LX obtained for PC+LX-FDC-ODTs after 10 min were about 79% and 74%, respectively. These results were higher than the amount of dissolved PC or LX obtained for marketed drugs (dissolved PC after 10 min= about 54% for Lipidalon®; dissolved LX after 10 min= about 46% for Lornoxicam®). As a result of the in vivo pharmacokinetic study, the authors determined that the percent relative bioavailability values of PC+LX-FDC-ODT to the marketed products were 286.7% for PC and 169.73% for LX. They emphasized that PC+LX-FDC-ODT is a promising dosage form for immediate co-delivery of both APIs [30].

In another study, FDC-ODT containing amlodipine (5 mg) and valsartan (40 mg) for the treatment of hypertension was prepared by direct compression method. They used synthetic or natural superdisintegrants (synthetic superdisintegrants: croscarmellose, and crospovidone; natural superdisintegrants: banana powder, and gallen gum) in the formulation. The hardness and disintegration time values of FDC-ODT formulations are in the range of 2.9 to 4.2 kg/cm^2 and 23.1-400 sec, respectively. They found that the best disintegration time results were obtained for the formulations containing crosspovidone, and the disintegration time decreased (from 50 sec to 23.1 sec) as the amount of crosspovidone increased (from 45 mg to 135 mg). The formulation containing crosspovidone were quickly disintegrate compared to the formulations containing the other superdisintegrants [31].

Studies in which FDC-ODT formulations were prepared for the treatment of diabetes are also included in the literature. Type 2 diabetes, in which the body's ineffective use of insulin due to peripheral tissue insulin resistance, impaired

insulin production and/or secretion by β cells of pancreatic islets (various degrees of beta-cell dysfunction), is a chronic metabolic disorder that has an increasing prevalence and has become a significant healthcare burden all over the world [32–34]. Type 2 diabetes management includes the use of oral hypoglycemic agents [biguanides (mainly Metformin); sulfonylureas (glyburide, glipizide, glimepiride, gliclazide); meglitinides (nateglinide, repaglinide); thiazolidinediones (pioglitazone, rosiglitazone), alpha glucosidase inhibitors (miglitol, acarbose, voglibose), DPP-4 inhibitors, SGLT2 inhibitors, and bromocriptine] and insulin (it is widely used in combination with oral hypoglycemic agents), as well as lifestyle changes (such as a healthy diet and regular physical activity) and obesity treatment [35,36]. FDC-ODTs can be prepared especially for elderly patients with diabetes and diabetic patients with impaired swallowing function to ensure less tablet intake and ease of use and to improve compliance.

Gulsun et al. [24] prepared MET and Glyburide (GLY)-containing FDC-ODT formulations by two different methods [direct compression (COMP) and lyophilization (L; freeze-drying) methods] using different excipients in these formulations. They performed quality control tests for MET+GLY-FDC-ODTs prepared by COMP or L methods (500 mg MET+ 5 mg GLY-COMP-FDC-ODTs and 250 mg MET+ 2.5 mg GLY-L-FDC-ODTs). In this study, highly porous FDC-ODTs were obtained using L technique, and the hardness, friability, and disintegration time values of MET+GLY-L-FDC-ODTs were 66.54±2.68 N, 0.38%, and 30 sec, respectively. For MET+GLY-COMP-FDC-ODTs, these values were determined as 221.60±40.82 N, 0.24%, and 80 sec, respectively. Although the hardness of MET+GLY-COMP-FDC-ODTs is higher than the preferred hardness value range (30–80 N [37]) for ODTs, these tablets disintegrated in a relatively short time, as expected from ODTs. In addition, MET+GLY-L-FDC-ODTs had a shorter disintegration time than MET+GLY-COMP-FDC-ODTs due to the higher porosity and easier water uptake of L-FDC-ODTs. The authors also determined the water absorption ratio, which is a significant parameter for the water uptake rate and disintegration of ODTs. They reported that the water absorption ratio for MET+GLY-COMP-FDC-ODTs were determined as 1.30±0.05, but this ratio could not determine for MET+GLY-L-FDC-ODTs that disintegrated very quickly without swelling. Moreover, the permeability study across the Caco-2 cell monolayer, which is widely used for drug permeability screening, as well as for the evaluation of the effects of the excipients in the formulation on the drug permeability, was performed. According to Biopharmaceutics Classification System, MET and GLY are classified as Class III (high water solubility and low permeability) and Class II (high permeability and poor water solubility) drugs, respectively. As a result of the permeability study, they reported that unlike COMP-FDC-ODTs, L-FDC-ODTs caused an increase in the permeability of MET and this result may be due to the potential effect of the excipients in the

formulations on Caco-2 permeability. On the other hand, both COMP-FDC-ODTs and L-FDC-ODTs did not affect the permeability of GLY [24].

Mitiglinide, a rapid-acting insulin secretion stimulating agent, and Voglibose, an alpha-glucosidase inhibitor (it lowers postprandial blood glucose levels), are used in the treatment of Type 2 diabetes [22]. Ono et al. [38] showed that an FDC of voglibose (0.2 mg) and mitiglinide (10 mg) significantly reduced postprandial glycemic excursions in Japanese patients with Type 2 diabetes.

Sotoyama et al. [22] prepared FDC-ODT containing mitiglinide and voglibose, ODT containing mitiglinide, ODT containing voglibose, and three corresponding blank-ODTs (without APIs; placebo-ODTs). The hardness and *in vitro* disintegration time values of all prepared ODTs were found to be in the range of 35.7-92.0 N and 18.4-28.7 sec, respectively. Then, they performed two independent clinical trials with healthy subjects to evaluate the clinical pharmaceutics characteristics of ODTs and FDC-ODT (such as disintegration time, the ease of intake of ODTs, the amount of water required for their uptake, palatability of ODTs). In the first trial performed to evaluate the ease of intake of ODT and the amount of water required for their intake, only placebo-ODTs were given to healthy volunteers with 23.0±0.86 years of mean age (8 men and 5 women) to avoid administering APIs. For this purpose, they conducted "a two-phase randomized crossover trial", consisting a phase of taking placebo-ODTs corresponding to ODTs containing single API (two tablets in total) simultaneously and another phase of taking a placebo ODT corresponding to FDC-ODT (only one tablet). As a result of this trial, they found that FDC-ODT, unlike ODTs, could facilitate ODT intake and reduce the water amount required for ODT intake. Furthermore, the second trial was performed on healthy subjects (8 men and 5 women; 23.4±1.6 years of mean age), and the sweetness, bitterness, and general flavor of FDC-ODT or ODTs were evaluated during disintegration and after spitting. For this, "a two-phase randomized crossover trial", consisting a phase of taking an ODT containing mitiglinide and an ODT containing voglibose (two tablets in total) and the other phase of taking an FDC-ODT containing mitiglinide and voglibose (only one tablet). They determined that the disintegration time were 27.9 sec for the phase of taking two ODTs containing single API and 25.3 sec for the other phase of taking an FDC-ODT, respectively. It was found that there was no difference between the FDC-ODT and ODTs in terms of taste assessment (except for the post-spitting sweetness score). It was emphasized that FDC-ODT containing mitiglinide and voglibose can contribute to improving the compliance of patients with Type 2 diabetes [22].

In another study, an FDC-ODT containing MET and glibenclamide was prepared by the melt granulation technique to overcome both the tablet burden, and swallowing problems, occurring at a later stage of diabetes. First of all, the authors prepared eight preliminary FDC-ODTs using two APIs (MET-250 mg/tablet and glibenclamide-2.5 mg/tablet), polyethylene glycol 6000 (PEG 6000; 7 mg or 24.5

mg/tablet), aspartame (1.75 mg/tablet), crospovidone (7 mg or 35 mg/tablet), sodium lauryl sulphate (3.5 mg/tablet), magnesium stearate (3.5 mg/tablet), colloidal silicon dioxide (1 mg/tablet), and microcrystalline cellulose (73.75 mg or 56.25 mg or 45.75 mg or 28.25 mg/tablet). PEG 6000 was used as a binding agent in the FDC-ODTs, and crospovidone was used as a superdisintegrant. Then, the hardness and wetting time values of these preliminary FDC-ODTs were determined in the range of 4.11-10.15 kg/cm^2 and 28-96 sec, respectively. In addition, the effects of 3 independent variables [compression force and the amounts of crospovidone and PEG 6000] on response variables [friability, disintegration time and percent APIs release (at 30 min)] was investigated by applying a two-level full factorial experimental design. Increasing the compression force and the amount of PEG 6000 caused a meaningful increase in the disintegration time of the FDC-ODTs while causing a significant decrease in their friability (%) values. Moreover, it was stated that the disintegration time of FDC-ODTs decreased significantly with increasing the amount of crospovidone, but their friability (%) values did not show a significant change. Based on this information obtained from the preliminary study, the authors further studied the effects of crospovidone, PEG 6000, and compression force on the disintegration time and friability of FDC-ODTs and optimized the formulation using a central composite design. Accordingly, the desired optimum conditions were met when the amounts of PEG 6000 and crospovidone were 3.82% and 9.83%, respectively, and the compression force was 10.6 kN. The predicted friability and disintegration time values of the optimum FDC-ODT were 0.302% and 18.7 sec, respectively. Moreover, the experimental values obtained for FDC-ODT prepared using these optimum conditions were within 5% of the predicted values. As a result, it has been reported that ODTs with faster disintegration time and sufficient mechanical strength have been successfully formulated [23].

3. CONCLUSION

FDC-ODTs have the advantages of providing better patient compliance and increased efficacy, especially in dysphagic patients and the patients on multiple drug therapy. However, it appears in the Orange Book that only FDC-ODTs containing carbidopa and levodopa have been approved by the FDA. In addition, more studies are needed to demonstrate the safety and efficacy of FDC-ODTs, as many FDCs' safety, efficacy, and rationality are still questionable.

Conflict of Interest

Author has no personal financial or non-financial interests.

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