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Review Article

An Overview on Fixed Dose Combinations

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ABSTRACT

Fixed dose combinations have become an important alternative to monotherapies in the treatment of diseases as hypertension, diabetes, *Helicobacter pylori*, AIDS- HIV infections and tuberculosis, asthma and COPD (Chronic Obstructive Pulmonary Disease) by offering several advantages including patients compliance, simple dosage schedule, superior efficacy and tolerability, reduced risk of adverse events, cheaper shipment & packaging activities. This article covers the advantages and disadvantages of FDC'sas well ascritical issues during evaluation of FDC's such as Efficacy, Safety, Bioavailability and Stability.

Key-words: bioequivalence; fixed-dose combination; stability.

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INTRIDUCTION

Fixed-dose combination products (FDCs) are medicines which contain two or more active ingredients in fixed proportions in the same formulation.They are also called as "Fixed Ratio Combinations"[1].Two or more pre-approved active substances are presented on the market in a single product, in fixed-doses. Today, the formulation in fixed-dose combinations and clinical development studies are increased for their use in treating various diseases.

The fixed-dose combinations are usually used for cardiovascular diseases (hypertension, hypercholesterolemia), diabetes, infectious diseases (Helicobacter pylori, AIDS- HIV infections and tuberculosis), psychiatric disorders (depression and Alzheimer's) and respiratory diseases (asthma and COPD) including allergies and in the fields of ophthalmology and dermatology. There are 131 products approved by the FDA from 1990 until 2013. Today, this number has increased with the addition of new products approved by the FDA. The distribution of approved products by therapeutic category is shown in Table 1. As shown in the Table, the therapeutic field working with the 35 products the most is the cardiovascular field[2,3].

Table 1 Approved FDC Products by Therapeutic Category (2)

Therapeutic Category	Approved Products
Cardiovascular	35
Endocrinology	28
Infectious Disease	17
Central Nervous System	11
Respiratory	9
Allergy	7
Opthalmology	6
Dermatology	5
All other (<5 approvals)	13

Delivery route of most of the approved FDC products are oral dosage forms (multi-layered tablets,compression coated, tab in tab, inlay technology as shown in Figure 1); other forms are topical, inhalation, injectable and ophthalmic delivery[2].

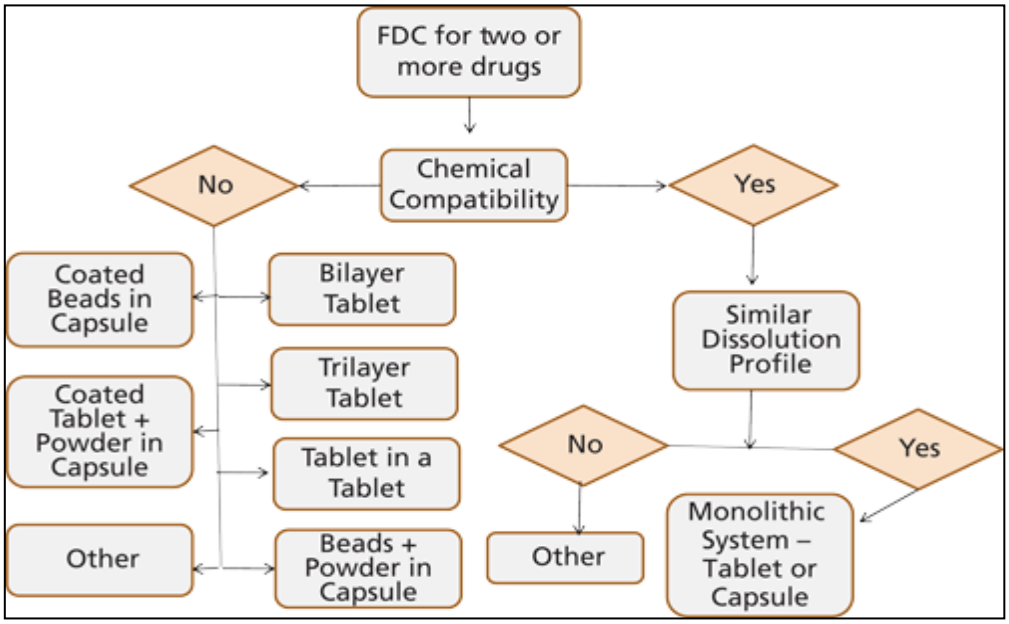

Figure 1: Processes in oral dosage forms (3)

Evaluation parameters of oral dosage forms are; stability indicating assay, dissolution, residual solvents, related compounds, impurity and content uniformity. In order to register the FDC product these parameters should be evaluated and meet the acceptance criteria[4].

According to WHO Guidelines; *"New fixed-ratio combination products are regarded as new drugs in their own right. They are acceptable only when (a) the dosage of each ingredient meets the requirements of a defined population group, and (b) the combination has a proven advantage over single compounds administered separately in terms of therapeutic effect, safety or compliance. They should not be treated as generic versions of single-component products"* [5].

So, FDC products should be evaluated as a new drug and safety, efficacy, tolerability and bioavailability should be justified.

Table 2: Registered Fixed Dose Combinations[5]

Product	Company	FDA Approval
Adderall	Shire	1996
Suboxone	Reckitt-Benckiser	2002
Avalide	Sanofi	1997
Diovan HCT	Novartis	1998
Exforge	Novartis	2007
Lotrel	Novartis	1995
Micardis HCT	Boehringer-Ingelheim	2000
Vytorin	Merck	2004
Janumet	Merck	2007
Yasmin	Bayer	2001
Atripla	Gilead	2006
Combivir	GlaxoSmithKline	1997
Epzicom	GlaxoSmithKline	2004
Tuvada	Gilead	2004
Zosyn	Pfizer/Taiho	1993
Advair	GlaxoSmithKline	2000
Combivent	Boehringer-Ingelheim	1996
Symbicort	AstraZeneca	2006
Complera	Gilead	2011

Advantages of Fixed Dose Combinations

Fixed-dose formulations can offer enough advantages compared to traditional monotherapy.

Patients compliance:FDC may increase patients compliance by taking less tablets on daily basis *(eg.,* 3–4 tablets/day instead of the 15–16 tablets/ day) compared to monotherapy[6,7]. Medication compliance improved by reducing pill burden of patients[8].

Simple dosage schedule: In the treatment of some diseases, such as tuberculosis, 9-16 tables per day may be required to be used. Patients might experience challenges in remembering and using the drug; it is a condition that can create confusion and put patients in distress. With the use of fewer tablets per day, FDA offers a more basic and easy to use schedule[9].

Greater efficacy compared to monotherapy: Data obtained from the studies with FDC combinations showed that FDC combinations have superior efficacy compared to monotherapy[10,11].

Reduced risk of adverse events:In a study, 5 adverse effects were noticed among 1775 hypertensitive patients. Decrease in incidence of adverse effects with FDC compared to the corresponding free-drug combination was noted, except for one case[12].A different meta-analysis reports that the adverse effects associated with the use of 2 drugs combined were less than those associated with those of the 2 drugs given independently[12].

Synergistic effect: Fixed dose combinations come together sometimes to create a perfect combination that has a synergistic effect[13].With Paracetamol's quick onset action andTtramadol's prolonged analgesic effect, it has been seen that the fixed dose combination of these two drugs create a synergistic analgesic effect[14,15].

Inhibition of microbial resistance:Infectious pathogens develop antimicrobial resistance against drugs. Inherently, microbes may be resistant to anti-infective agents or may develop resistant toanti-infective agents. This resistance can be prevented by different mechanisms generated by different drugs.Fixed dose combinations are more effective to eliminate or slow down antimicrobial resistances compared to monotherapydrugs and free dose combinations[16]. Tuberculosis patients treated with Rifampicin Mono drug, and when the treatment involves a short period of use, resistant micro-organisms immediately develop resistance to the drug. In the fixed-dose combination of Rifampicin containing isoniazid, the development of micro-organisms developing resistance to Rifampicin and their spread is slowed down[9].

Cheaper shipment & packaging activities: Reducing costs and simplifying the logistics flow of purchasing and distribution of complex antimicrobial regimes are acceptable targets in reaching public health outcomes inlow incomecountries. FDCs can successfully contribute to all of these elements, under condition that they do not put the therapeutic outcomes at risk[5].A possible outcome of using FDCs is the reduction of the overall costs of delivering treatment to patients and preventing shortages of individual drugs, by decreasing the cost of managing the drug supply[5].

Disadvantages of Fixed Dose Combinations

Reduced dosage flexibility:Fixed-dose antihypertensive combination products have the disadvantage of lacking the dosing flexibility for its individual components. However, since Amlodipine and Atorvastatin both have several dosage strengths (dose range: 5-10 mg Amlodipine/ 10-80 mg Atorvastatin), these drugs will not be concerned. Furthermore, fixed-dose combination antihypertensive/dys-lipidemic therapy may not provide a sufficient amount of drug to treat illnesses like angina (in cases where Amlodipine is necessary with doses higher than 10 mg) that can be found together with hypertension[17].

Drug interactions: Drug interactions may occur between active ingredients and excipients which are used in the FDCs according to chemical properties of the substances under the environment (acidic/basic/humidity etc…). Drug interactions are important issues because they may change the therapeutic effect, and may cause the potential incompatibilities and moreover affect the stability.In the fixed-dose combinations ofArtesunate (ART) and Amodiaquine hydrochloride (AMQ), drug interactions occur between active ingredients according to potential incompatibilities of the different chemical compounds, particularly the Artemisinins. In order to solve this problem, they have been produced as bi layer tablets to limit the contact between them and to prevent the degradation[18].

In case of Rifampicin directly interacting with Isoniazid, the interaction will be between the imine group of Rifampicin and the amino of Isoniazid.This causes chemical instability between two drugs. In order to prevent this interaction, modified tablet in tablet formulation has been developed[19].

***Misidentifying the causative ingredient when the patient experiences side effects*:**
If an FDC is believed to be the source of an adverse drug interaction, to find the active ingredient responsible for this reaction may be difficult. In order tosolve challenge, the treatment is initiated with the monotherapy of the drugs; the patient is then monitored for a while and in the case no side-effects are observed, the combination drug therapy can then be administered[20].

Critical Issues During Evaluation of FDC'S

Safety/Efficacy

Whereas the safety is an important sign with regards to the administered of the drug, the efficacy is an important sign with regards to the therapeutic advantage of the FDC compared to monotherapy. Effectiveness and tolerability of fixed dose combination of Amlodipine/Valsartan in treatment of hypertension Egyptian patients were evaluated. The results of this study indicated that single pill combination of Aamlodipine/Valsartan effectively reduced BP (Blood Pressure) with high tolerability profile[21].

Fixed-dose combination of Amlodipine and Valsartan (Exforge®) has been shown to be more effective in lowering BP than Amlodipine and Valsartan mono drugs in randomized trials with comparable side effect profile. Amlodipine and Valsartan fixed-dose combination is well tolerated and simplifies antihypertensive regimen enhancing patient adherence and a better BP control compared to monotherapy[22].

A fixed-dose combination of the orally inhaled Umeclidinium bromide (UMEC) and Vilanterol administered as a maintenance treatment for patients with COPD. The study results confirm that both agents were well tolerated and significantly improved lung function compared with placebo over 24 h in patients with COPD[11].

The efficacy and safety of Acarbose plus Metformin fixed-dose combination (FDC) compared with Acarbose monotherapy for Type-2 diabetes. The study findings confirmed that Acarbose/Metformin FDC has superior antihyperglycemic efficacy than Acarbose monotherapy[10].

Bioavailability/Bioequivalence (BA/BE)

The common approach for the approval of the FDCs is the bioequivalence between the FDC and the mono drugs previously used. The demonstration of bioequivalence between the FDCs and the mono drugs can be very difficult and sometimes, especially insoluble molecules in mono-drugs can complicate the biopharmaceutical and pharmacokinetic behaviors. The BE condition and the acceptance criteria for FDC components are listed in FDA, EMEA and in local regulations[23]. The bioequivalence study was conducted between Triamterene–Hydrochlorothiazide fixed dose generic product and reference product in healthy volunteers. Results obtained from this study showed that the test and reference products were bioequivalent[24].

Bioavailability was evaluated in a study of Amlodipine/Benazepril tablet versus capsule formulation. The results of this bioavailability comparison study in this population of healthy male volunteers suggest that the tablet and capsule formulations of combination Amlodipine-Benazepril are bioequivalent. Both formulations were well tolerated[25].

Oral Bioavailability of 4-Drug Fixed-Dose Combination containing Rifampicin, Isoniazid, Ethambutol and Pyrazinamide compared with the separate mono drugs in healthy male volunteers. The results

obtained from this study show that the combined formulation was bioequivalent to separate formulations of Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide at the same dose levels[26].

Stability

It is possible that having different pharmaceutically active ingredients may start interactions or incompatibilities that may lead to destabilization; in order to overcome this problem, some modifications should be done during development in order to assure that the product will remain stable during the period defined in the regulations.

The study indicatesthat Rifampicin interacts with Isoniazid and especially in acidic medium of stomach degrades substantially. If enteric coating polymers are intruded in the manufacturing of the Isoniazid by covering it so that physical contact between these two drugs can be prevented in the stomach, the interaction and degradation of Rifampicin can be reduced and the stability can be enhanced by modifying the release of Isoniazid in intestinal pH[27].

The presence of Hydrochlorothiazide in fixed dosage form affects the Cilazapril stability and the Cilazapril degradation reaction accelerates significantly, shortening of the reaction induction time, andincreasing the observed reaction rate constant. Since further Cilazapril destabilization is related to the elevation of temperature and relative humidity values, the Cilazapril-Hydrochlorothiazide pharmaceutical formulations should be preserved in dry and low temperature environmental conditions. It has been proven that protection against Cilazapril decomposition in the presence of Hydrochlorothiazide was provided by OPA/Alu/PVC//Alublister[28].

CONCLUSION

The use of FDC therapy has been widely accepted in recent years due to its convenience and advantage they provide for treatments. Instead of taking two or more drugs, the use of a single medication has eased the patient's life as well as physicians in prescribing drugs. Since they are the combination of pre-approved drugs, they can be easily administered to patients. The synergistic effect induced by two drugs and with different mechanisms, many problems such as the development of resistance to the drug, stability and side effects can be prevailed. It offers a simple and feasible dose schedules for some patients, such as tuberculosis, who are required to use many tablets during the day. In addition to these advantages, the lack of flexibility in dosage, side effects due to one of the components in the content of the drug and the interactions with other drugs have caused restrictions on the administration of the drug. Although the interactions of the drug has been attempted to be solved by different manufacturing processes, studies on this issue are still continuing.In the light of studies carried out in recent years and the approved products, FDC combinations will be preferred to be used in the treatment of various diseases in the coming years due to largely achieved criteria in anticipated different mechanisms, pharmacokinetic compliance, reduction in the number of drugs, additive effect, reduced side effects, superior efficacy and tolerability, profiles of bioavailability similar to monotherapy and acceptable stability criteria.

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