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Fixed-Dose Combinations: Innovations, Formulation Strategies, and Regulatory Challenges

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ABSTRACT
FDCs (fixed-dose combinations) are used in medicine formulations comprising a single dosage form with two or more active components, offering benefits such as improved patient adherence, reduced pill burden, and modified drug profiles.Key types of FDC formulations include hard capsules, bilayer tablets, multilayer tablets, hot-melt extrusion (HME), and 3D-printed tablets. Hard capsules, such as those containing tamsulosin and dutasteride, offer quick drug release and stability. Bilayer tablets combine immediate and sustained drug release, improving patient convenience, especially in chronic conditions like type 2 diabetes. Multilayer tablets, with controlled release patterns, are used for treating conditions requiring multiple dosing schedules. HME enables targeted and modified drug delivery, while 3D-printed tablets allow precise, customized dosing. These innovative FDC formulations contribute to enhanced drug efficacy, safety, and patient adherence, highlighting the importance of advanced technologies in modern pharmaceutical development.Approval of Fixed-Dose Combinations (FDCs) requires essential documents like chemical data, therapeutic rationale, and drug-drug interaction lists. In India, Treasury challan fees depend on the active substances' approval duration. Regulatory bodies emphasize safety, efficacy, and consistent drug release, especially for diseases like malaria and HIV/AIDS, avoiding narrow therapeutic index ingredients.
Key Words: FDC, API, Bilayer Tablets, Pharmaceutics

I. INTRODUCTION

In pharmaceutical technology, the phrase "fixed-dose combination" (FDC) denotes a combination of medications that contain a minimum of two A single dosage form containing active pharmaceutical ingredients (APIs) that is produced & marketed as aproduct with fixed dose.

FDC are particularly appealing to patients who are on many medications since they improve drug adherence and lessen pill burden. FDCs can also alter the pharmacokinetic and pharmacodynamic profile of medications, which can alter their in vivo behavior as compared to monotherapy. (1)

These benefits of combined treatment could be brought about by the use of only suitable, fixed-ratio, multiple-target medication combinations that, when taken together, lower a number of risk variables without increasing the likelihood of adverse repercussions for the pertinent diseases.

AIDS, malaria, TB, and cardiovascular (CV) disorders have all been linked to all been effectively treated with FDC drug products. The World Health Organization (WHO) and regulatory bodies in many nations have acknowledged the substantial contributions these products have made to improving public health through improved patient care and cost-effective compliance. (2)

A recent study found that a combination product increased the medication compliance rate compared to dual therapy regimens, which is an extra advantage for patients.(3)

When compared to conventional pharmaceutical processing methods, it offers the following benefits: easier dose modification, decreased dose dumping, modulation of drug release, delivery of incompatible medications, and increased patient compliance for fixed dose combination formulation.(4)

Even though there are disagreements over the use of FDC medications, numerous pharmaceutical companies can record billion-dollar earnings and create a new market by launching new FDCs. More data on the compounds' safety and effectiveness would be accessible if all of the FDC product's active pharmaceutical ingredients had already received approval for use in humans. This would be beneficial for both drug developers and

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health authorities. There are notable discrepancies and a lack of alignment in the regulations governing fixed-dose combinations (FDC) between the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). In the US, a combination of set doses drug is characterized as "a drug product in which two or more separate drug components are combined in a single dosage form." This definition is akin to that of the EMA; however, the phrase "combination product" is uniquely defined by the US FDA. It refers to a product that consists of two or more components, which may include combinations of drug/device, biologic/device, drug/biologic, or drug/device/biologic. (5)

FDC products are generally designed to address a specific disease, exemplified by antiretroviral FDCs used in HIV treatment, such as Truvada® (comprising tenofovir and emtricitabine) and Atripla® (which includes efavirenz, tenofovir, and emtricitabine). Nevertheless, some FDCs are formulated to manage multiple conditions, as seen with Juvisync™ (a combination of sitagliptin and simvastatin) aimed at treating type 2 diabetes and elevated cholesterol levels. Regulatory bodies have provided various guidelines for the industry concerning the development of FDC products.

Utilizing a combination of medications can also improve tolerability by lowering the risk of side effects by enabling each treatment to be taken at lower dosages than would be necessary if taken alone. (6)

The growing popularity of FDC development and marketing is partially attributable to the fact that evidence-based guidelines for many chronic clinical illnesses call for the simultaneous use of numerous medicines in intricate regimens.

The pharmacological activity and modes of action of the APIs that will be utilized in the creation of an FDC ought to be distinct or comparable. APIs must also treat closely related diseases or the same disease utilizing distinct modes of action, and they must have few drug-drug interactions in order to be considered as candidates for FDC formulation.(7)

The pharmaceutical industry's introduction of novel combinations two or more active components combined in one tablet) could serve as an example.

- Hard capsules composed of pellets, microcapsules, mini-tablets, or liquid mixtures encapsulated in microcapsules
- Bilayer tablets
- Multilayer tablets
- Oral dose forms that are gastrically retained (floating capsules, hydrodynamically balanced systems, raft-forming systems, expandable) • Delivery systems that use co-extrusion and hot-melted extrusion
- Three-dimensional (3D) printing technology

Pharmacological mechanisms, biopharmaceutical properties, pharmacokinetics, metabolic pathways, drug-drug interactions, clinical experience, manufacturing feasibility, and the necessary dosages of each API are typically taken into consideration when choosing the active pharmaceutical ingredients (APIs) for FDC formulation (7).

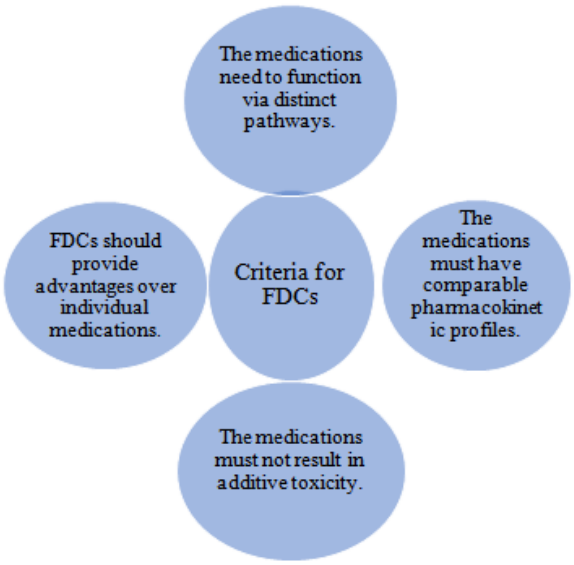

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Table. 1 Benefits and limitation of fixed dose combination(8)

Benefits	Limitation
Lower doses of medications improve treatment tolerance, reducing adverse effects and enhancing safety profiles.(9)	FDCs may result in reduced efficacy, unexpected side effects, added unnecessary medications, and inappropriate dosages. (2)
Simplified therapy leads to better therapeutic outcomes without requiring increased efficacy or safety. (2)	FDCs have limited flexibility in dosage and a variety of strength combinations are developed to compensate, but they may not be suitable for patients requiring frequent dose adjustments.
FDC products combine multiple medications with different mechanisms (e.g., anti-hypertensive, anti-viral), enhancing clinical value.	Due to the combination of drugs in a single dosage unit, it can be challenging to pinpoint the source of adverse drug reactions.
Combining medications like misoprostol and diclofenac in FDCs improves safety and tolerability, e.g., Arthrotec® tablets.	Pharmacists may struggle to track patient regimens, especially when drugs like metformin are contraindicated in specific conditions, such as elevated blood creatinine levels.
FDC products reduce production costs and streamline distribution, offering a cost-effective solution for pharmaceutical companies.	Restrictions on certain medications in FDCs, like the acetaminophen limit, may be overlooked, leading to potential overdose risks when combined with other drugs.
FDC products help pharmaceutical companies maintain their product pipeline, especially amid the decline of blockbuster drugs. (10)	The large size of FDC tablets may be challenging for young or elderly patients to swallow. (10)

Types of FDC formulations

Hard Capsules with Combinations of Fixed Doses

The two-part hard capsule, which was created in the 19th century, remains a common medicinal dosage form business. It is also an appropriate dosage form for administering FDC. In 1834, France granted the very first patent for the production of capsules along with their own capsules. These were capsules of hard gelatin. They used a cold brass rod to solidify hot liquid gelatin as their production method. The capsules were well-known both in France and elsewhere very fast. In 1835, 3.5 tons of gelatin were consumed in France alone.

Gelatin and hydroxypropyl methylcellulose (HPMC) capsules are the two primary types of capsules utilized as dosage forms in the pharmaceutical industry(9)(11). Traditionally, gelatin capsules are made from animal products. They dissolve quickly in all biological mediums, allowing for the medication to be released in 5–10 minutes. Compared to gelatin capsules, HPMC is a plant-based capsule that is more flexible and stable. The introduction of HPMC has made it easier to fill hygroscopic materials, which was difficult with conventional gelatin capsules. Technological developments in capsule filling have led to a natural evolution of the combination capsule products. Formulation scientists can now accomplish a mixture of liquid filling for capsules and powder filling. The spheres and pellets can be mixed with liquid, or small capsules filled with liquid can be put into bigger capsules filled with liquid. Hard capsules are used as medication containers in several successful FDC products. (9)

Bilayer tablets

In order to effectively treat a condition, bilayer pills combine combining two medications—either the same or different into one dosage.

Over the past ten years, the development of controlled or sustained drug delivery systems has accelerated due to a significant amount of focus being placed on the marketing of novel therapeutic molecules, since an increasing number of these molecules are being combined to treat various diseases that call for diverse dosing schedules. Patients comply with bilayer tablets, which are beneficial for either introducing two drugs in succession or releasing the same medication continuously and instantly as an initial dose and a maintenance dose.

Enhanced patient convenience because fewer daily doses are required compared with the standard delivery method, which improves the

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effectiveness of the medication regimen. It is in charge of separating incompatible components and preserving chemical and physical stability.(12)

To combine One medication unit containing an SR & IR dose, a number of FDC bilayer tablets with two dosages have been produced. The complexity of dosage and the possibility of improper administration can be decreased by this effective pharmaceutical formulation (Mandal and Pal, 2008). Most individuals with type 2 diabetes mellitus (T2DM) usually need more than two oral dose forms to control their blood glucose levels (Blonde et al., 2014, Han et al., 2019). In patients with poorly managed glycemia, changing medications or increasing the dosage of a prescription drug that is currently in use Infrequently produces the expected results. When a T2DM patient has poor glycemic control, adding another antidiabetic medication to the current prescription frequently results in better glycemic control. The several combination therapies have shown improvement in glycemic control in comparison with monotherapy (13)

Example

1. The suggested bilayer tablets were found to be an effective method for delivering the intended sustained atenolol release for an extended duration of up to 12 hours and the atorvastatin's rapid release in the current study. Of the total weight of the sustained-release and fast-release layers, 10% w/w xanthan gum and 10% w/w guar gum were used to create the sustained-release layer of these tablets. The Atorvastatin-CD solventresult of evaporation was present in a drug/CD molar ratio of 1: 3, which was discovered to be beneficial for improving the dissolution characteristics of atorvastatin in acidic media.

2. Oral combo therapy is necessary for diabetic patients to have adequate glycemic control. Metformin is the first-line treatment for diabetes, whereas one dipeptidyl peptidase-4 inhibitor with less adverse effects is saxagliptin. The objective of this study is to apply QbD, or quality by design) to create a bilayer tablet of saxagliptin and metformin inFDC that will provide both immediate and sustained release of saxagliptin and metformin, ultimately leading to improved patient compliance.

Methods: Using QbD, the bilayer tablet was created in four stages. The first step involved defining the bilayer tablet's quality target product profile (QTPP) and recognizing the essential quality attributes (CQAs) using a risk estimation matrix&Taguchi design. The second step involved optimizing the immediate-release saxagliptin layer, the third step involved optimizing the sustained-release metformin layer, and the final step involved preparing and characterizing the bilayer tablet. (14)

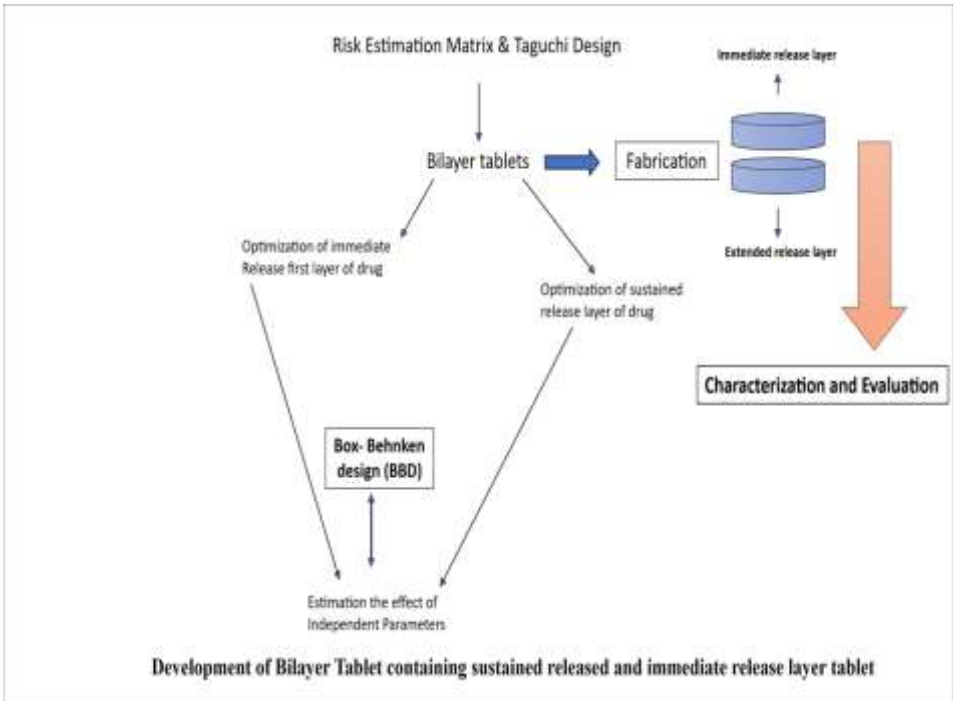

Fig. 1 schematic diagram of formulation of bilayer tablet

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Multilayer tablets

A multi-layer pill may be created by combining two or more incompatible medications. Because the active components have regulated release patterns, multi-layer tablets are preferred. When it comes to the same active ingredient, modified/controlled release formulations are more advantageous than quick release dosage forms. Modified or regulated drug release products are made to maximize treatment plans and increase patient compliance and convenience. Maintaining a consistent level of drug administration is the primary goal of controlled release systems.

Powdered materials are compressed under compression force to create monolayer and multilayer tablets. Despite having many common technological aspects, the process of manufacturing a multi-layer tablet is sensitive. In its final single body, layered Tablets consist of two or more separate layers separated by an interface, making them heterogeneous systems. The release kinetics in these systems are largely controlled by the makeup of each layer. The quantitative and qualitative composition of the final layered tablets, as well as their propensity to bend after each layer of tablet compression, determine their properties, including hardness and lamination tendency.(15)

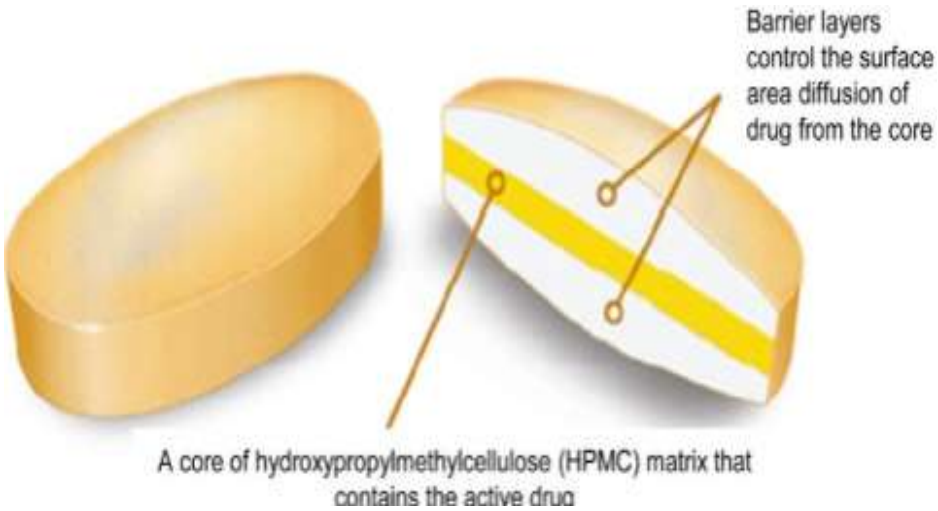

Fig.2 Diagram of Multilayer Tablet (15)

MULTI-LAYER TABLETING CONSIDERATIONS

The feeder and the suction produced by the downward sliding punch promote the powder flow during the first layer of a multi-layer tablet's filling. These stations are moving quickly beneath the feed frame on a high-speed press, and in well-designed tablet presses, the downward-moving punch doesn't start to draw down until it is beneath the feed frame. A suction is produced by the lower punch's quick downward motion. This effect only aids in the first layer's filling in a multi-layer tablet; hence, the flow properties of the second or any following layers play a significant role in maintaining weight. Once the weight has been adjusted, moderate forces are used to tamp the first layer. (typically,well below 1 kN). Special upper punch tooling with longer tips might be required since the first layer is positioned at the bottom end of the die. The lower punch position and first layer thickness determine the maximum fill depth that can be reached for future layers. The lower punch should be positioned to prevent excessive over-filling of the second layer, which will reduce excessive movement in the next processes. The lower punch raises the tablet to get the proper filling volume for the second layer after the first layer has been tamped and filled. The initial layer needs to be sufficiently strong to withstand that modification while also retaining enough surface roughness and porosity to guarantee good adhesion between the layers.After filling and dosing of all layers, the finalcompression step takesplace. (16)

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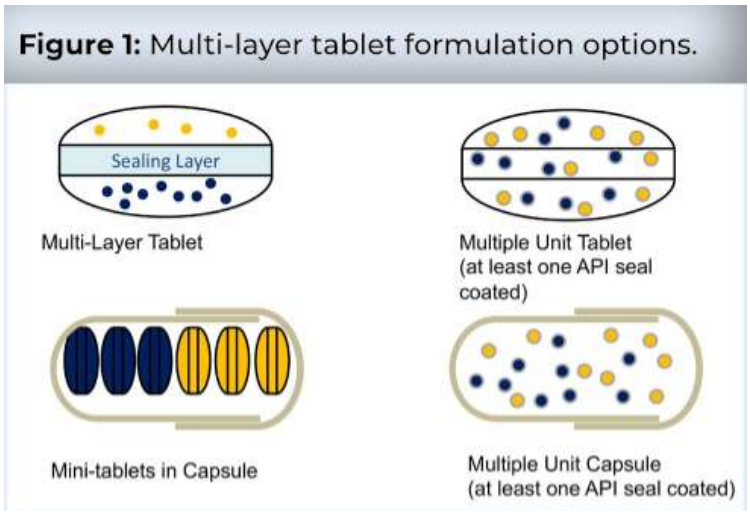

Fig.3 Multilayer tablet formulation option (16)

Hot-melt extrusion

In order to create molecular dispersions of active pharmaceutical ingredients (APIs) into different polymer or lipid matrices, HME has so far emerged as a revolutionary processing technology. This has made it possible for the method to distribute drugs in a time-controlled, modified, extended, and targeted manner. Thanks to HME, materials can now be used to mask the bitter taste of active substances.

Since the extrusion process was first used in industry in the 1930s, HME has attracted a lot of attention from the pharmaceutical industry and academia in a range of applications for pharmaceutical dosage forms, such as tablets, capsules, films, and implants for drug delivery via oral, transdermal, and transmucosal routes. As a result, HME is an excellent alternative to other popular techniques like roll spinning and spray drying.

HME not only satisfies the objective of the US Food and Drug Administration's (FDA) process analytical technology (PAT) system for developing, analyzing, and regulating the manufacturing process via quality control measures throughout the active extrusion process, but it is also a proven manufacturing process.(17)

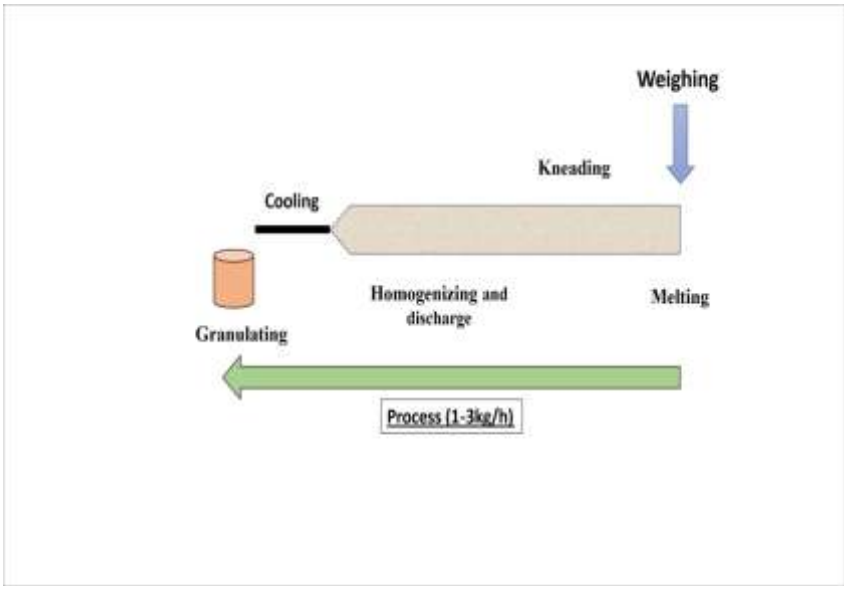

Fig.4 Schematic diagram of Hot melt extrusion formulation

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Example

Capsule-in-capsule dosage form

Each medication has a distinct polymeric carrier. Kollidon 12 PF was chosen for nifedipine, whereas Kollidon SR and VA 64 were chosen for indomethacin. 11 mm twin-screw co-rotating extruders (Waltham, Massachusetts, USA: Thermo Fisher Scientific) were used for the hot-melt extrusion procedures. Three mixing zones and four conveyance zones made up a typical screw design. Additionally, a screw speed of 100 rpm (for NIF formulations) and 75 rpm (for IND formulations) were used, along with an extrusion temperature of 180 °C.(18)

3D-Printed tablet dosage form

For the NIF and IND formulations, two physical combinations were made. 10% NIF, 10% (w/w) Polyplasdone, and 80% polyethylene oxide N80 made up the first, whereas 30% IND, 45.5% HPMC E4, 19.5% HPC LF, and 5% Kollidon CL made up the second. 11 mm twin-screw co-rotating extruders (Thermo Fisher Three mixing zones with a conventional screw design (Scientific, Waltham, MA, USA) and four conveying zones chosen for all formulations—were used to extrude NIF and IND filaments. For both formulations, the screw speed was maintained at 100 rpm, and the extrusion temperatures were 140 °C for NIF and 180 °C for IND. (18)

Challenges for FDC

1. Dosage ratios and proportionality of active ingredients.
2. Number of active component dosage strengths.
3. Physicochemical mismatch between the FDC formulation's active ingredients or active ingredients and excipients
4. Drug–drug interactions.
5. Alterations in the active ingredients' pk profiles and drug release (or dissolution).
6. Requirements for the development of multiple concurrent analytical and testing techniques for active components.
7. Requirements for developing novel medication delivery and combination formulation technologies.
8. Rise in the bulk volume (or weight) of the medication.
9. Unfavourable aspects of manufacturing and processing.
10. A rise in quality characteristics.
11. Increase in stability testing items. (2)
12. This approach is not recommended if there is a high chance of be failure.
13. Certain medications are known to have either beneficial or detrimental effects on diet. Compared to when fasting, when administered with a high-fat meal, the drug's bioavailability is greatly enhanced in the event of good food effects. When administered with high-fat meals, the bioavailability is considerably reduced for the adverse dietary effect. (10)

Case Studies

Ritonavir and Protease Inhibitors in a Fixed-Dose Combination

The FDC for ritonavir and indinavir demonstrated the purposeful application of DDI potential to encourage the combination use of the two drugs. Ritonavir was thought to improve the bioavailability of indinavir, which was demonstrated to be largely processed by CYP3A, in this particular instance of the use of CYP3A inhibition. When indinavir and ritonavir were administered together, Indinavir's systemic exposure rose 3.5 times more than when indinavir was administered alone, according to a DDI study evaluating exposure after indinavir/ritonavir treatment. One distinction in the study design was that while the combination trial was carried out with a low-fat diet present, the indinavir monotherapy pharmacokinetic investigation was carried out while fasting (19)(20).

Therefore, this study suggested the most plausible reason was CYP3A4 inhibition for the increased indinavir exposure, even though it was challenging to determine whether this was due to a synergistic effect of both CYP3A4 inhibition mediated by ritonavir, increased absorption mediated by reduced fat, or both. The possible CYP3A4 inhibition-mediated bioavailability enhancement by ritonavir might have been better understood by a comparable investigation of the combination conducted under fasting conditions. The notable increase Compared to the trough concentrations of indinavir (0.13 mg/L) without ritonavir, the trough concentrations of indinavir (1.40 mg/L) with ritonavir were more than 10 times greater, was another noteworthy factor that supported CYP3A4 inhibition by ritonavir. (19)(20). By Kakuda et al. assessed a similar method of boosting the bioavailability of darunavir using the CYP inhibition potential of ritonavir by performing a pharmacokinetic study in healthy subjects and comparing the bioavailability of darunavir when administered with ritonavir as an FDC vs. monotherapy of darunavir (20). According

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to the data, darunavir's bioavailability when combined with ritonavir was 1.7 times more than when used alone, indicating a major role for CYP3A-mediated metabolism and DDI potential. (19)(21)(20).

A Fixed Drug Eruption Caused by an Ofloxacin-Ornidazole Fixed-Dose Combination:

A 25-year-old man came in with a history of recurrent skin eruption episodes after taking a fixed-dose combination of 200 mg and 500 mg tablets of loxacin and ornidazole on his own. When he took the offending medication for an acute gastroenteritis (AGE) episode two years ago, he became aware of the firstepisode. In the first episode, the anterior region of the thigh, upper abdomen, and chest were affected by erythematous, violaceous, round to oval, flat-topped, rounded maculopapular lesions. After consulting with a local physician, he was prescribed topical corticosteroid ointment and oral antihistaminic medication.At first, the patient was unaware that the medication he was taking was the source of the lesions. He then observed that the same area of the body used to have comparable lesions that would show up there, last for a few days to weeks, and then go away with the affected area's hyperpigmentation remaining distinct from the surrounding skin. In addition to the older hyperpigmented lesions, he also described a few more recent ones. (22)

Documents Are Required for Manufacture/Import and Marketing Approval of FDCs.

Form 44

- If all active substances A Treasury challan of INR 15,000 will be given if they have been authorized in India for more than a year; if any are currently ingredients have been accepted for a period of less than a year, the challan will be INR 50,000. However, if the applicant has already filed an application and a challan of $50,000 for approval of any single active component that is less than a year old, only a challan of $15,000 is needed.
- Complete chemical and pharmaceutical data: for all solid oral dosage forms.
- A therapeutic explanation and rationale for combining them in the suggested ratio, accompanied by relevant literature.
- A list of known and/or anticipated drug-drug interactions involving the active substances listed in the FDC, together with an explanation of the consequences. A qualified individual should draft and sign this on the applicant's behalf.
- Data from published clinical trials that demonstrate the FDC's safety and effectiveness at the same level as those conducted in other nations, if relevant. (23)

Several Essential Conditions for FDC Product Registration Mentioned by Different Regulatory Bodies

- ✓ Every element must contribute to the stated impact
- ✓ Each component's dosage needs to be such that the mixture is both safe and useful
- ✓ A component may be added as a specific application of the first requirement, either to improve the principal active ingredient's safety or efficacy or to reduce the possibility of abuse
- ✓ The length of time that medications take to work shouldn't vary greatly; Combinations of fixed doses for malaria, TB, and HIV/AIDS
- ✓ Drugs should not have narrow therapeutic index or critical dosage range. (24)

II. CONCLUSION

This review article concludes that Fixed-Dose Combination (FDC) formulations are generally safe to use and significantly enhance patient compliance by reducing the pill burden. FDCs offer the advantage of dual synergistic effects, improving therapeutic outcomes. Various formulation techniques, including bilayer tablets, multilayer tablets, and hot-melt extrusion methods, have been successfully utilized to develop FDCs. These innovative approaches contribute to optimized drug delivery, stability, and controlled release, making FDCs a valuable tool in modern pharmaceutical treatments.

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