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Review Article

Fixed-Dose Combination drugs as Tablet in Tablet: A review

P.PAVAZHAVIJI [1*], A. N. RAJALAKSHMI[2]
[1,2]Department of Pharmaceutics, Mother Theresa Post Graduate and Research Institute of Health Sciences, Indira Nagar, Gorimedu, Puducherry - 605006, India
*Corresponding Author
Email: pavazhaviji@gmail.com
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ABSTRACT
The Pharmaceutical industry has become more interested in developing fixed-dose combinations (FDCs) in recent years. FDCs have been used successfully in a variety of clinical areas, including diabetes, HIV/AIDS, and cardiovascular diseases etc. FDCs are intended to extend the product life cycle and enhance patient compliance by decreasing cost. Active Pharmaceutical ingredients are chosen for FDC development based on variety of purposes such as Pharmacokinetic profile, drug-drug interactions, mechanism of action, and manufacturability for successful development. Tablet in tablet technology has gained popularity in recent years for creating modified release products. The compression coating or solvent-free-coating technology is also known as Tablet in Tablet technology. Tablet in Tablet technology is presently the finest alternative technology for the formulation of bilayer tablets for physical separation of active medicines and used to avoid chemical incompatibilities and to produce different drug release patterns such as rapid release, sustained release, controlled release, delayed release, and pulsatile release. This review mainly focuses on combining the techniques of both FDC and Tablet in Tablet formulations which offer a wide variety of benefits such as increased patient compliance, convenience, separation of incompatible ingredients, avoiding close interaction of two drugs, achieving various drug release patterns and maximizing the potency of both drugs over conventional oral dosage forms.

Keywords: Fixed dose combinations, Tablet in tablet technology, Compression coated tablet, Bilayer tablet, delayed release.

INTRODUCTION

FDC

According to Food and Drug Administration, a fixed dose combination product is defined 'as a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product'[1].

Combination drug, also known as fixed dose combinations (FDCs), is Two or more active drugs are combined in a single dosage form that is designed and developed in fixed doses. Individual components' dual or multiple mechanistic actions on distinct therapeutic targets make fixed-dose combination regimens attractive because of the potential for synergistic efficacy. In addition, the unfavorable effects of one of the fixed-dose components can be offset by the positive benefits of the other.

Fixed dose combination products are permitted only when the dose of each ingredient satisfies the demands of a specific population group and when the combination offers a recognized therapeutic, safety, or compliance advantage over the separate components.The pharmaceutical industry has become more interested in developing fixed-dose combinations (FDCs) in recent years. FDCs are intended to extend the product life cycle and increase patient compliance.FDCs have been used successfully in a variety of clinical areas, including diabetes, HIV/AIDS, and cardiovascular diseases[2].FDCs are very common in the Indian Pharmaceutical market, and there is a growing popularity in recent years[3].

The reason for FDCs should be based on a number of factors such as :

The drugs in the combination should act in different ways. The pharmacokinetics must not differ significantly. Within the combination, the substances must not have supra-additive toxicity.

Advantages

Combination medicines combine the advantages of combination therapy with the advantages of lowering the number of pills to be taken, resulting in improved patient

compliance. Manufacturing costs are lowered than compared to the costs of making individual products. When one drug is combined with another, the adverse effects of the first medicine are decreased. Example: levodopa + carbidopa. FDCs can aid in the enforcement of chronic infectious disease care, such as drug resistant strains, treatment failure, and public health risks.
Combining one drug with another will boost the efficacy in a synergistic way. Example: Estrogen+Progesterone,
Sulfamethoxazole+Trimethoprim[4].

Disadvantages

Any component's dose cannot be changed on its own. It is hard to pinpoint a single chemical that has either negative or positive effects. There are more adverse effects in certain fixed dose combinations than others. Example: Nimesulide+Paracetamol .One of the medicines in the combo may be ineffective. Example: Vitamin+Iron. If unneeded drugs are used, the cost will rise. Example: Ibuprofen +Paracetamol+Caffeine[4].

Types Of Fixed Dose Combinations (Fdcs)

FDCs are classified based on the number of constituent drugs present in a product are given in Table 1.

FDCs are classified based on therapeutic effect

Rational: The plasma half-life, peak plasma concentration, and volume of distribution of two or more drugs in a fixed dose combination (tablet, capsule, syrup, powder, and injection) must be the same.
Irrational: An "irrational drug combination" is a drug combination that is illogical in terms of plasma half-life and drug pharmacokinetics.
Absurd: If there is no rationale or justification for combining drugs, there would be no improvement in effectiveness over individual drugs.
Rejected/banned: Formulations have severe side effects and no more therapeutic efficacy than the individual molecule[3].

Formulations In Which Fdc Drugs Are Available

Tablets

Film coated tablets, Bilayered tablets, Trilayered tablets, Tablet in tablets, coated beads in tablets, Chewable tablets, Dispersible tablets

Capsules

Capsule in capsule, Beads and powder in capsule, coated beads in capsule, coated powder in capsule.

Formulation Design And Development Of Fdc Products

FDC product formulation and process development are typically more difficult than single entity product formulation and process development. In general, Active Pharmaceutical ingredients (APIs) are chosen for FDC development based on variety of purposes, and as a result of fundamental understanding of their mechanism of action, drug-drug interactions, Pharmacokinetic profile, and manufacturability for effective development. While choosing APIs, synergistic therapeutic results are desired but difficult to show. Formulation design and development of FDC products are given in Fig. 1.

Monolithic tablet

The monolithic system is the most basic FDC formulation choice. When two or more APIs are chemically compatible with each other and have a similar dissolution or targeted release profile, manufacturing them as a monolithic system in a solid oral dosage form is likely the best choice. The monolithic FDC tablet is comprised of two or more active formulations that have been combined together and compressed into a single layer tablet[7].

Bi-layer tablet

The active components are layered in a bi-layer FDC tablet. Tablet presses with two or more feeding systems and compression rolls are required to compact bi-layer or multi-layer FDC tablets[8].

Trilayer tablet

Trilayer tablet consist of three layers, a trilayer tablet's first layer is for rapid drug release, while the second layer is for long-term drug release. These two layers are separated by an intermediate barrier layer. This is a better option for delivering two drugs that interact with each another. It is made up of two different granulations that are compacted to form a single tablet with three layers; to give the tablet a distinct appearance, each layer is usually a different color. To avoid contamination, dust extraction is required during compression[9].

The core tablet-in-tablet

The core tablet-in-tablet FDC is the most advanced, consisting of a tablet core formulation encircled by a second outer formulation. This FDC tablet is suitable for a quickly dissolving outer layer and a slowly eroding inner layer, with a core: core coat weight ratio of at least 1:4.

Tablet in capsule

Tablet in capsule is a multipurpose and multiple unit system that comprises a hard gelatin

capsule containing adaptable mini-tablets. It may be made by making Rapid-release Mini-Tablets, Sustained-release Mini-Tablets, Pulsatile Mini-Tablets, and Delayed-onset Sustained-release Mini-Tablets with different release lag times and embedded in capsules. The system may be developed to hold two different or similar medicines in immediate and delayed release mini-tablets. Two tablets in a capsule are ideal for the sequential release of two medicines in combination, for separating two incompatible substances, and for sustained release drug administration in which one tablet in the capsule is immediate release as the first dosage and the second is the maintenance dose[10].

Beads in capsule

Beaded capsules are a type of dosage form that contains hundreds of small beads and made up of uncoated beads for immediate release and coated beads for delayed drug release, resulting in a multiple-unit dosage form with varied release properties. The size and shape of the beads within capsules are generally similar. Alternatively, they might be beads of varied sizes on other release patterns[11,12].

Powder in capsule

The majority of capsule filling materials are as powders, consisting of active ingredient and different types of excipients. Excipients are chosen based on a number of factors, including the active drug's characteristics, dose, solubility, particle size, shape, and capsule size[13].

Capsule in capsule

A formulated capsule (liquid-filled or dry-filled) is nested within an outer liquid-filled capsule. Capsule-in-capsule allows a variety of release patterns and may be utilized to overcome stability concerns like moisture absorption.

Tablet-In-Tablet Technology (Compression-Coating Technique)

Tablets are the most popular solid dosage form for oral delivery. Due to its various advantages, controlled or modified release formulations have risen in favor in medical therapy. Although less common; tablet in-a-tablet technology has gained popularity in recent years for creating modified release products. Tablet in Tablet technology is now the best alternative for bilayer tablet formulation for incompatible drugs for developing modified release products. By using specially designed tableting equipment; the granular materials are compressed around a preformed tablet core. The compression coating or solvent-free–coating technology is also known as Tablet in Tablet. Compressed Tablet-In-Tablet diagram given in Fig. 2

In Tablet in Tablet dosage form, the internal core and outer layer are the two components. The internal core is a compact tablet that is made with tooling that is somewhat smaller than that used to make the outer coat. After the production of the internal tablet core, it is located (centrally) another die that is fairly filled with a portion of coating powder and is bigger than the core tablet. The leftover coating powder is then applied to the surface of the central tablet and compressed, resulting in a tablet within a tablet. This procedure will result in problems, such as the core tablet tilting during the changeover to another die. The coat is typically water soluble and disintegrates rapidly after oral delivery to achieve immediate release. Process involved in Tablet in Tablet technology are given in Fig. 3

Advantages Of Tablet-In-Tablet Technology

In the core and outer layers, incompatible materials can be separated. It is used in the preparation of a modified release product. (Example: delayed release product). By using Tablet in Tablet technology, two different drugs can be targeted in two different regions of the gastrointestinal tract. In the press coating of the core and coating layer, the need for a separate tablet coating procedure can be eliminated. It is non-hazardous to the environment because it is a solvent-free coating. Pharmacokinetic interaction (drug-drug) between concomitantly taken drugs can be avoided in Tablet in Tablet dosage form by introducing a time interval in their release. A single Tablet in Tablet dosage form can provide an immediate and sustained release effect of a similar drug or drug combination.

Challenges Related To Tablet In Tablet Technology

The possibility of cross-contamination between layers. Between adjacent layers, the elastic modulus may be unequal. There may be insufficient layer binding and low interfacial strength due to the large elastic modulus ratio between neighboring layers. The device's long-term physical and chemical integrity during storage is a difficulty. It is difficult to swallow due to the large tablet size. When the core tablet is not in the center of the device, the coating performance varies.

Various Drug Release Patterns Involved In Tablet In Tablet Formulation

Immediate release:

Immediate release tablets are designed to dissolve and release the medication without the

use of any regulating elements such as coating or another formulation approach. Disintegrants are used in tablets to ensure that they dissolve quickly in the stomach after swallowing.

Delayed release

Delayed release oral dosage formulations will regulate the drug's release at the site of delivery, such as when it reaches the small intestine (enteric-coated dosage forms) or colon (colon-specific dosage forms). Delayed release systems release a bolus of medication at a predetermined time and location; that is, the drug is not released immediately after intake, for example enteric-coated tablet. The primary goal of using delayed release products is to shield the drug from gastric fluids, minimize gastric irritation caused by drugs that are especially irritating to the stomach, or make gastrointestinal transit easier for drugs that are best absorbed from the intestine.

Controlled release

Controlled release is a drug delivery system that maintains a constant level of drug in the blood and tissues for a long time[23].

Sustained release

Sustained release is a drug delivery system that allows for the gradual release of a drug over a long period of time after a single dose has been administered[24,25].

Pulsatile release

The pulsatile effect is defined as the release of a drug in a "pulse" after a lag period, must be designed so that the lag period is followed by a full and rapid drug release. Such systems are often known as time-controlled systems the drug delivered is independent of the environment. These systems have a unique mechanism for rapidly and completely releasing the drug after a "lag time," i.e., a period of "no drug release" Though most delivery systems are intended for constant drug release over time, pulsatile delivery systems are distinguished by a planned drug release, as constant blood levels of a drug are not always desired. The drug is available at the site of action at the appropriate time and in the right amount due to pulsatile mechanisms[26,27].

Formulation Consideration Of Compression-Coating Technique

Amount of Compression-coating

The amount of coating applied is the most significant factor in achieving uniform coating in compression coated tablets. Generally, Compression coated tablet requires a coating material which is about twice the weight of the core tablet or more, the volume must be greater than that of the core itself. If the core tablet contains low density materials, such as fats and waxes, to provide a consistent volume of coating material for covering the core and adherence of core and coating, the amount or weight of coating must be even greater. Using a new compression technique (one-step dry coated tablet manufacturing method; OSDRC-system), it was recently possible to increase drug loading by lowering the compression coat[28].

Position of core in coated layer

The main drawback of this system is to centralize the core in the compression coated tablets. The reproducibility of drug release from compression coated tablet is questionable, since the faults of press-coating may occur. Examples of press-coating faults are unequal coating, cocking and off-center. However, these drawbacks have been recently overcome by the novel compression tools (OSDRC-system) which placed a core tablet in a certain position. X-ray computed tomography as noninvasive and rapid characterization method in online processing control for Press Coated Tablets (PCT)[29].

Compression force and Compressibility of materials

The coating material has a significant impact on the compressibility of coated tablets. To achieve adequate mechanical strength, the powder coat's cohesion and plasticity are required. The cohesiveness of the coating surrounding the edge of the core is determined by its strength and plasticity reactions to the core's expansion after the final tablets have been released from the die. The final compression force applied to prepare compression coated tablets need to be higher than the compression force that is delivered to the core in order to guarantee core-coat adhesion. Tablets with an adhesive coating can be used as a core to guarantee compression coat and core adherence[30].

Interaction between drug and compression coat

When gellable coating materials are utilized for drug release control, the interaction of the drug and the coating must be taken into account. Compression coated tablets allow the drug to diffuse through the swelling coat. This process might enhance some possible interactions between drug and the coat. The difference in drug release of the enantiomers of verapamil hydrochloride from compression coated tablets containing chiral polymers (pectin, galactomannan and sclera glucan) as the coat has been found[31].

Recent Technologies Used In Compression Coating Method

One-Step Dry Coated Tablet manufacturing method (OSDRC), Dividable compression-coated tablets, Inlay tablets.

CONCLUSION

FDC products and Tablet in Tablet products both provide a number of benefits. Thus, combining two or more fixed dose combinations of drugs into a Tablet in Tablet has the potential to improve patient compliance, convenience, separation of incompatible ingredients, avoid close interactions between two drugs, and maximize the potency of both drugs over conventional oral dosage forms. To better utilize this technology, more research need to be conducted and more products need to be commercialized.

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Table 1: Fdcs Are Classified Based On The Number Of Constituent Drugs Present In A Product

Type	Brand name	Drug name	Strength
Two dose combination drugs	Augmentin	Amoxicillin + Clavulanic acid	250 mg, 125 mg
Three dose combination drugs	Rinizide	Isoniazid + Pyrazinamide + Rifampicin	100 mg, 375 mg, 150 mg
Four dose combination drugs	Sinarest	Paracetamol + Phenylephrine hydrochloride + Chlorpheniramine maleate+ Caffeine	500 mg, 10 mg, 2 mg, 30 mg

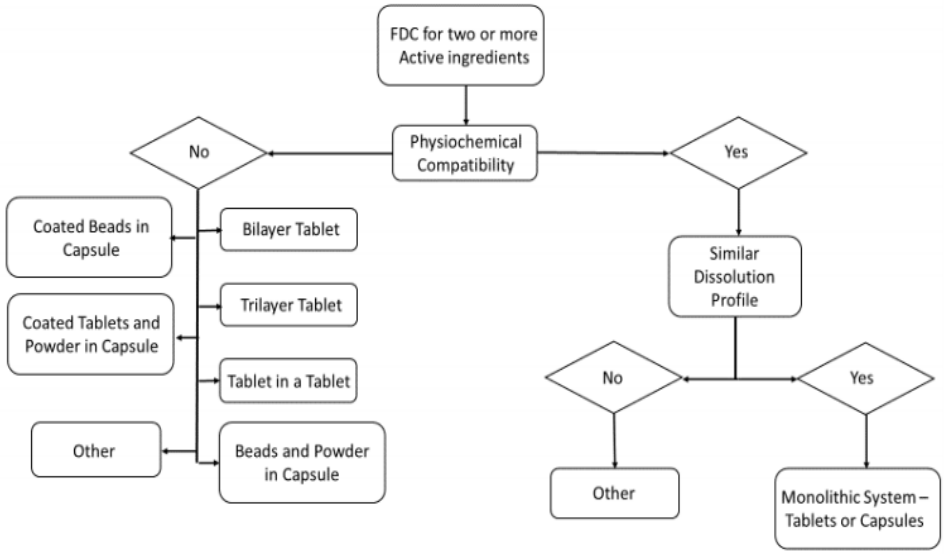

Fig.1: Formulation design and development of FDC products

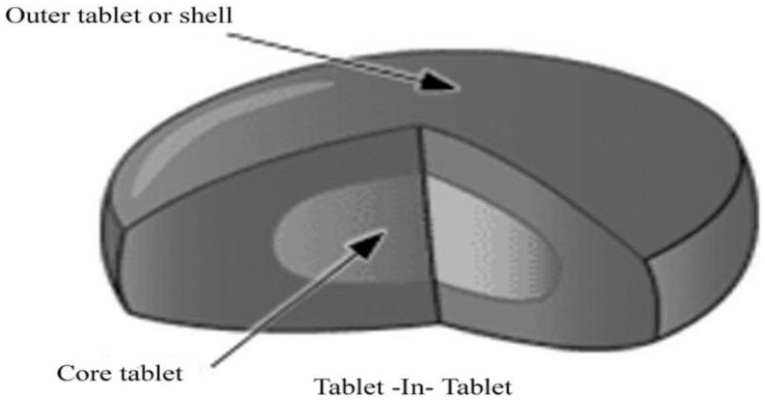

Fig. 2: Tablet-In-Tablet

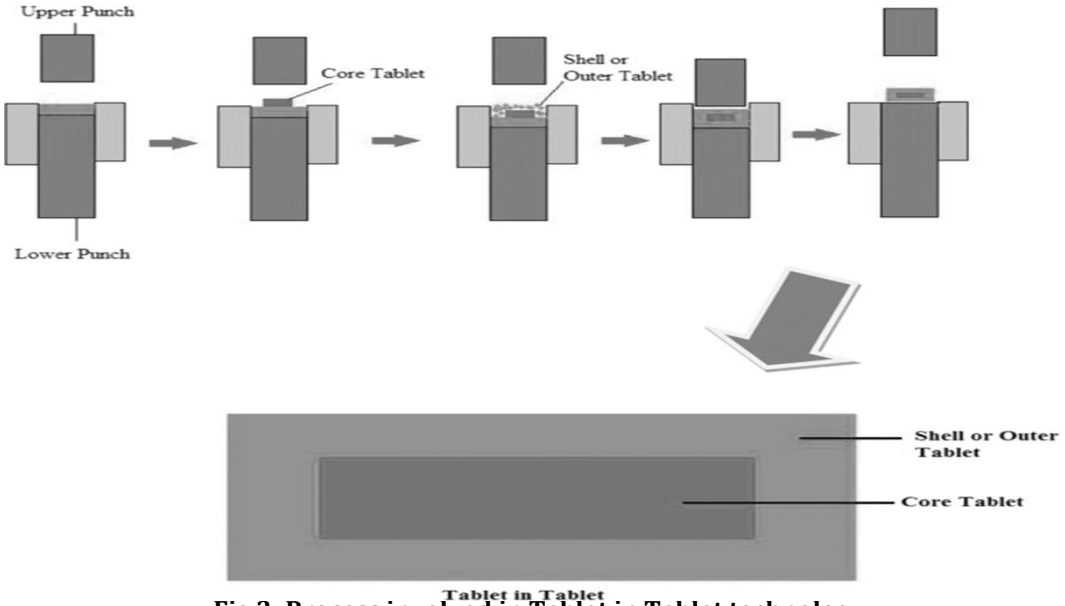

Fig.3: Process involved in Tablet in Tablet technology