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# ADVANCES IN THE DEVELOPMENT OF INNOVATIVE DOSAGE FORMS FOR FIXED-DOSE COMBINATIONS OF ACTIVE PHARMACEUTICAL INGREDIENTS

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## ABSTRACT

The review article delves into the recent advancement in Fixed-Dose Combination of Active Pharmaceutical Ingredients. An attempt is made to explore the strides made in enhancing drug stability, which is paramount for maintaining efficacy and extending shelf life. These fixed dose combinations and enhancing therapeutic success. FDCs are often employed in the management are aimed at streamlining treatment regimens, enhancing drug compliance, of chronic diseases such as diabetes, hypertension, and infective disorders, where the management of the condition using a combination of drugs is effective. Improved convenience, reduced pill burden, and potential cost savings are the primary benefits of FDCs. The development of fixed-dose combinations (FDCs) resulted from efforts to address the incompatibility of active ingredients. The use of several novel formulation technologies for FDC medications including multilayer tablets, bilayer systems, and 3D printing, is covered in this review. **Conclusion**: In conclusion, the developments in FDC provide creative answers to the ever-changing demands of contemporary medicine.

**KEYWORDS:** Fixed dose combination (FDC), bilayer, multilayer tablets, gastric retention of oral dosage forms, 3D printing.

## INTRODUCTION

Fixed-dose drug combinations, or FDCs, are combinations of two or more active drugs in a single dosage form. There are currently a number of FDCs available, but some of the more popular combinations include medications that affect the respiratory system analgesics,

antihypertensive, antidiabetic, and antibiotics. Patients may benefit from using these medications in a number of ways, such as lower treatment costs and better pharmacotherapy-related health outcomes. Given that many patients with long-term conditions like diabetes and hypertension frequently need medication involving several medicines. This helps patients by giving them access to safer, more approachable and simpler-to-apply medications. The pharmaceutical industry's introduction of novel combinations (two or more active ingredients in a single tablet) could serve as an example. Examples include

- Pellet-containing hard capsules, microcapsules, mini-tablets, or the encapsulating of liquid mixtures;
- Bilayer tablets;
- Multilayer tablets;
- Gastric retention of oral dose forms (expandable, raft-forming, hydrodynamically balanced, and floating capsules);
- Three-dimensional (3D) printing technology.

**Advantages**

- Complimentary mechanism of action and synergistic effects. Lower dosages of specific medications enhance treatment tolerance and lessen the likelihood of adverse effects.
- Using fewer pills and streamlining the dosage regimen.
- Reduced or decreased medical expenses. Typically, the cost of an FDC formulation is equal to or less than the sum of the costs of its constituent parts.
- Quicker achievement of therapeutic goals, improved glycemic management, pain reduction, and blood pressure regulation.
- Dispensing is convenient and simple. Reduces the default rate and increases adherence a number of logistical benefits, including planning, ordering, and medication administration.
- Lowering of tablet burden and a simple approach to treatment.
- Each of the aforementioned factors enhances the doctor-patient relationship, which enhances the efficacy of treatment.

**Disadvantages**

Components and excipients that impact solubility and dissolving Reduced dosage flexibility (dosage adjustment is difficult and specific doses for each constituent cannot be changed).

- In certain circumstances, it is preferable to begin and stabilize patients on individual pills prior to initiating the equivalent FDC product.
- It might be difficult to determine which medication is causing a patient's side effects because some unpleasant effects are shared by several active components. It can also be difficult to determine the cause of potential undesired behaviors.
- Either too much or too little. There is unintentional duplication of single-agent prescriptions and FDC.
- Logic is one of the major problems with FDCs; numerous research from Latin America, India, and portions of Asia have demonstrated that many FDCs lack logic. Additionally, the government of various nations has outlawed a number of FDCs.
- Combining one or more broad-spectrum antibiotics (FDC) can also have serious adverse effects, including as antibiotic-associated diarrhea and an increased risk of antibiotic resistance.
- When developing multi-drug formulations, formulation scientists face difficulties such incompatibilities between active.

## 1. HARD CAPSULES IN FIXED DOSE COMBINATIONS

Invented in the 19th century, the two-piece hard capsule remains a common dosage form in the pharmaceutical industry even today. It is also an appropriate dosage form for administering fixed dose combinations (FDCs).[1] In the pharmaceutical sector, gelatin and hydroxy propyl methyl cellulose (HPMC) capsules are the different types of capsules utilized as dosage forms include gelatin capsules, which are traditionally derived from animal sources.[2] They provide quick disintegration in all biological mediums, allowing for 5–10 minutes of drug release. Compared to HPMC capsules, gelatin 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. Advance in capsule filling technology have led to a natural evolution of the combination capsule products. It is feasible to combine spheres and pellets with a liquid or to encase smaller liquid-filled capsules within larger liquid-filled capsules. In several successful FDC products, the drug is enclosed in hard capsules. Some examples include

### 1.1 Encapsulation of Liquid combination

Combodart/Jalyn was the first FDC ever created to cure moderate to severe benign prostatic hyperplasia (BPH) and to prevent acute urine retention.[3] Tamsulosin hydrochloride, an

alpha-blocker, and dutasteride, an alpha-reductase inhibitor, make up the product. Tamsulosin offers immediate symptom relief by lowering smooth muscle tone in the prostate and bladder neck, whereas dutasteride slows the advancement of BPH by preventing the synthesis of dihydrotestosterone, the hormone that stimulates the male prostate to grow. **Figure 1** depicts the product's structure as a component of the distribution system.

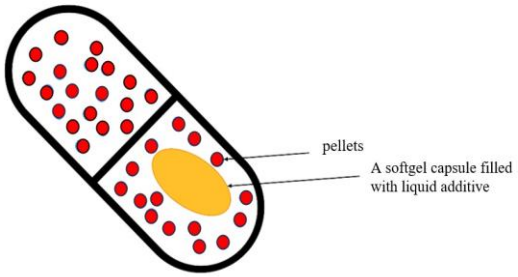



**Figure 1: shows the Combodart/Jalyn's structure: a liquid ingredient in a softgel capsule. The described softgel capsule was encased within a hard size-00 HPMC capsule. The HPMC capsule, which comes with the softgel in the finished dose form, is filled with pellets from the other component.**

### 1.2 Cardiovascular Polypill

A "polypill" is a fixed-dose combination medication that contains multiple ingredients intended to reduce multiple cardiovascular risk factors at once. Three blood pressure-lowering medications (for example, a thiazide, alpha blocker, and an angiotensin converting enzyme inhibitor), and a statin make up a primary prevention polypill that may reduce cardiovascular disease by almost 75%.[4] Regardless of pretreatment levels, the goal was to concurrently lower blood pressure, serum homocysteine, low density lipoprotein cholesterol, and platelet function four cardiovascular risk factors.

In the 1950s, the initial combination drugs for hypertension were reserpine or hydralazine. The 1960s witnessed the advent of drugs that combined a diuretic with reserpine, and methyldopa and a diuretic. In reaction to the worldwide increase in cardiovascular illness, enormous efforts have been undertaken over the last ten years to produce a range of cardiovascular polypills. When discussing therapies for noncommunicable illnesses in 2001, experts from the Wellcome Trust and the World Health Organization pointed out that taking a single pill can significantly save drug costs and promote patient compliance.[5]

The Fuster-CNIC-Ferrer CV Polypill is a multi-layered product that is presented in capsule form and was produced using Ferrer's patented technology.[6]

Ferrer researchers started developing the polypill in 2007, and the first tablet was launched in 2014. The cardiovascular polypill includes 100 mg of aspirin, 2.5, 5, or 10 mg of ramipril, and 20 mg of atorvastatin. Polypill treatment lowers mortality in patients with established cardiovascular disease, according to studies.[2,3] The method preserves the biopharmaceutical and pharmacokinetic characteristics of the individual components while successfully avoiding their physicochemical incompatibilities **Figure 2**

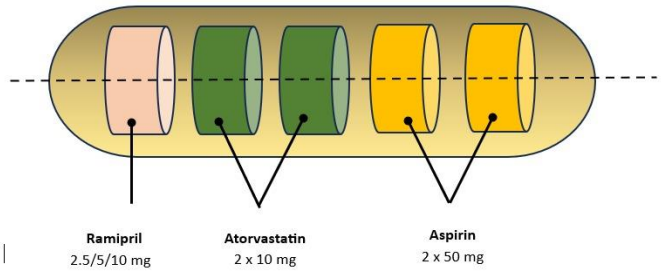



**Figure 2: The technology called Fuster-CNIC-Ferrer CV Polypill (Trinomia®, Sincronium®, and Iltria®).**

### 1.3 Inhalation Combinations

Capsules are considered to be the most suitable dosage form for FDCs.[7] Capsules are inert and available in different sizes. They are available in different sizes and are inert. Medications can be inhaled using hard capsules; the patient breaks the capsule and inhales to allow the powder to reach their lungs.[8] Combination therapy is superior to a single agent in dry powder inhalation technology based on capsules. A good example would be an association between Budesonide and formoterol.[9]

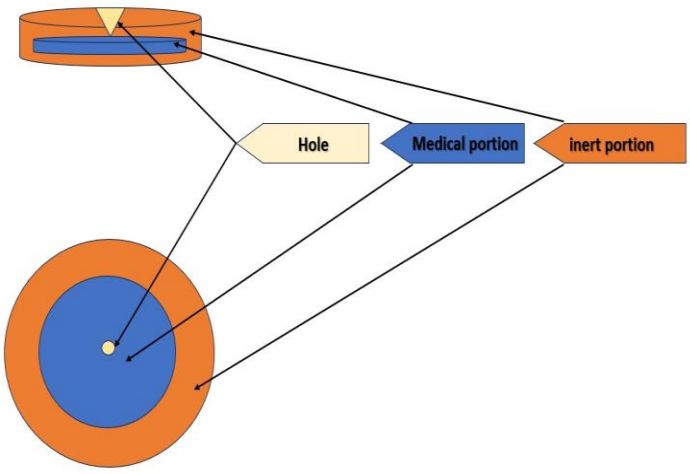
### 1.4 Fixed-Dose Combination Softgel

Unigel™ is a patented fixed-dose combination oral dosage form in which a large, soft gelatin capsule houses tablets, granules, pellets, or capsules. The strength of this approach lies in that it permits the utilization of active ingredients with different release profiles or chemical incompatibilities. Mixing of components, at least one of which is liquid or semi-solid, is also feasible.

**Figure 3. Unigel™ technology, which enables the use of various delivery systems such tablets, capsules, microgranules, or pellets, enclosed in a single soft capsule known as "softgel," for fixed-dose combination medications.**

## 2. BILAYER TABLETS

William Brockedon, a 19th-century British author, painter, and inventor, was granted a patent in 1843 for a machine that compacted potassium and sodium carbonates into lozenges and tablets.[10] Dong Han Won et al. formulated a two-layer fixed-dose tablet having a high dose of metformin hydrochloride in the extended-release layer and a small quantity of evogliptin tartrate in the immediate-release layer. This was achieved through the Quality by Design (QbD) concept, which assumes that quality should be "built-in" into the product via a well-considered, properly designed, and then permanently monitored technological process.[11]



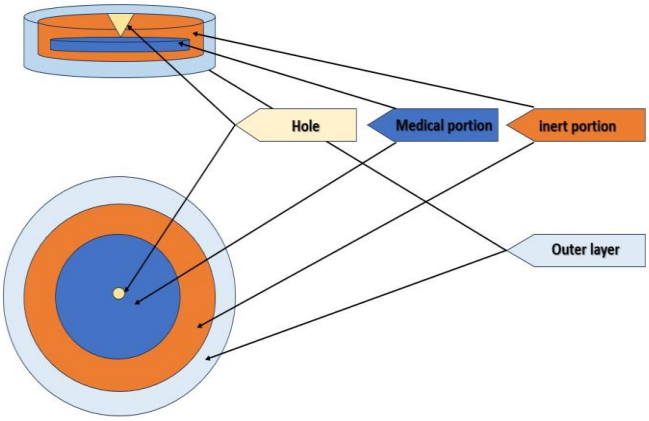



**Figure 4: A bilayer tablet conforming to the 1964 Stephenson patent.**

**Advantages of the bilayer tablet**[12,13,14]

Optimum protection against inter-layer contamination

- The two layers are visibly different from each other.
- Less compression force in order to avoid capping and separating the two distinct layers.
- Most inexpensive and easiest to package and strip.
- Best for large-volume production;
- Least amount of hang-up to swallow.
- Having an embossed or monogrammed punch face makes it possible to identify the product quickly and easily without requiring an additional label.

## 3. MULTILAYER TABLET

The creation of new controlled release formulations with multiple functions for the effective delivery of medication has taken a new direction with multilayer tablets. Since bilayer tablets physically compartmentalize active pharmaceutical ingredients (APIs) and allow multiple drug release profiles, they may be a crucial option for averting chemical incompatibilities between APIs. Even though most pharmaceutical ingredients are incompatible with each other, formulators can prevent interaction in multilayer tablets by placing an inert barrier layer between incompatible matrices. The multilayer tablet suits both sequential release of two drugs from a single drug form and to effect sustained release of a drug, whereby the maintenance dose is released in a slow manner by the other layer while the loading dose is released instantly by the first layer. When anti-hypertensive, anti-diabetic, anti-inflammatory, or analgesic drugs are in question—where combination therapy is commonly utilized—the application of bilayer pills is a totally new concept. Pharmaceutical companies are developing

bilayer tablets now for several reasons such as marketing, extension of patents, and improving therapy efficacy.

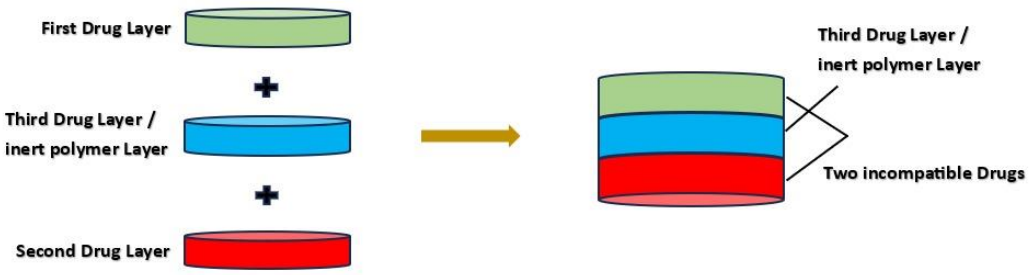



**Figure 5: Multilayer tablet structure diagram.**

## 4. ORAL SUSTAINED RELEASE DOSAGE FORM

The pharmaceutical industry has long attempted to establish oral sustained release dosage forms which are more convenient to administer, persist longer, have better pharmacokinetics, and need less dosing.[15,16] For the first time during the 1980s, Cargill et al. demonstrated that oral dosage forms were able to be retained in the stomach for a period of 24 hours consistently in a beagle dog with erosion governing release.[17]

## 5. FLOATING CAPSULES

Using a technique that releases the drug component slowly and evenly at the site of action is crucial to providing absorption for the needed duration. The stomach or proximal small intestine is where absorption occurs. Floating capsules, a promising technological solution, are designed for this purpose.[18] This group include effervescent floating systems, raft-forming systems, and hydrodynamically balanced and non-effervescent tablets, among other non-effervescent floating systems.[19]

## 6. HYDRODYNAMICALLY BALANCED SYSTEM (HBSs)

This medication is a floating form that floats on the stomach contents' surface to extend the drug's release. Drugs are blended with hydrocolloids like hydroxypropyl methylcellulose (HPMC) K4M, K15M, and K100M to form a hydrodynamically balanced system. HBSs are also produced from hydrogenated vegetable fats and low-density fatty acid sources. These systems function by remaining in the stomach for hours at a time, which enhances the poorly soluble drugs' bioavailability and solubility in a high pH environment. Oth et al. developed a

bilayer floating dosage unit made of HPMC to deliver misoprostol locally at the level of the stomach mucosa. Because it makes it more difficult to pass through the pylorus hole, using a big capsule lengthens the gastric retention period.[20]

Furthermore, numerous types of floating pill systems that release CO2 have been developed. The extended-release tablet in this method is housed in two layers in the form of a seed. The outermost coating is a swellable membrane layer containing PVA, shellac, and other ingredients, while the innermost coating is effervescent containing sodium bicarbonate and tartaric acid. Cisapride was the active pharmaceutical ingredient of a bilayer floating gastric retention tablet developed by Wei et al. Sodium bicarbonate was utilized to fortify the floating layer. Upon immersion in simulated gastric fluid, the pill floated at the surface and discharged the drug in a controlled manner. A greater HPMC content was required for delayed drug release.[21]

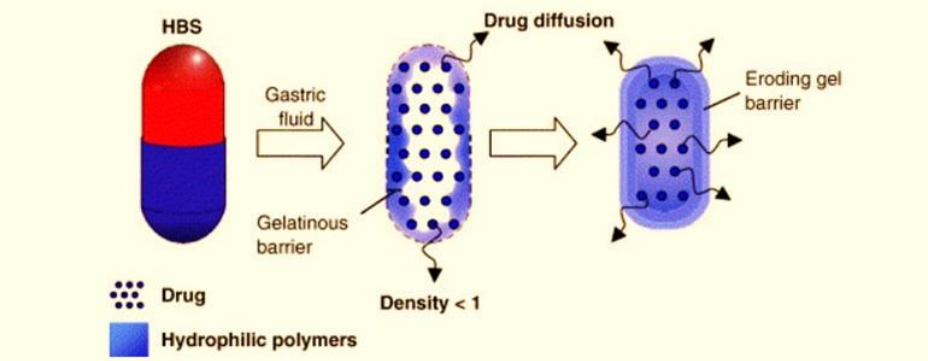



**Figure 6. Designing a float capsule for a hydrodynamically balanced system (HBS). HBS capsules' mode of action is based on gelatin mass with a specific density less than 1.**

Rouge et al. developed buoyant mini-tablets by either incorporating a sodium bicarbonate gas-generating ingredient or by swelling the excipient. The addition of a sodium bicarbonate gas-generating agent to the floating layer and wet granulation improved significantly the displacement of the atenolol-containing mini-tablets. Atenolol mini-tablets with Eudragit NE30D: RS 70:30 and 7% sodium bicarbonate ensured adequate buoyancy and drug release rate within less than six hours.

## 7. RAFT-FORMING SYSTEMS

To achieve buoyancy and extended drug release, the raft-forming process employs gel-forming polymers and effervescent excipients. Such systems consist of tablets or liquids that, upon contact with gastric fluids, are capable of gelling due to a pH change or increased

temperature (cation-induced gelation, for instance). The formed thick gel achieves buoyancy and controlled drug release uses as it remains intact in the stomach for many hours. The oesophagus and stomach may get blocked by floating rafts. Due to this property, such formulations are ideal to treat gastric esophageal reflux disease. Antacids like aluminum hydroxide, simethicone, and calcium carbonate are released through Raft systems.

Gaviscon® is an over-the-counter raft forming preparation, which may be employed to alleviate indigestion and heartburn. It is liquid or pills form. Sodium alginate, calcium carbonate, and sodium bicarbonate are involved in its raft-forming process.

**8. EXPANDABLE**

To maintain a longer gastric retention time, expandable drug delivery systems are designed to increase or change their size in the stomach so that the drug is not allowed to move through the pyloric sphincter. Due to their water-absorbing capacity and volume increase by swelling, hydrophilic polymers such as HPMC, PEO, and Carbopol® are commonly employed in swelling expandable system[22] Gastro-retentive drug delivery can be achieved in a number of different ways. These involve extensible, raft-forming, hydrodynamically balanced, or floating systems, and combinations of such technologies.

**9. THREE-DIMENSIONAL (3D) PRINTING TECHNOLOGY**

He created, patented, and sold the first 3D printing equipment in 1983, Charles Hull is regarded as a pioneer in the field. Hull's 3D printing method was based on stereolithography, which hardened the liquid resin by moving a laser across its surface. Until the correct shape was produced, this process was carried out numerous times, layer by layer. Charles Deckard submitted a patent application for selective laser sintering (SLS) in 1988. In the SLS process, the material transitions from a solid (powder) to a liquid and then back again to a solid state as a sinter.[23]

Scott Crump filed a fused deposition modeling patent in 1989. With this technique, hardening materials are layered onto an object to build up the desired form.[23,24] A new age of pharmaceutical manufacturing started in August 2015 when the FDA approved the first 3D printed medicine product.[23,25]

### 9.1 Fused Deposition Modeling (FDM)

In the FDM technique, the material applied (polymer) is forced through a heated nozzle to its melting point. Under the direction of a computer program, the nozzle moves automatically and controls the flow of material. When the API degradation temperature is similar and the high melting points of the polymers are being used, the technological solution described above is also better. The stability of the API is maintained while complete dispersion in the polymer matrix is achieved by reducing the process temperature.

Layer by layer, the model is developed, similar to stereolithography. This enables the development of many dosage forms with the polymer being part of its composition, such as implants, zero-order release tablets, etc.[26,27] Gioumouxouzis et al. developed an FDM-3D printed bilayer oral solid dose with glimepiride for immediate drug delivery and metformin for extended medication delivery. Glimepiride and metformin were loaded in polyvinyl alcohol (PVA) and Eudragit® RL sustained release layers, respectively.[28]

### 9.2 Semi-Solid Extrusion (SSE)

A category of 3D printing known as semi-solid extrusion (SSE) employs material embossing to create objects of any shape and size by depositing layers of paste or gel consecutively one upon the other. The application of disposable syringes allows for the attainment of key quality requirements of pharmaceutical uses, and the low printing temperatures of SSE 3D printing render it suitable for drug delivery and biological applications compared to other extrusion-based methods.[29,30]

### 9.3 Inkjet Printing

The 3D printing method referred to as inkjet printing employs a powder as a substrate upon which different combinations of ink and active ingredient with different droplet sizes are sprayed layer by layer until they freeze into a solid dosage form.[26,31]

### 9.4 Powder Bed Technology

The possibility of merging numerous active compounds in a single dosage form is facilitated by 3D printing, which lessens the dosage taken by the patient but brings the benefit of an immediate and sustained release of the active ingredient.

By developing an extremely porous material, the zip Dose technology not only allows for the administration of a tremendous quantity of medicine with high dispersion and solubility,

providing each patient with a dosage tailored to them. By using a compressed powder which is saturated with an active substance in several layers, the zip Dose technique guarantees that the drug form will rapidly dissolve as soon as it comes into contact with a limited quantity of water. The pharmaceutical industry improved patient treatment options with Aprecia's release of zip Dose technology in 2015 and the commercial success of Spritam® (levetiracetam), the first oral anti-epileptic tablet to be 3D printed. Large tablets may be hard for children and the elderly to swallow twice a day. However, skipping the next dose of a drug can cause a seizure. Manufactured with a 3D printer and zip Dose technology, Spritam® is an oral disintegrating tablet (ODT) that significantly improves patient convenience by delivering high doses of the drug—up to 1000 mg in a single dose.[32]

## CONCLUSION

More advanced drugs became more accessible due to innovations in applied pharmacy, enabling the creative enhancement of previously approved drugs. The development of oral dosage forms that continuously release the API for extended periods of time (days or weeks) can transform health care, significantly decrease patient burden in the treatment of chronic illness, and enhance therapeutic efficacy. Multi-layered, multiarticulate, and monolithic systems are the three most prevalent types of FDCs. Three primary manufacturing methods employed by industrial pharma companies today are compression of bilayered tablets, hotmelt extrusion coupled with spray coating, and combined wet and dry granulation method.[25]

Personalized drugs are increasingly important in the clinical environment today, and 3D printing is especially well-suited to producing complex, customized 3D solid dose forms that cannot be made with conventional techniques. One of the latest trends in 3DP is the use of responsive materials that can change their properties over time or due to external stimuli. The fourth dimension, or structural change through time, has created a new term referred to as "4D printing."

The disadvantages of traditional FDC drugs are overcome by 4D printing, such as incompatibility of active drug, low bioavailability, and failure to alter the dosing of individual components in specific patients. 4DP can potentially generate an expandable drug1 delivery system for gastric retention FDCs based on shape memory polymers in a predetermined manner via swelling and deswelling, self-folding or self-unfolding. Moreover, the release of FDC drugs can be adjusted to every individual patient's own altered pH in numerous

gastroenterological disorders. We are confident that the next tech revolution in fixed-dose combinations towards personalized medicine could happen with the lifting of regulatory barriers concerning 4D printing technology.

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