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Solid Dosage Forms with Fixed-Dose Combinations of Active Pharmaceutical Ingredients: Therapeutic Importance and Review of Formulation Strategies

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Abstract

Fixed-dose combination (FDC) products contain at least two active pharmaceutical ingredients (APIs) in a single dosage form. Monolithic, multilayer, and multiparticulate formulations are widely employed in the manufacture of solid fixed-dose combination products, such as tablets and capsules. Among the technologies used in production, active film coating, compression coating and liquid dispensing technology are the most widely employed, with increasing attention being given to 3D printing of FDC products. Selecting the appropriate formulation strategy for the development of these drugs is crucial to minimising their disadvantages. Clinically, they offer improved efficacy, safety, and tolerability in the treatment of conditions such as hypertension, type 2 diabetes, tuberculosis, pain, various infections, hormonal disorders and contraception. From the patient's perspective, they provide practicality and simplify therapy by reducing pill burden, which leads to greater adherence and, consequently, improved therapeutic outcomes and quality of life.

Key words: fixed-dose combinations, formulation approaches, clinical significance

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Introduction

Fixed-dose combination in pharmaceutical technology refers to a formulation that contains two or more active pharmaceutical ingredients (APIs) combined in a single dosage form in fixed proportions (1). Therapy involving fixed-dose combinations offers numerous advantages, and their importance is recognised in the treatment of various diseases and conditions such as hypertension, type 2 diabetes, tuberculosis, pain management, bacterial infections, hormonal disorders, contraception (2). One advantage of these formulations is that combining APIs with different mechanisms of action can achieve a synergistic effect, resulting in improved therapeutic efficacy and tolerability (2). In such cases, lower doses of APIs are used, reducing the risk of side effects (1). From an economic perspective, FDC products have lower production costs compared to single-API dosage forms. This results in smaller quantities of excipients required for manufacturing and fewer packages needed. For example, in Spain, a generic fixed-dose combination tablet containing hydrochlorothiazide and ramipril is priced at €6.9, while the corresponding separate generic products cost a total of €8.1 (€3.3 for hydrochlorothiazide and €4.8 for ramipril), indicating a potential cost advantage of fixed-dose combinations (1). Additionally, using a single fixed-dose combination simplifies the treatment, leading to increased patient adherence and better therapeutic outcomes. These advantages demonstrate that monotherapy is no longer the most effective way to treat these diseases and preference is given to fixed-dose combination products (2). Many types of fixed-dose combinations are available on the market, including formulations for oral, inhaled, and parenteral administration (3). Despite these advantages and their wide availability, formulating such products can be very challenging. Combining APIs in a single dosage form inherently carries the risk of numerous physicochemical and pharmacodynamic interactions, and is especially challenging when different API doses or release characteristics are required (1). It is necessary to approach formulation carefully and to consider all the characteristics of each API.

Advantages and Disadvantages of Solid Dosage Forms with a Fixed-Dose Combination of APIs

Oral solid dosage forms, such as tablets and capsules, are the most common route of drug administration for treating many diseases (4). Several reasons exist for selecting a formulation that combines two APIs in fixed doses, including: synergism, protection of API from degradation, reduction of adverse effects, decreased development of API resistance, increased patient adherence, and lower production costs (2).

Despite the advantages listed above, there are also disadvantages to this approach. One of the main disadvantages of FDC products is the reduced possibility of flexible dosing, which affects treatment outcomes in various ways. This is particularly important in chronic diseases such as hypertension and type 2 diabetes mellitus, where it is necessary to adjust the therapeutic dose to achieve target values for parameters such as blood pressure and glucose. In the treatment of tuberculosis and various other

infections, while it does not directly affect treatment outcomes, it complicates dose adjustment according to the patient's body weight, often necessitating the breaking of tablets (5). To address this, they are manufactured in several commonly used dose combinations (3). 3D printing technology has been highlighted as a potential solution to this limitation, as it allows for advanced personalisation of therapy (1).

Another disadvantage of FDC products is the inability to adequately adjust the dose in patients with impaired function of certain organs. This limitation is particularly evident in the geriatric population, where liver and kidney function are reduced due to ageing. One example is chronic pain therapy, where opioid analgesics are often used. Because of the pronounced first-pass effect through the liver and slow elimination via the kidneys, elderly patients experience increased API concentrations in the blood, leading to the appearance of side effects (6).

Additionally, because APIs are administered in fixed doses, it is impossible to adjust therapy flexibly for patients whose needs change over time. For example, in hypertensive patients, continuing the same dose during summer may lead to an excessive drop in blood pressure, which is why dose adjustment should be considered (7). Patients with tuberculosis often lose body weight (8), and using the same doses can increase the risk of side effects, especially when pyrazinamide, which may cause hepatotoxicity, is included in the therapy (9).

Since an FDC product contains at least two APIs within the same dosage form, it is very difficult to identify which component caused an adverse reaction (3). Additionally, combining multiple APIs into a single tablet often results in a tablet that is too large, creating serious swallowing difficulties for children and elderly patients (3).

Furthermore, combining multiple APIs carries the risk of interactions between them, as well as reactions with excipients. This can negatively affect the stability of the API or reduce its therapeutic effect. To prevent this, it is necessary to consider all the properties of each API and design the formulation adequately (2).

Therapeutic Application

A summary of selected examples of registered FDC products in the Republic of Serbia for the indications discussed below is presented in Table I (10).

Table I Selected examples of registered FDC products in the Republic of Serbia (10)

Tabela I Odabrani primeri registrovanih FDC proizvoda u Republici Srbiji (10)

Indication	Active pharmaceutical ingredients	Dosage form	Benefits
Hypertension	amlodipine + valsartan	film-coated tablets	Combining two or more antihypertensives lowers blood pressure through different mechanisms, while adding acetylsalicylic acid further reduces the risk of other cardiovascular diseases
	amlodipine + valsartan + hydrochlorothiazide	film-coated tablets	
	bisoprolol + amlodipine	tablets	
	bisoprolol + hydrochlorothiazide	film-coated tablets	
	bisoprolol + acetylsalicylic acid	capsules	
	enalapril + hydrochlorothiazide	tablets	
Type 2 diabetes	metformin + dapagliflozin	film-coated tablets	Combining two antidiabetics lowers blood glucose through different mechanisms
	metformin + empagliflozin	film-coated tablets	
	metformin + sitagliptin	film-coated tablets	
	metformin + vildagliptin	film-coated tablets	
Various infections	amoxicillin + clavulanic acid	film-coated tablets	Combining penicillin with a beta-lactamase inhibitor prevents the degradation of penicillin.
Pain	paracetamol + tramadol	film-coated tablets	Combining two analgesics provides pain relief through different mechanisms, while adding omeprazole prevents the adverse effects of the analgesics
	paracetamol + ibuprofen	film-coated tablets	
	diclofenac + omeprazole	modified release capsules	

Hormonal disorders and contraception	drospirenone + estradiol	film-coated tablets	Combining estrogen and progestogen components achieves the desired therapeutic effect through different mechanisms, while optimizing the safety profile
	drospirenone + estetrol	film-coated tablets	
	drospirenone + ethinylestradiol	film-coated tablets	
	norgestrel + estradiol valerate	coated tablets	

Hypertension

Essential hypertension refers to persistently elevated blood pressure above 140/90 mmHg with no identifiable cause, which is associated with an increased risk of cardiovascular, cerebrovascular and renal complications (11). In many patients, monotherapy does not achieve target blood pressure, even when administered at the highest tolerated dose. Furthermore, monotherapy demonstrates only moderate control in stage 1 or 2 hypertension, which represents the majority of cases (12). Currently, the goal is to achieve lower blood pressure values, and one option for achieving this is the use of drugs containing fixed combinations of APIs. This method is effective because combining APIs with different mechanisms of action blocks multiple pathways, resulting in more efficient blood pressure reduction. Furthermore, one API used in combination therapy can reduce the side effects induced by the other API. For instance, the incidence of peripheral edema, which is a common side effect of calcium channel blockers, is significantly reduced when combined with angiotensin-converting enzyme (ACE) inhibitors. Similarly, electrolyte disturbances such as hypokalaemia, a side effect of diuretics, can be corrected by concomitant administration of ACE inhibitors or angiotensin II receptor blockers (12). Recent clinical practice guidelines recommend the use of fixed-dose combination for the treatment of high blood pressure (13). Starting antihypertensive therapy with an FDC of two APIs at low or standard doses delivers superior blood pressure control compared to standard monotherapy. Evidence from retrospective cohort studies further supports this approach, demonstrating that the use of FDC products is associated with increased adherence, accelerated achievement of optimal blood pressure levels, and decreased cardiovascular morbidity and mortality (14).

Type 2 Diabetes

Type 2 diabetes is a complex multifactorial metabolic disorder that affects multiple organ systems and is characterised by hyperglycaemia (15). Therefore, monotherapy is often inadequate in the treatment of type 2 diabetes, as it targets only one pathophysiological change, resulting in prolonged exposure to hyperglycaemia and an increased risk of diabetic complications. Consequently, combination therapy, which involves the use of active pharmaceutical ingredients with different mechanisms of

action, has become a cornerstone in the management of type 2 diabetes. According to the European Diabetes Association, combination therapy is recommended for all patients with HbA1c > 7% after 2–3 months of metformin monotherapy (16). As type 2 diabetes advances over time, most patients will eventually need combination therapy to manage their condition. Furthermore, patients with diabetes often have comorbidities such as hypertension and dyslipidaemia, and the use of fixed-dose combinations (FDCs) reduces the number of individual tablets patients need to take. FDCs have been shown to provide greater reductions in HbA1c and better glycaemic control than monotherapy (17). Evidence from a retrospective study of 1,421 patients has revealed superior glycemic control (indicated by HbA1c) with the FDC of metformin and glyburide compared to individual APIs, despite the use of lower average doses (17). FDC use has also been associated with significantly better adherence, especially in patients who previously used individual tablets (monotherapy). Better adherence reduces healthcare costs, as it lowers the risk of diabetic complications and therefore hospitalisation, thus reducing overall costs for patients with type 2 diabetes. In addition, in terms of drug prices, FDCs are significantly cheaper than the individual drugs (17).

Tuberculosis

Globally, tuberculosis continues to be a leading infectious disease, causing high rates of illness and death. Managing this infection involves a multi-drug regimen lasting at least six months, which can lead to low patient compliance and result in therapy failure and subsequent development of drug-resistant strains (18). Drug-resistant tuberculosis is very difficult and expensive to treat, and it refers to resistance to at least two first-line antituberculotics. Given the considerable costs and challenges in treating this condition, the priority is to prevent the development of resistance. The main advantages of using fixed-dose combination therapy over monotherapy are simplified treatment and a reduced risk of developing drug-resistant tuberculosis. For example, with monotherapy, in the initial phase of treatment, the patient must take 9 – 16 tablets per day for two months, and then, in the continuation phase, 3 – 9 tablets per day for four to six months. In contrast, with a fixed-dose combination of antituberculotics, only 3 – 4 tablets per day are needed throughout the entire treatment. It has also been shown that treating patients with rifampicin alone quickly leads to resistance, even when it is administered for a short period, while the combination of two antituberculotics, rifampicin and isoniazid, reduces the likelihood of developing resistance (19). The World Health Organization and the International Union Against Tuberculosis and Lung Disease recommend the use of fixed-dose combination formulations of essential antituberculotics to ensure adequate treatment of patients (19).

Pain

One of the most common reasons for visiting the doctor is pain. However, therapy is very challenging because the mechanism of pain is extremely complex and not sufficiently explained. It is rare for a single mechanism to cause pain, and fixed-dose combination analgesics may be more effective than monotherapy because they activate

multiple pain inhibition pathways (20). Fixed-dose combination analgesics contain two or more analgesics in a single tablet. Non-opioid APIs such as nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol, as well as strong and weak opioids, can be used, and the appropriate combination depends on the patient's age, comorbidities, type of pain, and efficacy-safety ratio. Ideally, two APIs with different mechanisms of action are combined, which may result in an additive or synergistic effect and offer advantages in treating multiple pain mechanisms. This approach allows effective pain treatment, while the lower doses of analgesics in combination products minimise the occurrence of side effects. In addition, the patient's tablet burden is reduced, contributing to better adherence, which is important in the treatment of acute pain to prevent progression to chronic pain that is more difficult to treat (21). As NSAIDs can cause gastrointestinal side effects, combining NSAIDs with proton pump inhibitors can reduce the risk of these side effects and make the treatment more acceptable to the patient (2).

Various Infections

Infections caused by multidrug-resistant bacteria that are difficult to treat are becoming increasingly common and represent a global health problem. One strategy to address this issue is to combine two or more antimicrobial APIs (22). Using fixed-dose combinations of antimicrobial APIs can reduce the risk of developing resistance, achieve a synergistic effect, and lower the minimum inhibitory concentration.

For example, in vitro and in vivo tests have shown that the combination of amoxicillin and clavulanic acid produces a synergistic effect, although clavulanic acid is a beta-lactamase inhibitor (1). Clavulanic acid is an irreversible inhibitor of beta-lactamases and thus protects amoxicillin from inactivation, contributing to increased efficacy. Clinical trials have shown that the fixed-dose combination of amoxicillin and clavulanic acid is clinically and bacteriologically superior to amoxicillin alone and at least as effective as several other comparator antibiotics, such as cephalosporins or doxycycline, in treating adults and children with the most common infections encountered in general practice, including urinary tract infections, upper and lower respiratory tract infections, otolaryngological infections, and skin and soft tissue infections (23).

Hormonal Disorders and Contraception

The oral contraceptive pill is the most popular method of contraception among women (24). Although the term "pill" is commonly used, it is actually a tablet. There are two types of oral contraceptive pills: combined hormonal pills and progestogen-only pills. The combined hormonal pill contains two components, an estrogen and a progestogen, and is the most commonly prescribed contraceptive pill. These pills can also be used for non-contraceptive purposes to treat conditions such as polycystic ovary syndrome, acne, hirsutism, and irregular or painful menstruation. The correct choice and dosage of the estrogen and progestogen components are very important to achieve the desired effects, as well as to minimise adverse reactions and the risk of adverse events (25). Combined oral contraceptive pills are generally the first choice in therapy, except when there are

contraindications to their use or when women cannot tolerate their side effects. One advantage of the combined oral contraceptive pill compared to the progestogen-only pill is more flexible dosing. Progestogen-only pills require stricter adherence, as they must be taken at the same time every day; being more than three hours late can reduce contraceptive efficacy. In contrast, with the combined oral contraceptive pill, reduced efficacy is expected only if the delay exceeds twelve hours (26).

Strategies for Developing Solid Dosage Forms with Fixed-Dose Combinations of APIs

The design of fixed-dose combinations typically involves three main formulation approaches: monolithic, multilayer, and multiparticulate technologies (1). Several strategies exist for designing solid pharmaceutical dosage forms, such as tablets and capsules, containing fixed combinations of APIs. The choice of strategy depends on various factors. When selecting a formulation design, it is necessary to consider the factors shown in Figure 1 (3). Currently, the main manufacturing technologies used in the pharmaceutical industry are active film coating, compression coating and liquid dispensing technology, while 3D printing of FDCs is also gradually attracting attention (1).

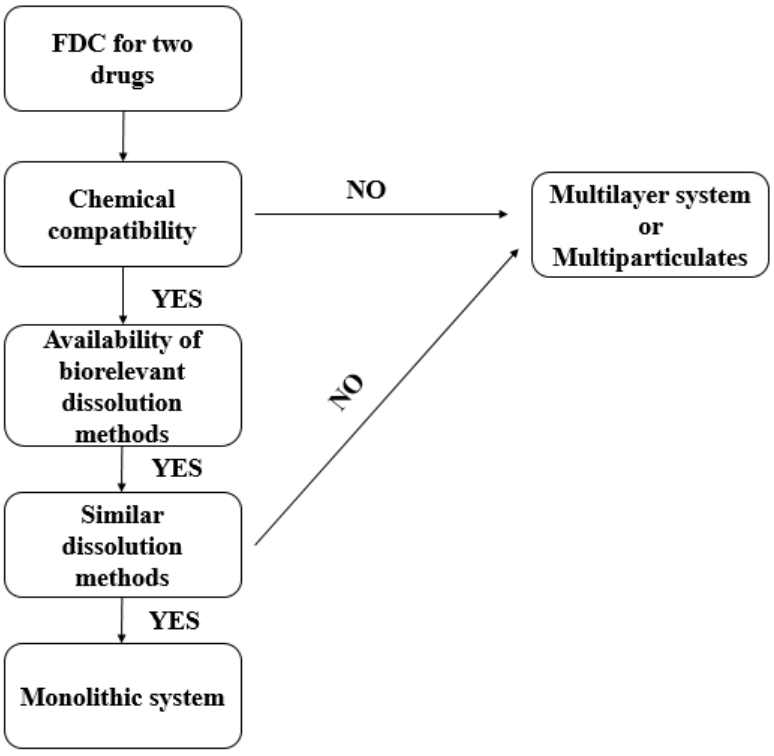

Figure 1. Decision tree for formulation design of fixed-dose combinations of two APIs (adapted from reference 3)

Slika 1. Stablo odluke dizajna formulacije kombinacije fiksnih doza dve lekovite supstance (prilagođeno prema referenci 3)

Monolithic Systems

Monolithic systems are usually single-layer tablet formulations, commonly used because they are easy to manufacture. This approach allows the development of both immediate- and modified-release preparations. However, a key requirement is that the APIs are chemically compatible, making this the main limiting factor. In addition to chemical compatibility, the APIs must have similar dissolution rate profiles and absorption mechanisms for this strategy to be applicable. The dose ratio of the APIs must also be considered, as a large difference in doses may increase the risk of segregation (1). Figure 2a) shows a monolithic system (1).

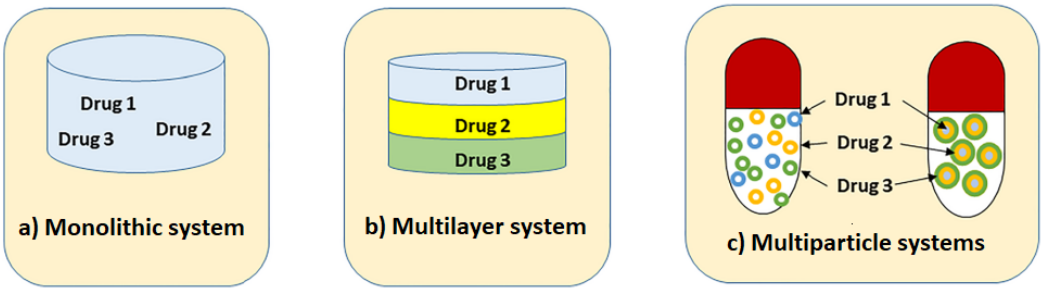

Figure 2. **a) Monolithic system, b) multilayer system, and c) multiparticle systems (adapted from reference 1)**
Slika 2. **a) Jednoslojni sistem, b) višeslojni sistem i c) višečestični sistem (prilagođeno prema referenci 1)**

Multilayer Systems

Multilayer systems are typically used when APIs are incompatible or have different dissolution rate profiles, necessitating their separation into layers (1). Most commonly, these are tablets containing two, three, or more layers of APIs. This approach allows for both immediate and controlled release of the same or different APIs within a single tablet. Manufacturing these systems is challenging, regardless of the chemical stability of the API, as it is difficult to produce a tablet with acceptable physical characteristics. Problems that may arise include inadequate hardness, which can result in excessive fragility – an undesirable outcome. To prevent this, it is important to consider the composition and weight of the layers. Similar composition and weight contribute to comparable physical properties of the powder for tablet compression, such as particle size distribution, density, and flowability, which improve tablet integrity. Delamination may also occur, either within a single layer or between layers. Causes include insufficient adhesion between layers, low moisture levels, air entrapment during compression, or excessive compression forces. To prevent delamination, it is necessary to optimise the compression of the first layer or adjust the compression zone in the die to a shallower position to prevent air ingress. Advances in technology have improved the production of bilayer tablets; machines such as Piccola-e, Fette, and Killian offer functions that monitor pre-

compression, perform automatic sampling of the first layer or automatically control the weights of the layers (3). Figure 2b) shows a multilayer system (1).

Multiparticulate Systems

Like multilayer systems, multiparticulate systems are commonly used when APIs are incompatible or have different release profiles, but here the principle of separation by particles is applied. The most widely used solid form of the multiparticulate system are capsules filled with coated pellets or granules (1), and several innovative dosage forms are also used in the formulation of drugs with a fixed-dose combination of APIs, such as capsules filled with mini-tablets or micro-capsules (27). There are many variations of such systems, from the simplest, where pellets coated with different APIs are contained within a single capsule, to more complex ones where a single API is located in the core of the pellet, and one or more APIs are present in the layers of the shell. Thus, the critical factors in the design of such systems are the composition of the core and the process of obtaining the core, as well as the process of coating the pellets (1). It is necessary to incorporate the API into the pellet. One way to achieve this is to coat the pellets in a fluidised bed device, where a solution or suspension of the API is sprayed as fine droplets and applied to the pellets, forming a layer of the API. If necessary, a layer that controls the release of the API can be applied after the API layer, and such systems are also suitable for combining APIs with different release rates. Another way to incorporate the API into the pellet is to mix the API with the ingredients during the pelleting process itself (3).

Such systems could, in theory, prove to be a good approach to formulating solid dosage forms with a combination of fixed doses of APIs; however, the complicated development of such products in practice, as well as the unique production of pellets and equipment, means that this strategy is less frequently used (3). Figure 2c) shows multiparticulate systems (1).

Active Film Coating

Another strategy in formulating solid dosage forms with a fixed-dose combination of APIs is the active film coating approach. In this method, one API is contained in the tablet core, while the other is incorporated into an active film shell surrounding the core. The active film coating is applied in a coating drum, where mixing, coating, and drying of the tablets occur. The tablets, rotating in the drum, are sprayed with a coating solution or suspension containing the API, coating agent, and solvent (2). It is important to consider the compatibility of the API and the coating agent when selecting a coating agent. The process is much easier if the API is water-soluble; if it is insoluble, the particle size must be considered to prevent nozzle clogging, and the suspension must remain stable during coating to ensure tablets with uniform content (28). The active film coating layer can serve various functions, including protecting the core from adverse external influences, masking taste, or controlling the release of the API. If there is an issue such as interaction at the interface between the core and the active film coating, this can be resolved by adding an inert intermediate layer as a barrier. This approach is suitable for

producing small-sized tablets, unlike multilayer tablets, and for manufacturing tablets with a disproportionate ratio of API doses, such as tablets containing a low dose of one API and a high dose of another (2). Figure 3 shows a tablet core with an active film coating (2).

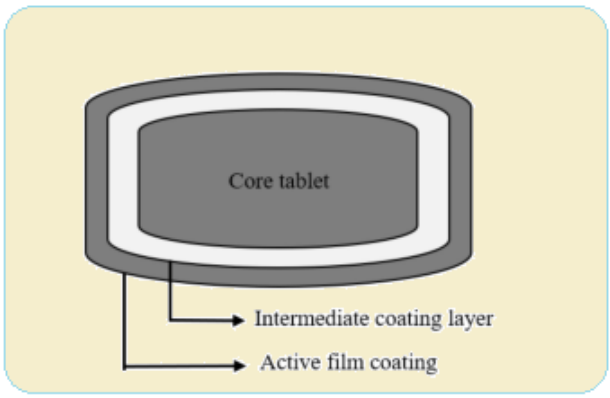

Figure 3. Active film-coated tablet (adapted from reference 2)
Slika 3. Tableta sa aktivnom filmskom oblogom (prilagođeno prema referenci 2)

Compression Coating

Compression coating is a process used to separate two incompatible APIs, placing one in the core and the other in the shell. This allows for different dissolution rates, such as immediate release of the API from the shell followed by prolonged release from the core. In this process, fine dry granules containing one API are compressed onto a tablet core containing the other API using specially designed tablet machines (29). This approach may be suitable for APIs that are sensitive to solvents or heat (3). Figure 4a) shows the compression coating process (1).

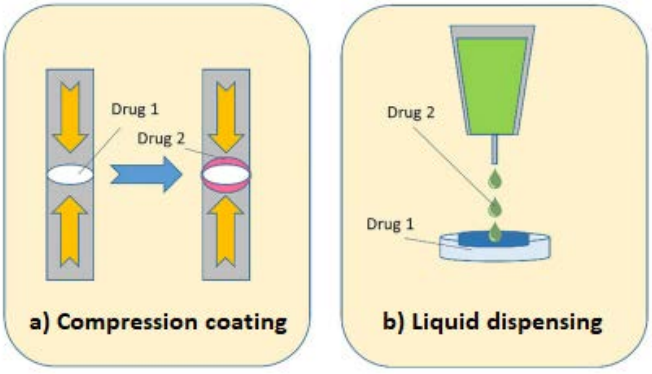

Figure 4. a) Compression coating, and b) liquid dispensing technology (adapted from reference 1)
Slika 4. a) Oblaganje kompresijom i b) tehnologija doziranja tečnosti (prilagođeno prema referenci 1)

Liquid Dispensing Technology

Liquid dispensing is an innovative technology used in the development and production of low-dose or highly potent APIs (30). In this method, a dosing liquid is applied to a biconcave tablet core. The liquid formulation is applied over the core to prevent absorption of the dosing liquid by the tablet core. The dosing liquid, which contains the API and a polymer dissolved in an organic solvent, is applied to the concave part of the tablet. After dosing, the organic solvent evaporates, and the polymer retains the API as a thin film (1). The same process can be repeated on the other side of the tablet core with a different API, allowing the development of a drug with a fixed combination of APIs (3). Figure 4b) shows the liquid dispensing technology (1).

Three-dimensional (3D) Printing

Current fixed-dose drugs lack the individualisation of therapy that is sometimes necessary in paediatric or geriatric patients, or in patients receiving polydrug therapy. 3D printing can be used to produce personalised drugs with a fixed combination of APIs according to the individual needs of the patient (1). It is possible to make a drug with the desired doses in the desired combination of APIs at the request of the patient, with the aim of optimising therapy (31). The most commonly used 3D printing techniques for pharmaceutical purposes are fused deposition modelling (FDM), pressure-assisted microsyringe (PAM), stereolithography (SLA), and selective laser sintering (SLS). Different manufacturing approaches are available for the successful 3D printing of FDC products with at least two APIs. The predominant strategy is a multilayer approach that uses a layered configuration, with immediate-release compartments forming the top and bottom layers. This sandwich-like structure ensures initial exposure to the medium while enclosing the sustained- or delayed-release compartments within the core. Although all previously mentioned methods can use this approach, FDM and PAM have the ability to print more advanced structures such as core, gradient or segmented tablets (1). Figure 5 shows the different approaches used in the 3D printing of FDC products (1).

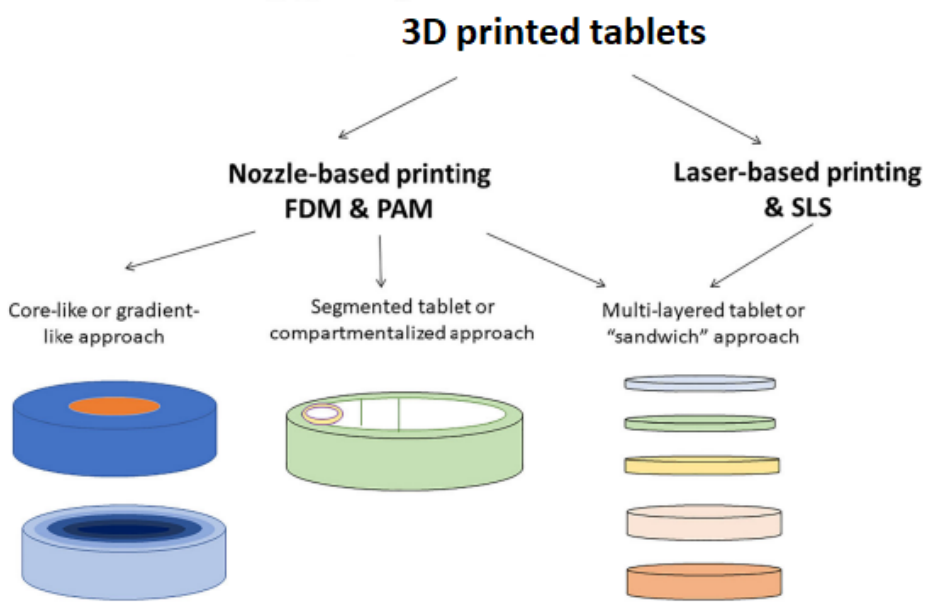

Figure 5. Different approaches used in 3D printing of FDC products (adapted from reference 1)

Slika 5. Različiti pristupi koji se primenjuju u 3D štampanju FDC lekova (prilagođeno prema referenci 1)

Although drug 3D printing technology is emerging as a solution to overcome the limitations of fixed doses in FDC products, its broader clinical application still faces significant obstacles. One major challenge is scalability, as this technology currently encounters difficulties even in production, let alone in creating drugs tailored to individual patient needs. The manufacturing process itself is extremely expensive and slow, making it economically unviable compared to traditional production methods (32).

Beyond economic constraints, regulatory requirements further complicate clinical application. In the pharmaceutical industry, validating such a process and demonstrating its reproducibility – ensuring that each printed tablet meets the required quality standards – is particularly demanding. Implementing quality control is also a significant challenge, as is aligning processes with GMP guidelines. Furthermore, regulatory bodies have not yet developed clear guidelines for the approval and monitoring of these drugs, which further restricts clinical application. The extent of these regulatory challenges is illustrated by the fact that only one 3D printed drug, Spritam®, has been approved on the market to date (32). For all these reasons, the transition from the theoretical advantages of personalised medicine to the clinical application of 3D printed drugs remains a long-term and complex process.

Conclusion

Therapy using FDC products offers numerous advantages, making them widely used in clinical practice. A suitable combination of APIs can achieve greater therapeutic efficacy, improved tolerability, and enhanced safety. FDC products also simplify treatment by reducing the number of tablets required, which is particularly important for patients undergoing polydrug therapy. For such patients, who often have multiple comorbidities, FDC products significantly improve adherence to therapy, leading to better therapeutic outcomes and improved quality of life. Their wide availability and affordable prices are additional benefits. However, despite these advantages, the formulation of FDC products can be challenging. Careful selection of formulation design and production technology can help overcome the disadvantages associated with FDC products.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

J.Đ.: Conceptualization, Supervision, and Writing – review & editing; **N.M.**: Writing – original draft.

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Čvrsti farmaceutski oblici sa kombinacijom fiksnih doza lekovitih supstanci: terapijski značaj i pregled formulacionih strategija

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Kratak sadržaj

Lekovi sa kombinacijom fiksnih doza (engl. *Fixed-Dose Combination*, FDC proizvodi) sadrže najmanje dve lekovite supstance u jednom farmaceutskom obliku. Monolitni, višeslojni i višečestični sistemi su najčešći tipovi čvrstih farmaceutskih oblika (tableta i kapsula) u kojima se formulišu FDC proizvodi. Od tehnologija koje se koriste u proizvodnji najčešće se koristi pristup aktivne filmske obloge i oblaganje kompresijom, a sve veća pažnja se poklanja 3D štampanju FDC proizvoda. Veoma je važan pravilan odabir formulacione strategije za razvoj ovih lekova kako bi se njihovi nedostaci sveli na minimum. Iz kliničke perspektive, ovi lekovi nude bolju efikasnost, bezbednost i podnošljivost u lečenju oboljenja i stanja poput hipertenzije, dijabetesa tipa 2 i tuberkuloze, u terapiji bola, raznih infekcija, hormonskih poremećaja i kontracepcije. Iz perspektive pacijenta, nude praktičnost i pojednostavljenje terapije kroz smanjenje broja potrebnih tableta i/ili kapsula, posebno kod pacijenata koji su na politerapiji zbog kompleksnih stanja i/ili komorbiditeta, što rezultira povećanim stepenom adherence kod pacijenata, a samim tim i poboljšanjem uspešnosti terapije i kvaliteta života pacijenata.

Ključne reči: lekovi sa kombinacijom fiksnih doza, formulacioni pristupi, klinički značaj