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Fixed dose combination, a model therapy optimization strategy: A review

Chukwunonso C Onwuzuligbo [1,*] and Amarachukwu U Onwuzuligbo [2]

[1] *Faculty of Pharmaceutical Sciences, Chukwuemeka Odumegwu Ojukwu University, Igbariam, Anambra State, Nigeria.*
[2] *Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.*

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Abstract

Therapy optimization involves a continuous improvement process of treatment interventions in the management of specific health challenges. Such optimization practices will not only help in achieving the desired treatment goals but will also improve the overall patients' quality of life. One of the available therapy optimization strategy is the use of fixed dose combinations over monotherapies or poly-pharmacy. Fixed dose combination (FDC) is combination product that includes two or more active pharmaceutical ingredients (APIs) with similar or different pharmacological activity and different mechanisms of action combined in a single dosage form, which is manufactured and distributed in fixed doses. Many advantages have been attributed to FDCs as a therapy optimization option. This is particularly important in the treatment of chronic diseases. This paper was designed to highlight an overview of fixed dose combinations, their advantages and disadvantages, examples of approved FDCs commercially available and FDCs' formulation options. Although several FDC products have been approved and are in use globally, there is still room for research and development of more FDCs with special emphasis on chronic comorbid disease conditions.

Keywords: Therapy; Optimization; Fixed dose combinations; Active pharmaceutical ingredients; Chronic comorbid disease conditions

1. Introduction

Fixed dose combination (FDC) was also referred to as fixed-ratio combination by [1], has been defined by several authors as a combination product that includes two or more active pharmaceutical ingredients (APIs) with similar or different pharmacological activity and different mechanisms of action combined in a single dosage form, which is manufactured and distributed in fixed doses [2,3]. This definition agrees with the postulation of Patel *et al.,* 2018, that the APIs to be used in the formulation of an FDC must have different mechanisms of action and similar or different pharmacological activities. Other criteria that qualify APIs as candidates for FDC formulation are; they must have minimal drug-drug interactions and treat closely related diseases or same disease using different mechanisms of action [4].

The decision of the active pharmaceutical ingredients (APIs) to be selected for FDCs formulation is usually based on factors such as approval status of the APIs, clinical experience, manufacturing feasibility, pharmacological mechanisms, biopharmaceutical properties, pharmacokinetics, metabolic pathways, drug-drug interactions and the required doses of the individual APIs [5].

2. Evolution of Fixed Dose Combination

Fixed dose combinations have been in use centuries ago, however the acceptance of the concept had a tumultuous period and devastating setback during the 1950s. Before the advent of potassium sparing diuretics, diuretic products

* Corresponding author: Chukwunonso C Onwuzuligbo

remove potassium alongside the intended removal of sodium; as a result, KCl was introduced into the diuretic products to replace the removed potassium. This seemed like an excellent idea until the cases of ulceration and puncturing of the stomach lining started emanating due to the presence of free-lying KCl in the stomach [6].

The use of several sulfonamides in a single dosage however, revived the concept of FDCs in the 20th Century. Also was the combination of estrogen and progestin as a single oral contraceptive tablet which appeared safest and most effective when compared with other alternatives [6]. The success of these early formulations opened the floodgates for FDCs resurgence leading to the most recent cocktails of highly active antiretrovirals (HAART) for management of HIV/AIDS patients. FDCs for treatment of Tuberculosis, Diabetes, Hypertension, Malaria, several FDC antibiotics etc. have saturated the global pharmaceutical space.

3. Clinical Application of Fixed Dose Combinations

Sequel to the resurgence of FDCs in clinical practice, there are currently a tremendous amount of FDC products approved and marketed worldwide for various therapeutic effects. Table 1. below enumerates some of the approved and marketed FDCs.

Table 1 Examples of Approved and Marketed FDCs

S/n	Therapeutic action(s)	Component drugs in fixed combination
1	Anti-Parkinson	Levodopa/Carbidopa
2	Anti-Convulsant	Gabapentin/Methylcobalamin
3	Analgesic	Acethylsalicylic acid/Caffeine; Paracetamol/Caffeine; Paracetamol/ Acethylsalicylic acid; Paracetamol/Ophenadrine; Paracetamol/Codeine; Paracetamol/Diphenhydramine; Paracetamol/Chlorpheniramine; Paracetamol/Ibuprofen; Paracetamol/Ibuprofen/Codeine; Diclofenac/Paracetamol
4	Anti-Rheumatism	Chondroitin//Glusosamine
5	Skeletal Muscle Relaxant	Methocarbamol/Paracetamol
6	Anti-Inflammation	Trypsin/Bromelain; Trypsin/Chymotrypsin
7	Local Anaesthetics	Lidocaine/Epinephrine
8	Antacids	Aluminium hydroxide/Magnesium hydroxide; Aluminium hydroxide/Magnesium hydroxide/Simeticone; Aluminium hydroxide/Magnesium hydroxide/Magnesium trisilicate/Simeticone; Magnesium trisilicate/ Aluminium hydroxide
9	Ulcer healing	Omeprazole/Clarithromycin; Omeprazole/Clarithromycin/Tinidzole; Rabeprazole/Amoxicillin/Clarithromycin
10	Anti-spasmodic	Dicyclomine/Dimethicone
11	Anti-diarrhea	Diphenoxylate/Atropine; Attapulgite/Pectin; Sulphaguanidine/Neomycin/Kaolin;
12	Anti-emetic	Domperidone/Omeprazole; Domeperidone/Rabeprazole
13	Anti-haemorrhoidal	Prednisolone caproate/Cinchocaine HCl; Tribenoside/Lignocaine
14	Diuretics	Chlortalidone/Reserpine; Torsemide/Spironolactone; Amiloride/Hydrochlorothiazide; Amiloride/Methyclothiazide; Triamterene/Hydrochlorothiazide
15	Anti-hypertensives	Atenolol/Chlortalidone; Nebivolol/Hydrochlorothiazide; Prazosin/Hydrochlorothiazide; Prazosin/Polythiazide; Reserpine/Clopamide/Dihydroergocristine; Reserpine/Dihydroergotoxine/Hydrochlorothiazide; Enalapril/Hydrochlorothiazide; Lisinopril/Hydrochlorothiazide;

		Ramipril/Felodipine; Candesartan/Hydrochlorothiazide; Losartan/ Hydrochlorothiazide; Telmisartan/ Hydrochlorothiazide; Telmisartan/Amlodipine; Valsartan/ Hydrochlorothiazide; Amlodipine/Lisinopril; Amlodipine/Atorvastatin; Amlodipine/Valsartan; Amlodipine/Valsartan/ Hydrochlorothiazide
16	Anti-thrombotic & Myocardial Infarction	Clopidogrel/Aspirin
17	COPD Drugs & Anti-asthmatics	Salbutamol/Fluticasone; Salbutamol/Beclomethasone; Salbutamol/Ipratropium; Salbutamol/Theophylline; Salbutamol/Theophylline/Chlorpheniramine; Salmeterol/Fluticasone; Ephedrine/Hydroxyzine/Theophylline; Ephedrine/Theophylline
18	Expectorants & Cough Suppressants	Bromhexine/Terbutaline/Guaifenesin; Bromhexine/Guaifenesin/Salbutamol
19	Anti-histamine	Dimethindene/Phenylephrine
20	Anti-bacterial	Amoxicillin/Clavulanic acid; Ampicillin/Cloxacillin; Ampicillin/Flucloxacillin; Ampicillin/Sulbactam; Piperacillin/Tazobactam; Cefixime/Clavulanic acid; Ceftriaxone/Sulbactam; Imipenem/Cilastatin; Ciprofloxacin/Tinidazole; Sulfamethoxazole/Trimethoprim; Sulfathiazole/Sulfadiazine/Sulfamerazine
21	Anti-tuberculosis	Isoniazid/Ethambutol; Isoniazid/Thioacetazone; Rifampicin/Isoniazid; Rifampicin/Isoniazid/Ethambutol; Rifampicin/Isoniazid/Pyrazinamide; Rifampicin/Isoniazid/Pyrazinamide/Ethambutol
22	Anti-malarial	Artemether/Lumefantrine; Artesunate/Amodiaquine; Artesunate/Mefloquine; Artesunate/Sulfadoxine/pyrimethamine; Artesunate/Sulfamethoxypyrazine/Pyrimethamine; Dihydroartemisinin/Piperaquine; Artemisinin/Piperaquine; Artesunate/Tetracycline; Artesunate/Doxycycline; Artesunate/Clindamycin; Sulfadoxine/Pyrimethamine; Sulfamethoxypyrazine/Pyrimethamine
23	Anti-amoebic, anti-giardial & anti-trichomonal drugs	Ornidaole/Ofloxacin
24	Anti-viral	Lopinavir/Ritonavir; Efavirenz/Emtricitabine/Tenofovir; Emtricitabine/Tenofovir; Lamivudine/Nevirapine/Stavudine; Lamivudine/Zidovudine; Lamivudine/Nevirapine/Zidovudine
25	Anti-diabetic	Metformin/Glibenclamide; Metformin/Glimepiride; Pioglitazone/Glimepiride; Pioglitazone/Metfomin; Rosiglitazone/Metformin; Vildagliptin/Metformin
26	Anti-thyroid drugs	Iodine/Potassium iodide
27	Anti-fungi	Miconazole/Metronidazole; Clindamycin/Clotrimazole
28	Contraceptives	Ethinylestradiol/Levonorgestrel; Ethinylestradiol/Drospirenone; Ethinylestradiol/Norethisterone; Methyloestradiol/Methyloestrenolone; Medroxyprogesterone/Estradiol; Norethisterone/Estradiol
29	Eye/Ear/Nose/Throat Preparations	Chloramphenicol/Beclomethasone/Clotrimazole/Lidocaine; Chloramphenicol/Hydrocortisone; Ciprofloxacin/Dexamethasone; Gentamicin/Dexamethasone; Oxytetracycline/Polymyxin B; Sulfacetamide/Chloramphenicol; Antazoline/Naphazoline; Antazoline/Tetrahydrozoline; Betamethasone/Neomycin; Dexamethasone/Chloramphenicol; Dexamethasone/Neomycin; Fluorometholone/Tetrahydrozoline; Hydrocortisone/Neomycin; Potassium Iodide/Sodium Iodide; Hydrocortisone/Neomycin/Polymyxin B; Glycerol/Sodium Bicarbonate; Xylometazoline/Antazoline; Phenylpropanolamine/Chlorpheniramine/Paracetamol; Paracetamol/Cetirizine;

		Phenylpropanolamine/Chlorpheniramine/Caffeine/Paracetamol; Pseudoephedrine/Chlorpheniramine; Pseudoephedrine/Paracetamol/Chlorpheniramine; Pseudoephedrine/Dextromethorphan/Chlorpheniramine; Pseudoephedrine/Bromhexine; Glycerine/Thymol; Neomycin/Bacitracin/Amylocaine/Menthol
30	Topical Preparations	Neomycin/Bacitracin; Benzoic acid/Salicylic acid; Mesulphen/Sulphur; Econazole/Triamcinolone/Gentamicin; Miconazole/Dexamethasone/Neomycin; Betamethasone/Clioquinol; Betamethasone/Neomycin; Betamethasone/Neomycin/Clotrimazole; Clobetasol/Gentamicin/Miconazole; Clotrimazole/Dexamethasone; Dexamethasone/Neomycin; Hydrocortisone/Gentamicin; Hydrocortisone/Neomycin; Hydrocortisone/Oxytetracycline; Calamine/Zinc Oxide; Methylprednisolone/Neomycin/Sulphur/Aluminum Chlorohydroxide

4. Advantages of FDC Products

Some of the advantages of fixed dose combinations over traditional monotherapy are as follows; Synergistic/additive effect, Enhanced patient compliance, Cost reduction, Simple dosage schedule, Reduced risk of side/adverse effect, Inhibition of microbial resistance, etc.

4.1. Synergistic or Additive Effect

It has been shown that drugs in fixed formulation exhibit either synergistic or additive effects than their monotherapy counterparts. For example, the FDC of paracetamol and tramadol exhibits synergistic analgesic effect superior to the monotherapy of both drugs [1]. Paracetamol has a quick onset of action whereas tramadol has prolonged duration of action, the two together have enhanced efficacy and effectiveness than the individual drugs. Also, in the treatment of hypertension, the use of Angiotensin converting enzyme inhibitors (ACEi) such as ramipril and captopril in combination with thiazide diuretics such as hydrochlorothiazide in a fixed combination have shown to reduce blood pressure more substantially than with individual therapy of the drugs alone [2]. Because of their different mechanisms of action, a combination of the two classes exhibit better blood pressure control than the individual therapies.

4.2. Enhanced patient compliance

FDC products reduced the pill burdens and dosing frequencies experienced by the patients by combining multiple APIs into a single product; and this has shown to encourage patients to be more compliant to treatment plans [7]. For example, a TB and HIV co-morbid patient will be exposed to treatment plan of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol for the treatment of the TB and Efavirenz, Emtricitabine and Tenofovir for the management of the HIV; making it a total of seven (7) drugs. But with FDC, Rifampicin, Isoniazid, Pyrazinamide and Ethambutol are combined as a single tablet while Efavirenz, Emtricitabine and Tenofovir are combined as a single tablet. Thus, with FDCs, the patient has an advantage of taking only two (2) tablets instead of seven (7), which most definitely enhances his compliance to treatment.

4.3. Reduction of Cost

FDC products provide cost reduction benefits to both the manufacturer of the product and the patient on whom the product is intended for [2]. For a diabetic patient with a prescription of Metformin and Glibenclamide, the cost of purchasing the two products having the APIs respectively will be much more compared to the cost of purchasing an FDC of the two APIs. Also, for the manufacturer, the production cost of the FDC will be cheaper compared to the cost of producing the individual products independently.

4.4. Simple Dosage Schedule

FDC provides the advantage of simplifying the dosage schedule for patients who are exposed to complicated treatment plans [1], for example tuberculosis (TB) patients. Treatment of TB involves two (2) phases; Intensive phase and Continuation phase. During the intensive phase, they are required to take four (4) medications (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol) for two (2) months whereas in the continuation phase, they are to take rifampicin and isoniazid for four (4) months, completing their six (6) months duration of treatment. FDC formulations of the various drugs will simplify the schedule for the patients and minimizes possibilities of errors in administration of the medications.

4.5. Reduced risk of side/adverse effects

Some FDC products have the benefits of possessing reduced risks of adverse or side effects compared to when the drugs are administered as monotherapies. Misoprostol when formulated with Diclofenac as an FDC, protects the gastrointestinal mucosa linings from gastrointestinal ulceration usually associated with NSAIDs [8].

4.6. Inhibition of microbial resistance

Several infectious pathogens develop antimicrobial resistance against anti-infective drugs. Microbes may inherently be resistant to anti-infective drugs or may develop resistant to anti-infective drugs during the course of treatment. This resistance can be prevented by different mechanisms generated by different drugs. Fixed dose combinations are more effective to eliminate or slow down antimicrobial resistances compared to monotherapies. The formulation of Rifampicin with Isoniazid in fixed dose inhibits or slows down the resistance developed by the *Tuberculosis bacilli* when treated with Rifampicin mono-therapy [1].

4.7. Cheaper shipment & packaging activities

Reducing costs and simplifying the logistics flow of purchasing and distribution of complex antimicrobial regimes are acceptable targets in reaching public health outcomes in low income countries. FDCs can successfully contribute to all of these elements, under condition that they do not put the therapeutic outcomes at risk. A possible outcome of using FDCs is the reduction of the overall costs of delivering treatment to patients and preventing shortages of individual drugs, by decreasing the cost of managing the drug supply [9].

4.8. Minimization of potential drug abuse

Sometimes, the drugs are combined to minimize the potential drug abuse, such as Suboxone® (buprenorphine and naloxone) and Lomotil® (diphenoxylate and atropine). Buprenorphine and naloxone are combined in Suboxone® to prevent the possibility of injecting the product by opioid addicts to get high on buprenorphine, a partial opioid agonist. Naloxone, an opioid antagonist, will generate withdrawal symptoms if Suboxone® is injected [10]. Similarly, diphenoxylate/atropine combination is used to counter opioid-like effect of diphenoxylate at high doses with anticholinergic effects of atropine [11].

5. Disadvantages of FDC Products

5.1. Dose inflexibility

The ability to titrate and adjust an individual component of the FDC to reach desired therapeutic outcomes is the primary challenge in FDC therapy in certain disease states, such as cardiovascular diseases and diabetes mellitus [12]. This is less of a concern in conditions such as malaria and TB but is a potential concern when prescribing anti-retroviral therapy based on patient weight, which can result in patients having to break tablets in half to achieve the prescribed dose in FDC products that are not available in the required strength.

5.2. Heightened possibility of drug interactions

Drug-drug and drug-excipient interactions are important considerations when formulating FDC products. Drug-drug interactions may influence bioavailability as is the case with rifampicin and isoniazid. Although rifampicin-isoniazid is a combination approved and recommended by the WHO, rifampicin has demonstrated instability in the presence of isoniazid when exposed to an acidic environment, which decreased the bioavailability of rifampicin [12].

5.3. Individual Drug Patents Hinder Development of Fixed-Dose Combination Products

Fixed-dose combination products often incorporate APIs with expired patents and seldom include new molecular entities. The approval of FDC products can be delayed based on the patent status of each individual component intended for inclusion in the proposed FDC product. Pharmaceutical companies have been known to develop and market an FDC product comprising an API that has a patent nearing expiry. This strategy is intended to extend the patent and exclusivity life of the API. Efforts are being made to exclude FDC products from single API patent restrictions and instead create a medicines patent pool to ease access to the proposed FDC regimen [13].

5.4. Development of Analytical Methods

Post-formulation, simultaneous determination of multiple APIs can require complex analytical techniques or the development of new analytical methods, which in itself can be a costly and time-consuming process requiring highly specialized equipment and expertise [14].

5.5. Time-Dependent Patient Compliance

Adherence to polypill regimens is significantly higher compared to multiple-pill regimens [15]. However, regardless of the number of tablets administered, there is a time-dependent decrease in compliance associated with treatment regimens extending beyond 18 months of therapy [16]. This suggests that whilst FDC therapy can improve patient compliance through easing the pill burden, ultimately, the nature of a chronic condition, i.e., the duration of the treatment period, is the greatest hindrance to patient compliance, more than the type of dosage form. With that said, it remains of utmost importance to design treatment regimens with patient convenience, and therefore compliance, in mind, to achieve the best therapeutic outcomes over an extended treatment period [12].

5.6. Fixed-Dose Combination Therapy Conflict with Personalized Medicine

There is a need to tailor treatment approaches to individual patient needs due to differences in genetic profiles, race, gender, age, epigenetic, as well as environmental factors. Patient weight, comorbidities, and inter-patient tolerance and side effects of therapy necessitate personalized treatment plans. A one-size-fits-all approach is a thing of the past in this regard and is thereby heavily undermined by FDC therapy that lacks dose flexibility [17].

5.7. Uncertainty over adverse effects

It is more difficult to accurately pinpoint the causative agent of an adverse drug event when several APIs are administered in the same dosage unit. For example, Inegy®, an FDC product that contains simvastatin and ezetimibe for the treatment of hypercholesterolemia, can cause an increase in liver enzyme activity. Both APIs in their respective individual formulations can also cause the same adverse effect and as a result it is difficult to pinpoint which API is causing it [2].

5.8. Large dosage form size

Since FDC products contain multiple drugs in the one tablet, it is a possibility that the tablet size may be too large to swallow, especially for pediatric and elderly patients. For example, in the case of, metformin, which is used in the treatment of type II diabetes, the usual unit dose is between 500 mg – 1000 mg. By adding an additional antidiabetic agent and excipients, the final tablet size may be too big to comfortably swallow [2].

6. Types of FDC Systems and formulation designs

FDC systems are basically classified into three types; monolithic or single layer FDC systems, multiple layers or multilayer FDC systems and multiparticulate FDC systems.

FDC systems formulation design and process development for FDC products are commonly more challenging than corresponding single entity products. In general, APIs are selected for FDC development based on several reasons and as a result a fundamental understanding of their pharmacological mechanisms, drug-drug interactions, pharmacokinetic profile and manufacturability are required for successful development. Synergistic therapeutic effects are desired when selecting APIs, but difficult to demonstrate [8]. Various manufacturing processes and formulations have been used successfully to produce FDC products from a commercial point of view. Fig. 2.1 shows a simplified decision framework on which a final formulation best suited to a potential FDC may be selected based on physicochemical properties of the APIs and desired dissolution profiles.

6.1. Monolithic FDC Systems

The single layer FDC system is the simplest FDC formulation choice. When two or more APIs are physicochemically compatible with each other and have dissolution or targeted release profiles that are similar, then the monolithic system in a solid oral dosage form is the most suitable option for the formulation. However, achieving bioequivalence for the FDC APIs may prove difficult for some systems when comparing the individual formulations to the FDC product. For example, if a BCS class II drug and a BCS class III drug were formulated into one monolithic FDC, even though they may be chemically compatible, the formulation matrix used for the BCS class III drug may impair the wetting and dispersion of the BCS class II drug making its bioavailability highly variable [8]. Such examples highlight the need for adequate

research to be undertaken prior to manufacturing [2]. Conventional FDC tablets and capsules are examples of monolithic FDC systems.

6.2. Multilayer FDC Systems

Multiple layers FDC systems are prepared by the repeated compression of powders. From a manufacturing point of view, they are a simple and convenient way of formulating incompatible drug compounds into a single solid dosage form. It is also a convenient way of enabling an immediate release formulation to be combined with a controlled release formulation. Drug compounds in the different layers may be the same API with different release profiles or, more commonly, contain two different APIs [18].

Once the chemical stability profiles of all drugs in multi-layered tablet FDCs are satisfactory, they can present some unique challenges in terms of obtaining acceptable tablet physical characteristics compared to conventional monolithic tablets. Some of the challenges associated with multilayer tablets may include insufficient overall tablet tensile strength, leading to excessive friability, delamination at the interface between layers, or capping within individual layers. Also, unsatisfactory weight control for the individual layers or the overall tablet, may lead to problematic content uniformity of the APIs [19].

6.3. Multiparticulate FDC Systems

This consists of numerous small discrete drug delivery units intended for oral delivery. Several terminologies such as mini-tablets, multiple units, beads, pellets, granules or spheroids have been used to describe this system. In the literature the size of these units has been reported as being as small as 150 μm and as large as 2 - 3 mm in diameter [20]. Multiparticulate systems may be made up with a single API or several, ranging from immediate release to modified release formulations. Multiparticulate systems are reliably administered as a single dose of the API/APIs using capsules, sachets or, after mixing with additional excipients and compression, in the form of tablets [21]. These types of systems offer many advantages including: flexibility for the choice of final dosage form e.g. capsules; flexibility in dose titration depending on how much API can be added individually; reduction in intra- and inter- subject variability due to reduced variation in gastric emptying and; easier dose-weight proportionality as compared to single dosage forms [20]. Pellets or spherical granules are usually made during an extrusion/spheronisation process, which has the advantage of having a narrower particle size distribution, and is the main manufacturing technology used in developing multiparticulate systems [22]. They also have the advantage of being able to be coated with one or several layers of film coating after production. Even though the extrusion/spheronisation process and the film coating of pellets, is considered well established, they are far from simple, with small changes in the formulation or process leading to significant effects on the attributes of the final formulation [23].

The film coating approach may be applied to produce various FDC products for several reasons. A simple film coat may provide protection of the API from light or moisture if these conditions have a detrimental effect on storage. Film coating may also be used for targeting drug release in a certain area of the gastrointestinal tract, such as a gastro-resistant film coating which prevents release in the stomach. Film coating technology may also be utilized to produce active film coats to prepare FDCs. The physical cores which are to be coated may be inert or may contain API. Layers of desired API may then be spray coated onto the core resulting in the FDC. The number of layers can vary from a single layer to several, depending on the number of APIs or the physicochemical interactions between the different layers that may be evident. One of the best examples of active film coating is in the product Claritin-DTM. This product is composed of an extended release pseudoephedrine core which is film coated with an immediate release loratadine and pseudoephedrine formulation. Upon oral administration, the coating dissolves immediately to release loratadine and pseudoephedrine to provide the initial dose followed by an extended release of pseudoephedrine from the tablet core [24]. The main difficulties with the active final coating approach are determining the end point of coating and content uniformity when coating is complete. For determining the end point, traditionally it was based on either the amount of coating material sprayed, or the weight gain of the core material. Due to the nature of spray coating, the core material potentially can change shape due to colliding off the wall of the container or the core material colliding off itself. This potentially results in an uneven distribution of the coating material. To overcome these problems, periodical sampling to perform assays has been introduced to determine the end point and content uniformity [8].

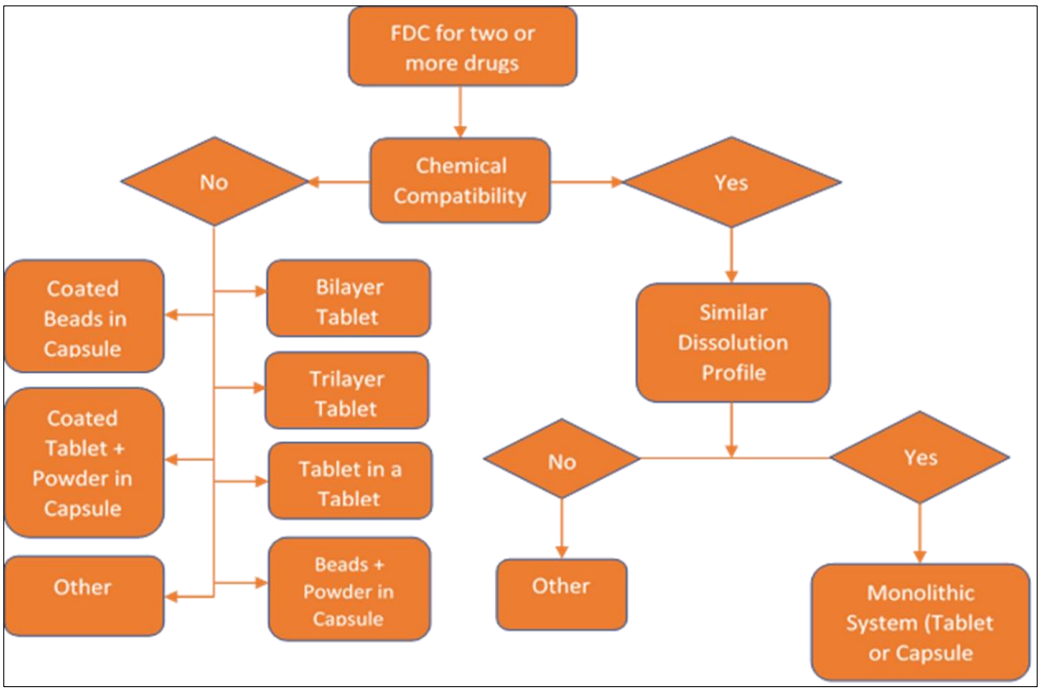

Figure 1 FDC systems formulation decision framework

7. FDC Formulation Approaches

When formulating solid oral dosage forms, the goals are same for both FDC tablets and monotherapy tablets; which is to establish a mass-production setup with a robust and quality-controlled approach resulting in acceptable and elegant looking preparations of consistent quality (e.g., uniformity of weight and uniformity of active ingredient) as well as a product with expected therapeutic effect, onset, intensity and duration of action. Several approaches may be employed when formulating these products, such as immediate-release fixed-dose combination dosage forms [12, 25-28], modified-release fixed-dose combination dosage forms (extended-release dosage forms, matrix-type drug delivery systems, multiple-unit pellet systems) [12, 25, 29-36], coating (delayed-release dosage forms, pH-responsive drug delivery systems) [12, 34, 37-43], layered tablets [12, 44-49], lipid-based formulations [12, 50-56], additive manufacturing [37, 57-59], multiple-unit delivery systems [12], layered tablets with drug-free layers [12]

8. Conclusion

Fixed dose combination has become a mainstay therapeutic alternative to patients faced with polypharmacy and high pill burdens, especially those patients with chronic comorbid health conditions. Although many FDC formulations have been approved by FDA and commercially available, yet there are still gaps left to be filled. A typical example of this gap is seen in the work of Onwuzuligbo *et al.* [60], where they identified the need for FDC formulations in the management of hypertension and diabetes mellitus comorbidity cases. This review paper succeeded in bringing together in one piece, the information required by pharmaceutical researchers interested in FDC to guide their FDC formulation decisions.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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