INTRODUCTION
People in the today's world leads a complicated life style with unhygienic conditions which usually causes increase in the chances of suffering from any type of various infectious diseases or any other sort of anatomical or physiological malfunctioning that may corresponds to cardiovascular, hormonal, gastrointestinal, central nervous system disorder. Subsequently, in order to treat such kind of disorder one has to depend upon either of the various medicinal agents which are prescribed either as a single drug or in the form of combination product/ fixed dose combinations (FDCs).

Combination products, also known as fixed dose drug combinations (FDCs) drug, are combinations of two or more active drugs in a single dosage form. The Food and Drug Administration, USA defines a combination product 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. The World Health Organization (WHO) lists nearly 325 essential drugs, including only 19 of such drug combinations (FDCs).

Some of the earliest FDCs have been widely accepted as rational combinations of drugs which are suitable for all of their target groups of patients, on the basis of their pharmacology or patient acceptability. Examples are the combination of estrogen with progestogen in combined oral contraceptives and levodopa with carbidopa to treat Parkinson’s disease. Many topical preparations, such as eye and ear drops and skin formulations, contain combinations which increase patient acceptability by reducing the number of products to be used.

Inappropriate drug combinations, where pharmacological claims for synergy are supported by little clinical evidence, e.g. the combination of caffeine with analgesics.

Mixtures of drugs which are of benefit to only a few patients. Examples are combinations of potassium sparing diuretics with thiazides and multi-component antacid mixtures.


Combinations of drugs for chronic conditions in which multiple drug regimens are recommended (e.g. HIV/AIDS). Such regimens place a significant pill burden on patients, particularly those with comorbidities, and FDCs in these patients may improve adherence.

Some formulations (e.g. asthma inhalers) contain two drugs but only one prescription charge is payable, which benefits patients who pay for their prescriptions.
bleeding from unsuspected peptic ulceration. FDCs of quinolones and nitroimidazoles (e.g. norfloxacin + metronidazole, ciprofloxacin + tinidazole, ofloxacin + ornidazole) have not been recommended in any standard books, but continue to be heavily prescribed in GI infections, pelvic inflammatory disease, dental infection, etc., to cover up for diagnostic imprecision and the lack of access to laboratory facilities. Such injudicious use of antibiotic FDCs can rapidly give rise to resistant strains of organisms, which is a matter of serious concern to the health care situation in our resource poor country. A glaring example is the emergence of ciprofloxacin-resistant Salmonella typhi strains which have made treatment of typhoid fever a difficult and expensive proposition in India today.

In India, a variety of NSAID combinations are available, often as over the counter products. These combinations are an easy way to sell two drugs when one (or even none) may be needed for the patient. The ‘combined’ pills are marketed with slogans like ‘ibuprofen for pain and paracetamol for fever’ and ‘ibuprofen for peripheral action and paracetamol for central action’. It is indeed very unfortunate that the medical fraternity in India has fallen prey to such gimmicks. The gullible patient then has to pay for the doctor’s complacence in terms of extra cost and extra adverse effects. There is no synergism when two drugs acting on the same enzyme are combined. Thus combining two NSAIDs does not and cannot improve the efficacy of treatment. It only adds to the cost of therapy and more importantly, to the adverse effects and the ‘muscle relaxants’ in some of these combinations are of questionable efficacy.

Combinations of NSAIDs/analogues with antispasmodic agents are also available in India. They are not only irrational but also could be dangerous. The antipyretic drug promotes sweating and thereby helps in heat dissipation. On the other hand, the anticholinergic antispasmodic drug inhibits sweating. Combining these two can result in dangerous elevation of the body temperature. Some such fixed drug combinations are now banned in India.

ADVANTAGES OF FDC PRODUCTS

- Simpler dosage schedule improves compliance and therefore improves treatment outcomes.
- Lower costs of manufacturing compared to the costs of producing separate products.
- Reduce complexity of a dosage regimen. It is seen that lesser number of tablets or medications a patient has to take, better will be his patient compliance.
- More convenient for the patient as he has to buy one drug compared to two.
- Reduces inadvertent medication errors.
- Only one expiry date simplifies dosing (single products may have different expiry dates).
- Procurement, management and handling of drugs are simplified.
- Potential for drug abuse can be minimized by using one drug of the combination for this purpose (i.e., excessive use of the antidiarrheal narcotic Diphenoxylate).
- Prevents and/or slows attainment of antimicrobial resistance by eliminating monotherapy.
- Allows for synergistic combination (e.g. Trimethoprim/Sulfamethoxazole combination allows each drug to selectively interfere with successive steps in bacterial folate metabolisms).
- Eliminates drug shortages by simplifying drug storage and handling, and thus lowers risk of being “out of stock.”

DISADVANTAGES OF FDC PRODUCTS

- Dosage alteration of one drug is not possible without alteration of the other drug.
- Differing pharmacokinetics of constituent drugs pose the problem of frequency of administration of the formulation.
- By simple logic there are increased chances of adverse drug effects and drug interactions compared with both drugs given individually.
- The greater are the number of ingredients, the less likely the prescriber or the physician is to know what FDCs are and what their adverse reactions are. A combination makes it more difficult to pinpoint the offending agent responsible for the adverse reaction.
- If a patient is allergic or has a side-effect to one component, the FDC must be stopped and replaced by separate medications.
- Reaction of one of the components (e.g., a rash to sulfamethoxazole in cotrimoxazole) may result in patient avoiding the “innocent” drug trimethoprim in the future.

SUCCESS FACTORS FOR FDC PRODUCTS FORMULATION

1. Formulation development challenges

A variety of issues potentially exist when combining multiple actives. It is not as simple as combining two or more actives in a tablet press or capsule. Understanding the chemistry, mechanism of action of each component, as well as drug substance pre-formulation characteristics, are paramount. An experienced formulator can make all the difference in helping you obtain / protect current IP, as well as make duplication by competitors extremely difficult. Speed to market is important, as well as holding off competitors. Below are just a few formulation considerations:

- Incompatibility
- Release profile differences
- Particle size
- Delivery challenges
- Regulatory requirements

2. Patent Feasibility

Obtaining patents is not as simple as submitting a concept that appears unique. The product must be innovative and show functionality. This is easier said, than done. Typically, patents are granted under the following criteria:

- Must be “novel” i.e. not publicly known
- Must be “inventive”, i.e. not obvious over what was already publicly known (“prior art”)
- Must be “utilizable”, i.e. has functionality

It should be noted that the “obviousness” hurdle is getting higher each year. If one’s have an idea or unique concept, chances are, so has somebody else. It is a good idea to research whether someone has gone down that road prior. The more successful combination products typically focus on unmet medical needs. To strengthen any patent, build innovation into the formulation. Generic companies are getting better at circumventing formulation patents.

3. Pricing & Reimbursement

- Premium pricing above mono-therapy is becoming more difficult.
- Increased unit sales should be the primary goal.
- Reimbursement is not typically an issue if combination product is not premium priced.
- Reimbursement at premium pricing will only hold if there is a clear beneficial outcome.
4. Physician Considerations
- Many physicians prefer to select relative dosing of combination components on an individual patient.
- Any need to titrate the drug dose can add complications.
- Identifying source of side effects can be difficult.
- Patient may potentially be exposed to drugs they do not really need.
- Conceptually, medication management & compliance should improve with patients. However, little evidence exists regarding compliance improvement.
- Physician’s increasingly see combination products as industry’s attempt to defend brand revenue against generic competition.

FDC PRODUCTS AND DISEASE MANAGEMENT

Anti-infective
Combination therapy is essential for the treatment of HIV/AIDS. The goals of HIV therapy are to maximally and durably suppress virus to allow recovery of the immune system and reduce the emergence of HIV resistance. At least three active drugs, usually from two different classes, are required to suppress the virus, allow recovery of the immune system, and reduce the emergence of HIV resistance. The FDC’s for the treatment of HIV should have the following criteria:
- Contain two or more components of a fully suppressive regimen
- Require a once or twice daily administration
- Have clinical efficacy and safety data that support use of the combination
- Be commonly used in treatment-naive patients
- Have drug interaction and toxicity profiles that allow for concomitant dosing
- Antiretroviral combination therapy defends against resistance by suppressing HIV replication as much as possible.

Antihypertensive
Several drug classes can be utilized in the treatment of hypertension: thiazide diuretics, β-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II (AII) receptor blockers, alpha (α) blockers and centrally acting agents. Both the British Hypertension Society 1999 guidelines and the American 6th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Blood Pressure of 1997 recommend that, in the absence of contra-indications or compelling indications for other agents, thiazide diuretics and β-blockers are the drugs of choice. These drugs have proved to be both safe and efficacious in numerous randomized control trials. Practice has been to begin treatment with one of these agents as monotherapy at a low dose. If this does not control blood pressure adequately then the physician is faced with three options.

Antihyperlipidemic
Out of various available FDC drugs as antihyperlipidemic, the comparative efficacy of the most popular marketed drugs is being discussed here. These are Vytorin and Advicor. Vytorin is a combination of another statin, simvastatin, and a newer drug ezetimibe, while Advicor is a combination of an HMG-CoA Reductase Inhibitor (statin) – lovastatin with an extended release formulation of niacin. All of the individual products are available separately and can be administered once daily. The FDCPs have multiple strengths available, although the dose of ezetimibe is constant at 10mg in Vytorin. For Vytorin, the difference in LDLc lowering compared to its component statin, simvastatin, was a mean of 14% across all doses. Differences with atorvastatin were dose-dependent with an inverse dose-response curve: differences of 11% at 10mg, 9 –12.5% at 20mg, 6.7% at 40mg and 5.7% at 80mg. Across all doses, the mean additional reduction in LDLc with Vytorin compared to rosuvastatin was 4%. With Vytorin compared to statin monotherapy, HDLC is increased an additional 0.4% to 4%.2,19,20 For Advicor, the difference in LDLc lowering compared to lovastatin monotherapy ranges from 10 to 24%, while the differences in comparison to simvastatin were 0 to 3%.22,23 Triglyceride reduction is also affected by adding niacin. The higher doses (2000mg/40mg or 1500mg/20mg) of Advicor were found superior to either drug alone for LDLc reduction. These studies also found that the addition of a second drug provided additional benefit compared to a single drug based on lipoprotein A and triglyceride levels.23,24,25

Antidiabetic
An observational study of a database of pharmacy prescription refills for 6,502 patients taking metformin and glibenclamide over six months showed no significant differences in concordance among newly treated patients receiving monotherapy, a combination of the two drugs or a FDC.26 However, patients switching to the FDC had improved concordance compared with those previously taking the two drugs separately (87% vs. 71%; p < 0.001) but the number of patients was small (n = 59). Another retrospective study with a FDC of metformin and glibenclamide did show better concordance compared with taking the two drugs separately (84% vs 76%; p < 0.0001, n = 1,421).27 In the latter study, improved HbA1C levels were also observed with the FDC, although these may have been due to different pharmacokinetic and pharmacodynamic properties of the FDC formulation observed by the authors, compared to the drugs administered separately.2 Patients who were at least 80% concordant with either therapy did not achieve significantly better glycaemic control than those who were less concordant with the same treatment.2 Elsewhere, only small increases in Hba1C were seen in patients who were nonconcordant with metformin (a 10% reduction in concordance produced an increase of 0.14% in HbA1c, p < 0.01).28 Another retrospective study of 11,532 patients with diabetes, found that non-concordant patients had higher rates of hospitalization (odds ratio (OR) 1.58; 95% confidence interval (CI) 1.38 to 1.81; p < 0.001) and higher all-cause mortality (OR 1.81; 95% CI 1.46 to 2.23; p < 0.001) than adherent patients.29

Antifertility (Contraceptives)
As per research a triphasic, combined oral contraceptive containing 30 - 40 - 30 micrograms Ethinylestradiol, and 50
- 75 - 125 micrograms Levonorgestrel was compared with a fixed dose combination containing 30 micrograms Ethinylestradiol and 150 micrograms desogestrel in a randomized multicentre trial in 193/199 women and 1063/1073 cycles, respectively. The duration of the trial was six months. Eleven centre’s in Denmark, Sweden, and Norway participated. Contraceptive reliability, bleeding control and side effects were evaluated and the result came as that - Three pregnancies occurred in the group using the triphasic regimen but none in the fixed dose regimen. Two of the three pregnancies were considered drug failures and the third a possible interaction. 30 It was concluded that it is safer and much more efficacious to use the contraceptives in the format of FDC. 

**Antituberculosis**

Anti-tuberculosis therapy (ATT) with multiple antimicrobials, administered individually or as fixed dose combinations (FDC) is the key to control of tuberculosis. Arguments in favor of FDC include better patient compliance, simplification of prescriptions, easier management of drug supply, reduced programmatic cost, and less chances of developing drug resistance. 31,32,33 WHO and other agencies also recommend FDC for delivering anti-tuberculosis drugs. 34

**Table: 1- RATIONAL FDC DRUGS**

<table>
<thead>
<tr>
<th>Generic combination</th>
<th>Category</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin + Clavulanic acid</td>
<td>Antibiotic</td>
<td>Tablet</td>
</tr>
<tr>
<td>Neomycin + Bacitracin</td>
<td>Antibiotic</td>
<td>Ointment</td>
</tr>
<tr>
<td>Cefadroxil + Clavulanic acid</td>
<td>Antibiotic</td>
<td>Tablet, Dispersible Tablet</td>
</tr>
<tr>
<td>Cefazidine + Tazobactam (as sodium)</td>
<td>Antibiotic</td>
<td>Injection</td>
</tr>
<tr>
<td>Cefixime + Cloxacin (as Sodium) + Lactobacillus (45 million spore)</td>
<td>Antibiotic</td>
<td>Tablet</td>
</tr>
<tr>
<td>Sulfamethoxazole + Trimethoprim</td>
<td>Antimicrobial</td>
<td>Tablet</td>
</tr>
<tr>
<td>Sulindoxone + Pyrimethamine</td>
<td>Antimicrobial</td>
<td>Tablet</td>
</tr>
<tr>
<td>Isoniazid + Ethambutol</td>
<td>Antitubercular</td>
<td>Tablet</td>
</tr>
<tr>
<td>Rifampicin + Isoniazid</td>
<td>Antitubercular</td>
<td>Tablet</td>
</tr>
<tr>
<td>Thiacetazone + Isoniazid</td>
<td>Antitubercular</td>
<td>Tablet</td>
</tr>
<tr>
<td>Benzoic acid + Salicylic acid</td>
<td>Antiseptic</td>
<td>Ointment, Cream</td>
</tr>
<tr>
<td>Ethinylestradiol + Levonorgestrel</td>
<td>Ant fertility</td>
<td>Tablet</td>
</tr>
<tr>
<td>Ethinylestradiol + Norethisterone</td>
<td>Ant fertility</td>
<td>Tablet</td>
</tr>
<tr>
<td>Levodopa + Carbidopa</td>
<td>Antiparkinsonism</td>
<td>Tablet</td>
</tr>
<tr>
<td>Ferrrous salt + Folic acid</td>
<td>Haematinics</td>
<td>Tablet</td>
</tr>
<tr>
<td>Lidocaine + Epinephrine</td>
<td>Local Anesthetic - Vasoconstrictor</td>
<td>Injection</td>
</tr>
<tr>
<td>Pantoprazole + Domperidone</td>
<td>GERD</td>
<td>Tablet</td>
</tr>
<tr>
<td>Temisartan + Amilodine (as Besylate)</td>
<td>Antihypertensive</td>
<td>Tablet</td>
</tr>
</tbody>
</table>

**Table: 2- IRRATIONAL FDC DRUGS**

<table>
<thead>
<tr>
<th>Generic combination</th>
<th>REASON of irrationality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nimesulide + Paracetamol</td>
<td>Nimesulide is banned in most countries. No documentary evidence of prominent effect of combination, Probability of myopathy may increase.</td>
</tr>
<tr>
<td>Atorvastatin + Nicotinic Acid</td>
<td></td>
</tr>
<tr>
<td>Cetrizine + Phenylpropanolamine + Pseudoephedrine</td>
<td>It has potential to cause paracetamol stroke, glaucoma and prostate enlargement.</td>
</tr>
<tr>
<td>Amoxicillin + Clavulanic acid</td>
<td>Amoxicillin is inactive against staphylococcus and clavulanic acid is not very active against streptococcus. One of the components is useless for any given infection. Increasing the chances of resistance.</td>
</tr>
<tr>
<td>Enalapril + Losartan</td>
<td>Two drugs affecting the same pathway do not add to efficacy.</td>
</tr>
</tbody>
</table>

**CONCLUSION**

The popularity of FDCs is increasing rapidly; particularly when more than one disease is found in a patient. Patients have already seen the benefit of combination products in areas such as oncology, cardiology, neurological, metabolic disorders, respiratory, HIV, as well as several other areas. On the other side, irrational FDCs may impose unnecessary financial burden on consumers. The time has come for all practitioners and consumers to raise this matter vociferously through all possible ways. Drug regulatory bodies should take urgent action to stop the free flow of irrational FDCs.

**REFERENCES**


32. Hong Kong Chest Service/British Medical Research Council. Acceptability, compliance, and adverse reactions when isoniazid, rifampin, and pyrazinamide are given as a combined formulation or separately during three-times-weekly antituberculosis chemotherapy. Am Rev Resp Dis, 1989; 140:1618-1622.


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