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Short Communication

Fixed dose combinations in India- what a way to go!

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ABSTRACT

Fixed dose combinations (FDCs) are generally considered desirable options in chronic diseases such as tuberculosis, cardiovascular diseases & diabetes, tropical diseases such as malaria & in HIV and in Cancer. FDCs are useful in chronic conditions especially when multiple disorders often co-exist The advantages of the FDC are basically patients compliance, simple dosage schedule, better efficacy, cheaper shipment & packaging activities. The drawbacks of FDCs are (a) Pharmacodynamic mismatch between the two ingredients, one drug having additive/antagonistic effect leading to reduced efficacy or enhanced side effects, (b) Pharmacokinetic disparity having peak efficacy at different time zone, (c) Chemical non compatibility leading to decreased shelf life, (d) Drug interactions due to common metabolizing pathways, and (e) limitations of dose titration of individual ingredients. As per Rule 122 E of Drugs and Cosmetics Act 1940, the FDCs are considered as New Drugs where the Central Drugs Standard Control Organization (CDSCO), ensures proper clinical data is submitted for the approval into the market. Appendix VI of Schedule Y (Drugs & Cosmetics Rules 1945) mentions the requirements for marketing approval of various types of FDCs.

1. Introduction

"A fixed-dose combination (FDC) is defined as the combination of more than one drug at a fixed ratio in a single dosage form for a particular indication".

FDCs are highly preferred in India due to patient compliance. The rational of combination is based on:

1. The drugs in the combination should acting by different mechanisms
2. The pharmacokinetics should not be dissimilar
3. The combination should not lead more side effects
4. There should be enhanced efficacy of the formulation [1]

The current 14th model list of essential drugs prepared by the WHO (March 2005) includes 312 formulation of which merely 18 are fixed dose drug combinations. [1]

In September 2018, the Government of India banned the manufacture, sale and distribution of 344 Fixed-Dose Combination drugs (FDCs), 1670 brands, with sales of 38 billion Rupee, after a protracted legal battle with manufacturers, which were marketed for past 30 years, the approval of these drugs was solely based on patient compliance and none of these were marketed in ICH regions. The Drug Technical Advisory Board (DTAB) recommended that 'there was no therapeutic justification' for the active ingredients in the banned FDCs and accordingly these combinations 'may involve a risk to exposed population. This had been a major challenge for the health policy in India. [2] Currently there are 51 FDC newly approved from CDSCO, in 2022, the therapeutic areas being hypertension, hyperlipidaemia, asthma, antivirals, bronchial asthma, antiepileptic, antimicrobials. [3] CDSCO has provided guidelines on FDC evaluation and approval

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as per their guidance in 2013. Global regulatory status of the FDC has to be made clear in the application and highlighting the same in the covering letter of the application, as per Form 44. The manufacturer/sponsor have to submit application on Form 44 for permission of new drug approval under the provisions of Drug and Cosmetics Act 1940 and Rules 1945. Form 44 is an application for grant of permission to import or manufacture a new drug. FDCs come under the category of New Drugs. The guidelines for domestic as well globally approved FDCs to be evaluated are provided in CDSCO website. For the approval of a new FDC, it is required to demonstrate all the possible advantages of the new combination against the disadvantages. The common approach for the approval of the FDCs is the bioequivalence between the FDC.[4] Cost of development of FDCs is much less as compared to the Innovator drugs, these can be evaluated through direct Phase IV studies in India and if the components of FDCs are already marketed and in US they take advantage of the FDA's 505(b) (2) approval pathway.[5]

Malaria: Artesunate**/**Mefloquine 25**/**50mg FDC **(**Fixed Dose Combination) Tablets are indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria, in the setting of either P. falciparum mono-infection or mixed infections in children and infants of 5 kg and above. African children with acute P. falciparum malaria and artesunate-mefloquine combination therapy over a period of 63 days showed no serious drug-related neurological or neuropsychiatric events. Less than 4% showed mild to moderate transient drug-related neurological or neuropsychiatric disorders.[6]

The FACT development project carried out a large pivotal Phase III trial with the support of the CRO Cardinal Health Inc. for data management and final report generation. Artesunate (AS) and amodiaquine (AQ) have distinct mechanisms of action and their pharmacokinetic/ pharmacodynamic (PK/PD) characteristics are complementary: AS rapidly and substantially reduces the parasite burden and has a very short half-life (20-45 minutes.[7] Both dihydroartemisinin-piperaquine (DP) and sulphadoxine and pyrimethamine (SP) have been used for malaria prevention in pregnant mothers. Fixed dose combination (FDC) artemether (ART)/lumefantrine (LUM) tablets available in African countries.[8]

FDCs for the Antiretrovirals for the Treatment of HIV, are the following therapeutic groups as per the recommendation of Centre of Drug Evaluation & Research.

Two-drug nucleoside analogue components (to be used with a protease inhibitor or NNRTI).

Three-drug regimens, consisting of two NRTIs and a protease inhibitor or NNRTI.

Triple regimen (or two-drug component) studied for at least 48 weeks in trials evaluating changes in HIV-RNA and CD4 cells1.[9]

1. *Hypertension:* From 2017, a systematic review of the evidence of efficacy and safety of two-drug BP-lowering combinations for the management of hypertension in adults has been established. American College of Cardiology, and other professional organizations recommend combination therapy as initial treatment, when SBP/DBP is 20/10 mm Hg above goal BP, with ACEI or ARB, CCB, and thiazide/thiazide-like diuretics. Drug combinations are essential to prevent long term complications of hypertension[10]
2. *Asthma:* The clinical place of triple therapy FDC inhalers in the management of severe asthma is becoming more established. The studies found that adding a LAMA- long-acting muscarinic antagonist to ICS- Inhaled corticosteroids + LABA- Long-acting beta-agonists modestly improves lung function compared to ICS + LABA.[11]
3. *Diabetes:* The following are IDF 2017 recommendations for Dual and Triple Therapy for Type 2 Diabetes mellitus.In principle a second glucose-lowering drug is added if monotherapy with metformin is not sufficiently effective to reach the glycated hemoglobin A_{1c} target or fails afterwards.
   The best choice of add-on is an SU (except glibenclamide/glyburide), a DPP-4 inhibitor, or an SGLT-2 inhibitor. An alpha-glucosidase inhibitor can be used as well, though there are increased incidences of gastrointestinal side effects. A GLP-1 receptor agonist can be used if weight loss is a priority.[12]
4. *Anti-tubercular drugs:* The WHO Model List of Essential Drugs includes two-drug formulations (INH + RIF and INH + ethambutol), three-drug formulations (INH + RIF + ethambutol and INH + RIF + pyrazinamide) and a four-drug formulation (INH + RIF + ethambutol + pyrazinamide)[13]
5. *Breast cancer:* FDC of capecitabine (1800 mg per day) and cyclophosphamide (80 mg per day) is effective and well-tolerated in the management of patients with Metastatic breast cancer. This shows high disease control rates and good safety profile in Metastatic breast cancer patients."
   Phesgo the injectable formulation combines breast cancer drugs Perjeta (pertuzumab) and Herceptin (trastuzumab) with hyaluronidase, to treat early and metastatic HER2-positive breast cancer.[14]

2. Discussion

India has highest number of FDCs approval, from 1961 onwards. Historically, in India FDCs have been approved based on justifications provided by Pharmaceutical sector

Table 1: Global top selling FDCs in US [15]

Brand	Molecules	Indication	Approval Year
Advair Discus	luticasone/salmeterol	Asthma/COPD	2000/ GSK
Hyzaar/Cozaar	Losartan/HCT	Hypertension	1995/Merck & Co.
Truvada	Emtricitabine /tenofovir	HIV/AIDS	Gilead/2004
Atripla Tablets	Efavirenz/ emtricitabine/ tenofovir	Tenofovir HIV/AIDS	2007/Gilead/BMS
Vytorin	Ezetimibe /simvastatin	Lipid regulation	2004/Merck/SP
Symbicort /DPI/MDI	Budesonide/formoterol	Asthma/COPD	2006/Astra Zeneca
Avandamet Tablets	Rosiglitane/metformin	Diabetes	2002/GSK
Kaletra soft gel	Lopinavir /ritonavir	HIV/AIDS	2000/Abbott
Epzicom	Abacavir /lamivudine	HIV/AIDS	2005/Shire
Combivir Tablets	Lamivudine /zidovudine	HIV/AIDS	1997/Shire
Ristfor Tablets	Sitagliptin/metformin	Diabetes	2010/ Merck(EU)
Duodart	Dutasteride/tamsulosin	BPH	2010/ GSK
DuoCover/DuoPlavin tablet	Clopidogre/aspirin	ACS/MI	2010 /BMs
Azor Tablet	Amlodipine amlodipine /olmesartan	Hypertension	2009/ Daiichi Sankyo
EMBEDA Abuse resistant capsule	Morphine /naltrexone	Pain	2009/ Alpharma
Lipsovir cream	Acyclovir /hydrocortisone	Herpes	2009/ Medivir
Copalia HCT	Amlodipine /valsartan/ hydrochlorothiazide	Hypertension	2009/ Novartis
ACTOplus met XR Tablets	Metformin/pioglitazone	Diabetes	2009/ Takeda

Table 2: FDCs included in national essential medicinelist [16]

(Trimethoprim + Sulfamethoxazole) Co-trimoxazole
Stavudine Lamivudine + Nevirapine +
Zidovudine +Lamivudine
Isoniazid+ Thiacetazone
Sulfadoxine + Pyrimethamine
Bacitracin+ Neomycin
Ethinylestradiol + Levonorgesterol
Ethinylestradiol + Norethisterone
Carbidopa+ Levodopa
Lignocaine hydrochloride + Adrenaline
Acriflavin + Glycerin
Salicylic acid +Benzoic acid
Aluminum hydroxide + Magnesium hydroxide
Oral rehydration salts (sodium chloride, trisodium citrate dehydrate, potassium chloride, glucose)

Table 3: Demerits of FDCs [17]

Difficulty in dose titration
Increased Cost
Drug interactions may occur between active ingredients and excipients which are used in the FDCs
If an FDC is believed to be the source of an adverse drug interaction, to find the active ingredient responsible for this reaction is difficult.

and respective key opinion leaders justifying their scientific stand, thus hundreds of FDCs have flourished, though which did not stood scientific justification were weeded out, nearly 344 by September 2018.

The FDCs in India were developed as the generic drug companies focussed on their development, as there was no inherent new drug pipeline in country, which is endorsed in Indian Journal of Pharmacology — Vol 48, Issue 4, August 2016, 347-348. Dr Y.K. Gupta.

Though compliance is strong feature in favour of FDCs, the disadvantages are: Fixed-dose anti hypertensive combination products have the disadvantage of lacking the dosing flexibility for its individual components. Drug interactions may occur between active ingredients and excipients which are used in the FDCs.

The efficacy is an important sign with regards to the therapeutic advantage of the FDC compared to monotherapy. Tuberculosis patients treated with Rifampicin mono drug therapy involving a short period of use, shows resistant micro-organisms. Similarly the effectiveness of Fixed dose Multiple drug therapy has been proved by its role in the elimination of leprosy and the acceptability by the patients and public health-care administrators worldwide. FDCs may offer better treatment through improving patient compliance.

Most of antimicrobial, drug combinations, do not have scientific justifications such as Ampicillin + Cloxacillin, Ciprofloxacin + Metronidazole, Ofloxacillin + Tinidazole, these are not approved in neighbouring countries such as Nepal & Bangladesh.

NSAIDs are amongst the most widely used drugs internationally. Almost 12 billion NSAID tablets/capsules were sold in India in 2012. Out of 124 NSAID-FDC products available in the market, only 34 were officially approved by CDSCO. Some triple drug combinations are thus withdrawn. Nimesulide formulations are not approved by EMA or US FDA.

Tonics are widely used and their basic aim is well-being. Most of time they have multiple ingredients, all of which may not be required to treat particular anemia or condition, and they are marketed at high price. These are more frequently prescribed in many concomitant conditions to improve sense of wellbeing. (These come under category of extravagant prescribing).

Irrational FDCs impose unnecessary financial burden on consumers. Doctors who prescribe such combinations could be the centre of controversy when subjected to litigation in consumer forums, as these combinations do not find mention in standard medical texts or in interactive forums.

Single drugs should used and combined with necessary medication for the desired benefits. FDCs therapy can be considered for chronic conditions, where there is actual need of combination therapy. The policy guidelines for FDCs are circulated by CDSCO, India in their website. Many guidelines on FDCs are available issued by various regulatory bodies worldwide, depending on the same FDCs are available in those countries.

3. Source of Funding

None.

4. Conflict of Interest

None.

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