A Brief Review On Fixed Dose Combination

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Abstract- *A combination drug or a fixed-dose combination is a medicine that includes two or more active ingredients combined in a single dosage form. A combination drug or a fixed-dose combination (FDC) is a medicine that includes two or more active ingredients combined in a single dosage form.[1] Terms like "combinationdrug" or "combination drug product" can be common shorthand for an FDC product (since most combination drug products are currently FDCs), although the latter is more precise if in fact referring to a mass-produced product having a predetermined combination of drugs and respective dosages (as opposed to customized polypharmacy via compounding[2]). And it should also be distinguished from the term "combinationproduct" in medical contexts, which without further specification can refer to products that combine different types of medical products—such as device/drug combinations as opposed to drug/drug combinations.[3] When a combination drug product (whether fixed-dose or not) is a "pill" (i.e., a tablet or capsule), then it may also be a kind of "polypill" or combopill. Initially, fixed-dose combination drug products were developed to target a single disease (such as with antiretroviral FDCs used against AIDS). However, FDCs may also target multiple diseases/conditions. In cases of FDCs targeting multiple conditions, such conditions might often be related—in order to increase the number of prospective patients who might be likely to use a given FDC product. This is because each FDC product is mass produced, and thus typically requires having a critical mass of potentially applicable patients in order to justify its manufacture, distribution, stocking, etc.*

Common combination drugs:-

Adderall: Treats attention deficit hyperactivity disorder (ADHD) and narcolepsy

Aspirin/paracetamol/caffeine: Treats pain, especially migraines and tension headaches

Caffeine/ergotamine: Treats headaches, such as migraines

Nonmaterial/ritonavir (Paxlovid): Treats and manages COVID-19

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I. INTRODUCTION

Fred-dose combination products (FDCs) are mediums which contain two or more active ingredients.Formalation They are called pretended on the market in a swaged product, in fixed-doses. Today, the formulation in hade-dose combinations and clinical development studies are increased for their use in treating various diseases.

The fed-dose combinations are usually used for cardiovascular diseases (hypertensions, hypercholesterolemia), diabetes, infectious diseases (h pylori, AIDS- IV infections and niherculests), psychiatric disorders (depression and Alzheimer's) and respiratory diseases (asthma and COPD) Including allergy release and in in the lurgies' fields et ophthalmology 1 dermatology. There id dermatology. The ducts approved by the FDA from 1990 90 until 2013. Today, this murders moved with the addition of new products approved by the FDA.

Regulation of FDC products:-

As per the Drugs and Cosmetic Act 1940, any new drug and the authorization to market a drug is to be given by the drug control general of India (DCGI). Before the approval of any drug, the iron Central drugs standard control organization (CDSCO) undergoes a process with respect to their quality, safety and efficacy. It is an accepted fact that FDC's is treated since a new drug for the reason that by combining two or more drugs. The safety, efficacy and bioavailability of the individual active pharmaceutical ingredients may change. The drugs from the angle of safety, effectiveness and rationality.Globally, there is a rising movement to license FDC's products for the market place. Appendix VI of Schedule Y specifies the necessities for authorization for marketing of variety of types of FDC's. to FDA guidelines apply manufacture/import and marketing approval of FDC's as a complete pharmaceutical product considered as new drug as per Rule 122 € of Drugs and Cosmetics Act 1940 and their Rules 1945.A clear explanation with an appropriate therapeutic rationale of the particular combination of active substances proposed will be the basis of approval. It is not always necessary to generate new information. Confirmation may be obtained from the scientific literature subject to its being of sufficient value. In case of FDC's where all the active ingredients are approved

individually, if a clinical trial is necessary, confirmatory study toestablish efficacy, preferably by similar comparisons in which the FDC's is compared to its individual substances may be considered when possible a placebo arm may be incorporated group. clinical trials of the FDC's with reference treatment may be essential, particularly when the therapeutic explanation talks more on the FDC's superiority over a reference treatment. An application for a marketing authorization may comprise entirely original data, entirely data from the literature and both original data and data from the literature (hybrid). For FDC's it is likely that hybrid submissions will be the most ordinary kind. Chemical and pharmaceutical data should be always completely innovative, unless there is enough explanation with literature when partial data can be inoriginal.

Advantages of FDCs:-

Decreased pill burden
Better adherence
Prescription errors less likely
Patients unable to take partial regimen
Experience of FDCs with other diseases such as tuberculosis, malaria etc.
6)Practical for management in large programs (improved drug supply systems)
7)Cheaper in generic form (e.g., in resource-limited setting .

Better treatment:- A reduced pill burden during the intensive phase, with only three or four FDC pills required per err day instead of the current 7-8 pills required for the single drug regimen. The large number of pills in the current regimen increases the chance that patients will miss taking a specific dose, which can lead Incomplete treatment, or worse, monotherapy with a single drag, increasing the risk of developing drug resistance. This risk can be mitigated with introduction of I FDCs, slace the essential drugs of the regimen are combined in a single pill.

Better adherence leads to better treatment outcomes and helps avoid treatment failure and relapses. This is especially true for people with HIV-TB co-infection wish are daily antiretroviral therapy (ART), Poor adherence to either DOTS or ART can lead to drug resistance and in turn lead to p lead to poor treatment outcomes for both TB and HIV. In addition, people living with HIV who are on ART are also mast in need of daily FICs (already being implemented for ART), to reduce their over pill burden, simplify treatment literacy and improve levels of adherence.

Better case management 1] FDCs simplify the drug supply chain by reducing the number of formulations' that must be ordered and distributed, particularly to peripheral parts of the country.

FDCA be cheaper than other regimens because program costs for procurement and distribution are lower. High-volume procurement by the government of India could further reduce costs.

Patient compliance:-FDC may increase patients compliance by taking less tablets on daily basis (cg. 3-4 tablets/day Instead of the 15-16 tablets/day) compared to monotherapy.

Disadvantages of FDCs,:-

Does not accommodate lead-in dose.
Difficult to use when dose adjustments are needed (eg, renal failure).
Need to stop FDC for adverse drug reaction to one component.
Limited availability of pediatric formulations.

More expensive if generic version of one or more components available (developed countries).

Products have the disadvantage of lacking the dosing flexibility for its individual components, However, since Amlodipine and Atorvastatin have several dosage strengths (dose range: 5-10 mg Amlodipine/10-80 one mg Morvastatin) these drugs will not be concerned.

Furthermore, Exec-dose combination antihypertensive/dys-lipidemic therapy may not provide a sufficient amount of drug to treat illnesses like angina (in cases where Amlodipine is necessary with doses (hagher than 10 mg) that can be found together with hypertension.

Drug interactions :-Drug interactions may car between active ingredients and excipients which are used in the FDC's according substances under chemical properties of the environment(acidic/basic/humidity).

Drug Interactions Important causes because they may change the therapeutic effect, and may cause the potential incompatibilities and moreover affect the stability.

Most FDCs have the following demerits:-

Dosage alteration of one drug is not possible without alteration of the other drug.
Differing pharmacokineticsofconstituent 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.

FDCs are Rational or Irrational:-

Many FDCs being introduced in India are usually irrational. The most pressing concern with irrational FDCs is that they expose patients to unnecessary risk of adverse drug reactions, for instance, paediatric formulations of nimesulide + paracetamol. Nimesulide alone is more antipyretic than paracetamol, more anti-inflammatory than aspirin, and equivalent in analgesia to any of the NSAIDS alone [6], so efficacy gains are unlikely with added paracetamol. However, the patients may be subject to increased hepatotoxic effects from the combination. FDCs of diclofenac + serratopeptidase do not offer any particular advantage over the individual drugs despite the claim that serratopeptidase promotes more rapid resolution of inflammation [3]. On the other hand, the patient is exposed to greater risk of gastrointestinal (GI) irritation and serious 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 [7, 8], but continue to be heavily prescribed drugs 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 typhus strains which have made treatment of typhoid fever a difficult and expensive proposition in India today [3].In India, a variety of NSAID combinations are available, often as over the counter products [9]. 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 [10] and the ‘musclerelaxants’ in some of these combinations are of questionable efficacy.

Combinations of NSAIDS/analgesics with antispasmodic agents are also available in India [9]. 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.

Functions:-

Transgenic mice engineered to constitutively express FDC-SP, the number and size of GCs formed after immunization with a T-dependent antigen significantly decreased. The position of these GCs is normal, but they do not form centers of highlyproliferating B cells, which us thought be due to FDC-SP affecting the development of GCs. The mechanism by which FDC-SP exerts its effects upon GC development is not currently known. The formation of FDC networks appears to be normal in transgenic mice, as does T cell response.[4].

FDC-SP is an amphipathic molecule, similar to surfactant proteins A and D, which are thought to be involved in the innate immune system of the lung. These proteins allow for the phagocytosis of bacteria by binding to them. Stathrin has been proposed to have similar properties, which itself possesses similar properties to FDC-SP. Stathrin can bind oral bacteria, so it has been proposed that FDC-SP acts as part of a host defense mechanism against oral pathogens.[3]FDC-SP is thought to bind target cells through a specific receptor in a similar manner to cytokines and chemokines. Although it shares no sequence homology with chemokines or cytokines, FDC-SP has several properties in common with several inflammatory mediators, including molecular mass and amino acid composition. The FDC-SP gene is also located next to a group of praline-rich salivary peptide genes, which themselves are next several to CXC chemokine genes. FDC-SP has an effect on B cell migration when used in conjunction with L cells, and migration is significantly increased when the B cells are stimulated with anti-CD40 plus IL-4. The addition of anti-CD40 causes the B cells to resemble those found in the GC. Pertussis toxin inhibits the action of G proteins and B cells treated with the toxin were observed to migrate poorly in response to FDC-SP.

Conclusion:-

Determining whether a FDC has benefits to a health care organization requires careful review of the evidence, practicality, and cost. Clear indications of improved outcomes,

reduced costs, safety, and convenience to patients are important considerations.

Produce a synergistic effect if each of the drugs impinges on a different target or signaling pathway that results in reduction of required drug.

REFERENCES

[1] World Health Organization (WHO). Global tuberculosis control: WHO report 2012. WHO/HTM/TB/2012.6.

[2] World Health Organization (WHO). Multidrug and extensively drug-resistant TB

[3] (M/XDRTB): 2010 global report On surveillance and response. WHO/HTM/TB/2010.3

[4] Murchison DA. How drug resistance emerges as a result of poor compliance during short course chemotherapy.

[5] . 4)Effectiveness and tolerability of fixed dose combination of Amindipine/valsartan in treatment of hypertension in the real-life setting among Egyptian patients, The Edgy Heart 1, 2014; 66:1-35.

[6] Aslan S, Fixed-dose Combination Therapy in Hypertension: Focus on Fixed-dose

[7] Combination of Amlodipine and Valsartan (Exmore) Cline. Medic Therap.1 2009; 15211529.

[8] Mitral A Wu Y Challenges and Opportunities in Achieving Bioequivalence. For Fixed-Dose Combination Products, AAPS Journal, 2012:14(3):646-655. [31] Mehrdad H. Shahbazi M. Azimi Bioequivalence evaluation of a triamterene trend hydroch hydrochloride chlorothiazide generic product: A new bioequivalence index for fixed-dose combinations. Regal TopicalPharm, 2011:59: 149-156.

[9] Chine K.1, Chau CL, Su T.C, Bioavailability Study of Fixed-Dose Tablet Versus Capsule Formulation of Amlodipine Plus Benazepril: A Randomized, Single-Dose, Two-Sequence.

[10] Two Period. Open-Label, Crossover Study in Healthy Volunteers, Orr. There. Res. Cline. Exp. 2005: 66(2):69-79. 33] MacKeigan P. Roderick F, and Mahajan It.

[11] Use of fixed dose combination drugs in India central regulatory approval and sales of FDCs containing non-steroidal anti- inflammatory drugs, Metformin, or Psychotropic Drugs. PLOS Medicine, 2015; (12): 1-28.

[12] Department-Related Standing Committee on Health and Family Welfare (2012 May) 594 report on the functioning of the Central Drugs Standard Control Organization (CDSCO).

[13] A. Nehr-Nielsen, M. De Bruin, M. Thomsen, C. Piper, T.Lange, O. Bjerrum, et al.

[14] Body of evidence and approaches applied in the clinical development programmed of fixed-dose combinations in the European Union from 2010 to 2016.

[15] A. Gupta, S. Arshad, N. Pouter. Compliance, Safety, and Effectiveness of Fixed-Dose Combinations of Antihypertensive Agents Hypertension, 55 (2) (2010), pp. 399-407.