

**A STUDY OF PREVAILING SCENARIO OF FIXED-DOSE DRUG COMBINATIONS (FDCs) AVAILABLE IN INDIAN MARKET**Dr. Sumit Patel<sup>1</sup>, Dr. Rima Shah<sup>2</sup>, Dr. Sagun Desai<sup>3</sup><sup>1</sup>Assistant professor, Pharmacology (MD), GCS Medical Collage, Ahmadabad, Gujarat<sup>2</sup>Assistant Professor, Pharmacology (MD), GMERS Medical College, Gandhinagar, Gujarat<sup>3</sup>Professor in Pharmacology (MD), SBKS Medical Institute & Research Center, Sumandeep Vidyapeeth, Piparia, Vadodara, Gujarat, India**\*Corresponding author e-mail:** [dr.sumitpatel@gmail.com](mailto:dr.sumitpatel@gmail.com)**ABSTRACT**

**Aim:** To study the prevailing scenario of FDCs available in Indian market. **Methodology:** This was an observational, analytical and cross sectional study. This study involved analysis of currently available FDCs in Indian Drug Review (IDR) for essentiality and rationality. Information about number of drugs per FDC, their dosage form, ingredients, category, essentiality and rationality of FDCs was collected. **Results:** A total of 16599 drugs and 6485 (39.07%) FDCs were present in IDR. More than four ingredients were found in 102 (1.56%) FDCs. The highest number of drugs and FDCs were found in category of antimicrobial drugs. More than 70% FDCs were found to irrational. **Conclusion:** In India, irrational FDCs are freely available. There is a concern regarding the production, prescription, and use of irrational FDCs. Considering the enormous use of drugs in Indian population, it is high time that pharmaceutical companies, health care professionals and regulatory authorities join hands and prescribe guidelines for the manufacture and sale of FDCs.

**Key words:** Fixed-dose Drug Combinations (FDCs), Rationality, Essential Medicine List**INTRODUCTION**

A Fixed-dose Drug Combination (FDCs) is defined as “a formulation of two or more active ingredients combined in a single dosage form in fixed doses”<sup>(1)</sup>. According to WHO, FDC is a combination of two or more actives in a fixed ratio of doses<sup>(2)</sup>. Use of FDCs is associated with many advantages like synergistic or additive action and increased efficacy (e.g., cotrimoxazole – combination of sulfamethoxazole and trimethoprim), reduced side effects (e.g., levodopa with carbidopa, thiazides with potassium sparing diuretics), reduced pill burden as well as cost and better patient compliance (e.g., anti tubercular drug combinations, anti retroviral drug combinations). On the other hand, incompatibility of pharmacokinetics, inflexible dose ratio, increased toxicity and cost, contraindication of one component of the FDC contraindicates the whole preparation and

difficult to find the drug responsible for toxicity (if any) are major problems associated with the FDCs<sup>(1)</sup>.

Use of FDCs is wide scale and global in nature. The World Health Organization (WHO) Model list of Essential Medicines for adults (17th list, March 2011)<sup>(3)</sup> includes 358 essential medicines with only 24 FDCs and the National list of Essential Medicines (3<sup>rd</sup> list, 2011)<sup>(4)</sup> of Government of India includes 348 essential drugs, including 16 FDCs only. There are more than 80,000 formulations available in the Indian market either as single drug formulation or as FDCs<sup>(5)</sup>. In 2008, estimated FDC market in India was about Rs. 3,000 crore to 3,500 crore<sup>(6)</sup>. In European countries like Spain, the use of FDCs was found to be up to 56% of total medicines prescribed<sup>(7)</sup>. During the last decade, more than one-third of all the new drug products introduced worldwide were FDCs<sup>(7)</sup>. Parliamentary standing committee on health and

family welfare noted that a very large number of FDCs are introduced in to Indian market without prior clearance from CDSCO<sup>(8)</sup>. The end result is that many FDCs in the market have not been tested for efficacy and safety. This can put patients at risk.

To the best of our knowledge no study from India is available showing the total number of formulations marketed in the country and the number, and percentage of FDCs thereof. This study was therefore planned to estimate the number of drug formulations available in India, to find out the percentage of FDCs and to assign them the status as essential or non-essential and rational or irrational on the basis of standard criteria.

## MATERIALS AND METHODS

This study was carried out with the objectives of analyzing Fixed-dose Drug Combinations (FDCs) currently available in Indian market for their essentiality and rationality. This was an observational, analytical and cross sectional study and was conducted from November 2010 to May 2012, over a period of 18 months, at the department of Pharmacology, S.B.K.S Medical Institute and Research Centre, Sumandeep Vidhyapeeth, Piparia, Vadodara, Gujarat.

Analysis had been carried out using the latest issue (ISSN 0971-8125, Vol.XVI, Issue no.6) of Indian Drug Review (IDR). It is a commonly used drug index by medical professionals for information on currently available drugs in Indian market. IDR lists the drug formulations in generic index in alphabetical order. All such listed formulations were counted to find the total number of formulations. The FDCs among them were counted separately and were expressed as percentage of total formulations. FDCs, except those listed outside the generic index and containing ayurvedic or herbal products or any other ingredients belonging to other healthcare systems, were segregated and excluded.

FDCs were analyzed for their number of ingredients, their therapeutic class based on action on body system and its essentiality and rationality. There are no uniform worldwide acceptable criteria or uniform principles to judge rationality of FDCs. Various studies<sup>(9-16)</sup> conducted globally have identified rationality criteria to analyze FDCs, which have been utilized in the present study, viz-

- Active pharmaceutical ingredient (API) of the combination should preferably be in the 17<sup>th</sup> model list of essential medicines (WHO EML 2011) or in 3<sup>rd</sup> the national list of essential medicines (NLEM) of India

- Combination should have advantage of established evidence of efficacy and safety over single compounds administered separately
- Overall cost of the combination should preferably be less than the combined cost of the individual components.
- Dose and proportion of each API present in FDC should be appropriate for its intended use
- The pharmacokinetic (PK) properties of individual drugs should be matching
- Individual drugs should have different mechanism or/and site of action.

The majority of these criteria are also recommended by WHO. Each FDC was evaluated using above mentioned criteria and categorised as rational, semirational or irrational as mentioned below:

- Rational FDCs:** FDCs which matched exactly with those given in either EML of WHO or NLEM of India were considered rational. Those FDCs which contained either a substitute of essential medicine or other identical drug from the group and met the above six criteria were also considered as rational. E.g: FDC of ampicillin with sulbactam is though not listed in either of the above two lists, it was considered rational since ampicillin is a substitute of amoxicillin (aminopenicillin) and sulbactam is that of clavulanic acid (beta lactamase inhibitor) and this FDC meets all the above five criteria.
- Semirational FDCs:** All those FDCs which did not match with FDCs listed in either EML of WHO or NLEM of India but still demonstrated a synergistic or additive pharmacodynamic profile and at the same time did not have the potential to cause any increase in adverse effects were considered semi rational, even though they were not strictly meeting pharmacokinetics or cost criteria. E.g: the combination of two antihypertensives (atenolol plus amlodipine, enalapril plus hydrochlorothiazide) or the combination of two diuretics (spironolactone plus frusemide) are not listed either in EML of WHO or NLEM of India, they were rated as semirational.
- Irrational FDCs:** When a FDC was not found to serve any PD or PK advantage, or did not have additive or synergistic effect or was shown to have the potential of causing enhanced adverse effects, it was considered as irrational FDC irrespective of purported advantages of cost or convenience. In other words, all those FDCs which could not be rated as rational or

semirational were accorded the status of irrational FDCs. E.g: paracetamol plus ibuprofen, ciprofloxacin plus tinidazole, cough mixtures containing combinations of antitussives, antihistaminics, expectorants etc.

## RESULTS:

Upon evaluation, a total of 16599 drugs and 24069 formulations were listed in the IDR. Total 6485 FDCs were listed constituting 8713 formulations. The FDCs constituted 39.07% and 36.20% of total drugs and total formulations respectively (Figure 1).

The WHO EML has listed a total of 358 drugs of which only 24 (6.70%) are FDCs. Similarly the NLEM has listed a total of 348 drugs of which only 16(4.60%) are FDCs. On comparing the number of FDCs in WHO EML and NLEM with that of IDR, we found that the number of FDCs in IDR was significantly more (39.07% vs 6.70%,  $p < 0.0001$ ) and (39.07% vs 4.60%,  $p < 0.0001$ ) respectively (Figure 2).

Majority of FDCs contained 2-8 ingredients/active molecules. The number of ingredients per FDC was compared between IDR, WHO EML and NLEM. There was no FDC in WHO EML containing more than four ingredients where as only one FDC in NLEM contained six ingredients. No statistically significant difference in number of ingredients per FDCs was found except that FDC containing six ingredients was significantly higher ( $p = 0.03$ ) in NLEM than the number in IDR (Table 1).

All 6485 FDCs in IDR were analyzed to find out their rationality status. All the FDCs matching the ones in WHO EML or NLEM were rated as rational. Of the total 6485 FDCs in IDR, only 491 (7.65%) and 419 (6.46%) of FDCs matched those in WHO EML or NLEM respectively. Three hundred thirty nine (5.23%) FDCs were common to both WHO EML and NLEM. A large number of FDCs (5914, 91.19%) did not match FDCs either in WHO EML or NLEM. (Figure 3). Overall 571 out of 6485 (8.80%) FDCs were found to be rational since they matched the ones in WHO EML or/and NLEM. Out of the 6485 FDCs, 1256 (19.37%) fell under the category of semirational. Remaining 4658 (71.83%) FDCs were considered irrational (Table 2)

When these 6485 FDCs were categorized depending on their action on body systems and analysed for their rationality status, the maximum number of rational FDCs was found in the category of antimicrobials (29.14%), followed by nutritional products (12.22%), drugs acting on central nervous system (6.60%), drugs acting on endocrine system (3.89%) and gastrointestinal system (0.15%). In remaining nine categories, of 3020 FDCs not a single

FDC was found to be rational (Table 3). In the group of semirational FDCs, the list was topped by FDCs acting on cardiovascular system (95.24%), closely followed by FDCs acting on endocrine system (95.05%) (Table 3). A whopping number of FDCs (4658, 71.83%) was found to be irrational. In nine out of fourteen categories of FDCs, more than 80% of FDCs were found to be irrational. All 100% of FDCs belonging to ear nose and throat and miscellaneous category were found to be irrational. This was followed by FDCs acting on gastrointestinal system (96.34%), respiratory system (94.75%), musculoskeletal system (94.23%), genitourinary system (92.50%), skin (90.71%), eye (86.67%) and central nervous system (81.25%). The lowest number of irrational FDCs was found in the category of endocrine system (1.06%) and cardiovascular system (4.76%).

## DISCUSSION

Rational use of medicines in therapeutics is a much bigger felt need than ever before. Rational use of medicine means use of a right medicine, in the right manner, at right time, in the right type of patients, at a right cost i.e. "the rule of right" <sup>(9)</sup>. Among many reasons of irrational use of medicines, one is the use of unnecessary Fixed-dose Drug Combinations (FDCs). The aim of the present study was to find out the scenario of FDCs in India.

In this study, it is observed that a typical drug index like IDR contains 24069 formulations of 16599 drugs and combinations. Of these, 8713 (36.20%) and 6485 (39.07%) were in the form of FDCs respectively. This was significantly higher ( $p < 0.0001$ , Figure 2) then the number of FDCs both in WHO EML (24 out of 358, 6.70%) and NLEM (16 out of 348, 4.60%). It appears that FDCs are highly popular in the Indian pharmaceutical market and are particularly flourishing in the last few years <sup>(17)</sup>. This phenomenon does not seem to be confined to India only. More than one-third of the new drug products introduced in the world during the last decade were FDCs <sup>(18)</sup>. According to one study 10% of the new products were FDCs in Japan <sup>(7)</sup>.

It was observed that a large number of FDCs in all the three lists contained two, three or four ingredients (98.44%, 100% and 93.7% in IDR, WHO EML and NLEM respectively) without having significant difference with regard to number of ingredients. Multiple ingredients in a formulation increase the risk of drug interactions, adverse drug reactions and even the cost. When the number of active ingredients is increased in the FDC, it becomes necessary for the prescriber to have information about

pharmacokinetics and pharmacodynamics of each and every ingredient and their adverse reactions<sup>(19)</sup>.

The most important qualitative aspect of a FDC is its essentiality and rationality status. Base on the criteria mentioned in methodology, only 8.80% FDCs were found to rational, 19.37% FDCs were semi-rational and rest 71.83% were irrational. This is a matter of concern since this factor alone can account for prevalence of irrational use of medicine in India.

On analyzing the therapeutic class, the highest number of FDCs was found in the category of antimicrobials (1575/6485, 24.29%) in IDR. As against this, the number of antimicrobial FDCs was 17 (70.83%) in WHO EML and was significantly higher ( $p < 0.0001$ ). Though the number of antimicrobial FDCs in NLEM was not significantly different ( $p = 0.13$ ), it was substantially higher than in IDR (43.75% vs 24.29%). Most of the FDCs in WHO EML and NLEM were for only tuberculosis, malaria and HIV infections. Use of single antimicrobial agent in the treatment of chronic infections (e.g. tuberculosis, AIDS, leprosy) for longer duration increases the risk of development of drug resistance. Primary multidrug resistance for tuberculosis and HIV was estimated to be 0-17% and 0-25% respectively<sup>(20)</sup>. FDCs of antimicrobial agents cause reduction of chances of resistance to particular drug and the total duration of treatment with improved therapeutic response. Therefore this higher number of antimicrobial FDCs in WHO EML and NLEM is understandable and justifiable. More alarming fact observed during the study that only 459(29.14%) of antimicrobial FDCs were found to be rational in IDR. More than 70% FDCs in antimicrobial category were found to be irrational (Table 3). A large number of FDCs in IDR contained quinolones and nitroimidazoles. Such FDCs are indicated for gastrointestinal infections, pelvic inflammatory disease, dental infection, etc. These combinations are irrational as the patient may suffer from diarrhoea caused by one type of causative organism at a particular time, and thus not requiring two antimicrobials<sup>(21)</sup>. These FDCs can rapidly give rise to resistant strains of organisms<sup>(22,23)</sup>. Similarly the FDCs of ampicillin/ amoxicillin with cloxacillin are available in large number and prescribed commonly in the Indian subcontinent. A study done in a teaching district hospital of Nepal showed that fixed dose combination of ampicillin and cloxacillin was the most commonly prescribed FDC<sup>(24)</sup>. Both these antibiotics share the same mechanism of action and when combined they do not produce any synergism<sup>(10)</sup>. Fixed ratio of two drugs does not allow flexibility of changing the dose of one without altering that of the other. The 59<sup>th</sup> report (2012) of parliamentary standing committee on functioning of CDSCO has

recommended that those unauthorized FDCs that pose risk to patients and communities, such as a combination of two antibacterials, needed to be withdrawn immediately due to danger of developing resistance that affects the entire population<sup>(8)</sup>.

Next to antimicrobials, FDCs acting on musculoskeletal system made up 16.30% of total FDCs in IDR as per the analysis. There are no FDCs listed in WHO EML or NLEM in the category of musculoskeletal system. Thus, not a single FDC in this category was considered rational. Combining two NSAIDs may increase the side effects of both the NSAIDs<sup>(7)</sup>. Such FDCs containing two NSAIDs are widely prescribed by doctors or are used by general public as self medication. This practice needs to be condemned. Combining NSAIDs with a proteolytic enzyme like serratiopeptidase does not offer any therapeutic advantage over the NSAID alone despite the claim that serratiopeptidase promotes rapid resolution of inflammation<sup>(21)</sup>. In fact, enzyme like serratiopeptidase or alpha chymotrypsin orally has no value since they are digested in the gut and lack sufficient evidence-base for antiinflammatory activity. Therefore combination of such enzyme with NSAID is irrational<sup>(10)</sup>. Similarly, combinations of NSAIDs and skeletal muscle relaxant may be considered irrational. Centrally acting skeletal muscle relaxants are used for the treatment of spastic muscular conditions which also relieve pain associated with spasm. Thus, combination of NSAIDs with a skeletal muscle relaxant does not provide any therapeutic advantage<sup>(25)</sup>. Combinations of analgesics are considered as rational, only when active ingredients demonstrate synergistic analgesic action; reduce the dose of each drug in the combination or when they act by different mechanism of action or at different site<sup>(25)</sup>. Therefore sixty one (5.77%) FDCs in IDR which contained combination of NSAID and opioid analgesic were considered semirational because their site and mechanism of action are different and their pharmacokinetic and pharmacodynamic profiles are complementary to each other which increase the analgesic effect at less dose of individual drug and decrease the risk of side effects caused by individual drug<sup>(26)</sup>. A large number (94.23%) of FDCs in this category was found to be irrational. This is a matter of serious concern since analgesics are easily available as OTC drugs in India, many of which are FDCs. The OTC sale of analgesics in India was \$258.6 million in 2009<sup>(27)</sup>. Availability of such FDCs as OTC drugs is likely to be misused and over used leading to harmful effects, besides wasting of the money.

All 100% of FDCs acting on ear nose and throat, 96.34% of FDCs acting on gastrointestinal system, 94.75% of FDCs acting on respiratory system,

92.50% of FDCs acting on genitourinary system, 90.71% of FDCs acting on skin, 86.67% of FDCs acting on eye, 81.25% of FDCs acting on central nervous system and 44.44% of FDCs of nutritional products were found to be irrational. This situation needs to be deplored considering the fact that many of these products are commonly prescribed by doctors of first contact or general practitioners. It was interesting to find that not a single FDC from the category of cardiovascular and metabolism qualified to be labeled as rational, while only 11(3.89%) from the category of endocrine system were found to be rational. On the other hand 95.24% of cardiovascular FDCs, 95.05% of endocrine FDCs and 71.43% of FDCs affecting metabolism were found to be semirational (Table 3). It may be pointed out that FDCs in these categories are largely used by specialists in the field.

India with population of 120 crore plus people is a second largest country in the world and has 4<sup>th</sup> largest pharmaceutical industry<sup>(28)</sup>. At the same time India is the country with significant drug use problem. There is a concern regarding the irrational production, prescription, and use of FDCs. The rationality of a fixed dose combination is the one of the most controversial and debatable issues in today's clinical practice. The Indian laws have not been properly defined to grant marketing approvals for the FDCs by state or central drug controlling authorities. Therefore, the state drug controlling authorities have continuously been approving various FDCs, lacking pharmacodynamic or pharmacokinetic advantages and acceptable rationale<sup>(14)</sup>. Recently in May 2012, the parliamentary standing committee on health and family welfare has noted in its fifty-ninth report on the functioning of the central drugs standard control organisation (CDSCO) of India that some state drug authorities have issued manufacturing licenses for a very large number of FDCs without prior clearance from CDSCO<sup>(8)</sup>. Availability of a large number of FDCs, many of which are irrational and often harmful, demands serious thinking and action on part of the policy makers, producers and prescribers. This situation has arisen probably because the pharmaceutical industry in India has been manufacturing and marketing FDCs which are non essential, often irrational and sometimes harmful to the recipients<sup>(17)</sup>. Questions may arise why do pharmaceutical companies indulge in manufacturing irrational combinations? Why do physicians prescribe irrational combinations? Why the regulatory authorities do approve these irrational FDCs? There are more questions than answers regarding irrational FDCs<sup>(29)</sup>. In a study done by Gulati et al, over 70 dangerous FDCs are being sold in India under more than 1,000 brand names<sup>(30)</sup>. The prescribers can help

resolve the situation by consciously not prescribing such FDCs and the drug control authorities by not granting permission for such FDCs. Medical experts worldwide have expressed serious concerns over the increased marketing of drug combinations by pharmaceutical companies, particularly in the developing countries<sup>(31)</sup>. Considering the enormous use of drugs in Indian population, it is the high time that pharmaceutical companies, health care professionals and regulatory authorities join hands and prescribe guidelines for the manufacture and sale of FDCs. It is the need of the hour that hospitals should constitute drugs and therapeutics review committees to promote rational prescription of FDCs. The major strength of the present study is that to the best of our knowledge this is a first effort on such a large scale to analyse the scenario of FDCs available in India. There have been some patchy efforts in the past in this direction but they had been restricted to only certain groups of drugs and had failed to quantify the FDCs. This is perhaps the first time that we have been able to show that FDCs constitute 39.07% of total drugs across the categories. Moreover we could also quantify drug category wise FDCs and showed that more than 70% of FDCs are irrational. On the flip side, the study had some inherent limitations as well. The most important limitation is the fact that against estimated 80000 to 100000 drug formulations in India market, we could account only for about 24000 listed in the IDR. Thus this cannot be called the perfect study in the true sense as actual number and percentage of drugs and FDCs could not be arrived at. However the findings of the study are likely to be very close to the real figures. The second limitation is perhaps limited application of statistics. More vigorous statistical analyses could have been done to bring forth subtle and finer issues.

## CONCLUSION

In India, irrational FDCs are freely available and also prescribed by physicians. FDCs account for around 40% of all drugs and 70% of them could be considered as irrational. There is a concern regarding the production, prescription, and use of irrational FDCs. Considering the enormous use of drugs in Indian population, it is high time that pharmaceutical companies, health care professionals and regulatory authorities join hands and prescribe guidelines for the manufacture and sale of FDCs. It is the need of the time that hospitals should constitute drugs and therapeutic review committees to promote rational prescription of drugs in general and that of FDCs in particular.

**Table 1: Analysis of number of ingredients in the FDCs and its comparison with WHO-EML and NEML:**

Number of ingredients	Drug lists				P value IDR vs NLEM
	Number of FDCs in IDR, n (%)	Number of FDCs in WHO EML, n (%)	p value IDR vs WHO EML	Number of FDCs in NLEM, n (%)	
2	4822(74.36)	17 (70.83)	0.87	12 (75.00)	0.95
3	1115(17.19)	05 (20.83)	0.84	02 (12.50)	0.87
4	446(6.89)	02 (8.34)	0.78	01(6.25)	0.92
5	81(1.25)	00	0.58	00	0.65
6	17(0.26)	00	0.80	01 (6.25)	<b>0.03</b>
7	2(0.03)	00	0.93	00	0.94
8	1(0.01)	00	0.95	00	0.96
>8	1(0.01)	00	0.95	0	0.96
<b>TOTAL</b>	<b>6485 (100)</b>	<b>24 (100)</b>		<b>16 (100)</b>	

**Table 2: Analysis of Rationality Status of FDCs in IDR:**

Status of FDCs	Number of FDCs (%)
Rational	571(8.80)
Semirational	1256(19.37)
Irrational	4658 (71.83)
<b>Total</b>	<b>6485 (100)</b>

**Table 3: Category-wise status of FDCs in IDR:**

Category of FDCs	Status of FDCs, n (%)			Total
	Rational	Semirational	Irrational	
FDCs acting on cardiovascular system	00	460 (95.24)	23 (4.76)	<b>483</b>
FDCs acting on musculoskeletal system	00	61(5.77)	996(94.23)	<b>1057</b>
Antimicrobial FDCs	459(29.14)	13(0.83)	1103(70.03)	<b>1575</b>
FDCs acting on central nervous system	19(6.60)	35(12.15)	234(81.25)	<b>288</b>
FDCs acting on gastrointestinal system	01(0.15)	23(3.51)	632(96.34)	<b>656</b>
FDCs acting on genitourinary system	00	09(7.5)	111(92.50)	<b>120</b>
FDCs acting on respiratory system	00	33(5.25)	596(94.75)	<b>629</b>
FDCs acting on skin	00	34(9.29)	332(90.71)	<b>366</b>
FDCs acting on eye	00	20(13.33)	130(86.67)	<b>150</b>
FDCs acting on ear nose and throat	00	00	171(100)	<b>171</b>
FDCs acting on endocrine system	11(3.89)	269(95.05)	03(1.06)	<b>283</b>
FDCs of nutritional products	81(12.22)	294(44.34)	288(43.44)	<b>663</b>
FDCs affecting metabolism	00	05(71.43)	02(28.57)	<b>07</b>
Miscellaneous FDCs	00	00	37(100)	<b>37</b>
<b>Total</b>	<b>571</b>	<b>1256</b>	<b>4658</b>	<b>6485</b>

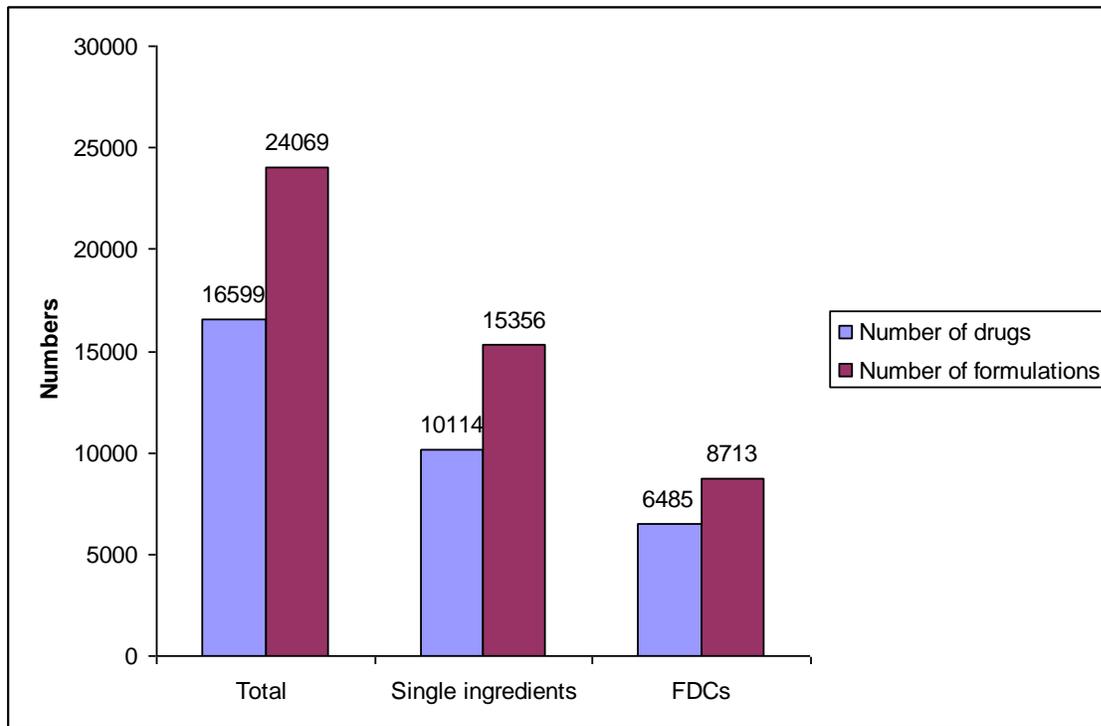


Figure 1: Number of drugs and formulations in Indian Drug Review (IDR):

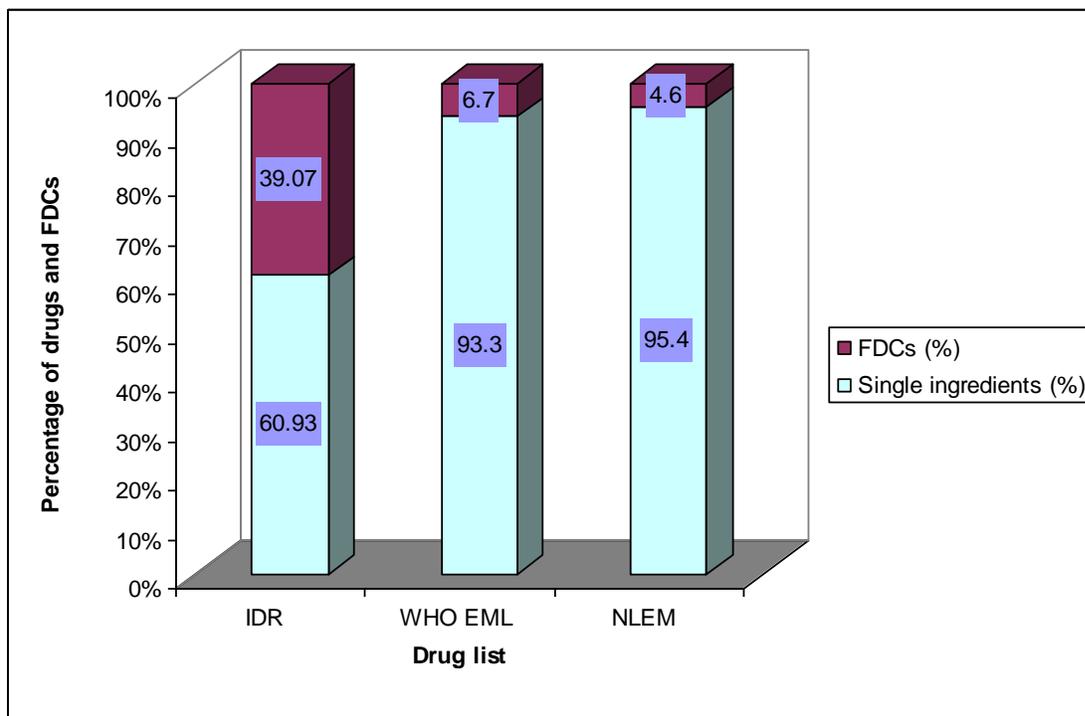
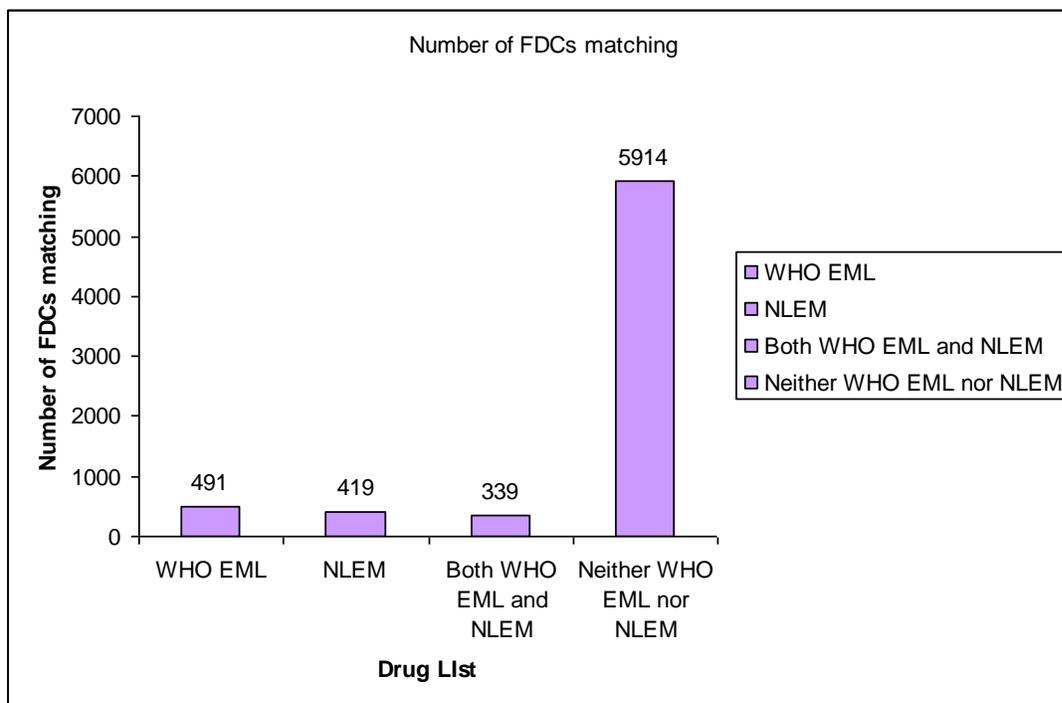


Figure 2: Percentage of drugs and FDCs in WHO EML, NLEM and IDR:



**Figure 3: Matching of FDCs in IDR (n=6485) with that of WHO EML and NLEM:**

## REFERENCES

1. Prajapati B, Singhal MM, Dwivedi VK, Gupta V. The Role of Fixed dose combinations (FDCs) Drugs in Various Diseases. *Journal of Natura Conscientia* 2010; 1(2): 211-19.
2. World Health Organization (WHO). Introduction to drug utilisation research/WHO. International Working Group for Drug Statistics Methodology, WHO Collaborating. centre for Drug statistics Methodology, WHO collaborating centre for Drug Utilisation Research and Clinical Pharmacological services. Geneva: WHO press, World Health Organization; 2003.
3. World Health Organization (WHO) Model List of Essential Medicines for adults 17<sup>th</sup> List (updated), March 2011 [cited 2011 August 9]. Available from: <http://www.who.int/medicines/publications/essentialmedicines/en/index.html>
4. National list of essential medicines, 2011 (cited 2011 sept 07). Available from: [http://www.whoindia.org/LinkFiles/Essential\\_Medicine\\_List\\_Essential\\_Medicine-2011.pdf](http://www.whoindia.org/LinkFiles/Essential_Medicine_List_Essential_Medicine-2011.pdf)
5. Sreedhar D, Subramanian G, Udupa N. Combination drugs: are they rational? *Curr Sci* 2006; 91: 406
6. Kumar SP. Fixed dose combinations (FDCs). *Rational Drugs*, January-June 2008; 31 & 32:1-3.
7. Poudel A, Palaian S, Shankar PR, Jayasekera J, Izham MIM. Irrational fixed dose combinations in Nepal: Need for intervention. *Kathmandu Univ Med J*, 2008; 6(3): 23:399-405
8. Department-related parliamentary standing committee on health and family welfare, 59<sup>th</sup> report on the functioning of the central drugs standard control organisation (cdsco) rajya sabha secretariat, new delhi, may, 2012
9. Desai SV, Essential drug and rational drug therapy: edi: arun phatak, *Bulletin of the society for rational therapy* 2001 jan;12(1)
10. Why some leading drugs in the Indian market should not be sold but are still sold, FDCs of ampicillin and cloxacillin: A lay person's guide to medicines, locost, vadodara, 2006:154
11. J.d.lakhani, s.v.desai et al. Multivitamins drugs-it's irrational use, department of medicine, pharmacology and paediatrics, medical collage, baroda; 1<sup>st</sup> February, 1987.
12. Drugs banned in India [cited in February 2009] Available form: [www.cdsco.nic.in/html/Drugsbanned.html](http://www.cdsco.nic.in/html/Drugsbanned.html)
13. Shankar PR, Partha P, Nagesh S. Prescribing patterns in medical outpatients. *Int J Clin Pract* 2002; 56:549-51.

14. Shewade DG, Pradhan SC. Auditing of prescriptions in a government teaching hospital and four retail medical stores in Pondicherry. *Indian J Pharmacol.* 1998; 30:403-10.
15. Saranjit Singh , Mariappan TT, Sankar R, Sarda N, Baljinder S, A critical review of the probable reasons for the poor variable bioavailability of rifampicin from anti-tubercular fixed-dose combination (FDC) products, and the likely solutions to the problem, *International Journal of Pharmaceutics* 2001 ;228: 5-17.
16. Agrawal S, Singh I, Kanwal JK, Shantaram B, Chaman LK, Ramesh Panchagnula, Bioequivalence trials of rifampicin containing formulations: extrinsic and intrinsic factors in the absorption of rifampicin, *Pharmacological Research* 2004;54: 317-27
17. Das BP, Sethi A, Rauniar GP. Antimicrobial utilization pattern in a teaching District Hospital of Nepal. *JNMA J Nepal Med Assoc.* 2004; 43: 119-24
18. Cohen E, Goldschmid A, Gaty M. Fixed-Dose combination Therapy in the United States, Britain and Israel. *Isr Med Assoc J* 2001; 3: 569-71
19. Kulkarni SK. Fancy, Fallacy and Facts about Fixed Dose Combinations. *Drugs Bulletin*, April 1983
20. Gassh B. Irrational use of antibiotics, *Indian Journal of practicing doctors*, 2008, 5(1).
21. Anand S, Asha AN, Bhosale U, Sarasija S. Emergence of irrationality of fixed dose combinations. *Pharma times* 2008; 40(9): 17-21.
22. Rosenthal PJ. Antiprotozoal drugs. In: *Basic and clinical pharmacology*, 9th edition, ed. Katzung BG. Boston, New York: MA:Mc Graw-Hill, 2004; 875-8
23. Philips MA, Stanley SL, chemotherapy of protozoal infection; In: Brunton L, editor. *Goodman and Gillman's The pharmacological basis of therapeutics* 12th ed. New York: Mcgraw-Hill; 2011; 1419.
24. Demeules J, Rollason V, Piguat V, Dayer P. Clinical pharmacology and rational of analgesic combinations. *Eur J Anaesthesiol* 2003; 20 (28): 7-12.
25. Eesha BR, Mohan L, Satish kumar MC, Shankar PR. Fixed dose drug combinations in therapeutics: an overview. *The journal of Medicine Use in Developing Countries* 2010; 2(1):27-42.
26. Jain NK, Akarte A, Deshmukh PT, Kannoja P, Garud N, Yadav A. Rationality of fixed dose combinations: An Indian scenario. *The pharma research* 2009; 01: 158-168.
27. Cough and Cold Preparations Market in India to 2014 (OTC Healthcare). *Research and Markets* [online]. 2011 Feb [Cited 2011 Sep 15]. Available from: URL: [http://www.researchandmarkets.com/reports/1583741/cough\\_and\\_cold\\_preparations\\_market\\_in\\_india\\_to\\_research\\_and\\_market](http://www.researchandmarkets.com/reports/1583741/cough_and_cold_preparations_market_in_india_to_research_and_market)
28. Dr. Mukesh Hindoliya, Dr. Pramod Kumar Sharma, Dr. S.P. Dhaneria: Prescribing Trends of Fixed Dose Combinations in Teaching and Non Teaching Hospitals of Ujjain District: *Journal of Pharmacy Research.* 2012; 5(7); 3503-3505
29. Sreedhar, D Janodia D, Ligade S, Mohapatra Susovan, Ganguly Rajesh, Udapa N. Fixed Dose Combination: Rational or Irrational. *Current Science* 2008;95: 581-583
30. Gulhati C M. Irrational Fixed Dose Combination: A Sordid Story of Profits Before Patients, *Indian Journal Of Medical Ethics*: 2003
31. Pradeep DT, Purohit S. Rationality of Fixed Dose Combinations: Necessity to weed out the Irrational Combinations Mushrooming in Pharmaceutical Industry. India; *Pharmacinfo. net* [updated 2008 January 20; cited 2008 March 1]. Available from: <http://www.pharmainfo.net/reviews/rationality-fixed-dose-combinationsnecessity-weed-out-irrational-combinations>