

## AN ANALYSIS OF BANNED FIXED-DOSE COMBINATIONS IN INDIA

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## ABSTRACT

**Objective:** The objective of the study was to analyze the nonsteroidal anti-inflammatory drugs (NSAIDs) and respiratory fixed-dose combinations (FDCs) recently banned in India.

**Methods:** This observational study was conducted at the Department of Pharmacology, B. J. Medical College, Ahmedabad, Gujarat. The data were collected from the report on the banned FDCs submitted by the drug technical advisory board subcommittee. Total 195 FDCs belonging to NSAIDs (33) and respiratory group (162) were assessed for class, number of active pharmacological ingredients, formulations, indications, and reasons for banning.

**Results:** The mean number of drugs in FDCs of NSAIDs was 2.6, while in respiratory FDCs, it was 3.6. The most common NSAID formulation was uncoated tablet (15, 30%) while it was syrup in respiratory (49, 30%). The most common reasons for banning these FDCs were safety concerns (153, 78.4%), followed by mismatched pharmacodynamics in respiratory FDCs and mismatched pharmacokinetics in NSAIDs FDCs. The NSAIDs FDCs were marketed for pain (70%) while respiratory FDCs were marketed for cough and cold (62%). Most common NSAIDs FDCs contained NSAID with NSAID (18%), while in respiratory FDCs combinations of a cough suppressant, expectorant, and soothing agents (10%) were present.

**Conclusion:** Evaluation of FDCs is essential to prevent the marketing of irrational FDCs.

**Keywords:** Nonsteroidal anti-inflammatory drugs, Respiratory, Banned fixed-dose combinations, Irrational fixed-dose combinations.

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## INTRODUCTION

Fixed-dose combinations (FDCs) are in which it consists of two or more approved drugs combined in a single dosage form in a fixed ratio, manufactured, and distributed in a specified dose to treat either a single ailment or multiple comorbid conditions [1]. The central drugs standard control organization (CDSCO) defines FDCs as products containing one or more active ingredients used for a particular indication(s) [2]. The FDCs are justified when they demonstrate clear benefits in terms of potentiating therapeutic efficacy, reducing the incidence of the adverse effect of drugs, having the pharmacokinetic advantage, better compliance by reducing the pill burden, reducing the dose of individual drugs, and decreasing the development of resistance and are cheaper than individual drug because of reduced cost from packaging to distribution [3]. FDCs have certain disadvantages. For example, dose titration of individual drugs is not possible; drug interactions may lead to alteration of the therapeutic effect, incompatible pharmacokinetics, and increased toxicity [4]. The therapeutic categories for which a higher number of FDCs are marketed in India are cough, cold, and fever preparations; analgesics and muscle relaxants; and antimicrobials [3]. The Indian medicine market has become the world leader of FDCs. The estimated number of FDCs in India is over 6000 [3]. This competitive structure of pharmaceutical industries is expected to provide high-quality medicines at a lower rate, but woefully, in India, the scenario was noticed to be pessimistic. This mushrooming of FDCs has led to irrational prescriptions. Increasing numbers of irrational FDCs in developing countries like India lead to an unnecessary financial burden, increase the occurrence of adverse drug reactions, including allergy, hospitalization, and ultimately reducing the quality of life [5]. Hence, CDSCO has banned 349 FDCs in late 2018 in compliance with the judgment of the Supreme Court on 15.12.2017. CDSCO had appointed a drug technical advisory board (DTAB) subcommittee to relook at FDCs and gave its recommendation their ban or otherwise [6]. DTAB is the highest statutory decision-making body on technical matters

related to drugs in the country. It is constituted as per the Drugs and Cosmetics Act, 1940. This study is done with an objective to carry out an in-depth analysis of the banned FDCs in terms of a number of active pharmacological ingredients, indications, reasons for banning, formulations, and a pharmacological group of banned FDCs. We hope that the results of the study will provide an in-depth understanding of the need and logistics for other similar irrational FDCs in the Indian market.

## METHODS

This was an observational study, conducted at the Department of Pharmacology, B. J. Medical College, Ahmedabad, Gujarat. The data were collected from the report of the DTAB sub-committee appointed on February 19, 2018, to examine the matters related to 344 plus 5 FDCs in compliance with the Hon. Supreme Court order dated December 15, 2017 [6]. Data were entered into Microsoft Excel® sheet and categorized as follows: Number of ingredients, indications for use of the FDC, reasons for banning, formulations, and pharmacological groups of the FDCs. As this data are available in the public domain, ethics committee approval was not sought. Banned nonsteroidal anti-inflammatory drugs (NSAIDs) and respiratory FDCs were analyzed as a representative sample. Each group of FDC was assessed for the number of active pharmacological ingredients, indications, reasons for banning, formulations, and pharmacological group of FDCs. Relevant literature of the constituent medicines in each FDC was reviewed from standard text and reference books for additional information. In addition, authentic web sources such as Pub Med database, Google Scholar, and Cochrane database were also used.

## RESULTS

A total of 349 FDCs were banned by the DTAB subcommittee. Of these, we analyzed 195 FDCs belongs to NSAIDs (33, 9.45%) and the respiratory group (162, 46.4%). The results are as follows:

### The number of ingredients

These FDCs contained two to seven drugs. The mean number of drugs in NSAIDs FDCs was 2.6, while that in respiratory FDCs was 3.6. The majority of FDCs (64, 32%) contained three or four drugs. Four drug combinations were frequent in respiratory FDCs while in NSAIDs FDCs of three drugs combination were highest (Fig. 1).

### Dosage formulation

These banned FDCs were available as different dosage formulations. Among NSAIDs, the most common formulation available uncoated tablets (15, 30%) followed by film-coated tablets (9, 27%) and tablets (7, 21%). While in respiratory FDCs, the most common formulation was syrup (49, 30%), followed by uncoated tablet (28, 17%) and tablet (19, 12%).

### Pharmacological constituent groups in the FDCs

The banned NSAIDs and respiratory FDCs are formulations that are a combination of different drug groups. In NSAIDs FDCs most common is with other NSAIDs (18%) and gastroprotective agents (18%) such as H2 blockers and proton-pump inhibitors (PPIs), followed by opioid analgesics and proteolytic enzymes (Table 1).

In respiratory FDCs most common combination is of expectorant, cough center suppressant and soothing agent followed by expectorant and cough center suppressant, bronchodilator, and expectorant (Table 2).

### Reasons for marketing

The banned FDCs were marketed for various indications. The most common reason for FDCs of NSAIDs was a relief of pain (23, 70%) while that for respiratory FDCs were for relief of cough (33%). The other reasons are mentioned in Tables 3 and 4.

### Reason for banning

The DTAB committee has categorized the reason for banning into four major categories. These include pharmacokinetic and pharmacodynamic mismatch, lack of efficacy, and safety concerns. Fig. 2 illustrates the reason for banning the respiratory and NSAIDs FDCs. The most common reason mentioned for banning the FDCs from both groups is safety concerns (153, 78.4%), followed by pharmacodynamic mismatch (76, 39%) and pharmacokinetic mismatch (65, 33%). Out of 162 respiratory FDC, 74 (46%) were banned due to pharmacodynamic mismatch. The most common group was the combination of cough center suppressant, expectorant, and soothing agent. In NSAIDs, two FDCs were banned due to pharmacodynamic mismatch. Similarly, 53 (33%) respiratory FDCs were banned due to pharmacokinetic mismatch. The most common group was the combination of cough center suppressant,  $\alpha$ 1 adrenergic agonist, and zinc. In NSAIDs, 12 FDCs were banned due to pharmacokinetic mismatch.

## DISCUSSION

According to the WHO guidelines, a fixed-dose combination is a combination of two or more ingredients in a fixed ratio of doses [7]. The Drugs and Cosmetics Act, 1940 and Rules, 1945 regulate the drugs in India. The CDSCO, after due examination of data on rationality, safety, and efficacy, gives marketing approval according to the Drug and Cosmetic Act (1940) [8]. Nonetheless, in the past some state, drug authorities have issued manufacturing licenses for a very large number of FDCs without prior clearance from CDSCO, resulting in an availability of many FDCs, which have not been tested for efficacy and safety, putting patients at risk.

### A descry of chronology of the parliamentary report on banning FDCs

In the year 2007, the central government passed the order to the state drug controllers to withdraw 294 FDCs which were licensed without the approval of the DCGI [9]. In 2013, CDSCO issued a list of guidelines for the approval of FDCs and asked the manufacturers for the safety and efficacy of the FDCs licensed before October 2012 [9,10]. In 2014, the Ministry of Health And Family Welfare constituted a committee under the leadership of Prof. C. K. Kokate. In 2015, Prof. C. K. Kokate committee

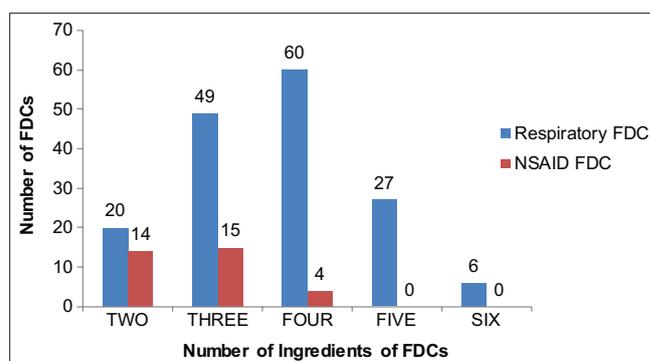


Fig. 1: Number of ingredients of fixed-dose combinations of nonsteroidal anti-inflammatory drugs and respiratory group (n=195)

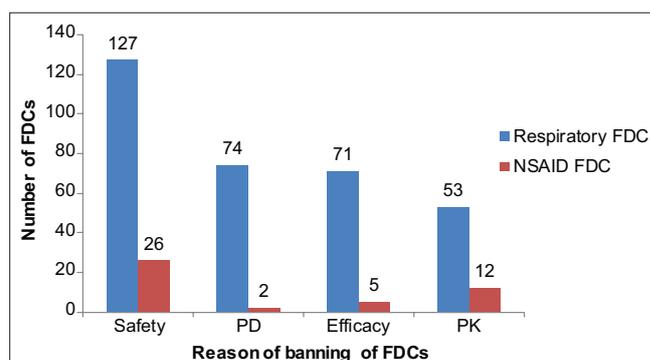


Fig. 2: Reason for banning of fixed-dose combinations (n=195)

Table 1: Pharmacological constituent groups in FDCs of NSAIDs group

S. No.	Pharmacological constituent groups	Number of FDC (%)
1.	NSAID+NSAID	6 (18)
2.	NSAID+Gastroprotective agents	6 (18)
3.	NSAID+Opioid analgesic	3 (9)
4.	NSAID+Proteolytic enzyme	3 (9)
5.	NSAID+Others*	15 (46)

\*Others include combinations with anticholinergic, antihistaminic, CNS stimulant, muscle relaxant, zinc, anticoagulant, D2 receptor antagonist. FDCs: Fixed-dose combinations, NSAIDs: Nonsteroidal anti-inflammatory drugs

Table 2: Pharmacological constituent groups in FDCs of respiratory group

S. No.	Pharmacological constituent groups	Number of FDC (%)
1.	Expectorant+Cough center suppressant+Soothing agent	16 (10)
2.	Expectorant+Cough center suppressant	15 (9)
3.	Bronchodilator+Expectorant	11 (7)
4.	Cough center suppressant+Expectorant+ $\alpha$ 1 adrenergic agonist	11 (7)
5.	Cough center suppressant+Expectorant+ $\alpha$ 1 adrenergic agonist+NSAID	10 (6)
6.	Cough center suppressant+Cough centre suppressant	5 (3)
7.	Cough center suppressant+ $\alpha$ 1 adrenergic agonist+NSAID+Zinc	5 (3)

FDCs: Fixed-dose combinations, NSAID: Nonsteroidal anti-inflammatory drug

**Table 3: Marketing indications for FDCs of NSAIDs (n=33)**

S. No.	Indications	Number of FDCs (%)
1.	Pain	23 (70)
2.	Inflammation	19 (57)
3.	Fever	7 (21)
4.	Migraine	2 (6)
5.	Dysmenorrhea	1 (3)
6.	Post-operative edema	1 (3)
7.	Gastrointestinal spasm	1 (3)

FDCs: Fixed-dose combinations, NSAIDs: Nonsteroidal anti-inflammatory drugs

**Table 4: Marketing indications for FDCs of respiratory group (n=162)**

S. No.	Indications	Number of FDCs (%)
1.	Cough	55 (34)
2.	Cold	45 (28)
3.	Nasal congestion	15 (9)
4.	Allergic rhinitis, sinusitis	13 (8)
5.	Asthma	10 (6)
6.	Chronic obstructive pulmonary disease	10 (6)
7.	Flu	7 (4)
8.	Respiratory tract infection	3 (2)
9.	Tropical pulmonary eosinophilia	2 (1)

FDCs: Fixed-dose combinations

submitted the detailed recommendation against each FDCs [11]. In 2016, 344 FDCs were prohibited under section 26A of the Drugs and Cosmetics Act, 1940. Hence, the various pharmaceutical industries appealed to the Delhi, Chennai, and Bengaluru High Courts to put a stay on the ban order passed by CDSCO. In 2017, the Supreme Court directed the Central Government to evaluate the claims by DTAB or its subcommittee. In 2018, with the DTAB subcommittee recommendations, the Central Government has prohibited the manufacture for sale, sale, and distribution of 349 FDC in the public interest [6,12]. We carried out an in-depth analysis of these 349 FDCs to find out the number of active pharmacological ingredients, indications, reasons for banning, formulations, and a pharmacological group of FDCs [13].

These banned FDCs contained two to seven drugs. In NSAIDs FDCs, three-drug combinations were highest, while in respiratory FDCs four-drug combinations were highest. A recent review panel of the US FDA on cough and cold medications has concluded that there is no justification of having more than three pharmacological groups in one FDC [14]. There is no evidence of the effectiveness of antihistamines combined with decongestants, analgesics [15]. We also found that constituents from the same pharmacological group have also increased, which has no rationality in combining FDCs. As the number of ingredients increases, drug-drug interaction also increases and leads to irrational prescriptions and adverse drug reactions [16]. Furthermore, in NSAIDs FDCs, the gastrointestinal agents are added in anticipation of its gastric side effects. In addition, many FDCs were combined with serratiopeptidase, an enzyme claimed to promote the rapid resolution of inflammation. To our surprise, we could not find any evidence in published literature such as standard books or reviewed scientific journals supporting this claim. Critical analysis of antimicrobial and respiratory FDCs available in the Indian market done by Shah *et al.* in 2015 using the tool found that majority of FDCs had a score less than seven indicating irrationality [17].

These FDCs were available in all dosage formulations targeting all age groups including pediatrics and geriatrics. The most common formulation in NSAIDs FDCs was an uncoated tablet, while in respiratory FDCs it was Syrup. Other formulations available were tablets, capsules, drops, and injections. There are no added advantages of different formulations of the same FDCs but it allows a company to

extend and maintain patents or increase market share, which is potent financial incentives.

These banned FDCs were marketed for different reasons. Like NSAIDs, FDCs were commonly marketed for pain and respiratory FDCs for cough and cold. These are sold without a prescription and contain multiple constituents targeted to treat symptoms that a patient may not be suffering from. Thus, unnecessarily exposing the patient to the side effects as well as adding to the cost of treatment. Further, most of these medications have unproven efficacy [18-20]. It is indeed very unfortunate and unethical to expose innocent patients to medicines with unproven efficacy and safety.

The DTAB subcommittee has categorized the reason for banning these FDCs in four categories, which include pharmacokinetic and dynamic mismatch and lack of efficacy and safety concern. The majority of FDCs are banned for safety concerns. This fact is alarming since it brings forth the fact that these FDCs were marketed without taking safety concerns into consideration. These FDCs are prescribed high in number and sometimes they are available over the counter, due to lack of regulatory checks. Some FDCs when combined could cause greater side effects. Like, NSAID when combine with other NSAID would lead to a greater incidence of severity of gastrointestinal adverse effects. The study found that NSAIDs FDCs containing nimesulide were also available, while it was already banned for use below 15 years of age due to its hepatotoxicity [21]. When NSAIDs are combined with central muscle relaxant or anticholinergic drugs, as was found in this study, it leads to an increased incidence of drowsiness [22]. In respiratory FDCs, there were combinations of antihistamines, decongestants, and anticholinergic agent's leads to adverse effects such as sedation, psychosis, impaired learning and memory, and cardiac arrhythmias [23].

The second common reason for the banning of these FDCs was a pharmacodynamic mismatch. Like in NSAIDs FDCs, there was also a combination of NSAID, anticholinergic, and prokinetic agents. In this combination, each ingredient has different therapeutic uses and adding them together does not appear to provide any additive or synergistic effect for any given indication. Anticholinergic and prokinetics are likely to antagonize each other's actions. While in respiratory FDCs, there were combinations of cough center suppressants and expectorants. They are pharmacodynamically antagonistic. Expectorants act by increasing the production of the demulcent respiratory tract fluid and protect the irritated mucosa, while cough center suppressants inhibit the cough reflex by directly suppressing the cough center in the medulla [24]. We also found that FDCs containing zinc, anticoagulant, and serratiopeptidase which does not have any justification or rationality.

The third common reason for the banning of these FDCs was lack of efficacy. We found that in both groups (NSAIDs + Respiratory), there were some combinations in which either drugs from the same group and in some other combinations drugs having opposite actions were combined. Like cough center suppressant and expectorant. Available literature does not suggest any advantage of these types of combinations. The pharmaceutical companies are required to provide data related to the efficacy of this type of combinations [6]. However, in most cases, convincing scientific/clinical evidence/justification is lacking.

The fourth common reason for the banning of these FDCs was a pharmacokinetic mismatch. When drugs are to be combined, their pharmacokinetics should be matched. However, we find that in both groups it was not matched and it may be the reason for banning these FDCs. For example, in NSAIDs FDCs, there was the combination of NSAIDs and PPI and in respiratory FDCs; there were combinations of antihistamines,  $\alpha$ 1 adrenergic agonist, and expectorants. In the NSAID group, NSAID is given 3-4 times a day, while PPI is administered once a day. In addition, PPI is given on an empty stomach whereas NSAID should be given after food. In respiratory FDCs, expectorant is given 3-4 times a day whereas antihistaminic is administered once a day [6,25].

The study has its limitations. It is an observational study. We have analyzed only NSAIDs and respiratory FDCs. Data available in the public domain alone were used. We have not done a cost analysis and we did not have information on manufacturing/distribution licenses granted by state drug authorities, nor the pharmacological justifications provided by the manufacturers for marketing these FDCs. Nonetheless, we believe that such an analysis and the existing regulations could provide an impetus for a similar initiative to weed out other similar FDCs in the market, as well as prevent the introduction of similar ones in the future.

### Recommendations

Only a handful of FDCs has been banned. We suggest that all other FDCs available in the market should undergo a similar evaluation for a possible ban, as applicable, in the larger interests of patient care in India.

### CONCLUSION

FDC products mushroomed in India mostly for marketing gains, without any scientific basis. A sinewy regulatory system and refurbished policies are required to have been deep-rooted into the Indian pharmaceutical market. Pharmaceutical companies in India should follow the draconian regulations and not compromise the efficacy and safety of the product.

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### AUTHOR'S CONTRIBUTIONS

Shruti Patel: Conceptualization, formal analysis, Writing – original draft, Writing – review and editing.

Samidh Shah: Conceptualization, Supervision, Writing – review and editing.

Chetna Desai: Supervision, Writing – review and editing.

### CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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