Perspective

Irrational ophthalmic fixed-dose combinations for dry eye syndrome

Nilima A Kshirsagar, Renuka Munshi[1], Sandeep B Bavdekar[2], Rohit Saxena[3]

Dry eye syndrome (DES) is a common disorder with rising incidence due to increased use of digital devices. While multiple treatment options are available, some are not efficacious or sometimes even safe for use in DES. This is particularly true for Fixed Dose Combinations (FDCs) that may contain ingredients having no rational for their use or may actually be harmful. Various committees appointed by the Government have reviewed several FDCs marketed in India and found some of them to be irrational and recommended for their removal. This paper discusses the contents of some of these FDCs marketed for DES with an aim to ensure that prescribers are mindful of their ingredients and whether there is adequate data about their efficacy and safety and prescribe them only if they consider them necessary for managing the patient.

Key words: Fixed-dose combinations, FDCs, Drug Technical Advisory Board [DTAB], Dry eye, eyedrops, irrational ophthalmic drops

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1169_22

Quick Response Code:

Dry eye syndrome (DES) is a disorder of pre-ocular tear film that results in damage to the ocular surface. It is a common disorder with prevalence ranging from 8–35% worldwide.[1] Recently, there has been a further increase in its incidence due to the greater use of visual display terminals and face masks during the COVID-19 pandemic and consequent lockdowns and "work-from-home" situations.[2] It manifests with a dry and gritty feeling of the eyes, burning or itching sensation, excessive tearing, pain, photophobia, and redness of the eyes in some cases. These symptoms may be associated with a stringy eye discharge and blurred vision. The presence of epithelial erosion, punctuate keratopathy, and filamentary keratitis indicate a moderate severity DES, whereas the presence of sequelae such as corneal ulcer or opacity indicates the presence of severe DES. The treatment aims to provide symptomatic relief, restore the tear film over the ocular surface and prevent corneal damage and includes modalities such as education, environmental or dietary modifications, artificial tear substitutes, punctal plugs, topical and/or systemic anti-inflammatory agents, and even surgery.[1]

Due to the high prevalence, eye drop purportedly indicated in the management of DES are among the most frequently prescribed eye drops. The treatment is not only initiated by the ophthalmologists and medical practitioners, but also by patients themselves. It is therefore essential that the drugs available in the market are efficacious, safe, and appropriate. However, it has been observed that eye drops with indications mentioned as "dry eye" actually are not safe or efficacious (report of the sub-committee appointed by the Drug Technical Advisory Board [DTAB]).[3]

This subcommittee was appointed to review fixed-dose combinations considered irrational. Fixed-dose combinations (FDCs) are pharmaceutical products that have two or more active ingredients in fixed quantities. These combinations are made for potentiating the therapeutic efficacy, providing pharmacokinetic advantage, reducing treatment cost, reducing the dose of constituent drugs, and/or enhancing patient convenience (by reducing the number of tablets the patient has to consume in a day). It is imperative that these combinations be based on rational therapeutic principles and evidence.[3] The 59th report of the Parliamentary Committee on the functioning of the Central Drugs Standard Control Organization (CDSCO), presented to the Rajya Sabha and noted that a large number of FDCs marketed in India flouted regulatory norms.[4] Various committees appointed by the Government of India, the Drugs Controller General of India, and the DTAB reviewed several FDCs marketed in India. The sub-committee appointed by the DTAB has published its report regarding 349 FDCs including three related to

Department of Clinical Pharmacology, Emeritus Scientist, ICMR, New Delhi, [1]Department of Clinical Pharmacology, TN Medical College and BYL Nair Hospital, Mumbai, Maharashtra, [2]Department of Clinical Pharmacology, Surya Children's Hospital, Mumbai, Maharashtra, [3]Pediatric Ophthalmology and Strabismus Services, Dr. R. P. Centre for Ophthalmic Sciences, AIIMS, New Delhi, India

Correspondence to: Prof. Rohit Saxena MD, PhD, Pediatric-Ophthalmology and Strabismus Services, Dr. R. P. Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India. E-mail: rohitsaxena80@yahoo.com

Received: 09-May-2022 Revision: 10-May-2022
Accepted: 01-Jun-2022 Published: 30-Sep-2022

Cite this article as: Kshirsagar NA, Munshi R, Bavdekar SB, Saxena R. Irrational ophthalmic fixed-dose combinations for dry eye syndrome. Indian J Ophthalmol 2022;70:3687-9.

DES.[3] The contents of these three FDCs are summarized in [Table 1]. Assessment of additional 37 FDCs being done by the subcommittee also contains the same ingredients.

Additional ingredients in other similar FDCs (as per public notice),[5] are benzalkonium chloride, hydroxypropyl methylcellulose, methylcellulose, tetrahydrozoline, and antipyrine.

Table 2: Possible reasons, advantages, and disadvantages of some of the ingredients

Ingredient	Pros and cons
Carboxymethyl- cellulose*	Demulcent action. Evidence of efficacy and safety in the treatment of DES available.[1] Use recommended by standard treatment guidelines.[5]
Naphazoline*	A sympathomimetic agent with vasoconstriction action. Mentioned in the USFDA monograph. Can get absorbed systemically and cause headache, hypertension, anxiety, and exacerbates arrhythmia.
Phenylephrine*	Sympathomimetic with vasoconstriction action. Can get absorbed and cause hypertension, tachycardia, and syncope.
Menthol‡	Not approved for ophthalmic use by the CDSCO. Not mentioned in the USFDA monograph for ophthalmic preparations.
Camphor‡	Not approved for ophthalmic use by the CDSCO. Not mentioned in the USFDA monograph for ophthalmic preparations.
Chlorobutanol‡	Detergent-type of preservative that has broad anti-microbial activity. Not mentioned in the USFDA monograph for ophthalmic preparations. Can lead to allergic reactions in a subset of patients.
Boric acid‡ and borax‡	Preservative with anti-bacterial action. Concentration used in FDCs is sub-optimal. Not mentioned in the USFDA monograph for ophthalmic preparations.
Chlorpheniramine*	Anti-histaminic action. Useful in allergic conditions.
Zinc sulfate	Astringent action. Mentioned in the USFDA monograph. Can cause irritation and excessive lacrimation.

*Mentioned in the USFDA monograph for ophthalmic preparations. †Vasoconstrictor agents: Can cause mydriasis and need to be discontinued if eye pain, irritation of the eyes, changes in vision, and redness persist for over 72 h. They are to be used with caution in patients with narrow-angle glaucoma. Their overuse can cause increased redness. ‡No plausible reason for including these agents in the eye drops for the treatment of DES

The US FDA monograph,[6] lists various ophthalmic ingredients though menthol, camphor, boric acid, and chlorobutanol borax are not mentioned. Three types of ingredients in the eye drops are useful for the treatment of DES: Ophthalmic demulcents, vasoconstrictors, and astringents. Demulcents lubricate and protect the mucous membranes when applied locally. These include cellulose derivatives (Carboxymethylcellulose sodium 0.2–2.5%, hydroxyethylcellulose 0.2–2.5%, hydroxypropyl methylcellulose 0.2–2.5%, and methylcellulose 0.2 to 2.5%), dextran-70 0.1%, gelatin 0.01%, and polyols (e.g., liquid glycerin 0.2 to 1%, polyethylene glycol 300: 0.2–1%, polyethylene glycol 400: 0.2 to 1%, polysorbate 80: 0.2–1%, polyvinyl alcohol 0.1 to 4%, and povidone 0.1–2%). The monograph also lists ephedrine hydrochloride as 0.123%, naphazoline hydrochloride as 0.01–0.03%, phenylephrine hydrochloride as 0.08–0.2%, and tetrahydrozoline hydrochloride as 0.01 to 0.05% as the ingredients with vasoconstrictive actions. Ophthalmic astringent agents (e.g., zinc sulfate 0.25%) precipitate protein and thereby help in the clearance of mucus from the ocular surface.

The pros and cons of some of the ingredients in the FDCs preparations are listed in [Table 2].

Carboxymethyl cellulose has a definite role in the management of DES as it lubricates the eye and protects the eye from injury. Naphazoline and phenylephrine are vasoconstrictors and are presumably added to reduce the redness of the eyes due to congestion. They have sympathomimetic activity and overlapping adverse effect profiles. All patients with DES may not have redness and hence FDC containing both the agents can potentially cause harm without any possibility of getting a therapeutic benefit. It is not correct to have two drugs with similar effects, a similar mechanism of action, and overlapping adverse effects in a single FDC. It is possible that they have additive or even synergistic actions; however, it is also possible their concurrent presence will increase the frequency and severity of side effects. Hence, such additions if at all done should be based on clinical evidence generated through clinical trials. Similarly, carboxymethyl-cellulose has been shown to be effective and safe in the treatment of DES and vasoconstrictors may have a role in aggravating cases of DES. Therefore, before preparing an FDC, empirical data should be generated to show if simultaneous use of carboxymethyl-cellulose and a vasoconstrictor agent (say naphazoline or phenylephrine) adds to therapeutic efficacy without significant addition to the risks involved.

Table 1: Ingredients in FDCs with indications mentioned by the firms for symptoms suggestive of dry eyes/Dry eye syndrome

	Ingredients
1	Naphazoline, menthol, camphor, phenylephrine, carboxymethyl cellulose (indications-ocular congestion, itching (redness) with dry eye.
2	Naphazoline, chlorpheniramine, zinc sulfate, boric acid, chlorobutanol (indications-for temporary relief of redness, burning, irritation, and discomfort due to dryness of the eye or due to exposure to wind, dust, sun, and computer).
3	Borax, boric acid, naphazoline, menthol, camphor, methylhydroxybenzoate (indication-redness and minor irritation of the eye caused by dusty atmosphere, wind, swimming, smoke, air pollutants, close work).

Camphor, menthol, chlorobutanol, boric acid, and borax have no role in the treatment of DES, camphor, and menthol are not approved for ophthalmic preparations, and there is no reason for their addition to FDC for dry eye. Chlorpheniramine is an anti-histaminic with anti-allergic action and though the dry eye can be a consequence of chronic ocular allergy, chlorpheniramine does not have any role in its treatment and may increase the dry eye symptoms. It is possible that chlorpheniramine has been added for the purpose of treating allergic conjunctivitis if the correct diagnosis has not been made. However, this is irrational. These drugs have no capacity to provide any benefit; however, on the contrary, their presence is capable of causing adverse effects.

The question that may arise in the minds of readers is why do pharmaceutical companies make such preparations with multiple agents? This is probably to show the uniqueness of their product over other preparations available in the market. The next question that arises is how did these FDCs, which have no evidence of efficacy and safety, get into the market in the first place and what is the remedy for it? An FDC when it is proposed to be manufactured and marketed for the first time in the country is considered a "new drug" and the CDSCO approves such an FDC only when sufficient data are generated to show that it is safe to use the FDC and that it has therapeutic advantages over single drug. However, licensing authorities of various states approved many FDCs, just because the proposer showed that the individual ingredient was approved by the CDSCO. In this communication, we have discussed only three ophthalmic preparations purportedly indicated in the treatment of DES. However, it is possible that similar FDCs are also marketed for other ophthalmic ailments, as well. Marketing and use of such FDCs with questionable credentials, where there are no data on safety and efficacy pose a threat to the patients' health. Banning them through government actions and court rulings is one way of dealing with the problem. Another solution is to ensure that prescribers are mindful of the ingredients of the FDC and check for themselves, if all the ingredients are necessary for managing the patient and whether there is adequate data about the efficacy and safety of the FDC. The pharmaceutical industry would be better off considering the pharmacology, disease process, standard treatment guidelines, potential benefits, and risk of ingredients while proposing an FDC. If the combination of ingredients is considered hypothetically potentially to be of benefit, then suitable clinical trials need to be conducted to generate relevant data. These clinical trials should be planned to demonstrate the superiority of FDC over single ingredients for efficacy/safety. In case the FDC is proposed for the treatment of two diseases that co-exist in a large population compared to the occurrence of a single disease then they should have valid data from the Indian population to prove. They should also be mandated to show that frequency of administration of the ingredients matches and that there is no pharmacokinetics/pharmacodynamics (PK/PD) pharmaceutical interaction that increases the risk.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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