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Alcaftadine: A Review of Characteristics, Physical Properties, Selection of Analytical Methods, Impact of Solvent and Decision of Selecting Analytical Methods towards Green Chemistry

Patel H*, Patel D, Meshram D
Department of Pharmaceutical Quality Assurance, Pioneer Pharmacy Degree College, Nr. Ajwa Crossing, Sayajipura, Vadodara, Gujarat, India
****Corresponding Author***
Email Id: patel.dhara.j@gmail.com

ABSTRACT

Qualitative and quantitative estimation plays a key role in ensuring the safety and efficacy of drugs in different matrices. A detailed literature survey is one of the most essential requirements for all focused research activities. Alcaftadine is used to prevent eye irritation brought on by allergic conjunctivitis. Alcaftadine is a broad-spectrum antihistamine displaying a high affinity for histamine H1 and H2 receptors and a lower affinity for H4 receptors. It also exhibits modulatory action on immune cell recruitment and mast cell stabilizing effects. Alcaftadine was approved by the U.S. Food and Drug Administration in 2010 under the trade name Lastacaft. The objective is to survey the characteristics and properties of Alcaftadine, as well as hold a discussion on the existing analytical methods to green chemistry and their impacts for both the operator and the environment. For the literature survey, data searches were conducted by scientific papers in the literature as well as in official compendium. The characteristics and properties are shown, also, methods using liquid chromatography techniques, titration, absorption spectrophotometry in the ultraviolet and the infrared region. Most of the methods presented are not green chemistry oriented. It is necessary the knowledge of researcher involved in the optimization of the methods applied through the implementation of green chemistry to determine the Alcaftadine.

Keywords: *Alcaftadine; Analytical Methods; Estimation; Matrices.*

ABBREVIATIONS

USP: *United State Pharmacopoeia*
ICH: *International Conference on Harmonization*
FDA: *Food and Drug Administration*
RP-HPLC: *Reverse Phase High Performance Liquid Chromatography*
LC-MS-MS: *Liquid chromatography - Mass spectrometry – Mass spectroscopy*
UPLC-MS/MS: *Ultra Performance Liquid Chromatography Tandem Mass Spectrophotometry*
IR: *Infrared spectroscopy*
UV: *Ultra violet spectroscopy*

CONJUNCTIVITIS

Conjunctivitis is one of the most commonly treated disorders of the eye. It is one type of inflammation or swelling of the conjunctiva. The conjunctiva is the thin transparent layer of tissue that forms outer anterior surface of the eyeball. There are two types of conjunctiva present in the eye one is palpebral conjunctiva, which is lines the inner aspect of the eyelids and second one is the bulbar conjunctiva, which is passes from the eyelids onto the surface of the eyeball, where it covers the white part of the eye that is sclera but not the cornea. Viral or bacterial infections are the source of the conjunctivitis. Sometimes it can also developed due to an allergic reaction to air irritant such as pollen,

smoke, chlorine content in swimming pools, ingredients used in cosmetics or other products that contact the eyes, such as contact lenses. Chlamydia and Gonorrhea which are sexually transmitted disease are less common cause of conjunctivitis [1-4].

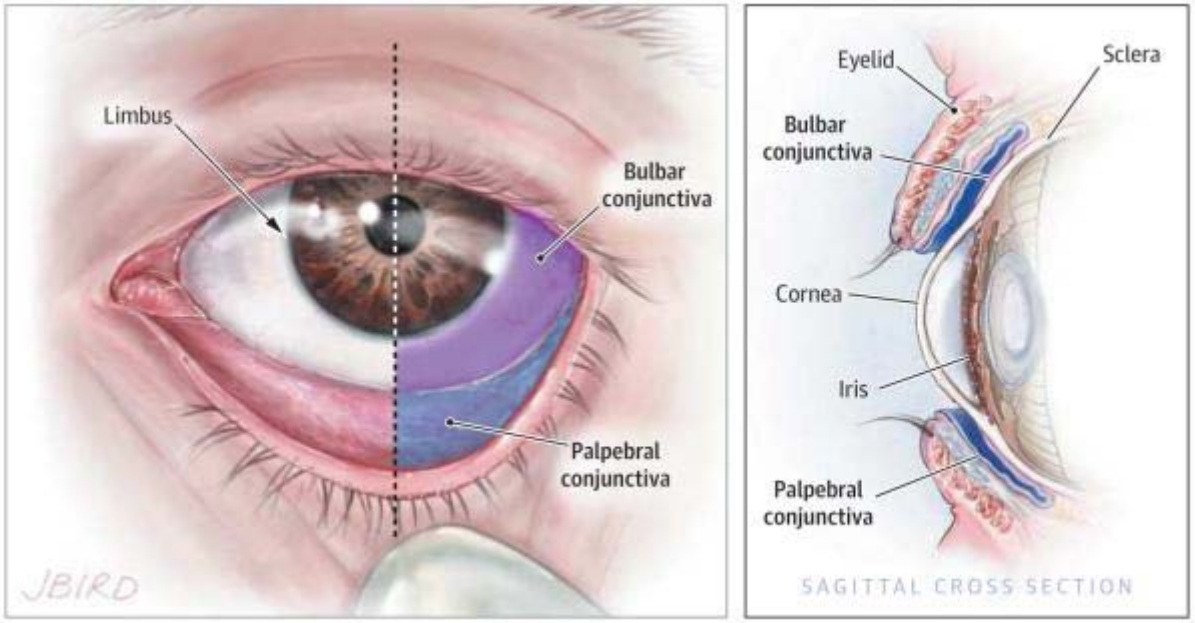
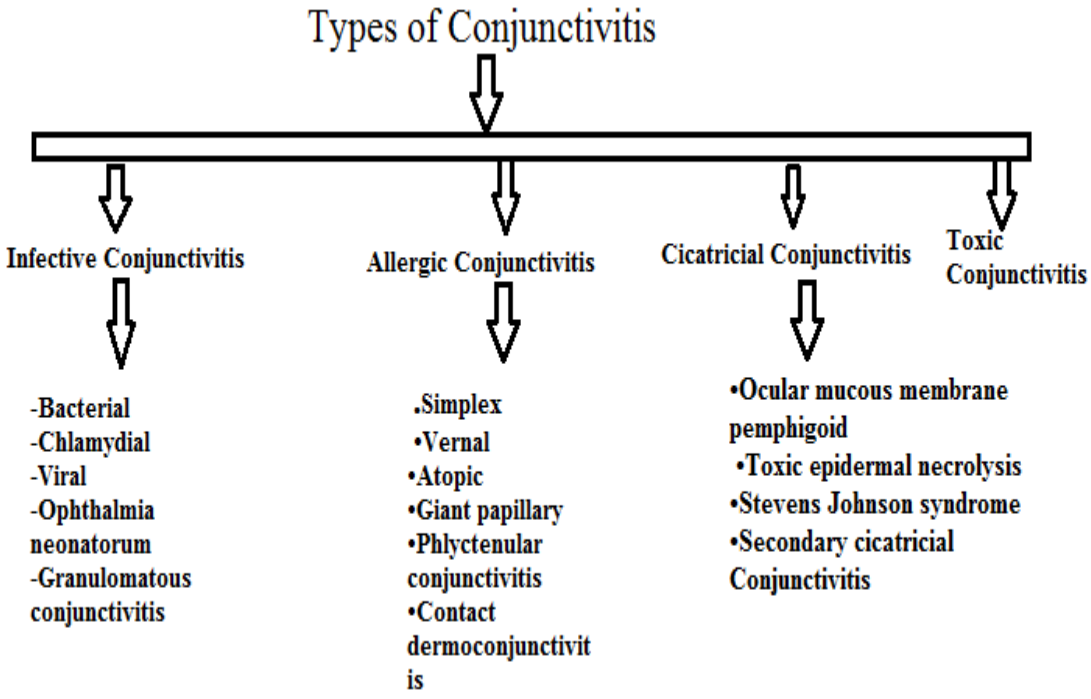


Fig 1. Anatomy of Eye and Eye lid

Types of Conjunctivitis [5-8]

There are three main types of conjunctivitis: allergic, infectious and chemical. The cause of conjunctivitis varies depending on the type.



Treatments [9-12]

There are a number of treatments available for the symptoms of allergic conjunctivitis.

Table 1: List of Drugs used for the treatment of Allergic Conjunctivitis

Sr No.	Class	Drug
1.	Decongestant	Naphazoline Oxymetazoline Phenylephrine hydrochloride
2.	Antihistamines	Emedastine Levocabastine Alcaftadine
3.	Antihistamine and decongestant combination	Antazoline Tetryzoline
4.	Dual-acting antihistamines/mast cell stabilizer	Azelastine Epinastine Ketotifen
5.	Mast cell stabilisers	Lodoxamide Sodium cromoglycate
6.	Corticosteroids	Dexamethasone Flurometholone Prednisolone sodium phosphate

Physicochemical Properties, Taxonomy, Mechanism of Action and Pharmacokinetic Parameters of Alcaftadine [13-15]

Alcaftadine ($C_{19}H_{21}N_3O$) is a new drug candidate for allergic eye disease treatment. Alcaftadine is an antihistamine that reduces the effects of natural chemical histamine in the body. Histamine can produce symptoms such as itchy or watery eyes. Alcaftadine ophthalmic (for the eyes) is used to prevent itching in the eyes caused by allergies. Alcaftadine ophthalmic should not be used to treat eye irritation caused by contact lenses. This drug was approved in July 2010. It is chemically known as 2-(1-methylpiperidin-4-ylidene)-4, 7-diazatricyclo [8.4.0.0³] tetradeca-1(14), 3, 5, 10, 12-pentaene-6-carbaldehyde (Figure 2). Molecular weight of alcaftadine is 307.389 g/mol. Physical properties and taxonomy are mentioned in table 1 and 2, respectively.

Table 2. Physical Properties of Alcaftadine

State	Solid
Water solubility	0.33 g/L
Pka	7.16
Log p	3.202
Boiling point	556.247 °C at 760 mmHg.
Density	1.24

Table 3: Taxonomy of Alcaftadine

Kingdom	Organic compounds
Super class	Organ heterocyclic compounds
Class	Benzazepines
Direct parent	Benzazepines

Alternative parent	Carbonylimidazoles/azepines/aryl-aldehydes/piperdines/ N-substituted imidazoles/ benzenoids/ heteroaromatic compounds/ trialkyamines /azacycliccompunds/ azacycliccompounds/ organopnictogencomponds
Substituent's	Benzazepine/ azepine / imidazole -4 – carbonyl group / aryl – aldehyde / N – substituted imidazole / piperdine / benzenoid / imidazole / azole / heteroaromatic compound tertiary aliphatic amine / tertitary amine / azacycle / organic oxide / amine / organooxygen compound / organo nitrogen compound / aldehyde / organonictogen compound / organic oxygen compound / organic nitrogen compound / hydrocarbon derivative / aromatic heteropolycyclic compound
Molecular framework	Aromatic heteropolycyclic compounds.
External descriptors	Piperidines, tertiary amino compound, aldehyde, Imidazobenzapine.

Fig 2: Chemical Structure of Alcaftadine

Mechanism of Action of Alcaftadine

Alcaftadine is a topically active, H1-receptor antagonist and an inhibitor of histamine release from mast cells. After topical ocular administration, Alcaftadine inhibits histamine-stimulated vascular permeability in the conjunctiva, thereby preventing the formation of ocular edema and wheal. Alcaftadine has also been shown to decrease chemotaxis and activation of eosinophils.

As a result of these pharmacologic actions, Alcaftadine relieves ocular pruritus associated with allergic conjunctivitis.

Figure 3 explains the mechanism action of Alcaftadine.

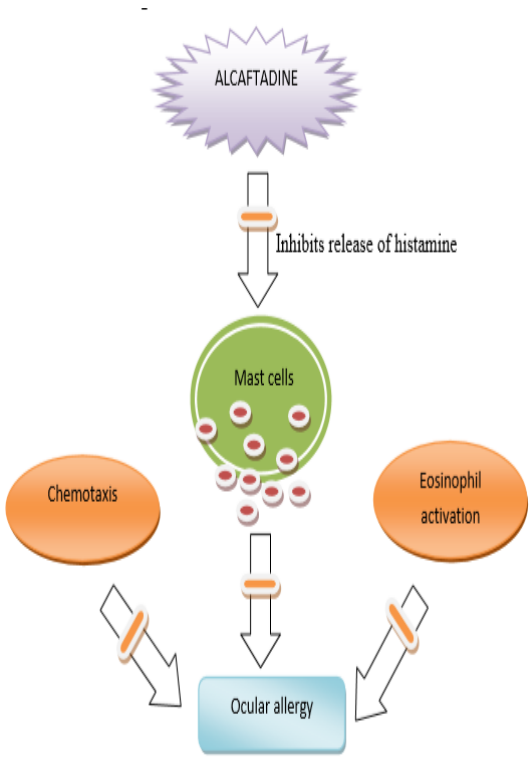


Fig 3: Mechanism action of Alcaftadine

Pharmacokinetic of Alcaftadine

The metabolism of Alcaftadine is mediated by non-CYP450 cytosolic enzymes to the active carboxylic acid metabolite. Pharmacokinetic parameters are discussed in table 4.

Table 4: Pharmacokinetics Parameters of Alcaftadine

Absorption	Minimal
Peak Plasma Time	0.25 hr; active metabolite 1 hr
Bioavailability	30-60%
C_{max}	1hours
Plasma protein binding	39.2% active metabolite 62.7%
Metabolism	Non-CYP450 cytosolic enzymes

Table 5: List of Available Marketed Formulations of Alcaftadine [16]

Name	Manufacturer	Form
ALCAREX EYE	Ajanta Pharma Ltd	Drops
CAFTA EYE	Sun Pharmaceutical Industries Ltd	Drops
ALCAFT EYE	Micro Labs Limited	Drops
LASTACAFT EYE	Allergan India Pvt Ltd	Drops

Table 6: Reported Analytical Methods for Estimation of Alcaftadine in Bulk, Pharmaceutical Formulation and Biological Fluids

Author	Title	Method	Description	Ref. No.
Mishra PR, *et al.* (2015)	Alcaftadine in ophthalmic dosage forms	**UV Spectrophotometry**	**Wavelength**: 252 nm **Solvent**: Methanol (95%) **Linearity**: 5-30 µg/ml **Detecto**r: UV	17
Mishra PR, *et al.* (2015)	Alcaftadine in ophthalmic dosage forms.	**UV Spectrophotometry**	**Zero order derivative** **Wavelength** :266 nm and 296 nm **Linearity** :1-16 µg/ml **Solvent** :Methanol **First order derivative** **Wavelength :** 257 nm and 277 nm **Linearity** : 1-16 µg/ml **Solvent** :Methanol	18
Mishra PR, *et al.* (2016)	Alcaftadine in ophthalmic dosage forms.	**HPLC**	**Stationary Phase**: C_{18} (250 × 4.6 mm, 5 µm) **Mobile Phase**: Methanol: water, (50:50% v/v) **Flow rate**: 1.2 ml/min **Retention time** : 3.15 min **Linearity**: 1-16 µg/ml **Wavelength**: 230 nm	19
Chavan BB, *et.al.* (2018)	Alcaftadine in ophthalmic dosage forms.	**UPLC**	**Stationary Phase:** C_{18} (100 × 2.1 mm, 1.7 µm) **Mobile Phase**: (10 mM, pH 5.0)Ammonium acetate and methanol **Wavelength** : 284 nm **Detector**: PDA detector	20

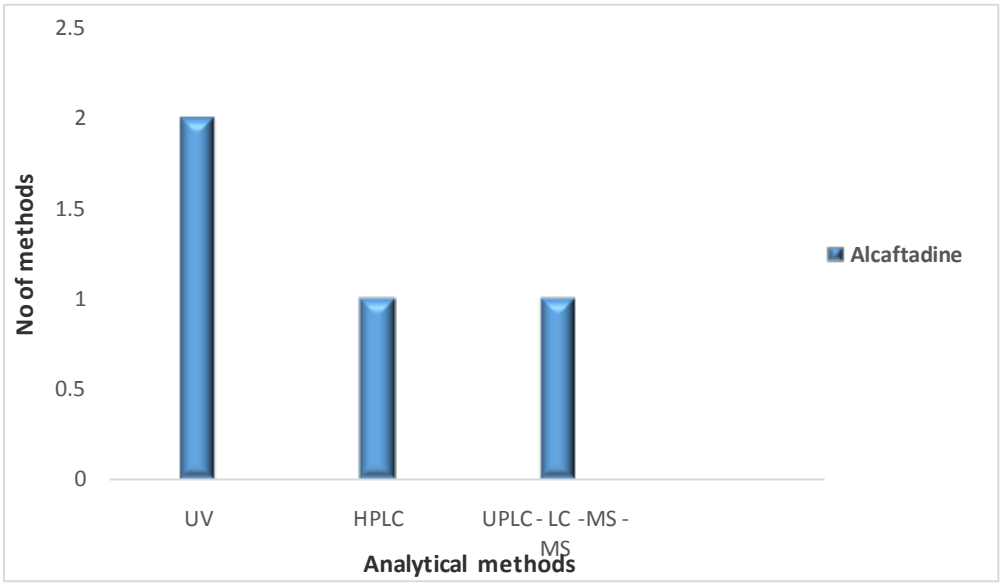
Analytical Methods for Estimation of Alcaftadine in Bulk Drug, Pharmaceutical Formulation and Biological Fluids

Many different analytical methods have been reported for estimation of Alcaftadine. Reported analytical methods have been discussed in table 6.

Clinical Studies of Alcaftadine and Selection of Analytical Method [21,22]

Hilde *et al* worked on clinical pharmacology of Alcaftadine, a novel

antihistamine for the prevention of allergic conjunctivitis. Pharmacokinetic studies showed that both the parent compound and the carboxylic acid metabolite reach peak serum levels within minutes of administration and fall below detectable levels within 3 h of dosing. Based upon pharmacokinetic and phase 1 study, the novel antihistamine Alcaftadine is an appropriate drug for use as an ophthalmic formulation for prevention and treatment of ocular allergic conditions such as allergic conjunctivitis. Alcaftadine ophthalmic solution 0.25% was recently approved for use by the FDA. Topical administration of Alcaftadine 0.25% ophthalmic solution was well tolerated and had an acceptable safety profile. The quantification of Alcaftadine in biological samples is very important for conducting pharmacokinetic studies, bioavailability, bioequivalence and consequently for the therapeutic monitoring of this substance. In the analyzed literature, there is a predominance of determination by high-performance liquid chromatography (HPLC), but also determinations using liquid chromatography of ultra-efficiency, ultraviolet absorption spectroscopy, infrared spectroscopy, NMR, thermal methods and X-ray spectroscopy. It is necessary to emphasize the absence of more analytical methods in the literature and pharmacopoeias. This absence is dangerous and can trigger many public health problems. Thus, the pharmaceutical industry must have analytical methods for evaluating the quality of the final product before release to the consumer market. If quality control does not exist or it is ineffective, products with a doubtful content will be found in the market. The consequence of this is patients without treatment improvement who will return to the health services, which will be overloaded. Another question is the type of analytical method. The big pharmaceutical and chemical industries have money to invest in technology; however, the small and medium pharmaceutical and chemical industries or even independent or unrelated laboratories to large companies are not equipped with the latest technologies. Therefore, varied methods are needed with the purpose of the industry or laboratory choosing the most appropriate to their reality. An end item that also impacts this multi-dimensional view is cost. The choice of type of analysis has a direct impact on the cost of this final product. So, it is important to know the impact of an analytical decision (Graph 1.).



Graph 1. Analytical Method

Impact of Analytical Decisions [23-43]

The innovation in the field of green chemistry is rising significantly and is becoming a big challenge for chemists to develop new products, processes and services that achieve the necessary social, economical and environmental objectives due to an increased cognizance of environmental safety, checking environmental pollution, sustainable industrial ecology and cleaner production technologies worldwide.

In green analytical chemistry, sample preparation and LC analysis need special attention because hazardous solvents are often used European medicine agency (EMA) mentioned that solvents like methanol, acetonitrile and tetrahydrofuran are ranked by as hazardous solvents and because of their inherent toxicity, safe detoxification of the waste solvents is essential, which may lead to high to very high disposal costs. Possibilities toward green LC include reducing solvent use, switching to more benign solvents and/or eliminating organic solvents.

Many solvents used in the analytical methodologies are volatile organic compounds (VOCs), that are hazardous air pollutants (HAPs), flammable, toxic and/or carcinogenic [e.g., the majority of analytical methods certified by the US Environmental Protection Agency (EPA) and Food and Drug Administration (FDA) use corrosive and toxic chemicals, with no other options currently available.

They also pose serious environmental, health, and safety (EHS) concerns, including human and eco-toxicity issues, process safety hazards, and waste management issues. Buffer solutions are not toxic to the environment and the operator, but they can decrease the life of equipment and accessories, such as chromatographic columns and this impacts the cost of the analysis. The proposal is to try to change the solvent used by another less toxic or try to decrease the amount of solvent. However,

the reality is that analysts and operators do not try to change processes or do not want to improve the process. They test directly, for example, methanol and acetonitrile automatically. Drugs that are poorly soluble in water can be solubilized first in ethanol or methanol (for example) and diluted in water. This is very common in laboratories that work toward green chemistry. The solvent is still used, but it is a less toxic solvent (ethanol, for example) and in a smaller amount (since the water was used as diluent). This contemplates the solvent required for HPLC technology and the solubility of poorly soluble drugs. This is the thought. During the development of the method considered green there is concern in the choice of solvents with low toxicity (for example, ethanol and water), as well as to use them in low concentrations in addition to the effort to work with reduced samples, through the miniaturization of the samples.

If this is not possible, work must be done through on recovery of toxic solvents, as these materials cannot be disposed of directly into the environment. Decrease the process steps and the pre-treatment of the samples are also a part of the green chemistry, because these activities directly influence in the amount of reagents used, the time of analysis or reaction, the number of materials required and cost involved.

The choice of equipment should also be important, it is recommended to use those that require the least amount of solvent, less time for analysis, lower energy consumption, lower costs for the company and lower final product prices as for example the HPLC or capillary electrophoresis. In capillary

electrophoresis, samples are used around nL and in HPLC it is used around ml. Each method has its advantages and disadvantages. The choice must not be by the most famous method or by the method that everyone is using, but the ideal one for your analysis or for what you want to study.

Thus, the universities become reference research centers in the area contributing to achievement of this objective. Among the methods surveyed, most of them do not fit the theory of green chemistry, being toxic waste generators, for example the organic solvents as acetonitrile and methanol.

CONCLUSION

Alcaftadine is used for allergic conjunctivitis. The wide use of this drug contributes to the development of studies that need carry out their analytical and bioanalytical quantification.

The existing methods in the literature for quantification of alcaftadine in raw material, pharmaceuticals and biological systems can still contemplate more the thought of green chemistry, whether in the choice of solvent, method, amount of sample, number of steps… The improvement of methods of analysis must be constant.

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