Analytical Chemistry Research 3 (2015) 1–12

Contents lists available at ScienceDirect

Analytical Chemistry Research

journal homepage: www.elsevier.com/locate/ancr

Analysis for commonly prescribed non-sedating antihistamines

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ARTICLE INFO

Keywords:
Cetirizine
Ebastine
Fexofenadine
Ketotifen
Loratadine

ABSTRACT

A comprehensive review with 185 references for the analysis of commonly prescribed members of an important class of drugs, non-sedating antihistamines (NSAs), is presented. The review covers most of the methods described for the analysis of cetirizine (CTZ), ebastine (EBS), fexofenadine (FXD), ketotifen (KET) and loratadine (LOR) in pure forms, in different pharmaceutical dosage forms and in biological fluids. The review covers the period from 1991 till now.

Contents

Abbreviations: NSAs, non-sedating antihistamines; CTZ, cetirizine; EBS, ebastine; FXD, fexofenadine; KET, ketotifen; LOR, loratadine; NBD-Cl, 4-chloro-7-nitrobenzo-2-oxa-1,3diazole; DDQ, 2,3-dichloro-5,6-dicyano-p-benzoquinone; CLA, chloranilic acid; CAT, chloramine-T; MAG, malachite green; XFF, xylene cyanol FF; NBS, *N*-bromo-succinimide; TCNE, Tetracyanoethylene; FDSFS, first derivative synchronous spectrofluorimetric method; SDSFS, second derivative synchronous spectrofluorimetric method; FIA, flow injection analysis; NPs, nanoparticles; IS, internal standard; DMF, dimethyl formamide; FID, flame ionization detector; CI, chemical ionization; beta-CD, beta-cyclodextrin; CZE, capillary zone electrophoresis; MWCNT, multi-walled carbon nanotube.

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http://dx.doi.org/10.1016/j.ancr.2014.11.003
2214-1812/

1. Introduction

H1-receptor antagonists (H1-antihistamines) that competitively block histamine at H1-receptors have been used in the treatment of allergic conditions for many years. Clinically useful H1-antihistamines such as phenbenzamine, pyrilamine, and diphenhydramine were introduced in the 1940s. Currently, H1 antihistamines constitute the second most commonly used class of medications after antibiotics, with more than 40 varieties used in clinical practice worldwide [1].

H1-antihistamines are traditionally classified into six groups, based on their chemical structure to [2]:

a- *Alkylamines:* drugs within this group typically possess significant sedative actions, although paradoxical stimulation can occur, especially in children. Brompheniramine and chlorpheniramine are typical alkylamine antihistamines.
b- *Monoethanolamines:* they have pronounced sedative and antimuscarinic actions but a low incidence of gastrointestinal effects. Examples include clemastine and diphenhydramine.
c- *Ethylenediamines:* these antihistamines are selective H1-antagonist. They cause moderate sedation (despite having weak CNS effects), gastric disturbances, and skin sensitization. Antazoline, mepyramine and tripelennamine are examples.
d- *Phenothiazines:* phenothiazine antihistamines have significant sedative, and pronounced antiemetic and antimuscarinic effects. Promethazine is a typical example.
e- *Piperazines:* this group of antihistamines possesses moderate sedative and significant antiemetic actions. Piperazine derivatives include cetirizine, cyclizine, and hydroxyzine. Cetirizine causes less sedation than other members of this group.
f- *Piperidines:* they cause moderate or low sedation and are highly selective for H1 receptors. Examples include azatadine, cyproheptadine, and non-sedating antihistamines (astimazole, desloratadine, ebastine, fexofenadine, loratadine, and terfenadine).

This classification is, however, of limited clinical relevance, and currently H1-antihistamines are classified as [1]:

a- First generation; also known as 'sedating antihistamines', First-generation H1 antihistamines such as alimemazine, chlorphenamine, clemastine, cyproheptadine, hydroxyzine, and promethazine are non-selective in binding to the H1 receptor. Most of these drugs have weak antimuscarinic anticholinergic effects, some have alpha-adrenergic blocking effects (promethazine), and others can inhibit both histamine and 5-hydroxytryptamine activity (cyproheptadine). Owing to their lipophilicity, relatively low molecular weight, and lack of recognition by the P-glycoprotein efflux pump, first-generation H1 antihistamines readily penetrate the non-fenestrated capillaries of the central nervous system (blood brain barrier) and bind to central H1 receptors, interfering with the actions of histamine on these receptors. *b- Second generation*, which are relatively non-sedating. Second-generation H1-antihistamines such as cetirizine (CTZ), Ebastine (EBS), ketotifen (KET), loratadine (LOR) are newer drugs that are much more selective for peripheral H1 receptors as opposed to the central nervous system H1 receptors and cholinergic receptors. This selectivity significantly reduces the occurrence of adverse drug reactions, such as sedation, while still providing effective relief of allergic conditions. The reason for their peripheral selectivity is that most of these compounds are zwitterionic at physiological pH (around pH 7.4). As such, they are very polar, meaning that they do not cross the blood–brain barrier and act mainly outside the central nervous system, that is why they produce very little or no sedation.

c- Third generation antihistamines includes some newly produced non-sedating antihistamines that are selective isomers or active metabolites of older second-generation antihistamines, and intended to have increased efficacy with fewer adverse drug reactions. Third-generation H1-antihistamines such as desloratadine, that results via an oxidative process of LOR. This is metabolite does not reach the CNS in significant concentrations. Another drug belongs to this group is fexofenadine (FXD) which is the carboxylic acid metabolite of terfenadine. FXD accounts for the antihistaminic properties of terfenadine but does not have the antiarrhythmic side effects of terfenadine.

The older first generation antihistamines are associated with troublesome sedative and antimuscarinic effects, and are often termed 'sedating antihistamines'. The newer generations of antihistamines, which are essentially devoid of these effects, are correspondingly termed as 'non-sedating antihistamines' (NSAs) [2].

NSAs are of potential value in the management of allergic rhinitis in which they relieve nasal and conjunctival itching, sneezing and rhinorrhoea. They are also useful in the treatment of acute and chronic urticaria [1]. NSAs down regulate allergic inflammation directly by interfering with histamine action at H1-receptors on sensory neurons and small blood vessels. They also decrease the antigen presentation, expression of pro-inflammatory cytokines and cell adhesion molecules, and chemotaxis. In a concentration-dependent manner, they inhibit mast cell activation and histamine release; although their mechanisms of action involved have not yet been fully delineated, down regulation of the accumulated intracellular calcium ion seems to play a role [3].

In the last few years, there was no comprehensive review published covering all different analytical techniques used for the determination of NSAs. So the present review comprises references covering the period from 1991 till now. The high importance of this class of drugs prompted us to review the most important recent methods for their analysis in pure forms, in different pharmaceutical dosage forms and in biological fluids.

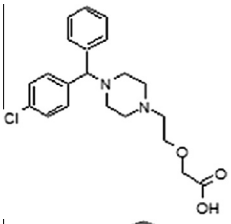
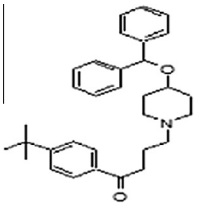
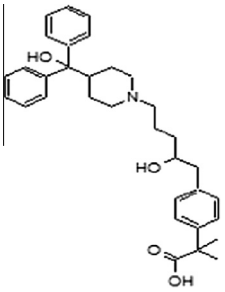
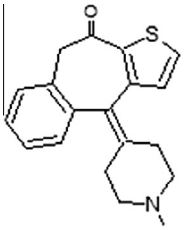
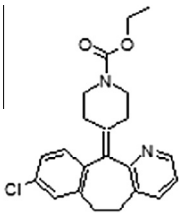
2. Chemistry

Our review is concerned with the second- and third-generation antihistamines which have quite similar pharmacological effects. We selected the commonly prescribed NSAs, namely cetirizine (CTZ), ebastine (EBS), fexofenadine (FXD), ketotifen (KET) and loratadine (LOR). Chemical structures, nomenclatures and molecular weights of these drugs are shown in Table 1 [4]. Structurally they all have the same nucleus (piperidine) except cetirizine which is a diaryl substituted piperazine [5].

3. Pharmacokinetics of NSAs

The pharmacokinetics of the H1 antihistamines has proved to be of great importance especially for the second- and third-generation drugs. Since pharmacokinetics demonstrates the lack of their sedative effect due to their poor distribution to the CNS [6]. Several second- and third-generation drugs are long-acting with duration of action from 12 to 24 h. Table 2 summarizes the differences in route of administration, bioavailability, metabolism, plasma protein binding and excretion between the individual compounds [7,8].

Table 1
Chemical structures of the studied non-sedating antihistamines (NSAs).

Drug (abbrev.)	Chemical structure	Chemical name	M.Wt.	Generation
Cetirizine **(CTZ)**		(±)[2[4[(4Chlorophenyl) phenyl methyl]-1-piperazinyl]ethoxy]acetic acid	388.89	2nd
Ebastine **(EBS)**		4-(4-Benzhydryloxy-1-piperidyl)-1-(4-tert-butylphenyl) butan-1-one	469.658	2nd
Fexofenadine **(FXD)**		(*RS*)-2-[4-[1-Hydroxy-4-[4-(hydroxy- diphenyl-methyl)-1-piperidyl]butyl]phenyl]-2-methyl-propanoic acid	501.656	3rd
Ketotifen **(KET)**		4-(1-Methylpiperidin-4-ylidene)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one	309.426	2nd
Loratadine **(LOR)**		Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine carboxylate	382.88	2nd

4. Official methods of analysis

The European pharmacopoeia 2014 [9] and British pharmacopoeia 2009 [10] have introduced titrimetric, spectrophotometric and chromatographic methods for determination of CTZ, EBS, FXD, KET and LOR (Table 3). United States pharmacopoeia (USP) 2008 [11] has introduced chromatographic methods (High Performance Liquid Chromatography HPLC and High Performance Thin Layer Chromatography HPTLC) for separation and quantitative determination of FXD and LOR in pure and pharmaceutical dosage forms. USP 2008 suggested an HPTLC method for assay of FXD and pseudoephedrine hydrochloride extended-release tablets by using silica gel plate, a mixture of toluene:dehydrated alcohol:ammonium hydroxide (50:45:5, v/v/v) as a developing solvent system and UV detection at 254 nm. Also, LOR oral solution and tablets are estimated by HPTLC, using ethyl ether and diethylamine (40:1, v/v) as a developing solvent system.

The reported HPLC methods in USP (2008) for separation and quantitative determination of FXD and LOR in pure and pharmaceutical dosage forms are summarized in Table 4.

5. Reported methods of analysis

5.1. Titrimetric methods

Titrimetric assay for the determination of CTZ has been developed, based on the measurement of the chloride from hydrochlorides using diphenylcarbazone-bromothymol blue as indicator [12]. A coulometric titration of KET in tablets has been also reported, involving the reaction of KET with iodine in alkaline medium using biamperometric end-point detection [13].

5.2. Spectroscopic methods

5.2.1. Ultraviolet spectrophotometric methods

Direct UV, derivative and chemometric spectrophotometric methods have been used for the analysis of different NSAs in their pure and pharmaceutical dosage forms. Simple UV spectrophotometric and absorbance ratio methods were developed for the estimation of CTZ hydrochloride in combination with ambroxol hydrochloride in tablets [14–16]. UV spectrophotometric methods

were applied to the determination of LOR hydrochloride in tablets and suspension [17,18]. Derivative spectrophotometric method was used for the assay of three binary mixtures of pseudoephedrine with CTZ, FXD and LOR. This method is based on the use of the first derivative of the ratio spectrum [19]. CTZ was determined by the measurement of its first (1D) and second (2D) derivative amplitudes at 239 nm and 243–233 nm, respectively [20]. The acid-base properties of CTZ have been studied using multiwavelength spectrophotometric titration method [21]. On the other hand, UV-spectrophotometric absorption correction and simultaneous equation methods have been developed for the analysis of EBS and Phenylephrine HCl in bulk and combined tablet [22]. Derivative spectrophotometry, 1D and 2D were used to measure FXD in the presence of its alkaline or acidic oxidative degradation products [23]. A method for the determination of FXD and pseudoephedrine in their combined tablet formulation has been developed, employing the partial least squares analysis of spectral data in their pharmaceutical preparation [24]. LOR and pseudoephedrine sulfate were estimated by first-, second- and ratio spectra derivative spectrophotometric methods [25–28]. Furthermore, stability-indicating methods have been reported for the determination of LOR in the presence of its degradation products developed by 1D ratio spectra, at 236, 262.4 and 293.2 nm and by second-derivative spectrophotometry, at 266 nm [29]. Also, 2D spectrophotometry has been described for the simultaneous determination of LOR and montelukast in their pharmaceutical formulations, the zero-crossing technique was applied at 276.1 nm for LOR, but tangent method was used at 359.7 nm for montelukast [30].

5.2.2. Visible spectrophotometric methods

The reported visible spectrophotometric methods for the determination of NSAs could be classified according to the following reactions:

(I) Charge-transfer complexation.
(II) Redox reactions.
(III) Ion pair formation.
(IV) Miscellaneous.

5.2.2.1. Charge-transfer complexation. Charge transfer complexation has been reported for the spectrophotometric determination of the cited NSAs, where they act as n-donors with either π-acceptor or σ-acceptor.

El Walily et al. [20] described a spectrophotometric procedure for the assay of CTZ sodium based on measuring the absorbance of the chromogen formed between CTZ sodium salt in polar solvent (dimethyl formamide) and chloranil at 556 nm. On the other hand, FXD hydrochloride was determined by 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole (NBD-Cl), forming an orange colored product measured at 469 nm [31]. El-Kousy and Bebawy [32] developed a method for the determination of KET and LOR based on the formation of radical ion using 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ), the color formed was measured at 588 nm. LOR was estimated by charge-transfer complex formation with Chloranilic acid (CLA) as a π-acceptor, and the resultant complex was measured at 520 nm [33].

5.2.2.2. Redox reactions. Narayana [34] proposed a spectrophotometric assay of FXD hydrochloride in bulk and dosage forms using chloramine-T (CAT) and two dyes malachite green (MAG) and xylene cyanol FF (XFF). This method entailed the addition of a known excess of CAT to FXD hydrochloride in acidic medium followed by the determination of the residual oxidant by reacting it with a fixed amount of MAG, measuring the absorbance at 615 nm, or 612 nm with XFF. On the other hand, KET fumarate was determined in bulk and pharmaceutical samples by the formation of colored species by the coupling of the diazotized sulphanilamide with the drug at 520 nm or by oxidizing it with excess *N*-bromo-succinimide (NBS) and determining the consumed NBS with decrease in color intensity of celestine blue at 540 nm or by the reduction of Folin–Ciocalteau reagent at 720 nm [35].

5.2.2.3. Ion pair formation. El-Kommos et al. [36] proposed a simple spectrophotometric method for determination of CTZ, EBS, FXD, KET and LOR in pharmaceutical preparations using erythrosine B. The formed pink-colored complex was measured at 550 nm without solvent extraction. Two spectrophotometric methods were reported for determination of CTZ, FXD and LOR in pure and commercial dosage forms using ion pair complexation [37]. The first method is based on the reaction of these drugs with bromocresol purple dye to form extractable ion-pair complex and subsequently measured spectrophotometrically. Secondly, eosin gives ion-pair complex, measurable directly without extraction. An Extractive spectrophotometric method was developed for the assay of CTZ hydrochloride in bulk drug, pharmaceutical preparations, and biological fluids [38]. The method is based on the formation of a chloroform soluble ion-pair complex using thymol blue in an acidic buffer at 413 nm. Also, CTZ dihydrochloride present in pure and different pharmaceutical preparations was estimated by the formation of extractable yellow ion-pair complex with methyl orange at pH 4.0, measured at 424.5 nm [39]. Furthermore, CTZ hydrochloride in pharmaceutical formulations was determined

Table 2
Pharmacokinetic properties of some non-sedating antihistamines (NSAs).

Drug Pharmacokinetic data	CTZ	EBS	FXD	KET	LOR
Route of administration	Oral	Oral	Oral	Oral/ophthalmic	Oral
Bioavailability	Well absorbed	Well absorbed	30–41%	60%	Almost 100%
Metabolism	Excreted mainly unchanged	Hepatic (CYP3A4-mediated), to carebastine	Hepatic CYP450	Hepatic CYP3A4, oxidation	Hepatic CYP2D6, CYP3A4
Elimination half-life (h)	8.3	15–19	14.4	12	8
Duration of action (h)	12–24	24	12–24	12	24
Time to maximum plasma concentration (h) after single dose	1.0 ± 0.5	2	1–3	2–4	1.2 ± 0.3
Plasma Protein binding %	~93%	Greater than 95%	60–70%	75%	97–99%
Excretion	Urine (mainly), hepatic or excrement (Small amounts)	2–3% renal/more than 90% fecal as metabolite (carebastine)	Fecal (~80%) and renal (~11%) as unchanged drug	Mainly renal as inactive metabolite with a small amount of unchanged drug	40% as conjugated metabolites into urine Similar amount into the feces

Table 3
Official methods of analysis of the studied NSAs in European pharmacopoeia 2014 and British pharmacopoeia 2009.

Method		Cetirizine	Ebastine	Fexofenadine	Ketotifen	Loratadine
Titrimetry	Titrant End point	0.1 M NaOH Potentiometrically	0.1 M $HClO_4$ Potentiometrically		0.2 M $HClO_4$ Potentiometrically	0.3 M $HClO_4$ Potentiometrically
UV/visible spectrophotometry		λ_{max} at 231 nm				
Thin-layer chromatography		– Stationary phase, TLC silica gel GF_{254} – Mobile phase, ammonia/methanol/methylene chloride (1:10:90, v/v/v) – Detection, UV at 254 nm			– Stationary phase, cellulose – Mobile phase, water/anhydrous formic acid/diisopropyl ether (3:7:90, v/v/v) – Detection, UV at 254 nm, Spraying with $KMnO_4$ in 1.4%v/v H_2SO_4, in daylight by transparency	
Liquid chromatography		With related substances: – Stationary phase; silica gel – Mobile phase; dilute H_2SO_4/water/ acetonitrile (0.4:6.6:93, v/v/v) – Detection; at 230 nm	With related substances: – Stationary phase; nitrile silica gel – Mobile phase; acetonitrile/phosphoric acid adjusted to pH 5.0 with NaOH solution (35:65, v/v) – Detection; at 210 nm	– Stationary phase; silica gel BC – Mobile phase; acetonitrile/a buffer (glacial acetic acid and ammonia, pH 4) (20:80 v/v) – Detection; at 220 nmWith related substances: – Stationary phase; phenylsilyl silica gel – Mobile phase; acetonitrile/a buffer (glacial acetic acid and ammonia, pH 4)/triethylamine (350:650:3, v/v/v) – Detection; at 220 nm	With related substances: – Stationary phase; octadecylsilyl silica gel – Mobile phase; (A) triethylamine/ water. (B)triethylamine/ – methanol – Detection; at 297 nm	With related substances: – Stationary phase; spherical end-capped octadecylsilyl silica gel with very low silanol activity – Mobile phase; methanol/potassium dihydrogen phosphate (pH 2.80 ± 0.05) with phosphoric acid/acetonitrile (30:35:40, v/v/v) – Detection; at 220 nm
Gas chromatography						– Stationary phase; poly (dimethyl) siloxane – Carrier gas; helium – Detection; flame ionization

Table 4
HPLC methods in USP (2008) for determination of FXD and LOR.

Drug	Column/stationary phase	Mobile phase	Detection
FXD	4.6 mm × 25 cm, packing phenyl groups bonded with porous silica	Phosphate-perchlorate buffer and acetonitrile (65:35, v/v) as a mobile phase adjusted to pH 2.0 with phosphoric acid	UV, 220 nm
FXD hydrochloride capsules	4.6 mm × 10 cm, packing octadecyl silane bonded to porous silica or ceramic	Acetonitrile and phosphate-perchlorate buffer (700:300, v/v) adjusted to pH 2.0 with phosphoric acid	UV, 220 nm
FXD hydrochloride tablets	4.6 mm × 10 cm, packing octadecyl silane bonded to porous silica or ceramic	Acetonitrile and phosphate-perchlorate buffer (7:3, v/v)	UV, 220 nm
FXD and pseudoephedrine hydrochloride extended-release tablets	4.6 mm × 25 cm, packing sulfonated fluorocarbon polymer coated on a solid spherical core 4.6 mm × 5 cm, packing sulfonated fluorocarbon polymer coated on a solid spherical core connected in series to a 4.6 mm × 25 cm, packing phenyl groups bonded with porous silica	Monobasic sodium phosphate-phosphoric acid buffer (pH 2.00 ± 0.05): acetonitrile (55:45, v/v) Methanol : acetate/1-octanesulphonate buffer adjusted with glacial acid to pH of 4.6 (35:65, v/v)	UV, 210 nm UV, 215 nm

by the formation of extractable complex with Alizarin red S at pH 3.2. This complex was passed through anhydrous Na_2SO_4, and measured at 440 nm [40]. Spectrophotometric methods have been developed and validated for the determination of FXD hydrochloride in pure form or pharmaceutical formulations using bromophenol blue, bromothymol blue, bromocresol green and bromocresol purple [41]. These methods involved the formation of colored chloroform extractable ion-associate complexes in acidic medium. The extracted complexes showed absorbance maxima at 411, 414, 409, and 411 nm, for the above-mentioned dyes respectively. Kumar et al. [42] described a method for the determination of FXD hydrochloride in bulk and pharmaceutical dosage forms. The method is based on the formation of chloroform-extractable pale yellow color complex formed with bromothymol blue at pH 2.6, which can be estimated at 412 nm. KET fumarate in tablet formulation has been estimated by the formation of chloroform extractable colored complexes with 2-nitroso-napthol-4-sulphonic acid, rhodizonic acid and azocarmine G [35,43]. The extracted complexes showed

absorbance maxima at 436.5, 489.5 and 540 nm, respectively. El-Kousy and Bebawy [32] described a method for estimation of KET and LOR, based on the formation of orange red ion pair complexes with molybdenum thiocyanate measured at 469.5 nm in dichloromethane. Furthermore, a visible spectrophotometric method has been developed for estimation of LOR from tablet formulation via formation of chloroform extractable colored complex with bromophenol blue at 413 nm and with cobalt thiocyanate at 624.5 nm [44].

5.2.2.4. Miscellaneous. Basavaiah and Charan [12] proposed a spectrophotometric method for assay of CTZ. To a fixed concentration of mercury (II)-diphenylcarbazone complex, different amounts of the drug were added and the decrease in absorbance of the formed complex was measured at 540 nm. Gazy et al. [37] developed a spectrophotometric method for determination of CTZ, FXD and LOR; through the base-catalyzed condensation of mixed anhydrides of organic acids (citric acid/acetic anhydride) where the tertiary amino group in these drugs acts as the basic catalyst.

5.2.3. Flow injection analysis

A flow injection chemiluminescence (CL) method was established for the determination of KET. CL was observed when potassium hexacyanoferrate (III) reacted with the mixture of calcein and KET [45]. Also, flow injection method was introduced for determination of KET fumarate in pure samples and in its pharmaceutical preparations by using PVC membrane selective electrodes, where KET tetraphenylborate was used as ion exchanger over the pH range 2.0–8.0 [46]. A mixture of LOR and pseudoephedrine sulfate was determined in pharmaceutical samples using non-linear second-order data generated by a pH-gradient flow injection analysis (FIA) system with diode-array detection [47].

5.2.4. Spectrofluorimetric methods

Gazy et al. [37] suggested spectrofluorimetric method for determination of CTZ, FXD and LOR in pure and their commercial dosage forms. This method was based on the reaction of these drugs with eosin giving ion-pair complex, measurable directly without extraction. CTZ, EBS, and FXD were determined through charge transfer complexation of these drugs with some π acceptors namely CLA, tetracyanoethylene (TCNE), and DDQ to give highly fluorescent derivatives [48]. A rapid and simple fluorimetric procedure for the determination of trace amounts of CTZ hydrochloride in pharmaceutical formulations has been developed, through measuring the fluorescence intensity at $\lambda_{ex.}$ 230 nm, $\lambda_{em.}$ 297 nm [49]. Also, CTZ dihydrochloride was determined by measuring its anti-fluorescence quenching effect on rhodamine B-sodium tetraphenylborate system at $\lambda_{ex.}$ 491, $\lambda_{em.}$ 610 nm [50]. Furthermore, a stability-indicating micelle-enhanced spectrofluorimetric method for determination of LOR in dosage forms was developed. This method is based on investigation of the fluorescence spectral behavior in a sodium dodecyl sulphate micellar system [51]. On the other hand, validated stability-indicating spectrofluorimetric methods were developed for the determination of EBS in pharmaceutical preparations depending on reaction with its tertiary amino group [52,23]. First method involves condensation of the drug with mixed anhydrides (citric and acetic anhydrides) producing a product with intense fluorescence, which was measured at $\lambda_{ex.}$ 388 nm, $\lambda_{em.}$ 496 nm [52]. The second method described the quantitative fluorescence quenching effect on eosin upon addition of the studied drug, at $\lambda_{ex.}$ 457 nm, $\lambda_{em.}$ 553 nm. This method was extended to third method where the first and second derivative synchronous spectrofluorimetric method (FDSFS & SDSFS) were used for the simultaneous analysis of EBS or FXD in presence of alkaline, acidic, and UV degradation products [23]. A sensitive fluorimetric method was reported for the assay of FXD hydrochloride in a pharmaceutical formulation and biological fluids using silver nanoparticles as a fluorescence probe where the drug caused considerable quenching of the emission band of silver NPs due to the formation of complex [53]. On the other hand, the interactions between LOR and bovine and human serum albumin were studied using tryptophan fluorescence quenching method [54].

5.2.5. Chemiluminescence methods

A method has been developed for the analysis of FXD in pharmaceutical formulations, using a tris (1,10-phenanthroline)-ruthenium(II) $[Ru(phen)_3^{2+}]$ peroxydisulphate chemiluminescence system in a multichip device [55]. Also, the luminescence sensitization of europium (Eu^{3+}) by complexation with FXD HCl has been studied at $\lambda_{ex.}$ 276 nm, $\lambda_{em.}$ 615 nm [56].

5.2.6. Atomic absorption spectrometric methods

El-Kousy and Bebawy [32] developed an atomic absorption spectrometric method for the determination of KET and LOR. This method depends on the reaction of these drugs with cobalt thiocyanate reagent at pH 2 to give ternary complexes. These complexes are readily extracted with organic solvent and estimated by indirect atomic absorption method via the determination of the cobalt content in the formed complex after extraction in 0.1 M hydrochloric acid.

5.3. Chromatographic methods

5.3.1. Thin layer chromatographic methods

Many reported TLC-spectrodensitometric methods [29,57–64] for separation and determination of NSAs in pure, pharmaceutical dosage forms and in biological fluids are listed in Table 5.

5.3.2. High-performance liquid chromatographic methods

There is an impressive increase in the use of high-performance liquid chromatography for determination of NSAs in the last thirty years. HPLC has been used frequently in all fields of NSAs research. These methods are based on different stationary phases (silica, C_8, C_{18}, cyanopropyl and Alpha1-acid glycoprotein), different mobile systems and using UV, fluorescence or tandem mass for detection. There are many reported HPLC methods for separation and quantitative determination of NSAs in pure, pharmaceutical dosage forms (Supplementary Table 6) [14,25,30,65–102] and in biological fluids (Supplementary Table 7) [103–156].

5.3.3. Gas chromatographic methods

GC/MS assay for the anti-anaphylactic agent KET in human plasma was described. This method is based on negative ion chemical ionization, utilizing the electrophoric nature of the underivatized drug [157]. On the other hand, GC/MS with selected ion monitoring has been used for the quantification of KET and its metabolites in human plasma and urine samples [158,159]. A validated GC/MS method for determination of total amount of KET in human plasma has been described using pizotifen as an internal standard (IS) [160]. Furthermore, a sensitive gas–liquid chromatographic (GLC) method has been developed for the determination of LOR and its active metabolite in human plasma, using a nitrogen-phosphorus detector and a fused-silica capillary column [161]. GC/MS method for the determination of LOR and pheniramine in human serum has been developed [162]. Capillary gas chromatography methods were proposed for the determination of residual organic solvents-diethyl ether, iso-propyl alcohol, acetonitrile, 2-methylpropanol-2, ethyl acetate, tetrahydrofuran, cyclohexane, triethylamine, toluene in LOR samples. A capillary column was used with temperature programmed control and dimethyl formamide (DMF) as the solvent [163]. Also, Agilent capillary column was used with flame ionization detector (FID) detector and nitrogen as the

carrier gas [164]. Furthermore, LOR was subjected to GC-chemical ionization (CI)-MS analysis, with He carrier gas, and temperature programming from 70 °C to 300 °C at 20 °C/min [165].

5.4. Capillary electrophoretic methods

A capillary electrophoretic method for the determination of CTZ in Zyrtec® tablet, syrup, and oral drops was developed using 10% methanol at pH 8.5. The voltage applied, 28 kV produced signals that were detected at 200 nm using phenobarbital sodium as an IS [166]. A sulfated beta-cyclodextrin (sulfated beta-CD)-mediated capillary electrophoresis method was described for the enantioseparation of CTZ in bulk and human plasma samples and enantiomeric purity evaluation of levocetirizine (R-enantiomer) in pharmaceutical tablets using a chiral cefazolin as an IS. The enantioseparation of the drug was performed in a borate buffer (5 mM, pH 8.7) with 1% w/v sulfated beta-CD as chiral selector at 10 kV [167]. Also, Enantioselective analysis of CTZ in pharmaceuticals by cyclodextrin-mediated capillary electrophoresis was developed using FXD as an IS [168]. On the other hand, chiral separation of CTZ in tablets was studied by CD-mediated CE using a 75 mM triethanolamine-phosphate buffer (pH 2.5) containing 0.4 mg/mL heptakis (2,3-diacetyl-6-sulfato)-beta-CD and 10% acetonitrile. Online UV detection was performed at 214 nm, at 20 kV [169]. Capillary zone electrophoresis (CZE) method has been developed for the simultaneous separation and determination of CTZ dihydrochloride, paracetamol, and phenylpropanolamine HCl in tablets using 10 mM sodium tetraborate (pH 9.0) and an uncoated fused-silica capillary at the applied voltage of 20 kV. UV detection was performed at 195 nm, with Ibuprofen as IS [170]. Nojavan and Fakhari [171] developed a method for chiral separation and quantitation of CTZ and hydroxyzine by maltodextrin-mediated CE in human plasma**.** Capillary electrophoresis method with UV detection was developed and validated for the quantitation of FXD hydrochloride in capsules using an uncoated fused-silica capillary at 20 kV potential and 20 mM $Na_2B_4O_7{\cdot}10\ H_2O$ buffer [172]. Mikus et al. [173] used capillary electrophoresis for determination of FXD in tablets with and without CDs as analyte carriers. A capillary electrophoretic method was developed for the determination of LOR in tablets using 24 mmol/L glycine as a carrier cation, 1.6 mmol/L citric acid and 84 mmol/L acetic acid as counter ions at pH 3.2 with UV detection at 240 nm [174]. Capella-Peiró et al. [175] used a full factorial design to optimize the experimental conditions of a CZE method aimed at achieving simultaneous separation and quantification of the antihistamines brompheniramine, chlorpheniramine, cyproheptadine, diphenhydramine, doxylamine, hydroxyzine, and LOR in urine and serum samples, using phosphate buffer pH 2.0 and 5 kV at 214 nm.

5.5. Electrochemical methods

A method was successfully applied to the determination of CTZ in pharmaceutical preparations using direct potentiometric method [176]. Javanbakht et al. [177] developed a biomimetic potentiometric sensor using molecularly imprinted polymer for the CTZ assay in tablets and biological fluids. A multi-walled carbon nanotube (MWCNT) film-modified glassy carbon electrode (GCE) was constructed for the determination of CTZ dihydrochloride in urine samples using cyclic voltammetry (CV). The MWCNT film has shown an obvious electrocatalytic

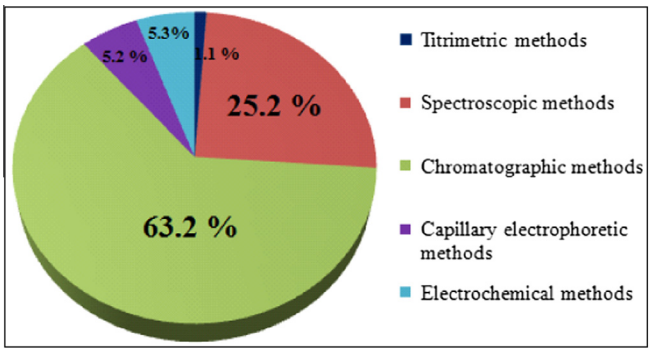
Table 5
TLC-densitometric methods for determination of the studied NSAs in pure, pharmaceutical dosage forms and in biological fluids.

Drug(s)	Stationary phase	Mobile phase	Analytical wavelength (nm)	References
CTZ				
CTZ with pseudoephedrine (stability-indicating study)	Silica gel 60 F_{254}	Ethyl acetate–methanol-ammonia (7:1.5:1, v/v/v)	240 nm	[57]
CTZ. 2 HCl with ambroxol HCl in tablets (stability-indicating study)	Silica gel 60 GF_{254}	CCl_4–Chloroform–Methanol (3:5:2, v/v/v)	230 nm	[58]
CTZ with ambroxol in tablets	Silica gel 60 F_{254}	Methanol–0.067 m KH_2PO_4 (35:65, v/v)	231 nm	[59]
CTZ	Silica gel 60 F_{254}, aluminum oxide 60 F_{254}	Chloroform–ethyl acetate (1:1, v/v)	254 nm	[60]
FXD				
FXD with				
Pseudoephedrine	Silica gel 60 F_{254}	Ethyl acetate:methanol:ammonia 33%; (7: 2: 1, v/v/v).	217 nm	[61]
Acetaminophen	Silica gel 60 F_{254}	Ethyl acetate:methanol:ammonia 33%; (7:2:1, v/v/v)	233 nm	[61]
KET				
KET	Aluminum oxide 60 F_{254}	Ethyl acetate–butan-2-one-toluene, (7:3, v/v).	254 nm	[60]
KET fumarate in tablets	Silica gel 60 F_{254}	Ethyl acetate–methanol–liquid ammonia (150:15:1, v/v/v)	301 nm	[62]
KET with				
Pseudoephedrine	Silica gel 60 F_{254}	Ethyl acetate:methanol:ammonia 33%; (15:1:2, v/v/v)	218 nm	[61]
Acetaminophen	Silica gel 60 F_{254}	Ethyl acetate:methanol:ammonia 33%; (15:0.3:2, v/v/v)	272 nm	[61]
LOR				
LOR and preservatives in syrups (LOR–sodium benzoate mixtures)	Silica gel 60 F_{254}	n-Butyl acetate–carbon tetrachloride–acetic acid–acetonitrile (3:6:0.2:3, v/v/v/v)	240 nm	[63]
(LOR–methylparaben–propylparaben mixtures)	Silica gel 60 F_{254}	Ethyl acetate–n-hexane–methanol–ammonia–diethylamine (1:4:0.8:0.4:2, v/v/v/v)	275 nm	
LOR in presence of degradation products, tablets and syrups, (stability-indicating study)	Silica gel 60 F_{254}	Chloroform–ethyl acetate–acetone (5:7:7, v/v/v)	200–400 nm	[64]
		Ammonia–methanol (3:200, v/v)	246 nm.	[29]
LOR with				
Pseudoephedrine	Silica gel 60 F_{254}	Ethyl acetate:methanol:ammonia 33%; (15:0.3:2, v/v/v)	218 nm	[61]
Acetaminophen	Silica gel 60 F_{254}	Ethyl acetate:ammonia 33%; (15:2, v/v)	251 nm	[61]

activity towards oxidation of CTZ, since it facilitates the electron transfer and significantly enhances its oxidation peak current [178]. On the other hand, the electrochemical oxidation of CTZ dihydrochloride at different pHs and concentrations using CV and differential pulse voltammetry with a GCE was studied. This study indicated that CTZ was susceptible to oxidation. The best results were obtained in phosphate buffer of pH 8 [179]. Khater et al. [180] constructed new modified carbon paste electrodes for determination of KET fumarate in its pure and pharmaceutical preparations. Furthermore, an electro-analytical method has been developed for the determination of the KET in biological fluids by continuous square wave adsorptive stripping voltammetry on a ultra-gold microelectrode in aqueous solution with phosphate buffer as supporting electrolyte (pH 2.3) and an accumulation potential of 300 mV [181]. Li et al. [182] proposed an electrochemiluminescence method for determination of KET fumarate on GCE modified with platinum-multi-walled carbon nanotube modified electrode. Also, ion-transfer voltammetry at a nitrobenzene/water interface was performed to study the ion-transfer reaction and the adsorption of histamine and KET. Ion-transfer voltammograms showed that KET gave an anodic wave at a potential less positive than that of histamine [183]. Ghoneim et al. [184] described the polarographic behavior of LOR in human plasma at the mercury electrode using buffer solution of pH 6, and a sensitive differential pulse stripping voltammetric method based on controlled adsorptive accumulation of LOR on a hanging mercury drop electrode for its direct determination at nanomolar concentrations without nitration of the drug using 0.1 M sodium hydroxide solution as a supporting electrolyte, accumulation potential −1.2 V and pulse amplitude 100 mV. Norouzi and Ganjali [185] introduced the fast Fourier transformation continuous cyclic voltammetry at a gold microelectrode in a flowing-solution system for determination of LOR in pharmaceuticals, the parameter values were set to 80 V/s for the scan rate, 0.7 s for the accumulation time, 300 mV for the accumulation potential, and 2 for the pH.

6. Conclusion

Our review article is a comprehensive review of different methods for the analysis of commonly prescribed non-sedating antihistamines. The review covers most of the methods described for the analysis of cetirizine, ebastine, fexofenadine, ketotifen and loratadine in pure forms, in different pharmaceutical dosage forms and in biological fluids. The review covers the period from 1991 till now. Chromatographic, spectroscopic, electrochemical, and titrimetric methods are presented. 63.2% of the reported analytical methods are chromatographic methods as shown in the following chart:



Disclosure

All the authors of the paper do not have a direct financial relation with the commercial identity mentioned in the paper.

Conflict of interests

All the authors declare that there is no conflict of interests in their submitted paper.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ancr.2014.11.003.

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