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Review

Advances in Simple and Chiral-HPLC Methods for Antiallergic Drugs and Chiral Recognition Mechanism

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Abstract: Among many diseases, allergy appears to be a serious problem for human beings. Various forms of allergic disorders make people tense, leading to some other health issues. Many medications, including nonracemic and racemic ones, are used to treat this problem. It is important to have exact analysis strategies just to see any medication side effects, plasma profiles, and working efficiency. Therefore, efforts are made to review simple and chiral HPLC methods for antiallergic drugs; HPLC is the best analytical technique. The highlights in this article include the world scenario, causes of allergy, the effect of allergy on the economy, the mechanism of allergy in humans, classes of antiallergic drugs, simple drugs, chiral drugs, analysis by HPLC, and the chiral recognition mechanism. Moreover, attempts are also made to highlight the management of allergies and future perspectives.

Keywords: antiallergic drugs; HPLC; simple and chiral analyses; chiral stationary phases

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1. Introduction

Since ancient times, allergy has been of great concern globally [1]. Generally, allergy is not a serious disease but disturbs the peace of mind, work, and economy of a country [2]. Sometimes, allergies may be a life-threatening problem. For example, anaphylaxis involves a life-threatening hypersensitivity reaction. There are various types of allergies concerning different objects such as foods, seasons, pets, metals, aerosols, and much more. The food products showing allergies are milk, egg, wheat, fish, shellfish, peanut, sulfite, soy, casein, etc. The seasonal factors are spring, summer, fall, and winter allergies. The spring season is a good source of pollen production and ragweed pollen production [3]. The most common allergic pets are dogs and cats. Other sources of allergy are poison ivy, hives (urticaria), oak, sumac, dust, hay fever, chemicals, sun reactions of the skin, allergic conjunctivitis (pink eye), drugs, cosmetics, insect stings (bee stings), mold, pollen, nickel, etc. Symptoms are mild, such as itching, rhinitis, itchy red spots on the skin, rashes, and watery or itchy eyes, on first exposure to an allergic source. Contrarily, the symptoms may be worse on continuous exposure to the allergens. Severe symptoms include diarrhea, chest tightness, abdominal pain, difficulty in swallowing, dizziness, anxiety, facial blushing, vomiting, heart palpitations, bulging of the face/eyes/tongue, faintness, wheezing, breathing difficulty, and insentience [4].

The exact reason for allergy is not known so far, but some factors may be responsible, including mechanization, suburbanization, air contamination, climate variation, and the hygiene hypothesis [5,6]. Additionally, climate change is supposed to be responsible for spreading allergies, for instance, allergic conjunctivitis, anaphylaxis, asthma, and allergic

rhinitis. It has been noted that there is a close relationship between climate change and allergy [7–9]. The effect of allergenic pollen on the development of allergies greatly relies upon annual volume duration and intensity of exposure, as well as the allergenicity of pollen. In general, tree pollen is the most abundant contributor to the greatest annual production of aeroallergens, followed by weeds and grasses [6]. On the other hand, air quality and food materials show some implications. Similarly, the increasing number of vehicles, power plants, and industries in cities upsurging CO_2 levels in the environment is also a big factor [10]. Changes in temperature and weather global warming are also responsible for increasing allergies in humans such as fungal bacteria that cause allergies and asthmatic reactions [11].

2. World Scenario

A large number of populations in the world are struggling with different types of allergic disorders. About 50 million people in the United States are struggling with an allergy of some kind. According to the Centers for Disease Control and Prevention, USA, food allergies are reported in 4% of adults and 4–6% of children. The symptoms of food allergies are very public, particularly in babies and children [12]. About 16.4 and 7.0 million adults and children have been found to have asthma. It has been reported that about 3600 patients with asthma die every year [13].

2.1. Asia

A thorough search of the literature through PubMed using strategies such as "Food allergy and each Asian country, Food allergy and Asia" and "Food anaphylaxis and Asia" was published between 2005 and 2012. It was observed that in Asia, shellfish is supposed to be the most widely popular food allergen, due to the presence of a large quantity of seafood in this region. The symptoms differ commonly, from oral signs to a hypersensitivity reaction (anaphylaxis) for a similar individual. Moreover, house dust parasite tropomyosin might be a key sensitizer, as the data suggest. Additionally, the two most common food allergies found in Asian infants and young children are cow's milk and egg hypersensitivity [14].

2.2. Europe

A combined study of allergy was included for infant to adult age groups. The overall estimates of a self-lifetime trend of reaction to cow's milk are 6.0%, wheat 3.6%, egg 2.5%, peanut 1.3%, tree nuts 2.2%, shellfish 1.3%, and soy 0.4%, whereas the trend of food allergy to cow's milk and tree nuts was a maximum of 0.6%, compared to 0.5% soy, 0.3% egg, 0.2% wheat, 0.1%, peanut, 0.2% fish, and 0.1% shellfish, respectively [15].

2.3. Australia

Unfavorably allergic diseases are the most widely recognized among the constantly developing conditions in Australia. These include drug, food, and insect reactions such as anaphylaxis, asthma, hay fever, and eczema. About 4.1 million people in Australia (19.6%) have been struggling with at least one type of allergic disorder [16]. In Australia, about 20% of the population is sensitive to allergy diseases, and this is continuously increasing. In the last few decades, the number of anaphylaxis patients has risen by 300% [17,18].

Allergy to food-prompted anaphylaxis has doubled in the last few years, and 10% of babies are affected by food allergies [19]. Moreover, 5% of adults might be oversensitive to drugs [20]. The lack of public consciousness about the impact of allergies on humans is a great concern. Overall, 18% of the population of Australia has allergic rhinitis, which reduces the quality and efficiency of human life. Because of the above facts, it may be predicted that by the end of 2050, the number of allergic patients in Australia will increase by 70% to 7.7 million [16,21].

2.4. America

The symptoms of hay fever are well known to others, such as puffy eyes, eye touchiness, runny and stuffy nose, sneezing, inflammation, and itchy nose and throat. A total of 18.0 million adults and 7.1 million people in the lower age group, especially children, struggle with hay fever allergies, and there are 13.1 million yearly doctor's visits for allergies [22]. The total medical cost of allergic rhinitis each year is USD 11.2 billion [23]. In addition, around 4 million individuals missed or had low-efficiency workdays, and every year, around USD 700 million is lost from production because of hay fever responses [24,25].

3. Causes of Allergy

Although the exact reasons for occurring allergies are not known so far, human allergies may be due to pet dander, insect stings such as bees, certain types of foods (nuts or shellfish), medications (penicillin or aspirin), plants, and pollen. Furthermore, development, suburbanization, air contamination, climate change, pollen, and the hygiene hypothesis are also responsible for the allergic disorder in humans [2,5].

4. Effect of Allergy on Economy

The American population is affected by allergies, which affect their value of life at school and work [6,26]. Due to allergies, humans cannot pay attention to their work. Therefore, the productivity of work or their results are reduced. Each year, asthma causes around 14.4 million missed school days and costs USD 15.6 billion in medical treatment, and loss of earnings amounts to USD 5.1 billion [1].

5. Mechanism of Allergy in Humans

An organism's immune system can eliminate antigens after its exposure. It follows various mechanisms to maintain normal health. During this period, we can observe a localized inflammatory response that eliminates antigens without much trouble. Sometimes these responses get worse and provoke several deleterious effects, which may be followed by death. This unwanted immune response is known as hypersensitivity or allergy. Based on the response, hypersensitivity is divided into various forms. Broadly, there are two types of response: (i) immediate hypersensitivity and (ii) delayed hypersensitivity. For instance, asthma is a common example of hypersensitivity. In most cases, its attack is initiated by blood or airborne allergens, dust, pollen, and some types of fumes, while in some cases, asthma is associated with the weather (in cold) or hectic exercises. Mast cell degranulation, along with some mediators, constricts bronchiociliary smooth muscles and lowers windpipe inflammation, which is due to inverted or disturbed expression levels of some proteins responsible for constriction or relaxation [14,27].

Allergy begins in humans; mast cells and basophils have become the main target cells of acute hypersensitivity reactions. Histamine is found in mast cells as well as basophils, and is a significant tool in the body's cache for struggling against infection. Histamine (Figure 1), chemically known as [2-(imidazol-4-y1) ethylamine], is obtained from the amino acid histidine after decarboxylation. It is present in all organs and tissues of the human body. Histamine plays a key role in biological actions and works like a chemical messenger to transfer information from one cell to another one.

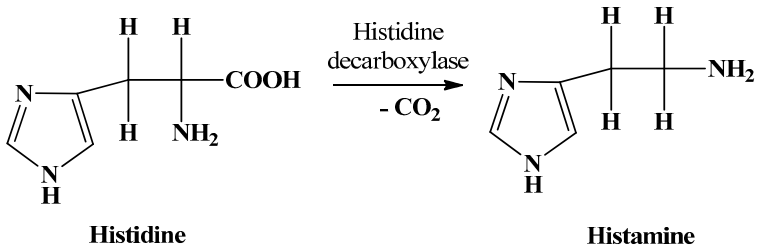


Figure 1. Mechanism of action of antiallergic drugs.

It takes minutes to days of alerting exposure to the mast cells and basophils for them to become primed immunoglobulin E antibodies. Protein molecules are attached to a ragweed pollen particle that has been inhaled; the same symptoms occur, as shown in Figure 2. Furthermore, IgE antibodies jump to the outsides of basophils, and then mast cells are acquainted with the protein surface signs of the allergen. In addition to this, IgE antibodies react to the protein surface markers by binding, and the rest of the IgE antibodies are close to the basophils or mast cells [28,29].

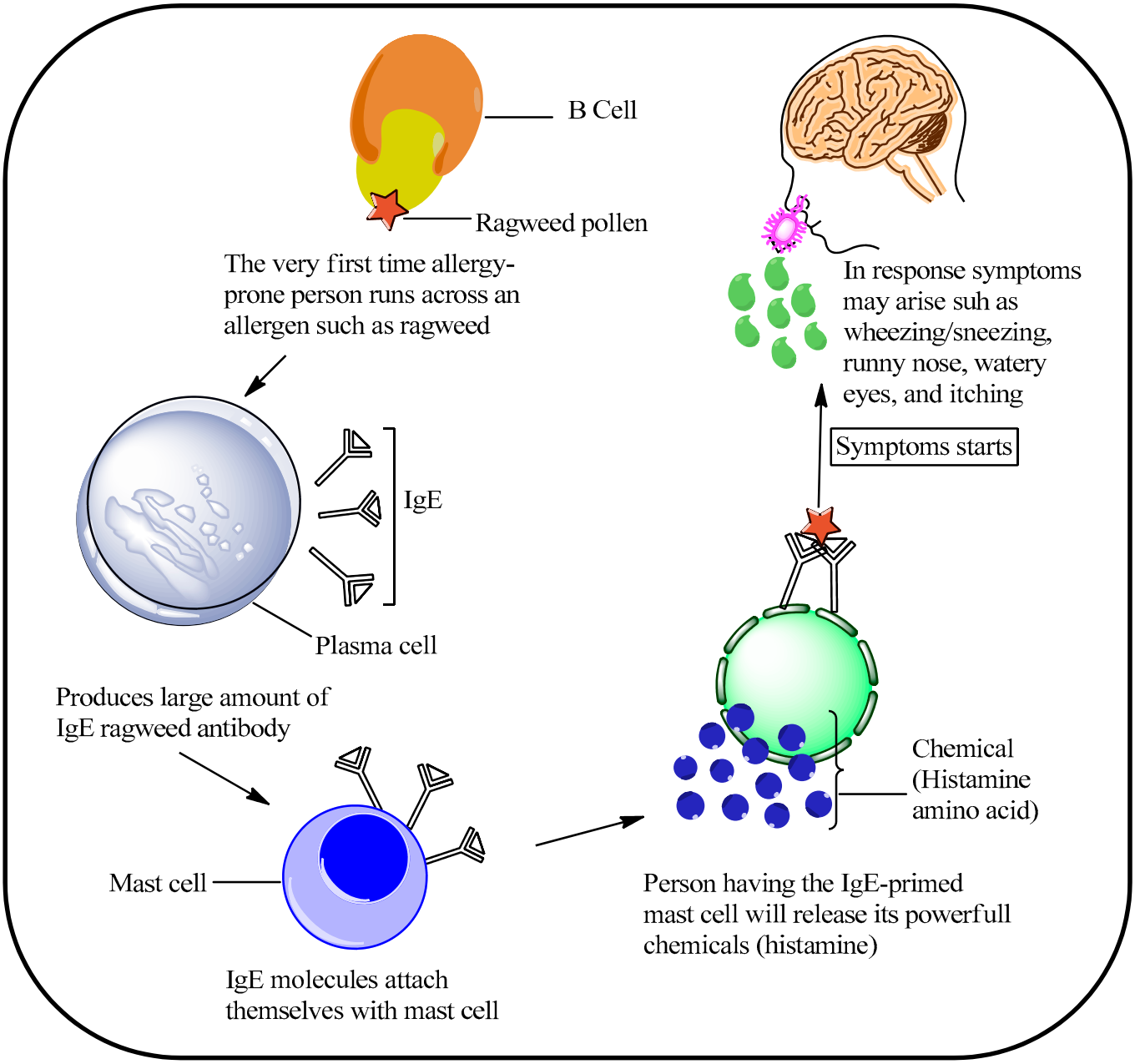


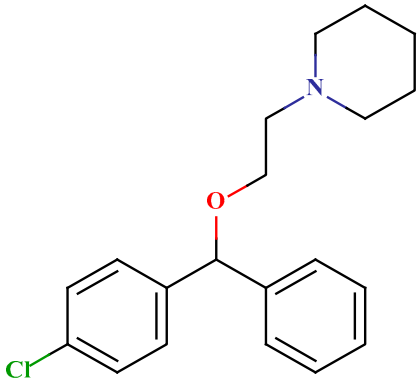
Figure 2. Pictorial presentation of the general allergic pathway (excessive immune response) in humans.

6. Classes of Antiallergic Drugs

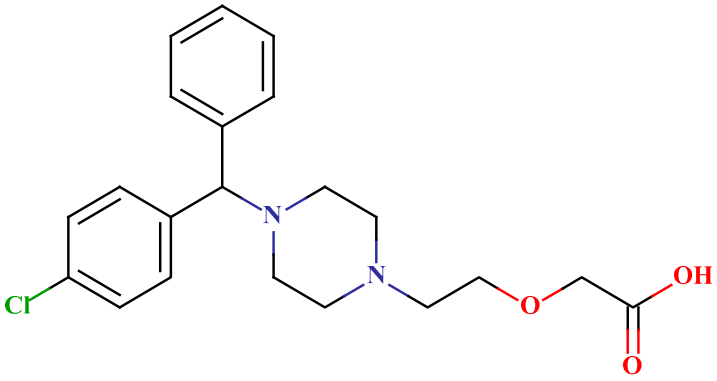
Antiallergic drugs are available in the market with different brand names and are further divided into two classes, such as:

6.1. Simple Drugs

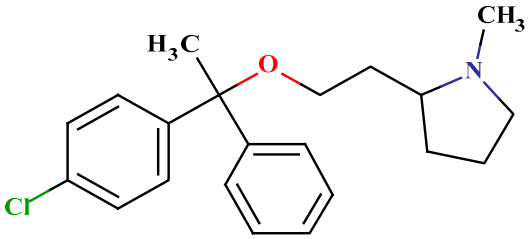
Loratidine, olopatadine, ketotifen, diphenhydramine, loratadine, domperidone, ebastine, ibudilast, bilastine, azelastine, etc., shown in Figure 3.



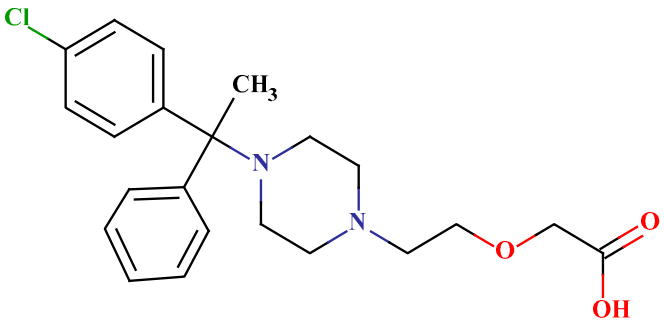
Cloperastine



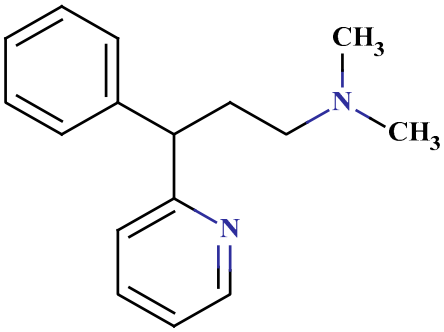
Cetirizine



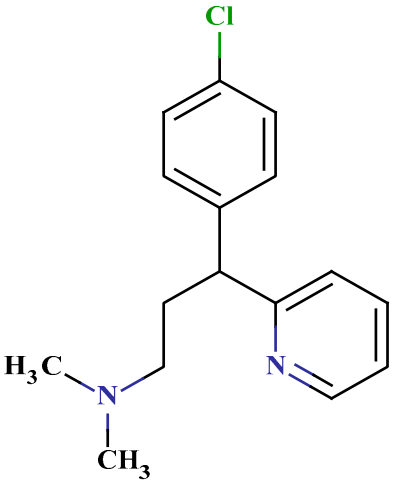
Clemastine



Levocetrizine

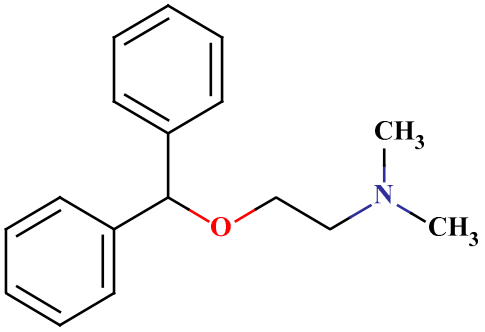


Pheniramine

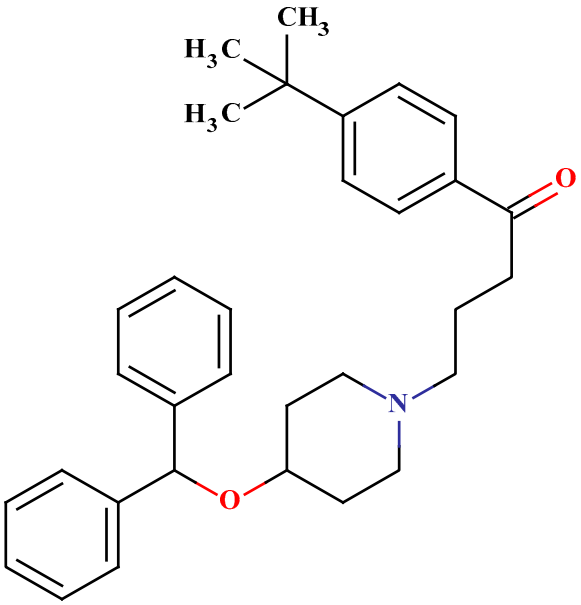


Chlorephiniramine

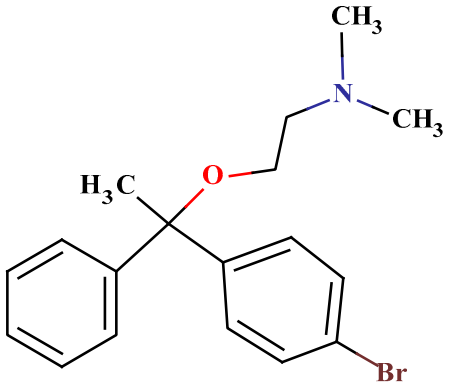
Figure 3. *Cont.*



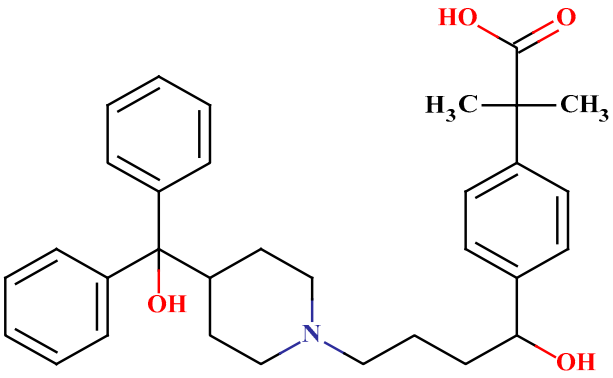
Diphenhydramine



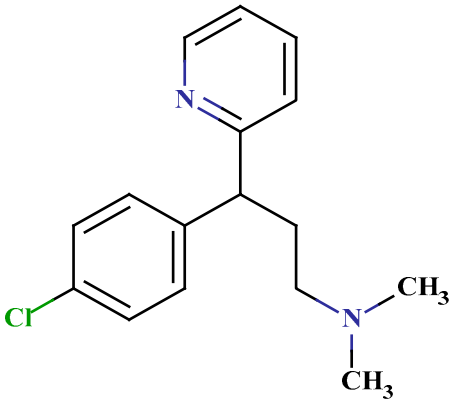
Ebastine



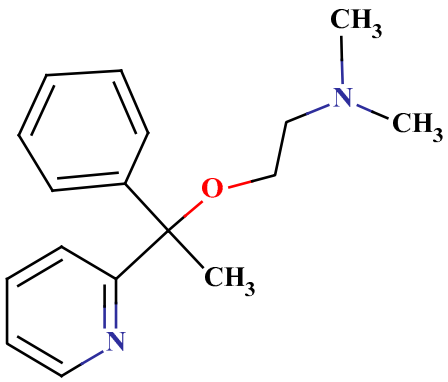
Embramine



Fexofidine

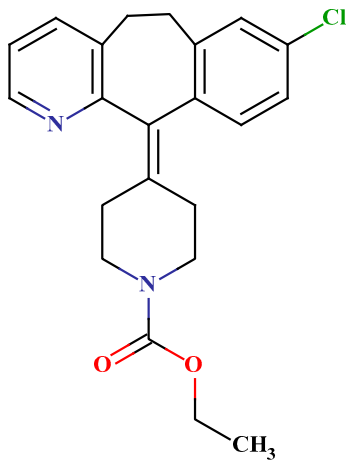


Dexchlorpheniramine

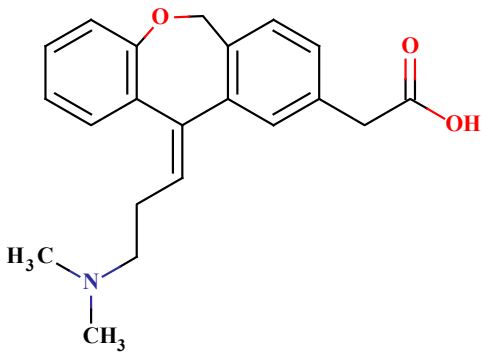


Doxylamine

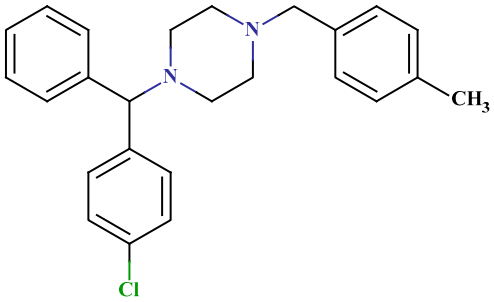
Figure 3. *Cont.*



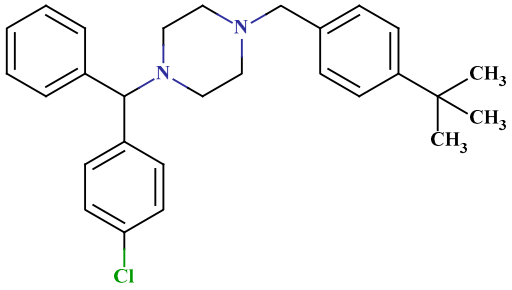
Loratidine



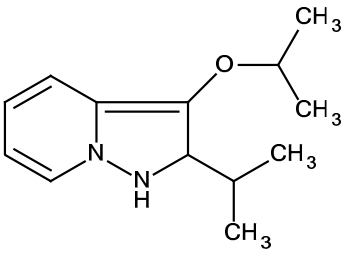
Olopatadine



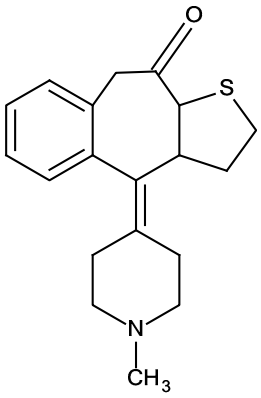
Meclizine



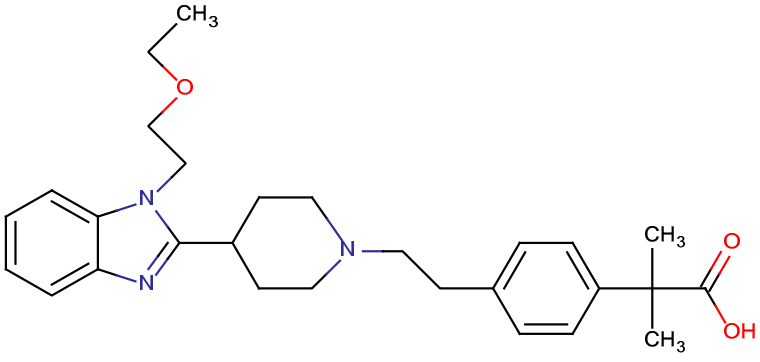
Buclizine



Ibudilast

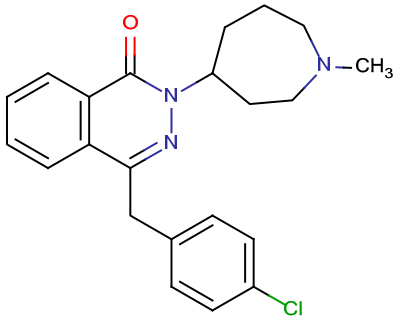


Ketotifen



Bilastine

Figure 3. *Cont.*



Azelastine

Figure 3. Chemical structures of antiallergic drugs.

6.2. Chiral Drugs

Cetirizine, pheniramine, chlorpheniramine, clemastine, levocetirizine, fexofenadine, embramine, dexchlorpheniramine, doxylamine, meclizine, buclizine, and cloperastine, shown in Figure 3.

7. Analyses of Antiallergic Drugs by HPLC

7.1. Sample Preparation

Sample preparation is an essential and critical part of analyzing any drug product. Sample preparation for analyzing the drug product in a biological sample is mandatory, because several impurities are present along with the drug of interest [30]. The drug concentration in the sample is very low, for instance, nano- to picogram levels. For that reason, sample preparation is required before the analysis to obtain the contamination levels of the drugs [31]. To get rid of these complications, very simple, fast, and reliable sample preparation techniques are used. The basic parts of an analysis of drugs and pharmaceuticals in human plasma are drug extraction, purification, and preconcentration. Additionally, the sampling of blood, preservation, and extraction is also essential. Moreover, the solid phase extraction (SPE) method is used to extract the drug product from a wide variety of matrices such as blood plasma, urine, water samples, beverages, soil animal tissue, etc. SPE is a very fast and sensitive extraction method, with the highest concentration of drug recoveries, i.e., 90–95%. For fast and selective sample preparation-cum-purification before chromatographic analysis, SPE is used. The SPE method is very economical because of the low consumption of solvent [32,33]. Considering the above features, SPE has become the first choice of about 80% of chromatographers for sample preparation globally [34]. Among columns, disks, and cartridges, cartridges have been frequently used for extraction purposes [35].

7.2. Separation and Identification

Separation and identification of antiallergies by HPLC were divided into two parts, viz. simple and chiral. The details are discussed in the following subheadings.

7.2.1. Simple

There are various techniques available on the market for drugs and pharmaceutical analyses. Among them, the HPLC technique appears as the best choice for analysts because of its good reproducible, effective, and selective results. Moreover, the availability of different types of columns for drug analysis makes HPLC the priority [36,37]. Similarly, the separation of antihistamine drugs by HPLC is carried out, which is given herein (Table 1). For the determination of phenylephrine HCl, paracetamol, and cetirizine hydrochloride in pharmaceutical tablet dosage form, an (HPLC-DAD) method has been developed and validated by Dewani et al. [38], utilizing mobile phase (10 mM phosphate cradle: pH 3.3 and acetonitrile on Kinetex-C18 column). The calibration curves were found to be linear, and ranged from 5–15, 250–750, and 2.5–7.5 µg/mL for phenylephrine HCl, paracetamol, and cetirizine hydrochloride, with correlation coefficient >0.9996. The developed method

promises potential application in the analysis of the pharmaceutical mixture of a marketed preparation tablet. Another HPLC method (accurate and specific) was described by Sher et al. [39] to determine drugs such as cetirizine HCl, chlorphenamine maleate, buclizine, domperidone, loratadine, and meclizine in dosage form and human serum, involving pyridoxine (internal standard), with mobile phase: a mixture of 0.01 M sodium salt of heptane sulphonic acid salt buffer and acetonitrile. Furthermore, the flow rate set was 1.0 mL/min with UV detection at 230 nm. A C_{18} column was used for this analysis. The authors have determined the separation of some antiallergic reference standard drugs by HPLC, for example, pyridoxine, chlorphenamine maleate, domperidone, cetirizine, loratadine, meclizine, and buclizine. LODs were in the range of 0.52 to 5.16 ng/mL. The key objective of their study was to optimize the sample preparation, standard preparation, pharmacokinetics, and force degradation study of these antiallergic drugs. These were extracted from the human plasma of different volunteers. The typical separation of the reported drugs was conceded in pharmaceutical formulation. Before the analysis of these antiallergics into human plasma, a blank sample was also carried out. Thereafter, a spiked drug plasma sample was injected into the HPLC and the typical chromatogram was achieved at 230 nm for pyridoxine, chlorphenamine maleate, domperidone, cetirizine, loratadine, meclizine, and buclizine.

Table 1. Separation of antiallergics.

S.N.	Name of Drugs	Mobile Phase	Column	Other Conditions	Ref
1	Phenylephrine hydrochloride, paracetamol, and cetirizine hydrochloride	10 mM phosphate buffer (pH 3.3) and acetonitrile	Phenomenex Kinetex-C_{18}	1 mL/min at 230 nm; recoveries from 101 to 102.40%	[38]
2	Chlorphenamine maleate, loratadine, Cetirizine HCl, domperidone, buclizine, and meclizine	Heptane sulphonic acid salt buffer in water and MeCN	symmetry C_{18}	1 mL/min at 230 nm; LOD from 0.52 ng/mL to 5.16 ng/mL	[39]
3	Cetirizine dihydrochloride	0.2 M K_2HPO_4 (pH 7) and ACN (65:35, *v*/*v*)	Eclipse XDB C_8	1 mL/min at 230 nm; LOD and LOQ were 0.25 and 0.056 µg/mL	[40]
4	Cetirizine dihydrochloride	50 mM KH_2PO_4 and ACN (60:40, *v*/*v*)	Symmetry C_{18}	1 mL/min at 230 nm; LOQ was 1 µg/mL. LOD) was 0.2 µg/mL with recovery of 99%	[41]
5	Nimesulide, phenylephrine hydrochloride, caffeine anhydrous, and chlorpheniramine maleate	Methanol and buffer (55:45, *v*/*v*, pH 5.5)	RP-Hypersil phenyl (4.6 mm × 25 cm)	1 mL/min at 214 nm; LOD from 0.45 to 9.34 µg/mL; recovery from 99.03 to 100.30%	[42]
6	Fexofenadine	Buffer and Methanol (30:70, *v*/*v*)	Symmetry-C_{18} (150 × 4.6 mm), 5 µm	at 254 nm; LOD = 9.92 ng mL	[43]
7	Ambroxol hydrochloride, cetirizine hydrochloride, methylparaben, and propylparaben	0.01 M phosphate buffer and 0.1% triethylamine as a solvent-A and ACN as a solvent-B (mixture of both)	Agilent Eclipse plus C18 (50 × 2.1 mm), 1.8 µm)	at 237 nm; LOQ from 0.12 to 0.18 µg/mL); recovery of more than 99%	[44]
8	Pseudoephedrine, Paracetamol, and Cetirizine	25 mM Na_2HPO_4 (pH 5.0)-MeOH-ACN (30:60:10, *v*/*v*)	Hypersil C_{18}	1 mL/min. at 240 nm; LOD from 0.836 to 2.512	[45]
9	Pseudoephedrine, Fexofenadine, and Cetirizine	TEA solution (0.5%, pH 4.5) MeOH-ACN (50:20:30, *v*/*v*)	Zorbax-C_8 (150 × 4.6 mm) 5 µm	218 and 222 nm; LOD from 0.10 to 1.75 µg/mL; recovery 97.52 to 100.98%	[46]
10	Desloratadine HCl and Loratadine	0.1 M SDS, 1% octanol, 10% n-propanol and 0.3% TEA in 0.02 M phosphoric acid, pH 3.0	Cyano Propyl bonded stationary-phase	1 mL/min at 247 nm; LOD was 0.8 and 0.2 µg/mL; LOQ was 2.3 and 0.6 µg/mL for both drugs	[47]
11	Ketotifen, olopatadine, cetirizine, and ibudilast	Acetonitrile-rich mobile phase	Polymer column (MSpak GF)	0.2 mL/min at 260 nm; LOD = 0.5 ng/mL; recovery 51.7–95.5%	[48]
12	Cetirizine	ACN-water-CH_3COOH-TFA (93:7:1:0.025, *v*/*v*)	Betasil silica (50 × 3, 5 m).	0.5 mL/min; recoveries 84.5 to 88.0%	[49]

Table 1. *Cont.*

S.N.	Name of Drugs	Mobile Phase	Column	Other Conditions	Ref
13	Desloratadine HCl	Methanol-0.03 M Heptane sulphonic acid sodium-Glacial acetic acid (70:30:4, *v*/*v*),	Diamonsil BDS C_{18}	1 mL/min at 247 nm	[50]
14	Desloratadine HCl	MeOH-ACN-Phosphate buffer 0.01 mol/L (35:35:30, *v*/*v*) (pH-5.5)	Hypersil CN Column (150 mm × 5 mm), 5 µm	0.8 mL/min at 241 nm; LOQ5.0 ng/mL	[51]
15	Cetirizine dihydrochloride	0.05 M dihydrogen phosphate-ACN-MeOH-THF (12:5:2:1, *v*/*v*)	Hypersil BDS C_{18} (4.6 × 250 mm), 5 µm	1 mL/min at 230 nm; LOD and LOQ were 0.10 and 0.34 µg/mL	[52]
16	Loratadine HCl	ACN-water-0.5 M KH_2PO_4-H_3PO_4 (440:480: 80:1, *v*/*v*)	Supelcosil LC18-DB column	1 mL/min. at 200 nm; LOQ was 0.5 ng/mL	[53]
17	Bilastine	Formic acid and MeOH(1:1 ratio)	Gemini C_{18} column (150 × 4.6), 5 µm	0.8 ml/min at 282 nm; LOD and LOQ were 0.08931 µg/mL and 0.27063 µg/mL	[54]
18	Azelastine	Potassium dihydrogen phosphate buffer and acetonitrile (50:50, *v*/*v*);	Spherisorb CN column (250 × 4.6 mm, 5-µm)	1.0 mL/min at 290 nm; LOD and LOQ were 0.81 µg/mL and 2.44 µg/mL Recovery = 99 and 102%	[55]

Borges et al. [40] developed a new RP-HPLC method for the stability of cetirizine dihydrochloride, by using 0.2 M K_2HPO_4 (pH 7.0) and acetonitrile (65:35, *v*/*v*) mobile phase. Eclipse XDB C_8 (150 × 4.6 mm, 5 µm) column was used with 1.0 mL/min flow rate and detection at 230 nm. The LOD and LOQ were 0.25 and 0.056 µg/mL, respectively. The developed stability-indicating methods can be utilized for cetirizine dihydrochloride oral lyophilized dosage form. Souri et al. [41] developed and validated an HPLC method to examine the cetirizine dihydrochloride degradation in acidic and oxidative conditions using mobile phase as a mixture of 50 mM KH_2PO_4-acetonitrile (60:40, *v*/*v*) on a symmetry C_{18} column. The developed and validated method was found to be linear and range from 1–20 µg/mL of cetirizine dihydrochloride with a correlation coefficient >0.999 and intra- and interday precision <1.5%. From the experimental data of the drug, it was concluded that the drug was unstable in 2 M HCl and 0.5% H_2O_2. LOQ was 1 µg/mL. LOD was 0.2 µg/mL with a recovery of 99%. Kumar et al. [42] developed and validated an explicit and accurate RP-HPLC method for the rapid determination of phenylephrine HCl, nimesulide, caffeine anhydrous, and chlorpheniramine maleate. A mixture of methanol and buffer (55:45, *v*/*v*, pH 5.5) was used as a mobile phase on the RP-Hypersil phenyl column (4.6 mm × 25 cm). A flow rate of 1.0 mL/min with detection at 214 nm was achieved. The retention times of these drugs, namely nimesulide, phenylephrine hydrochloride, caffeine anhydrous, and chlorpheniramine maleate were 7.47, 3.94, 4.55, and 17.15 min. The linearity for all the reported drugs was obtained in the range between (300–800 µg/mL) nimesulide, (15–32 µg/mL) phenylephrine hydrochloride, (16–32 µg/mL) chlorpheniramine maleate, and (30–180 µg/mL) caffeine anhydrous, respectively.

LODs were in the range of 0.45 to 9.34 µg/mL. This simple, precise, economical, rapid, and reproducible method could be employed for the determination of the aforesaid drugs in commercial uses. Sujana et al. [43] described an RP-HPLC method for the estimation of fexofenadine in bulk and tablets. The separation was carried out on a Symmetry C_{18} (15 cm × 4.6 mm i.d., 5 µm) column using a mixture of potassium dihydrogen phosphate buffer (pH 3.0) and methanol (30:70, *v*/*v*) as mobile phase and detected at 254 nm. LOQ and LOD values for fexofenadine were 9.92 and 3.03. The proposed method followed ICH guidelines and may be used in routine analysis of reported drugs in pharmaceutical tablet forms. Trivedi et al. [44] described a stability-indicating RP-UPLC method for simultaneous determination of ambroxol HCl, cetirizine HCl, methylparaben, and propylparaben in liquid pharmaceutical formulation. The separation was achieved on an Agilent Eclipse plus C_{18} (50 mm × 2.1 mm, 1.8 um) column using gradient elution with a mixture of 0.01 M phosphate buffer, 0.1% triethylamine, and acetonitrile as mobile phase, with detection at 237 nm. LLOQs were 0.12 to 0.18 µg/mL, with a recovery of more than 99% for each drug. All the drugs were well separated, with twelve known

impurities/degradation products together with one unknown degradation product within 3.5 min of retention time. Sivasubramanian and Lakshmi [45] developed and validated a linear, reproducible, specific, sensitive, and rugged HPLC technique for the optimization of cetirizine, paracetamol, and pseudoephedrine on a Hypersil C_{18} column using isocratic mode. The flow rate was 1.0 mL/min and the mobile phase comprised of 25 mM phosphate buffer (pH 5.0)-methanol-acetonitrile (30:60:10, v/v) at 240 nm. The linearity range for paracetamol, cetirizine, and pseudoephedrine was found to be 100–600, 1–6 and 12–72 µg/mL, separately and respectively. The LOD was 0.921, 0.151, and 0.321 µg/mL and the LOQ 2.512, 0.502 and 0.836 µg/mL for paracetamol, cetirizine, and pseudoephedrine. The created strategy was straight, reproducible, explicit, delicate, and tough. Karakus et al. [46] developed and validated a specific, accurate, precise RP—HPLC method to determine the antihistaminic-decongestant pharmaceutical dosage forms containing a binary mixture of pseudoephedrine HCl with fexofenadine HCl or cetirizine dihydrochloride using a Zorbax C_8 (15 cm × 4.6 mm, 5 µm) column, and detection was achieved at 218 and 222 nm, respectively. The mobile phase consisted of TEA solution 0.5%, pH 4.5-methanol and acetonitrile (50:20:30, v/v). The method was linear between the concentration range from 30–240 and 1.25–10 µg/mL, and the limits of detection for pseudoephedrine hydrochloride and cetirizine dihydrochloride were 1.75 and 0.10 µg/mL, separately. Similarly, the linearity range for pseudoephedrine HCl and fexofenadine HCl binary mixture was 10–80 and 5–40 µg/mL, and the limit of detection was 0.75 and 0.27 µg/mL, respectively. The connection coefficient was greater than 0.999, and RSD was under 1%. LOD values were 1.75 and 0.10 µg/mL for PSE and CET; LOD values were 0.75 and 0.27 µg/mL for PSE and FEX. The % recovery for PSE and CET was 97.52 to 98.40, and for PSE and FEX it was 100.98 to 98.97. The developed method can be applied to the quantitative analysis of the reported drugs. A rapid HPLC method was developed by El-Sherbiny et al. [47] for the pharmaceutical preparation of loratadine and/or its analog desloratadine using a microemulsion as the eluent. The separation was achieved using a column packed with cyanopropyl-bonded stationary phase followed by detection at 247 nm with a flow rate of 1.0 mL/min. The mobile phase: 0.1 M sodium dodecyl sulfate, 1% octanol, 10% n-propanol, and 0.3% triethylamine in 0.02 M phosphoric acid (pH 3.0). Validation of the developed method was carried out in terms of linearity, specificity, LOQ, LOD, precision, and accuracy. LOD was 0.8 and 0.2 µg/mL for loratadine and desloratadine, Similarly, LOQ was 2.3 and 0.6 µg/mL for both drugs. Fujimaki et al. [48] developed an HPLC-tandem mass spectrometry technique for the analyses of four antiallergic drugs—ketotifen, olopatadine, cetirizine, and ibudilast—in human plasma utilizing polymer column (MSpak GF). An acetonitrile-rich portable stage was utilized to elute the analytes. The observed recoveries of the ketotifen, cetirizine, olopatadine, and ibudilast spiked into plasma were 51.7–95.5%, and the detection limit was 0.5 ng/mL. Interestingly, the correlation coefficient (r) for the tested drugs was in the range of 0.9997, −0.999, 0.9997, and 0.998, with a concentration range of 1–100 ng/mL and a detection limit of 0.5 ng/mL. Songa et al. [49] described bioanalytical technique inbuilt solid phase extraction (SPE) and hydrophilic interaction liquid chromatography-tandem mass spectrometry (HILIC–MS/MS) for cetirizine determination. An SPE 96-well plate using polymer sorbent (Strata X) was utilized for the extraction of cetirizine. The mobile phase used consisted of acetonitrile-water-acidic acid trifluoro acetic acid (93:7:1:0.025, v/v), and 0.5 mL/min was the flow rate. Further, the extracted samples were separated on Betasil silica columns (50 × 3.5 mm). The method was validated over the range from 1.00–1000 ng/mL cetirizine in human plasma. The interday precision and accuracy of cetirizine exhibited <3.0% RSD and <6.0% relative error. The extraction recoveries were 85.8, 84.5, and 88.0% at 3, 40, and 800 ng/mL, respectively. A recovery of 84.1% was obtained for (IS). This HILIC-MS/MS technique may be used for cetirizine in any biological samples. Qia et al. [50] described the LC method for the analysis of desloratadine in drug substances and pharmaceutical preparations. The mobile phase consists of methanol, 0.03 mol/L heptane sulphonic acid sodium, and glacial acetic acid (70:30:4, v/v) on a Diamonsil BDS C_{18} column. The flow rate was 1.0 mL/min, with

detection at 247 nm. The developed method was validated as per these parameters, for example, selectivity, linearity, LOD, LOQ, accuracy, precision, and solution stability. This technique can be applied for synthetic process control and desloratadine determination in drugs and pharmaceutical preparations. Liu et al. [51] established an HPLC determination of desloratadine by using Hypersil CN column (150 mm × 5 mm, 5 µm) with mobile phase: methanol-acetonitrile-phosphate buffer (35:35:30, *v*/*v*) with pH 5.5; the flow rate was 0.8 mL/min and detection was at 241 nm. The LOQ and calibration range were 5.0 ng/mL and 5.0–800.0 ng/mL, respectively. Furthermore, this method can be utilized for bioequivalence studies of desloratadine fumarate (test), and desloratadine tablets (reference preparation). Jaber et al. [52] developed and validated the HPLC method for the analysis of cetirizine dihydrochloride (CZ) and its related impurities. The mobile phase used was 0.05 M NaH_2PO_4-ACN-MeOH-THF (12:5:2:1, *v*/*v*) on Hypersil BDS C_{18} (25 cm × 4.6 mm, 5 µm) The detection was achieved at 230 nm with a flow rate of 1.0 mL/min. The limits of detection and quantitation for CZ were 0.10 and 0.34 µg/mL, respectively, and CZ-related impurities were observed in the range of 0.08–0.26 µg/mL and 0.28–0.86 µg/mL, separately. The developed method was specific, stability-indicating, accurate, and precise, and can be used for CZ and its related impurities. Kunicki [53] discussed a specific HPLC method for the analysis of loratadine in a human plasma sample. The mobile phase consists of ACN-water-0.5 M KH_2PO_4-H_3PO_4 (440:480:80:1, *v*/*v*) on the Supelcosil LC-18-DB column, and the detection was set at 200 nm. The limit of quantification was 0.5 ng/mL. The precision was good over the range from (0.5–50 ng/mL). Prathyusha et al. [54] developed and validated the RP-HPLC method to obtain the purity of Bilastine in pharmaceutical and bulk dosage forms. The mobile phase used was a mixture of formic acid and methanol (1:1 ratio) using the Gemini C_{18} column (150 × 4.6 mm i.d. 5 µm particle size). The detection was set at 282 nm with a flow rate of 0.8 mL/min. The LOD and LOQ were observed at 0.08931 µg/mL and 0.27063 µg/mL, respectively. The developed method can be further applied for the determination of Bilastine for any mixture of the pharmaceutical dosage form. Patel and Pasha [55] developed a simple, precise, accurate, and stability-indicating RP-HPLC method for the determination of azelastine hydrochloride (AZL) in nasal spray preparation. The chromatographic separation was achieved on the Spherisorb CN column (250 × 4.6 mm, 5-µm) using potassium dihydrogen phosphate buffer and acetonitrile (50:50, *v*/*v*) as mobile phase. The flow rate was set to 1.0 mL/min and detection was achieved at 290 nm. LOD and LOQ were 0.81 µg/mL and 2.44 µg/mL. The % recovery was observed between 99 and 102%. Alali et al. [56] developed and validated a new LC-MS method for the exact amount of ketotifen (unchanged and conjugated) in human plasma. The internal standard Pizotifen was utilized in this investigation. The chromatographic condition was accomplished using reverse phase gradient mode with the switching column technique. The precision was linear and observed between the range of 0.5 to 20.0 ng/mL in human plasma. The percentage recovery was 98.04 and 95.13% for ketotifen and pizotifen, respectively. Li et al. [57] developed analytical methods for the determination of isoniazid and cetirizine in animal and human plasma, respectively. The developed methods had good accuracy, linearity, and precision over the range of 10–2000 and 1–1000 ng/mL of isoniazid and cetirizine in plasma. Chen et al. [58] developed a specific LC-MS-MS method for the optimization of ketotifen and its significant metabolite, ketotifen N-glucuronide in human plasma. Liquid–liquid extraction and the analysis were performed on an LC-MS-MS inbuilt with an electrospray ionization (ESI) interface. The LLOQ for ketotifen was 10.0 pg/mL, the interday precision was beneath 8.2%, and accuracy was between 2.4–3.4% for all samples.

Fujita et al. [59] developed a fast, sensitive, and selective method to optimize plasma concentrations of olopatadine HCl (A) and its metabolites, such as M1 (B), M2 (C), and M3 (D) by opting for HPLC with EI tandem mass spectrometry. Olopatadine and its metabolites together with the internal standard, KF11796 (E), were isolated from plasma by the SPE method.

The mass spectra of Ketotifen, cetirizine, olopatadine, and ibudilast were achieved using HPLC-MS, and HPLC-MS-MS are represented in along with its fragmentation mode. These antiallergic drugs presented protonated molecular ions $[M+H]^+$ at m/z 310, 389, 338, and 231, separately, by using HPLC-MS in full scanning mode. In the case of ketotifen, which showed the main important product (desired) ion at m/z 96 (collision energy, −40 eV), it was most likely equivalent to $[C_6H_8N + 2H]^+$. Similarly, for olopatadine, the mass spectra gave a major fragment ion at m/z 165, similar to the breaking of the dibenzoxepin ring. Moving forward for olopatadine, the product ion at m/z 247 was because of the loss of the CH_3CH_2NH and COOH groups. Cetirizine demonstrated a base peak that appeared at m/z 201 as a result of a piperazine side chain. Additionally, protonated ibudilast gave product ions at m/z 189 and 161, separately, because of the loss of an isopropyl group and an isobutyryl group [59]. The above drugs were pointed into human plasma. The chromatograms with distinct peaks for each drug showed little impurity. The elution of peaks of ketotifen, olopatadine, cetirizine, and ibudilast at different retention times was at 26.6, 26.9, 27.8, and 30.2 min; recoveries of these drugs from (biological) plasma samples were optimized by the current methodology without an additional internal standard (IS). The recoveries of ketotifen, olopatadine, cetirizine, and ibudilast were 51.7–95.5% from the plasma samples, and these results were found to be satisfactory. In these experiments, ibudilast 500 ng/mL plasma was taken as the IS to determine ketotifen, olopatadine, and cetirizine. Furthermore, ketotifen 50 mg/mL was used as the IS for the determination of ibudilast. The linearity for the above-cited drugs was the set range from 1–100 mg/mL, and the detection limit was fixed to 0.5 mg/mL for plasma [59].

7.2.2. Chiral

Nowadays, due to continuous development in analytical techniques, liquid chromatography has become the first choice for chiral separation. The main reason is its large number of applications, such as simple, selective, efficient, and reproducible results. The vast availability of a range of chiral stationary phases (CSPs) further boosted the good reputation of chiral HPLC methods in the area of enantiomeric separation of drugs and pharmaceuticals. Different CSPs are available on the market based on different chiral selectors, i.e., polysaccharides, cyclodextrins, antibiotics, proteins, macrocyclic glycopeptides, ligand exchangers, crown ethers, Pirkle's types, etc.) [60–62]. Comparative to all the above chiral selectors, polysaccharide CSPs are showing tremendous remarkable results due to their selective, sensitive, and reproducible performances. A fast enantioselective LC-ESI-MS method for assurance of levocetirizine and pseudoephedrine in dog plasma in presence of dextrocetirizine was developed by Ryu and Yoo [63]. The chromatographic separation was performed with an Ultron ES-OVM chiral column using ammonium acetate and acetonitrile (9:1, v/v) as mobile phase. The calibration curves were observed as linear over the concentration range from 1–200 and 5–1000 mg/mL for levocetirizine and pseudoephedrine. This method can effectively opt to carry out pharmacokinetic study after oral administration of the drugs such as pseudoephedrine (12 mg/kg), cetirizine (0.5 mg/kg), and levocetirizine (0.25 mg/kg) in the dog plasma. The LLOQ for levocetirizine is 5.9–15.0% and 7.7–17.9% for pseudoephedrine. Rustichelli et al. [64] introduced a new HPLC method for stereoselective chromatographic separations of terfenadine followed by its active metabolite fexofenadine using the Chiralcel column in the normal phase. Isopropyl alcohol and n-hexane 5:95, v/v containing 0.01% diethylamine were used as the mobile phase with a 0.4 mL/min flow rate and UV detection at 225 nm. Recently, our group, Ali et al. [65], developed enantiomeric separation of drugs such as pheniramine, oxybutynin, cetirizine, and brinzolamide enantiomeric drugs on amylose-based columns. The mobile phase used consisted of n-hexane-2-propanol-DEA (85:15:0.1, v/v) and n-hexane-2-propanol-DEA (70:30:0.2, v/v) for pheniramine and cetirizine on AmyCoat (150 mm × 4.6 mm) and Chiralpak AD (250 mm × 4.6 mm id), separately and respectively. The flow rate was 0.5 mL/min, and detection was achieved at 220 and 225 nm for pheniramine and cetirizine. The retention factors for both drugs were 3.25 and 4.34, and 6.10 and 6.60, respectively. The separation and resolution factors for both drugs were 1.33 and 1.09, and 1.09 and 1.63, respectively. The LOD for pheniramine and

cetirizine ranged from 1.0–2.5 ng/mL; LOQ was 5.0–10.0 ng/mL, respectively. The enantiomers -(R) and -(S) of these drugs are well resolved by using Amylose-based columns. The chiral separation of antiallergic drugs is given in (Table 2).

Table 2. The chiral separation of antiallergic drugs.

S. N.	Drug Name	Mobile Phase	Column	Other Conditions	Ref
1	Levocetirizine and pseudoephedrine	10 mM aqueous NH_4OAc and acetonitrile (9:1, *v*/*v*)	Ultron ES-OVM chiral column	1 mL/min; LOQ for levocetirizine 5.9–15.0% and 7.7–17.9% for pseudoephedrine	[61]
2	Terfenadine and fexofenadine	Isopropyl alcohol and n-hexane (5:95, *v*/*v* containing 0.01% diethylamine)	Chiralcel (250 mm × 4.6 mm, 5 µm)	0.4 mL/min at 225 nm	[62]
3	Pheniramine and cetirizine	2-PrOH-n-Hexane-DEA (15:85:0.1, *v*/*v*), and 2-PrOH-n-hexane-DEA (30:70:0.2, *v*/*v*)	AmyCoat (150 mm × 4 6 mm, 5 µm) and Chiralpak AD (250 × 4.6 mm, 5 µm)	0.5 mL/min at 220 and 225 nm; LOD ranged from 1.0–2.5 ng/mL; LOQ were 5.0–10.0 ng/mL	[63]
4	Terfenadine and active metabolite fexofenadine	IPA and n-Hexane (5:95, *v*/*v*) containing 0.01% DEA	Chiralcel column	0.4 mL/min at 225 nm	[64]
5	pheniramine, oxybutynin, cetirizine, and brinzolamide	n-hexane-2-propanol-DEA (85:15:0.1, *v*/*v*) and n-hexane-2-propanol-DEA (70:30:0.2, *v*/*v*) a	AmyCoat (150 mm × 4.6 mm) Chiralpak AD (250 mm × 4.6 mm id)	0.5 mL/min at 220 and 225 nm	[65]
6	Pseudoephedrine Sulfate	n-Hexane- Isopropyl alcohol- ethanol-DEA (980:10:10:1, *v*/*v*)	Chiralpak AD-H column (250 mm × 4.6 mm, 5 µm)	2.0 mL/min at 254 nm; LOD and LOQ were 0.04% and 0.16%	[66]
7	Doxylamine	Mobile phase consists of n-hexane-IAP-DEA (98:2:0.025, *v*/*v*)	Chiralpak AD-H column (250 mm × 4.6 mm, 5 µm)	1.0 mL/min at 262 nm	[67]
8	Flezelastine	Mixture of n-Hexane-IPA-DEA (88:12:0.5, *v*/*v*)	Chiralpak AD column (250 mm x 4.6 mm, 10 µm)	1.0 mL/min at 292 nm	[68]
9	Cetirizine, doxylamine and hydroxyzine	n-Hexane-ethanol-DEA (90:10:0.1, *v*/*v*); n-hexane-isopropanol-DEA (60:40:0.1, *v*/*v*); and n-hexane-isopropanol-DEA (90:10:0.1 *v*/*v*)	Chiralpak IC column	0.8 mL/min at 227 and 262 nm	[69]

Gokulakrishnanm and Balamurugan [66] achieved the best separation of both enantiomers of Pseudoephedrine Sulfate (UV detection at 254 nm, with a flow rate of 2.0 mL/min) by using an enantiomeric HPLC method on a Chiralpak AD-H column. LOD and LOQ were 0.04% and 0.16%, respectively. This method can be used for the determination of enantiomeric purity of bulk drug pseudoephedrine sulfate. Ozkırımlı et al. [67] developed and validated an HPLC-DAD method for the separation of doxylamine enantiomers using Chiralpak AD-H column, and the mobile phase consisted of n-hexane-2-propanol-diethylamine (98:2:0.025, *v*/*v*). Doxylamine was extracted with dichloromethane and hexane from plasma samples 1:2, *v*/*v*, and 87% yield. Paris et al. [68] developed an achiral HPLC and two chiral HPLC methods coupled with capillary zone electrophoresis (CZE) to examine in vitro metabolism of racemic flezelastine drug. A Chiralpak AD column was used for the chiral separation, which allowed for the separation of the N-dephenethyl metabolite. Zhou et al. [69] developed a stereoselective method for the enantioseparation of six antihistamines, namely doxylamine, carbinoxamine, dioxopromethazine, cetirizine, oxomemazine, and hydroxyzine. The chiral separation of cetirizine, doxylamine, and hydroxyzine was optimized using the Chiralpak IC column. The mobile phases used for doxylamine, cetirizine, and hydroxyzine were n-Hexane-EtOH-DEA (90:10:0.1, *v*/*v*); n-Hexane-IPA-DEA (60:40:0.1, *v*/*v*); and n-Hexane-IPA-DEA (90:10:0.1, *v*/*v*), separately and respectively. The flow rate was set at 0.8 mL/min. Yanru et al. [70] determined pheniramine enantiomers in rat plasma using the enantioselective HPLC-MS-MS method. The Chiralpak AGP column and mobile phase consisted of a 10 mM ammonium acetate buffer (pH 4.5) used for this study. The detection optimized by mass spectrometry and the transitions of m/z 240.97 → 195.84 and 275.21 → 229.85 were monitored for pheniramine and chlorpheniramine, separately. The lower limit of quantification pheniramine enantiomer was 1.0 ng/mL and the concentration range was 1–400 ng/mL. Chromatographic factors such as column temperature, mobile phase additive, flow rate, retention time, and resolution effects were also studied.

8. Chiral Recognition Mechanism

Chiral separation can be achieved using various chiral selectors such as polysaccharides, cyclodextrins, antibiotics, proteins, macrocyclic glycopeptides, crown ethers, ligand exchangers, Pirkle's types, etc., but among them, polysaccharide-centered chiral selectors are the top choice of analysts and scientists. Chiral columns such as Chiralpak AD and AmyCoat are both composed of amylose, whose structure is more helical in comparison to cellulose, etc. [65]. The best separation using such a chiral column is achieved because of the existence of chiral grooves inside. In addition to this, the spectroscopic fitting of enantiomers of chiral drugs occurs at different retention intervals. The exact fittings of the drug enantiomers occur because of the interaction of various forces such as hydrogen bonding, π-π interactions, steric effects, van der Waal's forces, etc. (Figure 4). It is the mobile phase that tends to carry out the drug enantiomers together. Therefore, after the struggle between mobile and stationary phases, the weak bonding enantiomer eluted first, as compared to the strongly bonding enantiomer.

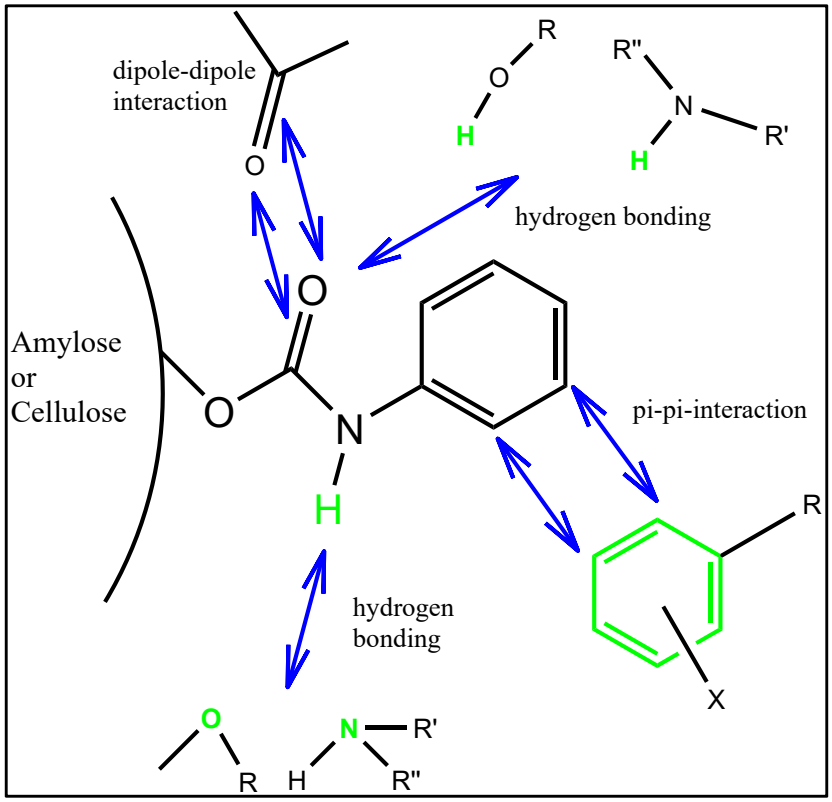


Figure 4. Chiral recognition mechanism.

9. Future Perspectives

The future of antiallergic drugs is an important factor from a human health perspective. It is crucial to study the pharmacokinetics and thermodynamics of racemic drugs. The simple and chiral profile of antiallergic drugs should be available before prescribing medication. Therefore, it is the demand of people that has compelled scientists to develop some novel chiral HPLC methods for antiallergies. At present, globally, people are excited to know the exact phenomenon of stereoselective bindings of the enantiomers, as well as its impact on humans. In light of the above facts, racemic antiallergics should be replaced by a single enantiomer that is more active than its counterpart, such as levocetirizine, which is an active molecule of racemic cetirizine. Additionally, there are several chiral molecules, as new drug entities are being monitored in phase I and IV clinical trials. Therefore, the current scenario demands the development of chiral-HPLC methodologies for antiallergies.

10. Conclusions

Some papers are available for the determination of chiral antiallergic drugs by HPLC. The separation of antiallergic drugs is well documented, but chiral separation is still a big area to focus. More research work has been required in this area for human welfare. Single-enantiomer (homochiral) drug products should be the main aim of pharmaceutical industries. A homochiral drug (single-enantiomer) is safe and should be prescribed and used. Therefore, there is a need for the development of the chiral-HPLC method for the examination of antiallergic drugs, as it tends to cause racemization in the body. Briefly, all the researchers, scientists, and academicians should focus on the above area and start working together to avail safe, effective, and economic medication to people globally.

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