Baghdad Science Journal

Volume 22 | Issue 8 Article 4

8-15-2025

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How to Cite this Article

Rasheed, Ashraf Saad and Mohammed, Mustafa J. (2025) "Evaluating the Selectivity of Novel ZIC-HILIC Columns and an Application for Determining Antihistaminic Drugs in Pharmaceutical Preparations," *Baghdad Science Journal*: Vol. 22: Iss. 8, Article 4.
DOI: https://doi.org/10.21123/2411-7986.5014

BAGHDAD SCIENCE JOURNAL 2025;22(8):2517–2526

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RESEARCH ARTICLE

Evaluating the Selectivity of Novel ZIC-HILIC Columns and an Application for Determining Antihistaminic Drugs in Pharmaceutical Preparations

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ABSTRACT

The hydrophilic interaction liquid chromatography (HILIC) conjugated with UV spectrometry was employed to the determination of two antihistaminic drugs (Acrivastine and fexofenadine) in pharmaceutical formulations using two lab-made zwitterionic HILIC stationary phases (ZIC-2 and ZIC-5). The study aimed to investigate the impact of separation parameters including acetonitrile (ACN) content, pH of the eluent, and acetate buffer concentration on the retention behavior of Acrivastine and fexofenadine. A mixture of 3.0 mM acetate buffer (pH 4.75) and ACN (30:70) was used as eluent, with a flow rate of 0.6 mL/min. The detection wavelength was controlled at 267 nm. The linearity of Acrivastine and fexofenadine is 0.09–13.5 and 0.09–9 μg/mL on the ZIC-2 and ZIC-5 columns, respectively. The proposed methods exhibited a high level of precision (RSD $\leq$ 0.82), these methods determined the LOD for Acrivastine in ZIC-2 and ZIC-5 to be (0.030–0.008 μg/ml) and LOQ (0.090–0.024 μg/ml), respectively. LOD values for fexofenadine were determined to be (0.050–0.020 μg/ml) for ZIC2 and ZIC5, respectively. Additionally, LOQ values were found to be (0.1515–0.060 μg/ml) for ZIC2 and ZIC5, respectively.

Keywords: Acrivastine, Antihistaminic drugs, Fexofenadine, Pharmaceutical Preparations, ZIC-HILIC

Introduction

The number of documented cases of allergic disorders has experienced a significant increase in the last 25 years.[1] The increased incidence of allergic diseases can be attributed to a combination of factors, including higher levels of air pollutants, the presence of natural environmental allergens, exposure to xenobiotics, and the influence of stress.[2] Antihistamines are employed in treating and controlling allergic conditions, providing effective relief for the itching symptoms arising from the release of histamine.[3] Although their primary site of therapeutic action is in the periphery, antihistamines can cross the blood-brain barrier. Once in the brain, antihistamines function by blocking histamine H1-receptors.[4] Acrivastine, Fig. 1, is a second-generation antihistamine known for its non-sedating properties, it is derived from the first-generation compound triprolidine.[5] Acrivastine (ACRV) significantly inhibits histamine-induced partial telangiectasia and increased permeability (edema).[6] Fexofenadine, Fig. 1, functioning as the active acid metabolite of terfenadine,[7] represents a non-sedating H1 antihistaminic drug.[8] Fexofenadine (FEXO) is essential in treating seasonal allergic rhinitis and chronic urticarial. Fexofenadine has been demonstrated to be helpful in the treatment of asthma.[9]

Received 21 November 2023; revised 26 April 2024; accepted 28 April 2024.
Available online 15 August 2025

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https://doi.org/10.21123/2411-7986.5014

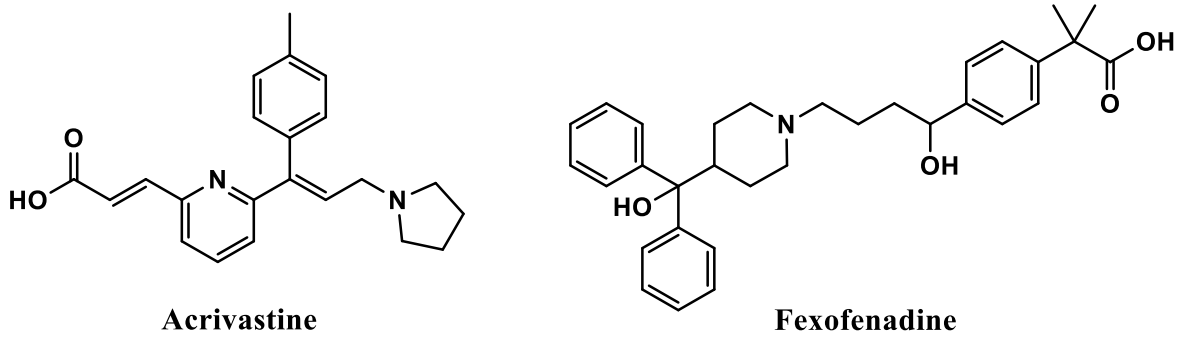

Fig. 1. Chemical structure of acrivastine and fexofenadine.

High-performance liquid chromatography (HPLC) is usually used to analyze drugs in pharmaceutical formulations[10–12] environmental samples,[13–15] and biological plasma.[16–18] Numerous HPLC methods have been documented for quantitatively determining acrivastine and fexofenadine in pharmaceutical preparations and plasma samples.[19–21] However, some of these methods exhibit prolonged analysis times and limited sensitivity. Based on literature from the past few years, it was observed that there is a notable absence of studies focused on analysing acrivastine and fexofenadine utilizing hydrophilic interaction chromatography (HILIC). In 1990, Alpert proposed the concept of HILIC,[22] and it has since gained increasing attention. HILIC has proven to be a highly effective method for separating polar compounds.[23] The stationary phase employed in HILIC is characterized by its polarity.[24] It consists of a silica or polymer support to which various functional groups, such as amino, amide, cyano, diol, and zwitterionic (ZIC), can be chemically attached.[25–27] HILIC employs a mobile phase consisting of polar solvents, typically a mixture of acetonitrile and water, with a higher proportion of the organic solvent.[28] The primary separation mechanism in HILIC is based on the analyte partitioning between the mobile phase's eluent and a water-enriched layer in the hydrophilic stationary phase.[29,30] Furthermore, the selectivity of the separation can be influenced by various other interactions, such as ion exchange, hydrogen bonding, and dipole-dipole interactions.[31,32] The first objective of this investigation is to offer additional insights into the separation mechanism of a ZIC-HILIC phase and the parameters influencing it. Previous works[33,34] examined the impact of the spacer length between charges on the separation of flavonoids and pharmaceuticals. They observed that as the distance between charges in the ZIC-HILIC column chains increased, the interaction between the analytes and stationary phases also increased. This investigation examines the influence of the chain length between the two charges by employing ZIC-2 and ZIC-5 columns. The investigation of this effect on estimating two antihistaminic drugs has not been previously established in the literature, so this will be a second objective for this study. The third objective of this investigation was to evaluate and apply two antihistaminic drugs, including acrivastine and fexofenadine in pharmaceutical preparations using HILIC coupled with ultraviolet detection, which, until now, have been examined using traditional chromatographic methods.

Materials and methods

Chemicals and reagents

Acrivastine and fexofenadine were obtained from Sigma-Aldrich. The HPLC-grade acetonitrile (ACN), acetic acid, and sodium acetate were provided by Carl Roth (Germany). All experiments utilized ultrapure water with a conductivity of 0.054 μs/cm obtained from (Millipore system-USA). Acrivastine tablets were obtained from Brown and Burk UK Ltd (8 mg, Acrivastine, UK, Sample 1), GSK plc (8 mg, Sermprex, UK, Sample 2), and Allergy Relief Plus Decongestant (8 mg, BENADRYL®, UK, Sample 3), respectively. Fexofenadine tablets were obtained from Sanofi India Ltd (120 mg, Allegra, India, Sample 1), QndQ Derm (120 mg, Fexgear, Indian, Sample 2), and Bosch Pharmaceuticals (60 mg, ALOC, Pakistan, Sample 3), respectively.

Chromatographic conditions

The analysis of selected drugs involved using the Merck-Hitachi HPLC system, which featured a separation center T-6300 along with an L-4200 UV/Vis detector and L6200 pump gradient pump. Data acquisition and analysis were conducted using the N2000 Photographic Workstation software. The chromatographic separation of two antihistaminic drugs

Table 1. Quantitative data of acrivastine and fexofenadine were obtained from the calibration graph.

	Columns			
	ZIC-2	**ZIC-5**	**ZIC-2**	**ZIC-5**
Parameter	**Acrivastine**		**Fexofenadine**	
Concentration range (μg/mL)	0.09–13.5	0.09–13.5	0.09–9	0.09–9
R^2	0.9998	0.9997	0.9997	0.9998
LOD (μg/mL)	0.030	0.008	0.050	0.020
LOQ (μg/ mL)	0.090	0.024	0.1515	0.060

(acrivastine and fexofenadine) was performed using lab-made stationary phases (ZIC-2 and ZIC-5, 100 mm 4.6 mm I.D.), as detailed in reference.[35] The numbers 2 and 5 in ZIC-2 and ZIC-5 indicate a specific number of methylene groups between the charged groups in the sulfobetaine monomers. The mobile phase utilized in this study consisted of a combination of 3.0 mM acetate buffer (pH 4.75) and ACN (30:70), the gradient elution system employed in this study, the analytes were detected at the UV 278 nm, the flow rate was set at 0.75 ml/min, and an injection volume of 10 μl was used.

Method validation

The validation of an analytical method is of significant importance in pharmaceutical analysis. An analyst aims to obtain accurate, precise, and reliable data. Therefore, the method validation process plays a crucial role in method development.[36,37] Currently, validation studies follow the guidelines of the International Council on Harmonization (ICH).[38] These parameters include linearity and range, detection and quantification limits, accuracy, and precision.

Linearity

The method's linearity was examined within the concentration range of 0.09–13.5 μg/mL for ACRV, and 0.09–9 μg/mL for FEXO. The evaluation of method linearity involved the calibration equation, featuring the determination coefficient (R^2) and slope, as detailed in Table 1.

Accuracy

The accuracy of the method developed in this study was assessed through a recovery investigation. Accuracy was tested using the standard addition method at three distinct levels: 50%, 100%, and 150%.[39] The percentage recoveries of ACRV and FEXO in the pharmaceutical preparations form were computed.

Precision

Precision was evaluated within the same day and over consecutive days, denoted as intra-day (repeatability) and inter-day precision (intermediate precision), respectively. Repeatability was evaluated by injecting a standard solution seven times within a single day, and intermediate precision was determined by injecting the same standard solution twice per day for three successive continuous days. The precision of ACRV and FEXO peaks was expressed by calculating the relative standard deviation (%RSD).

Preparation of standard solution

A stock solution of acrivastine and fexofenadine reference substance (100 μg mL^{-1}) was prepared by accurately weighing 10 mg of these drugs and dissolving them in ACN. Working solutions 0.09–13.5 μg mL^{-1} and 0.09–9 μg mL^{-1} for ACRV and FEXO, respectively. Were prepared by diluting the stock solutions with the mobile phase.

Preparation of sample solution

The average weight of seventeen tablets containing acrivastine and fexofenadine was determined by weighing each unit. Subsequently, the tablets were crushed to a fine powder. An appropriate amount of powder, corresponding to 20 mg of acrivastine and fexofenadine from each pharmaceutical preparation, was carefully transferred to a 100 mL volumetric flask. The volume was adjusted by mobile phase, followed by sonication for 10 min. Aliquots of this solution were subsequently diluted to obtain a final concentration of 50 μg mL^{-1}. Before injection, the solutions underwent filtration through a 0.45 μm membrane filter.

Results and discussion

This research establishes an alternative HILIC method for accurately determining acrivastine and fexofenadine in pharmaceutical preparations. Two

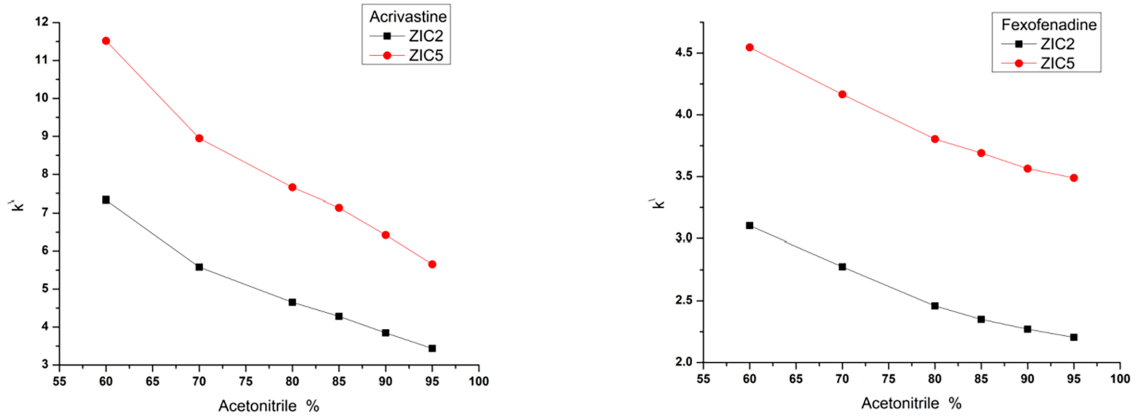

Fig. 2. Impact of ACN content on the retention factor of acrivastine and fexofenadine.

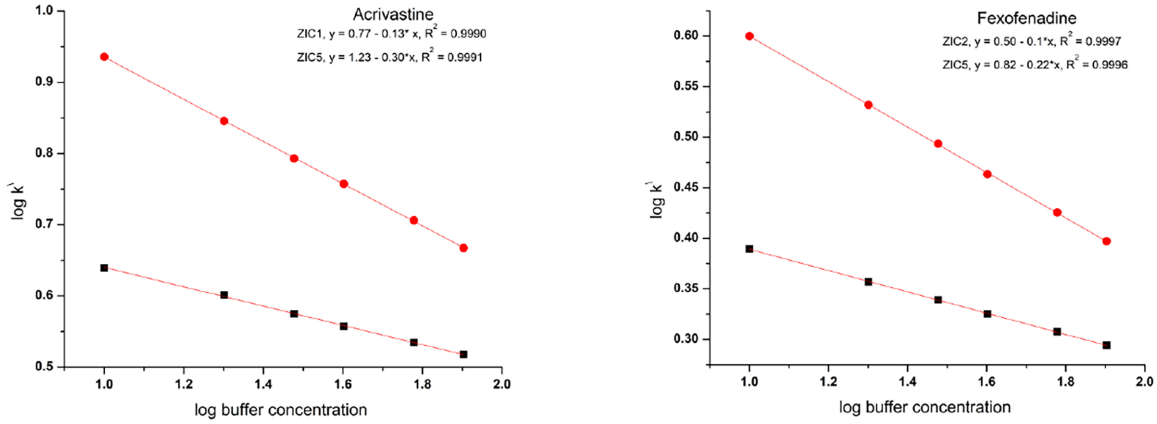

Fig. 3. Impact of eluent pH on the retention factor of acrivastine and fexofenadine.

lab-made columns (ZIC-2 and ZIC-5) were selected for this study with a mobile phase consisting of ACN and an acetate buffer. The investigation explored the effects of varying the mobile phase's organic solvent content, buffer concentration, and pH value. To gain insight into the separation mechanism of the drugs in HILIC, systematic variations of ACN content from 60% to 95% in the mobile phase, as well as in the eluent concentration from 10 to 80 mM and pH from 3 to 5.5.

Influence of ACN content on retention behavior

The composition of the mobile phase plays an essential role in the chromatographic separation. In HILIC separation, the mobile phase typically consists of a mixture of water and ACN, and it is essential to employ a mobile phase with an organic content (>60%) to ensure a significant hydrophilic interaction.[40] In this study, the impact of ACN content on retention was studied by altering the percentage of ACN in the mobile phase while keeping buffer acetate constant at (40 mM, pH 4.75). The retention factor of two antihistaminic models decreased when increasing the ACN percentage from 60% to 95%, as shown in Fig. 2. Acrivastine and fexofenadine demonstrate hydrophobic (RP) behavior, with the ACN eluent proportion rising from 60% to 95%. This behavior can be attributed to the log POW of ACRV and FEXO (1.62 and 2.58), respectively.

Influence of buffer concentration on retention behavior

Salts are commonly added into the mobile phase to regulate electrostatic interactions between analytes and the stationary phase.[41] Salts enhance the retention of analytes in HILIC by increasing the volume of the water layer immobilized on the surface of the stationary phase.[42] The retention behavior was examined using different concentrations of buffer acetate. The concentration of ACN was kept constant at 80%, while the buffer acetate concentration was varied from 10 to 80 mM (pH 4.9). The resulting chromatograms are shown in Fig. 3. The isoelectric points of ACRV and FEXO are 6.25 and 6.79,

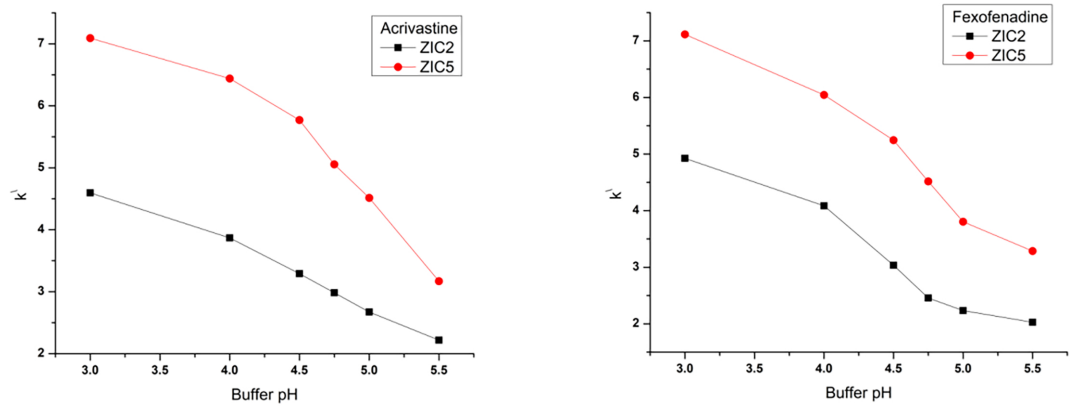

Fig. 4. Impact of eluent concentration on the retention factor of acrivastine and fexofenadine.

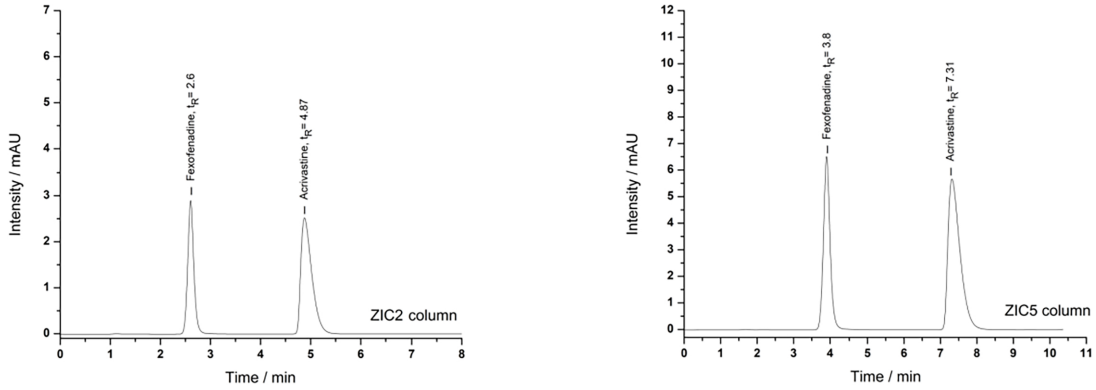

Fig. 5. Chromatograms of the (7 μg.mL^{-1}) acrivastine and fexofenadine by ZIC-2 and ZIC-5 columns.

respectively. As a result, they primarily exist in their cationic form. The interaction with the ZIC-2 and ZIC-5 columns depends on cation exchange for these two antihistaminic drugs, and when to increase buffer concentration more buffer cations become available to compete with both drugs, mainly when they are in their cationic form for exchange site on columns. This increased competition leads to a reduction in retention.

Influence of buffer pH on retention behavior

The selectivity in HILIC is significantly influenced by mobile phase pH.[43] It affects the ionization of analytes and/or functional groups on the stationary phase.[44] This is due to their sensitivity to pH variations, and any changes in ionization consequently affect the interaction between analytes and the stationary phase. It can also impact the thickness of the enriched aqueous layer that remains stagnant on the surface of the HILIC stationary phase.[45] The impact of mobile phase pH value was investigated by altering the pH within the range of 3 to 5.5 using an acetate buffer. In contrast, it maintains a constant ACN concentration of 90% and a buffer concentration of 35 mM. The retention time of ACRV and FEXO decreases when buffer pH increases from 3 to 5.5 Fig. 4. The pKa (7.77 and 9.21) and the isoelectric point (pI) (6.25 and 6.79) values for ACRV and FEXO, respectively. Regarding the pKa and pI values, this behavior can be attributed to the deprotonation of amino groups in two antihistaminic drugs, reducing the interaction between ACRV, FEXO, and the ZIC-HILIC columns.

Optimizing separation of acrivastine and fexofenadine

An optimization strategy was employed to determine the ideal chromatographic separation conditions for acrivastine and fexofenadine. The optimal conditions for separating two models of antihistaminic drugs (acrivastine and fexofenadine) were 30 mM acetate buffer, pH 5, and a mixture of ACN and acetate buffer at (70:30) ratio. Two models of antihistaminic drugs demonstrated the highest retention in the ZIC-5 column compared to the ZIC-2 column, as shown in Fig. 5. The significant difference in retention between the two ZIC columns is due to the presence of

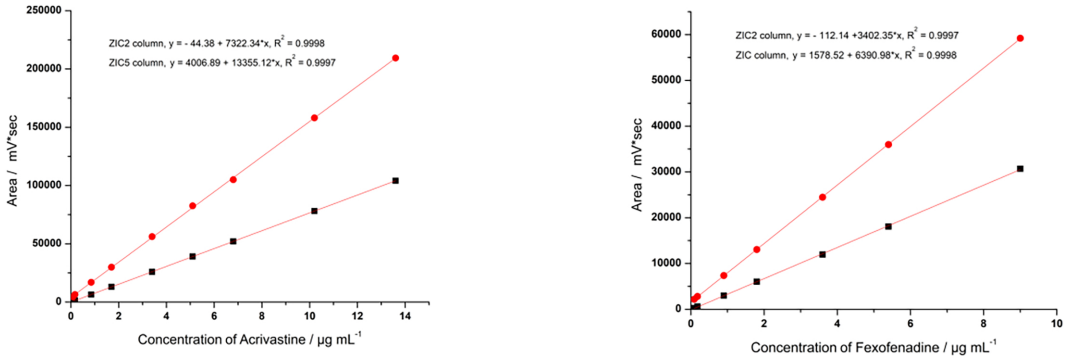

Fig. 6. Calibration curves for acrivastine and fexofenadine using ZIC-2 and ZIC-5 columns.

Table 2. The accuracy and precision of the suggested methods for the quantification of acrivastine and fexofenadine.

Intra-Day Analysis (n = 6)				Inter-to-Day Analysis (n = 6)		
			ZIC-2 Column			
ACRV Taken (μg/mL)	**ACRV Observed (μg/mL)**	**Recovery %**	**RSD (%)**	**ACRV Observed (μg/mL)**	**Recovery (%)**	**RSD (%)**
2.00	1.97	98.50	0.33	1.97	98.50	0.33
3.00	2.98	99.33	0.21	2.97	99.00	0.20
FEXO Taken (μg/mL)	**FEXO Observed (μg/mL)**	**Recovery %**	**RSD (%)**	**FEXO Observed (μg/mL)**	**Recovery %))**	**RSD (%)**
4.00	4.02	100.50	0.52	4.00	100.00	0.48
5.00	4.95	99.00	0.33	4.95	99.00	0.35
			ZIC-5 Column			
ACRV Taken (μg/mL)	**ACRV Observed (μg/mL)**	**Recovery %**	**RSD (%)**	**ACRV Observed (μg/mL)**	**Recovery (%)**	**RSD (%)**
2.00	2.02	101.00	0.29	2.00	100.00	0.32
3.00	2.96	98.66	0.22	2.96	98.66	0.25
FEXO Taken (μg/mL)	**FEXO Observed (μg/mL)**	**Recovery %**	**RSD (%)**	**FEXO Observed (μg/mL)**	**Recovery %**	**RSD (%)**
4.00	3.99	99.75	0.26	3.98	99.50	0.25
5.00	5.02	100.40	0.15	5.05	101.00	0.21

methylene groups located between charged groups.[46] The highest retention observed in the ZIC-5 column for the ACRV and FEXO can be attributed to the geometric arrangement of the sulfobetaine groups. These interactions arise from the varying flexibility of the sulfobetaine chains, enabling the formation of intra- and intermolecular ion pairs. As a result, spacers between the charges on the column are expected to impact the retention of pharmaceuticals.

Method validation

The calibration graphs for acrivastine and fexofenadine were created by plotting their concentrations against the corresponding peak areas. The range of concentrations for the two ZIC stationary phases is demonstrated in Fig. 6. The ZIC-HILIC mode obtains statistical information Table 2 regarding the calibration curves of acrivastine and fexofenadine. Table 3 summarizes %RSD and %recovery values obtained for two ZIC stationary phases on the same and different days. The calculation of the LOD and LOQ was performed in compliance with the ICH.[38] The low and high values for standard deviation and recovery refer to the accuracy of the proposed methods. The standard deviation demonstrates a relatively low, and the recovery value is high, suggesting a high level of accuracy in these methods.

Determination of ACRV and FEXO in pharmaceutical preparations

The suggested method in this study was applied to determine ACRV and FEXO in three pharmaceutical preparations. The findings are given in Table 4. The results were compared with those obtained from the

Table 3. Implementation of the suggested methods for the analysis of acrivastine and fexofenadine in pharmaceutical formulations.

Brand name	Started conc. (μg/mL)	Obtain (μg/mL)	%Rec.	%RSD n = 6
		ZIC-2 Column		
Acrivastine				
Semprex	3.00	2.98	99.33	0.21
Acrivastine	3.00	2.95	98.33	0.33
BENADRYL	3.00	3.02	100.66	0.68
Fexofenadine				
Allegra	4.00	3.95	98.75	0.82
Fexgear	4.00	4.02	100.50	0.74
ALOC.	4.00	3.98	99.50	0.32
		ZIC-5 Column		
Acrivastine				
Semprex	3.00	2.97	99.00	0.25
Acrivastine	3.00	2.94	98.00	0.56
BENADRYL	3.00	3.03	101.00	0.60
Fexofenadine				
Allegra	4.00	3.95	98.75	0.78
Fexgear	4.00	4.00	100.00	0.68
ALOC.	4.00	3.97	99.25	0.39

Table 4. The t and F tests were used to compare the suggested ZIC-HILIC technique to the standard method for acrivastine and fexofenadine calculation.

Applications	ZIC-2 method	ZIC-5 method	USP[39] method	t-Test (theor.)	F-Test (theor.)
Acrivastine					
Semprex	99.33	99.00	99.54	0.9891* (2.7764)	1.1445* (19.000)
Acrivastine	98.33	98.00	98.32	0.9172** (2.7764)	1.9546** (19.000)
BENADRYL	100.66	101.00	100.50		
Fexofenadine					
Allegra	98.75	98.75	99.00	0.9571* (2.7764)	3.0722* (19.000)
Fexgear	100.50	100.00	99.98	0.6650** (2.7764)	1.5776** (19.000)
ALOC.	99.50	99.25	99.67		

Note: Tabulated values t = 2.7764 and F = 19.000.

standard method[47] using the 95% confidence t-test and the F-test. The calculated t and F values did not exceed the theoretical values, suggesting no significant difference in the accuracy and precision between the two methodologies employed to determine ACRV and FEXO in pharmaceutical formulations.

Conclusion

The present research describes a simple, rapid, and selective chromatographic technique, which has been successfully developed and validated for determining ACRV and FEXO in pharmaceutical preparations. The chromatographic retention on the zwitterionic stationary phases exhibited characteristic hydrophobic interaction. In the HILIC mode, two antihistaminic drugs were separated effectively using the two lab-made ZIC-HILIC columns. The separation mechanism was notably influenced by hydrophobicity and electrostatic interactions. The selected drugs exhibited significantly higher retention on the ZIC-5 column than the ZIC-2 column. This difference is likely due to the longer spacer chain length between the internal and external quaternary amine and sulfonate groups in ZIC-5, resulting in enhanced retention. The ZIC-5 column exhibited higher sensitivity with lower LOD and LOQ than the ZIC-2 column for the selected drugs.

Acknowledgment

The authors thank the University of Baghdad, College of Science, Department of Chemistry for their endless support and for completing this research.

Authors' declaration

- Conflicts of Interest: None.
- We hereby confirm that all the figures and tables in the manuscript are ours. Furthermore, any figures and images, that are not ours, have been included with the necessary permission for republication, which is attached to the manuscript.
- We do not used laboratory animal in our research.

- Authors sign an ethical consideration's approval.
- Ethical Clearance: The project was approved by College of Science, University of Baghdad. And by education college AL-Iraqi University.

Authors' contribution statement

Both authors contributed to the design and implementation of the research, the analysis of the results, and the writing of the manuscript.

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تقييم أنتقائية اعمدة زويترأيون جديدة وتطبيقها في تقدير الادوية المضادة للهستامين في المستحضرات الصيدلانية

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المستخلص

تم أستخدام تقنية الكروموتوغرافيا السائل ذو التداخل المحب للماء المقترنة مع كاشف الاشعه الفوق البنفسجية في تقدير دواءين من الادوية المضادة للهستامين (أكريفاستين وفيكسوفينادين) في المستحضرات الصيدلانية باستخدام أطوار ثابتة من نوع الزويترايون مصنعة مختبرياً (ZIC-2,ZIC-5).هذه الدراسة تهدف الى التحقق من تأثير عوامل الفصل مثل نسبة الاسيتونيتريل ,الاس الهيدروجيني للطور المتحرك وتركيز وقاء الاسيتات على سلوك الاحتفاظ للاكرفاستين والفيكسوفينادين.تم أستخدام مزيج من وقاء اسيتات (3 مل مولاري,pH=4.75) والاسيتونيتريل (30:70 حجم/حجم) كطور متحرك وبمعدل جريان 0.6 مل/دقيقة. واستخدم طول موجة مكشاف 267 نانومتر.الاستجابة الخطية لأدوية ألاكريفاستين والفيكسوفينادين كانت 13.5-0.09 , 9-0.09 مكغ/مل لاعمدة ZIC-2,ZIC-5 , على التوالي.أظهرت الطريقة المقترحه مستوى عالي من المضبوطية(RSD ≥ 0.82) و تحددت حدود الكشف للأكريفاستين في الأعمدة الثابتة ZIC-2 و ZIC-5 بين (0.030 - 0.008 مكغ/مل)، وكانت حدود الكمية تتراوح بين (0.090 - 0.024 مكغ/مل) على التوالي. تم تحديد قيم حدود الكشف للفيكسوفينادين (0.050 - 0.020 مكغ/مل) لكل من الأعمدة ZIC-2 و ZIC-5 على التوالي. بالإضافة إلى ذلك قيم حدود الكمية كانت تتراوح بين (0.1515 - 0.060 مكغ/مل) لكل من الأعمدة ZIC-2 و ZIC-5 على التوالي.

الكلمات المفتاحية: أكريفاستين، الادوية المضادة للهستامين، فيكسوفينادين، المستحضرات الصيدلانية وزويترأيون-كروموتوغرافيا السائل ذو التداخل المحب للماء.