A COMPREHENSIVE ASSESSMENT OF ANALYTICAL TECHNIQUES FOR QUANTIFYING THE ANTIHISTAMINIC DRUG KETOTIFEN FUMARATE

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Abstract

The Allergic conjunctivitis is conjunctiva inflammation induced by allergens. Seasonal fluctuations induce tear production, redness, swelling, and itching. All of them constitute systemic allergic reactions. Up to 40% of the population may have allergic conjunctivitis, yet very few seek medical attention. Antihistamines or medicines that decrease mast cellular proliferation may relieve allergic conjunctivitis itching. This practice will help you manage allergic conjunctivitis. This demonstrates the team's commitment. Antihistamines, mast cell stabilizers, NSAIDs, and corticosteroids treat allergic conjunctivitis. This newer version of H1-antihistamines doesn't induce tolerance. Mast cell stabilizers may reduce eye sensitivities by restricting mast cells from emitting histamine. Molecularly generating ketotifen from benzocycloheptathiophene.

Keywords: "analysis" "antihistaminic." "ketotifen fumarate"

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1. Introduction

The molecular formula of ketotifen is represented as 4,9-dihydro-10H-benzo[4,5]. Its complete name of just this chemical in the chem realm is cyclohepta[1,2-b] thiophen-10-one. A gemstone that's also highlighted by its icy white and beige tones. It has been observed with ketotifen is soluble in DMSO, DMF, and ethanol when it is contained at a concentration of 25 mg/ml (fumarate). The substance fumarate doesn't really dissociate in water and has a hard time working in other liquids too though.

Approaches such as emission spectra, chromatography, critical assessment, capillary electrophoresis, and chemometrically assisted methods can be used to calculate the amount of ketones existing in dosage forms and biological fluids, etcetera.Figure 2 is a summary of the analytical methods used to figure out KETO levels. Figure 3 shows how the number of ways to test for KETO changed from 1978 to 2022.(Sokol et al., 2013)

This objective seeks to simplify, contextualise, and discuss the many analytical procedures that can be used to measure KETO in a variety of compositions and biological matrices. This will fulfil assignment criteria (Figure 4). Volumetric analysis, optical methods, chromatographic, electro analysis tools, linear electrochemical techniques, bioanalytical methods, and chemometric analysis were frequent studies. Capillary electrophoretic and electro analytical tests are many other.

2. Volumetric Approaches

2.1 Evaluation via Titrimetry

In the field of science, titration is implemented as a quantitative method of analysis. How much of a renowned chemical must be introduced to a solution whose concentration has been established in order to validate the reaction The method was evaluated in light of the ICH recommendations

3. Integrating Optical Approaches

3.1Spectroscopic techniques in the UV/visible area

A spectrophotometer is an external device of light that somehow a sample emanates at a multitude of wavelengths. Measurement tool that is extremely exact. Spectrophotometry is a testing tool that is designed when other, more complex and costlier methods, like GLC or HPLC, are inaccessible. These speedy, minimal, and simple methods come with lots of pros.

Spectrophotometric methods can be used on their own or in conjunction with other drugs in order to calculate the value of ketones. It was reported by Salem, Rofaida A, and others that the linearity of the material produced when alkali and formic acid are coupled is 10-1000 at 472 nm.

Table 1 Spectrophotometry

METHODS	MATRICES	SOLVENT/ REAGENT	LAMBDA MAX(nm)	LINEARITY /RANGE	LOD	LOQ	%RSD	CORRELATION COEFFICENT	REF
flurimetry	tablets	NMNCL with alkali ,formicacid	472	10-1000	N/A	N/A	N/A	N/A	(Journal & Paper, 2013)
UV	tablets		409	0.2-12	N/A	N/A	N/A	N/A	
UV	tablets		451	0.08-10	N/A	N/A	N/A	N/A	
UV	bulk/tablet	cerium (4)sulfate	298	0.1-50	1.136	N/A	<0.8 %	0.9975	(Turkey & Ibraheem, 2016)
Chemiluminescence	bulk	tris(1,10 phenanthroline)ruthenium(II)-Ce(IV) in sulfuric medium	N/A	0.34-34.00	0.09	N/A	4.60 %	N/A	(Mokhtari et al., 2015)

UV	bulk/tablet/capsule	bremocresol purple(5,5dibromo-o-cresolsulfophthalein	399	five - 15	N/A	N/A	1.06 - 1.56 %	0.9998	(Zagorodniy et al., 2015)
UV	bulk	methanol	298	10-100ng/ml	4ng/ml	7ng/ml	N/A	0.9997	(Muralidharan et al., 2012)
UV	bulk	methyl orange	N/A	2 TO 32	10 to 100	N/A	<2 %	0.9998	(Bolotov et al., 2011)
electrochemiluminescenc	bulk	glassy carbon electrode with modified pt/multiwalled C nanotube	N/A	1.0 × 10-7 to 1.0 × 10-4 mol/L	2.4 × 10-9 mol/L	N/A	2.10 %	0.9969	(Li, Liyong; Gao, Wenyan; Hu, Dachun; Cai, Zhuo; Li, Yanqing Li, Liyong; Gao, Wenyan; Hu, Dachun; Cai, Zhuo; Li, 2010)
UV	bulk	bromocresol green buffer pH3 in choloroform	423	5.15-61.91	N/A	N/A	<2.31 %	0.9995	(Amanlou et al., 2007)
Chemiluminescence	bulk	potassium hexacyanoferrate3,calcein	N/A	f 6.0×10-9 to 2.0×10-7 g mL-1	3×10-9 g mL-1	N/A	1.80 %	n/A	(Fei & Jiuru, 2007)
Chemiluminescence	bulk	luminol with ferricyanide in NaOH medium	N/A	t 1.0 x 10-8-1.0 x 10-6 g/mL	5.7 x 10-9 g/mL	N/A	2.60 %	N/A	(By He, Shuhua; Tian, Kaijiang; Zhang, Shuqiong; Yu, 2005)

3.2 Methods that rely on spectrofluorometric analysis

Because to its accuracy, low cost of equipment, and widespread accessibility in the overwhelming bulk of quality control laboratories, it can often be ranked one of the most valuable substantive processes. This is because acquiring this perspective is one of the most fruitful methods to taking. In order to isolate KETO and to quantify its presence in a mixture with other treatments, spectrofluorometric techniques have been widely reported and demonstrated. Find the methods you're seeking for here.

4. Chromatographic protocols

4.1 Optimal Liquid Chromatography

It is the most extensively used chromatographic separation technique medication compounds. LC is an effective strategy and for its sensitivity, persistence, and efficiency.

Improving and calibrating a HPLC method for the analysis of ketotifen fumarate in a pharmaceutical formulation were published by semreen, m. H. Et al. The hypersil c18 column is employed for the separation process. Keto is the research subject for multiple medications in other studies. Salbutamol seems to have a linearity range of 10-60 g/ml, whereas keto seems to have a range of 5-30 g/ml.

ANALYTE	MATRIX	METHOD	STATIONERY PHASE	MOBILE PHASE	FLOW RATE	DETECTION	RETENTION TIME	LINEARITY	LOD	LOQ	RSD	REF
KETO	N/A	TLC	Sorbfil 2x2 cm plates	concd. sulfuric acid, iodine vapors, Marqui reagent, Dragendorff reagent, cobalt thiocyanate, 2,4-dinitrophenylhydrazine, diazotated sulfanilic acid)	N/A	254 nm	N/A	N/A	N/A	N/A	N/A	(By Bolotov, V. V.; Akhmedov, E. Yu.; Miroshnichenko, 2011)
KETO	pharmaceutical prepns	ION EXCHANGE CHROMATOGRAPHY	ketotifen tetraphenylborate (Keto-TPB)	sodium tetraphenylborate (NaTPB) Na[C24H20B], dibutyl phthalate (DBP), dioctyl phthalate(DOP), tricresyl phosphate (TCP), ethylhexyl adipate (EHA), poly vinyl chloride (PVC) of high relative molecular weight and tetrahydrofuran (THF)	N/A	N/A	N/A	5.6 × 10-6 to 1.0 × 10-2	2.37 × 10-6		0.73%	(Khater et al., 2009)

Table 2 Chromatography Single Entity

Table 3 Chromatography Hplc Single Component

COLUMN	MOBILE PHASE	WAVELENGTH	FLOW RATE	CT	LINEARITY	LOD	LOQ	RSD	REF
YILITE Hypersil ODS2 C18	0.05 mol·L-1 potassium dihydrogen phosphate soln. 1% triethylamine and 0.005 mol·L-1 sodium heptanesulfonate	264	1.0 mL·min-1	30°C	N/A	N/A	N/A	N/A	(By He, Wen-bin; He, Zuo-min; Pan, Zhi-wen; Xu, 2015)
Thermo C18	methanol:10 mM ammonium acetate (30:70 %vol./vol. pH: 3.5	298	1mL/min	N/A	10-50mg/ml	1.0 ng/ml	5.0 ng/ml	N/A	(Selvadurai et al., 2012)
Agilent Eclipse SB C18 column	methanol-0.1% H3PO4 soln. (50:50)	301	1.0 mL/min	ambient	0.02026-1.0130 µg	N/A	N/A	1.56%	(Chen, Jiangtao; Liao, 2011)
C18 column	0.75% phosphoric acid-methanol	254	N/A	N/A	0.6-6 µg	N/A	N/A	< 1.2%	(Liu, Zhijie; Li, Donghui; Rao, Jinhua; Zhang, Jing; Feng, 2011)
Hypersil ODS C18 column	water-methanol-triethylamine (375 : 625 : 0.35)	300	N/A	N/A	0.01-0.6 mg/mL	N/A	N/A	1%	(Li, Miao; Hu, Bing; Shan, 2005)

C8 column	methanol, triethylamine phosphate buffer and THF (43:55:2, vol./vol./v)	297	1.2 mL/ min	N/A	0.73–145.43 µg/mL	N/A	0.60 µg/mL	0.28 %	(Elsayed, 2006)
Hypersil C18 column	potassium dihydrogen phosphate in water, and acetonitrile (70: 30, v/v)	298	1.5 ml/ min	N/A	0.6023 to 1.017 mg/ml	N/A	N/A	0.55 %	(Semreen, 2005)
µBondapak C18	phosphate buffer :methanol: acetonitrile:trimethylamine (29.8:45:25:0.2)	299	1 mL min -1	N/A	1.0 to 25 gg m L - 1	4 to 1	1 pg m L - 1	N/A	(Nnane et al., 1998)

Table 4 Hplc Combained

ANALYTE	**COLUMN**	**MOBILE PHASE**	**DETECTION**	**FLOW RATE**	**COLUMN TEMPERATURE**	**LINEARITY**	**LOD**	**LOQ**	**RSD**	**CORRELATION COEFFICIENT**	**REF**
KETO&SAL	250*4.6 mm C18 (Hypersil BDS)	pH 3.5 (0.1% triethylamine): Acetonitrile (60:40)	N/A	1.0 mL per min	25° C	5-15 µg/mL for KETO and 10-30 µg/mL for SAL	N/A	N/A	N/A	KETO 0.9988 and SAL 0.9989	(Kashyap & Srinivasa, 2013)
KETO,THE	N/A	Phosphate Buffer: Methanol (pH-3.0) (60:40 %V/V)	295 nm	1.0 ml/ min.	N/A	0.25-0.75 µg/mL	KETO 0.0348 µg/mL,THE 3.4735 µg/mL	KETO 0.1055 µg/mL,THE 10.5260 µg/mL	<2%	N/A	(Chaudhari, 2014)
SAL,KETO	a Thermo Hypersil Gold ODS-C18 (250 mm × 4.6 mm, 5.0 µm)	Methanol: KH2PO4 buffer (0.025M) at pH 3.25 with ortho phosphoric acid in the ratio of 45:55 vol./vo	280 nm	1 mL/ min	(25 ± 2°C)	10-60 µg/mL for SAL and 5-30 µg/mL for KETO	N/A	N/A	less than 2	N/A	(Choudhari et al., 2014)
OFL,	N/A	N/A	N/A	N/A	N/A	OFL was 30-300 mg/L-1	N/A	N/A	OFL 1.08 %	N/A	(Wu, Mingchai;

KETO, EPH						,KETO was 20-200 mg/L-1 ,EPHwas 100-1000 mg/L-1			KETO 1.61 %and EPH 1.23 %		Xie, Lixiao; Yi, Lin'gao; Dai, 2017)

KETO ketotifen fumarate, SAL salbutamol, THE theophylline, EPH ephedrine,OFL olfloxicin

5. Strategies for Electrochemical Analysis

Numerous tests, including titrimetric analysis, spectrometry, chromatography, and immunoassays, are typically performed in clinical laboratories. Due to the need for specialized and cumbersome analytical instruments, it is typical for analysis times to be protracted. Consequently, these equipment are inappropriate for the routine bedside measurements that are performed. Specifically, the use of electroanalytical techniques to the assessment of the samples drew attention owing to the reliability, selectivity, and pricing of this methodology. In particular, the application of these techniques to the analysis of the samples prompted intrigue.

Table 5 Electrochemical

METHODS	CHEMICAL	ELECTRODES	LINEARITY	LOD	LOQ	RSD	RECOVERY VALUE	REF
Potentiometric	sodium tetraphenylborate (NaTPB)	PVC membrane selective electrodes	10-7 to 10-2 mol L-1	N/A	N/A	0.63 %	N/A	(Frag et al., 2011)
voltammetry	phosphate buffer	ultra-gold microelectrode (Au UME)	2.0 × 10-7 to 5.0 × 10-12 M w	2.0 × 10-12 M	N/A	N/A	99.89%	(Daneshgar et al., 2009)
voltammetry	N/A	Ag/AgCl ref. electrode	5 × 10-8 to 1 × 10-6 mol/l-1	s 7 × 10-10 mol/l-1 a	N/A	1.03 %	99.9% ± 1.8	(Al-Ghamdi, Ali F.; Al-Ghamdi, Ahmad H.; Al-Omar, 2008)
cyclic voltammetry	phosphate buffer	C paste electrode (CPE)	N/A	N/A	N/A	N/A	N/A	(Tabrizivand et al., 2007)
Coulometry	KI, NaOH,biamperometric indicator	platinum electrodes	N/A	0.25–2 mmol	N/A	0.20 %	N/A	(Ciesielski et al., 2005)

6. Technology based on capillary electrophoresis

Capillary electrophoresis (CEs) is a highly sensitive separation technique devised using insights from high-performance liquid chromatography (HPLC). CE allows for efficient biomolecule separation, whereas HPLC quite often fails in this regard. CE methods that combine electrochromatography and electrophoresis reside. KETO, a benzocycloheptathiophene derivative, was introduced to the pharmaceutical market in the 1970s. UV/Vis spectroscopy and HPLC have been used to explore it.

Separations were executed using an uncoated fused-silicon capillary (50 cm * 50 mm) with linearity ranging from 3.0 10-8 to 5.0 10-8 g mL-1; Zhou, Min, et al. observed this combination of KETO and 5 mM Ru (bpy)3 2+ in 100 mM phosphate buffer (pH 8.0).

But even though recent advances in KETO detection have been made, there is still a long way to go before new technology can achieve greater sensitivity and overcome obstacles for instance the demand for an organic solvent in sample preparation.

Table 6 Capillary Electrophoresis

ANALYTE	MATRIX	STATIONERY PHASE	SOLVENT	DETECTION	LINEARITY		LOD	LOQ	RSD	REF
KETO	SYRUP	N/A	50 mmol·L-1 KH2PO4	301nm	16.08-80.40 µg·mL-1		N/A	N/A	N/A	(Xu, 2012)
KETO	TABLET	uncoated fused-silica capillary (50 cm * 50 mm)	5 mM Ru(bpy)3 2+ in 100 mM phosphate buffer (pH 8.0)	ECL	3.0 × 10-8 to 5.0 × 10-6 g mL-1		2.1 * 10-8 g mL-1	N/A	2.8	(Zhou et al., 2011)

7. Hyphenation

To optimize the efficiency between both methods, experts often adopt coupled chromatographic and spectral strategies. Chromatography can then be used to isolate a pure or substantially pure fraction of a chemical component from the mixture. If you really need to identify something precise, you could use spectroscopy, which is a technique that uses either benchmark spectra or a catalog of spectra to generate selected information. Multi-residue analysis of 210 medications in pork was undertaken by Yin, Zhiqiang et al. using ultra-high-performance liquid chromatography-tandem mass spectrometry. Separation and quantification of KETO as a different compound were undertaken using ultra-high performance liquid chromatography-mass spectrometry (UHPLC-MS/MS) with 0.1% formic acid (A) and methanol as carriers (B). The separation was executed on an Agilent Eclipse XDB-C18 column at a LOD of 4-505 g/kg and a LOQ of 10 g/kg.

Table 7 Hyphenation

ANALYTE	METHOD	MATRICES	EXTRACTIONTECHNIQUE	STATIONERYPHASE	MOBILE PHASE	DETECTION	INTERNALSTD	FLOW RATE	LINEARITY	LOD	LOQ	RSD	REF
KETO	UHPLC/MS/MS	PORK ANIMAL TISSUE	SIMPLE EXTRACTION	Agilent Eclipse XDB-C18	0.1% formic acid (A) and methanol (B)	ESI-MRM	N/A	0.3 mL/min	N/A	4-505 µg/kg	< 10 µg/kg	< 20 %	(Yin et al., 2016)
KETO	LC-	N/A	N/A	Grace Smart C18 colu	Acetonitrile, 10 mM disodium	230 nm	Salbut	1 mL/	KETO 1-30 µg/m	N/A	N/A	N/A	(Kabra et al., 2014)

ANDCET	UV			mn (250 × 4.6 mm, 5 µm)	hydrogen phosphate buffer (pH 6.5) 45:55 % v/v		amol sulfate	min.	L and CET 10-300 µg/mL				
KETO,PSH	TLC–densitometry	N/A	N/A	silica gel G 60 F254 (20 × 5 cm)	Ethyl acetate–methanol–ammonia 33%; (15:1:2)	218 nm	N/A	(2 µL)	KETO 0.5–6.0,pseudoepinephrine0.5–6.0	0.15 for KETO,0.81 for pseudoepinephrine	0.45 for KETO and 2.45 for pseudoepinephrine	3.45 %for ket,6.45 % for pse	(El-Kommos et al., 2014)
KETO,ACE	TLC–densitometry	N/A	N/A	silica gel G 60 F254 (20 × 5 cm)	Ethyl acetate–methanol–ammonia 33%; (15:0.3:2)	272 nm	N/A	(2 ml)	0.1–2.0 for KETO,0.04–0.8 for ace	0.03 for KETO , 0.01 for ace	0.10 for KETO 0.04 for ace	± 1.6 for ket,± 2.3 FOR ACE	(El-Kommos et al., 2014)
KETO	LC/MS/MS	N/A	N/A	Luna C18 column	10 mM ammonium formate (pH = 3) , acetonitrile (5:95, v/v)	MRM	oxybutinin	t0.2mL/min	N/A	N/A	N/A	N/A	(Nam, Kyung-Don; Tak, Sung-Kwon; Park, Ji-Sun; Cho, Min-Ho; Yim, Sung-Vin; Shim, Wang-Seob; Cho & Park, Mi-Sun; Lee, 2012)
KETO	HPLC/MS/MS	protein and/or macromol. matrix compds	N/A	new polymer column (MSpak GF),	acetonitrile	selected reaction monitoring	N/A	N/A	1-100 ng/mL	0.5 ng/mL	N/A	N/A	(Fujimaki et al., 2006)

KETO ketotifen, CET cetirizine , PSH Pseudoepinephrine.

Table 8 Miscellanous

ANALYTE	METHOD	MATRIX	DETECTION	LOD	LOQ	RSD	REF
KETO	DENSITOMETRY	N/A	228 nm	N/A	0.2-5 microg/spot	N/A	(Wyszomirska et al., 2013)

8. Discussion

KETO has been utilized in drug manufacturing, UV/VIS spectroscopy, and HPLC since 1976. KETO insolubility makes bioanalytical or capillary electrophoretic studies tricky. Sample solution consisted MeOH and ACN.Recent advances in KETO determination have been hindered by the need to upgrade sophisticated equipment to strengthen sensitivity and tackle issues such the cost-effective use of organic solvent in sample preparation.

9. Conclusion

This research is aimed at spectrophotometric and spectrofluorometric chromatographic characterization of KETO in both standalone and in combination with other drugs, following its evolution and development through time. Liquid chromatography is frequently used for both solitary and combined KETO analysis. Though there are established protocols for determining and managing KETO levels, most procedures still do not adhere to environmentally benign principles. Therefore, efforts will be made to create biological matrices and dosage forms that limit negative impacts on the environment. As a result, less potentially harmful organic effluents are needed.

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