A COMPREHENSIVE ASSESSMENT OF ANALYTICAL AND BIOANALYTICAL TECHNIQUES FOR QUANTIFYING THE ALPHA ADRENERGIC AGONIST PHENYLEPHRINE

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Abstract

Nasal congestion lead to tissue hypertrophy and blood vessel occlusion. Congestion might trigger a "runny nose." Blockage or impaired sensory processing generate congestion. Mucosal inflammation exacerbate congestion and allergy symptoms.(Seidel & Faubel, 1999) Inflammation, triggered by so many physiologically active agents and cell types, could lead to congestion and difficulty in breathing (including histamine, TNF-, interleukins, and cell adhesion molecules). Inflammation can damage nasal congestion, venous engorgement, and tissue swelling/edema. Rhinosinusitis affects tens of millions of Americans annually and costs US employers $6 billion in health care costs. Nasal congestion's social and economic burden is high. Adrenergic (phenylephrine) and intranasal corticosteroids are prescribed (beclomethasone dipropionate).

Keywords: Phenylephrine; Spectrophotometry; Chromatography; pharmaceutical formulations; biological matrix.

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1. Introduction

Direct-acting adrenergic agonists are chemicals that bind directly to adrenergic receptors and turn them on. These compounds can be very specific for certain types of adrenergic receptor subtypes or can bind to many different types. An alpha-1 adrenergic agonist is used to treat low blood pressure during anesthesia, septic shock, prolonged local anesthesia, and hemorrhoids. The important classes of adrenergic agonist are exemplified by direct acting (1) selective [phenylephrine] (2) nonselective [oxymetazoline], mixed acting [ephedrine], indirect acting (1) releasing agent [amphetamine] (2) uptake inhibitors [cocaine] (3) MAO inhibitors[selegiline] (4) COMT inhibitors[entacapone] Adrenergic agonists only work on the α1 adrenergic receptor. This causes noradrenaline and adrenaline to be released, and it also reduces swelling and mucus production. Phenylephrine (PHE) is the most unique and well-known α1 agonist. PHE therapy is linked to better vasoconstriction, morbidity and detumescent.

It is a monohydrochloride of 3-hydroxy-[(methylamino)methyl]benzene.(Cheng, 2004) The molecular weight of C9H13NO2•HCl is 203.66 g/mol..(Amer et al., 2008) White, odourless microcrystalline powder. pH of 1percent .as a result acrid water is 5. It's insoluble with water, methanol, ethanol (96%) and DMSO or dimethyl formamide (DMF). IP, BP, and USP applaud PHE. Pure PHE, dosage forms, biological fluids, and pharmaceutical mixes may be investigated utilizing spectrophotometry, chromatography, electro progressive development, and capillary electrophoretic methods. Figure 2 portrays PHE monitoring stages(Myers & Iazzetta, 1982). Figure 3 portrays PHE methodological approaches spanning 1977-2022.The objective of this project is to supply, summarise, and explain the several analytical approaches that may be used to quantify PHE either in the their natural form or in mixture with some other active constituents in formulations and biological matrices . Broad categorization of observations: The tools of volumetric analysis, chromatography, electroanalysis, capillary electrophoresis, bioanalysis, and chemistry come first.(Rajaei et al., 2013)

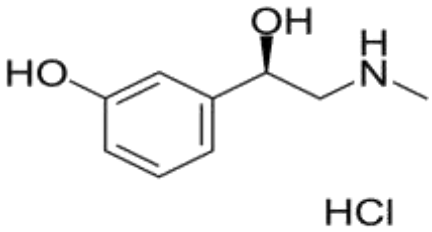

Figure 1. Structure of phenylephrine

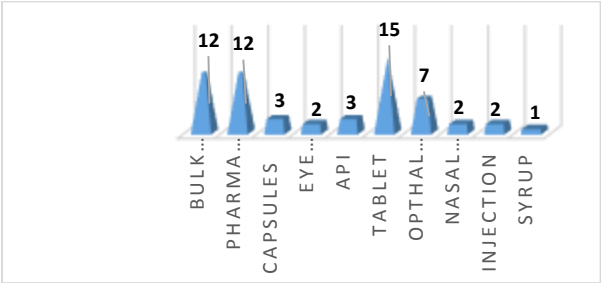

Figure 2. Number of phenylephrine-tested matrices

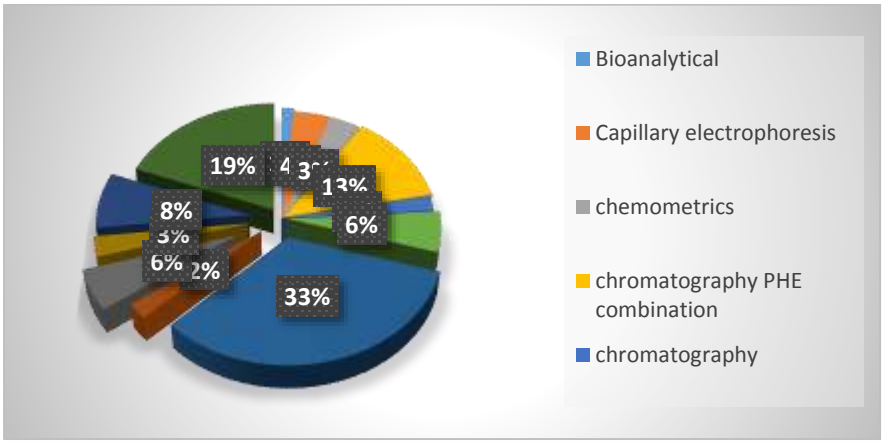

Figure.3 Techniques for trying to analyze phenylephrine in perspective of their incidence

Database sources: Science direct, Elsevier, Web of science, Springer, Taylor and Francis, Scopus and PubMed

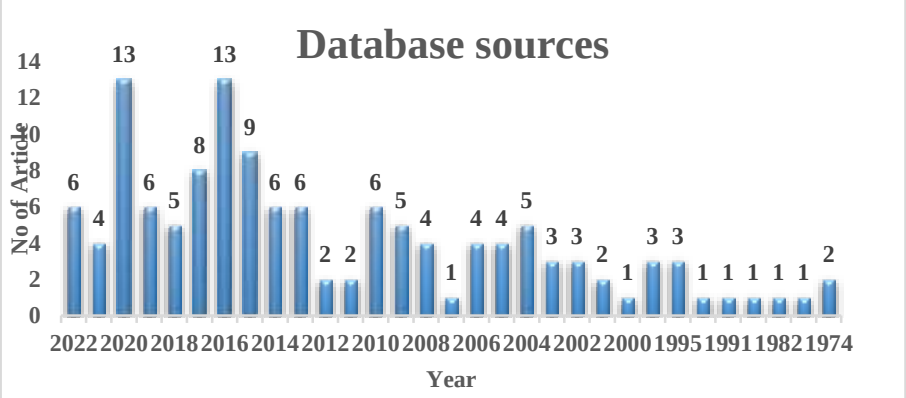

Figure 4 Phenylephrine annual publication

2. Optical Methods

Uv/Vis Spectrophotometric Methods

Spectrophotometry measures a material's reflecting or transmitting qualities as a function of wavelength. Spectrophotometric approaches for drug testing can be utilized in quality control labs without expensive equipment like GLC or HPLC. These methods are simple, cheap, and time-efficient. Jose R. C. Rocha noticed that PHE blended with 0.01M NaHCO3 formed a significant 500 nm absorbance condensation product. Tests absorb water. This study's t-test and F-test results revealed no statistically significant difference at the 95% confidence level. PHE also investigated commercial drugs. Simple procedure. 41 times, PHE strategies are discussed.(Verma & Mishra, 2018)

Table 1 Spectrophotometry Single Entity

METHOD	MATRICES	SOLVENT	LAMBDA MAX (nm)	LINEARITY	LOD	LOQ	correlation coefficient	REF
UV	bulk/tablets	NBS,Indigo Carmine,hcl	520	0.8-5.6	1.4593	1.4593	0.999	(Sasikala et al., 2016)
UV	Capsule	N/A	288.8	20-100 µg/mL	N/A	N/A	N/A	(A. S. Joshi et al., 2015)
UV	bulk/tablets	C7H7CINO2SNa and rhodamine-B dye	557	N/A	N/A	N/A	N/A	(Kondamadgu & Gandu, 2016)

UV	INJECTION	1% solution of Mesatonum,0.1M HCL	273	80-120 %	N/A	N/A	N/A	(Kryvanych et al., 2014)
UV	SYRUP	(4-AAP),copper(II) in the presence of sodium tetraborate buffer soln. of pH 9.00	480	2.0-50.0 µg/mL	N/A	N/A	N/A	(Al-Sabha, 2010)
UV	NASAL DROPS	1 mol/dm-3 NaOH (pH 13.5)	291	10-100 µg/cm-3	0.892 µg/cm-3	2.969 µg/cm-3	N/A	(Savic, Ivana; Nikolic, Goran; Bankovic, n.d.)
UV	pure , pharmaceutical formulations	haematoxylin in alk. medium with 10 min after heating at 65°	640 to 620	0.5–30 µg/m	N/A	N/A	N/A	(Ahmed & Amin, 2007)
UV	PHARMACEUTICAL DOSAGE	Na2Co3 1% (m/v) in water. 4-AAP 0.4 % (m/v) in water. C6N6FeK3 2% (m/v) in 1% Na2Co3,g Dowex 50W X8 ion-exchange resin	500	5.8–160 mg L−1	N/A	5.8 mg L−1	N/A	(Knochen & Giglio, 2004)
UV	Sequential injection	4- AAP , C6H6FeK3	503	0.5-17.5 mg l -1	0.09 mg l -1	N/A	N/A	(Beyene & Van Staden, 2004)
colorimetric method	Pharmaceuticals	0.01M NaHCO3	500	0.95 and 9 mg/L,	0.2 mg/L	0.7 mg/L	0.9998	(Rocha et al., 2002)
UV	pharmaceutical prepns	C6H7NO and KIO4	640	15 to 100 µg ml -1	N/A	N/A	N/A	(Abbas, M. N.; Mostafa, n.d.)

NBS,N-Bromosuccinamide ; $C_7H_7ClNO_2SNa$ chloramine-T ;4-AAP, 4-aminoantipyrine Na_2CO_3 Sodium carbonate;$C_6H_6FeK_3$,potassium ferricyanide; C_6H_7NO p-aminophenol;KIO_4potassium periodate.

Table 2 Spectrophotometry Combined Entity

ANALYTE	**METHOD**	**MATRICES**	**SOLVENT**	**DETECTION WAVELENGHT(nm)**	**LINEARITY**	**LOD**	**LOQ**	**CORRELATION COEFFICIENT**	**REF**
KETO ,PHE	deriv. spectrophotometry with the zero-crossing	binary mixt ,ophthalmic soln	MeOH , 0.1 M NaOH	KETO341, PHE 248.5	2—24 KETO and 2—32g/mL PHE	0.38 KETO ,0.52PHE	1.15 KETO ,1.57 PHE	0.99983KETO , 0.99985PHE	(Bel al et al., 20

	techniq ue								16)
KE TO ,P HE	ratio spectra derivati ve spectro photom etry	bina ry mixt ,opht halm ic soln	Me OH , 0.1 M Na OH	KETO 265 , PHE243.5	4— 28KET O , 4— 32PHE	0.65 KETO, 0.42PHE	1.97 KET O 1.28P HE	0.99970 KETO , 0.99992PHE	(B el al et al ., 2 0 1 6)
KE TO ,P HE	UV	bina ry mixt ,opht halm ic soln	Me OH , 0.1 M Na OH	KETO260—284 ,PHE235—260	4—28 KETO , 4— 32PHE	0.50 KETO, 0.42 PHE	1.52 KET O 1.27 PHE	0.99982 KETO , 0.99992PHE	(B el al et al ., 2 0 1 6)
KE TO ,P HE	Ratio spectra derivati ve UV	imm ediat e relea se table t	H2 O	KETO 290 , PHE227	4-20 KETO ,12-60 µg/ml PHE	0.261 KETO 0.433 PHE	0.792 KET O , 1.30P HE	0.9958 KETO ,0.9987PHE	(R . P ar m ar et al ., 2 0 1 5)
PH E ,PY H	UV	phar mac eutic al dosa ge form s	2, 4- dini tro phe nyl hyd razi ne	N/A	2.5 - 30 µg mL-1 PHE and 5 - 20 µg mL-1PYRID OXINE	0.3 PHE, 1.95 µg mL-1 PYRIDOX INE	0.95 PHE, 0.64 PYRI DOX INE	N/A	(K ri s h n e g o w d a, 2 0 1 5)

DYH, BEN, GUA and PHE	UV	quaternary mixture CAPSULES	MeOH ,H2O	N/A	N/A	N/A	N/A	N/A	(Darwish et al., 2015)
EBS , PHE	UV	bulk, pharmaceutical dosage forms	MeOH	241.0 (ZCP of PHE)for EBS and 232.0 (ZCP of EBS) forPHE	4-24 µg/mL	N/A	N/A	0.9994 EBS and 0.9991 PHE	(Suratiya, Sonu; Bhati, Sanjay sinh; Patel, Aska; Patel, Grishma; Panc

									holi, n.d.)
EBS and PHE	UV	combined dosage form	MeOH	EBS 231.61, PHE 242.21	5-40 µg/mL	0.84 µg/Mlebs 0.94 µg/mL PHE	2.54 µg/Ml EBS ,2.85 µg/Ml PHE	N/A	(B. N. Patel et al., 2014)
PHE and LEVO	UV	Pharmaceutical dosage	MeOH	PHE 271-281 , LEVO225-235	2-10µg/mL to 10 µg/ml	0.1180 PHE, 0.1212 LEVO	0.3601 PHE, 0.3672LEVO	0.9985PHE, 0.999LEVO	(Archit et al., 2014)
PARA, AMB,LEVO, PHE	UV	TABLET	MeOH	PARA 305.5 , ABM321 , LEVO 244 , PHE 280	20–140 μg/mL for PARA, 10–70 μg/mL for AMB, LEVO, and PHE	0.0352 μg/mL PARA,0.0373 μg/mL AMB, 0.0645 μg/mL LEVO, and0.0557 μg/mL, PHE	0.1070 μg/ml PARA, 0.1132 μg/mL AMB, 0.1954 μg/mL LEVO and 0.1687 μg/m	0.9992 PARA, 0.9990AMB, 0.9990 LEVO, 0.9995PHE	(Anandakumar & Veerasundari,

							L PHE		2014)
LEVO,PHE	UV	combined tablet dosage form	H2O	240 (zero crossing point of PHE) was used for quantification of LEVO and 283.2 (zero crossing point of LEVO)	4–24 μg/mL for LCT and 8–48 μg/mL for PHE	0.19 LCT, 0.64 (μg/mL)PHE	0.57 LCT, 1.94 (μg/mL)PHE	N/A	(K. Parmar et al., 2013)
CHLOR,PHE	UV	bulk and capsule dosage form	H2O	CHLOR 261 and PHE 272	2 - 12 µg/mL for CHLOR and 5 - 30 µg/mL for PHE	0.115 CPM, 0.200(µg/ml)PHE	0.348 CPM, 0.608 (µg/ml)PHE	0.9991CPM, 0.9994PHE	(Wadher et al., 2013)
PARA, CHLOR,PHE	UV	bulk and tablet dosage form	MeOH	PARA 258 ,CHLOR262 , PHE 239	4 to 24 μg/mL	PARA 0.0462 , CHLOR 0.3512 , PHE 0.0793	PARA 1.6081, CHLOR 0.6858 , PHE 0.5063	PARA 0.997 , CHLOR 0.996 , PHE 0.993	(Hapse et al., 2013)
IBU,PHE	uv	bulk and combined dosa	0.1 N NaOH	IBU 248 and PHE 237	IBU12–72 μg/mL and PHE 1.5–22 μg/mL	IBU1.285596 , PHE 0.443122	IBU 3.895744 , PHE 1.342793	IBU 0.9972 and PHE 0.9981	(M. Patel

		ge form							et al., 2013)
AMB, LEVO, PHE	UV	bulk and tablet dosage form	MeOH	AMB 248 ,LEVO 230, PHE 217	AMB 5 - 35 µg/ml, LEVO 4 - 28 µg/ml and PHE 2 - 28 µg/ml	N/A	N/A	N/A	(B&M, 2013)
CET,PHE	UV	tablets	H2O	PHE 273.5, CET232.0	12 to60 μg/mL	PHE 1.58, CET 0.64	PHE 1.58 ,CET 1.94	PHE 0.999,CET 0.999	(Wankhede et al., 2012)
CET,PHE	UV	tablet	H2O	PHE 232.0, CET 242.5	12 to60 μg/mL	PHE 2.76, CET2.95	PHE 8.36, CET 8.94	PHE 0.999,CET 0.998	(Wankhede et al., 2012)
ACE, PHE, CET ,C	UV	pharmaceutical dosage form	0.1 N NaOH	ACE 259 , PHE 233 ,CET 231 , CAFF273	0-40 µg/mL	N/A	N/A	N/A	(R. S. Jo

AFF									shi et al., 2016)
EBS,PHE	UV	tablet dosage form	N/A	EBS 252, PHE 216	5- 35 µg/mL EBS and 5-35 µg/Ml PHE	N/A	N/A	N/A	(Soni et al., 2011)
PHE, CHLOR	UV	pure and solid dosage forms	0.1 N NaOH	PARA 256.8 ,PHE 236.8 ,CHLOR222.4	0-35 µg/mL for all drugs.	N/A	N/A	N/A	(Geiss & Gumbsheimer, 2021)
PARA ,PHE ,CHLOR	UV	PHARMACEUTICAL PREPARATION	MeOH :H2O mixture (50: 50, v/v).	210–310	N/A	N/A	N/A	N/A	(Samadi-Maybodi & Hass

									aniNejad-Darzi, 2010)
PHE and TRP	UV	ophthalmic dosage form	HCl and H2O	PHE284.0,TPC 241.2	PHE 25-125, TPC4-20	PHE 1.138 ,TPC1.283	PHE 3.449 ,TPC 3.889	PHE0.9999, TPC 0.9996	(Sardana&Mashru, 2010)
PHE and TRP	UV	ophthalmic dosage form	HCl and H2O	PHE260.8- 268.2 , TPC246.2- 271.2	PHE 25-125 , TPC4-20	PHE 1.272, TPC 1.037	PHE 3.856 , TPC 3.142	PHE 0.9995, TPC 0.9999	(Sardana&Mashru, 2010)
PHE and TRP	UV	ophthalmic dosage	HCl and H2O	PHE 270.8 , TPC 240.4	PHE25-125 ,TPC4-20	PHE 1.173, TPC 0.416	PHE 3.557 , TPC 1.262	PHE 1.0000 , TPC 0.9998	(Sarda

		form							na & Mashru, 2010)
CHLOR, PHE and PHP	UV	tablet	H2O	CHLOR 273.8, 269.5, 262.2, 265.9 ,PHE 286.5,PP 220.0	CHLOR 2-12, PHE 1-8, PP 5-30	CHLOR 0.3, PHE 0.2, PP 0.5	CHLOR 1.0, PHE 0.8, PP 1.5	CHLOR 0.9994 ,PHE 0.99997 ,PP 0.99993)	(Kazemipour & Ansari, 2005)
PHE, DYH and NAP and MEP	SPECTROPHOTOMETER WITH PLS or NAP/CLS programs.	nasal solutions.	Nacl,H2O	PHE230–290, DIPH 210–270 ,NAPH 200–310,METH 220–270	PHEl21 0.00–8.00,DIPH 0.00–8.00 ,NAPH0.00–8.00 ,METH 0.00–1.00	N/A	N/A	PLS (PHE0.9994,DIPH 0.9987, NAPH 0.9991, METH 0.9992) , NAP/CLS (PHE 0.9994, DIPH 0.9987, NAPH 0.9992 , METH0.9992)	(Goicoechea & Olivieri, 2001)
PHE, CH	SPECTROPHOTOM	ophthalmic	H2O	PLS(PHE 252–322,CHL 251–350 ,ANT240–310, MET	N/A	N/A	N/A	N/A	(Col

P, MEP and THI	ETER WITH PLS or HLA programs	solutions		240–310 , THI 240–310), HLA/GO (PHE253–322,CHL 250–350, ANT 220–320, MET 240–350, THI 240–350)					lado et al., 20000)
PARA ASC, CAFF, PHE .	UV	TABLET	NaOH ,CHCL 3	250 to 300	50-150%	N/A	N/A	N/A	(Muszalska et al., 20000)
ACE .PHE) and CAFF	spatially offset Raman spectroscopy (SORS)	API	N/A	785	5% to 100%	N/A	N/A	N/A	(Olds et al., 2012)
ANT ,PHE	UV	eye drops	0.1 N H2 SO 4, C2 H5 OH	320 to 220	Ephedrine.HCL 40-60,PHE 5.0-7.5,Antazoline. HC1 5.0-7.0	N/A	N/A	N/A	(Koranyet al., 1985)

Spectrofluorometric Method

The extensive usage of spectrofluorometric in quality control settings may be attributed to its portability, reliability, and flexibility of use. PHE were isolated via spectrophotometric methods, either or in association with other pharmaceuticals.(Elokely et al., 2011)

Table 3 Spectroflurimetric Determination Alone And Combined Entity

ANALYTE	MATRICES	SOLVENT	EXCITATION AND EMMSION WAVELENGHT(nm)	LINEARITY(µg mL-1)	LOD (µg mL-1)	LOQ (µg mL-1)	CORRELATION COEFFICIENT	REF
PHE	pharmaceutical formulations	0.5 mol L-1 formaldehyde soln	N/A	0.25 to 15.0	0.027	0.09	0.9999	(Al Lawati et al., 2011)
PHE	pharmaceutical tablets.	large excess of paracetamol, slightly acid aq. soln. (HCl)	277	0.80 - 2.00	0.08	0.27	N/A	(Arancibia, J. A.; Nepote, A. J.; Escandar, G. M.; Olivieri, n.d.)
GUA, PHE	pharmaceutical tablets	methanolic solns	275	0.1-2	0.027 (D1, GUA), 0.025 (D2, GUA), 0.031 (D1, PHE) and 0.033 (D2, PHE)	0.089 (D1, GUA), 0.083 (D2, GUA), 0.095 (D1, PHE) and 0.097 (D2, PHE) µg/mL	N/A	(Maher et al., 2015)
OXMPHE ,PARA	pharmaceutical tablets	acid aq. soln. (pH = 2)	(excitation maxima appear at 280 and 272),emission maxima lie at 310 and 302)	0-6.40 and 0-1.00		N/A	N/A	(Nepote & Olivieri, 2001)

PHE, phenylephrine;PARA,paracetamol;GUA, gaufesnin,PYH Pyridoxine hydrochloride, DYH diphenhydramine HCl, BEN benzonatate,TRP tropicamide,PHP phenylpropanolamine HCl,NAP naphazoline, MEP methylparaben, CHP chloramphenicol,THI thimerosal,ASC ascorbic acid,ANT Antazoline, EPH ephedrine, OXM Oxatomide

Chromatographic Methods

Table 4 Chromatography Single Entity

ANALYTE	METHOD	COLUMN	MOBILE PHASE	DETECTION(nm)	FLOW RATE	CT	LINEARITY	LOD	LOQ	RSD	REF
PHE	HILIC	a Kinetex HILIC 100 mm x 4.5 mm, 2.6 mm particle size column	ACN—25 m mol L1 ammonium acetate inH2O adjusted with CH3COOH to pH 4.0 (87:13, v=v)	215	1 mL min 1	30 C	N/A	N/A	N/A	N/A	(Jovanović et al., 2015)

PHE	TLC	Silica gel 60F25,Silica gel 60/kieselguhr F25	GAA + n-butanol + H2O (1 : 4 : 1, v/v/v)	N/A	N/A	N/A	N/A	0.25, 0.50	N/A	N/A	(Pyka & Cazes, n.d.)
PHE	MEKC	uncoated fused silica capillary, 52 cm total length	tris-borate 20 mM with 30 mM SDS	214	0.5 psi for 5 s	N/A	5 to 30 mg/ml	1.0 mg/ml	3.5 mg/ml	0.15 to 0.50%	(Buiarelli et al., 2008)

HILIC Hydrophilic Interaction Liquid Chromatography;MEKC micellar electrokinetic capillary chromatography; ACNacetonitrile; GAAGlacial acetic acid

Table 5 Chromatography Combined Entity

ANALYTE	**METHOD**	**COLUMN**	**MOBILE PHASE**	**DETECTION(nm)**	**FLOW RATE (mL/min)**	**CT (°C)**	**LINEARITY**	**LOD**	**LOQ**	**RSD**	**REF**
PHE, PARA, GUA.	HPLC	Onyx Monolithic C18 R (100 × 4.6 mm	phosphate buffer pH 7.0/ethanol	220	2	N/A	PHE 5.0–80.0 PARA 10.0–800.0 GUA 10.0–600.0	PHE 1.39 PARA 3.09 GUA 3.14	PHE 4.20 PARA 9.37 GUA 9.53	PHE 99.70 ± 1.851 PARA 99.86 ± 1.507 GUA 100.27 ± 1.735	(Yehia & Mohamed, 2016b)
PHE and EBS	HPLC	kromasil C18 (250 ×4.6 mm, 5µp article size) column	Phosphate buffer (adjusted to pH 5.0 with dil. OPA): ACN: MeOH in the ratio of 30:45:25 %vol./vol.		0.8	N/A	N/A	N/A	N/A	N/A	(Yunoos, Mohammad; Sankar, n.d.)
ASE,	ME	fused-	BGE (pH 8.6;	210	N/	25	Aesculin	Aesculin 2.0	Aesculin 6.6Aesculeti	84 ± 1.9% (AL), 91 ±	(Pincová et al.,

ASL, and PHE	KC	silica capillary (50 µm id, total length 64.5 cm, effective length 8.5 cm	adjusted with 0.1 M NaOH) contained 20 mM boric acid, 60 mM SDS and 5% (v/v) of MeOH		A		0.01–0.5 Aesculetin0.01–0.5 PHE 0.0125–0.625 mg/ml	Aesculetin1.3 PHE3.4(mg/mL)	n 4.4 PHE 11.2	2.1% (AT), and 73 ± 3.6% (PE)	2015)
AD and PHE	CHIRALSEPERATION	CHIRALCEL OD-H and CHIRALCEL OJ-H	N-hexane and isopropanol (contg. different ratios of methanol, trifluoroacetic acid and diethylamine)	280	0.8	25	N/A	N/A	N/A	N/A	(Wang, Yan; Chen, Wen-jing; Zhou, Ying; Huang, Min; He, Wen-yi; Yao, Qing-qiang; Zhang, Qi-ming; Deng & Zhang, n.d.)
PHE, PHM,DYH,PRMCAFF,PHP	UHPLC	Waters Acquity BEH C18 column (2 mm × 100 mm, 1.7 µm)	two organic buffers, an ammonium formate buffer 0.025 M of pH 3 and an ammonium acetate buffer 0.025 M of pH 4, and two organic modifiers acetonitril	254	0.5	50	0.008–0.8 mg/ml	PHE 0.34 PARA 0.016 Salicylic acid 0.41 Codeine phosphate 0.032 CAFF 0.095 Acetyl salicylic acid 0.093 CHLOR 0.020 Quinine sulphate 0.017 Diphenhydramine.HCl	PHE 1.14 ,PARA 0.054 ,Salicylic acid 1.37, Codeine phosphate 0.11 ,CAFF 0.32 Acetyl salicylic acid 0.31,CHLOR 0.068 Quinine sulphate 0.055 Diphenhydramine.HCl	PHE 1.64,PARA 0.72 ,Salicylic acid 1.13 ,codeine phosphate 0.18, CAFF 1.65 acetyl salicylic acid 0.87 CHLOR 0.92 quinine sulfate 1.72diphenhydramine	(Deconinck et al., 2011)

			e and methanol					0.22 Promethazine.HCl 0.084	0.73 Promethazine.HCl 0.28	hcl 1.57 promethazine 1.22	
SAM, PARA, PHE and BRM	UFLC	Kinetex C18 column	MeOH-0.5% triethamide soln	N/A	1	N/A	PHE 0.10-10.33, brompheniramine maleate 0.05-4.82 , CAFF 0.04-4.10 , PARA 0.30-30.50 and salicylamide0.30-30.44 µg	N/A	N/A	N/A	(Zhong, Yani; He, Guotao; Fu, n.d.)
PHE, PARA (6 5 + 1, wt./wt.), ASC(5 + 1, wt./wt.)	ion-pair	XTerra RP18 column, 3 µm particle size, 50 × 3.0 mm id	aqueous 10 mM sodium octane-1-sulfonate adjusted with phosphoric acid to pH 2.2–acetonitrile (800 + 200, v/v).	excitation 275 and emission wavelengths of 310	0.3	30	0.2–20.0 mg/L	0.06mg/l	0.2mg/l	1.63	(Dousa & Gibala, 2010)
PHE, PARA (6 5 + 1, wt./wt.), ASC	HILIC	100 ´ 4.6 mm id, 3 mm particle size, Luna HILIC column	aqueous 5 mM potassium dihydrogen phosphate adjusted with phosphoric acid to pH 2.5–ACN (250 + 750, v/v)	excitation 275 and emission wavelen	0.8	25	0.2–20.0 mg/L	0.07 mg/l	0.23 mg/l	1.63	(Dousa & Gibala, 2010)

(5 + 1, wt./wt.)				gths of 310							
DEX, PHE, CX	HPLC	Luna 5 µm CN column (250 × 4.6 mm i.d.)	AC N–12 mM ammonium acetate in ratio of 60:40 (v/v) for Mix 1 and 45:55 (v/v) for Mix 2. pH 6.0 using CH3COOH	214	2	ambient temperature	DEX 5–20PH 5–20 CX 2–10µg/ml	DEX 2.41 × 10–2 PHE 2.43 × 10–2 CX 5.49 × 10–2(µg/mL	DEX 8.04 × 10–2 PHE 8.13 × 10–2 CX 1.83 × 10–1	DEX 0.86 PHE 0.87 CX 1.95 %	(El-Gindy et al., 2010)
PHE, GUA, and CHLOR	gradient liquid chromatography	C8 column	0.005 M heptane sulfonic acid sodium salt (pH 3.4) and ACN	210	N/A	N/A	PHE 30-180, GUA 120-1800, and CHLOR 10-60 µg/mL	N/A	N/A	N/A	(Amer et al., 2008)
PHE, CHLOR, ME	liq. chromatog.	7.5 cm Novapak silica column	930 mL MeOH with 70 mL of a 0.5% aq. soln. of 1-pentanesulfonic acid, sodium salt.	255 excitation and 285	1	N/A	N/A	N/A	N/A	N/A	(Cieri, 2019)

T	(LC)			emission							
PRE, SUFand PHE	MEKC	fused silica capillary (57 cm/ 75 mm ID)	5 mM phosphate /5 mM borate buffer, pH 8.2; 40 mM SDS	PARA 245, PHE 200 and SUL 195 nm	N/A	25	0.3 to 60 mg l1	SUL 0.09 PHE 0.09 PARA 0.34	SUL 0.29 PHE 0.32 PERA 1.21	N/A	(Lemus Gallego & Perez Arroyo, 2003)
PRE, NAP, PHE	MEKC	a fused-silica capillary (57 cm6 75 lm ID	MeOH;H2O (50: 50)	600	N/A	25	PHE 0.4 – 56.8 PRE 0.8 – 56.5 NAF 0.2 – 39.9 (mg L – 1)	PHE 0.09 PRE 0.22 NAF 0.03 (mg L – 1)	PE 0.32 PRE 0.73 NAF 0.13 (mg L – 1)	< 2.5%	(Gallego & Arroyo, 2003)
PRE, ZNB, and PHE	MEKC	a fused-silica capillary (57 cm6 75 lm ID	5 mM phosphate -5 mM borate buffer (pH = 8.2), 40 mM SDS	N/A	N/A	25	N/A	N/A	1.0 mg L-1	N/A	(Lemus Gallego & Arroyo, 2003)
PHE,CHLOR	RPLC	C8 (Eclipse XDB-C, 1503 4.6 mm id,C18	0.05 mol l21 SDS–6% v/v pentanol or 0.15 mol l21 SDS–2%v/v pentanol at pH 7	190–700	1	25 ± 0.2	5–50 mg ml2	N/A	N/A	N/A	(Gil-Agustí, Capella-Peiró, et al., 2001)

		(Kromasil, 1203 4.6 mm id									
PHE, CHLOR	RPLC	C18 column	sodium dodecyl sulphate (SDS) and pentanol,	260	1	25 ± 0.2	0.5–50 g ml−1	N/A	0.02	N/A	(Gil-Agustí, Monferrer-Pons, et al., 2001)
CHLOR, MET, and PHE	HPLC	250 x 4.6 mm Phenomenex CN 5analytical column	70% (vol./vol.) soln. of MeCN in water contg. 2% (vol./vol.) HOAc and 0.005 M Na 1-heptane sulfonate	262	2	N/A	5-500 mg mL 1	N/A	N/A	N/A	(Metwally, 2016)
PHE	HPLC	a strong cation-exchange column	methanol-glacial acetic acid (55:44:1 v/v) containing enough heptanesulfonic acid sodium salt to yield a 0.005 M solution	N/A	2	N/A	40ng-100MUg	40ng	N/A	N/A	(Koziol et al., 1979)

EBS ebastine; AD adrenaline; CAFF caffeine; DEX Dextromethorphan hydrobromide; CX Carbinoxamine; CHLOR chlorpheniramine maleate; MEKC micellar electrokinetic capillary chromatography;reversed-phase liquid chromatographic (RPLC), ASE aesculin, ASL aesculetin,PHM pheniramine maleate,PRM promethazine,PHP phosphate,SAM salicylamide,BRM brompheniramine,MET methscopolamine nitrate , PRE prednisolone acetate, SUF sulfacetamide,ZNB Zn-bacitracin

High Performance Liquid Chromatography

To segregate chemical mixtures empirically, HPLC is the benchmark. LC has good sensitivity, endurance, and precise. PHE is indicated both by itself and in conjunction with other drugs .(Kokilambigai et al., 2021) Katarina Marakova et al. made available online multidrug capillary electrophoresis and triple quadrupole mass spectrometry. Separation and analysis were carried out using Cosmosil C18 (4.6 mm 250 mm, 5 m). Other analysis evaluates PHE for multiple pharmaceuticals. Paracetamol linearity ranges are 0.15 to 0.25, 7.5 to 12.5 mg/ml, and 0.06 to 0.10 mg/ml for chlorpheniramine maleate.

Table 6 HPLC Single Entity

COLUMN	MOBILE PHASE	WAVELENGTH(nm)	FLOW RATE (mL/min)	CT	LINEARITY(µg mL-1)	LOD(µg mL-1)	LOQ(µg mL-1)	CORRELATION COEFFICIENT	RSD	REF
Kinetex C18 column	(pH 3.0–9.0) were prepared using potassium dihydrogen phosphate, phosphoric acid, sodium 115 hydroxide and KOH	220	2	22 ± 1 ° C	5.0 - 200.0	1.05	3.19	0.9998	N/A	(Yehia & Essam, 2016)
Cosmosil C18 (4.6 mm × 250 mm, 5 µm	MeOH-H_2O-CH_3COOH (30:70:1, vol./vol./v)	257	1	N/A	2.0 to 22.0	0.08	0.28	0.999	below 2.0 %	(Krishnamoorthy, 2020)
Kromasil C18 (250 mm×4.6 mm, 5 µm)	MeOH-ACN-sodium heptane soln. (1: 1: 8)	280	1	30 ° C	PHE 100-400	0.13	N/A	N/A	N/A	(Sun, Kegang; Shi, Jianguo; Jiang, n.d.)

MeOH Methanol; CH_3COOH acetic acid; ACN acetonitrile CYC cyclopentolate hydrochloride,PAP 4-aminophenol,NIM Nimesulide

Table 7 HPLC Combined Entity

ANALYTE	COLUMN	MOBILE PHASE	DETECTION	FLOW RATE (mL/min)	CT	LINEARITY	LOD	LOQ	RSD	REF
CYC and PHE	Waters Spherisorb ODS2 C18 anal. column (5 µm particle size)	0.1% heptane-1-sulfonic acid sodium salt in MeOH-water (80 + 20, vol./vol.)	210 nm	1	N/A	PHE 4–400 µg/mL clo 20–400 µg/mL			PHE 1.00 % CLO	(Rezk et al., 2017)

									0.62%	
EBS, PSU, PHE	ODS reversed-phase column from Merck Millipore; 50 mm × 4.6 mm i.d. silica-based monolithic column		254 nm for both EBS and PSU and 274 nm for PHE	1	ambient temperature	EBS 5.0–50.0, PSU 40.0–500.0 and PHE 10.0– 100.0 µg/mL	EBS 3.8, PSU 30.6 and PHE 7.5 µg/mL	EBS 4.7,PSU 39.4 and PHE 10.2 µg/mL.	N/A	(Ibrahim & Wahba, 2017)
KETO, CHLOR and PHE	Inertsil ODS C18 (150 × 4.6 mm, 5µm) column	Buffer(TBAHS) and MeOH in proportion of 60:40 %v/v	215	1	room temperature	1.2-3.6 µg/ml PHE, 5-15 µg/ml of KETO and 2-6 µg/ml of CPM	0.393 µg/ml for KETO, 0.154 µg/ml for PHE and 0.278 µg/ml for CPM	1191 µg/ml for KETO, 0.467 µg/ml for PHE and 0.842 µg/ml for CPM	less than 2%	(Nikul M. Rahevar*, Mitali H. Jasani, Ankit B. Chaudhary, Parth R. NayakNikul M. Rahevar*, Mitali H. Jasani, Ankit B. Chaudhary, n.d.)
PARA, PHE, CHLOR, (PAP)	Eclipse XDB C18 column (250 4.6 mm i.d., size 5 µm)	potassium dihydrogen phosphate buffer (pH 2.5) and CAN	265 CHLOR and 278 PARA ,PHE and 4-aminophenol.	1.4	35 oC	190-455 µg/ml (PAR), 3-7 µg/ml (PHE), 1.2-2.8 µg/ml (CPM) and 0.25-20 µg/ml (PAP)	PAP 0.0576 µg/ml.	N/A	less than 2%	(Dung & Hai, 2016)
PHE, CHLOR and	Hypersil BDS C8 column (4.6 X	TEA and 1-octane sulfonic acid sodium salt) (pH adjusted to 3.2 using orthophosphoric	220	1	25 ± 2° C	N/A	PHE 0.19,CHLOR 0.32 and	PHE 0.62, CHLOR 0.97 and	less th	(S. A. Kumar et al., 2016)

DEX HBr	250 mm; 5 µm)	acid) and CAN					DEXO 0.58 µg/mL	DEX 1.90µg /mL.	an 2 %	
PHE ,CET and (NIM)	Primesil-C18 column (4.6 x 250 mm i. d., particle size 5 mm)	70% MeOH, 30% aqueous contained 0.05% orthophosphoric acid as mobile phase adjust pH at 3	225	0.7	ambient temperature	PHE, CET 1-5µg/ml ,NIME 20-100µg/ml	N/A	N/A	less than 2	(Maaz et al., 2016)
PARA , PHE , CAFF AND LEVO	reverse phase Kinetex C18 packing column (4.6 mm×250 mm, 5 µm particle size;	10mM phosphate buffer (pH 3.3) and MeOH	230	1	N/A	PHE 2.5 to 10 PAR 250 to 750CAF 15 to 45 LEV 1.25 to 3.75 (µg/ml)	PHE 0.13 PARA 0.51 CAF 0.05 LEVO 0.05(µg/ml)	PHE 0.39 PARA 1.53 CAFF 0.15LEVO 0.15 (µg/ml)	less than 2	(Dewani & Patra, 2015)
PHE AND CET	Princeton SPHER C18 column (250 mm x 4.6 mm id, 5 µ particle size)	(0.1 M Ammonium dihydrogen phosphate pH 5.2 ± 0.05) : ACN (50:50% v/v	225	1	ambient temperature	PHE 10-60 CET 5-30 (µg/ml)	PHE 0.176, CET 0.248 (µg/ml)	PHE 0.533, CET 0.750 (µg/ml)	less than 2 %	(Deo et al., 2015)
AMB , CHLOR and PHE	C-18 (250mm × 4.6mm i.d with particle size of 5 µm)	MeOH : ACN (50%:50%) and phosphate buffer 5 pH containing 0.75% TEA set by HCOOH40%:60%v/v)	261	0.95	N/A	range of 32-48 µg/ml (R2 = 0.998)AMB, 6.4-12.8 µg/ml (R2 = 0.997) CHLOR and 11.2- 22.4 µg/ml (R2 = 0.990)PHE.	AMB 11.58µg/ml , CPM 0.66 µg/ml, PHE 7.04 µg/ml	AMB 35.092 µg/ml , CPM 2.02 µg/ml , PHE 21.36 µg/ml	N/A	(Bagada et al., 2014)

PHE and IBU	Agilent XDB C-18 column (4.6 x 150mm , 5 µ particle size)	0.1 % orthophosphoric acid and ACN 0.01/95/5, 2.5/95/5, 6/10/90, 8/10/90, 8.1/95/5 and 13/95/5	210	1	30 °C	5 - 25 µg/mL of PHE and 100 - 500 of IBU µg/mL	PHE were 0.03895 ,IBU were 0.338187 µg/mL a	PHE 0.11803 µg/Ml, IBU 1.024809 µg/mL,	less than 2 %	(Vemula & Sharma, 2014)
PARA , PHE , CET	a Kinetex-C18 (4.6, 150 mm, 5 mm) column	10 mM phosphate buff er (pH 3.3) and CAN	230	1	N/A	PHE 5–15 µg/ml, PARA 250–750 µg/ml and CET 2.5–7.5 µg/ ml.	N/A	N/A	± 2 %	(Dewani, Shelke, et al., 2014)
EBS AND PHE	BDS hypersil C18 column	Phosphate buffer (pH:3.5):MeOH(60:40)	272	1	N/A	5-15 µg/ml and for EBA and PHE	EBA (µg/ml) : 5.00 PHE (µg/ml) : 1.83	EBA (µg/ml) : 15.18 PHE (µg/ml) : 5.56	less than 2 %	(K. Parmar et al., 2014)
PHE and EBS	Thermo BDS Hypersil C18 column (250 mm × 4.6 mm, 5 µm)	MeOH: Phosphate buffer (30:70v/v), pH 4.0±0.05	215	1	ambient temperature	5-15 µg/mL (r2 = 0.9994) (PHE) and 5-15 µg/mL (r2 = 0.9947) (EBS)	PHE were 0.46 µg/ml ,EBS were 1.41µg /ml ,	PHE 1.12 µg/ml, EBS 3.41 µg/ml	EBS0.986, PHE0.730	(Yadav & Jain, 2014)
PARA , GUA ,AMB , PHE , and CHLOR	228 mm x 4.6 mm, 5 µm C18 column	0.01M sodium perchlorate, monohydrate, pH 3.0, B CAN	228	1.5	25°C	0.0008-0.0012 mg/mL (r2= 0.999) PHE, 0.04-0.06 mg/mL (r2= 0.999) PARAl, 0.008-0.012 mg/mL (r2= 1.000) GUA, 0.0024-0.0036 mg/mL (r2= 1.000) AMB, and 0.00016-0.00024 mg/mL (r2=	N/A	N/A	N/A	(Kolhal et al., 2014)

						1.000) CHLOR				
PHE, PARA, CAFFand CHLOR	a C-18 Phenomenex column (150 mm · 4.5 mm i.d., particle size 5 lm	ACN,MeOH and 10 Mm phosphate buffer 16:22:62 (v/v) (pH of buffer 2.5 ± 0.02, adjusted with ortho phosphoric acid	280	1	N/A	PARA 250 to 750 lg/ml, PHE 7.5 to 22.5 lg/ml,CAFF 10 to 45 lg/ml and CHLOR 1.0 to 3 lg/ml	N/A	N/A	N/A	(Dewani, Barik, et al., 2014)
ACE, PHE and DEX	inertsil C-18 column 250 mm length, 4.5 mm inner diameter and 5 µm particle size	0.05 percent orthophosphoric acid and MeOH in a proportion of 45:55	225	1.5	30° C	50 to 150 percent	N/A	N/A	N/A	(Bhortake & Lokhande, 2014)
PARA, GUA, PHE, CHLOR AND BRH	Symmetry C8 (150 X 4.6mm, 3.5µ) column	buffer 10mM KH2P04 and 3.7mM of an ion pair reagent, octane-1-sulphonic acid sodium salt. The pH of the mobile phase A was adjusted to 4.0 with ortho phosphoric acid and the mobile phase B consisted of a mixture MeOH and ACN in the ratio of 3:2	220	1	N/A	32 to 488µg/ml,GUA was 10 to 150µg/ml, PHEwas 5 to 75µg/ml, CHLOR was 2 to 30µg/ml and bromhexine was 8 to 120µg/ml.	0.5µg/ml	1.5µg/ml	less than 1.0 %	(Nalini et al., 2014)
PHE and LID	Lichrosphere RP18 250mm x 4.6mm, 5µm column	ACNand buffer, pH 3 in the ratio of 25: 75, v/v	254	1	N/A	4-44 µg/mL of PNL and 12.5-75 µg/mL of LID	PNL 0.756µg/mL and LID 0.692µg/mL	PNL 2.495µg/mL and LID 2.0998 µg/mL	less than 2.0	(Gurrala et al., 2014)

PHE and LEVO	Thermo Hypersil C18 column (250×4.6 mm i.d., 5 µm particle size)	0.05M Dibasic phosphate in the ratio of 70:30v/v	230	N/A	N/A	4-14 µg mL-1 for PHE and 2-12 µg mL-1 for LEV	PHE 0.34 µg mL-1 LEV 0.23 µg mL-1.	PHE 0.98 µg mL-1, LEV 0.70µg mL-1	N/A	(Sunitha & Ilango, 2014)
CHLOR ,IBU, and PHE	Sunfire C 18 column (5 μm × 250 mm × 4.6 mm)	ACN : MeOH: phosphate buffer (50 : 20 : 30, v/v/v; pH 5.6) and adjusted with 0.01% O-phosphoric acid	220	1	N/A	CPM 0.5–2.5 IBU 25–125 PHE 1.25–6.25 (μg/Ml	CPM 0.0321 IBU 0.1198 PHE 0.0679 (μg/mL	CPM 0.5 IBU 25 PHE 1.25 (μg/mL	less than 2%	(Sanchaniya et al., 2013)
CET and PHE	C18 (250 mm × 4.6 mm i.d) column with 5 µm particle size	ACN: Water	222	1	N/A	5-25 µg/mL CET ,PHE	CET 0.26 µg/mL and PHE 0.51µg/mL	CET 0.81µg/mL and PHE 1.54 µg/mL	N/A	(Bhadra, Sulekha; Sevak, n.d.)
PHE ,CHLOR	250 mm × 4.6 mm, 5µm particle, C8 column	0.01M phosphate buffer: ACN (70: 30). pH of the mobile phase was adjusted at 3 with 50% orthophosphoric acid.	230	1	N/A	5-60 µg mL-1	CHLOR 0.36, PHE 0.28 µg mL-1	N/A	N/A	(Sehrawat, Renu; Khatak, Mamta; Kumar, Anil; Khatakb, n.d.)
PHE, GUA, BRH and CET	Qualisil, C18 column, 250 mm × 4.6 mm, 5µm	0.05M KH2PO4-1.0% HCl Buffer: ACN (62:38) pH was adjusted to 2.5 by TEA	254	1	N/A	PHE 0.2-1.0 µg/mL,GUA 2-10 µg/mL,BROM 0.16-0.8 µg/mL and CET 0.1-0.5 µg/Ml	N/A	N/A	N/A	(Article, 2014)
CHLOR , PARA and PHE	Princeton C8 analytical column (250 x 4.6mm, 5µm particle size)	.01M Na2HPO4 buffer: ACN,pH 3with 50% orthophosphoric acid	230	1	N/A	5-60 µgmL-1)	CPM 0.36 PCM 0.36 PHE 0.28	CPM 1.1PCM 1.1 PHE 0.86	0.06%	(Sehrawat et al., 2013)
CHLOR,	Inertsil ODS	0.05M dibasic phosphate buffer:	215	1.5	30	CPM 3.2-4.8 PE 4-6 PCM	CPM 0.29,P	CPM 0.4,PH	<2	(Redasani et al.,

PHE, PARA AND CAFF	C18 colum	ACN (93: 07; v/v			° C	400-600 CAFF 24-36 µg/ml	E 0.41, PCM 38, CAFF 2.4	E 0.51, PCM 49, and CAFF 3.3		2013)
PHE and GUA	Zorbax reverse phase C18 column (150 x 3.0mm, 3.5µm)	5mM ammonium acetate: ACN (80:20% v/v)	222	1	N/A	PHE 1-5µg/Ml, GUA15-75µg/mL	PHE 0.11µg/mL and GUA 0.08µg/mL	PHE 0.34 µg/mL and GFN 0.26µg/mL	less than 2%	(Suma et al., 2013)
PHE, AMB AND LEVO	n Octadecyl Silane C18 column (250 mm × 4.6 mm, 5.0µ),	0.01M Sodium dihydrogen phosphate monohydrate buffer [pH 3.0, adjusted with Ortho Phosphoric Acid and 1.1 gm of Octane sulfonic acid sodium salt]: ACN: MeOH(60:30:10)	230	1	30 °C	PHE 0.104 mg/ml to 0.303 mg/ml; AMB 0.6 mg/ml to 1.804 mg/ml and LEV 0.051 mg/ml to 0.150 mg/ml,	N/A	N/A	N/A	(Padmakana Malakar*, n.d.)
TRP ,PHE	C18 column ,	MeOH 0.03 mol/L-1 octane sulfonate sodium soln. (1:1), adjusting to pH 3.0 with phosphorus acid	263	1	30 °C	PHE 0.054 0-0.504 0 mg/mL-1 TRP 0.050 21-0.502 1 mg/mL-1	N/A	N/A	N/A	(Tong, Yanhua; Wang, n.d.)
NIM, PE, CHLOR AND CAFF	Hypersil phenyl column (4.6 mm × 25 cm)	pH 5.5 consisting of MeOH and buffer (55:45, v/v)	214	1	N/A	NS 300-800 PE 15-32 CPM 16-32 CF30-180 (µg/mL)	NS 3.08 PHE 0.84 CPM 1.14 CF4.55 (µg/mL)	NS 9.34 PHE 2.54 CPM 3.45 CF0.45 (µg/mL)	N/A	(A. Kumar et al., 2012)
CAFF, CHLOR and PHE	clipse XDB-C8 column. A Lichrospher CN column	mobile phase was 0.01 M KH2PO4:MeOH:ACN:isopropanol (74:8:9:9, v/v/v/v)	215	1	35 C	MIT 90.021, COD 234.174, CAFF73.986, CHLOR 7.053 and PHE 1.486 mg/L,	MIT 1.00,COD CAFF 0.005, CHLOR PHE 0.200D (mg/L)	MIT 3.00, COD CAFF 0.010, CHLOR PHE 0.400 (mg/L)	N/A	(Chittrakarn et al., 2012)
CHL	Zorbax	ACN-phosphate	280	0.	N	CHLOR 10-	N/A	N/A	le	(Al-

OR , DEX HBr and PHE	C18 (4.6 cm × 250 mm, 5 µm)	buffer pH 3.5 (15:85, vol./vol.)		9	/ A	50, DEX 10-50 and PHE 5-45 µg/mL,			s s t h a n 2 %	Shaalan, 2012)
DEX , PHE , and CRB	ACE C18 column (Advance Chromatography Technologies, Scotland) 250 × 4.6 mm, 5 µm	MeOH-sodium perchlorate soln. (5: 95, vol./vol.)	274	1. 4	3 5° C	DEX, PHEN ,CAR 0.8–40.0 0	0.09 µg/mL for DEX, 0.006 µg/mL PHE and 0.19 µg/mL CAR	0.28 µg/mL for DEX, 0.02 µg/mL PHE and 0.58 µg/mL CAR	N / A	(Palabiyik & Onur, 2012)
PHE , GUA, AMB, and SAL	250 mm × 4.6 mm C8 column	pH 3.0 phosphate buffer and 1:1 MeOH–CAN	273 PHE,GUA and 225 AMB and salbutamol	1	a m bi en t	50–250 µg mL−1 PHE, 250– 1250 µg mL−1 forGUA, 75–375 µg mL−1 for AMB, and 5–25 µg mL−1 for salbutamol	N/A	N/A	le s s t h a n 2 %	(S. Joshi et al., 2011)
PARA,PHE ,CHLOR	Agilent Zorbax SB-CN column	0.02 M phosphate buffer (pH:4) and ACN (85:15,v/v)	365	1. 5	2 2 ° C	20 and 120 µg/mL PARA, 8 and 48 µg/mL for oxolamine citrate, 0.4 and 2.4 µg/mL PHE, 0.16-0.96 µg/Mlchlor	N/A	N/A	le s s t h a n 2 %	(Pirol et al., 2011)
PARA and PHE	Synergi Polar RP (4 µm, 150 × 4, 6 mm I.D.) column	5:95, %vol./vol., contg. 65 mM phosphoric acid	220	1	N / A	PHE 5-30, PARA 100-600 (µg/mL)	PHE 0.877 ,PARA 27.75 (µg/mL)	PHE 2.658, PARA 84.09(µg/mL)	le s s t h a n 2 %	(Çubuk Demiralay et al., 2010)

PHE, AMB and LEVO	n reversed phase Luna C8 (5 µm, 250 × 4.6 mm i.d.) phenomenex	phosphate buffer of pH 3.0 and solvent mixt. (MeOH:ACN in the ratio of 1:2)	273 and 230	1	N/A	Phe 100.18%, GP 99.92%, AMBH100.26%, andLCZH 100.22%	N/A	N/A	N/A	(S. Joshi et al., 2011)
PHE, DEX and LIN	Agilent C18 column (4.6 m × 150 mm, 5 µm)	0.02 mol/L diammonium hydrogen phosphate:ACN (vol./vol. 75:25)	240	N/A	N/A	N/A	N/A	N/A	N/A	((测定复方盐酸去氧肾上腺素喷鼻液中 地塞米松磷酸钠 盐酸去氧肾上腺素 和盐酸林可霉素的含量, n.d.)
PHE and CHLOR	Analytical column, Spherisorb, 5 lm, 4.6 · 150 mm	MeOH:water:ACN(70:22:8 (v/v/v)	280	0.9	Ambient temperature (20–22C)	PHE 0.15–15,CHLOR 0.03–5(lg/ml)	PHE 3.75,CHLOR 2.50(lg/ml)	PHE 10.08, CHLOR 4.32 (lg/ml)		(Al-Shaalan, 2010)
ACE, PHE AND CRB	: The analytical column was a reversed phase Luna Phenomenex C18 (5 µm, 300 mm x 3.9 mm)	60%MeOH and 40% potassium monobasic phosphate aqueous solution (62.46 mmol L-1) added with 1 mL phosphoric acid, 0.50 mL triethylamine and 0.25 g sodium lauryl sulfate.	220 PHE,CAR and at 300 ACE	1	27°C	N/A	ACE a 12.50PHE 0.36ACE b 20.95CAR 0.99*	ACE a 41.69 PHE a1.18ACE b 69.86CAR b3.10**	N/A	(Bastos & De Oliveira, 1951)

ACE, PHE, DEX and CHLOR	silica column (PerfectSil Target, 250 4.6 mm, 5 mm)	MeOH: water (containing 6.0 g of ammonium acetate and 10 ml of triethylamine per liter, pH adjusted to 5.0 with orthophosphoric acid), 95:5%(v=v)	25, 42, 20, 227	1.2	30 C,	ACE 162.5–650 PHE , 2.5–10,DEX 7.5–30, and CHLOR 1–4 mg=ml	N/A	N/A	N/A	(Heydari, 2008)
PHE, PARA, CHLOR and DEX	ACE C18 column (250 · 4.6 mm, 5 lm particle size)	(A) ACN and (B) sodium perchlorate solution (pH 3, 0.01 M). The initial ratio of mobile phase components (A/B) was 5:95	204	1.4	35 C	PHE 0.48–52 CHLOR 0.48–44 PARa 4–240 DEX 0.4–19 (lg mL)1)	0.03 lg mL)1 for PHE, 0.08 lg mL)1 for CHLOR, 0.10 lg mL)1 for PARA and 0.13 lg mL)1 for DEX.	0.08 lg mL)1 for PHE, 0.24 lg mL)1 for CHLOR, 0.29 lg mL)1 for PARA and 0.38 lg mL)1 for DEX	N/A	(Palabıyık & Onur, 2007)
ACE, PHE and CHLOR	HS PEG (polyethylene glycol) column (Supelco, Alcobendas, Madrid, Spain), 15 cm × 0.46 cm	20 mM phosphate buffer at pH 7.0/ACN 80:20 (v/v)	210 PHE,CHLOR and at 305 ACE	1	35 ◦C	ACE 0.13889–0.69444 ,PHE 0.00278–0.01389, CHLOR 0.00111–0.00556 (mg ml−1)	N/A	N/A	N/A	(Marín & Barbas, 2004)
ACE, PHE and CHLOR	1530.46 cm, 5 mm, Discovery HS PEG poly(ethylene glycol) column	20 mM phosphate buffer, pH aliquot was filtered using a 0.45-mm syringe filtra- 7.0– acetonitrile (90:10, v/v). The phosphate buffer tion disk to the vials for injection into the HPLC was prepared from H PO by adding NaOH to reach 3 4 system. In all cases three replicates were	215 PHE ,CHLOR , 310 FOR ACE	1	35 ◦C	PHE 0.15–0.25 ACE 7.5–12.5CHLOR 0.06–0.10mg/ml	PHE 0.0002 to 0.006, CHLOR 0.0001 to 0.002 mg/ml.	ACE 0.01 to 0.07 mg/ml, PHE 0.0002 to 0.006 mg/ml	N/A	(García et al., 2003)

		processed. pH 7.0								
PPA in addition To PHE and CHLOR	Daisopak SP-120-5-ODS-BP column (250 4.6 mm i.d., 5 m, Daiso)	MeOH–ACN–CH3COOH (0.1 M)–TEA (20:20:60:0.6, v/v/v/v) containing HSA (0.5 mM) as an ion pair.	254	1	N/A	2.5–1000 M	0.48 and 0.13 M for PPA and PHE, respectively, and 0.14 M for CAFF and CPA.	N/A	N/A	(Nakashima et al., 2002)
PARA,PHE, and CHLOR	CN RP analytical column from Waters (Milford, MA) (125 Å, 10 µm, 3.9 × 150 mm	phosphate buffer (pH 6.22) and ACN (22:78, v/v). The phosphate buffer was prepared by dissolving 1.36 mL orthophosphoric acid in 1 L water. Triethylamine was added to the phosphate buffer solution in order to adjust the pH to 6.22	265	1.5	22° C,	PARA 25–120PHE 0.3–10CHLOR 0.2–3 (µg/Ml	PHE 0.0325 µg/mL and CHLOR 0.0279 µg/mL	PHE 0.251 µg/mL CHLOR 0.184 µg/mL	N/A	(Senyuva & Ozden, 2002)
ACE,PHE and CHLOR	5 m particle SymmetryShield RP8 (Waters, Madrid, Spain) column (250×4.6 mm	A: phosphate buffer 40 mM at pH 6.0 and solvent B: acetonitrile. The phosphate buffer was prepared from KH2PO4 by adding KOH to reach the pH 6.0.	215 PHE,CHLOR 280 ACE	1	35 °C	CAPSULES ACE 0.154 to 0.461 mg/ml, PHE 3.04 to 9.13 g/ml and CHLOR 1.30 to 3.89 mg/ml. IF SACHETES ACE 0.195 to 0.583 mg/ml	1.2×10−4 mg/ml PHE and 1.5×10−4 mg/ml CHLOR	N/A	N/A	(Marín et al., 2002)
CHLOR (2.0 mg), PHE (5.0 mg), CAFF (15.0 mg) and ACE (500 mg)	inertsil ODS - 3, (250 × 4.6 mm) 5 µm	0.01M potassium dihydrogen phosphate and acetonitrile (85:15)	215, 300	N/A	N/A	N/A	N/A	N/A	N/A	(Kanumula et al., 2001)
PHE,	µBondapak	MeOH-pH 7.2 phosphate buffer		N/	N/	N/A	N/A	N/A	N/	(Wang, Da Peng;

TET and CHB	C18 column	(70:30		A	A				A	Tu, Yu Hsing; Allen, Loyd V., n.d.)
PHE, PAP and GUA	octadecylsilane columns used were packed 8 in the lab (25 cm X 4-mm i.d.)	350 ml of MeOH, 625 ml of water, and 25 ml of pentanesulfonic acid sodium salt in glacial acetic acid"? The methanol concentration had to be adjusted to between 25 and 40%	270	2	N/A	N/A	N/A	N/A	N.A	(Schieffer & Hughes, 1983)

CRB carbinoxamine maleate,LIN lincomycin hydrochloride,TET tetracaine hydrochloride,CHB chlorobutanol

Planar Chromatography (Thin Layer Chromatography - TLC)

A breakthrough is high-performance thin-layer chromatography (TLC). TLC resolution improves increasing automation, and so does quantitative data integrity. HPTLC can analyse several samples with minimal to no solvent. Analyzing, exposing, and disposing of hazardous organic effluents is less affordable, leading in less pollution to the environment. (Sherma, 2010)We provide HPTLC methods for determining PHE concentrations in pure form as well as in medicines. Classical chromatography is enhanced by high performance thin-layer chromatography (TLC). TLC resolution increases with automation, as does quantitative information quality. Due to its high throughput and low solvent demands, HPTLC was appropriate for swiftly analysing a large amount of samples. Less money is spent on analysing, exposing, and disposing of hazardous organic effluents, which is good for the environment. The following are HPTLC techniques for detecting PHE in isolation and in medicaments.

Table 8 HPTLC Alone And Combined Entity

Analyte	**matrices**	**MOBILE PHASE**	**CHAMBER SATURATION (MIN)**	**DETECTION(NM)**	**RF**	**LINEARITY (µG BAND−1)**	**LOD (µG BAND−1)**	**LOQ (µG BAND−1)**	**CORRELATION COEFFICIENT**	**RSD**	**REF**
KETO, PHE	bulk drug and in combined dosage forms	CHCL3–MeOH–NH3(7:3:0.1, v/v) and (7.5:2.5:0.1, v/v)	30	273	KETO 1,622.25 , PHE 2,723.41	KETO 0.20–0.60, PHE 0.60–1.95	KETO 0.03 , PHE0.15	KETO 0.10 , PHE 0.50	KETO 0.9991 , PHE 0.9993	N/A	(El Yazbi et al., 2016)
KETO,	bulk drug	CHCL3-MeOH-NH3	30 at	261	KETO	KETO 0.12-0.50, PHE	KETO	KETO	KETO	less than	(Yazbi et

PHE , CHLOR	and in combined dosage form	(7.75:2.25:0.1, vol./vol.)	room temperature (25 ± 2 °C)		2.06x 10-8 PHE 1.14x 10-7 CPM 8.52x 10-7	0.075-0.27, and CPM 0.09-0.27	0.04, PHE 0.01 , CPM 0.01	0.12, PHE 0.03 , CPM 0.03	0.9994 ,PHE 0.9987, CPM0.9992	2%	al., 2016)
KETO, PHE	Combined Dose Formulation	C4H10 O: C2H5OH: NH3 (6:3.5:0.6, vol./vol./v)	30	288	0.30PHE and 0.67 KETO	1026-6156 ng per band for PHE and 300-1800 ng per band for KETO	PHE 89.36 ng per band, KETO 136.46 ng per band	PHE 295.5 ng per band, KETO 73.74 ng per band	N/A	less than 2 %	(Bhole et al., 2015)
AMB, PHE, CHLOR, PARA, GUA	tablet dosage form	C7H8: CH3OH: GAA(1.4:8.3:0.3, vol./vol./v)	N/A	277	N/A	AMB 1000-10000 ng band-1, PHE 200-2000 ng band-1, CPM 100-1000 ng band-1, PARA 100-1000 ng band-1 ,GUA 500-3000 ng band-1	N/A	N/A	N/A	N/A	(Kardile et al., 2015)
PHE , NIM, CET,CAFF	bulk and pharmaceutical dosage form	C7H8: C4H8O2: CH3OH: HCOOH (16:2:4:0.8, vol./vol./vol./vol.)	20	212	N/A	PARA , NIM ,CET,CAFF 200-1400 ng band-1, PHE 100-1400 ng band-1.	N/A	N.A	N/A	N/A	(Vidhate et al., 2015)
BRH ,PHE	tablet dosage form	MeOH: strong NH3(100: 1.5, vol./vol.	N/A	265	Rf value of PHE 0.32 and BROMO 0.43	0.8-3.6 µg/spot for brompheniramine maleate and 2.0-9.0 µg/spot PHE	N/A	N/A	PHE 0.9992 and BPM 0.9997	BROMO 1.5 and PHE 1.1	(Janwitayanuchit & Lukkanatinapoorn, 2014)
CET , PHE	Fixed Dose	C7H8: C4H8O2: MeOH: NH3 (5:2:3:0.4	N/A	254	PHE 0.3130 ± 0.05	2-12 µg	PHE 0.306 ng/band	PHE 0.928 ng/band	PHE 0.99937, CTZ	below 2 %	(Wankhede et al.,

	Combination Tablets	vol./vol./vol./vol.).			and CTZ 0.49 ± 0.05		CTZ 0.598 ng/band	CTZ 1.815 ng/band	0.99992.		2013)
PARA, C6H8O6, CAFF, PHE	mixtures in commercial tablets	CH2CL2 - C4H8O2 - C2H5OH - HCOOH(3.5 + 2 + 4 + 0.5) (I) and CH2CL2 - C4H8O2- C2H5OH(5 + 5 + 1)	N/A	274 CAFF,PE, 264 C6H8O6, 254 PARA	N/A	N/A	N/A	N/A	N/A	PARA 2.7, CAFF 3.45, ASC 2.02, PHE 2.72	(El Sadek et al., 1990)

KETO, ketorolac ;PHE , phenyephirine;CHLOR , ;NIM ,nimesulide ;CET, cetrizine;GUA,gaufasine;$CHCL_3$,chloroform;MeOH ,methanol;NH_3 ammonia;$C_4H_{10}O$,n butanol;C_2H_5OH, ethanol;GAA glacial acetic acid;C_7H_8 toluene;$C_4H_8O_2$,HCOOH formic acid,BRH brompheniramine maleate

Electroanalytical Methods

Practitioners apply titration, spectrometry, chromatography, and immunoassays. Transmitting heavy, specialized analytical undertaking this project bedside measurements difficult and moment.(Sánchez et al., 2012) Electroanalysis is efficient, sensitive, and expense. Electroanalysis may evaluate PHE alone or in mixture.

Table 9 Electroanalytical Alone And Combined entity

ANALYTE	**METHOD**	**INDICATOR ELECTRODE**	**SOLVENT**	**LINEARITY**	**LOD**	**LOQ**	**REF**
PHE	Conductometric Titration Method	N/A	bismuth (III) tetraiodide	0.4-2.5 mg (8-50 µg/mL)	2.5 (µg/ml)	N/A	(Hasan et al., 2015)
PARA, CET and PHE	voltammetry	a multiwalled carbon nanotube-platinum nanoparticles nanocomposite modified carbon paste electrode	Cobalt (II)nitrate hexahydrate, iron (III) nitrate nonahydrate, ethylene (99.99%), chloroplatinic acid hydrate ,phosphate buffer (pH = 5.5)	PCT 3.51 × 10-7-5.61 × 10-5 M, CTZ 1.9 × 10-7-1.93 × 10-4 M ,PHE 2.9 × 10-7-5.69 × 10-5 M	PCT 2.79 × 10-8 M, CTZ 5.86 × 10-8 M , PHE 2.83 × 10-8 M	N/A	(Kalambate & Srivastava, 2016)
PARA, PHE and DEX	Voltammetry	carbon paste electrode (3 mm diameter CPE), a KCl- saturated calomel reference electrode (SCE)	N/A	PA 1.0 × 10-7-1.0 × 10- 3 M, PHE 8.0 × 10-6-8.0 × 10-5 M and DEX 8.0 × 10-6-8.0 × 10-4 M,	PA 1.5 × 10-8, PHE 9.5 × 10-7 and DX 2.9 × 10-6 M,	N/A	(Amiri et al., 2014)
PHE	pulse voltammetry	INP-Nafion-modified CPE	Ferric chloride (FeCl3·6H2O), ferrous chloride(FeCl2·4H2O), ammonia solution (25 wt. %), sodiumhydroxide, hydrochloric acid (37 wt.%	5 µM-130 µM	0.76 µM	N/A	(Pourghobadi & Niazi,

							2014)
PHE	differential pulse anodic stripping voltammetry	carbon paste electrode (CPE	Polyethylene glycol tert-octyl phenyl ether , Graphite powder	0.04-100 µM	0.0097 µM	N/A	(Gholivand et al., 2013)
PHE	Potentiometry	Ion-selective membrane electrodes	dibutyl phthalate (DBP), phospohotungstic acid (PTA), sodium tetraphenylborate (NaTPB), acetophenone (AP), 2-nitro-phenyloctyl ether (2-NPOE), oleic acid (OA), tetrahydrofuran (THF)	1.0 × 10-5-1.0 × 10-1	N/A	N/A	(Giahi et al., 2010)
PHE	differential pulse voltammetry	moleculary imprinted polymer glassy carbon electrode	0.003M K2HPO4, CAN	N/A	N/A	N/A	(Yao et al., 2009)
PHE and CHP	cyclic voltammetry	poly(4-aminobenzene sulfonic acid) modified glassy carbon electrode	0.1 M NaH2PO4–Na2HPO4 (pH 7.0)	PHE 1 × 10-7 to 1.5 × 10-5 M , CPT 2 × 10-6 to 4.5 × 10-5 M	PHE 1 × 10-8 , CPT1 × 10-7 M	N/A	(F. Huang et al., 2008)

PARA paracetamol; CET cetirizine; PHE phenylephrine ;DEX detromethophan,CHP chlorprothixene,DIX dioxopromethazine

Capillary Electrophoretic Methods

HPLC results was utilized to construct a capillary electrophoresis (CEs) technique. CE is preferable than HPLC for distinguishing biomolecules. Electrophoresis and electrochromatography are often used together. (Voeten et al., 2018)Capillary electrophoresis of PHE and other drugs (DEX, PARA, and CHLOR) has been presented by Palabiyik, who still presented multivariate optimization and validation of the method (chlorpheniramine maleate). Describe the supplementary CE methodologies was using to verify PHE.

Table 10 Capillary electrophoresis alone and combined entity

ANALYTE	**MATRICES**	**METHOD**	**STATIONERY PHASE**	**SOLVENT**	**DETECTION**	**LINEARITY**	**LOD**	**LOQ**	**REF**
PHE	pharmaceuticalproducts	CZE	Agilent 7100 CE instrument, fused silica capillary (59.5 cm total length, effective length	Tetraborate buffer, 0.1 M NaOH solution	214nmUV-DAD	5 to 30(µg/mL)	1.715(µg/mL)	5(µg/mL)	(Franco & Jasionowska, 2013)

			49.5 cm						
PHE	pharmaceuticalproducts	CE	N/A	50 mmol/L borate buffer (pH 10.00)	amperometric detection	2-100 µmol/L	0.8 µmol/L	N/A	(Y. Huang et al., 2010)
DEX, PHE, PARA and CHLOR	pharmaceuticalpreparation	CE	ACE C18 column (Advance Chromatography Technologies, Scotland) 250 × 4.6 mm, 5 µm	Na2HPO4·12H2O (pH 8, 0.1 M)	200 nm	4.0 – 20.0 µg mL–1 for DEX, 4.0 – 20.0 µg mL–1 forPHE, 1.6 – 8.0 µg mL–1 for CHLOR and 50.0 – 600.0 µg mL–1 for PARA	DEX 1.94, PHE 1.46, CHLOR 0.007, PARA 12.34	DEX 4.00, PHE 4.00, CHLOR1.60,PARA 50.00	(Palabiyik & Onur, 2010)
ACE, PHE, and CHLOR	capsules	CE	0.5 mM SDS at 30 kV in an uncoated silica capillary	0.5 mM CTAB,MeOH/water 1:1 (v/v)	200 nm	ACE 12.5–125 (mg ml−1),PHE 6.25–125(mg ml−1),CHLOR 25–125(mg ml−1)	N/A	N/A	(Marín & Barbas, 2004)
DIXa nd PHE	eyedrops	capillary isotachophoresis	N/A	10-2 M NH4OH with acetic acid as counterion added to pH 5.4,railing electrolyte was 5x10-3 M β-alanine.	N/A	N/A	N/A	N/A	(Kubacák et al., 2004)
PHE	API	capillary isotachophoresis	N/A	(20 mM 4-aminobutyric acid-HOAc or 5 mM caproic acid as following ion, pH 4.72, and 20 mM KOAc-3% hydroxypropyl Me cellulose, pH 4.95, [cationic sepn.] or 7 mM HCl contg. glycylglycine counterion-0.3% hydroxypropyl Me cellulose-0.2% Triton X-100, pH 2.97, [anionic sepn.] as leading electrolyte).	254 nm	N/A	N/A	N/A	(Klein, Hans; Teichmann, n.d.)

Bioanalytical Methods

In contrast to PARA, CHLOR, and DEX, PHE is also employed to improve nasal congestion. Biological phenomena must be directly measured. Dr. Juan C. Dominguez-Romero has done research in time-of-flight mass spectrometry. PHE may be assessed both alone and in blends via bioanalytical methodologies.(Tijare et al., 2016)

Table 11 Bioanalytical Alone And Combined Entity

ANALYTE	METHOD	MATRIX	EXTRACTION TECHNIQUE	EXTRACTION SOLVENT	STATIONERY PHASE	MOBILE PHASE	DETECTION	FLOW RATE(mL/min)	LINEARITY	LOD	LOQ	REF
PES, PHE	HILIC	LS180 human intestinal cells	centrifugation	ACN	100 × 4.6 mm Nucleodur HILIC, 3 m column	A: ACN: MeOH: Buffer (72: 8: 20) B: 100%ACN	excitation wavelength of 268 nm and emission wavelength of 293 nm	0.8	0.0625 M–32 M for PES and 0.39–200 M for PHE	N/A	PHE 0.39,PES 0.063	(Shah et al., 2017)
PHE	(LC-TOFMS).	urine	N/A	MeOH/MECN(1:1), HPLC MILLIQ WATER, HCOOH	XDB C18 ANALYTICAL COLUMN OF 4.6mm*50mm	H2O with 0.1 M HCOOH and ACN	m/z range 50-1000 positive ion mode, 50-1100 negative ion mode	0.5	0.25-125mg/l	0.2	0.2	(Domínguez-Romero et al., 2015)

HILIC hydrophilic interaction liquid chromatography ; LC-TOFMS : liquid chromatography -time of flight mass spectroscopy; ACN :acetonitrile ;HCOOH: formic acid ;MeOH :methanol ;PES phenylephrine 3-O-sulfate

Chemometrics

Stacking spectra precludes identification of the active medicinal component in formulations and biological fluids. Numerical and graphical algorithms correct the original absorption spectra. Al-Shaalan et al. employed chemo metric-assisted spectrophotometric and HPLC-UV to quantify PHE and CHLOR (chlorpheniramine maleate). Chemo metrics employed partial least squares (PLS). Applying chemo metrics is straightforward.(Biancolillo & Marini, 2018)

Table 12 Chemo metric Alone and Combination Entity

ANALYTE	METHOD	STATIONERY PHASE	MOBILE PHASE	DETECTION(nm)	LINEARITY	LOD(µg/ml)	LOQ(µg/mL)	REF
PARA, GUA, PHE and PP	(PLS)	N/A	N/A	200.0–400.0	PARA 40– 50 µg mL-1, GUA 16–20 µg mL-1, PHE 1–9 µg mL-1	N/A	N/A	(Yehia & Mohamed, 2016a)

PHE and KETO	CLS, PCR, and PLS	N/A	N/A	244-274	N/A	N/A	N/A	(Elfatatry et al., 2019)
AMB, GUA, CET and PHE	(CLS), I (ILS), (PCR)	N/A	N/A	N/A	N/A	AMB 1.01 , GUA 1.07 , CET 0.48 and PHE 2.11	AMB 2.9 , GUA 3.2 ,CET 1.4 and PHE 6.3	(Arora, Madhur; Ritika; Sharma, n.d.)
PHE and CHLOR	(PLS)	analytical column , Spherisorb, 5 lm, 4.6 · 150 mm i.d	MeOH: H2O :ACN (80: 12:8 vol)	270	PHE D1 20–150 DD1 20–150 CLS 10–70 PCR 5–35 HPLC 0.15–15, CHLOR D1 10–60,DD1 10–60, CLS 2–10, PCR 1–6 , HPLC 0.03–5	PHE D1 5.44 , DD1 5.70 , CLS 4.75, PCR 5.79, HPLC 3.75, CHLOR D1 9.72, DD1 3.43, CLS 6.44, PCR 8.64 , HPLC 2.50	PHE D1 15.34, DD1 12.65, CLS 13.05, PCR 15.86, HPLC 10.08, CHLOR D1 40.64, DD1 7.54 , CLS 19.54 , PCR 24.90, HPLC 4.32	(Al-Shaalan, 2010)
PARA, PHE and CHLOR	(PCR) ,(PLS)	N/A	N/A	200 to 400	N/A	N/A	N/A	(Khoshayand et al., 2010)

PARA paraacetamol ; GUA Guaifenesin; KETO ketorolac tromethamine ;AMB ambroxol hydrochloride ; CET cetirizine hydrochloride; CHLOR chlorpheniramine maleate;PLS Partial Least Squares; CLS Classical Least Square; PCR principal component regression; ILS Inverse Least Square; MeOH methanol ;H_2O water,PP p-aminophenol

3. Discussion

PHE has been utilized in drug manufacturing, UV/VIS spectroscopy, and HPLC since 1938. PHE's insolubility makes bioanalytical or capillary electrophoretic studies tricky. Sample solution consisted MeOH and ACN.TOF-MS drug analysis for pharmaceutical formulations must adopt HPLC with UV detection. Modern chemo metrics can estimate a drug's effectiveness.Recent advances in PHE 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.

4. Conclusion

This research is aimed at spectrophotometric and spectrofluorometric chromatographic characterization of PHE 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 PHE analysis. Though there are established protocols for determining and managing PHE 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.

Abbreviations

- PHE – Phenylephrine
- ACN – Acetonitrile
- SAL- salbutamol
- KETO- ketotifen
- EtOH - Ethanol

- HCl - Hydrochloric acid
- HPLC –high performance liquid chromatography
- HPCE - High performance capillary electrophoresis
- HPTLC - High performance thin Layer Chromatography
- KH_2PO_4 - Potassium dihydrogen phosphate
- LC-MS - Liquid chromatography/mass spectrometry
- MeOH - Methanol
- PARA - Paracetamol
- UV/Vis - Ultra Violet/Visible
- TLC – Thin Layer Chromatography

Conflict of Interest

Authors declare no conflict of interest

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