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A Review on Analytical Methods for Piperazine Determination

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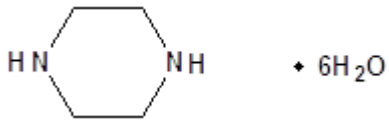
Abstrac, Piperazine compounds mediate their anthelmintic action by generally paralyzing parasites, allowing the host body to easily remove or expel the invading organism. It is an anthelmintic drug in human as well as in veterinary medicine. This review article represents the various analytical methods which have been reported for estimation of piperazine. Colorimetric , spectrophotometric techniques and chromatographic methods like high-pressure liquid chromatography [HPLC] and revered phase high-pressure liquid chromatography [RP HPLC], gas chromatography [GC], liquid chromatography–mass spectrometry [LC-MS] and another methods were reported.

Keywords: piperazine , anthelmintic drug , spectrophotometric techniques, chromatography

Introduction

Piperazine is an organic compound that consists of a six-membered ring containing two opposing nitrogen atoms.



piperazine hexa hydrate

Piperazine exists as small white crystals with a saline taste. Piperazine is freely soluble in water and ethylene glycol, but insoluble in diethyl ether. It is a weak base with two pKb of 5.35 and 9.73 at 25° C . piperazine can be synthesized by reacting alcoholic ammonia with 1,2-dichloroethane,by the action of sodium and ethylene glycol on ethylene diamine hydrochloride, or by reduction of pyrazine with sodium in ethanol[1,2].

First, it used as a solvent for uric acid to produce a soluble urate , the use of piperazine as an anthelmintic agent was first introduced in 1953. Upon entry into the systemic circulation, the drug is partly oxidized and partly eliminated as an unchanged compound. Piperazine are used in the treatment of worm

infections (common roundworms; ascariasis and pinworms ; oxyuriasis) . It's an action to paralyze the worms and then passed in the stool [3].

Analytical Methods

A. The official method:

The official method, used for the determination of piperazine in its formulations, is the gravimetric method with 2,4,6-trinitrophenol (picric acid) in the latest editions of most Pharmacopoeia [4].

B. Reported Method:

I. Colorimetric and Spectrophotometric methods:

Colorimetric methods were developed for the determination of piperazine in pharmaceutical formulations and commercial preparations [5,6,8] . Charge transfer reaction also was applied for the spectrophotometric determination of piperazine in pharmaceuticals [7,9-14]. Coupling reaction was developed for the determination of piperazine in pharmaceutical formulations [15]. Complex formation reaction were applied to real piperazine samples [16-18 , 21] .Table (1)

Table 1: Summary of colorimetric and spectrophotometric methods

Title	Reaction	Reagent	Wave Length (nm)	Linearity or LOD	pH	Ref.
Colorimetric determination in pharmaceutical formulations	Charge transfer	aqueous 1,2-naphthoquinone-4-sulphonate	490	20-120 µg/ml	7.5	5
Spectrophotometric determination in pharmaceutical preparations	Coupling reaction	2,6-dichloroquinonechlorimide	525	6.4-51.2 µg/ml		15
Spectrophotometric determination of piperazine and its salts in pharmaceuticals.	-	nitrous acid	239	1-15 µg/ml	2.3-2.6	19
Utility of chloranil in assay of piperazine	Charge transfer	Chloranil	540	2.5-12.5 mg %		7
Colorimetric	Condensation	Folin's amino acid	490	0-200		8

determination of piperazine in pharmaceutical formulations	reaction			µg/ml		
Determination of pure and dosage forms of piperazine	Charge transfer	benzoquinone and its halo derivatives	506	13-120 µg/ml		9
Colorimetric determination of piperazine	Charge transfer	*p*-benzoquinone	516	2–10 µg/ml	5.4	6
Spectrophotometric method for the determination of piperazine	Oxidative coupling	phenothiazine and N-bromosuccinimide in aqueous methanol	595	0.5–5 µg/ml		20
The use of dichlone as a reagent in pharmaceutical analysis	Charge transfer	Dichlone	505	3.06 µg/ml		10
Spectrophotometric determination of some chlorobenzoquinones with piperazine	Charge transfer	2,5-dichloro-, 2,6-dichloro- and 2,3,5,6-tetrachloro-1,4-benzoquinones	387-409	2-15 µg/ml		11
Spectrophotometric estimation of piperazine in dosage forms	Charge transfer	2,3-dichloro-1, 4-naphthoquinone	580	0.5- 3 µg/ml		12
Spectrophotometric analysis of certain drugs	Charge transfer	o-chloranil	540	10-400 µg/ml		13
spectrophotometric methods for the determination of amino compounds	Complex formation	Cu-nitrilotriacetic acid		0.1-2.6 µg/ml		21
Gravimetric and spectrophotometric methods for the determination of piperazine	Ion pair complex	picrolonic acid	343	$1*10^{-6}$ to $7*10^{-5}$ mol l^{-1}	7.5	16
Spectrophotometric determination of piperazine	Complex formation	chloranilic acid	345	1-10 µg/ml		17

Spectrophotometric determination of piperazine	Charge transfer	3,5-dibromo-2-methyl-p-benzoquinone	642	2-8 µg/ml	14
Spectrophotometric Assay of Piperazine Hexahydrate	Proton transfer	3,5- Dinitrosalicylic Acid	410	0.5-20 µg/ml	18

II. Chromatographic Methods :

Separation and identification of piperazine is showed by the paper chromatography [22]. Separation and identification of piperazine by thin – layer chromatography [23,24] . The HPLC for piperazine estimation [25-33,40-42]. GC method for the determination piperazine in pharmaceutical drug substances, chicken and pig tissues [34,35,42] . RP HPLC for analysis of trace quantities of piperazine in aqueous solutions and in human plasma [36,37] . Capillary GC for the determination of piperazine in working atmosphere, human urine and pharmaceuticals [38,39] . Table (2)

Table 2: Summary of chromatographic methods for piperazine determination

Title	Method	Mobile phase	Stationary phase	Wave length	Ref.
Separation and identification of piperazine	Paper chromatography	Propanol-ethanol-water (1:6:4)			22
Separation and identification of piperazine	Thin-Layer chromatographic Separation	Acetic acid – methanol – ethanol (3:1:1)	Silica gel		23
Separation and determination of piperazine	Thin-Layer chromatographic Separation	n-butanol-acetic acid-water (4 : 1 :l)	Silica gel 60 F-254 pre-coated TLC plates (E. Merck, Darmstadt, G.F.R.), 20 x 20 cm, layer thickness 0.25 mm,	254	24
Analysis of trace quantities of piperazine in aqueous solutions	Reversed –phase high – performance liquid chromatography	Acetonitrile/ultrapure water	-	254	36
Determination of	Capillary gas		A Duran 50		38

piperazine in working atmosphere and in human urine	chromatography with Nitrogen and mass-selective detection		borosilicate glass capillary column (15 m x 0.32 mm I.D.) coated with PS-255 as stationary phase (film thickness 0.75 µm)		
Determination of piperazine ferulate in human plasma	Reversed –phase high – performance liquid chromatography	Phosphate buffer - methanol	Ultrasphere ODS column	254	37
Determination of piperazine in human plasma	High-performance liquid chromatography-electrospray ionization tandem mass spectrometry	10 mM ammonium acetate solution (pH 3.0)-methanol (50: 50, v/v).	Agilent ZORBAX SB-C (18) column		25
Determination of Piperazine in Vortioxetine Hydrobromide	High-performance liquid chromatography–mass spectrometry	formic acid and acetonitrile	Waters SunFire C8 column		26
Determination of piperazine residues in whole eggs, albumen, and yolk	High-performance liquid chromatography – fluorescence detection	Acetonitrile/ultrapure water	a Waters Athena C18 column (2.1 mm 250 mm, 5 mm) at 25 C.		27
Determination of piperazine in pharmaceutical drug substances	Gas chromatography	The carrier gas used was Helium at a flow of 2 mL/min	DB-17, 30 m, 0.53 mm and 1µm film thickness		34
Piperazine in an active pharmaceutical ingredient	High-performance liquid chromatography - UV	A mixture of Acetonitrile, Methanol and diethyl amine in the ratio of 90:10:0.1(v/v/v)	Chiralpak IC (Diacel) of dimensions 250 X4.6 mm, 5µm	340	28
Determination of Piperazine Residues in the Presence of other Secondary and Primary Amines	High-performance liquid chromatography with diode array detection	hexane-2-propanol mixture in the gradient 90:10–70:30% v/v	SG-MIX (125 4.6 mm I.D.; dp ¼ 5 mm particle size	335 and 365	29
Quantification of piperazine in animal products	High-performance liquid chromatography with fluorescence detection	acetonitrile	C18 129 column (Waters Xbridge; 4.6 mm × 250 mm, particle size, 5 µm;	338 and 523	30
Quantification of piperazine in chicken and pig tissues	Gas chromatography–electron onization tandem mass spectrometry	The carrier gas used was Helium at a flow of 1 mL/min	Amine(30mx0.25 mm i.d.0.25 µm)column		35
Detection of piperazine in chicken	High-performance liquid chromatography-fluorescence detector	ultrapure water and acetonitrile (5:95,	Athena C18 (4.6 mm × 250 mm,	330 and 531	31

tissues and pork	(HPLC-FLD)	V/V)	id.: 5 µm) column		
Determination of Piperazine in Pharmaceutical drug substances	High performance liquid chromatography (HPLC) with evaporative light scattering detection (ELSD).	acetonitrile , deionized water and 0.1% trifluoroacetic acid	An Alltech Alltima Cyano (250 4.6 mm) column6		32
Determination of residual piperazine used in bulk drugs	High-performance liquid chromatography-UV detection	0.01 M KH_2PO_4 (PH7.3) , Acetonitrile	Nucleosil C18	254	33
Determination of residual piperazine in pharmaceuticals	Capillary gas chromatography		30 m x 0.3 mm i.d fused silica column coated with a 3.0 µm film of 5% cross linked Ph-Me silicone		39
Assay of piperazine in some pharmaceutical formulations	Cation-exchange high-performance liquid chromatography	0.07 M KH_2PO_4 (pH 3.0) buffer-triethylamine (100:0.01)	A 250x4.6 mm I.D. 10 /xm Ultrasil CX cation-exchange column	254	40
Quantification of Piperazine in Chicken Muscle	Ultra-performance liquid chromatography electrospray ionization mass spectrometry	ammonia water/ acetonitrile = 1:9, v/v).	UPLC HSS T3 column (100 × 2.1 mm; 1.8 µm)		41
Determination of aliphatic and alicyclic amines in water	Gas chromatography	helium as carrier gas (1.0 ml/min)	DB-5 fused-silica capillary column (30 mx0.25 mm I.D., 1µ m film thickness,		42
Determination of aliphatic and alicyclic amines in water	High-performance liquid chromatography /fluorescence detection	acetonitrile	a Macherey-Nagel ET 150 mm/8 mm/4 mm Nucleosil packed with 5 lm C18 material.	280 and 335	42

III. Alternative Methods :

Various methods have been employed for the determination of piperazine or its salts in pharmaceutical preparations, such as non-aqueous titration [43-45], gravimetric [46,47,16], polarographic [48] , volumetric [49], infrared spectrophotometry [46,50] and capillary electrophoresis [51].

Conclusion

Presented systematic review covers the current analytical methods for the determination of piperazine and its salts in pharmaceutical and biological samples like plasma, tissues, human urine. HPLC method

were found to be most widely used for piperazine . The presented information is useful for the future study for researcher involved in formulation development and quality control of piperazine.

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