ANALYTICAL METHODS FOR QUANTITATIVE ESTIMATION OF CHLORPHENIRAMINE MALEATE: A REVIEW

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ABSTRACT

Background: Chlorpheniramine Maleate is a first-generation alkylamine antihistamine used in the prevention of the symptoms of allergic conditions such as rhinitis and urticarial. Chlorpheniramine maleate was FDA approved in the united state as a prescription-only productin 1948, and laterin 2010, it got approval as an over-the-counter medication.
Design, synthesis of chlorpheniramine maleate has one asymmetric carbon atom,exists as racemic mixture of R and S forms and does not show optical rotation. It is a histamine H1 receptor ant agonist used as an anti-histamine.
Method: Various analytical techniques for the quantification of chlorpheniramine maleate for bulk, pharmaceutical formulations and biological samples have been reported. Assay methods include UV-spectroscopy, high performance liquid chromatography, high performance thin layer chromatography.
Result: Literature review reveals that methanol is the most commonly used solvent for the analysis of chlorpheniramine maleate by spectroscopic technique. For estimation of chlorpheniramine maleate by high performance liquid chromatography, methanol and acetonitrile are the commonly used organic solvents in the mobile phase and phosphate buffer or triuroacetic acid is used to maintain the pH of the mobile phase. Protein precipitation technique is used widely for extraction of the chlorpheniramine maleate from biological samples though liquid-liquid extraction and solid phase extraction has also been reported in fewer articles. The electroanalytical techniques reported for the analysis of the drug have provided methods with lower analysis time.
Conclusion: Amongst all the developed analytical methods, HPLC has been reported extensively for the quantitation for chlorpheniramine maleate.

Keyword Chlorpheniramine Maleate, analytical methods, HPLC

1. INTRODUCTION

Antihistamines are pharmaceutical agents which act by stimulating histamine action in the H1-receptors, there by antagonizing most of the smooth muscles to alleviateor prevent the symptoms of hay fever and other allergies and put a stop to motion sickness, nausea, vomiting, and dizziness. In addition, since antihistamines may cause drowsiness as a side effect, some of them may be used as an opponent to insomnia. Some antihistamines are used in the handling of nervous and emotional conditions to help control anxiety and to relax patients before surgery.[1] The less sedating behavior of new antihistamines have led to higher doses, which may contribute to asthma therapy by increasing vascular permeability.[2–6] Chlorphenamine, a histamine H1 receptor antagonist has been proven to reverse chloroquine resistance in Plasmodium falciparum [7] and is recommended for runny noses and seasonal allergies. Although cetirizine and levocetirizine are both important second generation antihistamines, their study has revealed that the antihistaminergic activity of the racemate is primarily due to levocetirizine.[8] Chlorpheniramine maleate (CPM), (R/S)-3-(4-chlorophenyl)-N,N-dimethyl-3-(pyridin-2-yl)propan-1-amine maleate 2-chloropyridine (Fig. 1)[9] is a first-generation alkyl amine antihistamine, act by antagonizing H1-receptors. It is commonly used in pharmaceutical preparations for symptomatic relief of the common cold and allergic rhinitis with mild sedative property. [10] It is commonly formulated as tablets, injections and syrups as single component preparations and is one of the popular ingredients in other formulations such as cough remedies and creams. Numerous UV, HPLC and HPTLC based methods have been reported[11-16] and NMR spectroscopy,[17] polarographic method, [18] electrokinetic chromatography, [19] for estimation of these drugs alone as well as in combination with other drugs in pharmaceutical dosage forms. But no method had yet been reported for simultaneous estimation of these two drugs using HPLC in

bulk drug and pharmaceutical dosage forms. Therefore, the present work was aimed to new developed synthesis and validate new HPLC method for estimation of CPM in pharmaceutical dosage forms

The molecular weight of chlorpheniramine maleate is 390.9g/mol and it Is appears as odourless, white crystalline solid or white powder with bitter taste**.** It is freely soluble in water soluble in alcohol and in chloroform,slightly soluble in ether and in benzene.

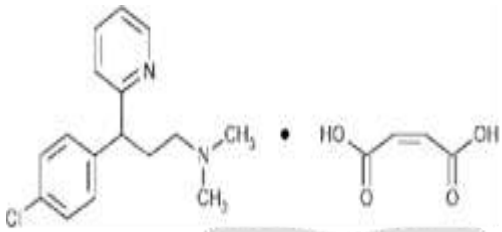

Fig No.1: Chlorpheniramine Maleate

2.SAMPLE PREPERATION

CPM is unstable in the presence of light and moisture thus the monograph in the pharmacopoeia indicates special storage condition. As per the Indian Pharmacopoeia CPM is required to be stored protected from light as well as moisture and at a temperature 37°C. US Pharmacopoeia indicates preserve the API in tight containers (12). Thus, sample preparation is required to be done in amber glassware. It has been mentioned to use freshly prepared solvents always for the drug (10-11). Methanol has been used as a diluent for majority of the spectrophotometric method of analysis for CPM. Extraction of the drug from the biological sample includes sample preparation via protein precipitation, liquid-liquid extraction and solid phase extraction (44-57). Acetonitrile has been reported extensively for the sample preparation by protein precipitation

3.ANALYATICALMETHODS

4. UV SPECTROPHOTOMETRY In the literature, different UV –Spectrophotometric method has been explored for the quantitative estimation of CPM in combination with drug, including simultaneous equation method, Q-absorbance Ratio method and derivative method. Water is commonly used as a solvent for CPM in the spectrophotometric method have reported method for estimation of CPM alone while other have reported simultaneous estimation with other API. Table1 list

The spectrophotometric method for analysis of CPM.

Table1: Reported spectroscopic method for determination of chlorpheniramine maleate individually or in combination with other drugs from the Pharmaceutical Dosage Form

Sr.No	API	Combined Drug	Solvent	Method	λmax	Reference
1	Chlorpheniramine Maleate	Paracetamol Phenylephrine HCL	0.1N NaOH	Spectrophotometric method	222.4 nm	1
2	Chlorpheniramine Maleate	Dextromethorphan HBr	Methanol	UV-Spectrophotometric method	262.6 nm	2
3	Chlorpheniramine Maleate	-	Distilled H_2O Sulfuric acid(0.25 mol/L)	UV-Spectrophotometric method	265 nm	3
4	Chlorpheniramine Maleate	Diethylcarbamazine citrate	Distilled H_2O	UV-Spectrophotometric method	261 nm	4
5	Chlorpheniramine Maleate	Phenylephrine HCl, phenylpropanolamine HCl	Distilled water	UV-Spectrophotometric method	269.5 nm	5
6	Chlorpheniramine Maleate	-	HCL, Acetate buffer, phosphate buffer, distilled water	UV-Spectrophotometric method	261 nm	6
7	Chlorpheniramine Maleate	Phenylephrine HCL, Caffeine, Paracetamol	Methanol, ethanol, 0.1N HCL	UV - Spectrophotometric method	263 nm	7
8	Chlorpheniramine Maleate	Diphenylamine hydrochloride	Potassium Permangnate.	UV-Spectrophotometric method	250 nm	8
9	Chlorpheniramine Maleate	Phenol Propanolamine Hydrochloride	Distilled Water	UV-Spectrophotometric method	261.6 nm/257	9
10	Chlorpheniramine Maleate	-	Distilled Water	UV-Spectrophotometric method	257 nm	10
11	Chlorpheniramine Maleate	Tincture Ipecac	Acetic Acid,	UV-Spectrophotometric method	254 nm	11
12	Chlorpheniramine Maleate	Caffeine	Distilled Water	Spectrophotometric method	261 nm	12

13	Chlorpheniramine Maleate	Phenylephrine HCl, Caffeine	Methanol Ethanol HCL	UV-Spectrophotometric method	263 nm	13
14	Chlorpheniramine Maleate	Methscopolamine nitrate	Methanol Distilled Water	Multiwavelength Spectrophotometric method	265 nm	14
15	Chlorpheniramine Maleate	Phenylephrine Hydrochloride	-	UV-Spectrophotometric method	262 nm	15
16	Chlorpheniramine Maleate	Phenylephrine Hydrochloride	0.1N NaOH equimolar solution in methanol	UV-Spectrophotometric method	271.6 & 250.2 nm	16

5.HPLC METHOD:

Among the chromatography method employed for the analysis of pharmaceuticals, high performance liquid chromatography is the most widely used technique. Several assay procedures and analysis related substance mentioned in the pharmacopeia's comprise the HPLC technique. More than 15 HPLC method for the estimation of chlorpheniramine maleate have been summarized in table and several methods for estimation of the drug in biological samples have been summarized in table 2.

Sr. no	API	Combined Drug	Solvent	Method	λmax	Reference
1	Chlorpheniramine Maleate	Ibuprofen Phenylephrine hydrochloride	Methanol: Phosphate buffer: Acetonitrile (20:30:50)	HPLC	220 nm	17
2	Chlorpheniramine Maleate	Phenylephrine Hydrocholoride	Acetonitrile & Phosphate buffer (55:45v/v)	HPLC	255 nm	18
3	Chlorpheniramine Maleate	Paracetamol Pseudoephedrine, Bromhexine	Triethylamine-phosphatic acid buffer & MeOH(35:65)	HPLC	215 nm	19
4	Chlorpheniramine Maleate	Caffeine Acetaminophen	Acetonitrile ion pair solution and tetrahydrofuran (13:14:87v/v)	HPLC	215 nm	20
5	Chlorpheniramine Maleate	Acetaminophen, Phenylephrine,	Methanol	RP HPLC	227 nm	21

		Dextromethorphan				
6	Chlorpheniramine Maleate	Distilled Water	RP-HPLC	HPLC	270 nm	22
7	Chlorpheniramine Maleate	Phosphate buffer (pH6.22) acetonitrile (22:78v/v)	HPLC	HPLC	265 nm	23
8	Chlorpheniramine Maleate	Phenylephrine hydrochloride	Methanol/Phosphate buffer (50 ml 0.2 m Monobasic Potassium Phosphate	HPLC	269.0 nm	24
9	Chlorpheniramine Maleate	-	Acetonitrile methanol, tetrahydrofuran, hex sulphonic acid Sodium	HPLC	235 nm	25
10	Chlorpheniramine Maleate	Paracetamol, Caffeine	Methanol 0.05 M dibasic phosphate buffer (pH 4.0) inration30:70v/v	HPLC	215 nm	26
11	Chlorpheniramine Maleate	Dexamethasone	Methanol: Chloroform: 0.1NHCl	HPLC	254 nm	27
12	Chlorpheniramine Maleate	Ascorbic acid Acetaminophen Caffeine	Double distilled Water	HPLC	215 nm	28
13	Chlorpheniramine Maleate	Codeine Phosphate	Mix of acetonitrile &methanol & 1%phosphoricacidinthe ration78:10:12	HPLC	254 nm	29
14	Chlorpheniramine maleate	Caffeine Paracetamol Glyceryl glycolate	Acetic Acid glacial bi-n-butyl amine	HPLC	255 nm	30
15	Chlorpheniramine maleate	Aminophylline	H_2SO_4: Methanol (60:40v/v)	HPLC	264 nm	31
16	Chlorpheniramine Maleate	Oxolamine Citrate Phenylephrine Hydrochloride	0.02 m phosphate buffer (pH:4) Acetonitrile (85:15v/v)	HPLC	356 nm	32
17	Chlorpheniramine Maleate	Paracetamol, Ambroxol, Guaifenesin Phenylephrine Hydrochloride	A. 0.01m Sodium per chloride Monohydrate B. Acetonitrile	HPLC	228 nm	33

18	Chlorpheniramine Maleate	Paracetamol, Guaiphenesin, Phenylephrine HCl, Bromohexane HCl	A. Buffer10 ml KH_2PO_4 & 3.7 mm ion pair reagent. C. Mix of methanol & acetonitrile(3.2)	HPLC	220 nm	34

6. HPTLC Method:

Sr. No.	API	Combined Drug	Solvent	Method	λ max	Reference
1	Chlorpheniramine Maleate	Tartrazine	Methanol & water(1:1)	HPTLC	217 nm	35
2	Chlorpheniramine Maleate	-	Distilled Water	HPTLC	277 nm	36
3	Chlorpheniramine Maleate	Ambroxol Hydrocholoride Phenylephrine Hydrochloride, Paracetamol Guaiphenesin	-	HPTLC	277 nm	37
4	Chlorpheniramine Maleate	Paracetamol, Caffeine, Phenylephrine	Methanol: n-Butanol: Toluene: Acetic acid [8:6:4: 4:0,2V/V)	HPTLC	212 nm	38

7. Review of HPLC method for estimation of Chlorpheniramine maleate in Biological Sample

Sr No	Matrix	Internals Standard	Mobile Phase	Flow rate	Column	λ max	Reference
1	Human plasma	Graphene oxide /Fe3O4 polythionie	H2So4(98%) Thionine acetate (85%) HCl (37%w/w)	-	C18	262 nm	39
2	Biological	-	30:70(v/v) ethanol: H2O mixture0.1% w/v.	0.8ml	C18	190-1100 nm	40
3	Biological Matrix	-	Methanol Potassium dihydrogen Phosphate buffer (60:40v/v)	08ml	C18	230 nm	41
4	Plasma Saliva Urine	-	20% Acetonitrile in 0.0075ml phosphate buffer	2ml/min	C18	254 nm	42
5	Human Plasma	Paracetamol, Amantadine Hydrocholoride, caffeine	Methanol: water [0.5% formic acid 20:80v/v	-	C18	250 nm	43

8.CONCLUSION

This review is aimed at focusing on the thorough Literature survey of the various analytical techniques Reported for the assay of chlorpheniramine maleate from Different sample matrices. The literature review Supports the fact that for estimation of chlorpheniramine maleate from biological samples where the Concentration of the drug is in very small amount, the Choice of detector becomes crucial. Reported methods Show that only fluorescence detector (up to nanogram Level) and mass spectrometer (up to picogram level) are Effective for detection of the drug in the biological Matrix. PDA detector has been reported for estimation of the drug in bulk and pharmaceutical dosage form Only.The conventional Spectroscopy has been used for assay of the drug individually or in combination With other API from bulk or a dosage form where the Concentration of the analyte is higher in comparison to the biological sample. The presence of multiple drugs in a formulation causes a crucial challenge to the Analyst during the selection of spectrophotometric Methods of analysis. The review has summarized the Simultaneous estimation methods developed for the Assay of chlorpheniramine maleate in presence of multiple Drugs in a formulation.

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