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A REVIEW ON THE DETERMINATION OF MIDODRINE HYDROCHLORIDE IN BULK AND MARKETED FORMULATIONS BY USING DIFFERENT ANALYTICAL TECHNIQUES

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ABSTRACT

Midodrine Hydrochloride is a Anti hypotensive used for the elevation of supine blood pressure. Midodrine involves the constriction of the blood vessels and increasing the blood pressure. Midodrine hydrochloride is a prodrug which forms an active metabolite Desglymidodrine which activates alpha adrenergic receptors of the arteriolar and venous vasculature thereby increasing the vascular tone and correspondingly blood pressure. Many analytical methods have been reported for the estimation of Midodrine hydrochloride in bulk and marketed formulations. High performance Liquid Chromatography, Ultra Violet Spectrophotometry, High Performance Thin Layer Chromatography etc. have been employed in the analysis. High Performance Liquid Chromatography and Ultra Violet Spectroscopy is been used most widely.

KEYWORDS: Midodrine Hydrochloride, High Performance Liquid Chromatography, Stability Indicating Analytical Methods.

INTRODUCTION

Midodrine Hydrochloride(MD) is an Antihypotensive/Vasopressor agent. Its chemical name is 2-amino N-[2-(2,5-dimethoxyphenyl)-2-hydroxy-ethyl]-acetamide. Melting Point is 200 to 203°C.pKa value is 7.8(0.3% aqueous solution). pH is 3.5 to 5.5(5% aqueous solution). It is readily soluble in water and sparingly soluble in methanol. It is an odorless white crystalline powder. It is mainly used in the treatment of orthostatic hypotension. It is also used in the

treatment of Cirrhosis and Hepato renal syndrome. Marketed brands are Bramox, Gutron, Amatine.

Many analytical methods have been reported for Midodrine Hydrochloride in formulation, Biological samples as well as in stability samples. The methods are mostly based on Ultra violet spectrophotometry(UV) and High Performance Liquid Chromatography(HPLC). In the present work, some of the most recently published works on the estimation of Midodrine Hyrochloride have been reviewed.

ESTIMATION OF MIDODRINE IN BIOLOGICAL SAMPLES

Reverse phase HPLC method have been reported by Barth *etal*. The estimation was carried out by using C18 column, Mobile phase is Acetonitrile 40mmol/L, Formic acid in 60:40 v/v and 1.4 ml/min flow rate. The experiment is carried out at 25± 2°C. Sample preparation is by Liquid-Liquid extraction using ethyl acetate as extraction solvent. The method was found to be linear in the range 0.4 – 40 µg/ml.[4]

Yoshida *etal* have developed a method for the estimation of Midodrine hydrochloride and its metabolite desglymidodrine in culture medium plasma using similar C18 column but the mobile phase used was Acetonitrile: Methanol: Water(10:30:60 v/v) with fluorescence detection using 400nm excitation wavelength and 485 nm emission wavelength. Here also the sample preparation was done by Liquid-Liquid Extraction using ethyl acetate as solvent. The elution has been carried out at 23 ±3°C and 1.4 ml/min flow rate and the detection was carried out by Ultra violet detection at 290 nm. The method was found to be linear from 0.4 - 40 mcg/ml.[5] Bio-analytical methods for the estimation of Midodrine Hydrochloride are given in table 1.

Table 1.

Parameters/Attributes	Method 1	Method 2
Column	Lichsorber 100 Reverse Phase 18 column(250x4.6mmx5mm)	TSK Gel ODS-120T(1250x4.6nm id X 5µm Particle size
Mobile Phase	Acetonitrile(40mmol/L): Formic Acid(60:40%v/v)	Acetonitrile: Methanol: Water (10:30:60%v/v)
Buffer	-	-
Flowrate	1.4 ml/min	1.0ml/min
Temperature	25±2°C	23±3°C
Retention Time	2.2 min(Shaken Conditions) 1.9 min(Static Conditions)	

Linearity	0.4-40.0 mcg/ml	
Sample Preparation	Liquid-Liquid Extraction using Ethyl acetate as solvent.	Liquid-Liquid extraction from plasma.
Resolution	1.52	
Reference	4	5

STABILITY INDICATING ANALYTICAL METHODS

Stability indicating analytical methods (SIAMs) are essential for the stability studies in order to estimate Midodrine hydrochloride in the presence of degradation product in stability samples. Sattar et al has been reported the HPLC methodfor selective determination of Midodrine in the presence of oxidative degradation product. They have used C18 column, 0.05 M potassium dihydrogen phosphate: acetonitrile (80:20%v/v) as mobile phase. The buffer is adjusted to pH 7 using sodium hydroxide. The elution was carried out at ambient conditions at the flow rate of 1ml/min. The eluent is monitored by UV detector at 290nm. For method development, Stress degraded samples were prepared by refluxing with 2M HCl for 13 hours. Under the chromatographic condition, Midodrine hydrochloride eluted at 2.1 min and its degradation product eluted at 3.7 min.[6]

Stability indicating analytical methods has been reported by Jain etal. Stress degraded samples were prepared by refluxing with 0.1 N NaOH for 30 min or 0.1N HCl for 30 min. For oxidative degradation, the sample is heated with 30% Hydrogen peroxide solution for 30 min at 80°C, whereas for hydrolytic degradation, the sample is heated with water at 30min at 80°C. The chromatographic separation has been carried out by using C18 column. Acetonitrile: 0.02% Triethylamine (pH 3) in the ratio of 38:62%v/v at 0.6ml/min flow rate. The detection is carried out at 289nm.Retention time of Midodrine Hydrochloride is 3.564 min. Alkaline hydrolyzed sample exhibited these additional peaks at 7.216 min, 8.369 min & 10.458 min whereas in oxidative hydrolysis, 2 actual peaks are found, one at 4.346 min & other at 5.927 min whereas in Acid degradation, No additional peaks found indicating the sample is stable at these conditions.[7]

Table 2.

PARAMETERS	METHOD 1	METHOD 2
COLUMN	Zorbax C18 column (250mmX4.6mm : 5 µm)	C18(250mm X 46m)5µm
MOBILE PHASE	0.05 M Potassium Dihydrogen phosphate: Acetonitrile 80:20v/v)	Acetonitrile: Buffer
BUFFER	Sodium Hydroxide pH(7.0±0.1)	Triethylamine(0.02%)pH 3
FLOW RATE	1 ml/min	0.6 ml/min
DETECTION	UV (290nm)	UV(289nm)
TEMPERATURE	Ambient	Room Temperature(25±2°C)
STRESS CONDITION	Acid Degradation by refluxing with 2M HCl for 13 hours & Neutralized.	Alkaline Hydrolysis (0.1N NaOH)30 min. Acid Hydrolysis (0.1N HCl)-30 min Oxidative degradation 100ml 30% Hydrogen peroxide - 80°C-30 min. Hydrolytic Degradation 100ml water- 80°C-30 min
RETENTION TIME	Midodrine – 2 min DMAE - 3.7 min	Alkali : 7.216 min 8.369 min 10.458 min Acid : 3.564 min Oxidative : 4.346 min 5.927 min Hydrolysis : 3.569
LINEARITY	30-150µg/ml	19.98 – 99.9 µg/ml
REFERENCE	6	7

HPTLC is a rapid separation method to analyze wide variety of drugs. The method has advantage over other chromatographic methods and the analysis time is short. It is used in both quantitative and qualitative purpose. Stability Indicating Analytical Method using High Performance Thin Layer Chromatography(HPTLC) has been reported by Salunke et al. The separation is carried out using precoated Aluminium Silica Gel plates (Merck 60F254). The Mobile phase used is Methanol: n-Butanol: Water (2:2:6%v/v). Rf value of Midodrine was found to be 0.30±0.002.[8] HPTLC method for the estimation of Midodrine Hydrochloride are given in table 2.

Table HPTLC (Table 2).

PARAMETERS/ATTRIBUTES	METHOD
COLUMN	Merck TLC Aluminium sheets precoated with silica gel $60F_{254}$
MOBILE PHASE	Methanol: Water: n-Butanol (2:2:6)
Rf VALUE	0.30±0.2
LINEARITY	400-1200ng/band.
STRESS CONDITION	Acid & Base hydrolysis Oxidation Thermal Degradation Photolytic degradation Hydrolysis
CHAMBER	10 X 10 cm Twin trough chamber
REFERENCE	8

ULTRA VIOLET METHODS.

The reported Ultra violet methods are Direct Ultra Violet spectrophotometry, Area under curve(AUC) method or First order derivative method. In Direct UV spectrophotometry, the absorbance is measured at 289nm, the absorption maxima of Midodrine hydrochloride in water.[1] Different methods based on measuring the Area under curve have been reported. In all the methods, Water is used as the solvent. The difference is only the range of wavelength selected for analysis. The range selected are 285 to 295 nm, 200-400nm,278-299nm. The linearity was found to be about 10-90mcg/ml. Derivative spectrophotometry is based on the measurement of the response at 312nm of first derivative ultraviolet spectra. Here also, Water is used as the solvent and the method is linear from 19.98-99.90 mcg/ml. A comparative account of ultraviolet spectrophotometry methods for the estimation of Midodrine Hydrochloride are given in table 4.

Table UV(Table 4).

PARAMETERS/ ATTRIBUTES	METHOD 1	METHOD 2	METHOD 3
METHOD	(A) Absorbance Maxima Method (B) Area Under Curve(AUC) Method	Area Under Curve Method	First Order derivative method
λ Selected	(A) 289nm (B) 285-295nm	289 nm	312nm
Solvent Used	Water	Water	Water
Linearity	10-90mcg/ml	12-84mcg/ml	19.98-99.90mcg/ml
Reference	3	1	2

CONCLUSION

The present review highlights on various analytical methods reported on Midodrine Hydrochloride. HPLC/HPTLC/UV Spectrophotometry methods were used for the analysis of the drug. HPLC methods are most commonly used for the analysis both in Bio analysis and Stability indicating methods. Amongst the reported methods, lowest run time of 3.564min has been achieved by using mobile phase Acetonitrile and Triethylamine buffer of concentration 0.02% w/v with flow rate 0.6ml/min. However there is no report based on scientific approach using Design of Experiment which may give better experimental parameters The chromatographic methods are more specific, sensitive and economic than other methods. The presented information is useful for the researchers.

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