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AZITHROMYCIN: A LITERATURE REVIEW ON ANALYTICAL AND BIO-ANALYTICAL METHODS

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ABSTRACT

This review work is a compilation of previously published methods for analysing azithromycin alone or in combination with other drugs. Many spectroscopic techniques, such as derivative techniques and chromogenic techniques, were used. New and improved chromatographic method that employs biological fluids and pharmaceutical formulations is also available. Aside from these few methods, LC-MS/MS and HPTLC are also available. In today's analytical research world, the quality by design or design by expert technique is used to obtain a better method for method validation. This concise review work can assist an analyst in selecting the most appropriate method for developing and validating the best analytical method.

KEYWORDS

Azithromycin, Analysis, Analytical method development and Validation.

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INTRODUCTION

A revolution in human health has been discovered as pharmaceuticals develop on a daily basis. These pharmaceuticals will perform best if they are free of impurities and pure. At regular intervals, various chemical and instrumental methods for producing impurity-free drugs were developed. Impurities can form at any stage of the process, from bulk drug manufacturing to finished product packaging and storage (degradation). Impurities are most likely to occur during transportation and storage. As a result, impurities must be detected and quantified in these conditions. For detection and quantification

analytical instrumentation and methods plays an important role[1].

For therapeutic process monitoring intermediate pharmaceutical analysis becomes an important tool as it includes different stages like testing of bulk drugs, intermediate products, drug formulations, degradation products, chemical stability of drugs and toxic contents of a drug materials. Polypharmacy is now a valuable therapy for many patients. As a result, testing of combined formulations and assay of biological samples are important for improving polypharmacy therapy quality control.

Antibiotics are medications that are used to treat bacterial infections in humans and animals. They kill bacteria or make it difficult for them to grow and multiply[2].

Macrolide is an antibiotic in the same class as Clarithromycin, Azithromycin, Fidoximycin and Erythromycin. The macrolides inhibit bacterial growth and are frequently used to treat common bacterial infections. More technically, the Macrolides are a group of antibiotics produced by various streptomycin strains, which are spore formation of bacteria which slowly grow in soil or water and have a complex (macrocyclic) chemicals structure as a branching filament mycelium. They inhibit the synthesis of protein[3]. Detail about the macrolide antibiotics given in Table No.1.

AZITHROMYCIN

From all these macrolide derivatives in this present journal, about azithromycin (AZM) is discussed briefly. AZM chemically, (2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R) -11-[(2S, 3R, 4S, 6R) -4- (dimethylamino) -3 - hydroxyl -6- methyloxan -2- yl] oxy -2- ethyl -3, 4, 10 trihydroxy -13- [(2R, 4R, 5S, 6S) -5- hydroxyl -4- methoxy -4, 6- dimethyloxan -2- yl] oxy 3, 5, 6, 8, 10, 12, 14 - heptamethyl -1- oxa- 6- azacyclopentadecan -15- one (Figure No.1) is an antibiotic drug belongs to macrolide class[4-6]. Macrolides are inhibiting the bacterial protein biosynthesis and they are thought to do this by preventing peptidyl transferase from adding the growing peptide attached to tRNA to the next amino acid (similarly to chloramphenicol) as well as inhibiting bacterial ribosomal translation[7-8].

(2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R) -11-[(2S, 3R, 4S, 6R) -4- (dimethylamino) -3 - hydroxyl -6- methyloxan -2- yl] oxy -2- ethyl -3, 4, 10 trihydroxy -13- [(2R, 4R, 5S, 6S) -5- hydroxyl -4- methoxy -4, 6- dimethyloxan -2- yl] oxy 3, 5, 6, 8, 10, 12, 14 - heptamethyl -1- oxa- 6- azacyclopentadecan -15- one.

Several analytical methods based on UV, RP-HPLC, LC-MS/MS was reported for the pharmacokinetic determination of AZM in plasma and urine of humans, rats and dogs. This review paper focuses the analytical procedure available for the estimation of AZM i.e. electrochemical methods, UV/VIS- spectrophotometric methods, HPLC/LC-MS, GC-MS, CE/CE-MS. The details about the previous studies are discussed in Table No.2, 3 and Table No.4.

Quality by design

For improving the analytical method presently Quality by Design technique is used widely. Quality by design (QbD) which is discussed in ICH Q8, [1] Q9 and Q2 is well established for the development and manufacture of pharmaceuticals[25].

Benefits of Quality by Design Method

It helps in the development of a robust method. As per design setup sources of variability can be better controlled. Method Transfer success is greater when a method is transferred from research level to quality control department. This technique gives a space for the invention of new techniques by continuous improvement throughout the lifecycle[26].

Table No.1: Details of Macrolide

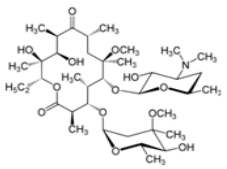
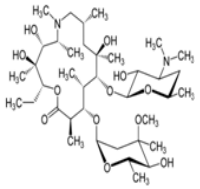
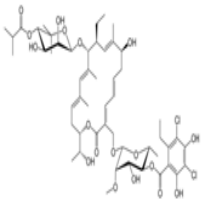
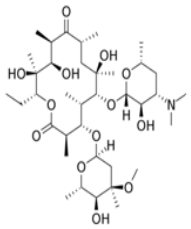
S.No	Drug	Structure	IUPAC Name	Molecular weight	Solubility
1	Clarithromycin		(3R, 4S, 5S, 6R, 7R, 9R, 11R, 12R, 13S, 14R)-6-[(2S, 3R, 4S, 6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-12, 13-dihydroxy-4-[(2R, 4R, 5S, 6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-7-methoxy-3, 5, 7, 9, 11, 13-hexamethyl-oxacyclotetradecane-2, 10-dione	748g/mol	Soluble in acetone, slightly soluble in methanol, ethanol and acetonitrile and practically insoluble in water
2	Azithromycin		(2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)-11-[(2S, 3R, 4S, 6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-2-ethyl-3, 4, 10-trihydroxy-13-[(2R, 4R, 5S, 6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-3, 5, 6, 8, 10, 12, 14-heptamethyl-1-oxa-6-azacyclopentadecan-15-one	749g/mol	Soluble in ethanol and DSMO, minimally soluble in water
3	Fidoximycin		[6-[[12-[3, 4-dihydroxy-6, 6-dimethyl-5-(2-methylpropanoyloxy)oxan-2-yl]oxy-11-ethyl-8-hydroxy-18-(1-hydroxyethyl)-9, 13, 15-trimethyl-2-oxo-1-oxacyclooctadeca-3, 5, 9, 13, 15-pentaen-3-yl] methoxy]-4-hydroxy-5-methoxy-2-methyloxan-3-yl] 3, 5-dichloro-2-ethyl-4, 6-dihydroxybenzoate	1058g/mol	Soluble in ethanol, methanol, DMF, DMSO and Limited water solubility
4	Erythromycin		(3R, 4S, 5S, 6R, 7R, 9R, 11R, 12R, 13S, 14R)-6-[(2S, 3R, 4S, 6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-7, 12, 13-trihydroxy-4-[(2R, 4R, 5S, 6S)-5-hydroxy-4-methoxy-4, 6-dimethyloxan-2-yl]oxy-3, 5, 7, 9, 11, 13-hexamethyl-oxacyclotetradecane-2, 10-dione	733.9g/mol	Soluble in organic solvents such as ethanol, DMSO and dimethyl formamide (DMF)

Table No.2: Summery of methods related to HPLC technique

S.No	Stationary Phase (Column)	Mobile Phase (with ratio)	pH	Wave length	Flow rate	Reference
Azithromycin with Levofloxacin						
1	C18 (100 x 4.6mm, 5µm)	Mixture of ammonium acetate buffer and Methanol in the ratio of 30:70%v/v	6	262nm	1ml/min	9
2	C18 (100 x 4.6mm, 5µm)	Mixture of orthophosphoric acid and methanol in the ratio of 40:60%v/v	2.4	269nm	0.8ml/min	10
Azithromycin with Ambroxol HCl						
3	C18 (100 x 4.6mm, 5µm)	Mixture of dipotassium hydrogen orthophosphate and acetonitrile in the ratio of 68:32%v/v	6.5	215nm	1.5ml/min	11
4	C18 (100 x 4.6mm, 5µm)	Mixture of acetonitrile and mono basic potassium phosphate buffer in the ratio of 68:32%v/v	8.5	220nm	2ml/min	12
Azithromycin, Spiramycin with Erythromycin						
5	C18 (100 x 4.6mm, 5µm)	Mixture of acetonitrile, 2-methyl2-propanol, hydrogen phosphate buffer, in the ratio of 33:7:100 % v/v/v	6.5	210nm	1ml/min	13
Azithromycin with Cefixime						
6	C18 (100 x 4.6mm, 5µm)	Mixture of methanol: buffer in the ratio of 85:15% v/v		275nm	1ml/min	14
Azithromycin as Single Formulation						
7	C18 (100 x 4.6mm, 5µm)	Mixture of methanol, acetonitrile and phosphate buffer in the ratio of 60:30:10% v/v/v	8	212nm	1ml/min	15
8	C18 (100 x 4.6mm, 5µm)	Mixture of methanol, phosphate buffer in the ratio of 90:10 %v/v	8	215nm	1.5ml/min	16
9	C-8, 250mm x 4.6mm, 5µ	Mixture of 0.0335M Phosphate Buffer and Methanol in the proportion 20:80%v/v	7.5	210nm	1.2ml/min	17

Table No.3: Summery of Analysis of Sitagliptin by UV-Spectroscopy methods

S.No	Drug	Method	Description	Reference
1	Spectrophotometric Method Development and Validation of Azithromycin in Tablet Formulation	Spectroscopic Method	Detection wavelength: 275nm in 0.1M Hydrochloric acid Linearity range: 1-4mg/ml Co-relation Co-efficient: 0.9985% Recovery range: 99.9268-101.1156% %RSD: ≤2%	18
2	Spectrophotometric and High Performance Liquid Chromatographic Determination of Cefpodoxime Proxetil and Azithromycin Dihydrate in Pharmaceutical formulation	Spectroscopic Method	Detection wavelength: 218nm in 0.2 N NaOH Linearity range: 10-50µg/ml Co-relation Co-efficient: 0.9978% Recovery range: 99.63-101.7% %RSD: ≤2%	19
3	Simultaneous Uv Spectrophotometric Method For The Estimation Of Azithromycin And Cefexime In Combined Dosage Form	Spectroscopic Method	Detection wavelength: 275nm and 240nm l for Azithromycin and Cefexime respectively in methanol. Linearity range: 2.5-12.5µg/ml and 2-10µg/ml for Azithromycin and Cefexime respectively Co-relation Co-efficient: 0.999% Recovery range: 99.8-100.53% %RSD: ≤2%	20
4	Azithromycin determination using spectrophotometer molecular methods and degradation using an advanced oxidation process.	Spectrophotometer Molecular Methods	Detection wavelength: 226nm in H2SO4 Linearity range: 20-100µg/ml Co-relation Co-efficient: 0.9885% Recovery range: 99.93-101.6% %RSD: ≤2%	21
5	Simultaneous estimation of Azithromycin and Cefixime in A Pharmaceutical Ingredients Spectrophotometry	Spectroscopic Method	Detection wavelength: 235nm and 288nml for Azithromycin and Cefexime respectively in methanol. Linearity range: 10-50µg/ml and 2-10µg/ml for Azithromycin and Cefexime respectively Co-relation Co-efficient: 0.996 and 0.998 for Azithromycin and Cefexime respectively. % Recovery range: 100.28-100.33 and 99.68-100.29% for Azithromycin and Cefexime respectively %RSD: ≤2%	22
6	Development of the UV Spectrophotometric Method of Azithromycin in API and Stress Degradation Studies	Spectroscopic Method	Detection wavelength: 208nm in 0.1 N HCl Linearity range: 10-50µg/ml Co-relation Co-efficient: 0.99% Recovery range: 99.72% %RSD: ≤2%	23
7	Selective spectrophotometric methods for the determination of azithromycin in pharmaceutical formulation	Spectroscopic Method	Detection wavelength: 415nm in ethanol Linearity range: 2-20µg/ml Co-relation Co-efficient: 0.999% Recovery range: 99.72% %RSD: ≤2%	24

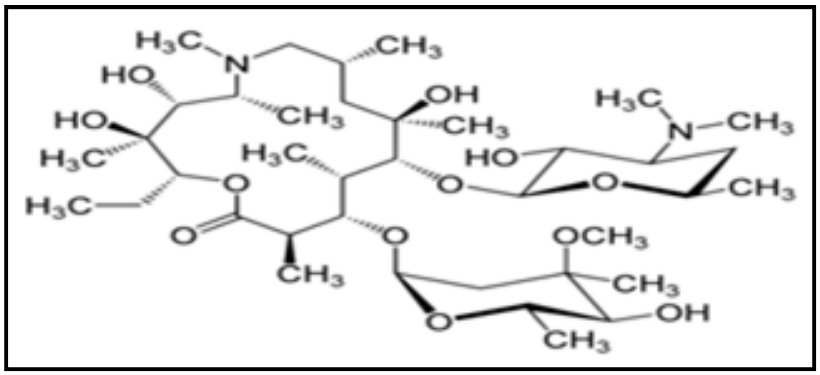


Figure No.1: Chemical structure and IUPAC name of AZM

CONCLUSION

This study shows reported chromatographic and spectrophotometric methods; developed and validated for the assessment of AZM. According to this review, the various spectroscopic and chromatographing techniques for AZM are available for the individual component and the combination and it has also been concluded that most of the chromatographic methods have more resolution through a mobile phase containing phosphate buffer, methanol and acetonitrile. It was observed that most common formulation of AZM used was (ex. AZITHRAL). For chromatographic method flow rate is observed in the range of 0.8-1.5ml/min to get good retention time. For most of the spectroscopic methods common solvent is methanol. Hence this all methods found to be simple, accurate, economic, precise and reproducible in nature. But from this review it was clear that available methods can be improved by using Design of Expert (DOE) technique, which will give more accurate and precise result.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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