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ANALYTICAL AND BIOANALYTICAL METHODS FOR ESTIMATION OF TIGECYCLINE ALONE AND IN COMBINED DOSAGE FORMS: AN OVERVIEW

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ABSTRACT

This review work is a compilation of information from previous publications on analytical techniques for tigecycline, either alone or in combination with other medications. Numerous spectroscopic techniques, such as derivative and chromogenic techniques, were employed. It is also possible to use newly created and improved chromatographic techniques with pharmaceutical formulations and biological fluids. A few LC-MS/MS and HPTLC techniques are also available in addition to these two techniques. The quality by design or design by expert technique is now used in the world of analytical research to obtain an improved method for method validation. This succinct review article can help an analyst decide which approach is best for developing and validating the best analytical method.

KEYWORDS

Tigecycline, Analysis, Analytical method development, HPLC and UV.

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INTRODUCTION

Human health has undergone a revolution as pharmaceuticals continue to advance daily. If these drugs are pure and free of impurities, they will function at their peak. To produce drugs free of impurities, various chemical and instrumental techniques were developed on a regular basis. Impurities can appear at any stage, from the production of bulk drugs to the packaging of finished goods and all the way to storage (degradation). Impurities may frequently appear during the two stages of transportation and storage. Impurities must therefore be identified and measured under these

circumstances. Analytical tools and techniques are crucial for detection and quantification[1].

Intermediate pharmaceutical analysis, which covers a variety of stages including testing of bulk drugs, intermediate products, drug formulations, degradation products, chemical stability of drugs, and toxic contents of a drug materials, becomes a crucial tool for therapeutic process monitoring. Today, polypharmacy is a highly beneficial treatment for many diabetic patients. Therefore, quality control testing of combined formulations and assay of biological samples are crucial for improving polypharmacy therapy.

Drugs called antibiotics are prescribed to treat bacterial infections in both humans and animals. They either eradicate bacteria or make it difficult for them to proliferate and spread[2].

Carbapenems, like penicillins and cephalosporins, belong to the beta lactam class of antibiotics that kill bacteria by binding to penicillin-binding proteins and inhibiting bacterial cell wall synthesis[3]. Tetracycline is used to treat bacterial infections such as pneumonia and other respiratory tract infections; infections of the skin, eye, lymphatic, intestinal, genital and urinary systems; and infections spread by ticks, lice, mites, and infected animals[4]. No elevated risk of acute pancreatitis has been seen in short-term clinical trials with Lymecycline, methacycline, minocycline, rolitetracycline and doxycycline are semi-synthetic tetracyclines. There is a substance from the glycylcycline subclass called tigecycline. Finally, in 2012, a group of more recent tetracyclines, including ervacycline, sarecycline, and omadacycline, were taken off the black triangle list[5]. Lymecycline, methacycline, minocycline, rolitetracycline, and doxycycline are semi-synthetic tetracyclines. There is a substance from the glycylcycline subclass called tigecycline. Ervacycline, sarecycline, and omadacycline are among a group of more recent tetracyclines in this group. The Tetracyclines class of medications are described in detail in Table No.1.

Tigecycline

In this journal, tigecycline is briefly discussed among all of the tetracycline-class medications. Biologically, tigecycline (4S, 4aS, 5aR, 12aR)-9-[[2-(tert-butylamino)acetyl]amino]-4, 7-bis(dimethylamino)-1, 10, 11, 12a-tetrahydroxy-3, 12-dioxo-4a, 5, 5a, 6-tetrahydro-4H-tetracene-2-carboxamide (Figure No.1) is The Actinobacteria species Streptomyces produces the broad-spectrum polyketide antibiotic tetracycline. By reversibly attaching to the bacterial 30S ribosomal subunit and preventing incoming aminoacyl tRNA from binding to the ribosome acceptor site, it has a bacteriostatic effect on bacteria. Additionally, it partially binds to the bacterial 50S ribosomal subunit and has the potential to change the cytoplasmic membrane, allowing for the leakage of intracellular components from bacterial cells.

It was reported that several analytical techniques based on UV, RP-HPLC, and LC-MS/MS were used to determine the pharmacokinetics of tigecycline phosphate in human plasma and urine as well as that of rats and dogs.

The analytical techniques used to estimate tigecycline, including electrochemical methods, UV/VIS spectrophotometric methods, HPLC/LC-MS, GC-MS, and CE/CE-MS, are the focus of this review article. Table No.2 discusses the specifics of the earlier studies.

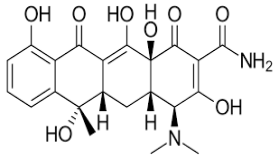
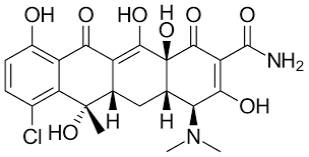
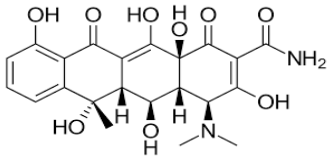
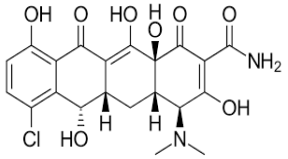
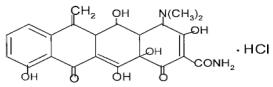
Quality by design

For pharmaceuticals, several analytical methods are available to enhance the quality[13-17]. But currently, the Quality by Design technique is widely used to improve the analytical method. For the development and production of pharmaceuticals, quality by design (QbD), which is covered in ICH Q8, [1,] Q9, and Q2, is well-established.

Benefits of Quality by Design Method

It aids in the creation of a reliable methodology. The sources of variability can be better controlled according to the design setup. Method the success of a method transfer from the research level to the quality control department is higher. This method creates a space for the development of novel techniques through ongoing improvement over the course of the lifecycle.

Table No.1: Details of tetracyclines class drugs

Drug	Structure	IUPAC Name	Moleculur Weight	Solubility	Duration of Action
Tetracycline		(4*S*, 4*aS*, 5*aS*, 6*S*, 12*aR*)-4-(dimethylamino)-1, 6, 10, 11, 12*a*-pentahydroxy-6-methyl-3, 12-dioxo-4, 4*a*, 5, 5*a*-tetrahydrotetracene-2-carboxamide	444.4g/mol	Ethanol and alkali hydroxide	Short acting (half life 6-8 hours)
Chlortetracycline		(4*S*, 4*aS*, 5*aS*, 6*S*, 12*aR*)-7-chloro-4-(dimethylamino)-1, 6, 10, 11, 12*a*-pentahydroxy-6-methyl-3, 12-dioxo-4, 4*a*, 5, 5*a*-tetrahydrotetracene-2-carboxamide	478.9g/mol	Soluble in water, methanol, ethanol and DMSO.	Short acting (half life 6-8 hours)
Oxytetracycline		(4*S*, 4*aR*, 5*S*, 5*aR*, 6*S*, 12*aR*)-4-(dimethylamino)-1, 5, 6, 10, 11, 12*a*-hexahydroxy-6-methyl-3, 12-dioxo-4, 4*a*, 5, 5*a*-tetrahydrotetracene-2-carboxamide	460.4g/mol	Very slightly soluble in water, freely soluble in 3N HCL and in alkaline solutions, sparingly soluble in alcohol.	Short acting (half life 6-8 hours)
Demeclocycline		(4*S*, 4*aS*, 5*aS*, 6*S*, 12*aR*)-7-chloro-4-(dimethylamino)-1, 6, 10, 11, 12*a*-pentahydroxy-3, 12-dioxo-4*a*, 5, 5*a*, 6-tetrahydro-4*H*-tetracene-2-carboxamide	464.9g/mol	It is soluble in organic solvents such as DMSO and dimethyl form amide which should be purged with an inert gas. The solubility of demeclocycline in these solvents is approximately 1 and 1.4mg/ml respectively	Intermediate acting (half-life 12 (hours)
Methacycline		(4*S*, 4*aR*, 5*S*, 5*aR*, 12*aR*)-4-(dimethylamino)-1,	442.4g/mol	Insoluble in EtOH; ≥51.73mg/mL in DMSO;	Intermediate acting (half-life 12

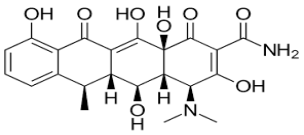
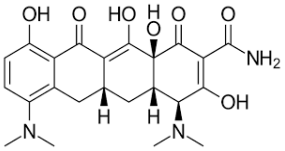
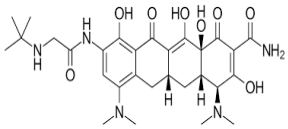
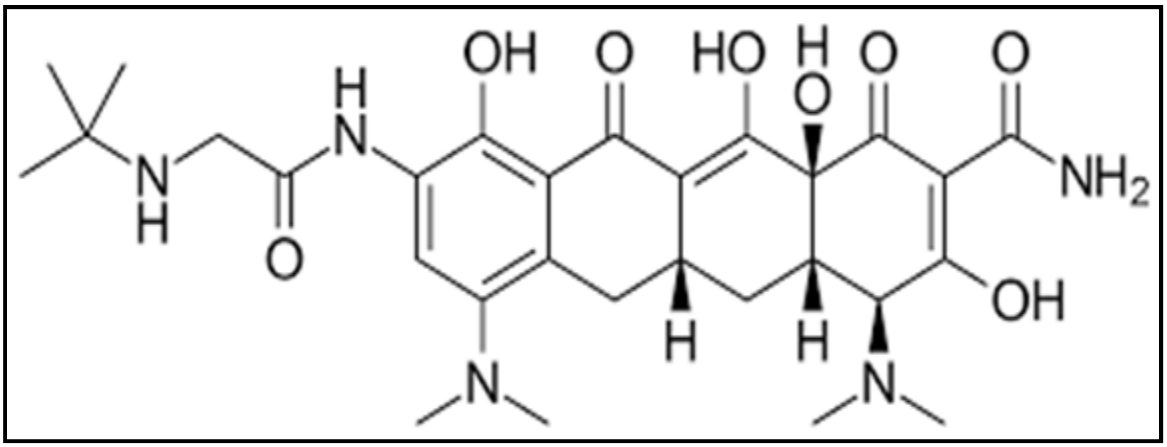
		5, 10, 11, 12*a*-pentahydroxy-6-methylidene-3, 12-dioxo-4, 4*a*, 5, 5*a*-tetrahydrotetracene-2-carboxamide		≥7.09mg/mL in H2O	hours)
Doxycycline		(4*S*, 4*aR*, 5*S*, 5*aR*, 6*R*, 12*aR*)-4-(dimethylamino)-1, 5, 10, 11, 12*a*-pentahydroxy-6-methyl-3, 12-dioxo-4*a*, 5, 5*a*, 6-tetrahydro-4*H*-tetracene-2-carboxamide	444.4g/mol	Very slightly soluble in water; sparingly soluble in alcohol; freely sol in dilute acid and alkali hydroxide soln; practically insoluble in chloroform and ether	Long acting (15-18 hours)
Minocycline		(4*S*, 4*aS*, 5*aR*,12*aR*)-4, 7-bis (dimethylamino)-1, 10, 11, 12*a*-tetrahydroxy-3, 12-dioxo-4*a*, 5, 5*a*, 6-tetrahydro-4*H*-tetracene-2-carboxamide	457.5g/mol	1g in about 60ml H20 and about 70ml alcohol; soluble in solution of alkali hydroxides and carbonates; practically insoluble in chloroform and ether/hydrochloride. Soluble In water, 52,000mg/l at 25°C.	Long acting (15-18 hours)
Tigecycline		(4*S*, 4*aS*, 5*aR*, 12*aR*)-9-[[2-(*tert*-butylamino) acetyl]amino]-4, 7-bis(dimethylamino)-1, 10, 11, 12*a*-tetrahydroxy-3, 12-dioxo-4*a*, 5, 5*a*, 6-tetrahydro-4*H*-tetracene-2-carboxamide	585.6g/mol	Tigecycline is soluble in water (0.45mg/mL) and DMSO (>3mg/mL).	Long acting (15-18 hours)

Table No.2: Details of HPLC analytical method development

S.No	Stationary phase (column)	Mobile phase (with ratio)	Ph	Wavelength	Flow rate	Reference
1	Thermo Scientific™ Acclaim™ Polar Advantage II (PA2) Guard Cartridge, 5µm, 4.6 × 10mm (P/N 069699)	DI water	-	UV absorbance at 247nm	1.0mL/min	6
2	Phenomenax C18 column (250 × 4.6mm, 5µm)	a mixture of acetonitrile and acetic acid (0.1% aqueous solution, in the ratio 20:80	3.5	250nm	0.4ml/min.	7
3	Atlantis T3 column (Waters) (150 x 3mm), with a 3µm particle size, maintained at 40C	consisted of phase A (0.1% formic acid in water) and phase B (0.1% formic acid in acetonitrile)	-	-	450µl/min	8
4	HSS T3 (2.1 × 100mm, 3.5μm) chromatographic column using isocratic program	a mobile phase comprising of 80% solvent A (water containing 0.1% formic acid (v/v) with 5mM ammonium acetate) and 20% solvent B (acetonitrile). The needle rinsing solution of the autosampler was methanol: ultrapure water (v/v, 70: 30).	-	-	0.3mL/min	9
5	The chromatographic column was an ACQUITY UPLC HSS T3, 1.8 mm, 2.1· 150mm protected by a Waters ACQUITY UPLC Column In-Line Filter (Waters).	Mobile phases were mobile phase A (20mM of potassium dihydrogen phosphate buffer at pH 3.2 with orthophosphoric acid) and mobile phase B (acetonitrile, 100%).	3.2	350nm	0.4mL/min	10
6	A Phenomenex Luna C18 150mm × 4.5mm column (5m) (Torrance, CA) preceded with a Bondapak C18 Guard-Pak precolumn (Waters, Milford, MA). EZChrom Elite chromatography data system (Scientific software, San Ramon, CA) was employed to quantify the peak areas.	The mobile phase was composed of 25: 75 (v/v) acetonitrile-phosphate buffer (pH 3.0, 0.023M) with 4mM 1-octanesulfonic acid.	3.0, 0.023M	244nm with a sensitivity of 0.002 aufs for HBSS samples, and 350nm with a sensitivity of 0.001 aufs	1mL/min.	11
7	stationary phase is Agilent ZORBAX Eclipse XDB C18 (250mm × 4.6mm, 5µm) column,	Methanol and 10mmol Triethylamine Buffer at pH 6.1 in the ratio of 75:25 (v/v) as mobile phase	6.1	231nm	1.0Ml/min	12



(4S, 4aS, 5aR, 12aR)-9-[[2-(tert-butylamino) acetyl]amino]-4, 7-bis(dimethylamino)-1, 10, 11, 12a-tetrahydroxy-3, 12-dioxo-4a, 5, 5a,6-tetrahydro-4H-tetracene-2-carboxamide

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

CONCLUSION

This study presents reported spectrophotometric and chromatographic techniques that were created and verified for the evaluation of tigecycline. The different spectroscopic and chromatographic methods for tigecycline are available for both the individual component and the combination, according to this review. It has also been determined that the majority of the chromatographic methods have more resolution thanks to a mobile phase made up of phosphate buffer, methanol, and acetonitrile. It was noted that the most popular form of tigecycline was (ex. TIGAPHAR). For chromatographic methods, flow rates between 0.8 and 1.5ml/min have been found to produce good retention times. The most common solvent for most spectroscopic techniques is methanol. As a result, all of the methods were discovered to be straightforward, accurate, affordable, precise, and repeatable. However, it is evident from this review that the use of the Design of Expert (DOE) technique can enhance the currently used methods and produce results that are more accurate and precise.

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CONFLICT OF INTEREST

The authors affirm that they do not have any competing interests.

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