International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 5 Issue 7 ǁ November 2016 ǁ PP. 39-44

Analytical Determination of Tricyclic Antidepressant Drug Amitriptyline by Sectrophotometry Using *β*-Cyclodextrin-PEG System in Pharmaceutical form.

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Abstract: *A new and simple procedure for the spectrophotometric determination of the tricyclic antidepressant drug amitriptyline has been developed. This method is very simple as there is no requirement of prior separation of the complex and reagents are commonly available. The method is based on enhancement of sensitivity of the* $[AMIYTP]^+$ *β-cyclodextrin and PEG molecules involved in formation of molecules inclusion complex, in presence of polyethylene glycol (PEG) medium. The mole ratio of* $[AMIYTP]^+$ *β-cyclodextrin and PEG molecules in inclusion complex were determined by the curve fitting method. The value of molar absorptivity of {[AMIYTP: (β CD)] PEG} complex in term of the drug lies in rage of (2.20 - 2.23)* $\times 10^4$ $L{\cdot}mole^{-1}{\cdot}cm^{-1}$ *at absorption maximum 242 nm. The slope, intercept and correlation co-efficient were found to be 14.21, 0.0046, and 0.998, respectively. The effect of analytical variables on the determination of the drug and composition of the ion associated complex are discussed in the paper. This method is applicable in the determination of amitriptyline in the pharmaceutical preparations.*

Keywords: *Amitriptyline; PEG; β-Cyclodextrin; Spectrophotometric Determination; AMIYTP-β-Cyclodextrin Complex; Pharmaceuticals.*

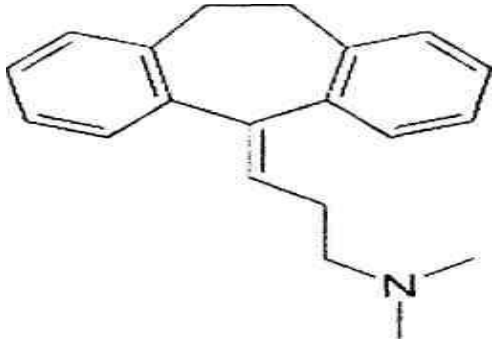
I. Introduction

Antidepressant medication is used to treat depression, a mood disorder, characterized by such symptoms such as sadness, decreased appetite, difficulty in sleeping, fatigue and a lack of enjoyment of activities previously found pleasurable. An antidepressant is a psychiatric medication used to alleviate mood disorders such as major depression and dysthymia while everyone experiences episodes of sadness at some point in their lives depression is distinguished from this sadness when symptoms are present most day for period of at least two weeks. Antidepressants are often the first choice of treatment for depression. Although the cause of depression is unknown, researchers have found that some depressed people have altered levels of neurotransmitters, chemicals that enable nerve cells to communicate. For little activity among neurotransmitters in the areas of the brain that control mood and emotion is thought to contribute to depression. Antidepressants interact with neurotransmitters in different way. They can change the rate at which the neurotransmitters are either created or broken down within the body. They can block the process by which neurotransmitters are recycled and reused, a process called "reuptake" by blocking re-absorption of neurotransmitters into the nerve cells. Finally antidepressants can interfere with the binding of a neurotransmitter to neighboring nerve cells, thus leaving the neurotransmitter available. Depression is one of the most serious and frequent problems of contemporary society. Frequently, as a remedy for this state, physicians prescribe tricyclic antidepressants with or without amitriptyline and imipramine. These medications are mostly prescribed by psychiatrists and other physicians, and their effectiveness and adverse effects are the subject of many studies. The amitriptyline and imipramine are very important pharmaceutical compounds. The interest in first generation TCAs (amitriptyline, imipramine) drug is due to its great medicinal and pharmaceutical importance. Now a days various generation of antidepressant drugs are being used for the treatment of variety of depression moods, but TCAs is the most prescribed drug due to its effectiveness and low cost. However it has some undesirable side effects. Therefore, it became the substance of interest for our research, keeping in view its beneficial aspect. The present work deals with the first generation antidepressant (TCAs) drugs i.e. Amitriptyline. These substances share a basic chemical structure comprising a three ring compound and an alkyl amine side chain. The present study also aims to reach such outcome with micellar mixed micellar polymer and cyclodextrin with first generation tricyclic antidepressant. The therapeutic action of a drug needs the confluence of different factor to occur. Molecular complexation in an artificial model system is an universally and widely used tool in the interpretation of a number of biological mechanisms. Tricyclic antidepressant drugs are very popular pharmaceuticals used for liver and nervous cancer. Many pharmacologically active compounds are amphiphilic or hydrophobic molecules, which may undergo

different types of association and whose site of action in the organism is the plasma membrane. Amphiphilic compounds bear an ionic or non-ionic polar head group and a hydrophobic portion. In aqueous medium they are able to organize themselves as micelles, bilayers, monolayers, hexagonal or cubic phases.

Analytical procedures capable of both identifying and quantifying these drugs are needed in forensic toxicological practice. Imipramine hydrochlorides, [IMI] HCl, Amitriptyline hydrochloride [AMIYTP] HCl, are members of the dibenzazepine class of the drugs. They are important tricyclic antidepressant commonly used in the treatment of emotional and psychiatric disorder [R.F. Doerge, Wilson and Gisvolds 1982]. Their efficacy in alleviating depression has well stabilized. The vast pharmaceutical success of these medicinal agents has made dibenzazepine a major area of research in heterocyclic chemistry [A. Rosowsky, 1984, R.K. Smalley**,** 1984**,** British Pharmacopoeia, 1984, United States Pharmacopoeia, 2002] and an important branch of commercial importance in pharmaceutical science.

cyclodextrins (CDs) are considered as one of the most suitable artificial receptors for the vectorization of guest hydrophobic molecules (drug, dyes, detergents, pesticides, etc.) in aqueous media [4-6]. In fact, the use of CDs as a new family of pharmaceutical excipient and drug carriers has become an increasingly accepted method for many therapeutic molecules [7]. Various analytical methods have been reported for de-termination of amitriptyline including spectrofluoromet-ric [8], fluorospectrophotometric [9-14] flow injection method [15] atomic absorption spectroscopic [16], con-ductometric [17,18], high performance liquid chroma-tographic [19,20], voltammetric [21] and chroma-tographic [22] methods.



Scheme 1.1 [AMIYTP] Cl: Chemical Name: [3-(10,ll-dihydro-5H-dibenzol [a,d] cyclohept-5-ylidene) propyldimethylamine]

The conventional batch process solvent extraction is a tedious and time consuming procedure. Therefore it seems necessary to develop a sensitive, simple and fast identification and determination of Amitriptyline. The proposed method is based on the enhancement of sensitivity of [AMIYTP: *β*CD] complex in presence of polythene glycol (PEG) medium. The optimization of analytical variables is discussed in this paper. The method is simple, sensitive and reproducible. This method has been applied for determination of amitriptyline in pharmaceutical preparations.

II. Experimental

2.1. Reagents

All chemicals used were of analytical grade reagent (Merck). The standard solution of amitriptyline (l000 ppm) was prepared by dissolving its 1.000 g in 1 liter deionized double distilled water. The working solutions were prepared by the appropriate dilution of the stock solution. Solutions used were prior filtered. The *β*-cyclodextrin 1000 ppm (8.81×10^{-4} M) solution was prepared by dissolving its 0.1gm in 100 ml deionized double distilled water, and further diluted to 800 ppm (7.04×10^{-4} M) with double distilled water. The PEG solution 1000 ppm (2.5×10^{-3} M) was prepared by dis-solving its 0.1 gm in 100 ml deionized double distilled water, and it was further diluted to 20 ppm (5×10^{-5} M) with deionized distilled water. All working solutions employed were prior filtered and degassed, by the de-gassing unit.

2.2. Equipment

Systronics UV -VIS double beam spectrophotometer –2201 matched with 1 cm quartz cell were employed to determine the absorbance. Source and sample positions are software optimized to keep the unit always at its peak performance.

2.3 Procedure for determination of Amitriptyline

Aliquots 2 ml of the standard solution of amitriptyline having varying concentrations from 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0 ppm were taken in 10 ml volumetric flasks. In each volumetric flask 2 ml of β-CDs solution and 2 ml of PEG solution are added. Then make up the solution up to the mark on volumetric flask with double distilled water. Then measured their absorbance at 242 nm against the reagent blank, and prepared the calibration graph by plotting absorbance versus concentration of amitriptyline. Fig (3.1), (Table 3.1).The similar procedure was repeated with sample solution, which was prepared from pharmaceutical product. The concentration of Amitriptyline in the sample solution was computed by using the calibration curve prepared under similar condition.

III. Result and Discussion

3.1 Reaction mechanism and composition of complex

Amitriptyline gives ion-associate species with β-CD and PEG system and the absorbance increases with increase in the concentration of amitriptyline. Amitriptyline cation reacts with β-CDs to give an inclusion complex. Their stochiommetry are 1:1 indicating that the complex is formed by the association of a molecule of β-CD per each molecule of $[AMIYTP]^+$, as usually found for most cyclodextrin / drug complexes. Considering this 1:1 stochiommetry the molecular encapsulation process can be represented by eq.3.1

$$.m\,[AMIYTP]^+Cl + n\,\beta\,CD \quad \{[AMIYTP]m\,(\beta CD)_n\}^{m+}Cl\ldots \qquad \text{eq.3.1}$$

Where n =1 to 2.

This reaction has been used for the determination of cationic antidepressant drug Amitriptyline in presence of PEG molecule. The solubilization as well as the viscosity of an aqueous solution of polymer bound system is higher than the solution of pure polymer. The expected reaction in the PEG medium can be expressed as eq.3.2

$$m[AMIYTP]^+CI + n\,\beta\,CD + \chi\,PEG \quad \{[AMIYTP]m(\beta CD)_n(PEG)\chi]\}^{m+}Cl\ldots \qquad \text{eq.3.2}$$

Where, value of 'χ' may vary from 3-4 and
$[AMIYTP]^+$ = cation of the drug Amitriptyline

The mole ratio of $[AMIYTP]^+$ to β-CD and PEG molecules involved in formulation of molecules inclusion complex, were determined by the curve fitting method by plotting $\log(A_{eq.}/A_{max.}-A_{eq.})$ vs. Concentration. $A_{eq.}$ = Absorbance of the complex when reagent was in equilibrium, Amax. = Absorbance when reagent was in constant excess.

The value of slope for β- CD and PEG were found to be ratio 0.140 and 0.436, respectively. Curve- fitting method suggested the molar ratio of β-CD and PEG and drug cation in the complex to be in 1:3 ratios. As per the curve-fitting method, the composition of the inclusion complex is expected to be as eq.3.3

$$[AMIYTP]^+CI + \beta\,CD + 3PEG \quad \{[AMIYTP](\beta CD)(PEG)_3\}^+Cl\ldots.. \qquad \text{eq.3.3}$$

3.2 Absorption Spectra

The $\{[AMIYTP](\beta\,CD)(PEG)_3\}^+Cl$ complex exhibit the absorption maximum at 242 nm. The position of λ_{max} is changed when the PEG is added and absorbance was increased. The absorption maxima of only{ [AMIYTP] (□ CD)} complex were found to be at 250 nm, fig3.4.The position of λmax. is change when the PEG is added and the absorbance was increased. The $\{[AMIYTP](\beta\,CD)(PEG)_3\}^+Cl$ complex exhibits the absorbance maximum at 242 nm. In presence of the drug / PEG, hyper chromic and hypso chromic shift due to formation of molecular inclusion complex.

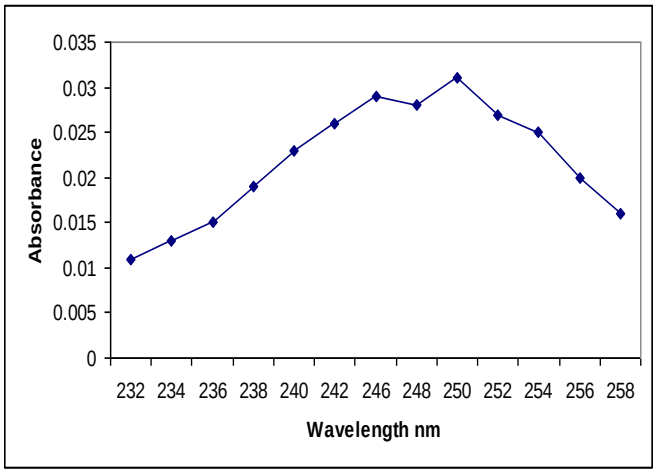
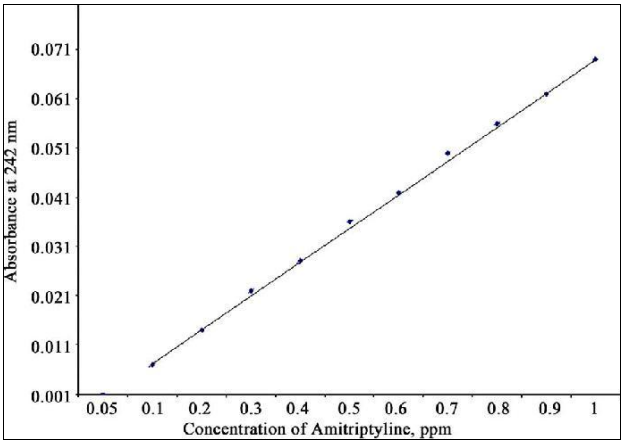


Fig 3.1 Absorption spectra of {[AMIYTP] (β-CD)}$^{+}$ ions – associate complex ions concentration of Amitriptyline 0.5 ppm



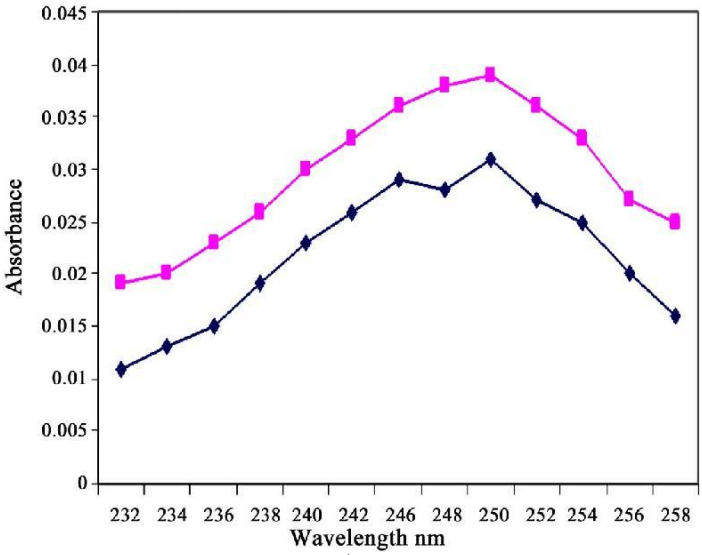


Figure 3.2 Absorption spectra of {[AMIYTP](*β*-CD)}$^{+}$Cl and {[(AMIYTP](*β*-CD)] $(PEG)_3$}$^{+}$Cl Ions-associate

Table-1. The result of analysis of Amitriptyline tablets by proposed and official method.

S.No.	Pharmaceutical Product	Recovery, mg		Error, %
		Official Method	Proposed Method	
1.	Amit 25, 25 mg	25.3 ± 0.03	24.87 ± 0.16	1.6%
2.	Amitriptyline Hydrochloride tablet 25mg	25.2 ± 0.25	24.72 ± 0.32	1.9%

Table 2. Comparison with other established spectrophotometric method

S.No.	Method	λ_{max}, (nm)	Working (ppm)	Range,R.S.D* (%)	Correlation Co-efficient
1.	Extraction spectrophotometer ammonium reinkate method	523	0.1 - 6.0	0.8	0.994
2.	Proposed spectrophotometric {AMIYTP(βCD)$(PEG)_3$}$^+$Cl ion associate complex method	242	0.1 - 1.0	2.0	0.998

IV. Conclusion

The method was successfully applied for the determination of amitriptyline in the pharmaceutical preparations. The method is very simple as there is no requirement of prior separation or extraction of the complex and the re-agents are cheap and commonly available in routine laboratories. The results obtained from the proposed method were comparable with the established methods. The method has good potential in simplicity and sensitivity.

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