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METHOD DEVELOPMENT AND VALIDATION OF TRAZODONE HYDROCHLORIDE (HCL)-REVIEW

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ABSTRACT

Trazodone Hydrochloride (TRZ) is a well-known chemical compound that is used as an antidepressant that belongs to selective serotonin reuptake inhibitors (SARI). This medication is used to treat depression. It may help to improve your mood, appetite, and energy level as well as decrease anxiety and insomnia related to depression. Trazodone is available in the form of 25 mg, 50 mg, 100 mg, 150 mg, and 300 mg tablets for oral ingestion. An extended release formulation at 150 mg and 300 mg as tablets is also available. The existing available literature reports explain there are different analytical method available for estimation of trazodone hydrochloride single as well as combination with other antidepressant. the different analytical method include RP-HPLC, UV, Spectrophotometric method are available for estimation of trazodone hydrochloride the existing available literature report do not include any systematic assay method for analyte quantification to reflect the accurate purity characteristic of sample to get average accurate results, hence there is a scope to develop assay method for estimation of trazodone hydrochloride dosage form

INTRODUCTION

Method development and validation aspect by assay method

Accurately reflect the purity characteristic of sample, assay procedure are intended to measure the analyte present. By using Analytical methods development and validation assume imperative parts in the discovery, improvement and preparation of pharmaceuticals. Method development is the way toward demonstrating that a analytical strategy is satisfactory for use

to measure the concentration of an active pharmaceutical ingredient (API) in a particular formulated dosage form which enables simplified methods to be utilized to check that an analytical procedure, precisely and reliably will convey a reliable estimation of an active ingredient in an compounded preparation. The analytical strategy validation is important for analytical technique improvement and tested widely for specificity, linearity, exactness, accuracy, precision, range, detection limit, quantization limit, and robustness. In outline, analytical method development and validation permits to affirm that an exact and reliable potency estimation of a pharmaceutical preparation can be performed. Method validation often evolves from method development. Method development can take number of forms. At one extreme, it may involve adapting an existing method, making minor changes so that it is suitable for a new application. It requires a lot of effort, and there is a degree of doubt initially to whether the method will be successful. It involves working on various ideas simultaneously and then finally picking one of those. Various st eps involved in method development and validation are:

Method development plan definition
↓
Background information gathering
↓
Laboratory method development
↓
Generation of test procedure
↓
Methods validation protocol definition
↓
Laboratory methods validation
↓
Validated test method generation
↓
Validation report.

A well-developed method is always to validate. While using any analytical technique for the estimation of the drug it needs a proper method to be developed. Let us take an example of most complex analytical technique, i.e., high performance liquid chromatography (HPLC) which is complex in the sense that there are a wide variety of equipments, columns, eluents, and other parameters for operation which makes it so. There are various aspects which should be kept in mind while developing a method for HPLC. They are explained as follows:

- Selection of the HPLC method which includes choosing either of the two, reverse phase or normal phase HPLC depending upon the nature of the sample, for example, for polar analytes we use reverse phase HPLC so that we obtain better retention and resolution and

for low or medium polarity samples we generally prefer normal phase chromatography.

- Then, choosing a proper mobile phase for the given analyte is the most crucial stage in developing a method for HPLC. A mobile phase which has the capability of pulling the analyte from the column is chosen. When dealing with weak acids and bases, we have to adjust the pH also as it aspects the retention.
- A stationary phase is generally C18 bonded in the case of reverse phase HPLC and cyano-bonded in the normal phase.
- Then, the detectors are selected based on the nature of the analyte. We observe that whether it has chromophores which will enable their detection in UV while using UV-detectors.

Fluorescence detectors are used in the case of trace analysis and in preparative HPLC refractive index detectors are used

1.1 Historical assumptions of assays

Historically insufficient attention has been paid to assay development, how it impacts the product, on-going release testing and product control. Simple coefficient of variation (CV) calculations for assay precision is a necessary but insufficient measure of assay goodness and may be misleading as CV has no relationship to product acceptance and release testing limits. Assays and measurement systems must be viewed as a process. The measurement process is made up of methods, software, materials and chemistry, analysts, sample preparation, environmental conditions and instrumentation/equipment. Quality risk management and statistical data analysis techniques should be used to examine the process of measurement and identify factors that may influence precision, accuracy, linearity, signal to noise, limits of detection and quantification and/or any other assay attributes to achieve optimal assay results.

1.2 History

Trazodone was developed in Italy, in the 1960s, by Angelini Research Laboratories as a second-generation antidepressant. It was developed according to the mental pain hypothesis, which was postulated from studying patients and which proposes that major depression is associated with a decreased pain threshold. In sharp contrast to most other antidepressants available at the time of its development, trazodone showed minimal effects on muscarinic cholinergic receptors. Trazodone was patented and marketed in many countries all over the world. It was approved by the Food and Drug Administration (FDA) in 1981 and was the first non-tricyclic antidepressant approved in the US

1.3 Interaction

Concomitant use of trazodone with inhibitors of CYP3A4 can result in substantially increased plasma concentrations of trazodone and increase the potential for adverse effects. In one study, concomitant use of ritonavir (200 mg twice daily for 2 days) and trazodone (a single 50-mg dose) in healthy individuals increased maximum plasma concentrations and decreased clearance of trazodone by 34 and 52%, respectively, and increased area under the plasma concentration-time curve (AUC) and half-life of trazodone by greater than twofold. Adverse effects (e.g., nausea, hypotension, syncope) also were observed with concomitant use of trazodone and ritonavir. The manufacturers of trazodone state that a reduction in trazodone dosage should be considered in patients receiving a potent inhibitor of the CYP3A4 isoenzyme (e.g., indinavir, itraconazole, ketoconazole, nefazodone, ritonavir) concomitantly with trazodone.

1.4 Pharmacodynamics

Trazodone is generally described as acting as a potent serotonin 5-HT2A and α1-adrenergic receptor antagonist, a weak serotonin reuptake inhibitor (SRI), and a weak antihistamine or histamine H1 receptor inverse agonist. Its 5-HT2A receptor antagonism and weak serotonin reuptake inhibition form the basis of its common label as a serotonin antagonist and reuptake inhibitor (SARI). Trazodone, both itself and via its major active metabolite *meta*-chlorophenylpiperazine (mCPP), also binds to a variety of other receptors.[1] It is an antagonist at most or all of the receptors it binds to except the 5-HT1A receptor, where it acts as a partial agonist similarly to buspirone and tandospirone but with comparatively greater intrinsic activity. Conversely, mCPP is a non-selective agonist of most of the serotonin receptors it binds to. A range of weak affinities (Ki) have been reported for trazodone at the human histamine H1 receptor including 220 nM, 350 nM,500 nM, and 1,100 nM

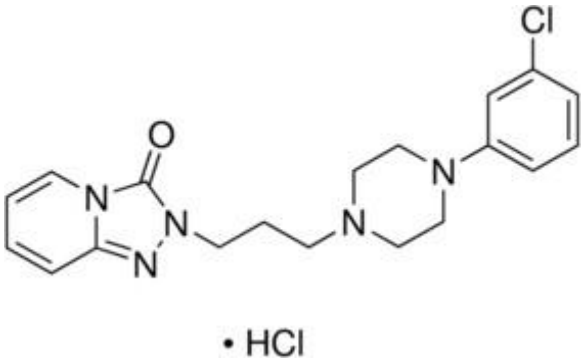
1.5 Pharmacokinetics

Trazodone is well absorbed after oral administration, with mean peak blood levels obtained at about one hour after ingestion. Absorption is somewhat delayed and enhanced by food. The drug is 89–95% protein-bound. Trazodone is extensively metabolized by the liver, with three or four major metabolites having been identified in the human body, particularly mCPP,[1] which may contribute to the side effect profile of trazodone and which probably accounts for trazodone's serotonergic effects. Levels of trazodone are about 10-fold those of mCPP with treatment. The mean blood elimination half-life of trazodone is biphasic: the first phase's half-

life is 3 to 6 hours, and the following phase's half-life is 5 to 9 hours. Metabolites are conjugated to gluconic acid or glutathione and around 70 to 75% of ^{14}C-labelled trazodone was found to be excreted in the urine within 72 hours. The remaining drug and its metabolites are excreted in the faeces via biliary elimination. Less than 1% of the drug is excreted in its unchanged form.

Drug profile

Trazodone Hydrochloride MF: $C_{19}H_{23}BrClN_5O$, MW: 452.8g/mol, IUPAC Name: 2-[3-[4-(3-bromophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3-one;hydrochloride, used to treat This medication is used to treat **depression**. It may help to improve your mood, appetite, and energy level as well as decrease anxiety and insomnia related to **depression**. Trazodone works by helping to restore the balance of a certain natural chemical (serotonin) in the brain. Serotonin and noradrenaline **are** chemicals in the brain that help improve your mood. When your levels **are** low, you **can** get depressed. **Trazodone** helps increase your levels of serotonin and noradrenaline so you feel better.



The main side effects associated with TRZ administration are: nausea, insomnia, agitation, dry mouth, constipation, headache, hypotension, blurred vision and confusion 8. The drug was first synthesized in 1966, has minimal anticholinergic and cardiovascular effects, and a marked sedative action 9. Analytical methods for the determination of trazodone in serum include spectroflurometry 10, gas chromatography with flame-ionization, nitrogen-phosphorous selective or mass spectrographic detection 11-14. HPLC method with ultraviolet, fluorescence or electrochemical oxidation detection 15-20 and UV 21-25 methods.

Trazodone has biphasic elimination, with a redistribution half-life of about one hour and an elimination half-life of **10-12 hours**. Trazodone is nearly completely metabolized hepatically by hydroxylation and oxidation to metabolites that are probably inactive.

1.3 Society and Culture

Generic names

Trazodone is the generic name of the drug and its INN, BAN, and DCF, while *trazodone hydrochloride* is its USAN, USP, BANM, and JAN.

Brand names

Trazodone has been marketed under a large number of brand names throughout the world. Major brand names include Desyrel (worldwide), Donaren (Brazil), Molipaxin (Ireland, United Kingdom), Oleptro (United States), Trazorel (Canada), and Trittico (worldwide).

Method Development and Validation Aspect

By using Analytical methods development and validation assume imperative parts in the discovery, improvement and preparation of pharmaceuticals. Method development is the way toward demonstrating that a analytical strategy is satisfactory for use to measure the concentration of an active pharmaceutical ingredient (API) in a particular formulated dosage form which enables simplified methods to be utilized to check that an analytical procedure, precisely and reliably will convey a reliable estimation of an active ingredient in an compounded preparation. The analytical strategy validation is important for analytical technique improvement and tested widely for specificity, linearity, exactness, accuracy, precision, range, detection limit, quantization limit, and robustness. In outline, analytical method development and validation permits to affirm that an exact and reliable potency estimation of a pharmaceutical preparation can be performed.

LITERATURE REVIEWS

By study of some searches and findings following samples are represents the line study related to the topic.

Title	Method	Description	Detection mode
1.Rp-Hplc Method Developmentand Validation Of Trazodone Hcl	RP-HPLC	Mobile phase: acetonitrile: methanol: water in the ratio 40:40:20v/v Column: kromasil 100SC18 (250mmx4.6nm)	255nm wavelength
2.isocratic hplc method determination of trazodone hcl and its three process related impurity	HPLC	Mobile phase: 300ml acetonitrile, 50 ml THF, 400 ml water and 250 ml methanol.	255nm wavelength
3.Validation Rp- Hplc	FESIBLE RP- HPLC	Mobile phase: Acetonitrile:	256nm

Method for Estimation of trazodone hcl in marketed formulation		methanol in the ratio 50:50v/v Column :C18 (5um,150nmx4.60nm)	wavelength
4.Development and Validation of Liquid Chromatographic Method for trazodone hcl	HPLC	Methanol 180 ml, acetonitrile 180 ml, tetrahydrofurane 40 ml, Column: (4.6 mmx 10 um)	252 nm wavelegth
5.Stability Indicating Assay of Trazodone Hydrochloride Using Hplc	HPLC WITH FLUROSENCE	-	-
6. Trace level quantification of 1-(3-	LIQUID CHROMATOGRAPHY TENDEM MASS	Mobile phase : Ammonium acetate :acetonitrile (30:70 v/v)	
Chloropropyl-4- (3-chlorophenyl) pyperazine hcl genotoxic impurity in Trazodone using lc-ms/ms.	SPECTROMETRY (LC-MS/MS)	Column : C18 symmetry (100mmx4.6mm,3.5um)	-
7.Development of hplc method coupled with fluorescence detection for simultaneous determination of trazodone hcl and donepezil hcl.	-	-	-

Instead of analytical part

There are various papers were studied on the trazodone hydrochloride

1. Main active metabolite in human plasma study i.e 3-(1-chlorophenyl) piperazine (m-cpp) was done.
2. Trazodone hydrochloride is also studied for their multiple uses that are decrease anxiety, insomnia related to depression, improving mood, appetite, and energy level as well as its worsening side effects such as suicidality and suicidal ideation in children, young adults and adolescent, also studied in pulled analysis of placebo controlled trials of antidepressant N=4,500 pediatrics and 77,000 adults), there was an increase risk of suicidal thought and behavior across patient.
3. There are certain studies like pharmacokinetic and pharmacodynamics activity of trazodone hydrochloride was also done.
4. As well as for different parameters like bioavailability comparison study also done.

CONCLUSION

The above study gives the analyte method for analysis of trazodone hydrochloride by using RP-HPLC methods and UV Spectroscopic methods. The validation parameter such as precision, accuracy, linearity, analysis time are perfomed. literature survey reveals that various methodologies are reported for development and validation of various drugs. These methods give ideas for development and validation of new analytical method.

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