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A REVIEW ON ANALYTICAL METHOD VALIDATION OF TAPENTADOL TABLETS

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ABSTRACT

Tapentadol is a novel centrally-actingopioid analgesic. Analytical method validation established by laboratory studies that the performance characteristics of the method meet the requirements for the intended analytical application. The user generates proof on the accuracy, precision, specificity, the limit of detection, the limit of quantitation, linearity, range, and robustness of the method for in-house application. For qualitative and quantitative testing of drug analytical method validation plays an important role for safety compliance while developing drug products. It attempts to summarize guidelines by different regulatory bodies and also a summary of the testing method published in different journals.

KEYWORDS

Tapentadol, HPLC, HPLC, UV and GMP.

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INTRODUCTION

Tapentadol Hydrochloride [3-[(2*R*, 3*R*)-1-(dimethylamino)-2-methylpentan-3-yl] phenol; Hydrochloride] is a novel opioid analgesic having two mechanisms of action. The first mechanism of action is agonist activity at μ opioid receptor and the second one is norepinephrine reuptake inhibitor. The physical appearance of Tapentadol Hydrochloride is light brown solid. The molecular formula of Tapentadol Hydrochloride is $C_{14}H_{24}ClNO$ having a molecular weight of 257.8, melting point 209 – 210□, and boiling point 323.493□ at 760mmHg.

Tapentadol HCl is used to treat moderate to severe short-term pain. It belongs to a class of drugs known as opioid analgesics. It works in the brain to

change how the body feels and responds to pain. The dosing regimen should be individualized according to the severity of pain and previous treatment experience. Patients should start treatment with single doses of 50mg Tapentadol tablet administered every 4 to 6 hours. Higher starting doses may be required depending on the severity of pain and the patient's previous history of analgesic requirements. On the first day of dosing, an additional dose may be taken as soon as one hour after the initial dose, if pain persists. The dose should then be titrated individually to a level that provides adequate analgesia and minimizes undesirable effects under the close supervision of the prescribing physician. Total daily doses greater than 700mg Tapentadol on the first day of treatment and maintenance daily doses greater than 600mg Tapentadol have not been studied and are therefore not recommended.

Pharmacokinetic Properties

After oral administration Tapentadol is rapidly and completely absorbed. At fasting, absolute bioavailability after single-dose administration is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after administration of tablets.

Throughout the body, Tapentadol is widely distributed. Following intravenous administration, the volume of distribution (V_d) for Tapentadol is 540 ± 98L. The serum protein binding is low and amounts to about 20%.

The metabolism of Tapentadol is huge. About 97% of the core compound is metabolized. The metabolism of Tapentadol occurs by conjugation with glucuronic acid to produce glucuronides.

Tapentadol and its metabolites are excreted nearly 99% via the kidneys.

Side effects

Hives

Fast heartbeats

Chest pain

Difficult breathing

Tapentadol tends to slow or stop breathing and death may occur. Naloxone can be used or emergency medical attention should be provided if the patient has slow breathing with long pauses, blue-colored lips, or if you are hard to wake up.

Drug-Drug Interactions

Duloxetine, Venlafaxine, Amitriptyline, Desvenlafaxine and Escitalopram

Tapentadol with these drugs increase the risk of a rare but serious condition called serotonin syndrome (such as confusion, hallucination, seizure, extreme change in blood pressure, increase heart rate, fever, excessive sweating, shivering or shaking, blurred vision, muscle spasm or stiffness, tremor, incoordination, stomach cramp, nausea, vomiting, and diarrhea).

Pregabalin, Orphenadrine, Oxycodone, Quetiapine, Naloxone and Diazepam

Tapentadol with these drugs cause CNS depression and lead to serious side effects including respiratory distress, coma, and even death.

Topiramate

Tapentadol with Topiramate may increase side effects such as dizziness, drowsiness, confusion, and difficulty concentrating. Elderly people may experience impairment in thinking, judgment, and motor coordination.

Albuterol

Both Tapentadol and Albuterol can increase blood pressure and heart rate and combining them may enhance these effects[1].

Validation

As per USFDA validation is defined as "Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Validation is an important part of quality assurance that involves the systematic study of process, procedure and method aimed at determining whether they perform their intended functions adequately and consistently as specified. Itself validation does not improve processes, procedures, or methods but confirms that they have been properly developed and under command.

Stages in validation

There are three stages for action identifying with validation.

Stage 1

It includes the pre-validation qualification stage which covers entire processes identifying with product studies and improvement, formulation pilot batch, technology transfer, setting up stability conditions, managing of in-process, finished pharmaceutical formulations, equipment qualification, master documents, and process limit.

Stage 2

It is the process validation phase. The intention is to check that every installed limit of the essential process parameter is considerable and that satisfactory products can be manufactured even below the worst conditions.

Stage 3

It is known as the validation maintenance phase, it requires continuous review of all procedures related to archives, including validation of the review reports to guarantee that there have been no modifications, departure, failures, or alteration to the production procedure and that all SOPs, change control procedures has been observed[2].

Types of validation

Different types of validation in pharmaceuticals are[3,4]

Equipment Validation
Process Validation
Cleaning Validation
Computer System Validation
Analytical Method Validation
Facilities Validation
HVAC System Validation
Utilities Validation
Vendor Validation

Equipment Validation[5-8]

The action of proving and documenting that any premises, system, and equipment are properly installed and work correctly gives expected results. Most commonly Equipment Validation is known as Equipment Qualification. Qualification is the initial stage of validation, but individual qualifications do not constitute process validation.

There are four stages of Qualification.

Design Qualification (DQ)

Design Qualification is documented verification of the design of equipment and manufacturing facilities. It is aimed to specify that the equipment, system, or facility is designed in accordance with the requirements of the user and GMP guidelines. It confirms equipment description, the material of construction, utility connections, and verification of major components.

Installation Qualification

Installation Qualification is documented verification of equipment of system design and adherence to manufacturer's recommendations. It should provide documented evidence that the installation was complete and satisfactory. All the parameters are verified and documented as per the approved IQ protocol. The purchase specifications, drawings, manuals, spare parts list, and vendor details should be verified during IQ.

Operational Qualification

Operational Qualification should provide documented evidence that utilities, systems, or equipment and all its components operate in accordance with the operational specification. Typically OQ procedures include:

Brief identification information
Visual inspection parameters
Functioning of switches and indicator lights
Check and calibration of the sensor, probes, gauges, recorders, airflow rates, direction, pressure, temperature, etc.
Filter integrity and efficiency test
Cleaning procedure
Control panel testing
Safety features testing
Training for operators and supervisors

Performance Qualification

Performance Qualification should provide documented evidence that utilities, systems, or equipment and all its components can consistently perform in accordance with the specifications under routine use.

Performance Qualification is the final stage of qualification, which demonstrates how the

equipment or system will perform when challenged under simulated or actual production conditions. A series of tests are designed to demonstrate that the equipment or system is capable to perform consistently and meet required specifications under routine production operations.

Process validation[5-8]

USFDA defines process validation as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality characteristics".

WHO GMP defines process validation as "establishing documented evidence, which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes".

The European Commission (EC) guideline defines process validation as "establishing documented evidence that the process operated within established parameters can perform effectively and produce a medicinal product meeting its predetermined specifications and quality attributes".

There are four types of Process Validation.

Prospective process validation

It is a preplanned scientific approach and includes the initial stages of formulation development, process development, setting of process specifications, developing in-process tests sampling plans, designing of batch records, defining raw material specifications, completion of pilot runs, transfer of technology from scale-up batches to commercial size batches, listing major process is executed and environmental controls.

In prospective Validation, the validation protocol is executed before the process is put into commercial use.

Concurrent process validation

It is similar to prospective validation except the operating firm will sell the product qualification runs to the public at market price. This validation involves in-process monitoring of critical processing steps and product testing.

A process where current production batches are used to monitor processing parameters. It gives of the present batch being studied and offers limited assurance regarding consistency of quality from batch to batch. Concurrent Validation may be the practical approach under certain circumstances.

Retrospective process validation

It is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information. The sources of such data are production, QA, and QC records.

Revalidation

It is the repetition of the validation process or part of it. This is carried out when there is any change in any of the critical process parameters, formulation, primary packaging components, raw material fabricator, major equipment, or premises. Failure to meet product and process specifications in batches would also require revalidation.

Cleaning validation

Cleaning validation guarantees that specified facilities, production sites, equipment, etc. are cleaned as per predetermined standards. This validation for production equipment prevents the product from contamination of previous product; detergent or microbial sources have been reduced to a pre-determined level. A documentation system must be established, which identifies the previous batch and shows that the equipment is properly cleaned[9].

Computer system validation

In this validation, a system that includes the input data, electronic processing, and output information to be used for automatic control or reporting is validated. Suitable installation qualifications and operational qualifications have illustrated the suitability of computer hardware and software to perform the specified task. The functions were computerized systems are used to control a GMP-related processor to store and retrieve data that have GMP implications, they are validated. Computerized system validation ensures adequate control to prevent unauthorized access or changes to data. In case computerized systems breakdown or failure may result in a permanent loss of critical records, then a backup system and a recovery plan

are provided. If changes to computerized systems are required then it is supposed made according to the "change control" system and have to be formally authorized, documented, tested, and subjected to the revalidation process[3].

Analytical method validation[10-16]

Analytical method development and validation are a part of analytical chemistry and analytical chemistry is defined as the study of separation, quantification, and identification of natural or artificial materials made up of one or more elements or compounds.

Analytical method validation is defined as the process by which it is established by laboratory studies that the performance characteristics of the method meet the requirements for the intended analytical application.

Analytical procedures to be validated

Validation of analytical procedures is of the four most common types.

Identification tests

Quantitative tests for impurities' content

Limit tests for the control of impurities

Quantitative tests of active moiety in samples of drug substance or drug product or other selected components in the drug product

Determination of performance characteristics

Accuracy/Recovery

The accuracy of an analytical procedure expresses the closeness of agreement between the value, which is accepted either as conventional true value or an accepted reference value and the value found, i.e. analytical result. The accuracy of an analytical method is indicated by the recovery of analytical results.

It is done by either spiking or taking in linear conc. of samples over the range of 80% to 120% of the target concentration with triplicate samples in each concentration.

Precision

Precision is the closeness among analytical results. It is expressed as a relative standard deviation. Precision is of three different categories.

Repeatability (under the same operating conditions over a short interval of time i.e. same day precision).

Intermediate Precision (within laboratories variations i.e. change of analyst, equipment, etc.).

Reproducibility (results at different laboratories).

Specificity

Specificity is the ability to assess unequivocally the target pathogen or analyte in the presence of components that might be expected to be present. It is investigated by injecting the blank (solvent)/placebo (matrix solution), standard solution, and sample solution to demonstrate the absence of interference with the solution of analytics.

Limit of detection

The Limit of Detection (LOD) is defined as the lowest concentration of an analyte in a sample that can be detected, not quantified.

Limit of quantification

Quantitation limits based on the visual inspection are determined by establishing the minimum level of analyte that can be measured with acceptable accuracy and precision.

Linearity

The linearity of an analytical procedure is its ability to obtain test results that are directly proportional to the concentration of an analyte.

Range

The range is the concentrations of analyte or assay values between the low and high limits of quantitation

Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate, variations in method parameters and provides an indication of its reliability during normal usage.

After all these tests by confirming ICH guidelines, the Analytical method development finally results in official test methods. This review is focused on several analytical methods such as UV, HPLC, and UPLC for the estimation of Tapentadol tablets[17,18].

Summary for analysis of Tapentadol tablets by UV method

S.No	Literature Topic	Method	Description	Ref.
1	A new Facile and Sensitive Method for estimation of Tapentadol	UV	Detection wavelength: 520nm in Water Linearity range: 50-250µg/ml Co-relation Co-efficient: 0.9989% Recovery range: 97.8-99.5% % RSD: 0.527%	19
2	Spectrophotometric Methods for Determination of Tapentadol Hydrochloride	UV	Detection wavelength: 282nm in Water Linearity range: 25-150µg/ml Co-relation Co-efficient: 0.9999% Recovery range: 98.9-99.82% % RSD: 0.97%	20
3	Development and validation of first order derivative spectrophotometric method for simultaneous estimation of paracetamol and Tapentadol hydrochloride in tablet dosage form	UV	Detection wavelength: 289nm (TAP) and 257.1nm (PCM) in 0.1 N NaOH Linearity range: 3-15µg/ml (TAP) and 15-35µg/ml (PCM) Co-relation Co-efficient: 0.9993% (TAP) and 0.9989% (PCM) Recovery: 98.9% (TAP) and 99.76% (PCM) RSD: 1.24% (TAP) and 1.02% (PCM)	21
4	Development and validation of RP-HPLC, UV-Spectrometric and Spectrophotometric Method for Estimation of Tapentadol Hydrochloride in Bulk and in Laboratory Sample of Tablet Dosage form	UV	Detection wavelength: 272nm using Methanol Linearity range: 20-100µg/ml Co-relation Co-efficient: 0.9995% Recovery: 99.93 -100.1% RSD: 0.65%	22

Summary for analysis of Tapentadol tablets by HPLC method

S.No	Literature topic	Method	Description	Ref.
1	Development and Validation of RP-HPLC method for estimation of Tapentadol Hydrochloride in bulk and tablet dosage form	RP-HPLC	Column: C18 column (150x4.6mm, I.D, 5µm) Mobile phase: Methanol: 0.1mM Dipotassium phosphate (pH 4, adjusted with Orthophosphoric acid) Flow rate: 1mL/min Wavelength: 280nm	23
2	Application of a Validated stability-indicating LC Method for the Simultaneous Estimation of Tapentadol and its Process-related impurities in bulk and its dosage form	LC	Column: C18 column (250x4.6mm, I.D, 5µm) Mobile phase: Methanol: 0.2 M Potassium dihydrogen orthophosphate (pH 6, adjusted with 1 M KOH) and Acetonitrile (80:20, v/v) Flow rate: 1mL/min Wavelength: 215nm (UV detection) Retention Time: 7.7 ± 0.05	24

3	Stability Indicating RP-HPLC Method for the determination of Tapentadol in Bulk and in pharmaceutical dosage form	RP-HPLC	Column: C8 column (250x4.6mm, I.D, 5µm) Mobile phase: A buffer containing a mixture of 10mM aqueous potassium dihydrogen orthophosphate (pH adjusted to 3): Acetonitrile (65:35, v/v) Flow rate: 1mL/min Wavelength: 217nm (UV detection) Retention Time: 3.8 minutes	25
4	ICH guideline practice: application of validated RP-HPLC-DAD method for determination of Tapentadol hydrochloride in dosage form	HPLC	Column: C18 column (250x4.6mm, I.D, 5µm) Mobile phase: 0.1% Formic Acid in water and Acetonitrile (75:25) Flow rate: 1mL/min Detector: PDA Retention Time: 5.34 minutes	26
5	Development and validation of RP-HPLC, UV-Spectrometric and Spectrophotometric Method for Estimation of Tapentadol Hydrochloride in Bulk and in Laboratory Sample of Tablet Dosage form	RP-HPLC	Column: C8 column (250x4.6mm, I.D, 5µm) Mobile phase: 50mM Phosphate buffer (pH 3.62) and Acetonitrile (70:30) Flow rate: 1mL/min Wavelength: 285nm Retention Time: 5.4 minutes	22

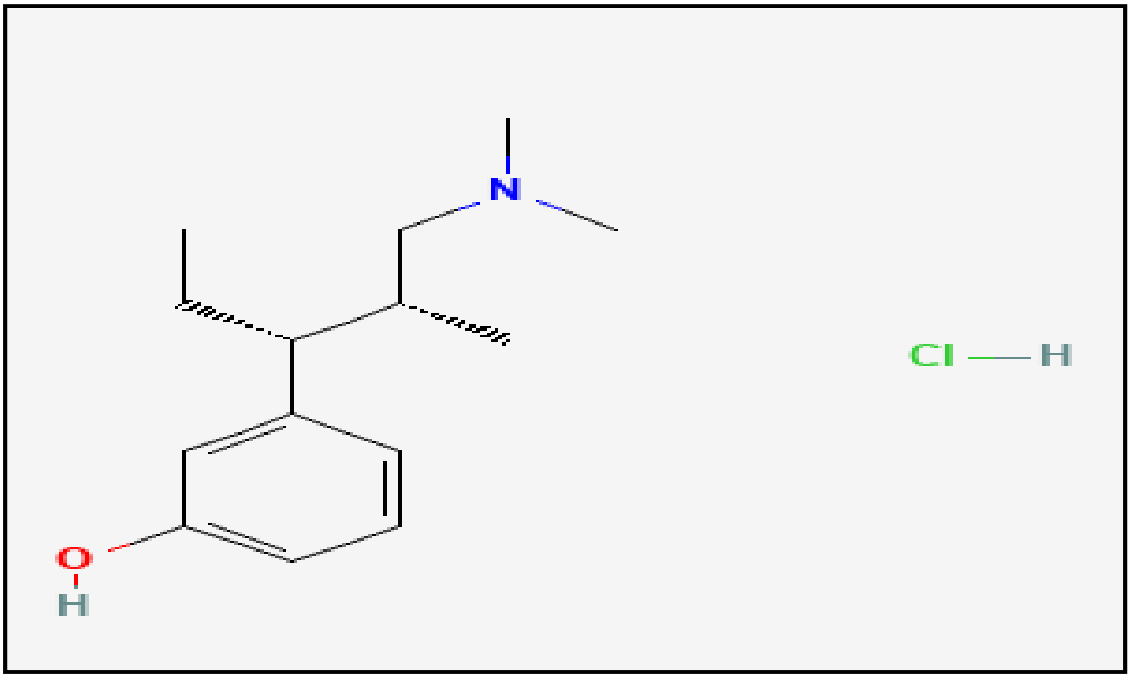

Figure No.1: Structure of Tapentadol hydrochloride

CONCLUSION

Various analytical techniques were available for the analysis of Tapentadol tablets. Some of the analytical techniques are the UV method and some are of the HPLC method for the same compound. In the HPLC method, there is the use of different detectors (UV, PDA) and different columns (C8, C18) of varying sizes and different mobile phases. It was noticed that a flow rate of 1mL/min was taken in all the literature to get a good retention time. For the UV method, Methanol and Water were used as a solvent. Hence it can be concluded that all the methods found to be simple, accurate, precise, and reproducible in nature.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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