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A Systematic Review on Analytical Methods of Antipsychotic Drug Aripiprazole

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ABSTRACT

Aripiprazole is a novel antipsychotic drug for the treatment of schizophrenia and schizo effective disorder. Aripiprazole belongs to the benzisoxazole derivatives. Aripiprazole is available in many salts and polymorphs forms. Analytical method development and validation are the continuous and independent task associated with the Quality assurance department. Analytical procedures play a critical role in equivalence and risk assessment, management, it helps in establishment of product specific acceptance. State that the analytical procedure is suitable for its intended purpose. The validation can provide significant improvement in precision and a reduction in bias error. It can further help to avoid costly and time consuming exercise. X-ray diffraction, IR spectroscopy and DSC could be used for differentiating the polymorphs of Aripiprazole some instrumental methods if analysis such as UV spectroscopy, HPLC, HPTLC, HPLC-UV method, Mass spectroscopy, capillary electrophoresis, chromatographic methods like gas chromatography, also they performed in biological fluid of human and experimental animal such as rat. Also, they include new stability indicating validated method for determination of Aripiprazole. The proposed review on analytical methods of antipsychotic drug Aripiprazole will be sufficient document evidence for the development of new analytical methods as well as for the routine quality control of the drug.

INTRODUCTION

Psychosis is a condition that effect your brain processes information. It makes you lose touch with reality. You may see, hear, or believe things that are not real. Psychosis is a symptom, not a disease. Mental or physical illness, substance abuse or extreme stress or trauma can be the cause. Young people are particularly likely to get it, but doctors don't know why. Even before what doctors call the first episode of psychosis (FEP), you can slightly change the way you think or act. This is called the prodromal period and could last for days, weeks, months, or even years.

Antipsychotics, also called neuroleptics or major tranquilizers used to manage psychosis (including delusions, hallucinations, paranoia, or thought impairment), primarily in schizophrenia and bipolar disorder.

Aripiprazole was approved in November 2002 by the United States Food and Drug Administration for the treatment of schizophrenia. Its introduction has been touted by some as a "third generation" antipsychotic because it was the first partial dopamine agonist anti-schizophrenia drug to be marketed. Other events since the launch of the aripiprazole product have been the emergence of second generation antipsychotics as mood stabilizers, almost all of which, including aripiprazole, have been approved by regulatory authorities for the indication of bipolar mania. Aripiprazole has been approved by regulatory bodies for the treatment of schizophrenia and bipolar I disorder. Although it is a partial dopamine agonist, relatively few comparative trials with other second generation antipsychotics have been published for schizophrenia, none available for bipolar disorder. Evidence to date suggests that in terms of efficacy for schizophrenia, aripiprazole is superior to placebo and haloperidol (long-term), similar to perphenazine and risperidone, and less than 1 "olanzapine.

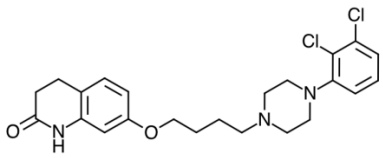

Figure No. 1: Chemical structure of aripiprazole

1. Analytical methods

Pharmaceutical analytical methods or different methods for identifying and quantifying a substance, the components of a pharmaceutical solution or mixture or the determination of the structure of the chemical compound used in the manufacture of the pharmaceutical product. The monitored components include process impurities, chiral or achiral drugs, residual solvents, breakdown products, excipients such as preservatives, extractables and leachables from the container and the closure or manufacturing process. Pharmaceuticals revolutionized human health. These pharmaceuticals would only serve their purpose if they are free from impurities and are administered in the proper amount. In order for the drugs to perform their functions. This review highlights the role of analytical instrumentation and analytical methods in assessing the quality of drugs. The review highlights a variety of analytical techniques such as titrimetric, chromatographic, spectroscopic, electrophoric and electrochemical and their corresponding methods which have been applied in the analysis of pharmaceuticals.

Therefore, system's performance can be measured for a set of possible system architecture and/or size of components.

Analytical techniques

- Titrimetry
- Chromatography
- Spectroscopy

From the stages of drug development to marketing and commercialization, analytical techniques play a big role, be it understanding the physical and chemical stability of the drug.

2. Biological specimens commonly used for the analysis of aripiprazole

Antipsychotic drugs (AP) are prescribed for a wide range of psychotic illnesses. With more than 35 access points currently available worldwide, this class of drugs has quickly gained importance in clinical and forensic settings. Due to their chemical properties, many PAs are present in human samples at very low concentrations, detection by gas chromatography-mass spectrometry (GC-MS), liquid chromatography - (tandem) mass spectrometry LC-MS (/ MS),

RP-HPLC, electrophoresis technology has enabled the precise detection and quantification of these compounds in various human samples. The validation of methods has been a particular objective of analytical chemistry in recent times. Detection and quantification of antipsychotic drugs can be done in different biological matrices, including human saliva, urine, blood, and in the plasma and brain of rats. Biological matrix used for screening, the concentration depends on many factors, namely the dose consumed, the quality of the product, the mode of consumption, the metabolism of the consumer's body weight and his state of health.

2.1. Saliva

Saliva is one of the interesting biological specimens for detecting a recent psychotropic drugs intake compared to urine. Indeed, saliva was approved as the screening method in 2011 by the Substance Abuse and Mental Health Services Administration (SAMHSA, USA).

2.2. Urine

Test of drug using urine are the most common types of tests used in medical professionals. Urine tests are more common because they are noninvasive, are fast, offer the advantage of providing a large sample volume, and are able to qualitatively detect a wide range of substances including aripiprazole. However, the urine needs to be properly stored to provide stable and valid results, and due to the privacy of providing samples, it can be altered before the analysis.

2.3. Blood

Blood is probably the only medium with the potential to indicate whether an individual is under the influence of aripiprazole, or not, at the time of collection. The detection window in the blood is narrower than urine, and the concentrations are lower. Therefore, a sensitive and very specific confirmation technique is mandatory for the detection of aripiprazole and their metabolites in the blood like HPLC or LC-MS/MS, gas chromatography, or GC-Mass spectrometry.

3. Sample preparation (pretreatment and extraction)

The pretreatment of the sample aims to isolate and concentrate the xenobiotic in a matrix while extracting as little as possible endogenous compounds before the analysis. This is certainly the most important step in the analytical process. The diversity of biological samples, entrusted to toxicology laboratories for analysis, shows complex matrices (blood, urine, hair, saliva, meconium, etc.). From this observation, it is well known why good preparation has a direct influence on the limit of detection, repeatability and reproducibility of the analysis. Over the years, various procedures have been developed, including liquid-liquid extraction (LLE), solid phase extraction (SPE), solid phase extraction in molecular phase (MISPE), microextraction (SPME and LPME), extraction by supercritical fluid (SFE), in solid phase extraction, ASPEC system (automated sample preparation with extraction columns), column switching, liquid-liquid dispersive microextraction (DLLME), no-extraction (biofluid dialysis using a semi-permeable gold membrane direct injection of raw samples after precipitation of proteins) and extraction of the sorptive tissue phase (FPSE) which combines extraction in SPME / SPE mode and a unique technological platform. In this review, we will describe the LLE and SPE methods.

3.1. Solid-Phase Extraction (SPE)

Solid phase extraction is based on the partitioning of the compounds between a liquid phase, the sample and a stationary phase, the adsorbent. It generally consists of four stages. It allows it to be humidified with an organic solvent and to activate the retention sites, seat of molecular interactions. A hydrophobic support is conditioned by an organic solvent (most often methanol) and then by a solvent whose ionic characteristics and pH are as close as possible to the solvent in the sample (generally water). The goal is to cause quantitative retention of the analytes of interest on the stationary phase, while the maximum of interference is eliminated by simple non-retention. For maximum efficiency, the sample flow rate should be moderate. The next step is washing. It is not systematic; it aims to eliminate weakly retained interference. It is necessary to choose solvents with low eluent forces (for example, a methanol/water solution) to elute only the interferents. This step for the so-called mixed phases can be multiplied by acting alternately on one of the mechanisms, for example, a first washing with a solution with a low eluent for our analytes then a second washing by modifying the pH of the mobile phase. These multiple washes very clearly improve the cleanliness of the extract contributing to the quality of the analysis. It is recommended at the

end of this step to dry the support to evaporate the traces of washing solvent. This step improves the extraction yield. The last step is elution. It is preferable to use the solvent having the lowest possible elution force capable of entraining all the molecules of interest, thus avoiding the elution of highly retained interferers. The choice of solvent is also guided by its ease of evaporation or its compatibility with the following analytical technique. However, it must be as effective as possible; its volume must be low to obtain a very important preconcentration factor. The solvent flow should be slow to promote elution. Finally, SPE has taken an important place in the preparation of samples over the years. The range of stationary phases and their conditioning are regularly enriched. This extraction method makes it possible to easily extract compounds that are difficult to extract because they are very polar, with organic solvents and which can therefore only be analyzed after simple precipitation. In addition, its automation which exists in different forms promises its wide use in the future by many laboratories.

3.2. Liquid-Liquid Extraction (LLE)

Liquid-liquid extraction (LLE) methods are commonly used in pharmacology/toxicology to purify and concentrate samples before chromatographic or other analyzes. Various physicochemical parameters govern the production of an LLE, specific to the solvents used and the solutes to be extracted. Knowledge of certain properties of the solvent such as its miscibility with water, the acidity constant, the dielectric constant, the dipole moment, the density, the volatility and its toxicity will allow the choice of this solvent alone or as a mixture for l extraction of a given substance. Likewise, knowledge of the properties of the solute such as the structure, the acidity constant, the lipophilicity, the nature and the complexity of the matrix in which it is found will optimize the extraction, the efficiency of which will be evaluated by the extraction yield. The mastery of all these variables will allow the operator to optimize the toxicology.

4. Methods commonly used for the Analysis of Antipsychotic drugs

Many methods for the determination of aripiprazole in biological samples have been reported in the literature. Some are qualitative and others are quantitative methods. Indeed, the methods developed are classified in chromatography (HPLC, TLC and GC) Photometric immunoassays (nuclear magnetic resonance and ultraviolet-visible) and electroanalytical methods (potentiometric, polarographic and voltammetric).In the event of suspected misuse

or acute intoxication with aripiprazole, toxicological analysis is often very useful for confirmation. The latter consists of three stages:

Step 1. Screening using enzyme-linked immunosorbent assays that allow rapid identification of the class of the affected drug.

Step 2. Identification by spectroscopic and / or chromatographic techniques, well adapted to the emergency but presenting certain limits.

Step 3. Quantification of the aripiprazole molecule by suitable chromatographic or spectroscopic techniques.

To obtain accurate and reliable results, relatively clean samples must be analyzed. Therefore, pretreatment of the biological sample is aessential factor for analytical method. It makes it possible to improve the reproducibility of the analysis, to lower the limit of quantification of the method by reducing the background noise and the concentration steps, by improving the fidelity and the precision of the analysis, and finally by increasing selectivity. In this regard, modern isolation techniques, for example, solid phase microextraction (SPME) or LLE which help to concentrate volatile or non-volatile compounds in samples before GC or HPLC analysis, solvent extraction after derivation and stationary phases of polar grafted silica, are very important[1].

5. ANALYTICAL METHODS FOR ARIPIPRAZOLE

1) Spectroscopic studies

The infrared spectrum, ultraviolet spectrum (UV), mass spectrum (MS), nuclear magnetic resonance (NMR) and of aripiprazole, a new antipsychotic drug, were reported and interpreted. All the 13C NMR and 1H NMR signals were assigned. Mainly, the ten different methylenes in this structure were analyzed based on the chemical shifts, coupling constants and correlations in 2D-NMR spectrum. By all these spectral techniques, the structure of antipsychotic drug aripiprazole was identified [2].

The spectroscopic determination was carried out at maximum absorption of 256 nm using 95% ethanol as solvent. In the UV spectroscopic method, the linearity over the concentration range of aripiprazole was found to be 5.30 µg / ml with a correlation coefficient of 0.9995. The results of the analysis were validated statistically and by recovery studies. The developed

method proved to be precise, selective and quick for the estimation aripiprazole in solid dosage form [3]. He proposed method for the determination of aripiprazole in solid dosage form has been shown to be precise, selective, fast and economical. Aripiprazole exhibited maximum absorption at 255.92 nm and obeys Beer's law in the concentration range of 5-30µg/ml. the proposed method for determining aripiprazole showed a molar absorbability of 0.74023 x10-4, a linear regression Y = 0.031X + 0.0156 with a correlation coefficient (r^2) of 0.9995.A relative standard deviation of 0.330% was observed during the analysis of six replicates (acetonitrile and 0.1 M HCl for dissolution and dilution respectively) methods for determining aripiprazole. The recovery percentage of 100.12 ± 0.52%, which indicates that the method developed, was simple, fast and precise.

2) RP-HPLC Method

A high performance liquid in reverse phase chromatography (RP-HPLC) was developed for the quantitative detection of aripiprazole in bulk and in pharmaceutical formulation. Separation and quantification have been performed on Sherisorb 5µ ODS column water 24.6 mm x 250 mm C18 using a mobile phase of acetonitrile: methanol: buffer (20:40:40 v/v/v) pH 3.5 at a flow rate of 1.0 ml/min with detection wavelength at 254 nm. The separation was carried out in 7.7 ± 0.1 min for the aripiprazole sample. The method shows good linearity between the ranges of 5 to 25 µg/ml. The intra and inter day the variation was found to be less than 2%. The average recovery of the drug from the solution was 103.67%. This method can be applied directly for the estimation of the drug content in pharmaceutical products formulation [4]. The developed method was validated and applied to pharmaceutical analysis for estimation of ARP in bulk and tablet formulation. This HPLC method is using as a common reagents. A simple sample preparation procedure is appropriate for analysis of ARP in pharmaceutical dosage form. This method has advantages of simplicity, precision, accuracy, sensitivity and quantification of ARP. The retention time is 7.7 min only so many samples also be analyzed in short period of time.

3) Development of an LC-MS/MS method for the simultaneous quantification of aripiprazole and dehydroaripiprazole in human plasma

Sensitive and precise method of liquid chromatography-tandem mass spectrometry (LC-MS / MS) for the simultaneous determination of aripiprazole and its active metabolite, dehydroaripiprazole in human plasma, was developed in using papaverine as an internal standard (IS). LC-MS/MS analysis was performed on a Finnigan LC-TSQ Quantum mass spectrometer using positive ion electrospray ionization (ESI (+)) and selected reaction monitoring (SRM). The dosages of aripiprazole and dehydroaripiprazole were linear over the ranges of 0.1 to 600 ng/ml and 0.01 to 60 ng/ml, respectively. The mean recoveries in the plasma samples were both greater than 85%. The intra- and inter-test precision and accuracy values are revealed within the limits of the test variability criteria according to the directives of the United States Food and Drug Administration [5].

4) Development and Validation of an LC–ESI-MS Method for Quantitative Determination of Aripiprazole in Human Plasma and an Application to Pharmacokinetic Study

A high pressure liquid chromatography–positive electrospray ionization tandem mass spectrometry method was developed and validated for the quantification of aripiprazole in human K2EDTA plasma using zolpidem tartrate as an internal standard. The analyte and internal standard were extracted from human plasma by solid-phase extraction using methanol. The eluted samples were chromatographed on a Grace Smart RP 18 4.6×100 mm, 3µ column by using a 95:5 v/v mixture of methanol and ammonium acetate buffer (30 mM, pH 5.0 ± 0.05) as a gradient mobile phase at a flow rate of 0.6 mL/min, and analyzed by mass spectrometry in the multiple reaction monitoring mode using the [M + H]+ ions m/z 448.03 → 285.14 for aripiprazole and m/z 308.13 → 235.25 for the internal standard (zolpidem tartrate), respectively. Calibration plots were linear over the concentration range of 0.20 to 60.01 ng/mL. Intra-day and inter-day precision (percent coefficient of variation) and accuracy (percent nominal) for quality control samples (0.60, 30.60 and 45.59 ng/mL) ranged between 2.28 and 8.93% and between 92.50 and 107.07%, respectively. Extraction recovery of aripiprazole from plasma was in the range 75.56–79.57%; mean recovery was 77.35%. The main pharmacokinetic parameters were Tmax = (4.00 ± 2.336) Cmax = (55.16 ± 13.490) and AUC = (1846.28 ± 484.686)[6].

A low sample volume, simple solid-phase extraction (SPE) technique is used for extraction, which has 0.20 ng/mL as the limit of quantification (LOQ) and short run time for the quantification of aripiprazole in human plasma. This assay has been successfully applied to a pharmacokinetic study involving the oral administration of 10 mg aripiprazole to 15 healthy human volunteers.

5) Gas chromatography-mass spectrometer

Gas chromatography–mass spectrometry (GC–MS) was developed and validated for the detection of aripiprazole and its main metabolite, dehydroaripiprazole, in plasma. Blood samples from seven psychiatric patients treated with aripiprazole (10–20 mg/day) underwent a solid-phase extraction (SPE) and N-methyl-N-trimethylsilytrifluoroacetamide (MSTFA) derivatization. The characteristic ions of mass spectra for aripiprazole and dehydroaripiprazole were m/z 306, 292, 218 and 304, 290, 218, respectively. Extraction recoveries from this method were 75.4% (n = 5) for aripiprazole and 102.3% (n = 5) for dehydroaripiprazole. The calibration curves of aripiprazole and dehydroaripiprazole were linear from 16 to 500 ng/ml (r^2 = 0.999) and 8 to 250 ng/ml (r^2 = 0.999), respectively. The respective limits of quantification (LOQs) for aripiprazole and dehydroaripiprazole evaluated in 0.5 ml of serum were 14.4 ng/ml and 6.9 ng/ml. Intra-assay and interassay precision and accuracy were within acceptable ranges. In this study, they also found that the mean trough concentrations in plasma at steady-state were 128.9 µg/l for aripiprazole and 30.1 µg/l for dehydroaripiprazole[7].

6) Ultra-performance liquid chromatography/electrospray ionization tandem mass spectrometry

Ultra-performance liquid chromatography/electrospray ionization tandem mass spectrometry (UPLC-ESI-MS/MS) method was developed and validated for the simultaneous quantification of this compound in rat plasma and brain homogenate. The analyte was extracted from rat plasma and brain homogenate using a weak cation exchange mixed-mode resin-based solid phase extraction. The compound was separated on an Agilent Eclipse Plus C(18) (2.1×50 mm, 1.8µm) column using a mobile phase of (A) 0.1% formic acid aqueous and (B) acetonitrile with gradient elution. The analyte was detected in positive ion mode using multiple reaction monitoring. The method was validated and the specificity, linearity, limit of quantitation (LOQ), precision, accuracy, recoveries and stability were determined.

The LOQ was 0.5 ng/mL for aripiprazole in plasma and 1.5 ng/g in brain tissue. The MS response was linear over the concentration range 0.5-100 ng/mL for aripiprazole in plasma and 1.5-300 ng/g in brain tissue. The precision and accuracy for intra-day and inter-day were better than 14%. The relative and absolute recoveries were above 72% and the matrix effects were low. This validated method was successfully used to quantify the rat plasma and brain tissue concentrations of the analyte following chronic treatment with aripiprazole[8].

7) Dried blood spot method combine with HPLC

Aripiprazole analyzed by ultra-high-performance liquid chromatography-tandem mass spectrometry using a C18 reversed-phase column with use of a mobile phase consisting of ammonium acetate/formic acid in water or methanol. The suitability of DBS for TDM was assessed by studying the effect of specific parameters: extraction solution, EDTA carryover, hematocrit, punching location, spot volume, and hemolysis. The assay was validated with respect to conventional guidelines for bioanalytical methods [9].

Volumetric Absorptive Microsampling

Volumetric absorbent micro-sampling (VAMS) is a recent micro-sampling technique used to obtain samples of dried blood and other biological matrices for application to a plethora of bioanalytical purposes. As such, it can be compared to the dried blood stain (DBS) technique which has been widely used for the past 40 years. However, VAMS has promised to bring some significant advantages over DBS, related to the accuracy of the sample volume, hematocrit dependence (HCT), pretreatment and automation. Although some aspects still need to be studied in depth, VAMS is increasingly recognized as a viable alternative to DBS and other dried microsampling techniques [10].

The method was linear, specific, without critical matrix effect, and with an average recovery of around 90%. Precision and imprecision were included in the acceptance criteria for samples with hematocrit values of 30% to 45%. EDTA or hemolysis did not distort the results and no punching transfer was observed. No significant influence on the volume of the spot or the location of the punch was observed. The antipsychotics were all stable in DBS stored for 10 days at room temperature and 1 month at 4 or -80°C. The method was successfully applied to quantify the 3 antipsychotics and their metabolites in patient samples.

8) Adsorptive stripping voltammetric methods

Anodic behavior of aripiprazole (ARP) was studied using electrochemical methods. Charge transfer, diffusion and surface coverage coefficients of adsorbed molecules and the number of electrons transferred in electrode mechanisms were calculated for quasi-reversible and adsorption-controlled electrochemical oxidation of ARP at 1.15 V versus Ag/AgCl at pH 4.0 in Britton–Robinson buffer (BR) on glassy carbon electrode. Voltammetric methods for direct determination of ARP in pharmaceutical dosage forms and biological samples were developed. Linearity range is found as from 11.4 µM (5.11 mg/L) to 157 µM (70.41 mg/L) without stripping mode and it is found as from 0.221 µM (0.10 mg/L) to 13.6 µM (6.10 mg/L) with stripping mode. Limit of detection (LOD) was found to be 0.11 µM (0.05 mg/L) in stripping voltammetry. Methods were successfully applied to assay the drug in tablets, human serum and human urine with good recoveries between 95.0% and 104.6% with relative standard deviation less than 10% Only a few analytical techniques, including HPLC with UV detection, LC-MS / MS, HPLC with tandem mass spectrometry, UPLC with tandem mass spectrometry, HPLC - MS, HPLC with switching column, column switching HPLC and capillary electrophoresis, were targeted for the determination of PRA in pharmaceutical samples or biological fluids. These methods are sufficiently sensitive but are also tedious and specific, very sophisticated instrumentation for routine analysis. Although ARP is an electroactive molecule on different electrodes, there are no studies dealing with the electrochemical behavior of ARP based on its oxidation or reduction to date. Voltammetric techniques, such as cyclic voltammetry (CV), differential pulse voltammetry (DPV) and square wave voltammetry (SWV), have been shown to be very sensitive for the determination of organic molecules, including drugs and molecules apparent in pharmaceutical and biological dosage forms. Fluid. T Sensitivity could be increased when pickling voltammetry is applied. Adsorbent stripping voltammetry (AdSV) has proven to be an effective technique for the determination of traces of a wide range of species which have an interfacial adsorption character on the surface of the working electrode. One of the objectives of the present study was to study the electrochemical oxidation behaviors of PRAs using voltammetric methods. Validated direct voltammetric determination and pickling methods for the determination of PRA in different samples, including pharmaceutical preparations, human serum and human urine. These methods are faster, easier to use and more economical than spectroscopic and chromatographic methods. The electrochemical behavior of ARP, antipsychotics and atypical antidepressants under GCE was studied for the first time. According to these investigations,

the ARP was oxidized on GCE by an almost reversible mechanism with contribution of adsorption and diffusion. These results can be used to study the absorption, distribution and metabolism, pharmacological, toxicological and pharmacokinetic parameters of the molecule studied. It may also be important to study other studies regarding its side effects, target, related organs, form and mode of excretion. Direct stripping and adsorption voltammetric methods for direct determination of PRA have been proposed. A high recovery percentage and low RSD values of the proposed methods indicate that these methods could be used to quantify PRA without interference from other ingredients. In addition, the voltammetric methods proposed that distinct advantages over other existing methods with regard to sensitivity, minimum detectability, applicability to biological samples without any pretreatment and time savings. In addition, no sophisticated instrumentation is required. Consequently, the voltammetric methods proposed that the potential to be a good alternative for the determination of PRA in different samples [11].

9) Thermal analysis

Five pure phase modifications of the antipsychotic drug aripiprazole were prepared and characterized by thermal analysis, vibrational spectroscopy and X-ray diffractometry. All modifications can be produced from solvents, from Form I in addition by heating from Form X degrees at about 120 degrees C (solid-solid transformation) and of form III by crystallization from the melt. The thermodynamic relationships between the polymorphs were evaluated on the basis of thermochemical data and visualized in a semi-schematic energy/temperature diagram. At least six of the ten polymorphic pairs are enantiotropically related and two monotropically. Form X degrees is the thermodynamically stable modification at 20 degrees C, form II is stable in a window of around 62 to 77 degrees C and form I above 80 degrees C (high temperature form). Forms III and IV are triclinical degrees I and X are monoclinic (P2 (1)) and form II orthorhombic (Pna2 (1)). Each polymorph has a distinct molecular conformation, and there are two basic hydrogen bonding synthons N-HO (catemers and dimers). Hirshfeld surface analysis was used to show the differences in intermolecular short contacts. High kinetic stability has been observed for three metastable polymorphs which can be classified as suitable candidates for the development of solid dosage forms [12].

10) Development of fixed dose combination tablets of aripiprazole plus divalproex sodium and their simultaneous determination using HPLC-UV

A large majority of psychiatric patients are treated effectively with a combination of drugs to improve efficacy and compliance, but due to limited research and development in a fixed-dose combination (FDC) in psychiatry, these products are not uses available. The purpose of this study is to prepare cost-effective FDC tablets containing aripiprazole and divalproex sodium. Two batches of combined fixed dose tablets, FDC1 and FDC2, were successfully prepared using the wet granulation technique. In addition, aripiprazole A1 and A2 tablets and Divalproex D1 tablets were also formulated as a reference for comparing the in vitro availability profile. A precise and simple isocratic HPLC method has been established and validated for the simultaneous quantification of aripiprazole and valproic acid in FDC tablets. A C18 reverse phase column (250×4.6 mm) in isocratic mode was used. The mobile phase consisted of acetonitrile and 0.32% KH2PO4 (60:40, v / v), the flow rate was adjusted to 1.0 ml/min and the detection was carried out at 210 nm. The average recovery percentage for aripiprazole and valproic acid was 96.0% and 95.5%, respectively, meeting official requirements. The newly developed FDC product can be used for better therapeutic results from the combined use of aripiprazole and valproic acid, which can improve patient adhesion [13].

11) X-ray diffraction

The existence of sixth polymorph of aripiprazole (APPZ) as characterised by single-crystal X-ray diffraction, and presents its structural and lattice energy comparison with five other polymorphs of APPZ in the Cambridge Structural Database (CSD). Incidentally, aripiprazole with six well characterized polymorphs happens to be the second most polymorphic system in the CSD after the classic ROY molecule which has a record number of seven polymorphs. The extensive polymorphism in the title compound is attributed to a very high degree of conformational freedom, significant differences in the hydrogen bonding and due to the influence of crystal packing effects. Further, the stabilization of a metastable conformer by more efficient crystal packing or a less efficient crystal packing by a more stable conformer are believed to contribute its rich polymorphic behavior. Besides these structural features, an interesting observation noted in APPZ system is that out of the six polymorphs three polymorphs crystallised in centrosymmetric space groups (all P=1) and the remaining three are in the non-centrosymmetric space groups (P21, P21 and Pna21). The presence or absence

of a specific hydrogen bonding motif in the crystal structure is correlated to the selection of the space group. Overall aripiprazole presents an interesting case study of packing, synthon and conformational polymorphism. The present study indicates the importance of exploring suitable crystallization conditions for a good polymorph screening in the early stages of drug development. importance of exploring suitable crystallization conditions for a good polymorph screening in the early stages of the drug development[12].The present study indicate the importance of exploring suitable crystallization condition for good polymorph screening in the early stages of drug development. Importance of exploring suitable crystallization conditions for a good polymorph screening in the early stages of drug development [14].

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12) Simultaneous determination of aripiprazole and its active metabolite, dehydroaripiprazole, in plasma by capillary electrophoresis combining on-column field-amplified sample injection and application in schizophrenia

Capillary-electrophoresis (CE) is one of the preferred techniques which have been frequently used in pharmaceutical quality control as well as clinical chemistry. The device has relatively high sensitivity, shorter analyzing time, and lower costs compared with HPLC. Furthermore, the precision of CE is as good as that of LC, and less effort for sample pretreatments is needed in CE. Urine and even plasma can be directly injected without further pre-treatments. Studies on using CE method for analysis of aripiprazole and its metabolites were limited. Musenga reported that a CE method with dual wavelengths was able to detect aripiprazole at 214 nm within 5 minutes (uncoated fused silica capillaries and a background electrolyte composed of 50 mM phosphate buffer at pH 2.5, 20 kV).

The authors used loxapine as the internal standard, and the plasma sample was pre-treated by using solid-phase extraction on cyano cartridges, with extraction yield rate higher than 91.3%.8 However, there are different detection modules available for CE. The CE machine used in the study of were equipped with dual wavelengths of 214 nm and 590 nm. The study used solid phase extraction, a complicated and expensive method, for sample condensation.

In this report, we describe the use of a liquid extraction method for sample condensation and the P/ ACE MDQ System to detect aripiprazole and its metabolites. The broader wavelength range of The P/ACE MDQ System, between 190 nm and 600 nm, provides a more sensitive and alternative platform for such purpose. 2. Methods 2.1. Chemicals and standards All reagents were analytical grade chemicals from Merck, including NaOH, HCl, phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate, methanol (MeOH), NaHCO3, dimethyl sulfoxide (DMSO)[15].

CZE combining the injection of amplified field samples (FASI) has been developed for the simultaneous determination of aripiprazole and its active metabolite, dehydroaripiprazole, in human plasma. Sample pretreatment using liquid-liquid extraction (LLE) (diethyl ether) with subsequent quantification by FASI-CZE was used. The separation of aripiprazole from dehydroaripiprazole was performed using a BGE containing 150 mM phosphate buffer (pH 3.5) with 40% methanol and 0.02% PVA as dynamic coating to reduce the interaction of the analytes with the capillary wall. Before loading the sample, a methanol plug (0.3 psi, 6 s) was injected to allow FASI for stacking. The samples were injected electro-kinetically (10 kV, 30 s) to introduce sample cations and the applied voltage was 20 kV with column detection at 214 nm. Several parameters affecting the separation and the sensitivity of the drug and its active metabolite were studied, in particular the reconstitution solvent, the organic modifier, the pH and the concentration of phosphate buffer. The linear ranges of the test drug method and its active metabolite, in plasma using amlodipine as an internal standard, were greater than 5.0-100.0 ng / mL. A female volunteer (25 years old) received a single 10 mg oral dose of aripiprazole (Abilify, Otsuka) and blood samples were taken over a 60 hour period for a pharmacokinetic study. The method was also applied to monitor the concentration of aripiprazole and dehydroaripiprazole in plasma collected after oral administration of 20 or 30 mg of aripiprazole (Abilify, Otsuka) per day at steady state in patient schizophrenia.

13) Absorbance Ratio Method of Vortioxetine and Aripiprazole in Synthetic Mixture by UV Spectrophotometry

The absorbance ratio method is a modification of the simultaneous equations procedure. In this study, absorbance ratio analytical method is developed in UV spectrophotometry of Vortioxetine and Aripiprazole in synthetic mixture. The measurements were carried out at wavelengths of 225 and 255 nm. The 255nm is the max of Aripiprazole and 225 nm is the isobestic point. The linear correlation of Isobestic point (r^2=0.997) was obtained in the range

of 2-20 µg/ml and for Aripiprazole the linear correlation range (r^2=0.998) was obtained in the range of 2-32 µg/ml. The method was successfully used for absorbance ratio method of Vortioxetine and Aripiprazole in synthetic mixture form without any interference from excipients and prior separation [16].

14) Identification of degradation products in Aripiprazole tablets by LC-QToF mass spectrometry

This method include separation, identification and proposed structures of degradation products formed during the degradation analysis of aripiprazole in its final dosage form by high performance liquid chromatography (HPLC) coupled with a quadrupole time mass spectrometry in flight (QToF - MS). The drug product was subjected to stressful conditions including acid, basic, thermal, oxidation, moisture and photolytic degradations. Aripiprazole was found to be stable under all conditions, except thermal degradation and peroxide. The degradation impurities were first separated by HPLC and then identified using the QToF mass spectrometry. QToF mass spectrometer provided high mass precision order for strangers impurities and their fragment ions to explore elemental composition. Based on fragmentation model, possible structures of unknown impurities have been proposed. AT to our knowledge, no method was available to identify impurities degradation of aripiprazole tablets by liquid chromatography-mass spectrometry [17]. This demonstrated clarity identification of unknown impurities formed during degradation studies of aripiprazole tablets and was performed byLC - QToF - MS. The aripiprazole tablet formulation experiences severe degradation under thermal degradation conditions of 105°C for 3 days. Three unknown impurities at RRTs of 0.45, 1.06 and 1.1.4 have been detected during degradation studies. From QToF–MS and the MS/MS fragmentation scheme, the structures of unknown impurities in the drug product aripiprazole were elucidated and named 1-but-3-enyl - 4- (2,3 - dichloro - phenyl) -piperazine (0.45 RRT), aripiprazole N - oxide (1.06 RRT) and 7- but - 3 - enyloxy - 3,4 - dihydro - 1H - quinolin - 2 - one (1.14 RRT). Finally, QToF mass study is a useful technique for structure elucidation of unknown impurities in aripiprazole tablets.

15) Sensitive determination of aripiprazole using chemiluminescence reaction of tris(1,10-phenanthroline)ruthenium(II) with acidic Ce(IV)

Aripiprazole (ARP) is an atypical antipsychotic drug used to treat schizophrenia and schizoaffective disorders. In this study, a new method using the chemiluminescence (CL) of tris (1, 10-phenanthroline) -ruthenium (II), Ru (phen) 32+, was developed for the rapid and sensitive determination of PRA in pharmaceuticals and human plasma. The method is based on the fact that the weak chemiluminescence produced in the reaction of Ru (phen) 32+ and Ce (IV) acid is increased in the presence of PRA. Under the selected experimental conditions, the calibration curves were linear from 1.8 to 18.0 ng mL -1 (r2 = 0.9951) and from 18 to 35 900 ng mL -1 (r2 = 0.9987). The limit of detection (LOD) was 0.9 ng mL-1 (S/N=3). In the proposed method, the LOD was approximately 100 times lower than the therapeutic concentration of PRA. The percentages of relative standard deviation (% RSD) for 11 repeated measurements of 180 and 720 ng mL -1 of PRA were 4.5 and 5.2% respectively. The sampling rate for analysis was 70 samples per hour. The proposed method was successfully applied to the dosage of commercial tablets containing the drug, and the results were consistent with those obtained with the reference method. The method was further applied to the determination of the drug in plasma samples. The possible reaction mechanism to LC was also briefly discussed [18].

CONCLUSION

Different analytical methods were used to study antipsychotic drug aripiprazole. This review mainly concerned with analytical methods categories as chromatographic method, titrimetric method, spectrophotometric method and electrochemical techniques, thermal methods, RP-HPLC, LC-ESI-MS, GS-MS, and UPLC-IE-TMS, spectroscopic methods and thermal analysis, electrophoresis, x-ray diffraction, methods are also included in this review.

The LC-MS-MS method was to quantify aripiprazole using zolpidem as IS. The sample turnover rate of 3.70 min per sample make it a procedure in high-throughput bioanalysis of aripiprazole. The developed method can be useful for Bioavailability and bioequivalence studies and routine therapeutic drug monitoring with precision and accuracy.

In Capillary electrophoresis, validated Capillary electrophoresis developed in this study provides a reliable assay for quantifying of aripiprazole and dehydroaripiprazole in blood samples of psychiatric patients and showed better stability in detection over higher

concentrations. Applying the technique obtained from this study to clinical use could be used as a reference for monitoring aripiprazole's therapeutic effect and minimizing side-effects in clinical response. The patients' compliance for treatment responses and quality of life would increase.

Adsorptive stripping voltammetric analysis, the electrochemical behavior of ARP, antipsychotics and atypical antidepressants under GCE was studied for According to these investigations, the ARP was oxidized on GCE by an almost reversible mechanism with contribution of adsorption and diffusion. These results can be used to study the adsorption, distribution and metabolism, pharmacological, toxicological and pharmacokinetic parameters of the molecule studied.

In dried blood spot with HPLC, the method with an average recovery of around 90%. Precision and imprecision were included in the acceptance criteria for samples with hematocrit values of 30% to 45%. EDTA or hemolysis did not distort the results and no punching transfer was observed. The method was applied to quantify the 3 antipsychotics and their metabolites in patient samples.

UPLC/EITMS, method was successfully used to quantify the rat plasma and brain tissue concentrations of the analyte following chronic treatment with aripiprazole. This review provides detailed information about the analytical method which is quantified aripiprazole as a safe drug with antipsychotic effect.

Determination of aripiprazole using chemiluminescence reaction of tris(1,10-phenanthroline)ruthenium(II) with acidic Ce(IV).The method was further applied to the determination of the drug in plasma samples. The possible reaction mechanism to LC was also briefly discussed.

Identification of degradation products in Aripiprazole tablets by LC-QToF mass spectrometry was also reported can be also used for the unknown impurities formed during degradation studies of aripiprazole tablets and was performed by LC - QToF – MS.

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