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Review Paper

Tadalafil Review on Analytical Methods Developed for Pharmaceutical Formulations

Seffrin D P, Gokulakrishnan D, Kavitha R*

Assistant professor, Department of Pharmaceutical Analysis,KMCH College of Pharmacy, Coimbatore – 48.

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ABSTRACT

Tadalafil is a phosphodiesterase- 5 (PDE- 5) inhibitor that has been well-known in the treatment of erectile dysfunction, pulmonary arterial hypertension, and benign prostate hyperplasia. The growing clinical use of tadalafil has led to the need to identify effective analytical mechanisms to determine the drug in the pharmaceutical preparations and in the biological samples. Some of the analytical methods that have been reported in the determination of tadalafil include UV-visible spectrophotometry, high-performance liquid chromatography (HPLC), reverse phase high-performance liquid chromatography (RP-HPLC), high-performance thin-layer chromatography (HPTLC), ultra-performance liquid chromatography (UPLC), liquid chromatography-mass spectrometry (LC-MS), and electrochemical. RP-HPLC is the most commonly used one of these because it has high sensitivity, precision, strength, and can be used in routine quality control. Recent developments in analytical chemistry focus on green analytical methods, chemometric optimization, and Analytical Quality by Design (AQbD) methods to improve the performance of methods and regulatory discipline. The review outlines the different analytical methods which have been described in the determination of tadalafil in pharmaceutical dosage forms and key aspects of the methods, chromatographic conditions, validation parameters, benefits and limitations. The paper also addresses the new trends in the field of analytical analysis and views on tadalafil analysis in the future.

INTRODUCTION

Tadalafil is phosphodiesterase type 5 (PDE-5) which has a 36 hours extension period following a dosage and a half-life of 17.5 hours [1]. The investigation of five tadalafil trials in a total of 1215 men with ED involved in six studies recently terminated on the safety and efficacy of tadalafil [2]. Tadalafil is a PDE 5 that is used to treat erectile disorder. The production of nitric oxide

***Corresponding Author:** Dr. R. Kavitha
Address: *Assistant professor, Department of Pharmaceutical Analysis,KMCH College of Pharmacy, Coimbatore – 48..*
Email ✉: kavithasureshd1@gmail.com
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gas, which is released locally through sexual stimulation, is vital in causing the vasodilation of the erectile tissues because it activates guanylyl cyclase that increases intracellular levels of cyclic guanosine monophosphate (cGMP) and relaxes vascular smooth muscle. An erection is the result of the smooth muscular relaxation and blood flow into the penile tissues. Therefore, Tadalafil is applicable in male erectile dysfunction.

The drug Tadalafil acts in the absence of sexual stimuli. Due to their effectiveness, safety and ease of use, the oral phosphodiesterase type-5 (PDE-5) inhibitors have become the prescribed treatment of erectile dysfunction in most countries. Tadalafil (Cialis; Lilly-ICOS, Indianapolis, IN), a PDE-5 selective inhibitor, became the first of a series of the second-generation PDE-5s to be introduced into the market in February 2003, and was approved by the European Union to treat erectile dysfunction [5].

As one of the most exasperating and unresponsive disorders amongst urologic professionals, ED is now extensively regarded and covered in the general care setting. The latest tadalafil (Cialis ®; Eli Lilly and Company, Indianapolis, IN, USA) is a PDE5 inhibitor that performs in a similar way as sildenafil and vardenafil (Levitra 2; Bayer AG, Germany), but differs primarily in proving to be longer-acting. The last innovation in the treatment of ED therapy in January 2008, Eli Lilly announced that tadalafil as a once-a-day dose has been approved by the Federal Drug Administration (FDA) to use in the management of erectile dysfunction [3].

The most common dosage for Tadalafil is in the form of tablet in 2.5,5,10 or 20 mg of active component with other pharmaceutically inert fillings. However, newer and better oral drug delivery technology is the oral dis integrating strips (ODS) [6].

Here in the review, different techniques are presented analytically to estimate Tadalafil in biological and pharmaceutical matrices. Figure 1 represents the chemical structure of Tadalafil.

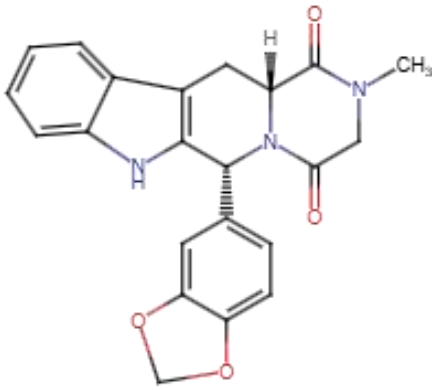

Figure 1

Chemical and Physicochemical Properties of Tadalafil

Property	Description
Chemical Name	(6R,12aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1', 2':1]pyrido[4-b]indole-1,4-dione
Molecular Formula	C22H19N3O4
Molecular Weight	389.40 g/mol
Therapeutic class	PDE-5 inhibitor
Solubility	Slightly soluble in water, soluble in organic solvents
UV absorption maxima	220–230 nm and 290–295 nm

Its hydrophobic nature requires organic solvents such as acetonitrile and methanol in chromatographic methods [9]. Poor solubility also affects dissolution behaviour and analytical extraction efficiency [17].

Estimation Tadalafil: Methods of analysis.

UV -Visible Spectrophotometric Techniques.

One of the easiest and most common analysis procedures applicable in estimating tadalafil in

bulk medicines and therapeutic dosing forms is the UV-Visible spectrophotometry. The principle is founded on the fact that tadalafil absorbs ultraviolet light using the chromophoric groups in its structure to generate a typical absorption maximum (284 -295 nm) [9,22].

In such approaches, tadalafil abides by the law of Beer Lambert in a certain concentration range; which is usually 2-20 mg/mL enabling its quantification depending on the absorbance data [9]. The method has very low sample preparation requirements and is often run in solvents like methanol, ethanol or acetonitrile to maximize solubility [10].

A number of studies have documented successful use of UV spectrophotometry procedure to perform quality control on tadalafil tablets on routine basis with acceptable levels of accuracy (98102) and precision (error with standard deviation less than 2 percent) [22]. In order to enhance selectivity, particularly in combination formulations, variant spectrophotometric techniques, and concomitant equation techniques have also been designed, which allows the separation of two or more overlapping spectra [22,28].

UV spectrophotometry has some weaknesses despite having its benefits. It has no particularity with the existence of excipients, impurities, or other co-formulated medicines, thus unsuitable in complicated preparations like those found in biological samples [10]. Also, it has less sensitivity than chromatographic methods such as HPLC or LC-MS/MS [25].

In general, UV VIS spectrophotometric procedures can still be used to analyze tadalafil in pharmaceutical preparations that are rapid, cost-effective, and routine but are normally used to supplement the more sophisticated techniques used to confirm, as well as bioanalytical purposes [10,25].

Reverse Phase High Performance Liquid Chromatography (RP-HPLC).

One of the most applied services of analysis used in the pharmaceutical analysis to separate drug substances, identify, and determine their quantities is Reverse Phase High Performance Liquid Chromatography (RP-HPLC). In RP-HPLC the stationary-phase is non polar (usually the C18 or C8 bonded silica), whereas the mobile-phase is relatively polar, typically a combination of water, buffers, methanol or acetone naphthons [10,27].

The RP-HPLC separation mechanism is mainly relying on hydrophobic interactions of the analyte and the stationary phase. Compounds that are non-polar are retained more and those that are polar elute quickly. However, Tadalafil has a lipophilic nature and, therefore, is well retained and resolved when the chromatographic conditions are favourable [9,10].

RP-HPLC analysis of tadalafil is typically done using C18 column, a mobile phase such as acetonitrile and buffer (pH 3 -5), a flow rate of about 1 mL/min, and UV detection with wavelength of 230-295 nm [10,11]. Such conditions are a great means of peak symmetry, resolution and reproducibility.

RP-HPLC techniques have been widely used in:

- Determination of tadalafil in bulk and in dosage form.
- Parallel estimation in combination therapies.
- Stability-indicating work under stress environment.

Validated RP-HPLC procedures are very accurate (98102%), have a precision, expressed as percent relative standard deviation (%RSD) less than 2% and linear (R 2 = 0.999), which is ideal in routine quality control [5,18]. Moreover, stability-indicating RP-HPLC means can separate tadalafil and its decay products in an effective way, being specific, and being in compliance with regulation [11].

In spite of its merits, RP-HPLC has some weaknesses such as high solvent use and cost of operation. Nevertheless, recent advancements in green analytical chemistry and optimisation based on AQbD have enhanced the efficiency of the method and minimised the environmental impact [12,18].

Summing up, RP-HPLC is a powerful, stable and multifunctional method of analyzing tadalafil in pharmaceutical preparations and can be regarded as a conventional method of the quality analyses laboratory.

Stability-Indicating Methods

RP-HPLC techniques that indicate stability can be used to resolve tadalafil and its degradation products in stress conditions [11].

Recent research produced various pathways of degradation as oxidative and acidic degradation with LC-MS/MS confirmation [11].

Ultra Performance Liquid Chromatography (UPLC)

Ultra Performance Liquid Chromatography (UPLC) is a superior chromatographic method that has several advantages over the traditional High-Performance Liquid Chromatography (HPLC) in regards to speed, sensitivity and resolution. UPLC with columns packed with sub-2 µm particle sizes, which help in improving the separating efficiency and enabling a faster analysis with less solvent usage. UPLC techniques have been extensively used in estimations of tadalafil; at both pharmaceutical preparation and biological sample analysis, UPLC procedures offer fast run times (typically under 6 minutes) and higher peak resolution [7,8]. Further improvements in sensitivity and selectivity are achieved by the combination of UPLC and mass spectrometry (UPLC-MS/MS) to detect nanograms of complex biological samples including plasma and urine [7,24]. Also, UPLC techniques have been efficient in impurity profiling, degradation analysis, and in detecting counterfeit drugs since it has great resolving power and reproducibility [8]. In general, UPLC is an extremely effective and dependable instrument of analysis in contemporary pharmaceutical research, which compares with the contemporary tendencies of high-throughput and environmentally-friendly analytical methodology [12].

High Performance Thin Layer Chromatography (HPTLC):

High Performance Thin Layer Chromatography (HPTLC) is a sophisticated type of thin-layer chromatography that has better resolution, stability and detectability of the drug constituents, such as tadalafil. It uses precoated silica gel plates that have finer particle sizes and automated loading of samples, such that multiple samples could be analyzed with precision and concurrently. HPTLC in the estimation of tadalafil usually uses mobile phases like toluene, ethyl acetate and methanol, and densitometric statistics in the UV at 280 nm and 295 nm. This method is especially beneficial to the daily quality control because of its low consumption of solvents, cost-efficiency, and the possibility to consider multiple samples simultaneously. Nonetheless, HPTLC has a rather low sensitivity and selectivity compared to RP-HPLC and LC-MS/MS, which restricts its use in trace-level and bioanalytical works. HPTLC is a useful preliminary screening and impurity profiling method, as well as an effective method of estimating combination drug formulations, despite these restrictions [13,25,28].

Liquid Chromatography-Mass Spectrometry (LC-MS/MS).

The Liquid Chromatography–Mass Spectrometry (LCMS/MS) can be considered a gold standard in the quantitative analysis of tadalafil in biological samples because it is highly sensitive, selective, and accurate. This is a hyphenated method that

allows the separation power of liquid chromatography with the detection power of tandem mass spectrometry, which allows accurate identification and quantification of even trace levels (ng/mL) of a complex biological sample like plasma and urine [14,24]. The sample preparation may generally be based on protein precipitation, liquid-liquid extraction, or a solid phase one in order to decrease the matrix effects and the recovery of the analyte [24]. The tadalafil LC MS/MS methods have shown to be highly linear when choosing over a large set of concentration ranges (e.g. 5-1000 ng/mL), it is highly precise (100%RSD) and accurate within the acceptable regulatory limits [14]. In addition, multiple reaction monitoring (MRM) enhances specificity by selectively recording transitions of target ion, thus the procedure is very appropriate in pharmacokinetic and bioequivalence studies [26]. These merits can be taken as the strength allowing LC on MS/MS to be the analysis method of choice in bioanalysis, despite the elevated cost and advanced equipment used.

Spectrofluorimetric Methods

The spectrofluorimetric techniques have proved to be very sensitive analysis methods used in the determination of tadalafil especially when they are present in biological mediums at low concentration where an analysis method capable of detecting them is required. These techniques are founded on the quantification of native or generated fluorescence of tadalafil in the optimum conditions, which often involve excitation and emission wavelengths to obtain high signal and low interference levels. Spectrofluorimetry has much lower limits of detection (LOD) and quantification (LOQ) compared to UV spectrophotometry, which implies that it is useful in analyzing traces. Recently, the application of surfactants, derivatization reagents, and the micellar system to increase the fluorescence content of tadalafil and the sensitivity and selectivity of the methods were reported. Also, spectrofluorimetric methods have so far been effectively used in pharmaceutical preparations with acceptable accuracy and precision; but they can be unsuccessful in the practical use of complex matrices due to the quenching effect and interference of excipients or endogenous substances. Nevertheless, these achievements notwithstanding, the method is still a viable option to consider in fast and cost-efficient analysis in the cases where high sensitivity is a necessity [15,22,24].

Electroanalytical Methods

The use of electroanalytical techniques has presented itself as a potential alternative in ascertaining tadalafil because it is highly sensitive, fast responding, and has few requirements regarding sample preparations. Cyclic voltammetry, differential pulse voltammetry, and square wave voltammetry are some of the techniques that have been studied in relation to pharmaceutical and biological analysis. The modes of operation of these methods are based on the fact that tadalafil is an electroactive drug that can be quantified by oxidation reduction processes on the electrode surface. The current developments include utilization of altered electrodes such as carbon nanotube, graphene-based and metal nanoparticle coated electrodes, which have greatly improved sensitivity, selectivity and limit of detection. The strengths of electroanalytical methods are that they are inexpensive, handheld, and can be used on site. Nevertheless, their use is not wide-spread due to difficulties in controlling factors like electrode degradation, excipient / biological matrices interference and reproducibility. Nevertheless, electrochemical methodology still receives interest as a supplementary approach to chromatographic technique, specifically in the

design of miniaturized and miniaturized-size and point-of-care CAM sensors [15,16,29].

Stability-Indicating Methods

Stability-indicating procedures refer to critical analytical processes aimed at the precise determination of an active pharmaceutical ingredient (API) in the presence of its degradation products, impurities and excipients. These techniques are especially essential to safety, efficacy, and shelf-life assurance of drugs, to which regulatory provisions like ICH Q2(R2) require them [19]. Stability experiments are usually conducted on tadalafil by exposing the drug to all kinds of stress forces such as acidic and alkaline hydrolysis, oxidative degradation, thermal stress, and photolytic exposure to determine its degradation properties [11,17]. The most commonly used technique among them is RP-HPLC that uses a high-resolution capability and can adequately separate tadalafil and its degradation products to confirm the specificity of the method [10,11]. Countries like LC hyphenated methods like LC17is further utilized to identify and elucidate the structure of the degradation products assisting in making the stability investigations more reliable [14,17]. The recent studies have also focused on the creation of the eco-friendly and AQbD-based stability-indicating methods that enhance the method robustness and minimized the environmental impact [12,18]. In general, stability-indicating procedures are important in the pharmaceutical analysis in maintaining the quality and regulatory conformity of tadalafil preparations at their entire life cycle.

Degradation Conditions

- Acidic hydrolysis
- Basic hydrolysis
- Oxidative degradation
- Thermal degradation
- Photolysis

Oxidative degradation is a distinct sensitivity of tadalafil formation of numerous degradation products [17].

Green Analytical Chemistry

Green Analytical Chemistry (GAC) aims at reducing the environmental effect of analytical processes without compromising the performance, accuracy and reliability of the methods. It focuses on the minimization or removal of hazardous solvents, energy usage and production of waste by utilizing friendly solvents, miniaturization methods and effective design of analytics. In pharmaceutical analysis, GAC principles have been used more and more in the design of chromatographic methods, typically minimizing the use of organic solvents, using aqueous or micellar mobile phases and so Analytical Quality by Design (AQbD) has been used to minimize conditions in chromatographic methods with limited experimentation. The recent evidences have revealed that green RP-HPLC procedures to estimate tadalafil could reach the same sensitivity and accuracy as the traditional ones with a reduced environmental impact [12,23]. Moreover, the analysis and subsequent confirmation of environmentally sustainable practices are assisted by the implementation of the sophisticated tools like greenness assessment metrics (e.g., Analytical Eco-Scale, GAPI). GAC therefore does not only increase the efficiency of analysis, but also makes pharmaceutical analysis in tune with the objectives and expectations of global sustainability [12,18,23].

Bioanalytical Methods

In order to determine tadalafil in biological fluids (plasma, serum and urine), bioanalytical techniques are needed to quantitatively determine the drug. They are mostly utilized in pharmacokinetic, bioavailability, and bioequivalence research, where a high level of

sensitivity and selectivity is needed because of low concentration of the drug in the biological fluids [14,24].

1. LC–MS/MS Methods

The most commonly and popular method of tadalafil bioanalysis is liquid chromatography-tandem mass spectrometry (LC -MS/MS).

Sensitivity: ng/mL range

Specificity: High (selective ion monitoring)

Run time: Typically, 3–6 minutes

The LC-MS/MS techniques have a good level of re-producibility and precise measurements with minimal interference by the biological components present in the body. A proven methodology has shown that there is a linear range of 5-1000 ng/mL, with a heavy degree of precision and accuracy [14].

The method reports a chromatographic separation coupled with mass detection and through this method tadalafil can be identified with high levels of reliability and stable even in the complexity biological matrices [24].

2. Methodologies in Sample Preparation.

Bioanalysis requires an effective sample preparation to eliminate proteins and other disruptive elements.

Common techniques include:

Protein Precipitation (PPT):

Things to be simple and quick; solvents such as acetonitrile or methanol.

The majority of crude oil reserves produced by the Canadian oil sands are extracted via liquid-to-liquid extraction (LLE).

Has cleaner extracts and increased sensitivity.

Solid Phase Extraction (SPE):

Has good recovery and reproducibility.

Among them, SPE is superior because it is more selective and cleaner, in particular, in LC MS/MS analysis [24,26].

3. UPLC–MS/MS Methods

Ultra-performance liquid chromatography in association with MS/MS provides:

- Faster analysis time
- Improved resolution
- Automated solvent use.

The UPLC-MS/MS techniques are especially practical in the high-throughput pharmacokinetic investigations and big sample analysis [7].

4. Validity in Bioanalysis.

The bioanalytical techniques should go in accordance with regular requirements like:

- US FDA Bioanalytical Method Validation Guidance (2023)
- EMA Guidelines (2023)

The most important validation parameters are:

- Selectivity
- Accuracy and precision
- Recovery
- Matrix effect
- Stability

The validated methods are able to give reliable results to the biological matrices that can be reproducibly determined through quantification [20,21].

5. Bioanalytical Methods Applications.

The bioanalytical methods are commonly used in:

- Pharmacokinetic studies
- Bioequivalence studies
- Drug monitoring in therapeutics.
- Drug interaction studies

The LCMSMS-based techniques have been effectively applied to the analysis of plasma concentration time profile of tadalafil to offer critical information on dose optimization [14].

Quality with Design Analytical Quality by Design (AQbD)

Analytical Quality by Design (AQbD) represents a methodology of analytical method development that is systematic and science- and risk-driven, and it focuses on predefined goals, in-depth knowledge

of method variables and strong performance during the method life cycle. Basing its concepts on the principles of Quality by Design, AQbD will start with defining of the Analytical Target Profile (ATP) which is further on par with identification of Critical Method Attributes (CMAs) and Critical Method Parameters (CMPs). The risk assessment tools, like failure mode and effects analysis (FMEA) are applied to determine what could be the cause of variability, whereas Design of Experiments (DoE) is utilized to develop a method operable design region (MODR) in which the method is consistent within its performance requirements. AQbD improves the strength of the method and minimizes variation and variability compared to conventional trial-and-error methods, promotes regulatory flexibility and life cycles. Governmental bodies like International Council of harmonisation and US Food and drug administration promote the use of AQbD to improve reliability, reproducibility and continuous improvement of the drug analysis procedures in pharmaceutical analysis [18,21].

Method Validation

Analytical method validation is an important procedure that will guarantee reliability, accuracy and reproducibility of an analytical method in the purpose it will be used. It is done based on a set of guidelines set forth by the International Council for Harmonisation, specifically ICH Q2(R2), and the suggestions made by the US Food and Drug Administration and the European Medicines Agency [19,21] as well.

The method validation shows the appropriateness of an analytical procedure to the quantitative determination of pharmaceutical and biological matrices drugs [22].

Key Validation Parameters

1. Specificity

Specificity is the capability of analytical method to detect the analyte response under the influence of impurities, degradation products and matrix components. It implies the technique is able to determine and detect tadalafil correctly and in good quantity [22].

2. Linearity

Linearity describes the capacity of the technique to give linear results to the concentration of analyte within a certain proportion. This is typically being indicated through the correlation coefficient (R 2), which must be 0.999 and above of a good method [18].

3. Accuracy

Accuracy represents the proximity of assent between the evaluated worth and the factual worth. It is normally tested using recovery investigations at varying concentrations (e.g., 80-,100-, and 120-percent) and must be in the range of 98-102 percent [22].

4. Precision

Precision defines that which is used to describe the reproducibility of the method in a normal operating condition and is defined as percent relative standard deviation (RSD).

- Repeatability (intra-day)
- Intermediate precision (inter-day precision)

The expected value of a lower percentage of RSD should not exceed 2% [22].

5. Limit of Detection (LOD)

LOD is the minimum concentration of analyte that can be detected without necessarily being quantifiable. It will be computed as a signal to noise ratio (usually 3:1) [19].

6. Limit of Quantification (LOQ)

LOQ represents the lowest concentration of an analyte which can be quantitatively measured with reasonable precision and accuracy. This is

normally established at a ratio of 10:1 of signal to noises [19].

7. Robustness

Robustness is an analysis of the ability of the method to be insensitive to small yet intentional changes in method parameters including pH, flow rate and temperature. It implies the stability of the approach in the normal operation [18].

8. Ruggedness

Ruggedness evaluates how the method can be reproducible in varying conditions like varying analysts and instruments and also in various laboratories [22].

9. Range

The range is defined as the difference between the high and low concentration of analyte, which are known to be measured with acceptable accuracy, precision and linearity [19].

DISCUSSION

The determination of tadalafil analytically has changed considerably through the years as a result of improvement in pharmaceutical analysis as well as the rising pressure of the regulatory authorities. Various methods of analysis have been discussed, and each one possesses its unique benefits based on the use, sensitivity needs, and the complexity of the matrix.

In spite of being easy and cost-effective, UV-visible spectrophotometric techniques can be used in bulk drug and simple formula quality control only because of their lack of specificity and interference with both excipients and co-formulated medications. They are not suitable to more complex formulations and more sensitive biological matrices where greater selectivity is critical.

Reverse Phase High Performance Liquid Chromatography (RP-HPLC) is still the most popular method of tadalafil estimation in pharmaceutical dosage preparations. It is known to be popular due to its strength, reproducibility as well as having the capacity to offer accurate and precise results. Its applicability is further enhanced by the fact that stability indicative RP-HPLC methods are available and in fact the latter can be used to efficiently separate tadalafil and its degradation products under different stress environments. Also, the tadalafil estimation method by RP-HPLC has had a successful application of the simultaneous tadalafil estimation through combination therapies which are becoming more prevalent in clinical practice.

Ultra Performance Liquid Chromatography (UPLC) is an imperative enhancement over the traditional HPLC, as it is fast, provides a better resolution and reduced solvent usage. These strengths are very much in line with the present trends of high-throughput and environmental friendly analytical processes. The instrumentation and maintenance being more expensive however may not allow it to be widely adopted in the normal laboratories.

High Performance Thin Layer Chromatography (HPTLC) is a less sensitive method to HPLC-based because it offers a cheaper option to screen and analyze numerous samples concurrently. This is because it is simple and has low solvent consumption hence it is appropriate when doing preliminary analyses but not high precision and sensitive such as advanced ones.

Mass Spectrometry Liquid Chromatography-Mass Spectrometry (LC-MS/MS) has become the new standard of bioanalytical estimations of tadalafil. It has high sensitivity and specificity, and thus can accurately be quantified on trace levels in biological samples, (i.e., plasma and urine). This renders it to be essential to pharmacokinetic, bioavailability and bioequivalence researches. The complex sample preparation methods as brought by the incorporation of solid phase extraction are

even further improved by the fact that they reduce matrix effects on the various methods.

The electroanalytical and spectrofluorimetric methods have been proposed as useful substitutes; they are highly sensitive and need fewer sample preparations. Their application is however limited to the problems of interference, difficulty in reproducibility and common validation when compared to chromatographic techniques.

Another interesting development in the recent years is the introduction of green concept of analytical chemistry that has aimed at minimizing the use of solvents and minimizing the environmental impact. The accessibility of non-toxic chromatography and micellar system allows showing that sustainable analysis can be achieved without negatively impacting the analytical performance.

Moreover, the introduction of Analytical Quality by Design (AQbD) has had a major enhancement on methods development processes. At last, by including risk analysis and design of experiments, AQbD provides strong and trustworthy analysis techniques with lower variability. Regulatory agencies continue to promote this method of systematizing efforts in pharmaceutical analysis and it is likely to become standard practice.

Irrespective of these developments, there exist some challenges. Tadalafil has poor aqueous solubility, which may influence the extraction efficiency, sensitivity of the method, although there is also the issue of matrix interference with bioanalytical analysis. To solve these problems, further developments of the sample preparation procedures and analysis instruments are necessary. In general, the selection of analysis methodology is determined by the purpose of application. RP-HPLC is suitable when it comes to quality control routinely, and LC-MS/MS cannot be omitted in bioanalysis. New methods and advances in analytical procedures should also help improvement even more analytical work, and the estimation of tadalafil becomes more efficient, reliable, and environment-friendly.

CONCLUSION

In short, numerous analytical techniques are developed in the estimation of tadalafil in pharmaceutical products and biological samples. RP-HPLC is the most widely used method of routine quality control because of the reliability, accuracy, and cost-effectiveness of the method, and LC-MS/MS is the method of choice in the case of bio analytics since the method is much more sensitive and selective. Most of the recent developments such as UPLC, green methods of analysis and Analytical Quality by Design (AQbD) have enhanced the robustness of methods and their efficiency as well as environmental sustainability. Although this has been met with poor solubility and matrix interference, new inventions continually revolve around the analysis technology, which will continue to improve the precision, sensitivity, and applicability of tadalafil analysis to pharmaceutical and clinical studies.

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