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Advances in quality assessment and analytical techniques for losartan potassium: A comprehensive review

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Abstract

Losartan Potassium, a medication that blocks angiotensin II receptors, is commonly prescribed for managing high blood pressure and kidney issues in diabetic patients. Monitoring its quality and therapeutic performance is essential, especially due to concerns about inconsistent bioavailability and the presence of harmful nitrosamine contaminants. This review provides a critical evaluation of the physicochemical, spectrophotometric, and chromatographic methods used to assess the quality and purity of Losartan Potassium. The study highlights gaps in current methodologies and underscores the need for more robust analytical approaches, such as HPTLC-MS, to improve detection and quality assurance.

Keywords: Losartan Potassium; Quality Assessment; Analytical Methods; Chromatography; HPLC; HPTLC; HPLC-MS; HPTLC-MS; Spectrophotometry; Nitrosamine Impurities

1. Introduction

Losartan potassium with the chemical name as [2-butyl-4-chloro-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol mono potassium salt], Its molecular formula is $C_{22}H_{22}ClKN_6O$, with a molecular weight of 461 and a melting point of between 183.5 to 184.5 °C. [1] It was first approved by the U.S. Food and Drug Administration (FDA) in 1995, marketed under the brand name Cozaar and various generic formulations [2]. With the chemical structure below:

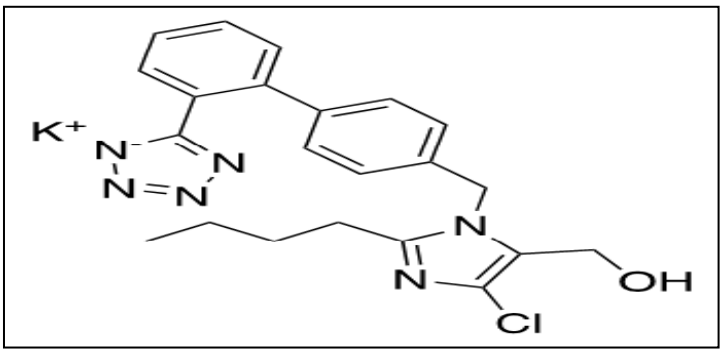

Figure 1 Chemical Structure of losartan potassium [1][2].

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As an orally effective, non-peptide antihypertensive agent from the biphenylyltetrazole class, Losartan functions by inhibiting AT1 receptors of angiotensin II. This action helps dilate blood vessels and lowers the risk of cardiovascular complications and kidney damage, particularly in individuals with diabetes. It offers effective blood pressure control and cardiovascular protection, often preferred due to its tolerability profile[3]. Igboasoiyi, Egeolu, & Memberr Assessing the quality of losartan is paramount to guarantee its efficacy, safety and crucial for blood pressure control [4]. Growing concerns surround the bioavailability of generic losartan potassium formulations, potentially leading to inadequate blood pressure control with suboptimal dosing. This raises questions about their interchangeability with the innovator brand [4]. The presence of multiple generic brands with varying bioavailability has been reported in Nigeria [5]. And this creates a challenge for clinicians and pharmacists in selecting a suitable brand or alternative. Moreover, the presence of nitrosamine impurities, which are potential carcinogens, has been reported in some losartan potassium products. These impurities can arise from the manufacturing process or degradation of the active pharmaceutical ingredient (API). Therefore, losartan potassium poses unique challenges in terms of quality assessment due to its varying bioavailability and susceptibility to nitrosamine impurities [6].

Despite its therapeutic benefits, ensuring the pharmaceutical quality of Losartan potassium is critical, particularly following global recalls due to the detection of carcinogenic nitrosamine impurities, concerns over the quality of different brands, bioequivalence variations, and the presence of carcinogenic nitrosamine impurities necessitate rigorous quality control [7]. Various analytical techniques have been developed to assess the physicochemical properties, potency, and impurity profile of Losartan Potassium [8]. This review critically examines these methods, evaluates their effectiveness and proposes the need for advanced approaches for quality assurance.

2. Analytical Methods for Quality Assessment

The quality of Losartan Potassium is evaluated through physico-mechanical tests, spectrophotometric analysis, and chromatographic techniques.

2.1. Physico-Mechanical Testing

Various techniques including physico-mechanical evaluations following United States Pharmacopeia (USP) and International Conference on Harmonization (ICH) guidelines have been conducted. These include hardness and friability tests which ensure tablet integrity during handling; weight variation and thickness tests assess tablet uniformity and disintegration time test evaluates tablet breakdown in the body [9][5].

2.2. UV-Spectrophotometric Testing

UV-spectrophotometry involves color-based techniques that depend on particular chemical interactions to produce measurable absorbance at set wavelengths, ensuring consistent results when carried out under standardized conditions [10][11]. It also uses colorimetric techniques by relying on color development with specific reagents in visible spectroscopic investigations [12], as well as Raman spectroscopy [13], which is a rapid, non-destructive technique for solid dosage form. Spectrophotometric methods were also employed to evaluate the quality of losartan potassium tablets through the dissolution profile, performed according to USP and FDA specifications [9][5]. Dissolution Testing measures drug release rate in various pH media of 0.1N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8, and water, highlighting bioavailability concerns[9][5]. Findings of the studies reported that all brands met USP physico-mechanical properties specifications. Only Qiu et al use the four dissolution media but all the methods had limited sample size [8]. For dissolution undertaken by Igboasoiyi et al., in Nigeria, reported that one brand passed dissolution specifications (>80% at 30 minutes) in 0.1NHCl while another brand failed dissolution specifications (<80% at 30 minutes) in distilled water bringing about concerns for the validity of the test and bioavailability of these brand [5].

2.3. Chromatographic Methods

Chromatographic techniques provide superior sensitivity, selectivity, and impurity profiling. The primary chromatographic methods include High-Performance Liquid Chromatography (HPLC) is a gold standard for quantitative analysis, High-Performance Thin-Layer Chromatography (HPTLC) is a rapid and cost-effective alternative, Gas Chromatography (GC) -it is use for volatile compounds and impurities and Liquid Chromatography-Mass Spectrometry (LC-MS) – reported as a powerful tool for nitrosamine impurity detection. Various analytical methods have been developed and validated for the estimation of losartan potassium in pharmaceutical preparations. These methods include: reversed-phase high-performance liquid chromatography RP-HPLC [14][8] Reversed-Phase Ultra-Performance Liquid Chromatography RP-UPLC [15], High-Performance Tin Layer Chromatography HPTLC [16][17], liquid chromatography tandem mass spectrometry LC-MS/MS [18]. Two review studies by Ramu&Chittela (2018)[19] and Reddy et al. (2023)[20] highlighted various analytical methods for estimating losartan potassium in pharmaceutical

preparations. The methods used include RP-HPLC, HPTLC, LC-MS and ultra performance liquid chromatography-mass spectrometry UPLC-MS and reported that Acetonitrile is the most commonly used solvents for chromatographic methods while methanol is the most commonly used solvent for spectroscopic methods. Key findings of chromatographic methods showed that HPLC and HPTLC methods have been developed and validated for the quantification of losartan potassium analysis. Only Qiu et al., 2014 [8] method simultaneously estimated losartan and its nitrosamine impurities. Analytical techniques are crucial for ensuring the quality and safety of losartan potassium tablets

3. Impurity and Stability Concerns

Both the U.S. FDA and the EMA have detected nitrosamine contaminants in various angiotensin receptor blocker (ARB) medications, prompting international product recalls. Studies indicate that Losartan Potassium is prone to degradation under acidic conditions, thermal stress, and oxidation. U.S Food and Drug Administration (2021)[6] emphasized the need for risk assessment strategies to detect and quantify these impurities. HPLC-MS and HPTLC-MS are recommended for impurity profiling to ensure drug safety. The review of existing literature indicates that while HPLC and spectrophotometry remain the dominant analytical methods, HPTLC-MS presents a superior alternative due to its ability to detect low-level impurities and degradation products. Dissolution studies, when coupled with in-vitro-in-vivo correlation (IVIVC), provide reliable bioequivalence data, potentially reducing the need for in-vivo pharmacokinetic studies. However, gaps remain in the standardization of dissolution media, as many studies use only distilled water instead of the four official USP dissolution media. Additionally, many quality assessments focus solely on physicochemical properties without considering impurity detection, particularly for nitrosamines and impurity levels, highlighting the need for stringent quality control measures

4. Discussion

The review of existing literature indicates that while HPLC and spectrophotometry remain the dominant analytical methods, HPTLC-MS presents a superior alternative due to its ability to detect low-level impurities and degradation products. Dissolution studies, when coupled with in-vitro-in-vivo correlation (IVIVC), provide reliable bioequivalence data, potentially reducing the need for in-vivo pharmacokinetic studies. Studies reveal discrepancies in dissolution profiles among brands, highlighting bioavailability concerns. However, gaps remain in the standardization of dissolution media, as many studies used either one or two dissolution media instead of the four official USP dissolution media. In one of the studies (Igboasoiyi et al.), highlighted a discrepancy in the officially reported insolubility of losartan potassium in acids (HCl), yet one brand was indicated to dissolve in 0.1 N HCl by more than 80% and was reported to passing the dissolution test. This raises concerns about accuracy of the dissolution test results, validity of using 0.1 N HCl as a dissolution medium for losartan potassium and potential errors in the study's methodology or interpretation of results. Therefore, further investigation or clarification is needed to resolve this inconsistency. Additionally, many quality assessments focus solely on physicochemical properties without considering impurity detection. These methods face limitations due to overlapping peaks, matrix interferences and limited impurity detection capabilities. It also showed food/drink (e.g., cola, grapefruit juice, milk) altering dissolution and potentially affect biological availability. Most of the studies use the physico-mechanical and spectrophotometric methods without validating using multiple brands and primary standards to evaluate the quality of losartan potassium tablets render these methods unsuitable for quality control purposes.

From literature, the chromatographic methods, particularly HPLC and HPTLC, play a crucial role in the analysis of losartan potassium tablets due to their and high sensitivity and specificity. Chromatographic methods enable accurate detection and quantification of losartan potassium and its impurities [14][8]. Chromatographic methods can identify and quantify nitrosamine impurities, which is critical for ensuring the safety of losartan potassium tablets [18]. Robustness and reliability these methods provide reliable and reproducible results, making them essential for quality control and regulatory purposes [20]. Flexibility and versatility, made the methods to be adapted for various sample types, including bulk drugs, tablets and dissolution samples [16][17]. Chromatographic methods are widely accepted, recommended and complied by regulatory agencies, such as the USP, for the analysis of pharmaceuticals, including losartan potassium tablets [20]

4.1. Recent Developments

HPTLC-MS is emerging as a promising technique, offering simultaneous quantitative and mass-to-charge ratio determination. This approach is essential given the recent discovery of carcinogenic nitrosamine impurities in ARBs, including Losartan Potassium.

5. Conclusion

Ensuring the quality and efficacy of Losartan Potassium requires robust analytical methods. Physicochemical and spectrophotometric tests provide basic quality control, but chromatographic techniques (HPLC, HPTLC, and LC-MS) are essential for accurate and simultaneous quantification and impurity detection. The recent nitrosamine contamination issue underscores the need for advanced methods like HPTLC-MS for routine monitoring.

Future studies should focus on Advanced analytical techniques like HPLC-MS, HPTLC-MS, TLC-MS should be developed and employed for losartan API and impurity detection, quantification and for effective quality control measures.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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