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PHARMACEUTICAL ANALYTICAL REVIEW OF SORAFENIB

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ABSTRACT

Background: Sorafenib is an oral multi-kinase inhibitor used for treating advanced renal cell carcinoma, hepatocellular carcinoma, and thyroid cancer. Despite its efficacy, Sorafenib's chemical complexity and susceptibility to degradation under stress conditions necessitate robust analytical methodologies. Effective quality control is critical to ensuring its safety, potency, and stability in pharmaceutical formulations. **Aim:** To explore and review the various analytical methods developed for Sorafenib, focusing on chromatographic techniques, impurity profiling, and stability-indicating studies to support regulatory compliance and quality assurance. **Research Methodology:** This review highlights chromatographic methods such as HPLC and UPLC, with emphasis on mobile phase optimization, forced degradation studies, and impurity profiling. Spectroscopic methods like UV-Vis, FTIR, NMR, and MS are discussed for their roles in structural elucidation and degradation product identification. Stability studies conducted under acidic, basic, oxidative, thermal, and photolytic stress conditions are detailed to assess Sorafenib's behavior under various environmental challenges. **Conclusion:** Advanced analytical methods, including UPLC and LC-MS/MS, provide robust platforms for impurity profiling and stability evaluation of Sorafenib. These approaches ensure compliance with regulatory standards, supporting its safe and effective use in pharmaceutical applications.

KEYWORDS: Sorafenib, Impurity profiling, Stability studies.

INTRODUCTION

Sorafenib is an oral multi-kinase inhibitor approved for the treatment of advanced renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), and thyroid cancer. By targeting multiple kinases involved in tumor cell proliferation and angiogenesis, Sorafenib plays a pivotal role in the management of these malignancies. Despite its widespread therapeutic use, its complex chemical structure and susceptibility to degradation necessitate robust analytical methods for quality assurance and regulatory compliance.

Analytical chemistry in the pharmaceutical industry ensures the identity, purity, potency, and stability of drugs. This is particularly important for Sorafenib due to its degradation under various stress conditions, which can lead to the formation of impurities that compromise its efficacy and safety. This review provides an in-depth discussion of the analytical methods developed for Sorafenib, with a focus on chromatographic techniques, impurity profiling, and stability studies.

Chemical Structure and Physicochemical Properties: Sorafenib (chemical name: N-(3-trifluoromethyl-4-chlorophenyl)-N'-(4-(2-methylcarbamoyl pyridin-4-yloxy) phenyl) urea) has a molecular weight of 464.82 g/mol. It is slightly soluble in water and exhibits higher solubility in organic solvents like methanol and acetonitrile. These properties influence the selection of analytical techniques, particularly in chromatographic separations.

Analytical Challenges

The primary challenges in analyzing Sorafenib include

1. **Degradation under Stress Conditions:** Sorafenib is prone to hydrolysis, oxidation, and photolysis, requiring stability-indicating methods for detecting degradation products.
2. **Impurity Profiling:** Regulatory authorities mandate impurity identification and quantification to ensure safety and efficacy.
3. **Matrix Interference:** The analysis of Sorafenib in biological fluids or complex formulations often involves interference from excipients or endogenous substances.
4. **Sensitivity Requirements:** Low detection and quantification limits are critical for impurity analysis and pharmacokinetic studies.

CHROMATOGRAPHIC METHODS

High-Performance Liquid Chromatography (HPLC): HPLC remains a cornerstone technique for the analysis of Sorafenib due to its versatility and ability to separate drug components from impurities. Various studies have reported the use of reverse-phase HPLC (RP-HPLC) with C18 columns for this purpose.

- **Mobile Phase Composition:** Methanol and acetonitrile are commonly used in combination with aqueous buffers to achieve optimal separation. For example, methanol: acetonitrile (55:45 v/v) with a pH-adjusted buffer enhances peak resolution.
- **Detection Wavelength:** Sorafenib exhibits maximum absorbance at 240 nm, making UV-visible detection a preferred method.
- **Validation Parameters:** HPLC methods for Sorafenib are validated for precision, accuracy, linearity, specificity, robustness, and system suitability.

Ultra-Performance Liquid Chromatography (UPLC): UPLC offers enhanced resolution, reduced run times, and lower solvent consumption compared to traditional HPLC.

- **Stationary Phase:** C18 columns with smaller particle sizes (1.7 µm) are employed for superior separation.
- **Forced Degradation Studies:** UPLC methods have been developed to assess Sorafenib under acidic, basic, oxidative, wet heat, and photolytic conditions, revealing degradation products effectively.
- **Impurity Profiling:** The higher sensitivity of UPLC facilitates the detection and quantification of impurities at trace levels, meeting stringent regulatory requirements.

Gas Chromatography (GC): Although not commonly used for Sorafenib due to its limited volatility, GC can be employed for residual solvent analysis in bulk drug substances. The method involves derivatization to enhance volatility and detectability.

SPECTROSCOPIC TECHNIQUES

UV-Visible Spectroscopy: UV spectroscopy is frequently employed for the preliminary quantification of Sorafenib due to its simplicity and cost-effectiveness. The absorption maximum at 240 nm serves as a reliable parameter for its detection.

Fourier Transform Infrared (FTIR) Spectroscopy: FTIR is used to identify functional groups in Sorafenib and its degradation products. Characteristic peaks corresponding to the urea and phenyl functional groups provide structural insights.

Nuclear Magnetic Resonance (NMR) Spectroscopy: NMR spectroscopy is applied for the structural elucidation of Sorafenib and its impurities. It offers detailed information about the chemical environment of atoms within the molecule.

Mass Spectrometry (MS): MS, often coupled with chromatographic techniques (LC-MS), is utilized for molecular weight determination, structural elucidation, and impurity profiling. LC-MS/MS is particularly valuable in pharmacokinetic studies to quantify Sorafenib in biological matrices.

Stability Studies: Stability studies are essential for determining the shelf life and storage conditions of Sorafenib. Stability-indicating methods differentiate the drug from its degradation products under forced degradation conditions, including.

1. **Acidic Hydrolysis:** Conducted using HCl solutions, revealing degradation via hydrolysis of the urea moiety.
2. **Basic Hydrolysis:** Performed using NaOH solutions, leading to cleavage of susceptible bonds.
3. **Oxidation:** Involves exposure to hydrogen peroxide, resulting in oxidative degradation.
4. **Thermal Stress:** Evaluates stability under elevated temperatures, mimicking accelerated storage conditions.
5. **Photolytic Degradation:** Assesses the impact of light exposure on drug stability.

Validation of Analytical Methods: Validation ensures the reliability and reproducibility of analytical methods. Key validation parameters for Sorafenib analysis include.

1. **Linearity:** Demonstrated over a concentration range (e.g., 8–40 µg/mL), with correlation coefficients above 0.998.
2. **Precision:** Intraday and inter day variations yield %RSD values within acceptable limits (<2%).
3. **Accuracy:** Recovery studies at different spiking levels confirm recoveries close to 100%.
4. **Specificity:** The ability to separate Sorafenib from impurities and degradation products.
5. **LOD and LOQ:** Limits of detection and quantification ensure sensitivity, with values as low as 0.838µg/mL and 2.540µg/mL, respectively.
6. **Robustness:** Minor changes in chromatographic conditions (e.g., flow rate, temperature) do not significantly affect method performance.

Impurity Profiling: Regulatory guidelines, such as ICH Q3A and Q3B, mandate the identification and quantification of impurities in drug substances and products. Impurity profiling for Sorafenib involves.

1. **Structural Characterization:** MS and NMR techniques are used to identify unknown impurities.
2. **Quantification:** Chromatographic methods quantify impurities at trace levels (<0.1%).
3. **Toxicological Evaluation:** Impurities are assessed for potential toxicity to ensure patient safety.

Applications in Pharmaceutical Analysis

1. **Quality Control:** Routine analysis of Sorafenib in bulk and finished products to ensure compliance with pharmacopeial standards.

2. **Stability Testing:** Monitoring degradation and ensuring appropriate shelf-life assignments.
3. **Pharmacokinetics:** Quantification of Sorafenib in plasma and other biological matrices for drug metabolism and pharmacokinetic studies.
4. **Regulatory Submissions:** Supporting documentation for new drug applications (NDAs) and abbreviated NDAs (ANDAs).

Challenges and Future Perspectives

1. **Matrix Complexity:** Developing methods to address interference from biological fluids or formulation excipients.
2. **Emerging Technologies:** The application of advanced techniques such as capillary electrophoresis, microfluidics, and high-resolution MS for enhanced analysis.
3. **Green Analytical Chemistry:** Emphasizing eco-friendly solvents and methods to minimize environmental impact.

CONCLUSION

The analytical evaluation of Sorafenib plays a crucial role in ensuring its quality, efficacy, and safety. Advanced techniques like UPLC and LC-MS/MS provide robust platforms for impurity profiling, stability studies, and pharmacokinetic analysis. Continuous advancements in analytical methodologies will further enhance the accuracy, sensitivity, and eco-friendliness of Sorafenib analysis, aligning with the growing regulatory and environmental expectations.

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