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Advancements in Torsemide Capsule Formulations: A Comprehensive Review

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Abstract

Torsemide (known as torasemide in Europe) is a novel sulfonylurea loop diuretic approved for treating edema associated with congestive heart failure, renal dysfunction, and hepatic disease, and for hypertension, either alone or combined with other antihypertensive. As a weakly basic loop diuretic within the pyridine sulfonylurea group, torsemide is particularly effective for managing hypertension and edema related to heart failure, renal, or hepatic disorders. However, it's limited solubility in water and bitter taste present challenges. To address these issues, torsemide was preformulated into a solid dispersion using suitable water-soluble carriers and flavoring agents, enhancing drug absorption, reducing peak plasma level fluctuations, and minimizing side effects. This method also allows the development of flexible oral dosage forms, enabling the formulation and blending of different, even incompatible, drug substances into a single dosage form. Torsemide and Amiloride Hydrochloride, both diuretic-class antihypertensive drugs, are marketed together in tablet form to treat essential hypertension and manage primary hypertension and edema associated with congestive heart failure. This research aimed to develop stability-indicating RP-HPLC methods for analyzing Torsemide and Amiloride Hydrochloride in combined dosage forms. In veterinary medicine, managing congestive heart failure (CHF) often relies on empirical methods, highlighting the need for a more quantitative approach to assess diuretic responsiveness. Understanding the relationship between diuretic measures, particularly urinary sodium excretion, and clinical outcomes is essential. Longitudinal studies are critical for refining these measures and optimizing treatment protocols. These advancements will improve CHF management in companion animals, enhancing their quality of life and prognosis. By bridging current knowledge gaps and focusing on quantitative diuretic responsiveness, both human and veterinary medicine can achieve better health outcomes through more precise and effective treatments for conditions like CHF.

Keywords: Torsemide, Diuretic responsiveness, Stability-indicating RP-HPLC, Congestive heart failure (CHF). Pharmaceutical formulation

Introduction

Torsemide (known as torasemide in Europe) is a novel sulfonylurea loop diuretic that has recently gained approval for treating edema associated with conditions like congestive heart failure, renal dysfunction, and hepatic disease. Additionally, it is prescribed for hypertension, either as a standalone treatment or in combination with other antihypertensive medications. Research indicates that torsemide primarily works by inhibiting the Na+-K+-2Cl- reabsorptive pump in the medullary portion of the thick ascending limb of the loop of Henle. One of the key advantages of torsemide is its consistently high bioavailability, which facilitates a seamless transition from intravenous to oral administration on an equivalent milligram-to-milligram basis [1]. Furosemide and torsemide are among the most frequently prescribed loop diuretics in medical practice. According to a review, torsemide may offer superior outcomes compared to furosemide due to its beneficial impact on the renin-angiotensin-aldosterone system. Firstly, torsemide holds a pharmacological edge over furosemide, and using them in combination can decrease the necessity for furosemide. Secondly, clinicians often resort to using multiple diuretics to address diuretic resistance. Lastly, despite torsemide being more expensive than furosemide in China, combining these medications might lower costs for heart failure patients compared to using torsemide alone, while also providing potential advantages over furosemide [2]. Torsemide is a loop diuretic that helps the body expel excess salt through urine by preventing its absorption. It is commonly used to treat congestive heart failure and edema. Torsemide falls under the Biopharmaceutical Classification System (BCS) class IV, meaning it has low permeability and low solubility. Its oral bioavailability ranges approx. 50%. The drug's poor aqueous solubility and dissolution rate can adversely affect its bioavailability. Torsemide was estimated spectrophotometrically using UV methods at 290 nm. Pre-formulation studies using FTIR showed no interaction between the drug and polymers, and stability studies confirmed that the drug did not degrade within the formulation. Thus, torsemide was chosen for formulation development to enhance its overall bioavailability, focusing on its absorption throughout the intestine. Sustained release floating granules of torsemide were prepared using the melt granulation technique, designed to ensure sustained drug release in the intestine for prolonged absorption. The developed formulation exhibited a notably enhanced drug release profile compared to the marketed formulation, particularly across different pH levels in the gastrointestinal tract. The main objective in designing and refining the controlled release system for torsemide was to enhance its bioavailability by prolonging its retention time in the stomach without direct mucosal contact [3]. The first method developed for the simultaneous determination of torsemide and spironolactone, along with their related compounds, involves stress degradation using a Quality by Design (QbD) approach combined with LC-MS. Both torsemide and spironolactone are susceptible to degradation in acidic, basic, and oxidative conditions, yet remain stable when exposed to water. The application of the QbD approach ensured the robustness of the method [4]. Torsemide possesses certain characteristics that may render it a preferable choice over furosemide, even when clinical outcomes appear similar. Its longer half-life and greater protein-binding capacity contribute to less frequent urination, offering potential advantages in certain patient populations. Furthermore, torsemide is believed to exert

positive effects on cardiac remodeling by inhibiting aldosterone receptors and reducing collagen cross-linking through decreased myocardial expression of active lysyl oxidase. These potential benefits may become more apparent with longer-term follow-ups. The upcoming TRANSFORM-HF biomarker sub-study is anticipated to shed light on the underlying mechanistic distinctions between torsemide and furosemide, further elucidating their comparative efficacy and safety profiles. [5]. Torsemide, a non-antibacterial sulfonamide, belongs to a drug class rarely associated with Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Although torsemide-induced TEN is exceptionally rare, there is only one documented case to date. Similarly, only one other instance of SJS/TEN induced by a non-antibacterial sulfonamide diuretic has been reported. In this specific case, torsemide was identified as the causative agent due to its classification as a sulfa drug, unlike spironolactone. The patient's severe liver disease was a significant factor in considering torsemide as the likely culprit. Torsemide undergoes extensive hepatic metabolism, primarily via pathways involving liver-prevalent enzymes. Additionally, torsemide tightly binds to plasma proteins such as albumin. These factors contribute to the patient's susceptibility to adverse reactions associated with torsemide use [6].

Historical Development of Torsemide Formulations

Torsemide, categorized as a weakly basic loop diuretic within the pyridine sulfonylurea group, is commonly employed in the management of hypertension and edema. It proves particularly effective in cases associated with heart failure, renal, or hepatic disorders. Despite its therapeutic benefits, torsemide poses challenges due to its limited solubility in water and its bitter taste. Consequently, it was chosen as the focal drug for this study. To overcome these hurdles, the drug was preformulated into a solid dispersion using suitable water-soluble carriers and flavoring agents [7]. Although furosemide continues to be the predominant loop diuretic utilized in clinical settings, the enhanced bioavailability and prolonged half-life of torsemide indicate its potential superiority in managing signs and symptoms of congestion. Nevertheless, the existing data is insufficient to consistently advocate for torsemide over furosemide to achieve optimal symptom relief and enhance the quality of life in patients with heart failure [8]. In the study, torsemide, a poorly water-soluble drug, was chosen as the focus. To enhance its solubility, torsemide was incorporated into a solid dispersion using a variety of solubilizers. These solubilizers were first dissolved in water, after which the drug was added, resulting in a clear yellow solution. The excess water was then evaporated from this solution, yielding a solid dispersion. This dispersion was subsequently dried thoroughly, pulverized, and packaged [9]. Typically, edema associated with nephrotic syndrome is treated with 100 mg of torsemide co-administered with an aldosterone antagonist. No pharmacokinetic interactions have been reported when torsemide is co-administered with digoxin, spironolactone, carvedilol, or cimetidine. Short-term studies have demonstrated that oral administration of torsemide at doses ranging from 5 to 20 mg per day reduces the severity of edema and decreases mean body weight more effectively than a placebo or 40 mg of furosemide in patients with chronic congestive heart failure (CHF). Additionally, a daily dose of 20 mg of torsemide has been shown to reduce pre-existing edema more effectively than 40 mg of furosemide in patients with chronic CHF [10]. The availability of torsemide, a widely used loop diuretic in heart

failure (HF) management, suggests that it may offer favorable biochemical and molecular effects on myocardial fibrosis. This implies that torsemide could potentially be beneficial, especially in heart failure with preserved ejection fraction, where a single medication could alleviate congestion while also mitigating or even reversing myocardial fibrosis. Confirming additional anti-fibrotic and clinical outcome benefits of torsemide beyond its primary role as a diuretic would be valuable [11].

Novel Excipient Technologies in Torsemide Capsules

Acute toxicity studies conducted on a novel polymer showed no observable physiological changes in rat behavior, and the rats remained healthy throughout the study. The formulated CC tablets underwent pre-compression and post-compression evaluations, as well as stability studies. All parameters were found to be within the specified limits outlined in the pharmacopeia. Interestingly, the formulation containing starch tartrate exhibited faster drug dissolution compared to other formulations. Further evaluation of the optimized formulation through FTIR and DSC analysis revealed no significant incompatibilities between the active ingredient and excipients. Stability testing conducted on the optimized formula confirmed its stability over time [12]. The newly developed HPLC method exhibited a limit of quantification of 2 µg/ml and a lower limit of detection of 10 µg/ml, indicating its novelty, simplicity, linearity, precision, reliability, sensitivity, and repeatability. This method facilitates routine quality control of both bulk and tablet dosage forms with ease. Regarding the assay of Torsemide, the technique demonstrated linearity across a concentration range of 100 µg/ml, with Torsemide exhibiting a retention time of 2 minutes. The accuracy of the analysis was confirmed through recovery tests and statistical analysis. The detection limit and quantitation limit of Torsemide were determined successfully. Overall, the study's results underscored the utility of the proposed RP-HPLC method for the routine analysis of Torsemide in both bulk medication and its pharmaceutical dosage form [13]. A robust and accurate RP-HPLC method has been devised and validated to simultaneously analyze Eplerenone and Torsemide in pharmaceutical formulations, following ICH guidelines. This method employed a Shiseido column and utilized a mobile phase consisting of Acetonitrile, Methanol, and Water. The absorbance measurements were recorded accordingly. Additionally, a reverse-phase high-performance liquid chromatographic technique was developed and validated for the quantification of Spironolactone and Torsemide. The stability of Torsemide was evaluated under diverse stress conditions as prescribed by the ICH guidelines [14]. Patients experiencing a sudden increase in blood pressure often face significant declines in functional ability and acute restlessness. To help manage these symptoms, a patient-friendly fast-dissolving tablet (FDT) has been developed. Torsemide, a loop diuretic belonging to the pyridine sulfonyl urea class, is used to treat hypertension and edema associated with congestive heart failure. It can be administered alone or in combination with other diuretics, such as thiazides [15, 16].

Controlled Release and Targeted Delivery Systems

Pellets disperse effectively in the gastrointestinal tract, enhancing drug absorption, reducing fluctuations in peak plasma levels, and minimizing side effects. This method prevents high local concentrations of the drug. Pellets

offer flexibility in developing oral dosage forms, allowing for the formulation and blending of different drug substances, even incompatible ones, into a single dosage form. Additionally, immediate-release and controlled-release pellets can be combined to achieve the desired release pattern [17]. The study focuses on formulating controlled release tablets of Torsemide using an appropriate polymer matrix. These tablets, compared to their immediate release counterparts, offer comparable systemic exposure but notably delay the absorption rate and minimize fluctuations in plasma concentrations. This design aims to enhance both the efficiency and tolerability of Torsemide medication [18]. The treatment of acute and chronic diseases has been effectively achieved through the administration of drugs using a variety of pharmaceutical dosage forms. These forms range from traditional tablets and capsules to more advanced delivery mechanisms such as transdermal patches, inhalers, and injectables. The primary goal of these dosage forms is to ensure the accurate delivery of the drug to the intended site of action, optimizing therapeutic outcomes while minimizing side effects. Significant progress has been made in drug development by employing the concepts and techniques of controlled and targeted drug delivery systems. Controlled drug delivery systems are engineered to release medication at a specified rate, ensuring consistent drug concentrations in the bloodstream over an extended duration. This approach not only boosts the therapeutic effectiveness of the medication but also enhances patient adherence by reducing the need for frequent dosing. Examples of such systems include sustained-release tablets, implants, and osmotic pumps [19, 20].

Analytical Techniques for Evaluation of Torsemide Capsules

The development and validation of analytical methods are crucial for providing reliable data for regulatory submissions. These methods play a crucial role in various applications, including quality control release testing, stability sample testing, and reference material testing, and supporting specifications. Utilizing analytical methods to establish evidence ensures a high level of confidence, which is essential in the drug discovery process. Torsemide and Amiloride Hydrochloride, both diuretic-class antihypertensive drugs, are marketed together in tablet form to treat essential hypertension and manage primary hypertension and edema associated with congestive heart failure. This research aimed to develop stability-indicating RP-HPLC methods for analyzing Torsemide and Amiloride Hydrochloride in combined dosage forms. The study involved systematic method development, assessing the impact of the organic modifier, buffer pH, buffer concentration, and column temperature. The developed method is recommended for routine monitoring during process development and quality control analysis [21]. A reverse-phase high-performance liquid chromatography (RP-HPLC) method was developed to quantify Torsemide and Spironolactone and to investigate their forced degradation. This development employed Analytical Quality by Design (QbD) principles. The chromatographic conditions were optimized using a full factorial experimental design. Analysis of variance (ANOVA) was used to evaluate the statistical significance of the independent variables, and perturbation plots were utilized to visualize the findings. Design of experiments (DoE) provided valuable tools for optimizing variable parameters in the development of HPLC methods. The method developed demonstrated high precision, accuracy, and robustness. The forced degradation study confirmed the method's effectiveness in detecting degradants. Applying the AQbD approach

during method development proved to be an effective strategy for enhancing the efficiency and quality of analytical method development [22]. UV spectrophotometry is crucial in pharmaceutical analysis, assisting in the identification and quantification of raw materials and pharmaceutical products. Despite its importance, a method for assessing the stability of Torsemide has not yet been described. Spectrophotometry is advantageous due to its speed, simplicity, and reliability, making it a valuable analytical tool. Consequently, it was considered worthwhile to develop and validate spectrophotometric methods for determining Torsemide in the presence of its degradation products in powdered forms, laboratory-prepared mixtures, and pharmaceutical formulations. While chromatography stands as a powerful and versatile tool for separating and quantitatively analyzing multiple components within a mixture in a single procedure, previous chromatographic methods for Torsemide analysis did not address stability assessment. This research endeavors to fill this gap by developing and validating stability-indicating methods for determining Torsemide. Specifically, TLC-densitometric and HPLC methods are employed for this purpose [23]. A well-developed method should be easily validated, facilitating its application to preclinical samples, formulation prototypes, and commercial samples. In this study, a validated RP-HPLC method was established for determining Torsemide. Validation parameters such as accuracy, precision, specificity, linearity (correlation coefficient) were observed. The method demonstrated simplicity, accuracy, precision, specificity, and selectivity. Tablet formulations were successfully analyzed using the developed methods. The validation results met the requirements outlined by ICH and USP. This study underscores the benefits of employing the ICH approach in establishing drug estimation methods [24, 25].

Future Trends and Emerging Technologies

In the current management of congestive heart failure (CHF) in veterinary patients, there's often a reliance on a trial-and-error method. Diuretic doses are determined through empirical means, and treatment efficacy is gauged based on clinical signs of congestion, which might not become apparent until well into the treatment course. We suggest that adopting a quantitative approach to assess diuretic responsiveness and pinpoint specific causes of resistance in dogs and cats could lead to better outcomes, akin to what's observed in human medicine. The concept of diuretic responsiveness aligns with fundamental pathophysiological and pharmacological principles, enabling the evaluation of proposed or ongoing treatment without waiting for congestion signs to emerge. Nonetheless, significant knowledge gaps remain that must be addressed before fully understanding quantitative diuretic responsiveness. A crucial aspect is obtaining a clearer understanding of the relationship between measures, particularly urinary sodium excretion, and both short- and long-term outcomes. Longitudinal studies are crucial for addressing pertinent issues such as the optimal timing of measurement, the impact of individual variability and treatment history, and how to use these measures to guide treatment decisions in veterinary patients with CHF. These efforts will contribute to a more nuanced and effective approach to managing CHF in companion animals, ultimately enhancing their quality of life and prognosis [26, 27]. The pragmatic approach of the trial may have overlooked potential mechanistic benefits of torsemide usage not directly tied to the primary endpoint. Therefore, further exploration into the effects of torsemide versus furosemide on heart failure (HF)-specific

outcomes, especially in patients with a high risk of diuretic resistance, remains valuable. However, until such data are accessible, achieving complete decongestion in HF patients is likely more critical than the specific diuretic agent employed. Recent findings from the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial indicate that initiating therapy with intravenous acetazolamide in hospital settings can effectively address this objective. This evidence-based approach stands as one of the few available options for achieving comprehensive decongestion in HF patients. [28-31].

Conclusion

In conclusion, Torsemide, also known as torasemide in Europe, is a novel sulfonylurea loop diuretic that has demonstrated efficacy in treating edema associated with conditions such as congestive heart failure, renal dysfunction, and hepatic disease, as well as in managing hypertension. Its therapeutic benefits are somewhat challenged by its limited water solubility and bitter taste, which has led to innovative approaches such as solid dispersion formulations to enhance its bioavailability and patient compliance. This study focused on developing stability-indicating RP-HPLC methods for analyzing Torsemide and Amiloride Hydrochloride in combined dosage forms, addressing a critical need for robust analytical methods in quality control and process development.

Moreover, the management of congestive heart failure (CHF) in veterinary medicine often relies on empirical methods, highlighting the necessity for a more quantitative approach to assess diuretic responsiveness. Understanding the relationship between diuretic measures, particularly urinary sodium excretion, and clinical outcomes is essential. Longitudinal studies are imperative to refine these measures and optimize treatment protocols. Such advancements will not only improve the management of CHF in companion animals but also enhance their quality of life and prognosis.

By bridging the gap in current knowledge and focusing on quantitative diuretic responsiveness, both human and veterinary medicine can benefit from more precise and effective treatments for conditions like CHF. The development of comprehensive and reliable methods for drug analysis, alongside a deeper understanding of diuretic response mechanisms, represents a significant step forward in achieving better health outcomes across species.

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