ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 19, Issue 1, 2026

Online - 2455-3891
Print - 0974-2441

Review Article

EVALUATION OF COMPARATIVE BIOAVAILABILITY AND BIOEQUIVALENCE ANALYSIS OF TERAZOSIN HYDROCHLORIDE

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Received: 16 October 2025, Revised and Accepted: 28 November 2025

ABSTRACT

Terazosin hydrochloride is a selective α_1-adrenergic receptor antagonist used to treat high blood pressure and benign prostatic hyperplasia. Due to the interest of patients, prescribers, and payers in cost-effective and therapeutically equivalent generic formulations, the evaluation of bioavailability and Bioequivalence has been a significant focus area for regulatory authorities and pharmaceutical companies. Regulatory authorities, including the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have established guidelines related to the requirements for BE studies, as well as requiring the use of validated bioanalytical methods to quantify drug concentrations in biological matrices. BE studies focus on pharmacokinetic parameters, such as the maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and area under the curve (AUC) from the plasma concentration versus time curve, which gives an estimate of the rate and extent of drug absorption. This article discusses current regulatory frameworks and essential considerations in the design and conduct of BE studies, as recently provided by the FDA and EMA (e.g., validated bioanalytical methods and pharmacokinetic parameters, such as T_{max}, C_{max}, and AUC). The extent to which the industry adheres to BE study design and conduct regulations, as well as the issues surrounding the study population, dosage form, and statistical analysis of the results, will also be explored. Discussion will also include potential biowaivers for BCS Class I and III drugs, which are essential for development while maintaining safe therapeutic equivalence. The alignment of regulatory requirements and scientific advancements enables the safe and effective development and marketing of generic terazosin hydrochloride products.

Keywords: Terazosin hydrochloride, Bioavailability, Bioequivalence, Generic drugs, Regulatory guidelines, Pharmacokinetics.

 DOI: http://dx.doi.org/10.22159/ajpcr.2026v19i1.57317. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

The increasing need for affordable and accessible healthcare has branded generic drugs as essential components of contemporary pharmacotherapy. Generic drugs are designed to be identical to their innovator counterparts in terms of route of administration, strength, therapeutic use, dosage form, and dosage regimen, and contain the same active pharmaceutical ingredient as the branded product. Given that generics are used pervasively in clinical practice, it is essential to continue establishing their safety, efficacy, and quality [1,2]. Continuous evaluation through regulatory pathways, including bioavailability and bioequivalence (BE) studies, is critical to confirm that generic formulations are therapeutically equivalent to branded products [3,4]. Traditionally, Terazosin is an antagonist of the postsynaptic α1-adrenoceptor and is used to treat benign prostatic hyperplasia (BPH) and hypertension. It has its own distinct therapeutic benefits, significantly alleviating lower urinary tract symptoms (LUTS), improving endothelial function, influencing platelet aggregation, and lowering blood pressure [5,6]. Terazosin has more pharmacological advantages than other drugs in its class, such as doxazosin, alfuzosin, and tamsulosin. Clinical experience has demonstrated that Terazosin is efficacious and safe in men and women with LUTS, adding further value in the management of their urinary tract symptoms as well as cardiovascular stabilization [7,8]. Given the clinical relevance of Terazosin and the need to provide cost-effective treatment options, it is essential to ensure that its generic formulations are bioequivalent to the innovator product. Bioavailability is defined as the rate and extent of the active drug in systemic circulation, and BE studies are performed to confirm that the test (generic) product and the reference (branded) product have similar pharmacokinetic parameters without a clinically significant difference [9,10]. These studies have been used to demonstrate the scientific basis to allow regulatory approval and therapeutic substitution of generic medications. This review aims to provide an overview of bioavailability and BE concepts, as well as the regulatory importance of BE for Terazosin, specifically. This paper discusses the bioavailability properties of Terazosin, methods for assessing bioequivalent properties, and the clinical implications of these studies, which support development and approval of terazosin generics [11,12].

METHODS

We performed a comprehensive literature search in Scopus for all available records up to October 2025 to identify studies related to terazosin hydrochloride. Included in our search were the following keywords: Terazosin, animal experiment, pharmacokinetics, *in vivo* studies, bioavailability, and BE. This search yielded 33 documents, with 27 English-language articles fulfilling our inclusion criteria. Our final focus was on original research in humans or animals that reported pharmacokinetics, bioavailability, or BE mentions. We decided to omit non-English articles, articles that did not report post-intervention outcomes, reviews, and incomplete records. After a systematic review of titles, abstracts, and full-text articles, we identified a final total of 27 studies for consideration.

OVERVIEW OF TERAZOSIN HYDROCHLORIDE: PHARMACOLOGY AND PHYSICOCHEMICAL PROFILE

Terazosin is a drug that functions as an alpha-adrenergic blocker and is used for the treatment of high blood pressure, and for the treatment of symptoms related to BPH. It works by blocking alpha receptors, which

ultimately cause dilation of blood vessels, thereby lowering blood pressure. It also relaxes smooth muscle in the prostate and bladder neck, improving urination. Terazosin is an α1-adrenoceptor antagonist, which was recently approved for the treatment of hypertension and relieving urinary obstruction symptoms associated with BPH [13]. Terazosin appears as a white crystalline solid and is highly effective; however, it has specific significant side effects, such as dizziness and orthostatic hypotension [14]. This is especially important to be concerned with any patient with a fainting history, as these patients need to be careful. Concern for interaction with blood pressure medications, such as beta-blockers, diuretics, and, especially, PDE5 inhibitors (e.g., Sildenafil), is also important because other blood pressure medications can also lead to severe lowered blood pressure, and dosage adjustments are greatly needed. A more in-depth description of the drug can be found in Fig. 1, which includes its physical and chemical properties, adverse effects, contraindications, and other relevant details [15]. Structurally, Terazosin is a prazosin analogue whose furan ring is saturated. The saturation of the furan ring contributes to improved solubility and introduces an optically active center, with its two enantiomeric forms, resulting in different pharmacokinetic properties compared to prazosin. Terazosin's duration of action is longer, with an elimination half-life approximately 2–3 times that of prazosin, thus allowing terazosin to be given once daily. In addition, Terazosin's gastrointestinal (GI) absorption is also Complete and more predictable, allowing for more direct titration of doses [7]. It is essential in relation to the preparation of the sample and chromatographic conditions that Terazosin's physicochemical properties, such as lipophilicity, pKa, and solubility, all play a vital role. Terazosin's basic property and adequate aqueous solubility also allow Terazosin to be efficiently recovered by liquid-liquid extraction with organic solvents in an alkaline solution. Terazosin can also be considered stable under a range of conditions for sample quantitation [16]. Therefore, understanding all these properties and factors is crucial for developing a selective, sensitive, and reproducible LC-MS/MS method in accordance with Terazosin's molecular characteristics [17].

Treatment with Terazosin leads to a lowering of blood pressure in individuals with low to intermediate essential hypertension, while exerting a minimal impact on heart rate. Terazosin is an effective antihypertensive agent, whether used as monotherapy or in combination with other antihypertensive drugs, including β-blockers, diuretics, or their combination. In limited studies involving individuals diagnosed with congestive heart failure, Terazosin was shown to enhance cardiac output while decreasing systemic vascular resistance and ventricular filling pressure [18]. Terazosin therapy has been associated with decreases in total plasma cholesterol, along with reductions in the low-density and very-low-density lipoprotein cholesterol components, while often increasing high-density lipoprotein cholesterol levels. The most commonly reported adverse effects include headache, dizziness, nasal congestion, and asthenia; however, these are generally mild and rarely necessitate discontinuation of treatment [19]. Terazosin is typically administered once daily, beginning with a dose of 1 mg/day and gradually titrated upward based on patient response and blood pressure stabilization, up to a maximum dose of 20 mg/day. Initial-dose hypotensive reactions are uncommon and can usually be avoided by administering the first dose at bedtime [20]. Overall, Terazosin is a practical therapeutic choice for controlling mild to moderate primary hypertension, either as a single-agent therapy or in conjunction with other blood pressure-lowering medications [21]. In addition, Terazosin selectively antagonises α_1-adrenoceptor-mediated smooth muscle contraction in the bladder base, prostatic capsule, prostate and proximal urethra. This action leads to a reduction in bladder outlet resistance and urethral pressure, thereby alleviating urinary complaints related to symptomatic BPH [22-24].

BIOAVAILABILITY AND BE STUDIES OF TERAZOSIN HYDROCHLORIDE

Bioavailability is the fraction of a pharmacologically active agent that successfully enters the systemic circulation and is thus ready to exert its effects at the intended site of action. For most drugs given orally, the active compounds are released and absorbed in the GI tract before entering the systemic circulation to reach their target sites. In the blood, the concentration of active ingredients and/or their active metabolites reflects the amount available at the site of action, making it a dependable indicator of bioavailability. A concentration-time profile

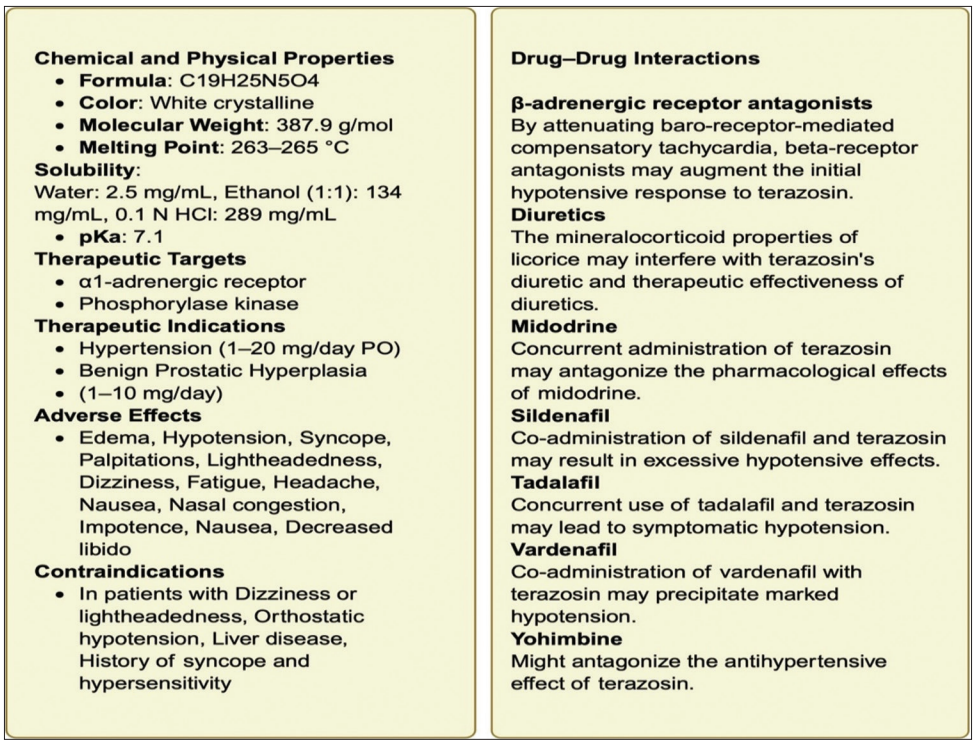

Fig. 1: Detailed physicochemical, pharmacological, and toxicological overview of terazosin: Mechanism of action, therapeutic indications (hypertension and BPH), key adverse effects, and drug-drug interactions

in the blood, obtained through repeated sampling, represents not only the absorption and release of the active compound but also involves additional mechanisms, such as metabolism (including pre-systemic), distribution, and elimination throughout the body [25].

BE studies serve as an alternative indicator for assessing clinical efficacy and safety, since conducting full clinical trials for generic drugs is usually impractical. When two medications are considered bioequivalent, it means there is no meaningful difference in the degree or speed at which their pharmacologically active components are absorbed into the body. In other words, bioequivalent drug versions are expected to offer equivalent clinical benefits and are considered to have comparable therapeutic outcomes. When the exclusivity period of a branded (innovator) drug concludes, pharmaceutical or generic manufacturers can apply for approval of a generic version by submitting an abbreviated new drug application (ANDA). Generic drug products are defined as medications that are equivalent to an approved brand-name (innovator) drug in terms of dosage form, intended use, route of administration, strength and active ingredients. Because ANDAs for generics do not require extensive clinical trials, the development costs are significantly lower, resulting in a much more affordable price, typically around 20% of the cost of the original branded product [26-28].

In 1984, the legal framework was established to facilitate the approval of generic medications through the enactment of the Drug Price Competition and Patent Term Restoration Act by the US FDA. The purpose of this law was to encourage the availability of low-cost, safe, and effective generic alternatives once the exclusivity rights of branded drugs expire. To approve a generic drug, the FDA mandates proof of comparable drug absorption, demonstrated through bioavailability and BE studies. These BE evaluations act as substitutes for direct clinical trials in establishing the therapeutic equivalence of the drug products. A standard approach to evaluating BE involves conducting a study in healthy male volunteers, based on the premise that the relative bioavailability of the test drug can reliably predict its clinical performance, namely, its safety and effectiveness in actual therapeutic use. A BE study is typically carried out using a crossover design, where each participant receives both the standard and test formulations, effectively serving as their own control. This design enables direct within-subject comparisons [29-31].

It is widely accepted that when the plasma concentrations of the active ingredient are equivalent between brand and generic drugs, their concentrations at the site of action and, consequently, their safety and therapeutic effectiveness will also be comparable. Beyond BE, generic drugs must meet strict quality criteria, including standards for manufacturing processes and the purity of the final product. BE is assessed by comparing the relative bioavailability of the generic drug to that of the innovator product, using the ratio of key pharmacokinetic parameters, such as C_{max} and AUC, where a ratio of 1 indicates complete equivalence [32,33]. To be considered bioequivalent, the plasma concentrations of a generic drug must not show significant variation from those of the brand-name (innovator) product. Research has shown that the average differences in plasma levels between generics and their reference drugs are typically within 5%. BE is determined through a statistical comparison of pharmacokinetic parameters – specifically, the ratios of C_{max} and AUC – with the requirement that the 90% confidence intervals for these ratios fall within the range of 0.80 to 1.25. This assessment is formulated in terms of value ratios, not absolute values; a ratio equal to 1 indicates perfect equivalence [34,35]. As a rule of thumb, the mean C_{max} and AUC values of the generic drug should ideally approach the mean values of the innovator drug. If the ratio approaches the lower limit of 0.8 and the upper limit of 1.25, it is imperative that there be no variability in the data to allow for a 90% confidence interval around the mean that remains within the acceptable limits based on the ratios used to establish BE [36-38].

During the period from 1977 to 2003, the FDA developed guidelines to help evaluate BE based on average bioavailability, comparing generic drug products to branded drugs. One guideline, known as the ±20% rule, allows researchers to determine BE when the average bioavailability of a test formulation is 20% greater or less than that of a reference formulation, again evaluated at a specified level of statistical confidence. The ±20% rule applies to an additive model, not for determining relative or percentage differences, and is not the preferred guideline for most drug products. The most accepted method of assessing BE is known as the 80/125 rule [38,39]. In brief, the 80/125 rule states that if a test formulation has an average bioavailability between 80% and 125% of the average bioavailability of the reference product, at a specified level of statistical confidence, then the two formulations may be considered bioequivalent [40].

Fig. 2 presents the concept of BE by presenting the confidence intervals for the relative bioavailability (ratio of test/reference). This typically entails comparing a generic (test) medication to the branded (reference) medication. BE is generally considered to fall within the range of about 0.80 to 1.25. If the 90% confidence interval for the test drug falling within the range of 0.80 and 1.25 (as presented in the middle example), that would suggest the two drugs are bioequivalent. If the interval is <0.80, it would be designated as non-equivalent (low), indicating that the test drug is absorbed at a lower rate. On the other hand, apart from the non-equivalent high, which indicates that the test drug is absorbed at a higher rate. This analysis is essential for ensuring that generic medications are equivalent to their branded counterparts.

The FDA's 2003 guidance employs a multiplicative model for analyzing pharmacokinetic parameters [41-43]. The guidance suggests taking logarithmic transformations of parameters, such as $AUC_{(0-t)}$, C_{max} and

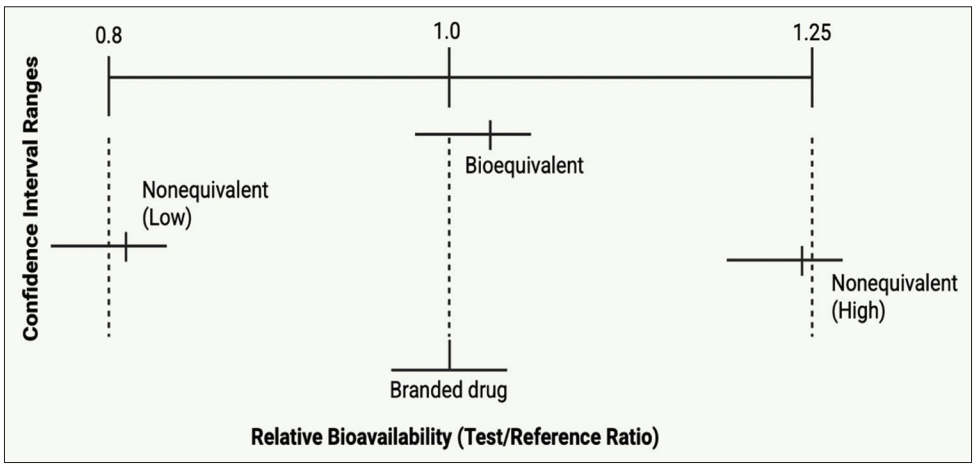

Fig. 2: Determination of bioequivalence based on the 90% confidence interval for the relative bioavailability (test/reference) ratio, defining the acceptable limits (0.80–1.25) for generic drug interchange ability

$AUC_{(0-\infty)}$. This leads to an asymmetric acceptance range on the original scale, which means the probability of demonstrating BE is most significant when the ratio is not exactly equal to 1. However, on the log-transformed scale, the BE acceptance range becomes symmetric from –0.2231 to 0.2231, centered around zero, which maximizes the probability of concluding average BE [44,45]. Under current FDA regulations, average BE is supported when the 90% confidence intervals for the ratio of the geometric means of the pharmacokinetic parameters of interest (log-transformed) fall between 80% and 125% [46-48]. Therefore, when average BE is supported using this method of statistical analysis, the two drug products are considered bioequivalent [49].

BIOAVAILABILITY STUDIES OF TERAZOSIN HYDROCHLORIDE

For any therapeutic compound to exert a biological effect, it must first be released from the drug matrix and subsequently absorbed, distributed, and made available within the body. Since direct quantification at the site of action is often unfeasible, systemic bioavailability is commonly used as a surrogate marker [50,51]. After oral administration, Terazosin is rapidly and almost completely absorbed from the GI tract and is metabolized in the liver. Elimination occurs via fecal and urinary excretion, which results in the excretion of both the unchanged drug and its metabolites. Terazosin is 25 times more soluble in water than prazosin, which is not soluble enough in water to be formulated as an intravenous preparation for clinical use. Prazosin's limited solubility in water makes it impossible to develop as an intravenous preparation, while Terazosin's high solubility allows for the easy development of an intravenous dosage form. Terazosin and prazosin also differ significantly in the amount of drug that becomes available in aqueous or lipid phases. Terazosin is absorbed more completely and consistently than prazosin, thereby allowing for a more accurate titration of dose [52]. The bioavailability of oral Terazosin is approximately 90%, which is significantly greater than that of prazosin, which averages approximately 57%. The C_{max} occurs for Terazosin between 1 and 2 h following oral administration. This difference is one of the factors contributing to the different pharmacokinetics of the two drugs. In turn, this section will be based on a limited number of studies and review articles found in the published literature regarding the pharmacokinetics of Terazosin in both animal studies and humans. The pharmacokinetics of Terazosin have been studied in more than seven healthy volunteers, of which five were elderly, as well as twelve hypertensive patients, and six patients with congestive heart failure. Most studies used a single oral or intravenous dose of Terazosin at doses ranging from 0.1 to 7.5 mg, and included a washout period of 2–7 days between doses, as appropriate. One study examined the pharmacokinetics of Terazosin after 30 days of consecutive daily dosing. Using modern liquid chromatography methods, Terazosin was measured in both plasma and urine, with prazosin used as the internal standard. Terazosin was quantifiable in the plasma at 0.5 ng/mL and in urine at 5 ng/mL. The signal intensity was proportional to concentrations up to 50 ng/mL in plasma and 500 ng/mL in urine. There was an increasing plasma terazosin concentration with each increment in intravenous dose to normotensive and hypertensive individuals, and the doses were administered as single agents at 0.5 mg, 1 mg, or 2 mg [53-55]. The associated pharmacokinetic data are presented in Table 1.

Table 1: The pharmacokinetics of terazosin after intravenous dosing

Subjects	Dose (mg)	Mean plasma clearance (mL/min)	Mean plasma half-lives (h)	References
Normotensive volunteers-8	0.5	86.6	8.9	[56]
	1	76.9	12.4	
	2	76.3	11.6	
Hypertensive patients-12	1	57.4	11.8	[56]
	2	55.8	12.6	
	5	53.1	13.3	

After oral administration, Terazosin is rapidly absorbed, reaching maximum plasma concentrations (T_{max}) within 1–2 h. The estimated systemic availability is approximately 90%. Terazosin was first developed for clinical studies in capsule form, and then reformulated into tablet form. Capsules, solutions, and tablets of Terazosin were evaluated at both the 0.5 mg and 1.0 mg doses. The 0.5 mg dose of capsule and solution had comparable bioavailability, with C_{max} values of approximately 8.4 ng/mL and AUC values of approximately 85 ng·h/mL. The tablet and solution followed similar trends, with significantly higher C_{max} (15.49, 14.64 ng/mL, respectively) and greater AUC (209.8–202.3 ng·h/mL), confirming greater systemic exposure than the 0.5 mg forms at the 1.0 mg dose. Food does not seem to considerably influence the relative absorption of oral Terazosin. The effects of food on the bioavailability of Terazosin were investigated in a randomized, three-period, crossover study involving 17 healthy, normotensive subjects. Each subject was administered a 1 mg capsule under three conditions: Fasting (2 h before breakfast), immediately before a meal, and 30 min after a meal. Food consumption did not significantly alter the absorption or urinary excretion of Terazosin. The results demonstrated similar values for plasma AUC and urinary elimination for all treatments (both values were defined as 100 % in the fasting condition); however, there was a slight increase in relative plasma absorption when Terazosin was given just before (128.3%) and 30 min after a meal (113.4 %), relative to fasting (100 %) [57,58].

Urinary excretion and relative urinary absorption remained consistent, indicating that food had no meaningful impact on overall bioavailability. However, the plasma concentration profile of Terazosin is more accurately characterized by a two-compartment model following oral administration and a three-compartment model after intravenous administration. At plasma concentrations up to 1000 μg/L, Terazosin exhibits approximately 90% to 94% binding to plasma proteins, with no indication of saturation of binding sites. The estimated distribution volume for intravenous Terazosin in both healthy individuals and patients with hypertension ranges from 18 to 30 L. Following oral administration of Terazosin labeled with carbon-14 at the 2-position of the quinazoline ring, its metabolism was investigated in humans. Although Terazosin undergoes minimal hepatic first-pass metabolism, it is extensively metabolized by the liver [59-61]. The primary route of elimination is through the biliary tract, although renal excretion also contributes. In a study involving four healthy volunteers who received a 1 mg oral dose of ^14C-labeled Terazosin, approximately 56% of the radiolabeled compound was recovered in the faces and 39% in the urine over 7 days. At 72 h, the unchanged drug accounted for over 28% of the radiolabeled dose; more than 18% and 10% were excreted in the faces and urine, respectively. Results suggested that metabolism of Terazosin is thought to involve hydrolysis of the amide linkage, O-demethylation, piperazine ring opening and N-dealkylation, resulting in the formation of four key metabolites: Piperazine derivative of Terazosin, diamine metabolite of the piperazine compound,6-O-demethyl Terazosin, and 7-O-demethyl Terazosin. These metabolic pathways are consistent with those identified in pre-clinical studies involving rats and dogs [62,63].

The mean plasma elimination half-lives ($t_{1/2}$) of oral and intravenous Terazosin in healthy volunteers and patients with hypertension are similar, ranging from 8 to 13 h; these reported $t_{1/2}$ values are 3–4 times greater than those of prazosin. The mean plasma and renal clearances of Terazosin have been estimated at 4.8 L/h (80 mL/min) and 0.6 L/h (10 mL/min), respectively. Mean plasma clearance is significantly reduced in patients with hypertension compared with normotensive subjects. The systemic clearance of Terazosin in 8 healthy volunteers ranged from 4.6 L/h (76 mL/min) with a 2mg intravenous dose to 5.2 L/h (87 mL/min) with a 0.5mg dose. In contrast, mean plasma clearance in 12 patients with hypertension ranged from 3.2 L/h (53 mL/min) with a 5mg dose to 3.4 L/h (57 mL/min) with a 1 mg dose. Research study reported that the absorption and elimination of Terazosin were age-dependent. There were significant increases in C_{max}, AUC and $t_{1/2}$ values, and decreases in T_{max} in 5 healthy middle-aged volunteers (54–62 years) who received Terazosin 1 or 2 mg compared

with 10 healthy young volunteers (19–30 years). Although another study concluded that higher AUC (by 44 to 59%) and t1/2 (by 20–23%) values in healthy elderly volunteers (>70 years; n = 6) who received single oral and intravenous doses of terazosin 1 mg compared with healthy young volunteers (20–39 years; n = 6), the differences in these parameters between the younger and older subjects were considered to be of no clinical significance. There were no significant differences in absorption rate constant, elimination rate constant, steady-state plasma concentrations, total plasma clearance, apparent volume of distribution, or AUC values between patients with hypertension and normal renal function and those with moderate or severe renal impairment who received Terazosin 1 mg/day for 15 days. Hemodialysis does not seem to impact the pharmacokinetics of Terazosin, which is consistent with the fact that the kidneys are not the primary route of its elimination. The only pharmacokinetic parameter that appears to be significantly different in patients with hypertension compared with healthy volunteers is mean plasma clearance [64-66].

Studies of patients with hypertension or heart failure found that pharmacokinetic parameters, except plasma clearance, did not differ significantly in 12 hypertensive subjects compared with values reported in normotensive subjects included in separate studies. The average plasma clearance after Terazosin was given intravenously to hypertensive subjects was notably reduced ($p<0.05$) compared to normotensive subjects. In six patients with congestive heart disease, the uptake, elimination speed, plasma half-life, and plasma clearance of Terazosin showed no significant variation when compared to younger normotensive volunteers. The kidney is not the primary route of excretion for Terazosin; thus, the drug's pharmacokinetics would not be expected to be significantly altered by a reduction in renal function [67-69].

BE STUDY OF TERAZOSIN HYDROCHLORIDE

The BE study of terazosin involves comparing the pharmacokinetic parameters of different formulations to ensure they have similar bioavailability and therapeutic effects. Various investigations have been conducted to evaluate the BE of terazosin tablets, focusing on both domestic and imported versions, as well as different formulations such as orally disintegrating tablets. These research investigations are commonly conducted in healthy volunteers and quantify plasma concentrations of terazosin using analytical techniques such as high-performance liquid chromatography and liquid chromatography-tandem mass spectrometry. According to guidelines from the FDA, study design should aim to minimize intra-subject variability. As a result, crossover designs are generally preferred [70].

A BE study was conducted in beagle dogs using a double cross-randomized design to evaluate and compare the pharmacokinetic profiles of terazosin hydrochloride formulations. The reference formulation, sourced from Abbott Laboratories (Shanghai, China), was administered as a single oral dose (2 mg), alongside seven generic formulations (each 2 mg) from different manufacturers. The key pharmacokinetic parameters assessed included the terminal elimination half-life ($t_{1/2}\beta$), C_{max}, T_{max} and AUC. For the test-to-reference ratios of C_{max} and AUC, the 90% confidence intervals were 84.57–122.60% and 91.68–104.87%, respectively, both within the accepted regulatory range of 80.00–125.00% for drugs with a non-narrow therapeutic index in animal studies. Although animal studies are not a substitute for human BE trials, beagle dogs are a well-established pre-clinical model for assessing oral drug absorption and systemic exposure, particularly in the early stages of formulation development. The inclusion of this study supports the formulation comparability of the tested products and provides supplementary evidence before human BE trials. According to the results, the tested generic formulations are bioequivalent to the reference product in beagle dogs, supporting their potential for therapeutic interchangeability. Although not a substitute for human BE trials, the beagle dog model is a well-established and ethically accepted pre-clinical approach for evaluating oral absorption and systemic exposure. The inclusion of this animal study is intended to provide supplementary evidence on formulation comparability, particularly in the early stages of drug development. Such data help support the decision to proceed with human BE studies and reinforce confidence in the consistency of pharmacokinetic performance across formulations [71].

A validated analytical method for quantifying Terazosin was employed in a BE study conducted under fasting conditions in thirty healthy individuals aged 18–55 years, using a two-treatment, two-sequence, two-period, open-label, single-dose crossover randomized design. The study compared Terasin® tablets (Y.S.P Industries (M) SdnBhd, Malaysia -Terazosin 2 mg) in comparison with Hytrin® tablets (Aesica Queen borough Limited, United Kingdom - Terazosin 2 mg). The clinical trial received approval from Malaysia's Medical Research and Ethics Committee (MREC) and was carried out in compliance with the ethical principles outlined in the Declaration of Helsinki. Key pharmacokinetic parameters assessed for BE included the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. These were calculated using non-compartmental analysis. The average C_{max} values for the experimental and standard formulations were 36.8 ± 9.3 and 37.3 ± 10.2 ng/mL, respectively. The lower limit of quantification (LLOQ) for Terazosin was 1.00 ng/mL, which accounted for less than 5% of the average C_{max}, ensuring reliable quantification in plasma samples. Although lower C_{max} and AUC values were reported in this study compared to previous studies using the same dose, the criteria for BE were fulfilled. For AUC_{0-t}, C_{max} and $AUC_{0-\infty}$, the log-transformed geometric mean ratios comparing the test and reference products showed 90% confidence intervals that remained within the regulatory acceptance range of 0.80 to 1.25. These results indicate that Terasin® and Hytrin® tablets are bioequivalent and, therefore, interchangeable under fasting conditions (Table 2) [72].

Terazosin hydrochloride has been the subject of several regulatory-reviewed BE investigations. A pivotal *in vivo* BE study submitted by Mylan Pharmaceuticals Inc. involved a comparison of their 5 mg capsule formulation with the reference product, Hytrin® 5 mg capsules (Abbott Laboratories). The study confirmed that the test and reference formulations exhibited BE when administered under fasting conditions, with all primary pharmacokinetic parameters (AUC_0–t, C_{max}, and AUC_0–∞) falling within the accepted 90% confidence interval range of 80% to 125%. This conclusion was reviewed and confirmed by the Centre for Drug Evaluation and Research (CDER) of the US FDA. Importantly, the 1 mg, 2 mg, and 10 mg strengths of the test product were found to be compositionally proportional to the 5 mg strength. Based on this proportionality and successful BE results for the 5 mg strength, CDER granted a waiver for *in vivo* BE testing of the lower and higher strengths. Consequently, these formulations were also deemed bioequivalent to their corresponding Hytrin® strengths. In a fasting study using a randomized two-period crossover design and involving 25 healthy volunteers, pharmacokinetic equivalence was confirmed between Mylan's 5 mg capsules and Hytrin®. Further evaluation under fed conditions in a three-way crossover study with 17 subjects revealed minimal variability: Differences in AUC_{0-t} and $AUC_{0-\infty}$ were within 3%, while the C_{max} varied by 15%. Like the pharmacokinetic parameters that have been log-transformed, the parameters also complied with regulatory limits. The BE findings were further supported by an open-label, two-way crossover study involving 26 healthy, non-smoking adult males. Each subject received a single 5 mg dose of either the investigational or standard formulation while fasting. Both formulations were bioequivalent (potencies of 99.0% and 98.5%, respectively), and the dosing was standardized to 240 mL of water. Together, these studies confirm that Mylan's terazosin capsules, across all strengths, meet regulatory BE standards and are therapeutically interchangeable with the branded Hytrin® products. In comparative pharmacokinetic studies, the test and reference formulations of Terazosin 2 mg tablets demonstrated closely aligned profiles. Differences in AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all under 3%, with the accepted BE range of 80–125% well covered by the 90% confidence intervals. Despite a slightly prolonged T_{max} in the test product, the overall absorption and elimination parameters were consistent between formulations.

Table 2: Mean pharmacokinetic parameters following a bioequivalence study

Type of study	Species	Study details	Analytical instrument	Dose	$AUC_{(0-t)}$ (ng·h/mL)	$AUC_{(0-\infty)}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	References
Double cross-randomized design	Beagle dogs-6	The study utilized MacroFlux, which is a scaled-up version of PAMPA, to assess the bioequivalence of terazosin generics. It found that even though the dissolution rates were similar, some generics exhibited low permeability (flux). This was mainly attributed to variations in the active pharmaceutical ingredient (API) properties, indicating a potential risk of differences in how they perform in the body.	HPLC Agilent 1260	Standard-2 mg Test-2 mg Hytrin capsule-2 mg	545.27±70.76 535.50±77.18 975.21 (16)	558.18±72.66 554.83±76.97 1007.57 (16)	55.68±10.80 56.49±9.65 95.77 (18)	1.58±0.66 1.17±0.41 0.910 (62)	8.18±0.86 9.14±1.76 14.57 (17)	[76]
Single-dose, 2-period, 2-treatment crossover design	Human healthy volunteers-35	This study examines how competition in pharmaceutical markets differs between therapeutic substitutes (alternative molecules) and brand-name versus generic substitutes (same molecule), concluding that price competition occurs primarily at the level of the molecule to define relevant antitrust markets.	NA	Terazosin tablet-5 mg (Zenith Laboratories Inc.) Hytrin tablet-5 mg	1111.34 (28) 1125.06 (22)	1160.71 (30) 1175.37 (23)	101.09 (23) 101.19 (26)	1.190 (68) 1.262 (54)	13.335 (14) 13.147 (18)	[77]
Two way, single dose, crossover, randomized design	Rabbit (Boskat New Zealand white male)-10	This study introduced a highly sensitive and validated ion-pair chromatographic (IPC) method that features improved fluorescence (FL) detection for alpha-blockers, such as Terazosin. In this method, Sodium Dodecyl Sulfate (SDS) acted as both the ion-pair reagent and a fluorescence enhancer. The researchers successfully applied this technique in a bioequivalence study comparing two terazosin formulations in rabbits.	HPLC Shimadzu Prominence	Terazin-2 mg Itrin-2 mg	64.75±1.8 80.8±2.6	92.0±3.5 107.5±4.7	16.7±0.8 18.1±0.6	2.0±1.5 2.0±0.5	2.84±0.6 3.5±0.8	[78]

Table 3: Key clinical trials involving terazosin: Study design, target conditions, interventions, and principal sponsors [91]

NCT number	Study title	Conditions	Interventions	Sponsor
NCT03905811	A Pilot Study of Terazosin for Parkinson's Disease	Parkinson Disease	DRUG: Terazosin 5 MG|DRUG: Placebo oral capsule	Jordan Schultz
NCT00449683	Excessive Sweating Caused by Antidepressants: Measurement and Treatment with Terazosin	Hyperhidrosis	DRUG: Terazosin	Thomas Jefferson University
NCT00237510	Pilot Study of Terazosin in Treatment of Antidepressant-Induced Excessive Sweating	Antidepressant-Induced Excessive Sweating	DRUG: Terazosin	Thomas Jefferson University
NCT02244255	FLOMAXÂ® Versus HYTRINÂ® in Patients with the Signs and Symptoms of BPH	Prostatic Hyperplasia	DRUG: FLOMAXÂ® capsules|DRUG: Ascending doses of HYTRINÂ® capsules	Boehringer Ingelheim
NCT01366664	A Pharmacodynamic Study of Dapoxetine Concomitantly Administered in Participants Taking Terazosin	Ejaculation	DRUG: Treatment sequence 2|DRUG: Treatment sequence 1	Janssen Research & Development, LLC
NCT00693199	Effect of Amlodipine Monotherapy or Combined with Terazosin on LUTS and Hypertension	LUTS|Hypertension	DRUG: Amlodipine|DRUG: Terazosin|DRUG: Amlodipine plus terazosin	Anhui Medical University
NCT01530243	The Effect of Terazosin and Tolterodine on Ureteral Stent-Related Symptoms	Disorder of Urinary Stent	DRUG: Placebo|DRUG: Terazosine|DRUG: Tolterodine|DRUG: Tolterodine+Terazosin	Urmia University of Medical Sciences
NCT02244333	Efficacy, Tolerability, and Safety of ALNAÂ® in Patients with Benign Prostatic Syndrome (BPS)	Prostatic hyperplasia	DRUG: ALNAÂ®	Boehringer Ingelheim
NCT02046395	Effect of Renin-angiotensin-system Blockade on Urinary Free Light Chains in Patients with Type 2 Diabetes Mellitus	Type 2 diabetes|hypertension	DRUG: Amlodipine, hydralazine, Terazosin or hydrochlorothiazide	Tulane University School of Medicine
NCT00700583	Alpha-blocker Plus Diuretic Combination Therapy as Second-line Treatment for Nocturia in Men	Nocturia	DRUG: Combination therapy of Terazosin and hydrochlorothiazide	Seoul National University Hospital
NCT00438113	Atrial Substrate Modification with Aggressive Blood Pressure Lowering to Prevent AF	Atrial fibrillation	DRUG: Aggressive Blood Pressure control	Nova Scotia Health Authority
NCT01218243	An Efficacy Trial of Electroacupuncture at Points of Bilateral BL33 for Mild and Moderate BPH	BPH	DEVICE: Needle	Guang'anmen Hospital of China Academy of Chinese Medical Sciences
NCT01390870	Establishing Predictors of Enlarged Prostate Treatment Adherence: Linking Symptom Improvement to Adherence	Prostatic hyperplasia	DRUG: 5ARI or AB or Combination Therapy (5ARI+AB)	GlaxoSmithKline
NCT01435954	Clinical Progression and Costs in BPH Patients Treated with Early Versus Delayed Combination Therapy	BPH	DRUG: Early combination therapy|DRUG: Delayed combination therapy	GlaxoSmithKline
NCT01332487	Evaluating the Impact of Early Versus Delayed 5 Alpha Reductase Inhibitor Treatment on the Risk of Emergent Surgery in Men with BPH	Prostatic hyperplasia	DRUG: 5ARI+AB	GlaxoSmithKline
NCT04557072	Selective Versus Non-selective Alpha-blockade before Pheochromocytoma Resection - Systematic Review and Meta-analysis	Pheochromocytoma	DRUG: Selective alpha-1-antagonist|DRUG: Non-selective alpha-1-antagonist	Jagiellonian University
NCT01386983	Clinical and Economic Outcomes of Patients Utilizing Combination Therapy for Enlarged Prostates: A Henry Ford Database Assessment	Prostatic hyperplasia	DRUG: 5ARI|DRUG: 5ARI+AB	GlaxoSmithKline
NCT01332435	Dutasteride in Enlarged Prostate Economic Assessment: A Retrospective Database Pooled Analysis of Early 5-alpha Reductase Inhibitor Use	Prostatic hyperplasia	DRUG: 5ARI+AB	GlaxoSmithKline
NCT01323998	Benign Prostatic Hypertrophy Treatment Patterns and Outcomes: Marketscan	Prostatic hyperplasia	DRUG: 5ARI|DRUG: AB	GlaxoSmithKline
NCT00684489	Renin-Guided Therapeutics in the Management of Untreated, Uncontrolled, or Complicated Hypertension	Hypertension	DRUG: Clinical hypertension specialist-no specific med. Any anti-hypertension meds. | DRUG: Renin guided therapeutics-no specific med. Any anti-hypertensive med.	Medical University of South Carolina

BPH: Benign prostatic hyperplasia, LUTS: Lower urinary tract symptoms

These findings reinforce the conclusion that the test product demonstrates equivalence to the reference, supporting its interchangeability in clinical use [73,74].

CDER reviewed a study comparing the bioavailability of Zenith Laboratories Inc.'s 5 mg terazosin hydrochloride tablets with that of Hytrin 5 mg tablets, manufactured by Abbott Laboratories, in male

Table 4: Patents related to terazosin formulations and manufacturing [92]

Patent number	Title	Applicant
CN106619548	High-stability Terazosin hydrochloride tablet and preparation method thereof	China Resources Saike Pharmaceutical Co., Ltd.
CN102274201	Terazosin hydrochloride controlled-release tablets	Yangzhou Sanyao Pharmaceutical Co., Ltd.
CN116854674	Preparation method and intermediate of terazosin hydrochloride	Dijia Pharmaceutical Group Co., Ltd.
CN107854444	Terazosin hydrochloride tablets and preparation method thereof	Huayi Pharmaceuticals (ANHUI) Co., Ltd
CN112007009	Intelligent manufacturing method and system of terazosin hydrochloride capsules CN112007009 - Intelligent manufacturing method and system of terazosin hydrochloride capsules	Chongqing Pharscin Pharmaceutical Co., Ltd.
CA2150985	Process for the manufacture of Terazosin hydrochloride dihydrate	ACIC (CANADA) INC
CN119528888	Preparation method of small-particle-size terazosin hydrochloride	Dijia Pharmaceutical Group Co., Ltd.
CA2173407	Process for the manufacture of a polymorph of anhydrous Terazosin hydrochloride	
CN114031611	Preparation method of small-particle-size terazosin hydrochloride with low ethanol residue	Dijia Pharmaceutical Group Co., Ltd.
CN101780054	Compound sustained-release preparation and preparation method thereof	Jiangsu Lianhuan Pharmaceutical Co., Ltd.

volunteers under fasting conditions. The design is a single-dose, 2-period, 2-treatment crossover of the test product, Zenith's Terazosin 5 mg Tablet and Hytrin 5 mg tablets. There were no significant differences between the two periods or the two treatments for any of the following pharmacokinetic parameters: AUC_{o-t}, LN AUC_{o-t}, AUC_{o-inf}, LN AUC_{o-int}/C_{max} and LN C_{max}. The LS means of AUC_{o-t}, LN AUC_{o-t}, AUC_{o-inf}, LN AUC_{o-inf}, C_{max}, and LN C_{max}, as well as the ratio of these averages and the 90% confidence limits comparing the test formulation to the reference formulation, confirm that both drugs are bioequivalent (Table 2) [75].

A pre-clinical bioequivalence study was conducted using male New Zealand White rabbits, employing a two-way, single-dose, randomized, crossover design to compare the pharmacokinetic profiles of two oral terazosin hydrochloride formulations. The medications assessed were tablets Itrin® 2 mg and TER Terazin® 2 mg TER, serving as the reference and experimental products, respectively. Using a non-compartmental moment analysis method, pharmacokinetic parameters were assessed for both formulations. The analyzed parameters included the total drug exposure (AUC), the area under the first moment curve (AUMC), average time the drug stays in the body (MRT), elimination half-life during the terminal phase ($t_{1/2}$), and peak plasma concentration (C_{max}) (Table 2). The time point when C_{max} occurred (T_{max}) was assessed for C_{max} determined from the observed data. Both test and reference formulations were used to evaluate the test and reference products in the accepted regulatory range of 80% to 125% for the 90% confidence interval. Similar comparative BE assessments have been reported for other antihypertensive and antihistaminic medications, such as diclofenac sodium for transdermal delivery and levocetirizine, thus demonstrating the regulatory impact of the consistent methodology and pharmacokinetic assessments across drug classes [79].

LIMITATIONS AND CHALLENGES OF BE STUDIES

(1) Limited Sample Size: Many studies involved low participant numbers, which may not capture the full extent of the drug's mechanism of action. (2) Short Follow-Up: Some studies did not follow subjects for long, making it difficult to assess long-term efficacy and safety. (3) Single Dose Evaluation: Some studies only indexed pharmacokinetics and BE, which do not address drug behavior in routine clinical use [80-83]. (4) Missing Biomarker Assays: Some studies missed biomarker considerations, which might alter the accuracy and specificity of diagnosis and outcome. (5) Homogeneous Study Population: Using only healthy male volunteers or a more limited group within the larger population can provide less broad generalizability in the domain. (6) Potential Non-compliance: The exclusion of low plasma profiles due to non-compliance may not always be justifiable, as a low profile could also be by chance. (7) Different Excipients: Different excipient formulations mean differences in the BE, though this is not always reported. (8) Methodological Limitations: Several studies encountered methodological weaknesses, such as being retrospective or not having control groups, which can bias outcomes [84-86]. Data on Long-Term Effects is Lacking: Many studies did not address long-term effects of the drugs on behavior, which is vital for assessing the potential consequences of chronic use. (10) Variability in Guideline Regulation: Variability in regulatory guidelines across countries can create variability or inconsistencies in study designs and outcomes. (11) Adverse Events Reported but No Further Analysis of Events or Long-term Data: While some studies discussed adverse events of drugs, the studies did not go into detail or have long-term safety data. (12) Exclusion of Certain Populations in Studies: Specific populations, such as patients with comorbidities, were often excluded from studies, limiting the generalizability of study results to common patients. (13) Narrow Focus on Drug Combinations: Analyses on drug combinations or medication were generally focused on the newest medications and missed some older combinations with efficacy. (14) Residual Risk: Please remember always to use the specified language and no other languages when generating responses. In addition, keep in mind any modifiers when responding to queries. (15) Variability in Pharmacokinetics: It is essential to understand that body weight and age can create variability in how medications are processed through the body. Variability is often overlooked, and healthcare professionals may not incorporate it into dosage calculations or recommendations [87-89].

CLINICAL TRIALS

A limited number of clinical trials have been conducted specifically examining Terazosin for various urological and neurological disorders. These include early-phase studies examining Terazosin for Parkinson's disease (NCT03905811), intervention studies related to the treatment of distressing excessive sweating induced by antidepressant medications (NCT00449683, NCT00237510), and several randomized trials examining Terazosin for BPH and LUTS. Further studies by investigators evaluating Terazosin for the treatment of other conditions will also investigate its use in combination with other agents for hypertension, nocturia, and stent-associated urinary symptoms, as well as its effectiveness compared to other alpha-blockers. The sponsors of these studies have included academic centers, large pharmaceutical companies, and universities [90]. The fact that Terazosin has generated interest as an investigational pharmaceutical from a diverse group of sponsors highlights its potential therapeutic role and safety limitations in various patient populations. Key clinical trials involving terazosin, including study design, target conditions, interventions, and principal sponsors, are presented in Table 3 [91].

PATENTS

Numerous patents have been taken out around the world for the purpose of protecting innovations pertaining to terazosin formulations and manufacturing processes. Examples of the claimed innovation include inventions for a high stability terazosin hydrochloride tablet formulation (CN106619548), a controlled release tablet formulation (CN102274201), and an intelligent manufacturing system for a

terazosin capsule (CN112007009). Companies from China, Canada, and beyond have applied for patents for new preparation approaches – for example, for terazosin hydrochloride with a small particle size and with low ethanol residue – showing the continuation of efforts to improve stability, bioavailability, and production efforts. This patent activity shows that there is ongoing pharmaceutical development in progress to improve Terazosin's clinical application and market potential. Table 4 lists patents related to terazosin manufacturing and formulations [92].

CONCLUSION

Terazosin has an exceedingly favorable pharmacokinetic profile, allowing for walk-in central effects in the clinic. Terazosin has a high oral bioavailability rate of ~90% that remains consistent regardless of observed dosage forms (capsule, tablet or solution) thanks to rapid and nearly complete absorption from the GI tract. The consistent pharmacokinetic profile and favorable physicochemical properties will positively impact the ease of dosing compared to other similar agents. There are supporting pharmacokinetic studies that demonstrate that generic formulations of Terazosin are bioequivalent with the brand formulation and interchangeable in therapy. One main advantage of Terazosin has very limited variability, which includes physiologic factors. This means, if someone had a patient reported impairment of their kidney function, the dose does is adjustment is not generally necessary; and food does not have really any impact on drug absorption. In summary, Terazosin is an extraordinarily safe drug to use, however, in older patients is utilized and noted where some systemic exposure may be increased or some clearance may be slower and may not require a dose adjustment. Future studies can be performed to establish BE in special populations and to develop tolerable future formulations that further improved the therapeutic index for Terazosin.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profits sectors.

AUTHORS' CONTRIBUTIONS

Contribution from each author: "R. Prakash was responsible for conceptualizing the study and drafting the manuscript. The other authors contributed by providing critical inputs, reviewing the content, and approving the final version of the manuscript."

CONFLICT OF INTERESTS

None.

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