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Evaluation of *In Vitro* Dissolution Consistency of Domestic and Original Finasteride Tablets and Establishment of *In Vivo-In Vitro* Correlation Model using GastroPlus™

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Abstract:

Objective: To evaluate the quality consistency between domestic finasteride tablets and the original reference formulation by comparing their *in vitro* dissolution behavior, and to analyze the *in vitro-in vivo* correlation using computer simulation technology. *Methods:* Following the methods outlined in the 2015 edition of the *Chinese Pharmacopoeia* (unchanged in the 2020 edition), the *in vitro* dissolution behavior of the domestic formulations and the reference formulation was examined in four different dissolution media: pH 1.2 hydrochloric acid solution, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and water. Additionally, the GastroPlus™ software was used in combination with the *in vitro* dissolution test results to establish an *in vitro-in vivo* correlation model for finasteride tablets. *Results:* Under the selected conditions, products from three out of 15 domestic pharmaceutical companies demonstrated dissolution curves in all four media that were similar to those of the reference formulation. However, software analysis suggested that the *in vitro* dissolution curves were not consistent with the simulated *in vivo* behavior. *Conclusion:* The dissolution curves of most generic finasteride tablets showed certain differences compared to the reference formulation, indicating that the manufacturing processes and formulations of domestic finasteride tablets need improvement. Further research is required to establish biorelevant dissolution conditions that reflect *in vivo* release behavior.

Keywords:

Finasteride tablet
Dissolution
Consistency evaluation
Computer simulation

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1. Introduction

Finasteride is a synthetic steroidal compound that acts as a specific inhibitor of the intracellular enzyme type II 5α-reductase, which is involved in the metabolism of the androgen testosterone to dihydrotestosterone (DHT). It has the effect of inhibiting testosterone metabolism. This drug is available in two specifications, 5 mg and 1 mg. The former is indicated for the treatment and control of benign prostatic hyperplasia and related symptoms, while the latter is used for the treatment of male pattern baldness. Common adverse reactions include sexual dysfunction, breast discomfort, and skin rash [1,2]. It was first developed by Merck & Co., Inc., USA in 1991. Currently, there are 29 domestic manufacturers of finasteride tablets in China.

With the implementation of the consistency evaluation of generic drugs, dissolution curve technology has been widely used in the quality evaluation of orally administered solid formulations of chemical generic drugs in China [3,4]. To investigate the quality consistency between domestic finasteride tablets and the original preparation, this study selected the finasteride tablets produced by Merck & Co., Inc., USA, which were announced by the National Medical Products Administration, as the reference preparation to determine the *in vitro* dissolution curves of both. Additionally, the computer simulation technology GastroPlus™ was utilized to establish an *in vivo-in vitro* correlation model [5,6], evaluate the correlation between the *in vitro* dissolution curves and *in vivo* release curves of finasteride tablets, and provide a reference for establishing a biologically relevant dissolution method in the next step.

2. Instruments and reagents

2.1. Instruments

Waters e2695 high-performance liquid chromatograph (quaternary pump, autosampler, column oven, DAD detector), Empower 2 chemical workstation (Waters Corporation, USA); SOTAX AT-Xtend dissolution tester (SOTAX AG, Switzerland); XS205DU electronic balance (Mettler Toledo, Switzerland), Milli-Q deionized water generator (Millipore Corporation, USA), GastroPlusTM software (Simulations Plus, Inc., USA, Version 8.6).

2.2. Reagents

Finasteride reference substance (National Institutes for Food and Drug Control, batch number: 100611-201503, content: 99.7%); original finasteride tablets (Merck Sharp & Dohme Ltd., UK, specification: 5 mg, batch number: S007878); domestic generic finasteride tablets from 15 manufacturing enterprises, totaling 15 batches (specification: 5 mg), all were samples from the national evaluative inspection in 2019; finasteride drug substance (Hubei Gedian Renfu Pharmaceutical Co., Ltd., batch number: FTD180902); hydrochloric acid, glacial acetic acid, sodium acetate, potassium dihydrogen phosphate, and sodium hydroxide (analytical grade), acetonitrile (chromatographically pure), and water was ultrapure water.

3. Methods and results

3.1. Study on dissolution curve method

An excessive amount of finasteride was placed in a 25 mL conical flask, and 10 mL of nine different pH solvents were added separately, in triplicate. The flasks were tightly sealed and shaken in a 37℃ constant temperature water bath for 24 hours. After centrifugation, the supernatant was collected and filtered, and the subsequent filtrate was used for measurement. The solubility of finasteride drug substance was investigated in nine different media: hydrochloric acid solution (pH 1.0, 2.0), citrate buffer (pH 3.0, 5.0), acetate buffer (pH 4.0), phosphate buffer (pH 6.0, 7.0, 8.0), and water. The solubility in different pH media was determined and the results are shown in **Figure 1**. The data revealed a pH-independent solubility characteristic.

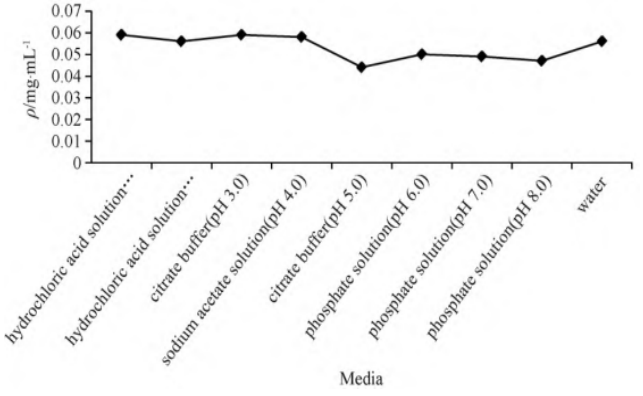

Figure 1. The solubility of finasteride in media of different pH values

3.2. Establishment of in vitro dissolution curve test method

3.2.1. Dissolution test conditions

Referring to the dissolution test method for finasteride tablets in the 2015 edition of the *Chinese Pharmacopeia* (there were no changes to this item in the 2020 edition) [7], dissolution curve studies were conducted using hydrochloric acid solution (pH 1.2), acetate buffer (pH 4.5), phosphate buffer (pH 6.8), and water as dissolution media, with a volume of 900 mL, at 50 rpm, and a temperature of 37 ± 0.5℃.

3.2.2. Chromatographic conditions

The chromatographic column used was SHISEIDO CAPCELL MGII C18 (4.6 mm × 150 mm, 5 μm), with acetonitrile-water (45:55) as the mobile phase. The flow rate was 1.0 mL/min, the column temperature was 35℃, the detection wavelength was 210 nm, and the injection volume was 100 μL.

3.2.3. Solution preparation

Approximately 12.5 g of finasteride reference substance was accurately weighed and placed in a 50 mL volumetric flask. 10 mL of methanol was added to dissolve the substance, and the solution was diluted to the mark with dissolution medium and mixed well. 2 mL of this solution was accurately measured and placed in a 100 mL volumetric flask, diluted to the mark with dissolution medium, and mixed well to obtain the reference solution. Dissolution samples were taken at 5, 10, 15, 20, 30, 45, and 60 minutes, and the dissolution medium was replenished in a timely manner. The samples were filtered, and the subsequent filtrate was used as the test solution.

3.2.4. Linear relationship

Approximately 20 mg of finasteride reference substance was accurately weighed, dissolved in 10 mL of methanol, and diluted with water to prepare a series of concentration solutions. These solutions were measured under the chromatographic conditions described in **3.2.2**. The regression equation was found to be y = 207,986x + 2,352.5, with a linear range of 0.2078 to 6.2331 μg/mL and a correlation coefficient (r) of 0.9998. The results showed a good linear relationship between the concentration of the reference solution and the peak area within the range of 0.2078 to 6.2331 μg/mL.

3.2.5. Specificity investigation

A blank excipient solution without the main drug was prepared according to the prescription ratio and filtered, and the subsequent filtrate was measured under the chromatographic conditions described in **3.2.2**. The excipients did not interfere with the determination of finasteride, indicating good specificity of the method.

3.2.6. Recovery rate

Samples were accurately weighed at 50%, 80%, and 100% of the labeled amount of finasteride reference substance and corresponding amounts of blank excipients according to the prescription ratio. An appropriate amount of water was added, and the mixture was shaken to dissolve the finasteride. The solution was then diluted to the appropriate concentration with water, mixed well, and filtered, and the subsequent filtrate was measured under the chromatographic conditions described in **3.2.2**. The average recovery rate was found to be 99.4% with a relative standard deviation (RSD) of 1.0% (n = 9). The results showed that the recovery rate met the methodological requirements and could be used for dissolution determination.

3.2.7. Solution stability

Test solutions in four dissolution media were taken and measured under the chromatographic conditions described in **3.2.2** at 0, 4, 8, 12, and 20 hours. The RSD was less than 1.5% for all measurements, indicating that the solutions were stable within 20 hours.

3.3. Drawing of in vitro dissolution curves

Generic and original preparations were tested according to the dissolution conditions described in **3.2.1**. Samples were taken at 5, 10, 15, 20, 30, 45, and 60 minutes and measured under the chromatographic conditions described in **3.2.2**. Dissolution curves were then plotted, as shown in **Figure 2**.

The results showed that among the four dissolution media, the dissolution amount of the original preparation could reach over 85% at 15 minutes; only three domestic manufacturers' finasteride tablets had a dissolution

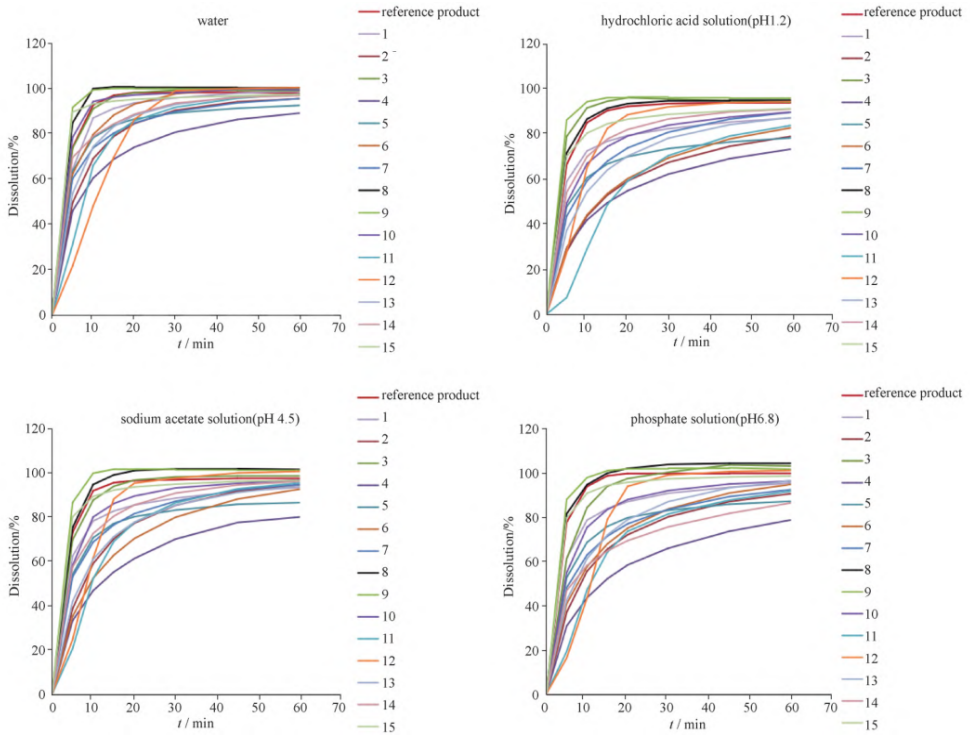

Figure 2. Dissolution curves of original and generic finasteride preparations in dissolution media with different pH values

amount greater than 85% at 15 minutes, indicating that only three generic preparations had similar dissolution curves to the original preparation under the set conditions. Most domestic preparations had the lowest dissolution amount in hydrochloric acid solution (pH 1.2) and the highest dissolution amount in water. Therefore, using hydrochloric acid solution (pH 1.2) as the dissolution medium for consistency evaluation can effectively identify differences between domestic preparations and reference preparations.

3.4. Study on the establishment of an in vitro-in vivo correlation model for finasteride tablets using GastroPlusTM software

3.4.1. Construction of the GastroPlusTM basic model

Combining the relevant physicochemical properties of finasteride and the pharmacokinetic (PK) parameters reported in the literature [8-10], an *in vivo* absorption curve model for finasteride preparations was constructed. The model's predicted simulated drug concentration-time curve was compared to the actual drug concentration-time curve reported in the literature (**Figure 3**) to assess the model's accuracy. The prediction results of the constructed model were remarkably similar to the measured drug concentration-time curve. The predicted

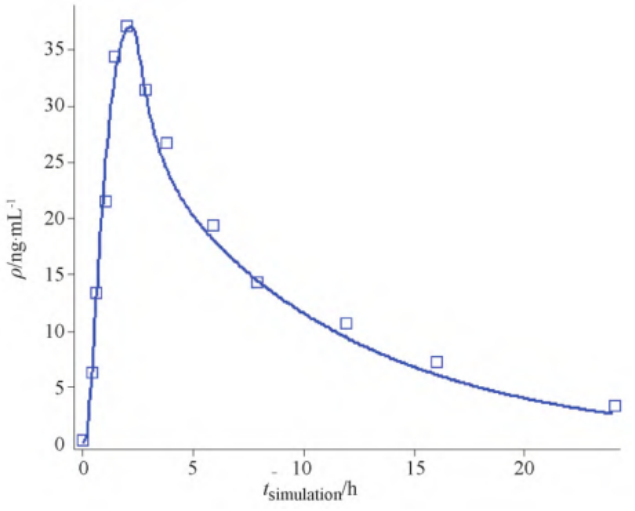

Figure 3. The actual PK curve and simulated PK curve of finasteride tablets (line-simulated PK curve; □-actual PK curve)

main PK parameters (c_max, t_max, AUC) closely matched the measured values, with prediction deviations falling within the bioequivalence range of ±25%, demonstrating the model's accuracy. Consequently, the parameters utilized in this model can be further applied to establish an *in vitro-in vivo* correlation model.

3.4.2. In vitro-in vivo correlation analysis of finasteride tablets

Analysis utilizing the gastrointestinal absorption model in GastroPlus™ software (**Figure 4**) revealed that the primary absorption sites of finasteride after oral administration are in the duodenum and jejunum. The simulated *in vivo* release and absorption curves after oral administration of 5 mg of finasteride tablets (**Figure 5**) indicated that, due to finasteride's poor hydrophilicity, the drug exhibits slow release characteristics in the gastrointestinal tract after oral administration, achieving complete release after approximately two hours. The light blue absorption curve closely follows the *in vivo* release curve, suggesting that the released drug is quickly absorbed into intestinal cells and completes the absorption process after the release ends. Hence, improving the drug release process has minimal impact on overall exposure in the body but may affect the drug's peak time and concentration, especially the peak time.

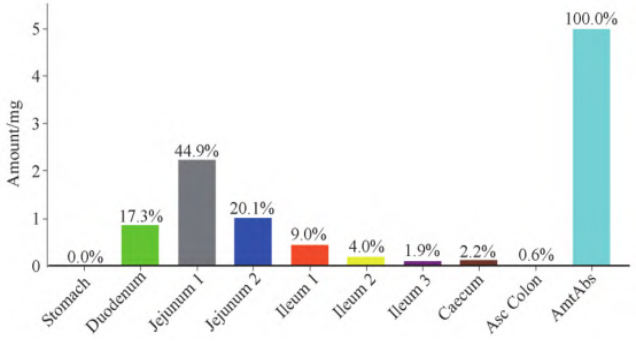

Figure 4. Absorption of the drug in the gastrointestinal tract

Dissolution data for generic and original finasteride tablets in four different pH media *in vitro* were imported into GastroPlus™ software to simulate *in vivo* behavior and analyze the *in vitro-in vivo* correlation. Comparing the measured data with the reference *in vivo* release curve, it was observed that the drug's *in vivo* release rate was significantly slower than the results obtained under the aforementioned dissolution conditions (**Figures 2** and **5**). The reference preparation demonstrated slow release characteristics in the gastrointestinal tract, releasing only 50% of the prototype drug at 60 minutes, whereas it achieved complete release in the four media at the same time. This indicates that the *in vitro* dissolution rate was notably faster than the *in vivo* release process. Therefore, the current dissolution conditions inadequately reflect the drug's *in vivo* release characteristics, suggesting a poor correlation between *in vitro* and *in vivo* dissolution. Future research could focus on optimizing dissolution conditions to develop biologically relevant dissolution methods.

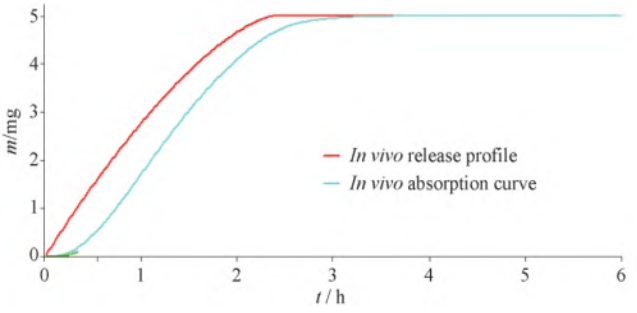

Figure 5. Dissolution and absorption profiles of finasteride tablets *in vivo*

4. Discussion and conclusion

This study compared the dissolution behavior of domestically produced finasteride tablets with reference preparations by measuring their dissolution curves in four different dissolution media: pH 1.2 hydrochloric acid solution, pH 4.0 acetate solution, pH 6.8 phosphate solution, and water. Using hydrochloric acid solution (pH 1.2) as the dissolution medium for consistency evaluation effectively screened for differences between domestic preparations and reference preparations. The results showed that among the generic drugs from 15 manufacturers, only three manufacturers' preparations had similar *in vitro* dissolution behavior to the original preparation. This suggests that most domestically produced finasteride tablets have certain differences in process level and prescription compared to the original preparation, which need to be further improved.

The results of GastroPlus™ software analysis indicate that *in vitro* dissolution behavior is not correlated with *in vivo* biological behavior. Therefore, based on initial analysis, the currently set dissolution conditions are more suitable for quality control of the drug and cannot establish a one-to-one correspondence with the *in vivo* release process. Dissolution conditions still need further research and development to establish biologically relevant dissolution methods. The findings in section **3.4.2.** suggest more gentle dissolution conditions,

physiologically relevant dissolution methods such as flow-through cells, and a transition of dissolution media from pH 1.2 to pH 6.8 to reflect the drug's *in vivo* release environment. Additionally, considering the non-pH-dependent solubility characteristics of the drug under physiological pH conditions, conventional hydrophilic media may not distinguish differences in drug release *in vivo*. Therefore, simulated gastric fluid (SGF) and fasted state simulated intestinal fluid (FaSSIF), which mimic gastrointestinal fluids, may exhibit more biologically relevant behavior. Gentle rotation speeds may also establish biologically relevant dissolution conditions that reflect *in vivo* release behavior.

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Disclosure statement

The authors declare no conflict of interest.

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