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Consistency Evaluation of the Dissolution of Toremifene Citrate Tablets

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ABSTRACT

Introduction: Endocrine therapy plays a pivotal role in the comprehensive treatment of breast cancer, and toremifene citrate tablets are a commonly used agent, with proven clinical efficacy. However, the dissolution of toremifene citrate is highly pH-dependent, which may lead to fluctuations in bioavailability, necessitating dissolution profile similarity evaluation to ensure therapeutic consistency of generic tablets with the original preparation. **Methods**: This study established a dissolution test method for toremifene citrate tablets to assess in vitro dissolution consistency of test tablets (self-developed) with the reference listed drug (RLD). According to the *Chinese Pharmacopoeia*, dissolution testing was conducted using a paddle apparatus with four media: pH 1.2 hydrochloric acid (HCl) solution, 0.02 mol/L HCl solution, pH 4.0 acetate buffer, and water. The dissolution profiles were determined using UV spectrophotometry, followed by similarity analysis. **Results**: The method demonstrated strong specificity, excellent linearity, and negligible membrane adsorption, as well as high precision, accuracy, solution stability, and robustness, thereby meeting all methodological requirements for dissolution testing. Three batches of the test tablets and the RLD exhibited mean cumulative dissolution rates > 85% at 15 minutes in pH 4.0 acetate buffer and 0.02 mol/L HCl. In water and at pH 1.2 with HCl, the similarity factor (f_2) exceeded 50 compared to the RLD batch, confirming the consistency of the dissolution curve. **Conclusion**: This validated method is suitable for dissolution testing and in vitro equivalence assessment of toremifene citrate tablets.

Keywords: Toremifene citrate tablets, original preparation, generic preparation, dissolution curve, consistency evaluation

INTRODUCTION

Breast cancer remains a major global health concern. Within the comprehensive treatment strategies for breast cancer, endocrine therapy plays a pivotal role, especially for postmenopausal patients with estrogen receptor-positive (ER+) breast cancer (*1*–*4*). Toremifene citrate tablets, a commonly used drug in this field, contain the active ingredient toremifene citrate, a non-steroidal triphenylethylene derivative (*5*, *6*). It competitively binds to estrogen receptors, blocking estrogen-induced tumor cell proliferation and effectively inhibiting cancer growth, demonstrating significant clinical efficacy (*7*, *8*).

As a typical poorly water-soluble drug, toremifene citrate exhibits markedly different dissolution behaviors across various media. Studies indicate that the drug shows negligible dissolution in pH 6.8 phosphate buffer, but significantly improved release in modified media containing surfactants

or ethanol (*9*). This pH-dependent dissolution profile suggests that the bioavailability of toremifene formulations may be substantially influenced by variations in patients' gastrointestinal environments, potentially leading to clinical efficacy variability. Therefore, evaluating the dissolution curve similarity between generic and reference toremifene tablets is crucial to ensuring consistent and reliable therapeutic outcomes.

Currently, only the *Chinese Pharmacopoeia* provides quality standards for this drug, and the Japanese Orange Book and United States FDA Dissolution Database provide dissolution methods (*10*–*12*). However, differences exist among these standards regarding dissolution media (composition and volume), methodology, and detection wavelengths.

Based on existing guidelines, this study established an ultraviolet (UV) spectroscopy-based method to assess the in vitro dissolution profiles of toremifene citrate tablets in media of varying pH levels. The aim was to compare generic preparations and the original research drugs, providing a reference for dissolution curve analysis in bioequivalence studies. Key parameters including dissolution medium selection, rotational speed, sampling time points, and detection wavelength were optimized to ensure method reliability (*13*).

METHODS

Chemicals and Reagents

Toremifene citrate tablets (self-developed test tablets: batch nos. 190301D02, 190302D02, 190303D02, expiry date: 2024.03, Fuan Pharmaceutical Group, Ningbo Team Pharmaceutical, Co. Ltd., China; and reference tablets: batch nos. 1819950, 1717571, 1896319S1, expiry date: 2023.02, Orion Corporation, Finland) and reference substance (batch no. 420014-201401, purity 99.8%) were sourced from National Institutes for Food and Drug Control. Hydrochloric acid (HCl), sodium acetate, acetic acid, potassium dihydrogen phosphate, and sodium hydroxide (AR, National Pharmaceutical Group Chemical Reagent, Co. Ltd., China) were used without further purification either before or during the experiment. Ultrapure water was prepared in-house using an Arium Comfort II purification system (Sartorius Company).

Dissolution Method and Evaluation

The dissolution tests were performed according to the compendial method for toremifene citrate tablets, i.e., paddle apparatus (Agilent 708-805DS and SOTAX) at 50 rpm with four media: pH 1.2 hydrochloric acid (HCl, 900 mL, 0.02 mol/L HCl (1000 mL), pH 4.0 acetate buffer (900 mL), and water (900 mL). The dissolution media were prepared in accordance with *Chinese Pharmacopoeia* (the pH 1.2 HCl leaching solution uses pH 4.0 acetate buffer as the diluent). Samples (4 mL) were taken at 5, 10, 15, 30, 45, and 60 min and filtered for UV analysis (SHIMADZU, UV-2600). The cumulative dissolution for each product was calculated.

Method Validation

Validation of adsorption of the filter membrane, specificity, linearity, range, accuracy, precision, durability, and solution stability of the dissolution method was conducted in accordance with the principles set out by the International Council on Harmonization (*14*).

Specificity

Specificity of the UV detection method was assessed within the wavelength range of 200–400 nM using 0.02 mol/L HCL, pH 4.0 acetate buffer, mixed medium (40 mL of pH 1.2 HCl and 60 mL of pH 4.0 acetate buffer), water, blank excipient solution, reference substance solution, and test sample solution. The detection wavelength was 277 nm in pH 1.2 HCl, pH 4.0 acetate buffer, and water. In 0.02 mol/L HCl, the detection wavelength was 234 nm.

Linearity

Linearity of the method was assessed by making a series of linear solutions with concentrations of 20%, 40%, 60%, 80%, 100% and 120% using each dissolution medium as follows.

0.02 mol/L HCl solution

Precisely weigh 0.01567 g of toremifene citrate reference substance and place it in a 100-mL vessel. Add 30 mL of methanol to dissolve it, then add approximately 70 mL of 0.02 mol/L HCl solution. Ultrasonicate and intermittently shake for 10 min, then dilute to the mark with the medium. Shake well. Precisely measure 1, 2, 3, 4, 5, and 6 mL of the solution into separate 50-mL vessels, dilute to the mark with 0.02 mol/L HCl solution, and shake well.

Aqueous solution

Precisely weigh 0.01539 g of toremifene citrate reference substance and place it in a 50-mL vessel. Add 10 mL of methanol to dissolve it, then add water to approximately 30 mL. Ultrasonicate and intermittently shake for 10 min, then dilute to the mark with water. Shake well. Precisely measure 1, 2, 3, 4, 5, and 6 mL of the solution into separate 50-mL vessels, dilute to the mark with water, and shake well.

pH 4.0 acetate buffer solution

Precisely weigh 0.01527 g of toremifene citrate reference substance and place it in a 50-mL vessel. Add 4 mL of methanol to dissolve it. Then, add the pH 4.0 acetate buffer to approximately 30 mL. Sonicate the solution while intermittently shaking it for 10 min. Next, dilute it to the mark with the pH 4.0 acetate buffer and shake well. Precisely measure 1, 2, 3, 4, 5, and 6 mL of the solution into separate 50-mL vessels and dilute to the mark with pH 4.0 acetate buffer and shake well.

pH 1.2 HCl solution

Precisely weigh 0.01540 g of toremifene citrate reference substance and place it in a 50-mL vessel. Add methanol to dissolve it and dilute it to the mark, then shake well. Precisely measure 1, 2, 3, 4, 5, and 6 mL of the solution into separate 50-mL vessels. Add the mixed medium (40 mL of pH 1.2 HCl and 60 mL of pH 4.0 acetate buffer) to dilute to the mark, then shake well.

The linear correlation coefficient of each medium should be greater than 0.999.

Adsorption of Filter Membrane

Adsorption of the filter membrane was studied in each of the four dissolution media (1000 mL of 0.02 mol/L HCl, 900 mL of pH 1.2 HCl, 900 mL of water, and 900 mL of pH 4.0 acetate buffer). The dissolution test was performed for 30 minutes in each of the four media. Aqueous filter membranes (0.45-μm, polyethersulfone) from different manufacturers were used for one-time

filtration. The 0.02 mol/L HCl solution, pH 1.2 HCl solution, and water were discarded with 2, 5, and 10 mL of the initial filtrate, and the pH 4.0 acetate buffer solution was discarded with 5, 10, and 15 mL of the initial filtrate. The absorbance value was detected by UV light. When filtering different volumes, the change in absorbance between the test sample solutions and reference should be less than 5%.

Accuracy

The accuracy of the method was investigated using pH 1.2 HCl, pH 4.0 acetate buffer, water, and 0.02 mol/L HCl. The 80% and 100% recovery rates of each medium should be between 98% and 101%, the 50% recovery rate of each medium should be between 95% and 102%, and the relative standard deviation (RSD) should be less than 5.0%.

Precision

The precision of the method was determined using six samples of the standard and sample solutions (RSD should not exceed 2.0%). Intermediate precision tests were performed in the same laboratory by different operators on different days using different instruments.

Robustness

The robustness of the method was studied by modifying the dissolution parameters, including speed of the paddle with standard medium (50 ± 5 rpm), temperatures of dissolution medium (37 ± 2 ℃), no degassing of dissolution medium, different rinsing volumes, and different detection wavelengths (± 2 nm), and brand of dissolution instruments. When comparing the dissolution results with the normal conditions, the difference in average dissolution should be less than ± 5%. The mean difference in cumulative drug release at the 15-minute time point must be less than ± 10%.

Stability

The standard solution was stored at room temperature for 0, 2, 4, 8, and 24 hours, and the absorbance was measured at the corresponding wavelength at each time point. For the standard solution stored in the refrigerator (2–8 ℃), it was taken out, diluted, and measured at 1, 2, 3, and 5 days.

The sample solution was prepared according to the dissolution method and stored at 37 ℃ for 1 hour and then at room temperature for 2, 4, 6, and 8 hours. The absorbance was measured at the corresponding wavelength at each time point. For pH 1.2 HCl, due to the solution becoming turbid at room temperature after 1 hour, it needed to be heated to clarify and then diluted and measured immediately.

For both solutions, the change in absorbance compared with the 0-hour measurement should be less than 2.0%.

To assess long-term stability after 6 months of room temperature storage, three batches of each test product and the reference formulation were subjected to dissolution testing.

Date Analysis

All data were analyzed using Microsoft Excel 2016. Data are presented as the percentage of cumulative drug release (mean or median) with RSD. The relationship between the concentration of toremifene and its absorbance in different media was evaluated using linear fitting. For the comparison of dissolution curves, the similarity factor f_2 (sum of squared residuals method) was calculated.

RESULTS

Specificity

Both the test and control solutions have maximum absorption at 273 and 235 nm, and the absorption spectra of the test and control are consistent. The interference of blank excipients was less than 1%. That is, the specificity of each medium is good in the specified wavelength range (Supplementary Tables S1 and S2).

Linearity

Toremifene citrate demonstrated excellent linearity ($r \geq 0.9997$) across multiple media, with concentration ranges of 2.12–12.69 μg/mL in 0.02 M HCl ($r = 0.9997$), 4.15–24.93 μg/mL in water ($r = 0.9999$), 4.12–24.73 μg/mL in pH 4.0 acetate buffer ($r = 1.000$), and 4.16–24.95 μg/mL in pH 1.2 HCl ($r = 0.9998$). These results confirm robust linear relationships in all tested dissolution media, which met the requirements for a strong linear relationship (Figure S1).

Adsorption of Filter Membrane

Both self-prepared and reference formulations demonstrated comparable filter membrane adsorption characteristics across tested media. When employing primary filters (Agilent/SOTAX) followed by secondary filters (Jiangsu Green Union/Shanghai Anpul) with a 10-mL initial filtrate discard, absorbance variations remained below 5%, confirming negligible drug adsorption. Consistent results between test and reference formulations validate that a 10-mL rinse volume in automated dissolution testing ensures accurate dissolution profile determination (Tables S3–S6).

Accuracy

The recovery rates in different media were within the range of 97.65%-101.39%, and RSD values were less than 1.1% (Table S7). That is, the dissolution determination method of each medium of this product had high accuracy.

Precision

The average recoveries of the 12 sample solutions were 99.7%, 99.4%, 99.2%, and 100.4%, and RSD values were 0.56%, 0.65%, 1.2%, and 0.73%, respectively, in water, 0.02 mol/L HCl, pH 1.2 HCl, and pH 4.0 acetate buffer, respectively (Table S8). The dissolution method met the standard for good precision.

Robustness

The dissolution method demonstrated robust performance under varied conditions (agitation speed ± 5 rpm, medium temperature 37 ± 2 °C, non-deaerated medium, volume 900 or 1000 mL, and rinse volumes 5–37.5 mL), with average deviations within ± 5% compared to standard

conditions. After 15 minutes of dissolution, the release profiles across different instruments also showed ≤ 5% variability, confirming inter-instrument consistency. Furthermore, wavelength variations (234 ± 2 nm) yielded < 5% deviation in dissolution measurements, validating method robustness for wavelength selection. These results collectively affirm the reliability and ruggedness of the dissolution methodology in 0.02 mol/L HCl (Tables S9–S11).

Stability

The sample solutions exhibited stability for 8 hours at room temperature in water, 0.02 mol/L HCl, and pH 4.0 acetate buffer after an initial 1-hour incubation at 37 °C, whereas pH 1.2 HCl solutions required immediate dilution post-clarification due to turbidity. Reference standard solutions remained stable for 24 hours in water and pH 1.2 HCl, and 8 hours in 0.02 mol/L HCl and pH 4.0 acetate buffer at room temperature. Refrigerated stock solutions retained stability for 5 days (water and pH 1.2 HCl) and 3 days (0.02 mol/L HCl), but pH 4.0 acetate buffer stock solutions showed > 2.0% absorbance variation after 1 day, necessitating same-day use (Tables S12 and S13).

Plotting of the Dissolution Curve

As shown in Figures 1 and 2, cumulative drug release of the three test products and the reference formulation exceeded 85% within 15 minutes in acetate buffer pH 4.0 and 0.02 mol/L HCl at 0 months and after 6 months of long-term storage. The f_2 values for three batches of test products were greater than 50 when compared with the reference formulation in water and pH 1.2 HCl (Table 1), and the dissolution curves showed the same pattern of in vitro drug release Two batches of the reference formulation did not satisfy the f_2 value in pH 4.0 acetate buffer and 0.02 mol/L HCL or the amount of drug released was greater than 85% at 15 minutes; however, differences in cumulative dissolution at each time point were less than 10%.

Table 1. Comparison of f_2 Values with the Reference Formulation (Batch 1819950)

Batch	Water		pH 1.2 Acid Solution	
	0 month	6 months	0 month	6 months
190301D02	71	98	72	78
190302D02	88	69	75	73
190303D02	73	62	75	75
1717571	55		89	
1896319S1	66		57	

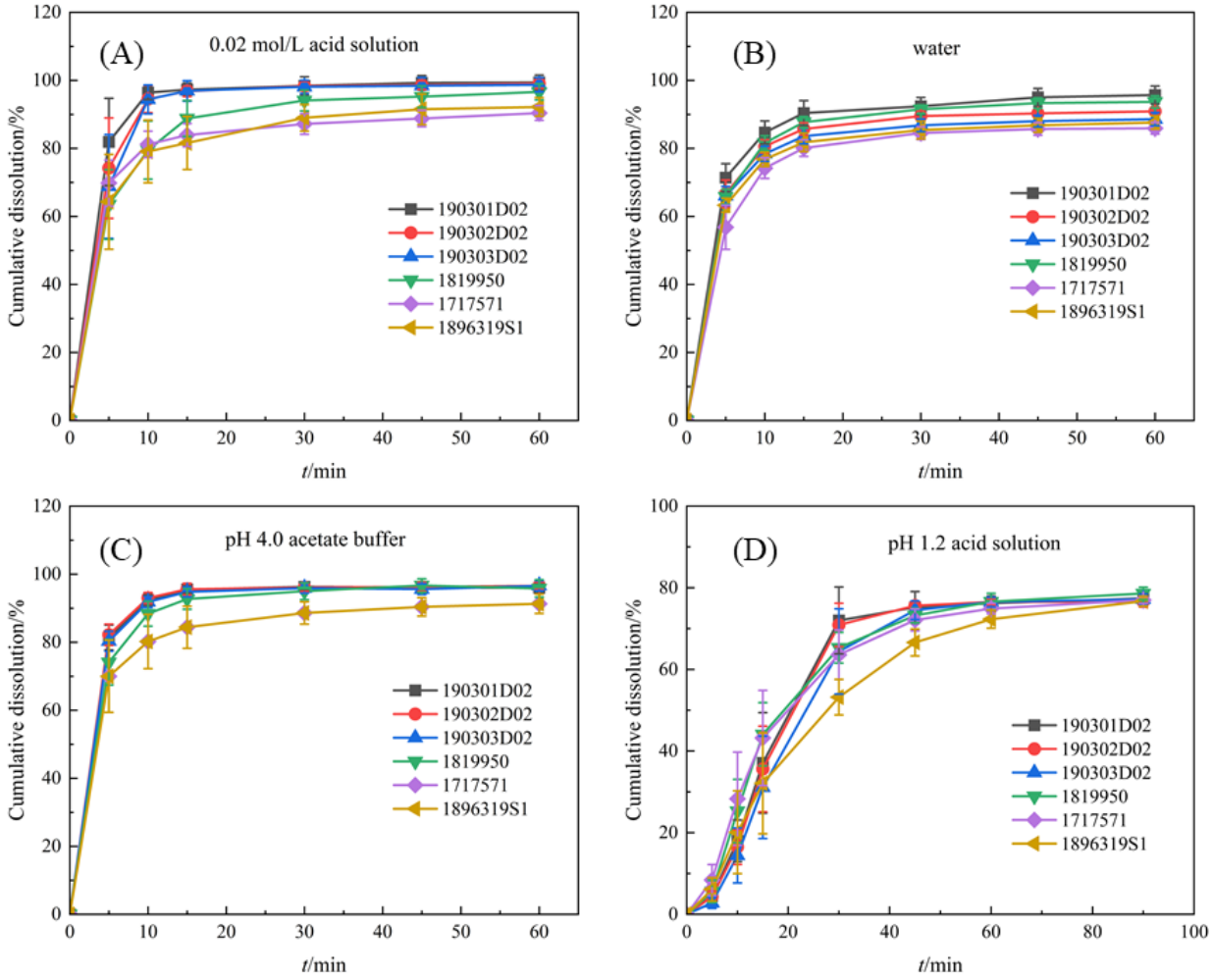

Figure 1. Dissolution curves of toremifene citrate tablets in four dissolution media verified at 0 month.

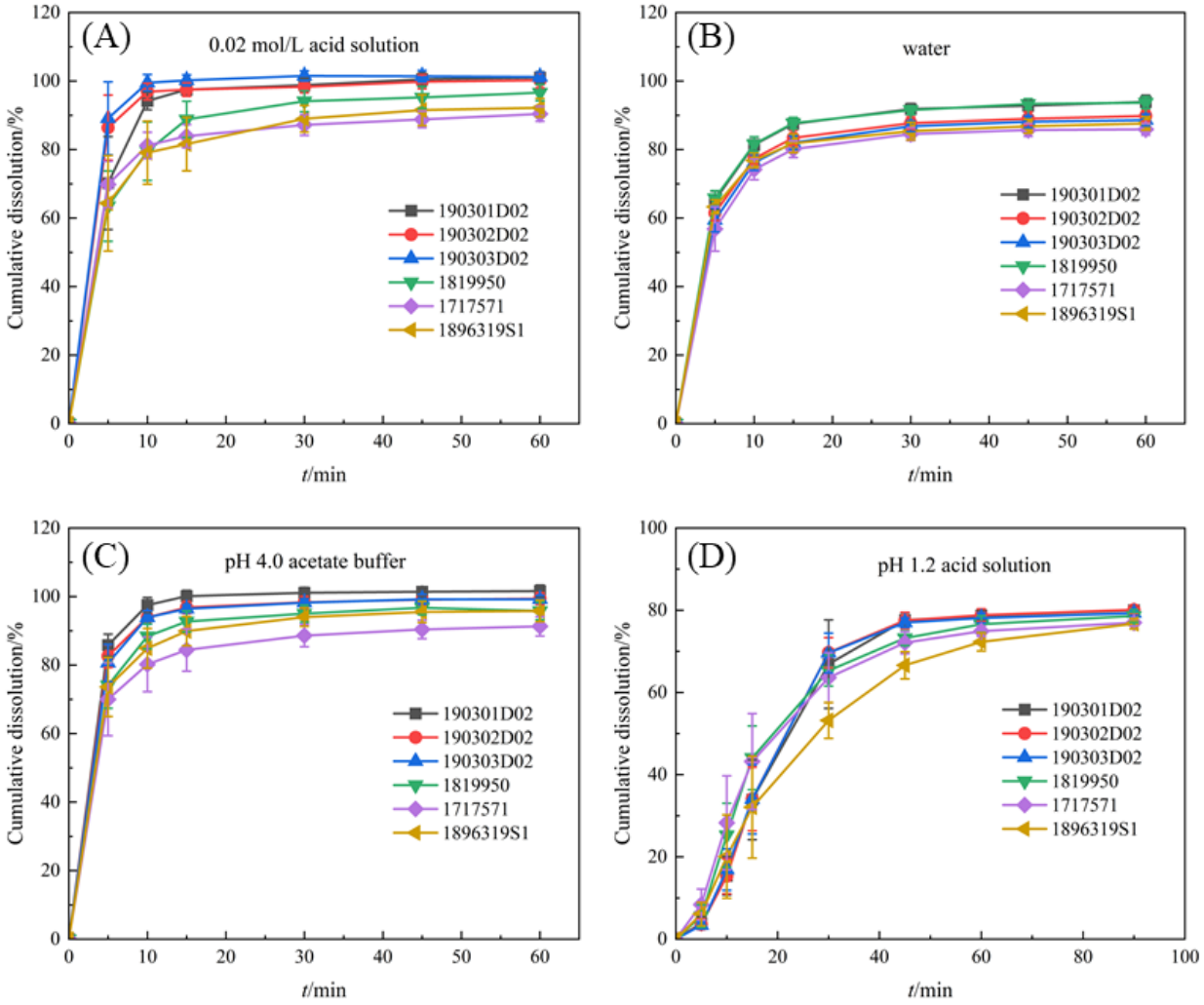

Figure 2. Dissolution curves of toremifene citrate tablets in four dissolution media verified at 6 months for long-term stability.

DISCUSSION

Solubility of API

The solubility of toremifene citrate API in water, pH 1.2 HCl, pH 4.0 acetate buffer, 0.02 mol/L HCL, and pH 6.8 phosphate buffer medium (37 ℃) were investigated (Table S14). The results showed that the solubility of this product is greater than 0.3 mg/mL in both pH 1.2 HCl and pH 4.0 acetate buffer , which is consistent with the solubility published in the Japanese Orange Book, i.e., the solubility of toremifene citrate is pH-dependent.

Regulatory Differences in Dissolution Testing

The dissolution testing requirements for toremifene citrate tablets highlight key differences between FDA and National Medical Products Administration (NMPA) regulations. While the FDA emphasizes in vitro-in vivo correlation (IVIVC) and allows flexibility in method selection (e.g., accepting single-medium testing for BCS-classified drugs), the NMPA mandates stricter multi-

medium dissolution profiling (e.g., pH 1.2, 4.0, 6.8, and water) for consistency evaluation of generic preparations. This study adopted the NMPA approach, which aligns with the *Chinese Pharmacopoeia* and includes robustness validation across diverse pH conditions, which is critical for toremifene's pH-dependent solubility.

Advantages of NMPA's framework:

1. Comprehensive Media Selection: Testing in four media (versus the FDA's typical one or two) ensures better predictability of in vivo performance under varying gastrointestinal conditions, reducing bioavailability variability risks.
2. Rigorous Similarity Criteria: The NMPA's requirement for $f_2 > 50$ in multiple media (versus FDA's focus on BCS-based waivers) guarantees tighter quality control for generics, as demonstrated by the consistent dissolution profiles of test and reference batches in this study.
3. Process Robustness: NMPA's emphasis on method validation (e.g., filter adsorption, stability) minimizes operational variability, enhancing reproducibility, which is a strength reflected in this study's < 5% deviation across instruments and conditions.

These differences underscore the NMPA's conservative yet scientifically robust approach, which may offer greater assurance of therapeutic equivalence for complex drugs like toremifene citrate. Future harmonization efforts could integrate the FDA's IVIVC flexibility with the NMPA's multi-medium rigor to optimize global generic drug standards.

Investigation of the Dissolution Method

Selection of dissolution apparatus

Upon inquiry, only the *Chinese Pharmacopoeia* contains the quality standard of toremifene citrate tablets, while the Japanese Orange Book and the FDA dissolution database contain the dissolution method., and these three sources have slight differences in the medium type and volume, method, and detection wavelengths (Table S15) (*10*–*12*). This study compared the results obtained using a paddle apparatus (50 rpm) and basket apparatus (100 rpm) with 1000 mL of 0.02 mol/L HCl solution as a dissolution medium. As shown in Figure 3A, the dissolution rate at 30 minutes was more than 85% with both methods, and the results after 30 minutes were basically the same. However, cumulative drug release with the basket method at 100 rpm for 5 minutes was greater than 85%, indicating that the initial dissolution rate was too fast. Therefore, the final dissolution medium was 1000 mL of 0.02 mol/L HCl solution, and the method of dissolution was the paddle apparatus at 50 rpm.

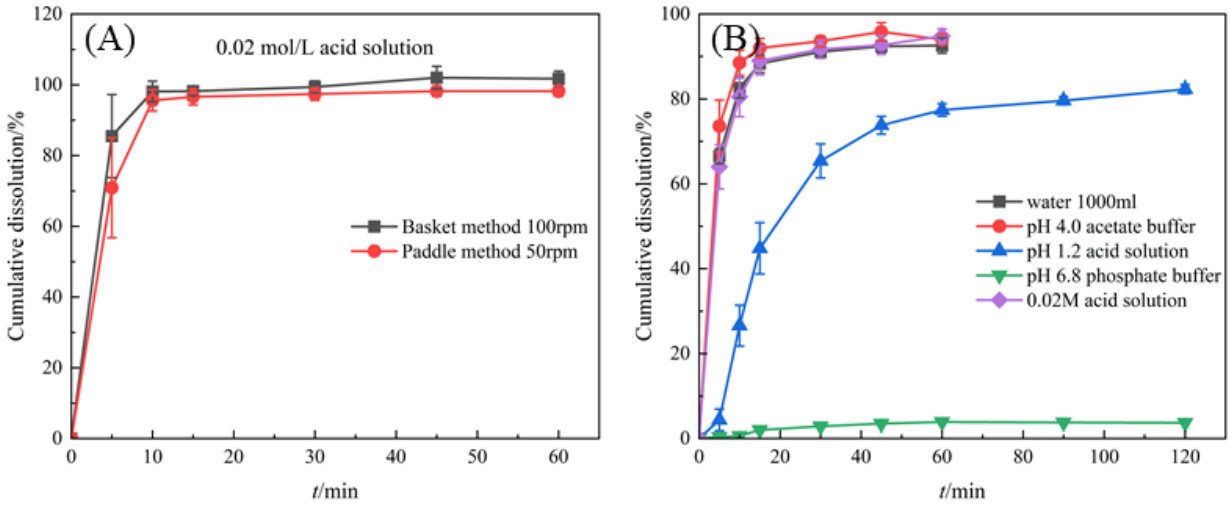

*Figure 3. (**A**) Cumulative drug release in 0.02 mol/L hydrochloric acid solution with different dissolution methods. (**B**) Cumulative drug release of the reference formulation using the paddle method with different dissolution media.*

Selection of diluents

After the test solution of pH1.2 HCl is taken out, if it is left for more than 1 hour below room temperature (25 °C), the solution will precipitate or become turbid, which affects the accuracy of the dissolution curve. According to solubility data in the Japanese Orange Book, toremifene citrate has the highest solubility in pH 4.0 acetate buffer (Table S16). Dissolution results in pH1.2 HCl and pH 4.0 acetate buffer was similar, so the pH 1.2 HCL solution used pH 4.0 acetate buffer as diluent. The other three dissolution media had good stability, so they all used the corresponding medium as a diluent.

Selection of control preparation methods

Because of the low solubility of the product in each medium, the control was dissolved in a small amount of methanol and then diluted with a dissolution medium. The absorbance of the product was measured at 277 nm using a 1-cm cuvette. When the concentration of the control product was 20 μg/mL of toremifene, the absorbance was about 0.5, and the absorbance was in the range of 0.3–0.7. Therefore, the concentration of the control product in pH 4.0 acetate buffer, pH 1.2 HCl, and water was determined to be 20 μg/mL of toremifene. Referring to the concentration specified in the *Chinese Pharmacopoeia* method (8 μg/mL toremifene), the absorbance is about 0.4 (range 0.3–0.7), so the concentration of the control product in 0.02 mol/L HCl is the same, 8 μg/ml.

Determination of medium for comparison of dissolution curves

The dissolution curve for toremifene citrate tablets was determined by paddle method using the same reference preparation in five different media: pH 4.0 acetate buffer (900 mL), pH 1.2 HCl (900 mL), pH 6.8 acetate buffer (1000 mL), 0.02 mol/L HCl (1000 mL), and water (900 mL). The results showed that the sample was almost insoluble in pH 6.8 acetate buffer for 120 minutes,

and the average cumulative dissolution in pH 4.0 acetate buffer, water, and 0.02 mol/L HCl for 30 minutes was more than 80%; therefore, the sampling time was determined to be 30 minutes (Fig. 3B). In pH 1.2 HCl, the dissolution plateau was reached at 60 minutes, and there was no significant increase at 120 minutes. Therefore, the four media selected were pH 4.0 acetate buffer (900 mL), pH 1.2 HCl (900 mL, 0.02 mol/L HCl (1000 mL), and water (900 mL). The dissolution profiles of the reference formulation were compared with those of the test product. The dissolution profiles of the reference formulation in each medium are shown in Fig. 3B.

Data Analysis and Interpretation

This study validated the in vitro dissolution consistency between the test formulations and the reference listed drug (RLD) through multidimensional data. In four dissolution media, the three batches of test formulations and the RLD (BE batch 1819950) showed mean cumulative dissolution rates above 85% at 15 minutes in pH 4.0 acetate buffer and 0.02 mol/L HCl, consistent with the pH-dependent dissolution characteristic of toremifene citrate (Figs. 1 and 2). In water and pH 1.2 HCl media, the f_2 values between test formulations and the RLD were all greater than 50 (Table 1), with values ranging from 55–88 at baseline and 62–98 after 6-months of storage, indicating high consistency in dissolution profiles across batches and no significant impact of long-term storage on dissolution behavior.

Method validation data showed linear correlation coefficients (r) above 0.999 in all media, recovery rates of 97.65–101.39% (RSD < 1.1%), and filter membrane adsorption below 5%, demonstrating excellent specificity, accuracy, and precision (Tables S7–S13). In robustness tests, dissolution degree deviations remained less than ± 5% under parameter variations (agitation speed ± 5 rpm, medium temperature 37 ± 2 °C), and inter-instrument differences in dissolution curves were less than 10%, confirming the method's stability across different laboratory environments.

Notably, non-BE batches of the RLD (1717571, 1896319S1) did not meet the $f_2 > 50$ criterion in pH 4.0 acetate buffer and 0.02 mol/L HCl, but the differences in mean cumulative dissolution at each time point were less than 10%. Combined with $f_2 > 50$ results in water and pH 1.2 media, this suggests consistent dissolution behavior across RLD batches, with differences possibly due to minimal release variations in low-solubility media. Collectively, these data confirm the in vitro dissolution equivalence between test formulations and the RLD, providing a reliable basis for subsequent in vivo bioequivalence studies.

CONCLUSION

Consistency evaluation of generic versus original medicines can effectively improve the quality of generic products, improve the success rate of drug in vivo bioequivalence tests, and reduce the total medical cost to patients. In this study, UV spectrophotometry was used to determine the dissolution rate of toremifene citrate tablets in four media. The method was feasible, and the dissolution profiles were similar for three batches of test and reference products. This research contributes to the consistent evaluation of toremifene citrate tablets, supporting the development of clinically equivalent generic alternatives with predictable therapeutic performance.

DISCLOSURES

The authors received no financial support for this work and have no conflicting interests.

SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be requested by contacting the corresponding author.

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