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Consistency Evaluation of Dissolution of Generic and Original Preparations of Sulindac Tablets

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ABSTRACT

Introduction: Sulindac is a non-steroidal anti-inflammatory drug (NSAID) primarily used to alleviate pain and inflammation associated with various arthritides (e.g., rheumatoid arthritis, osteoarthritis) and soft tissue injuries. To ensure consistent drug release and therapeutic efficacy, a reliable dissolution method must be established for quality control. This research systematically investigates and validates the dissolution method for sulindac tablets. **Methods:** The 0.2-g strength was selected for dissolution method validation, including investigation of specificity, linear range, filter membrane adsorption, accuracy, precision, robustness, stability, and recovery rate. Dissolution profiles for self-made tablets (0.1 g and 0.2 g) and the reference listed drug (RLD) were evaluated in multiple dissolution media (0.1 mol/L hydrochloric acid, pH 4.5 acetate buffer, and pH 6.8/pH 7.2 phosphate buffer). **Results:** The dissolution method validation demonstrated that all indicators met the requirements, including no interference from blanks, a good linear relationship, negligible membrane adsorption, excellent precision and stability, a satisfactory recovery rate, and strong robustness. In phosphate buffer (pH 6.8 and 7.2), the dissolution profiles of the test products and RLDs were similar (f_2 > 50). **Conclusion:** The validated dissolution method is accurate and reliable, effectively facilitating the dissolution testing and quality evaluation of sulindac tablets.

Keywords: Sulindac tablets, original preparation, generic preparation, dissolution curve, consistency evaluation

INTRODUCTION

Sulindac, a nonsteroidal anti-inflammatory drug (NSAID), exerts its therapeutic effects by inhibiting cyclooxygenase enzymes, thereby reducing prostaglandin synthesis (*1*, *2*). It is clinically administered for the management of rheumatoid arthritis, osteoarthritis, and acute pain (*3*). Sulindac can also be used in the treatment of colorectal polyps in familial adenomatous polyposis (*4*, *5*). Sulindac and its derivatives are a new type of anticancer drug (*6*, *7*). Recently, research has found that sulindac can also improve the stiffness and quality of life for patients with breast cancer after taking aromatase inhibitors (*8*). The bioavailability

and therapeutic efficacy of sulindac tablets are profoundly influenced by their dissolution characteristics, as the drug's release rate in the gastrointestinal tract directly affects systemic absorption and clinical outcomes (*9*).

In pharmaceutical development, a validated dissolution method serves as a critical tool for evaluating formulation quality and ensuring batch-to-batch consistency, as drug absorption following oral administration hinges on the drug's release from the product, its dissolution and solubilization under physiological conditions, and gastrointestinal permeability. Given the pivotal role of the first two steps, in vitro dissolution holds significant relevance for predicting in vivo performance, and evaluating dissolution profiles is a key quality measure for solid oral dosage forms like tablets and capsules. Moreover, demonstrating dissolution profile similarity between self-made formulations and reference listed drugs (RLDs) is a fundamental requirement for bioequivalence assessment and regulatory compliance, particularly within the framework of generic drug consistency evaluation (*10*–*12*).

This study focuses on sulindac tablets (0.1-g and 0.2-g, with proportional excipients and identical manufacturing processes) to achieve two objectives: systematically validate the dissolution testing method for specificity, linearity, precision, and robustness; and compare dissolution profiles between self-made batches and RLDs across four media (0.1 mol/L hydrochloric acid [HCl], pH 4.5 acetate buffer, pH 6.8/pH 7.2 phosphate buffers). These efforts aim to establish a reliable analytical method and provide scientific evidence for the quality equivalence of self-made tablets to the reference preparation.

METHODS

Chemicals and Reagents

The test product was self-manufactured sulindac tablets (Fuan Pharmaceutical Group Qingyu Tang Pharmaceutical Co., Ltd):

- 0.1 g dose: batch 20240401 (expiry date: 2024.04.15), 20240402 (expiry date: 2024.04.16), 20240403 (expiry date: 2024.04.17)
- 0.2 g dose: batch 20240101 (expiry date: 2024.01.19), 20240102 (expiry date: 2024.01.22), and 20240103 (expiry date: 2024.01.25)

The RLD was sulindac tablets from Teva Pharmaceuticals:

- 0.2 g dose: batch 0197A231 (expiry date: 2024.07) and 1403F231 (expiry date: 2026.01).

The reference substance was sulindac from United States Pharmacopeia (batch 12J345, purity: 99.7%).

Chemicals and reagents included HCl, sodium acetate, acetic acid, potassium dihydrogen phosphate, and sodium hydroxide; all were of analytical reagent grade and purchased from National Pharmaceutical Group Chemical Reagent Co., Ltd. All solvents and reagents were used without further purification before or during the experiment. Ultrapure water was prepared using an Arium Comfort II purification system from Sartorius Company.

An electronic balance (XP26, XS205DU) and pH meter (Five Easy plusFE28) from Mettler Toledo International Co., Ltd. were used for the experiments.

Investigation of Solubility of API

The solubility of sulindac API was determined in pH 1.0 HCl solution, pH 4.5 acetic acid buffer solution, pH 6.0 phosphate buffer solution, pH 6.8 phosphate buffer solution, and pH 7.2 phosphate buffer solution (37 °C), as shown in Table 1. The results showed that sulindac was almost insoluble in pH 1.0 HCl and pH 4.5 acetic acid buffer solution. As the pH increased, the solubility increased, indicating that the compound exhibits significant pH dependence.

Table 1. Solubility Results for Sulindac

Medium	Solubility Determined by this Method (mg/mL)
0.1 M Hydrochloric Acid Solution	0.006
pH 4.5 Acetate Buffer	0.027
pH 6.0 Phosphate Buffer	0.411
pH 6.8 Phosphate Buffer	1.993
pH 7.2 Phosphate Buffer	2.598

Selection of Dissolution Method

The *Chinese Pharmacopoeia*, *United States Pharmacopeia*, and *British Pharmacopoeia* include quality standards for sulindac tablets (Table 2) (*13*–*15*). The dissolution methods, dissolution media, and volume flow rates specified in all three Pharmacopeias are consistent, and the detection methods all use UV detection. The *British Pharmacopoeia* adopts the specific absorption coefficient calculation method for the assay of sulindac tablets, whereas the *Chinese Pharmacopoeia* and *United States Pharmacopeia* employ the external standard method for quantitative determination. Thus, the dissolution methods in the pharmacopoeias of various countries are fundamentally equivalent. Therefore, the dissolution method for this product was directly selected from the *Chinese Pharmacopoeia*.

Table 2. Comparison of Three Dissolution Methods for Sulindac Tablets

	ChP (2020)	*BP*	*USP*
Dissolution Method	Paddle method	Paddle method	Paddle method
Rotation Speed	50 rpm	50 rpm	50 rpm
Medium	pH 7.2 phosphate buffer	pH 7.2 phosphate buffer	pH 7.2 phosphate buffer
Volume	900 mL	900 mL	900 mL
Detection Method	UV, 326 nm, external standard method	UV, 327 nm, absorption coefficient method	UV, 326 nm, external standard method
Sampling Time	45 min	45 min	45 min
Standard	80% of the labeled amount	80% of the labeled amount	80% of the labeled amount

ChP: Chinese Pharmacopeia; BP: British Pharmacopeia; USP: United States Pharmacopeia; UV: ultraviolet.

Dissolution Test

The dissolution test was conducted using the paddle method (Agilent, 708-805DS) at 50 rpm. The dissolution rate was determined by ultraviolet (UV)-visible spectrophotometry (UV-2600, SHIMADZU) at a detection wavelength of 326 nm.

Solution Preparation

The dissolution media were 900 mL each of 0.1 mol/L HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and pH 7.2 phosphate buffer, prepared in accordance with the *Chinese Pharmacopoeia* (*16*).

Dissolution Method Validation

The method validation included verification of the adsorption of filter membrane, specificity, linearity, range, accuracy, precision, robustness, and solution stability. The studies were conducted in accordance with the principles set out by the International Council on Harmonization (ICH) (*17*).

Specificity

For specificity, the blank solvents and blank excipients in the UV spectrum should not interfere with the determination of the sample. The UV absorption spectra of the test solution and the reference solution should be consistent; at a wavelength of 326 nm, the absorbance of the blank solvent and blank excipient should be less than 2% of the absorbance of the reference solution.

Linearity Range

The linear correlation coefficient should be greater than 0.999, with a linear regression of 5–160% of the labeled amount in each medium.

Adsorption of Filter Membrane

The test solution was filtered through each dissolution medium using primary and secondary filter heads; 2, 5, and 10 mL of the initial filtrate were discarded, respectively. Secondary filtration was performed using filter heads from Chongqing Haopu and Shanghai Anpul. The absorbance change should be less than 5.0%.

Accuracy

The accuracy of the method was investigated in each dissolution medium (n = 9). At 80–100% dissolution in each medium, the recovered drug should be 98–101% of the label claim; at 50% dissolution, the recovered drug should be 95–102% of the label. The RSD of nine samples should be less than 5.0%.

Precision

The precision was examined by measuring absorbance of the reference solution six times. Intermediate precision tests were performed in the same laboratory by different operators on different days using different instruments. The relative SD (RSD) of the measurements for each medium should be less than 2%. For the 12 tablets in the precision study, the RSD should be less than 5%.

Robustness

Robustness was evaluated for the same batch of samples using different brands of dissolution apparatus (Agilent vs. SOTAX), different rotational speeds (50 ± 5 rpm), different dissolution medium temperatures (37 ± 2 °C), different rinsing volumes (± 2 mL), and without degassing of the dissolution medium. The average dissolution rate difference compared with normal conditions should be less than ± 5%.

Sample and Standard Solution Stability

For stability, the absorbance of sulindac in each medium and the reference solution were compared at 0 h and after 24 hours of storage at room temperature. The absorbance change should be less than 5.0%.

Dissolution Evaluation and Analysis

For the dissolution evaluation, 12 tablets each from three batches of self-produced and two batches of reference preparations were tested in 900 mL of each dissolution medium (0.1 mol/L HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, and pH 7.2 phosphate buffer). Samples were taken at 5, 10, 15, 30, 45, and 60 min and filtered for UV analysis. The cumulative dissolution for each product was calculated.

The similarity of dissolution profiles between self-produced and reference preparations was evaluated using the similarity factor (f_2) method, with a threshold of $f_2 \geq 50$ indicating acceptable similarity. This method is widely recognized in pharmaceutical regulatory guidelines for assessing in vitro dissolution profile consistency of generic drugs.

RESULTS

Adsorption of Filter Membrane

For the test solutions of the generic drug product and the RLD, absorbance changes were all less than 5.0% after filtration through primary and secondary filter heads, with discarding the initial filtrate volumes of 2, 5, and 10 mL, in 0.1 mol/L HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and pH 7.2 phosphate buffer. This indicates that neither the primary nor secondary filter heads exhibit significant adsorption of the drug in the generic product or reference product.

Specificity

Both the test and control solutions exhibited maximum absorption at 326 nm, with their absorption spectra showing good consistency. The absorbance of the blank excipient was less than 2% of the absorbance of the test solution, indicating good specificity within the specified wavelength range.

Linearity

Figure 1 shows excellent linearity ($r \geq 0.9999$) across multiple media: 0.50–16.30 µg/mL in 0.1 M HCl, 0.51–30.83 µg/mL in pH 4.5 acetate buffer, 0.50–16.30 µg/mL in pH 6.8 phosphate buffer ($r = 1.000$), and 0.50–16.30 µg/mL in pH 7.2 phosphate buffer. These results confirm robust linear relationships in all media, which met the requirements.

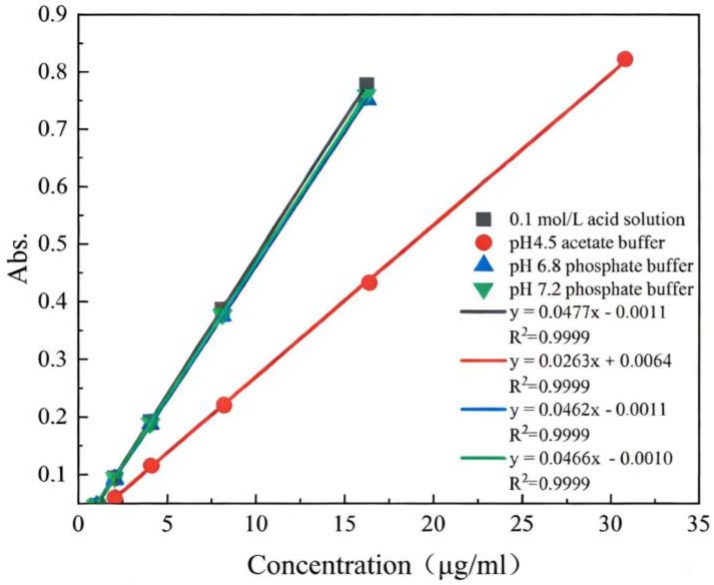

Figure 1. Linear results of the dissolution test.

Accuracy

The recovery rates in different media were within the range of 98.67–100.01%, and the RSDs were all less than 1.87%. That is, the dissolution method had high accuracy in each medium.

Precision

The test substance was almost insoluble in both 0.1 mol/L HCl and pH 4.5 acetate buffer; thus, no RSD comparison was conducted. The RSDs of the 0.2 g specification in pH 6.8 and pH 7.2 phosphate buffer were 0.43% and 0.84%, respectively. The RSDs of the 0.1 g specification in pH 6.8 and pH 7.2 phosphate buffer were 0.61% and 0.85% respectively. The RSDs of the 12 samples in pH 6.8 phosphate buffer solution and pH7.2 phosphate buffer solution were all less than 5%, which met the standard. Thus, this method had good precision.

Robustness

The dissolution method showed good robustness under varied conditions: agitation speed ± 5 rpm, medium temperature 37 ± 2 °C, and rinse volumes 5–10 mL (i.e., average dissolution deviation ± 5% vs. standard conditions). Additionally, post-15-minute dissolution profiles across instruments had ≤ 5% variability, confirming inter-instrument consistency. Wavelength variations (326 ± 2 nm) caused < 5% dissolution deviation, validating wavelength robustness. Collectively, these results demonstrate that the dissolution method has sufficient robustness and reliability.

Solution Stability

The reference standard solutions were found to remain stable for 24 hours at room temperature across all tested media, with absorbance variations of less than 5.0% compared to the initial (0 h) measurements. Similarly, the sample solutions in all media exhibited stability for 24 hours at room temperature, as the absorbance changes were within 5.0% of the initial values.

Dissolution Profiles

As shown in Figures 2 and 3, dissolution studies conducted in 0.1 M HCl revealed minimal drug release across all formulations. Specifically, the 0.2-g test batches (three lots) and the reference bioequivalence (BE) batch (0197A231) exhibited cumulative dissolution of less than 10% at all time points, with no appreciable change beyond 30 minutes. A comparable dissolution pattern was observed for the 0.1-g test batches relative to the corresponding reference formulation. In pH 4.5 acetate buffer, cumulative dissolution remained below 20% for all 0.2-g and 0.1-g test formulations, with variation not exceeding 5% after 30 minutes when compared to the BE reference.

In pH 6.8 phosphate buffer, the 0.2-g test batches demonstrated dissolution profile similarity to both reference batches, with similarity factors (f_2) exceeding 50. An f_2 value greater than 50 between the two batches confirms their internal consistency. For the 0.1-g test batches, $f2$ values were greater than 50 when compared with the 0.2-g BE batch, indicating dissolution equivalence across strengths.

In pH 7.2 phosphate buffer, rapid dissolution was observed, with both 0.2-g test and reference formulations achieving ≥ 85% drug release within 15 minutes, thereby satisfying the criterion for profile similarity without necessitating f_2 analysis. The 0.1-g test formulations demonstrated equivalent kinetics, also reaching ≥ 85% release at 15 minutes, confirming dissolution profile similarity across dose strengths.

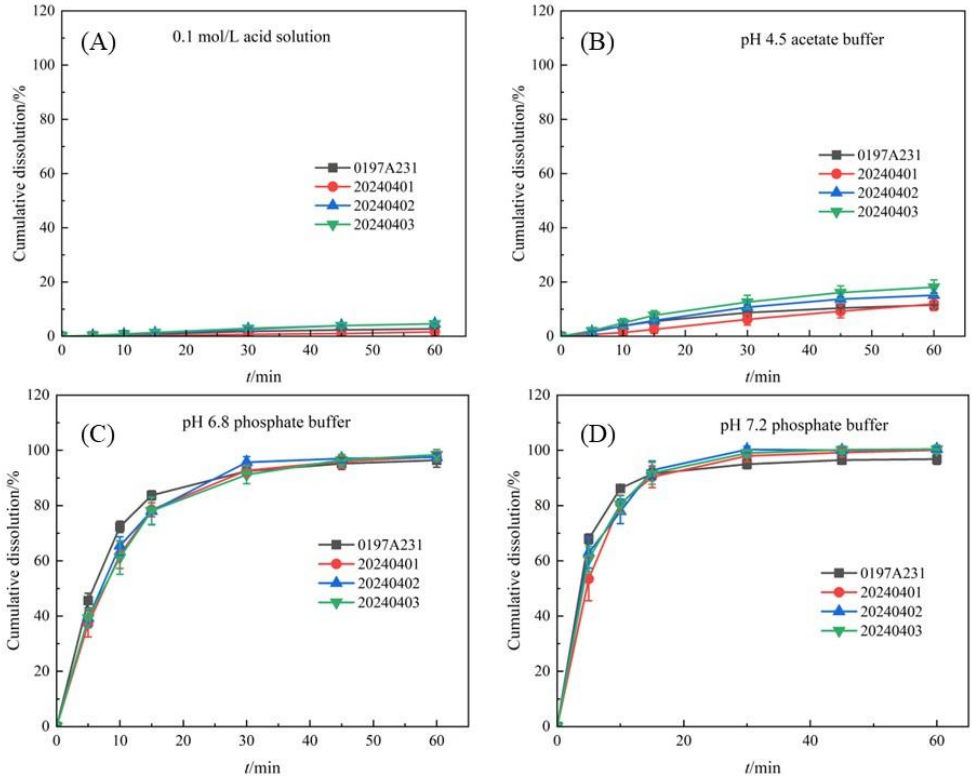

Figure 2. Dissolution curves of 0.1-g sulindac tablets (reference product: 0197A231; test products: 20240401, 20240402, 20240402) in four dissolution media.

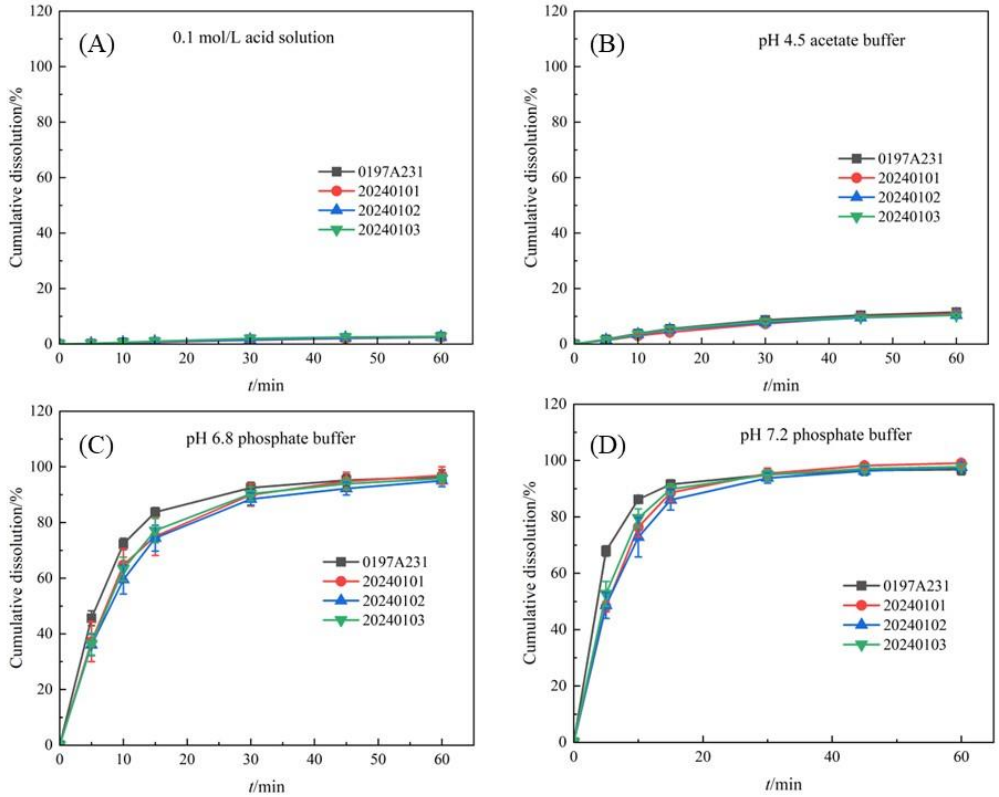

Figure 3. Dissolution curves of 0.2-g sulindac tablets (reference product: 0197A231; test products: 20240101, 20240102, 20240102) in four dissolution media.

DISCUSSION

This study systematically established and validated a dissolution testing method for sulindac tablets (0.1-g and 0.2-g) and compared their dissolution profiles with the RLD across multiple physiological media. The findings not only confirm the reliability of the developed method but also provide critical insights into the formulation quality and in vitro performance of the self-manufactured sulindac tablets, which holds practical significance for generic drug development and consistency evaluation.

Method validation — a cornerstone of analytical method development for ensuring accuracy, precision, and robustness in routine quality control — met all requirements of ICH guidelines and pharmacopoeial standards, confirming suitability for sulindac tablet dissolution testing.

Specificity evaluation showed no interference from blank solvents or excipients at 326 nm (blank absorbance < 2% of the reference solution); this is critical for avoiding false-positive or inaccurate sulindac quantification. The linearity results ($r \geq 0.9999$ across all media) covered a concentration range of 5–160% of the labeled amount, ensuring the method's ability to accurately quantify drug release even in extreme scenarios (e.g., incomplete dissolution or slight over-release). Notably, filter membrane adsorption — a common source of error in dissolution testing — was negligible (< 2.0% absorbance change) across all tested media and filter types. This eliminates concerns about drug loss during sample filtration and guarantees the accuracy of dissolution data. The precision (RSD < 5% for 12 replicate samples) and intermediate precision (RSD < 2% across operators, instruments, and days) further confirm

the method's reproducibility. Variations in rotation speed, medium temperature, rinse volume, and instrument brand yielded dissolution deviations less than ± 5%, indicating the method's robustness under routine laboratory fluctuations. Additionally, solution stability (absorbance change < 5% over 24 h at room temperature) allows flexibility in sample handling, reducing time pressure for immediate analysis. Collectively, these validation results demonstrate that the developed method is accurate, reliable, and robust for routine dissolution testing of sulindac tablets.

The solubility and dissolution profiles of sulindac tablets exhibited significant pH dependence, which aligns with the physicochemical properties of sulindac (weak acid with pH-dependent solubility). In acidic media (0.1 mol/L HCl, pH 1.0; pH 4.5 acetate buffer), both the self-manufactured tablets and RLDs showed minimal drug release (cumulative dissolution < 10% in pH 1.0 and < 20% in pH 4.5). This is attributed to the poor solubility of sulindac in acidic environments (as confirmed by the solubility study), which is consistent with previous reports on weak acid NSAIDs. In contrast, in neutral to slightly alkaline media (pH 6.8/pH 7.2 phosphate buffers), dissolution was significantly enhanced: all formulations achieved ≥ 85% release within 15 minutes in pH 7.2 buffer, and the 0.2-g self-manufactured batches showed dissolution profile similarity to RLDs ($f_2 > 50$) in pH 6.8 buffer.

This pH-dependent dissolution behavior has important implications for in vivo performance. The human gastrointestinal tract transitions from acidic (stomach, pH 1.0–3.0) to neutral (small intestine, pH 6.0–7.5), meaning sulindac tablets are likely to remain undissolved in the stomach and undergo rapid dissolution in the small intestine, where absorption primarily occurs. The consistency in pH-dependent dissolution between self-manufactured tablets and RLDs suggests similar in vivo absorption kinetics, which is a key prerequisite for bioequivalence. Furthermore, the 0.1-g test tablets showed dissolution equivalence to the 0.2-g RLD ($f_2 > 50$ in pH 6.8 buffer and ≥ 85% release in 15 minutes in pH 7.2 buffer), confirming that the proportional excipient composition and identical manufacturing process across specifications do not affect dissolution performance. This is a critical consideration for ensuring dose-proportional bioavailability.

A potential limitation of this study is the focus on in vitro dissolution behavior; although this is a well-established surrogate for in vivo performance, the findings cannot fully predict bioavailability. Future studies could complement these findings with in vivo bioequivalence trials to confirm the clinical relevance of the observed dissolution similarity. Additionally, while the current method is based on the *Chinese Pharmacopoeia*, comparative studies with dissolution methods using different media volumes or rotation speeds (e.g., 500 mL media for small-volume dissolution apparatus) could further expand the method's applicability.

CONCLUSION

The validated dissolution method for sulindac tablets is accurate, robust, and suitable for routine quality control. The pH-dependent dissolution behavior of self-manufactured tablets is consistent with that of RLDs, and dissolution profile similarity across specifications confirms formulation consistency. These results provide strong scientific evidence for the quality

equivalence of self-manufactured sulindac tablets to the reference preparation, supporting their application in generic drug consistency evaluation and clinical practice.

DISCLOSURES

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SUPPLEMENTAL MATERIAL

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

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