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Method Validation of HPLC for Dissolution Profile Characterization in Various Media and Tofacitinib Citrate Tablets Consistency Evaluation

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ABSTRACT

Introduction: This study aimed to establish a dissolution method for tofacitinib citrate tablets to evaluate the consistency of in vitro dissolution with the reference listed drug (RLD) according to the *Chinese Pharmacopoeia*. **Methods**: Dissolution tests were conducted using a basket apparatus at 100 rpm with 900 mL of 0.1 mol/L hydrochloric acid solution, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and water as dissolution media. The experiments were performed on two fully automated dissolution systems, Agilent and Sotax. Dissolution was analyzed using high-performance liquid chromatography (HPLC), and the dissolution profiles were compared for consistency. **Results**: The results of the method validation met the requirements for dissolution testing. The method exhibited strong specificity, good linearity, no membrane adsorption, excellent precision, high accuracy, good solution stability, and robustness. Cumulative dissolution of both the test and RLD tablets exceeded 85% within 15 minutes in all four dissolution media, and their dissolution profiles were consistent. **Conclusion**: This study developed and validated a method to determine the dissolution of tofacitinib citrate tablets, which serves as a suitable approach for in vitro consistency evaluation.

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

INTRODUCTION

Tofacitinib citrate is a selective Janus kinase (JAK) inhibitor approved for the treatment of rheumatoid arthritis (RA), particularly in patients who have had an inadequate response to conventional disease-modifying antirheumatic drugs (cDMARDs) (*1*). By inhibiting the JAK-STAT signaling pathway, tofacitinib citrate blocks the signal transduction of multiple inflammatory cytokines (*2*). For oral solid dosage forms, the drug dissolution profile is a critical factor influencing absorption and bioavailability. Therefore, the consistency of dissolution profiles is essential for evaluating the quality and therapeutic equivalence between generic drugs and the reference listed drug (RLD) (*3*).

Currently, only the United States Food and Drug Administration (FDA) has published the dissolution conditions for tofacitinib citrate but has not provided an analytical method for dissolution testing, which imposes certain limitations on the in vivo and in vitro evaluation of this drug as well as subsequent clinical studies (*4*).

Previous investigations of tofacitinib citrate have primarily focused on formulation development and in vitro-in vivo correlation (IVIVC). Kushner et al. established a level A IVIVC for tofacitinib modified-release tablets utilizing osmotic delivery technology, demonstrating the critical role of in vitro dissolution characterization in predicting in vivo performance (*5*). More recently, Wang et al. reported a new polymorph of tofacitinib citrate and conducted in vitro equivalence studies of its sustained-release tablets, further highlighting the importance of dissolution profile comparison for formulation development (*6*). While Kaleswararao et al. developed a reverse phase high-performance liquid chromatography (RP-HPLC) method for cleaning residue determination of tofacitinib citrate, no validated HPLC method has been specifically reported for the quantitative analysis and comparative assessment of tofacitinib citrate dissolution profiles across multiple media (*7*).

Based on the dissolution conditions published by the FDA, this study aimed to establish a method to analyze and compare the in vitro dissolution profile of tofacitinib citrate tablets in multiple media using HPLC.

METHODS

Chemicals and Reagents

Tofacitinib citrate tablets (5 mg) from Fuan Pharmaceutical Group, Ningbo Team Pharmaceutical, Co., Ltd. (Ningbo, China) (batches: YJ200101, YJ200102, YJ200103) were used as the test product, and the RLD was Xeljanz (batch: X99288) from Pf Prism CV (Rotterdam, The Netherlands).

Tofacitinib Reference Standard was obtained from Fuan Pharmaceutical Group Ningbo Team Pharmaceutical Co., Ltd. (batch: Y031-190902WS, purity: 99.7%). Hydrochloric acid (HCl), sodium acetate, acetic acid, potassium dihydrogen phosphate, and sodium hydroxide (analytical reagent grade) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China), and acetonitrile (HPLC grade) was purchased from TEDIA (Fairfield, OH, USA). Water was purified water prepared in-house.

Solubility Analysis

This equilibrium solubility of tofacitinib citrate API was investigated at room temperature in a series of dissolution media with different pH values (Mettler Toledo, Five Easy plus FE28 pH meter), aiming to evaluate whether its solubility meets the requirements for subsequent dissolution testing.

Preparation of Dissolution Media

Considering the solubility of the API, the selected dissolution media were 0.1 mol/L HCl, acetate buffer pH 4.5, and phosphate buffer pH 6.8. All media were prepared according to the methods specified in the *Chinese Pharmacopoeia* (*8*).

Preparation of Reference Standard Solution

To obtain the reference standard stock solution, approximately 30 mg (0.03082 g) of tofacitinib citrate reference standard was accurately weighed (XS205DU electronic balance, Mettler Toledo) and transferred to a 100-mL volumetric flask, then dissolved and diluted to volume with diluent, and mixed well. To obtain the working reference standard solution, 3 mL of the stock solution was precisely pipetted into a 100-mL volumetric flask, then diluted to volume with the dissolution medium, and mixed well. This was prepared separately for each medium.

Preparation of Test Sample Solution

For the dissolution test, one tablet was placed into 900 mL of dissolution medium maintained at 37 ± 0.5 °C. The basket method was used at a rotation speed of 100 rpm. At the 15-minute time point, a sample of the solution was withdrawn. Approximately 5 mL of the withdrawn solution was filtered through a 0.45 μm PES membrane (for aqueous media) or a 0.45 μm PTFE membrane (for the water medium). The filtrate was the test sample solution. This was prepared separately for each medium.

High-Performance Liquid Chromatography (HPLC) Method Development

This study independently developed a HPLC method for dissolution analysis using the 1260 HPLC system from Agilent (Santa Clara, CA, USA) with a column (150 × 4.6 mm, 5 μm) packed with octadecylsilane-bonded silica maintained at 30 °C. The mobile phase consisted of 0.02 mol/L dipotassium hydrogen phosphate aqueous solution (adjusted to pH 4.0 with phosphoric acid) and acetonitrile in a ratio of 70:30. The detection wavelength was set at 290 nm, the flow rate was 1.0 mL/min, the injection volume was 10 μL, and an isocratic elution mode was employed. The retention time for tofacitinib was approximately 3 min.

During the method optimization phase, a column length of 250 × 4.6 mm (5 μm) was initially investigated, and the retention time for tofacitinib reached 50 min. Subsequently, the column length was reduced to 150 × 4.6 mm, which decreased the retention time to 3 min, thereby significantly improving detection efficiency.

Three different diluents were evaluated. Diluent 1 consisted of approximately 70% of the total volume of 0.1 mol/L HCl, then diluted with acetonitrile and water (30:70). Diluent 2 was acetonitrile and 0.1 mol/L HCl (30:70). Diluent 3 was acetonitrile and 0.1 mol/L HCl (10:90). The amount of drug content extracted using was 98% for all three diluents, so diluent 2 was selected for further use.

The composition of the mobile phase was also studied. When 0.02 mol/L dipotassium hydrogen phosphate solution (pH 4.0) and acetonitrile in a ratio of 80:20 were used as the mobile phase, the retention time for tofacitinib was found to be 7 min. Consequently, the original mobile phase ratio was maintained.

Method Validation

The dissolution method validation evaluated filter membrane adsorption, specificity, linearity, accuracy, precision, robustness, and solution stability according to the *Chinese Pharmacopoeia* 2020 Edition, Part IV, General Rule 0931, Method 2 (*8*).

Adsorption of Filter Membrane

The adsorption of the filter membrane was studied under various dissolution conditions: 5 minutes at 100 rpm, 15 minutes at 200 rpm, and single versus two-stage filtration.

For each study, one tablet of each product was placed in 900 mL of dissolution medium. After 5 minutes at 100 rpm, or 15 minutes at 200 rpm, samples (1, 3, 5, 8, and 10 mL) were withdrawn and filtered using polyethersulfone (PES) or polytetrafluoroethylene (PTFE) (0.45 µm) filters. The process was repeated using the primary filter of the dissolution apparatus, followed by filtering a 5-mL sample of the subsequent filtrate using a PES or PTFE filter.

Specificity

Specificity was evaluated by HPLC. It was required that the blank solvent did not interfere with the main component, the theoretical plate number of the main peak was greater than 2000, the tailing factor was less than 1.5, and the resolution from any impurity peak was greater than 1.5.

Linearity

To assess linearity, 0.6, 1.2, 1.8, 2.4, 3.0 mL, and 3.6 mL of reference standard solution was precisely pipetted into separate 100-mL volumetric flasks. Each was diluted to volume with the respective dissolution medium and mixed well. This was prepared separately for each medium. The linear correlation coefficient of each medium was required to be greater than 0.999.

Accuracy

Three portions each of approximately 15, 24, and 30 mg of tofacitinib citrate reference standard were accurately weighed. Each portion was transferred to a separate 100-mL volumetric flask. An appropriate amount of the blank excipients of the product was added to each of the aforementioned flasks. The mixtures were dissolved and diluted to volume with diluent and mixed well. Then 3 mL of each solution was filtered through an organic membrane filter, and the subsequent filtrate was precisely pipetted into separate 100-mL volumetric flasks. Each was diluted to volume with the respective dissolution medium and mixed well.

Recovery rates for the 50%, 80%, and 100% spiking levels in each medium are required to be between 95% and 102%, and the relative standard deviation (RSD) must be less than 5.0%.

Precision

Six consecutive test sample solutions were analyzed to evaluate the repeatability of the method. To study intermediate precision, the same procedure was repeated by different personnel, on different days, and using different analytical instruments. The RSD of the results must be less than 2.0%.

Robustness

Tests were conducted using normal chromatographic conditions with the variation of the following parameters: medium rotation speed (± 5 rpm), dissolution medium temperature (37 ± 2 °C), non-degassed dissolution medium, different rinse volumes (5 ± 1 mL), and dissolution

apparatuses from two different manufacturers.

For the same batch of samples, when comparing dissolution test results obtained under varying conditions to those under normal conditions, the mean dissolution difference must be less than ± 5%. When comparing dissolution apparatuses from different manufacturers, the difference in the mean cumulative dissolution at time points after 15 minutes must be less than ± 10%.

Solution Stability

To evaluate the stability of tofacitinib citrate in each medium, 3 mL of filtrate resulting from the adsorption studies (200 rpm for 15 mins; single-stage filtration) was collected. These solutions were placed at room temperature, unprotected from light, for specified time intervals (e.g., 0, 2, 4, 8, 12, 24 hours). After each interval, the solution was obtained as the stability test sample. The variation in peak area for each medium compared to the 0-hour sample must be less than 2.0%.

Dissolution Test and Analysis

In accordance with the established dissolution test method, one of each tablet was placed into 900 mL each of medium (0.1 mol/L HCl, pH 4.5 acetate buffer solution, pH 6.8 phosphate buffer solution, or water) maintained at 37 ± 0.5 °C (*3*). Two fully automatic dissolution testers were used (Agilent 708-805DS or SOTAX) (basket apparatus) at 100 rpm. Samples (1.5 mL) were withdrawn at 5, 10, 15, and 30 minutes, and analyzed by HPLC for the dissolution profile comparison. The similarity factor (f_2) was used to evaluate the similarity of dissolution profiles.

RESULTS

Solubility

The solubility (calculated as tofacitinib, mg/mL) was highest in 0.1 mol/L HCl, reaching approximately 13.18 mg/mL at 24 hours. In buffer media pH 2.2–6.0, solubility ranged from 0.09–2.74 mg/mL, showing a general decreasing trend as the pH increased. Solubility was lowest in pH 6.8 phosphate buffer, measuring only 0.27 mg/mL at 24 hours and decreasing further over time. In water, the solubility was approximately 1.24 mg/mL at 24 hours.

These results indicate that the solubility of tofacitinib citrate is significantly pH-dependent, being higher in acidic environments and markedly lower in near-neutral conditions. In all tested media, the equilibrium solubility of the API was far greater than the required sample concentration for dissolution testing (approximately 0.0056 mg/mL). Therefore, the API is soluble in the dissolution media covering pH 1.0–6.8 and in water, and does not pose a limitation for detection of the formulation's dissolution behavior, thereby meeting the requirements for dissolution method development (*7*).

Method Validation

Adsorption of Filter Membrane

No significant adsorption difference was observed between the two membranes in 0.1 mol/L HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer media. However, in the aqueous

medium, the PTFE membrane demonstrated less adsorption compared to the PES membrane. For both single- and two-stage filtration, the change in peak area was less than 2.0% after discarding 5–10 mL of the initial filtrate. Consequently, the PTFE membrane was selected for the aqueous medium, and the PES membrane was used for all other media, with a 5-mL rinse volume employed prior to sample collection. These results are available as supplemental material (Tables S1–S4).

Specificity

The specificity test demonstrated that neither blank solvents nor blank excipients interfered with the analysis of the test sample across all media. The chromatographic performance was satisfactory, with the main peak exhibiting over 2000 theoretical plates, a tailing factor of less than 1.5, and good resolution from adjacent impurity peaks. These findings confirm the strong specificity of the method.

Linearity

As shown in Figure 1, in all media, within the concentration range of tofacitinib citrate, from 1.14008–6.84046 µg/mL (equivalent to 21–123% of the test sample concentration), the peak area showed a good linear relationship with the concentration, and the correlation coefficients (*r*) were all greater than 0.999.

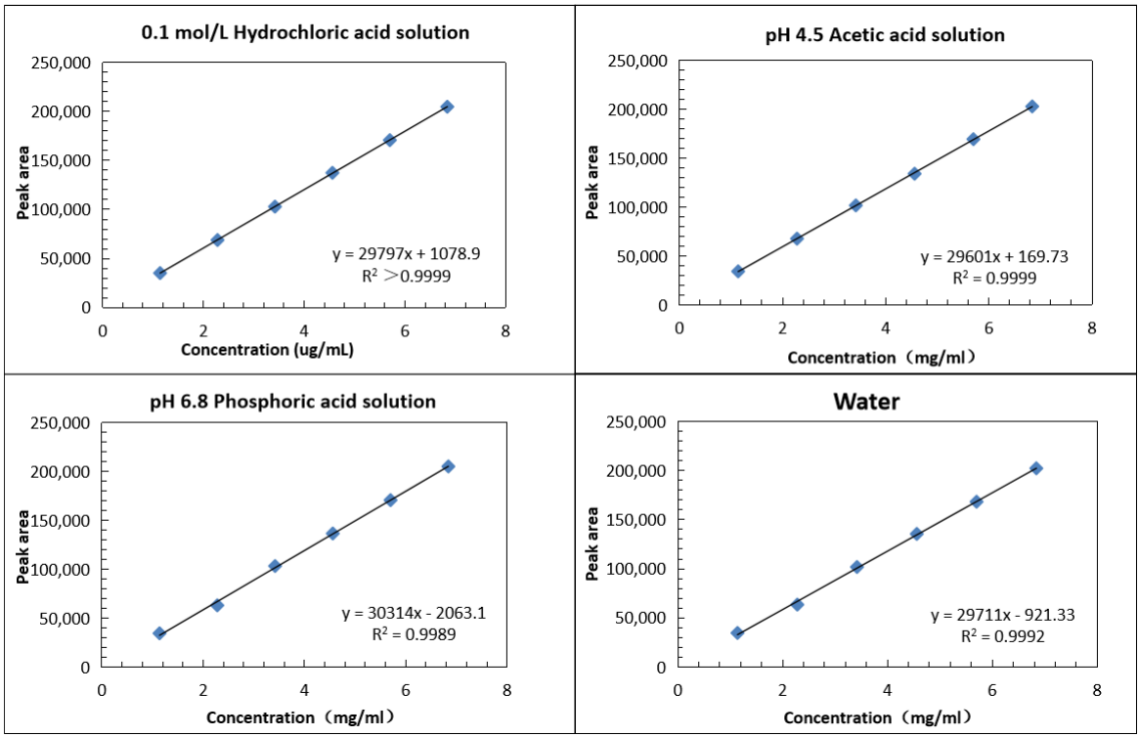

Figure 1. Linear plots of four dissolution media.

Accuracy and Precision

The recoveries in all four dissolution media ranged from 95% to 102%, with RSD values below 5.0% for all nine preparations, indicating that the method has good accuracy for determination of tofacitinib citrate dissolution.

As shown in Tables 1 and 2, the method demonstrated good precision for detecting the dissolution of this product, with all RSDs in each medium being less than 2.0%, and all RSDs of precision samples were less than 5%.

Table 1. Method Precision Evaluation

Replicate	Final Dissolution (%)			
	0.1 mol/L HCl	pH 4.5 acetate buffer	pH 6.8 phosphate buffer	Water
Repeatability assessment				
1	100.2	98.1	101.1	94.1
2	100.1	98.2	100.2	94.2
3	100.3	98.5	100.3	94.4
4	100.4	98.6	100.9	94.5
5	100.0	99.0	100.5	94.1
6	100.1	98.1	101.0	94.2
Mean	100.2	98.4	107	94.3
RSD	0.15	0.38	0.41	0.18
Intermediate precision assessment				
1	102.2	100.1	99.5	99.2
2	103.1	100.1	100.2	98.4
3	101.2	100.5	101.1	98.5
4	102.7	99.8	100.8	96.6
5	102.3	98.5	97.5	97.2
6	102.5	99.7	100.1	97.8
Mean	102.3	99.8	99.9	98.0
RSD	0.56	0.67	1.2	0.91

HCl: hydrochloric acid; RSD: relative standard deviation.

Table 2. Dissolution Results Obtained by Different Operators

Medium	Op	Final Dissolution (%)						Mean (%)	RSD (%)
		1	2	3	4	5	6		
0.1 mol/L HCl	A	100.2	100.1	100.3	100.4	100.0	100.1	101.3	1.07
	B	102.2	103.1	101.2	102.7	102.3	102.5		
pH 4.5 acetate buffer	A	98.1	98.2	98.5	98.6	99.0	98.1	99.2	0.84
	B	100.1	100.1	100.5	99.8	99.5	99.7		
pH 6.8 phosphate buffer	A	101.1	100.2	100.3	100.9	100.5	101.0	100.3	0.99
	B	99.5	100.2	101.1	100.8	97.5	100.1		
Water	A	94.1	94.2	94.4	94.5	94.1	94.2	96.1	2.12
	B	99.2	98.4	98.5	96.6	97.2	97.8		

HCl: hydrochloric acid; Op: operator; RSD: relative standard deviation.

Robustness

As shown in Tables 3 and 4, the robustness of the method was evaluated under modified conditions including in speed, temperature, non-degassed medium, and rinsing volume. Under these varying conditions, the differences in mean dissolution compared to the normal conditions were within 5.0%, indicating acceptable robustness for these parameters. However, a significant difference was observed when using the Agilent and SOTAX dissolution apparatus. Dissolution profiles for the same batch showed differences in cumulative dissolution exceeding 5.0% at all time points (e.g., 8% at 5 minutes). Therefore, it is critical to use the same brand of dissolution apparatus (Agilent is recommended) throughout the study to ensure consistent results.

Table 3. Method Robustness Evaluation with Modified Dissolution Conditions

Tested Conditions		Final Dissolution (%)						Mean Dissolution (%)	Difference (%)
		1	2	3	4	5	6		
Normal conditions		100	97	99	100	98	99	99	-
No degassing		100	101	99	99	100	100	100	1
Temperature (°C)	35	92	97	96	95	91	97	95	4
	39	94	96	96	96	97	92	95	4
Speed (rpm)	95	93	99	96	97	96	95	96	3
	105	92	92	95	93	93	100	94	5
Rinsing volume (mL)	4	95	96	96	96	97	96	96	3
	6	97	96	96	94	97	97	96	3

Table 4. Method Robustness Evaluation with Different Equipment

Time (min)	AGILENT		SOTAX		Difference (%)
	Cumulative dissolution (%)	RSD (%)	Cumulative dissolution (%)	RSD (%)	
5	93.3	3.49	101.4	0.71	8
10	96.0	1.51	101.8	0.65	6
15	96.1	1.27	101.8	0.69	6
30	96.4	1.40	102.0	0.62	6

Solution Stability

With the exception of the aqueous medium, the peak area variations for both PTFE and PES were less than 2.0% after 22 hours. In water, when filtered with PTFE, peak area variation remained below 2.0% after 3 hours, whereas filtration with PES resulted in a peak area variation exceeding 2.0% after 3 hours. The peak area changes in all media were less than 2.0% at 45 minutes. In conclusion, at room temperature, the samples were stable for 22 hours in all media except water, in which stability was maintained for 3 hours only when filtered with PTFE.

Dissolution Profiles

As shown in Figure 2, both the self-prepared product and the RLD dissolved rapidly in the four

media, with dissolution exceeding 85% within 5 minutes. Therefore, the similarity factor (f_2) was not calculated for comparison. Comparing three media is sufficient to meet the requirements for sample investigation. Consequently, the study of the aqueous medium will be discontinued, and only the dissolution profiles in 0.1 mol/L HCl, pH 4.5 acetate buffer solution, and pH 6.8 phosphate buffer solution will be examined in future studies.

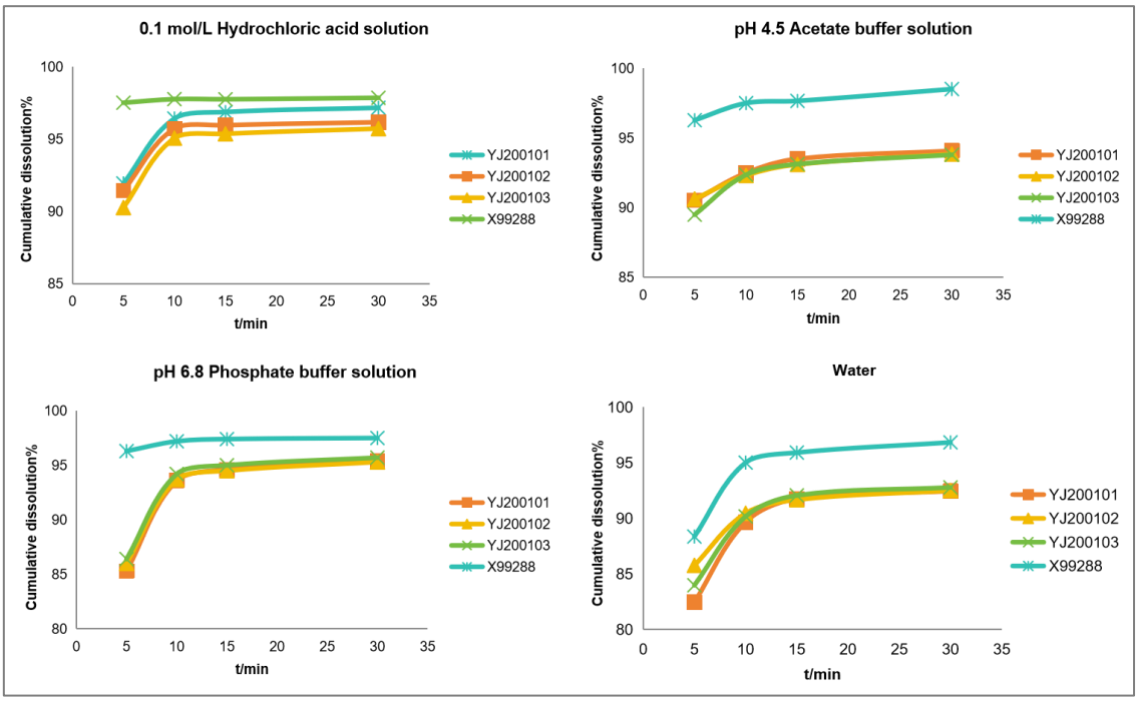

Figure 2. Comparison of the dissolution profiles for self-prepared tofacitinib citrate tablets (YJ200101, YJ200102, YJ200103) and the reference listed drug (X99288) in four dissolution media.

DISCUSSION

This study established an in vitro dissolution determination method based on *Chinese Pharmacopoeia* 0931 (method 2) through multidimensional validation (*8*). Compared with single medium measurement, evaluating multiple dissolution media is more suitable for the in vivo dissolution scenario, addressing the defect of traditional standards that cannot comprehensively evaluate the dissolution characteristics of formulations (*9*).

After optimizing the membrane selection (PTFE membrane for water medium and PES membrane for the rest), the peak area change was less than 2.0%, effectively avoiding the interference of membrane adsorption on the measurement results. The finding that tofacitinib citrate is stable in non-aqueous media for 22 hours and the aqueous medium is stable within 3 hours provided a key basis for the experimental operation. The linear range covers the concentration of the test sample from 21% to 123%, with a correlation coefficient $r > 0.999$, a recovery rate of 95–102%, and a precision RSD < 5%. In the robustness study, parameter fluctuations other than instrument brands have an impact of < 5% on the results. The established method has strong specificity, high accuracy, and good repeatability, and can be reliably used for dissolution determination.

Consistency Evaluation of Dissolution Behavior

The comparison of dissolution curves reveals a high degree of consistency between the generic drug and the RLD; both showed rapid dissolution characteristics in the three non-aqueous media (> 85% in 5 minutes). Thus, the dissolution behavior can be confirmed to be consistent without the need for f_2 factor calculation. This result is consistent with the ADME characteristic of rapid oral absorption of tofacitinib citrate, suggesting that generic drugs may have similar in vivo absorption rates as the original formulation (*10*).

The human bioequivalence study of tofacitinib citrate tablets conducted by Liu et al. confirms that this drug is a fast-releasing formulation (*11*). Under fasting conditions, the median time to maximum plasma concentration (Tmax) for both the test and reference (Xeljanz) formulations is 0.75 hours (range 0.33–3 hours), which falls within the fast-release range. This finding is consistent with the in vitro dissolution profiles obtained in the present study. The half-life is only 2.4–2.9 hours, indicating rapid clearance. To maintain effective therapeutic concentrations throughout the day, such drugs typically require multiple daily administrations. This represents the typical pharmacokinetic profile of immediate-release tablets, which is in sharp contrast to once-daily sustained-release tablets. The same literature mentions that the postprandial Tmax is 1.5–2.25 hours, showing a delay compared to the fasting state. This is because food, especially high-fat meals, delays gastric emptying. For an immediate-release drug that is primarily rapidly dissolved and absorbed in the stomach and upper small intestine, this delay is an expected and typical effect, further confirming its immediate-release characteristics.

Although rapid dissolution is also observed in aqueous media, the decision to cancel the investigation of aqueous media has been fully validated for consistency, ensuring the scientific rigor of the evaluation and simplifying the subsequent research process (*12*–*14*).

CONCLUSION

Conducting consistency evaluations between generic and RLDs serves as an effective strategy to enhance generic drug quality and increase the success rate of in vivo bioequivalence studies. In this study, a comprehensive HPLC method was established and validated for determining the dissolution of 5-mg tofacitinib citrate tablets. The method proved to be feasible and reliable. The dissolution profiles of multiple self-made batches and the RLD were found to be similar in the three key dissolution media (0.1 mol/L HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer), exhibiting rapid and consistent dissolution behavior with that of the original drug, thereby demonstrating consistent quality of the generic and original products.

DISCLOSURES

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

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