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Evaluation of In Vitro Dissolution Behavior of Ibuprofen Suspensions Based on the Flow-Through Cell Method

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ABSTRACT

Introduction: Ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID), is recommended for pediatric fever and pain management. Due to its low water solubility, pH-dependent solubility, and the nature of suspension formulations, understanding the in vitro release behavior of ibuprofen suspensions is critical. The paddle method for dissolution testing has limitations, while the flow-through cell method, which simulates in vivo pH changes, offers advantages for evaluating drugs with pH-dependent solubility. **Methods:** An in vitro release testing method for ibuprofen suspension was established using the flow-through cell method. Key parameters such as membrane filters, glass bead dosage, flow rates, and dissolution media, were optimized. The dissolution profiles of generic and reference ibuprofen oral suspensions were determined using both the paddle and flow-through cell method and evaluated according to the similarity factor (f_2). Particle size and crystal shape were analyzed via microscopy and laser diffraction. **Results:** The optimized flow-through cell method demonstrated strong discriminatory power, with dissolution profile similarity results aligning with consistency evaluation outcomes for quality and efficacy of generic drugs in China. The method could effectively distinguish between generic formulations that passed and those that failed the consistency evaluation. However, the paddle method may risk misjudgment, as having similar dissolution profiles may not guarantee consistency. **Conclusion:** This research established a dissolution profile determination method for ibuprofen suspensions based on the flow-through cell method, overcoming the limitations of the paddle method. It provides a precise tool for quality control and consistency evaluation of generic ibuprofen suspensions.

KEYWORDS: Ibuprofen suspension, flow-through cell method, dissolution profile, similarity factor (f_2), consistency evaluation, apparatus 4

INTRODUCTION

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is a first-line medication for pediatric fever and pain management as recommended by both the World Health Organization (WHO) and the United States Food and Drug Administration (FDA) (*1–6*). As of October 2023, information from the data query website of the National Medical Products Administration in China shows that many manufacturers in China have obtained approval for ibuprofen suspensions, and the quality has drawn much attention due to Ibuprofen's low solubility in water, high demand in pediatric use, and the nature of the suspension formulation.

The dissolution profile is a critical quality attribute (CQA) for ibuprofen suspension. The commonly used paddle method for dissolution testing has limitations like unfixed sampling position and inappropriate dissolution medium selection (*7, 8*). Because ibuprofen's solubility varies with pH, a pH 7.2 dissolution medium may not effectively evaluate product quality differences. In contrast, the flow-through cell method has advantages such as a fixed sampling position, and it can simulate in vivo pH changes (*9–13*). Thus, the flow-through cell method is suitable for evaluating liquid formulations and drugs with pH-dependent solubility, and it is valuable for generic drug quality consistency evaluation (*14–19*).

This study aims to optimize and establish an in vitro release testing method for ibuprofen suspension using the flow-through cell apparatus. The method will be used to assess the similarity of dissolution profiles between reference and generic products, compare the results of the paddle and flow-through cell methods, and investigate the

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influence of factors like particle size, crystal shape, and formulation on in vitro release behavior. This will support in vitro release research and quality control of ibuprofen suspension and contribute to generic drug quality consistency evaluation.

METHODS

Materials

Ibuprofen reference substance (Batch No.100179-202308, content: 100.0%) was obtained from the National Institute for Food and Drug Control, Beijing, China. Fifteen batches of ibuprofen suspensions (2%) (coded "B1"–"B15") from eight manufacturers (coded "C1"–"C8") were purchased from pharmacies in Sichuan, China. The product of manufacturer C1 (Shanghai Johnson & Johnson Pharmaceutical Enterprise), a locally produced originator drug, served as the reference preparation, and the others (C2–C8) were generic drugs. All products were used at least 12 months prior to expiration. The chemicals and reagents used to perform the experiments included sodium hydroxide pellets (NaOH) (Kermel, China), potassium dihydrogen phosphate (KH2PO4) (Guanghua, China), sodium acetate (CH3COONa) (Kelong, China), glacial acetic acid (CH3COOH) (Guanghua), and hydrochloric acid (HCl) (Chuandong, China).

Aqueous buffer solutions (pH 1.4 HCl, pH 4.5 acetate, pH 6.0 acetate, pH 6.5 phosphate, and pH 7.2 phosphate) were used as dissolution media and were prepared in compliance with the *Chinese Pharmacopoeia* (ChP) (*20*).

The filter membranes used to perform the experiments included polyethersulfone (PES) (0.45 µm; PALL, USA), mixed cellulose ester (MCE) membrane (0.8 µm; JINTENG, China), glass fiber (2.7 µm and 0.7 µm; WHATMAN, UK), and polycarbonate track-etched (PCTE) membranes with various pore sizes (5, 8, and 10 µm; WHATMAN), and defatted cotton (Winner, China).

Equipment

The instruments used in this study included a pH meter (Mettler Toledo, S210), a liquid chromatograph (Agilent 1260 Infinity), an electronic balance (Sartorius CPA225D), two dissolution testers (SOTAX, CE 7smart and AT 7X), a laser particle size analyzer (Malvern Mastersizer 3000), and a microscope (Olympus BX43). All instruments were calibrated or verified annually following laboratory guidelines. The two dissolution testers, installed by the vendor, underwent 3Q (design qualification, installation qualification, and operational qualification). Subsequently, they were mechanically calibrated and performance-verified annually by an accredited laboratory. A Performance verification test of the Sotax AT 7X dissolution tester was carried out using salicylic acid tablets (national pharmaceutical reference substance of China) in accordance with their instruction manuals.

Dissolution Profile Determination Based on the Flow-Through Cell Method

For the flow-through cell method, the dissolution tests were conducted on Sotax CE 7smart system coupled with a CP7-35 piston pump and C 615 fraction collector. The closed-loop configuration was used, with a pump pulse of 120 r/min. The suspension was thoroughly mixed, and approximately 2.5 mL was transferred into a needle-free syringe. The syringe was weighed before and after the transfer to determine the exact sample volume based on weight and density. The sample was then introduced into a standard flow-through cell with an inner diameter of 22.6 mm. The cell was prepared by filling the conical section with 7 g of 1-mm glass beads and placing a ruby bead at the bottom. A filter membrane combination, consisting of defatted cotton (2.5 cm diameter, 0.1 g) and a glass fiber membrane (2.7 µm), was assembled on top of the cell. The experiment was conducted at a temperature of 37 ± 0.5 °C with a flow rate of 8 mL/min. HCl solution (pH 1.4) was used as the medium during the first 5 minutes of the test, then phosphate buffer (pH 6.5) was used. Samples were taken at a volume of 40 mL every 5 minutes from 0–30 minutes and 60 mL every 15 minutes from 30–120 minutes.

Optimization of the Flow-Through Cell Method

Filter membranes were selected based on the graded filtration principle to prevent tubing blockage while retaining undissolved ibuprofen particles. Flow rate, glass bead dosage, and sample volume were optimized by comparing the dissolution behavior of the reference drug (coded "C1B2") and a generic drug (coded "C6B11") that passed the consistency evaluation through calculating the similarity factor (f_2). Under the finally selected conditions, the f_2 factor of C1B2 and C6B11 should be relatively high. According to data from the Japanese National Institute of Health Sciences, the solubility of ibuprofen at 37 °C varies significantly with pH (pH 1.2: 0.053 mg/mL; pH 5.5: 0.433 mg/mL; pH 6.8: 2.010 mg/mL; water: 0.077 mg/mL), indicating that its dissolution behavior is heavily influenced by pH (21). To simulate the gastrointestinal pH environment of the human body, this study employed a multi-phase dissolution medium, with an acidic phase followed by a neutral phase. The pH values were based on the HCl condition (pH 1.4) in simulated gastric juice and the pH range (pH 5.0–6.5) of biorelevant dissolution media, including fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) (*22–24*). Different pH-variable dissolution protocols were

investigated, and the one with the highest f_2 was chosen. Two types of dissolution media were used as follows. For dissolution medium 1: HCl solution (pH 1.4) was used for the first 5 minutes; then acetate-acetic acid buffer (pH 4.5) was used from 5–10 minutes; then phosphate buffer (pH 6.5) was used from 10–120 minutes. For dissolution medium 2: HCl solution (pH 1.4) was used from 0–5 minutes, then phosphate buffer (pH 6.5) was used from 5–120 minutes.

Validation of the Flow-Through Cell Method

The dissolution method was validated for specificity, linearity, limit of quantitation, accuracy and solution stability according to International Council for Harmonization (ICH) guidelines (*25*). All validation parameters were within acceptable limits.

For filtration membrane and glass bead adsorption, an appropriate amount of ibuprofen suspension (Batch B2) was accurately weighed, dissolved, and diluted in phosphate buffer (pH 6.5) to prepare solutions with approximately 0.2 mg/mL and 1.0 mg/mL of ibuprofen, simulating sink and non-sink dissolution conditions, respectively. These solutions were treated by two methods: centrifugation and filtration through degreased cotton combined with a 2.7-µm glass fiber membrane, followed by chromatographic analysis. The membrane adsorption rate (%) was calculated as follows:

$$\frac{\text{Peak area of centrifuged sample} - \text{Peak area of filtered sample}}{\text{Peak area of centrifuged sample}} \times 100\%.$$

Under both concentration conditions, the membrane adsorption rate should not exceed 2%.

Moreover, the prepared solutions were vortexed or shaken with glass beads, then filtered through the degreased cotton-glass fiber membrane combination. The results were compared with samples without glass beads, processed identically. The glass bead adsorption rate (%) was calculated as follows:

$$\frac{\text{Peak area of sample without glass beads} - \text{Peak area of sample with glass beads}}{\text{Peak area of sample without glass beads}} \times 100\%.$$

The glass bead adsorption rate should also be no more than 2%.

Dissolution Profile Determination Method Based on the Paddle Method

According to the United States Pharmacopeia (USP), the dissolution of ibuprofen suspensions is determined using the paddle method. Dissolution curves in different media were measured by USP apparatus 2 (paddle). A 2.5-mL sample was used, and 900 mL of dissolution medium was employed with a stirring speed of 50 rpm. Samples were collected at 5, 10, 15, 20, 30, 45, and 60 minutes. The dissolution media included HCl solution (pH 1.4), water, acetate-acetic acid solutions (pH 4.5 and pH 6.0), and phosphate solutions (pH 6.5 and pH 7.2).

High-Performance Liquid Chromatography (HPLC) Analysis

Ibuprofen was analyzed and quantified by high-performance liquid chromatography (HPLC) using an Agilent 1260 Infinity system. Separation was achieved on a C18 column (Agilent, 250 × 4.6 mm, 5 µm) with a mobile phase consisting of methanol, acetonitrile, water, and phosphoric acid (65:10:25:0.03, v/v/v/v) at a flow rate of 1 mL/min. Detection was carried out at 220 nm, and the injection volume was 10 µL.

Evaluation of Dissolution Profile Similarity

The similarity of dissolution profiles between reference and generic formulations was evaluated using the similarity factor (f_2), the f_2 values must be between 50 and 100 (*26*, *27*). Alternatively, similarity can be established without f_2 comparison if both formulations achieve ≥ 85% drug release within 15 minutes.

Particle Size Analysis

The particle size distribution of ibuprofen suspensions, a critical factor influencing drug safety, efficacy, and stability (*28–30*), was characterized using microscopy (Olympus BX43) and laser diffraction (Malvern Mastersizer 3000 with Hydro MV wet dispersion unit) (*31–33*). Microscopy revealed both particle size and the crystal shape, while laser diffraction quantified the size distribution. For laser diffraction analysis, a saturated ibuprofen solution (0.5% Triton X-100) was prepared as the dispersion medium. Suspension samples (2 mL) were processed through two cycles of centrifugation (3000 rpm, 10 min) and redispersion in 6 mL medium. The final dispersion (2 mL) was analyzed under following conditions: 1500 rpm for 5 min; refractive indices of 1.550 (sample) and 1.33 (medium); sample absorbance of 0.01; non-spherical mode; obscuration range 3-12%. Triplicate measurements (10 s sample, 10 s background) were performed for each sample.

RESULTS

Flow-Through Cell Method

Optimization Results

During the assessment of multiple membrane combinations, such as PES (0.45 µm), MCE (0.8 µm), glass fiber (2.7 and 0.7 µm), and combinations of PCTE (5, 8, and 10 µm) with glass fiber (2.7 and 0.7 µm), various degrees

of blockage were detected. Particle size analysis revealed that particles larger than 2.7 µm accounted for over 99.6% of all samples (with the reference sample showing 100.0%). Although the 2.7-µm glass fiber membrane could theoretically retain undissolved ibuprofen effectively, samples from some manufacturers still caused pipeline blockages, likely due to viscous excipients like a large dosage of sucrose, glycerin, and cellulose. To overcome this, defatted cotton was added before the membrane. It effectively intercepted undissolved substances, solving the blockage problem. The final membrane combination was defatted cotton (2.5-cm diameter, 0.1 g) and the 2.7-µm glass fiber (2.7 µm) membrane.

The similarity factor f_2 between the reference formulation (batch B2) and the consistency-evaluated generic (batch B11) varied with different flow rates and glass bead quantities (Table 1). The optimal conditions were determined as a flow rate of 8 mL/min and 7 g of glass beads, which resulted in a higher f_2. Regarding sample volume, 10-mL loading caused significant tubing blockages, 5-mL loading led to some blockages, and 2.5-mL loading had no blockages. Thus, 2.5 mL was chosen as the final loading volume. In different pH-altering dissolution media, the f_2 values differed. Dissolution medium 2 (f_2 = 70) demonstrated better similarity between reference (B2) and generic (B11) batches compared to medium 1 (f_2 =52), so medium 2 was selected as the optimal medium (HCl solution pH 1.4 for first 5 minutes, then phosphate buffer pH 6.5 from 5–120 minutes).

Table 1. Optimization of Flow Rate and Glass Bead Dosage Based on The Flow-Through Cell Method

Flow Rate (mL/min)	Glass Bead Dosage (g)	Similarity Factor (f_2)
8	2	57
8	7	71
4	2	38
4	7	58

Formulation C1B2 was the reference; acceptable range for f_2 is 50–100.

Validation Results

The method demonstrated excellent specificity, with complete separation of ibuprofen from adjacent peaks and no interference from dissolution medium or excipients. Linearity was established over 0.0021–0.6270 mg/mL (y = 23249x + 52.85, r = 0.9999), with a limit of quantitation (LOQ) of 0.209 µg/mL. Method accuracy was confirmed by recovery rates of 100.0–102.1% across four concentration levels. No adsorption on membranes and glass beads was detected under both sink and non-sink conditions. Solution stability was studied, with an RSD of 0.7% for sample solutions over 24 hours and 0.3% for reference solutions over 7 days. These results validated the accuracy, reliability, and applicability of the established method.

Dissolution Profile Similarity Based on the Flow-Through Cell Method

The dissolution profiles and f_2 values obtained using the flow-through cell method are detailed in Figure 1 and Table 2.

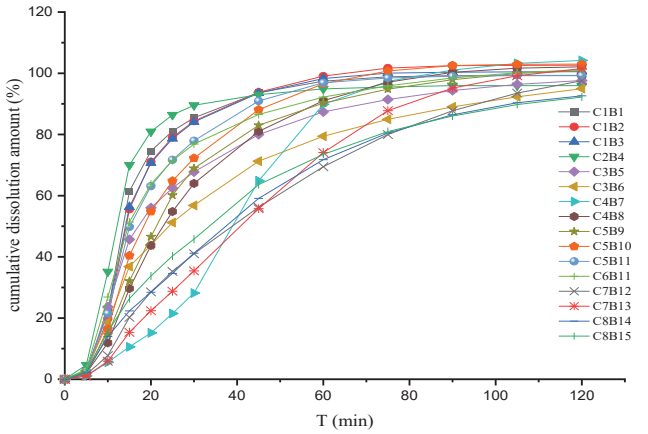

Figure 1. Dissolution profiles based on the flow-through cell method.

Three batches of the locally produced originator product (B1, B2, and B3) from manufacturer C1 served as the reference. To ensure no more than one point with cumulative release exceeding 85% was included, dissolution amounts from the first six time points were selected for calculating the similarity factor (f_2) between each generic formulation and the reference. Among the reference batches, B1 exhibited slightly faster dissolution compared to B2 and B3. Particle size analysis revealed that B1 had a smaller particle size (D_{90}: 47.7µm) compared to B2 and B3 (D_{90}: 66.1 and 65.9 µm, respectively),

Table 2. Similarity Factor (f_2) Based on the Flow-Through Cell Method

	Reference Products			Generic Products											
	C1B1	C1B2	C1B3	C2B4	C3B5	C3B6	C4B7	C4B8	C5B9	C5B10	C6B11	C7B12	C7B13	C8B14	C8B15
C1B1	N/A	74	76	58	41	31	16	31	34	40	62	21	19	21	24
C1B2	74	N/A	92	51	44	33	17	33	37	44	70	23	20	22	26
C1B3	77	92	N/A	52	45	33	17	34	37	44	72	23	20	22	26

Acceptable range for f_2 is 50–100. C1B1-C1B3: reference products (three batches [B1-B3] from one manufacturer [C1]); C2B4-C8B15: generic products (12 batches[B4-B15] from 7 manufacturers [C2-C8]).

suggesting that dissolution rate differences may be related to particle size.

Products from manufacturer C2 (B4) and C6 (B11) had f_2 values greater than 50 when compared to the reference (B2), indicating good dissolution profile similarity. B4 showed a slightly higher dissolution rate than the reference, while B11 was slightly lower. Other batches had f_2 values below 50, with slower dissolution rates compared to the reference. As of December 2023, the C6 ibuprofen suspension completed bioequivalence trials and passed consistency evaluation, whereas the C3 product failed. Other companies are either in the process of evaluation or have not yet submitted applications. Using the flow-through cell method, the C6 product (B11) showed f_2 values greater than 50 compared to the reference, and the C3 products (B5 and B6) had f_2 values below 50. These results indicated the method's discriminative power and correlation with consistency evaluation outcomes.

Dissolution Profile Similarity Based on the Paddle Method

Dissolution profiles obtained using the paddle method under varying pH conditions are illustrated in Figure 2. In HCl solution (pH 1.4) and water, cumulative dissolution at 60 minutes was low. Acetate-acetic acid buffer (pH 4.5) improved dissolution, but some batches remained below 80%. In contrast, acetate-acetic acid buffer (pH 6.0), phosphate buffer (pH 6.5), and phosphate buffer (pH 7.2) resulted in cumulative dissolution rates exceeding 90% for all batches.

Using C1B2 as the reference, f_2 values for each generic were calculated (Table 3). Lower pH levels resulted in lower dissolution amounts due to inadequate sink conditions, whereas higher pH levels reduced discriminative power. In phosphate buffers (pH 6.5 and 7.2), all samples showed cumulative dissolution greater than 85% at 15 minutes, indicating similarity to the reference. The paddle method identified four generic products (from C2, C3, C6, and C8) with dissolution profiles similar to the reference across various pH conditions. Notably, the C3 product, which failed consistency evaluation, showed similar dissolution profiles using the paddle method, potentially leading to misjudgment.

Particle Size Analysis

Microscopy and laser diffraction results revealed diverse crystal shapes (plate-like, polyhedral, granular, needle-like, and short rod-like) among manufacturers, likely due to differences in API sources and formulation processes (available as supplemental data). The C6 product, which passed consistency evaluation, exhibited plate-like crystals and a particle size distribution (D_{90}) similar to the reference. The C2 product had short rod-like crystals with a slightly larger D_{90} than the reference. The C5 and C7 products showed thicker plate-like and polyhedral crystals with significantly larger D_{90} values compared with the reference. The C3 and C8 products had granular crystals with low D_{90} values, and the C4 product featured aggregated needle-like crystals with a much larger D_{90} than the reference.

Differences in crystal shape and particle size distribution may impact dissolution behavior and bioequivalence. CQAs of ibuprofen suspensions, including particle size distribution, crystal shape, and solubilizer content, are summarized alongside dissolution profile results in Table 4.

DISCUSSION

In the paddle method, smaller particle sizes correlated with faster dissolution. The reference formulation, with smaller particles, showed rapid dissolution across all media. Generics with smaller particles were more likely to achieve similar dissolution profiles. However, the C3 product, despite having similar dissolution profiles, failed consistency evaluation, highlighting the method's limitations. The paddle method's vigorous stirring may not fully reflect the impact of formulation differences beyond particle size. Relying solely on this method for consistency evaluation risks misjudgment, as similar dissolution profiles may not guarantee consistency.

In the flow-through cell method, the C2 and C6 products showed dissolution profiles similar to the reference, with fast dissolution rates. The C6 product had crystal shapes and particle sizes consistent with the reference, facilitating similar dissolution profiles. The C2 product, despite having different crystal shapes and a slightly larger particle sizes, achieved similar dissolution due to a higher concentration of solubilizer (polysorbate 80, 0.3% vs. 0.05% in the reference). The flow-through cell method comprehensively reflected the effects of crystal shape, particle size, and formulation on dissolution behavior. It demonstrated excellent discriminatory capacity, with dissolution profile similarity results aligning with consistency evaluation outcomes. This method addresses the paddle method's limitations, such as sample positioning issues and inadequate reflection of pH-sensitive dissolution behavior.

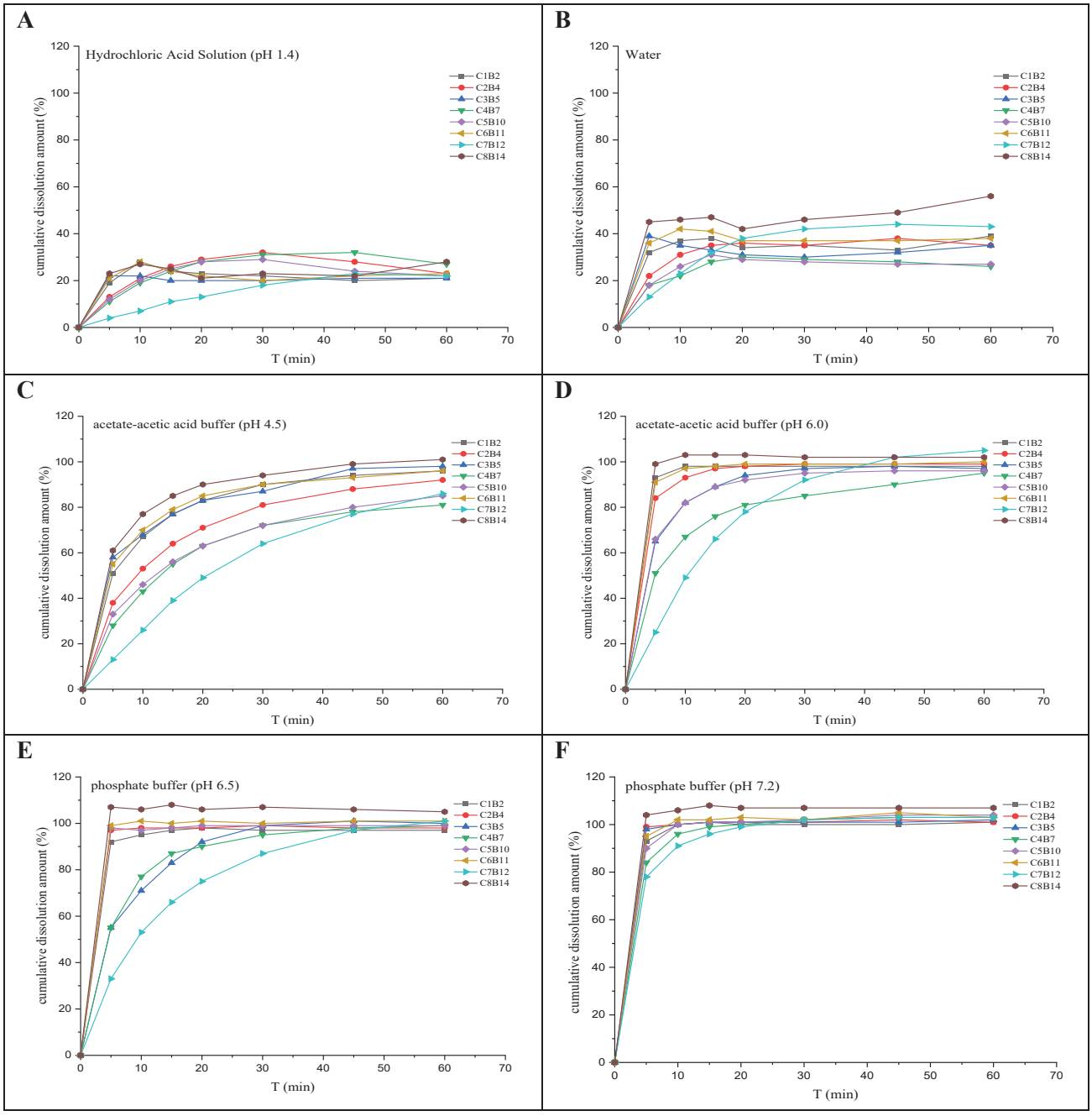

Figure 2. Dissolution profiles in different media based on the paddle method: (A) pH 1.4; (B) water; (C) pH 4.5; (D) pH 6.0; (E) pH 6.5; (F) pH 7.2.

Table 3. Similarity Factors (f_2) Under Various Dissolution Conditions Based on the Paddle Method

Parameter	Medium	C2B4	C3B5	C4B7	C5B9	C6B11	C7B12	C8B14
f_2	pH 1.4	58	73	54	61	91	45	84
	Water	63	69	50	53	71	47	50
	pH 4.5	53	72	36	36	80	24	56
Cumulative Dissolution > 85% at 15 min	pH 6.0	Yes	Yes	No	Yes	Yes	No	Yes
	pH 6.5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	pH 7.2	Yes	Yes	Yes	Yes	Yes	Yes	Yes

C1B2 was used as the reference; acceptable range for f_2 is 50–100. C2B4-C8B14 represent the generic products (7 batches [B]] from 7 manufacturers [C]).

Table 4. Summary of Critical Quality Attributes and Dissolution Profiles Similarity

	Reference Product Manufacturers			Generic Product Manufacturers				
Attribute	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**
Crystal shape	Plate-like	Short rod-like	Granular	Needle-like	Plate-like and polyhedral	Plate-like	Plate-like and polyhedral	Granular
Particle size (D_{90})	66.1 µm	146.0 µm	51.5 µm	268.2 µm	217.9 µm	97.8 µm	145.8 µm	69.3 µm
Polysorbate 80 content (w/w)	0.05%	0.3%	0.1%	0.1%	0.3%	NA	0.4%	0.05%
Similarity (Paddle)	Reference	Yes	Yes	No	No	Yes	No	Yes
Similarity (Flow-Through Cell)	Reference	Yes	No	No	No	Yes	No	No

NA: Polysorbate 80 content unavailable for C6; D90: particle size at undersize values of 90%; Yes: dissolution profiles similar to reference; No: dissolution profiles dissimilar.

CONCLUSIONS

This study provides a technical foundation for quality control and consistency evaluation of ibuprofen suspensions. The flow-through cell method offers a precise assessment of product quality differences, particularly in vitro release, supporting quality enhancement and consistency evaluation of generics.

SUPPLEMENTAL MATERIAL

Supplemental data are available for this article and may be requested by contacting the corresponding author.

DISCLOSURES

The authors received no financial support for this work and have no conflicts of interest.

REFERENCES

1. Wahba, H. The antipyretic effect of ibuprofen and acetaminophen in children. *Pharmacotherapy* **2004**, *24* (2), 280-284. DOI: 10.1592/phco.24.2.280.33138.
2. Goldman, R. D.; Ko, K.; Linett, L. J.; Scolnik, D. antipyretic efficacy and safety of ibuprofen and acetaminophen in children. *Ann. Pharmacother*. **2004**, *38* (1), 146-150. DOI: 10.1345/aph.1C391.
3. de Martino, M.; Chiarugi, A.; Boner, A.; Montini, G.; De' Angelis, G. L. Working towards an appropriate use of ibuprofen in children: an evidence-based appraisal. *Drugs* **2017**, *77* (12), 1295-1311. DOI: 10.1007/s40265-017-0751-z.
4. Morozova, T. E.; Andrushchishina, T. B.; Antipova, E. K. [Ibuprofen: safety and efficiency of its use in wide clinical practice] [Article in Russian]. *Ter. Arkh*. **2013**, *85* (3), 118–124.
5. Kanabar, D. J. A clinical and safety review of paracetamol and ibuprofen in children. *Inflammopharmacology* **2017**, *25* (1), 1–9. DOI: 10.1007/s10787-016-0302-3.
6. Ziesenitz, V. C.; Zutter, A.; Erb, T. O.; van den Anker, J. N. Efficacy and safety of ibuprofen in infants aged between 3 and 6 months. *Paediatr. Drugs* **2017**, *19* (4), 277–290. DOI: 10.1007/s40272-017-0235-3.
7. Rivera-Leyva, J. C.; García-Flores, M.; Valladares-Méndez, A.; Orozco-Castellanos, L. M.; Martínez-Alfaro, M. Comparative Studies on the Dissolution Profiles of Oral Ibuprofen Suspension and Commercial Tablets using Biopharmaceutical Classification System Criteria. *Indian J. Pharm. Sci*. **2012**, *74* (4), 312–318. DOI: 10.4103/0250-474X.107062.
8. Gray, V.; Kelly, G.; Xia, M.; Butler, C.; Thomas, S.; Mayock, S. The science of USP 1 and 2 dissolution: present challenges and future relevance. *Pharm. Res*. **2009**, *26* (6), 1289–1302. DOI: 10.1007/s11095-008-9822-x.
9. Medina Lopez, J. R.; Domínguez-Reyes, A.; Hurtado, M. Comparison of generic furosemide products by in vitro release studies using USP apparatus 2 and 4. *Dissolut. Technol*. **2021**, *28* (1), 14–22. DOI: 10.14227/DT280121P14.
10. Singh, I.; Aboul-Enein, H. Y. Advantages of USP Apparatus IV (flow-through cell apparatus) in dissolution studies. *J. Iran. Chem. Soc*. **2006**, *3* (3), 220–222. DOI: 10.1007/BF03247211.
11. Paprskářová, A.; Možná, P.; Oga, E. F.; Elhissi, A.; Alhnan, M. A. Instrumentation of flow-through USP IV dissolution apparatus to assess poorly soluble basic drug products: a technical note. *AAPS PharmSciTech* **2016**, *17* (5), 1261-1266. DOI: 10.1208/s12249-015-0444-4.
12. Bhattachar, S. N.; Wesley, J. A.; Fioritto, A.; Martin, P. J.; Babu, S. R. Dissolution testing of a poorly soluble compound using the flow-through cell dissolution apparatus. *Int. J. Pharm*. **2002**, *236* (1), 135–143. DOI: 10.1016/S0378-5173(02)00027-3.
13. Abdelfattah, F. M.; Taha, N. F.; Abdou, A. R.; Mursi, N. M.; Emara, L. H. Prediction of in vivo performance of ibuprofen immediate-release products using different dissolution models. *J. Appl. Pharm. Sci*. **2022**, *12* (8), 193–201. DOI: 10.7324/JAPS.2022.120820.
14. Medina, J. R.; Cortes, M.; Romo, E. Comparison of the usp apparatus 2 and 4 for testing the in vitro release performance of ibuprofen generic suspensions. *Int. J. Appl. Pharm*. **2017**, *9* (4), 90–95. DOI: 10.22159/ijap.2017v9i4.19926.
15. Emara, L.; Emam, M.; Taha, N.; El-Ashmawy, A.; Mursi, N. In-vitro dissolution study of meloxicam immediate release products

using flow through cell (USP apparatus 4) under different operational conditions. *Int. J. Pharm. Pharm. Sci*. **2014**, *6* (11), 254–260.

16. Hashem, H.; Abdou, A.; Mursi, N.; Emara, L. Comparative in vitro dissolution study on metformin market products using different dissolution apparatuses. *Int. J. Pharm. Pharm. Sci*. **2019**, *11* (9), 65–72. DOI: 10.22159/ijpps.2019v11i9.34711.
17. Kaló, Z.; Holtorf, A.-P.; Alfonso-Cristancho, R.; Shen, J.; Ágh, T.; Inotai, A.; Brixner, D. Need for multicriteria evaluation of generic drug policies. *Value Health* **2015**, *18* (2), 346–351. DOI: 10.1016/j.jval.2014.12.012.
18. Wei, Y.; Zhu, J.; Qiao, J.; Zhang, D.; Chen, Y. The Impact of the consistency evaluation policy of generic drugs on R&D investment intensity of pharmaceutical companies—an empirical study based on the difference-in-differences model. *Front. Public Health* **2022**, *10*. DOI: 10.3389/fpubh.2022.902025.
19. Liu, Q.; Huang, Z.; Mao, Z. Has the consistency evaluation policy of generic drugs promoted the innovation quality of Chinese pharmaceutical manufacturing industry? An empirical study based on the difference-in-differences model. *Front. Public Health* **2023**, *11*, 1265756. DOI: 10.3389/fpubh.2023.1265756.
20. 8004 Buffers. In *Pharmacopoeia of the People's Republic of China*: Vol. IV. China Food and Drug Administration, China Medical Science Press, 2020; pp 424–425.
21. [Ibuprofen Tablets] [in Japanese]. Japan National Institute of Health Sciences (NIHS). http://www.nihs.go.jp/drug/ecqaged/bluebook/a/o_Ibuprofen_Tab_01.pdf (accessed Feb 25, 2025)
22. Bou-Chacra, N.; Melo, K. J. C.; Morales, I. A. C.; Stippler, E. S.; Kesisoglou, F.; Yazdanian, M.; Löbenberg, R. Evolution of choice of solubility and dissolution media after two decades of Biopharmaceutical Classification System. *AAPS J*. **2017**, *19* (4), 989–1001. DOI: 10.1208/s12248-017-0085-5.
23. Fuchs, A.; Leigh, M.; Kloefer, B.; Dressman, J. B. Advances in the design of fasted state simulating intestinal fluids: FaSSIF-V3. *Eur. J. Pharm*. **2015**, *94*, 229–240. DOI: 10.1016/j.ejpb.2015.05.015.
24. Dahlgren, D.; Venczel, M.; Ridoux, J. P.; Skjöld, C.; Müllertz, A.; Holm, R.; Augustijns, P.; Hellström, P. M.; Lennernäs, H. Fasted and fed state human duodenal fluids: characterization, drug solubility, and comparison to simulated fluids and with human bioavailability. *Eur. J. Pharm. Biopharm*. **2021**, *163*, 240–251. DOI: 10.1016/j.ejpb.2021.04.005.
25. ICH Q2(R2) Guideline on validation of analytical procedures; EMA/CHMP/ICH/82072/2006. Committee for Medicinal Products for Human Use, European Medicines Agency, 2023.
26. Hoffelder, T.; Leblond, D.; Van Alstine, L.; Diaz, D. A.; Suarez-Sharp, S.; Witkowski, K.; Altan, S.; Reynolds, J.; Bergeron, Z.; Lief, K.; Zheng, Y.; Abend, A. Dissolution profile similarity analyses-statistical principles, methods and considerations. *AAPS J*. **2022**, *24* (3), 54. DOI: 10.1208/s12248-022-00697-y.
27. Novick, S.; Shen, Y.; Yang, H.; Peterson, J.; LeBlond, D.; Altan, S. Dissolution curve comparisons through the F_2 parameter, a Bayesian extension of the f_2 statistic. *J. Biopharm. Stat*. **2015**, *25* (2), 351–371. DOI: 10.1080/10543406.2014.971175.
28. Bommireddi, A.; Li, L. C.; Stephens, D.; Robinson, D.; Ginsburg, E. Particle size determination of a flocculated suspension using a light-scattering particle size analyzer. *Drug Dev. Ind. Pharm*. **1998**, *24* (11), 1089–1093. DOI: 10.3109/03639049809089954.
29. Nutan, M. T. H.; Reddy, I. K. General principles of suspensions. In *Pharmaceutical Suspensions: From Formulation Development to Manufacturing*; Kulshreshtha, A. K., Singh, O. N., Wall, G. M., Eds.; Springer New York, 2010; pp 39-65.
30. Larsson, M.; Hill, A; Duffy, J.. Suspension stability; why particle size, zeta potential and rheology are important. *Ann. Transact. Nordic Rehology Soc*. **2012**, *20*.
31. Xu, R. Light scattering: a review of particle characterization applications. P*articuology* **2015**, *18*, 11–21. DOI: 10.1016/j.partic.2014.05.002.
32. Levoguer, C. Using laser diffraction to measure particle size and distribution. *Met. Powder Rep*. **2013**, *68* (3), 15–18. DOI: 10.1016/S0026-0657(13)70090-0.
33. Shekunov, B. Y.; Chattopadhyay, P.; Tong, H. H. Y.; Chow, A. H. L. Particle size analysis in pharmaceutics: principles, methods and applications. *Pharm. Res*. **2007**, *24* (2), 203–227. DOI: 10.1007/s11095-006-9146-7.