Assessing Ibuprofen in Mini-Tablets Using the Axcend Focus LC® Micro-HPLC-UV System

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Abstract

This study compares two analytical methods—UV spectrophotometry and micro-HPLC-UV—for quantifying ibuprofen content in pediatric mini-tablets. While both methods demonstrated acceptable linearity, accuracy, and precision in validation, the spectrophotometric method failed to detect a polar unknown compound observed in real formulations. In contrast, the micro-HPLC-UV method, utilizing the Axcend Focus LC®, successfully identified this impurity, revealing critical insights into formulation-related variability. The findings highlight the essential role of chromatographic techniques in reliably detecting unknown impurities and ensuring accurate quantification in pediatric drug formulations.

Introduction

Pediatric formulations must ensure accuracy, safety, and ease of administration. Mini-tablets (2 mm, 10 mg) offer numerous advantages, including dose flexibility, improved swallowability, and high patient acceptance.

In this study, we studied the formulation of mini-tablets loaded with ibuprofen, a common NSAID used as a model active principle ingredient (API) and available as a racemic mixture. The mini-tablets were produced via a Design of Experiments (DoE) approach with varied excipient ratios and

compaction pressures. An initial UV spectrophotometric method, based on 222 nm detection, indicated lower-than-expected API recovery, prompting the development and validation of a micro-HPLC-UV method derived from the USP Ibuprofen Tablets monograph. The study aimed to compare the two methods and assess equivalence using the Two One-Sided Test (TOST).

Experimental

Materials and Chemicals

- **API & Excipients:** Ibuprofen (EP RS), Parteck® ODT (mannitol/croscarmellose sodium), magnesium stearate
- **Solvents & Reagents:** Methanol, acetonitrile (≥99.9%, gradient grade), phosphoric acid (85%), Milli-Q® water
- **Filters:** PVDF Millex®-LH 0.45 µm membrane filters
- All consumable materials, including the Purospher® STAR RP18-endcapped capillary column, were obtained from Merck KGaA (Darmstadt, Germany)

Instrumentation

- **UV-Vis:** Perkin-Elmer Lambda 365+ spectrophotometer; 1 cm quartz cuvettes; λ = 222 nm
- **Chromatography:** Axcend Focus LC micro-HPLC system
    - Column: Purospher® STAR RP18-endcapped, 50 × 0.3 mm, 2.0 µm
    - Elution: Isocratic; Flow rate: 7 µL/min; Temperature: 40°C
    - Mobile Phase: ACN/H_2O (0.05% H_3PO_4), 50:50 v/v
    - Detection: λ = 255 nm; Injection volume: 250 nL (manual)

Sample Preparation

Thirteen mini-tablet batches were manufactured (including placebo and optimized batches). Tablets were disintegrated in 1:1 methanol/water via ultrasonication (15 min), stirred (15 min), filtered, and subjected to both spectrophotometric and chromatographic analysis.

Method Validation

Following ICH Q2 (R2) guidelines, as shown in Table 1, both methods were validated for:

- **Specificity**
- **Linearity**
- **Precision** (repeatability and intermediate)
- **Accuracy** (recovery range: 95-105%)

Table 1. Methods' Validation Figures

Parameter	Spectrophotometry @ 222 nm	Micro-HPLC-UV @ 255 nm
Specificity	Specific	Specific (selective)
Linearity (5 points, range 10-40 µg/mL)	Absorbance (AU) vs. Ibuprofen concentration y = (0.042 ± 0.01) · x + (0.03 ± 0.02) Residuals ~ N(0, 4E-3), r > 0.999	Peak area (mAU · s) vs. Ibuprofen concentration y = (0.530 ± 0.009) · x + (-1.1±0.2) Residuals ~ N(0, 0.1), r > 0.998
Quantification limit (µg/mL)	6	6
Repeatability (RSD%, N=6, one day)	3%	8%
Intermediate precision (RSD%, N=6, two days)	5%	13%
Accuracy (REC%, N=3 @ 10, 25, and 40 µg/mL)	99-104%	96-98%

Results & Discussion

Specificity

Spectrophotometry was specific for ibuprofen at 222 nm in methanol/water but failed to detect an unknown peak found in authentic formulations. Micro-HPLC-UV at 255 nm revealed a polar impurity absent from artificial or placebo samples.

Accuracy & Recovery

Artificial samples and spiked placebos yielded acceptable recoveries (95–105%). However, real mini-tablet batches showed ibuprofen recoveries consistently below nominal values (Table 2).

Table 2. Ibuprofen Assay Recoveries in Mini-Tablets' Batches

Batch #	Spectrophotometry @ 222 nm	Micro-HPLC-UV @ 255 nm
1	69.1	58.9
2	101.0	102.5
3	63.8	44.0
4	84.3	75.0
5	64.0	42.4
6	93.3	77.7
7	97.2	86.3
8	87.9	76.9
9	107.8	93.7
10	95.0	78.0
Optimized	86.5	87.1

Equivalence Assessment

Using the TOST approach, the methods failed to show equivalence in real samples due to confidence intervals exceeding ±10% bounds (Figure 1). The discrepancy was attributed to an unknown, non-absorbing compound at 222 nm, revealed only via micro-HPLC-UV (Figures 2 & 3).

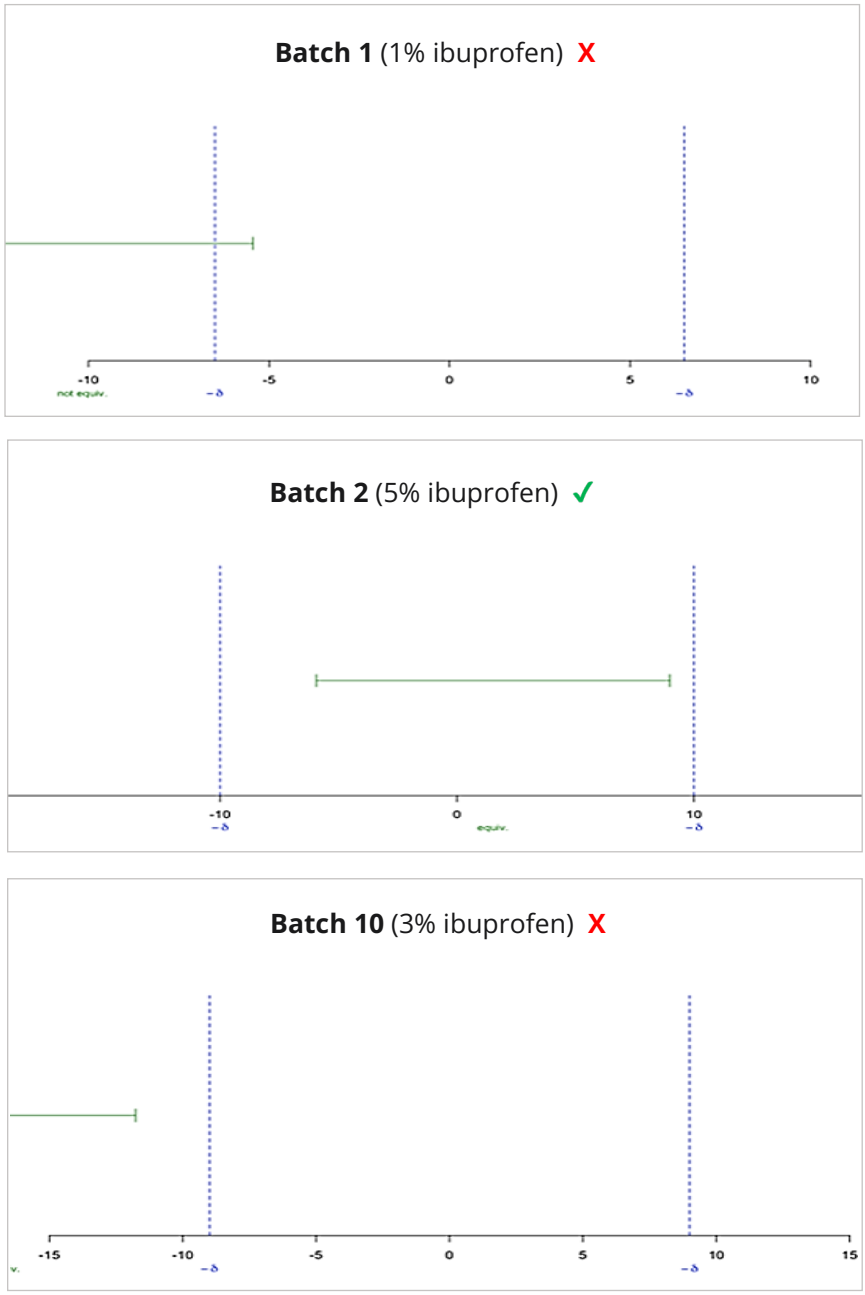
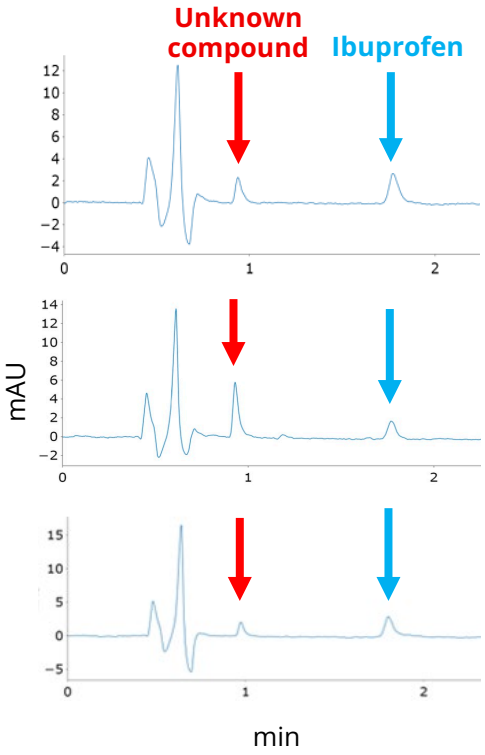


Figure 1. An example of the TOST results for three batches.

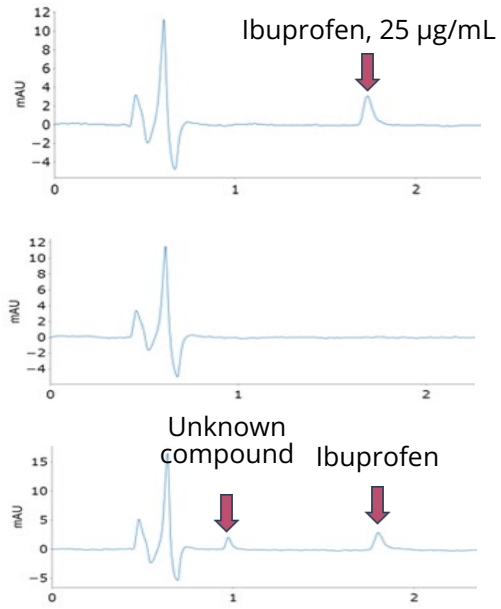


Batch 1
Excipients/ibuprofen = 99:1%, w/w
100 MPa

Batch 3
Excipients/ibuprofen = 99:1%, w/w
300 MPa

Batch 2
Excipients/ibuprofen = 95:5%, w/w
100 MPa

Figure 2. Chromatograms of mini-tablets solutions: the abundance of the unknown peak is proportional to the excipients/ibuprofen ratio and to the compaction pressure.



Placebo mini-tablet
spiked with ibuprofen, 25 µg/mL

Placebo mini-tablet

Batch 2 mini-tablet
Excipients/ibuprofen = 95:5%, w/w

Figure 3. Micro-HPLC-UV method selectivity and an example of mini-tablet assay. An unknown compound is found in all batches of mini-tablets manufactured.

Impurity Behavior

The impurity's abundance correlated with both compaction pressure and the ratio of ibuprofen to excipients used in manufacturing. This suggests a process-related origin and highlights the sensitivity of micro-HPLC-UV to detect such byproducts.

Precision

While both methods demonstrated satisfactory intermediate precision for this study, only the spectrophotometric method approached the rigor typically required for QC use (Table 1).

Conclusions

Two validated methods were used to quantify ibuprofen in pediatric mini-tablets. The spectrophotometric method was faster and more cost-effective but lacked the specificity needed to detect unknown impurities. In contrast, micro-HPLC-UV (using the Axcend Focus LC) successfully identified a polar compound affecting API recovery, demonstrating its utility for rapid monitoring in preformulation studies. Our findings highlight the critical role of chromatographic analysis in pharmaceutical formulation development, particularly when impurities generated by the formulation process may be present. Further investigations using LC-MS/MS are underway to characterize the impurity and optimize the manufacturing process.

References

1. USP Ibuprofen Tablets Monograph. DOI: https://doi.org/10.31003/USPNF_M39890_01_01. June 10, 2025.