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Spectrometric Smartphone-Based System for Ibuprofen Quantification in Commercial Dosage Tablets

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API
active pharmaceutical ingredient
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dispersive liquid-liquid microextraction
IBU
ibuprofen
LOQ
limit of quantification
TRI
transmission, reflection, intensity

ABSTRACT

A rapid and portable analytical methodology has been developed for ibuprofen (IBU) quantification in commercial dosage tablets using a spectrometric smartphone-based system. The analytical methodology employs point-of-use approaches both for sample preparation and detection, demonstrating its potential utility for portable quality control of pharmaceutical products. In this work, IBU is dissolved in methanol and then treated with a Co(II) aqueous solution, forming a blue complex which is extractable by dispersive liquid-liquid microextraction. Then, the sample's absorption spectrum is directly measured by a spectrometric smartphone-based system using cartridge made of polyoxymethylene for solvent compatibility. The main experimental factors affecting the dispersive liquid-liquid microextraction of Co-IBU complex were optimized using a multivariate analysis. Under optimized conditions, a working range between 20 and 80 μg mL^{-1} was obtained with a correlation coefficient of 0.996 for 5 calibration points. The limit of detection and limit of quantification obtained were 4 and 12 μg mL^{-1}, respectively. The performance of the proposed methodology was evaluated in commercial tablet dosage forms, and the results demonstrate the ability of the method to determine IBU in samples representative of those used in real-world quality control applications. Recovery values between 97% and 105% were obtained, which are comparable to those obtained via standard titrimetric methodology.

Introduction

Nonsteroidal anti-inflammatory drugs are among the most frequently prescribed drugs worldwide, and they are used for relief of inflammatory pain conditions in both acute (e.g., headache, postoperative pain, and orthopedic fractures) and chronic (e.g., rheumatoid arthritis, osteoarthritis, and gout) disease.[1]

Ibuprofen (IBU), (*R,S*)-2-(4-isobutylphenyl) propionic acid, is a white crystalline powder that is partially insoluble in water but easily dissolved in acetone, methanol, and chloroform, while it is partially soluble in dilute hydroxide and carbonate solutions. It has become one of the most common nonsteroidal anti-inflammatory drugs, and the general acceptance of its safety led to its approval by the US Food and Drug Administration in 1984 for nonprescription, over-the-counter sale to consumers (<1200 mg/d).[2] Since then, its utilization as a general analgesic has led it to become the third most popular pharmaceutical in the world, with an annual global production reported as 10^6 kg.[3]

As with any pharmaceutical product, achieving stringent quality controls over both the quantity of the active pharmaceutical ingredient (API) and quality of that product is essential to ensuring that end-user dosage is in agreement with national standards. Several factors can result in a loss of potency and quality. For instance, IBU may be synthesized via different chemical pathways, resulting in different process impurities remaining in the API and final drug products.[4] Furthermore, during shipping and storage,

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different degradation impurities may be formed due to environmental variations in temperature and humidity.[5] Quality control of both API and final consumer products is an essential component of all pharmaceutical manufacturing.

Quality control of raw materials and consecutive monitoring of potency and safety of pharmaceutical products constitutes an important current subject of investigation in the pharmaceutical sector. The decomposition process can result in a loss of potency and quality or in a loss of safety of drugs and drug formulations due to creation of minor ineffective or toxic degradation products.

The pharmacopoeias for different countries report conflicting methods for IBU determination in pharmaceutical product quality control. For instance, the method used throughout the United Kingdom and the European Union is based on an acid-base titration in nonaqueous media (a solution of methanol and sodium hydroxide) and is measured by observing the color change of phenolphthalein as a visually observable indicator. This classic method of titration is quite time consuming and agent intensive. In the US pharmacopoeia, standard procedures dictate the use of HPLC with UV-visible absorption spectroscopy. While this procedure is less labor intensive, it requires considerably more expensive instrumentation, thereby increasing analysis costs.

Several methods for the quantification of IBU in pharmaceutical products have been described in the literature. The most recent methods include the use of spectrophotometry,[6] spectrofluorimetry,[7] HPLC with UV detection,[8] and capillary electrophoresis.[9] These methods are attractive choices for the analysis of IBU in terms of their limit of quantification (LoQ), which can extend to concentrations less than 0.05 $\mu g\ L^{-1}$. These improvements in detection sensitivity involve inherent tradeoffs, including the dependence on sophisticated, costly, and bulky instruments compounded by time-consuming analysis, and the need for expensive reagents in high volumes.

In other usage cases when portability and low-cost, high-sensitivity detection is necessary, researchers have looked to take advantage of smartphone-based systems to measure a variety of analytes including biomarkers, target DNA, viruses, drugs, allergens, ascorbic acid, molecular beacon, proteins, among others.[10-22] Modern smartphones make use of miniaturized high-quality cameras and more powerful microprocessors than the desktop computers of even a decade ago while maintaining reasonable affordability and ease of use compared with standard laboratory equipment. In fact, smartphone-based systems have recently been demonstrated for several chemical analysis for quality control applications that include methanol[23] and ethanol[24] determinations in sugar cane spirits, sulfadiazine and sulfasalazine determinations in pharmaceutical and veterinary formulations,[25] ascorbic acid determination in commercial vitamin C tablets,[26] iodine determination in biodiesel,[27] and even furfural quantification for beer freshness assessment.[28] These smartphone-based systems offer several advantages including (1) their ability to use a low volume of reagents and samples, (2) cost-effectiveness, (3) shortened analysis time, (4) high portability for on-site and in-field analysis, (5) simple operational steps and familiar user experience, and (6) high-throughput capabilities. Nevertheless, the use of a spectrometric smartphone-based system for IBU quantification has not been previously reported.

In this article, we demonstrate the first use of a spectroscopic smartphone-based system as a simple, fast, portable, and low-cost analytical procedure of IBU in commercial dosage tablets. The demonstrated methodology uses strategies compatible with a point-of-use approach for both sample preparation and portable, high-sensitivity readout: centrifuge-less dispersive liquid-liquid microextraction (DLLME) and a smartphone-based spectrometric device. The DLLME offers a simple, easy-to-use, low-reagent volume technique that allows for both the reduction in byproducts generated and a much higher enrichment factor when compared with traditional liquid−liquid extraction techniques.[29] In this work, we have optimized the chemical assay via a multivariate optimization and then used the developed assay to accurately measure IBU concentrations in commercial IBU tablets, successfully demonstrating comparable results to those obtained by a conventional titrimetric method.

Analytical Methodology

Spectrometric Smartphone-Based System

The transmission, reflection, intensity (TRI)-analyzer used in this work is the result of the evolution of diverse prototypes already described elsewhere,[11,18,19] and it has been previously introduced for multimodal analysis of absorptive, fluorescence, and photonic crystal-based measurements.[10,30] Briefly, the TRI-analyzer instrument comprised a 3D-printed cradle for a commercially available smartphone that enables the rear-facing camera to function as a spectrophotometer. The system gathers light from the white light-emitting diode that is ordinarily used for flash illumination into an optical fiber. The light emerging from the opposite end of the fiber is directed through a cartridge, and after passing through it, the light is reflected back by a mirror, so the white light makes 2 passes through a liquid test sample. When the liquid sample contains material that absorbs some of the light-emitting diode wavelengths, the intensity of the reflected spectrum will be reduced at those specific wavelengths. The back-reflected light is gathered into a second optical fiber that directs the light through a transmission grating that is placed in front of the phone's rear-facing camera, thus dispersing the wavelength components in one direction to generate a spectrum on the image sensor's pixels. The cartridge contains multiple liquid compartments in a serial configuration that can be passed through the measurement head in a linear sequence, and when at least one of the liquid compartments is filled with colorless material (such as pure water), the spectrum from a test sample can be directly compared with a negative control spectrum to generate an absorption spectrum. Although the TRI-analyzer can perform 3 different classes of spectroscopic measurements, we will use the system solely to measure the absorption spectrum of the test sample via optical transmission.

Reagents and Samples

A stock solution (2000 mg L^{-1}) of S-ibuprofen (Sigma-Aldrich, St. Louis, MO) was prepared in methanol (Fisher Scientific, Fair Lawn, NY) and stored at 4°C. Working solutions were prepared by dilution of the stock standard solution. Chloroform (Sigma-Aldrich) was used as an extractant solvent, and methanol was used as a dispersant. A stock cobalt (Co(II)) solution (10% [w v^{-1}]) was prepared by dissolving $CoCl_2 \cdot 6H_2O$ (Sigma-Aldrich) in water and stored at 4°C. Working solutions was obtained by diluting the stock cobalt solution. Diluted sodium hydroxide solution, prepared from solid NaOH pellets (Fisher Scientific), was used for pH adjustment. Sodium chloride was purchased from Sigma-Aldrich. D-glucose was purchased from Merck (Darmstadt, Germany), while $MgCl_2 \cdot 6H_2O$ was purchased from Sigma-Aldrich.

Pharmaceutical Sample Analysis

Two different commercial IBU products were analyzed: 200 mg ibuprophen tablets from Major Pharmaceuticals, Inc. (tablet 1) and Supervalu, Inc. (tablet 2). For each sample, 5 tablets were weighed, finely powdered, and then homogenized. From these powders, 3 samples each of 200.0 mg IBU (the weight of one tablet) were dissolved in 50 mL of methanol for both the standard (titrimetric) and

proposed methodologies. As the proposed methodology was designed to use smaller volumes, aliquots of 100 μL were measured. Sodium hydroxide solution (0.100 M) was prepared and standardized using potassium hydrogen phthalate (Sigma-Aldrich). Phenolphthalein solution 0.5 wt. % in ethanol:water (1:1) (Sigma-Aldrich) was used throughout as a colorimetric indicator. In addition, for the method described here, spiked samples with 15 μg mL^{-1} of IBU were analyzed to characterize the limit of quantification (LOQ).

Distilled, deionized water (18.3 MΩ cm) from a Millipore water purification system (Millipore Corporation, Bedford, MA) was used for producing all aqueous solutions. All stock solutions were stored at 4°C, and all working solutions were prepared immediately before each experiment.

Multivariate Optimization

Cobalt(II) forms a complex with IBU. Physical studies of Co(II) ibuprofenate ($Co_2(Ibu)_4(H_2O)_2$) show that 2 cobalt atoms bridge 4 deprotonated carboxylate groups and 2 water molecules in the coordination sphere.[31] Thus, Co-IBU complex extraction can be influenced by several modifiable experimental factors that were optimized by multivariate analysis. The main experimental factors affecting the extraction include extractant solvent volume, dispersant volume, sample pH, salt concentration (NaCl), and cobalt concentration. We employed a two-step multivariate technique: (1) a Plackett-Burman design for screening followed by (2) a circumscribed central composite design (CCCD) for optimization. This study was carried out using the TRI-analyzer platform (Spectrometric Smartphone-Based System), and a model 10 mL sample containing 80 μg L^{-1} of IBU was used to optimize the assay procedure. For both steps, 12 experiments were randomly performed to nullify the effect of extraneous factors. The peak measurement intensity at a wavelength of $\lambda = 585$ nm, where Co-IBU complex exhibits a strong absorbance band, was used as the response function in designing both the Plackett-Burman and CCCD studies.

Extractant volume of chloroform was studied in the range of 75-100 μL as microextraction procedure must use an extractant volume equal or below 100 μL.[32] In addition, the study was carried out by varying the dispersant volume in the range of 200-400 μL due to the fact that those amounts of methanol showed enough dispersive effect to form a cloudy solution. Furthermore, the effect of the pH was studied in the range 5-7. The basic media was not evaluated to avoid the precipitation of the cobalt(II) hydroxide. The vast excess of sodium chloride added was to improve the extraction of the analyte and promoted a fast phase separation. Finally, a huge excess of cobalt salt was used to guarantee the formation of the Co-IBU complex.

Data Processing

A multivariate optimization strategy was performed to determine the optimum conditions for the microextraction method. Statgraphics statistical computer package "Statgraphics Centurion XVI" (Warrenton, VA) was used to construct the experimental design matrices and evaluate the results. Image analysis software is developed with computational software (Matlab, MathWorks, Natick, MA) to process spectral data acquired by the smartphone. Details about spectrum processing has been previously explained by Long et al.[10]

DLLME Procedure

Using the results of our multivariate analysis, our final DLLME protocol calls for a mixture of 80 μg mL^{-1} of IBU, 5% (w v^{-1}) of cobalt salt, and 5% (w v^{-1}) of NaCl solutions mixed well in a15-mL test tube, with a pH corrected to 7 and a final volume adjusted to 10 mL. pH measurements were performed with a pH meter (model

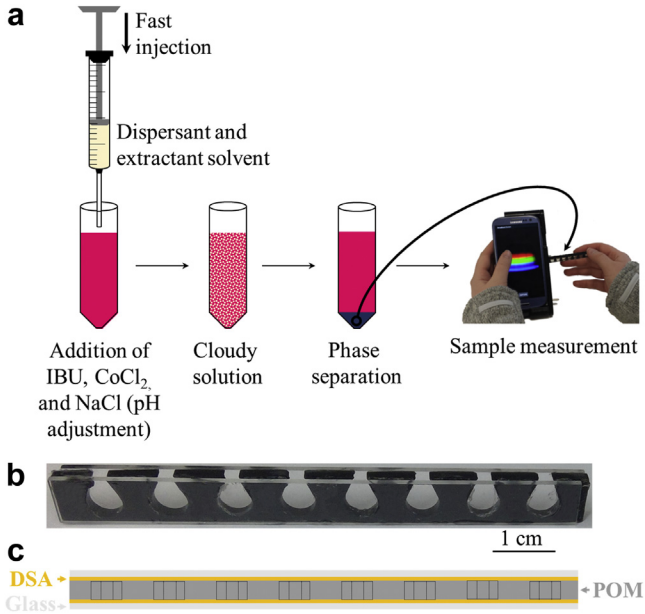

Figure 1. (a) Scheme of the analytical procedure for IBU quantification. (b) Photography of the cartridge used throughout the work. (c) Scheme of the top view of the cartridge made of glass substrates with double-sided adhesive (DSA) and polyoxymethylene (POM) which is completely resistant to chloroform.

Orion 3 Star; Thermo Scientific, Waltham, MA). Then, a mixture of 99 μL of extractant solvent (i.e., chloroform) and 319 μL of dispersant volume (methanol) are added using a syringe. A cloudy solution immediately forms, and the phase separation is allowed to proceed for 1 min. Chloroform was chosen over nontoxic solutions (e.g., undecanol) as it allows phase separation to occur without centrifugation, allowing for a truly portable sample preparation. Afterward, the aqueous phase is removed, and the organic phase is retrieved with a pipette and analyzed by the smartphone-based system (Fig. 1). A novel component of this work is the direct measurement of the organic phase using a custom cartridge that integrates a linear series of fluid compartments made of polyoxymethylene, which has excellent chemical resistance to most organic solvents (Figs. 1b and 1c). From the beginning to end, the overall procedure lasts less than 5 min.

Results and Discussion

Optimization of the Experimental Factors

Table 1 shows the experimental factors and levels used in both Plackett-Burman and circumscribed central composite

Table 1
Experimental Factors and Levels of the Plackett–Burman and Circumscribed Central Composite Designs

Plackettt–Burman Design	Level	
Factors	Low (−1)	High (+1)
Extractant volume (μL)	75	100
Dispersant volume (μL)	200	400
Sample pH	5	7
[NaCl] (%,w v^{-1})	5	10
[$CoCl_2$] (%,w v^{-1})	5	10

Circumscribed Central Composite Design	Level			Star Points ($\alpha = 1.4142$)	
Factors	Low (−1)	Central (0)	High (+1)	−α	+α
Extractant volume (μL)	80	90	100	76	104
Dispersant volume (μL)	200	300	400	159	441

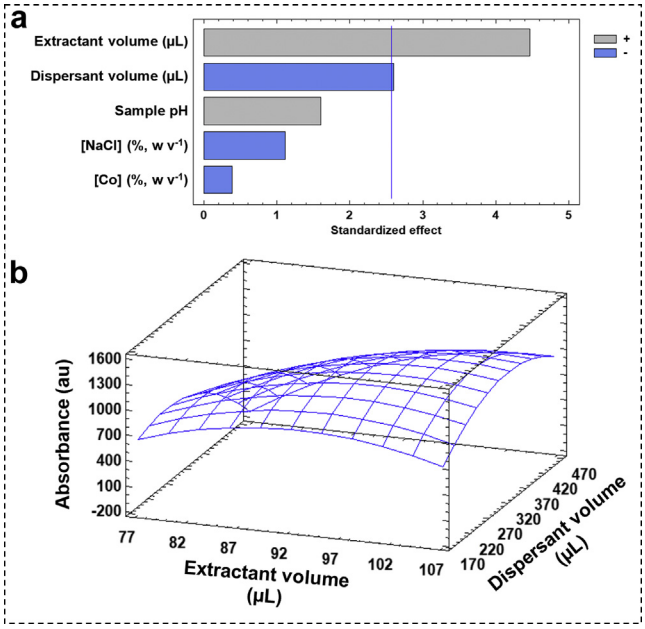

Figure 2. (a) Pareto charts obtained in the screening study of the experimental factors affecting the DLLME. (b) Response surface from circumscribed central composite design.

optimizations. The results obtained from the screening study (Plackett-Burman design) are shown in the Pareto chart in Figure 2a. In this chart, gray bars indicate a positive influence in the response function for the DLLME procedure when increasing the value of the experimental factor, whereas blue bars indicate a negative influence. The vertical line indicates the 95% confidence interval and the factors with a statistically significant influence with respect to the selected response function extend past this threshold. As observed, the extractant solvent and the dispersant volumes have a significant influence in DLLME. On the other hand, the sample pH, $CoCl_2$ concentration, and NaCl addition are not statistically significant factors in the procedure optimization and as such can be fixed at reasonable values. Sample pH was fixed at its highest level and the other 2 nonsignificant factors ($CoCl_2$ and NaCl concentration) were fixed at their lower limits for subsequent extractions.

The extractant solvent and the dispersant were each assessed at 5 different volumes using a CCCD. Table 1 shows the experimental factors and volumes selected for the CCCD. Results of this study are illustrated in Figure 2b as a response surface, showing the variation in the absorption of the Co-IBU complex as a function of the extractant solvent and the dispersant volumes.

Increasing the extractant solvent volume in DLLME leads to an increase in the quantity of tiny droplets dispersed throughout the aqueous solution, thereby increasing the interfacial contact area and consequently the extraction efficiency. On the other hand, increasing the extractant solvent volume also leads to an increase in the analyte-enriched phase (i.e., dilution) and therefore to a decrease in the analyte concentration in the organic phase. The observed optimum value of 99 µL for extractant solvent volume is a direct consequence of these competitive effects.

The dispersant volume should be controlled to ensure adequate extractant solvent dispersion, thus leading to the formation of fine droplets that are responsible for maximizing extraction efficiency for the DLLME. However, an excess of dispersant may increase the dilution of the organic phase, thus resulting in a lower extraction efficiency.

In summary, the optimum experimental conditions for our procedure were selected as the following parameters for subsequent experiments: extractant solvent volume, 99 µL; dispersant volume, 319 µL; sample pH, 7; $CoCl_2$ concentration, 5% w v^{-1} and NaCl concentration, 5% w v^{-1}.

Analytical Figures of Merit

Analytical figures of merit of the combination of DLLME and the spectrometric smartphone-based system were evaluated to assess the analytical capability of this procedure for the quantification of IBU in pharmaceutical products. Under optimized conditions, the working range was established between 20 and 80 µg mL^{-1}, and the absorption spectra were measured (Figs. 3a-3c). The calibration curve was constructed using 5 concentration levels, evaluated in

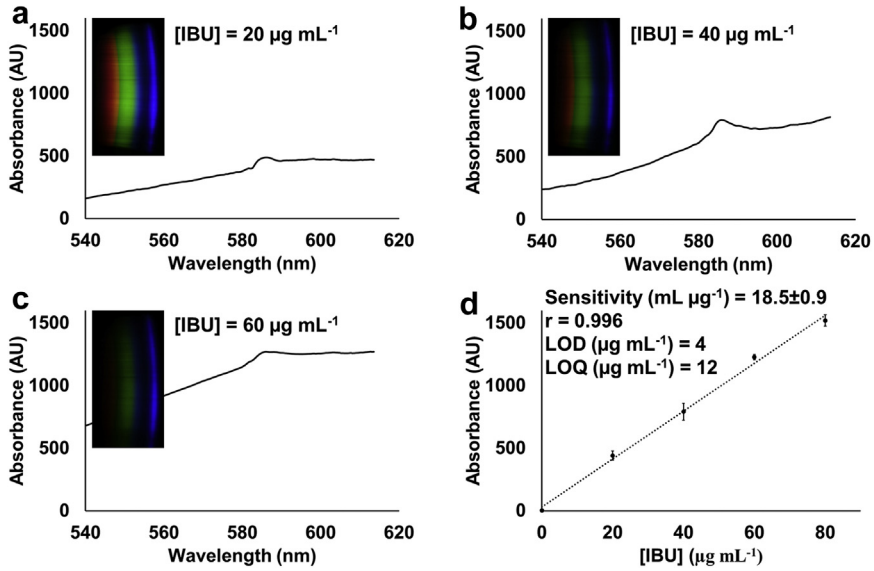

Figure 3. (a-c) Sample absorption spectra and raw RGB image data (insets) for 20, 40, and 60 µg mL^{-1} calibration standards of IBU, respectively. (d) Calibration curve measuring the absorbance at 585 nm of calibration standards from 0 to 80 µg mL^{-1} and the analytical figures of merit (insets) evaluated.

Table 2
Comparison of the Reported Analytical Methods With the Present Work

Method	Portable System	LOQ	Reference
Ratio spectra derivative spectrophotometry	No	300 μg mL^{-1}	33
Second-order derivative spectrophotometry	No	104 μg mL^{-1}	34
Ratio difference spectrophotometry	No	41.47 μg mL^{-1}	35
First-order derivative UV-spectrophotometry	No	30 μg mL^{-1}	36
Flow injection spectrophotometry	No	12.2 μg mL^{-1}	37
Colorimetric determination based on gold nanoparticle aggregation	No	0.10 μg mL^{-1}	38
Kinetic spectrophotometry	No	0.10 μg mL^{-1}	39
Solid-phase extraction coupled by UV spectrophotometry	No	0.028 μg mL^{-1}	40
Spectrometric smartphone-based system	Yes	12 μg mL^{-1}	This work

triplicate. The resulting calibration curve demonstrates a high level of linearity with a correlation coefficient (r) of 0.996 ($N = 5$). The sensitivity of the instrumental measurements estimated by the slope of the calibration curve was 18.5 ± 0.9 mL μg^{-1}. The limit of detection and the LOQ were estimated by using the mean signal of the blank ($n = 3$ replicates) plus 3 and 10 times its standard deviation, respectively. The limit of detection was calculated to be 4 μg mL^{-1}, and the LOQ was 12 μg mL^{-1} (Fig. 3d).

Comparison With Previously Published Spectrophotometric Methods and a Smartphone-Based System

Several analytical methods for IBU quantification using spectrophotometric systems have been published, though none of them are portable smartphone systems (Table 2). It should be noted that, as a result of the combination of DLLME and spectrometric capability of the smartphone-based system, our observed LOQ values of IBU in this work are significantly better than those obtained using benchtop spectrophotometer instruments.[33-36] One research work obtained comparable LOQ values using a complex and nonportable flow injection system.[37] Few works using nonportable systems reported significantly lower LOQ than what was obtained using the proposed method, and we believe that in each case our demonstrated methodology provides significant improvements. First, the proposed method does not require gold nanoparticles that makes cheaper the analysis, and the methodology does not depend on the low colloidal stability of gold nanoparticle solution.[38] Second, our proposed method is significantly faster than aggregation-based, solid-phase microextraction, or kinetic spectrophotometry techniques.[38-40]

Interference Study

Typical excipients used in pharmaceutical dosage include binders, fillers, glucose, and some salts of sodium and magnesium.

Table 3
Effect of Interference Species on the Determination of 40 μg mL^{-1} of IBU

Interference Species	RE (%)[a]	Tolerance Level[b]
Glucose	−5	750
$MgCl_2$	5	750
NaCl	−7	500

[a] Relative error defined as RE (%)=(C_f–C_t)/C_t*100.
[b] Defined as $C_{interferent}/C_{IBU}$.

Table 4
Determination of IBU in Table Dosage Forms

Samples	Labeled Concentration (μg per Tablet)	Titrimetric Method		Proposed Method	
		Found Value (μg per Tablet)[a]	Recovery (%)	Found Value (μg per Tablet)[a]	Recovery (%)
Tablet 1	200	214 ± 4	107 ± 2	204 ± 10	102 ± 5
Tablet 2	200	207 ± 4	103 ± 2	210 ± 19	105 ± 9

[a] Data are expressed as the mean ± SD, $n = 3$.

Binders, such as gelatin, and fillers, such as talc and silicon dioxide, are insoluble in methanol, which we used for dissolving the pharmaceutical preparations. For this reason, only glucose and salts of magnesium and sodium were evaluated for potential interference in this study.

To assess the selectivity of our method, the interference of these excipients were studied. Four different concentration ratios were studied ($C_{excipient}/C_{IBU}$ = 250:1, 500:1, 750:1 and 1000:1) in the quantification of 40 μg mL^{-1} IBU, and the resultant tolerance limits are shown in Table 3. The tolerance limit is defined as concentration ratio causing a relative error of ±10% from pure IBU. Both glucose and $MgCl_2$ were found to have the same upper tolerance limit ratio (i.e., 750:1), while NaCl has an upper tolerance limit of 500:1. The anticipated $C_{excipient}/C_{IBU}$ ratios for pharmaceutical dosages are much lower than the ratios investigated in this interference study, typically on the magnitude of 0.05:1-0.1:1.

Real Sample Analysis

Table 4 shows the results obtained for the determination of IBU in 2 commercial tablets. The results were compared with those obtained by standard reference methods of the British and European pharmacopeias, and a high level of agreement was found (recovery values ranged from 103% to 107%). In addition, both tablets were spiked at concentrations near that of the determined LOQ, 15 μg mL^{-1} of IBU (Table 5). No significant difference between the concentrations added and those measured via our proposed methodology were found with either commercial tablet, with recovery values ranging from 97% to 105%.

Conclusion

In this work, a spectrometric smartphone-based system has been successfully combined with a novel, optimized DLLME procedure for the quantification of IBU in pharmaceutical tablets. These results demonstrate that the combination of DLLME and a spectrometric smartphone-based system can improve the figures of merit even beyond those of recent conventional benchtop laboratory spectrophotometers. This promising analytical methodology would be suitable for a routine and rapid IBU quality control and can be performed in virtually any location or field environment.

Table 5
Determination of IBU in Table Dosage Forms

Samples	Stock Solution (μg mL^{-1})	Spiked Solution (μg mL^{-1})	Proposed Method	
			Found Value (μg mL^{-1})[a]	Recovery (%)
Tablet 1	40	–	41 ± 2	102 ± 5
	40	15	53 ± 5	97 ± 9
Tablet 2	40	–	42 ± 4	105 ± 9
	40	15	57 ± 5	104 ± 9

[a] Data are expressed as the mean ± SD, $n = 3$.

DLLME naturally improves the sensitivity of the chemical assay and results in a much smaller analyte volume, which is ideal for analysis via the spectroscopic smartphone system. Finally, the approach does not depend on expensive instrumentation and the simple operating procedures and familiar user interface of a smartphone provide for the analysis of samples by nonspecialists outside the laboratory environment, thereby decreasing analysis costs and labor requirements for analytical labs. Given that this smartphone-based system offers advantages of low-cost, compactness, and near real-time analysis, this approach has significant potential as a new tool for monitoring IBU quality, especially in low- and middle-income countries, where there is an urgent need for quality control standards and techniques to measure impurities via continuous monitoring, allowing for more effective advocacy against fake and counterfeit drugs.[41,42]

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