# CONTENT UNIFORMITY DETERMINATION OF IBUPROFEN INTACT TABLETS BY REFLECTANCE NIR SPECTROSCOPY

**BY**

Ahmed Shawky Abouzaid[1], Maissa Y. Salem[2], Eman S. Elzanfaly[2], Ahmed E. El Gindy[1], Ahmed Ibrahim[3]

**FROM**

[1]Analytical Chemistry Department,Faculty of Pharmacy, Misr International University, Km 28 Cairo Ismailia Road, Cairo, Egypt

[2]Analytical Chemistry Department, Faculty of Pharmacy, Cairo University, EL- Kasr El Aini St., Cairo, Egypt 11562

[3]School of Pharmacy, University of Maryland, 20 N. Pine Street, Baltimore, Maryland, USA 21201

**Keywords**

Content uniformity; Ibuprofen; NIR reflectance; PLS regression model

**Abstract**

Content uniformity (CU) is a critical quality attribute in tablet manufacturing process. The active pharmaceutical ingredient (API) is usually determined off-line techniques such as, high performance liquid chromatography (HPLC) which is a slow, destructive technique and requires sample preparation. Therefore, Near Infrared (NIR) spectroscopy was employed as a process analytical technology (PAT) tool to determine the API and consequently the content uniformity of tablets. NIR spectroscopy is a fast, non-destructive technique and requires minimal sample preparation. The purpose of this work was to develop and validate NIR reflectance method for the determination of the ibuprofen content (mg) for the content uniformity for ibuprofen tablet. Partial least squares (PLS) model for the NIR reflectance was constructed by using calibration laboratory tablets with different ibuprofen (IBU) contents spanning from 146.47 mg to 243.91 mg. The predictive performance of the proposed method was evaluated by traditional chemometric criteria. The corresponding values for the root mean square error of prediction (RMSEP) were equal to 0.96% for NIR reflectance method. Besides, the proposed NIR method was successfully validated and implemented for the determination of the content uniformity for three batches that represent three levels of IBU content (160 mg, 200 mg and 240 mg).

## 1. Introduction

Content uniformity (CU) is a critical quality attribute in tablet manufacturing process**(Djuris et al., 2013)**. The CU is essential to guarantee the correct amount of active pharmaceutical ingredient (API) in every dosage unit. The API is usually determined by high performance liquid chromatography (HPLC), which is a slow, destructive technique and requires sample preparation**(Blanco et al., 2006).** Besides, with the issuance of the process analytical technology (PAT) guidance for industry in September 2004, the FDA is encouraging the pharmaceutical manufacturing to move from off-line laboratory tests to timely measurements executed directly in or near the process environment**(Food &Drug Administration, 2004).** Therefore, Near Infrared (NIR) spectroscopy is currently used as a process analytical technology (PAT) tool to determine the API and consequently the content uniformity of tablets **(Blanco & Alcalá, 2006; Moes et al., 2008; Pestieau et al., 2014).** NIR spectroscopy is a rapid, nondestructive and requires minimal sample preparation**(Blanco et al., 2008).** Besides, this technique has been applied for thedetermination of the chemical properties (e.g. active ingredient) and the physical properties (e.g. particle size) of the samples**(Ciurczak et al., 1986; Frake et al., 1997).** Moreover, NIR spectroscopy can be used in-line, at-line, on-line and off-line measurements**(Burggraeve et al., 2013)**. In NIR spectroscopy**(Osborne et al., 1993; Siesler et al., 2008; Williams et al., 1987)**, the samples are irradiated with NIR radiation. Some of this NIR is absorbed by the molecules, bringing them to a higher vibrational state. Only vibrations resulting in changes in dipole moment of a molecule can absorb NIR radiation. Vibrations of R–H, O–H, N–H, C–H and S–H bonds have strong overtones, as the dipole moment is high. Therefore, they are strong NIR absorbers.

For NIR analysis, there are two main NIR measurement modes: reflectance and transmittance**(Sánchez et al., 2016)**.In reflectance mode, the instrument detects the diffused reflectance energy of the NIR radiation from the sample. Usually penetration depth of the NIR radiation is less than 1 mm. Therefore, only a portion of the sample is analyzed in this mode. However, the NIR spectrum is obtained in full range (up to 2500 nm) with good signal to noise ratio.

Ibuprofen**(USP 35-NF, 2012)** is 2-(4-isobutylphenyl) propanoic acid, is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic. It has following structure formula, as shown in **Figure1.**

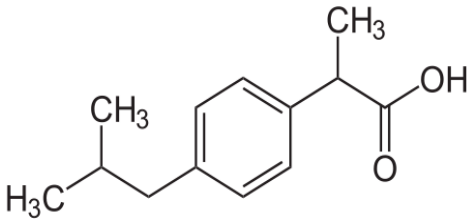


**Figure 1:** Structure formula of ibuprofen

Several analytical methods for the determination of the content uniformity in intact tablets have been developed. Blanco et al.**(Blanco et al., 2006)** demonstrated the application of NIR spectroscopy as a process analytical technology to determine the tablet hardness, content uniformity and dissolution test.Moes et al.**(Moes et al., 2008)** applied the NIR spectroscopy as a process analytical technology to determine the content uniformity.Li et al.**(Li et al., 2009)**studied the content uniformity of low-dose tablets, which include 6.25% w/w API, using principal component analysis. Luo et al.**(Luo et al., 2013)** used the diffuse reflectance NIR spectroscopy with PLS to monitor naproxen tablet content uniformity. Peng et al.**(Peng et al., 2014)** developed the NIR spectroscopy to analyze the content uniformity of low-dose tablets. Pestieau et al.**(Pestieau et al., 2014)** demonstrated the application of NIR spectroscopy as a process analytical tool to evaluate the conformity of paracetamol tablets. Wahl et al.**(Wahl et al., 2014)** used the inline NIR spectroscopy with PLS to monitor the active pharmaceutical ingredient and excipients.Chavez et al.**(Chavez et al., 2015)**developed NIR spectroscopy to determine the active content of non-coated pharmaceutical tablets. Yang et al.**(Yang et al., 2015)** used the NIR spectroscopy with PLS to monitor the content uniformityof the ambroxol hydrochloride tablets.

Therefore, our goal was to develop and validate NIR reflectance method to determine the content uniformity for ibuprofen tablet. For this purpose, PLS model for the NIR reflectance was applied to determine ibuprofen content (mg) in tablets. Besides, to apply the proposed NIR method to determine the content uniformity for three batches having three levels of IBU content (160 mg, 200 mg and 240 mg). Samples are considered uniform if the drug content of each sample was within the limits established by both the European Pharmacopoeia (15% around the nominal content) and the US Pharmacopoeia (15% around the manufacturer's label claim), and the relative standard deviation (RSD %) for the average of each batch was below the level required by the US Pharmacopoeia (6%) **(Blanco et al., 2006).**

## 2. Experimental

### 2.1. Materials and reagents:

Ibuoprofen USP (Lot # IB1F115), active ingredient was obtained from Spectrum chemical company, California, USA.Ludipress® (Lot # IB1F115) and Polyvinylpyrrolidone (Kollidon CL®, Lot # 99807536W0) were obtained from BASF, New York, USA. Methanol was purchased from Decon labs, Pennsylvania, USA. Magnesium stearate (lot # L06615), Hyqual® vegetable source was obtained from MACRON Chemicals Pennsylvania, USA.

### 2.2. Instruments:

#### 2.2.1. NIR spectrophotometer:

Metrohm NIRS XDS MasterLab (Metrohm, Florida, USA) was used for reflectance measurements.

#### 2.2.2. HPLC:

The HPLC system (Shimadzu HPLC) consisted of pump (type LC-10AS), a UV/VIS detector (typeSPD-10A), an autoinjector (type SIL-10A) and a reversed-phase column (ThermoScientific® RP C18)

### 2.3. Procedure:

#### 2.3.1. Preparation of calibration and validation samples

A total of 34 tablets were prepared in order to expand the IBU content ranges by

±25% around their respective nominal content in the formulation spanning from 146.47 mg to 243.91 mg. Twenty-four tablets were used for calibration and ten tablets were used for validation.

The tablet formulation was developed for direct compression and based on ibuprofen as active pharmaceutical ingredient. The tablet formulation studied contained ibuprofen (IBU) content of 200 mg (57%) as active principle, Ludipress content of 144 mg (41%) as major excipient, kollidon CL of 3 mg (1%) and magnesium stearate of 3 mg (1%) as minor excipients. Ludipress is an excipient derived from lactose (93%), Kollidon 30 (3.5%), and Kollidon CL (3.5%). It thus combines the properties of a filler, binder, disintegrant, and flow agent.

Three different active pharmaceutical ingredient (IBU) contents were manufactured: 80%, 100% and 120% of a predetermined dosage (200 mg of IBU) at a compaction pressure of 10kN. To obtain these different contents, the content of the IBU was increased or decreased relative to the target content. The quantity of Ludipress (main excipient) was adapted to maintain a tablet weight of 350mg while the quantity of KollidonCl and magnesium stearate remained constant.

The IBU, Ludipress and KollidonCl were mixed in a 16 qt V-blender (Patterson Kelly Co., PA, USA) for 10 min without lubricant (magnesium stearate) at 30 rpm. The lubricant was then added and mixed during 1 min.

The blends were compressed at 10 kN compression force with an instrumented Stoke B2 rotary press (Key International, NJ, USA) rotating at 30 rpm. Flat face bevel edge tablets were obtained using round punches with a diameter of 10 mm. Targeted tablet weight was fixed at 350 mg.

### 2.3.2. Measurements

#### NIR spectroscopy

Tablets were placed in a NIRS Multi-tablets tray (4×5, 10 mm tablets) and scanned in reflectance mode. Reflectance measurements were made from 400-2500 nmwith data collected every 0.5 nm.

#### HPLC

The HPLC method was used as a reference method. The HPLC conditions were

chosen as per the reported HPLC method for the assay of ibuprofen **(Farrar et al., 2002).**The detection was performed at 220 nm. The mobile phase consisted of a mixture (60:40) of acetonitrile and water (pH adjusted to 2.6 with phosphoric acid. The flow rate of the mobile phase was set at 2 ml/min. Each tablet was weighed, dissolved in 50 ml of methanol, sonicated for 15 min and diluted to 100 ml with the same solvent. Five milliliter of this solution was then diluted to 100 ml with the mobile phase. This solution was filtered through a 0.22 μm PDVF filter then twenty microliter of the prepared solution was injected.

**2.4. Software and multivariate data analysis**

Data handling, principal component analysis (PCA) and partial least squares (PLS) routine work were done using SOLO8.0® (Eigenvector Research Inc., Washington, USA).

Partial least squares (PLS) models were applied to the NIR spectra.In order to build PLS model, the raw data was preprocessed using one or a combination of two preprocessing methods; mean centering (MC), autoscaling (AS) and Savitzky-Golay's first derivative (D1). The root mean square error of prediction (RMSEP) and number of latent variables (LVs) were used to evaluate the performance PLS models**(Mazurek & Szostak, 2006; Szostak & Mazurek, 2004)**.

**2.5. Method validation**

The proposed NIR method was validated in accordance with some ICH guidelines **(International Conference on Harmonisation (ICH), 2005).** The method linearity, accuracy and precision (both repeatability and intermediate precision) were measured for the proposed methods. In addition to, the traditional chemometric criteria were calculated to evaluate the predictive ability of the developed PLS models**(De Bleye et al., 2012).**These criteria are regression coefficient ($R^2$), the root mean squared error of cross-validation (RMSECV) and of prediction (RMSEP) for external validation set, not involved in the calibration set.

## 3. Results and discussions

### 3.1. NIR spectra

The NIR reflectance spectra for the active ingredient (IBU), the major excipient (ludipress) and the laboratory tablet are shown in **Figure 2**.

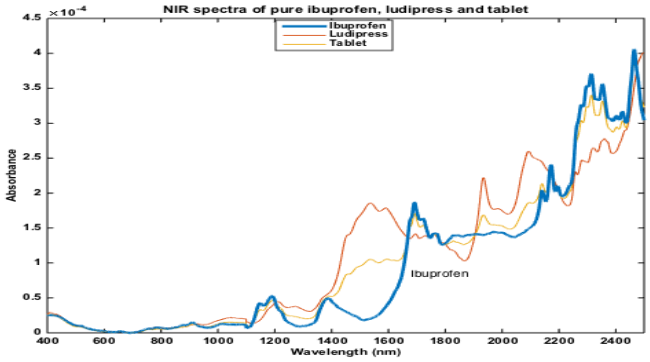


**Figure 2:**NIR reflectance spectra of pure ibuprofen, Ludipress (main excipient) and laboratory tablet.

The spectrum of pure IBU showed pronounced signals over the entire spectral range and the most intense bands for IBU were found in the regions 1100-1200 nm (2$^{nd}$ overtone of CH) corresponding to $CH_3$ group, 1350-1420 nm (CH combination) corresponding to $CH_3$ group, 1688-1870 (1$^{st}$ overtone of OH and 1$^{st}$ overtone of CH) corresponding to OH group and $CH_3$ group, and 2240-2440 nm (CH stretch and C=O stretch) corresponding to $CH_3$ group and C=O group**(Schwanninger et al., 2011).**

Spectra regions from 1100-1200 nm, 1350-1400 nm, 1688-1870 nm and 2240-2440 nm of the calibration samples were selected and analyzed using principal component analysis (PCA) where 3 PC's explained 99.57% variability in the data with PC1, PC2 and PC3 capturing 94.70%, 4.15% and 0.72% variability, respectively, as shown in **Figure 3**. As can be seen, the greatest source of variability in the spectra was the IBU content (PC1 94.70%).

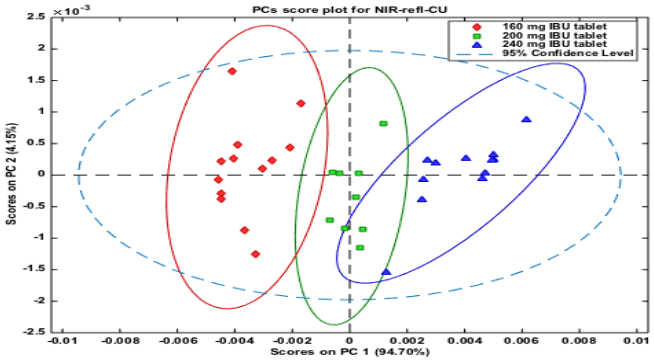


**Figure 3:**PC1 versus PC2 scores plot for NIR reflectance spectra of the calibration samples.

### 3.2. Model Calibration

Spectra regions from 1100-1200 nm, 1350-1420 nm, 1688-1870 nm and 2240-2440 nm were selected to build the PLS model for the NIR reflectance to remove the irrelevant spectral part, while keep dealing with IBU bands, as shown in **Figure 4**.

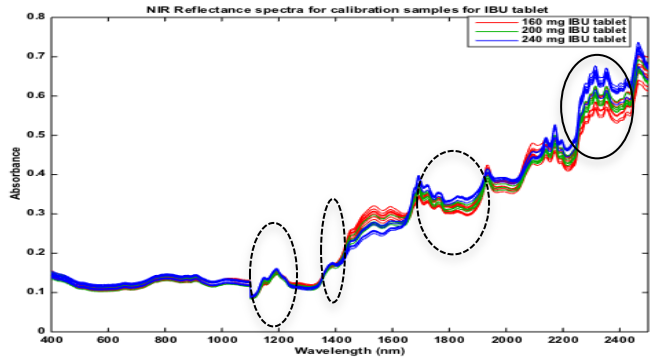


**Figure 4:** NIR reflectance spectra for the calibration samples. Selected spectral ranges (1100-1200 nm, 1350-1420 nm, 1688-1870 nm and 2240-2440 nm)

In order to build PLS model for NIR reflectance, the raw data was preprocessed using different spectral preprocessing methods; mean centering (MC), autoscaling (AS) andSavitzky-Golay's first derivative (D1). PLS models were fitted and their predictive performance was evaluated by the root mean square error of prediction (RMSEP) and number of latent variables (LVs).

The selected PLS model for NIR reflectance was the one obtained by applying Savitzky-Golay's first derivative with mean-centering (D1-MC) it decreased the number of latent variables used in the model by 40% (from 5 LVs to 3 LVs) with the same value

of RMSEP (1.83%), (see **Table 1**).

**Table 1**: The performance of different tested PLS models for determination of ibuprofen content (mg) for content uniformity.

| | **PLS** | **LV** | **RMSEC(%)** | **RMSECV(%)** | **RMSEP(%)** |
|---|---|---|---|---|---|
| **NIR reflectance**[a] | Raw data | 5 | 1.92 | 2.98 | 1.83 |
| | AS | 4 | 2.59 | 3.35 | 1.37 |
| | MC | 5 | 1.82 | 2.82 | 1.76 |
| | **D1-MC**[b] | **3** | **2.24** | **3.06** | **1.83** |

[a]Selected spectral ranges (1100-1200 nm, 1350-1420 nm, 1688-1870 and 2240-2440 nm).

[b]Selected preprocessing method.

### 3.3. Model Validation

The linearity of the proposed methods was demonstrated by establishing the regression plot between the IBU contents (mg) predicted by the proposed method and those determined by the reference HPLC method.Twenty-four tablets were used as calibration samples. Regression plot for the calibration samples for NIR reflectance was characterized by regression coefficient value of 0.949, as shown in **Figure 5(a)**.Internal validation of the models by venetian blindmethod resulted in RMSECV values equal to 3.06% for NIR reflectance. Ten tablets were used as validation samples. Regression plot for the validation samples for NIR reflectance was characterized by regression coefficient value of 0.955, as shown in **Figure 5(b**).The range of the proposed methods was 146.47 (mg) and 243.91 (mg). The NIR reflectance model was only valid within this range.

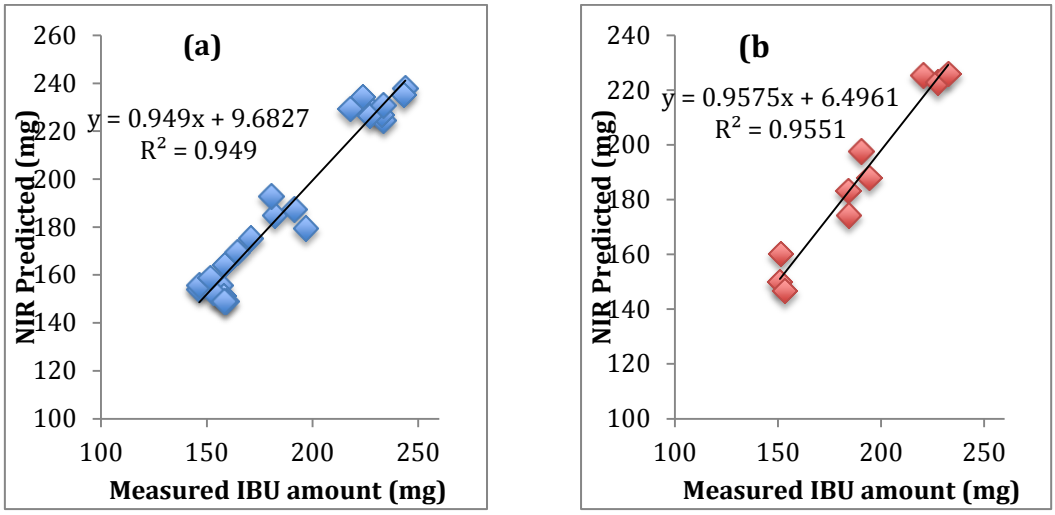


**Figure 5(a-b):** Regression plot between IBU amounts (mg) predicted by NIR method and the HPLC measured for (a) calibration samples and (b) validation samples using PLS model.

To establish the accuracy of the proposed method, a paired t-test for independent samples was performed between the tablet IBU contents (mg) predicted by the proposed method and those determined by the reference method (HPLC). The analysis was carried out for the ten validation tablets. The test confirmed the absence of significant differences between the two methods; as the $t_{exp}$(0.719) for NIR reflectance was less than the $t_{tab}$(2.26) at the 95% confidence level for the proposed method. **Table 2** shows the accuracy results.

**Table 2**: Accuracy of the proposed NIR method for the determination of IBU content (mg) in the validation set for content uniformity.

| **Validation samples** | **NIR reflectance predicted (mg)** | **HPLC measured (mg)** | **Recovery (%)** |
|---|---|---|---|
| **1** | 225.38 | 220.60 | 102.17 |
| **2** | 183.26 | 184.04 | 99.58 |
| **3** | 160.26 | 151.46 | 105.81 |
| **4** | 150.02 | 150.93 | 99.40 |
| **5** | 146.70 | 153.29 | 95.70 |
| **6** | 187.97 | 194.41 | 96.69 |
| **7** | 174.32 | 184.37 | 94.55 |
| **8** | 197.72 | 190.37 | 103.86 |
| **9** | 222.74 | 227.64 | 97.85 |
| **10** | 225.97 | 232.67 | 97.12 |
| **Accuracy** | **Mean** | | 99.27 |
| | **RSD (%)** | | 3.69 |
| | **t-test** | | 0.719(2.26)★ |

*The values in parentheses are the corresponding tabulated values at p=0.05.

**Measured by the reported HPLC method

The precision of the proposed methods was determined by measuring the repeatability and intermediate precision for the ten validation samples, as shown in **Table3.**

The root mean squared errors, together with regression and validation parameters for determination of IBU content (mg) in the validation set by the proposed NIR method were summarized in **Table 3**.

**Table 3**: Root mean squared errors,together with regression and validation parameters for determination of IBU content (mg) in the validation set by the proposed NIR method for content uniformity.

| Parameter | PLS (3) model★ |
|---|---|
| **Root mean squared errors ★★** | |
| RMSEC (%) | 2.24 |
| RMSECV (%) | 3.06 |
| RMSEP (%) | 1.83 |
| **Regression parameters** | |
| Range (mg) | 146.47 to 243.91 |
| Slope | 0.958 |
| Intercept | 6.50 |
| Regression coefficient ($R^2$) | 0.955 |
| **Accuracy** | |
| Mean ± SD | 99.27 ± 3.66 |
| **Precision** | |
| Repeatability (RSD %) | 0.10 |
| Intermediate precision (RSD%) | 0.12 |

*The number of latent variables (LVs) is represented in parentheses.

**Root mean squared error of calibration (RMSEC), root mean squared error of cross-validation (RMSECV) for the complete dataset and root mean squared error of prediction (RMSEP) for the test subset

### 3.4. Application to pharmaceutical formulation

The proposed NIR method was applied to determine the content uniformity for three batches (10 tablets for each batch) that represent the three levels of IBU content; batch 1 (each tablet claimed to contain 160 mg of IBU), batch 2 (each tablet claimed to contain 200 mg of IBU) and batch 3 (each tablet claimed to contain 240 mg of IBU), as

shown in **Figure 6**. The results for the ten tablets from each batch were within the limits established by both the European Pharmacopoeia (15% around the nominal content) and the US Pharmacopoeia (15% around the manufacturer's label claim), and the relative standard deviation (RSD %) for the average of each batch was below the level required by the US Pharmacopoeia (6%)**(Blanco et al., 2006)**. These results confirm that the proposed NIR method can be an effective alternative to the current HPLC reference method for determining content uniformity in pharmaceutical tablets containing 200 mg of IBU for the entire dosage interval from 80% to 120%.

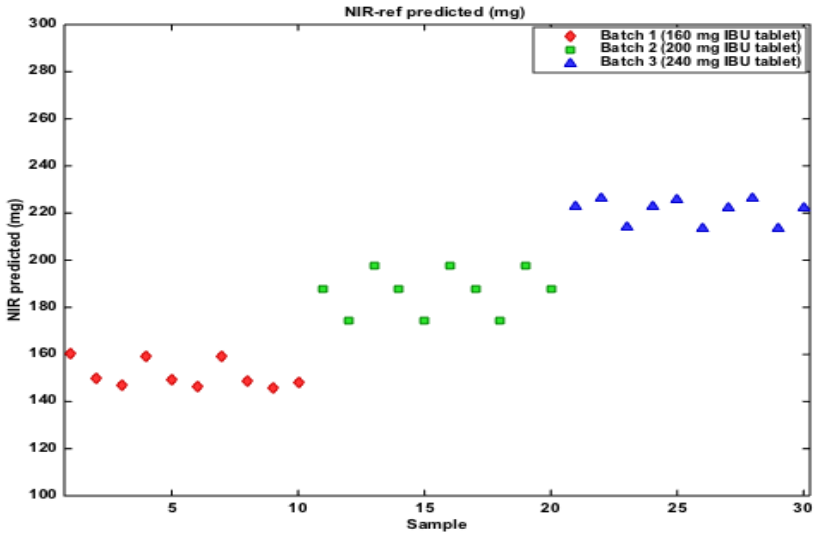


**Figure 6:** Ibuprofen contents (mg) predicted by the proposed NIR reflectance method for the tablets obtained from three batches.

## 4. Conclusion

The main objectives of this study were to develop and validate the NIR reflectance in conjunction with partial least squares (PLS) for the determination of ibuprofen (IBU) content for content uniformity of ibuprofen tablet. PLS calibration model was constructed using different IBU contents spanning from 146.47 mg to 243.91 mg. The PLS was characterized by RMSEP values of 0.96% for the NIR reflectance. Besides, the proposed NIR method was successfully implemented for the determination of the content uniformity for three batches that represent three levels of IBU content (160 mg, 200 mg and 240 mg).

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## تعيين تماثل المحتوى للأقراص الدوائية السليمة من قبل الأشعة تحت الحمراء القريبة المنعكسه

**للسادة الدكاترة**

أحمد شوقى أبوزيد[١] ، مايسة سالم[٢] ، إيمان الزنفلى[٢] ،أحمد الجندى[١] ،أحمد ابراهيم

**مـــــــــن**

[١]قسم الكيمياء التحليليةكلية الصيدلة جامعة مصر الدولية

[٢]قسم الكيمياء التحليليةكلية الصيدلةجامعة القاهرة

[٣]قسم الكيمياء التحليليةكلية الصيدلة جامعة ماريلاند بالولايات المتحدة الامريكية

**الكلمات الدالة**

تماثل المحتوى، الأشعة تحت الحمراء القريبة المنعكسه، ايبوبروفين، طريقة المربعات الصغرى الجزئية

**الملخص العربي**

تماثل المحتوى هو خاصية ذات أهمية حاسمةفي عملية تصنيع الأقراص الدوائية. وعادة يتم تعيين المادة الفعالة النشطة عن طريق تقنيات خارج خط الأنتاج مثل كروماتوجرافيا السائل ذات الأداء العالي و تعتبر هذة الطريقة بطيئة ومدمرة و تتطلب تحضير عينات. لذلك تم استخدام الأشعة تحت الحمراء القريبة كتقنية من تقنيات التكنولوجيا التحليلية العملية لتعيين المادة الفعالة النشطة وبالتالي تماثل المحتوى للأقراص الدوائية. و تعتبر الأشعة تحت الحمراء القريبةتقنية سريعة وغير مدمرة وتتطلب الحد الأدنى من تحضير العينة.الهدف من هذا الجزء هو تطوير والتحقق من صحة طريقة الأشعة تحت الحمراء القريبة المنعكسه لتعيين محتوى ايبوبروفين (ملغ) للتأكد من تماثل المحتوى للأقراص ايبوبروفين. تم إنشاء طريقة الأشعة تحت الحمراء القريبةبالتزامن مع طريقة المربعات الصغرى الجزئيةباستخدام محتويات مختلفة من أقراص ايبوبروفين من ١٤٦.٤٧ ملغ إلى ٢٤٣.٩١ ملغ للتأكد من تماثل المحتوى للأقراص ايبوبروفين. تم تقييم الأداء التنبئي لطرق المقترحة عن طريق المعايير الكيمومترية التقليدية و كان متوسط جذر مربع تنبؤ الخطأ ٠.٩٦٪ للأشعة تحت الحمراء القريبة المنعكسه. وبالإضافة إلى ذلك، تم التحقق من صحة طريقة الأشعة تحت الحمراء القريبة المقترحة و تطبيقها للتأكد من تماثل المحتوى لثلاث دفعات من أقراص ايبوبروفين تمثل ثلاث مستويات من محتوى ايبوبروفين (١٦٠ ملغ، ٢٠٠ ملغ، ٢٤٠ ملغ).