Quantitation of Active Pharmaceutical Ingredient through the Packaging Using Raman Handheld Spectrophotometers: A Comparison Study

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Handheld Raman spectroscopy is actually booming. Recent devices improvements aim at addressing the usual Raman spectroscopy issues: fluorescence with shifted-excitation Raman difference spectroscopy (SERDS), poor sensitivity with surface enhanced Raman scattering (SERS) and information only about the sample surface with spatially offset Raman spectroscopy (SORS). While qualitative performances of handheld devices are generally well established, the quantitative analysis of pharmaceutical samples remains challenging.

The aim of this study was to compare the quantitative performances of three commercially available handheld Raman spectroscopy devices. Two of them (TruScan and IDRaman mini) are equipped with a 785 nm laser wavelength and operate in a conventional backscattering mode. The IDRaman has the Orbital Raster Scanning (ORS) option to increase the analyzed surface. The third device (Resolve) operates with an 830 nm laser wavelength both in backscattering and in SORS modes.

The comparative study was carried out on ibuprofen-mannitol-microcrystalline cellulose ternary mixtures. The concentration of ibuprofen ranged from 24 to 52 % (w/w) while the proportions of the two excipients were varied to avoid cross-correlation as much as possible. Analyses were performed either directly through a glass vial or with the glass vial in an opaque polypropylene flask, using a validated FT-NIR spectroscopy method as a reference method. Chemometric analyses were carried out with the Partial Least Squares Regression (PLS-R)

algorithm. The quantitative models were validated using the total error approach and the ICH Q2 (R1) guidelines with +/- 15% as acceptance limits.

Keywords:

handheld spectrophotometers, Raman spectroscopy, Spatially Offset Raman Scattering, comparison of quantitative performances, quantitation through packaging

1. Introduction

There is a growing concern toward using vibrational spectroscopy in pharmaceutical quality control [1,2]. Raman spectroscopy is considered as an important analytical tool beside Near-Infrared (NIR) and High Performance Liquid Chromatography (HPLC) [3–5]. This technique is based on the interaction between the energy of a monochromatic light and a sample inducing light scattering. It is characterized by many advantages that may be summarized in its minimal sample preparation requirement, its ability to be used on-site via handheld instrument and the possibility to analyze the sample through clear glass and bottles made from polyvinyl chloride (PVC) or polypropylene (PP). Nevertheless, there are drawbacks that present challenges using the Raman technique. Some of these drawbacks are: sample auto-fluorescence that may overwhelm the signal coming from the analyzed sample, the challenges of analyzing heterogeneous samples because of the small analyzed volume and of carrying out a qualitative or quantitative analysis of a compound in a mixture through a package material such as blisters or plastic bottles [6–8].

The last cited challenge of analyzing a drug substance through package material could be overcome using a specific measuring configuration mode called spatially offset Raman scattering (SORS). The main difference between SORS and backscattering Raman is that the scattered light is collected at a spatially offset location situated a few millimeters from the illumination site. This configuration allows collecting photons that have gone deep in the sample leading to spectra predominantly composed of content's signal [9,10]. To obtain the SORS corrected spectra, the outer (container) spectrum is scaled and removed from the offset spectrum in order to obtain a clean spectrum of the content [11]. SORS has already proved its usefulness in many sectors. For instance, in the pharmaceutical field, it was used to detect various types of raw materials in a range of non-transparent sealed containers and it further allowed detecting counterfeits [10]. For food analysis, it was demonstrated that SORS is able to detect the internal maturity of tomatoes or to detect chemical markers that are responsible for the adulteration and falsification of spirit drinks through bottles [12]. The obtained results showed that SORS is well suited to conduct analyses through different types of containers and samples. In the present study, only offset spectra were used (without SORS correction).

Raman spectroscopy data must be analyzed with appropriate chemometric tools to extract relevant qualitative or quantitative information. Partial least squares regression (PLS-R) is a multivariate

data analysis method that is used to carry out the quantification of the target component in a mixture and can deal with interferences and overlapping bands [13,14].

The objective of the present study was to compare the quantitative performances of three handheld Raman spectrophotometers for the analysis a pharmaceutical powder sample directly through a glass vial and through a glass vial placed inside a polypropylene (PP) container. The pharmaceutical sample is a ternary mixture composed of ibuprofen, mannitol and microcrystalline cellulose. The prepared samples were analyzed by three handheld Raman spectrophotometers using different measurement technologies. Beside the handheld Raman devices, the samples were also analyzed with a benchtop NIR spectrophotometer used as reference equipment to check the sample preparation and detect possible outliers. The quantitative performance of the selected devices were evaluated based on accuracy profiles [15–17].

2. Material and methods

2.1. Instrumentation

The analyses were carried out on three handheld Raman instruments from different manufacturers. The first handheld Raman device is the TruScan spectrophotometer (Thermo Scientific, Waltham, MA, USA) utilizing a 785 nm excitation wavelength and covering the 250 to 2875 cm^{-1} Raman shifts range. The second device is the IDRaman mini (Ocean Optics, Largo, FL, USA) with a 785 nm excitation wavelength and covering the 400 to 2300 cm^{-1} spectral range and characterized by the option of Orbital Raster Scanning that increases the analyzed surface. The last device is the Resolve™ (Agilent Technologies, Santa Clara, CA, USA) utilizing an 830 nm excitation wavelength covering the 200 to 2000 cm^{-1} spectral region. This device can be used in two modes: conventional Raman spectroscopy and SORS. On the one hand, raw SORS data (ambient, zero and offset spectra) were extracted using the Resolve Database Data Viewer v0.0.8. Before being processed, raw offset spectra were corrected by removing the ambient spectra. However, no removal of the zero position spectra was performed. On the other hand, the backscattering spectra were pre-processed inside the device (baseline correction) and were subsequently imported directly from the latter.

The samples were also analyzed with a Fourier transform near infrared multipurpose analyzer spectrophotometer (MPA, Bruker Optics, Billerica, MA, USA). The spectra were collected with the Opus software V6.5 (Bruker Optics). Each spectrum was the average of 32 scans and the resolution was set at 8 cm^{-1} over the spectral range from 12500 to 4000 cm^{-1}.

2.2. Sample preparation

Different ternary mixtures of ibuprofen (Sigma-Aldrich, Belgium), microcrystalline cellulose (Sigma-Aldrich, Belgium) and mannitol (Sigma-Aldrich, Belgium) were realized to build both calibration and validation sets. Ibuprofen was chosen as test molecule because of its moderate Raman scattering character. This permits obtaining a balanced signal between ibuprofen and excipients.

For the calibration set, the concentration of ibuprofen varied at five levels: 24, 32, 40, 48 and 52 % (w/w) covering the range of 60 – 130 % around the target concentration of 40 % (w/w) (equivalent to 200 mg of ibuprofen). The amount of excipients added was varied in order to keep the total sample weight constant at 500 mg in each mixture. Correlation of the API to the excipients was minimized equally by varying the proportion of the excipients at each ibuprofen concentration level. An equal mass mixture with each of the three components at 33.3 % w/w was also added leading to a total of 26 calibration samples (see Table S1).

The validation set consisted of five concentration levels of ibuprofen (28, 34, 40, 46 and 52 % w/w)) covering the range between 70-130 % of the target ibuprofen concentration. The ratio between the excipients was varied leading to 15 validation samples per series (see Table 1). Three series of validation were realized independently with new sample preparation and restart/recalibrate each device on each new series.

Once weighted, the powders were finely grinded in a pestle and mortar to ensure homogeneous mixtures and placed in glass vials. Each mixture was analyzed in triplicate.

Both calibration and validation samples were analyzed directly through the glass vial (thickness of 1 mm) and through the glass vial placed in an opaque white PP container (thickness of 1mm). The analysis of the mixtures through the packaging was performed with all handheld Raman instruments. FT-NIR spectra were only acquired in reflectance mode on the glass vial.

2.3. Multivariate data analysis

The regression model was developed based on the partial least square (SIMPLS) algorithm using the PLS Toolbox V8.2.1 (Eigenvector Research INC, USA) running on Matlab (R2018b) (The Mathworks, USA). The Y block used was composed of actual weights and the same Y block was used for all instruments. Different preprocessing techniques were investigated and compared based on the root mean square difference of prediction (RMSEP). The combination of standard normal variate (SNV) normalization with mean centering proved to be the most suitable for FT-NIR data, while the combination of the Savitzky-Golay 1st derivative (polynomial order: 2, window size: 15), SNV and mean centering provided better predictions for Raman spectroscopy.

The accuracy profiles were computed using the results from the three validation series composed of three replicates at five concentration levels measured on each device using e-noval V4.0b (Pharmalex Belgium SA, Mont-Saint-Guibert, Belgium) with 95% β-expectation tolerance intervals [16,18–20]. The acceptance limits were set at +/- 15 % of relative total error following the European Pharmacopoeia general monograph 2.9.40 on the uniformity of dosage units.

3. Results and discussion

Actually, handheld Raman spectrophotometers are designed for qualitative analysis since the acquisition time is optimized at each measurement to obtain a sufficient signal to noise ratio [2]. Moreover, quantitation of active ingredients becomes a challenge when this is to be performed through thick and opaque containers. During this study, different ternary mixtures of ibuprofen/mannitol/MCC were prepared following the scheme described in section 2.2. Figure 1 shows the Raman spectra of each raw material and of the ternary mixture of ibuprofen/MCC/mannitol in the proportions 4/3/3, respectively. Once the samples were prepared and placed in the glass vials, they were first analyzed by FT-NIR spectroscopy. The obtained NIR spectra were then processed by PLS-R allowing us to ensure that the mixtures were correctly prepared (the detected outliers were removed and prepared again). The computed PLS-R model based on FT-NIR data has been validated and the accuracy profile computed. The beta-expectation tolerance intervals (β = 95%) was well included in the previously set +/- 15 % of relative total error.

Once the samples were verified by FT-NIR, they underwent analyses by the different handheld systems directly through the glass vial and through the glass vial placed in the PP container (see photos in supplementary materials).

3.1. Analysis of samples through glass vial

Figure 2 shows the baseline corrected spectra acquired on each device in backscattering mode through the glass vial for a mixture of ibuprofen/MCC/mannitol in the proportions 4/3/3, respectively. The mixture and ibuprofen spectra were recorded through a thin plastic bag to avoid any interference from the glass. The dashed red lines indicate the main spectral features of ibuprofen and the blue dashed line indicates the main peak of mannitol. No specific peak associated to cellulose was observable because cellulose is a weak Raman scatterer and its features are masked by the other components. Nevertheless, cellulose disturbs the global signal due to a high fluorescence background. On this Figure 2, it is possible to see that the signal measured with each device exhibits a spectrum directly correlated to the mixture spectrum with the main spectral features of ibuprofen and mannitol. The spectra recorded with the TruScan and the IDRaman mini also exhibit a spectral perturbation between 1300 and 1500 cm^{-1} due to the fluorescence of glass with the 785 nm incident laser source.

The spectra obtained with each instrument (ID Raman mini, TruScan, Resolve) were modelled using PLS models. Several pre-processing and spectral ranges were tested. The best pre-processing and spectral range were selected based on the RMSEP and the bias computed on the validation set. Once the final PLS model selected, the accuracy profiles were computed for each device. Table 2 summarizes the final parameters used for the PLS models and their respective figures of merit. Each Raman spectroscopy model used the Savitzky-Golay [21] first derivative as pre-processing. Indeed, most devices use a 785 nm laser as light source. However, glass exhibits a high fluorescence background when irradiated by a 785 nm light and the use of the first derivative helped managing the fluorescence.

The computed accuracy profiles are shown in Figure 3 and the values of the validation criteria are reported in table 3. As can be noticed, all the selected devices provided good results as their 95% β-expectation tolerance intervals are included inside the acceptance limits of +/- 15%. This means

that 95% of future measurements will have an accuracy (total error) of less than +/- 15%. These results indicate that for formulations with a well-balanced signal of both excipients and API in a transparent container, satisfying quantitative performances may be obtained using Raman handheld devices in their native configuration (auto-exposure).

3.2. Analysis of samples through glass vials placed in a polypropylene container:

Figure 4 shows the baseline corrected spectra acquired on each device in backscattering mode and SORS mode (for the Resolve) through the glass vial placed in the PP container for a mixture of ibuprofen/MCC/mannitol in the proportions 4/3/3, respectively. The dashed red lines indicate the main spectral features of ibuprofen and the blue dashed line indicates the main peak of mannitol. Compared to the spectra shown on Figure 2, the spectra recorded through the PP container show no spectral features associated with ibuprofen nor mannitol except for the SORS spectra. It is worth noting that the SORS spectra presented here and subsequently used in the quantitative modelling are only the offset part of the spectrum. Indeed, usually final SORS spectra are obtained after removal of the zero spectrum (equivalent to the backscattering recorded spectrum) from the offset spectrum to remove the residual container spectral features. Since the SORS correction parameters (baseline correction and removal of the scaled "zero offset" spectrum) are computed for each spectrum separately, this led to additional random error on the quantitative models. Therefore, to avoid errors when removing the zero offset, this step was skipped and the offset spectrum was directly used.

Once again, PLS models were built for each device and several pre-processing and spectral ranges were tested. Accuracy profiles were computed based on the predicted values from the PS models. The results are summarized in Figure 5 and the parameters values of the validated models are presented in table 3. None of the backscattering devices was able to quantify ibuprofen through the PP container because no (or very few) signal originating from the sample was measured in this configuration. Indeed, after applying the mean centering prior to the modelling, no residual signal was observed, only noise. That means that all spectra were the same for each validation and calibration sample because only the PP signal was recorded.

However, the Resolve operating in the SORS mode was able to achieve satisfying quantitation of the sample through the PP container since its accuracy profile was completely included in the acceptance limits. Furthermore, SORS measurements are more representative of the sample since the recorded signal has gone through a higher sample volume.

4. Conclusion

The aim of this study was to carry out a comparison study between conventional backscattering and Spatially Offset Raman Scattering (SORS) Raman handheld instruments. This comparison has been performed measuring a ternary mixture of ibuprofen/MCC/mannitol directly through a glass vial and with the glass vial placed in a PP container. PLS models were built for each device and each measurement configuration. The predicted values obtained from the PLS models on a validation set were used to compute accuracy profiles following the ICH Q2 R1 guidelines on validation with ±15% as acceptance limits.

By measuring through the glass vial, the Raman spectra showed clear features associated with both the API and the excipients leading to satisfying quantitative performances. The subsequent models and predictions were validated and their accuracy profiles were included inside the a priori defined acceptance limits. This confirms the fact that it is possible to obtain reliable quantitative information with handheld devices with their auto-exposure default configuration. However, it is worth noting that this is only true for the studied formulation with a well-balanced signal between the API and excipients.

However, none of the backscattering Raman handheld devices was able to quantify the mixture when it was placed in an opaque 1 mm PP and 1 mm thick glass containers. To be able to pass through the packaging, the SORS measurement configuration was necessary and allowed to obtain a valid PLS model.

These preliminary results pave the way to reliable quantitative Raman measurements directly in the field through opaque containers.

Acknowledgments

This project has been supported by the European funds of regional development (FEDER) and by Walloon as part of the operational program “Walloon-2020.EU”.

The financial support of this research by the Walloon Region of Belgium in the framework of the Vibra4Fake project (convention n°:7517) is gratefully acknowledged.

This work was supported by the National Fund for Scientific Research, FNRS-F.R.S. (1.A030.17 - FC6921).

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Figures:

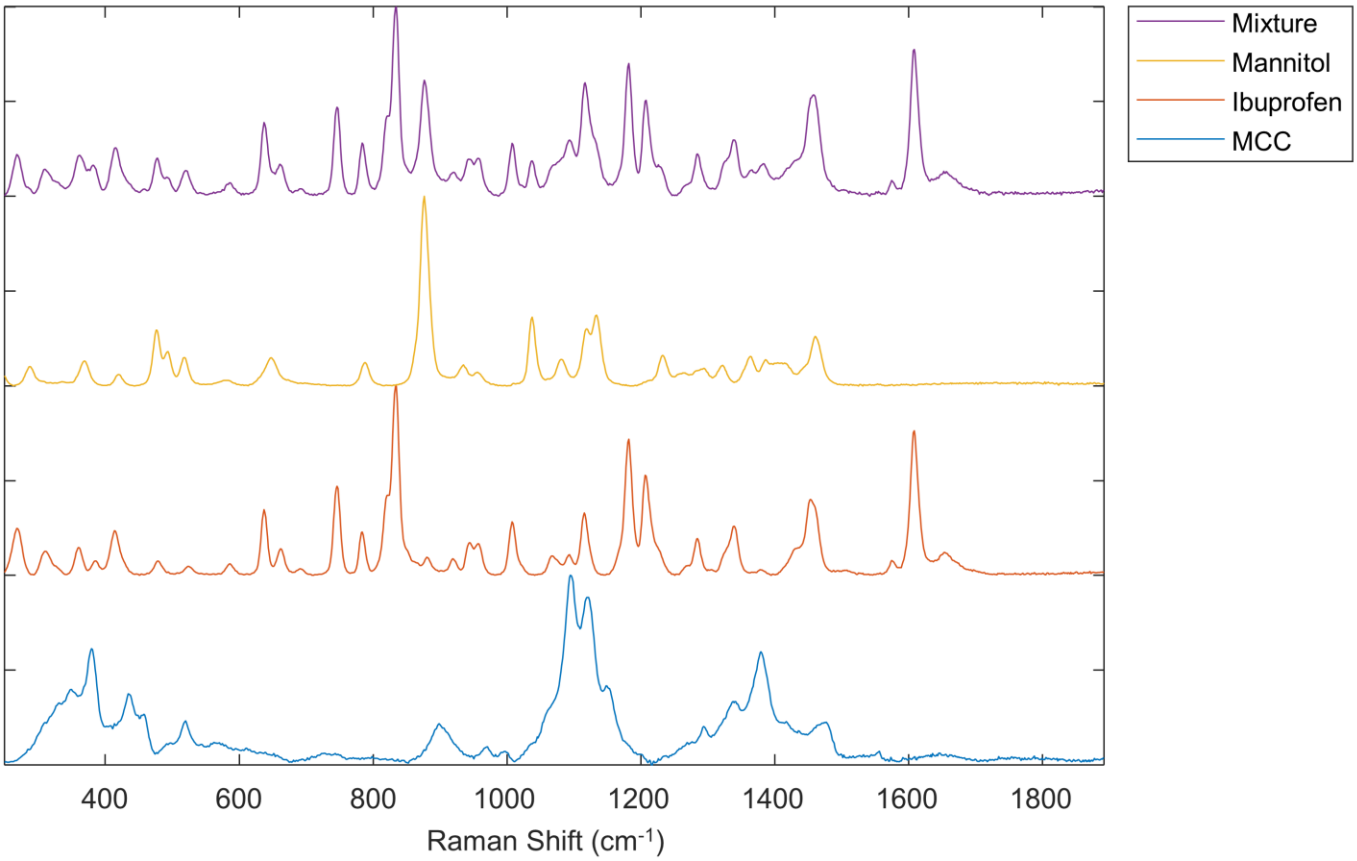


Figure 1: Raman spectra of raw materials and ternary mixture ibuprofen/MCC/mannitol in the proportions 4/3/3 respectively. The spectra were acquired with the TruScan in "signature" mode through a thin plastic bag and were baseline corrected by asymmetric least squares[22][22][22][23][23] with parameters: lambda 10^5, p: 10^{-3}.

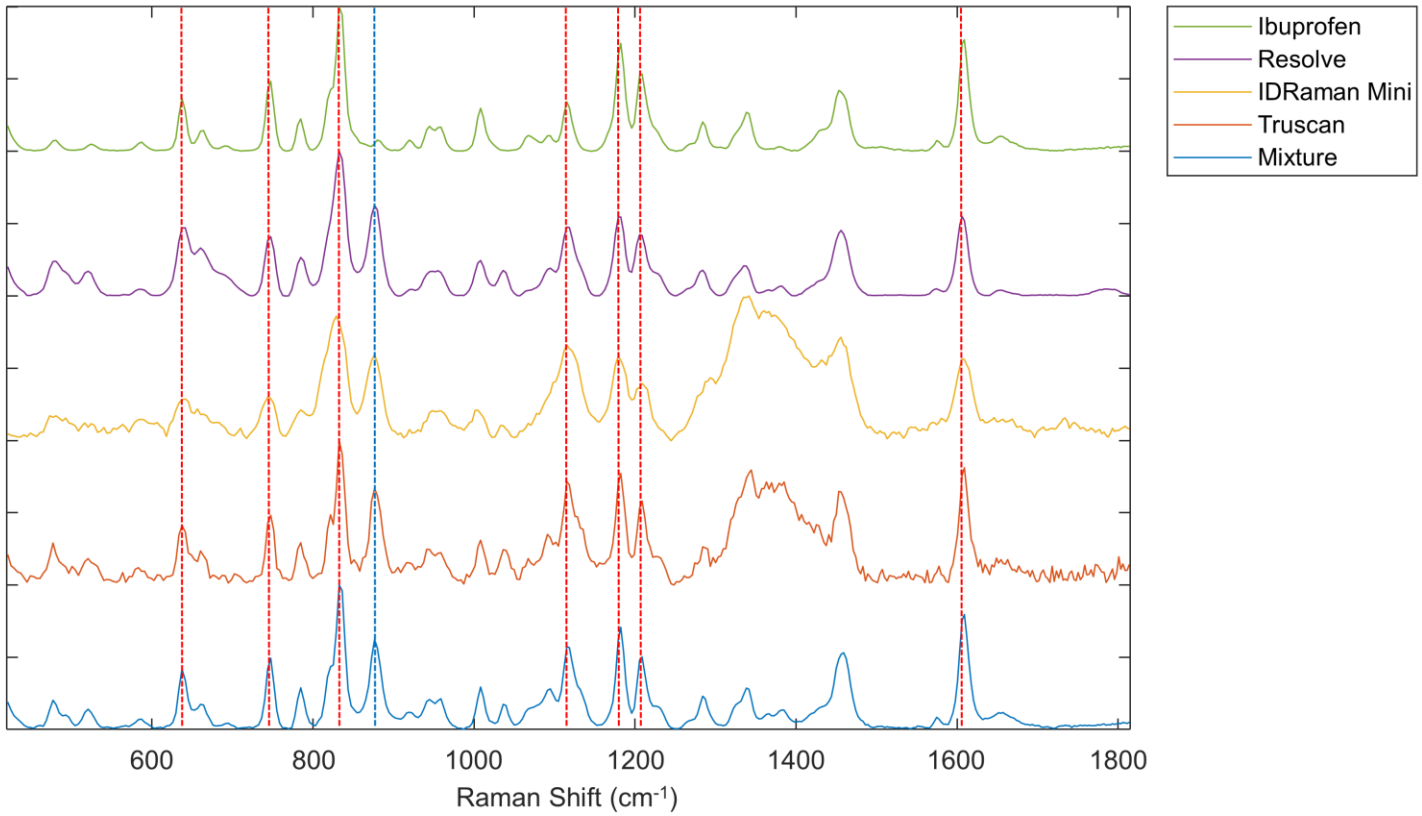


Figure 2: Raman spectra of a ternary mixture ibuprofen/MCC/mannitol in the proportions 4/3/3 respectively. The spectra were acquired with each handheld device in the backscattering mode through the glass vial. The spectra were baseline corrected by asymmetric least squares with parameters: lambda 10^5, p: 10^{-3}. Reference spectra of ibuprofen and the ternary mixture were acquired as described in Figure 1. Ibuprofen and mannitol spectral features are marked by dashed red and blue lines respectively.

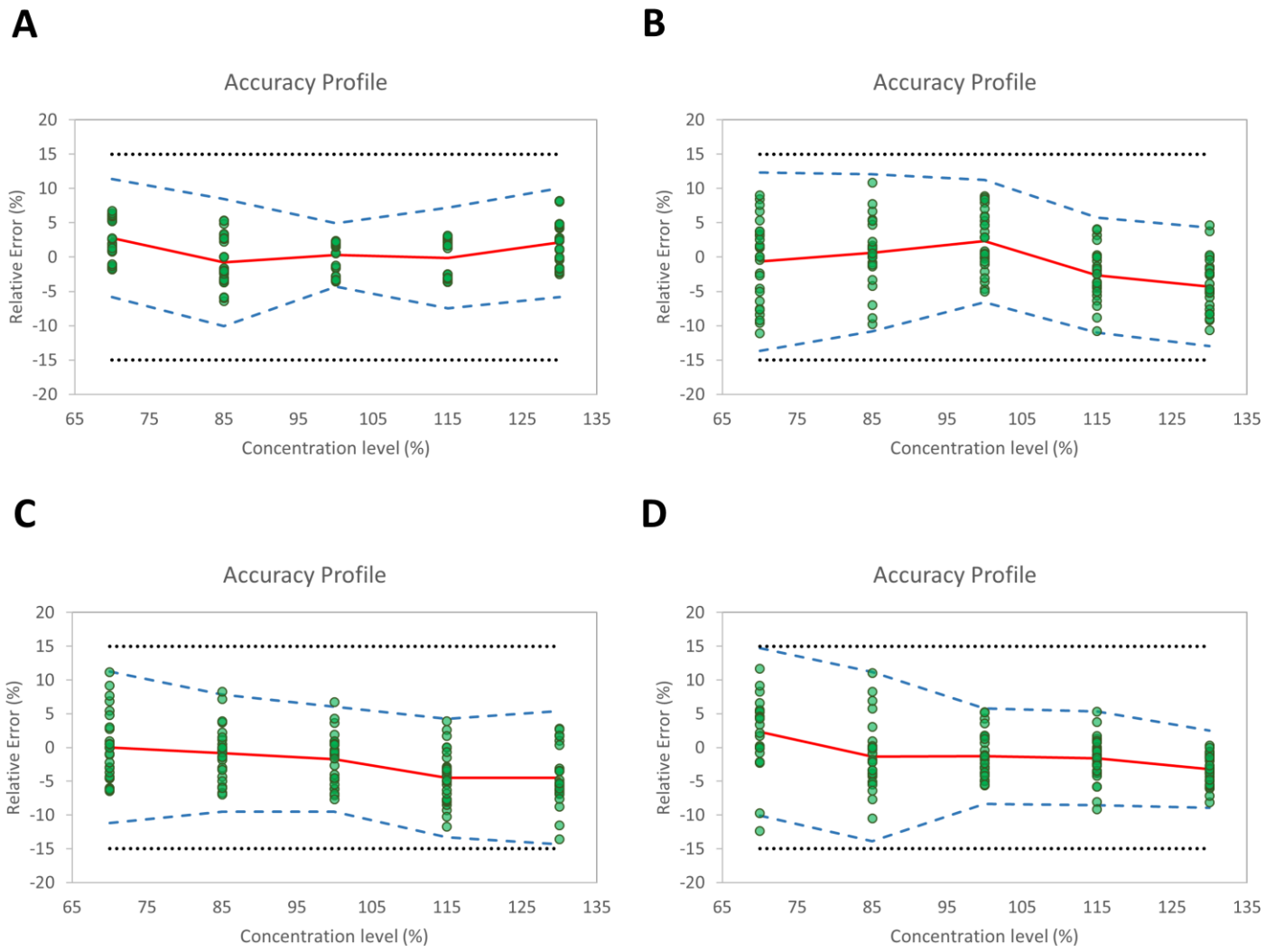


Figure 3: Accuracy profiles obtained with each handheld device (A: MPA, B: TruScan, C: IDRaman Mini, D: Resolve) in backscattering mode through the glass vial. The plain red line is the relative bias, the dashed blue lines are the β-expectation tolerance limits (β = 95%) and the dotted black lines are the acceptance limits set at 15%. The green dots represent the relative errors of each validation results.

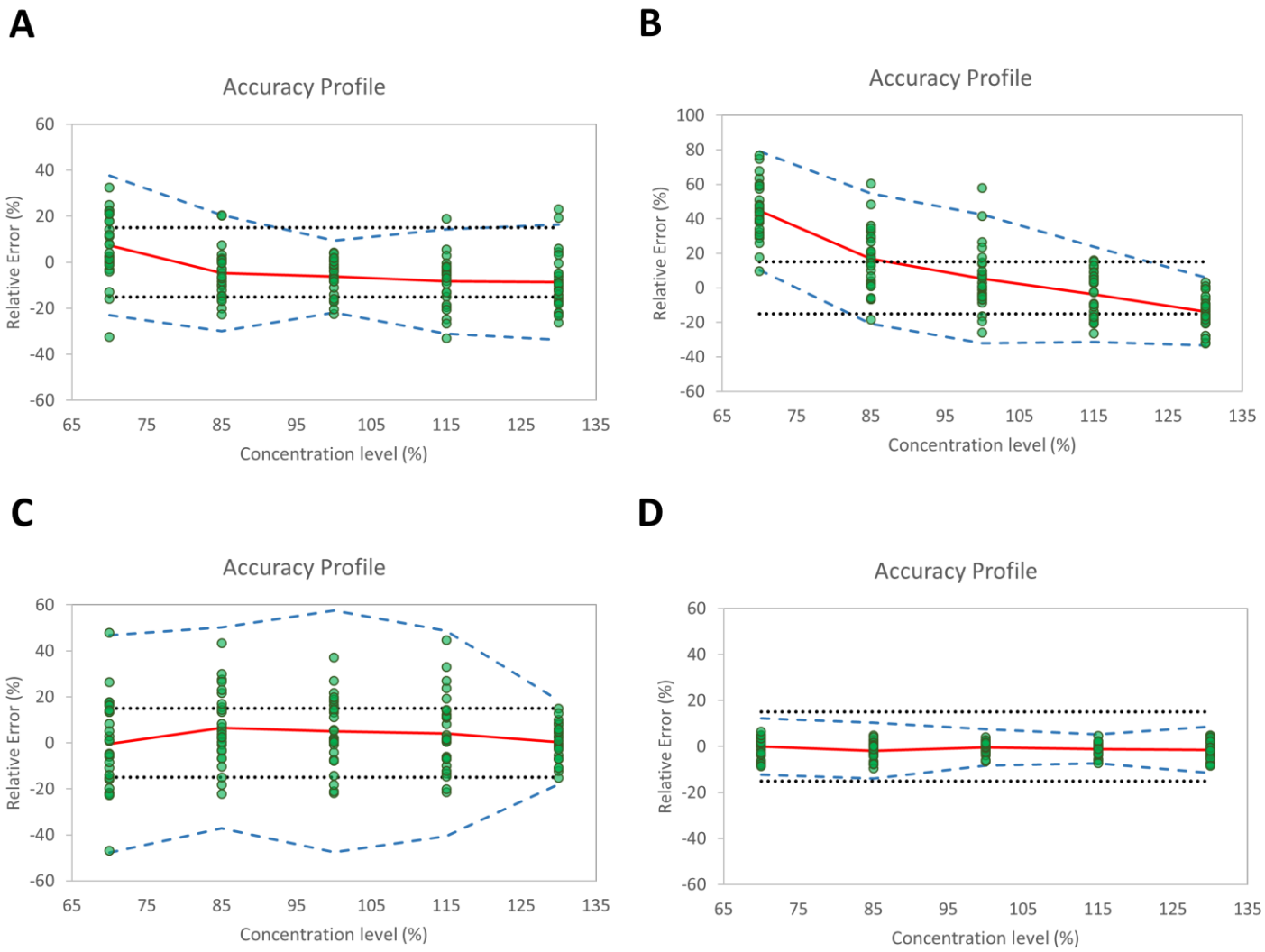


Figure 4: Raman spectra of a ternary mixture ibuprofen/MCC/mannitol in the proportions 4/3/3 respectively. The spectra were acquired with each handheld device in the backscattering mode and the Resolve in SORS mode through the glass vial placed in the polypropylene container. The spectra were baseline corrected by asymmetric least squares with parameters: lambda 10^5, p: 10^{-3}. Reference spectra of ibuprofen and the ternary mixture were acquired as described in Figure 1. Ibuprofen and mannitol spectral features are marked by dashed red and blue lines respectively.

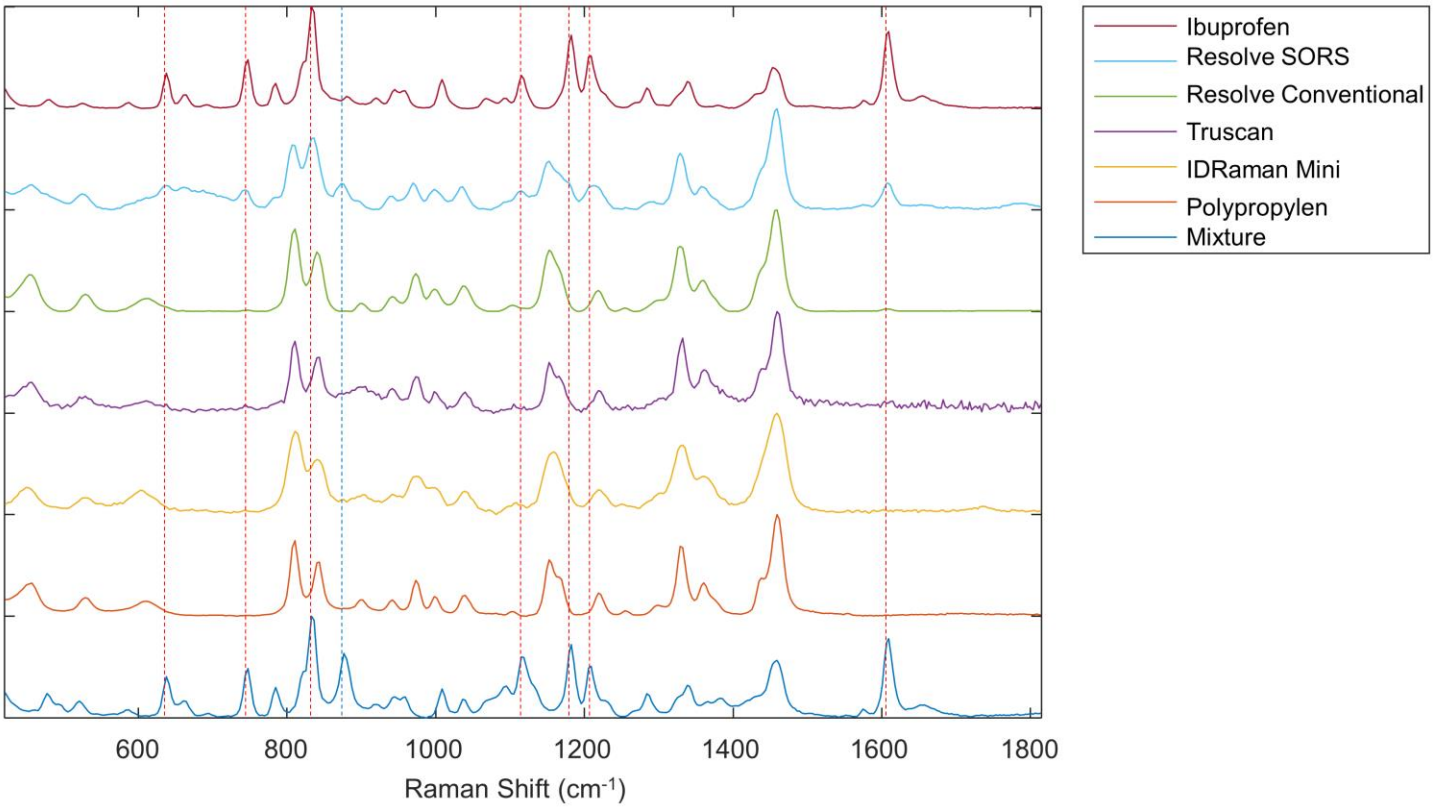
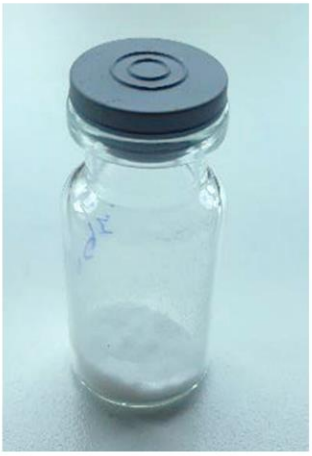


Figure 5: Accuracy profiles obtained with each handheld device (A: TruScan, B: IDRaman Mini, C: Resolve backscattering and D: Resolve SORS) mode through the glass vial placed in the opaque polypropylene container. The plain red line is the relative bias, the dashed blue lines are the β-expectation tolerance limits (β = 95%) and the dotted black lines are the acceptance limits set at 15%. The green dots represent the relative errors of each validation sample.

Figure S1

Polypropylene container used

Vial container used



Vial and Polypropylene container used

Vial in the Polypropylene container used

Table 1: composition of validation samples

	Quantity of compounds (mg)				Concentration (% w/w)		
Concentration level	**Ibuprofen**	**MCC**	**Mannitol**	**Total**	**Ibuprofen**	**MCC**	**Mannitol**
70 % label claim	140	36	324	500	28	7.2	64.8
		108	252			21.6	50.4
		180	180			36	36
85 % label claim	170	231	99		34	46.2	19.8
		297	33			59.4	6.6
		33	297			6.6	59.4
100 % label claim	200	90	210		40	18	42
		150	150			30	30
		210	90			42	18
115 % label claim	230	243	27		46	48.6	5.4
		27	243			5.4	48.6
		81	189			16.2	37.8
130 % label claim	260	120	120		52	24	24
		168	72			33.6	14.4
		216	24			43.2	4.8

MCC: microcrystalline cellulose

Table 2: Regression model parameters and figures of merit of handheld Raman devices and FT-NIR

	Resolve			TruScan RM		IDRaman mini		FT- NIR
Sample	Glass vial + PP	Glass vial + PP	Glass vial	Glass vial + PP	Glass vial	Glass vial + PP	Glass vial	Glass vial
Mode	SORS	Backscattering	Backscattering	Backscattering	Backscattering	Backscattering	Backscattering	Reflection
Spectral Range (cm^{-1})	1152-1608	400-1700	400-1700	1000-1600	400-1700	600-1700	400-1700	9000-4000
Pre-processing	SG1D (2,15); SNV; MC			SG1D (2,15); SNV; MC		SG1D (2,15); SNV; MC		SNV; MC
Latent Variables	6	7	3	6	3	5	3	5
R^2 calibration	98.7	97.2	96.0	98.7	94.0	99.8	98.7	99.0
RMSEC (mg)	5.6	8.5	10.1	5.9	12.4	2.4	5.6	5.3
R^2 Cross Validation	97.8	89.3	95.7	58.8	92.3	37.2	95.0	98.7
RMSECV (mg)	7.4	16.6	10.5	32.3	14.2	40.6	11.0	5.9
R^2 prediction	93.0	83.1	92.3	66.4	91.6	9.5	96.5	95.5
RMSEP (mg)	12.7	19.8	12.6	27.0	12.7	45.4	13.6	9.0

SG1D: Savitzky-Golay first derivative (polynomial order, window size)

SNV: standard normal variate

MC: mean centering

Table 3: ICH Q2 (R1) validation criteria values of the PLS models.

	Concentration level	SORS (glass vial + PP)	Resolve (glass vial)	TruScan RM (glass vial)	IDRaman mini (glass vial)	FT-NIR
Trueness Relative bias (%)	70	0.665	2.319	-0.647	0.034	2.790
	85	-1.226	-1.315	0.637	-0.848	-0.771
	100	-0.377	-1.289	2.332	-1.726	0.291
	115	-1.688	-1.587	-2.632	-4.516	-0.150
	130	-3.030	-3.197	-4.335	-4.484	2.138
Intra-assay precision Repeatability (RSD %)	70	3.308	5.813	5.953	5.206	2.338
	85	3.400	4.872	5.002	3.984	3.346
	100	2.406	3.375	4.244	3.707	2.205
	115	2.883	3.308	3.873	3.884	2.230
	130	3.483	1.968	3.586	3.617	2.777
Between-assay precision Intermediate precision (RSD %)	70	4.824	5.813	6.117	5.283	3.276
	85	3.400	5.525	5.251	4.071	3.971
	100	2.468	3.375	4.244	3.707	2.205
	115	3.331	3.308	3.922	4.089	2.932
	130	4.103	2.415	3.928	4.277	3.372
Accuracy Relative β - expectation tolerance limits (%)	70	[-12.52 , 13.85]	[-10.11 , 14.75]	[-13.64 , 12.35]	[-11.20 , 11.27]	[-5.82 , 11.40]
	85	[-8.41 , 5.95]	[-13.85 , 11.22]	[-10.79 , 12.06]	[-9.53 , 7.83]	[-10.04 , 8.50]
	100	[-5.60 , 4.85]	[-8.36 , 5.78]	[-6.58 , 11.25]	[-9.49 , 6.04]	[-4.33 , 4.91]
	115	[-9.25 , 5.87]	[-8.52 , 5.34]	[-10.99 , 5.73]	[-13.28 , 4.25]	[-7.48 , 7.18]
	130	[-12.47 , 6.41]	[-8.92 , 2.53]	[-12.97 , 4.30]	[-14.35 , 5.38]	[-5.79 , 10.07]

Table S1: composition of calibration samples

Concentration level	Total mixture weight (mg)	Ibuprofen (% w/w)	Excipients (% w/w)	Excipient proportions									
				Proportion 10:90		Proportion 30:70		Proportion 50:50		Proportion 70:30		Proportion 90:10	
				MCC	Mannitol	MCC	Mannitol	MCC	Mannitol	MCC	Mannitol	MCC	Mannitol
				(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)
60% label claim	500	24	76	38	342	114	266	190	190	266	114	342	38
80% label claim	500	32	68	34	306	102	238	170	170	238	102	306	34
100% label claim	500	40	60	30	270	90	210	150	150	210	90	270	30
120% label claim	500	48	52	26	234	78	182	130	130	182	78	234	26
130% label claim	500	52	48	24	216	72	168	120	120	168	72	216	24
Equal mass point	500	33.33	66.67	166.67 mg of MCC – 166.67 mg of Mannitol									

MCC: microcrystalline cellulose