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Vibrational spectroscopy in analysis of pharmaceuticals: Critical review of innovative portable and handheld NIR and Raman spectrophotometers

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Abstract

The fast pace of changes occurring in the pharmaceutical world emphasizes the need for powerful technologies that allow checking the quality of pharmaceutical products. Infrared and Raman spectroscopies have shown great potentialities for drug analysis in the last decades and consequently caught the attention of the scientific world as well as of industrial developers, leading to major technological advancements. These fast, eco-friendly, and non-destructive techniques help gather essential information about the samples under examination with consistent advantages. This review focuses on the application of portable/handheld NIR and Raman spectrophotometers in the analysis of pharmaceutical products for both in-process and quality control tests. Moreover, analytical methods developed by several authors are described in order to illustrate the applications explored until now.

Keywords: chemometrics; falsified drugs; handheld; IR spectroscopy; pharmaceutical analysis; portable; quality control; Raman; SERS; SORS

Abbreviations: API, active pharmaceutical ingredient; FIR, far infrared; IR, infrared; LOD, limit of detection; MIR, mid-infrared; NIR, near-infrared; Ph. Eur., European pharmacopoeia; SERS, surface-enhanced Raman scattering; SORS, spatially offset Raman scattering; USP, United States Pharmacopeia

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1. Introduction

Vibrational spectroscopy techniques based on infrared (IR) and Raman spectrophotometers are becoming common practice in the pharmaceutical industry in both manufacturing and quality control laboratories. Identification of raw materials and finished products as well as polymorphism characterisation and quantification of active pharmaceutical ingredients (APIs) and excipients are the main applications found in scientific literature. Infrared and Raman spectroscopies allow for both qualitative and quantitative analyses to be carried out and their application have been efficiently demonstrated to be convenient and appropriate in the context of drug testing. The reason behind the success of these techniques is their convenience; they require no (or almost no) sample preparation, they are non-destructive, and they do not require any (or just a small amount of) solvents. All these aspects result in techniques that are eco-friendly, timesaving, and - with the coming of new portable and handheld devices - applicable for in situ analyses [1]. The miniaturisation of vibrational spectrophotometers permits measurements to be performed directly in the field of interest. Figure 1 shows the number of annual publications related to the application of these devices in many fields. A clear increasing trend in the number of publications can be observed since 2010 revealing the increasing usage of portable and handheld devices. One of the advantages of this approach is the possibility to minimise the time needed for analyses, for instance before accepting an incoming material or approving a batch of production before its progression in the manufacturing stream. Confirming the interest for such devices, the European Pharmacopeia (Ph. Eur.) and the United States Pharmacopeia (USP) added them to their Raman spectroscopy monograph (Ph. Eur. 2.2.48 and USP <1120>).

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1.1. Raman spectroscopy

The Raman phenomenon has been described almost 90 years ago, but only in recent years has the use of Raman spectroscopy become generalised in various fields, such as the food industry and the archaeological science/chemistry [2–6]. For Raman analysis, a monochromatic light is used to interact with the sample. Inelastically-scattered light (approximately 1 in 10 million photons) contains information correlated to the vibrational modes of the chemical species that constitute the sample, resulting in a very selective technique. [7].

However, Raman spectroscopy presents some issues such as the negative effect of fluorescence and the lack of sensitivity. Attempts to overcome these limitations have been made and alternative methodologies have been developed, both of which are discussed below. For pharmaceutical applications, the best compromise between fluorescence and signal intensity is the use of 785 nm laser for excitation. This explains why most handheld systems are equipped with such laser wavelength (e.g. Thermo Fisher's Truscan™, B&W Tek's Nanoram™, Metrohm's MIRA™, SciAps's Inspector 300™, and TSI's ASSURx™).

Surface-enhanced Raman scattering (SERS) is an alternative Raman technique that has been increasingly applied throughout the last decade [8]. It consists in using roughened metallic surfaces, mainly silver and gold colloids, on which the analyte is adsorbed in order to increase the Raman scattering. The Raman scattering resulting from this technique can be 10^3-10^6 times greater than by using conventional Raman analyses. Sensitivity issues can therefore be dealt with.

Spatially offset Raman spectroscopy (SORS) is another methodology, introduced by Matousek *et al.* in 2005, that allows drug products to be directly analysed through opaque packaging and without any sampling preparation process [9]. It consists in performing the

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analysis on the container surface at different spatial offsets from the illumination zone. The spectra obtained contain the relative Raman contributions of both packaging and content that are then separated by using a scaled subtraction to obtain the pure Raman spectrum of the sample's individual regions [9].

This way, incoming pharmaceutical materials, for instance, can be tested without opening the container or liner, guaranteeing their integrity and preventing some phenomena such as cross-contamination or operator exposure to high potent APIs. The suitability of SORS in this context has already been demonstrated for detecting various pharmaceutical compounds in different non-transparent containers. (Agilent's Resolve^{TM} handheld device or RapID portable device). [10,11].

Conventional Raman handheld or portable devices can perform some analysis through most transparent (or semi-transparent) containers such as plastic bags and glass bottles. However, SORS technology can analyse materials through opaque or thick containers such as multilayer paper sacks, barrels and big bags. The performance of the equipment is dependent on the Raman scattering properties of the analysed materials. If the analysed compound is a high Raman scatterer, good performances may be obtained even through thick containers using the portable RapID device. Nevertheless, some containers, such as cardboard barrels or metallic containers, remain inaccessible even for SORS technology.

1.2. Infrared spectroscopy

While Raman spectroscopy is based on the scattering phenomenon, IR spectroscopy is based on the absorption of light. IR spectroscopy is divided according to the spectral range in near infrared (NIR) (0.8 – 2.5 µm, respectively 12,500 – 4,000 cm^{-1}), mid-infrared (MIR), (2.5 – 25 µm, respectively 4,000 – 400 cm^{-1}) and far infrared (FIR) (25 – 1,000 µm,

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respectively 400 – 10 cm^{-1}) spectroscopy. Although the FIR spectral region shows some interest regarding solid state characterisation of the sample – this region being mainly influenced by crystal lattice vibrations – it is rather difficult to access, also considering no handheld or portable device is available with FIR spectroscopy. Nevertheless, this region (400-10 cm^{-1}) can be easily accessed through Raman spectroscopy. Although handheld devices are generally limited to 175-200 cm^{-1}, low frequencies can be easily accessed by setting specific configurations (specific notch filters) on portable devices (e.g. up to 65 cm^{-1} with iRaman plus from B&W Tek).

Handheld NIR spectroscopy can be performed in a reflective mode using "point-and-shoot" configuration due to weaker absorption of NIR light. On the other hand, MIR spectroscopy is generally performed with an attenuated total reflectance (ATR) crystal interface. It therefore requires sample handling and cannot be used to interrogate materials through packaging. A detailed review of portable spectroscopy technologies may be found in [12].

1.3. Comparison between Raman and IR: advantages and disadvantages

Due to the complementarity of their spectral information, IR and Raman spectroscopies are often jointly used. Advantages and disadvantages of each technique are discussed in this section.

First, it is important to underline that both allow performing with very little or no sample preparation. In many cases, samples can be directly analysed in their original state, without altering their nature [13]. Second, these non-invasive techniques are suitable for many pharmaceutical purposes, which are described in the second part of this review. The main difference between these techniques is the sample volume interrogated. Indeed, when using an ATR interface (for MIR spectroscopy), the penetration depth of light is of 0.5-2 µm

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depending on the crystal and the wavenumber considered. NIR spectroscopy in reflectance mode and Raman spectroscopy have a penetration depth of several millimetres (1-3 generally) depending on the sample nature, the wavelength and the light power. Beside penetration depth, the sample volume interrogated also depends on the spot size, usually smaller for Raman devices (1-2 mm) than for NIR devices (5-10 mm). The interrogated sample volume is therefore typically of ~10 μm^3 for ATR-IR, ~10 mm^3 for Raman spectroscopy and 75 mm^3 for NIR spectroscopy. These considerations on analysed sample volume may be crucial depending on the application. Indeed, the analysis of raw pure material may be performed with small volume technologies (e.g. Raman) because their homogeneity is usually good. On the other hand, pharmaceutical finished products may be relatively inhomogeneous and therefore using a larger sampled volume or performing the analysis at different spatial points may lead to more reliable results. Orbital raster scanning (ORS), a technology integrated to Metrohm's MIRA device, addresses the issue by moving the laser spot over a larger sample region.

Contrarily to wet techniques such as liquid chromatography, these techniques do not involve the use of organic solvents and their analysis time is considerably reduced. Furthermore, the simplicity of their application allows analyses to be carried out by minimally trained staff. All these aspects result in significant time and cost savings, and in more eco-friendly techniques. Notably, water being a weak Raman scatterer, Raman spectroscopy permits analyses to be conducted in aqueous solutions with limited interferences, unlike IR [14]. By contrast, NIR spectroscopy collects information about moisture and varying hydration states in samples with increased efficiency [15].

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As for every technique, the spectroscopic ones present some limitations - some of which have been already mentioned - that can challenge operators. Focusing the attention first on Raman spectroscopy, lack of sensitivity arises as a major issue. As discussed in 1.1., for analyte molecules that do not present a strong Raman effect, this issue can be overcome by means of SERS measurements, obtaining in some cases enhancement factors of 10^6 [16]. Another significant limitation in Raman spectroscopy is the fluorescence interference (intrinsic or imputed to the presence of impurities) that can entirely mask Raman scattering. A frequently used mitigation approach consists in shifting the laser wavelength to the NIR spectral range (e.g. 1,064 nm for Rigaku's Progeny™ or 1,030 nm for SciAps's Inspector 500™), for which fluorescence is less observed. Another recently proposed solution is the use of shifted-excitation Raman difference spectroscopy [17], also available in handheld systems (Bruker's Bravo™).

With NIR spectroscopy, the signal arises from combination and overtone bands. It is also much less distinctive, especially for higher overtones (i.e., at shorter wavelengths). The complex interpretation of spectra therefore requires allocating resources to the conception of chemometric models and having highly trained staff.

1.4. Chemometric tools

Nowadays, the use of chemometric methods with vibrational spectroscopy is well documented in the pharmaceutical field (general monographs Ph.Eur. 5.21 and USP <1039>).

Although raw material identification with handheld Raman spectrophotometer may be performed by the application of a correlation coefficient, it is inefficient for similar compounds or when comparing generic final products. Therefore, for most applications of Raman spectroscopy and almost all NIR spectroscopy application, multivariate data analysis

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(chemometrics) is either supervised or unsupervised depending on the application (see Figure 2).

When applying chemometrics, spectral pre-processing is often the first step to ease access to the sought information. Pre-processing steps include mathematical transformation such as baseline corrections, smoothing, normalisation, derivation, etc., that can be possibly combined. These are fundamental for NIR and Raman spectroscopies, which may present significant variability due to factors such as variation of chemical-physical properties of samples, measurement process, as well as instrument changes.

As shown in figure 2, multivariate data analysis methods are divided in two main categories: unsupervised, for which only spectral data is collected as information; and supervised methods, for which an input is necessary (qualitative or quantitative information to be related to spectral data).

For detailed information on identification and confirmation algorithms for handheld spectrophotometers, the readers are referred to [18].

2. Qualitative applications

2.1. Raw material identification

In the pharmaceutical industry, raw materials are the starting point of every processing or manufacturing campaign. The incoming materials are first stocked in a quarantine area for approval before processing. Acceptance of the materials then requires conducting several analytical tests in respect of the recommendations given by pharmacopoeia monographs. These (often destructive) analytical tests are performed in QC laboratories (sometimes located far from the manufacturing plant) and require samples of the materials. The sampling stage may also be a very complicated part of the testing when working with high potent compounds

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due to the precautions needed to open the containers while protecting both the operator and the material. The sampling and analysis steps are therefore time-consuming and risky operations that delay the whole process.

This is why, in order to reduce the lead-time, the industrial sector asked for fast and reliable analytical tools enabling the identification of materials. This way, the incoming raw materials could be processed according to pharmacopoeia monographs, keeping the risk of batch reject at an acceptable level. It appeared that vibrational spectroscopy was well suited to that purpose [19]. Even if both Fourier transform-IR and Raman spectroscopies may be used as incoming raw material verification tools, the preference is given to handheld Raman spectrophotometers. This choice is driven by several reasons. While Raman spectroscopy gives very distinctive spectra allowing visual confirmation, it is also sensitive to polymorphism and salts forms of compounds and its interfacing (point-and-shoot configuration) shows low levels of sensitivity to most transparent packagings. MIR spectroscopy, on the other hand, can also provide distinctive spectral features allowing fast and reliable identification. However, the interfacing with the ATR crystal requires complex sample handling. While NIR spectroscopy shows good interfacing properties (point-and-shoot configuration), its weaker ability to select the best spectral regions and to develop the algorithm as well as its approximate spectral features for checking the final result [20] made it a second choice.

However, as we mentioned earlier, Raman spectroscopy suffers from many other drawbacks such as the possible fluorescence of some samples and the difficulty to perform analysis through opaque containers. To circumvent these limitations, some technological advancements have been made and new handheld devices are now available in the market (e.g. Bruker's Bravo™ for fluorescence mitigation and Agilent's Resolve™ for SORS

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measurements). Up to now, no single instrument combines these features and the end-user must choose the device that better fits its own application based on risk assessment.

2.2.Process Analytical Technologies (PAT)

Launched in 2004, the FDA's guidance on Process Analytical Technologies (PAT) [21] introduced the on-line and in situ monitoring of manufacturing processes in the pharmaceutical industry. Going one-step further, many companies are now engaged in continuous manufacturing (CM) as stated in the newly published ICH Q13 concept paper [22]. Both PAT and CM rely on the implementation of new technologies to monitor both critical process parameters and quality attributes [23]. Handheld and portable devices are playing a major role in this framework. Indeed, the portability of these devices combined with the versatility of their interfacing (through probes, optic fibres…) make them suitable for in situ monitoring of chemical and pharmaceutical processes [24].

Due to its poor sensitivity to water, Raman spectroscopy is the preferred technology for some processes such as monitoring chemical synthesis, polymerisation reactions as well as for the vast majority of bioprocess monitoring.

Nevertheless, because of the sensitivity of NIR spectroscopy to physical parameters such as moisture, particle size, and bulk density etc., its use can be key to ensuring the final quality of the pharmaceutical product. This technique also allows gathering essential information related to these parameters [25,26].

2.3. Pharmaceutical product identification

Pharmaceutical product identification is another major field of application of portable and handheld vibrational spectroscopy devices. In 2018, the World Health Organisation stated

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that approximately 10% of pharmaceutical products in low and middle-income countries were falsified or substandard [27]. Falsified medicines are defined as "medical products that deliberately/fraudulently misrepresent their identity, composition or source" and substandard medicines as "authorised medical products that fail to meet either their quality standards or specifications, or both" [27].

Although such products can sometimes be easily detected (even visually), pharmaceutical inspectors do need field detection devices to authenticate or analyse pharmaceutical products in most cases [28].

In this context, two main questions may be asked:

- Is the product faithful to its description (product identification)?
- What are the contents of the product investigated (product investigation)?

The answer to these questions may be partially found in portable/handheld spectroscopic systems, as discussed hereafter.

2.3.1. Product identification:

In the case of product identification, the analyst will compare the measured spectrum against a database of reference finished products spectra using a specific algorithm. This database must be built using samples provided by trusted sources that must be representative of the natural variability of the product. Full information from the manufacturer is required since the same product from different manufacturing sites may exhibit different spectral features (see Figure 3). Due to the importance of physical parameters on the NIR spectra, NIR spectroscopy outperforms Raman spectroscopy in the context of finished products identification.

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The reader should also pay attention to the fact that handheld devices cover different optical frequency ranges. Some devices cover the third and second overtone spectral region (e.g. SCiO: 700-1,100 nm), others the third, second, and first overtone (Innospectra's NIR-S-G1, and Viavi's MicroNIR: 900-1,700 nm) while others are mainly focused on the first overtone and combination bands region (e.g. Thermo Fisher's Microphazir: 1,600-2,400nm). This might be of great importance depending on the analysed product and may lead to confusing results if the major differences are found outside spectral range used. Another aspect that must be taken into account is the interface between the device and the sample. SCiO spectrophotometer requires "unblistered" tablets that must be placed in a specific holder; MicroNIR has a specific probe for tablets; NIR-S-G1 has a relatively small measuring window while MicroPhazir has a relatively large one. These practical aspects may lead to unreliable results if the presentation of the sample is too variable (e.g. if the sample size is smaller than the measuring window). Before starting a study or implementing a handheld/portable solution for routine analysis, these practical aspects should be investigated (e.g. using a benchtop device covering the full spectral range) and solved.

2.3.2. Product investigation

Investigation analyses are more focused on public health aspects than on intellectual property protection. In this framework, Raman spectroscopy outperforms NIR spectroscopy. Indeed, due to its lower sensitivity to physical differences between formulations, Raman spectra may provide valuable information on the presence of the active compounds for different brands or generics. Following the same idea, if the correct API has been replaced by another compound, the Raman spectrum of the product may be matched against a pure compounds database and inform the analyst about the actual detected compound and its

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related risk [29,30]. However, several limitations can arise at this point. In fact, low-dosed compounds (e.g., hormones) in drug products may not be detected as well as fixed-dosed combinations with a high Raman scatterer compound masking the signal of lower-dosed API (e.g. detection of the presence of artemether in artemether/lumefantrine combinations) [31]. To overcome the low-dose issue, it is also possible to use SERS technology together with handheld devices for identification of APIs [32,33].

Another limitation may come from opaque tablet coatings (e.g. presence of TiO_2) or sugar coatings, that may block the access to the signal of the tablet core. The operator may then use different lenses (e.g. long range or short-range lenses) to focus the laser beam inside the tablet in order to decrease the spectral influence of the coating and increase the spectral signature of the core [34] (see Figure 4).

3. Quantitative applications

3.1. Quantitation of API and excipients

Quantitative abilities of vibrational spectroscopy have no longer to be demonstrated for benchtop devices [26,35,36]. Indeed, both IR and Raman spectroscopy signals are directly proportional to the number of IR - or Raman - active molecules. Regarding MIR and Raman spectroscopy, univariate analysis based on band area or intensity may be used when applicable (there must be no interfering signal from the environment). However, factors such as the refractive index, density, temperature and polarity of the environment surrounding the compound of interest may influence both band position and band area [35]. Combined to the fact that the vast majority of pharmaceutical samples exhibit spectral band overlap, these perturbing factors make multivariate statistical analysis of spectra necessary for almost all vibrational spectroscopy applications [37].

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In the pharmaceutical industry field, most quantitative applications of vibrational spectroscopy have been performed using benchtop systems, the recent trend being the development of at-line and on-line systems for process analytical technology control both in new NIR spectroscopy reflexion geometries [38,39] and transmission Raman spectroscopy [40,41].

Most quantitative applications for handheld or portable devices are related to the control of raw materials and finished products. Indeed, because of miniaturisation, spectral resolutions and covered spectral ranges are reduced compared to benchtop systems, leading to limited quantitative applications of handheld/portable devices. Moreover, transmission spectroscopy is only envisaged on portable devices for liquid samples (placed in cuvettes/vials). Both handheld and portable devices analyse solid samples in reflexion mode, therefore leading to less accurate results compared to those obtained in transmission mode. Obviously, the absence of transmission spectroscopy for solid dosage forms excludes the quantitative analysis of homothetic (same ratio API/excipients but different size) or multi-layered tablets.

Nevertheless, portable devices show relatively good quantitative performances. Raman portable devices have been used to detect contamination of glycerine with diethylene glycol with a limit of detection (LOD) of 0.32% across five similar instruments [42]. More recently, expired Tamiflu capsules were analysed with different Raman portable devices. The capsule content was dissolved in water at concentration ranges from 3 to 7.5 mg/mL. The results exhibited average assay values within 0.3% of those obtained from high-performance liquid chromatography analysis [14]. Finally, a portable Raman device was used to monitor the ciprofloxacin tablet dissolution as a field deployable solution, showing performances comparable to those of chromatographic techniques [43].

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Compared to portable and benchtop devices, the quantitative performances of most handheld Raman and NIR spectrophotometers in their default configuration are rather poor [44]. Indeed, most commercially available handheld Raman devices are configured for qualitative applications and performed by non-qualified operators. In this context, the exposure time is optimised for each sample in order to obtain the best signal-to-noise ratio in an acceptable measurement time. However, the exposure time is a critical parameter that must be determined prior to calculating quantitative measurements. Figure 5 shows the spectra of ibuprofen tablets of strength 400, 600 and 800 mg. The spectra were measured through the blister with a benchtop Raman system with fixed acquisition time (Fig 5A) and a handheld Raman device with automatic exposure time (Fig 5 B). As one can see, when the API signal masks the excipients signal, the auto-exposure time makes it impossible to distinguish both. These automatic parameters had a negative impact on the capacity of handheld devices to detect substandard medicines [28,45], which the emergence of antimicrobial medicine resistance has made a main issue of concern [46]. Thermo Fisher's Truscan™ now optionally embeds a chemometric toolbox (Trutools™ from Eigenvector Research Inc.) that enables the setting of exposure times as well as chemometric models (e.g. PCA, PLS, PLS-DA). Although no comparative study establishes the quantitative performances of commercial handheld devices, the quantitative performance of handheld devices seems promising according to Sorak *et al.* [1]. However, some handheld NIR devices help setting acquisition parameters and exhibit relatively good quantitative performances compared to benchtop and portable systems [47–50].

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3.2. Quantitation of physical factors

Another major interest of the pharmaceutical industry in vibrational spectroscopy is its sensitivity to physical factors such as polymorphism, particle size or moisture.

Moisture analysis is one of the oldest applications of NIR spectroscopy in the pharmaceutical industry [51]. Benchtop devices exhibit very good quantitative performances (LOD up to 0.005% v/v). Very few applications of portable or handheld devices are reported in the literature to determine moisture in pharmaceutical samples. However, the reported performances seem to show satisfying performances [52]. Due to the weak Raman activity of water, the moisture analysis is limited to IR-based devices.

One of the most important physical factors of pharmaceutical powders is the polymorphism phenomenon, especially for weak soluble APIs (e.g. biopharmaceutical classification system BCS 2). Both IR and Raman spectroscopy may characterise polymorphic forms of pharmaceutical raw materials [53–55]. Since the difference between two polymorphic forms may substantial (occurrence or disappearing of peaks [56]) or weak (change in peak width [57]), the sensitivity of both techniques is material-dependent and is therefore difficult to generalise.

In a calibration transfer study on the detection and quantitation of mebendazole polymorphs in pharmaceutical raw materials, the portable NIR devices exhibited LOD values of ~3.6% w/w whereas benchtop exhibited LOD of ~1.8% w/w [58]. The root mean square errors of prediction were statistically comparable around 2.1% w/w. Another study used portable Raman spectroscopy in association with differential scanning calorimetry to characterise salmeterol xinafoate polymorphs [59].

When analysing polymorphs with Raman spectroscopy, the low-frequency bands (< 100 cm^{-1}) are the most interesting part of the spectrum as they are related to crystal lattice

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vibrations [60]. However, reaching such part of the spectrum traditionally requires setting special configurations (several monochromators or ultra-narrow notch filters) even for benchtop instruments. Carriere *et al.* developed a portable Raman device capable of detecting Raman bands up to ~5 cm^{-1}, therefore enabling on-field detection of polymorphs [61].

4. Data handling:

Data handling is one of the major issues that arise when using handheld or portable devices. Indeed, both qualitative and quantitative applications rely on spectral databases and their management. Actually, most available devices enable the use of commercially available databases for the identification of pure raw materials. However, analyses based on such commercial databases are not without risk [62]. Furthermore, the pharmaceutical industry also often works with its own-patented products and must build its own databases. While most devices offer this possibility, several issues remain.

The transferability of databases or chemometric models between devices of the same brand may suffer from poor device-to-device reproducibility [26,42]. This highlights the need for more complete standardisation of handheld devices by manufacturers but also by users when building the databases/models. For Raman spectroscopy, this standardisation also shows good results for inter-brand databases transfers [63]. This aspect is very much valued by the pharmaceutical industry. Indeed, a pharmaceutical manufacturer may have different manufacturing sites and use different brands of handheld/portable devices across its different manufacturing sites. Therefore, it is very time/money consuming to build and maintain a different spectral database for each manufacturing site and each spectrophotometer. The standardisation of spectra may enable the construction and maintenance of the spectral database in a central laboratory on e.g. a benchtop system and its subsequent transfer to the

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manufacturing sites. NIR-based calibration models have been successfully transferred from benchtop to portable and handheld devices using a piecewise direct standardisation or a direct standardisation [50,58,64,65]. However, no study has yet established the long-term stability of transferred models. Furthermore, once transferred, these must be maintained and updated on each device.

Another issue is the weak embedded intelligence of handheld devices. Indeed, most of them are configured for qualitative analysis without showing any potential for quantitative analysis (except now for the Truscan™ with the Trutools™). However, even the qualitative analyses are generally performed by correlation coefficient, hit quality index or even p-values. These comparators are easy to implement but rather inefficient when it comes to detecting small spectral variations [66]. Spectral data analysis externalisation on cloud servers is foreseen as one of the future major development in the portable/handheld spectrophotometers field. Indeed, the centralisation of the database ensures that all users operate the latest version; it also allows its deployment on different manufacturing sites and enables the use of up-to-date statistical tool. This way, it is possible to enrich the spectral database with any scanned product and to update/maintain the chemometric models. However, once again, the standardisation of measurements is the keystone of such developments.

5. Conclusion and perspectives:

The utility of vibrational spectroscopy in the analysis of pharmaceutical materials has been widely demonstrated. Handheld and portable spectrophotometers constitute valuable pieces of the analyst's toolbox since they enable the deployment of on-site qualitative and quantitative methods for a faster and safer control of raw materials or finished products. These

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tools will certainly play a major role in the future of pharmaceutical material analysis and control.

The spectral performances of handheld devices are generally inferior to the ones of benchtop devices. This might be explained by the characteristics of these devices, as miniaturisation and portability constraints do not allow obtaining such performances. However, these lower performances might also be explained by the weak standardisation of the devices, which impacts the quality of model transfer from benchtop to portable/handheld devices. Fortunately, this standardisation might be undertaken by the user and ultimately lead to satisfying results. Directly linked to this standardisation of data comes the need for centralisation of data storage and processing on cloud servers to enable multi-site and multi-brand model deployment and maintenance.

Another aspect that has not yet been studied is the analysis of bio-pharmaceutical products with handheld devices. Indeed, the actual growth in market share of bio-pharma and bio-similar products is one of the major challenges that the pharmaceutical industry will have to take up. The question is: what are the analytical performances of portable/handheld devices with biological products? Some recent studies tend to show that portable devices have a major role to play in this field [67].

Other developments will possibly come from newer vibrational spectroscopies (e.g. Terahertz spectroscopy) [68] and from the combination of several spectroscopies (e.g. NIR & Raman or MIR & Raman (e.g. Thermo Fisher's Gemini)) aiming at better exploiting the complementarity of both information and offsetting respective weaknesses. In addition, the field of applications, limitations and performances of new advances such as SERS and SORS need to be clarified and compared to existing methods.

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Figure captions

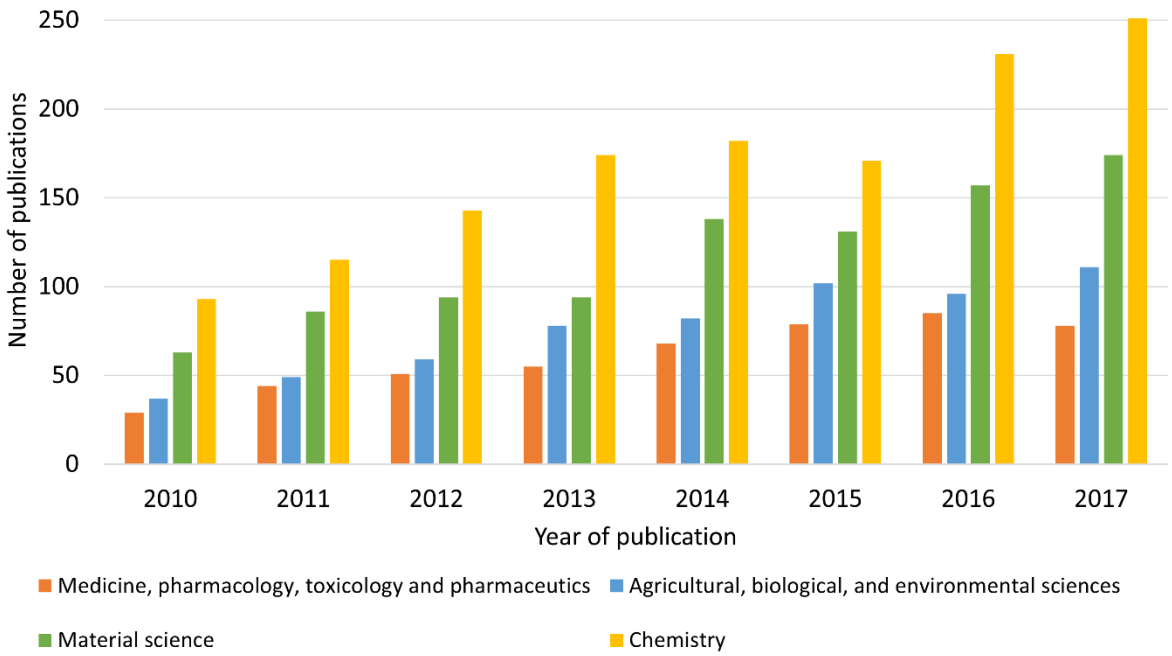

Figure 1

Number of publications by year related to portable/handheld NIR and Raman spectrometers, searching "portable OR handheld OR ATR OR attenuated total reflectance AND NIR OR Raman OR MIR OR near-infrared OR mid-infrared" for article title, abstracts and keywords and sorting papers among different subject areas, Scopus database (2010-2017).

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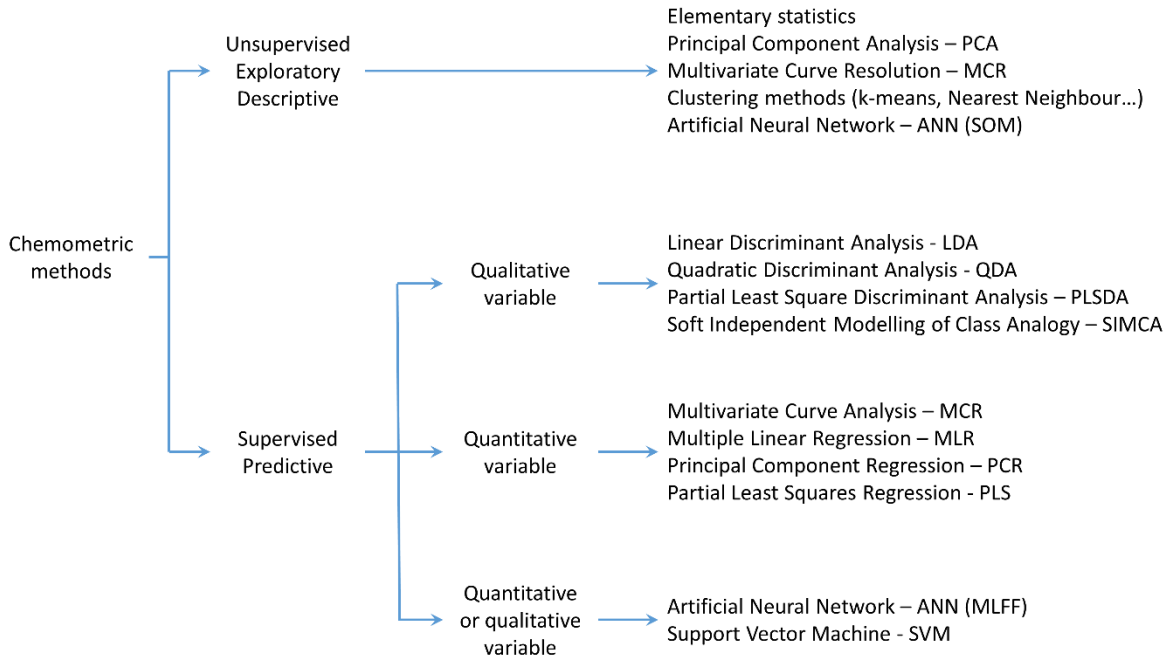

Figure 2

Flowchart of chemometric methods (adapted from Chapter 04/2016:52100 of the European Pharmacopeia).

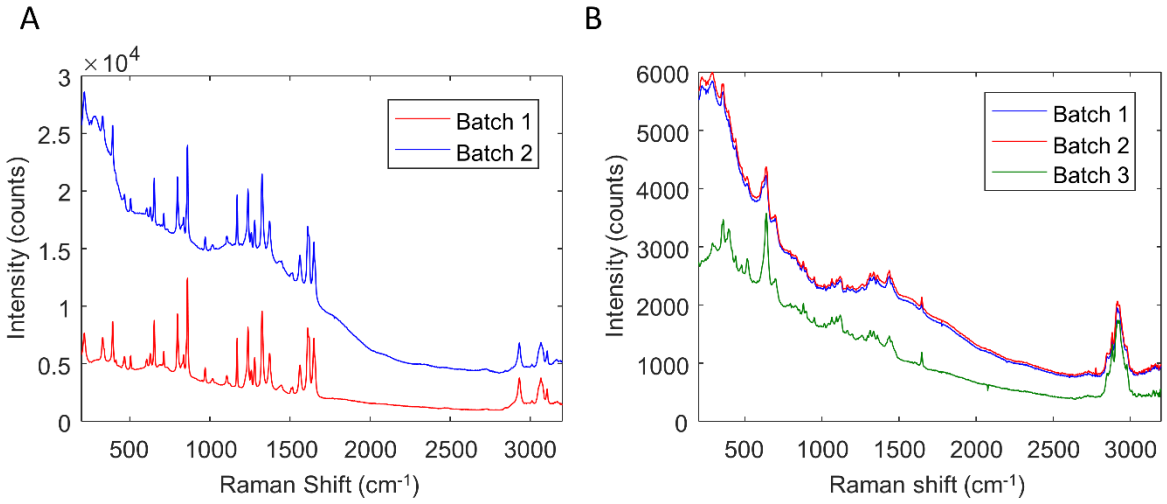

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Figure 3

Raman spectra of same-brand (A) paracetamol tablets and (B) simvastatine tablets from different batch numbers. The spectral differences are likely linked to different manufacturing sites and different raw materials.

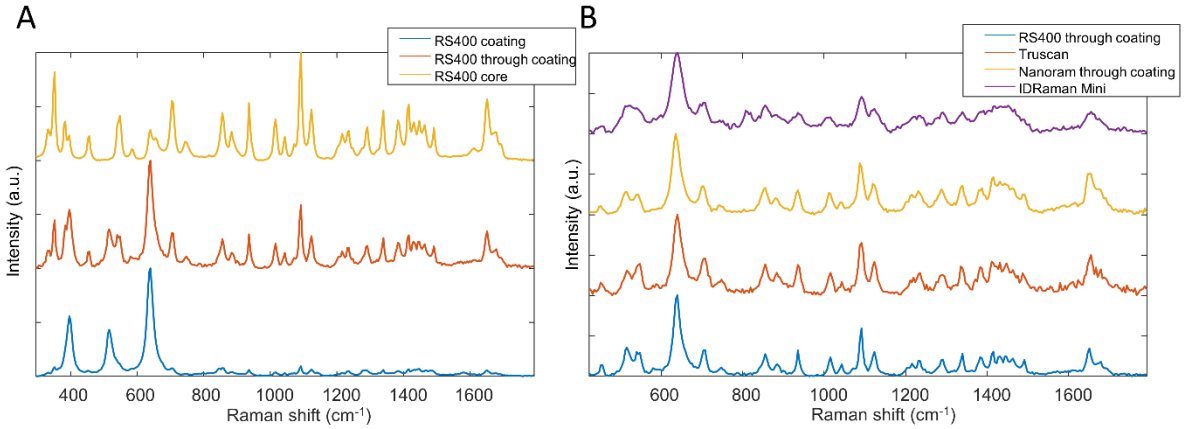

Figure 4

A: Raman spectra acquired on a pharmaceutical coated tablet with a benchtop device (RamanStation 400, Perkin Elmer). Blue spectrum is acquired focusing the laser beam on the outer part of the tablet. Coating signal (titanium dioxide) is masking the core signal. Red spectrum is acquired when focusing the laser beam inside the tablet through the coating (6 mm focal distance probe directly on the tablet surface). Orange spectrum is acquired on the core of the tablets after breaking it into two parts.

B: Attention must be paid to the focal distance in order to obtain comparable Raman spectra with both benchtop and handheld devices. Blue spectrum is the same as red spectrum of Fig 4A. Red and purple spectra are acquired with Truscan and IDRaman Mini handheld devices in their default configuration. Orange spectrum is acquired with NanoRam handheld device placing the lens directly against the tablet surface.

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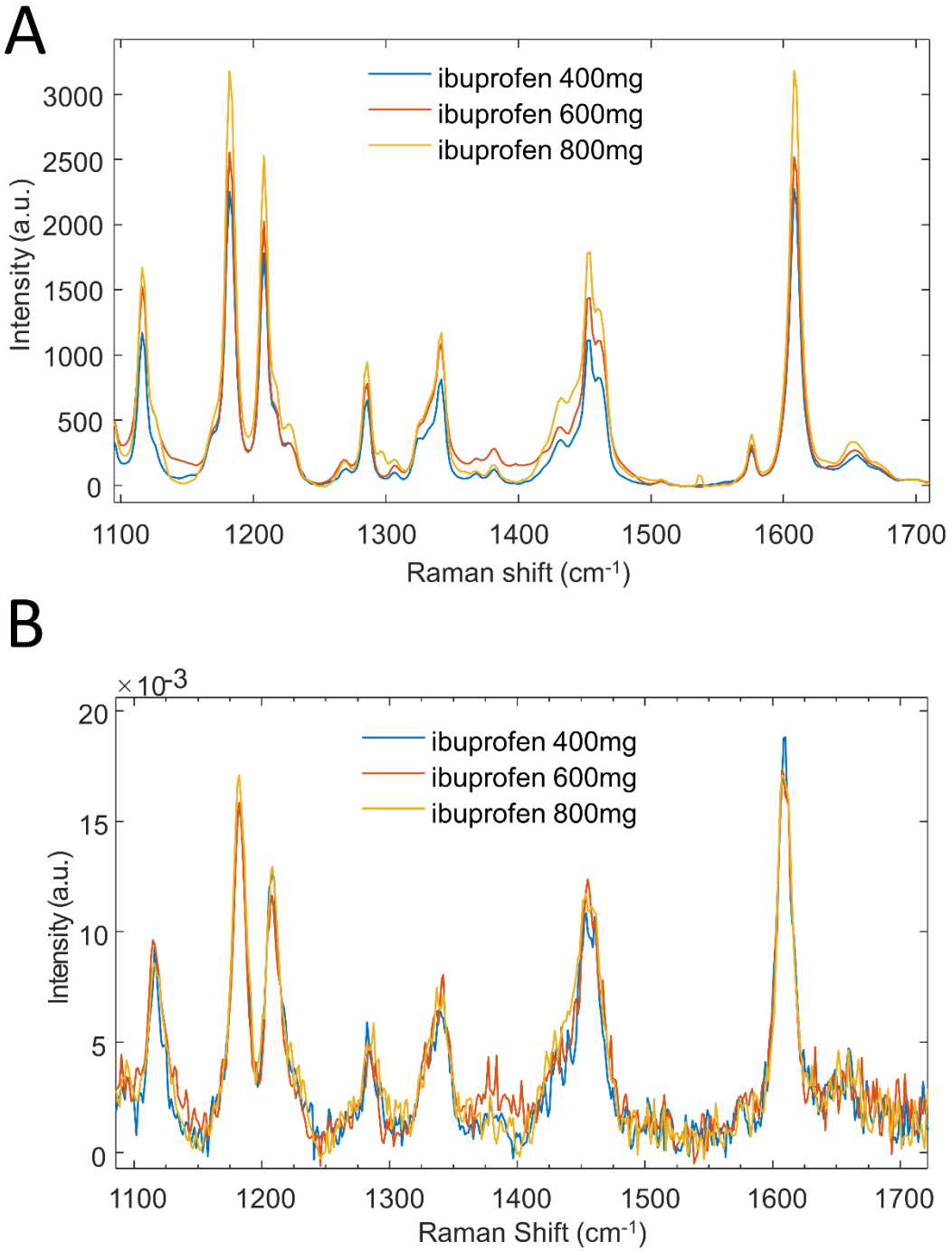

Figure 5

A: Raman spectra acquired with a benchtop device (RamanStation 400, Perkin Elmer) with fixed acquisition times (15 sec) on ibuprofen tablets of different strengths. The spectra were baseline corrected by Asymmetric least squares (λ: 10^5, p: 10^{-3})

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739 B: Raman spectra acquired with a handheld device (Truscan, Thermo Fisher) with
740 automatic acquisition times on ibuprofen tablets of different strengths. The spectra were
741 baseline corrected by Asymmetric least squares (λ: 10^5, p: 10^{-3}).