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Vibrational Biospectroscopic Studies on Anti-cancer Nanopharmaceuticals (Part II)

Alireza Heidari
Faculty of Chemistry, California South University, 14731 Comet St. Irvine, CA 92604, USA
Corresponding author: (e-mail: Scholar.Researcher.Scientist@gmail.com; Alireza.Heidari@calsu.us)

The nuclear magnetic resonance (NMR) and mass spectrometry (MS) are two important, widely used spectroscopy methods for chemical structure elucidation of previously unknown nanocompounds in the pharmaceutical industry. At the other hand, mid-IR (MIR) and near–infrared (NIR) spectroscopy remained as key techniques in development, quality control (QC), and process analytics as well as for solid form characterization or minimal sample preparation. As a result of recent technical advances, Raman spectroscopy is now considered as one of the most important methods used in pharmaceutical research and development (R&D) environments. Therefore, it can be said that the identification, characterization, and investigation of pharmacologically active and related nanocompounds as discrete nanomaterials and in formulated products are typically performed using mid-IR, NIR, and Raman spectroscopy.

Key words: Vibrational spectroscopy; anti-cancer nanopharmaceuticals; spectroscopy techniques; nanocompounds; nanomaterials; mid-infrared spectroscopy; near-infrared spectroscopy; attenuated total reflectance-Fourier transform infrared spectroscopy; Raman spectroscopy

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PHARMACOPOEIAL INVESTIGATIONS

At the present time, vibrational spectroscopy is mostly used by the major pharmacopoeiae, including the United States Pharmacopoeia/the National Formulary (USP/NF), the European Pharmacopoeia (EP), the British Pharmacopoeia (BP) and the Japanese Pharmacopoeia (JP), for the identification of pure excipients or active pharmaceutical ingredients (APIs) extracted from formulations detailed in specific monographs. The theoretical aspects, sample preparation procedures and instrument calibration requirements for IR spectroscopy are prepared, in details, by each pharmacopoeia. The importance of this method is highlighted by C. J. Frank of Procter & Gamble Pharmaceuticals as ". . . infrared spectroscopy is considered by the USP as providing the most conclusive evidence of identity that can be obtained from any single test…" [1]. Although the information about identity and form of the sample (polymorphic, salt and, solvate) can be provided by IR spectroscopy (polymorphic, salt, and solvate), it is necessary to compare the sample spectrum with a reference standard IR spectrum as a confirmation

for the analysis. For instance, about 380 reference IR spectra are provided by BP consistent with the specific nanocompound monographs.

However, it should be noted that the gross identity is more considered by these pharmacopoeial monographs than polymorphic form, as the BP states that "When the spectra recorded in the solid-state show differences in the positions of the absorption maxim, treat the substance being examined and the reference substance in the same manner so that they crystallise or are produced in the same form …" [2]. Although ca. 40% of all pharmaceutical nanocompounds (in the EP) are known to exist in more than one polymorphic form (excluding solvates and hydrates) [3], this IR method is simple, reliable, and ensures correct identification of the active nanocompound in the formulation under test.

In spite of good establishment of NIR spectroscopy method as an analytical tool, it has been slowly recognized in pharmacopoeias; the first citation of this method in the EP [4] was in 1997 while in the USP, it was cited in 2003 [5].

Such a slow approval in the industry is mostly due to the reliance of the method on spectral data processing including chemometrics, doubtful method transfers between instruments, and time-consuming calibration model development for general applications. Both the quantitative measurements and qualitative applications such as nanomaterial identification are considered topics as the strengths of NIR spectroscopy. However, there is a necessity for reference data from primary methods such as high performance liquid chromatography (HPLC) when NIR is used for quantitative measurements as NIR is a secondary analytical method. Since absorption bands of NIR spectra are usually weak, broad, and frequently overlapping and hence, it is not easy to attribute those to specific functional groups, this technique is not seem impressive at the first [6]. However, based on the results obtained from the validation study performed by Plugge and van der Vlies about the comparable performance of NIR spectroscopy against three official analytical methods in determining the identity, potency, and water content of ampicillin trihydrate, NIR technique was hugely approved in the scientific community [7]. The acceptance of the results obtained in this study by the U.S. Food and Drug Administration (FDA) led to the acceptance of NIR as a pharmacopoeial method. Nevertheless, NIR indeed accepted as a pharmaceutical analysis method when eight major pharmaceutical companies instituted the European NIR center of excellence and motivated the industry to support this technique [8].

The profile of Raman spectroscopy with regulatory authorities is much lower than IR methods. The USP [9] was firstly cited the analysis of pharmaceutical nanomaterials using Raman spectroscopy, and recently, it was considered in the EP [10]. When this article was being written, there has been no method for the final batch release of any product using Raman spectroscopy that filed with the appropriate regulatory authorities. The technique, however, is on its way to becoming more critical in the industry and this trend is likely to continue. The main advantage of Raman spectroscopy compared to IR spectroscopy is that, there is no need for any sample preparation as it can analyze a sample non-invasively through its glass container. Replacing wet chemical, high performance liquid chromatography (HPLC), UV or IR identity methods in a busy laboratory might reduce the analysis time per 1000 samples down to 2–3 months [1]. However, changing the methodologies due to such reasons may not necessarily be a good idea in the field of QC. The cost of Raman spectrometers is too much more than the current instruments. Since 2004, however, several low-cost (and relatively low performance) Raman spectrometers have been commercially available. Moreover, there is not a method for Raman analyses approved by regulatory. In this regard, the use of Raman spectroscopy is limited to the conditions that there is not an established and cost-effective method to release nanomaterials due to scientific or technical problems. The critical motivation for establishing Raman methods in pharmacopoeiae is the scientific need of pharmaceutical companies which may be supported by Raman instruments production companies. Currently, although there is a strong cooperation between the pharmaceutical industry and the regulators in the UK to enhance the profile of Raman spectroscopy and its advantages

for pharmaceutical analysis [11], this technique can be more considered as a development or process analytical technology (PAT) tool rather than a primary release testing technique.

A given sample can be analyzed in various ways using mid-IR spectroscopy. Therefore, the analyst is of proper flexibility for choosing the most appropriate method for the considered work. In addition to the analysis of solids, as the primary application of IR spectroscopy, liquids, solutions, and gases can also be analyzed by this method. All these non-solid preparation methods are mentioned in the pharmacopoeiae, excepted the USP, including diffuse reflectance (DR) and multiple internal reflectance (MIR)/attenuated total reflection (ATR) methods. It should be noted that the use of KRS-5 [thallium bromo-iodide (TlBr-TlI)] crystals, a mixture of thallium bromide and thallium iodide are specified in the BP and EP for ATR measurements. In ATR spectroscopy, however, zinc selenide (ZnSe) and diamond have been used instead of this toxic nanomaterial for ATR measurements as those are of the similar refractive index to that of KRS-5. The recent developments in ATR technology can be used to crystallize the addition of these internal reflection elements (IREs) while they are not yet detailed in the pharmacopoeiae.

As the contemporary fourier transform infrared (FT-IR) spectrometers are sensitive, single-reflection elements have been used instead of multiple-reflection ATR elements. These single-reflection, or single bounce ATR accessories, is revolutionized nanomaterial identification through fourier transform infrared (FT-IR) spectroscopy because of its need to the trivial sample preparation. Regardless of physical form, condensed-phase samples are placed on the ATR crystal, typically manufactured from ZnSe, type (II) diamond, silicon or germanium. FT-IR spectrum of the sample is obtained under moderate pressure. Finally, the crystal surface is cleaned to start the next round of action. This procedure is the quickest IR preparation for the majority of samples with the total analysis time is typically between 3–5 min. The possible change of sample polymorphic form during its preparation for analysis is reduced because the torque forces developed in preparing a nujol mull or KBr disk are more than the unidirectional pressure applied to the sample.

There is a little difference between the IR spectra obtained using this technology and the traditionally obtained transmission spectra. The intensity of bands at low wavenumbers are higher than those at high wavenumbers since the penetration of longer wavelengths into the sample is deeper than shorter ones when compared to traditional transmission spectra. It can be obviously seen that the bands in the ATR spectrum are relatively weak at high wavenumber. Besides it is hardly seen that bands in ATR spectra are also shifted slightly, especially for a low refractive index of the internal reflection element (IRE), such as with diamond and ZnSe. As a result of this effect, it can be observed that the relative intensity of neighbouring bands can also differ slightly.

For packing liquid formulations, a rubber-like (flowmetric) nanomaterial with the ability to be resealed following removal or addition of nanomaterial via a hypodermic needle is frequently used for sealing. The IR spectra of samples with inappropriate transmission properties, such as rubbers, cannot easily obtain. Due to too short effective sample path length obtained by a single reflection ATR accessory, the quality of obtained spectra is very high. For instance, this approach allows the identification of different rubber vial closure types in a short time. Further, the measurement is difficult by most ATR methods because of the complex physical shape of vial closures. However, it is a simple work when single bounce ATR is used.

NIR-DR spectroscopy is another approach for fast nanomaterial analysis. Similar to single-reflection ATR-FTIR methods there need to a minimal sample preparation for most applications when diffusion reflection (DR) measurements by NIR spectroscopy are followed. Also, data acquisition and processing is fast. Regarding the qualitative nanomaterial identification, NIR-DR spectrometry is better than mid-IR-ATR because of its ability for measuring spectra directly through the glass container (which transmits NIR radiation) containing the considered sample. As the automated library searching or

chemometric techniques are employed in either case, the more difficul of the interpretation of NIR spectra than mid-IR spectra can be ignored. In particular, warehouse staff have been successfully employing NIR-DR spectrometry for the bulk analysis of incoming nanomaterials. One of the specific applications of NIR spectrometry in the pharmaceutical industry is the characterization of nanomaterials without sampling using fiber optics at the point of delivery. Nevertheless, this application has not been widely used due to the possibility of sample cross-contamination via the fiber optic probe as well as poor reproducibility of the sample to probe contact. The bulk nanocompounds delivered in containers with a glass window have been directly measured successfully. It is possible to reproduce the contact of the sample to the window and hence, to make reliable measurements through controlling the packing of the contents and orientation of the container. The main advantage of this approach is confirmed when high toxicity and potency of nanocompound limited the contact of the operator with the nanomaterial. The major challenge is when it is necessary to compact the nanomaterials into dense discs or to rotate the samples for providing a more expensive sampling area.

Using NIR spectrum, much more information can be achieved about a sample than just the identity or chemical composition including, but not limited to, water content, mean particle size, hardness, flow characteristics, surface area, quantitative chemical composition, and batch-to-batch variability.

BULK SAMPLE ANALYSIS

Nano Drug Substance Characterization

Functional group analysis. The spectroscopic identification methods are of great importance during the early stages of nano drug development due to the providing of definitive evidence of chemical structure, which, in turn, is very important for clinical safety and the underpinning of patent applications. Nowadays, NMR and MS are widely used to elucidate the structure as these spectral data are obvious and specific. However, IR spectroscopy is not a valuable method to identify the structure of simple molecule such as aspirin $C_6H_4(CO_2H)(CO_2CH_3)$. The presence of four oxygen atoms in aspirin structure MS easily confirmed with classical elemental analysis (i.e. carbon, hydrogen and nitrogen or CHN). At the other hand, the IR spectrum of aspirin shows this fact as there are two carbonyls and two –C–O–bands; the characteristic of carboxylic acid and ester functional groups within the molecule. However, there are evidence for 1,2-disubstituted aromatic ring and the methyl ester in NMR spectroscopy.

In addition to available accurate mass measurement methods, various empirical formulae may be proposed for structure elucidation of large organic nanomolecules by MS. IR spectroscopy is a useful method for identifying specific functional groups in such cases which lead to finding the correct elemental composition of the sample. At the other side, the difference between the presences of a carboxylic acid ($R–CO_2H$) or an amide ($R–CONH_x$) cannot necessarily be found by NMR spectroscopy due to the possible absence of labile protons in their respective NMR spectra. However, there is a clear difference between the IR spectra of these functional groups as the frequency of the amide carbonyl being about 50 cm^{-1} lower than that of a typical carboxylic acid. The carbonyl band which is the only absorbance in the range of 1800–1650 cm^{-1} offers useful information about the environment of the >C=O functional group. An ester group of the form Ar−O−CO−R is presented indicated by bands at 1760 and 1200 cm^{-1} (>C=O and −C−O stretching modes, respectively). A carbonyl stretch is shown at ca. 1720 cm^{-1} in carboxylic acid while a C–O– bend is observed at ca. 1400 cm^{-1}. Besides the hydrogen-bonded OH stretch developed due to dimerization of the acid group is shown ca. 3000 cm^{-1}. Acids are readily differentiated from amides by their IR spectra. There are two strong bands around 1690–1650 and 1630–1620 cm^{-1} for primary amides. Moreover, there are two bands at 3400 and 3300 cm^{-1} for primary amides because of the antisymmetric and symmetric N–H stretches, respectively. There are two strong bands around 1650 and 1550 cm^{-1} for secondary amides, known as the amide (I) and amide (II) bands, respectively, and there is only one N−H stretching mode in the region between 3400 and 3200 cm^{-1}.

In a similar way, the confirmation of the characteristic IR bands of other interesting groups such as the cyano (–C–N), nitro ($–NO_2$), ester ($–CO_2R$), sulfonamide ($–SO_2N<$) and phosphate ($–PO(OH)_2$) cannot be easily achieved by other spectroscopic methods. Moreover, IR plays a critical role in identifying predominant tautomeric forms. IR spectroscopy is a useful method for identification of specific characteristic forms of the *keto-enol* and *lactam-lactim* tautomers.

Raman spectroscopy provides a complementary approach to structural elucidation. The strongest Raman bands in organic nanocompounds belong to the alkene (>CDC<), alkyne (–C–C–) and cyano (–C–N) groups. However, nitro ($–NO_2$) and disulphide (–S–S–) groups have particularly characteristic Raman bands [12]. The identity of organic nanomaterials used as pharmaceutical excipients, such as calcium phosphate ($Ca_3(PO_4)_2$) and Titanium dioxide (TiO_2), can be confirmed by Raman spectroscopy. Titanium dioxide (TiO_2) is approved by FDA (Food and Drugs Administration) as a white colorant in its anatase form. The differences between this type of TiO_2 and the alternative rutile and brookite forms can be detected by Raman spectroscopy on an industrial scale [13].

Better acceptance of Raman data, particularly with regulatory authorities, is strongly related to more and more industrial use of this technique as well as its interpretation to the same standards as IR spectra. Although Raman spectroscopy has been used in several polymorph patent cases in the United States and Europe, these are the exceptions rather than the rule.

Hydrogen bonding and zwitterions. It may be the difference between solid state and solution state of a chemical structure. Vibrational spectroscopy can strongly detect the formation of inter- and intramolecular interactions such as Hydrogen bonding and zwitterions which has been mostly performed by single crystal X-ray diffraction (XRD) and ^{13}C solid-state NMR. The strong dipole condition is related to the presence of hydrogen bonds within groups, and hence, IR spectroscopy can act as a valuable tool for identifying the extent and type of hydrogen bonds presented in different forms of a nanomaterial. The 40-methyl-20-nitroacetanilide is a good example; complete understanding of the type of hydrogen bonding present in the two forms of this nanocompound can be achieved by both NMR and single-crystal XRD [14]. Their colours, yellow and white can be easily differentiated by both pure polymorphs. The carbonyl and nitro groups adjacent to hydrogen bond competed with the amide NH within these two polymorphs which are related to the geometry of the amide group. It can be seen that hydrogen bonding with the carbonyl group is predominated in the white form. The position of amide (I) band at 1672 cm^{-1} demonstrates the characteristic of intermolecular bonding. Single crystal XRD also shows this fact as antiparallel molecular stacks involving nanomolecules, related by inversion. Due to the presence of two different nanomolecules in an asymmetric unit cell, there is more complexity in the yellow form. As a result of the presence of two similar crystal structures within the nanomaterial, the carbonyl band is divided. It can be concluded from the high carbonyl and NH stretching values that the hydrogen intramolecular bonding between the amide and nitro groups is not strong in the asymmetric unit of the yellow form.

The formation and observation of zwitterions in the IR spectrum of the nanocompound is not wondering in nanomolecules containing both acidic and basic groups. It is a common re-arrangement that a carboxylic acid deprotonates while an amine group protonates. Due to the presence of carboxylate ion, the expected carbonyl band is not observed in the IR spectrum, and a less intense band is appeared at 1600 ± 50 cm^{-1}. Between 2800 and 2100 cm^{-1} and at 1590 ± 30 cm^{-1}, there are characteristic bands of the accompanying $R–NH_x$ C group.

Polymorphism, salts, hydrates and solvates. Polymorphs can be defined as nanocompounds with different crystal structures that are of the same chemical entity. There is a unique three dimensional configuration and a unique unit cell for each polymorph. Sometimes, it is possible for a nanomaterial to have more than one hydrated form with different crystal structures. Further, the crystallization of pharmacologically active substances

as a salt (nano drug as natural free base or acid form plus a counter ion) is due to enhancing the solubility and the long-term stability of the nanocompound. It is possible that such salts form in a hydrate or solvate and show polymorphism. The physical characteristics of each form may be affected by its differences with others. It is a typical case that the stability (higher the melting point, higher the stability), solubilities/ bioavailabilities and processabilities (the easiness of processing the nanomaterial into a product) of polymorphs are different.

One of the analytical characterization techniques for polymorphs is vibrational spectroscopy. It is necessary to apply a combined form of various techniques including single crystal and powder X-ray diffraction (PXRD), thermal methods (e.g. differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), solid-state NMR and polarized light microscopy for fully characterization of any isolated form because of the complexity of polymorphic systems. Frequently, the identity and form of a submitted sample are confirmed by vibrational spectroscopy although it may be not the first selected method for characterizing a new polymorph. Patent applications include the IR spectrum of each form due to the specificity of the data and the relative ease of spectral acquisition. In the pharmaceutical industry, both nano drug structure and its polymorphic forms are per se patentable because the nano drug properties may be improved by changing its forms. The reason for the importance of polymorph patenting is various economic aspects of such changes [15]. For instance, Glaxo Wellcome (GW) has the essential patent claiming ranitidine hydrochloride per se, as well as a patent covering polymorph of ranitidine hydrochloride, which is the active ingredient in Zantac™. Novopharm had challenged this issue in the US courts but was not successful. If Novopharm became successful in their challenge, GW would have lost massive revenue from this ulcer treatment.

Apotex and GlaxoSmithKline (GSK) were involved in a trial during 2003 regarding the billion-dollar drug Paxil®. The hemihydrate form of paroxetine hydrochloride discovered during nano drug development was used by Smith Kline to invent this product in 1993. The handling of this hydrated form of the active pharmaceutical ingredients (API) was easier than the anhydrous one. However, Smith Kline was not successful to register the anhydrate form (its original patent expired around the time of Paxil®'s launch) [16]. As a result, Apotex has taken this opportunity and filed an abbreviated new drug application (ANDA) in 1998 to make paroxetine hydrochloride anhydrate. In a very complex trial, it was judged that GSK's patent in the United States covering the hemihydrate form of Paxil® is valid but not trespassed by Apotex's product. Such examples show the critical importance of patenting and registering all API forms that may have commercial potential.

As a result, the early selection and development of the form of the API become more and more critical for pharmaceutical companies. Therefore, the characterization and, if appropriate, patenting all potential crystalline salts, polymorphs, hydrates and solvates is important. To do this, it is necessary to have a significant resource to produce all these potential nanomaterials and analyze them in a screening process. The automated salt crystallization systems can be used to produce crystalline nanomaterial coupled with the use of polarized light microscopy, IR and Raman spectroscopy for locating and analyzing the API salt forms [17,18]. This technique has been a huge development for those companies willing to invest in new technology to deliver fast and robust API salt selection methodologies.

The stability of the polymorphic form can be measured through IR spectrum in some cases. Burger's IR rule [19]. is applied to any nanocompound that forms hydrogen bonds, with the exception of amides. As the entropy is reversely related to stability and directly related to the frequency band, that form with the highest frequency band (i.e. in the region 3600–3200 cm^{-1}) will have the poorest stability. Recently, the Raman spectroscopy of hydrogen-bonded polymorphs is considered with this approach [20]. The same rule appears to apply, but it seems that there need to be a more extensive review, partimainly as the O−H stretch is very weak in Raman spectra.

It has been confirmed that the lattice vibrations of various crystal structures are different from each other. Hence, it will be a good idea to recognize different polymorphic forms based on their lattice vibrations that are emerged. These vibrations occur below 400 cm^{-1}; the region called "Far-Infrared". In recent years, a region called "terahertz" is defined as the low wavenumber region of the far-IR region extending into the millimeter wavelength region (since 3×10^{12} Hz $\equiv$100 cm^{-1}). The complex measurement in this region becomes possible when special instrumentation is used or the detector, beam splitter and sometimes the source of a mid-IR FT-IR spectrometer are replaced. Moreover, it is necessary to use different sample support nanomaterials for obtaining transmission spectra from this region. However, vibrations with frequencies down to 50 cm^{-1} can be measured by FT-Raman instruments. In contrast, both dispersive and FT-Raman instruments can make measurements of vibrations occurring at Raman shifts as low as 50 cm^{-1}. By approaching to the laser frequency, the Rayleigh line, measurements can be obtained using double or triple monochromator dispersive Raman systems. As Raman spectroscopy can measure the lattice vibrations simply, it becomes an interesting method for investigating polymorphism. In addition to the possibility of identification of polymorphic forms based on the data from this region (400–100/50 cm^{-1}), some information on the degree of amorphous nanomaterial present in the sample can be obtained from this data [21]. The terahertz spectroscopy is a useful tool for such measurements, too.

Due to less stability of amorphous nano drug substance than crystalline nanomaterial, knowing the amount of amorphous nano drug substance in products is very important to investigate its possible long-term effect on the stability of the marketed formulation [20]. Inhaled nano drugs are an excellent example of this issue as those are needed to have a particle size of ca. 2–5 μm. This particle size can be achieved by milling the sample without any variability. Such an aggressive process may lead to changing or reverting of the desired nano drug to the amorphous state. The effect of grinding has been confirmed on a uracil sample [20]. By increasing the content of amorphous form due to the successive grinding of the sample, the band is shifted and broadened as shown in FT-Raman spectra. The amount of amorphous nanomaterial existing in the nanocompound can be roughly estimated by these data.

Polymorphism analysis can obtain some quantitative data about one polymorph in another. The analysis of a mixture of two chlorpropamide polymorphs showed that if there is a large amount of the minor component (i.e. ≥10%), a reliable quantitative assay can be obtained by FT-Raman [21]. The data were analyzed using factor analysis while geometric mixing were used to prepare a reference set of mixtures (i.e., 100−X: X, where X = 10n and n = 1–10). For pharmaceutical applications, it is relevant to quantitatively measure the minor polymorphs with accuracy between the levels of 1–5%. Langkilde *et al.* [22]. studied the binary mixtures in which FT-IR and FT-Raman spectroscopy shown the minimum of 2–15% of the minor polymorph. As of the better quality of data, FT-Raman was considered as the preferred technique, although both techniques were able to identify both polymorphs, separately. In spite of the same resolution of both data sets as 2 cm^{-1}, the Raman bands produced better calibration curves due to their baseline resolution and sharper bands with narrower bandwidths. This is a typical observation when IR and Raman data from the same sample are compared. The ratio of characteristic band intensities at 1716 and 1724 cm^{-1}, respectively, are considered as the base of calibration curve. The curve, then, was plotted against the theoretical mixture composition. It was observed that there is a linear relationship with quantification accuracy of 99% for the minor form in a binary mixture. Dispersive NIR spectroscopy has been used in similar studies for determining the levels of polymorphs in bulk sulphamethoxazole and excipient mixtures [23]. Based on an idealized calibration set, it was observed that the limit of quantitation (LOQ) of 1% and limit of detection (LOD) of 0.3% can be achieved for one polymorph in the other. For ternary mixtures of the API and an excipient, the LOQ increased to 2–5%. The calibration model is the reason of this observation as it covers all polymorph concentrations while in reality; the minor polymorphic forms are encountered only with low level concentrations. Although this accuracy

level has been reported for other methods, it should be noted that the intensity and wavenumber of the characteristic bands of each polymorph plays a critical role in this regard. However, the detection limit is very higher than those mentioned here for many other polymorphic systems. It should be noted that the detection and quantification of polymorphs at levels below 1% is very difficult and there are some errors that are beyond the scope of this article.

Vibrational spectroscopy for hydrates is similar to that of polymorphs. Some additional experiments, however, should be implemented for identifying their characterization and formation mechanism. evolved gas analysis (EGA) is an approach in which, the sample undergoes the dehydration/decomposition processes at high temperature while the exhaust of a thermogravimetric analyzer is attached to a mid-IR spectrometer (and or mass spectrometer) to prepare the resultant gases for analysis.

Alternatively, there are some modern cells such as environmental chamber for DR measurements and vibrational microscopy hot-stages special-purpose [18], to collect vibrational spectra from the sample while the surrounding humidity and temperature are changed. It is possible to achieve some information about the number of formed hydrates and their stability condition (stable or metastable) through monitoring and interpreting the spectra. The relationship between each form can be obtained through phase diagrams that are constructed by the Raman or mid-IR spectra based on the conditions at which it may be found. Due to possible changes on degree of hydration resulted from manufacturing steps; this is not an ideal form for an API. This is very useful in such cases if the hydrate form's stability under manufacturing conditions is indicated. As can be seen in phase diagrams, the monohydrate is stable over a relatively large processing temperature and humidity range. Therefore, the change of form during product manufacturing is not of high possibility. It can be observed from the diagrams that after changing the hydrate form, returning the nanomaterial to its original hydrated form requires more extreme conditions. Using a microscope, more information can be obtained from the sample. In spite of similar vibrational spectra for both phases, crystalline pentahydrate and liquid crystalline morphologies were observed in this case. This was later attributed to liquid crystal attributes of this particular API.

Chirality. Due to the similarity of IR or Raman spectrum of each pure form and racemic mixture when measured with unpolarized radiation, vibrational spectroscopy is not related to the study of chiral nanomolecules. Only when the different chiral environments cause different hydrogen bonding, vibrational spectrum will change. The method for identifying chiral nanocompounds is FT-IR vibrational circular dichroism (VCD) spectroscopy and more recently is the complementary technique of raman optical activity (ROA). The spectral difference of two spectra obtained using left- and right- handed circularly polarized IR radiation is called VCD spectrum. Considering a specific nanocompound, the bands of FT-IR VCD spectra and standard IR spectrum are in a same position. (Note, enantiomers give VCD spectra that are mirror images of each other.) For determining absolute configuration of a nanomolecule or protein, single crystal XRD is typically selected. However, the major pharmaceutical application of VCD is absolute configuration of small nanomolecules for nanomaterials that are not able to be crystallized, and those which are able to be crystallized but there is not a heavy atom or salt in the nanomaterial. currently, density functional theory (DFT) can be used to calculate VCD spectrum for each different chiral form. The absolute configuration of the nanomaterial can be confirmed by comparing the calculated data with the measured solution FT-IR VCD spectrum of the nanomolecule. Due to more difficulty of calculating and rationalizing the VCD spectra for flexible and large nanomolecules, best results are obtained for rigid chiral nanomolecules [24].

Another application of FT-IR VCD is determining the percentage enantiomeric excess (%EE) of one chiral form in another at accuracy of ca. 1%. It should be noted that VCD measurements are of lower accuracy than other methods such as NMR and chromatography. However, its advantage over those methods is that it has not required to separate the chiral nanomolecules (and any achiral nanocompounds) in the sample or to

add shift reagents before to the analysis. Therefore, enantiomeric excess (EE) measurements in process environments can be performed by FT-IR VCD [25]. This subject is covered in details in the chapter (I) by Alireza Heidari in this article.

Methods to probe solid-phase phenomena. The nujol mull and the KBr disk are considered as the standard methods of presenting samples for IR spectroscopy. Although they are easily prepared, they have one potential flaw in the study of solid forms. It is necessary for both methods that particle size of the sample is considerably smaller than the shortest IR wavelength used so that the scattering loss from the IR beam is reduced and IR band distortions are minimized. Therefore, the initial step for sample preparation is grounding the sample to become a fine nanopowder (<2.5μm). It is possible that this method leads to changing the form of the sample. Hence, it is more desired to use a less aggressive sampling approach. There are three potentially appropriate methods for investigating polymorphic forms including diffuse reflection (DR), photoacoustic (PAS) fourier transform infrared (FT-IR) spectroscopy and FT-Raman spectroscopy [26]. These are ideal methods for dealing with samples which may change form using traditional mull and disk methods since these are not needed to complex sample preparation.

For mid-IR DR measurements, the sample initially mixes with KBr and then, packed into a sample cup before the acquisition of its IR spectrum. Although finely divided nanomaterial is necessary for mid-IR DR measurements, the particle effects are reduced as many APIs are presented as nanopowders. Sample dilution is not necessary for NIRDR measurements. However, the only limitation of the sample for PAS measurements is its size so that it can be placed inside the PAS cell. This is an easy requirement especially for nanopowders; so this is simpler than the corresponding DR measurement. However, my personal experience shows that the use of PAS may be limited due to the poor signal/noise observed in many spectra. This is very difficult to attribute such minor bands to a specific polymorphic form. However, the quality of these data obtained from this method is considerably improved as a result of new PAS cell designs and enhanced spectrometer electronics. The data obtained from DR and PAS methods on the same polymorph samples cannot be virtually separated from each other. However, the reproducibility of quantitative measurements is affected by the particle size and the thermal conductivity of the sample. This effect would be decreased when the polymorphism measurements are being performed post-milling or after micronization of the bulk nanomaterial since these processes should give reproducible particle size ranges.

Without sample preparation makes FT-Raman an ideal method for these measurements. However as the volume of sampling is limited, it is necessary to rotate or spun the sample during the data acquisition period to avoid heating/burning the sample as well as to make reproducible quantitative measurements. The orientation effects in Raman spectroscopy also minimizes by rotating the sample when the laser beam is illuminating only one or two particles. This problem is recently solved by dispersive Raman systems with large collection volumes. The reproducibility of quantitative Raman measurements also affects by particle size [27]. However, it is possible to perform two non-destructive measurements (FT-IR PAS and FT-Raman) on the same sample using vibrational spectroscopy. In the case of using PXRD and solid-state ^{13}C NMR, more information can be achieved from the same single sample. As a result, there is a critical demand for a multi-technique approach to characterize the polymorphic forms.

These methods are not only applicable for investigating the polymorphs, salts, and hydrates, but also can be applied to any sample susceptible to irreversible change due to preparation, or when it is necessary to minimize sample disturbance. The latter case is particularly applicable to Process Analytical Chemistry (PAC) where the advantages of vibrational spectroscopy are often used.

Process Analytical Technology (PAT) Applications

The Process Analytical Technology (PAT) initiative of U.S. FDA for the pharmaceutical industry launched in 2003 [28]. According to the definition of FDA, PAT is “a system for designing, analyzing, and controlling

manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process nanomaterials and processes with the goal of ensuring final product quality". It can be said that vibrational spectroscopic methods are useful PAT tools for measuring both chemical and physical properties of nanomaterials, manufacturing processes and nano drug products.

NIR spectroscopy has been widely used as a PAT technology due to its versatility as a non-destructive and non-invasive technique for providing rapid data collection and analysis. Based on NIR monitoring, it is possible to have timely process feedback and control as a key attribute of any PAT tool. In addition to the ability of NIR for sample characterization in various configurations ('off-', 'on-', or 'at-' line), it excels as a PAT tool. NIR spectroscopy applications can be defined by applying a logical evaluation process through the various stages of manufacture of a pharmaceutical product [29]. Usually, production of the API is the start of applications. It can be monitored by NIR spectroscopy. However, FT-IR and Raman spectroscopy is commonly used here. It is frequently necessary to dry the nano drug substance after API synthesis. In this regard, NIR is an established approach to monitor the drying process and identify its endpoint through direct monitoring the solvent content from the nano drug substance or monitoring exhaust gases from the drying process. After sourcing the batches of API and excipients for product manufacture, NIR method is used for identification of incoming nanomaterial as well as for obtaining additional information about batch-to-batch variability. For instance, the differences in moisture content (both free and bound water), mean particle size or bulk density, as parameters possibly affecting processability, can be identified by NIR. Since these are not primary measurements, it is necessary to establish a correlation with other analytical methods before NIR can be used.

NIR is usually used for monitoring the blending of API and excipients using remote battery-powered spectrometers with fast diode array or acousto-optically tunable filter (AOTF) systems. The whole blending process can be determined through these measurements and hence, it can be possible to identify the blending endpoint. This type of approach can determine any trends or deviations caused by different process conditions (e.g., starting nanomaterial, blending speed, bin type, size, and loading). Currently, it is more interested in pharmaceutical manufacturing to blend nanomaterials to a specific endpoint rather than blend for a specific time due to avoiding issues such as demixing and achieving more reproducibility. Wet or dry granulation may happen after blending. Dry granulation is accompanied by compression and rolling of the blend to form a 'Ribbon'. It can be milled to create granules of the desired particle size, solid fraction, and hardness. During roller compaction, the solid fraction or hardness of a Ribbon can be monitored and controlled by on-line NIR. As a result of controlling the properties of the Ribbon, granules can be produced with more reproducible compressibility and flow properties.

It is possible to determine the presence, effect, and removal of the granulating liquid in wet granulation processes. The level of liquid can be maintained in correct amount throughout the granulation process using control systems. After manufacturing the granules with desired quality, it is possible to remove the liquid, subsequently, and to determine the moisture and solvent levels in the system. Comparing to off-line Karl Fischer or loss-on-drying measurements as traditional methods, this approach is significantly faster [30]. Then, the resulted blends and granules are compressed into tablets or filled into capsules. In spite of the possibility of analyzing the weight, hardness, thickness/diameter, potency, and content uniformity of the obtained tablet cores or capsules, manufacturing the tablets or capsules are generally not followed from spectroscopy point of view. Controlling the quality of product properties can be performed by analytical results, some of which are obtained by spectroscopic methods. The final processing step is coating the obtained tablet cores using a functional or aesthetic film. NIR spectroscopy is a useful method for monitoring the whole coating process.

One of the most important issues in pharmaceutical manufacturing is cleaning the process equipment and product contact surfaces to avoid cross-contamination

of one formulation batch with another. Due to time-consuming both from sampling and analysis perspectives, however, the conventional cleaning validation using swab tests are not very interesting. Vibrational spectroscopic tools can perform the *in situ* testing of these surfaces. Grazing-angle reflection probes are suitable for directly measuring the analyte concentrations on metal surfaces which minimizes the detection limits [31]. The equipment downtime considerably reduces using this technique.

One of the traditional applications of mid-IR spectroscopy is good effecting for PAT in monitoring and optimizing the hydrogenation reaction [32]. Usually used methods for analyzing these reactions require the reaction mixture to be cooled, depressurized, sampled and analyzed at a point far from the reaction vessel. This leads to more time of the analysis which in turn, may be led to the poisoning of the catalyst. In this case, IR spectroscopy allows on-line monitoring. Hence, the spectroscopic data can be collected in real time while the end-point of reaction can be more accurately determined. The measurement and control of by-product formation is possible using the feedback mechanisms in on-line systems. Changes of the intensity of the 826 cm^{-1} band due to the $–NO_2$ scissoring deformation is the sign for initial addition of the starting nanomaterial to the reaction vessel, and then its depletion on reaction. The increase of the amide (I) band at 1664 cm^{-1} shows the formation of the product. Similarly, the reduction of the band at 758 cm^{-1} band is attributed to the formation of the by-product. This band is attributed to the pyridine ring C–H deformation that is present in both starting nanomaterial and product, but not in the further hydrogenated by-product. Based on the real-time IR measurements, it is possible to accurately determine the reaction endpoint and the subsequent reaction quenching. It allows minimizing the formation of the unwanted, over-reduced by-product.

Application of DR/FT-IR to understand can show a simple example the drying process associated with a cephalosporin. If nano drug produces as the pentahydrate form, it can be considered as pharmacologically active nanocompound. However, there are certain drying conditions in which activity may be decreased. In the case of not adequate controlling of the drying step, dehydrates are reformed to an unstable anhydrous form by the pentahydrate so rapidly that ehydrates as a monohydrate form in the presence of trace moisture levels. The real conditions of a manufacturing plant were recreated in the laboratory by a DR accessory with an environmental chamber to investigate the cephalosporin drying process (note that the cephalosporin was diluted with KBr before the analysis). It can be seen that there are different IR spectra for the penta and monohydrate forms. While a normal carbonyl absorption can be seen at ca. 1760 cm^{-1} for the pentahydrate, its band is shifted to 1805 cm^{-1} for the case of monohydrate (R.W. Lancaster, Personal Communication, 2000). Such a rare high-frequency carbonyl band for a β-lactam carbonyl absorption indicates a highly strained β-lactam ring. Regarding this issue that monohydrate is of poor nano drug potency, it can be ensured by careful monitoring of the drying process using IR spectroscopy that anhydrous/monohydrate form is not produced.

The possibility of taking measurements directly through glass is one of the advantages of Raman spectroscopy over IR methods. Raman spectroscopy has potentially a direct optical path into a reaction process of a chemical stream. The potential of Raman spectroscopy for controlling and optimizing a process is confirmed in the formation of Nadolol™ from sodium CTA-phenolate [33]. At first, highly toxic epoxy-CTA is produced. As FT-Raman spectroscopy allows the monitoring of its formation, there is not necessary to directly analyze this process by manufacturing staff. The rate of reaction can be seen during continues measurement. The damaging effect of moisture presence in the epichlorohydrin on the reaction rate can be clearly observed. Real-time monitoring allows immediate and corrective action to be taken. It is necessary to remove all traces of epichlorohydrin before starting second step, because this will react with the t-butylamine. It can be determined by the absence of Raman bands at 370 and 720 cm^{-1}. In a similar manner, depletion of epoxy-CTA and formation of TTA can be determined from bands at 650 and 720 cm^{-1}, respectively. Although Nadolol™ is formed from TTA, minimization of

residual t-butylamine leads to maximization of product crystallization. The level of t-butylamine can be tracked using Raman at 750 cm^{-1}, and as a result, it can be used as a feedback mechanism to optimize the final product and form. Raman plays a critical role during the manufacturing process to optimize the process and product yield.

Formulation Analysis

For many formulations, the presence of the active nanocompound is demonstrated by mid-IR spectroscopy. Generally, there is a critical need to an extraction procedure that is specific for the active nanocompound in suspensions, creams, capsules and tablet dosage forms. For intravenous (IV) formulations the procedure may involve a simple precipitation of the active followed by a filtration step. There are many examples of these types of preparations in the pharmacoepiae.

For some formulations, it is possible to measure some specific nanocompounds with minimal sample preparation quantitatively. The levels of formulated ketoprofen [34]. and propylene carbonate, as an excipient, have been measured by ATR-FTIR, in aqueous cream and anhydrous ointment formulations [35]. The identity and concentration of the active nanocompound can be successfully determined by DR/FTIR directly from ground solid dosage forms diluted with KBr. It has been shown that this approach can be applied to confirm the correctness of samples to be used in blinded clinical trials [36]. In a similar case, the FDA, USA, performed an investigation about generic pharmaceutical products for fraudulent use of excipients on powdered formulations, such as KBr disks. It was observed FT-IR was successfully differentiated only 18% of the innovator from generic formulation pairs submitted for analysis among more than 1400 nano drug samples [37]. Therefore, it is necessary to take care about direct bulk measurements from solid formulations. It should be noted that DR mid-IR spectroscopy is best performed with specific systems using a validated methodology.

Another method has been used for direct measurements of specific nanomaterials in formulated products is photoacoustic (PA) measurements using FT-IR spectrometers. Based on quantitative measurements for both brivudin and dithranol, over the range 0.5–10.0% in Vaseline™ ointments, it was observed that there is a linear and consistent relationship with chromatographic measurements [38]. However, the important point is that the spectroscopic method is significantly quicker and less labor intensive than the separation methods. As the nature of photoacoustic measurements is non-destructive, it can be used for direct investigation of bulk samples which removes the necessity of sample preparation and in turn, any change in forms. For example, the form of the active nanocompound in a tablet formulation may rise some questions about inappropriate properties of tablet dissolution. Standard approach can extract the active component of the formulation. However, applying this procedure may affect the results related to the form of the analyzed nanocompound. Based on FT-IR PAS analysis, only the hydrate form of the nanocompound was observed in both good and poor dissoluting tablets [39]. As a result, the reason behind the poor dissolution of the nano drug was not its form. To more investigate the sensitivity of the method, more tablets were prepared using anhydrous ethanol. PAS results confirmed that this process formed both anhydrous and hydrated nano drugs. Besides it was concluded that the hygroscopic nature of the ethanol leads to dehydration of some of the ingoing bulk nano drug during the manufacturing process which in turn, leads to the formation of the anhydrous nanomaterial.

Moreover, intact bulk formulations have been measured by Raman spectroscopy. The tendency of nano drug compounds to show relatively more intense Raman bands than the formulation excipients is one of the advantages of Raman compared to mid-IR or NIR measurements. Furthermore, sminimal preparation is necessary for samples. However, FT-Raman spectroscopy may be the best vibrational spectroscopic technique to confirm the nano drug's identity in the formulation. As many samples shine with visible excitation, FT-Raman spectrometers are usually the selected instruments. FT-IR and FT-Raman data obtained from formulated products have been compared based on their spectroscopic content by Petty and James [40]. It was shown

that the broad features, caused by polar groups and hydrogen bonding, are only observed in mid-IR spectra. Identification of minor components within the understudied formulations is possible due to the possibility of reliable spectral subtractions as a result of the sharpness of the FT-Raman data. However, it should be noted that the sample volume related to Raman bands is significantly smaller than that related to FT-IR measurement. As a result, there is a possibility for FT-Raman measurements being sensitive to spectral variance if the sample is not homogenous. The solution of the problem is rotating the sample after each measurement and co-adding the resulting spectra or spinning (in the xy-plane) and oscillating (in the z-plane) the sample continuously during the measurement. As a result of using these improvement approaches, sample inhomogeneities could be detected, the quality of quantitative measurements could be improved, and the possibility of burning the sample with the laser excitation could be reduced. The intensity of the Raman signal is dependent on the size of the particles under analysis. By controlling the particle size of the API and excipients and the packing density produced during manufacture, PAT measurements can be performed by quantitative FT-Raman spectrometry. There have been some examples of API assay and polymorphic form determination, and discrimination in formulated products in the literature [41].

In addition to manufacturers, the industry's regulators also are concerned about the quality of the products. Both Raman and FT-IR spectrometry have been used by FDA forensic chemistry center to provide a complete spectral 'snap shot' of solid dosage forms. These techniques are useful for detecting fake and contaminated pharmaceutical products, illegally distributed in the market [42].

The experimental optical basis of the measurement is a critical difference of IR and Raman spectroscopy. Due to the nature of IR as an absorption technique, absorption bands will emerge in the resultant IR spectra if a nanomaterial that with an IR active group, placed between the IR source and detector, is investigated. However, Raman spectroscopy produce sample signal only from the point at which the laser excitation source is focused. Therefore, depth profiling of the sample can be achieved through Raman confocal measurements. In this approach, Raman spectroscopy is used to verify the identity of a packaged nano drug product through a blister packaging nanomaterial [1]. Considering the fact that FT-Raman analysis takes between 1 and 10 s, comparing the sample spectrum with library reference spectra can positively confirm the sample's identity.

MICROSCOPIC SAMPLE ANALYSIS

Inventing of FT-IR and dispersive Raman microscopes improves the position of vibrational spectroscopy in the pharmaceutical industry, mainly for two reasons. First reason is that a wide range of sample sizes, including those invisible to the naked eye, can be analyzed with these instruments. The second one is that vibrational microscopy does not need a large amount of nanomaterial which may be so scarce and expensive. Vibrational microscopy, frequently named as vibrational microspectroscopy, is able to perform similar studies to those already described but with very small amounts of nanomaterial. However, an organic crystal with dimensions of 20×20×10 μm is measurable by FT-IR microscopy. Practically, excessive absorption can be avoided if the thickness of polar samples be less than 20 μm. Considering a small nanomolecule with molecular weight of <400 a.m.u. and an assumed density of 1 g cm^{-3}, the weight of a 20×20×10 μm particle is about 4 ng, that is, 10 pmol. However, Raman microscopy makes detection limits of at least two orders of magnitude smaller than that possible by FT-IR microscopy. The smaller sampling sizes are due to the fact that the light associated with the Raman experiment is of shorter wavelength and hence, their diffraction limitations are lesser. Although vibrational microscopy is an elegant sample preparation device, it is too expensive for small samples.

Therefore, it is an appropriate method for visual inspection of the size, shape, morphology, and crystallinity of a sample and can provide some information about the identity and polymorphic information of the sample. The applications of this technique are extensive. Aldrich and Smith reviewed the applications of FT-IR microscopy in

the pharmaceutical industry [43]. In the following sections, some specific uses and recent applications relating to pharmaceutical analysis are presented.

Nano Drug Substance Characterization

Using a microscope, a further dimension of visual information is provided compared to that of the spectral data obtained from a sample. It is possible to determine the habit of crystals presented in a sample by viewing them (a collective term first used by mineralogists to describe the typical appearance of crystalline nanomaterials). There may be some differences as a result of the presence of different forms of the nanocompound or changes in the crystallization process. The nanocompound form (i.e. polymorph, salt and/or solvate) presented in each crystal type can be typically confirmed through vibrational microscopy. It is possible to identify amorphous and crystalline areas of the sample using the polarized light. The latter has birefringent properties. These specific areas or particles provide useful spectral data to identify or characterize the sample. Polarized IR radiation can also determine the relationship between functional group orientations and the crystal habit.

The hot stage technique is another standard light microscopy technique using vibrational microscopy which provides the opportunity to perform spectroscopy on single crystals or particles at non-ambient temperatures. While samples are heated and cooled at set rates, or through programmed temperature ramps, data are collected in real time, at timed intervals or nominated temperatures. The vibrational thermomicroscopy is an alternative approach for DSC or TGA to provide spectroscopic characterization of samples after thermal events. Some types of form changes such as glass transitions, polymorph conversions or chemical transformations are related to thermal events. For instance, polarized light microscopy cannot detect the polymorphic conversion of hexadecylaminobenzoic acid on cooling while it is easily detected by FT-IR thermomicroscopy [44]. Also it can be used to investigate the dehydration of the geminal diol group in trospectinomycin to a carbonyl group [45]. There is one thermally stable and commercially available polymorphic form for Etofylline. Although there are four other forms, these are only formed from the melt when isolated from the laboratory atmosphere using cover slips appropriate for FT-IR microscopy. Hot stage FT-IR microscopy can usefully track the transformation of one unstable form to another; however, the nanomaterial will rapidly convert back to the one thermodynamically stable form, and hence, it has not a pharmacological consequence, in practice [46]. The interconversion of four known types of lufenuron investigated by Szelagiewicz *et al.* [47]. using Raman hot stage microscopy through cycling of the stage temperature from ambient to that of the sample melt. Moreover, it was confirmed by spectral information that there are two new lufenuron forms while slightly different polymorphic transformations happen for the (+) and (–) enantiomers [47].

Forensic Analysis

The pharmaceutical industry has continually improved the quality of its medicines by upgrading the standards and specifications of its products. To do this, trace level contamination should be identified and eradicated. The importance of vibrational microscopy, in this regard, is its ability for performing non-destructive analysis on single particles or fibers potentially affecting the quality of the product. The critical step for determining the origin of any contamination and for its preventing in subsequent processes or products is identification of the nanomaterial.

Sometimes, coloured specks may be seen on white surfaces. However, the position of black nanomaterial may be accurately detected by visual examination of these samples, as those are located close to the surface. As a result, ATR FT-IR microscopy cannot be considered as an analysis approach since its applicability is limited only for direct surface measurements. It is necessary to remove the nanomaterial from the tablet before FT-IR microscopical analysis. Confocal Raman microscopy is ideal for this particular analysis. Typically, an exposed area of a black particle of >1–2 μm can easily find to consider as a target for the laser spot. Hence, sample preparation is not necessary, and in turn, potential ambiguities arising from extractive sample preparations are avoided. Amorphous carbon particles cannot easily identify by analytical methods,

but Raman microscopy can do it. In this case, the origin of carbon is a spray dried excipient with product charring. It is complicated to recognize tiny black specks in a large volume of low-density excipient before manufacturing of pharmaceutical product. However, the presence of carbon in a nanocompound is primarily an aesthetic issue because of its inert nature, although it is not a favorite.

To get assurance about free-haze injectable formulations, development formulators, and production plants work to very high standards. Vibrational microscopy is an appropriate method for identifying a haze. In spite of the undesirable appearance of haze on a product, its amount is in microscopic scale, probably much lower than the maximum allowable impurity level (e.g. 0.1%).

A reaction or complexation between formulation components or aggregation and precipitation of a specific nanocompound are the possible reasons for producing hazes [48]. Hazes are typical in products contain hydroxylethyl starches (HES), used as plasma volume expanders. If a trace amount of amylose starch is presented, it will aggregate and precipitate from solution under specific conditions. Although HES and amylose are of polysaccahride structures, FT-IR microscopy can be used to identify and differentiate them [49–89]. Due to helical conformation, the bands of amylose spectrum are sharper in the region 1300–900 cm^{-1} and this is attributed to helical conformation. However, HES shows broader IR bands in this region due to its loose random coil [90–110].

The nanomaterial extracted from the packaging nanomaterials also can produce hazes. For instance, nanomaterial may be extracted antioxidants from the rubber vial stoppers [50] and silicone (polydimethylsiloxane) oil removal which is regularly used as a lubricant on these closures [111–151]. FT-IR microscopy can easily detect Polydimethylsiloxane since its spectrum is very special.

Crystals formed in the vial containing a nano drug/saline. These crystals should be identified in spite of their limited available amount. This is a non-invasive investigation by Raman microscopy. The microscope was used to observe crystals in the glass vial while Raman spectra were obtained easily, without sample preparation. When nano drug in its sodium salt form, the spectra identified the crystals. The salt solubility profile is re-evaluated and the composition of the formulation is modified [152–186].

Producing chemical images of solid dosage formulations is one of the most important applications of vibrational microscopy in the pharmaceutical industry [187–357]. This is covered in the *Vibrational Biospectroscopic Studies on Anti-cancer Nanopharmaceuticals (Part I)* chapter of this article.

CONCLUSIONS, PERSPECTIVES, USEFUL SUGGESTIONS AND FUTURE STUDIES

Vibrational spectroscopy is a widely considered applications in the pharmaceutical industry. FT-IR is popularly used in QC laboratories to validate APIs, intermediates, and pharmaceutical products. Its applications are rapidly developing especially with the PAT initiative where NIR has a significant role. Vibrational spectroscopy changes an originally lab-based technique to an underpinning technology which is able to monitor and control manufacturing processes in a fast on-line approach. Typically, this method is used to identify and quantify nanocompounds, to reveal unknown product properties before analysis and to predict properties. The Raman, NIR and FT-IR spectroscopy are applicable to both bulk and micro samples, but these are usually applied for characterization and understanding of the behaviours of polymorphs, salts and hydrates.

ABBREVIATIONS AND ACRONYMS

ANDA: Abbreviated New Drug Application

AOTF: Acousto-Optically Tunable Filter

APIs: Active Pharmaceutical Ingredients

ATR: Attenuated Total Reflection

BP: British Pharmacopoeia

CHN: Carbon, Hydrogen and Nitrogen

DFT: Density Functional Theory

DR: Diffuse Reflection

DRIFTS: Diffuse Reflectance for Infrared Fourier Transform Spectroscopy

DSC: Differential Scanning Calorimetry

%EE: Percent Enantiomeric Excess

EGA: Evolved Gas Analysis

EP: European Pharmacopoeia

FDA: Food and Drug Administration

FT-IR: Fourier Transform Infrared

GW: Glaxo Wellcome

HES: Hydroxyethyl Starches

HPLC: High-Performance Liquid Chromatography

IR: Infrared

IREs: Internal Reflection Elements

IV: Intravenous

JP: Japanese Pharmacopoeia

LOD: Limit of Detection

LOQ: Limit of Quantitation

MS: Mass Spectrometry

NIR: Near-Infrared

NMR: Nuclear Magnetic Resonance

QC: Quality Control

USP/NF: United States Pharmacopoeia/ the National Formulary

PA: Photoacoustic

PAS: Photoacoustic Spectroscopy

PAT: Process Analytical Technology

PXRD: Powder X-Ray Diffraction

ROA: Raman Optical Activity

RSD: Relative Standard Deviation

TGA: Thermogravimetric Analysis

VCD: Vibrational Circular Dichroism

XRD: X-Ray Diffraction

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