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Review paper

IR-EcoSpectra: Exploring sustainable *ex situ* and *in situ* FTIR applications for green chemical and pharmaceutical analysis

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ABSTRACT

In various industries, particularly in the chemical and pharmaceutical fields, Fourier transform infrared spectroscopy (FTIR) spectroscopy provides a unique capacity to detect and characterise complex chemicals while minimising environmental damage by minimal waste generation and reducing the need for extensive sample preparation or use of harmful reagents. This review showcases the versatility of *ex situ* and *in situ* FTIR applications for substance identification, analysis, and dynamic monitoring. *Ex situ* FTIR spectroscopy's accuracy in identifying impurities, monitoring crystallisation processes, and regulating medication release patterns improves product quality, safety, and efficacy. Furthermore, its quantification capabilities enable more effective drug development, dosage procedures, and quality control practices, all of which are consistent with green analytical principles. On the other hand, *in situ* FTIR spectroscopy appears to be a novel tool for the real-time investigation of molecular changes during reactions and processes, allowing for the monitoring of drug release kinetics, crystallisation dynamics, and surface contacts, as well as providing vital insights into material behaviour. The combination of *ex situ* FTIR precision and *in situ* FTIR dynamic capabilities gives a comprehensive analytical framework for developing green practices, quality control, and innovation in the chemical and pharmaceutical industries. This review presents the wide range of applications of *ex situ* and *in situ* FTIR spectroscopy in chemical, pharmaceutical and medical fields as an analytical green chemistry tool. However, further study is required to fully realise FTIR's potential and develop new applications that improve sustainability in these areas.

1. Introduction

Fourier transform infrared spectroscopy (FTIR) is a powerful analytical technique used to identify and quantify the chemical composition of materials. Infrared spectroscopy (IR) is primarily based on detecting the vibrations of molecules stimulated by an infrared beam of light. It is based on the Fourier transform, a mathematical technique that decomposes a signal into its constituent frequencies. FTIR works by measuring the absorption of infrared radiation by a sample, which provides information about the molecular vibrations and functional groups present in the material, represented as distinctive spectra. This information can be used to identify a sample's specific chemical components, determine the material's purity, and even detect trace amounts of impurities. The light transmitted may be examined to ensure the quantity of energy absorbed at each wavelength. The data ensuring compound identification can be obtained by thoroughly examining absorption bands and comparing them to spectra of chemical references. The general principle of FTIR measurement is shown in Fig. 1. The attenuated total reflection (ATR) accessory allows the sample to be in direct contact with an internal reflection element (IRE) made of a high refractive index material. This IRE acts as a waveguide for the infrared light, and as the light propagates through the sample, it interacts with the sample's chemical functional groups, resulting in absorption bands that can be used to identify the sample's composition. Samples can be measured in either wet or dry state. Preferably, samples should be allowed to dry before testing to decrease water content and, hence OH interference in the IR spectra. Nonetheless, ATR permits samples to be measured in the form of liquids, solids and gases [1,2].

Medium IR spectrophotometers are calibrated to record spectra representative of the molecules in the range 4,000 cm^{-1} to 650 cm^{-1},

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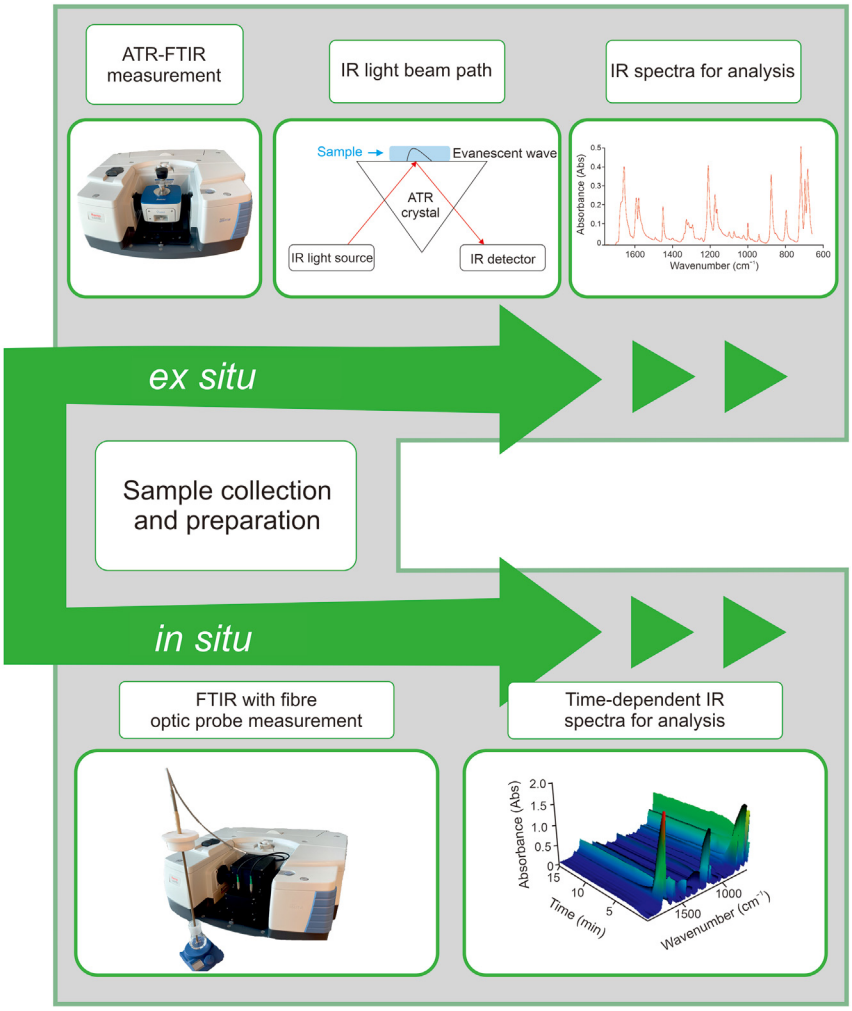

Fig. 1. The mechanism of *ex situ* and *in situ* attenuated total reflection-Fourier transform infrared spectroscopy (ATR-FTIR) use for analysis of various samples. IR: infrared.

or potentially up to 200 cm^{-1}. IR spectroscopy is a rapid technique that has been accepted as an analytical method due to its numerous advantages, such as being a green technique, having a lower environmental impact because it does not use organic solvents, and being an excellent alternative for the industry by reducing or even eliminating the generation of waste chemicals in routine procedures. Furthermore, it is a technique that requires little or no sample preparation and can also identify contaminants. Spectroscopy in the infrared range is recognised as a fundamental identification test capable of distinguishing compounds with minor structural changes and is one of the most commonly employed methods for identification [3,4]. To maintain accuracy and optimise findings, FTIR spectroscopy requires suitable spectrum processing. This is done immediately after data collection and is used to eliminate or decrease undesirable signals in spectra. Incorrect use of these processing stages can significantly influence data dependability [5]. Although FTIR offers multiple benefits, many other methods are frequently used in industrial and laboratory settings to perform analyses. Techniques such as Raman spectroscopy and high-performance liquid chromatography (HPLC), among others, serve this purpose; nevertheless, they pose particular comparative challenges in terms of use and green chemistry principles when juxtaposed with FTIR. Raman spectroscopy, frequently employed in chemical and pharmaceutical analysis, has distinct downsides compared to IR spectroscopy. Although Raman provides insightful information, it requires high sample concentrations and homogenous reaction mixtures. Fluorescence can obstruct basic Raman apparatus; therefore, it is essential to distinguish clearly between starting materials and products in Raman spectra. On the other hand, HPLC analysis provides the highest level of sensitivity for the separation and measurement of complex mixtures. However, disadvantages offset this benefit, including higher solvent consumption, longer run times, higher costs, greater waste production, and higher energy consumption. Therefore, considering the extensive advantages of FTIR spectroscopy regarding its green chemistry principles and its effectiveness in quick, low-preparation analyses suited to identifying substances, we have focused on reviewing this particular technique.

2. Brief history of FTIR

The history of FTIR spectroscopy dates back to the 1800s, when William Herschel discovered infrared radiation and later created IR spectroscopy [6]. Dispersive IR spectrometers, which employed prisms or gratings to scatter infrared light and quantify its absorption, were invented in the 1940s [2]. In the 1950s, FTIR spectroscopy was developed, employing interferometers to detect infrared light interference and provide spectral data [7]. Arthur Schawlow and Charles Townes pioneered the FTIR spectrometer in the 1960s, and they earned the Nobel Prize in Physics in 1981 for

their work on laser spectroscopy. The first commercial FTIR spectrometers were introduced in the 1970s, and they quickly became popular in the petrochemical and polymer sectors for examining organic molecules [8,9]. FTIR became a typical approach for identifying unknown substances in forensic investigations and drug analyses in the 1980s [10]. The invention of micro-FTIR also enabled IR spectroscopy on tiny samples, such as single cells and microorganisms [11,12]. The introduction of portable and handheld FTIR devices in the 1990s enabled on-site analysis in domains such as environmental monitoring and quality control in industrial plants. The method was also utilised to investigate biomolecules, food and agricultural goods, and cultural heritage items [13,14]. Advances in FTIR imaging techniques in the 2000s made it possible to visualise molecule distribution and structure inside samples, and the approach began to be employed in disciplines such as biological research and materials science [15,16]. It has been used to investigate anything from protein and DNA molecular structure to the composition of complex polymers and medications. As a result, in recent years, FTIR has become a vital tool for researchers and scientists working in a wide range of fields, including chemistry, biology, and materials science.

3. FTIR as a green and sustainable chemistry tool

The terms “green chemistry” and “sustainable chemistry” are commonly used interchangeably, which may result in the misunderstanding of the distinct meanings of these two fields. Green chemistry primarily concentrates on designing and optimising chemical processes to minimize hazardous substances. In contrast, sustainable chemistry encompasses a broader framework that integrates economic and societal considerations, emphasising a holistic approach to resource efficiency and environmental responsibility. Even though they both aim to reduce the environmental impact and promote responsible chemical practices, green and sustainable chemistry serve different purposes [17]. The likelihood of confusion highlights the importance of precise definitions and clarification of these concepts to ensure accurate discourse within the field of science.

Green chemistry is an approach to designing and developing chemical products and processes that are ecologically sustainable, cost-effective, and safe for human health. It entails the design, development, and implementation of chemical processes and products that reduce or eliminate the use and creation of hazardous compounds, as well as the reduction or elimination of waste and the conservation of energy and resources. Green chemistry seeks to support long-term expansion by decreasing the environmental effects of chemical products and processes while preserving their economic feasibility and performance [18]. Green chemistry is crucial because it reduces molecular pollution and the negative effects of hazardous by-products and reagents on people and the environment by improving the safety and efficiency of chemical operations [19]. Anastas and Warner [20] introduced the 12 principles of green chemistry in 1998. However, these were primarily intended for synthetic chemistry. Green analytical chemistry emerged as a branch of green chemistry around 1995, focusing on how analytical chemists can make their laboratory practices more environmentally sustainable [21]. It has gained considerable attention from chemists: besides improving instrumentation and methodologies to enhance the quality of chemical analyses, there is a growing effort to reduce the negative impact of chemical analyses on the environment and implement sustainable development principles in analytical laboratories. Green analytical chemistry should be acknowledged as a driving force for progress in analytical chemistry. The biggest challenge for the future of this field is finding a balance between improving the quality of results and making analytical methods more environmentally friendly [19,22,23].

On the other hand, sustainable chemistry is a more comprehensive approach, considering sociological and economic factors in addition to the fundamentals of green chemistry. Sustainable chemistry aims to increase the effectiveness of exploiting natural resources to satisfy human demand for chemical goods and services while safeguarding and improving environmental quality and human health. Although it adheres to the principles of green chemistry, it also emphasises societal welfare and economic development. In order to break the link between economic growth and environmental destruction, sustainable chemistry encourages ethical consumption and production. It adheres to the circular economic model, which aims to extend the lifespan of materials [24,25].

FTIR is recognised as a green and sustainable chemistry instrument in chemical and pharmaceutical analysis for several essential reasons. Firstly, FTIR analysis aligns with the principles of green chemistry by minimising the production of hazardous waste and decreasing the use of toxic chemicals. Reduced waste and chemical use make the analytical process safer and more ecologically friendly. Secondly, FTIR makes it possible to analyse materials in real-time, obviating the need for time-consuming sample preparation and conserving energy. By encouraging energy savings and expediting the analytical process, this function is in line with sustainable and green chemistry concepts. The expedited analytical procedure advances sustainability by reducing resource consumption and encouraging energy efficiency, which aligns with broader sustainability objectives. Additionally, the molecular structure of chemicals is effectively revealed by FTIR, which helps to create chemical and pharmaceutical procedures that are more ecologically friendly. This capability promotes green and sustainable chemistry ideals by encouraging the development of safer and more effective chemical processes that eventually contribute to a sustainable future. The alignment of FTIR with the 12 principles of green chemistry is shown in Table 1. In conclusion, FTIR is a valuable tool that embodies the principles of both green and sustainable chemistry in chemical and pharmaceutical analysis, because it can analyse samples without potentially dangerous chemicals, perform *in situ* analysis, and provide information for more environmentally friendly chemical processes.

4. Use of *ex situ* FTIR spectroscopy as a green analytical tool in the chemical and pharmaceutical industry

Ex situ FTIR spectroscopy involves analysing samples that are not part of the reaction or process being studied. Unlike *in situ* approaches, the samples are prepared separately and then analysed using FTIR.

Ex situ FTIR spectroscopy is used in the chemical industry for material characterisation, quality control, and pollution monitoring. It identifies impurities, by-products, and contaminants in raw materials and finished goods. Furthermore, it allows for the investigation of material features such as crystallinity, polymer composition, and surface functionalisation, all of which are important for the development of new materials and nanotechnology applications. This analytical technique is also used extensively in the pharmaceutical sector for drug development, stability testing, and pharmacokinetic investigations. It helps to ensure product quality, safety, and efficacy by analysing medication-excipient interactions and measuring drug content in dosage forms. Furthermore, *ex situ* FTIR spectroscopy is utilised to identify polymorphic forms, degradation products, and drug release patterns, giving crucial information for drug development.

Table 1
Alignment of Fourier transform infrared spectroscopy (FTIR) with the 12 principles of green chemistry.

No.	Green chemistry principle	Description of FTIR usage aligning with green chemistry principle
1	Prevent waste	FTIR prevents the formation of unwanted by-products by real-time monitoring and immediate adjustments to reaction conditions and controlling the purity of substrates.
2	Maximise atom economy	FTIR aids in achieving high atom economy by optimising reactions to minimise waste and maximise the conversion of starting materials into desired products.
3	Design less hazardous chemical syntheses	FTIR enables the identification and mitigation of the formation of hazardous intermediates or by-products.
4	Design safer chemicals and products	FTIR helps select reaction conditions that minimise the generation of toxic substances, as well as access the benefit-harm qualities of chemicals.
5	Use safer solvents and reaction conditions	FTIR helps choose greener solvents and auxiliaries by evaluating their interactions with reactants and products.
6	Increase energy efficiency	FTIR guides the selection of optimal reaction conditions, reducing energy consumption.
7	Use renewable feedstocks	FTIR monitors reactions involving renewable feedstocks and assesses their conversion into valuable products.
8	Avoid chemical derivatives	FTIR helps reduce the undesired derivatives by ensuring reactions proceed efficiently and by monitoring the purity of products.
9	Use catalysts, not stoichiometric reagents	FTIR assists in optimising catalyst usage by studying catalyst-reactant interactions.
10	Design chemicals and products to degrade after use	FTIR assesses the stability of products and materials, aiding in the design of substances that degrade more readily.
11	Analyse in real time to prevent pollution	FTIR's real-time monitoring helps prevent pollution by detecting and addressing issues during chemical processes.
12	Minimise the potential for accidents	FTIR provides early detection of potential hazards and enables timely interventions to prevent accidents.

The next section of the study will discuss the uses and improvements of *ex situ* FTIR spectroscopy in the chemical and pharmaceutical sectors, focusing on its contributions to environmentally friendly and efficient analytical practices. We aim to highlight the importance of *ex situ* FTIR spectroscopy as a beneficial tool in these critical areas by diving into individual case studies and significant research activities.

4.1. Identification, quality and quantity control

FTIR has been widely used to identify and monitor the purity of raw materials and finished products to ensure they meet the necessary standards. For example, the FTIR technique enabled the identification of a complex formation between β-cyclodextrin and curcumin, as the curcumin itself, being an active pharmaceutical compound, requires improvements in stability and solubility by using co-precipitation and other methods due to low water solubility [26]. Another great example is the validation results produced by Pedroso and Salgado [3], which suggested that the FTIR approach is suitable for measuring ertapenem sodium, a parenteral-β-methyl carbapenem antibiotic. This approach allows the characterisation and quantification of ertapenem sodium without the need for any organic solvent, because samples are synthesised in potassium bromide pellets as a unique reagent. As a result, this approach may contribute to reducing organic solvent waste in the mass pharmaceutical manufacturing process. Farouk et al. [27] used FTIR methods for the successful quality control of the diabetes medications such as repaglinide, rosiglitazone maleate, pioglitazone hydrochloride, and metformin hydrochloride, and to assess their application for in-process quality control and in identifying counterfeit medicine.

Quantity control is critical to ensuring the safety and efficacy of medications. The FTIR approach is a viable alternative to routine drug quality control analysis and is used to quantify various pharmaceuticals. The initial step in using FTIR for quantitative study is to prepare reference spectra of a known standard of the chemical of interest, which compares the sample's chemical composition. The resultant spectrum is compared to the reference spectrum to determine the chemical concentration in the sample. This can be accomplished through direct comparison or the use of mathematical methods such as partial least squares (PLS) regression or principal component analysis (PCA) to predict the link between spectral data and medication concentration. The FTIR spectrum of an unknown sample can be used to identify its concentration once the relationship between the spectral data and the drug concentration has been established. It is crucial to note that the accuracy of the FTIR quantitative analysis is affected by various factors, including the quality of the reference spectrum, the stability of the sample and reference, and the FTIR spectrometer's resolution. These aspects must be considered carefully to guarantee that the conclusions of the analysis are accurate and dependable. Despite being somewhat selective, IR spectroscopy offers demonstrative evidence of specific functional groups, simplicity, and cost-effectiveness compared to alternative instrumental methods, while maintaining good quantitative precision [28]. The FTIR method for quantifying ampicillin sodium [29] in powder for injection within the 1.0–3.0 mg/pellet concentration range was found to have good linearity, precision, accuracy, and robustness, making it suitable for routine quality control tests in the pharmaceutical industry. This makes it potentially interchangeable with other methods for the same purpose, such as HPLC, fluorimetry, and chemiluminescence spectroscopy. IR was also used to develop and evaluate a method for measuring ceftazidime [28] in powder for injection. The approach was based on aromatic ring absorbance measurements centred at 1,475–1,600 cm^{-1} and showed good linearity, precision, and accuracy at doses ranging from 0.5 to 7.0 mg. The excipient didn't affect the assay, and the average recovery percentage was 98.98% ± 0.70%. Other medications evaluated using the same methodology included cefuroxime [30] in powder for injection (with a linear range of 5.0–20.0 g/mL and good precision with relative standard deviation values close to 2% and below 5%), doxycycline in raw material [31] (linear throughout a concentration range of 0.5–2.5 mg with a correlation value of 0.9991 and detection and quantification limits of 0.125 and 0.378 mg, respectively), darunavir [32] in tablets (linear over a concentration range of 1.5–3.5 mg with a correlation coefficient greater than 0.9991 and detection and quantification limits of 0.12 and 0.36 mg, respectively) and others. Fahelelbom et al. [33] discovered that ATR-FTIR spectroscopy is an excellent approach for quantifying diclofenac sodium in tablet formulations. The tablet excipients did not interfere with the test, and the technique displayed good linearity with a correlation value of 0.9994 for drug concentrations ranging from 0.2% to 1.5% (*m*/*m*). The high percentage of recovery (99.81%, 101.54%, and 99.41%) and low detection and quantification limits reflect the method's high sensitivity and accuracy.

An interesting study, which included a comparison of FTIR combined with chemometrics tools and HPLC in conducting

quantitative analysis of ketoprofen/hyoscine and benzocaine/dextromethorphan HBr in their binary drug mixtures and pharmaceutical preparations, was conducted [34]. The statistical comparison revealed nearly identical results, demonstrating their suitability for commercial dose formulations. FTIR analysis emerged as a more environmentally friendly and cost-effective option than HPLC due to reduced solvent usage, portability, minimised waste production, faster operation, lower energy consumption, and increased operator safety. However, HPLC analysis provides superior sensitivity in separating and quantifying complex mixtures, yet this advantage comes with drawbacks, including increased solvent usage, extended runtime, higher expenses, greater waste generation, and increased energy consumption. Specific analytical requirements, sample characteristics, regulatory constraints, and sustainability objectives should determine the choice of analytical technique.

4.2. Crystallisation monitoring

Crystallisation monitoring is critical in the chemical and pharmaceutical industries because it has a direct impact on product quality, purity, and operational efficiency. Researchers may analyse crystallisation processes using *ex situ* FTIR as a vital analytical tool, guaranteeing efficient and regulated industrial practices while adhering to environmental sustainability norms.

Ex situ FTIR was used to investigate crystallisation processes, as evidenced by the analysis of the transition of amorphous paracetamol before and after the addition of trehalose and melibiose. Spectrum analysis revealed changes in molecule shape and intermolecular interactions in disordered materials, including both quench-cooled solids before grinding and the resulting powdered crystalline entities. Compared to their crystalline counterparts, amorphous materials exhibited larger and less defined peaks in their spectra [35]. Beyond pharmaceutical applications, FTIR spectroscopy shows considerable potential as an analytical tool for advancing protein crystallisation studies. This extends to exploring the influence of surface features on protein behaviour, addressing pivotal concerns related to protein structure and function [36]. Moreover, FTIR techniques enable the imaging and monitoring of crystallisation and melting properties in diverse natural plant-based oils, as exemplified by studies on *Physalis peruviana* [37].

4.3. Oxidation and stability control

The oxidation processes are crucial in chemistry, pharmacy, and biology, especially in the development of living organisms. The loss of electrons from a molecule or atom, frequently followed by oxygen being gained or hydrogen being eliminated, is defined as oxidation. After hydrolysis, oxidation is the second most prevalent pharmacological degradation mechanism, and it is essential in developing new materials and synthesising pharmaceuticals because it allows for the insertion of functional groups, changes in chemical structures, and the formation of valuable compounds. Controlling and identifying the oxidation mechanisms involved in drug metabolism is critical for drug development, dosage methods, and drug-drug interaction prediction [38], as well as for understanding chemical processes and optimising chemical synthesis [39].

In the study by Surapaneni et al. [19], the oxidation of (−)-menthol to (−)-menthone in different solvent systems using FTIR spectroscopy was investigated. The solvent systems (acetic acid, acetone, ethyl acetate, and dichloromethane) utilised in this reaction have a significant impact on the reaction kinetics and yield. Because of the enhanced solubility of the hypochlorite salt, which is a limiting factor in the oxidation reaction, the authors expected that the most polar solvent systems would result in the fastest reaction rate and maximum yield. The findings of the study revealed that the reaction utilising ethyl acetate, the least polar solvent, provided the maximum yield of (−)-menthone. Surprisingly, the reaction time was shortest in the ethyl acetate and acetic acid solvent systems, both of which are less polar than acetonitrile, the original solvent system utilised for this reaction. The authors characterised all of the reaction products as (−)-menthone using FTIR spectroscopy, which offered valuable insights into the effect of solvent choice. This discovery emphasises the significance of using green chemistry concepts when selecting solvent systems for chemical reactions.

Drug formulations frequently include a lipid phase dispersed in an aqueous medium, producing oil-in-water (o/w) emulsions. These emulsions are significant for monitoring lipid oxidation. The o/w oxidation mechanism is more complicated than that of bulk oil oxidation. Prooxidants and antioxidants that are both water- and oil-soluble can interact at the oil-water interface. As a result, there is a pressing demand for a precise and rapid analytical approach to measure oxidation in drugs and chemicals directly, and FTIR was found to be a valuable methodology for imaging omega-3 fatty acids oxidation,as demonstrated by Daoud et al. [40]. The combination of FTIR spectroscopy with recent advances in data processing and chemometrics makes it suitable for exploring the stability and applicability of biopharmaceuticals, such as the effective portrayal of biomaterials, monitoring of monoclonal antibody purification and biopharmaceutical bioactivity under stress conditions, investigation of structural stability of biopharmaceuticals, and many other applications [5].

4.4. Drug dissolution and release control

The investigation of drug release and solubility is highly significant in the search for new potential drug candidates. For preclinical testing, a proposed drug's solubility should be more than 10 μM. Early preclinical data analysis to identify the solubility could be useful in determining the need for resource-intensive formulation development [41]. Changes in the chemical structure resulting from drug ingredient degradation and dissolution, on the other hand, might lower drug potency, raising efficacy issues while posing a safety risk, as the degradation products may be hazardous. Forced degradation research is one of the first phases in developing any novel medicine, and it provides the first insights into its chemical stability. Researchers could use the FTIR data from the forced degradation study to assess the stability of the drug under various settings based on the number of degradation impurities generated, for example, the darunavir study performed by Modini et al. [42], and studies on doxofylline and deflazacort by Raju et al. [43,44].

Abd El-Halim et al. [4] attempted to correct zolmitriptan's (ZMT) poor permeability and undesirable side effects and increase its efficacy in treating acute migraines by utilising the synergistic effect of the lavender essential oil to create self-nanoemulsifying drug delivery systems. A continuous flow system with ATR-FTIR, pump, dissolving device, and computer approach was utilised to estimate the percentage of ZMT dissolved with time during dissolution and permeation tests. While standard analytical procedures, such as HPLC, necessitate frequent samples and constant replenishing of the solution withdrawn, continuous FTIR real-time monitoring can provide a comprehensive profile of the active pharmaceutical agent's dissolving pattern. The upgraded ZMT self-nanoemulsifying system produced nanosized globules with greater penetration than the ZMT solution during the initial disintegration. FTIR imaging was also employed to analyse solid dispersions of a poorly water-soluble medication in polyethylene glycol (PEG) and its

disintegration in water [45]. It was found that amorphous nifedipine initially crystallises within PEG-8000 for formulations with a drug content of at least 10% (*m*/*m*). The ATR-FTIR spectroscopic imaging gave a new insight into the mechanism of nifedipine dissolution from solid dispersions in water-soluble polymers, which is useful for optimising formulation manufacture.

In pharmaceutical studies, FTIR can be employed to examine the absorption and desorption of medication from various delivery systems. Scientists can trace the release of pharmaceuticals from formulations and understand their interactions with excipients by measuring changes in the IR spectra, which is critical for optimising drug delivery systems. Mesoporous silica as a drug delivery system for naproxen was tested by Žid et al. [46]. It was discovered that the adsorption and desorption properties of naproxen are affected by the pH of the solution as well as the surface functionalisation of the silica. By comparing the spectra of mesoporous silica, modified samples, and naproxen-loaded materials, the grafting of organic groups and effective adsorption of naproxen in the silica were clearly seen.

4.5. Nanoparticles formation control

Nanoparticles have registered essential advances in the chemical and pharmaceutical industry. Researchers can increase medication stability and bioavailability and target specific cells or tissues by encapsulating nanoparticles in pharmaceuticals as improved delivery systems. This can preserve medications from degradation, regulate their release rate, and help them pass cellular barriers. Nanoparticles can be designed to carry medications to damaged cells or tissues, reducing adverse effects and enhancing therapeutic effectiveness [47,48]. In addition, nanoparticles operate as catalysts in a variety of chemical processes. Because of their large surface area and unique surface features, they are effective in catalysing processes, reducing the need for costly and ecologically hazardous catalysts [49,50]. Green approaches were used to create ZnO nanoparticles with macropores in the study conducted by Bashir et al. [51]. FTIR examination revealed the creation of ZnO nanoparticles as well as the presence of phytochemicals that aid in the creation of formulations. More studies showed FTIR as a valuable technique for nanoparticle formation observation [52–58] and their crystallinity characterisation [59].

Despite the lack of real-time monitoring, *ex situ* FTIR spectroscopy remains an important instrument due to its ease of use, resilience, and capacity to analyse a diverse variety of materials with good consistency. *Ex situ* FTIR spectroscopy's merits as a green analytical method stem from its non-destructive nature, minimal sample preparation, and low waste creation. By saving resources and providing meaningful data without jeopardising the integrity of the analysed sample, the approach encourages sustainable practices.

5. Use of *in situ* FTIR spectroscopy as a green analytical tool in the chemical and pharmaceutical industry

In situ FTIR spectroscopy operates on identical principles to traditional FTIR, where an infrared light beam travels through a sample, and the absorbed energy creates a unique spectrum corresponding to the molecular vibrations inside the sample. In traditional *ex situ* FTIR spectroscopy, the sample is prepared separately and then analysed in the spectrometer. This method gives valuable information about the sample's original composition, but it does not capture dynamic changes throughout chemical reactions or processes. *In situ* FTIR spectroscopy, on the other hand, entails putting the sample immediately within the FTIR spectrometer or attaching the spectrometer to the reaction vessel. This enables continuous monitoring of the sample as it transforms, allowing a time-resolved examination of the reaction's progress. This analytical approach enables real-time sample examination, making it particularly suitable for researching dynamic systems and time-sensitive processes [60].

The various uses of *in situ* FTIR spectroscopy in the chemical and pharmaceutical sectors will be discussed in this part of the paper. We hope to illustrate the transformational influence of *in situ* FTIR spectroscopy as a green analytical technique by reviewing individual studies and important research activities.

5.1. Identification, quality, and quantity control

Similar to *ex situ* FTIR, *in situ* FTIR is often employed for sample identification, particularly in the pharmaceutical field. It plays a crucial role in verifying component purity, detecting potential impurities, and identifying products resulting from degradation processes, presented in various researches [61–65].

Moreover, *in situ* FTIR serves as a robust tool for quality and quantity control, ensuring consistency and adherence to manufacturing standards in both the chemical and pharmaceutical industries. An illustrative study by Chan et al. [66] involved generating ibuprofen formulations within PEG, encompassing ibuprofen concentrations ranging from 0% to 100%. This was accomplished using the micro droplet deposition method. The concentration of ibuprofen within the PEG matrix was determined through simultaneous measurement of all samples using *in situ* FTIR spectroscopic imaging. Through analysis of the FTIR spectra from these samples, insights were gained into the molecular state of the drug and the extent of polymer swelling as influenced by varying drug concentrations. Another excellent example was provided by Ho et al. [64], who used *in situ* FTIR spectroscopy to explore the formation of fucoidan/chitosan-based polyelectrolyte multilayers (PEMs), employing ATR-FTIR to monitor the sequential growth. The different peaks associated with each polymer increased in strength throughout each adsorption step, and spectral analysis allowed for the extraction of layer-specific spectra, facilitating the precise quantification of adsorbed mass at each stage of PEM synthesis.

5.2. Reaction kinetics and catalyst interaction control

The nuances of reaction kinetics are crucial to developing effective procedures and high-quality products in the field of chemical and pharmaceutical research. It is crucial to have a thorough understanding of reaction speeds, processes, impact of catalysts, and reaction parameters. In this case, *in situ* FTIR appears as a valuable tool, allowing researchers to grasp the complexities of reaction kinetics and make informed decisions on catalysts and reaction conditions to achieve maximum quality.

It is essential to comprehend the kinetics of a chemical reaction to forecast its course and modify the environment for desired results. By continuously observing molecule vibrations, *in situ* FTIR offers a dynamic insight into these dynamics. Data on concentration over time must be gathered in order to calculate reaction kinetics. Beer's law states that a component's absorbance in a mixture varies linearly with that component's concentration. As reactants transform into products, characteristic infrared absorption bands shift, intensify, or diminish. These spectrum changes, which *in situ* FTIR is capable of recording, provide a detailed account of reaction progression. Researchers can determine reaction rates, locate rate-limiting processes, and even uncover transient intermediates that escape standard investigations by calculating the pace of these spectrum variations. This ability to track reaction kinetics at a molecular level enables scientists to fine-tune reaction parameters

with accuracy [67–72].

In assessing reaction effectiveness and product quality, catalysts are crucial. Selectivity, yield, and reaction routes are all greatly influenced by the catalyst used. An exceptional vantage point to evaluate the interaction between reactants and catalyst surfaces is offered by *in situ* FTIR. Changes in IR spectra show adsorption mechanisms, species involved, and active sites as reactant molecules adsorb onto the catalyst. This knowledge is crucial for understanding how various catalysts affect reaction pathways and has been used in various studies for the past few years [73–78]. Additionally, real-time reaction monitoring enables scientists to pinpoint catalyst deactivation, regeneration potential, and ideal operational circumstances. According to the research conducted by Marinkovic et al. [79], electrochemical *in situ* FTIR technology was used to highlight the role of Rh in encouraging the cleavage of C–C bonds within the ternary $PtRh/SnO_2$ catalyst. Furthermore, *in situ* FTIR enabled quantitative confirmation of the increase in the total oxidation pathway that results in CO_2 generation.

Real-time evaluation of the effects of changes in temperature, pressure, concentration, catalyst, and solvent on the reaction kinetics and selectivity is made possible by *in situ* FTIR, which acts as a sentinel. Using this tool, researchers may quickly assess how these variables affect reaction rate, equilibrium position, and product dispersion. This quick feedback loop makes it easier to find the ideal circumstances for reactions that yield higher product quality.

5.3. Drug release control

Proper control of drug release from pharmaceutical formulations is an essential component of current drug delivery systems, with the goal of optimising therapeutic efficacy while minimising potential side effects, and *in situ* FTIR has proven itself as a powerful tool. Furthermore, FTIR imaging lends itself to the visualisation of drug release as a function of time. Unlike traditional dissolution studies, this spectroscopic imaging technology provides a new perspective on the alterations that occur within the pharmaceutical during disintegration. *In situ* FTIR imaging has shown significant potential in a variety of applications, including the investigation of multi-layered solid tablets, streamlined high-throughput investigations, the use of microfluidic devices, and the deployment of surface-enhanced *in situ* ATR-FTIR spectroscopy [80].

Ewing et al. [81] developed a method for studying drug release from pharmaceutical formulations using a combination of ATR-FTIR spectroscopic imaging and particularly constructed polydimethylsiloxane microfluidic devices. Under flowing conditions, the dissolution of micro-formulations such as ibuprofen and PEG was investigated, and the drug's behaviour and release were observed *in situ* at various pH levels. As seen in the spectroscopic images and ATR-FTIR spectra, the medication transformed from a molecularly distributed state to a crystalline form in the acidic solution. The microfluidic devices allowed many micro-formulations to be exposed to different aqueous conditions simultaneously, providing an efficient way of screening several micro-formulations in a single experiment. The study also stressed the importance of examing the drug's behaviour after its release, such as recrystallisation from a solution. When sodium ibuprofen was dissolved in a neutral solution and exposed to an acidic medium, the ATR-FTIR spectroscopic imaging data revealed a phase transition from sodium ibuprofen dissolved in a neutral solution to solid crystalline ibuprofen. The combination of ATR-FTIR spectroscopy and microfluidic devices provides a high-throughput analytical technique to investigate drug release and material behaviour under flowing conditions, with the possibility of further improvement as a reliable and robust method for studying a wide range of formulations and solutions.

In the study by Pudlas et al. [82], *in situ* FTIR spectroscopic imaging combined with a flow-cell device was used to examine the effect of different excipients on drug release from formulations. It was discovered that differences in drug release rates were primarily due to drug-polymer interactions, with the addition of sodium carbonate enhancing release by reducing these interactions and promoting the formation of a more water-soluble ibuprofen salt. Other successful examples of the use of *in situ* FTIR in drug dissolution imaging included studies investigating the release of antiviral drugs by Ewing et al. [83,84].

5.4. Crystallisation control

The ability of a molecule to take different crystalline shapes in its solid form is referred to as polymorphism. Polymorphs differ in their physical and chemical properties, such as lattice energy, melting point, heat of fusion, solubility, dissolution rate, density, and processability. These variances can affect pharmaceutical stability, formulation, potency, bioavailability, storage, and performance. In terms of intellectual property, a unique polymorph can obtain a patent if it exhibits enhanced properties over a previously patented polymorph, allowing competitors to legally offer the same drug molecule in a different crystal structure. Modifications in crystallisation settings, such as changing the operating temperature, solvent type, and solution pH, can lead to various polymorphic forms [85]. The process of polymorphism can be monitored effectively using *in situ* FTIR, which allows for real-time observation of molecular changes during crystallisation processes.

Cheng et al.'s study [86] emphasises the importance of amorphous calcium carbonate as a critical transitional stage in the $CaCO_3$ nucleation and crystallisation process. Understanding the detailed molecular-level metamorphism of amorphous calcium carbonate into definite crystals is critical for unravelling various biomineralisation phenomena. The researchers used *in situ* FTIR spectroscopy to examine the process of moisture-induced amorphous calcium carbonate crystallisation in their investigation. This technique is highly sensitive to changes in the vibrational properties of carbonates and water molecules, making it a viable tool for analysis. Another great example was presented by Chan et al. [66], who characterised the use of *in situ* FTIR imaging in combination with a controlled humidity cell to monitor the crystallisation of binary mixtures of two drugs under identical environments. Using an infrared focal plane array detector, the researchers investigated the influence of relative humidity on binary mixes of nifedipine and nitrendipine arrayed on the surface of a BaF2 window with varying molar ratios and amorphous nitrendipine. The study also examined the effect of sample thickness on imaging findings analysis, employing a unique approach to generate thickness-independent images. The FTIR spectroscopic imaging approach presented in this paper can be used in future high-throughput research on a large number of samples in a controlled setting. This method also revealed the ability to investigate numerous distinct medications and their mixes at the same time for crystallisation behaviour and polymorphism alterations. This high-throughput imaging investigation has the advantage of measuring each sample as a distinct chemical image, allowing the spectra of different polymorphs to be retrieved and evaluated individually without requiring spectral subtraction. There are also other valuable examples of studies where *in situ* FTIR was used for crystallisation control in the pharmaceutical industry, particularly in the polymorphic transformation of carbamazepine [87], rifampicin [88], and celecoxib [89], as well as in chemical analysis [90–92].

5.5. Absorption and desorption control

In situ FTIR spectroscopy is proved to be an effective analytical method for studying molecular interactions on solid surfaces. This technique is used in a variety of scientific investigations, assisting researchers in deciphering the complicated dynamics of molecule adsorption and desorption processes. *In situ* FTIR can provide insights into the delicate interplay between adsorbate molecules and the underlying surface, allowing for a better understanding of material behaviour under different situations. This skill has found application in a variety of fields, including catalysis, materials science, and environmental monitoring.

Surface interactions have benefited from the use of horizontal attenuated total reflection Fourier transform infrared spectroscopy (HATR-FTIR). This specific *in situ* technique involves carefully positioning a high refractive index crystal at an angle against the sample's surface, causing an evanescent wave that penetrates the material. This method allows for real-time, non-destructive investigation of surface layers without the need for elaborate sample preparation. Several research endeavours have harnessed the power of HATR-FTIR to delve into adsorption and desorption phenomena. For instance, a recent investigation explored the desorption of glyphosate from goethite induced by phosphate adsorption. Through a combination of HATR-FTIR spectroscopy and adsorption isotherm analyses, researchers established significant glyphosate desorption upon high surface coverage of phosphate. This effect manifested as pronounced desorbed glyphosate to adsorbed phosphate ratio of 0.60 [93]. Similarly, studies have explored the influence of humic acid on glyphosate's adsorption/desorption behaviour on goethite [94], as well as the adsorption of dimethyl sulphide on silver-modified bentonite [95], dimethylarsinic acid on iron-(oxyhydr)oxides [96], and major intermediates in CO_2 electrochemical reduction on CuO nanoparticles [97]. Studies are being conducted on the local structure of water on chemically and structurally diverse surfaces. *In situ* IR spectroscopy is also an excellent tool for examining adsorbed water, both qualitatively and quantitatively, due to its sensitivity to water and hydrogen bonding states [64,98,99].

In situ diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) is another useful tool for examining surface intermediates in real time. In contrast to HATR-FTIR, which uses a high refractive index crystal in direct contact with the sample's surface, *in situ* DRIFTS operates on a different concept. It entails using infrared radiation to illuminate finely divided or powdered samples and capturing the diffusely reflected light for examination. Using DRIFTS, researchers investigated the surface chemistry of Cu/TiO_2 composites during CO_2 photoreduction, revealing that Cu/Ti(H_2) exhibited over 50% higher CO_2 photoreduction activity compared to Cu/Ti(air), attributed to the synergy between Cu^{2+}, OH groups, and oxygen vacancies, which enhanced electron transfer, provided CO_2 adsorption sites, and facilitated CO_2 activation [100].

In contrast to *ex situ* methods, *in situ* FTIR spectroscopy appears to be a powerful technique for investigating surface intermediates in real time. These investigations exemplify the broader utility of *in situ* FTIR, particularly HATR-FTIR and DRIFTS, in exploring surface interactions and molecular dynamics. By enabling precise characterisation of molecular changes at solid surfaces, *in situ* FTIR significantly advances our understanding of material behaviour and drives innovation in areas as diverse as environmental science and materials engineering.

In contrast to *ex situ* methods, which require analysing samples removed from their original environment, *in situ* FTIR allows direct monitoring of molecular species adsorbed onto a solid surface during chemical reactions. This feature is extremely useful, since it allows for investigating reaction mechanisms, identifying transitory intermediates, and monitoring surface species dynamics under realistic reaction conditions. *In situ* FTIR has a distinct benefit in that it captures the precise details of molecular interactions and changes as they happen without disturbing the system. This real-time observation of surface intermediate behaviour allows for a better knowledge of catalytic processes, reaction pathways, and the roles of various surface species, ultimately paving the way for informed catalyst design and optimization. This enhances our understanding of complicated reaction processes and intermediate species. However, the procedure requires specialised equipment and can be experimentally complicated, causing difficulties in terms of correct sample handling and setup.

6. Combination of FTIR technique with other analytical techniques for optimization of chemical and pharmaceutical processes

Methodological synergy in chemical analysis involves integrating and combining different analytical techniques or methodologies to obtain complete and reliable information about an analytical sample. Researchers can capitalise on the merits of each strategy while accounting for their limitations by using diverse methodologies. This method can provide users with a better knowledge of the sample's composition, structure, characteristics, and behaviour. FTIR can also be combined with various analytical methods to optimise laboratory and industrial processes.

Gas chromatography (GC) is a powerful analytical method for separating and analysing volatile compounds in a sample. It can be combined with FTIR to observe the composition of the gas and liquid phases during a reaction [101–103]. For example, Ke et al. [104] created two gas-liquid separators to overcome the difficulties associated with using ATR-FTIR as an analytical method when a significant quantity of hydrogen gas is generated from the counter electrode. The self-optimising system has been proven with two reactions, as well as the performance and reliability of the gas-liquid separators.

Raman spectroscopy is another vibrational spectroscopy method that gives information about a sample's molecular structure. It can be used in tandem with FTIR to provide additional information about the chemical mixture and pharmaceutical formulations [105–108]. As a successful illustration, in optimising ultrasound-assisted extraction of bioactive compounds from *Acacia Seyal* gum using response surface methodology, a combination of Raman and FTIR Spectroscopy and GC was utilised effectively [109]. The Raman spectrum fingerprint identified polysaccharides like galactose and glucose, as well as proteins like lysine and proline, while the FTIR spectrum showed the presence of functional group peaks including alkanes, aldehydes, aliphatic amines, and phenol. The presence of D-galactopyranose, carotenoid, and lycopene antioxidant compounds was identified using GC spectroscopy.

Multivariate analysis methods such as PCA [110,111] and PLS [112–114] can be used to analyse the FTIR data. These methods can aid in identifying the most significant spectral changes that occur during the reaction, allowing the reaction conditions to be optimised. The combination of FTIR analysis and chemometric calculations is a promising analytical tool that aims to reduce the difficulty of analysing pharmaceuticals in a completely green performance. Compared to conventional methodologies such as HPLC, it can help decentralise analytical measurements with fewer obstacles in terms of short operation times, portability, lower cost, less organic waste, and enhanced operator safety. A side-by-side comparison of the potential of FTIR and HPLC techniques, combined with PLS regression for quantitative analysis of pharmaceutical active ingredient combinations in view of green analytical chemistry principles, was conducted in the study by Kelani et al. [34]. The analysis of ketoprofen/hyoscine and benzocaine/

dextromethorphan HBr in binary mixtures and pharmaceutical preparations using FTIR-PLS regression showed superior performance because it offers less solvent consumption, portability, less generated waste, shorter operating time, lower operation cost, lower energy consumption, and increased operator safety, and it is easily coupled with chemometric tools.

In addition to the techniques described previously, FTIR can be combined with other methods, such as flow cells [115,116] or microfluidic devices [117–119], to monitor and optimise chemical reactions in real time. These methods have a variety of benefits, including the ability to control reaction parameters, improve mass transfer, improve reaction kinetics, and provide information on the electrochemical behaviour of the reactants. Overall, combining FTIR with other techniques offers a powerful method for monitoring chemical reactions and optimising reaction conditions.

7. Use of FTIR spectroscopy in the medical industry for disease and medical conditions identification

The growth in diseases such as cancer and viral infections, as well as a lack of adequate, reliable, cost-effective, and high-throughput diagnostic technologies, has necessitated the development of alternative diagnostic instruments. FTIR spectroscopy is essential for comprehending a wide range of applications, from chemical characterisation and quality control to biomedicine. This approach is a rapid, non-invasive, label-free, reagent-free, and highly repeatable method for characterising biological molecules [120]. It enables automated and repeatable analyses, resulting in objective sample evaluation. FTIR can reveal the molecular structure and chemical content of biological substances such as proteins, lipids, nucleic acids, and carbohydrates. It may also identify changes in molecular composition associated with illness, providing unique signatures of biological materials such as tissues, cells, and biological fluids [121,122].

The use of ATR-FTIR spectroscopy in diagnosing viral infections [1] is being investigated by imaging spectral changes caused by the infection, which offer precise information about the infection's stage. The study of changes in the virus's genomic material during infection, known as MTPs, may be an essential technique for detecting viral infections. FTIR spectroscopy can identify changes in blood components such as total cholesterol and immunoglobulin after viral infection. Some studies [123–125] attempted to develop a novel diagnostic approach for coronavirus disease 2019 (COVID-19) based on saliva and plasma vibrational modes investigated by ATR-FTIR spectroscopy. They defined the COVID-19 biological fingerprint, enabling COVID-19 detection using a multivariate linear regression model, which may aid the future development of quicker and less expensive diagnostic instruments. The efficacy of FTIR spectroscopy for the rapid identification of infective virus particles was investigated by Lee-Montiel et al. [126], utilising poliovirus (PV1) and buffalo green monkey kidney cells. Their results demonstrated that the approach works best 8 h after infection and can accurately identify viral titers ranging from 10 to 10^6 PFU/mL. According to the study, this method of poliovirus identification and quantification might be applied to other viruses and modified for use in water safety monitoring and medical diagnostics. FTIR studies demonstrated a constant decline in the strength of the carbohydrate peak in conjunction with the growth of the herpes viral infection [127], as detected by optical microscopy. This drop in cellular glucose content was employed as a biomarker for the kinetics of herpes virus infection, and it might be utilised to establish a spectroscopic approach for assessing the progression of herpes virus infection. ATR-FTIR spectroscopy was also used to identify hepatitis C and B viruses [128] and dengue fever [129] caused by dengue arboviruses.

FTIR spectroscopy has been demonstrated to be a valuable tool for detecting and characterising various forms of cell death in leukaemia cells [130]. The study's findings indicate that FTIR spectroscopy can discriminate between apoptosis and necrosis based on changes in DNA conformation and protein secondary structure. There was an increase in β-sheet structures linked with apoptosis and a decrease in random coil formations during necrosis. Because of its capacity to offer discrete biochemical information with minimum sample processing and no need for reagents, FTIR spectroscopy appears to be a potential method for monitoring cell death in a clinical environment, according to the study. There have been reports of the use of FTIR spectroscopy in the diagnosis of certain cancer cells: colon cancer [131], breast cancer [121], lung cancer [132], skin cancer [133], etc.

Additionally, FTIR spectroscopy may be used to quantify urine components like protein, creatinine, and urea [134]. By giving information on bone composition and molecule quantities, FTIR spectroscopy can be utilised to diagnose bone illnesses linked to bone strength. Through FTIR spectroscopy, the researchers identified the contributions of mineral and collagen properties to stress fractures (SF) risk [135], analysing the biochemical profile differences between healthy bone and bone affected by an SF. According to ratio analysis and biochemical mapping, stress-fractured bones exhibited a higher collagen content, poorer maturity, mineralisation, carbonate and acid substitutions, and increased crystallinity compared to healthy bones.

8. Conclusion

This review aimed to provide strong evidence of FTIR spectroscopy as a practical, fast and selective technique, with the advantage of requiring small samples, having a viable budget in terms of instrumentation, increasing the ability to identify or characterise complex structures, minimizing the handling of toxic materials, and reducing the generation of organic waste solvents. The primary contribution of this work is to show examples of *ex situ* and *in situ* FTIR applications for substance identification and analysis that can now also be utilised in chemical, pharmaceutical and medical fields, while being "greener" than existing procedures. FTIR spectroscopy may be conveniently employed in routine drug and chemical testing and quantification. Moreover, this valuable technique may be employed in disease identification.

In all industries, *ex situ* FTIR spectroscopy is a reliable tool for material identification, quality control, and stability assessment. Its ability to characterise contaminants, monitor crystallisation processes, and manage medication release patterns highlights its critical role in product quality, safety, and efficacy. Furthermore, its quantification capabilities lead to more efficient drug development, dosing methodologies, and quality control practices, while its environmentally friendly characteristics are consistent with green analytical practices. *In situ* FTIR spectroscopy, on the other hand, emerges as a novel tool for dynamic analysis, allowing for real-time monitoring of molecular changes during reactions and processes. Its contributions range from monitoring drug release patterns and crystallisation dynamics to studying surface interactions and adsorption phenomena. The time-resolved examination of chemical reactions by *in situ* FTIR offers a unique perspective that complements *ex situ* approaches, leading to a better knowledge of molecular changes and material behaviour.

Together, the precision of *ex situ* FTIR in characterising and quantifying, combined with the ability of *in situ* FTIR to capture dynamic changes, creates a comprehensive analytical framework for advancing green practices, quality control and innovation in both chemical and pharmaceutical sectors. With their distinct advantages, these methodologies work in tandem to shape efficient,

sustainable and effective analytical strategies for the growth of research and industry. Overall, the prospects for using FTIR in greening chemical and pharmaceutical processes are promising. However, further research is needed to explore the potential of FTIR in these fields fully and to develop new applications that can further enhance the sustainability of chemical and pharmaceutical processes.

CRediT author statement

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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