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Current and potential applications of simultaneous DSC-FTIR microspectroscopy for pharmaceutical analysis

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Abstract

Quality control (QC) is the most important key issue in the pharmaceutical industry to ensure the quality of drug products. Many analytical instruments and techniques in pharmaceutical analysis are applied to assess the quality and quantity of the drugs. In the current and future trends, a combination of digitization, automation and hyphenation with high throughput on-line performance will be the topics for the future of pharmaceutical QC. The hyphenated analytical techniques have recently received great attention as unique means to solve complex analytical problems in a short period of time. This review article is an update on the recent potential applications of hyphenated technique developed from the coupling of a rapid separation or induction technique (differential scanning calorimetry; DSC) and an on-line spectroscopic (Fourier transform infrared; FTIR) detection technology to carry out an one-step solid-state analysis in pharmaceutical formulation developments, including (1) intramolecular condensation of pharmaceutical polymers, (2) intramolecular cyclization of drugs and sweetener, (3) polymorphic transformation of drugs and excipients, (4) drug-polymer (excipient) interaction, (5) fast cocrystal screening and formation. This simultaneous DSC-FTIR microspectroscopy can also provide an easy and direct method for one-step screening and qualitative detection of drug stability in real time.

Keywords: DSC-FTIR microspectroscopy, Hyphenation, One-step, Real time, Solid-state analysis

1. Introduction

According to the “Quality Guidelines” of ICH for the development of pharmaceutical drug products, understanding the physicochemical properties of active pharmaceutical ingredients (APIs) and excipients is an important prerequisite for successful development and manufacture of different dosage forms [1,2]. The physicochemical properties of both APIs and excipients include particle size, powder properties, moisture content, hygroscopicity, crystal properties, solubility, polymorphs, stability and their compatibility [3–5]. These properties play a crucial role in pharmaceutical development; it must pay more attention in the pharmaceutical

manufacturing processes [6–9]. Moreover, several manufacturing factors such as temperature, light, humidity, pressure, processing time, and solvents used have found to influence the solid-state characteristics of APIs and excipients, leading to alterations of the physicochemical properties, bioavailability and therapeutic efficacy of the APIs [10–12].

From the ICH guidance and US FDA regulation for drug development and manufacturing, a detailed characterization of the critical physical attributes of the pharmaceutical materials should make sure to comply with regulatory requirements [13,14]. It has been known that the solid state characterization of pharmaceutical solids can be analyzed by several analytical techniques [15–21]. Brittain et al. classified the physical properties of

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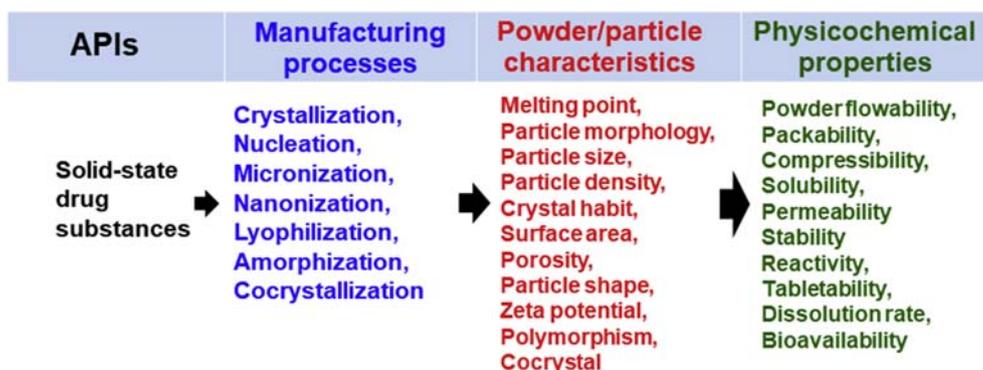
Table 1. Classification of physical characterization of pharmaceutical solids by various analytical approaches [Modified, with permission from Ref. [15]].

Molecular level	Particulate level	Bulk level
Spectroscopies Light Microscopy UV–vis spectroscopy (UV-VIS) Fluorescence spectroscopy Fourier transform infrared spectroscopy (FTIR) Raman spectroscopy Near-infrared spectroscopy (NIR) Solid-state nuclear magnetic resonance spectrometry (SSNMR)	Spectroscopies Terahertz pulsed spectroscopy (TPS) Terahertz Pulsed imaging (TPI) Fluorescence spectroscopy Dielectric spectroscopy X-ray photoelectron spectroscopy (XPS) Single-crystal X-ray diffraction (SCXRD) Particle morphology Polarized light microscopy (PLM) Scanning electron microscope (SEM) Atomic force microscope (AFM) Transmission electron microscopy (TEM) Particle size/distribution Particle size analyzer Diffraction Powder x-ray diffraction (PXRD) Thermal analysis Thermogravimetric analysis (TGA) Differential scanning calorimetry (DSC) Modulated differential scanning calorimetry (MDSC) Hot-stage microscopy (HSM) Zeta potential analyzer	Micromeritics Powder characteristics tester <ul style="list-style-type: none"> • Angle of repose • Cohesion • Aerated density • Uniformity • Dispersibility • Compressibility • Angle of Fall • Packed density • Angle of Spatula • Angle of difference • Particle size Powder flow analyzer Gas pycnometry Moisture analyzer Wall friction tester Tensile tester Contact angle goniometer

pharmaceutical solids into three main levels: (1) molecular level (properties associated with individual inorganic or organic molecules), (2) the particulate level (properties belonged to individual geometrical solid particles), and (3) the bulk level (properties associated with particulate assemblies) [15,19]. Table 1 lists the classification of physical characterization of pharmaceutical solids by various analytical approaches [15,17,19], in which the molecular-level properties are usually evaluated by using vibrational spectroscopy and solid-state nuclear magnetic resonance spectrometry (SSNMR); the particulate level properties are determined by particle morphology, particle size/distribution, thermal and diffractometric methods; and the bulk level properties are focused on surface area,

porosity and pore size distribution, and powder flow characteristics [15,21–23].

Since many APIs can exist in different pharmaceutical solid forms, the solubility, flowability, compressibility, physical and chemical stability, and reactivity of these APIs may be altered depending on manufacturing processes and/or under storage conditions of the final solid dose forms. Scheme 1 illustrates the manufacturing processes affecting solid state characterization of drug substances. Therefore, selecting an optimal solid form of an API is of considerable importance and also a key factor to maintain the selected solid form through formulation development, scale up, manufacturing processes, storage and usage of drug products. Particularly, the possibility of compatibility/



Scheme 1. Manufacturing processes affecting solid state characterization of drug substances.

interaction, and API stability after exposure to elevated humidity and temperature over time should be conducted [24–27]. It is therefore necessary to use the comprehensive solid-state analytical approaches for ensuring and maintaining maximum quality control of an original API in pharmaceutical drug products [6,28,29].

2. The most commonly used solid-state analysis of APIs in drug products

Newman and Byrn had reported that the solid APIs played an important role to impact the quality and consistency of the final solid oral dosage formulations [29]. Thus how to monitor and/or control the intact solid API continuously existed in drug product without any change from development to market and beyond is the most critical factor for successful drug development in the pharmaceutical industry [30–32]. In common, it is necessary to analyze each raw API, intermediate and final finished product at designated times to ensure the highest quality during pharmaceutical process development for supporting the regulatory filing activities [33,34]. Until now, many analytical techniques such as thermal, spectroscopic, and diffractometric methods have been often used to determine and confirm the original crystal form of API still existed in solid dosage forms after different pharmaceutical manufacturing processes [29–31,33–35]. Several unusual drug examples on the market had occurred undesired solid state conversion, resulting in poor bioavailability related problems or clinical failures [36,37].

Here, three most commonly used analytical techniques including thermal, spectroscopic, and diffractometric methods for solid-state analysis of APIs and drug products will be briefly described as follows.

2.1. Thermal analysis

Thermal analysis (TA) is one of the oldest analytical techniques for studying the thermal properties of different materials as a function of temperature or time [38,39]. In the field of pharmaceutical research,

TA has been often applied to investigate and characterize different pharmaceutical substances, such as physical stability (e.g., weight loss, loss of hydration/solvation, degradation and/or decomposition), phase transitions (e.g., melting, sublimation, polymorph conversion) and other complex phenomena (e.g., chemical reaction, vitrification, relaxation, etc.) [40–44]. Four common TA techniques used in the pharmaceutical fields are thermogravimetric analysis (TGA), differential thermal analysis (DTA), differential scanning calorimetry (DSC), and thermomechanical analysis (TMA). The primary differences in these TA techniques and the properties measured of the materials are listed in Table 2. Hot-stage microscopy (HSM) is another thermal method and can be used to visually examine many kinds of thermal transitions such as melting point, melting range, crystal nucleation, crystal growth, crystal transformations and others under a microscope, especially for the study of the visual color changes in the process of thermal transitions [45,46].

2.2. Vibrational spectroscopic technique

The vibrational spectroscopy commonly includes mid-infrared (MIR), near-IR (NIR), and Raman spectroscopy. Fourier Transform Infrared (FTIR) spectroscopy is mainly used to measure MIR light absorption (wavelengths 2.5–25 μm). Both FTIR and Raman spectroscopies are complementary techniques, and offer rapid and non-invasive analysis to provide specific fingerprinting spectra for analysis of molecules in different scientific and industrial fields [47–50]. These techniques are indispensable analytical techniques in pharmaceutical analysis and can substantially identify and characterize the drug substances and excipients in drug discovery and formulation development, as well as in on-line pharmaceutical process manufacturing [51–54].

Both FTIR and Raman spectroscopies provide characteristic fundamental vibrations and are applied to the elucidation of molecular structure, whereas NIR spectroscopy is based on molecular overtones and combinations of vibrational modes to measure the absorption of electromagnetic radiation within wavelengths from 750 to 2500 nm [55–58].

Table 2. Conventional TA techniques and the representative properties measured for materials.

TA Technique	Abbreviation	Representative properties measured
Thermogravimetric analysis	TGA	Decomposition, oxidation or loss of solvent or water
Differential thermal analysis	DTA	Melting points, glass transitions, phase changes
Differential scanning calorimetry	DSC	Melting points, heats of reaction, glass transition, heat capacity
Thermomechanical analysis	TMA	Expansion, contraction, penetration, softening, glass transition
Hot stage microscope	HSM	Thermal transition/crystal growth (Visual color change)

On the other hand, NIR spectroscopy as a powerful technique has recently been used for monitoring end-point of many pharmaceutical manufacturing processes, such as granulation, mixing or drying, since the NIR measurement not only requires no or little sample preparation but also is fast for online process control [59,60].

In recent years, two new techniques of Terahertz Pulsed spectroscopy (TPS) and Terahertz Pulsed imaging (TPI) instruments are now commercially available for rapid and non-destructive analysis in pharmaceutical industry [61,62]. Both Terahertz techniques have been available used for various pharmaceutical applications, such as (1) discrimination and quantification of polymorphism and crystallinity, (2) analysis of solid form transformation dynamics, (3) quantitative characterization of tablet film coatings: off-line and on-line, (4) tablet porosity measurement, (5) tablet coating and dissolution, (6) spectroscopic imaging and chemical mapping [61–66]. Fig. 1 shows different frequency ranges of the electromagnetic spectrum [67].

2.3. Diffractometric technique

X-ray diffraction (XRD) is a nondestructive technique used in solid state chemistry to characterize both organic and inorganic crystalline materials in various fields, as indicated in Fig. 2 [68,69]. XRD has a tremendous potential for solid state drug analysis in all stages of drug discovery and development, manufacturing and quality control of manufactured pharmaceutical products, in which XRD may

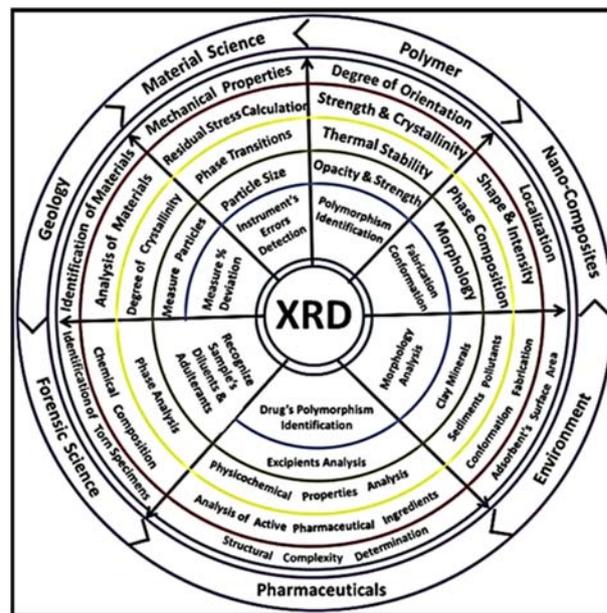
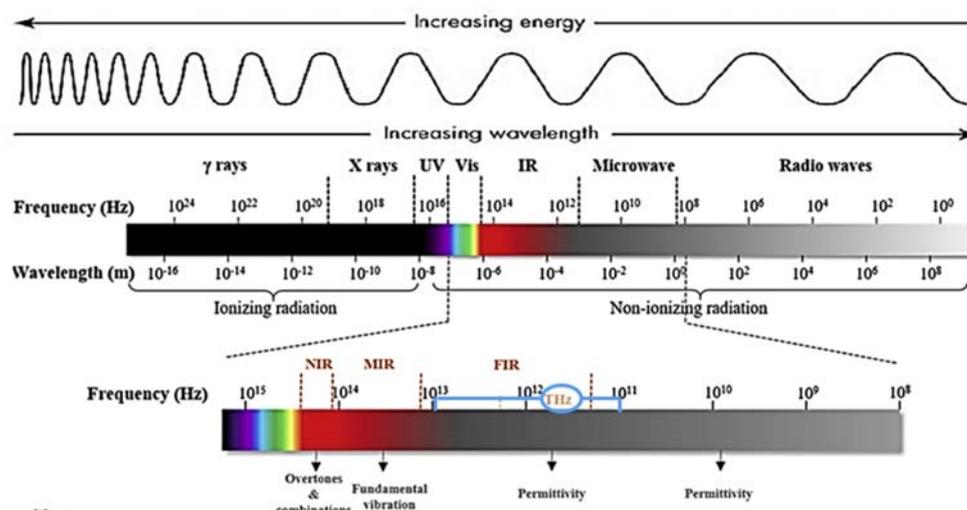


Fig. 2. Analytical applications of X-ray diffraction (XRD) in different fields [Reproduced from Ref. [68]].

provide more valuable pharmaceutical information on crystal structure, polymorphism, and degree of crystallinity and amorphous character of solid formulations, excipient compatibility, detection of impurities formed, stability studies, dosage uniformity, and manufacturing process control [70–72]. XRD is mainly based on Bragg's law, $2d\sin\theta = n\lambda$, Where d is the spacing between diffracting planes, θ is the incident angle, n is an integer, and λ is the beam wavelength. XRD patterns result from



Note:
 UV: Ultraviolet; Vis: Visible; NIR: Near infrared; MIR: mid-infrared; FIR: Far infrared;
 THz: Terahertz

Fig. 1. Different frequency ranges of the electromagnetic spectrum [Modified, with permission from Ref. [67]].

electromagnetic waves impinging on a regular array of scatters, as shown in Fig. 1 [67]. The XRD pattern is the fingerprint of periodic atomic arrangements in a given material and commonly employed on thick or powdered materials due to its penetration depth of X-ray, resulting in the enhanced performance for detection of internal structural properties of the material [73].

The XRD analyzer consists of three key elements, X-ray source, a sample, and a detector, to pick up the diffracted X-rays [69]. Several scattering techniques of X-ray crystallography have been reported: single-crystal diffraction, powder diffraction, fiber diffraction, small-angle and wide-angle X-ray scattering [74]. Two major techniques, powder X-ray diffraction (PXRD) and single-crystal X-ray diffraction (SCXRD), are the most common approaches used in pharmaceutical investigation [75,76].

PXRD can characterize the structural properties of powders or microcrystalline solid materials, whereas SCXRD may determine three dimensional arrangements of atoms in a crystalline chemical compound. Particularly, PXRD has always applied to the pharmaceutical industry via solid-state analysis of a drug substance or product in various stages of drug development and manufacturing process as follows: (1) API characterization and excipient identification (phase analysis and polymorph screening, crystallinity determination, control of ingredients), (2) determination of physical and chemical stability (compatibility studies, stability studies), (3) monitoring for solid form conversion upon manufacturing (process control, manufacturing and production), (4) verification of the solid form of the API in the drug product (batch/dosage uniformity, impurities product) [77–80].

3. Hyphenated analytical techniques applied to pharmaceutical analysis

In recent years, hyphenated analytical techniques have received considerable attention as unique analytical tools for solving various complex problems in pharmaceutical analysis [81–85]. The merits of hyphenated analytical techniques have remarkably broadened their applications in the analysis of biomaterials, natural products, cosmetics, pharmaceuticals and biomedical products. The hyphenated technique simply connects two or more analytical instruments together to enhance material characterization with an appropriate interface [86]. The term “hyphenated techniques” may range from the combination of separation–separation, separation–identification and identification–identification techniques [87]. The hyphenated analytical method has

been able to provide faster and more reliable results than that a traditional single instrumental method.

The technique developed by coupling a separation technique and an on-line spectroscopic detection (identification) technology is the most used hyphenated technique, thus Patel et al. had discussed the use of five available hyphenated techniques, e.g., gas chromatography–mass spectroscopy (GC–MS), liquid chromatography–Fourier transform infrared (LC-FTIR), LC-MS, LC-nuclear magnetic resonance spectroscopy (LC-NMR), capillary electrophoresis-MS (CE-MS), for pre-isolation analyses of crude extracts or fraction from various natural sources, isolation and on-line detection of natural products, chemotaxonomic studies, chemical fingerprinting, quality control of herbal products, and etc. [81]. The GC, LC and CE were as the separation tool in the hyphenated techniques, whereas FTIR, MS and NMR were utilized as identification tool. The combination of both separation tools with identification techniques has been demonstrated for years to qualify and quantify the unknown compounds in complex natural product extracts or fractions [81].

Ermer and Vogel had successfully introduced the applications of hyphenated LC-MS techniques in pharmaceutical analysis, in which LC-MS might systematically be applied to monitor and identify the impurity profiles during pharmaceutical development and scaling up for supporting the safety evaluation of batches used in clinical studies [88]. In addition, Pan et al. had reviewed and discussed the current analytical strategies for chemical and structural identification of pharmaceutical impurities [89]. Because the pharmaceutical impurities had pharmacological or toxicological effect, the presence of these impurities and their levels in drug products often had critical impacts on the quality of drug products and the safety of patients. Thus understanding drug impurities or drug degradation products in the formulated products must be conducted. The LC-MS had been widely used in the pharmaceutical industries due to its excellent sensitivity for the detection of trace level of impurities and degradation products observed in formulated dosage forms. Sometimes, other hyphenated analytical techniques such as LC-NMR, GC–MS, and size-exclusion chromatography (SEC)/chemiluminescent nitrogen detectors (CLND) were also used to identify and confirm the final structures of impurities as required during dosage form development.

In addition, the identification–identification modes of hyphenated techniques had also been applied to polymeric and pharmaceutical industries

by coupling TA techniques with spectroscopic technique [90–96]. TA techniques were commonly well-established techniques used for characterization of polymers and pharmaceuticals. A single TA technique simply measured the change of a specific property of materials as a function of temperature, whereas the hyphenated techniques coupled with different analytical techniques and equipped with a proper interface could enable user to determine more information from complex matrices [44,83,87,96]. Therefore, the application of the hyphenated analytical techniques in pharmaceutical analysis has offered great advances [84–88,97–101].

4. Simultaneous DSC-FTIR microspectroscopy

It had been reported that TA techniques could only measure the physical properties of materials; it was often incomplete and/or limited in its ability to address chemical composition and structure [102]. In order to overcome the limitation of TA techniques, coupling TA instruments with chromatographic or spectral instruments to increase the information collected during the experiment is one of the most important challenges [83–87,103]. Analysis of complex samples has been greatly assisted by the coupling of FTIR analysis to the TA experiment [91,94]. The combination of DSC and FTIR spectroscopy gives important spectroscopic and thermodynamic information for a solid or liquid sample upon heat treatments [90–94]. The DSC-FTIR technique is being more widely recognized as a powerful tool for understanding the thermal-dependent structural behaviour. The most promising research areas are probably polymers and the polymorphism of pharmaceuticals [90,91,94].

4.1. Introduction of DSC

DSC is a fundamental tool and also the most commonly used TA tool for investigating the temperature-driven phase changes of different materials. DSC can measure the transition such as the melting, crystallization, and glass transition of materials from polymers to foods and to pharmaceuticals [22,38–43]. DSC not only measures directly the endothermic or exothermic behavior of a material as a function of temperature, but also provides qualitative and quantitative information of thermodynamic parameters such as glass transition temperature (T_g), melting temperature (T_m), crystallization temperature (T_c), and thermal properties such as the enthalpy (H), heat capacity (C_p) [38–43,104]. However, Menard et al. pointed out that DSC lacked structural or chemical information

from its DSC thermogram [102,103], in which DSC only provided the thermal properties of solid materials. The structural or chemical information of solid samples must be obtained from other analytical methods.

4.2. DSC coupling with FTIR spectroscopy

Although DSC is a well-known analytical tool to measure the temperature-dependent phase changes and various kinetic parameters, it is also used to combine with a few analytical instruments only so far. DSC has only been found in conjunction with FTIR spectroscopy (DSC-FTIR), mass spectrometry (DSC-MS) or X-ray diffraction [90,91,105–108]. Two simultaneous DSC-FTIR combined systems had first been studied in 1986 by two groups of researchers to examine the structural changes of polypropylene during melting or to monitor the morphological transitions on the hydrogen bonding of polyurethanes, respectively [90,105].

The DSC coupling with FTIR spectroscopy deals with the thermal and spectral information to be derived simultaneously from a single sample. This simultaneous DSC-FTIR technique gives thermodynamic and spectroscopic information about a solid or liquid sample upon thermal treatment [44,90,91,105], in which DSC measured the endothermic and/or exothermic responses of the samples, while the FTIR analysis detected thermal changes in chemical and physical compositions. The possible merits of this DSC-FTIR combined system may be proposed as follows: (1) the same sample for both determinations; (2) the identical thermal and chemical environments; (3) real time response to both thermal and chemical events, and (4) a short analysis time [109]. Therefore, this DSC-FTIR coupled technique can be used easily and effectively to study the thermal and spectral properties of pharmaceuticals in real time.

4.3. DSC-FTIR instrument configuration

As described above, the hyphenation of DSC with FTIR microspectroscopy had first been used in 1986 [90,105]. This DSC-FTIR combined technique can simultaneously provide the thermodynamic and spectroscopic information of the sample under thermal treatment at the same time. In this approach, the whole instrument of DSC-FTIR microspectroscopic system used in my laboratory is shown in Fig. 3. This DSC-FTIR combined system involves the use of a miniature DSC cell positioned under the objective of an IR microscope in conjunction with FTIR spectroscopy. A computer

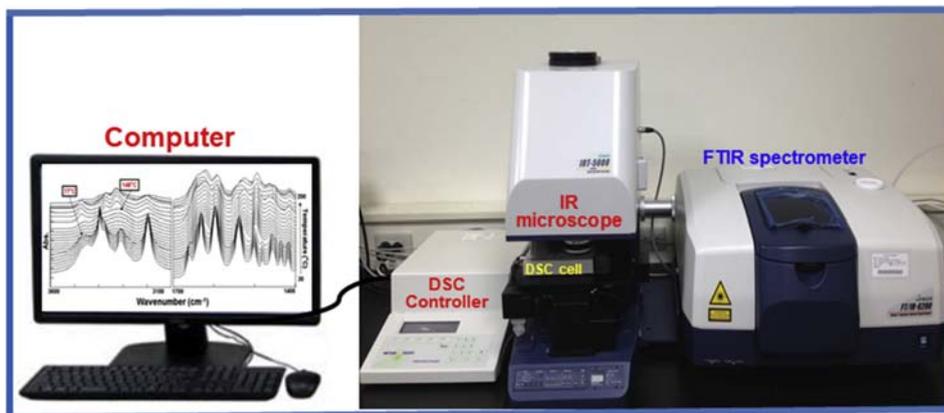


Fig. 3. The instrumental configuration of a DSC-FTIR microspectroscopic apparatus [Modified, with permission from Ref. [44]].

directly monitors DSC and FTIR analyses, and the overall operation permits the simultaneous collection of both data sets. In this combined system, DSC can measure the thermal responses of the samples, whereas FTIR analysis determines the changes in their structure simultaneously.

This FTIR microspectroscopy is commonly equipped with mercury cadmium telluride (MCT) as a detector in the narrow and mid-band wavelength range between 4000 and 650 cm^{-1} . The FTIR spectra are generated by co-addition of 256 interferograms collected at 4 cm^{-1} resolution. The MCT detector used with an IR microscope has a much greater sensitivity, which is suited to the measurement of micrometer sized samples common for microscopic measurements. However, the MCT detector has some disadvantages such as the requirement for liquid nitrogen cooling for measurements, a reduced absorbance linearity and a reduced wavenumber range for measurements. Recently, a new deuterated L-alanine triglycine sulphate (DLATGS) detector has been developed for IR microscopy with wide wavenumber range between 4000 and 450 cm^{-1} at ambient temperatures to meet various measurement purposes, especially focusing on an increased sensitivity [110].

In my laboratory, the hot stage microscopy is used as a DSC cell, which is a precise thermal measurement cell for simultaneous visual observation and heat flow measurements. In the instrument configuration, the IR beam passes through a hole in the DSC cell via the IR microscope to the MCT detector. The samples are generally mounted on an optically transparent medium of potassium bromide (KBr) pellet and then placed it in a hole in the DSC cell, which can be used as the transmission or reflectance mode. A careful alignment procedure is required

prior to the operation. This simple and time-saving system relies on a one-step continuous process and provides the correlation between thermal response and spectral information regarding structural changes occurring in the sample. Moreover, this combined system may also be acted as an accelerated stability testing apparatus to predict the thermal stability of samples. This unique DSC-FTIR combined system has been extensively applied to quickly investigate the thermal-induced structural changes and stability of foods, polymers, pharmaceuticals, excipients, and cocrystal formation [44,99,111].

4.4. DSC-FTIR microspectroscopy for rapid solid-state analysis of drugs and pharmaceutical polymers or excipients

The solid-state chemistry of drugs has received major attention from the pharmaceutical industry and has become an increasingly important benchmark in drug development because solid-dosage forms are the most commonly used preparations [98,99]. A better understanding of solid state properties of an API is essential for pharmaceutical drug development and should be the first priority in the design of oral solid dosage drugs. This DSC-FTIR microspectroscopy can simultaneously establish the correlation between the thermal response and the IR spectral information of structural changes of the drug sample. This technique not only can simulate the accelerated stability test, but also may simultaneously detect the decomposed products in real time. The current review attempts to provide a succinct update of DSC-FTIR microspectroscopy used on the investigation of the solid state analysis of different drugs and polymers or excipients (Table 3), the details are as follows.

Table 3. A DSC-FTIR microspectroscopy used for investigation of the solid state analysis of different drugs and polymers or excipients.

Intramolecular condensation	Intramolecular cyclization (DKP formation)	Polymorphic transformation	Drug-polymer (excipient) interaction	Cocrystal screening and formation
Silicone elastomer (Ref. [112])	Lisinopril dihydrate (Ref. [130])	Acetaminophen (Ref. [147,148])	Eudragit L-theophylline (Ref. [163])	Carbamazepine-glutaric acid (Ref. [188])
Eudragit L (Ref. [113–115])	Enalapril Maleate (Ref. [131,132])	Famotidine (Ref. [149])	Eudragit E-enalapril maleate (Ref. [164])	Indomethacin-saccharin (Ref. [188-184,194])
Eudragit E (Ref. [116])	Aspartame hemihydrate (Ref. [133,134])	Metoclopramide HCl monohydrate (Ref. [150,151])	Asparagine-glucose (Ref. [165])	Theophylline-citric acid (Ref. [190,191])
Eudragit S (Ref. [117])	Gabapentin (Ref. [138])	Indomethacin (Ref. [152,153])	Metoclopramide HCl monohydrate-KBr (Ref. [166])	Metaxalone-succinic acid (Ref. [192])
Eudragit L30D (Ref. [117])		Trehalose dihydrate (Ref. [154])	Human serum albumin (HSA)-ribose (Ref. [167])	Indomethacin-nicotinamide (Ref. [193,195])
Carbopol (Ref. [117])		Raffinose pentahydrate (Ref. [155])		Piroxicam-saccharin (Ref. [196])
PVA copolymer (POVACOAT) (Ref. [119])		Captopril (Ref. [160])		

4.4.1. Solid-state intramolecular condensation of pharmaceutical polymers

Lin et al. used a DSC-FTIR microspectroscopy to examine the curing kinetics of silicone elastomer via intramolecular condensation [112]. This DSC-FTIR microspectroscopy was a very rapid and convenient apparatus for determination of the curing kinetics of medical grade silicone elastomer (MDX-4-4210), in which the change in IR peak intensity of Si–H at 2162 cm^{-1} for the curing agent might be acted as a reaction marker. The IR peak intensity of the Si–H band was decreased with the increase in temperature during curing process, which might be attributed to the curing reaction occurred between Si–H (curing agent) and $\text{CH}_2=\text{CH}_2$ (elastomer), leading to reduction of the amount of Si–H groups in the reaction mixture. In addition, the curing temperature and normal hydrocarbon alcohols added significantly influenced the curing process of silicone elastomer, in which the curing reaction might be described by first-order kinetics.

Lin and co-workers had used DSC-FTIR microspectroscopy to extensively examine an intramolecular interaction occurred in a series of methacrylic acid copolymers such as Eudragit L, S, E, RL, RS, L30D, E30D, PVA copolymer, and carbopol by nonisothermal or isothermal method with transmission or reflectance model [113–119]. A 6-membered cyclic anhydride formation was respectively produced by heating each Eudragit L, S, E or L30D, PVA copolymer or carbopol via inter- or intramolecular ester condensation. Eudragit E as an example, the anhydride-related IR peak intensities at 1801 and 1763 cm^{-1} (asymmetric and symmetric

stretching vibration mode of the $\text{C}=\text{O}$ group in an anhydride structure) as well as 1007 cm^{-1} (asymmetric stretching mode of $\text{C}-\text{O}-\text{C}$ for a cyclic anhydride) appeared from 180°C and increased with the heating temperature, suggesting that the anhydride formation via ester condensation started above 180°C (Fig. 4) [116]. Moreover, the higher peak intensity ratio of $1763\text{ cm}^{-1}/1801\text{ cm}^{-1}$ also exhibited the predominant role of intramolecular ester condensation in anhydride formation for Eudragit E film. However, Eudragit RL, RS, or E 30D polymer revealed a higher thermal-stable behavior without ester condensation [118]. In addition, the T_g of different polymers was also easily and rapidly measured by DSC-FTIR analysis in a short time, as compared other techniques [120].

4.4.2. Solid-state intramolecular cyclization of drugs and sweetener

A better understanding of drug stability in various dosage forms and their regulatory requirements are essential for pharmaceutical researchers. The intramolecular aminolysis occurred in protein drugs is also an important stability problem for formulating these drugs with or without different excipients [121–123]. The intramolecular cyclization of amino and carboxylic acid, ester, or amide, groups at the N-terminus of a peptide or protein, to form diketopiperazine (DKP) is a key degradation pathway during peptide synthesis or long-term storage [121–125]. The detailed mechanism of DKP formation from dipeptide amides involves the nucleophilic attack of the N-terminal nitrogen at the amide carbonyl carbon-atom, between the second and

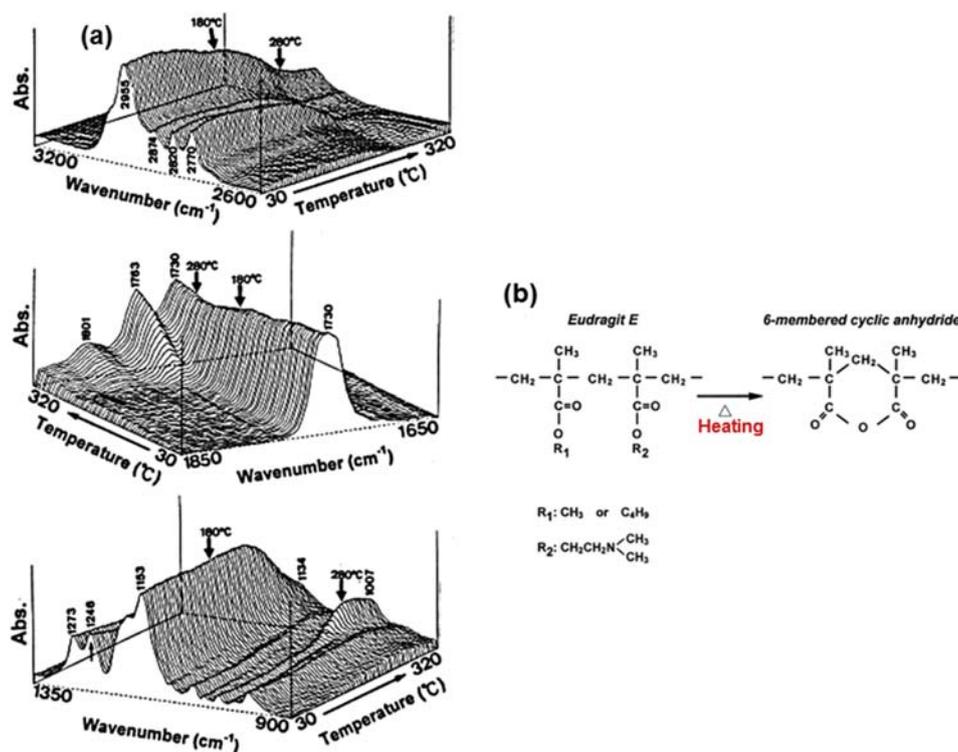


Fig. 4. Three-dimensional plots of reflectance FTIR spectra of Eudragit E film with respect to the temperature (a) and the scheme for six-membered cyclic anhydride formation via heating process (b) [Modified, with permission from Ref. [116]].

third amino acids. Until now, several analytical methods have been used to investigate the stability and DKP formation of these dipeptide drugs in solid and liquid states [99,126–129].

A simultaneous DSC-FTIR technique for real-time induction and detection of DKP formation from the pharmaceutical dipeptides including lisinopril dihydrate, enalapril maleate and aspartame hemihydrate had been examined by Lin and colleagues [99,130–134]. Lisinopril dihydrate as an example, the three-dimensional plots of FTIR spectra of lisinopril dihydrate as a function of temperature between 3700–2500 and 1800–1200 cm⁻¹ of wavenumbers is displayed in Fig. 5 [130]. A new peak at 1670 cm⁻¹ assigned to the carbonyl band of DKP formation was clearly evidenced. The water of reaction byproduct was liberated at a temperature >100 °C and appeared on the IR spectra near 3200–3400 cm⁻¹. Moreover, the peak at 1574 cm⁻¹ assigned to carboxylate was shifted to 1552 cm⁻¹ due to the DKP formation. The peak intensity at 1670 cm⁻¹ related to the DKP formation was changed slightly from 147 °C but significantly above 157 °C. Because both DSC and TGA methods are hard to show up lisinopril DKP formation, the DSC-FTIR microscopic system can be considered to be a useful technique to quickly and directly detect the

solid-state stability of drug [130]. The pathway of two consecutive dehydration processes and intramolecular cyclization of DKP formation in solid-state lisinopril dihydrate had been examined by this one-step DSC-FTIR microscopy, as shown in Fig. 6 [130]. The solid-state lisinopril dihydrate exhibited two step dehydration processes: the first process was from dihydrate to monohydrate at 76 °C and then the second process was from monohydrate to anhydrate at 99–101 °C. The DKP formation was continuously occurred after 147 °C via intramolecular cyclization in solid-state anhydrous lisinopril. The DKP formation might be as an impurity existed in pharmaceutical dosage forms. Similar results are also observed for enalapril maleate and aspartame hemihydrate [131–134].

In addition, Widjaja et al. had successfully used the multivariate data analysis approach based on entropy minimization and spectral dissimilarity to investigate the solid-state kinetics of intramolecular cyclization of enalapril maleate via thermal FTIR microscopy [135]. The infrared spectra of enalapril maleate and DKP were reconstructed. Their kinetic analysis revealed that the process of degradation required about 176.4–193.9 kJ/mol of activation energy based on fitting the fraction decomposed of enalapril maleate to seven nucleation models.

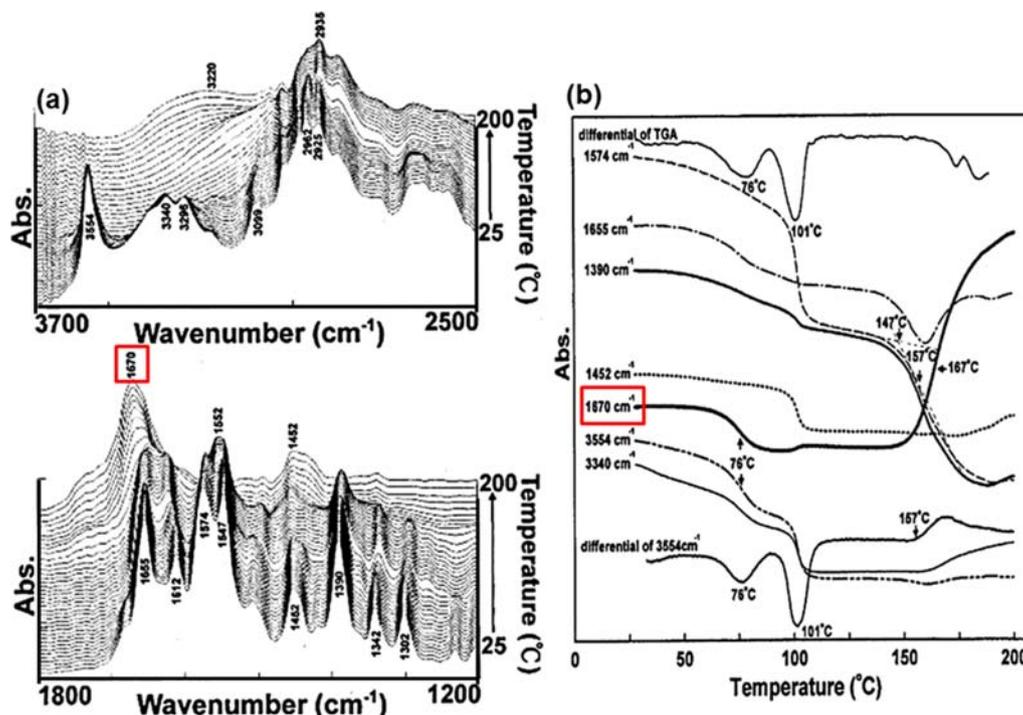


Fig. 5. Three-dimensional plots of FTIR spectra of solid-state lisinopril dihydrate a function of temperature (a) and temperature-dependent changes in peak intensity of the selected IR banks of lisinopril dihydrate (b) [Modified, with permission from Ref. [130]].

Moreover, Tan and Widjaja further interpreted the pathway of dehydration and intramolecular cyclization of lisinopril dihydrate in the solid state via isothermal FTIR microscopy by using advanced

multivariate chemometric approach [136,137]. The estimated activation energy of the intramolecular cyclization reaction of lisinopril was about 327 kJ/mol.

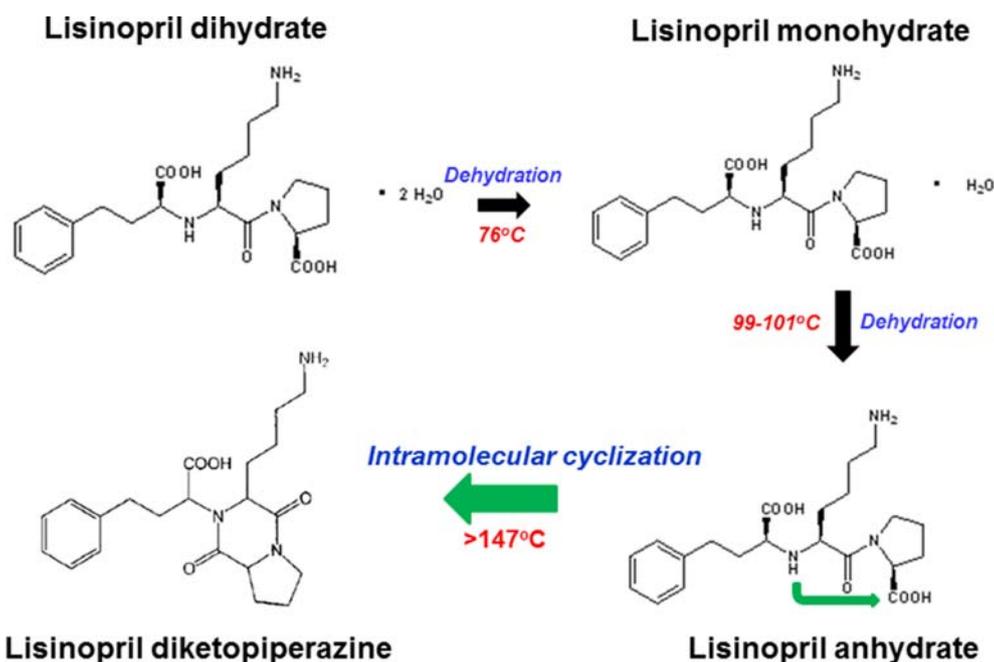


Fig. 6. The pathway of two consecutive dehydration processes and intramolecular cyclization pathway of DKP formation in solid-state lisinopril dihydrate [Modified, with permission from Ref. [130]].

The detailed intramolecular lactamization process of gabapentin (GBP) to form gabapentin-lactam (GBP-L) was also studied by Hsu and Lin via one-step DSC-FTIR microspectroscopy [138]. This DSC-FTIR microspectroscopy clearly evidenced that the IR spectral peak at 3350 cm^{-1} for water liberated was found and at 1701 cm^{-1} for lactam structure was formed due to the lactam formation of GBP. In addition, the intramolecular lactamization GBP was easily determined in the GBP sample prepared by embedding it into 2KBr method rather than 1KBr method.

4.4.3. Solid-state polymorphic transformation of drugs and excipients

The polymorphic forms of a drug have a profound impact on the physicochemical properties like dissolution and solubility, chemical and physical stability, flowability and hygroscopicity, resulting in a significant influence on the stability and bioavailability of drug products [37,139–141]. In recent years, the change of the polymorphic form of APIs has frequently caused problems in bioavailability and clinical failures once it is on the market [36,37,140–143]. Recently, many some advanced analytical techniques have been applied to characterize the polymorphs and polymorphic transformation [144–146]. In my researches, this one-step powerful DSC-FTIR combined system has been designed to quickly investigate the thermal-induced polymorphic interconversion processes of drugs involving acetaminophen, famotidine, gabapentin, indomethacin, metoclopramide HCl monohydrate, trehalose dihydrate, raffinose pentahydrate in the solid state, too [147–155].

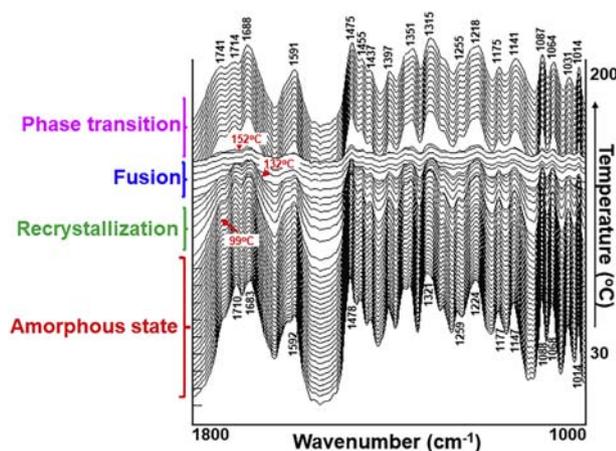


Fig. 7. Continuous phase transitional changes in the three-dimensional FTIR plot of amorphous indomethacin (IMC) in the solid state [Modified, with permission from Ref. [153]].

Indomethacin (IMC) as an example, IMC has several polymorphic forms and one amorphous form [156]. Fig. 7 displays the continuous phase transitional changes in the three-dimensional FTIR results of amorphous IMC measured by the simultaneous DSC-FTIR method [153]. It is evident that the thermal-related changes in IR peak intensity for several specific spectra were clearly observed. These spectral changes significantly differed from that of the spectral changes for γ -IMC (did not change). Four undulating regions of the IR peak intensities were obviously observed in the three-dimensional FTIR contour profile. There were no substantial changes in the contour profile of sharp IR peaks before $99\text{ }^{\circ}\text{C}$ (amorphous state). Once the temperature was $>99\text{ }^{\circ}\text{C}$, all the IR peak intensities were slightly increased as the temperature was increased from $99\text{ }^{\circ}\text{C}$ to $132\text{ }^{\circ}\text{C}$ due to the occurrence of recrystallization. Beyond $132\text{ }^{\circ}\text{C}$, all the IR spectral peaks became broader and less intense. However, the sharp IR peak intensities reappeared at temperatures $>152\text{ }^{\circ}\text{C}$. The less intense of IR peaks within $132\text{ }^{\circ}\text{C}$ – $152\text{ }^{\circ}\text{C}$ might be due to the fusion of the recrystallized IMC. The sharp IR peak intensities above $152\text{ }^{\circ}\text{C}$ should be corresponded to the phase transformation from the molten IMC to α -IMC and γ -IMC. The reappearance of the sharp IR peaks at 1741 and 1714 cm^{-1} was explained by this phenomenon. The thermal-dependent successive conformational changes of amorphous IMC sample were directly and clearly evidenced by DSC-FTIR microspectroscopy.

Another continuous process of solid-state dehydration, amorphization and recrystallization of metoclopramide hydrochloride monohydrate (MCP HCl H_2O) was also determined by this simultaneous DSC-FTIR microspectroscopic technique [150,151]. During the thermal treatment, three undulating regions of FTIR spectral peak intensities in the contour profile displayed a marked change. As shown in Fig. 8, there was a less significant change in the contour profile before $77\text{ }^{\circ}\text{C}$. Once the heating temperature was $>77\text{ }^{\circ}\text{C}$, all the IR peaks became broadened and weaker in intensities. However, the sharp IR peak intensities again appeared at temperatures $>148\text{ }^{\circ}\text{C}$. Both weak and less intense IR peaks from 77 to $148\text{ }^{\circ}\text{C}$ might be due to the amorphous formation after quick dehydration of MCP HCl H_2O , which resulted in a random structure in the crystal lattice. The starting temperature of $77\text{ }^{\circ}\text{C}$ was close to that of the thermal change at $78\text{ }^{\circ}\text{C}$ in the TGA and DSC curves. Given that the amorphous form of MCP HCl is unstable during heating, it quickly recrystallized near $148\text{ }^{\circ}\text{C}$ and sharpened the IR band from broad shape. Obviously, the

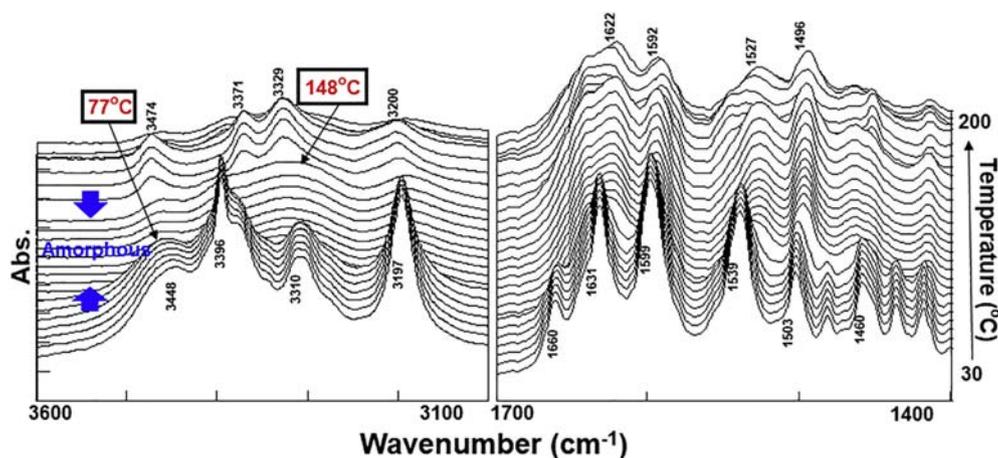


Fig. 8. Continuous phase transitional changes in the three-dimensional FTIR plot of solid-state metoclopramide hydrochloride monohydrate (MCP HCl H₂O) [Modified, with permission from Ref. [150]].

thermal-dependent 3D plot of the FTIR spectra clearly indicated both amorphization and recrystallization processes after dehydration of MCP HCl H₂O in a one-step determination. This suggests that one-step simultaneous DSC-FTIR microspectroscopy is useful for studying changes in the progressive processes of dehydration, amorphization and recrystallization of solid-state MCP HCl H₂O.

Lin and Cheng also used a thermal micro-Raman spectroscopy to determine the phase transformation of solid-state MCP HCl H₂O [157]. Three steps of phase transformation were dehydration, recrystallization, and new crystal formation, which were markedly correlated with the endothermic and exothermic results of DSC study and the observations of HSM. The results generally indicated that MCP HCl H₂O crystals were first dehydrated to form an anhydrous sample, then recrystallized and transformed to a new crystal form of MCP HCl anhydrate. Similar studies of famotidine under different compression pressures or milling processes were also examined by thermal micro-Raman spectroscopic mapping study [158,159].

Wang et al. also investigated the conformational isomerization of captopril in the solid state by DSC-FTIR microspectroscopy [160]. The results demonstrated that the intact captopril was existed as *trans* isomer form in the solid state by intramolecular hydrogen bonding, but after heating the captopril sample to >102 °C, several new bands at 1720, 1645, and 1610 cm⁻¹ were observed with the increase of temperature, indicating the coexistence of a *cis* isomer. However, the *cis* isomer could transform gradually to the *trans* isomer after cooling. The *trans*

isomer was more stable than the *cis* isomer, but the *cis* isomer was favored at the higher temperature.

4.4.4. Solid-state drug-polymer (excipient) interaction

The drug-excipient compatibility study is an important topic and process in the pre-formulation stage of drug development [26,27,161,162], in which the potential interaction between drug and polymer or excipient has impacts on the physical, chemical, bioavailability and stability of the drug dosage forms. In my laboratory, the drug-polymer interaction of theophylline and Eudragit L or enalapril maleate and Eudragit E in the solid state was also confirmed by using one-step DSC-FTIR microspectroscopy [163,164]. Due to the interaction between theophylline and Eudragit L was occurred, leading to having a higher glass transition temperature of the cast film than that of their physical mixture or Eudragit L-100 alone. An interaction between theophylline and Eudragit L-100 was also found in the physical mixture during DSC heating. Moreover, the formation of an acid anhydride by a crosslinking process also took place in Eudragit L-100 polymer at elevated temperature [163].

On the other hand, the mechanism of solid-state interaction between enalapril maleate and Eudragit E was also determined by this unique technique. When the weight ratio of both components was 1:1, Eudragit E might interact with the carboxyl group of maleic acid to exacerbate the degradation of enalapril maleate. However, the excess amount of Eudragit E might somewhat reduce the degradation of enalapril, due to the interaction that occurred between Eudragit E and carboxyl group of enalapril [164].

Hwang et al. also used this DSC-FTIR technique to investigate the stepwise reaction pathway of the solid-state Maillard reaction between glucose and asparagine [165]. It clearly found that the successive reaction products such as Schiff base intermediate, Amadori product and decarboxylated Amadori product in the solid-state glucose-asparagine Maillard reaction were simultaneously evidenced by this one-step DSC-FTIR microspectroscopy. The color changed from white to yellow-brown to dark brown, and appearance of new IR peaks confirmed the formation of Maillard reaction products.

Cheng et al. accidentally found that several new peaks at 3478, 3345 and 1618 cm^{-1} were gradually increased their intensities from 60 to 78 °C and then decreased with heating temperature in the three-dimensional contour profile of MCP HCl H_2O embedded in KBr pellet via determination with DSC-FTIR microspectroscopy (Fig. 9). However, there were no any new peaks found in the three-dimensional contour profile of MCP HCl H_2O embedded in KCl pellet [166]. These new IR peaks formed had been confirmed, due to the ion-exchange reaction occurred between MCP HCl H_2O and KBr. The possible mechanism of this ion-exchange reaction might be attributed to the occurrence between the HCl salt of MCP H_2O and a KBr matrix by heating to yield a mixture of HCl and HBr salts of the MCP sample in the presence of

hydrated water. The crystal hydrate played an important role to improve this ion-exchange reaction between MCP HCl and KBr. However, no ion-exchange reaction occurred between MCP HCl H_2O and KCl or between 150 °C-preheated MCP HCl and KBr. This solid-state ion-exchange reaction was only detected by this powerful DSC-FTIR microspectroscopy than other conventional methods.

In order to prevent the advanced glycation end products (AGEs) formation, the DSC-FTIR combined system as an accelerated method was also attempted to simultaneously determine the thermal-dependent conformational changes of human serum albumin (HSA) in the HSA-ribose mixture and also examined the onset of the structural transformation from α -helix to β -sheet structures with or without AGEs inhibitors used [167]. The results clearly indicated that native HSA had an onset temperature at 96 °C for the irreversible thermal-induced structural transition from α -helices to β -sheets; whereas HSA-ribose mixture exhibited its onset temperature near at 78 °C due to the early occurrence of ribosylation (Fig. 10). However, this onset temperature for the α -helix to β -sheet transition was gradually changed from 78 °C to 96 °C by adding the amount of sodium diclofenac or inositol, which was closed to that of the onset temperature of native HSA, implying that the thermal-induced

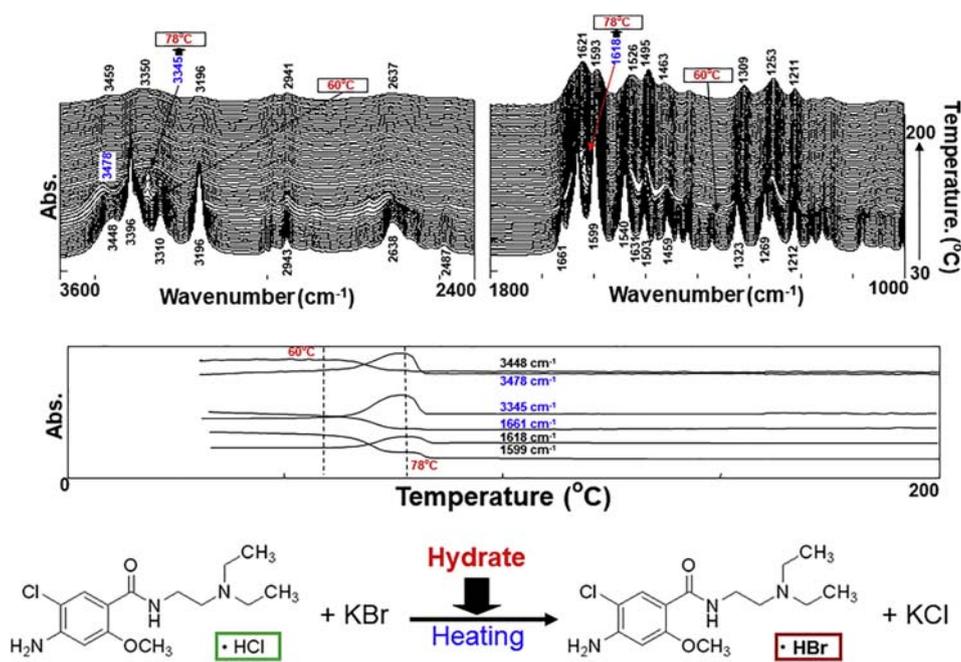


Fig. 9. Three-dimensional FTIR spectral plots and the thermally dependent changes in IR spectra of several specific peaks of metoclopramide hydrochloride monohydrate (MCP HCl H_2O) prepared in the KBr pellet and its pathway of thermally-induced ion-exchange reaction [Modified, with permission from Ref. [166]].

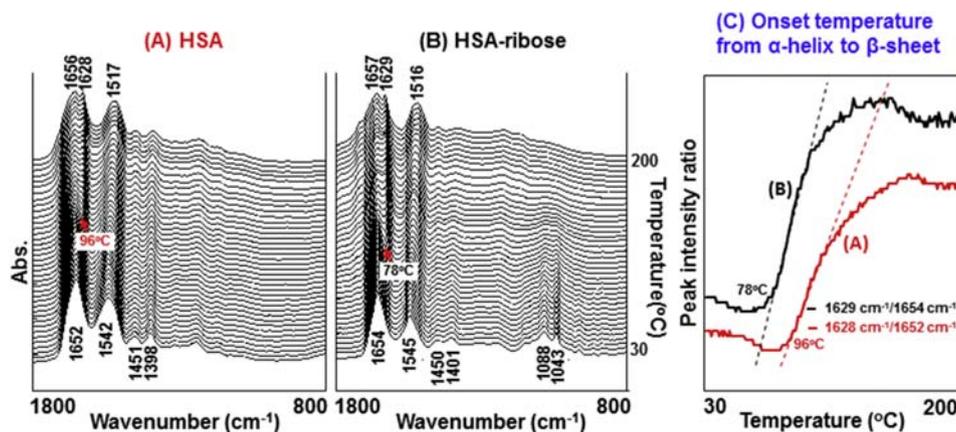


Fig. 10. Thermal-dependent FTIR spectral changes of native human serum albumin (HSA) (A) and HSA-ribose mixture (B), and the onset for conformational changes from α -helix to β -sheet (C). [Modified, with permission from Ref. [167]].

conformational transition from α -helix to β -sheet for HSA in the HSA-ribose mixture was effectively prevented by adding AGEs inhibitors (sodium diclofenac or inositol). This unique DSC-FTIR combined system could be a useful tool to quickly screen and evaluate the glycation-induced conformational changes of proteins in a one-step process.

4.4.5. Solid-state real-time cocrystal screening and formation

The characterization of an API is one of the most important stages in the preformulation development of a drug product. Unfortunately, not all of APIs can have ideal properties for their use as a pharmaceutical drug. Since more poorly water-soluble drug candidates are becoming increasingly popular in the drug development pipeline, many pharmaceutical technologies have been applied to enhance the dissolution and bioavailability of poorly water-soluble drugs [168–171], in which pharmaceutical cocrystals have recently gained increasing interest in the pharmaceutical industry [172–175]. Pharmaceutical cocrystals may provide a lot of desired physicochemical properties and patentability without altering the pharmacological properties, thus cocrystals have recently entered the scope of drug development within the supramolecular chemistry community [172,176,177]. With the advent of new regulatory guidance on pharmaceutical cocrystals from US FDA and EMA, pharmaceutical cocrystal as a promising drug candidate has become one of developing targets in the pharmaceutical industry [178–182].

There are many traditional processes and analytical techniques used for the preparation and identification of pharmaceutical cocrystals, however, these operations take considerable time to screen and prepare the cocrystals [172–177,183–187]. Here,

Lin and colleagues had first and successfully used this unique DSC-FTIR microspectroscopic approach to simultaneously and directly screen and detect pharmaceutical cocrystal formation in the following systems such as indomethacin-saccharin, indomethacin-nicotinamide, carbamazepine-glutaric-acid, metaxalone-succinic-acid and piroxicam-saccharin [188–199]. This powerful one-step DSC-FTIR combined technique provides an easy and direct method for one-step screening and qualitative detection of cocrystal formation in real time.

Indomethacin (IMC)-saccharin (SAC) cocrystal formation as an example [188,189,194,199], Fig. 11 shows the DSC curves and FTIR spectra of each component, physical mixture and solvent-evaporated sample of IMC and SAC. It clearly indicates that two endothermic peaks at 163 and 229 °C were observed in the DSC curves; both peaks might be attributed to the melting points of IMC and SAC, respectively. On the other hand, the solvent-evaporated sample showed an endothermic peak near at 184 °C, which was close to the melting point of IMC-SAC cocrystals at 182.6–184.2 °C respectively reported by Basavoju et al. and Padrela et al. [200,201]. The FTIR spectra of this solvent-evaporated sample is also displayed in Fig. 11, in which four unique FTIR peaks at 1734, 1714, 1682 and 1317 cm⁻¹ clearly appeared. The first three FTIR peaks were similar to that of the IR positions of IMC-SAC cocrystals [202], implying that the solvent-evaporated IMC-SAC sample was recognized as a cocrystal. It is interesting to note that these four unique FTIR peaks (1736, 1718, 1684, 1319 cm⁻¹) were also directly evidenced from the thermal-dependent three-dimensional FTIR spectral contour plot of the physical IMC-SAC mixture determined by a simultaneous DSC-FTIR combined technique after temperature above 154 °C. The

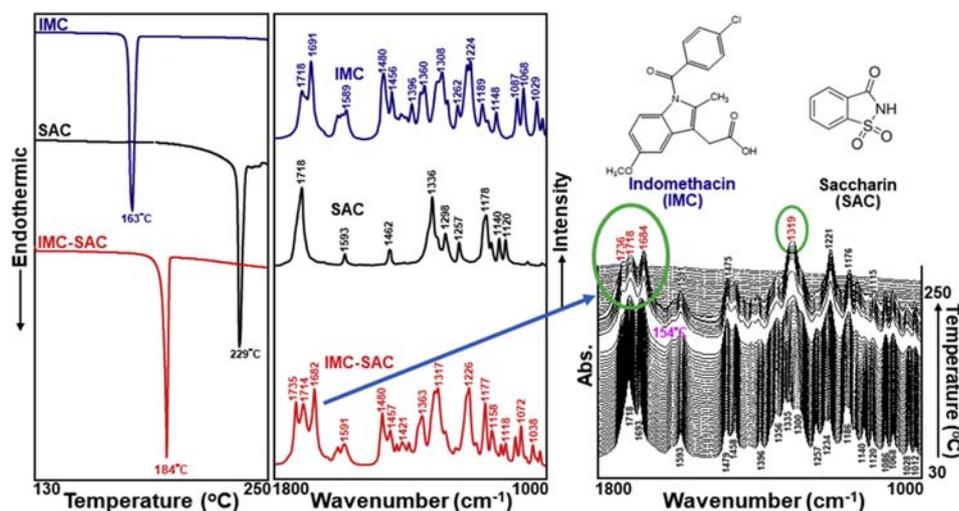


Fig. 11. The DSC curves and FTIR spectra of indomethacin (IMC), saccharin (SAC), and solvent-evaporated sample of IMC-SAC, as well as thermal-dependent 3D FTIR spectral plot of the physical mixture of IMC-SAC [Modified, with permission from Refs. [189,194]].

appearance of these new IR peaks was due to cocrystal formation between IMC and SAC by hydrogen bonding [200–202]. This implies that this powerful DSC-FTIR microspectroscopic system providing the spectroscopic and thermodynamic information can easily, directly and simultaneously produce, screen and detect the IMC-SAC cocrystal formation in real time.

The other indomethacin-nicotinamide cocrystals, carbamazepine-glutaric-acid cocrystals, metaxalone-succinic-acid cocrystals and piroxicam-saccharin cocrystals exhibited similar behavior and can be directly obtained by this one-step simultaneous DSC-FTIR combined technique [188,190–193, 195–199].

5. Conclusions

In the recent years, solid-state chemistry of drugs is of growing importance in the pharmaceutical industry for developing the useful API and stable dosage forms [3–5], in which advanced solid-state analytical approaches play a critical role in pharmaceutical process control to detect and ensure the maximum quantity of an API in dosage forms [28,29]. Although many analytical techniques have been respectively used, the hyphenated analytical techniques have received ever-increasing attention in recent years as a special means to solve complex analytical problems in drug analysis [81–85]. The hyphenated technique is the combination or the coupling of the different analytical techniques. There are many advantages for hyphenated technique, such as shorter analysis time, higher degree of automation, higher sample throughput, better

reproducibility, reduction of contamination, enhanced combined selectivity and higher degree of information [44,83,203].

Among various hyphenated techniques for pharmaceutical analysis, a combination of DSC and FTIR is a very useful technique for monitoring structural changes of sample under thermal treatment [91–93]. This unique DSC-FTIR combined technique gives spectroscopic and thermodynamic information of samples in the heating process. DSC measures the exothermic and endothermic responses of the samples, while the FTIR analysis observes their structural changes in chemical and physical properties. This powerful DSC-FTIR combined system has been considerably applied to quickly investigate the thermal-induced structural changes and stability of foods, polymers, pharmaceuticals, excipients, and cocrystal formation [99,110–120,130–134,147–155, 163–167,188–199].

In this review article, a series of DSC-FTIR microspectroscopic studies had been clearly introduced in the rapid solid-state analysis of pharmaceuticals, polymers and excipients including (1) intramolecular condensation of pharmaceutical polymers, (2) intramolecular cyclization of drugs and sweetener, (3) polymorphic transformation of drugs and excipients, (4) drug-polymer (excipient) interaction, (5) fast cocrystal screening and formation. This powerful one-step DSC-FTIR combined technique provides an easy and direct method for one-step screening and qualitative detection of drug stability in real time (Fig. 12). In Fig. 12, trehalose dihydrate as a representative example for quick DSC-FTIR microspectroscopic study. An IR peak intensity at 1687 cm^{-1} corresponded to the

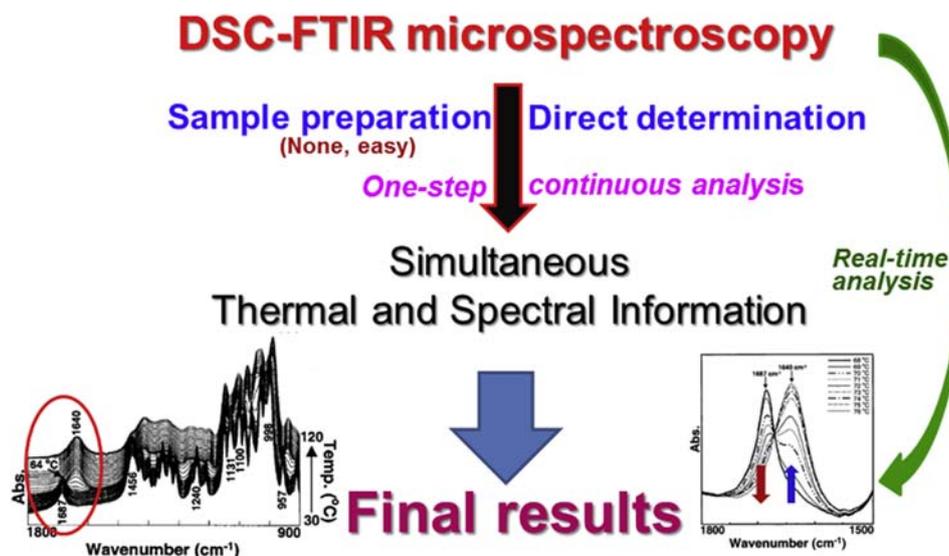


Fig. 12. The schematic flowchart of one-step simultaneous DSC-FTIR microspectroscopic analysis [Modified, with permission from Ref. [154]].

bending vibration mode of the solid-like water in trehalose dihydrate decreased sharply at 64 °C. Simultaneously, another IR peak intensity at 1640 cm⁻¹ due to the bending of liquid water quickly appeared and remained constant after 64 °C (left). This transitional temperature reflected the thermal-dependent transformation from solid-like water to liquid water in the trehalose dihydrate structure in the process of dehydration. A declining peak at 1687 cm⁻¹ and a rising peak at 1640 cm⁻¹ were only observed simultaneously from the DSC-FTIR microspectroscopic study in real time (right) [154].

In the near future, the hyphenated analytical technique will become an extremely versatile tool in pharmaceutical analysis by combining several analytical methods with automation and high-throughput (HT) analysis. Such hyphenation can enable simultaneous separation, identification, qualification and quantification of pharmaceutical components. Different hyphenated systems may be applied to solve many sophisticated analytical problems in various fields [82,85,92,204]. In the future mission, an integrated approach to ensuring sustainable development of HT analytical architecture and system can be introduced by an innovative technology, advanced equipment and new methodology with high-performance artificial intelligence (AI) systems to produce more accurate and reliable hyphenated instruments and measurements for pharmaceutical researchers in the pharmaceutical investigations and drug analysis [205–207].

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Conflict of interest

The author declares that there is no conflict of interest.

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