Indonesian J. Pharm. Vol. 23 No. 1 : 1 – 8
ISSN-p : 0126-1037

Review Article

APPLICATION OF FOURIER TRANSFORM INFRARED SPECTROSCOPY FOR QUALITY CONTROL OF PHARMACEUTICAL PRODUCTS: A REVIEW

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Submitted: 11-11-2011
Revised: 15-12-2011
Accepted: 20-12-2011

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ABSTRACT

Analysis of pharmaceutical products covers all aspects of quality control of active pharmaceutical ingredients (API) and finished products. Today, Fourier transform infrared (FTIR) spectroscopy, especially in combination with chemometrics software, has emerged as one of the promising analytical techniques to be used in pharmaceutical industry, for quality control of desired pharmaceutical products. Compared with other instrumental techniques, FTIR spectroscopy offers some advantages, namely it is rapid, simple in sample preparation, and not destructive. In this review, the application of FTIR spectroscopy for qualitative and quantitative determinations of API and monitoring drug release are described.

Key words: FTIR spectroscopy, quality control, pharmaceutical products.

INTRODUCTION

Infrared spectroscopy is one of the vibrational spectroscopic techniques, besides Raman spectroscopy (Che Man *et al*., 2010). It allows the wide wavenumbers covered, fast scanning, high resolution, non destructive, and not time consuming. In addition, this technique can be used for simultaneous analysis of complex sample mixtures without the use of hazardous solvents and chemical reagents. In this point of view, IR spectroscopy is clearly benefit to operators, environment, and reduces the cost of external treatment of chemical wastes (Moros *et al*., 2010). As a consequence, IR spectroscopy can be taken into account as one of the potential techniques in green analytical chemistry (de la Guardia, 2010).

In pharmaceutical industry, IR spectroscopy has gained the popularity not only in the ease and expeditiousness of the samples measured but also in the quality of results obtained (Blanco and Peguero, 2010). The pharmaceutical quality control of active pharmaceutical ingredients (API) includes (i) the qualitative analysis for the identification of raw materials, intermediate, and finished products as well as for the evaluation of the ability of API to occur in different crystalline forms, known as polymorphism; (ii) the quantitative analysis of API in several pharmaceutical dosage forms; and (iii) monitoring the stages in pharmaceutical products development such as homogenization of API in the mixture, drying, packaging, etc. (Roggo *et al*., 2007; Massart and Buydens, 1988). In this review, FTIR spectroscopy was highlighted for the qualitative, especially for monitoring polymorphism, quantitative determinations of API, and for the monitoring of drug release.

The important factor contributing to the success of FTIR spectroscopy as qualitative and quantitative tools is chemometric package (Lavine, 1998). Chemometrics is discipline of extracting chemically relevant information from data produced in chemical experiments by means of statistical and mathematical tools (Roggo *et al*., 2007; Rutan, 1992). In short, the most commonly used chemometrics techniques in vibrational spectroscopy include processing techniques (mean centering, derivatization, baseline correction), pattern recognition either using unsupervised (such as principal component analysis) or supervised pattern recognition techniques (like discriminant analysis), and multivariate calibrations, including partial least square regression (PLSR), principle component regression (PCR),

stepwise multiple linear regression (SMLR), and classical least square (Smith, 2002; Brereton, 2007). In addition, an experimental design was also covered in chemometrics for developing and quantifying the pharmaceutical products (Miller and Miller, 2005).

Qualitative analysis

The identification of polymorphism is very important aspect to be taken into consideration in the development and manufacturing of pharmaceutical products. It is well recognized that the changes in the polymorphic property of API can affect the bulk chemical properties, such as bioavailibility, dissolution, and stability (Aaltonen *et al*., 2008). Hence, the monitoring of polymorphic behavior is highly demanded.

Salari and Young (1998) used FTIR spectroscopy in combination with attenuated total reflectance (ATR) for the identification and quantification of ganciclovir polymorphs in pure three phases. Quantitative analysis of polymorphic mixtures is successfully carried out using partial least square (PLS) model. Each polymorph exhibits a characteristic FTIR specta at fingerprint region (1800–600 cm^{-1}), with significant differences, in which each polymorph can be readily identified. The R^2 obtained is > 0.98. Fiber-optic near IR was also used for monitoring the polymorphisms of SaC, an anti-hypertension agent. Sac was characterized as polymorphs I and II (SaC-I and SaC-II) and amorphous state (SaC-Am). The quantification was carried out using multivariate calibration of principle component regression (F´evotte *et al*., 2004).

FTIR spectroscopy in combination with PLS using KBr pellet as sampling technique was used to quantify the amount of amorphous cyclosporine in crystalline cyclosporine (Bertacche *et al*., 2006). The mixing of different percentages of crystalline cyclosporine with amorphous cyclosporine was used to obtain a set of standards, composed of cyclosporine samples characterized by different percentages of amorphous cyclosporine. Quantitative analysis of amorphous cyclosporine was performed at whole mid infrared region of 450–4000 cm^{-1}. PLS gave coefficient of correlation (r) value of 0.9971 for the relationship between actual and FTIR predicted values of amorphous cyclosporine. The standard errors of estimate and prediction obtained were of 0.3562 and 0.4168 %, respectively; indicating the good precision of the developed method.

The polimorphisms of several APIs such as sulfathiazole (Hu *et al*., 2010; Poll¨anen *et al*., 2005), mebendazole (Kachrimanis *et al*., 2010), acyclovir (Lutker *et al*., 2011), risperidone (Karabas *et al.,* 2007), and tranilast (Vogt *et al*., 2005) were also investigated.

Determination of active pharmaceutical ingredients (API)

One of the main advantages of FTIR spectroscopy for quantitative analyses of API is due to the possibility to simultaneously analyze some APIs using single spectral measurement (Moros *et al*., 2010). However, the co-existence of several APIs in pharmaceutical products meets several problems associated with the FTIR spectral overlapping. Fortunately, today, some chemometrics techniques can overcome this problem without any separation step of sample components (Gallardo-Velázquez *et al*., 2009).

Torrado *et al.* (2005) have used FTIR spectroscopy for quantitative analysis of dimmethicone in commercial tablets and capsules. Using absorbance measurement at 7.9 μm, dimethicone has been successfully quantified with recovery percentage of 98-102 %. The developed method was linear over the concentration range of 20-50 mg/mL in carbon tetrachloride. The United States Pharmacopeia (USP) also used this technique for quantitative analysis of simethicone.

FTIR-ATR was also proposed for direct determination of niflumic acid in the pharmaceutical gel with the aid of PLS calibration. The quantitative analysis was performed at frequency regions of 2300 – 1100 cm^{-1}. Using 14 factors, the coefficient of determination (R^2) for the relationship between actual and FTIR predicted values of niflumic acid is 0.9999, with root mean quare error of prediction (RMSEP) of 0.2 %. The percentage of recovery obtained is in the range of 96.60 – 101.02 % (Boyer *et al.* 2006).

Table I. Some active pharmaceuticals ingredients (API) determined with FTIR spectroscopy

API	Calibration	Figure of merit	References
Tianeptine	PLS	R^2: 0.99; RSD < 0.60 % RMSEC = 1.7 %; RMSEP = 2.0 %	Boret *et al.* (2011)
Ephedrine and pseudoephedrine	PLS	Frequency region: 1540–950 cm^{-1} SEP = 0.74 %	Dijiba *et al.* (2005)
Diazepam	Standard external	Frequency region: 16782 - 1672 cm^{-1}; RSD = 0.5 % LOD = 0.04 mg/tablet Recovery: 98 – 104 %	Moros *et al.* (2007)
Ibuprofen	Standard external	Frequency region: 1721.5 cm^{-1} RSD = 3.8 % LOD = 0.056 mg/tablet Recovery: 98 – 110 %	Matkovic *et al.* (2005)
Zidovudine	Internal standard	Frequency region: 2105 and 2931 cm^{-1}; linear concentration range: 0.8–2.0% w/w in KBr disc Recovery: 99.8%; RSD of 2.157%	Peepliwal *et al.* (2010)
Naltrexone	PLS	Frequency region: 830–1800 cm^{-1} RMSEC: 0.1823 %; RMSECV = 0.3330; R^2 = 0.9967	Khanmohammadi *et al.* (2009)

PLS = partial least square, RMSEC = root mean square error of calibration; RMSEP = root mean square error of prediction; RMSECV = root mean square error of cross validation; RSD = relative standard deviation; LOD = limit of detection

Due to the lack of chromophore, FTIR spectroscopy using transmission mode with KBr pellet is a method of choice for determination of roxithromycin in tablet dosage forms (Sherazi *et al.*, 2011). The calibration model was performed based on the absorption band of carbonyl group (C=O) at frequency regions of 1765 to 1705 cm^{-1}. The good relationship between actual value and FTIR predicted value of roxithromycin was obtained, with R^2 value of 0.9992, along with standard error of calibration (SEC) of 0.01 mg. The developed method is also accurate enough with acceptable recovery values.

Mazurek and Szostak (2011) have used FTIR spectroscopy with attenuated total reflectance as sampling accessory for determination of sodium diclofenac in tablet. The quantification was performed with multivariate calibration of PLS. The combined frequency regions of 1233.5–1615.9 and 2801.9–2976.4 cm^{-1} was exploited for such determination. Three standard release tablets and two sustained release tablets containing between 25 and 100 mg of sodium diclofenac were successfully determined with the recovery percentage of 99.1–101.3 %.

Multivariate calibration of PLS, coupled with FTIR spectroscopy has been used for simultaneous analysis of sulphamethoxazole (SMZ) and trimethoprim(TMP) in the mixture of raw material powders, used for the manufacturing of commercial pharmaceutical products (Silva *et al.*, 2009). The interval partial least squares (iPLS) and synergy partial least squares (siPLS) were exploited for choosing spectral range which provided the lowest prediction error, in comparison to the whole IR spectrum model. The considered concentration ranges were 400–900 mg/g SMZ and 80–240 mg/g TMP, respectively. Spectral data were scanned at 650 - 4000 cm^{-1} using resolution of 4 cm^{-1}. The results obtained by FTIR spectroscopy were comparable with official technique of HPLC using 15 commercial samples, containing SMZ and

TMP. A root mean square error of prediction (RMSEP) of 13.18 mg/g for SMZ and 6.03 mg/g for TMP was obtained after selection of better intervals by siPLS.

A novel FTIR spectroscopy has been developed for quantitative determination of levodopa and carbidopa in aqueous binary solutions, acidified by HCl. ATR-FTIR spectra at frequency regions of 1211-1315 cm^{-1} and 1488-1550 cm^{-1} were used. Using the proposed method, the R^2 and RSD values for levodopa and carbidopa obtained were (0.9965, 1.209 % w/w) and (0.9537, 0.813 % w/w), respectively (Khanmohammadi *et al.*, 2007).

FTIR method was also exploited for quantitative analysis of paracetamol. The analyte was hydrolyzed in the alkaline environment to produce *p*-aminophenol. The *p*-aminophenol was further oxidized using oxidizing agent of $K_3Fe(CN)_6$ to produce *p*-benzoquinone-monoimine which eventually oxidized to form *p*-benzoquinone. The analytical measurements were performed by exploiting OH-phenolic deformation at 1274.1 cm^{-1} and the aromatic ring vibration at 1498.2 cm^{-1}. The developed method was used for determination of paracetamol in marketed-tablet samples. The results obtained from FTIR are in agreement with those specified by producers (Ramos *et al.*, 1998).

Some impurities may exist in APIs. FTIR spectroscopy has been developed for determination of possible impurities in piracetam, namely 2-oxo-1-pyrrolidine acetic acid (PAc). The developed method was effective enough for the simultaneous analysis of PAc in piracetam and may be an alternative to HPLC technique. The FTIR spectral resolution was enhanced using the Fourier self-deconvolution, and the profiles were subsequently deconvoluted using a curve fitting procedure. The calibration curve for PAc was made using the relative areas of 1723 and 1696 cm^{-1} towards the carbonyl peak area in the region of 1750–1600 cm^{-1} (Karamancheva and Staneva, 2000).

Besides in pharmaceutical dosage forms, FTIR was also used for monitoring the levels of active drug substances in biological fluids. Crupi *et al.* (2002) investigated the benzodiazepine concentration in rat brain fluid. The CH-OH stretching vibration (3800-2400 cm^{-1}) was used for such analysis. The presence of band centered at 3495 cm^{-1} in treated samples confirms the occurrence of drug in brain tissue. Table I listed the use of FTIR spectroscopy for analysis of API in some pharmaceutical formulations. The calibration models and the figure of merit of analytical measurements were also compiled in this Table.

Besides for APIs quantification, currently, FTIR spectroscopy was also used for rapid analysis of water contents in super-disintegrant pharmaceutical excipients using ATR accessory. Using simple ordinary least square, water contents of the investigated three common superdisintegrants (crospovidone, croscarmellose sodium, sodium starch glycolate) was varied over a wide range (0–24%, w/w). Quantitative analysis of water was relied on the strong absorption of -OH vibration at frequency region of 3700 and 2800 cm^{-1} having R^2 alue of > 0.99 (Szakonyi and Zelkó, 2012).

The level contents of water in shampoo were investigated with FTIR-ATR using classical least square and inverse least square. The frequency regions of 3500–3000 cm^{-1} due to OH stretching and 1700–1550 cm^{-1} attributed from H-O-H bending were used for water determination (Carolei and Gutz, 2005). The level of water in soap formulation was also determined at frequency region of 3600 – 3200 cm^{-1} with the aid of PLS calibration (Rohman and Che Man, 2009).

We have developed FTIR spectroscopy for rapid analysis of lipid components namely lard in lotion cosmetics (Lukitaningsih *et al.*, 2012) as well as lard (Rohman and Che Man, 2011) and virgin coconut oil (Rohman *et al.*, 2009) in cream formulations. Quantitative analysis of these lipids was performed using PLS calibration, while the classification between cream/lotion with and without these lipids in their formulation was carried out with the chemometrics of discriminant analysis and principal component analysis.

Monitoring the drug release

FTIR spectroscopy with ATR has evolved as one of the standard techniques for monitoring the drug release across membranes and for determining the diffusion coefficients (Reinl *et al.*, 1995;). FTIR-ATR spectra in the

spectral range of 700 –1700 cm^{-1} has been used to study the drug particle release of ketoconazole in a liquid medium of paraffinum liquidum. This technique is able to provide the release process of drugs in semi solid formulations. Thus, it is possible to determine the diffusion coefficient of a drug in the liquid phase (Hanh *et al.*, 2000[a]). The same authors also used FTIR-ATR to determine the ketoconazole release suspended in vaseline with various amounts of paraffinum liquidum as donor and an artificial dodecanol-collodion (DDC) membrane as acceptor compartment. Based on spectral changes at 700-1700 cm^{-1} and correlated with Fick's second law, it is possible to derive the apparent dissolution coefficient (*K*dis) by numerical fitting of experimental data (Hanh *et al.*, 2000[b]).

FTIR-ATR has been used for measuring the dissolution of Excedrin tablet composed from paracetamol and salicylic acid in its formulation. Dissolution is the accepted methodology for measuring the API release from the dosage forms. This approach was found to be sensitive technique which can detect as low as 0.03 mg API/mL. FTIR spectra were subjected to baseline correction. For dissolution purposes, peak area at 1388 cm^{-1} and at baseline of 1370 cm^{-1} were used to calculate salicylic acid, meanwhile the absorption peak at 1246 cm^{-1} and baseline at 1276 cm^{-1} were selected for measuring paracetamol concentration (Kassis *et al.* 2010). FTIR-ATR was also used to simultaneously follow the diffusion of three drugs, namely cyanophenol, methyl nicotinate, and buthyl paraben as well as solvent across of silicone membrane. The diffusion of these drugs and the solvent was successfully explained with Fickian model. Using the absorbance changes at several frequencies and exploiting the penetration depth in ATR, the diffusion of these drugs can be predicted (McAuley *et al.* 2009).

Currently, FTIR spectroscopy in combination with ATR has been developed for screening technique in order to quantify the relative release of pamidronate (PAM) from films of polyelectrolyte (PEL) complex (PEC) particles (Müller and Keßler, 2012). A stepwise decrease of the band at frequency region of 1070 cm^{-1}, attributed from (O=P=O) vibration due to PAM is observed. This band can be used as qualitative tool for a retarded release of PAM from PAM loaded PEC particles. Furthermore, other bands like that around 1250 cm^{-1} coming from (O=S=O) vibration and C=S are nearly constant, which is a qualitative hint for the stability of the PEC matrix during PAM release.

FTIR-ATR spectroscopic imaging has been used to study tablets containing diclofenac sodium and HPMC (hydroxypropyl methylcellulose) in different dissolution media which influence the solubility of diclofenac. The release profiles obtained by flow-through dissolution test suggest the presence of particles (or precipitates) in the dissolution medium. This is consistent with the results obtained by FTIR spectroscopy imaging, which indicated that the proposed techniques are superior to the ordinary dissolution test, when applied to poorly soluble drugs (Der Weerd and Kazarian, 2005).

CONCLUSION

FTIR spectroscopy offers rapid and reliable method for quality control of pharmaceuticals products including identifycation of polymorphism of drugs, quantitative analysis of active pharmaceuticals, and monitoring the drug release from its formulation. This is due to the fact that IR spectroscopy is fingerprint technique especially in combination with the powerful chemometrics software. IR spectroscopy is also taken into account as green analytical technique due to its ability to exploit the minimum use of solvents and reagents.

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