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Potential application of UV reflection spectroscopy on solid pharmaceutical formulation analysis

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Abstract

An imaginary complex refraction index (extinction coefficient) has been deduced for a number of common pharmaceutical forms from their specular reflection spectra. It seems that reflectivity technique is preferred to the transmission one in those special case in which non-destructive analysis of samples is requested. Furthermore, the obtained results are independent of solvent effects and sample thickness.

Keywords: UV reflection spectroscopy; Pharmaceutical analysis; Solid phase investigation; Pharmacologically active compounds

1. Introduction

The measure of the reflection coefficient (R) of a material is one of the most simple and traditional methods to investigate the optical properties of its surface (Hussla and Philpott, 1986; Uram et al., 1986). As is well-known, for a given substance, R depends on its complex refraction $N = (n - ik)$, where the real part n is the so called index of refraction and the imaginary k is the extinction coefficient. Thus, a direct measurement of the reflectivity can lead to the knowledge of the absorption spectrum of a sample if R-data are processed by means of a particular numerical analysis, generally referred as Kramers-Kronig (KK) transform (Born and Wolf, 1970), in order to obtain the separate contribution of n and k to the reflection coefficient. KK analysis of reflectivity spectra allows one to obtain the absorption coefficient of the examined materials with the same precision and accuracy of a direct transmission measurement (Ishitani et al., 1982; Golden and Saperstein, 1983; Golden et al., 1984). The two techniques seem to be perfectly equal as regards the results (Golden et al., 1984). A fundamental characteristic of the reflection spectroscopy coefficient is the independence from the sample thickness (Tolstoi et al., 1984). Furthermore, this technique, as with others in solid phase (Villari et al., 1992, 1994) is non-destructive and the result are not dependent on the sampling

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methods. In this work, the reflectivity spectra of some compounds of large pharmaceutical interest are presented as a proof of the reliability of the technique.

2. Materials and methods

Acetylsalicylic acid (ASA), salicylic acid (SA), caffeine, cimetidine and 4-acetamidophenol are Sigma products (St. Louis, MO, USA) and were used without further purification. The commercial pharmaceutical products: Aspirina®, Cibalgina® and Tagamet® were purchased in a pharmacy.

The apparatus for the reflection experiments (200–400 nm) was assembled in our laboratories. The reflectivity setup consisted of a Xenon 150 W UV lamp (Oriel mod. 6254) and a monochromator (Oriel mod. 77250). The detector is another monochromator and a Hamamazu mod. R955 photomultiplier. A bundle of optic fibres (mod. SF 1000/1100M) was employed both for illumination of the samples and for the detection of the reflected light-beam. This particular configuration ensured a uniform illumination covering an area with a diameter of 4 mm at a distance of 1 cm from the sample surface. The resolution during the measurement was 1.0 nm and the reproducibility was characterised by 1% error in the case of the lowest measured reflectivity values to nearly 10^{-3}. The examined samples were commercial tablets which, not being suitable for analysis as found due to the non-planarity of the surface, were reduced to powder, homogenised and compressed again. In this way, reflection coefficients between 6% and 0.4% were obtained. Reflectivity measurements have been performed at room temperature, using an UV-coated Al mirror as a standard reference. Sample spectra were obtained by performing for each abscissa the ratio $R_{\text{true}} = R_{\text{sample}}/R_{\text{aluminium}}$.

3. Results and discussion

When an electromagnetic wave goes through a homogeneous medium, the intensity (I) is exponentially attenuated along the direction of propagation, in agreement with the equation:

$$I = I_0 \exp(-\alpha x) \tag{1}$$

where α is the adsorption coefficient, which is linked to the imaginary part of the complex refraction index (k) by means of the relation:

$$\alpha = 4\pi k/\lambda \tag{2}$$

where λ equals the wavelength of the electromagnetic radiation. The photon energy associated with the radiation is $E = h\nu = hc/\lambda$, where c is the light velocity and h is the Planck constant. Between the real and imaginary part of the complex refraction index (N) (between n and α) there is a relation by which it is possible to obtain the adsorption value by means of the measurement of the refraction index as a function of the wavelength. Experimentally, to measure the reflectivity (R) of the sample (close to the normal incidence) and to calculate the phase of the reflected field Θ is preferable.

The complex refraction index ($n - ik$) is related to the measured reflection coefficient by the relation:

$$\frac{n-1-ik}{n+1+ik} = R^{1/2}\exp(i\theta) \tag{3}$$

Θ being the phase angle determined, at an incident photons energy E by the integral (Wendlandt and Hecht, 1966):

$$\theta(E) = -\frac{E}{\pi}P\int_0^{\infty}\frac{\ln R(x)}{(x^2-E^2)}\mathrm{d}x \tag{4}$$

representing the change of the phase of the electromagnetic wave as a consequence of the reflection process. The symbol P in Eq. (4) refers to the integral Cauchy principal part, the integral being a singular function for $E = x$. The integration variable x is defined in the same range of E, and $R(x)$ is the measured reflectivity spectrum (Greenler et al., 1971).

Usually, Eqs. (3) and (4) are solved by means of a computer using the normal procedures of numerical analysis. Owing to its range of integration from zero to infinite, the integral (Eq. (4)) is broken into three parts: the experimental one (where the reflectivity is measured) between the limits E_1 and E_N, and two tails, for $E \leq E_1$ and $E \geq E_N$ respectively, where the reflection co-

efficient is described by two analytical functions which well fit the optical response out of the measurements range. However, such tails are critical and a wrong choice of their analytical behaviour leads to bad results (Greenler et al., 1971). In order to avoid this difficult, a different integration method may be used which is independent on the optical response simulation out of the experimental energies range.

Suppose we know Θ_0 at a certain energy E_0, its value is defined in Eq. (4) by:

$$\theta_0(E_0) = -\frac{E_0}{\pi} P \int_0^\infty \frac{\ln R(x)}{(x^2 - E_0^2)} dx \quad (5)$$

and subtracting Eq. (5) from Eq. (4), we get:

$$\theta(E) = \frac{E}{E_0}\theta_0(E_0) + \frac{E(E_0^2 - E^2)}{\pi} P \int_0^\infty \frac{\ln R(x)}{(x^2 - E_0^2)(x^2 - E^2)} dx \quad (6)$$

which consists in an expansion around the energy E_0.

As pointed out above, the most important feature of this type of integration is its independence of the high and low energy tails choice because of the more rapid convergence of the integral which goes to zero as E^{-4} instead of E^{-2} as in the case of Eq. (4). Thus, the tails may be well approximated by constant reflectivity spectra [$R = R(E_1)$ for $E \leq E_1$; $R = R(E_2)$ for $E \geq E_2$]. Details on the evaluation of the Θ value in Eq. (6) and on the overall procedure are reported elsewhere (Wendlandt and Hecht, 1966).

Knowledge of the $\Theta(E)$ spectrum allows the calculation of the optical constants of the examined sample, by means of the relations:

$$n(E) = \frac{(1 - R)}{[R - 2\sqrt{R}\cos\theta(E) + 1]} \quad (7)$$

$$K(E) = \frac{2\sqrt{R}\,sen\,\theta(E)}{[R - 2\sqrt{R}\cos\theta(E) - 1]} \quad (8)$$

Eqs. (7) and (8) give the real and imaginary parts of the complex refraction index. A computer program has been developed to perform the numerical integration (Eq. (6)).

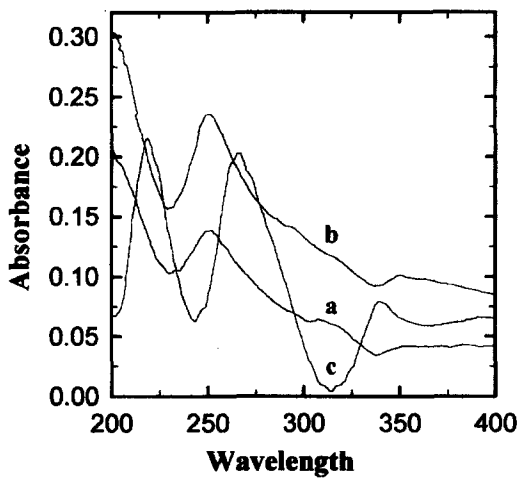

Fig. 1. KK-spectra of (a) Aspirina®, (b) acetylsalicylic acid and its hydrolytic degradation product, (c) salicylic acid, at room temperature.

The absorption spectra of the examined pharmaceutical formulations are reported together with those of their biological active compounds, in Figs. 1 and 2, and Fig. 3. Spectra of pure substances were used as a reference for their successive comparison with the absorption spectrum of each commercial tablet. The characteristic peak and shoulder positions, as deduced from the KK analysis of reflectivity data, are summarised

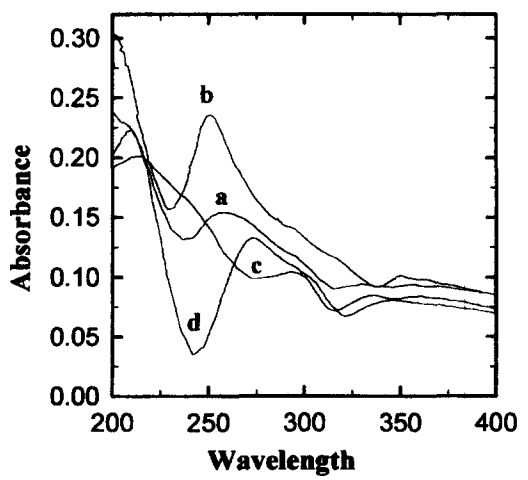

Fig. 2. KK-spectra of (a) Cibalgina® and the active compounds contained within: (b) acetylsalicylic acid, (c) caffeine and (d) 4-acetamidophenol, at room temperature.

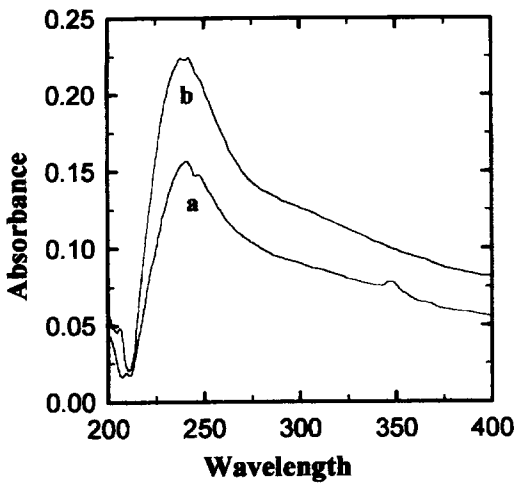

Fig. 3. KK-spectra of (a) Tagamet® and its pharmaceutically active compound, (b) cimetidine.

in Table 1, referring to the k extinction coefficient spectral features.

By comparing the Aspirina® tablet spectrum (Fig. 1) with that of the acetylsalicylic acid, very good agreement can be found between the main peak position of the two samples (Table 1). There seems to be no appreciable contribution from salicylic acid, which is contained both in acetylsalicylic acid, and Aspirina® as an impurity normally not higher than 0.05% (Villari et al., 1992, 1994).

In the case of Cibalgina® tablets (Fig. 2), the comparison is more difficult than the previous one, as the structures of the active principles nearly coincide or are not enough apart from each other (Table 1). The first group of the two peaks at 249 nm (acetylsalicylic acid) and at 275 nm (4-acetamidophenol) gives rise to the structure centred at 250 nm. It should be emphasised that 4-acetamidophenol and acetylsalicylic acid are present nearly in the same quantity in the tablet. This factor is the reason for the mean position of the observed k-maximum at 250 nm. A second group of absorption bands centred at 290 nm (acetylsalicylic acid), 298 nm (4-acetamidophenol) and 295 nm (caffeine) may be considered as the origin of the pronounced broad absorption positioned at about 291 nm. Owing to the great number of active substances, a derivative technique must be preferred in order to achieve the requested sensitivity to detect optical structures very close to each other and, hence, not distinguishable using the normal spectrophotometric techniques.

Fig. 3 shows the extinction coefficient spectrum of a Tagamet® tablet and one of its active compound (cimetidine). It is worth noting that the cimetidine absorption spectrum has been never reported, probably because the effect of the solvents, employed for solubilizing the compound to carry out the transmission measurements, is so great that it prevents the observation of the peak at 240 nm. In fact, this spectral position is coincidental with the beginnings of the strong ultraviolet absorption of the greatest part of the employed solvents. By comparing the two spectra, it is very easy to identify the presence of cimetidine in the

Table 1
Peak and shoulder positions obtained by means of KK-analysis of the reflectivity data[a]

Pharmaceutical formulations and their active compounds	Peak and shoulder position (nm)					
Aspirina®		**250**				
Acetylsalicylic acid		**249**			290	
Salicylic acid	**218**			**265**		340
Cibalgina®			**256**		291	
Acetylsalicylic acid		**249**			290	
Caffeine	212				**295**	
4-Acetamidophenol	206			**273**	298	
Tagamet®		**240**				350
Cimetidine		**239**				

[a] Each reflection spectrum was carried out at room temperature.
The values written with bold fonts represents the peak positions, whereas the shoulder positions are indicated by normal fonts.

Tagamet® samples. The slight difference between the two maximum absorption points is negligible, being very close to the experimental resolution.

The validity of this work must be viewed not in the originality of the results, because they have been obtained from well-known compounds, but rather in the potential application of the UV reflection technique that, in its simplicity, offers incontestable advantages in the field of qualitative spectroscopic analysis. With regard to any calculation difficulties in the numerical data-handling procedures, computer programs are commercialy available. This technique may also have the potential of being applicable to biological compounds (Leidberg et al., 1984, 1985).

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