International Journal of Anatomy and Physiology ISSN: 2326-7275 Vol. 8 (10), pp. 001-006, October, 2019. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Determination of enantiomeric compositions of ibuprofen by infrared spectrometry with catalytic amount of simple chiral recognition reagent

Xiaojing Chen[1,2], Xiangou Zhu[1,2] and Jun Jiang[1,2]*

[1]College of Chemistry and Materials Engineering, Wenzhou University, Chashan University Town, Wenzhou, Zhejiang Province 325035, People's Republic of China.

[2]College of Physics and Electronic Engineering Information, Wenzhou University, Chashan University Town, Wenzhou, Zhejiang Province 325035, People's Republic of China.

Accepted 13 May, 2019

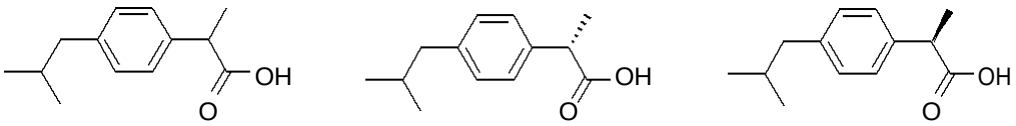
Catalytic amount of cheap chiral recognition reagent (quinine) combined with chemometric and infrared spectroscopy (IR) was used for quick and accurate determination of the enantiomeric compositions of ibuprofen. First of all, full spectrum was used as the input variable of partial least regression (PLS) to establish the calibration model, after which a good prediction rate of the average error of 4.65% was obtained. Then, wavelet transform (WT) algorithm, with strong compression ability, was employed to obtain a more concise model. The low-frequency coefficients were extracted by the simplest Harr wavelet function, and were used as the input variables to establish the calibration, after which a good prediction rate of the average error of 3.60% was obtained. All the results showed that the combination of partial least squares and infrared spectroscopy can be used for quick and accurate prediction of the enantiomeric excess (ee) value of ibuprofen.

Key words: Ibuprofen, enantiomeric compositions, quinine, infrared, wavelet transform.

INTRODUCTION

Analysis of the enantiomeric composition of chiral drugs is of great importance because the enantioisomers often showed different physiological and therapeutic effects. Generally, only one form of enantiomeric pair was pharmacologically active, while the other presented limited or even reverse effect (Williams, 1985; Islam et al., 1997). Ibuprofen (Figure 1), an important nonsteroidal anti-inflammatory drug (NSAIDs), was used to reduce fever and treat pain or inflammation caused by headache, toothache, menstrual cramps, or minor injury (Altman, 1984). The ibuprofen molecule contains a chiral center at the 2-position of the carboxylic acid, thus has two enantiomers (Figure 1a and b). Research found that the (S)-(+)-ibuprofen 1a is the pharmacologically active component, while the (R)-(-) isomer 1b is weakly active or even inactive *in vitro*, although the (R)-(-) enantiomer can convert into to the active (S)-(+) enantiomer in some extent through metabolic inversion *in vivo* (Kaiser et al., 1976). Besides, the (R) (-) enantiomer can be stored in fatty tissue as the glycerol ester, which may be potentially toxic, and the long-term effects are unknown (Hutt and Caldwell, 1983). To enhance the specificity and avoid the undesirable load on metabolism, (S)-(+)-ibuprofen has been introduced as an alternative of racemic ibuprofen by Merck in the form of its lysinate salt (Tung et al., 1991). Thus, determining the enantiomeric composition of ibuprofen is virtually important both in pharmaceutical industry and pharmacological research. When compared to the rapid development of asymmetric drug synthesis, the enantioselective analysis often remains the bottleneck, because it usually entails laborious and time-consuming chromatographic techniques (Armstrong et al., 1986). So, there is urgency for different methods to achieve rapid detection of enantiomeric composition of ibuprofen.

*Corresponding author. E-mail: junjiang@wzu.edu.cn. Tel: +86 577 88368280. Fax: +86 577 88368280.



racemic ibuprofen **1** (S)-(+) ibuprofen **1a** (R)-(-) ibuprofen **1b**

Figure 1. Racemic ibuprofen and its enantiomers.

A much different approach to analyze the enantiomeric composition of chiral compounds is based on infrared spectroscopy (IR), which can detect any changes induced by interactions between enantiomers and chiral recognition reagents. Combining this with the guest-host complexes and chemometric data analysis, a quick, facile and cheap way is offered to determine the enantio-meric purity (Tran et al., 2003, 2004; Zhou, 2006). Tran et al. (2003) reported the determination of enantiomeric compositions of amino acids by NIR through complexation with cyclodextrins (CDs) or sucrose, using partial least squares as data analysis method, to obtain good results (for example, the rel. errors of the prediction of enantiomeric excess (ee) of 2.0 mM Ala in 4.0 mM α-CD ranged from 0.66 to 16.94%). Subsequently, they extended this strategy to analyze the enantiomeric compositions of chiral pharmaceutical products, such as propranolol, etc, in which cyclodextrins (CDs) and sucrose were found again be good chiral recognition reagents (Tran et al., 2004). Zhou et al. (2006) applied this strategy to analyze the enantiomeric purity of M3 antagonist drug substance by employing CDs or L-tartaric acid as chiral recognition reagents. The prediction results were in good agreement with the gravimetric method (1.3% standard error) (Zhou, 2006). However, in most of the reported cases, one equivalent or much excess amount of chiral reagent was required to give rise to signal splitting, while these chiral reagents were commonly expensive or not easily prepared. Herein, we wish to report a practical rapid enantiomeric excess determination of ibuprofen through partial least regression technique, which just employs catalytic amount quinine as chiral recognition reagent. This common, cheap chiral alkaloid has not been applied in the IR to detect ee yet. Furthermore, wavelet transform (WT) has been found to be a very efficient technology in compressing analytical signals (Chen et al., 2009; Shao et al., 2003). Nonetheless, if WT can be combined with the partial least regression (PLS), the concise model can be obtained.

EXPERIMENTAL

Spectral acquisition and sample partition

IR spectra were collected using an ART (attenuated total reflectance) spectrometer (Nicolet is 10, Thermo Fisher Scientific 5525, USA). The collected wavelength of spectroscopy ranged from 650 to 1855 cm^{-1}, while a total of 2500 spectral data were obtained. A sample of (S)-(+) ibuprofen was purchased from Acros Organics, while racemic ibuprofen was purchased from Alfa Aesar A Johnson Matthey Company and used without further purification. The different levels of enantiomeric excess of ibuprofen (10, 20, 30, 40, 50, 60, 70, 80 and 90%) were prepared from accurately weighing and combining certain amount of (S)-(+)-ibuprofen and racemic ibuprofen. Thus, the mol ratio of quinine and ibuprofen was 1:5. While maintaining the overall concentration (0.08 mmol/ml, refers to ibuprofen) and sample volume constant (1 ml, $CHCl_3$), the experiment was repeated 5 times to ensure reproducibility, and a total of 45 samples were obtained. Finally, one of the samples extracted from each level of enantiomeric excess sample was used as the prediction set (9 samples), while the remaining 36 formed the calibration set.

Wavelet transform

Wavelet transform (WT) changes the original spectral into the wavelet domain, so that the information contained in the original spectra data can be represented by the wavelet coefficients. Due to the characteristics of WT, most of the coefficients with small amplitude can be regarded as noise or uninformative. Therefore, the original data can be compressed and explained by only a small amount of wavelet coefficients. Wavelets are a series of functions derived from the basis function (mother wavelet); hence, a wavelet is defined as:

$$\Psi_{a,\tau}(t) = \frac{1}{\sqrt{a}}\psi\left(\frac{t-\tau}{a}\right),\ a>0, \tau \in R \quad (1)$$

where a is a scaling variable, and b is a translation variable. WT depends on these two parameters that vary continuously over a set of real numbers.

Let $f(t)$ denote a function, so that the WT of $f(t)$ will be written as:

$$WT_f(a,\tau) = \frac{1}{\sqrt{}}\int_R f(t)\psi^*\left(\frac{t-\tau}{}\right)dt \quad (2)$$

where "$*$" denotes conjugation. In practice, the scale parameter a can be sampled along the dyadic sequence $(2^j)_{j\in Z}$, and the position parameter τ can be sampled as $(k2^j)_{k,j\in Z}$. Then the DWT can be obtained as:

$$WT_f(a,\tau) = 2^{-j/2}\int_R f(t)\psi^*(2^{-j}t-k)dt \quad (3)$$

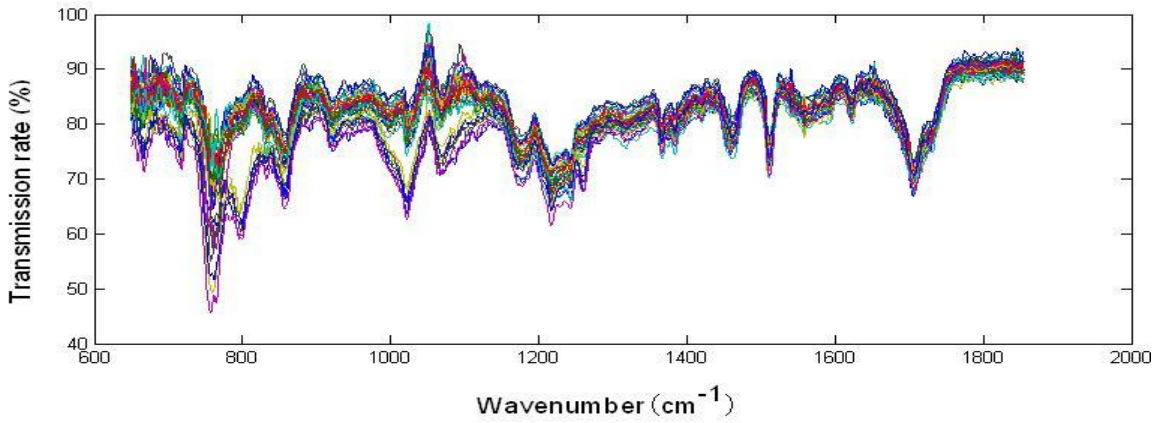


Figure 2. Original transmission spectra of different ibuprofen enantiomers.

$\{\phi \quad\}$ $\{\psi \quad\}$
Assuming $j,n \ n\in Z$ and $j,n\ n\in Z$ are orthonormal bases, the projection in these spaces will be characterized by:

$$c_j(k) = < f, \phi_{j,n} > \tag{4}$$

$$d_j(k) = < f, \psi_{j,n} > \tag{5}$$

So, the Mallat algorithm is as follows (Mallat, 1989):

$$c_{j-1}(k) = \sum_{n\in Z} c_{j(n)} \bar{h}_{n-2k} \quad k \in Z \tag{6}$$

$$d_{j-1}(k) = \sum_{n\in Z} d_{j(n)} \bar{g}_{n-2k} \quad k \in Z \tag{7}$$

where $\{c_j(k)\}$ is the approximate coefficient (low-frequency components) of the signal at the decomposition level of J, and $\{d_j(k)\}$ is the detailed coefficient (high-frequency components). Moreover, the reconstruction formula is as follows:

$$c_{j+1}(k) = \sum_{n\in Z} c_{j}(n) h_{k-2n} + \sum_{n\in Z} d_{j}(n) g_{k-2n} \quad k \in Z \tag{8}$$

PLS regression

Partial least squares regression is the most powerful regression technique in chemometics. It decomposes the predictor (X) and the dependent variable (Y) blocks in a single process.

$$X = TP + E \tag{9}$$

$$Y = YQ + F \tag{10}$$

where T and U are the X and Y score matrices; P and Q are the X and Y loading; and E and F are the residual, respectively. The linear inner relationship is constructed between the dependent and independent variable (T and U) respectively, according to:

$$U = TB \tag{11}$$

$$B = (T'T)^{-1}T'Y \tag{12}$$

where T' is T transpose matrix. When predicted, the unknown T of unknown X can be obtained according to P, and the unknown Y can be obtained as:

$$Y_{unknown} = T_{unknown} BQ \tag{13}$$

Software and calculation

All calculations were performed with homemade programs in MATLAB 7.6 (The Math Works, Natick, USA). The optimal number of PLS latent variables (LVs) was determined on the basis of minimum root mean square error of cross-validation (RMSECV).

RESULTS AND DISCUSSION

Transmission spectral investigation

The typical infrared spectra with different enantiomeric excess values are shown in Figure 2. It can be seen from Figure 1 that the trends with different spectral curves are very similar, which makes it very difficult to directly determine the enantiomeric excess value of ibuprofen. It can also be observed that the spectra contain a relatively large noise. At the same time, as there are large data contained in the spectral variables, chemometric approach is required to compress the spectral data.

PLS based on full spectrum

In the first stage of this study, a PLS regression model was built on the whole spectra without any processing. It can be seen from Table 1 that the prediction error was basically kept within 15%, and the largest prediction errors occurred in the prediction of enantiomeric excess values of 30 and 70%, which reached 11.38 and

Table 1. Prediction results of enantiomeric excess percentage of different ibuprofen enantiomers by PLS models by on full spectrum.

Analytes	Given[a]	PLS[b]	Error
1	10	8.56	1.44
2	20	15.64	4.36
3	30	41.38	11.38
4	40	41.60	1.60
5	50	48.52	1.48
6	60	61.04	1.04
7	70	59.25	10.75
8	80	71.21	8.79
9	90	90.90	0.90

[a]Enantomeric compositions of the solution prepared fom R- and S- ibuprofen.[b]predicted by PLS model.

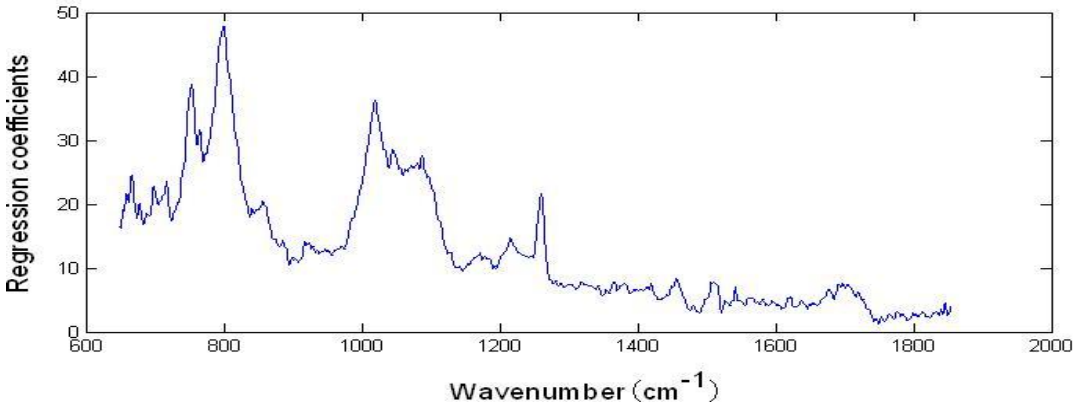


Figure 3. PLS model regression coefficients.

10.75% respectively, thereby showing that the predicted results were not ideal. Except for these two, other predication errors were within 10%, especially the prediction of 90% enantio-meric excess value, in which the error was minimized to 0.9%. Finally, the prediction results of enantiomeric excess values ranging from 0.1 to 0.9 were averaged, and the average prediction result of 4.65 was obtained. From the perspective of the overall prediction, these prediction results were satisfactory. Consequently, all the results showed that it was feasible to quickly predict enantiomeric excess value based on IR technology.

To study the contribution of each variable on its pre-diction model, the PLS model regression coefficients were listed and shown in Figure 2. The absolute values of the regression coefficients represented the different contributions to prediction models; as such, the larger absolute value of the regression coefficients means the larger contribution. From Figure 3, we can see that the wavelength of the greatest contribution is 800 cm^{-1}, followed by 1000 cm^{-1}. Wavelengths from 1400 cm^{-1} have little contribution to the model, because the absolute values of these wavelength coefficients are very low.

PLS on wavelet decomposition approximate coefficients

The preceding analysis shows that it is feasible to rapidly predict the enantiomeric excess value based on IR. However, the previous prediction model is based on the full spectrum. Due to the large data amount, the model is not simple enough. Particularly, in practical applications, it is time-consuming. Therefore, as a result of this defect, we must conduct compression on these large amounts of spectral data. Wavelet transformation has the merit of time-frequency in spectral signal analysis, which has been proven to be a powerful compression method. According to the principle of wavelet transformation, low-frequency and high-frequency information in the original signal can be obtained in wavelet decomposition domain, of which low-frequency information represents most of the information of the original spectral signal, while high-frequency information mainly represents noise information. High-frequency information of the original spectral obtained by wavelet transform is removed in the wavelet domain, while spectral signals are compressed. Thus, based on this concept, the wavelet transform

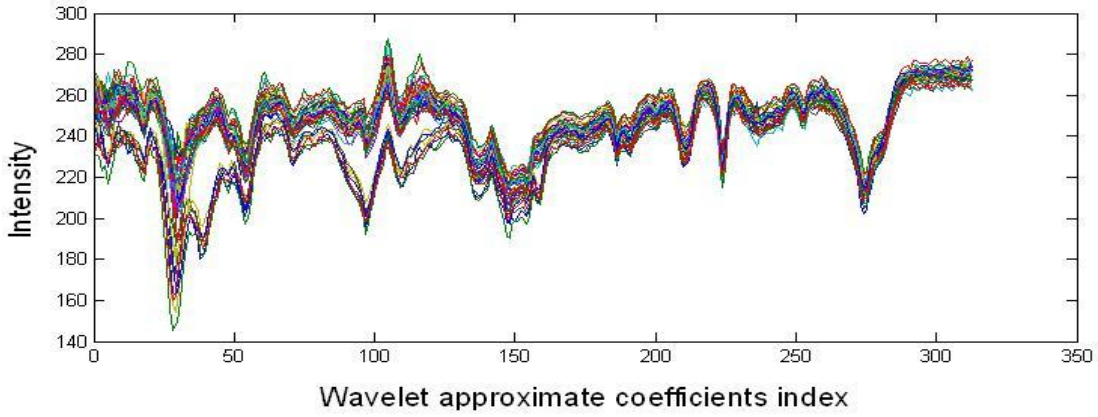


Figure 4. Wavelet approximate coefficients of ibuprofen spectral using Haar wavelet function and decomposition level 3.

Table 2. Prediction results of enantiomeric excess percentage of different ibuprofen enantiomers by PLS models via wavelet decomposition level 3.

Analytes	Given	PLS	Error
1	10	9.99	0.01
2	20	22.99	2.99
3	30	34.38	4.38
4	40	39.93	0.06
5	50	45.84	4.15
6	60	62.88	2.88
7	70	63.81	6.18
8	80	68.31	11.69
9	90	90.04	0.04

[a]Enantomeric compositions of the solution prepared from R- and S- ibuprofen. [b] predicted by PLS model.

algorithm was employed to decompose the ibuprofen IR spectra, and the decomposed low-frequency information was used as the input variables of PLS to establish the calibration model, which can not only make the model simple, but can also enhance the modeling prediction precision. Decomposition level 3 and the simplest Harr wavelet function (Db1) are adopted in this work. However, the low-frequency coefficients of decomposition level 3 are shown in Figure 4. It can be seen from Figure 4 that they are quite similar with the original spectra in Figure 2, which show that the low-frequency coefficients of decomposition level 3 properly retained the information features of the original spectra. After careful observation, changes of the coordinate axis can be found. Meanwhile, from the decomposition results, the data points reduced from 2500 to 331, which is only 1/4 of the original amount. The prediction results are shown in Table 2. As observed from the overall results, the prediction results were also satisfactory; in that the largest prediction error was for 80% enantiomeric excess value, reaching 11.69%. Except for this one, other errors were mostly within 5%, particularly for 10, 40 and 90% enantiomeric excess samples, in which the prediction error was almost close to 0. Similar with the previous practice, predicted errors were averaged, and the average error of 3.60 was obtained, which was better than the PLS model on the full spectrum. The better result was attributed to eliminate high-frequency noise information. Therefore, low-frequency coefficient information was employed as input variables of PLS, which can not only compress the data but also improve the prediction precision.

Conclusion

In this study, the feasibility of the rapid prediction on ibuprofen enantiomeric excess value by IR was explored. The calibration model on full spectrum using PLS regression technology was built and the average prediction error rate of 4.65 was obtained. The result shows that it is feasible to quickly determine the ee value based on IR technology. Due to the huge amount of data,

wavelet transform technology was used to compress the original spectra, and the decomposition level 3 low-frequency coefficient was used as input variables to build the PLS model. The average prediction error rate was obtained as 3.6, which showed that the wavelet transformation technology can not only compress the raw spectral data, but also improve prediction results. The obtained results proved that the IR non-equivalences of enantiomers of chiral drugs, induced by catalytic amount of chiral alkaloid, are enough to be accurately analyzed by PLS. However, all the results showed that the proposed strategy can be used as a rapid, cheap, accurate and practical way to determine enantiomeric compositions of ibuprofen.

ACKNOWLEDGEMENT

The authors are grateful for the financial support from NSFC (21002071), Department of Education of Zhejiang Province (Y201017083), and ZJNSFC (3110289).

REFERENCES

Altman RD (1984). Review of ibuprofen for osteoarthritis. Am. J. Med., 77: 10-18.

Armstrong DW, Ward TJ, Armstrong RD, Beesley TE (1986). Separation of Drug Stereoisomers by the Formation of β-Cyclodextrin Inclusion Complexes. Science, 232: 1132-1135

Chen X, Wu D, He Y, Liu S (2009). Detecting the quality of glycerol monolaurate: A method for using Fourier transform infrared spectroscopy with wavelet transform and modified uninformative variable elimination. Anal. Chim. Acta., 638: 16-22.

Chen X, Lei X (2009) Application of a Hybrid Variable Selection Method for Determination of Carbohydrate Content in Soy Milk Powder Using Visible and Near Infrared Spectroscopy J. Agric. Food Chem., 57: 334-340

Hutt AJ, Caldwell J (1983). The metabolic chiral inversion of 2-arylpropionic acids: A novel route with pharmacological consequences. J. Pharm. Pharmacol., 35: 693-704.

Islam MR, Mahdi JG, Bowen ID (1997). Pharmacological importance of stereochemical resolution of enatiomeric drugs. Drug Saf., 17: 149-165.

Kaiser, DG, Vangiessen, GJ, Reische, RJ, Wechte, WJ (1976) Isomeric inversion of ibuprofen (R)-enantiomer in humans. J. Pharm. Sci., 65: 269-273.

Mallat SG (1989). A Theory for Multi-resolution Signal Decomposition: the Wavelet Representation. IEEE Trans. Pattern Anal. Mach. Intell., 11: 674-693.

Shao XG, Leung AKM, Chau FT (2003). Wavelet: A New Trend in Chemistry, Accounts Chem. Res., 36: 276-283.

Tran CD, Grishko VI, Oliveira D (2003) Determination of Enantiomeric Compositions of Amino Acids by Near-Infrared Spectrometry through Complexation with Carbohydrate. Anal. Chem., 75: 6455-6462.

Tran CD, Oliveira D, Grishko VI (2004). Determination of enantiomeric compositions of pharmaceutical products by near-infrared spectrometry. Anal. Biochem., 325: 206-214.

Tung HH, Waterson S, Reynolds S, Paul E (1991). Resolution of Ibuprofen Via Stereospecific. Crystallization. AIChE Symp. Ser., 87: 64-71.

Williams K, Lee E (1985). Importance of drug enantiomers in clinical pharmacology. Drugs, 30: 333-354.

Zhou LL, Lin ZH, Welch CJ, Ge ZH, Ellison D (2006). Determination of the Enantiomeric Excess of an M3 Antagonist Drug Substance by Chemometric Analysis of the IR Spectra of Different Guest-Host Complexes. Chirality, 18: 306-313.