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Determination of polymorphic forms of ranitidine–HCl by DRIFTS and XRPD

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Abstract

The identification, characterization and quantification of crystal forms are becoming increasingly important within the pharmaceutical industry. A combination of different physical analytical techniques is usually necessary for this task. In this work solid-state techniques, diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) and X-ray powder diffractometry (XRPD) were combined to analyze polymorphic purity of crystalline ranitidine–HCl, an antiulcer drug, H2 receptor antagonists. A series of 12 different mixtures of Form 1 and 2 was prepared by geometric mixing and their DRIFT spectra and XRD powder patterns were obtained and analyzed, either alone or combined together, using Artificial Neural Networks (ANNs). A standard feed-forward network, with back-propagation rule and with multi layer perceptron architecture (MPL) was chosen. A working range of 1.0–100% (w/w) of crystal Form 2 in Form 1 was established with a minimum quantifiable level (MQL) of 5.2% and limit of detection of 1.5% (w/w). The results demonstrate that DRIFTS combined with XRPD may be successfully used to distinguish between the ranitidine–HCl polymorphs and to quantify the composition of binary mixtures of the two.

Keywords: Crystal; Polymorphs; Ranitidine

1. Introduction

The oral route is extensively used for administration of drugs. The most popular dosage forms are tablets and capsules where the drug is usually presented as a solid. Solid state properties of the active ingredient can influence the in vivo performance of the dosage form [1,2] and physical characterization of the solid state of a drug substance is necessary for successful development and approval of a pharmaceutical product. Polymorphism is the ability of a substance to crystallize in various arrangements of molecules [3]. The polymorphic behavior of organic solids can be of crucial importance in the pharmaceutical industry [4]. Properties varying between polymorphs include stability, crystal shape, compressibility, density, and dissolution rate. It is critical to select the

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optimum solid form for manufacture, to control the crystallization of drugs and to ensure that the approved form is produced consistently and is present in the formulation. Ideally, the drug substance should consist only of a single form because it is usually easier to control production to produce only one form.

Ranitidine hydrochloride (*N*-(2[({5-[(dimethylamino)methyl]-2-furanyl}methyl)thio]ethyl}-*N*′-methyl-2-nitro-1,1-ethenediamine hydrochloride), an anti-ulcer drug in current use is one of the 20 most frequently prescribed drugs (Fig. 1). Crystalline ranitidine is polymorphic and exists in two crystalline forms known as Form 1 and Form 2, and in several pseudopolymorphic forms [5]. Ranitidine hydrochloride Form 1 crystallizes from an ethanolic solution after addition of ethyl acetate [6]. Crystallization is difficult and expensive. Form 2 was reported and patented later. It crystallizes from isopropanol–HCl and is easier to be produced commercially [7].

Due to the patent issue [8] and its commercial value, manufacturers and researchers have paid special attention to both forms. The two forms have almost equal solubilities and there is no difference in bioavailability [9,10]. However, studies on their solid-state stability with different techniques have yielded slightly different stability results. Polymorphic transition may occur or accelerate upon humidity, temperature changes and mechanical forces, such as compression (the use of pressure in sample preparation for FTIR spectroscopy lead to a polymorphic transition) [11,12].

The aim of this work was to analyze polymorphic purity of crystalline ranitidine–HCl drug substance, by combining of two solid-state techniques, diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) and X-ray powder diffractometry (XRPD) via Artificial Neural Networks (ANNs). Neural networks are a wide class of flexible parameterized nonlinear regression and discriminant models used for empirical regression and classification modeling. Their flexibility enables them to discover more complex relationships in data than traditional statistical models, which often assume a linear dependence between predicted output variable and the given input variables. Hence, ANNs provide an analytical alternative to conventional techniques, which are often limited by strict assumptions of normality, linearity, variable independence etc. ANNs have been successfully used to classify spectra from various modalities including gamma ray spectroscopy [13] infrared spectroscopy [14,15], mass spectrometry [16], NMR spectroscopy [17,18] and X-ray fluorescence [19] over the last few years.

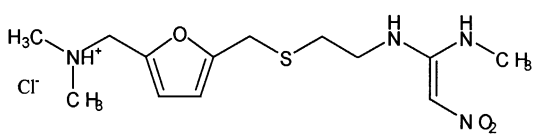

Fig. 1. Chemical structure of Ranitidine hydrochloride.

2. Materials and methods

2.1. Ranitidine hydrochloride

Samples of ranitidine–HCl Form 1 (Ch.-B 560018) and Form 2 (A.-Nr.32005)] were supplied by Dolorgiet Pharmaceuticals, St. Augustin, Germany. The polymorphic forms were characterized using elemental analysis, X-ray diffraction (XRD), Fourier transform-infrared spectroscopy (FTIR), DRIFTS, Raman spectroscopy (Raman), scanning electron microscopy (SEM) and light microscopy as described earlier [11].

2.2. Polymorphic mixtures

Different binary mixtures were prepared from the two polymorphic forms. The weight percent of Form 2 in the mixtures were 0, 1, 2, 5, 10, 20, 30, 40, 50, 60, 70, 100%. All the mixtures were mixed geometrically. Mixtures with 0, 1, 2, 10, 30, 40, 50, 70 and 100% of Form 2 were used for training and testing the ANN and with 5, 20, 60% of Form 2 were used as a validation data set. Each sample was prepared in triplicate.

2.3. Procedure for sample preparation

2.3.1. DRIFTS analysis

It is widely recognized that variation in particle size can have a significant influence on the diffuse

reflectance measurements [20]. Grinding could reduce the variation in particle size. However, grinding was avoided because it could induce polymorphic transitions [21]. We wanted to keep the method as simple as possible and to directly analyze the powdered samples with minimal pretreatment. Sample mixtures were dispersed as a 5% (w/w) mix in KBr (AR grade, BDH Laboratory Suppliers, Poole, UK), placed in the large sample cup (approximately 300 mg) using the supplied sample cup holder. A razor blade was used to smooth the sample surface. Spectra were measured immediately after mixing.

2.3.2. XRPD calibration analysis

In the preliminary experiments about 360 mg of powder samples were compressed using different pressures of 1, 2 and 4 tons. Resulting tablets were exposed to X-ray scans. The relative intensities of the major peaks remained constant indicating that the application of pressure did not induce any preferred orientation. In addition, a flat surface was achieved, minimizing negative interference due to sample curvature or irregular sample surface.

About 360 mg of binary mixtures was compacted as tablets (⌀16 mm) under a mass of 2 tons. It has been found earlier that this compaction does not lead to the polymorphic transition.

2.4. Apparatus

For analysis of the samples, a dynamic alignment FT-IR spectrophotometer (Bio-Rad FTS 175C, Bio-Rad Laboratories, Cambridge, USA) fitted with a diffuse reflectance accessory (Pike Technology Easidiff) was used. Spectra were captured using PC and Win-IR software. About 16 scans were averaged. A KBr background scan was performed routinely.

The XRPD scans were performed on a Philips wide angle XRPD with X-ray generator (PW 1130/00) and goniometer (PW1050, Philips, Almelo, The Netherlands). A copper target X-ray (wavelength 1.541Å CuKα) tube was operated at a power of 40 kV, 30 mA. The automatic divergence slit was set at 1° for the X-ray beam and at 0.1° for the receiving scintillation detector. The scans were carried out at a step size of 0.04° and counting time for 0.5 s per step within the ranges of 7–48° (2θ).

2.5. Pre-processing of the data

Using spectral intensities at all theta degrees of the diffractogram or at all wavenumbers from the DRIFT spectra directly as input data vectors had a weak correlation with weight fractions of polymorphs in mixtures. Reduction and transformation of the input data was necessary to enhance the ANN performance [22]. Transformation of the variable also reduced the number of outliers, and variance among values.

2.5.1. XRD patterns

The powder patterns were sampled between 15 and 29.4°(2Θ), the region containing the characteristic diffractions and 360 steps (2Θ) were recorded. These steps were further processed to reduce the data being fed to ANN and to smooth the noise in the diffractograms. The 360 steps were reduced into 72 (dB = 5), 36 (dB = 10) and subsequently into 18 (dB = 20) averaged intensities from 5,10 or 20 consecutive steps, respectively.

2.5.2. DRIFT spectroscopy

The original spectra were sampled between 660 and 3860 wavenumbers (cm^{-1}) and reduced to 1600 spectral intensities during the data recording. These spectral data were further processed to smooth the noise in the spectra. The 1600 absorbances were reduced into 160 averaged spectral values, each from ten consecutive wavenumbers (dB = 10), 64 (dB = 25) and 32 (dB = 50).

These data were used as inputs together with the corresponding weight fraction of Form 1 and 2 as output to train the ANN.

2.6. Optimal network architecture and training

A standard feed-forward network, with back-propagation rule and multilayer perceptron (MLP) model architecture [23] was used in this study.

Three ANNs models were trained and tested per each technique. For the DRIFT analysis, the ANN models consisted of 160 ($n = 10$), 64 inputs ($n = 25$) or 32 inputs ($n = 50$) for the averaged spectral value. For the XRD analysis, models had 72 ($n = 5$), 36 ($n = 10$) and 18 ($n = 20$) inputs, respectively. Seven models with combined inputs from DRIFTS spectra and XRPD diffractograms were trained and tested ($160 + 72$, $64 + 72$, $32 + 18$, $32 + 72$, $32 + 36$, $64 + 36$ and $54 + 72$).

Models had two output neurons, one for the percentage of each ranitidine–HCl crystal form. The number of hidden layers and hidden neurons was optimized.

ANN training was accomplished by cycling through the entire assembly of training examples and correcting the weights using the standard back-propagation rule to minimize the sum squared output error.

Weights and biases were initialized with random values at the start of each training run. During training, the performance of the ANN was evaluated with testing data. That is, 80% of the original sample data (mixtures containing 0, 1, 5, 20, 30, 40, 60, 70, 100% of Form 2) was used for the training and the other 20% of the data was used as the test set and back-propagated through the network to evaluate the trained network. The set used for testing was rotated and the results of the four runs were averaged.

Since training the ANNs can only compare the performance of the various types of network, models were validated on a third set of data. Predictions of the polymorphic composition of mixtures containing 2, 10 and 50% of Form 2 were used to validate neural network models.

Thus, three types of data sets are used:

training data: used to train network,

test data: used to monitor the neural network performance during training,

validation data: used to measure the performance of a trained application,

each with corresponding error. To calculate the rooted mean squared error (R.M.S., overall error) the individual errors are squared, summed, divided by the number of individual errors, and then square rooted.

3. Results and discussion

The requirement of analytical control implies reliable methods of detecting, distinguishing and quantifying polymorphs. The techniques used to assess polymorphism derive information from different means, and it is usually necessary to investigate polymorphism with multiple techniques.

XRPD is a powerful technique for the identification of crystalline solid phases, crystallinity and phase purity. Every crystalline solid phase has a unique XRD pattern as molecular repetition will give a unique set of reflection and generate a unique pattern. Change in crystal packing will lead to change in the form of molecular arrangement and repetition. Thus, different polymorphs will give a distinctive X-ray powder patterns. X-ray powder crystallography is, therefore, of great value for distinguishing and identifying polymorphs [24]. In a powder mixture, each crystalline phase produces its pattern independently of the other components in the mixture. Despite, XRPD is an underutilized analytical method for the determination of crystalline purity of solid phases and has found only limited application for the evaluation of drug product quality [25,26].

Non-destructive methods of analysis that allow rapid, sufficiently precise and reliable quality control have wide applications in many production systems. IR spectroscopy is a widely recommended identification method, wherein the spectrum of the test substance is compared with the spectrum of the reference standard [27]. Unfortunately, most of the identification methods currently listed are insensitive to the solid state of the drug in the dosage form. Methods based on IR spectroscopy have been the subject of considerable research, development and implementation in the pharmaceutical industry [28,29]. In recent years, much effort has been expended in the attempt to use IR spectroscopy in the quality control of solid pharmaceutical formulations [30]. Differences in crystal packing or conformational differences are mainly responsible for polymorphism. An infrared spectrum is unique for a compound and different polymorphs may show differences in their infrared absorbance due to differences at the molecular level [31]. Choice of

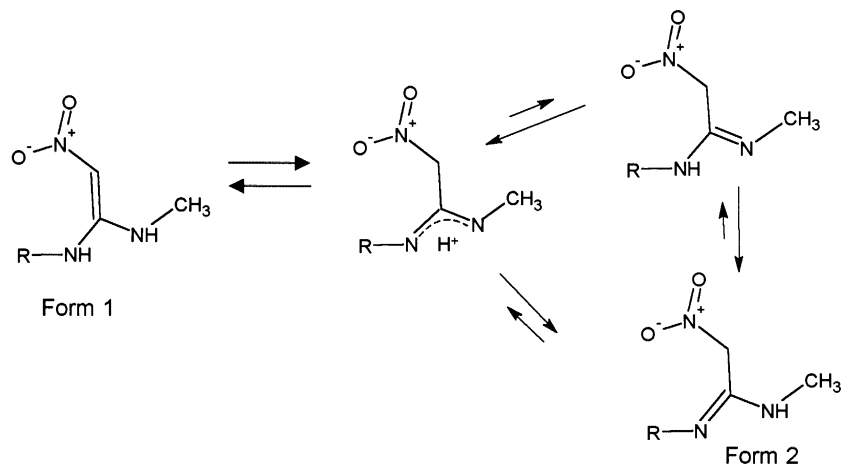

Fig. 2. Ranitidine tautomeric forms.

the routine sample presentation method for solid state IR spectroscopy includes mulls [32], disks [33], diffuse reflection [34] and attenuated total reflection (ATR) [35], since the running of solution spectra is excluded for distinguishing of polymorphs. The key factor in determining the sample procedure is the stability of the polymorphs. Disks or mulls are usually most appropriate, but DRIFTS is particularly suited for the examination of polymorphic systems as the preparation technique will minimize polymorphic interconverzion [36,37]. In this work, DRIFTS was implemented as the sampling method of choice to eliminate the possibility of polymorphic transformations during sampling preparations. Experiments had suggested that the reason for polymorphism of ranitidine–HCl is tautomerism [9]. Electron delocalization occurs at 2,2-diamino-1-nitroethylene residue. This structure can exist in three tautomeric forms. However, only two tautomers are stable and, therefore, we have two crystal forms (Fig. 2). DRIFT spectrum of Form 2 show additional peak at 2400 and peak at1610 cm^{-1} is split into two peaks. Imino group (C=NH) usually shows one broad peak or group of relatively sharp peaks at 2400 cm^{-1}, while peak at 1610 is characteristic for the C–N in plane bending of amino groups and for the vibration of conjugated acyclic double bonds (1600–1650). These spectral differences confirmed that two tautomeric forms are responsible for the polymorphic behaviors. Perhaps the electronic delocalization, present in Form 2, causes the differences in the spectra.

While DRIFTS detects properties associated with the molecular level, XRPD is a non-spectroscopic technique that determines the polymorphic form of a substance based on differences in the crystal packing. The XRPD patterns, and DRIFT spectra, of each polymorphic form of ranitidine–HCl are unique (Figs. 3 and 4). Predictions of the Form1/Form 2 polymorphic composition of mixtures were made with each technique and with combined data of the two techniques and compared with the theoretical values.

Better results were obtained with higher resolution spectra for a single technique. Best models had 160 (dB = 10) and 36 (dB = 10) inputs for the

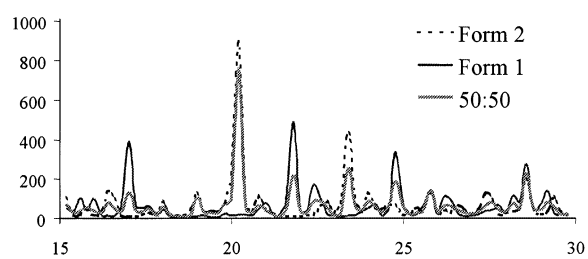

Fig. 3. X-ray diffractograms of the two polymorphic forms of ranitidine–HCl.

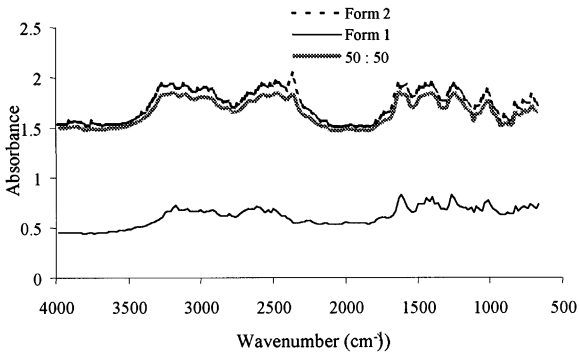

Fig. 4. DRIFT spectra of the two polymorphic forms of ranitidine–HCl.

DRIFT and XRPD technique, respectively. In case of DRIFT analysis, models had only one hidden layer, but for the XRD analysis better results were obtained with two hidden layers. Network structure was optimized by heuristic search. The criteria for judging the best model was rooted sum of mean squared error (R.M.S.) and relative error (ERR%) of model predictions (Tables 1 and 2).

Predictions were improved with the composite model created from combined inputs. Low-resolution DRIFT spectra and XRPD pattern were sufficient to achieve good results. Training the ANN with all available data would exhaust the network on training the irrelevant parts of the spectra. The best model had 36 inputs from the DRIFT spectra (dB = 50) and 32 inputs from XRD pattern (dB = 10) and one hidden layer with 24 hidden neurons (Table 3). Good prediction were obtained also by the model with 64 inputs from the DRIFT spectrogram (dB = 25) and 36 inputs from the X-ray diffractogram (dB = 10) and two hidden layers with four and two hidden neurons, respectively.

Plots of measured composition against predicted values with different techniques are shown in Fig. 5 and Fig. 6. In the case of Form 1 for the DRIFT spectra, XRPD pattern and the combination of both techniques linear regression analysis gave slopes of 1.011, 0.9621 and 1.007, intercept values of -0.519, -0.810 and -0.216 (Fig. 5). Coefficients of correlation were 0.998, 0.985 and 0.999. For the Form 2 linear regression analysis gave slopes of 1.019, 0.962 and 1.000, intercept values of -0.378, 4.572 and -0.153 and correlation coefficients of $r = 0.998$, 0.984 and 0.999, respectively (Fig. 6). In each case, intercept was not significantly different from zero and slope was not different from unity indicating no method bias and absence of proportional error.

The ANN model constructed from the XRD pattern was superior in predictions at lower concentration of one form (1 and 2% of Form 2), but the ANNs model constructed with the DRIFT spectral data had better overall averaged prediction.

The minimum quantifiable level (MQL) is determined from multiple measurements of the spectral response of a single sample mixture containing 1% of Form 2 ($n = 5$) and utilizing Eq. (1)[38]. Based upon a standard deviation (S.D.) of 0.76 and slope of 1.019 for DRIFT spectroscopy, an MQL of 7.5% for the Form 2 was calculated:

Table 1
Best ANNs structures for combined and single methods

Inputs			Hidden neurones		ANNs model[a]	R.M.S.		
DRIFT	XRD	Σ	1st layer	2nd layer		Training	Testing	Validation
32	72	104	11	0	104/11/2	0.06	1.64	1.41
32	36	72	24	0	72/24/2	0.09	0.72	0.81
64	36	100	4	2	100/4/2/2	0.24	2.34	0.44
160	0	160	24	0	160/24/2	1.79	3.37	1.91
0	32	36	1	2	36/1/2/2	1.23	8.14	1.31

[a] Number of inputs/hidden neurones/outputs.

Table 2
Averaged predictions with different ANNs for the validation data set

ANN structure													
		DRIFTS+XRPD							DRIFTS			XRPD		
		232/5/2/2	232/30/2	50/4/4	104/11/2	68/24/2	136/4/1/2	100/4/2	160/24/2	32/9/2	64/11/2	72/5/2/2	36/1/2/2	18/6/2
DRIFTS+XRPD inputs														
		160+72	160+72	32+18	32+72	32+36	64+72	64+30						
Theoretical		Predicted												
Form 2 (%)	2	5.25	2.20	4.99	1.19	2.19	6.24	2.26	3.88	7.45	5.87	4.53	3.42	5.09
	10	9.98	10.13	10.01	9.99	10.01	10.10	9.98	7.94	8.48	8.91	9.99	8.93	10.11
	50	32.25	37.24	52.93	51.80	50.00	50.21	49.99	53.23	66.72	49.56	11.36	44.64	90.21
Form 1 (%)	98	94.76	96.98	95.00	98.82	96.90	93.76	97.66	96.05	92.77	94.10	95.49	96.82	94.89
	90	90.03	89.95	89.97	90.00	89.99	89.90	89.94	92.10	91.73	91.03	90.01	91.30	89.93
	50	67.72	64.90	47.37	47.96	50.00	49.79	50.13	46.50	33.37	50.62	88.73	54.85	9.756
	ERR(%)[a]	41.58	13.35	29.37	10.27	1.41	38.42	4.38	24.20	62.40	37.38	49.40	17.46	53.29

[a] ERR (%) (Predicted − Actual)/Actual × 100 averaged.

Table 3
Determination of the polymorphic composition of synthetic mixtures of ranitidine–HCl by the combined DRFT and XRDP techniques and using 68/24/2 ANNs model

Sample number	Form 2 (%)	Found (%)	Recovery	Form 1 (%)	Found (%)	Recovery
1	0.00	0.25	[a]	100.00	99.8	99.80
2	1.00	1.06	106.00	99.00	98.97	99.97
3[b]	2.00	2.19	109.50	98.00	96.9	98.88
4	5.00	4.97	99.40	95.00	95.01	100.01
5[b]	10.00	10.01	100.10	90.00	89.99	99.99
6	20.00	19.99	99.95	80.00	80.01	100.01
7	30.00	30.09	100.30	70.00	68.51	97.87
8	40.00	39.99	99.98	60.00	59.97	99.95
9[b]	50.00	49.99	99.98	50.00	50.03	100.06
10	60.00	60.02	100.03	40.00	40.01	100.03
11	70.00	69.98	99.97	30.00	29.89	99.63
12	100.00	99.74	99.74	0.00	0.26	[a]
	Recovery (%)[c]		101.36			99.64
	S.D.[d]		3.26			0.72
	R.S.D. (%)[e]		3.22			0.72

[a] Cannot be calculated.
[b] Validation data set.
[c] Recovery = (amount found $\times 100$)/amount added.
[d] S.D. $= \sqrt{\frac{\Sigma_1^n (x_i - \bar{x})^2}{n-1}}$, where x_i is the measured value and n is the number of results to calculate the mean, $\bar{x}$ = mean value.
[e] R.S.D. (%) $= \frac{\text{S.D.} \times 100}{\bar{x}}$.

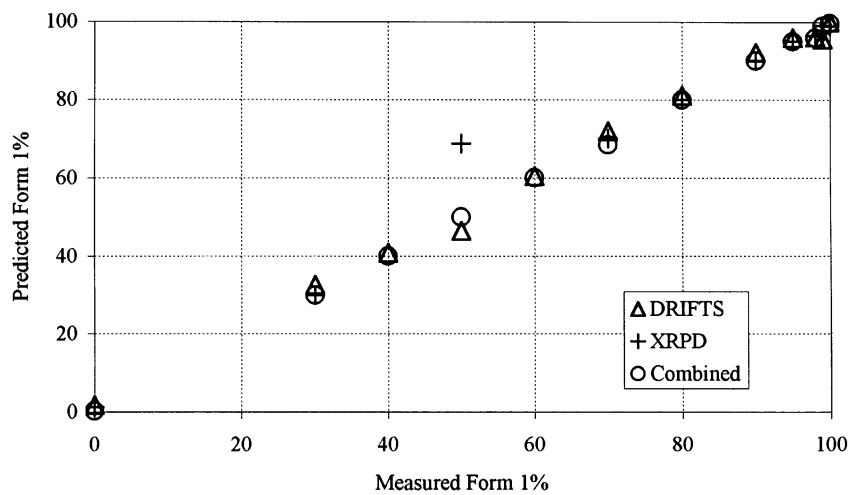

Fig. 5. Plot of values predicted by DRIFTS, XRPD and combined technique against theoretical polymorph Form 1 composition.

$$\mathrm{MQL} = \frac{10 \times \mathrm{S.D.}}{\mathrm{Slope}} \quad (1)$$

The limit of detection (LD) was calculated by multiplying the S.D. by three and then dividing by the slope of the calibration curve. Through this method of calculation, the LD was found to be 2.2% (w/w). For the XRP diffractometry MQL was 11.3% and LD was 3.4% (S.D. = 0.96, Slope = 1.09) and for combined technique MQL was 5.2 and LD was 1.5% (S.D. = 0.524, Slope = 1.001). It is obvious that calibration function obtained with combined data had constant variance over the entire concentration range and, therefore, higher precision and less deviation from linearity. Since S.D. for replicated samples containing 1% of Form 2 ($n = 5$) was smaller, MQL and LD were significantly smaller in comparison with single technique methods.

4. Conclusion

In conclusion, we have shown that the combination of DRIFTS and XRPD using ANNs can provide qualitative and quantitative information about the polymorphic composition of ranitidine–HCl drug substance. The method described can be used may be successfully applied to the in situ monitoring of the crystal nature of a ranitidine–HCl bulk drug sample.

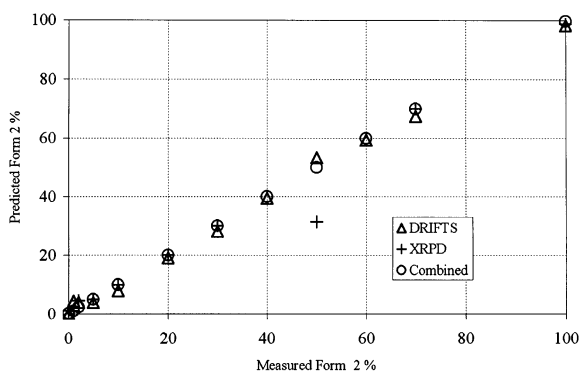

Fig. 6. Plot of values predicted by DRIFTS, XRPD and combined technique against theoretical polymorph Form 2 composition.

The technique can provide qualitative and quantitative information about the solid state of the ranitidine–HCl drug substance (crystal form). The method can be used in primary production for the bulk drug substance control. Polymorphic transition in solid state induced during pharmaceutical processing can be detected and even quantified.

References

[1] S.R. Byrn, in: Solid State Chemistry of Drugs, Academic Press, New York, 1982, pp. 7, 140–146, 332.
[2] S. Byrn, R. Pfeiffer, M. Ganey, C. Hoiberg, G. Poochikian, Pharmaceutical solids — a strategic approach to regulatory consideration, Pharm. Res. 12 (1995) 945–954.
[3] L. Borka, Reviw on crystal polymorphism of substances in the European Pharmacopeia, Pharm. Acta Helv. 66 (1991) 16–22.
[4] T.L. Threlfall, Analysis of organic polymorphs-a review, Analyst 120 (1995) 2435–2460.
[5] T. Madan, A.P. Kakkar, Preparation and characterization of ranitidine–HCl crystals, Drug Dev. Ind. Pharm. 20 (1994) 1571–1588.
[6] M. Hohnjek, J. Kuftinec, M. Malnar, M. Skreblin, N.A. Kajfez, N. Blazevic, Ranitidine. Analytical Profiles of Drug Substances, vol. 15, Academic Press, New York, 1986, pp. 534–561.
[7] D.L. Crookes, Crystalline ranitidine hydrochloride and pharmaceutical composition containing it, Chem. Abs. 97 (1982) 332.
[8] D.L. Crookes, UK Pat. 2084580B, 1982.
[9] J. Shen, D. Lee, R.G. Mckeag, Bioequivalence of two forms of ranitidine, NZ Pharmacy 15 (1995) 24–25.
[10] S.A. Bawazir, M.W. Gouda, Y.M. El-Sayed, Comparative bioavailability of two tablet formulations of ranitidine hydrochloride in healthy volunteers, Int. J. Clin. Pharm. 36 (1998) 270–274.
[11] J.T. Carstensen, M.K. Franchini, Isoenergic polymorphs, Drug Dev. Ind. Pharm. 21 (1995) 523–536.
[12] A. Foster, K. Gordon, D. Schmirer, N. Soper, V. Wu, T. Rades, Characterisation of two polymorphic forms of ranitidine–HCl, Int. J. Vibrational Spectrosc. 2 (1998) Ed. 2:12.
[13] P. Olmos, J.C. Diaz, J.M. Perez, P. Gomez, A new approach to automatic radiation spectrum analysis, IEEE Trans. Nucl. Sci. 38 (1991) 971–975.
[14] H. Hobert, K. Meyer, Infrared spectroscopic analysis of complex mixtures by classification and regression, Fresenius J. Anal. Chem. 344 (1992) 178–185.
[15] K. Tanabe, T. Tamura, H. Uesaka, Neural network system for the identification of infrared spectra, Appl. Spectrosc. 46 (1992) 807–810.

[16] R. Shadmehr, D. Angell, P.B. Chou, G.S. Oehrlein, R.S. Jaffe, Principal component analysis of optical emission spectroscopy and mass spectrometry: application to reactive ion etch process parameter estimation using neural networks, J. Electrochem. Soc. 139 (1992) 907–914.
[17] B. Meyer, T. Hansen, D. Nute, P. Albersheim, A. Darvill, W. York, J. Sellers, Identification of the H-1-NMR spectra of complex oligosaccharides with artificial neural networks, Science 251 (1991) 542–544.
[18] S.R. Amendolia, A. Doppiu, M.L. Ganadu, G. Lubinu, Classification and quantitation of H-1 NMR spectra of alditols binary mixtures using artificial neural networks, Anal. Chem. 70 (1998) 1249–1254.
[19] M. Bos, H.T. Weber, Comparison of the training of neural networks for quantitative X-ray fluorescence spectrometry by a genetic algorithm and backward error propagation, Anal. Chim. Acta 247 (1991) 97–105.
[20] M.P. Fuller, P.R Griffiths, Diffuse reflectance measurements by infrared Fourier transform spectrometry, Anal. Chem. 50 (1978) 1906–1910.
[21] M. Otsuka, N.J. Kaneniwa, Effect of seed crystals on solid-state transformation of polymorphs of chloramphenicol palmitate during grinding, J. Pharm. Sci. 75 (1986) 506–511.
[22] F. Drablos, Transformation for mass spectra, Anal. Chim. Acta 256 (1992) 134–151.
[23] H. White, Artificial Neural Networks: Aproximation and Learning Theory, Blackwell, Oxford, UK, 1992.
[24] R.S. Chao, K.C. Vail, Polymorphism of 1,2-dihydro-6-neopentyl-2-oxonicotinic acid: characterization, interconversion, and quantitation, Pharm. Res. 4 (1987) 429–432.
[25] K. Ashizawa, K. Uchikawa, T. Hattori, Y. Ishibashi, T. Sato, Y. Miyake, Pseudopolymorphism and phase stability in four solid forms of (6R,7R)-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-2-methoxy-iminoacetamid]-3-[(4-carbamoyl-1-quinuclidinio)methyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]oct-2-ene-2-carboxylate (E1040), J. Pharm. Sci. 78 (1989) 893–899.
[26] R.K. Cavatur, R. Suryanarayanan, Characterization of phase transitions during freeze-drying by in situ X-ray powder diffractometry, Pharm. Dev. Technol. 3 (1998) 579–586.
[27] US Pharmacopeia, XXIII, US Pharmacopeial Conversion, Rockville, MD, 1994, pp.107, 241, 266, 1277,1521.
[28] E. Dreassi, G. Ceramelli, P. Corti, P.L. Perruccio, S. Lonardi, Application of near-infrared reflectance spectrometry to the analytical control of pharmaceuticals: ranitidine hydrochloride tablet production, Analyst 121 (1996) 219–222.
[29] E. Dreassi, G. Ceramelli, P.L. Perruccio, P. Corti, Transfer of calibration in near-infrared reflectance spectrometry, Analyst 123 (1998) 1259–1264.
[30] E. Dreassi, G. Ceramelli, P. Corti, M. Massacesi, L. Perrucio, Quantitative Fourier transform near-infrared spectroscopy in the quality control of solid pharmaceutical formulations, Analyst 120 (1995) 2361–2365.
[31] W.P. Findlay, D.E. Bugay, Utilization of Fourier transform Raman spectroscopy for the study of pharmaceutical crystal forms, J. Pharm. Biomed. Anal. 16 (1998) 921–930.
[32] W.F. Potts, Chemical Infrared Spectroscopy, vol. 1, Wiley, New York, 1963.
[33] R.G. White, Handbook of Industrial Infrared Analysis, Plenum, New York, 1967.
[34] K. Krishnan, J.R. Ferraro, in: J.R. Ferraro, L.J. Basile (Eds.), Fourier Transform Infrared Spectroscopy, vol. 3, Academic Press, New York, 1982, p. 149.
[35] F.M. Mirabella, Internal Reflectance Spectroscopy, Marcel Dekker, New York, 1992.
[36] D.A. Roston, M.C. Walters, R.R. Rhinebarger, L.J. Ferro, Characterization of polymorphs of a new anti-inflammatory drug, J. Pharm. Biomed. Anal. 11 (1993) 293–300.
[37] S. Agatonovic-Kustrin, I.J. Tucker, D. Schmierer, Solid state assay of ranitidine hydrochloride as a bulk drug and as active ingredient in tablets using DRIFT spectroscopy with ANNs, Pharm. Res. 16 (1999) 1479–1484.
[38] K.A. Robinson, Chemical Analysis, Little, Brown and Company, Boston, 1986, pp. 754–758.