Solid State Assay of Ranitidine HCl as a Bulk Drug and as Active Ingredient In Tablets Using DRIFT Spectroscopy with Artificial Neural Networks

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Purpose. A new, simple, sensitive and rapid method was developed to analyse the polymorphic purity of crystalline ranitidine-HCl as a bulk drug and from a tablet formulation.

Methods. Diffuse reflectance infrared Fourier transform (DRIFT) spectroscopy was combined with Artificial Neural Networks (ANNs) as a data modelling tool. A standard feed-forward network, with back-propagation rule and with single hidden layer architecture was chosen. Reduction and transformation of the spectral data enhanced the ANN performance and reduced the complexity of the ANNs model. Spectral intensities from 1738 wavenumbers were reduced into 173 averaged spectral values. These 173 values were used as inputs for the ANN. Following a sensitivity analysis the number of inputs was reduced to 30, or 35, these being the input windows which had most effect on the output of the ANN.

Results. For the bulk drug assay, the ANN model had 30 inputs selected from a sensitivity analysis, one hidden layer, and two output neurons, one for the percentage of each ranitidine hydrochloride crystal form. The model could simultaneously distinguish between crystal forms and quantify them enabling the physical purity of the bulk drug to be checked. For the tablet assay, the ANN model had 173 averaged spectral values as the inputs, one hidden layer and five output neurons, two for the percentage of the two ranitidine hydrochloride crystal forms and three more outputs for tablet excipients and additives. The ANN was able to solve the problem of overlapping peaks and it successfully identified and quantified all components in tablet formulation with reasonable accuracy.

Conclusions. Some of the advantages over conventional analytical methods include simplicity, speed and good selectivity. The results from DRIFT spectral quantification study show the benefits of the neural network approach in analysing spectral data.

KEY WORDS: DRIFT spectroscopy; ANNs; ranitidine hydrochloride; crystal forms.

INTRODUCTION

The polymorphic behaviour of organic solids can be of crucial importance in the pharmaceutical industry. Properties varying between polymorphs include stability, crystal shape, compressibility, density, and dissolution rate. The different molecular packing may result in a substantially different dosage to the patient as the drug dissolves. The drug can become less effective or inactive, or toxic, or, in extreme cases, lethal (1). It is thus vital to control crystallisation of drugs and to ensure the approved polymorph is present in the formulation.

Ranitidine hydrochloride (N-(2[({5-[(dimethylamino) methyl]-2furanyl}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. Crystalline ranitidine is polymorphic and exists in two crystalline forms known as Form 1 and Form 2, and in several pseudopolymorphic forms (2). Ranitidine hydrochloride Form 1 crystallises from an ethanolic solution after addition of ethyl acetate (3). Form 2 crystallises from isopropanol-HCl (4). Scanning electron microscopy (SEM) photos in Fig. 1, show the morphology of the two samples and differences in their particle shape.

Due to the patent issue 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 (5,6). However, studies on their solid-state stability with different techniques (2,3,7) have yielded slightly different stability results.

In this study we investigated the capacity of Artificial Neural Networks (ANNs) as a data analysis tool to analyse Diffuse reflectance infrared Fourier transform (DRIFT) spectra for qualitative and quantitative estimation of ranitidine-HCl. Over the last few years ANNs have been successfully used to classify spectra from various modalities including gamma ray spectroscopy (8), infrared spectroscopy (IR) (9,10), mass spectrometry (11), nuclear magnetic resonance (NMR) spectroscopy (12,13) and x-ray fluorescence (14). Non-destructive methods of analysis that allow rapid, sufficiently precise and reliable quality control have wide applications in many production systems. Methods based on infrared spectroscopy have been the subject of considerable research, development and implementation in the pharmaceutical industry (15,16,17).

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 (18). IR spectroscopy is a widely recommended identification method, wherein the spectrum of the test substance is compared with the spectrum of the reference standard. The identification test of the drug in a dosage form is complicated by the presence of excipients and often requires extraction of the active ingredient so potentially valuable information about the solid state of the drug can be lost.

The main aim of this research involved two steps: to investigate the ability of ANNs to recognize and quantify two crystal forms of ranitidine hydrochloride polymorphic mixtures from DRIFT spectroscopy data and provide information about the solid state; to identify the crystal form and quantify the active ingredient in tablets.

Artificial Neural Networks

ANNs are computer programs designed to simulate the way in which human brain processes information. ANNs learn (or are trained) through experience with appropriate learning exemplars. The behaviour of a neural network is determined by the transfer functions of its neurones, by the learning rule, and by the architecture, itself. We have used a supervised network with a back-propagation learning rule. In this type of model, information from inputs (e.g., inputs = spectral data)

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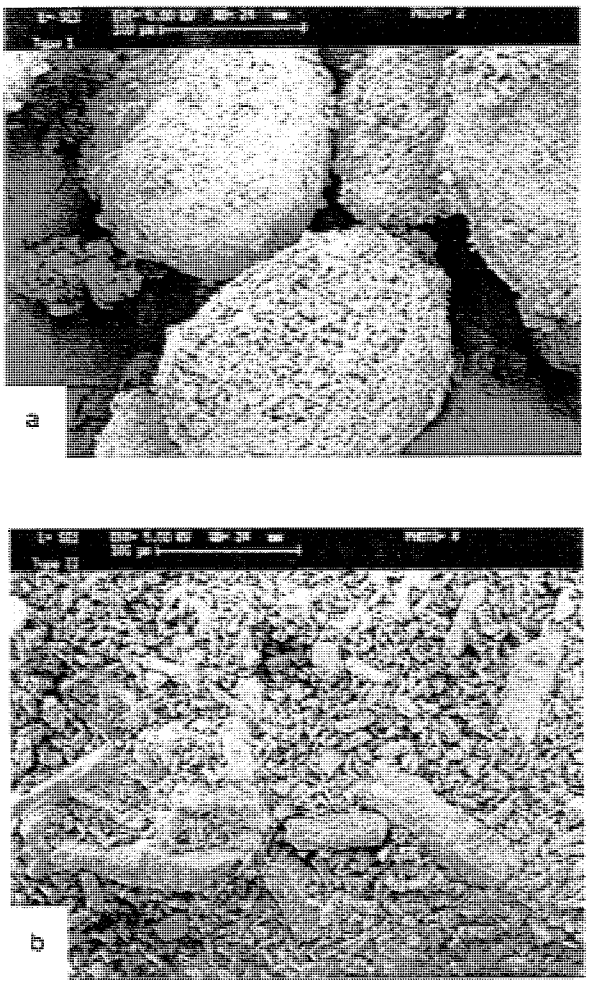

Fig. 1. SEM photos of Ranitidine-HCl Form 1 (a) and Form 2 (b).

is fed forward through the ANN to optimise the weights between neurons. The output of the neuron (e.g., output = level of Form 1) is related to the summed input by a sigmoid shaped transfer function. During training, optimisation of the network weights is made by back-propagation of error (e.g., difference between predicted and actual level of Form 1), and the interunit connections are changed until the error in predictions is minimised across many data sets and until the network reaches a specified level of accuracy. Once the network is trained and tested it can be given new input information (e.g. spectral data) to predict the output (e.g., level of Form 1).

Their most important advantage is in solving problems that are too complex for conventional methods. These problems include pattern recognition and forecasting.

MATERIALS AND METHODS

Ranitidine Hydrochloride

Samples of ranitidine hydrochloride Form 1 (Ch.-B 560018) and Form 2 (A.-Nr. 32005)] were supplied by Dolorgiet Pharmaceuticals, St. Augustin, Germany. The commercial tablets was obtained from the local market.

Table 1. Composition (% w/w) of Mixtures Used for the Tablet Assay Calibration

Avicell	Kollidon	Mg-stearate	Form 1	Form 2
0	0	0	99	1
0	0	0	98	2
0	0	0	80	20
0	0	0	70	30
0	0	0	50	50
40.2	2.7	0.7	56.4	0
39.7	3	1.5	55.9	0
33.7	9	7	50.2	0
25	25	25	25	0
20	20	40	20	0
100	0	0	0	0
0	100	0	0	0
0	0	100	0	0
0	0	0	100	0
0	0	0	60	40

Calibration Samples for the Ranitidine Hydrochloride Bulk Drug Assay

Binary mixtures were made from the two polymorphic forms with different proportions. The weight factions 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, 50, 70 and 100% of Form 2 were used for training and testing the ANN and with 5, 20, 40, 60% of Form 2 as a validation data set.

The samples were stored in a desiccator at room temperature and protected from light.

Calibration Samples for the Ranitidine Hydrochloride Tablet Assay

Individual tablet ingredients (two microcrystalline cellulose components and magnesium stearate) and two ranitidine hydrochloride crystalline forms at different weight ratios were weighed and mixed and their composition is given in Table 2. All the mixtures were mixed geometrically and stored in a desiccator at room temperature and protected from light.

These samples were used for training and testing the ANNs and tablet samples as a validation data set.

Table 2. Predicted Concentrations of Polymorphs in Mixtures

Form 1 (%)	Form 2 (%)	ANN*		ANN**	
95	5	97.64	6.09	95.06	4.5
80	20	78.54	22.36	74.73	24.9
60	40	60.68	39.75	59.41	40.12
40	60	42.59	57.03	39.95	61.13
	validation ERR(%)	2.9	9.8	1.9	9.2

* Trained with 173 inputs.

** Trained with 30 selected inputs (sensitivity greater than 1%).

$$\text{ERR}(\%) = \left(\frac{\text{Predicted} - \text{Actual}}{\text{Actual}}\right) \times 100$$

Tablet Samples

Each tablet was gently ground into a fine powder using a glass mortar and pestle. Ten samples were prepared.

Procedure for Sample Preparation

Sample mixtures were dispersed as a 5% (w/w) mix in KBr, placed in the large sample cup (approx. 300 mg) using the supplied sample cup holder and a razor blade was used to smooth the sample surface. Spectra were measured immediately after mixing.

Apparatus

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

Scanning electron microscopy was performed at 5 kV acceleration voltage using a Cambridge S360 SEM.

EXPERIMENTAL

ANN Software and Optimal Network Architecture

The MS-Windows based artificial neural network software, NNMODEL Version 1.404 (Neural Fusion) was used.

A standard feed-forward network, with back-propagation rule and multilayer perceptron (19) (MLP) model architecture with one hidden layer was chosen. The architecture of the ANNs when consisting of an input layer, one or more hidden layers and an output layer, is more powerful than perceptrons with no hidden layer and can compute any continuous mapping. A single hidden layer was used for simplicity, and because there is little evidence to suggest that a larger number of hidden layers improves performance (20).

During training and testing the number of hidden neurons was varied from 0 to 10 and training cycles from 0 to 2000 and ANN performance was tested after each addition. Model selection for an ANN requires choosing the number of hidden units and connections thereof for optimal performance.

For the bulk drug assay, two ANNs models were trained and tested. The first ANN had 173 inputs, with each input being the averaged reflectance across 10 consecutive wavenumbers. The second ANN had 30 inputs selected from a sensitivity analysis. Models had one hidden layer, and two output neurons, one for the percentage of each ranitidine hydrochloride crystal form.

For the tablet assay the first ANNs model had 173 inputs and second had 35 inputs selected from a sensitivity analysis. ANNs models had one hidden layer and five output neurones. Two output neurones were for the percentage of two ranitidine hydrochloride crystal forms and three more outputs for tablet excipients and additives.

Training

At the start of the training run, both weights and biases were initialized with random values. During training, the performance of the ANN was evaluated with testing data. That is 75% of the sample data was used for training and testing was done with the other 25% of the data. The set used for testing was rotated and the results of the four runs were averaged.

RESULTS AND DISCUSSION

It is widely recognized that variation in particle size can have a significant influence on the diffuse reflectance measurements (21). Grinding could reduce the variation in particle size. However, grinding was avoided because it could induce polymorphic transitions (22). We wanted to keep the method as simple as possible and to directly analyse the powdered samples with minimal pretreatment.

Common methods of building linear calibration models are multiple linear regression (MLR) (23,24), principal components regression (PCR) and partial least-squares (PLS) (25). For less noisy data it is always possible to obtain accurate calibration models using a limited number of wavelengths (26,27). If there is only two components in a mixture a minimum of two peaks can be used to determine the relative amount of each component in the mixture. In the multivariate case, when there is more than one independent variable, the general computational problem is to fit a line to a number of points. The conventional multivariate calibration approach involves a time consuming process of spectrum decomposition and reconstruction until a mathematically generated spectrum closely matches the measured spectrum (24,25). Full spectral classification techniques, PLS and PCR has shown less success in handling the low signal-to-noise ratio for complex mixtures. When applied to noisy data, they perform very poorly and performance of PLS is usually better that that of PCR (28). In such cases a more empirical approach such as ANN exhibits advantages. ANNs modeling technique has attracted increasing interest in recent years as a most promising candidate for classification and multivariate calibration problems.

The ANN approach employed pattern recognition on the entire low-resolution spectrum and modelled all peaks simultaneously. MLP models compute the output as a sum of non-linear transformations of linear combinations of the inputs. The number of weights and hidden units increases linearly with the number of inputs. The higher the dimensionality of the input space, the more training data sets are required. If the dimension of the input space is high the network uses almost all its resources to represent irrelevant portions of the input space. Careful feature selection and scaling of the inputs affects the complexity of the problem, as well as the selection of the best neural network model. In order to further reduce the amount of data and select the best ANN architecture, a pruning method was applied similarly to backward elimination in stepwise regression. Connections or units were eliminated during training based on sensitivity analysis, highest coefficient of multiple determination and minimal generalization error.

Each crystalline form presented to the sample produced a characteristic spectrum (Fig. 2). By presenting mixtures of polymorphs and mixtures with different ratios of tablet components to the system, a database of spectra was constructed. From this database, training and testing sets were generated.

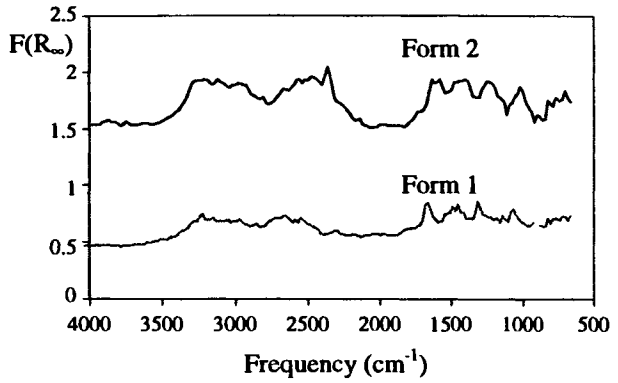

Fig. 2. DRIFT spectra of two ranitidine hydrochloride crystalline forms.

The training set was used to actually train the network and the test set was used to monitor overtraining the network. The error in mapping the training values decreased as the number of hidden neurones was increased. By increasing the number of hidden neurones, the ANN more closely followed the topology of the training group clusters on optimisation. However, above an optimum level, adding more hidden neurones resulted in tracing the training pattern too closely and the system was overtrained.

Another useful variation was to maintain the hidden layer but also allow direct connections from the input layer to the output layer. This would speed convergence if the relationships were simple. With direct connections each neurone had one additional weight as an input that allowed an additional degree of freedom when trying to minimise the training error

The testing error is not a good estimate of the generalisation error. One method for getting an unbiased estimate of the generalisation error is to present the ANN with a new, third set of data, that were not used at all during the training process. The relative error (ERR) (29) was used to compare generalisation ability of the models.

Using the spectral intensities directly as input data vectors had a weak correlation with structural properties. Reduction and transformation of the input data was necessary to enhance the ANN performance (30). Transformation of the variable also reduced the number of outliers, and variance among values. The original spectra were sampled between 650.16 and 3999.40 wavenumbers (cm^{-1}) and post processed to 1738 spectral intensities. These spectral data were further processed to smooth the noise in the spectrum. The 1738 reflectances were reduced into 173 averaged spectral values, each from ten consecutive wavenumbers (dB = 10). The system was trained to a satisfactory level with averaged spectral values as the inputs and sensitivity analysis was done on these inputs. Sensitivity reports show the sensitivity of the output variables, as a percentage, to the changes in the input variables. It shows the rate of change of the output with respect to the corresponding values of the inputs. The final ANNs were trained with inputs whose sensitivity was greater than 1%. The results of trained networks were compared and validated.

Polymorphs Mixture Assay

Direct connection between input neurones and output neurones improved the network performance. During training the coefficient of multiple determination increased from 0.277 for the model without direct connections between input and output layer to 0.998 for the model with direct connections and validation relative error decreased from 94.9 to 9.8% for Form 1 and from 28.2 to 2.9% for Form 2. The network was trained twice using 173 input and with 30 selected inputs on the basis of the sensitivity analysis. Results obtained with the selected inputs (sensitivity greater that 1%) and with three hidden neurons were not different from those using the 173 inputs. The level of Form 2 polymorph in mixtures of both crystal forms was varied from 1–100%. The results were in close agreements with the true values calculated from the masses of the polymorphs in the mixtures. At the same time, they were indicative of the good accuracy of the method. The mean ± S.D. recovery values were 96.61 and 99.32 for Form 1 and Form 2. Levels of Form 2 of 1% in the Form 1 were detected with the S.D. of 0.81. Linear regression analysis of theoretical composition against predicted values gave slopes of 1.019, intercept value of −0.378 and correlation coefficients of r = 0.998. The intercept was not significantly different from zero and slope was not different from unity indicating no method bias and absence of proportional error.

The minimum quantifiable level (MQL) was determined from multiple measurements (n = 5) of the spectral response of a single sample mixture containing 1% of Form 2 (31). Based upon a standard deviation of 0.81, a MQL of 7.9% and a detection limit (LD) of 2.4% (w/w) for the Form 2 was calculated.

The trained ANN successfully identified and quantified both forms in the mixtures used for the validation (Table 2). The mean recovery values were 102.14 and 98.09 of Form 1 and 107.00 and 104.17% of Form 2, for the ANN with 173 and 30 inputs respectively. Levels of 5 ± 0.54% of Form 2 were successfully detected with selected inputs.

Tablet Assay

The suggested method was applied to qualify and quantify the ranitidine hydrochloride crystal form present in tablet formulations, directly with minimal sample pretreatment. Since there was no need to extract the active ingredient from the dosage form, the identification was accomplished in the presence of excipients and additives (Fig. 3 and Fig. 4). ANN was trained with 173 (averaged reflectances) and with 35 input data

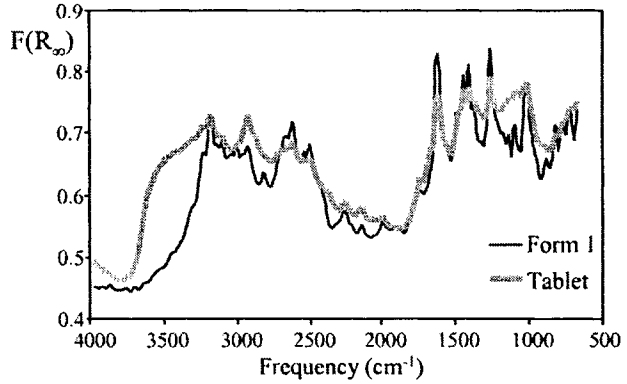

Fig. 3. DRIFT spectra of the ranitidine hydrochloride Form 1 and tablet powder.

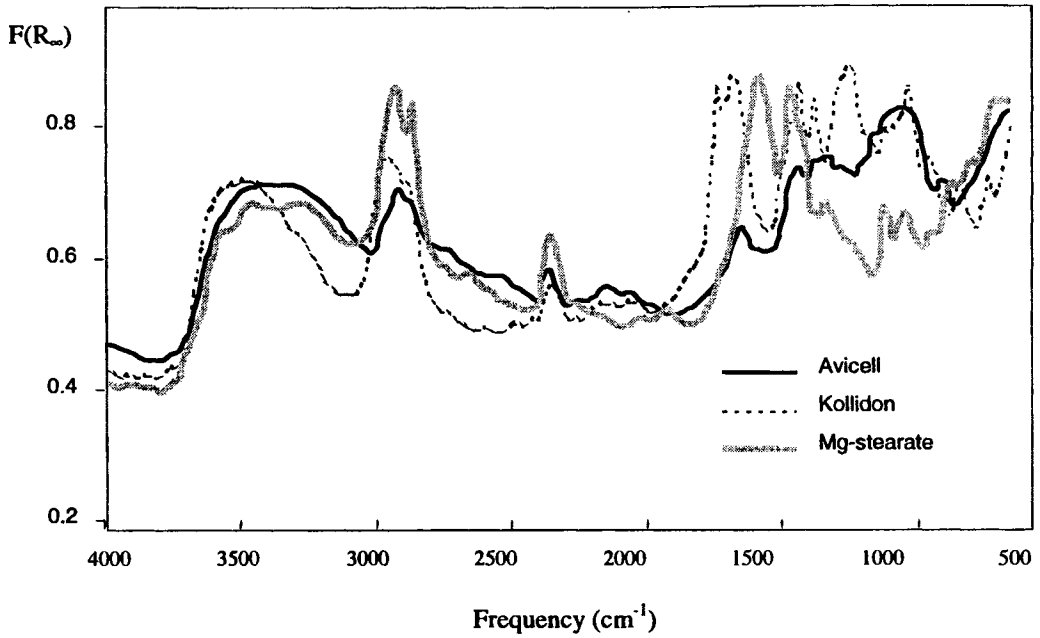

Fig. 4. DRIFT spectra of tablet excipients and additives.

(sensitivity greater than 1%) and with five output neurons one for each tablet ingredient. Direct connection between input and output neurons did not improve the network performance. This was an exceptional task to distinguish complex spectral patterns, identify and quantitate all tablet ingredients and the ranitidine hydrochloride crystal form present in tablet formulation.

The ranitidine hydrochloride tablet is a multicomponent tablet formulation with a significant overlap of the spectral pattern of ingredients. The ANN was trained to recognize specific patterns of constituents of the formulations from the overall spectral pattern. Better results were obtained for the network trained with 173 inputs. Less significant peaks increased the success of predictions over ANNs that contained only selected peaks (sensitivity > 1%), where peak selection based on selectivity reduced the importance of low intensity peaks. The test results showed that a sufficient number of hidden neurons was 3 to 5 to achieve good convergence on the training data (Table 3). The mean sum of squared error (SSE) was less than 0.03. The trained ANN successfully identified crystal form and quantified all ingredient from tablets despite interference from formulation matrix and suggested that the complex problem of quantifying drugs from mixtures having two or more components with overlapping spectra can be solved by DRIFT-ANN technique (Table 4).

Table 3. Effect of Number of Hidden Neurones in ANN Training for the Tablet Assay

Number of hidden neurones	2	3	4	5	6
Testing SSE	0.013	0.007	0.004	0.002	0.003
Training SSE	0.005	0.003	0.004	0.003	0.007
Training R^2	0.864	0.925	0.989	0.993	0.993

Table 4. Averaged Results (n = 10) of Predictions for Tablet Contents Obtained with ANN Having 5 Hidden Neurones and 1000 Training Cycles

	Avicell	Kollidon	Mg-stearate	Ranitidine-HCl Form 1	Ranitidine-HCl Form 2
Predicted (%)	41.09	4.03	1.24	54.11	−0.69
Expected (%)[14]	40.20	2.70	0.70	56.40	0.00
SD	6.77	0.69	1.88	7.32	1.69
RSD (%)	16.47	17.08	151.07	13.52	*
ERR	0.02	0.49	0.78	0.04	*

* Could not be calculated.

CONCLUSIONS

The results of this research have shown the benefits of the neural network approach in analysing spectral data. The simplicity of this method, together with the satisfactory recoveries and good selectivity, shows the potential of DRIFT-ANN to analyse polymorphic purity of crystalline ranitidine-HCl. The proposed method is not only simple and direct but it also provides information about the polymorphic form of crystalline ranitidine hydrochloride as a bulk drug and as an active ingredient from tablet formulation. The tablet formulation was analysed after minimal sample pretreatment and there was no need to extract the active ingredient from the excipients in the formulation when potentially valuable information about the solid state of the drug could be lost. For analysis of a commercial product the ratio of excipient to active drug substance should be constant. A further step would be to use calibration samples limited to varying only the Form 1/Form 2 concentration ratio, to achieve greater accuracy and to develop a more precise assay.

As shown, simultaneous identification and quantification of all tablet ingredients in the formulation was possible. The

simultaneous spectral determination and quantification of all ingredients has not yet been reported in literature.

Potential applications of the method are in monitoring polymorphic transitions or changes in the degree of crystallinity in the solid state induced during the pharmaceutical processing. These changes can be detected and even quantified. Furthermore it might be applied for the simultaneous identification of more than one active ingredient in the formulation.

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