PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : G01N 21/65, G01J 3/44	A1	(11) International Publication Number: WO 00/40950
		(43) International Publication Date: 13 July 2000 (13.07.00)

(21) International Application Number: PCT/SE99/02473

(22) International Filing Date: 22 December 1999 (22.12.99)

(30) Priority Data:
9900030-9 5 January 1999 (05.01.99) SE

(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

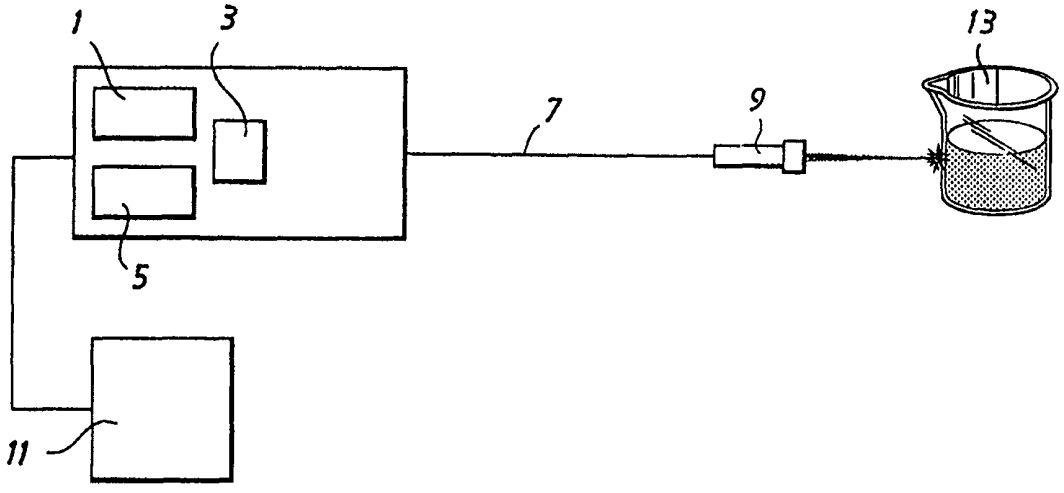
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: JOSEFSON, Mats [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). LANGKILDE, Frans [DK/DK]; Astra Hässle AB, S-431 83 Mölndal (SE). SVENSSON, Olof [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE).

(74) Agent: ASTRAZENECA AB; Intellectual Property, Patents, S-151 85 Södertälje (SE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: REACTION MONITORING



(57) Abstract

This invention relates to a method for monitoring a chemical reaction of pharmaceutical relevance, comprising the steps of: consecutively obtaining Raman spectrum samples of a solution of chemical constituents contained within a reaction vessel, by irradiating, with substantially monochromatic radiation, said solution and detecting the scattered radiation; processing said Raman spectrum samples by means of a multivariate data analysis (MVDA) for consecutively generating at least a first main component related to a latent variable indicative of the progress of the reaction wherein the multivariate data analysis is independent from calibration using reference measurements of objects having a known composition; and determining the extent of the chemical reaction on basis of said at least a first main component and optionally on basis of additionally one or more main components generated from one or more previously run reactions of the same kind.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

REACTION MONITORING

Technical field

The present invention relates to a method for monitoring a chemical reaction of pharmaceutical relevance.

Technical background

The manufacture of a pharmaceutical substance often involves a reaction process step, such as a synthesis, wherein original constituents react with each other after being mixed in a reaction vessel. During the reaction process, while the desired substance is formed, the original reactants are consumed. The reaction process step of the manufacturing process is a batch process and it is economically desirable to process a batch as fast as possible. Further, undesired by-products can develop in the reaction vessel if the manufactured substance is left in the reaction vessel after the reaction is completed. Therefore, it is desired to know when the reaction is completed.

A conventional method for determining when the reaction is completed is to measure the concentration of the substance produced. This is often combined with a measurement of the concentration of one or more of the original constituents. By experience it is known within what ranges the concentrations should arrive.

Different methods have been applied in order to measure the concentration of the substance produced and/or the concentration of one or more of the original constituents. Prior art methods include those based on spectroscopy, such as NIR (Near Infra-Red), MIR (Mid Infra-Red) and ATR (Attenuated Total Reflectance) in combination, or Raman spectroscopy. The resulting spectral information is related to said concentrations. The result is determined by measuring peak height and/or peak area for one or more peaks at significant wavelengths, and comparing the measurements to relevant references.

The above described prior art methods of determining the point of completion of the reaction involves a time delay which is added to the mean time required for completing a specific reaction.This is done in order to ascertain that the reaction is mostly completed

when the measurement is performed.. Thereby the variance of the reaction time period is taken into account. The addition of the time delay is performed in order to avoid making excessive measurements.

In order to reduce the time delay the above mentioned spectroscopic methods have been developed to enable continuous monitoring of the reaction process. Known methods include Raman spectroscopy wherein a single wavelength is irradiated towards the solution, which scatters a spectrum, called Raman spectrum. Raman is advantageous due to the relatively narrow peaks of the resulting Raman spectrum, which makes it easier to distinguish an individual peak related to a specific substance of the solution. The apparatus for performing such Raman monitoring is sufficiently fast in order to produce relevant spectra serving the purpose of the monitoring.

However, the evaluation of the spectra in order to determine the concentration of a substance still relies on a determination of the peak heights or areas. This in turn requires a relevant calibration of the spectra and a comparison of the calibrated spectra with a relevant reference spectrum. To enhance the calibration, multivariate methods, such as partial least squares regression, may be employed.

An example of a prior art method performing such an evaluation, though applied for quantitatively monitoring constituents of a chemical composition produced in a typical process, is disclosed in US-5 638 172.

Further, the prior art Raman monitoring suffers from the problem of distinguishing a specific peak when constituents of the solution cause several peaks at almost the same wavelength. This is common in reaction solutions of pharmaceutical relevance.

Summary of the invention

One object of this invention is to provide a method for monitoring a reaction, which method provides for an accurate determination of the extent of the reaction.

Another object of this invention is to provide a method for monitoring a reaction, which method can be used when several overlapping peaks occur.

Yet another object of this invention is to provide a method for monitoring a reaction, which method does not require a separate determination of a reference sample or spectrum.

The objects are achieved by a method for monitoring a chemical reaction of pharmaceutical relevance, in accordance with the present invention. The method comprises the steps of:

- consecutively obtaining Raman spectrum samples of a solution of chemical constituents contained within a reaction vessel, by irradiating, with substantially monochromatic radiation, said solution and detecting the scattered radiation;

-processing said Raman spectrum samples by means of a multivariate data analysis (MVDA) for consecutively generating at least a first main component related to a latent variable indicative of the progress of the reaction wherein the multivariate data analysis is independent from calibration using reference measurements of objects having a known composition; and

- determining the extent of the chemical reaction on basis of said at least a first main component and optionally on basis of additionally one or more main components generated from one or more previously run reactions of the same kind.

Since the present invention provides for continuous monitoring of the reaction and obtaining of consecutive Raman spectra, it is possible, by applying the MVDA, to easily follow the progress of the reaction. The changes of the conditions within the reaction vessel are efficiently detected by the MVDA and mirrored thereby in a single or a few main components. The main component(s) is then processed in order to determine how the changes proceed with time. The MVDA generates a result that is relative to constituents and physical properties internal to the reaction, and, consequently, no particular reference is needed.

An embodiment of the present invention is characteristic for the invention in that no calibration using reference measurements of objects having a known composition is needed. Principally, the only response variable used, if any, is the reaction time, or an amount proportional to the reaction time.

Further objects and advantages of the present invention will be discussed below by means of exemplary embodiments.

Brief description of the drawings

Fig. 1 illustrates schematically an arrangement for monitoring a reaction, such as a synthesis;
Fig. 2 illustrates Raman spectra obtained at different points of a first reaction;
Fig. 3 is a scores plot related to Fig. 2;
Fig. 4 is a loadings plot related to Fig. 2;
Fig. 5 illustrates Raman spectra of different compounds related to a second reaction;
Fig. 6 illustrates Raman spectra obtained at different points of the second reaction;
Fig. 7 is a scores plot related to Fig. 6;
Fig. 8 is a scores plot related to Fig. 6; and
Fig. 9 shows diagrams of a spectrum difference and loadings respectively.

Description of embodiments

In Fig. 1 an example of an arrangement for reaction monitoring is shown. The arrangement comprises a Raman spectrometer equipped with a charge coupled device (CCD) detector 1, a holographic transmission grating 3, a laser 5, an optical fibre 7, and an optical interface 9; and an evaluation device 11. Reference character 13 denotes a reaction vessel, the contents of which is monitored. The vessel 13 has a wall of glass through which the monitoring may be performed.

In the following a preferred embodiment of the monitoring method of this invention will be described.
In a preferred embodiment of the method according to the present invention, the reaction vessel contains a solution comprising different constituents, such as reactants, catalysts etc., which are required for producing a desired substance of pharmaceutical relevance, below simply referred to as the substance. The solution is generally stirred, subjected to a particular temperature, etc., in order to provide appropriate conditions for the reaction to take place.

The optical interface 9 is appropriately positioned either at a distance, determined by the focus, from the outer surface of the glass wall of the vessel 13 or within the vessel 13 lowered into the solution. Monochromatic radiation is irradiated by the laser 5 and led through the optical fibre 7 to the optical interface 9 coupling the radiation into the solution.

The solution scatters a spectrum, which is caught by the optical interface and led by the optical fibre to the CCD detector. The optical fibre may be appropriately constituted in any appropriate way as will be known to one skilled in the art. For example, said optical fibre could be constituted by a bundle of two or several fibres, one or more used for guiding the monochromatic radiation to the vessel and one or more other fibres used for guiding the scattered radiation back through the holographic transmission grating 3 to the CCD. The Raman spectrum thus sampled by means of the CCD detector is then processed by the evaluation device, which may be a general purpose computer executing a proper set of instructions for performing the processing or a special purpose computer specifically structured and/or programmed for performing the processing.

The processing of the CCD detector output, which in the following is referred to as the spectrum sample, aims at monitoring the reaction in order to accurately determine the extent of the reaction. For example, the determination of the extent of the reaction may be a determination of how far the reaction has proceeded or, ultimately, of the point of time when the reaction is finished. The processing comprises the main steps of:

a) obtaining a new spectrum sample;
b) applying chemometric methods to the spectrum sample in combination with previous spectrum samples for performing an MVDA, thus generating main components related to a latent variable indicative of the progress of the reaction;
c) using one or more main components of the analysis result for determining the extent of the reaction.

The steps are repeated during the whole reaction process. As will be described below, step c) comprises several alternative determinations which may be optionally combined.

The above defined step a) is simply performed by reading the output of the CCD detector. The output consists of a number of values, here labelled spectrum values, at different wavelengths.

In step b) an MVDA (multivariate data analysis) is performed. The prior art methods of monitoring a chemical reaction are based on the determination of peak height or area changes of one or more peaks related to a specific substance of the solution. For example, in prior art, the reaction may be determined to be finished when the peak height/area is no longer changing or when it has reached a predetermined value. Such measurements are

dependent on momentary conditions, such as laser intensity, changing from one sample to the other. Hence, the prior art methods require the spectrum sample to be calibrated against an explicitly known internal or external reference spectrum sample, in order to ascertain the peak values of specific peaks of the Raman spectrum. Alternatively, the calibration is made with a different independent analytical result for a similar sample. The described requirements make the prior art methods complex. In accordance to the present invention multivariate data analysis has been inventively used as a means for eliminating the need for such references.

There are a number of multivariate data analysis methods to choose from. However, in this preferred embodiment either principal component analysis (PCA) or partial least squares (PLS) is employed depending on the circumstances. Both PCA and PLS are projection methods which project points in a multidimensional space onto a space having fewer dimensions, preferably one or a few. The PCA projection is expressed in matrix form as:

$$\mathbf{X} = \mathbf{TP'} + \mathbf{E} = \mathbf{t}_1\mathbf{p}'_1 + \mathbf{t}_2\mathbf{p}'_2 + \ldots + \mathbf{t}_A\mathbf{p}'_A + \mathbf{E} \quad (1)$$

The spectrum samples are placed as rows in matrix X, having n rows and k columns. Thus, each row represents a spectrum sample and each column represents a single wavelength. The matrix X is approximated in terms of the product of two smaller matrices T and P'. These matrices capture the essential patterns of X. E is a noise matrix. If, for example, X is a 20x10 matrix, i.e. 20 spectrum samples and 10 wavelengths, then T is a 20xA matrix and P' is a Ax10 matrix. A represents the number of principal components resulting from the PCA. Mathematically what is done when decomposing the matrix X is to project a 10-dimensional space on an A-dimensional space, and the determination of the matrices T and P' is based on minimising the matrix E by means of least squares calculations. Thus, the Principal Component model (PC-model) is a plane that is spanned by the A rows of the matrix P'. Each principal component consists of two vectors, the score vector t and the loading vector p. The score vector t contains a score value for each spectrum sample, and this score value tells how the spectrum sample is related to the other spectrum samples in that particular principal component. The loading vector tells which spectral features in the original spectrum samples that are captured by the principal component studied. Generally, an appropriate number A of principal components is determined by means of e.g. cross validation. In this embodiment one or a few principal components are determined. As will be apparent below, the first principal components capture the largest variation in the matrix

X, which variation is closely related to the reaction process. Consequently, the first few principal components are usable for the desirable monitoring purposes of this invention.

PLS has been used as an alternative to the PCA. PLS is a projection and regression method involving the X matrix and a y vector (or matrix). In this embodiment the time that has lapsed from the start of the reaction is inventively used as y in connection with Raman spectroscopy. The PLS method works in a similar manner as PCA. A difference is that while PCA captures as much of the variation of X as possible in each component, PLS calculates components that both capture the variation of X and correlates to the variation in y.

The PLS method is to be further discussed with reference to the below equations 2-5. The loading weight vector w_a, where a denotes PLS component number a, shows the spectral features in X that correlate with y, calculated as in equation 2. The score vector t_a, which can be interpreted in the same way as in PCA, is calculated as in equation 3. A scalar coefficient c_a is then calculated (eqn. 4) which in turn together with t_a constitutes an equation for y, where f is a residual with non-modelled variation in y (eqn. 5).

$$\mathbf{w}_a = \frac{\mathbf{X}'_{a-1}\mathbf{y}_{a-1}}{\left\|\mathbf{X}'_{a-1}\mathbf{y}_{a-1}\right\|} \qquad (2)$$

$$\mathbf{t}_a = \mathbf{X}_{a-1}\mathbf{w}_a \qquad (3)$$

$$c_a = \frac{\mathbf{t}'_a\mathbf{y}_{a-1}}{\mathbf{t}'_a\mathbf{t}_a} \qquad (4)$$

$$\mathbf{y} = c_1\mathbf{t}_1 + c_2\mathbf{t}_2 + \ldots + c_A\mathbf{t}_A + \mathbf{f} \qquad (5)$$

The number of PLS components to be used is often selected with cross validation and/or independent test sample sets. As in the PCA case, we are here mainly interested in the first few PLS components.

In the following "main components" will be used as a common term for the principal components of the PCA and the similar components of the PLS or any other suitable multivariate data analysis.

As a preparation for the PCA or the PLS a standard normal variate (SNV) or related transform can be applied to the spectrum sample, as follows.

The Standard Normal Variate (SNV) transformation is a known technique used to reduce additive and multiplicative effects in spectra. The transformation is done for each spectrum individually according to the following equation:

$$x_{i,SNV} = \frac{(x_i - \bar{x})}{\sqrt{\frac{\sum_{i=1}^{k}(x_i - \bar{x})^2}{k-1}}} \qquad (6)$$

where $x_{i,SNV}$ is the transformed Raman intensity for wavenumber x_i, and $\bar{x}$ is the mean intensity of all the k wavenumbers in the spectrum. Equation 6 shall be repeated for all k wavenumbers in the spectrum.

One advantage with SNV is that there is no need to store any values for future transformations, as is the case with multiplicative signal correction (MSC).

The main components thus generated are related to latent variables of the spectrum samples, which latent variables are indicative of the progress of the reaction.

In step c) one or more of several different determinations are performed, basically by means of the first main component of the PCA or the PLS. Initially, an indication value inherent in said first main component is determined. This indication value is indicative of the extent of the reaction and may for example represent the concentration of a compound. What is actually used as the indication value is a score value of the score vector of the first main component. In order to secure that changes of score values of said score vector are related to the reaction progress, and not to, for example, changes of temperature, as occasionally being the case, the corresponding loading vector is evaluated in parallel.

The indication value, or, generally, a vector of indication values, i.e. the score vector, is then used in further one or more different ways, dependent on what evaluation is requested.

One way to proceed is to determine if the progress of the reaction follows a typical schedule by monitoring the pathway of the score trace generated by consecutive MVDAs. This score trace is compared with a predetermined pathway, for example, determined as a mean of several pathways generated during previously run reactions. If the present pathway deviates excessively from the predetermined pathway, then it is determined that reaction is

not proceeding typically. By means of this determination it is possible to stop erroneous reactions at an early stage, thereby saving time of manufacture.

Another way to proceed is to compare the present score vector with a predetermined set of score vectors covering the whole reaction process from the beginning to the end. The reaction extent represented by the predetermined score vector causing the smallest difference to the present score vector is taken as the extent which the present reaction has reached.

Yet another way to proceed is to use the score vector to determine when the reaction is finished. This is done by determining a rate of change of consecutive indication values, i.e. score values. The rate of change is related to the extent of the reaction in that the rate is zero when an equilibrium is reached, which of course is the case when the reaction is finished. Alternatively, a stop limit could be defined. When the rate of change decreases below said stop limit it is determined that the reaction is finished. At least if PCA is employed, also the score values could be used as indication values for determining the rate of change. In this way it is instantly and accurately determined that the reaction is finished, thereby saving time of manufacture.

In order to illustrate how the present method is actually performed a simple example is now to be described. For reasons of simplicity and clarity, this example does not pertain to a pharmaceutically relevant reaction, since such a reaction is most often more complex. Rather, it pertains to the hydrolysis of ethyl acetate, using water as solvent. The reaction scheme of this hydrolysis is: $CH_3COOCH_2CH_3 + H_2O \rightarrow CH_3COOH + CH_3CH_2OH$

In Fig. 2 four different diagrams of the Raman intensity versus wavenumber are shown for the hydrolysis at four different points of time during the reaction process. Arrows show the development of the Raman intensity, or peak height, at four different wavenumbers. It can be seen that the height of three of the peaks decreases with time while the height of one of the peaks increases with time. Decreasing peak heights represent the ethyl acetate and increasing peak heights represent both ethanol and acetic acid, since their peaks overlap each other.

In Fig. 3 the scores of the first main component, i.e. principal component, (PC1) are plotted for PCAs performed on Raman spectra obtained from the hydrolysis at different points. It is evident from the plot how the reaction proceeds. Fig. 4 shows a corresponding loading

plot determined on the complete X matrix. The loading plot illustrates spectral features responsible for the pattern of the score plot. The score plot is usable for determining the extent of the reaction as described above. For example, it is evident from the plot that at the end of the reaction the rate of change approaches zero.

Above the present invention is exemplified by means of a simple reaction. However, the full usefulness of the invention is obtained in a more complex case in which the peaks overlap, such as for a typical reaction of pharmaceutical relevance. In order to illustrate said usefulness another example will now be briefly described. The reaction in question is involved in the manufacture of metoprolol base. Metoprolol is the result of a reaction between Meepb, short for 1-(2,3-epoxypropoxy)-4-(2-methoxyethyl)benzene (or p-methoxyethyl-epoxypropoxybenzene), and Isopropylamine. The reaction takes place in an Isopropanol solvent. The reaction scheme is: $C_{12}H_{16}O_3 + C_3H_9N \rightarrow C_{15}H_{25}NO_3$.

In Fig. 5 the Raman spectra for the four compounds of the solution, during the ongoing reaction all present at the same time, are shown. It is to be noted that particularly the spectra of the Meepb and the Metoprolol base are very similar, and that the spectra of the other compounds substantially overlap with the Metoprolol base spectrum. This makes it extremely difficult to use the prior art methods for monitoring the reaction. As is illustrated in Fig. 6, the overlapping peaks result in a Raman spectrum having few and weak peaks changing during the progress of the reaction.

However, by employing the present invention it is possible to manage even this difficult situation. By applying MVDA, and more particularly PCA, to consecutive spectrum samples the score plot of Fig. 7 is obtained. Referring to the above description of the simple case, it is now clearly evident that the score plot is usable for reaction monitoring purposes, despite the likeness between the spectra of Meebp and Metoprolol and the high degree of peak overlap. Fig. 8 shows a score plot of a PLS-analysis, to be compared to the PCA score plot in Fig. 7.

The upper diagram of Fig. 9 illustrates the difference between a first spectrum sampled at the beginning of the reaction and a second spectrum sampled at the end of the reaction. The lower diagram of Fig. 9 illustrates a plot of the loadings of the first main component (PC1). The plot is based on the full X matrix. Note the similarity, which confirms that the loadings of the first component represent the spectral changes taking place during the reaction process.

Above the method is described for monitoring a single reaction. However, in addition, the present method, in contrary to prior art methods, enables monitoring of a plurality of reaction steps or reactions consecutively performed in one and the same reaction vessel. This is possible because of the capability to more or less instantly and accurately determine the extent of the reaction and, as a special case thereof, the point of completion.

Further, in another embodiment, the method of the present invention involves feedback control of the reaction. The feedback control is dependent on the results obtained by the MVDA. Thus, the PCA or PLS components are further evaluated in order to obtain knowledge of whether the chemical reaction proceeds as required or some parameter should be changed in order for it to proceed as required.

Consequently, if an excess reaction deviation is discovered, it is determined, on basis of said further evaluation of the PCA or PLS components, what parameters of the reaction should be changed in order to eliminate or decrease the deviation. More specifically, for example, the feedback control can be based on changes in scores and loadings which are in response to a change in temperature. The determination of whether the temperature has changed is based on, for example, the derivative of the scores plot for the first few PCA or PLS components. The thermostat environment surrounding the reaction vessel is then adjusted accordingly.

Above a preferred embodiment of the method according to the present invention has been described. This should be seen as merely a non-limiting example. Many modifications will be possible within the scope of the invention as defined by the claims.

It is here to be noted that the above described arrangement employed for performing the method of this invention may be optionally configured in order to adapt it to different environments, requirements of manufacture, etc., which will be apparent to those skilled in the art. Thus, for example, various gratings, detectors, etc. may be employed.

CLAIMS

1. A method for monitoring a chemical reaction of pharmaceutical relevance, c h a r a c - t e r i s e d in the steps of:

- consecutively obtaining Raman spectrum samples of a solution of chemical constituents contained within a reaction vessel, by irradiating, with substantially monochromatic radiation, said solution and detecting the scattered radiation;

- processing said Raman spectrum samples by means of a multivariate data analysis (MVDA) for consecutively generating at least a first main component related to a latent variable indicative of the progress of the reaction, wherein the multivariate data analysis is independent from calibration using reference measurements of objects having a known composition, and

- determining the extent of the chemical reaction on basis of said at least a first main component and optionally on basis of additionally one or more main components generated from one or more previously run reactions of the same kind.

2. A method as claimed in claim 1, c h a r a c t e r i s e d in that the step of determining the extent of the chemical reaction comprises the steps of:

- determining an indication value, indicative of said extent of said chemical reaction, inherent in said main component; and

- comparing said indication value with a set of predetermined limits for the indication values or relations between indication values characteristic of the reaction at different extents of said chemical reaction.

3. A method as claimed in anyone of the preceding claims, c h a r a c t e r i s e d in that the step of determining the extent of the chemical reaction comprises the steps of:

- determining successive indication values, indicative of said extent of said chemical reaction, inherent in said main component;

- determining a rate of change of said successive indication values; and

- determining that the reaction is finished when said rate decreases below a predetermined limit.

4. A method as claimed in anyone of the preceding claims, c h a r a c t e r i s e d in that the step of determining the extent of the chemical reaction comprises the steps of:

- determining successive indication values, indicative of said extent of said chemical reaction, inherent in said main component;

- determining a pathway followed by the successive indication values; and

- determining whether the reaction proceeds typically by comparing said pathway to a typical pathway.

5. A method as claimed in anyone of claims 2 to 4, c h a r a c t e r i s e d in that said indication value is a score value.

6. A method as claimed in anyone of the preceding claims, c h a r a c t e r i s e d in that the multivariate data analysis comprises a principal component analysis (PCA).

7. A method as claimed in anyone of claims 1 to 5, c h a r a c t e r i s e d in that the multivariate data analysis comprises a partial least squares (PLS) regression.

8. A method as claimed in anyone of the preceding claims, c h a r a c t e r i s e d in that the reaction is a metoprolol synthesis.

9. A method as claimed in anyone of the preceding claims, c h a r a c t e r i s e d in monitoring a series of two or more reaction steps consecutively performed in one and the same reaction vessel.

10. A method as claimed in anyone of the preceeding claims, c h a r a c t e r i s e d in the further step of controlling the reaction by means of feedback control based on evaluations of said at least a first main component.

Fig. 1

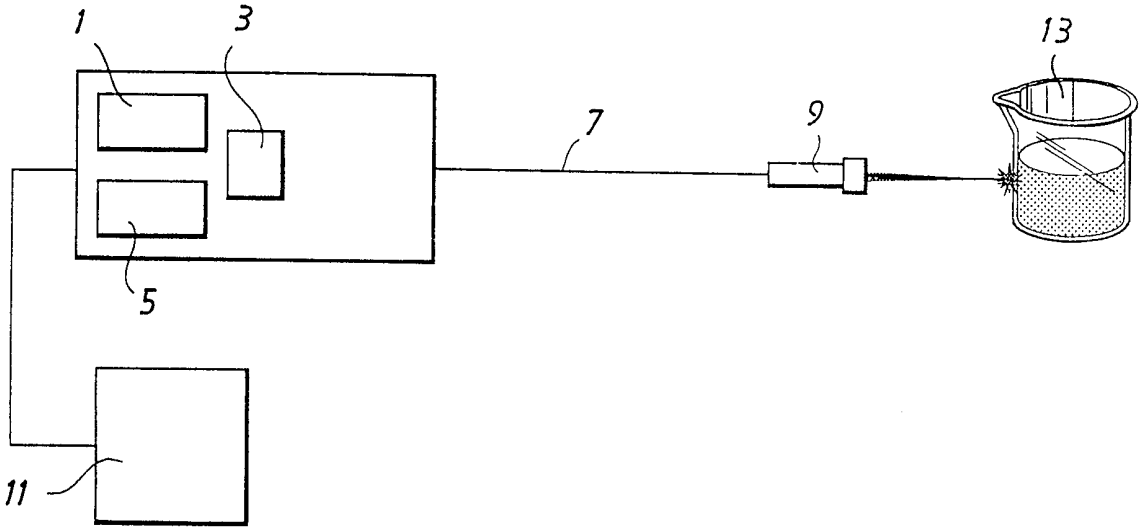

1
3
13
7
9
5
11

Fig. 2

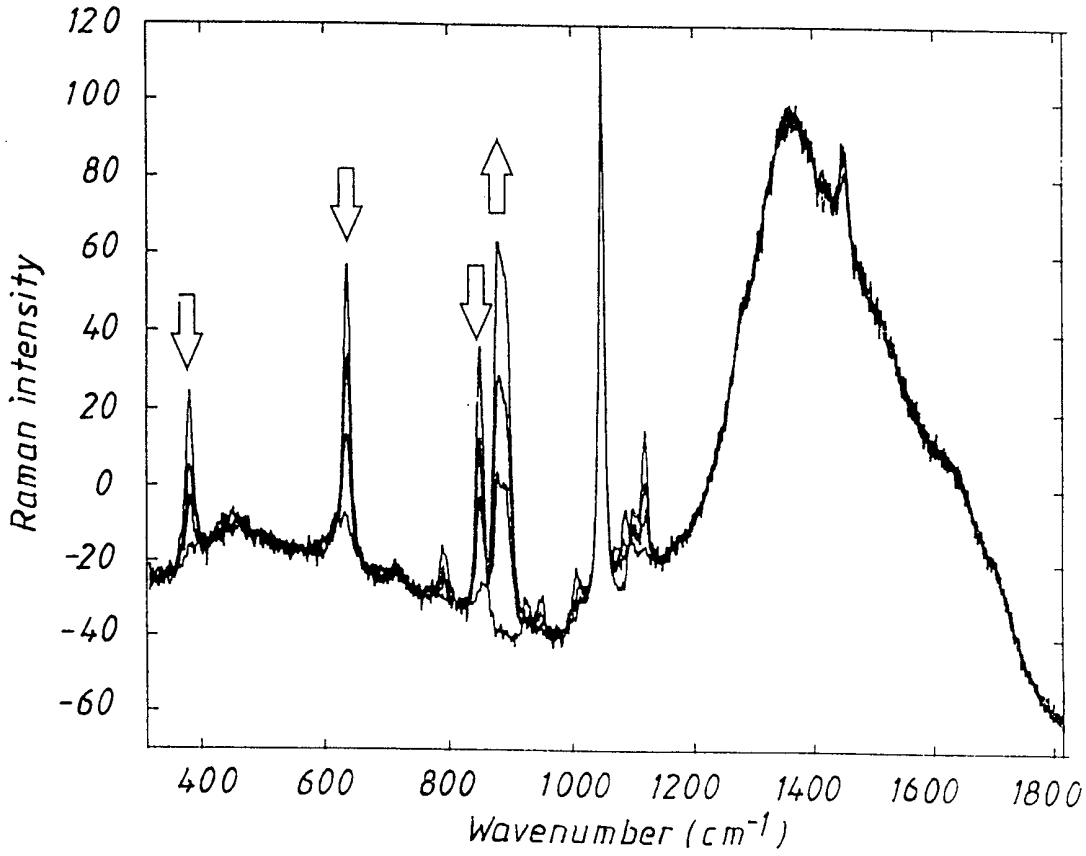

120
100
80
60
40
20
0
-20
-40
-60
Raman intensity
400
600
800
1000
1200
1400
1600
1800
Wavenumber (cm-1)

Fig. 3

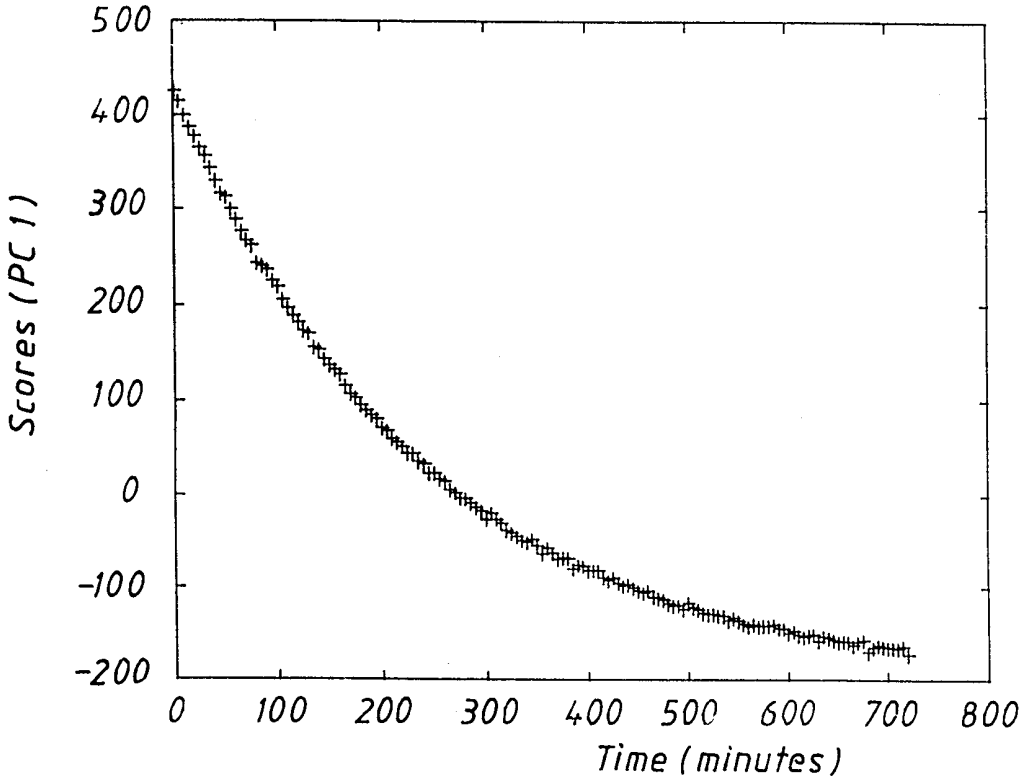

500
400
300
200
100
0
-100
-200
Scores (PC 1)
0
100
200
300
400
500
600
700
800
Time (minutes)

Fig. 4

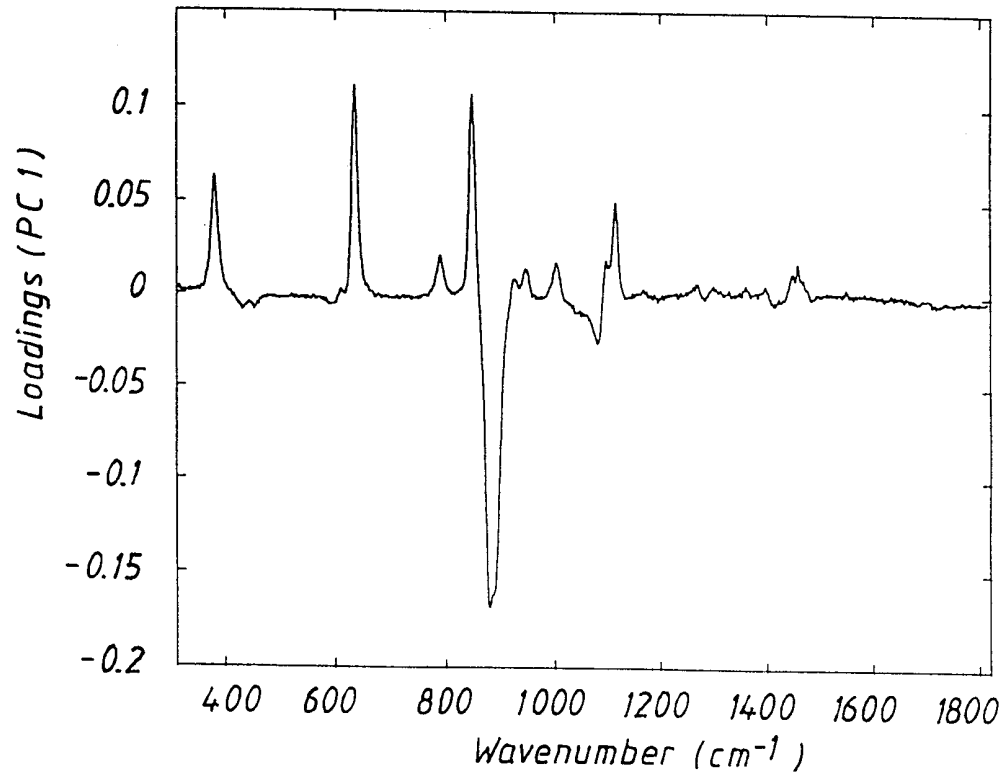

0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
Loadings (PC 1)
400
600
800
1000
1200
1400
1600
1800
Wavenumber (cm-1)

Fig. 5

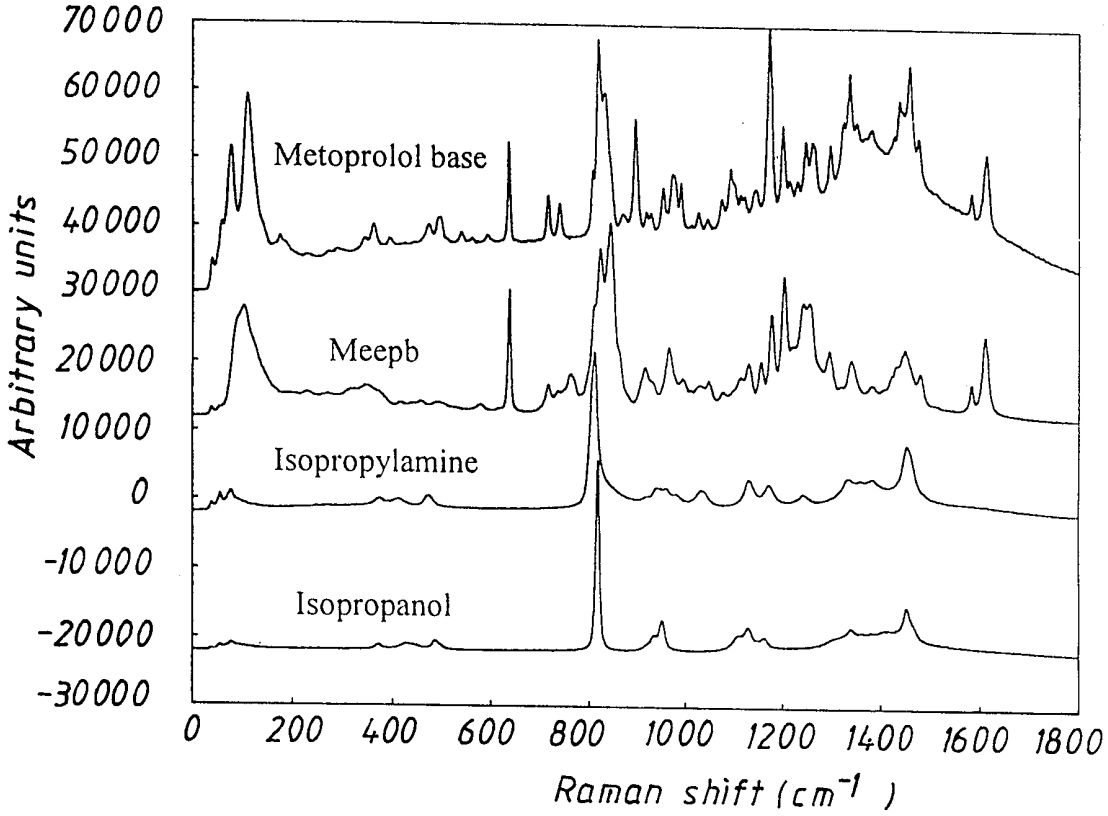

70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
-30000
Arbitrary units
Metoprolol base
Meepb
Isopropylamine
Isopropanol
0
200
400
600
800
1000
1200
1400
1600
1800
Raman shift (cm-1)

Fig. 6

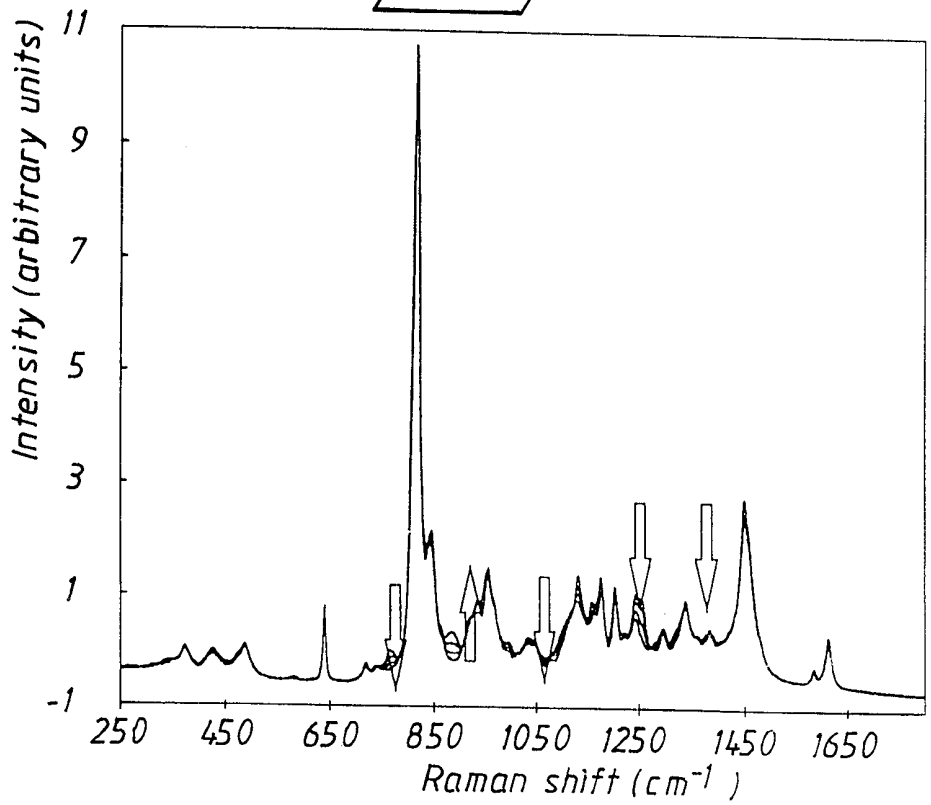

11
9
7
5
3
1
-1
Intensity (arbitrary units)
250
450
650
850
1050
1250
1450
1650
Raman shift (cm-1)

Fig. 7

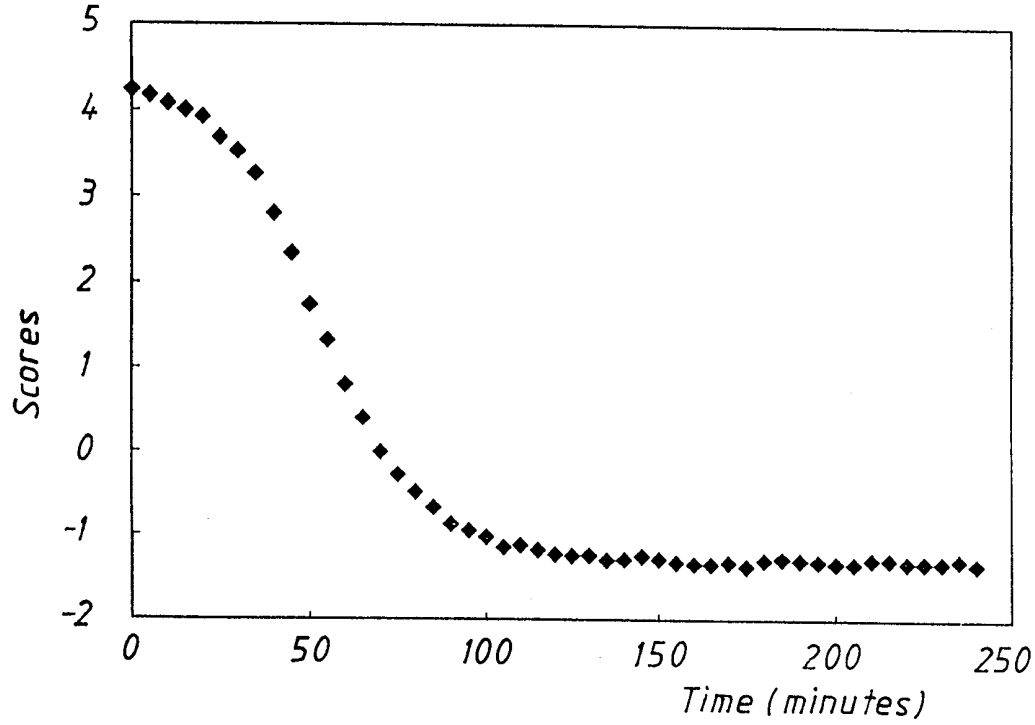

5
4
3
2
1
0
-1
-2
Scores
0
50
100
150
200
250
Time (minutes)

Fig. 8

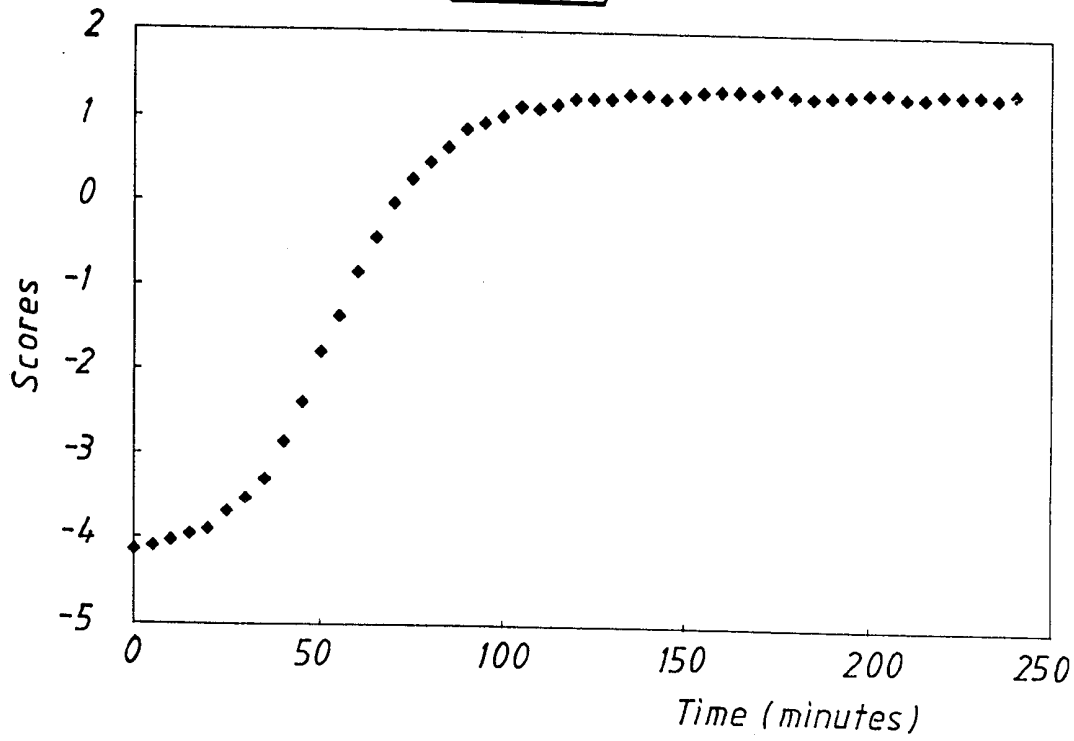
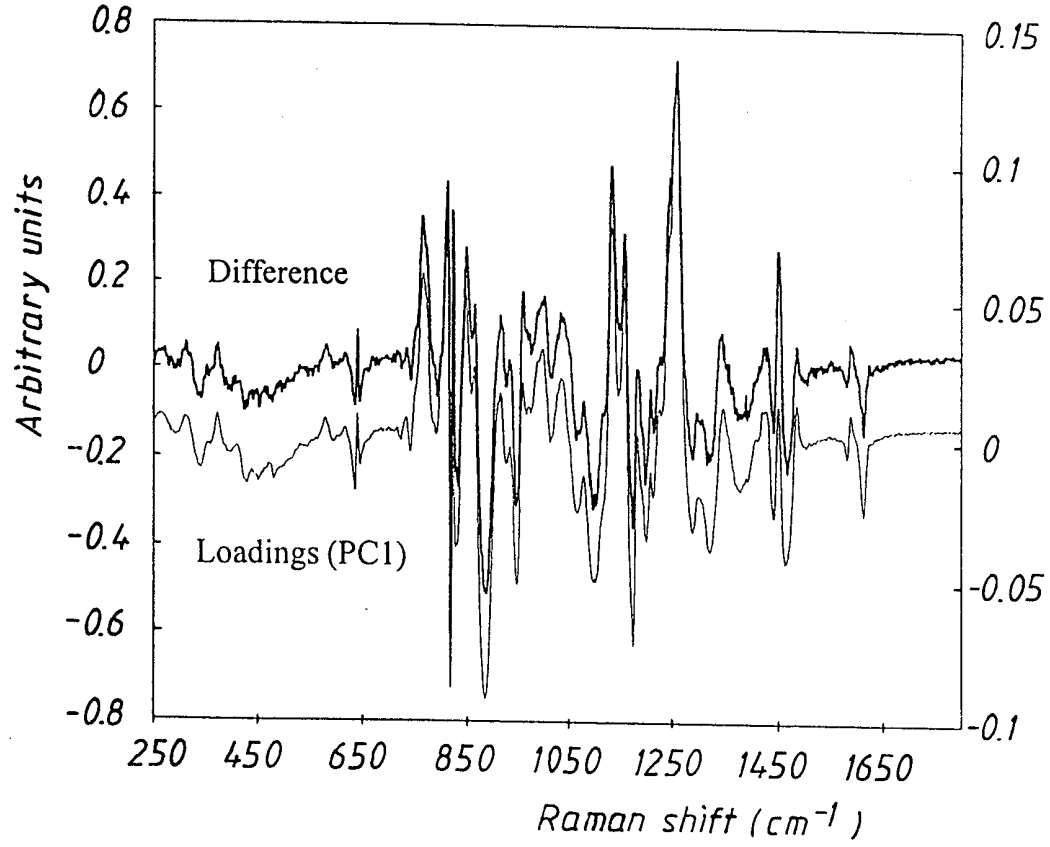

2
1
0
-1
-2
-3
-4
-5
Scores
0
50
100
150
200
250
Time (minutes)

Fig. 4


0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
Arbitrary units
Difference
Loadings (PC1)
0.15
0.1
0.05
0
-0.05
-0.1
250
450
650
850
1050
1250
1450
1650
Raman shift (cm-1)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02473

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: G01N 21/65, G01J 3/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: G01N, G01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC,WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5596196 A (J.B.COOPER ET AL), 21 January 1997 (21.01.97), column 2, line 64 - column 5, line 12; column 7, line 49 - line 61, figure 3, see example 3	1-10
X	US 5638172 A (D.C.ALSMEYER ET AL), 10 June 1997 (10.06.97), column 8, line 24 - column 10, line 61; column 14, line 6 - line 26; column 19, line 29 - line 35	1-10
A	US 5610836 A (D.C.ALSMEYER ET AL), 11 March 1997 (11.03.97), column 1, line 60 - column 2, line 5; column 3, line 1 - line 67; column 4, line 16 - column 7, line 10, see example 1	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 April 2000	12-05-2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Jonas Andersson /itw Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02473

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	DE 19810917 A1 (BüHLER AG), 16 Sept 1999 (16.09.99) --	1-10
A	EP 0751388 A2 (KYOTO DAI-ICHI KAGAKU CO.LTD.), 2 January 1997 (02.01.97) --	1-10
A	WO 9610009 A1 (EXXON CHEMICAL PATENTS INC.), 4 April 1996 (04.04.96) --	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 99/02473

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5596196 A	21/01/97	NONE	
US 5638172 A	10/06/97	US 5652653 A	29/07/97
		AU 682118 B	18/09/97
		AU 2588295 A	21/12/95
		BR 9507781 A	19/08/97
		CA 2190627 A	07/12/95
		CN 1149334 A	07/05/97
		CZ 9603451 A	18/02/98
		EP 0760938 A,B	12/03/97
		HU 76508 A	29/09/97
		HU 9603124 D	00/00/00
		JP 10501333 T	03/02/98
		PL 317399 A	14/04/97
		SK 136396 A	06/08/97
		US 5455673 A	03/10/95
		WO 9533189 A	07/12/95
		ZA 9504309 A	14/08/96
US 5610836 A	11/03/97	AU 2245997 A	22/08/97
		CA 2243677 A	07/08/97
		CN 1214767 A	21/04/99
		EP 0877923 A	18/11/98
		WO 9728436 A	07/08/97
DE 19810917 A1	16/09/99	WO 9947909 A	23/09/99
EP 0751388 A2	02/01/97	CN 1157919 A	27/08/97
		JP 9015155 A	17/01/97
		US 5796476 A	18/08/98
		JP 9079982 A	28/03/97
WO 9610009 A1	04/04/96	AU 3831195 A	19/04/96