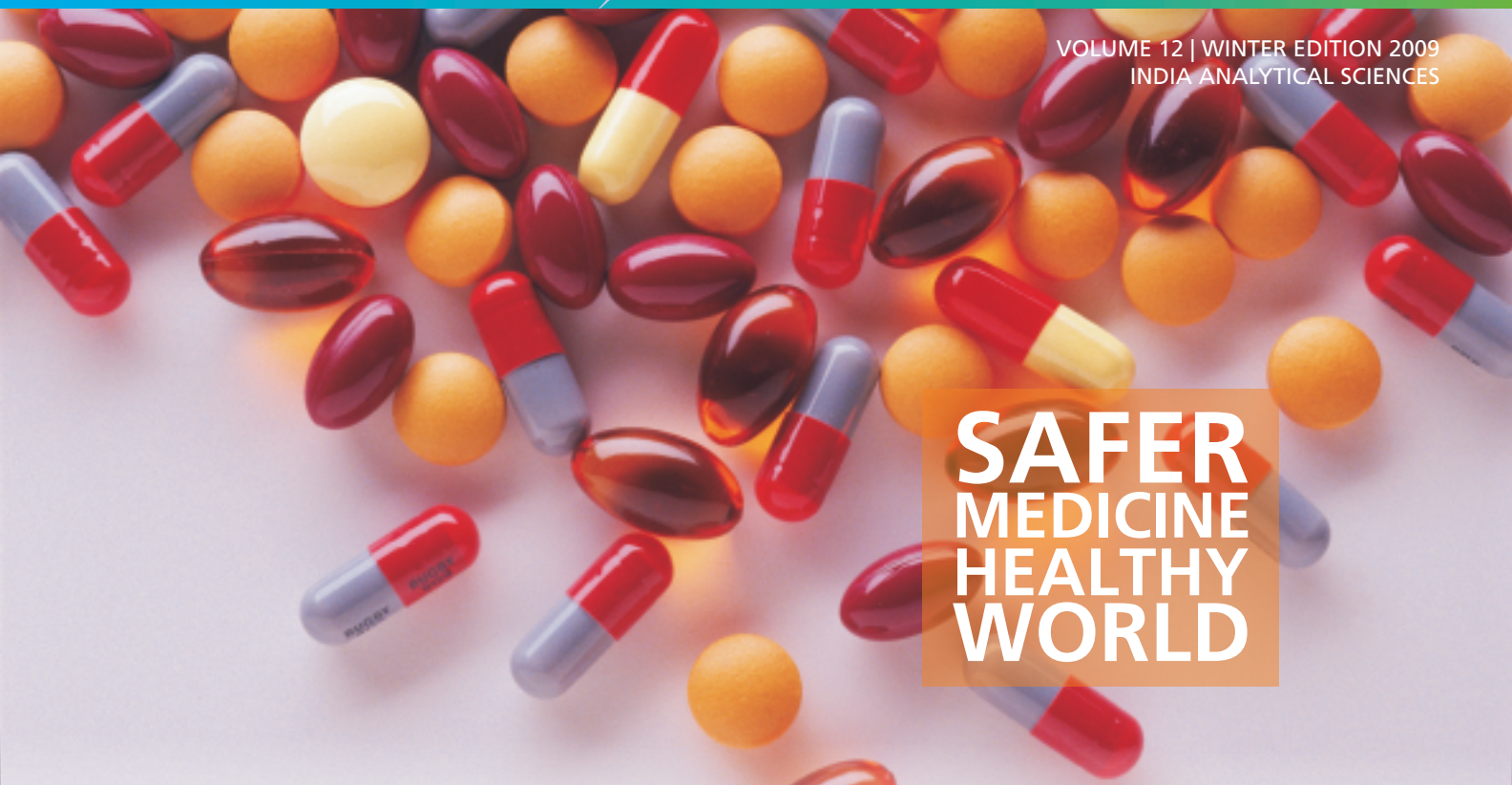
Fresh

PerkinElmer®
For the Better

HUMAN HEALTH | ENVIRONMENTAL HEALTH

VOLUME 12 | WINTER EDITION 2009
INDIA ANALYTICAL SCIENCES



SAFER MEDICINE HEALTHY WORLD

Hello readers,

It gives us immense pleasure to inform you that we are reaching to you through this newsletter; to keep you posted about the technologies and solutions. We started the 'FRESH' initiative in the beginning of the 2009 with a small note. However with your response and suggestions we got the energy to provide the right content and updates.

This winter edition is dedicated to the pharmaceutical and bio-pharma industries and researchers. This industry is governed by regulations and has also come up to the level for new research and developments to provide the safer and effective drugs and medicines to mankind.

PerkinElmer as a company is providing solutions for human health and environmental health through technology solutions. Our development team and application teams are engaged in providing simpler and easier solutions to pharma research and quality assurance.

As a technology leader; we have introduced various new products this year. The series of hyphenation techniques are the most promising solutions for the pharmaceutical industries worldwide. The affordable systems like IR Microscopy and TG-IR are the pride for any research or ADL laboratories.

Some applications based on the newer technologies are included in this issue of FRESH. We solicit your feedbacks and responses along with the business enquiries.

Wishing you all a Merry Christmas and a very happy, healthy and prosperous New Year.

WHAT'S Fresh inside...

PHARMAceutical EXPO 2009

December 11-13, 2009
Nirma University of Science & Technology, Ahmedabad

Visit us @ booth '17 A', hall 'H' at Pharmaceutical Expo 2009
11 - 13 December, 2009
Nirma University of Sciences & Technology, Ahmedabad

Fresh

PerkinElmer
For the Better

VOLUME 12 | WINTER EDITION 2009
INDIA ANALYTICAL SCIENCES

PHOTO-DEGRADATION OF PHARMACEUTICALS BY UV-DSC

Contribution from
K. Menard, A. Salamon, and P. Ye of PerkinElmer LAS, Shelton, CT
W. Brostow and N. Menard of U. North Texas, Denton, Texas

Introduction:

The photo-stability of pharmaceutical is an area of growing concern as the number of drugs found to be photosensitive is increasing [1]. As of 2005, the USP listed over 250 drugs that require protection from UV or Visible light [2]. The concerns with the photo stability of drugs are those of decreasing biological activity caused by loss of drug potency and light initiated reactions with excipients as well as unintended biological effects from degradation products, reactions with substrates, or with environmental oxygen. [1]. These concerns affect the handling, packing, and labelling of the drugs and vary according to the sensitivity of the compound. [3]

Determination of photo degradation is normally done by visual inspection, by repeating dissolution studies, or by chromatographic methods [4]. The disadvantage of these techniques is that they are either inexact in the case of physical inspection or time-consuming for the latter two techniques. However, more and more, regulatory agencies are requiring information on the photo-stability of drugs.[5] A faster and less cumbersome method for determining the presence of photo-instability and measuring the degree of degradation would be useful to help reduce costs and testing times.

Experimental:

Differential Scanning Calorimeters (DSC) coupled to a UV source have been used for years to study the photo-initiation of cures in materials[6]. This technique, called Photo-DSC or UV-DSC, takes advantage of the ability of the DSC to detect small changes in the material after irradiation of the sample with UV in situ. This note investigates the application of the Photo-DSC technique on samples of drugs with a range of photo-stabilities from poor to excellent.

Results and Disussion:

Samples of nifedrine, acetylsalicylic acid , acetaminophen, cetirizine, and pantoprazole were obtained from Aldrich-Sigma, St. Louis, Missouri in purities of 99% or better. All materials were stored in a dark dry box under nitrogen atmosphere at 5 C. 5-10 milligrams of sample was used for each run.

All DSC work was performed in PerkinElmer Diamond DSC with UV adapter. The UV source was an EFOS Omnicure 2000 with dual fibre optic light guides and a 200-450 nm filter

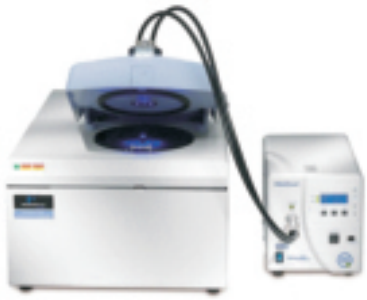


Figure 1 The PerkinElmer Diamond DSC (with Omnicure UV system)

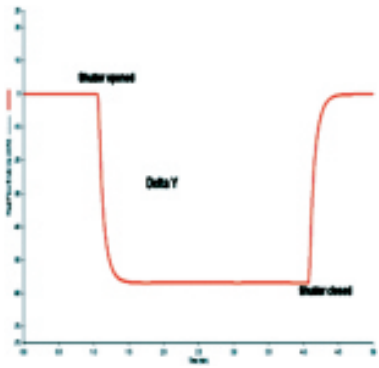


Figure 2 Calculation of UV energy striking a graphite target in the DSC

for 1.0 mW/cm2 of UV. Samples were run in open aluminium pans under 40 cc/minute nitrogen purge with the isothermal at 25 C and scanning rates from 20 to 300 C/minute. Cooling was supplied by either a PolySci chiller running at -20 C or by the Cryofill LN2 system. Pyris software's internal trigger was used to turn the Omnicure unit on.

The displacement of baseline when the reference pan is covered gives the energy from the beam actually striking the sample. This ability to exactly measure the light energy applied, with the highly stable isothermally performance and rapid response of this design, make dual furnace DSCs ideally suited to these studies.

Photostability runs were performed by placing a sample in a pan with a quartz lid and exposing it to UV light for a period ranging from 1 to 120 seconds. The sample was then run up though its melt and the differences from the unexposed samples compared (Figure3). All experiments were run in triplicate and the results averaged.

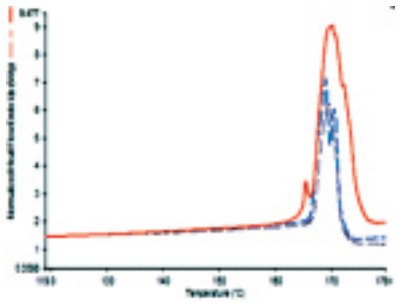


Figure 3 Nifedrine run at 20 c/min when exposed to no UV (red), 1 second of UV (blue), and 1.5 seconds of UV (black).

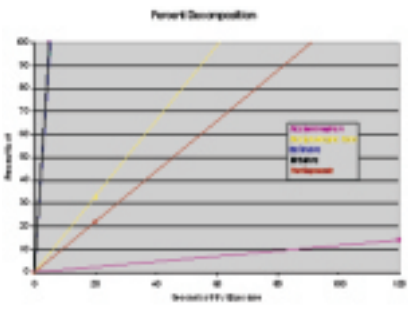


Figure 4 Decomposition of drugs under UV exposure.

Samples tested for photo stability not only degraded but as seen above changed peak shapes. This suggests that the material is also changing its polymorphic form, something undetectable by the standard methods of analysis. Both different degrees of photo-stability and the photo-initiated inter-conversion of polymorphic forms has is a known concern[7].

In the same manner different drugs were tested for their degradation per second as given in Fid.4 and Table given below..

Pharmaceutical	Degradation per Second
Acetaminophen	0.1%
Acetylsalicylic acid	1.7%
Cetirizine	19.0%
Nifedrine	20.0%
Pantoprazole	1.1%

Conclusion:

Photo-DSC or UV-DSC is a fast method for screening the photo-stability of drugs. Besides being relatively fast, the ability of DSC to detect the polymorphic forms of drugs makes it a useful complement to the normal techniques used for this test. Because of the advantages of double furnace DSC in isothermal stability and measuring the UV energy on the sample, these instruements are ideally suited for this application.

Summary:

Photostability testing for pharma-ceuticals is becoming more and more a requirement. This paper investigates the use of photo-DSC or UV-DSC for testing the photo-stability of drugs and drug formulations. Double furnace DSC has the advantage of being able to measure UV intensity directly as well as maintain stable isothermal. By irradiating the sample in the DSC and then scanning it, this method allows a fast evaluation of drug photo-stability.

Results show that Photo-DSC can detect the changes in drugs as the photo-degrade and track that degradation as a function of light intensity. In addition, the DSC appears to be able to see the changes in polymorphic form caused by UV exposure and this information would not accessible by chromatographic methods traditionally used. Coupling DSC to Raman Spectroscopy might represent a way to gain more information on these changes.

References:

(1) H. Tonneson, Photostability of Drugs and Drug Formulations, Taylor and Francis, Boca Raton, 2006, p. 1-7.

(2) U.S Pharmacopedia, Impurities Track, 26 September 2006, Retrieved on Feb 26th, 2009 from http://www.usp.org/pdf/EN/eventsEducation/asMeeting/2006Denver/presentations/track4session1and2.pdf

(3) A. Albini, Drugs Photochemistry, and Photostability, Royal Society of Chemistry, London, 1998.

(4) ICH Q1B, Photostability Testing of New Drug Substances and Products, IFPMA, Geneva, Switzerland, 1996.

(5) TCH Q1A, Stability Testing of New Drug Substances and Products, IFPMA, Geneva, Switzerland, 1992.

(6) JP. Fouassier, Photoinitiation, Photopolymerization and Photocuring, HanserGardner, Cincinnati, 1995.

(7) H. Tonneson, Photostability of Drugs and Drug Formulations, Taylor and Francis, Boca Raton, 2006, p.359.

VOLUME 12 | WINTER EDITION 2009
INDIA ANALYTICAL SCIENCES

VOLUME 12 | WINTER EDITION 2009
INDIA ANALYTICAL SCIENCES

Author:
Dr. Stuart Huckins
PerkinElmer Life & Analytical sciences

Pharmaceuticals - Homogeneity of Active Ingredient in a Solid Phase Drug Delivery System

Introduction:

Time release drug delivery systems are becoming increasingly important in modern pharmaceuticals.

Subcutaneous insertion of a drugloaded polymer avoids the need for repeated injections, and provides a much more constant delivery of drug. This is particularly significant in cases where the difference in concentration between therapeutic and toxic drug levels is quite small. Figure 1 shows the difference in tissue drug concentration for traditional and time-release systems. Such drug delivery systems are often based on a polymer or 'depot' within which the drug is included. Furthermore, the composition of the polymer itself is chosen to allow biodegradation of the polymer as shown in Figure 2, swelling to produce drug release, or response to physiological environment leading to drug release. The delivery system may be surgically implanted subcutaneously, applied as a surface patch, injected ultrasonically or inhaled.

In each case the structure and stability of the polymer and the concentration and homogeneity of active ingredient distribution must be characterized.

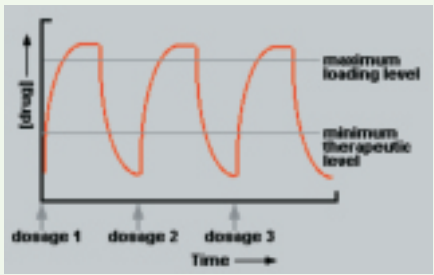


Figure 1a. Traditional dosing methods.

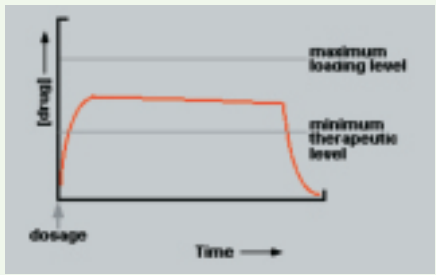


Figure 1b. Time-release delivery methods.

Figure 1.

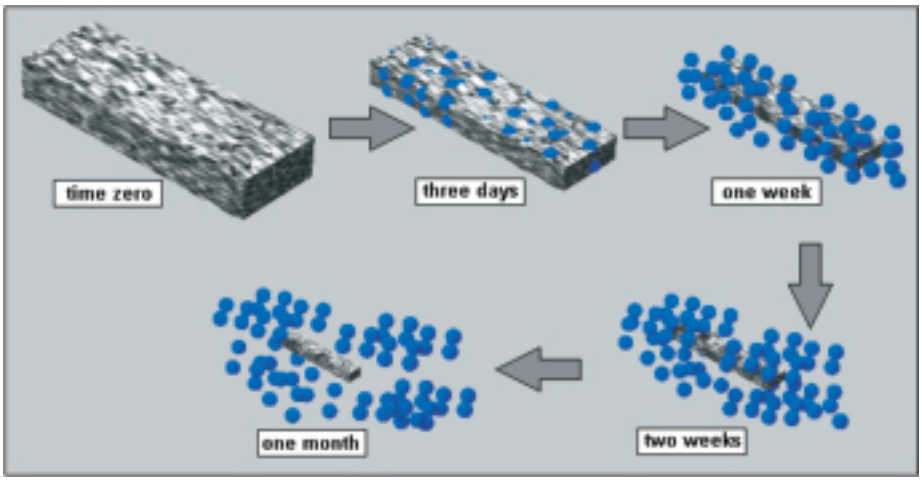


Figure 2. Controlled release of drug from a biodegradable polymer.

Results:

The survey scan in Figure 3a shows detail of the end of a typical drug delivery depot. Bubbles caused by the extrusion process can be seen over the entire surface of the depot. A vertical fault line can also be seen at 500 microns on the X axis. This particular depot sample contains the lowest concentration of active ingredient that will be used commercially.

The red area shown in Figure 3a was defined as a region of interest. Closer observation of this area shows several flat areas, identified by the arrows (Figure 3b).

Bubbles clearly visible in the picture are

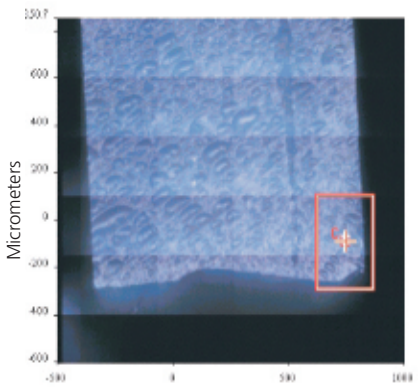


Figure 3a. Survey scan.

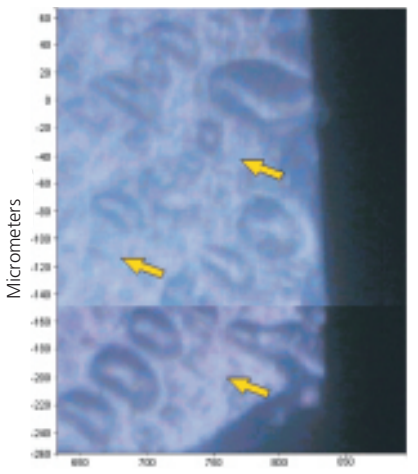


Figure 3b. High resolution visible map.

Figure 3.

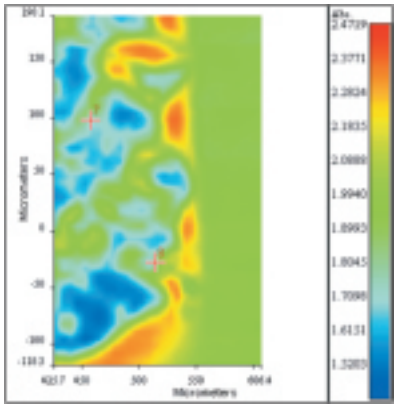


Figure 4a. Total absorbance map.

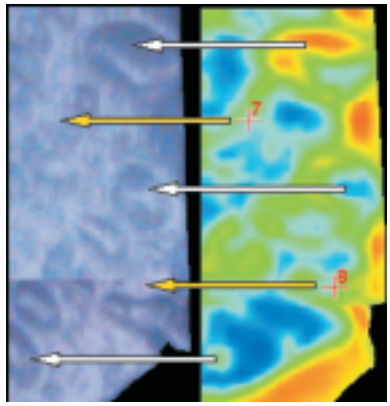


Figure 4b. Relating the total absorbance map to the visible image.

Figure 4.

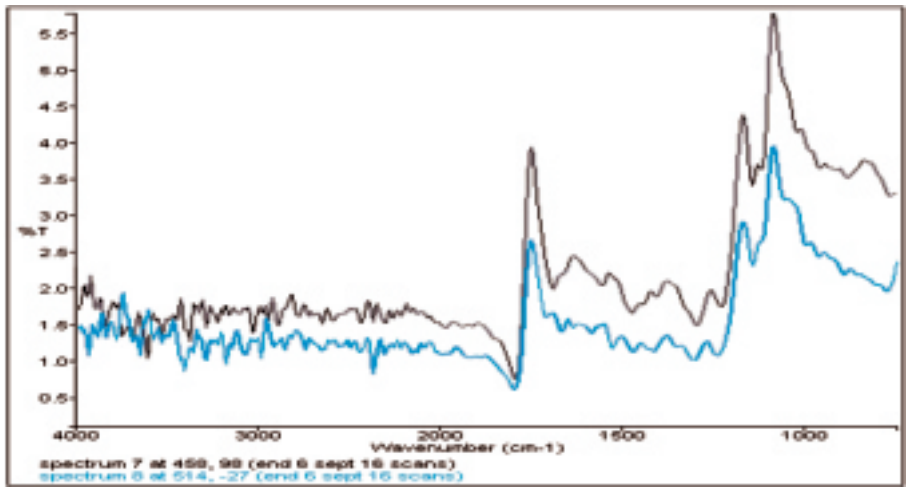


Figure 5. Spectra from Figure 3.

caused by the extrusion process and have nothing to do with drug distribution. Furthermore the bubbles are not of analytical interest since they represent material above or below the focal plane of the imaging system.

The identification and distribution of active ingredient throughout the depot are critical to manufacturing quality control of the product.

The infrared image of the selected sample area was collected at 8 wavenumber spectral resolution, 6.25 micron pixel resolution, 16 spectra per pixel. Data collection took 18 minutes.

Features in the total absorbance map can be easily related to the visible image as shown in Figure 4b. The two locations were then chosen from flat regions and spectra from these locations (marked as 7 and 8) were extracted (Figure 5).

Raw spectra showed artefacts due to the thickness of the sample, so the two spectra were transferred into Spectrum and treated with the Kramers-Kronig transform. This produced spectra that both clearly showed the carrier polymer, but only one showed the active ingredient's absorption band (Figure 6).

Conclusion:

Active ingredient distribution through the depot can clearly be analyzed, allowing accurate quality control of the drug delivery implant product. The Spectrum™ Spotlight is ideally suited to the measurement of time-release drug delivery systems. The sensitivity provided by the system allows for extremely rapid measurement of high quality results.

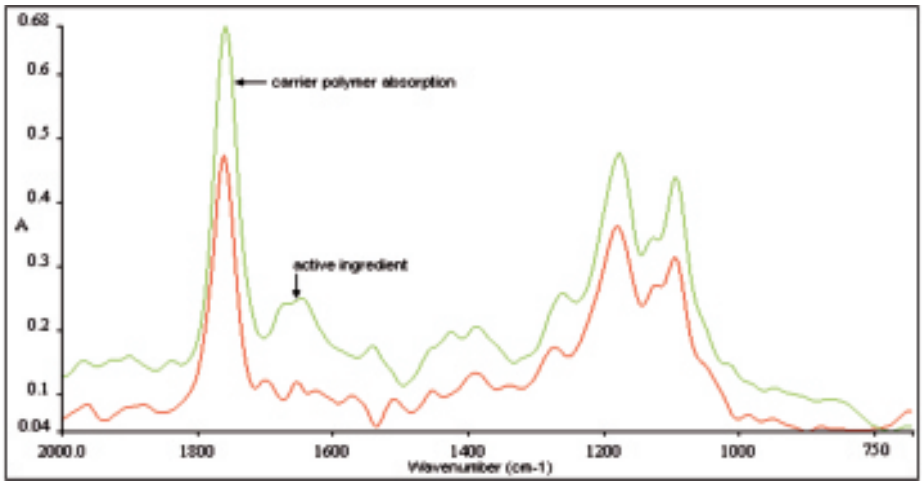
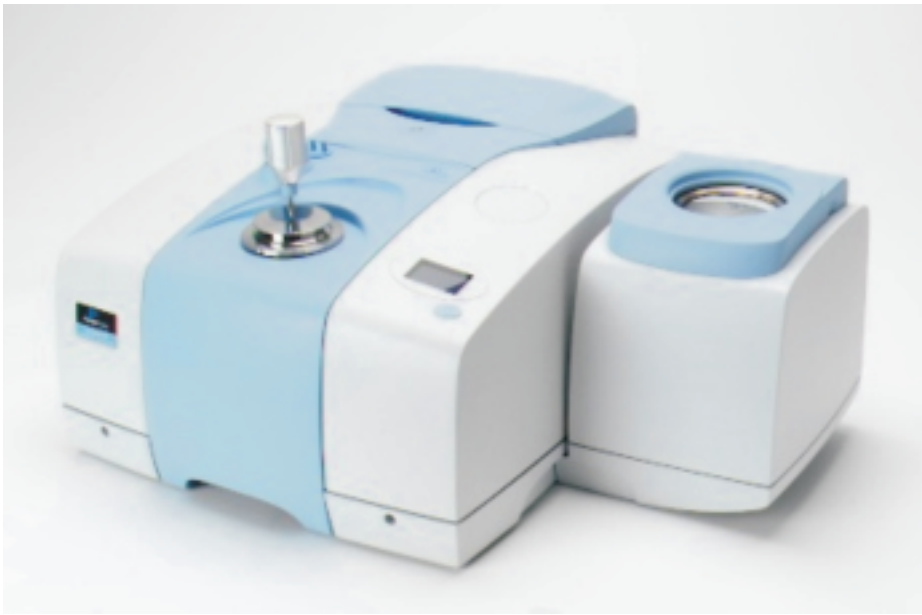


Figure 6. Kramer's Kronig transform applied to spectra from Figure 5.

VOLUME 12 | WINTER EDITION 2009
INDIA ANALYTICAL SCIENCES

Solid Materials Checking Using The Spectrum 100N/400 FT-NIR with NIRA Reflection Accessory



Versatility of Sampling:

The NIR Reflectance Accessory (NIRA) for the Spectrum 100N/400™ Near Infrared Testing System (NTS) System is designed for quick, easy sampling without compromising spectral quality. Sampling is simple as materials are measured directly in containers placed on the rugged sample platform. In the case of tablets, tablet blister packs, and transdermal patches, samples are placed directly on the sampling window where they are illuminated from below. Samples can also be measured in a range of containers, from conventional vials, plastic bags or bottles, to colored glass bottles. The original containers which the samples are transported to the instrument are more convenient, reproducible, and carry less risk of cross-contamination than using fiber-optic dipping probes.

To illustrate the versatility of NIRA sampling, a few examples and their resultant spectra are shown in this note.

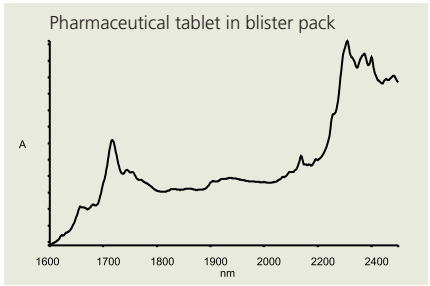


Figure 1: NIR spectrum of aspirin tablet in pack. It is unnecessary to remove a tablet from a blister pack before obtaining the spectrum using the ICRA. Simply place the sample you want, in its blister packing, directly on the sampling window.

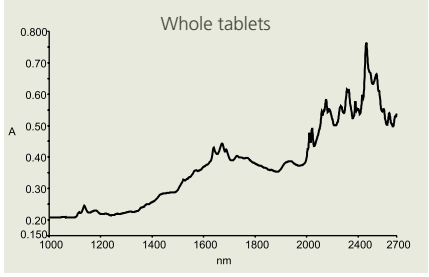


Figure 2: NIR spectrum of paracetamol tablet. The spectrum of a paracetamol tablet was obtained by simply placing the tablet on top of the sampling window.

Advantages of the NIRA Accessory:

By eliminating the need for any special sample preparation or accessory cleaning, the NIRA ensures more consistent measurement conditions. The large illumination area allows for the analysis of samples with varying (large) particle size and inhomogeneity is improved. A large sample area is measured, therefore decreasing the influence of inhomogeneities and providing a more representative sampling, for example polymer flakes and pellets.

For more granular and inhomogenous materials such as grains, an optical spinning sample cup is available to ensure the most representative sampling.

Reliability and Reproducibility:

The NIRA accessory eliminates the major problems associated with using fiber-optic probes for materials checking. Hand-held probes are inherently unstable. The NIRA, however, offers a robust sampling platform. The automated self referencing feature also eliminates the need to collect separate background spectra.

Test data for replicate spectra of calcium ascorbate from a commercially available fiber optic probe system and the NIRA are shown in Figures 5 and 6. The results from the NIRA show much less variability than those of the probe system.

Spectral Response:

Traditionally, NIR sampling has been confined to fiber optic and dispersive systems with spectra measuring between ca. 10000 – 2200 nm (10000 – 4545 cm-1). These systems typically provide the highest response in the short wavelength region.

The response from the NIRA is shown in Figure 7 along with that of a typical dispersive system. Sample spectra are shown in Figures 8, 9 and 10 with the high quality long wavelength information gained when using the NIRA.

One advantage to this response allows for sampling to occur in original colored glass bottles which typically show spectra with little useful information in the shorter range. By collecting data in the longer wavelength region where the glass is transparent, sample identity can often be verified without removal from the original container. The NIRA is optimized for operation in the longer wavelength range in order to maximize the information content available.

Resolution:

The NIRA delivers new levels of information in NIR spectra due to the higher resolution available. In addition to improving spectral interpretation, this offers improved accuracy for qualitative analysis, and assists in transferring multivariate calibrations between instruments.

Conclusion:

The NIRA offers simple but effective sampling solutions for materials testing without compromising spectral quality or time. The combination of optimized range and resolution reveals information which has been hitherto under-utilized in qualitative and quantitative applications. This extra level of spectral detail should provide new opportunities for analyses in terms of both easier sampling and improved spectral discrimination and quantitation.

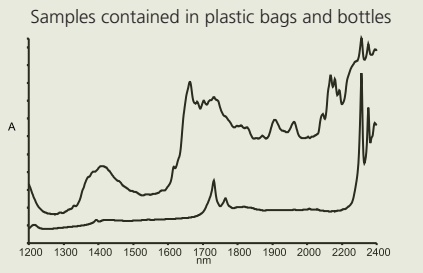


Figure 3: NIR spectra of a polyethylene bag (lower) and polybutlylene terephthalate (PBT) in a polyethylene bag (upper).This PBT sample was received in a polyethylene bag, and scanned intact.

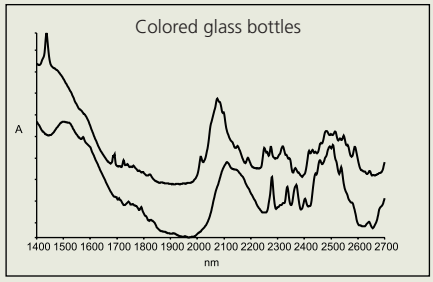


Figure 4: NIR spectra of sucrose (upper) and dextrose (lower) scanned in amber colored glass vials.

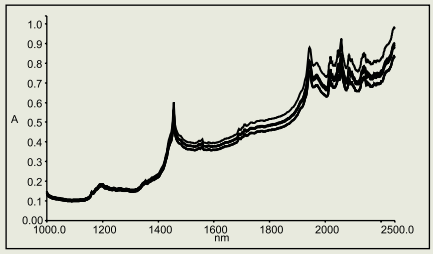


Figure 5: NIR spectra of calcium ascorbate in a glass bottle recorded using the NIRA.

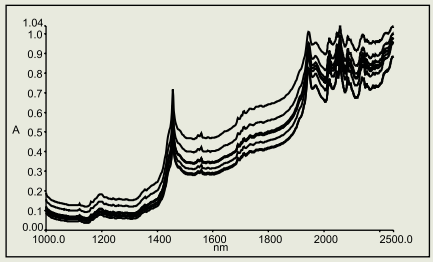


Figure 6: NIR spectra of calcium ascorbate recorded using a fiber optic solids probe.

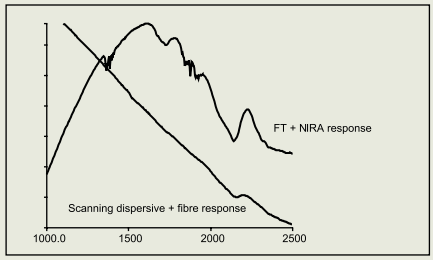


Figure 7: Typical response of the NIRA compared with a typical scanning dispersive instrument with a fiber probe.

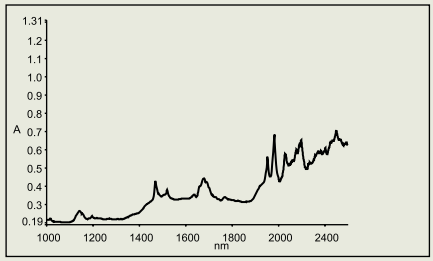


Figure 8: Tegretol tablet.

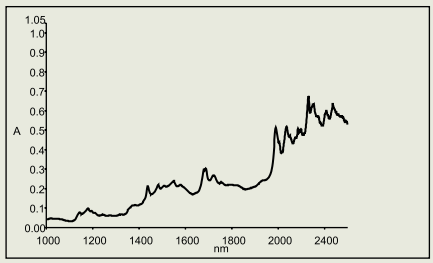


Figure 9: Procainamide tablet.

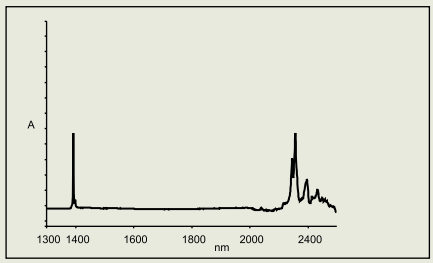


Figure 10: Talc.

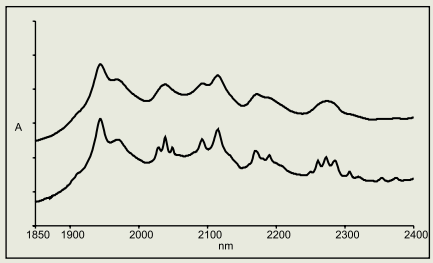


Figure 11: NIR spectra of calcium ascorbate at typical dispersive NIR instrument resolution 3 nm (upper) and FT resolution of 0.4 nm (lower).

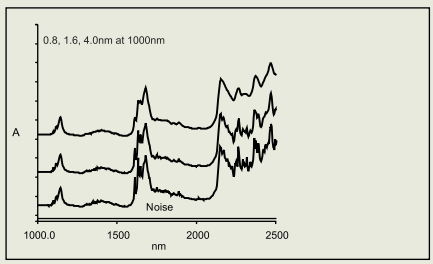


Figure 12: NIR spectra of Clotrimazole at 4, 1.6, 0.8nm resolution (upper – lower).The increased spectral information gained at higher resolution is real as the noise profile is shown on the same scale.

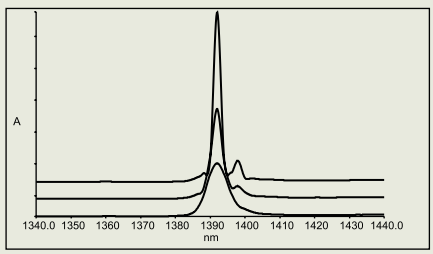


Figure 13: NIR spectra of Talc at 0.4 nm, 1.6 nm and 3.2 nm resolution (upper to lower).

VOLUME 12 | WINTER EDITION 2009
INDIA ANALYTICAL SCIENCES

The RamanStation & RamanMicro Systems

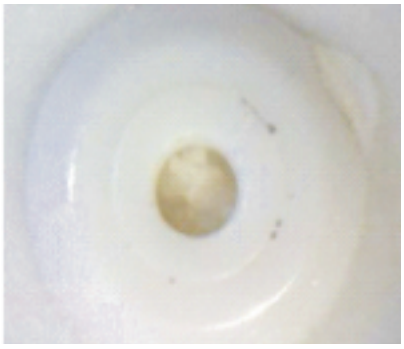
Modern Raman microscopy is being used in an ever-increasing number of application areas in a wide variety of analytical environments. in trouble-shooting laboratories where industrial problems related to manufacturing, quality control, environmental issues, etc. are investigated. In many cases, these analyses involve the unambiguous identification of rogue materials which can turn up in unusual and unwanted places. Some of the applications are listed below where the applications have provided the clues to address the problems and remedial actions.

Use of the RamanMicro 200 in the identification of an Aerosol Nozzle blockage

Identifying the cause of blockage in an aerosol nozzle is a common problem found in many products ranging from foodstuffs, paints, healthcare and medical equipment. The results of these blockages can be inconvenient, costly or even fatal. The current method of analysis of the blockage material is to remove it and identify it using an IR microscope. Since the blockage is slightly recessed into the nozzle it is not possible to analyze the sample in-situ using IR spectroscopy. The removal of the sample destroys its spatial integrity. It is of particular importance to identify the material that actually causes the blockage as opposed to the material that simply builds up behind the initial blockage. Since Raman spectroscopy is a noncontact analytical technique, it is ideal for this type of in-situ analysis.

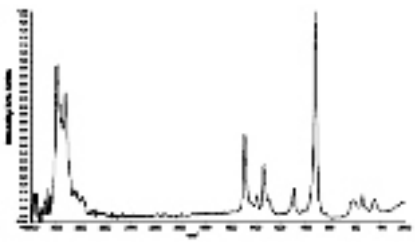
The resultant Raman spectra from the white surrounding polymer and the blockage are shown in Figures 2 and 3 respectively. The acquisition time for these spectra was 1 minute and the spectral resolution was 8 cm-1. The Raman spectra from the two most likely materials to cause the blockage are shown in Figure. The sample was turned over and the reverse side of the

- Combined macro-micro sampling functionality in a single system
- Ease of use - the permanently aligned optics for both macro and micro sampling ensure optimum performance for all modes of operation. Changing modes is as simple as a mouse click; no changing of optics required.
- A full range of macro and micro sampling options available
- Add a fiber optic probe for remote sampling or reaction monitoring
- No Raman expertise required to acquire high quality Raman data.
- A full suite of application software, including Library Search and Imaging, ensures that the maximum amount of useful information

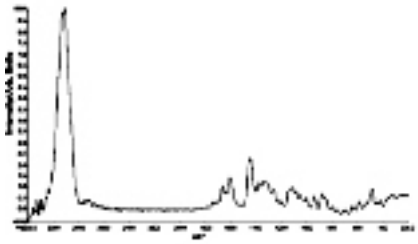


Visible image (x4 objective) of the blockage taken using the camera of the RamanMicro 200.

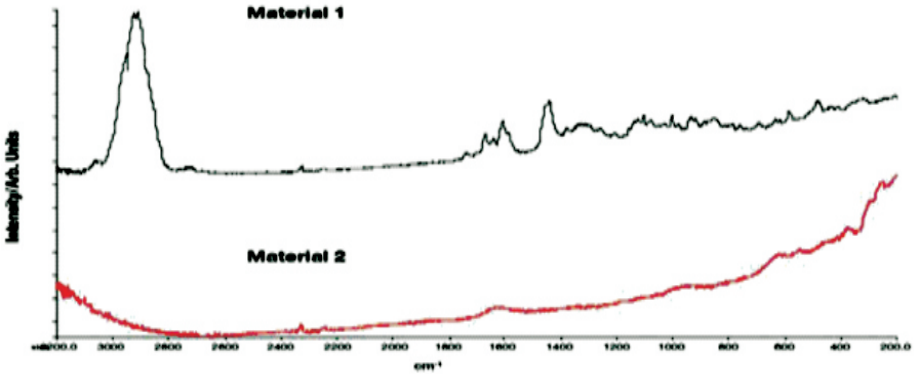
blockage analyzed using the same experimental conditions. The resultant spectrum was also that of Material. Finally, the entire blockage was removed and analyzed in bulk. This also indicated that only Material 1 was present. The conclusion is therefore, that the initial blockage was caused by Material 1 and any subsequent build-up of material behind this blockage was of the same material.



Raman spectrum of the white surrounding polymer



Raman spectrum of the blockage material



Comparison of the sample spectrum with the two most likely blockage materials shows that Material 1 is causing the blockage.

Analyses through plastic and glass containers (Raman Identicheck)

Analysis of materials through plastic bags becomes routine with the IdentiCheck. The spectra shown in Figure 1below are from exposed acetaminophen (paracetamol) and acetaminophen taken through a double-layer black plastic bag. The contribution due to the plastic bag is shown by the two small additional C-H bands at 2850 and 2887 cm-1 in the bottom spectrum. This contribution can be subtracted automatically by the software, but in practice this small effect has no adverse effect on the positive identification of the material. In a similar way, analyses can be made through clear or colored glass containers. For materials with a strong Raman spectrum, the effect of the glass container is minimal. This is shown in Figure 2 where the spectrum of nicotine liquid was recorded through a dark brown glass vial. There is no significant contribution from the glass container in this spectrum. In some other cases, the contribution from the glass can be more significant but the software allows spectral

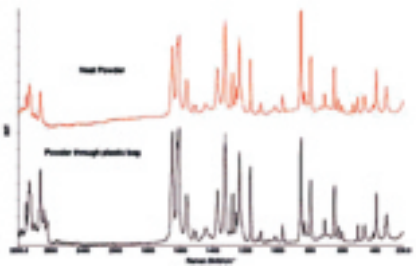


Figure 1. Raman spectra of acetaminophen (paracetamol).

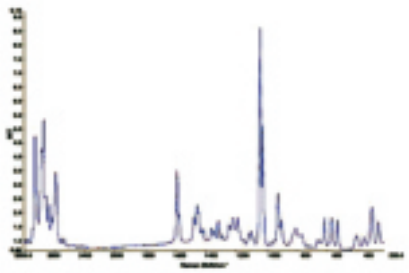


Figure 2. Spectrum of nicotine liquid through a brown glass bottle.

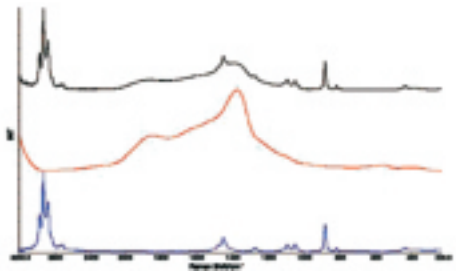


Figure 3. The top spectrum shows ethanol through the glass bottle, the middle spectrum is that of the glass bottle and the bottom spectrum is of ethanol after subtraction of the glass contribution

The Raman IdentiCheck comes in its own rugged travel case and is controlled via a laptop or tablet PC

subtraction of the glass. This is shown in Figure 3 where the spectrum of ethanol is recorded through a 2 mm thick glass bottle.

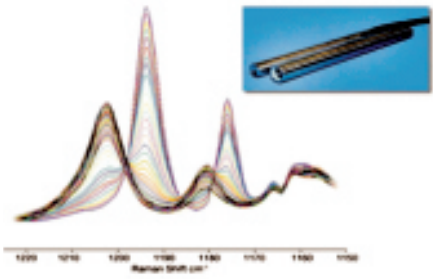
The Raman IdentiCheck combines the benefits of high performance in a convenient, trigger-probed system. In the pharmaceutical and healthcare industries. Compliance with regulatory requirements such as 21CFR Part 11 is intrinsic to the system via the Spectrum ES and the optional AssureID software packages.

A unique macro-micro Raman analysis system

The combination of the PerkinElmer® RamanStation™ 400 with the RamanMicro™ 300 provides an easy-to-use macro-micro sampling system designed to give the analyst high quality, reproducible results in seconds. The additional fiber optic functionality further extends the range of sample types that can be analyzed.

The macro compartment of the RamanStation 400 is equipped with a software controlled, motorized X, Y, Z sample stage, designed for easy sample manipulation, that can automatically align your sample in all three coordinates. A video camera enables autofocus of both the visible image and the Raman spectrum. The versatile sample holder accommodates single samples in capillary tubes, vials or cuvettes, or on microscope slides, while the X, Y, Z stage can hold all standard multiwell plates. Multi-tablet and powder-holding kits are also available.

A wide range of macro sampling options is available.



When performing reaction monitoring with fiber optic probe, an optional immersion sleeve can be added

Remote analysis

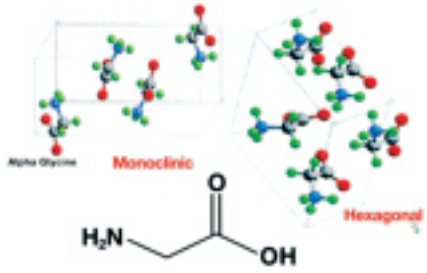
The RamanStation 400 can accommodate a choice of fiber optic probes for remote analyses. These probes can be used for reaction monitoring or remote analysis of bulk samples. In reaction monitoring, the probe is either immersed into the reaction solution or focused through an observation window in the reaction vessel. When immersed in solution, the optional immersion sleeve is used.

Raman Analysis of a Polymorph within a Polymorph

It has long been known that some molecules with the same chemical formula can have different chemical structures. These different structures are called polymorphs. There are two ways in which different crystal structures can arise: Arrangement (or packing) polymorphism and conformational polymorphism. Pseudo polymorphs are crystalline structures that also incorporate solvent molecules and are therefore not chemically identical to the true polymorphs. Arrangement polymorphism occurs when rigid molecules of the same conformation pack in different ways. The monoclinic and hexagonal forms of Glycine are examples of this type of polymorphism.

Conformational polymorphism occurs when flexible molecules with different conformations pack in different ways. An example is the two forms of Spiperone.

The differences in the crystalline structure of these polymorphs can affect the physicochemical parameters of the substance such as solubility, dissolution rate, density, hardness and shape. This in turn can impact on important pharmaceutical properties of



Different arrangement polymorphs of Glycine.

Different conformational polymorphs of Spiperone.

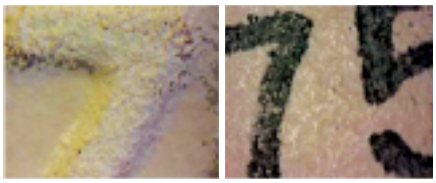
these polymorphs such as bioavailability and stability of a drug as well as the formulation technology of the dosage form. The differences between the solid polymorphs are lost on melting and dissolution.

The formation of different polymorphs is a controllable process within formulation. Factors such as solvent of crystallization, rate of cooling and degree of supersaturation can affect the crystallographic form produced. Powder processing, especially pressure in the form of grinding or milling can also change the polymorphic form. In the pharmaceutical industry it is therefore vital to manufacture the correct polymorphic form and to access its continued viability throughout its formulation, storage and subsequent usage. It is also of great commercial importance to pharmaceutical companies when filing patents for new products.

Raman spectra from the core of the tablets

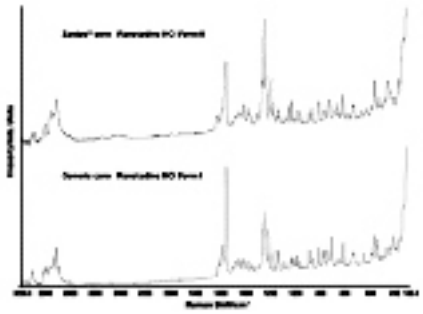
The outer coating of the tablet was removed prior to analysis. The resulting spectra are shown in Figure and are the result of a 1 minute accumulation time. They show a spectral range of

VOLUME 12 | WINTER EDITION 2009
INDIA ANALYTICAL SCIENCES

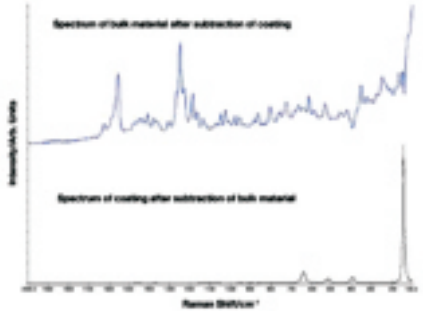


Surface of Zantac 75® relief and generic tablet.

Spectrum obtained from tablet coating.



The different forms of Ranatadine HCl found in the two tablets



Spectra of bulk material (Form II) and coating (Anatase) by z-axis analysis through Zantac 75® tablet

3200-100 cm-1 and have a spectral resolution of 4 cm-1. Although there will be a small contribution from minor excipients, these spectra are essentially the spectra of the Ranatadine HCl present in these tablets. It is clear that these two tablets contain the different polymorphic forms of Ranatadine, with the Zantac 75® tablet containing Form II and the generic tablet containing Form I. The reason for this difference almost certainly lies in historical patent restrictions. Both forms have been tested to ensure they have the same effects on the human body.

Ranatadine Hydrochloride is one such polymorphic molecule that can exist in two distinct forms and several other pseudo-polymorphic forms. It is a histamine type 2 receptor antagonist used in the treatment of peptic ulcers. Form I of the drug was first prepared in 1977 and the first U.S. patent registration was in 1978. In 1980 Form II of the drug was discovered and in 1985 the patent for Form II was registered in the U.S. In 1984.

In addition to Zantac 75®, there are many other generic drugs based on Ranatadine HCl available for the treatment of peptic ulcers. All of these products are in the form of a coated tablet and the active Ranatadine is present in a high dosage. The coatings on these tablets are relatively thick and often pigmented. Visible images, acquired using the RamanStation™ video camera, showing the coating on Zantac 75® (left) and a generic tablet (right) are shown.

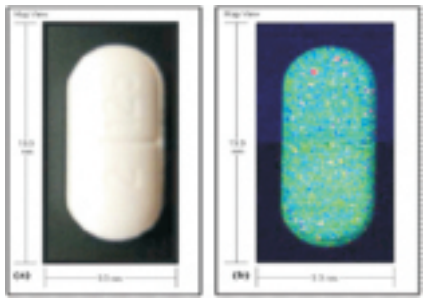
This study confirms that Raman spectroscopy is an ideal method for the analysis and identification of both organic and inorganic polymorphs.

Chemical Imaging of Solid Dosage Forms Using the RamanStation 400

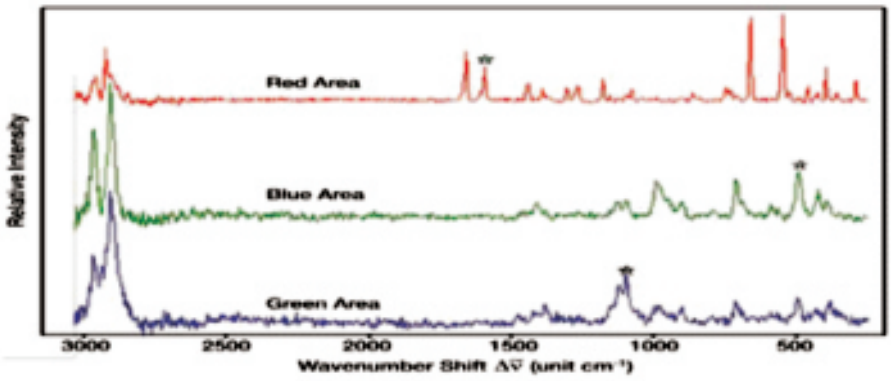
In Raman chemical imaging, the spectra are acquired in a grid pattern (or map) and processed using software to provide a two-dimensional representation of the sample composition. This map can be constructed from any number of spectral properties such as the intensities or areas of particular peaks of interest, but importantly, these spectral properties can be chosen to reflect the chemical composition. This means that the spectral maps can show variation in concentration or even properties like crystallinity across the mapped area.

Chemical imaging is an extremely powerful technique for characterization of solid dosage forms. The RamanStation 400 spectrometer allows large areas (tens of millimeters) to be mapped. The entire area is mapped with full coverage – rather than discrete, widely-spaced sample points. This data can be obtained rapidly with no compromise in spectral and spatial resolution while the Insight software allows quick and easy analysis of data using either univariate or multivariate (chemometrics) models.

For more details and application notes please write to marketing.india@perkinelmer.com



(a) Imodium Advanced® caplet and (b) chemical image of an Imodium Advanced® caplet.



Representative spectra from the Imodium Advanced® caplet chemical image, peaks marked were used to construct the image

VOLUME 12 | WINTER EDITION 2009
INDIA ANALYTICAL SCIENCES

Low-level Selenium Determination

Authors:
Kenneth R. Neubauer and Ruth E. Wolf
PerkinElmer Life & Analytical sciences
Headquarters Office: 710 Bridgeport Avenue
Shelton, CT 06484-4794 USA

Introduction:

Selenium is an essential element to human health at low levels (20-80 µg/L), but becomes toxic at elevated levels. Selenium exists in different forms that determine its toxicity and bioavailability. Current research is now focusing on the determination of individual selenium species or seleniumcontaining compounds. This can be done using ICP-MS as a selenium- specific detector for a chromatographic separation of the compounds. Since the critical levels of the individual compounds will be significantly less than the total selenium concentration, it is becoming more necessary to be able to make very low level selenium determinations. This application note discusses the use of the ELAN® Dynamic Reaction Cell™ (DRC™) ICP-MS for making low-level selenium determinations.

With conventional quadrupole ICP-MS, the most abundant isotope of selenium (80Se) cannot be used for the determination due to the interfering $^{40}Ar_2$ + dimer from the argon plasma which occurs at the same mass-to-charge ratio (m/z). As a result, selenium is normally determined using the ^{82}Se isotope, which is only 8.7% abundant. This limits the detection capability for

selenium to the 0.5- 10 µg/L range by conventional ICP-MS.

Using the ELAN DRC ICP-MS, this limitation can be overcome by removing the $^{40}Ar_2$ + interference. This allows the most abundant isotope of selenium, ^{80}Se, to be used in the determination, resulting in detection limits that are on the order of a thousand times better than those obtainable by conventional ICP-MS.

Experimental:

The instrument used was the ELAN DRC ICP-MS. The ELAN DRC eliminates the Ar_2 + background, so that selenium can be determined at levels below 100 ppt. The background reduction described in this application note was achieved using methane as the reaction gas. The flow rate of the reaction gas was optimized using the automated routines in the ELAN software to maximize selenium signal transmission while minimizing the $^{40}Ar_2$ + background. In addition, the dynamic bandpass tuning parameters of the quadrupole inside the reaction cell were adjusted to eliminate any unwanted secondary reaction products.

Results:

Figure 1 shows the mass spectrum of 50 ppt selenium in 1% nitric acid compared with the theoretical isotope ratios. The accurate agreement of theoretical and measured abundance of all isotopes indicates that the Ar_2 + is virtually eliminated. Further evidence of this reduction is seen in Figures 2 and 3, which show ^{80}Se and ^{78}Se calibration curves using 1, 5, 10, and 20 ng/L standards. The linearity of these low-level curves further verifies the removal of the Ar_2 + interference. The detection limits obtained using DRC ICP-MS are presented in Table 1.

The quantitative determination of selenium in a Certified Reference Material (CRM), Trace Metals in Drinking Water (High-Purity Standards, Charleston, SC) is shown in Table 2.

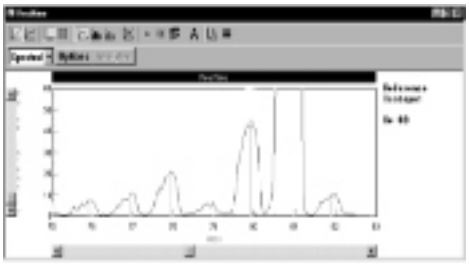


Figure 1. Spectrum of 50 ng/L Se in 1% HNO_3.

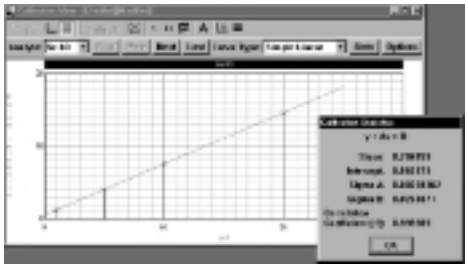


Figure 2. Calibration curve for ^{80}Se.

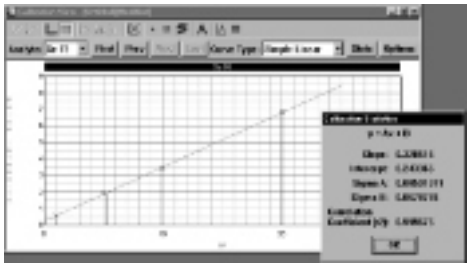


Figure 3. Calibration curve for ^{78}Se.

The CRM was diluted 1,000 times to reduce the selenium concentration to 10 ng/L. Accurate recoveries for selenium were obtained at the 10 ng/L level for both the ^{78}Se and ^{80}Se isotopes. Further evidence of the accuracy in other matrices is shown in Table 3. The data in Table 3 illustrate that the DRC ICP-MS technique is also applicable to chloride-containing matrices. Excellent recoveries for a 50 ng/L spike were obtained in 1000 mg/L NaCl.

Conclusions:

The results of this study indicate that the ELAN DRC ICP-MS can accurately determine low selenium levels with a detection limit of 1 ng/L or less. This is achieved by the complete elimination of the Ar^2 + interference using Dynamic Reaction Cell ICP-MS with a methane reaction gas and tunable DRC bandpass. Calibrations using 1, 5, 10 and 20 ppt selenium standards showed excellent linearity. Results for 10 ppt selenium reference material and spike recoveries for 50 ppt spikes in a NaCl matrix were both excellent.

The analysis time per sample using DRC ICP-MS was less than 30 seconds per sample. In addition, DRC mode elements can be determined in the same analysis as standard mode elements for analyte lists containing multiple elements. The ELAN DRC will automatically switch between DRC mode and standard mode during the data acquisition, so the sample tube is only sampled once by the autosampler. This means that productivity is not sacrificed when using DRC mode in an analysis.

Table 1: Detection Limits in 1% HNO_3

Spike Level (ppt)	^{80}Se IDL (ng/L) DRC Mode	^{78}Se IDL (ng/L) DRC Mode	^{82}Se IDL (ng/L) Standard Mode
1	0.7	1.2	131
5	0.9	1.5	Not Determined
10	1.7	1.5	Not Determined

Table 3: 50 ppt Se Spike Recoveries in 1000 mg/L NaCl

	^{80}Se (% Recovery)	^{78}Se (% Recovery)
Replicate 1	93	101
Replicate 2	98	98
Replicate 3	101	90
Mean	97	96
Standard Deviation	4	6

Table 2: Analysis of 10 ng/L Se in High-Purity Standards SRM - Trace Metals in Drinking Water

	^{80}Se (ng/L)	^{78}Se (ng/L)
Replicate	1	9.77 11.80
Replicate	2	9.26 9.24
Replicate	3	10.68 10.83
Mean	9.90	10.62
Standard Deviation	0.72	1.29

HUMAN HEALTH

ENVIRONMENTAL HEALTH

GAS AND LIQUID CHROMATOGRAPHY

DATA SYSTEMS INFORMATION MANAGEMENT (LIMS)

INORGANIC ANALYSIS

MATERIAL CHARACTERIZATION
MOLECULAR SPECTROSCOPY
THERMAL & ELEMENTAL ANALYSIS

SERVICES & CONSUMABLES

TRAINING AND APPLICATION SUPPORT

Drug Discovery
- Target Discovery
- Drug screening
- Preclinical evaluation
- Clinical evaluation

Research & Development
- Method Development
- Polymorphism studies
- Counterfeit detection
- Reverse engineering
- Compatibility studies
- Hyphenation techniques

Manufacturing
- At line monitoring
- Process analytical techniques(PAT)
- Raw Material Testing
- In Situ analysis
- Whole tablet analysis

Quality Control & Assurance
- Organic Volatile Analysis (VOC)
- Identification and confirmations of API
- Tablet dissolution testing Online/off line
- Mass spectrometric analysis
- Inorganic analysis for heavy metals

Validation & Qualifications
- GLP & GALP Regulations
- Validation Standards
- IQ/OQ/PQ services

Packaging
- Packaging films quality
- Tablet coatings studies
- Capsules and gelatin analysis.
- Blister packs and foils
- Analysis of collapsible tubes and caps.

PerkinElmer (India) Pvt. Ltd.
TradeStar Building, 8th Floor, "B" Wing
J.B. Nagar, Andheri (East), Mumbai-400059 India
Tel: 91 22 67601759 Fax:91 22 67601792
Marketing.India@perkinelmer.com

PerkinElmer®
For the Better

Fresh

PerkinElmer®
For the Better

HUMAN HEALTH | ENVIRONMENTAL HEALTH

VOLUME 12 | WINTER EDITION 2009
INDIA ANALYTICAL SCIENCES

WHAT'S **Fresh** inside...

Hello readers,

It gives us an immense pleasure to inform you that we are reaching to you through this newsletter; to keep you posted about the technologies and solutions. We started the 'FRESH' initiative in the beginning of the year 2009 with a small note. However with your response and suggestions we got the energy to provide the right content and updates.

This winter edition is dedicated to the pharmaceutical and bio-pharma industries in India and abroad. This industry is governed by regulations and also has come up to the level for the new research and developments to provide the safer and effective drugs and medicines to the mankind.

PerkinElmer as a company is providing solutions for the human health and environmental health through the technology solutions. Our development team and application teams are engaged in providing the simpler and easier solutions to the pharma research and quality assurance.

As a technology leader; we have introduced various new products this year. The series of hyphenation techniques are the most promising solutions for the pharmaceutical industries worldwide. The affordable systems like IR Microscopy and TG-IR are the pride for any research or ADL laboratories.

Some applications based on the newer technologies are included in this FRESH. We solicit your feedbacks and responses along with business enquiries.

Wishing you all a Merry Christmas and a very happy, healthy and prosperous New Year.

Fresh

PerkinElmer®
For the Better

HUMAN HEALTH | ENVIRONMENTAL HEALTH

VOLUME 12 | WINTER EDITION 2009
INDIA ANALYTICAL SCIENCES

Hello readers,

It gives us an immense pleasure to inform you that we are reaching to you through this newsletter; to keep you posted about the technologies and solutions. We started the 'FRESH' initiative in the beginning of the year 2009 with a small note. However with your response and suggestions we got the energy to provide the right content and updates.

This winter edition is dedicated to the pharmaceutical and bio-pharma industries in India and abroad. This industry is governed by regulations and also has come up to the level for the new research and developments to provide the safer and effective drugs and medicines to the mankind.

PerkinElmer as a company is providing solutions for the human health and environmental health through the technology solutions. Our development team and application teams are engaged in providing the simpler and easier solutions to the pharma research and quality assurance.

As a technology leader; we have introduced various new products this year. The series of hyphenation techniques are the most promising solutions for the pharmaceutical industries worldwide. The affordable systems like IR Microscopy and TG-IR are the pride for any research or ADL laboratories.

Some applications based on the newer technologies are included in this FRESH. We solicit your feedbacks and responses along with business enquiries.

Wishing you all a Merry Christmas and a very happy, healthy and prosperous New Year.

SAFER MEDICINE HEALTHY WORLD

WHAT'S **Fresh** inside...