



### Sun and fun for everyone – SPF determination with UV-VIS spectra

The sun protection factor SPF will be one of the most important topics in the near future. FAMEs in aviation turbine fuel – a risk?

FAMEs in diesel fuel have an unintended side-effect: Potential contamination of jet turbine fuel! »Best supporting actor«

HS-20: The new powerful Headspace partner for GC analysis playing alongside the leading actors and bringing out the best in them.



## Sun and fun for ev

### APPLICATION

Sun and fun for everyone – SPF determination with UV-VIS	-
spectra	2
Practical test: Lead in circuit boards – RoHS II – new guidelines	4
Heavy metals in the food chain – Determination with the high- speed self-reversal method for background compensation	8
Where's the difference? Volume-based vs. number-based particle size measurement	10
»Best supporting actor« – The new generation headspace sampler	12
Read the lips – FTIR spectros- copy of cosmetics and pharma- ceuticals	14
FAMEs in aviation turbine fuel – a risk?	16
Technical failure or 'human factor'? Measurement inaccuracies in X-ray	
fluorescence spectroscopy	19
LATEST NEWS	
Experimental compartment	6
TOC analyzer in quality control – A customer report from the pharmaceutical industry	11
Global structure – Global Design	20

PRODUCTS

New accessory for the UV series – Micro cell holder 18



he sun protection factor SPF will be one of the most important topics in the near future. Due to changes in the global climate, temperatures and exposure to sun will increase. Humans and animals will be sunburnt more easily than in the past.

30 years ago a sun blocker with an SPF of 10 was regarded as a high protection factor. Nowadays, a protection factor of 50 produced especially for children is normal. It is difficult to find a reliable procedure for controlling the production of such mixtures in lotions, milks and creams.

What does SPF stand for?

Sun protection is needed against exposure through UV-A and UV-B radiation from natural sunlight. UV-A is by definition the range of 380 to approx. 315 nm and UV-B is the range from 315 down to 280 nm on the wavelength scale.

The target of a cream is to work as a cutoff filter. The exposure time for the skin is reduced. SPF 10 simply means that the treated skin can stay 10 times longer in the sun than under normal conditions.

The usual sun blockers are often prepared with  $TiO_2$  which gives the creams and lotions their white color.  $TiO_2$  is a white pigment and by nature an ideal reflector of the radiation. But this is only one aspect of such complex mixtures.

There is a particular focus on sun transmission which is able to pass the sun blocker film. In principle,



Figure 1: Preparation of a sample onto the PMMA polymer plate following recommendations of COLIPA documentation



### eryone SPF determination with UV-VIS spectra



the sun blocker products can be guidelines describe a method for

prepared in a capillary cell with very low thickness. But the spectra resulting from these measurements all show different signal structures, preventing comparison based on the SPF factor.

the preparation of samples, simulation of the skin, measurement technique and analysis of the results.

30 and 50+ SPF in the spotlight

The COLIPA Guidelines define a common understanding of SPF products for all suppliers. The

A PMMA polymer plate simulates the skin surface on which 32 mg of cream is distributed. The plate



Figure 3: SPF calculation for four UV-VIS spectra from a sun blocker defined as SPF 50+, the graph shows absorbance and transmission spectra, comment lines and inputs required as well as calculated results

surface has a specified roughness of approx. 5 µm and is suitable for collecting the transmittance of light by UV-VIS spectroscopy combined with an integrating sphere. The measurement procedures are described in the COLIPA method.

This method demands many repeat measurements and calculations of sum parameters from the data points of the spectra. Its

#### Conclusion

The UV-VIS-spectrophotometer UV-2600 combined with ISR-2600 integrating sphere is ideal for this application: the same system analyzes the color of the sun cream as well as the packaging. The samples measured here are labeled with SPF 30 and SPF 50+, difficult to measure with older technologies but easy with the UV-2600 spectrophotometer.

Item	Comment
Wavelength Range (nm)	290.00 to 400.00
Instrument Type	UV-2600 Series
Measuring Mode	Transmittance
Slit Width (nm)	5.0

Tabble 1: Measurement parameters for UV-2600 in combination with the ISR-2600 integrating sphere

SPF characteristics	Calculated values		
	Label 60	Label 30	Standard
SPF	63.12	30.69	18.86
SPF label	60	30	16
SPF UVA range (320 - 400 nm)	46.77	18.49	19.35
SPF UVB range (290 - 320 nm)	66.82	34.24	18.79
Unretained UVA average T %	8.16	18.55	12.23
Unretained Short UVA average T %	2.23	5.46	4.94
C factor	0.988	0.993	0.944
SPF adjusted	50	30	16
UVAPF0	30.33	10.93	14.78
Critical lambda (pre-irradiation)	379 nm	372 nm	380 nm

Table 2: Calculated SPF results from typical UV-VIS spectra of sun crèmes. Calculation equations are described in the COLIPA document.

mathematical results are the SPF value and the critical wavelength. The sample and calculation result is shown for a material labeled with SPF 50+. In this example, four measurements were carried out (shown in Figure 2).

These spectra were entered into the SPF calculator software and the result of the SPF 50+ sample is shown in figure 3.

These simple samples were not irradiated with an UV lamp. Table 2 shows a selection of values for all three samples. In table 1 the most important parameters are shown.

### Literature

 In vitro method for the determination of the UVA protection factor and "critical wavelength" values of sunscreen products, COLIPA Guidelines, March 2011

### Practical test: Lead in circui

ICP-OES spectroscopy – RoHS II – new guidelines



Figure 1: Electronic circuit boards - examples of sample material

p to now, lead constituted about 60 percent by weight as a component in solders, used in the manufacture of circuit boards for electrical and electronic equipment. Under the RoHS directive, the continued use of these solders is now only allowed in exceptional cases, so substitution products are on the increase. On this occasion, a test was carried out to determine the presence of lead in solders used in various circuit boards (Figure 1) in electrical and electronic equipment. Shimadzu's ICPE-9000 emission spectrometer with inductively coupled plasma was used for this investigation (Figure 2).

In addition to lead, other elements can be determined simultaneously in a single measurement using the ICPE-9000, which provides a wealth of information on a given sample within a very short time. The emission of sample atoms in the wavelength range of 167 nm to 800 nm is separated within an evacuated spectrophotometer and detected using a large high-resolution CCD chip. Due to the vacuum, the spectrometer of ICPE-9000 does not have to be flushed with inert gas and additional a minitorch reduces operation costs significant because of its low argon consumption rate of 10 L/min which is sufficient for stable operation of the analytical plasma.



Figure 2: ICPE-9000 simultaneous ICP-OES spectrometer with low operating costs

### t boards

Prior to measurement, a suitable sample preparation procedure is required to convert the heterogeneous circuit boards into liquid homogeneous samples. For this purpose, each circuit board is ground using various mills into a fine powder which is subsequently acid-digested in a microwave sample preparation system.

The prepared sample can now be measured directly. To ensure accu-

lematic in terms of RoHS II. This illustrates the importance of clarification of vague definitions (see info box) such as, for the source material, 'homogeneous material': A "material of uniform composition throughout or a material, consisting of a combination of materials, that cannot be disjointed or separated into different materials by mechanical actions such as unscrewing, cutting, crushing, grinding and abrasive



Figure 3: Emission profiles of the calibration for lead at 220.353 nm (left) and a possible source of the lead: Solder to attach electrical components to electric circuit boards (right).

racy of the results, the analytical emission lines used for evaluation were examined in detail with respect to interference influences. As an example, emission profiles of the lead calibration are shown in figure 3.

#### Results

One can reasonably expect that high lead content is due to several small contamination sources such as soldered joints. Since the results were based on total solder mass including plastic materials, the 'undiluted' contamination sources could exhibit an even higher lead concentration, making the use of these products even more probprocesses." [1] In this way, not even a single soldered joint may exceed the limit value if the distribution of an electrical or electronic equipment to and within Europe is to be further maintained.

#### References

 [1] http://eur-lex.europa.eu/LexUriServ/ LexUriServ.do?uri=OJ:L:2011:174:008 8:110:DE:PDF

### Hazardous substances ban for electrical and electronic equipment

RoHS stands for Restriction of Hazardous Substances and regulates the use of certain hazardous substances in electrical and electronic equipment, namely lead, mercury, cadmium, chromium VI and two special brominated flame-retardants.

While the first RoHS directive (2002/95/EG) has been in force since 1 June 2006, its successor directive RoHS II (2011/65/EU) [1] applies as of January 2013. Despite discussions on changing of limit values or inclusion of additional elements, the original values remain in force. For instance, the limit value for lead remains unchanged at 0.1 percent by weight. However, variations in the scope of the instruments types have been taken into consideration. Recently, medical devices or monitoring and control instruments are also covered under the directive.

In addition, vague terms have been defined in more detail, such as the scope of parties responsible in the product chain as opposed to just the 'manufacturer' in RoHS-I.

Sample	Pb [g/kg]
A	30.3
В	41.1
С	8.47
D	11.9
E	0.616
F	34.9
G	46.4

Table 1: Lead content of the electrical circuit boards

## Experimental compartment

lthough pharmacy is one of the oldest academic disciplines, it is in its present form a relatively young science. In today's pharmaceutical sciences, drug and active ingredient development is focused on ensuring that only specific substances unfold their effects following medication - side effects caused by interfering substances and impurities are undesirable. For this reason it is important to use the purest possible substances and purified tools and materials in the production of pharmaceuticals.

To ensure that equipment is free from undesirable foreign substances, cleaning of instrument surfaces is validated using various methods. For instance, the final rinse water after a cleaning process can be analyzed for possible contaminations. Likewise, a material surface can be wiped with a suitable medium and subsequently be analyzed for possible impurities.

Various parameters are used for such analyses. TOC (Total Organic Carbon) is one of the most informative analytical methods. The TOC parameter is a measure of organic contamination in a matrix.

TOC – the dirt trap

The TOC is an excellent analytical parameter to indicate and ensure that the instruments are free from traces of 'previous' drug batches. The TOC not only mirrors the presence of drugs, but also indicates other contaminants such as those originating from cleaning agents.

TOC determination is carried out via oxidation of the organic compounds to carbon dioxide. The carbon dioxide is subsequently transferred to an NDIR detector and measured. Oxidation is carried out in various ways – either Cleaning validation, Henry's law and diffusion associated with airborne molecular contamination



Figure 1: Experimental setup before and after closing the compartment

via chemical reaction of the organic compounds in the presence of sodium persulfate under UV irradiation, or via catalytic combustion at 680 °C.

Cleaned surfaces are, however, not permanently cleaned and then usable at all times. They can be contaminated again through various environmental influences. This also applied to the rinsing water. When carrying out cleaning validation, it is important to take these environmental influences into account.

### Organic compounds diffuse into water

A simple experiment carried out in a previous study has shown that the carbon content of water (Total Organic Carbon, TOC) that is in contact with air increases time-dependently. It was concluded that airborne, molecular organic compounds diffuse into water. The relevance to cleaning validation is given in the context that aqueous rinsing solutions after being in contact with air, may no longer comply with the TOC limit values for purified water. This is to be expected in terms of physics and subject to the laws of Fick, Dalton and Henry.

Simply stated: mobile compounds diffuse into media and between media such as air and water until they reach uniform distribution (Fick's laws). In closed systems, for instance in an air compartment, the total pressure is the sum of the partial pressures (Dalton's law). If a water surface is present in the air compartment, the gaseous molecular compounds diffuse into the water phase according to their partial pressures (Henry's law).

This represents the physics in terms of the model for 'ideal gases.' From another point of view, it could be that these laws apply to every airborne, molecular organic compound and, therefore, also to evaporated or sublimated organic compounds. On the other hand, the earlier study already implied the first experimental confirmation of this assumption.

Experimental setup: the compartment

Recently, a simple experiment using camphor, water and air in a closed container has been repeated: the metal relic of the past measured 700 x 360 x 380 mm  $(L \times W \times H)$  and the total volume was approximately 97 liter. A beaker containing 1 g of solid camphor (melting point 179.75 °C) was placed in the center of this metal box. Two beakers, each containing 50 mL of ultrapure water, were placed symmetrically in the center on either side of the camphor beaker. Two stainless steel trays, each with dry surface measuring 250 cm<sup>2</sup>, were placed on either side of the three beakers.

Questions needing to be verified experimentally over an appropriate time period were:

- Can camphor be detected following sublimation and diffusion?
- Does diffusion take place in the water medium?
- Is the stainless steel surface impinged by camphor?

The box was closed with a cover, and this experimental setup within the airtight container was left at room temperature for 14 days.

On first opening, 1 mL of the inner air was withdrawn using a gastight syringe and analyzed for camphor using direct-injection gas chromatography. The water in the two beakers was analyzed separately for TOC content. In addition, camphor was determined via UV spectrophotometry. The surfaces of the stainless steel trays were rinsed with methanol and camphor was determined via UV spectrophotometry.

#### Results

The results were as follows:

- Camphor could be detected using gas chromatography as being present in the closed air compartment as an airborne, molecular organic compound.
- Camphor was detected in water via UV spectrophotometry.
- The measured TOC content in both water samples was consistently found to be 400 ppm and 399 ppm.
- Camphor could not be detected at the trace level on the stainless steel surfaces using UV spectrophotometry.

An initial interpretation was as follows:

- As expected, camphor sublimates at room temperature and is distributed evenly in the air compartment in the form of airborne molecular organic gas (Fick's law).
- According to Henry's law, molecular gas-phase camphor diffuses into the water.
- The airborne camphor molecules cannot diffuse into the metal lattice of the stainless steel trays and 'wander' through the lattice imperfections like ions according to Henry's law. In this experiment, the reactivity of the surfaces and the other thermodynamic boundary conditions of the experiment did not lead to resublimation of gaseous camphor or solidification of UVactive degradation and reaction products on the stainless steel surfaces.

### Relevance for cleaning validation

The above represents the physics aspect with the anticipated results.

What is the relevance of this simple experiment for cleaning validation? Here are the conclusions:

- 1. Solids sublimate depending on their vapor pressure and, from the perspective of cleaning validation, become airborne molecular contaminants (AMC).
- 2. In principle, diffusion of gaseous molecular substances including organic contaminants takes place in the air and in adjacent media such as water and solids. Substances and organics can turn into airborne molecular contaminants, even when they are stored further apart.
- 3. When purified water is used for rinsing, its carbon content can increase due to diffusion of airborne molecular organic contaminants. Exceeding the limit values of 500 µg C/L is then only dependent on the duration of air contact and the dimension of the water surface that is in contact with air.
- 4. When purified water is used for rinsing, its conductivity increases due to diffusion of carbon dioxide. Exceeding of the limit value of 5.1 μS/cm at 25 °C by the secondary product carbon dioxide depends on the duration of air contact and the dimension of the water surface in contact with air. This analogous conclusion, which has been experimentally verified elsewhere, is mentioned here for the sake of completeness.
- 5. In the present experiment, sublimation of gaseous camphor was not detected on the stainless steel surfaces after 14 days at room temperature.
- 6. Conclusion 5<sup>th</sup> results do not rule out that secondary reactions can be initiated by reactive surfaces, contaminants and gaseous water ('humidity') and cause the formation of deposits with further solidification.
- The results according to conclusion 5 do not rule out that temperature differences can cause the formation of solids ('depositions') due to condensa-

tion and solidification, whereby condensed water with its established phase transitions in accordance with Henry's law can also act as a medium and 'vehicle.'

The relationships and considerations mentioned here can be used in the substantiation of expected values and acceptance criteria, as well as for the determination of the shelf life of cleaned and dried stainless steel equipment. As a limitation, it should be pointed out that in production plants, not only airborne molecular contamination but also airborne particular contamination must always be taken into account. Due to mass transport, particular contamination is even more relevant than airborne molecular contamination.

#### Conclusion

In the simple experiment described, the phase transitions solid phase —> gas phase —> water phase were verified using camphor as an example.

With respect to the integrity of formulations and equipment surfaces in contact with air during pharmaceutical production, at least several hundred known pharmaceutical raw materials and several thousand additional organics can be potential molecular airborne contaminants of the pharmaceutical products. Subsequent reactions of the airborne contaminants – taking place in the air, with atmospheric oxygen, water molecules, via catalysis on metal surfaces and finally also in contact with particles - seems hardly comprehensible in terms of numbers.

It is reassuring that all of this has not, so far, presented any significant limitation in the development of pharmaceutical production processes. Contaminants as well as contaminants resulting from subsequent secondary reactions are, in many cases, already present at levels below any perception and detection capabilities. In exceptional cases however, contaminants that have reached a product via diffusion, have already led to complaints of an organoleptic nature without any direct analytical detectability. The idea that air and cleaned surfaces are 'clean' in the sense of 'free from foreign substances' should clearly be abandoned.

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# Heavy metals in the food chain

Determination with the high-speed self-reversal method for background compensation



ly, control of elements at trace and ultra-trace concentration levels is carried out using atomic absorption spectrometers such as the Shimadzu AA-7000. This fully automatic double beam dual atomizer system is equipped with the GFA-7000 graphite furnace featuring digital control, and the ASC-7000 sample preparation station (see figure 1).

The AA-7000 concept allows fully automatic changeover from flame to graphite furnace mode and element-specific optimization of the atomizer position. The system includes two methods of background correction for the determination of heavy metals in samples of complex matrices when using flame and graphite furnace atomization. The Deuterium background correction is useful for compensation of spectral interferences generated by molecular absorption and particulatecaused scattering. In addition, the high-speed self-reversal technique (high current pulse technique) is useful for compensation of interferences caused by overlapping absorption lines and structured background.

All drinking water and wastewater is monitored continuously according to the European drinking water regulation and the law for indirect introduction of wastewaters. In addition, food is controlled through the German foodstuffs and requirements law where the determination of heavy metals such as lead and cadmium is strictly controlled in § 35 LMBG L00.00-19/3.

Determination of Cadmium in food and soil samples

High concentrations of Cadmium in contaminated soils can be dan-

eavy metals such as cadmium, chromium and lead are natural components of the earth's crust and are typically present in our environment in higher or lower concentration levels. They enter the human body via food, drink and air. Some of these heavy metals, so-called trace elements such as Chromium, Iron, Cobalt, Copper, Manganese, Zinc and Tin are essential in low concentration levels to the human body, as they are important for the metabolism. However, at higher concentrations they are harmful and poisonous to the human body.

Typical heavy metal poisoning is caused by drinking water contamination from lead pipes, air contamination from industrial emission sources, or intake via the food chain in the form of contaminated vegetables, meats and fish.

### Cadmium in drinking water

Water for human consumption has to fulfil the European drinking water regulation, where the maximum allowable concentration levels of the essential and toxic elements are clearly defined. Typical-



gerous as it can enter the food chain through plants. According to the European food safety authority, foodstuffs are the main source of cadmium exposure for the non-smoking general population [1]. The types of food contributing for the major part to dietary cadmium exposure, primarily due to high consumption, are cereals and cereal products, vegetables, nuts and potatoes as well as meat and meat products. High cadmium concentrations are expected in vegetables grown on soils close to industrial areas such as smelters.

In order to analyze food and soil samples, the analytical procedure begins with sample digestion using a microwave digestion system with a typical sample weight of approximately 250 mg in a mixture of 1.5 mL nitric acid (70 %) and 4.5 mL sulfuric acid (70 %). The sample solutions are transferred into a 10 mL flask and filled up to volume accurately. Quantitative determination of cadmium is done using a fully automatic sequence programmed on AA-7000, with a calibration curve from a stock standard solution with matrix matched acid concentration using the ASC-7000 sample preparation station in combination with the autodiluter.

Table 1 shows the instrumental parameters using conventional hollow cathode lamps and the recommended currents for low and high current measuring mode

Element	Cd	Cd
Wavelength [nm]	228.8	228.8
Slit width [nm]	0.7	0.7
Atomization	Graphite furnace	Graphite furnace
Lamp current D <sub>2</sub> BGC* [mA]		8
Lamp current SR BGC* [mA]	10/100	
Atomization temperature [°C]	2100	2100

Table 1: Instrumental parameters for determination of cadmium with different background compensation methods

using the high speed self reversal method which has been selected because of the complex matrix. The high-speed self-reversal method is able to compensate for spectral interferences caused by high iron concentrations on the cadmium line. Even arsenic interferences are also compensated for.

To apply the technique of the high-speed self-reversal background compensation, the cadmium hollow cathode lamp current is modulated in two modes. In the low current mode at 10 mA, absorption of element and background signals is measured while in the high current mode at 100 mA only the background signal is detected. Because the high current mode determines only the background absorption, the difference between the absorption of both types of light provides accurate background compensation and measurement of the atomic absorption of the target element. Further experimental work on cadmium determination in heavy matrix samples has been published by Waterlot and Douay [2].

#### **Summary**

Fully automatic atomic absorption spectrometers such as the AA-7000 are the right tools for solving a wide range of application problems in environmental and food analysis. Since the list of contaminants and their maximum contaminant level is expected to be even more stringently controlled in future, there is a real need for system configurations with lowest detection limits and highest precision. Shimadzu offers total hardware and software solutions for accurate determination of contaminants in water, food and soil samples, demonstrating competence and know-how of a market leader in spectroscopy.

#### References

- http://www.efsa.europa.eu/en/efsajournal/ pub/980.htm
- [2] Christophe Waterlot and Francis Douay, Talanta 80 (2009) 716-722

# Where's the difference?

Volume-based vs. number-based particle size measurement



figure 2: Volume-based particle size measurement

**S** himadzu offers a broad variety of particle size instruments, which support the well-established laser diffraction method, able to cover the measurement range of 0.5 nm to 3,000 μm. Additionally and exclusively Shimadzu offers the patented induced grating method.

A wide range of accessories enables measurements of highly concentrated, dry or small-volume samples. The phrases "volume based particle size distributions" and "number based particle size distributions" often appear when discussing the results of particle size measurements.

What is the difference between number and volume based result?

When looking at particle size distributions, "number-based" and "volume-based" change the scaling of the y-axis. If not explicitly mentioned, the scaling is "volumebased" as it is the more typical scaling. But "number-based" is also quite common.

Here's the difference: Let's assume that a sample solution contains particles with an average radius of 50 µm respectively 100 µm. The ratio of these particles is 1:1. When looking at "number-based" results two peaks will appear: One peak is at 50 µm and the second at 100 µm. The ratio of these peaks is 1:1.

When changing to a "volumebased scaling" the ratio of these peaks changes to a ratio of 1:8. The peak at 100  $\mu$ m is now eight times larger in comparison to the peak at 50  $\mu$ m.

### Here's the explanation

When looking at number-based results, the number of particles is taken into account. At a mixture of 1:1, the intensity of the lines is self-explanatory.

When looking at volume-based results, the volume of the particles is considered. The software implies that all particles are spheres and calculates their volumes according to

 $V = \frac{4}{3} \pi r^3$ 

Using particles with 50 µm and 100 µm radii (1:1 mixture) results in following equations:

 $V = \frac{4}{3} \pi (50 \ \mu\text{m})^3 = 523598 \ \mu\text{m}^3$  $V = \frac{4}{3} \pi (100 \ \mu\text{m})^3 = 4188790 \ \mu\text{m}^3$ 

Dividing 4188790 by 523598 results in 8. So 1:8 is the ratio of the peaks at 50  $\mu$ m and 100  $\mu$ m in the example above.

In the analysis of an unknown sample containing larger and smaller particles and "volumebased" analysis is chosen, it is possible that the peak at lower particle sizes cannot be seen. On the other hand, it is much easier when reporting with a numberbased scaling to find the smallest particles of the sample solution.

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# TOC analyzer in quality control

A customer report from the pharmaceutical industry

**T** illotts Pharma AG in Rheinfelden, Switzerland has installed a Shimadzu TOC-L analyzer for their quality control. The company produces and markets pharmaceutical products, medical devices and diagnostics for focused gastroenterological treatments and applications. In their "Tillotts Newsletter, issue 6" they describe applications and their experiences with the TOC analyzer.

In July 2011 a new TOC analyzer was installed and qualified in Quality Control. This equipment is used for measuring the Total Organic Carbon (TOC) content in liquid, solid or gaseous samples. It can be used in many applications for example cleaning validations, to verify the effectiveness of cleaning procedures and analysing the purity of different water qualities e.g. waste water, drinking water and water for pharmaceutical use.

The TOC content is a very important sum parameter and implemented in many monographs in all pharmacopoeias. The TOC analysis is an unspecific method determining all organic components that can be oxidised to carbon dioxide (CO<sub>2</sub>) which is determined quantitatively and very precisely by IR absorption. The advantage is that all components are measured in one run and that even unknown compounds like impurities are captured. In contrast other methods like chromatography (HPLC) or spectroscopy (UV, IR) detect and quantify a specific component only like the active substance (e.g. mebeverine hydrochloride) or a cleaning agent.

There are two different kinds of preparation methods: the wet chemical oxidation and the combustion catalytic oxidation method. The commercially available TOC analyzers all have very wide measuring ranges over several decades of e.g. 4 µg/L up to 30,000



Figure 1: TOC-L

mg/L for the actual type TOC-L<sub>CPH</sub> of Shimadzu. This is facilitated by diluting the sample solution. The calibration of the analytical method is done by means of a standard solution with a certified content of organic carbon of 1,000 mg/L. Of course, an SST (system suitability test) is performed with two independent references (benzoquinone, saccharose) to show the proper function of the whole system.

Summary description of the TOC analyzer in QC

### **Model:** Shimadzu TOC-L<sub>CPH</sub> (see figure 1)

**Type:** combustion type analyzer **Software:** compliant to 21 CFR Part 11 (FDA) – Use of normal or sensitive catalyst, analyzing down to a limit of detection in ppm to ppb range\*

Autosampler ASI-L: for effective and efficient working

Automatic sample acidification/sparging Automatic dilution function: if the TOC content is too high for direct measuring

\* $ppm = parts per million (10^{-6}),$  $ppb = parts per billion (10^{-9})$ 

### Conclusion

The new TOC-LCPH analyzer of Shimadzu was installed and qualified without problems. It was used since then in cleaning validations (showing in three runs the validity of the general cleaning procedure) and in the verification of a single cleaning procedure e.g. after the custom manufacturing of capsules for a clinical trial where only one batch of placebo and verum were produced. Here, the result of the cleaning is available on the next day and enables a quick decision whether a second cleaning is necessary or not and therefore avoiding long times of cessation in production. It is a very useful piece of

equipment that is also quite robust; after some initial trials we are now familiar with its routine use. It has a wide measuring range and the analysis can be performed very quickly with high precision. The handling of the TOC system (equipment and software) is easy, so an effective and efficient working is possible.

"Last but not least, we chose Shimadzu because of having a partner with great experience and reliable service not only in TOC analysis but other analytical techniques (IR, UV) that gives support in technical aspects, methods and qualification. We have a service contract in place like for other analytical equipment."

### »Best supporting actor«

HS-20 – The new generation headspace sampler



Figure 1: HS-20 headspace autosampler with the GC-2010 Plus

The Tony awards, the Goya or Molière prizes, Polish or German Film prizes, Academy awards, Golden Globe awards or the César – they all award prizes for best supporting actors or actresses playing alongside the leading actors and bringing out the best in them. And not just human actors but also robots, such as R2D2 or cars ('Herbie') can shine in supporting roles.

What is true for theatre and film also applies to technology: in analytical instrumentation, the leading systems unfold even more of their full potential when paired with high-quality peripheral systems. A new actor on the analytical scene is the HS-20 headspace autosampler, supporting GC analysis (Figure 1).

In headspace analysis, samples are typically heated in 10 - 20 mL gastight sample vials. Depending on the nature of the sample (matrix), volatile substances diffuse into the gas phase. When a defined volume of this gas phase is withdrawn and subsequently injected into a gas chromatograph, the results allow conclusions to be drawn on the composition of the actual sample. Headspace techniques (HS) are especially popular for samples that cannot be measured via gas chromatography without prior sample preparation. Examples are traces of organic compounds on solids, for instance fire accelerants on building components, or odorintensive substances in plastics, residual solvents in drugs, but also drinking water.

### Large sample volumes for trace analysis

The great advantage of HS lies in the available sample volume of several milliliters. Whereas in conventional liquid injection only a few microliters of a sample can be evaporated, a much higher sample volume is available in HS analysis. With virtually quantitative diffusion of volatile substances from the sample volume into the gas phase upon heating, HS allows injection of significantly more of the substance amount compared to the volume possible via liquid injection of the same sample.

In this way, headspace analysis can significantly decrease detection limits. The concentration equilibrium of a component between the liquid or solid and the gas phase is essentially influenced by the incubation temperature and the matrix, i.e. the chemical composition of the liquid or solid phase (Figure 2).



Figure 2: Phase equilibria in the headspace vial

### Automation included

Another advantage of HS versus sample extraction is its complete automation, in which modern HS autosamplers enable highly complex and very detailed and controllable sample preparation. As the gaseous sample comes into contact with a variety of surfaces in the autosampler's sampling system, deactivation of these surfaces is essential in order to meet the high analytical demands of trace analysis.

The HS-20 headspace sampler sets new standards in meeting of these demands. Designed as 'transfer line HS system' it complements the syringe-based HS AOC-5000 Plus sampler. While the latter allows a flexible choice of injection techniques (liquid, headspace, solid-phase micro-extraction [SPME] and in-tube extraction [ITEX]), the HS-20 is firmly connected to the GC system via a transfer line, offering better precision and more headspace analysis options.

A large incubation oven allows simultaneous sample preparation of up to twelve samples. It is furnished with a sample tray holding 90 samples (Figure 3), where 10 and 20 mL HS sample vials, screw or crimp vials can be placed in any order. For rapid gas phase equilibration, the samples are shaken during incubation. The incubation temperature of the oven can be set to up to 300 °C and kept constant using an air circulation system (similar to a GC oven). An incubation time of up to 1,000 minutes is possible.

Excellent recovery rates and reproducibility

The inert transfer line, optimized for connection to Shimadzu's GC-2010 series, enables transfer of high molecular weight as well as surface-active substances to the GC system with superior recovery rates and reproducibility (Figures 4 and 5). All lines in the HS-20 with direct sample contact can be heated up to 300 °C – the transfer line optimized for the GC-2010 can be heated to 350 °C. This enables a 100 % recovery rate for the usual test with n-alkanes up to C24.



Figure 3: Air circulation incubator oven and sample tray of the HS-20

But beyond this, the HS-20 sets new standards as evidenced by the recovery rates of over 50 % for n-C32. Further proof of the inertness of the HS-20 is the very low carry-over rate for surface-active substances, for instance a carryover of less than 0.0001 % for 1,3-dimethyl-2-imidazolidinone (DMI) and for acetic acid.

The HS-20 offers a 'multiple headspace extraction' (MHE) function for detection of matrix effects or quantification of volatile components in solids (i.e. plastics). Up to 10 headspace extractions per vial are possible. Volatile components can be quantified from the decrease of the peak areas from extraction to extraction. Essential here is constant pressurization of the vials. Prior to each measurement, the sample vial is pressurized to a predetermined pressure using an inert gas, essential to attain accurate results in MHE – and also a factor for good reproducibility in conventional HS analysis. For pressurization, the HS-20 uses the proven electronic pneumatics of the GC-2010.

#### Casting – the optimal cast list

The HS-20 is available in several versions. In addition to the standard model, a 'HS-20 Trap' version is also available. This model allows enrichment of multiple extractions from one sample vial onto a cold trap filled with an adsorbent (e.g. Tenax TA) for the detection of low trace amounts. The trap is cooled down to -30 °C using a Peltier element, which enables freezing of the multiple extracts obtained from one sample vial and subsequent focused transfer onto the separation column via





rapid heating. Using repeated extraction, the amount of sample used in the analysis can be significantly increased, opening up new possibilities especially for trace analysis.

The software directs the analysis

The HS-20 can be controlled easily via the supplied software. Alternatively, drivers can be integrated within the GC software packages (for instance LabSolution). In this case all parameters of the autosampler method, along with the GC method, are stored in the chromatogram data file and can be viewed at any time. At the same time, internal diagnostic results of the sampler are also retrievable, for example when checking whether a vial has maintained pressure after pressurization or whether it has been closed properly (Figure 6). Used in combination with Shimadzu's GC and GCMS systems, the HS-20 trap system signifies the start of a new era in headspace trace analysis.

Item	Output
Pretreatment Result	Normal end.
Injection 4	1
Max Pressure at Pressurizing (Injection 1)	99 kPa
Min Pressure at Pressurizing (Injection 1)	99 kPa
r	

Figure 6: Results of the internal HS-20 diagnostics. Comparing the 'maximum pressure' immediately following pressurization to the 'minimum pressure' after a set waiting period for reaching equilibrium does not reveal any difference. This demonstrates that the vial was closed properly.



### Read the lips

FTIR spectroscopy of cosmetics and pharmaceuticals

osmetics and perfumes are offered as powders, liquids, creams and emulsions. Some products and their functions overlap with medical substances.

Infrared spectroscopy is an analytical tool which differentiates between them, both cosmetics and toiletries as well as medicinal ingredients.

One part of the human body needs special care – the lips. They are very sensitive towards environmental influences, for example exposure to the sun, food or viruses such as herpes. These all affect the lips and can cause painful reactions. This article focuses on lip balm, available as cream or balsam.

Special care for lips

In the dry atmosphere indoors during the winter, lips tend to dehydrate and need special care. The same effect occurs in sunlight in winter or summer. Under these conditions, water in a lip cream is unhealthy. Instead, a fatty product is needed for protection of the lips in order to avoid sunburn. Particularly in snow-covered mountains regions the burn effect is even more dangerous and the lips demand care products with a higher proportion of fat with UV filters.

Medical creams are independent of this subject. Their role is to transport embedded medicine into the lips to stop or avoid the appearance of diseases such as herpes (herpes labialis).

In order to demonstrate the simple differences between pharmaceutical and cosmetical ingredients, some lip creams were measured using FTIR spectroscopy equipped with a single ATR (Attenuated Total Reflectance) accessory. Small portions of balsam and creams were placed on the measurement window (2 mm in diameter) of the single reflection ATR unit. The accessory used is based on the diamond window.

FTIR methods applied

FTIR spectroscopy is a powerful tool which can be applied to a wide range of sample types. The majority of the samples can be read using an ATR accessory in the instrument. Compared to other techniques, ATR eliminates most of the sample handling time required. In most cases, a sample can simply be dispensed to the ATR crystal and detection can start without any further preparation. In this context, the diamondequipped ATR version is useful since the high pH-value of many creams can attack the convention-



Figure 1: Four different infrared reflection spectra from diverse lip balsams and creams: black shows lip balsam, green a UV protection lip cream, blue a medicine against herpes while the red line shows a pharmaceutical lip cream containing dexpanthenol and ceramides.

al ZnSe crystal normally used in the ATR accessory.

Samples were applied directly to the measurement window. For data acquisition, default resolution was used with wavenumber ranges 4,000 - 400 cm<sup>-1</sup>, Happ-Genzel Apodization and 4 cm<sup>-1</sup> resolution with an accumulation of 40 scans for the signal averaging (multiplex advantage of the FTIR technique).

The benefit which ATR provides is excellent throughput and performance - combined with Shimadzu's FTIR Spectrophotometer with exceptionally high throughput of light and very high signal-to-noise ratio. Introducing a liquid or powder sample to the accessory simply requires dispensing the material into the small measurement window.



spectra mainly belong to the fatty acid molecular groups.

The third spectrum is a typical profile of a water-based spectrum. Strong and broad signals in the region of -OH structures are visi-



not only water is the base of the pharmaceutical product Bepanthol. Near to the broad signal of water, a sharp signal in the range of the fatty acids at 1,740 cm<sup>-1</sup> makes a difference. This signal is recognized in the spectra for the balsam and the UV protection cream. It is the one for fatty acids. In addition, Bepanthol includes Dexpanthenol and Ceramides.

The fourth spectrum shows that

#### Conclusion

FTIR is an exceptionally versatile technique offering high levels of sensitivity and specificity while needing very little time or effort to perform. The sequence from measurement to library match takes only a few clicks of the mouse, and samples can be measured in a few seconds simply by dispensing solids or liquids onto the single-crystal ATR. Some samples can be measured with greater sensitivity using a multiple-bounce ATR design.

The infrared comparison shows spectra for four products relating to the ingredients of the creams and balsam. The spectra are dominated by water and fat or waxstyle materials. Where the content of the pharmaceutical ingredient is more than 1 %, identification is possible.

Instruments: FTIR: IRAffinity-1 Accessory: DuraSampIIR, diamond based single reflection unit Structure analysis: IRAnalyze version 1.3 Libraries: Sadtler, Shimadzu

Figure 3: The chemical structure of Acyclovir, by name 2-Amino-9-(2-hydroxyethoxymethyl)-3H-purin-6-on.

### The spectra of balsam and creams

According to the label, the lip balsam is a mixture of detergents blended with beeswax. A library search connects the spectrum to fat, oils and waxes. It shows the typical fatty acid signal at 1,740 cm<sup>-1</sup>.

The lipstick with UV protection and the balsam are reduced in the main spectrum to fat, oils and wax. The balsam spectrum contains more infrared information which seems to be of inorganic material, most probably  $TiO_2$  or some other salt as the cream is white in color. The whitener must be either digestible for the human body or harmless in order to move through the body without complication. ble (strong 3,300, strong 1,600 and broad weaker signal around 2,100 cm<sup>-1</sup>). In the fingerprint range some additional signals show the ingredients mixed with the waterbased cream. Not all of the signals relate to the typical fat signals, because the 1,740cm<sup>-1</sup> signal for fatty acids is missing. In this case, paraffin and Vaseline instead of fatty acids form the base of the cream. The different alcohols in this cream have related signals at about 1,044 and 1,082 cm<sup>-1</sup>. The pharmaceutical ingredient Aciclovir with 5 % (weight %) is included in the cream.

The signal at 1,380 cm<sup>-1</sup> can be the vibration of the -(C-N) molecular group. Other reference signals of amine structures overlap with the water signals and cannot be seen directly.



Figure 4: Structures of Ceramide (above) and Dexpanthanol (below); above the typical structure of a ceramide is shown whereas R equates to a fatty acid.



# FAMEs in aviation turbine fuel — a risk? GC/MS analysis of Trace Fatty Acid Methyl Esters

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urrent and growing international governmental requirements to add fatty acid methyl esters (FAMEs) to diesel fuel have had an unintended sideeffect of leading to potential FAMEs contamination of jet turbine fuel in multi-fuel transport facilities, with industry-wide concern. The contamination of aviation fuel with fatty acid methyl esters can arise through the use of multi-product pipelines or tanks for fuel supply and distribution. FAMEs can adsorb onto the surface of the pipeline, contaminating fuel that follows, including aviation turbine fuel (AVTUR).

There are two main issues with introduction of FAMEs content

into diesel fuel that impact on jet fuel:

1: FAMEs are active and tend to stick to metal or glass surfaces. This creates new risks of cross contamination where supply

Nominal std conc. (mg/Kg)	Volume WSS (µL)	Volume dodecane (µL)	Volume internal standard (µL)
100	1000	0	10
80	800	200	10
60	600	400	10
40	400	600	10
20	200	800	10
10	100	900	10
8	80	920	10
6	60	940	10
4	40	960	10
2	20	980	10
0	0	1000	10

Table 1: Volumetric dilutions for preparing standards in the range 0 - 100 mg/kg from the 100 mg/kg working standard



chains handle both jet fuel and biodiesel.

2: FAMEs are non-hydrocarbon fuel components. But jet fuel specification states explicitly that only hydrocarbon components or approved additives are allowed.

The international jet fuel specifications (e.g. DEF STAN 91-91) limit FAME content to less than 5 mg/kg (mg/kg w/w). Levels above 5 mg/kg render the fuel out-of-specification.

Current methods for determining FAME content in aviation fuel use a polar type GC column for the separation with mass spectrometry (MS) for detection. The test sample of AVTUR is run together with an internal standard on the GC-MS to separate the polar FAME relative to the non-polar hydrocarbon matrix of the jet fuel and any mineral diesel contamination. Due to natural background of high-end naphtha components present in some samples, complete separation is not possible and a multiple selective ion monitoring (SIM) is performed. The ions used in the SIM method are indicative of the FAMEs and not the background hydrocarbon matrix of the fuel, therefore distinguishing FAMEs from hydrocarbon aviation fuel.

### **Experimental**

The analysis was performed on a Shimadzu GCMS-QP2010 SE with a split/splitless injector. A 1.0 µL splitless injection introduced the standards and the samples with the aid of an AOC-20i

autosampler and chromatographic separation was achieved on a 60 m x 0.25 mm Øi x 0.50 µm HP-INNOWAX column.

Detailed instrument parameters are presented below:

Instrumental conditions

### GC oven temperature programme

Initial temp 150 °C and hold for 5 min.

Ramp at 12 °C per min until 200 °C and hold for 17 min. Ramp at 3 °C per min until 252 °C and hold for 6.5 min. Total run time: 50 min.

### Sample injection

Splitless injector, temperature 260 °C. Sample volume 1 µL.

#### **MS** Conditions

Ion source temperature: 200 °C Interface temperature: 255 °C Detector Voltage: 0.83 kV

SIM measurement: See table 3

### Procedure

The experimental procedure was carried out according to IP 585/10. A stock standard solution of 1,000 mg/kg of FAMEs as well as a 1,000 mg/kg of internal standard (C17:0 d33) were prepared in dodecane. A 100 mg/kg working standard of FAMEs was then prepared as well as all standards derived from it according to table 1.

Two calibration plots for each fatty acid methyl ester were used,

covering the working ranges 0 mg/ kg to 10 mg/kg (using the 0, 2, 4, 6, 8, 10 mg/kg standards) and 0 mg/ kg to 100 mg/kg (using the 0, 20, 40, 60, 80, 100 mg/kg standards). The lower working range should be applied for all FAMEs present in any sample at less than 10 mg/kg. The 0 mg/kg to 100 mg/kg calibration range shall be applied for all FAME species present in any sample at greater than 10 mg/kg. In figure 1, a chromatogram of a 10 mg/kg standard of FAMEs is shown.

Correlation coefficients of all fitted calibration curves were excellent as can be seen in table 2 and figure 2. The total FAME concentration is calculated by summing the concentrations obtained for

the six specified FAMEs using the specified calibration ranges.

As a fixed volume of sample is injected, the density of the samples will vary and differ from the dodecane used to prepare the standards. A density correction factor is therefore applied to the concentrations calculated from the standard calibration according to with the equation:

Total FAME, mg/kg = (measured FAME, mg/kg) x (density of dodecane)/(sample density).

Quantitation as well as implementation of density correction factor was performed automatically by the GCMS solution program.





(HELLAS)



Although the method requires a
0.5 mg/kg detection limit for each
substance (signal to noise 10:1),
the instrument achieved much
higher sensitivities (signal to noise
from 50 to 200:1 depending on
the substance) with a low detector
voltage (0,83 kV) as can be seen in
figure 3.

Conclusions

The Shimadzu GCMS-QP2010 SE was proven to be an excellent platform for the determination of FAMEs in aviation turbine fuels according to the IP 585 test method. The method showed excellent linearity at both high and low concentration levels as well as high sensitivity even with low detector voltage. All method parameters, internal standard calibration curves and density correction factor were successfully implemented in the GCMS Solution software, allowing automatic quantification of the samples. Finally, this meth-

FAME	R <sup>2</sup> (0 - 10 mg/Kg)	R² (0 - 100 mg/Kg)
C 16:0	0.993	0.997
C 17:0	0.995	0.996
C 18:0	0.997	0.996
C 18:1	0.997	0.997
C 18:2	0.998	0.997
C 18:3	0.998	0.995

Table 2: Correlation coefficients of the calibration curve

FAMEs to be detected	SIM ions to be used for quantification
C 16:0	227, 239, 270, 271
C17:0 (d33) Internal standard	317
C 17:0	241, 253, 284
C 18:0	255, 267, 298
C 18:1	264, 265, 296
C 18:2	262, 263, 264, 294, 295
C 18:3	236, 263, 292, 293

Table 3: SIM measurement

od has been successfully implemented in Motor Oil (Hellas) Corinth Refineries S.A., one of the largest petroleum companies in Greece and to our knowledge the only Greek laboratory performing it.

#### References

[1] IP 585:2010, Determination Of Fatty Acid Methyl Esters (Fame), Derived

From Bio-Diesel Fuel, In Aviation Turbine Fuel – GC-MS With Selective Ion Monitoring/Scan Detection Method, The Energy Institute, London, UK

- [2] JIG (Joint Inspection Group), Bulletin No 21, November 2008. www.jigonline.com
- [3] Ministry of Defence, Defence Standard 91-91, Issue 6, April 2008, **UK Defence Standardization**

### PRODUCTS

### New accessory for the UV series

ew micro cell holders extend the wide range of accessories for the UV-2600/UV-2700 spectrophotometry series. This UV-VIS-NIR spectroscopy instrument series owes its high performance to the patented 'LO-RAY-LIGH®' diffraction gratings.

Micro cell holders for integrating spheres

With the introduction of the UV-2600, the ISR-2600Plus integrating sphere has been implemented, a unique feature for this instrument class enabling measurements in the near-infrared range up to 1,400 nm. For both this new integrating sphere and Shimadzu's entire model range, an additional accessory is now available for the measurement of small samples. Until now, small samples had to

be embedded in barium sulfate (BaSO<sub>4</sub>) as part of the sample preparation process, which is not necessary using the new micro sample holders. They are supplied in a pack of three holders for various sample sizes.

Table 1 lists the dimensions of the various samples. The samples can be round ( $\emptyset$ ) or square ( $\Box$ ). Small lenses, filters or glasses can be fixed securely - they are locked inside the holder very easily via sliding elements. The sliding elements also function as masks for the measurement of smaller samples. The holders are fixed to the

corresponding measurement positions of the integrating sphere, enabling both transmittance and reflectance measurements.



Figure 1: Micro sample holder for samples of 10-14 mm internal diameter or rectangular shaped samples; maximum diameter of the light beam for transmittance measurement is 5 mm

Sample holder	Sample size
Large samples	Ø 10 - Ø 14 · 🗆 10 - 🗆 14 mm
Medium samples	Ø 6 - Ø 14 · 🗆 6 - 🗆 12.5 mm
Small samples	Ø 3 - Ø 9 · 🗆 4 - 🗆 8 mm

Table 1: Dimensions of the micro sample holders for Shimadzu's integrating spheres

# Technical failure or 'human factor'?

Measurement inaccuracies in X-ray fluorescence spectroscopy



Figure 1: Energy dispersive X-ray fluorescence spectrometer EDX-800P

n elemental analysis, ICP, AAS and EDX methods differ in terms of sample preparation complexity, lowest possible detectable concentrations, the number of simultaneously measurable elements and the overall measurability of an element. While ICP and AAS offer better detection limits, sample preparation can usually be omitted when using EDX. Carbon to uranium or sodium to uranium can be measured in solid as well as in liquid samples. Depending on the element and sample, the detection limit reaches down to the single digit 'ppm range.'

After selecting a suitable method for an analytical question, it is important to be able to determine the accuracy of the measurement results. Sometimes the analytical method or the measurement instrument are blamed for nonoptimum measurement results or too high overall standard deviations.

The total measurement error, however, is the sum of many individual errors. The first error often arises during sampling. In this step, it is important to obtain a sample which is as representative as possible. Furthermore, the sample should be homogenous, and all elements present in the sample must be available for the applied measurement method. It can, however, still be possible that the sample itself changes the measurement result, either as a result of interaction between the sample components or due to interaction with the measurement method. Weighing errors or errors due to incorrect calibration distort the final result in addition.

The instrument error is often the smallest factor contributing to the total error of a measurement result.

In the present case, a potassium/manganese mixture was finely ground, pressed into a tablet and measured 20 times using Shimadzu's EDX-800P. The sample was not repositioned in the sample chamber, thereby excluding errors arising from possible sample inhomogeneity. A standard deviation of the measurement results of 0.2 % was achieved. This reflects the measurement accuracy of the instrument in the present case.

Looking at the total error of an EDX measurement, 5-fold up to

10-fold higher standard deviations are quite realistic. It is a recurring challenge for the experimenter to reduce these errors as much as possible using suitable sampling and sample preparation methods. This is a challenge in which Shimadzu is happy to assist.

Measurement	K (ppm)	Mn (ppm)
1	37.2	62.8
2	36.9	63.1
3	37.1	62.9
4	36.9	63.1
5	36.9	63.1
6	37.0	63.0
7	36.9	63.1
8	37.0	63.0
9	36.8	63.2
10	37.1	62.9
11	36.7	63.3
12	37.0	63.0
13	36.8	63.2
14	36.8	63.2
15	36.8	63.2
16	36.7	63.3
17	37.2	62.8
18	36.6	63.4
19	36.8	63.2
20	36.8	63.2
Average	36.9	63.1
Standard deviation	0.2	0.2

Table 1: Measurement results: K/Mn mixtures

# Global structure – Global Design



Figure 1: New website following Global Design guidelines

»Excellence in Science« is Shimadzu's promise to customers worldwide. With its strongly networked company structure reaching across continents, Shimadzu serves the needs of internationally active companies, small businesses or large enterprises alike.

In order to reach prospects and markets in times of global business relationships with a consis-



Figure 2: First issue with new design

tent brand recognition, Shimadzu has developed a new Global Design for all its communication channels – advertisements, brochures, mailings etc. Shimadzu's website and the 'Shimadzu News' apply this new design as well.

Shimadzu Europe website

The new web presence has been implemented for the European business units 'Analytics' and 'Medical Technology' – white, subtle, clear structuring and large images characterize Shimadzu's design of the front-page with a large key-visual related to current topics of analytics. The design of the inner pages is minimalist and has been optimized regarding reader-friendliness and readability.

In three issues per year, the Shimadzu News articles cover new applications, products and developments in analytical instrumentation and materials testing. The Shimadzu News is also available as iOS App and Web App.



Figure 3: Clear and well structured - the new interior design of the Shimadzu News

new look. This way, the corporate as well as the product brands can be experienced consistently. The websites of the individual European subsidiaries will be released shortly.

Shimadzu News

»The times they are a-Changin« – so do the 'Shimadzu News.' Since its first issue, this wellestablished print medium has periodically adapted and updated its content and look over the years. The new Global Design has been applied for the recent facelift.

In fact, the first issue featuring the new look was already published at the end of 2012. One of the most obvious changes is the



Shimadzu News iOS-App



Shimadzu News WebApp