



ACHEMA 2000 22. – 27. May 2000 Frankfurt am Main/Germany

The opening ceremony of the 26th ACHEMA was performed in the Congress Center at the Frankfurt Exhibition Grounds. From Monday, May 22, 2000 the gates to the world's biggest chemical engineering Exhibition-Congress and International Meeting on Chemical Engineering, Environmental Protection and Biotechnology was opened to the public for 6 days. The special trend reports of ACHEMA 2000 exhibition (no 1-19) were prepared for publication by authorities from DECHEMA. In this issue of *Chemical Industry JI. (Hemijska industrija)* trends covering Production-integrated environmental protection in the chemical industry, Life Sciences in the service of mankind, and Particle Technology-nanoparticles are prepared.

Trends covering Process Identification (PI), Process Instrumentation and Control, Process Safety, and Plant Engineering Tools were published in No 6 of *Chemical Industry JI.*, while trends covering the Pumps and valves, Pumps, fitting and seals, Compressors, drives and seals, and Trends in Automation in No 7-8, Packaging (New Materials and Technologies) and Environmental management in No 10, and trends covering Pharmaceutical Technology, Trends in pharmaceutical industry, Genetic Engineering, and Industrial Biotechnology in No 11.

PRODUCTION-INTEGRATED ENVIRONMENTAL PROTECTION IN THE CHEMICAL INDUSTRY

Sustainable environmental protection at work is the result of a variety of efforts within the company – production-integrated environmental protection is an important component. At ACHEMA 2000 more than a 1000 exhibitors from different exhibition groups presented components and solutions to problems in the field of production-integrated environmental protection.

The chemical industry is seen worldwide as one of the main causes of environmental pollution. The potential risk but also the level of environmental protection in this sector is high. Terms such as Responsible Care and Sustainable Development are automatically associated with the environmental politics of the chemical industry. German chemical companies have taken the lead in these policies. They are part of the worldwide chemical initiative known as Responsible Care and have committed themselves to constantly improving health, environmental protection and safety policies.

In the seventies and eighties rapid implementation of environmental protection requirements was primarily achieved by end-of-the-pipe solutions, i.e. processes located downstream from the production process which are used to clean off-gases and waste water and to dispose wastes. At the end of the eighties an attempt was made to come up with an integrated concept which tackles the problem of environmental protection at its source. It makes sense to avoid environmental pollution during the production of a product, especially since end-of-the-pipe solutions are financially worthwhile only if a certain degree of clean up is reached. The costs however increase exponentially in relation to the reduction of emissions.

Avoid emissions and preserve resources

The aim of production-integrated environmental protection is not only to reduce emissions to the environment, but also to preserve resources. To this end,

completely new processes must be developed or established methods optimized to reduce the amounts of by-products, non-converted raw materials or auxiliary substances, and preventing or reducing emissions. For example, the reaction of the raw materials used can be improved, the selectivity of the reaction can be increased or the number of steps in the process reduced. The introduction of recirculating production cycles or the optimization of plant and control technology contribute to better environmental protection.

A poll showed that the R&D projects for production-integrated environmental protection in the chemical industry differ depending on the product range of the company. Industrial companies which produce bulk chemicals place the emphasis on process control. Companies which are closer to the end-user, such as producers of bodycare products, focus more on the use of resources. In every case it needs to be verified whether the proposed process is technically, environmentally and economically feasible.

Ecological efficiency analysis as a decision-making tool

The analysis of ecological efficiency, for example, is a useful tool. It can help a company decide which products and processes are worth investing in. The method involves analyzing the entire lifecycle of a product or manufacturing process in terms of five categories: the consumption of raw materials, energy consumption, emission in air and water and during disposal, the toxicity and the risk potential. All these data combined give the degree of environmental pollution. Economic data is also collected. The economic and ecological data are then plotted on the two axes of a graph showing the ecological efficiency of the product or process. Using this method it was possible, for example, to optimize the production of indigo and the dying process for blue jeans. The highest ecological efficiency is demonstrated by the process in which a 40% solution of pre-reduced indigo and a new electrochemical dying technique were

used. This method enables the use of hydrosulfite as a reducing agent to be avoided.

An example of production-integrated environmental protection, which has proven its worth, is modern adipic acid production. The preferred method used to be the strongly exothermic discontinuous oxidation of a mixture of cyclohexanol and cyclohexanone with nitric acid in stirrer tank. The heat released was absorbed by the cooling water. Nowadays the reaction is carried out continuously. The nitric acid is concentrated in the reaction mixture using the heat of reaction. The cooling water is circulated, separated from the wastewater. In this way, 50% less energy in the form of steam and 10% less nitric acid are required; the volume of wastewater is reduced by 98% (with much lower COD – chemical oxygen demand values), and the total yield of adipic acid is increased by 4%. Since 1993 a method has been in use whereby the nitrous oxide which is formed as a by-product is broken down to nitrogen by thermal reduction, and the energy released as steam is fed back into the supply system. This method of synthesis, regarded for a number of years as state-of-the-art, has been improved, both in terms of cost and the impact on the environment, by a new catalyst system. The purity of the adipic acid produced has also increased considerably, and this is a great advantage for all subsequent steps.

In 1998, the flow of reflux cooling water in a plasticiser plant of a chemical company was changed from a continuous to an open system. In this way the consumption of reflux cooling water has been lowered by 500,000 cubic meters per year, and the volume and degree of pollution of wastewater has also been significantly reduced. In the refinery which produces C4 products, the company has introduced a process information and control system which allows a better analysis of the process and, at the same time, a reduction in energy consumption of around 2%.

The process must be changed

In order to achieve production-integrated environmental protection, different technical components are required depending on the application. Filters and membrane systems, centrifuges or evaporation plants ensure that wastewater or solvents, for example, are cleaned and can be fed back into the system. AICHEMA 2000 presented many innovations in this field. Exhibits included a liquid-liquid phase separator which can separate organic solvents from wastewater using coalescence filters (microfibres) at a low cost and with minimal energy expenditure, as well as an emulsion splitting unit with heat recovery and resource circulation. A heat pump-boiler concentrates wastewater from the wash and cleaning processes in chemical production. Dry weights of between 20 and 40% are achieved. The distillate is fed back into the system. A process filter plant for product recovery in a drying process for the chemical industry, which, depending on the application, contains

various filters for the different air volumes being treated. Instrumentation and Control Systems presented at AICHEMA 2000 allow optimum dosage of flocculation aids e.g. and thus make an active contribution to production-integrated environmental protection.

Biotechnology provides new approaches for production-integrated environmental protection

Biotechnology processes often have many advantages compared with chemical synthesis and thus considerable potential for preventive production-integrated environmental protection. They allow mild reaction conditions at low temperatures and pressures, the use of aqueous media, as well as raw materials that are often cheaper, and they often enable greater selectivity and specificity in the conversion of reactants to products. This preserves both material and energy resources and reduces emissions.

Biotechnology, has, until now, been used primarily for the synthesis of highly expensive special and fine chemicals and chiral substances in the chemical and pharmaceutical industry. Genetically modified organisms, or enzymes produced by them, are also used for the production of drugs and diagnostics. A shift in the production of 6-amino-penicillic acid from a chemical to a biocatalytic process has made it possible to avoid the solvents dichloromethane, n-butanol and N,N-dimethylaniline as well as the toxic compounds phosphopentachloride and dimethyldichlorosilane. The energy consumption sank by 50%. According to a study, the main obstacles which have prevented biotechnology methods being introduced, are, above all, the lack of know-how and the fact that the enzymes needed are not present in the necessary quality and quantity.

In the production of detergents and cleansers large amounts of enzymes produced by biotechnology are used in cleaning products. This enables less detergent and lower washing temperatures to be used. Gene technology is used to produce large amounts of enzyme with high purity. For example, the saving in terms of raw materials, in the production of a protease by gene technology in 1996 was 82%, and the energy saving was 84% compared with the enzyme produced by the conventional method. Carbon dioxide emissions were reduced by 84% and organic wastes by 70%.

Innovations cost money

The chemical industry is convinced that innovations are essential if the current trends in production-integrated environmental protection are to continue. Many universities and research institutes demonstrated the latest approaches in production-integrated environmental protection. For example, a software program for designing process systems with high energy efficiency was presented, as well as a new membrane systems for different applications.

Integrated environmental protection processes often require longer research, development and approval times than new additive methods, and the costs are therefore higher initially, but in general the trend for production-integrated environmental protection in the chemical industry is positive. In 1994 and 1995 the operating costs for environmental protection in the big chemical companies in Germany were lower for the first time. This shows that the integrated measures can also be economically advantageous.

Only complex steps lead to success

It is important, however, to see production-integrated environmental protection as only one component – be it a very important one – in the complex interaction of all the environmental protection measures within the company. Thus it is virtually impossible to recognize the weak points and identify the optimization potential in the production process without a well-organized environmental management system, clear delegation of responsibility, the setting of concrete environmental goals, such as the ecoaudit, and without the implementation of material, energy flow and environmental efficiency analyses. All three aspects of environmental protection: production integrated environmental protection, product related environmental protection taking into account the use and disposal of products and downstream clean up measures must be investigated from ecological, economic and social points of view to find an optimal solution. The recovery of raw materials and the utilization of materials, wastewater and waste heat at both the intra- and intercorporate level, is particularly relevant in this context. And, above all, it is essential to preserve as much as possible resources such as water, energy, etc., in every part of the company.

Analysis, Automation and Miniaturisation

The classic image of analysis in Erlenmeyer flasks and test tubes is a thing of the past. Precise technology, electronics and data processing have become an essential part of analysis. As a result, detection limits are being lowered and the accuracy of analyses is increasing. At the same time online analysis is gaining significance in production. Many exhibitors at ACHEMA illustrated this trend.

Automation is increasingly becoming a focal point of analysis – both in the laboratory and production. In particular pharmaceutical and life science companies, searching for new drugs, are committed to faster techniques in the laboratory, but analytical laboratories also want to reduce costs of standard methods. Whereas the aim in the laboratory is often to analyze unknown components, in production the basic composition is already known. In this case, the analytical techniques must be suitable for production and automated. Process analysis has huge potential and Frost & Sullivan estimates the annual growth worldwide for process analysis equip-

ment to be 6.3 percent. In the year 2004 this market is predicted to have a turnover of \$US 1.4 billions worldwide.

Maintenance is an important aspect of process analysis. This is carried out on a daily basis by engineers, in a similar way as for pressure or throughput analyzers. Even a complicated gas analysis, which involves sample preparation, then measurement and finally disposal, then becomes just one measurement amongst many, and therefore has to be robust. Maintenance and regular status reports are part of the everyday workload. Although improved diagnostic methods make error recognition easier and thus reduce the effort required to remedy the problem, safety-dependent applications require very high reliability. For many analytical engineers the analysis fieldbus and its interfaces play a vital role. Several companies are currently working together to test the possibility of using a fieldbus and they are checking its functions in a scientific laboratory. They are trying to develop a common profile which will also apply to simple analyses, because as yet no uniform description of the device exists. Another problem is the data volume: it is not a problem to transfer one temperature value per data line, but the data lines available cannot cope with the huge data volume of an entire chromatogram. In order to service complex equipment such as HPLC or gas chromatographs remotely the Internet or Ethernet are increasingly being used for this purpose.

Another aspect of process analysis is the use of apparatus in explosive areas. 2-wire technology is therefore in demand, also because of its simple maintenance. Many manufacturers demonstrated the functions of their tried-and-tested equipment at ACHEMA on a 2-wire device.

Close to the process

An example of the successful integration of analysis in production is without doubt near infrared spectroscopy (NIR). Many areas of the food and chemical industry are using NIR spectroscopy as a means to check and control the production process in real time. NIR spectroscopy is based on the excitation of molecular vibration by electromagnetic radiation. The wavelength range lies between visible light and infrared radiation. The NIR spectrum of a substance is a suitable means of identification, in a similar way as a fingerprint. A database of known spectra is used as the basis and a mathematical evaluation is performed. A determination of the composition of a substance is also possible. The high speed of analysis, minimal and reliable sample preparation and a non-disruptive analysis make NIR spectroscopy the number one choice. Measurements in potentially explosive areas can also be carried out. The data can be transferred long distances via fibre glass lines. The recognition by the FDA (American Food and Drug Administration) that NIR spectroscopy is as versa-

tile as chromatography as a method of analysis has given further impetus to this technique.

Faith is good, certainty is better

The increasing integration of analyzers into the process has, however, led to another, laborious task. The volume of data accrued during the production process has now reached an all-time high. From the control of raw and starting materials through the intermediate check in production to the final check of the finished product – the sheer volume of data collected is immense. New systems are needed to document this data in a seamless and reproducible way, store it for the long term and make it rapidly available. Data control systems are not only necessary in production but also in the chemical laboratory, where the complexity of work has increased. Examples are the many quality assurance systems, such as ISO 9000, or the proof of environmental compatibility, which have led to a considerable amount of red tape. The documentation required is sometimes more time-consuming than the analysis itself. Thus LIM Systems (Laboratory Integration and Management Systems) are becoming more and more important. Interfaces to other systems used in production and administration as well as high usability are areas of the future. The central principle is: the LIMS must be adapted to the laboratory and not vice-versa. Without the application of object-oriented and modern development platforms, LIMS will not be suitable for future use. An Internet connection, which enables different production sites across the world to be reached, was an important theme at ACHEMA.

Automation in the laboratory

Automation is not only a buzz word in the process industry but also in the laboratory. Terms such as laboratory automation and process control are having an increasing influence, on the laboratory photometer for example. Machines which can handle a large number of samples and transfer their data online are required here. Connection to the Internet or an Intranet is essential. Many exhibitors presented their equipment at ACHEMA with this aspect in mind.

New developments in laboratory devices usually occur with an emphasis on cost-cutting, low maintenance, self-calibration and automation. This also applies to sample preparation. This has a major influence on the quality of the result. Although there are countless solutions to the automation of analyzers, the integration of sample preparation is usually not included. Automated preparation of samples which are toxic or a health hazard make a major contribution to health and safety at work. Even in smaller laboratories attempts will be made to automate the often laborious sample preparation procedures. Flexible structure and easy-to-use software are indispensable if an analyzer is to become established in practice. Although, in the case of low sample

volumes, full automation is rarely worthwhile, efforts are being made to automate at least a part of the process.

Miniaturization is in

The laboratory of today is decreasing in size, daily. Chemists are being confronted with ever smaller devices. Pumps, valves, chromatographs – they all fit on a single chip nowadays. New methods for the production of fluid canals as well as the integration of different functions in a small area are creating new possibilities in DNA sequencing, and in other chemical analyses, such as environmental protection or food technology, new opportunities are occurring. The miniaturization of analytical methods ensures that only minimal reagent volumes are required for samples and thus only very small amounts of waste products occur. Genome analysis is one of the most important fields where microfluid systems are applied. The polymerase chain reaction (PCR) for example, is used to copy DNA regions so that a sufficient amount of DNA is available for tests to be performed reliably. Several manufacturers will be providing a range of kits and reagents for quantitative PCR.

A classic piece of laboratory equipment, which, with the aid of electronics and miniaturization has become a high-tech instrument, is the pipette. The increase in PCR tests in recent years, which usually require 96-well or 384-well microtitre plates, has led to an dramatic increase in the number of electronic pipettes. These devices are controlled by a microprocessor. The plunger rises automatically drawing the liquid into the pipette tip. The controlled movement of the plunger provides greater accuracy and reproducibility, not to mention a reduction in the workload and time spent pipetting by the laboratory worker. Although the market for these pipettes is only just establishing itself, low prices and frequent applications in substance screening and molecular biology have increased demand. In a few years' time the electronic pipette will be on an equal footing with the mechanical pipette in many laboratories – not only in the pharmaceutical industry.

The biochip is on the march

If we are to discuss the future of analysis, then we have to mention the biochip. This is a grid-like arrangement of miniaturized DNA fragments on a support material. A biochip contains densely packed genetic information with which individual genes can be identified in cells. It is predicted that, in future, universal chips will be produced, which can save the entire genetic information of the human genome. Special chips for certain genes, for example a chip which recognizes the gene mutation which leads to breast cancer, have already been developed. In a few years' time, modern medical diagnostics without the biochip will be unthinkable. Despite its enormous potential, this technology is currently being applied only in research. It will require more inten-

sive testing by medical staff and analytical chemists before the biochip becomes part of everyday routine.

Biological systems as a model

The development of high-tech copies of our sensory organs – biosensors – could play a greater role in future. According to a study by Frost & Sullivan the turnover of this market sector in the European market will increase from \$US 113.5 millions (1997) to \$US 197.6 millions in 2004. The specific recognition and amplification of signals at the molecular level is a basic principle of the biological cell. During visual or olfactory detection the signal received (in the form of quanta of light or scent) is amplified millions of times by biochemical reactions, so that single events are registered. The sensory organs thus reach the physical limits in terms of detection. Nucleic acids, antibodies, biocatalysts based on enzymes and ion channels in the membrane are the "molecular machines" involved in signal processing.

Biosensors can be used to detect biochemical reactions. In this way blood tests can be carried out and pollutants detected in water and foodstuffs in a short space of time and at very low concentrations. In addition to their basic significance for the understanding of processes in the living cell, a knowledge of the mechanism of these "molecular machines" is required. The possibilities and potential of biosensors were demonstrated at ACHEMA.

LIFE SCIENCES: IN THE SERVICE OF MANKIND

ACHEMA 2000 presented a significant innovation – the 1st International Symposium on Synthesis, Screening and Sequencing as a part of the exhibition congress. This symposium and a special show from exhibitors provided a fascinating insight into tomorrow's world of pharmaceutical research and strengthen ACHEMA's position as the most important forum for chemistry, chemical engineering, laboratory technology and biotechnology.

Whether in the USA, Asia or Europe: if the pharmaceutical industry is to survive in the global marketplace it will have to drastically reduce the horrendous cost of developing a new drug – currently averaging US\$ 500 million. It will have to shorten the entire development and market launch process, so that maximum profit can be gleaned from a new drug and, at the same time, patent protection fends off copycat products.

This means that preclinical research must bring more products into the development pipeline, faster and at a lower cost. Miniaturization, automation and parallelisation are three key technologies here, which will play a vital role in determining the ability of a company to compete in years to come. The significance of this technological development was underlined at ACHEMA 2000 by a special exhibition group. More than 30 manufacturers presented equipment for parallel chemistry, high-throughput screening and sequencing in a special show.

PCR technology is driving genome research forward

Today, life science without gene technology would be unthinkable. Deoxyribonucleic acid (DNA) contains genetic information encoded in the sequence of its four building blocks, the nucleotide bases adenine, thymine, guanine and cytosine. In the mid-seventies molecular biologists began to systematically analyze DNA, in order to decode smaller sequences and obtain information about the function of single genes. Technically demanding sequencing methods were developed which allowed the sequences of hundreds of base pairs to be determined at once.

Improvements in the equipment, optimization of the biochemical reagents, and, in particular, the introduction of the polymerase chain reaction (PCR) opened up genomics as a research area. Attention was diverted from single DNA sequences to the entire genetic information of a species. PCR is a method which enables fragments of DNA to be copied millions of times with great precision in a test tube. Suddenly, the amount of biological material from which DNA was isolated, processed and analyzed was no longer a limiting factor. The PCR technique revolutionized the life sciences and its discoverer was awarded the Nobel Prize for Chemistry five years after the first publication.

In the field of sequencing, PCR enabled the process to be simplified, parallelised and miniaturized. In the classic sequencing method a separate reaction was carried out for each of the four bases per DNA fragment. The base sequence was determined by incorporating a radioactive base analogue, followed by separation with gel electrophoresis, exposure of the dried gel and development of an X-ray film.

The sequencing method commonly used today is a variant of PCR, where, in one reaction, a different fluorophore is used for each of the four bases. The most modern sequencing machines are designed in such a way that only a microtitre plate is required for the analysis of the DNA samples, the addition of reagents, the actual sequencing reaction, the separation by means of capillary electrophoresis and the fluorescence detection are fully automated. The latest hardware and software solutions were presented at ACHEMA 2000.

HUGO triggers technology leap

In 1988 the Human Genome Project (HUGO) was launched. The aim was to completely decode the human genome with its approximately 3.2 billion base pairs. This international project is supported by several centres worldwide and caused considerable controversy initially. It triggered a technology leap which led to advances in the apparatus and computing methods required for the project within a short space of time. Today, there is no doubt that the goal of the project will be reached. On the contrary, the "book of life" should be completed not as originally planned in 2005, but much earlier.

The decoding of the human genome is only the basis however, for the clarification of the really important questions in biology. The pharmaceutical industry is already investing millions in companies engaged in genome research in order, by cooperation, to be in on the act when the human genome is fully unraveled. It is hoping to identify as soon as possible genes which are important for the key diseases of modern civilisation.

It is all about shedding light on and understanding the interaction between genes in the human body. For example, why is a certain gene product highly activated in the disease state but deactivated in the normal state? Can a drug be found which interacts specifically with this control mechanism? Can a therapy be derived from this which not only treats the symptoms but also addresses the causes of the disease?

The inherited differences in a gene and their effect on its expression and the disease which results also need to be understood. The knowledge sought in this area could be used to identify genetically susceptible risk groups and to delay or even prevent the disease by means of preventive measures or to provide therapy tailored to the individual.

DNA chips and microarrays are conquering the market

An important fundamental of genome research are single nucleotide polymorphisms (or SNPs, pronounced "Snips"), which represent the most frequent variation in the genome and occur every 100 to 300 base pairs. It is assumed that SNPs in genetic population studies can very quickly provide important information about the connection between point mutations in the genome and inherited diseases. As a result, a boom in the discovery and detection of such SNPs has occurred. It is much easier and faster to isolate DNA samples from individuals within a population group, than to perform a complete genealogical study of a family member across several generations.

Important tools in this field are the DNA chips or DNA microarrays. These are regular arrangements of single DNA strands of known sequence on a silicon chip with an area of around 1 cm². From a technical point of view these are adaptations of methods from the semiconductor industry. Depending on how densely these chips are packed, many hundreds of thousands of single DNA strands can be attached to the chip, the loading technique used is either the ink jet principle or optical lithography. At ACHEMA 2000, in addition to the classic sequencing machines, chip technology tools were also presented: machines for loading DNA onto chips, chip readers with laser optics, and – of increasing significance – data processing programs.

Screening: searching for a needle in a haystack

When a new target molecule with potential for therapeutic use is identified and validated according to

certain criteria (for example from genome research) biochemical assays can be used to identify those structures in a substance library which interact specifically with the target molecule. For example, structures are sought which inhibit the activity of an enzyme or block the binding site of a receptor molecule.

Today, these screens (the proverbial search for a needle in a haystack) are carried out in microtitre plates. The biggest advantage of these microtitre plates is that 96 reaction vessels (wells) are integrated into a relatively small area (13 x 8.5 cm) as an 8 x 12 matrix. Miniaturization has led to the 384-well plate becoming standard and soon a 1536-well plate will be in routine use in screening. The transfer from the 96-well to the 1536-well plate brings with it not only a 16-fold reduction in the reaction volumes required, but also saves time. The potential reduction in costs is also high: with a sample size of 500,000 for example, one test costs around 250,000 Euro, whereas the same test with a 1536-well plate costs only 13,000 Euro.

Miniaturization brings advantages

The miniaturization of assays has clear advantages in terms of costs, and the technical problems are not insurmountable. Since a large part of a biochemical assay consists of pipetting small volumes of solutions accurately and rapidly into microtitre plates, machines used for this purpose must be parallelised sufficiently that the necessary speed is reached. This is especially important because with such small sample volumes, sample evaporation cannot be ignored.

Liquid handling machines are already available on the market which can pipette into 384 canals simultaneously with the necessary accuracy. In order to pipette small liquid volumes with greater precision the inkjet technique is being used today. However, there are currently no machines on the market which have the parallelisation necessary. Only highly specialized laboratories have this know-how.

High demands on detection

The many interactions and types of detection required demand a variety of assays. Several trends are evident and these will become more apparent in the coming years:

- radioactive assays are increasingly being replaced by fluorescence and luminescence assays
- homogeneous enzyme assays are being replaced by cell assays, in order to shed more light on complex interactions.
- physiological conditions in cells can be quantified more accurately using radiometric or kinetic measurements. The detectors must react to the high degree of miniaturization with greater sensitivity and faster reading times for each plate.

These readers, as they are called, are, in extreme cases, single channel machines. This means each well

is read in sequence, or they use a charge-coupled device (CCD camera) to photograph the whole plate at once. Whereas the measurement speed of a single channel reader (in particular with 1536-well plates) is affected, fringe effects and sensitivity problems play a role with the CCD camera image.

The latest developments are attempting to meet the dual demands of high sensitivity and speed by means of 96-fold parallel detection. For example, 96 mini lenses are arranged in the same order as the 96 wells of a 96-well plate. In this way a 384-well plate can be read in 4 steps and a 1536-well plate in 16 steps.

In synthesis only the best of the substance libraries will do

It is possible that, having screened several hundred compounds, not a single suitable structure remains which can then be optimized (in terms of efficacy, compatibility and availability) in a special chemical program.

The lack of chemical or structural diversity is often bemoaned in this context (the corresponding term "biodiversity" is used to describe the variety of species in the plant and animal kingdom). By diversity we mean that elusive property of a group of substances – the ability to span the chemical structure spectrum.

Today, attempts are being made, with the help of extremely complex mathematical model calculations, to approach the abstract term "chemical diversity". It is now generally accepted however, that substance libraries which have grown with the passage of time lack diversity, because in the past they were used for only a few therapeutic areas and expanded with only these areas in mind. It is difficult to fill this diversity vacuum.

Miniaturized parallel chemistry offers at least a partial solution. The times where chemists synthesized a single variant of a drug per week are gone. The never-ending time and cost pressure has led to parallelisation, automation and miniaturization gaining a foothold in this area too.

Combinatorial chemistry provides new opportunities

Combinatorial chemistry began around ten years ago with the synthesis of short peptides, linear chains of different amino acid building blocks. In modern combinatorial chemistry, on the other hand, synthesis methods are required in which as many different chemical structures as possible can be attached via the same functional group to the basic structure. One talks in terms of building blocks. Since in such cases the reaction conditions are identical or at least very similar, these syntheses can be carried out in parallel or automated. If the chemist succeeds in attaching several functional groups at once, then it is possible with combinatorial chemistry to synthesize a large number of structurally different substances. Thus in theory, a basic structure and 3 x 50 adducts can be used to synthesize 125,000 different compounds.

Using combinatorial chemistry, millions of different compounds can be synthesized, purified and prepared for screening in a short space of time. The screening robots currently used allow these substance libraries to be screened without human assistance. At ACHEMA 2000 even more powerful robots were presented.

Smart screens will improve efficiency

In future, ways to reduce the number of substances to be tested with smart screens will be sought. Genetic algorithms are the first attractive alternative. Starting with a relatively small number of random combinations, active structures are identified which are then iteratively optimized using special structure-activity calculations.

A second possibility is to combine the structural information contained by single compounds, or groups of similar substances, with data from older screens, and to use it to develop and maintain special databases. Knowledge of the three-dimensional structure of the target molecule will then make it possible to screen virtual substance libraries and to achieve iterative structural improvements in vitro. Hence it comes as no surprise to hear that there are already computer programs available which promise at least a partial solution to these problems.

PARTICLE TECHNOLOGY: NANOPARTICLES

Nanoparticles are destined to become big players in a host of applications, from microelectronics and medicines to catalysts and cosmetics. The many facets of nanotechnology were presented at ACHEMA 2000 by numerous exhibitors and in the special congress session "Chemical Nanotechnology".

A nanoparticle, also called a nanocrystal, has almost as many molecules on its surface as are hidden in its interior. Compared with micron- or submicron-sized particles, nanocrystals have lower melting points, increased light absorption and different electromagnetic properties. En masse, they form powders with huge surface areas – hundreds of square meters per gram. "Some people even believe that nanosize particles constitute another state of matter," says Sotiris Pratsinis, mechanical engineering professor at the Swiss Federal Institute of Technology (ETH; Zurich). "And people are suddenly realizing what you can do with these things."

Indeed, chemical manufacturers are incorporating nanoparticles into more products. And industrial and academic researchers are actively improving existing nanoparticle production technologies and developing new ones to increase yields, control the size and shape of particles, and improve their dispersion in host materials. According to the National Science Foundation (Washington, D.C.), the U.S. leads funding of nanoparticle research, spending about \$116 million/year, followed by Europe and Japan. Showa Denko K.K. (Tokyo) manufactures polyamide and polyacetal interspersed with

nanoparticles of synthetic mica. These composites are more flame retardant and 30–80% more rigid than competing types. Composites of PET and zinc oxide are also in the works, says Nikolas de Jaeger, head of colloid and particulate processes in chemical engineering at Agfa-Gevaert (Mortsel, Belgium). Incorporating nanoparticles of zinc oxide into plastic packaging protects edible contents from degradation by sunlight.

Catalysts are another potential market for nanoparticles. Since 1998, Nanophase Technologies Corp. (Burr Ridge, Ill.) has tested its NanoTek Palladium (Pd) as a catalyst. According to Joe Cross, chief executive officer of Nanophase, a catalyst with a 0.5% loading of nanosized Pd has a hydrogen uptake that is five times greater than current Pd catalysts.

Nanophase produces nanocrystals of Pd, TiO₂, aluminum oxide (alumina) and other materials by physical vapor synthesis (PVS). In this process, high-purity metal is vaporized by an electric arc. The resulting metal plasma reacts with an air-oxygen mixture, forming a metal oxide. The gas mixture also acts as a coolant, decreasing the temperature of the metal oxide, causing it to form nano-sized particles. This process is run at atmospheric pressure. The formed particles are spherical, and of high purity – over 99%. According to Cross, nanoparticle purity is high because there are fewer impurities in the process (e.g., high-purity metals for raw materials) compared with metal-oxide reactions, which are carried out in the liquid phase.

Two years ago, CeraMem (Waltham, Mass.) developed an economical process for the manufacture of nanoparticles by precipitating them in reverse micelles, or colloidal droplets, of water-in-oil microemulsions. Two water-soluble compounds that will react to form a very low-solubility product are dissolved separately into equal volumes of a microemulsion. The reactant pairs may be an acidic salt and a basic precipitating agent. The resulting microemulsions are then mixed together, causing the precipitation reaction to occur within the aqueous micelles, thereby mediating the size and size distribution of the product precipitates.

The chemistry of the microemulsion can be manipulated to obtain the desired nanoparticle diameters. Precipitated products may be any of a variety of compositions of commercial interest – including carbonates, halides, sulfides, chalcogenides and borides – as well as oxides and other precursors.

A drawback of producing nanoparticles from microemulsions is that nanoparticle concentrations are diluted by the large volume of reagent liquid needed for the colloidal micelle reaction. According to CeraMem vice-president Rich Higgins, production of 500 mL of zinc-oxide nanopowder requires 1,000 L of liquid. For increased concentrations, CeraMem has developed ceramic ultrafiltration membranes with tailored pore sizes that hold back precipitated particles, but permit fluid components of the microemulsion to pass through. The

result is highly concentrated nanoparticles that are available as either nonaggregated colloidal suspensions or weakly aggregated, fully dispersible powders. CeraMem expects that common oxides made with its membrane will cost \$5–20/kg, compared with \$50–200/kg for vapor-formed nanoparticles.

The cost of nanoparticles is expected to drop even further as continuous processes are brought onstream. For example, researchers at Sandia National Laboratories (Albuquerque, N.M.) have developed a continuous process for making silica nanostructures in sizes from 2–50 nanometers. Droplets of a homogeneous solution of soluble silica and surfactant in an ethanol water solvent are passed through a reactor. As the liquid is evaporated, the rest of the material "self assembles" into a completely ordered particle in about six seconds. The nanospheres, which fit inside each other like Russian dolls, have potential as encapsulants for military weapons and controlled drug delivery. They may also be useful as coatings on silicon chips. The spheres can absorb organic and inorganic substances, including small particles of iron that can be controlled by magnets and released as needed, says Sandia lead investigator Jeff Brinker.

Rhodia (Paris), BASF AG (Ludwigshafen, Germany), and Olivier y Batlle (Badalona, Spain) are collaborating with two non-commercial laboratories to develop a new continuous process for nanoparticle synthesis. Last March, the team started up a pilot unit of a rapid-contact technology. The apparatus mixes two reagent flows so quickly that their reaction precipitates nanoparticles. Downstream, the particles are agglomerated for filtration. The solids are then redispersed as nanoparticles. Rhodia is interested in developing an alumina-based nanocatalyst, while BASF expects that nanoparticles will give paints brighter, more-intense colors using a common red pigment.

Hard coatings that lubricate themselves are the goal of another international collaboration of industrial and academic partners, among them Daimler-Chrysler Benz AG (Munich), the European Commission's Institute for Advanced Materials (Ispra, Italy) and the Technische Universität Braunschweig (Braunschweig, Germany). The team is working on a process to embed nanocrystals of molybdenum disulfide (MoS₂), a solid lubricant, into a matrix of titanium nitride (TiN). Because nanoparticles of MoS₂ are easily contaminated by humidity, they will be made fresh in the first stage of the process, then blown directly into a second stage where TiN is being laid down. There, the nanoparticles will settle on a substrate, and TiN will fill in around them.

These novel nanoproducts are the tip of the iceberg, says Agfa-Gevaert's de Jaeger. "There is a general interest in making all sorts of materials that now exist as powders in industry into nanosize form, simply to explore their unexpected properties."

Nanoparticles improve gas sensors' performance

Metal-oxide gas sensors are based on the small changes in resistance caused when a metal oxide layer is exposed to oxidizing or reducing gases, such as carbon monoxide or hydrogen. Most industrial sensors use coatings of tin oxide particles, but have limited sensitivity because large SnO₂ particles have reduced reactivity. Chemists of the National Center for Scientific Research (CNRS; Toulouse, France) have found a way to make monodispersed SnO₂ particles of 20 nm dia., 1/25th as large as those achieved by conventional methods, such as sputtering or chemical vapor deposition.

The new method first makes Sn nanoparticles from organometallic precursors. Sn (II) amides are thermally decomposed for about 3 h using anisole solvent with a small amount of water. At 135 °C, the thermolysis yields 20 nm-dia. spherical Sn crystals covered with an oxide layer. The oxide layer prevents further growth. These particles are then oxidized at 200 °C to SnO₂ in two 6-h stages. MicroChemical Systems S.A. (Neuchâtel, Switzerland) is using the method to develop commercial gas sensors for such applications as leak detection, combustion and air-quality control, and fire detection.

Nanoparticles are being scrutinized intensely by microelectronic companies bent on shrinking components even smaller. For example, IBM (Armonk, N.Y.) has had research focusing on nano-enhanced materials and nanotechnologies for several years. Smaller companies are getting in on the act as well. Morgan Materials Technology Ltd. (Stourport-on-Severn, U.K.), Alcatel CIT (Marcoussis, France) and Spain's Scientific Research Council (CSIC) have teamed up with three European universities. The researchers are developing a technique that not only produces nanocrystals of metal within a specific size range, but makes particles that are either needle- or disc-shaped, rather than spherical.

Ciba Specialty Chemicals (High Point, N.C.) is using nanoparticles to encapsulate and transport vitamin E, amino acids and other active ingredients beneath the surface of the skin. Less than 30 nm in diameter, Nanotopes are 5-10 times smaller than conventional liposomes.

Flame processes are among the so-called gas-phase manufacturing methods for nanoparticles. These high-temperature techniques are divided into two classifications - gas-to-particle or droplet-to-particle - depending on how the particles are made. In gas-to-particle processes, such as flame methods, individual molecules of the product material are made by chemically reacting precursor gases or rapidly cooling a superheated vapor. Depending on the thermodynamics of the process, the molecules then assemble themselves into nanoparticles by colliding with each other, or by repeatedly condensing and evaporating into and from molecular clusters. Other gas-to-particle processes include hot-wall, evaporation-condensation, plasma, laser and sputtering types.

In droplet-to-particle processes, liquid atomization is used to suspend droplets of a solution or slurry in a gas at atmospheric pressure. Solvent is evaporated from the droplets, leaving behind solute crystals, which are then heated to change their morphology. Spray drying, pyrolysis, electrosprays and freeze-drying use the droplet-to-particle scheme. Typically, gas-phase technologies are used to make nanoparticles of inorganic molecules. Today, oxides including SiO₂, TiO₂, Al₂O₃, ZrO₂, GeO₂ and V₂O₅, have been produced as nanoparticles, as have Au, Fe, Cu and other metals.

For heat-sensitive organic materials, however, wet chemistry like that used to make the original nano-sols replaces hot gas-phase processes. Microemulsions, sol-gels and homogeneous precipitation are among the cooler routes for making nanoparticles for medicines and other uses.

Make powders of hard substances

A device for the controlled comminution of very hard substances has been developed by Super Fine Ltd. (Kiryat Shmona, Israel). Silicon carbide, for example, (with hardness of 9.3 Mohs), can be ground from an inlet size of 0.7-1.5 mm to 3.74 μm with a narrow size distribution. Such hard materials cannot be ground using conventional mills in a single pass, says Leonid Zisman, development manager at Super Fine, and would require many stages of milling with a large input of energy. Milling costs using the new process are said to be a factor of two-to-three times lower than the \$100-200/m.t. for conventional jet milling.

Conventional jet mills work by introducing a working fluid, via a Venturi jet, into the milling chamber. The high-speed gas (typically more than 150-300 m/s) interacts with added particles causing them to accelerate before they collide with a target, causing the particles to fragment. The new device works by a principle called resonance-whirl milling that was originally developed in Russia. Particulate solids are added at the top, and fall down the center of the chamber. A working fluid, such as air, is injected into the chamber tangentially, creating a vortex of particle material in the working fluid. Within the vortex, particles spontaneously disintegrate due to pressure variations in microcracks, experienced by the particles as they follow trajectories of different radii. The size of the particles can be controlled by providing an auxiliary discharge port, or using internal ribs or baffles within the chamber to adjust the motion of the particles.

Unlike conventional jet mills, there is no need for high speed injection. As a result, an air pressure of 3.5 bars is used in contrast with the 7-8 bars used in conventional jet mills, says Zisman. (The particle speeds are typically only 50 m/s - too slow for conventional jet mills). An industrial test is underway at an undisclosed firm in Israel, with a throughput of 200 kg/h of silicon carbide.

Fine particles with controlled size distribution, morphology and high purity are continuously produced in a segmented-flow tubular reactor (SFTR) developed at the Swiss Federal Institute of Technology (EPFL; Lausanne). The controlled precipitation has been able to produce calcium carbonate (CaCO_3) powder with average dia. of 2.02 μm . Conventional batch crystallization has less control over the fluid volumes, leading to back mixing and a broader size distribution. The technology could find applications for producing chemicals for the electronics industry, catalysts, and dense ceramics (such as CaCO_3 for bioceramics, like for bone transplants).

At EPFL, a 22-m long 4-mm-dia. tube serves as the reactor. To make CaCO_3 powder, for example, saturated solutions of calcium nitrate and potassium carbonate are mixed in a micromixer, developed at IMM GmbH (Mainz), which quickly disperses the two fluids before precipitation occurs. The well-mixed fluid then leaves the mixer and enters the tube where it is segmented by an immiscible fluid such as dodecane. This fluid also forms a film on the tube to prevent fouling. As the segmented fluids flow through the tube, the precipitation reaction takes place in the individual little batch reactors. Each little batch reactor follows absolute plug-flow, so

there is no back-mixing as occurs in conventional batch reactions, says researcher Marcel Donnet. Because of the controlled mixing and controlled reaction volume, powders of high purity are achieved. Also, different morphologies can be produced by adjusting reaction parameters, for example to make platelet or rod-shaped powders. The low-shearing forces involved have also led to new morphologies for CaCO_3 .

A project under the European Commission's Fifth-Framework research program has just begun to "scale-out" the process. The project, with participants from 6 European countries, includes two industrial partners (Kemgas Ltd. (Ferney-Voltaire, France) and Glass Keller AG (Basel). When the three-year project is completed, a pilot plant consisting of multiple mini- and micro-channel SFTRs, will produce 1 kg/h of well-defined powders of three different materials: a multi-cation ceramic, a metal oxalate and calcite from waste-lime recovery. In addition, to the pilot plant, a software package will be developed to model the precipitation to allow users to develop new products quickly.

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