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High-Pressure Technology

HP-Micronization (RESS) and HP-Spray Drying (GAS)

- High-pressure pilot units for RESS process (**R**apid **E**xpansion of **S**upercritical **S**olutions)
- High-pressure pilot units for GAS process (**G**as **A**nti-**S**olvent)
- Multipurpose pilot units for RESS, GAS and SFE
- Diamond nozzle set

Multipurpose high-pressure pilot unit for micronization (RESS), spray drying (GAS) as well as for the extraction of solids using supercritical gases as solvents (300 bar, 80 °C, 18 kg/h CO_2 flow, spray column 6.4 litre (ID 90 mm) with diamond nozzle, 1 litre stirrer vessel for product pre-treatment and as extractor, motorised piston pump for pulsation-free injection of liquid product, separator 1.2 litre).

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High-Pressure Technology

Advantages

- Production of very fine powders
- Production of very uniform powders
- Shape and size of crystals changeable in a wide range by modifying process parameters

Applications

- Formulation of pharmaceutical products
- Enrobing of active agents
- Production of colour pigments

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High-Pressure Technology

Multipurpose high-pressure pilot unit for micronization and spray drying (technical description)

This turn-key multipurpose pilot unit is assembled in a mobile frame and is built for the following operating conditions:

Extraction / spray pressure:	75 – 300 bar (higher pressures optional)
Extraction / spray temperature:	ambient – 80 ºC (higher Temperatures optional)
Separation pressure:	40 – 70 bar depending on the storage bottle pressure (higher pressures optional)
Separation temperature:	ambient – 60 ºC

In the spray drying or micronization mode, the Pilot Unit is operated semi-continuously during one stroke of the motorized piston pump P5. Extracting solutes from solid material, the unit is used in the batch mode.

The following **modes of operation** are possible:

A. High pressure spray drying (GAS-process)

In the **spray drying mode** (**G**as **A**nti-**S**olvent Process), the solid material (for instance an active agent) is dissolved in a conventional liquid solvent. A high pressure vessel B1 equipped with a magnetic stirrer is used to prepare the fluid mixture. In this stirrer vessel B1 the mixture is heated up to the desired spray temperature.

The motorised piston pump P5 which generates a well-defined and absolutely pulsation-free flow is used to pump the solution through the spray nozzle into the spray column B3.

While the very fine droplets which have been generated in the diamond nozzle fall down to the bottom of the column B3, the liquid solvent is extracted by CO2 flowing in co- or counter-current (depending on chosen mode of operation). The droplets are “dried” and reach the bottom of the column B3 as a very fine powder which is collected in an especially designed collecting basket.
The extracted liquid solvent is carried out of the column B3 by the supercritical CO2 and is separated from the gas inside the separator B2. The clean CO2 leaving the separator B2 is re-condensed and re-pumped up to the desired pressure.

The powder which has been collected during the experiment in the collecting basket can be removed by opening the quick opening closure at the bottom of the spray column B3 after the experiment.

B. Supercritical fluid extraction (SFE)

The stirrer vessel B1 can also be used as an extractor for solid products. In this case the magnetic stirrer has to be dismounted.

The solid product is introduced into the extractor B1 in a cylindrical basket with filter elements on both ends. These filter elements retain the product but are permeable for the solvent fluid and the dissolved extract. The solvent fluid dissolves the extract flowing upstream (or downstream) through the solid product. The extract is carried over to the separator B2 by the supercritical gas.

Before entering the separation vessel B2 the pressure is reduced by a control valve C1 lowering the solvent power of the carrier gas to practically zero. There are three distinct phases entering the separation vessel: Liquid CO_2, gaseous CO_2 and the extract. The extract drops to the bottom of the separator B2 from where it can be removed through a hand valve. In the separation vessel B2 a liquid level is maintained in order to improve the separation of the extract. The entering liquid CO_2 is evaporated continuously at moderate temperature.

The gas leaving the separator B2 is re-condensed and re-pumped as described before.

C. Combination of SFE and HP-micronization (RESS-process)

In the RESS mode (Rapid Expansion of Supercritical Solutions) the vessel B1 is used as an extractor.

The active agent is introduced into the extractor B1 in a cylindrical basket with filter elements on both ends. These filter elements retain the product but are permeable for the solvent fluid and the dissolved active agent.

The supercritical fluid, saturated with active agent, is then directly injected through a diamond spray nozzle into the spray column B3. The sudden and drastic decrease in solubility generates a huge number of crystallisation germs and thus a huge number of very fine particles.

The particles generated fall down to the bottom of the spray column B3, are collected in an insert and can be removed after the experiment.

Basically the high pressure pilot unit consist of a pressure generating section, of the spray column B3, the stirrer autoclave B1 and the separator B2.

In the condenser W3 the gas is condensed and in the following metering pump P1 brought up to the chosen extraction or spraying pressure. In the downstream heat exchanger W1 the solvent fluid is heated up to the required extraction or spraying temperature which means that the solvent fluid has reached the extraction or spraying conditions when entering the spray column B3 or the extractor B1.

The high capacity diaphragm metering pump P1 delivers contaminant free supercritical fluid. Its capacity is adjustable from 10 to 100. As an option the mass flow may be measured using a Coriolis mass-flowmeter.

The spray nozzle and the spray cone can be observed through the installed sight glasses and as an option can be transmitted on a TV-screen or sent to a Video recorder.

The vessels are easily accessible and the quick opening closures are hand operated.

For reliable scale-up and economic reasons the design of the system is based on pumping the supercritical fluid rather than compressing it in the non-relevant and costly gaseous state.

All relevant data are indicated on digital displays on the front panel flow sheet and, as an option, may be brought up to a recorder or to a Personal Computer.

Various additional options are available, such as larger spray columns/extractors with capacities of up to 20 litre; higher pressures, temperatures and mass flows.

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High-Pressure Technology

Motor-driven high-pressure syringe pump for pulsation-free injection.

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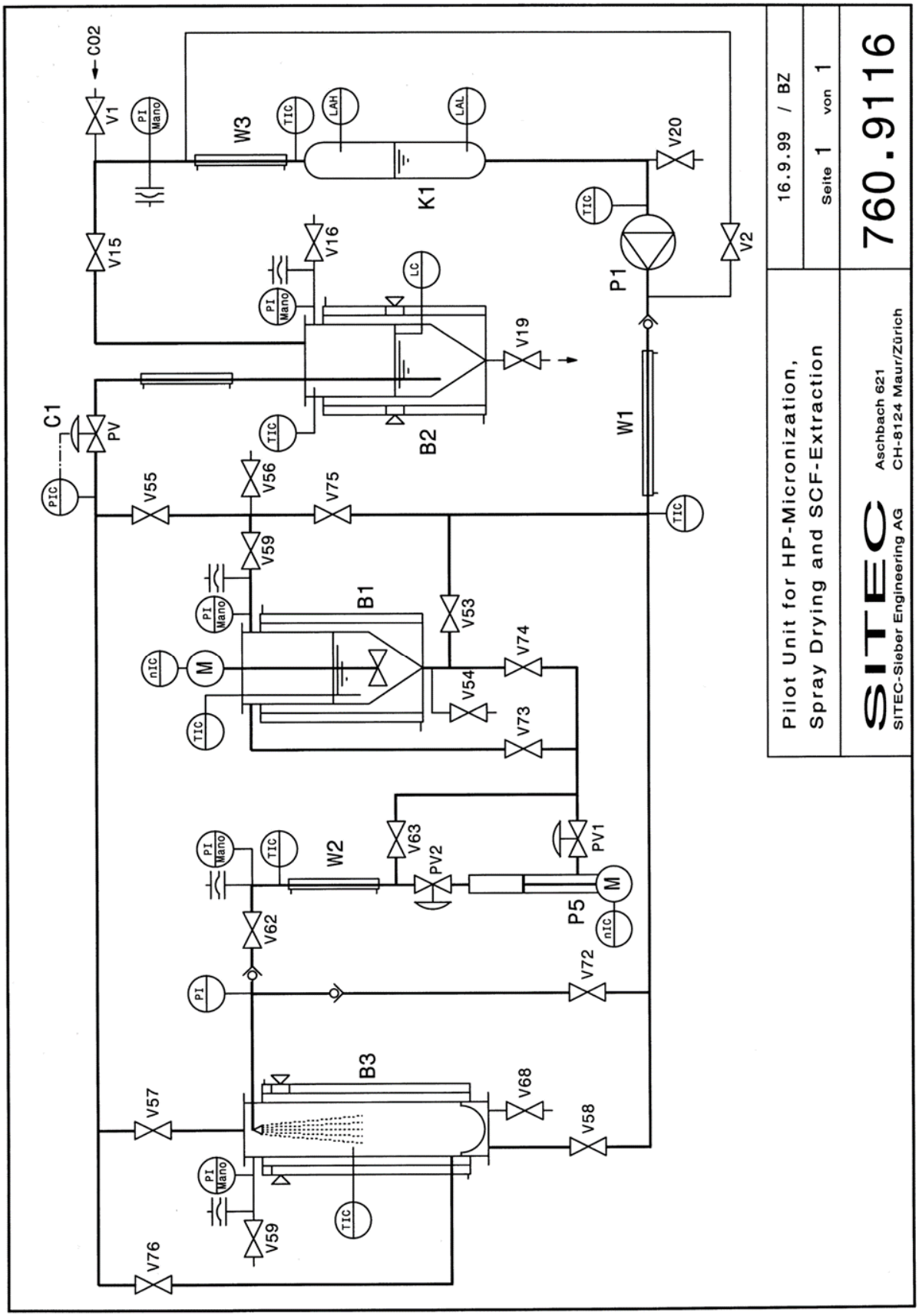
SITEC
High-Pressure Technology



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High-Pressure Technology

Questionnaire for micronization pilot units (RESS / GAS)

Operating pressure max.:		**300 bar**	500 bar	(700 bar)
Fluid (CO2) pump capacity max.:	10 l/h	☐	☐	☐
	18 l/h	☐	☐	☐
	30 l/h	☐	☐	
	50 l/h	☐	☐	
	100 l/h	☐		

Operating temperature max.: ☐ **80 °C** ☐ 120 °C ☐ 150 °C ☐ 200 °C

☐ .....

Supercritical solvent: ☐ **carbon dioxide (CO2)** ☐ .....

Stirrer vessel /
extractor capacities:

☐ **1 litre (with 600 ml basket insert for RESS/SFE)**
☐ 2 litre (with 1.2 litre basket insert for RESS/SFE)
☐ 4 litre (with 2.4 litre basket insert for RESS/SFE)
☐ 6 litre (with 3.9 litre basket insert for RESS/SFE)
☐ 10 litre (with 7 litre basket insert for RESS/SFE)
☐ 20 litre (with 14 litre basket insert for RESS/SFE)

☐ .....

Spray column diameter:

☐ **∅ 90 mm**
☐ ∅ 110 mm ☐ ∅ 160 mm

☐ .....

Spray column length:

☐ **1 m**
☐ 2 m

☐ .....

Liquid educt capacity:

☐ **3.5 l/h**
☐ 10 l/h ☐ 18 l/h

☐ .....

Options:

☐ Mass-Flowmeter for ☐ carbon dioxide (recommended)
☐ liquid educt
☐ co-solvent
☐ Intermediate separation system(s) ☐ 1 ☐ 2 ☐ 3
☐ Co-solvent system
☐ Data acquisition system by PC
☐ PLC control with integrated batch documentation
☐ Continuous recovery of ☐ extract ☐ co-solvent
☐ Preparation of rack for RETROFIT of a(n) ☐ extractor ☐ column ☐ separator
☐ Colour camera system with endoscope

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High-Pressure Technology

Contact Details

Last name: .....

First name: .....

Title / gender: .....

Company: .....

Department: .....

Street: .....

P.O. Box: .....

Zip code: .....

Town / city: .....

Country: .....

Phone: .....

Fax: .....

E-mail: .....

www. .....

Please fill in this form and return it to SITEC-Sieber Engineering AG.

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High-Pressure Technology

Diamond nozzle

The nozzle geometry effectively influences the particle size, the particle size distribution and the particle shape in high pressure spray drying and micronization processes (RESS and GAS process). The nozzle is one of the key components of such a system.

SITEC offers **diamond nozzle pellets** with the following features:

- **bore diameters d** from ∅ **300 µm** down to ∅ **15 µm**
- **aperture angles a** of atomizing cones from **8°** to **24°** (this angle is checked by spraying water into air)

Part No.: **741.0363-d-a**
(e.g. Part No. 741.0363-75-8 for bore diameter 75 µm and aperture angle 8 °)

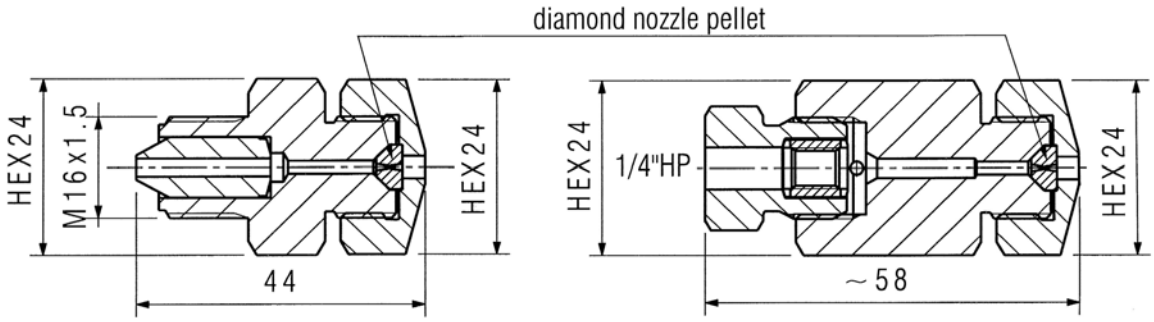
Standard bore diameters 15 µm, 75 µm, 150 µm with angle 8° on stock.

Advantages:

- long tool life (diamond insert)
- customized nozzle dimensions
- easy nozzle exchange

Spray cone of a diamond nozzle
(picture by Fraunhofer Institute)

The diamond nozzles (Part No. 741.0363-d-a) can be mounted into the following standard **nozzle holders** (different designs on request):



Part-No.: 742.0210 Part-No.: 742.0125

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High-Pressure Technology

Data acquisition and online visualisation

As a useful addition to the SITEC high-pressure pilot units, we are able to offer you a simple and also a very flexible data acquisition program. This program allows to visualise your process data online during the experiments and to save it on your hard disk for a later interpretation.

The data acquisition and visualisation program will be completely integrated in your high pressure pilot unit and is configured for a specific application. It is also possible to upgrade an existing high pressure pilot unit, but with a bigger expenditure.

Based on the SCADA Software SpecView from EUROTHERM (see overview hereafter) SITEC provides several windows specifically programmed for a certain application.

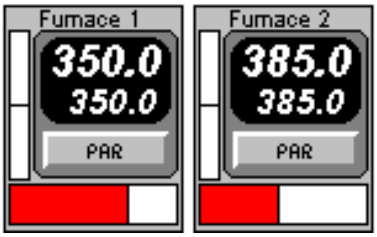
One window shows all the controller symbols and allows set-point adjustment or also alteration of control parameters. In addition, all monitoring signals are shown. On an additional screens all the data are graphically and digitally displayed.

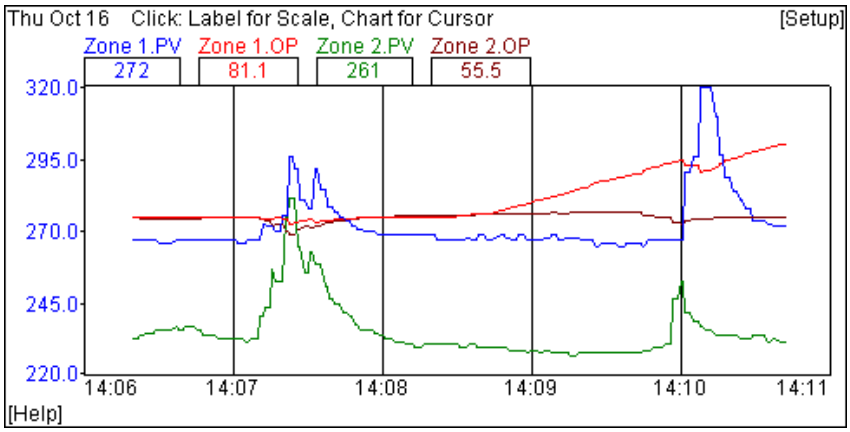
All the data are automatically stored always the data acquisition program is started. On request a certain section (time interval) can be extracted and exported to Microsoft Excel.

The full development package of SpecView which is also supplied allows to change an existing or to create a new user interface using easy to handle “drag and drop” methods. On request, we will gladly send you a more detailed description of this development package.

The communication PC <-> Pilot Unit is made via USB. The controllers are interconnected by a RS485 interface.

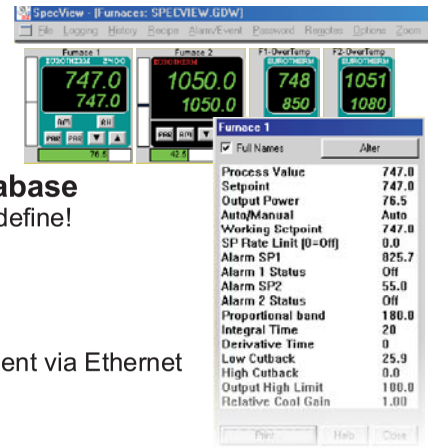
The system requirements for the installation of SpecView: Windows PC with Windows 95, 98, Me, NT, 2000, XP or 2003 Server operating system, 64MB RAM minimum (128MB recommended), USB interface.





CONNECT to Control and Measuring Instruments

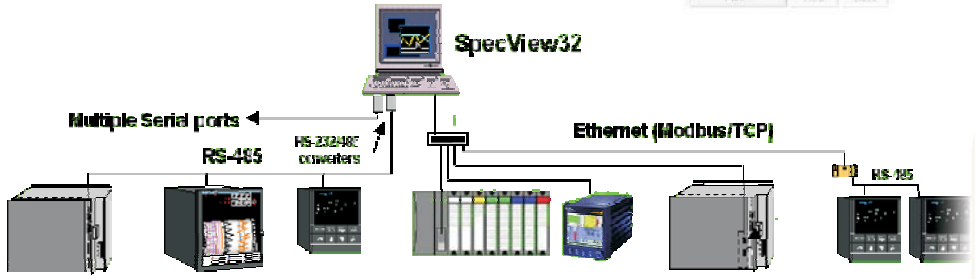
Simple Display and Logging Applications setup in minutes!



Auto-Detection of Connected Instruments

Pre-built Instrument View Database
- Over 1000 instruments - no tags to define!
- Access all instrument parameters

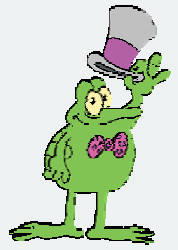
Concurrent Connections
- RS232/RS485 (up to 40 ports)
- TCP/IP, connect any RS485 instrument via Ethernet
- OPC



Temperature
Pressure
Flow
Level
Vacuum
Speed
Status
Power

Controls
Systems
Meters
Indicators
Remote I/O
Data Acquisition
PLCs

RS232 / RS485
Ethernet
Internet
OPC
Radio



SpecView

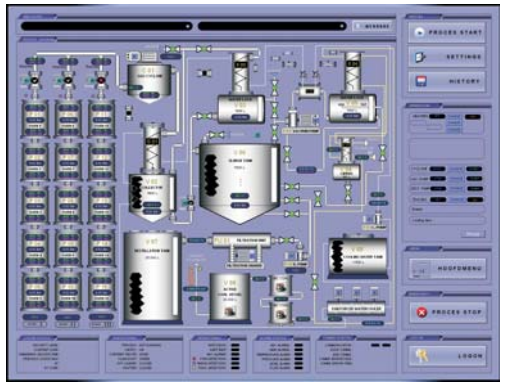
SCADA software for people with other jobs!

OPERATE Operator Interface (HMI)

Create easy to use HMI
- Unambiguous screens ensure error free operation

Touch Screen Compatible

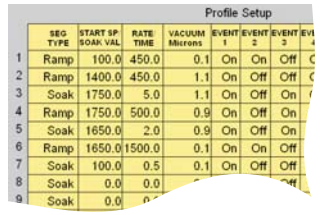
Visualize your process at a glance



Passwords
- Multiple password levels
- Restrict access to specified items
- Record user login

Events & Alarms
- All operator actions recorded
- Pop-up alarm window
- Remote notification: pager / E-mail / SMS

Recipes
- Multiple recipe screens
- Process snapshot
- Flexibility:
  - Full Access: select / review / edit / send
  - Read-Only: select / review / send
  - Single button send
- Bar code recipe selection



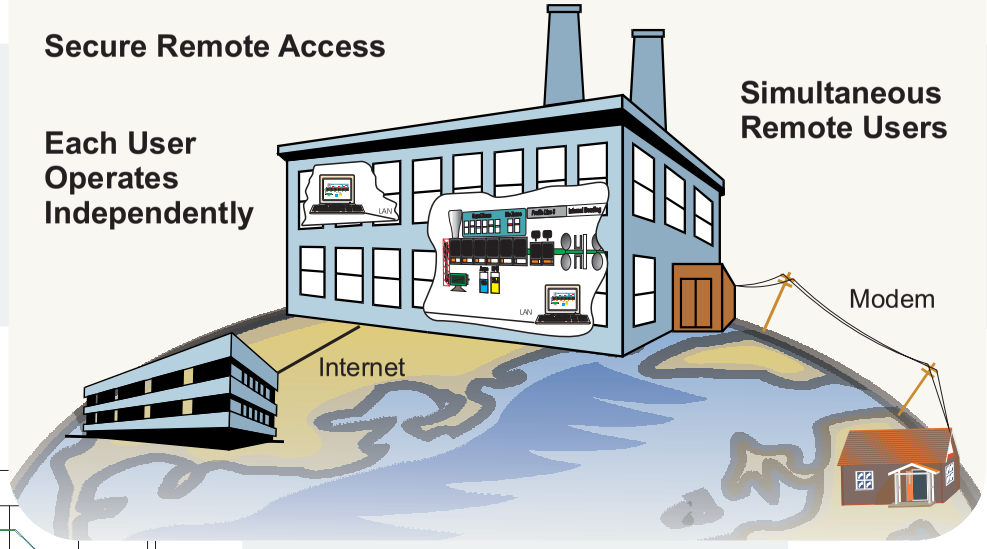
NETWORK Use SpecView from Office or Home

Multiple Operator Stations for Large Machines

Secure Remote Access

Each User Operates Independently

Simultaneous Remote Users



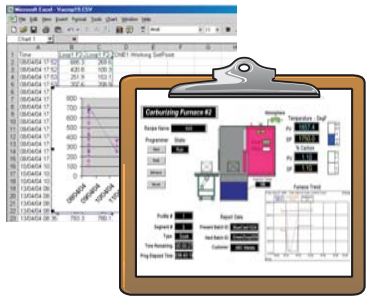
> SpecView is unique. Many of my customers configure the program unaided. Some choose to have some assistance and for those that want a turn-key installation SpecView gives me the tools I need.
>
> Rick Sabo, AQI Engineering

> Loy Instrument, Inc. has installed close to one hundred copies of SpecView. I have found that SpecView is unmatched by anything else on the market. Its versatility has allowed us to use it in everything from straight data logging to full scale SCADA systems. For the money, no other software on the market can touch it.
>
> Mark McDaniel, Loy Instrument Inc.

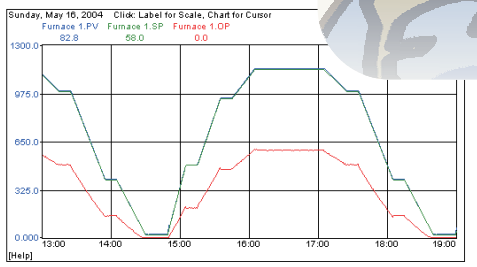
RECORD Data Management

Logging
- Record any item
- By time or event

User Variables
- Batch data, comments etc
- Integrate test data

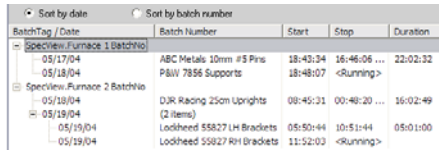


Trends
- Unlimited pens
- Unlimited charts
- Multiple time axes
- Automatic printing



Reports
- Log reports for spreadsheet analysis
- Batch "Clipboard" report
- Automatic process / shift reports

Batch Records
- Find data quickly and easily
- Multiple parallel batches



Alarm / Event
- Start, acknowledge & clear timestamps
- Alarm history
- All operator actions recorded

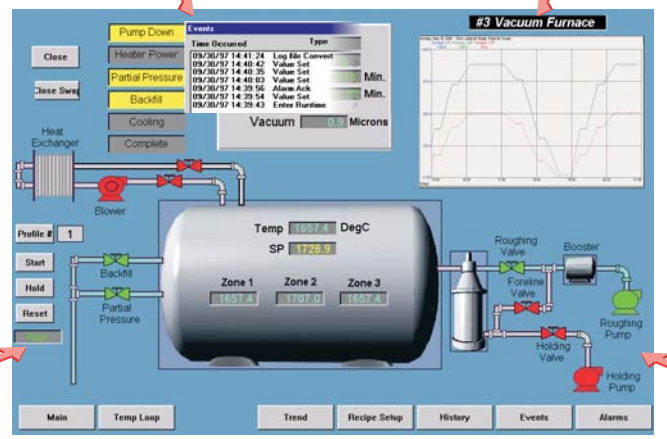
Historical Replay
- 'Video' replay of whole screen
- Review your process in 'Fast Forward'

> I received SpecView as a CD and manual. In a short time I had a configured the program to provide both data logging and an operator interface to a number of different control devices. I had no previous experience with this kind of software. SpecView made it easy.
>
> Lisa Reep, Corning

ANALYSE Explore and Troubleshoot

Event Window
- What did the operator do?
- ...and when?

Integrate
- Test measurements
- Operator comments
- Peripheral data



Visual Feedback
- "I wish I had been standing here when..."
- "Did the purge valve open correctly?"

Performance
- How many parts?
- Percentage downtime
- Correlate run-to-run data

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High-Pressure Technology

Process control with integrated batch documentation

This control allows you to master your processes by combing display, regulation, control and even batch documentation – all in one.

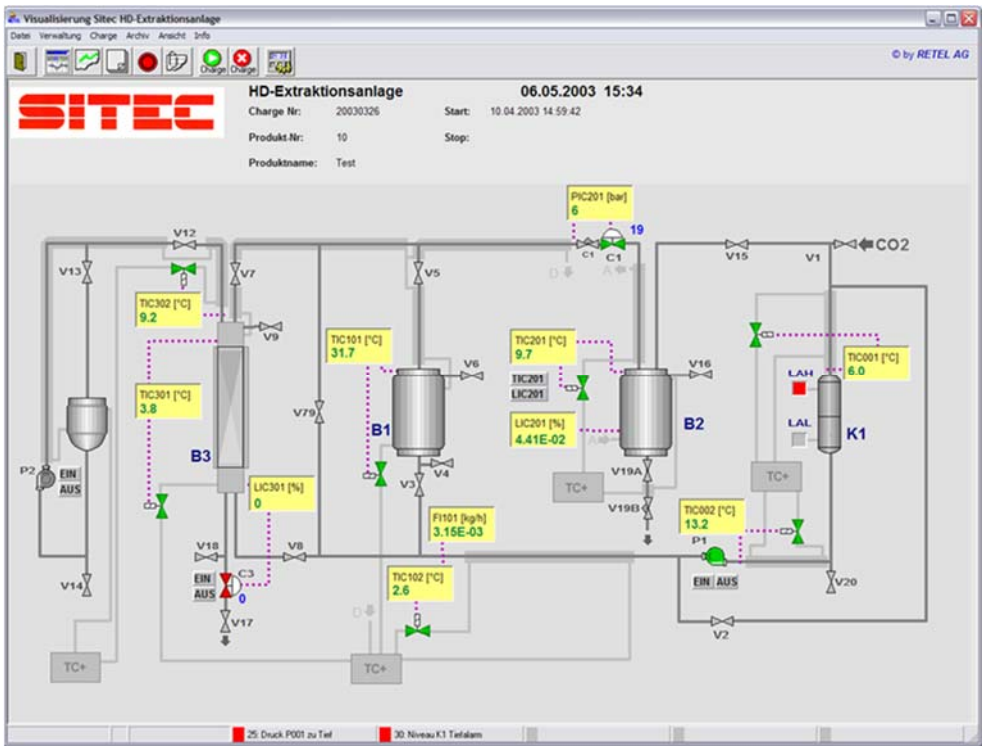
Advantages:

- **complete batch documentation**
- **trend display of process flow**
- **dynamic overview of the installation**
- **easy input of nominal values**
- **exportable into standard formats**
- **protocols and diagrams accessible over network**

The user-friendliness of the system operation is achieved by clearly arranged displays. This control system includes functions which otherwise are integrated in process control systems only.

The control system allows manual and – as an option – automatic control of the installation. All process parameters can be displayed.

The data of the current batch as well as the system overview is displayed on the main window. The operator can control the process over the display picture.



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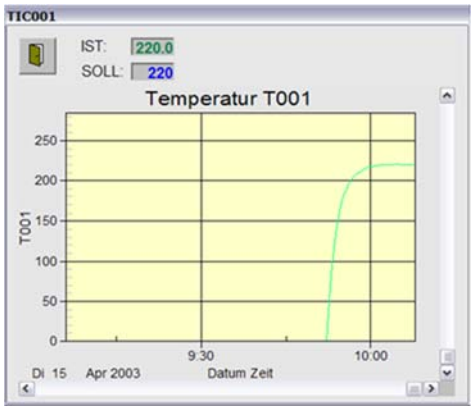
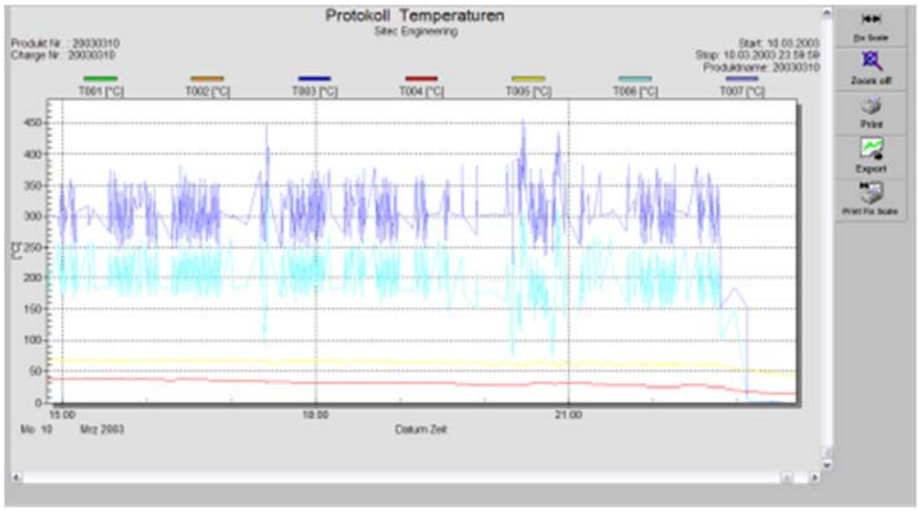
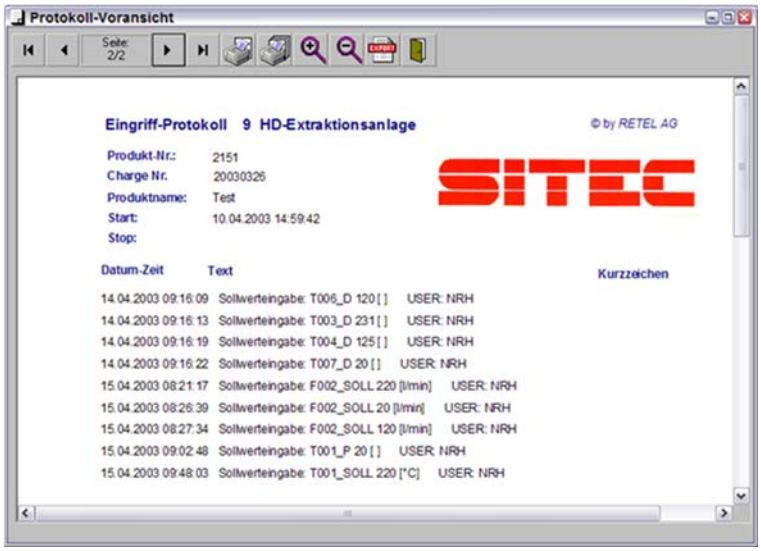
High-Pressure Technology



The automatic control circuits have special display windows with integrated diagrams and nominal value input.



Important process parameters are shown in a trend display. The trend display has a zoom and Fix Scale function and can be printed or exported into bmp, wmf, or jpg graphic formats.



With the help of the integrated logging program the process can be documented completely. All protocols are exportable in pdf, html, or txt formats.

- data protocol
- error protocol
- event protocol
- comment protocol

The batches recorded can be retrieved from the archive. All protocols and diagrams can be exported and re-printed as desired.

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High-Pressure Technology

Reference list for pilot plants

Rhône Poulenc, France	Chemical
University of Delft, Holland	Process engineering
University Wageningen, Holland	Agricultural research
BASF Ludwigshafen, Germany	Chemical
Salzgitter, Germany	Chemical
Hüls Chemie, Germany	Chemical
ENI, Italy	Petrochemical
Givaudan, Switzerland	Flavours and fragrances
Research Centre Karlsruhe	Environmental
Reemtsma, Hamburg, Germany	Tobacco
CNRS, France	Food research
TUBITAK, Turkey	Food research
SASOL, South Africa	Waxes
DEGUSSA-SKW, Trostberg, Germany	Hops, spices
Guinness, Ireland	Brewery research
English Hop Products, Great Britain	Hops
Fraunhofer Institute Pfinzthal, Germany	Process engineering
University of Bremerhaven, Germany	Food research
Novartis, Switzerland	Chemical
Firmenich, Switzerland	Flavours and fragrances
Haarmann & Reimer, Germany	Flavours and fragrances
University of Messina, Italy	Chemical engineering
MERCK, Germany	Chemical
University of Bari, Italy	Research
LIPI, Indonesia	Natural products
F.Hoffmann-La Roche, Switzerland	Reactions
University of Tübingen, Germany	Pharmaceutical research
National Technical University of Athens, Greece	Research
Inst. for “Nichtklassische Chemie”, Leipzig, Germany	Research
University of Halle-Wittenberg, Germany	Research
Janssen Pharmaceutica, Beerse, Belgium	Drug delivery research
MAINELAB, Angers, France	Drug delivery research
Semnan University, Semnan, Iran	Research
JSC “Interbridge”, Moscow, Russia	Research
Ecole des Mines d’Albi, Albi, France	Research
KRAFT Foods, UK	Coffee
Hochschule Niederrhein, Germany	Research
Solvay Solexis, Italy	Research (polymers)
EPFL, Switzerland	Research
University of Alicante, Spain	Research
King Fahd University of Petroleum, Saudi Arabia	Research
Inst. Nawozow Sztucznych Pulawy, Poland	Research
TU Bergakademie Freiberg, Germany	Research
3M, Seefeld, Germany	Research
FAPEX, Salvador de Bahia, Brazil	Research
University of Copenhagen, Frederiksberg, Denmark	Research
University Duisburg-Essen, Essen, Germany	Research
C. Illies, Hamburg, Germany (for China)	Research
AiFame GmbH, Wald-Schönengrund, Switzerland	Natural products

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Additional units in following countries:

Denmark
Turkey
Belgium
Italy
Canada
Greece
Spain
Brazil
Germany
Holland
Switzerland
India
Bulgaria
Iran
Saudi Arabia
China
South Africa
France
Great Britain
Ireland
Indonesia
Russia
Poland

Activities:

Flavours and Fragrances
Biotechnology
Chemical Industry
Coal Industry
Food Industry
Pharmaceutical Industry
Oil/Gas Industry

SUPERCRITICAL FLUIDS AS PARTICLE FORMATION MEDIA : FROM FUNDAMENTALS TO APPLICATIONS

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ABSTRACT

The use of supercritical fluids as particle formation media has only recently started to attract attention [e.g.,1]. Yet, arguably, it is precisely in materials processing that supercritical fluids will have the greatest technical impact. This is because of the possibility of processing materials as diverse as liquid crystalline polymers [2,3], proteins [4,5], bioerodible polymers [6-8], and inorganic oxides [9,10] into pure, solvent-free solid phases with interesting, often unique properties and morphologies. To date, two routes have been used to make particles from supercritical fluids: rapid expansion (RESS) [11,12] and the anti-solvent process (SAS) [13]. RESS is used to form fine particles of substances that are soluble in a supercritical solvent. SAS is used for sparingly soluble materials. In RESS, use is made of the sensitivity of a supercritical fluid's solvent power to small changes in pressure, to trigger precipitation mechanically (by sudden decompression), rather than thermally. The resulting large supersaturation, coupled with the rapid attainment of uniform conditions, leads to small particles with a narrow size distribution. In SAS, the solid of interest is dissolved in a liquid, and a supercritical fluid, acting as an anti-solvent, is added to precipitate the solid. Specific applications to be discussed include the formation of composite drug-polymer microparticles by RESS [8,14,15]; of biologically active protein powders by SAS [4,5]; and of polymer microfibers by SAS [2,3].

I. COMPOSITE PARTICLES

Drug-loaded microspheres in the 50-100 μm range, composed of a bioerodible polymer matrix containing a uniformly-dispersed therapeutic drug are of interest in controlled release applications [16]. Debenedetti and co-workers have studied the formation of such composite particles by co-precipitation during RESS. Single needles of lovastatin (an anti-cholesterol drug) were encapsulated in poly (D,L-lactic acid) [14,15]; more recently, these authors have used fluorescence microscopy to investigate the distribution of pyrene in poly (L-lactic acid) microspheres [8], and they have used a simple one-dimensional compressible flow model [11,8] to explain the transition from microparticles to microspheres in capillary RESS.

The direct encapsulation of drugs in bioerodible polymeric microspheres by RESS is especially attractive because it leads to solvent-free particles at mild processing conditions.

An important limitation of the technique is the low solubility of most bioerodible polymers and many therapeutic drugs in supercritical carbon dioxide, requiring the use of appreciable amounts of co-solvents, such as $CHClF_2$ [8,11]. Furthermore, as is generally the case with RESS, monodispersity and reproducibility are not easily attained.

II. PROTEIN POWDERS

Biologically active protein powders in the 1-5 μm range are of interest in controlled release applications, as well as for targeted delivery of therapeutic enzymes to the lungs. Existing micronization techniques such as spray drying, milling, and lyophilization tend to denature proteins. Debenedetti and co-workers have used the continuous SAS method to obtain insulin powders, using CO_2 as anti-solvent, and dimethylsulfoxide (DMSO) and dimethylformamide (DMF) as solvents [4]. The resulting powders had 90% of the particles smaller than 4 μm, and 10% smaller than 1 μm. The biological activity of the SAS-processed powders was indistinguishable from that of commercial insulin. Recently, these authors have investigated the secondary structure of SAS-processed insulin by amide I Raman spectroscopy [5]. They found extensive loss of α-helicity, suggestive of pronounced β-sheet-mediated aggregation. However, unlike irreversible aggregates, the insulin powders recover their biological activity upon reconstitution.

SAS-processed protein powders are a new frontier of supercritical research. Scientifically, they raise the interesting question of whether SAS allows the exploration of configurations that are not accessible by other processing routes, and from which the dry protein can refold reversibly upon redissolution. Were this to be the case, it suggests the exciting possibility of reversibly "switching-off" enzymatic activity. Another unexplored frontier is the direct microencapsulation of proteins in bioerodible polymers by SAS. Work is in progress in our laboratory on this concept.

III. POLYMER FIBERS

The continuous SAS process was employed on a series of para-linked aromatic polyamides [2,3], using DMSO as the solvent, and CO_2 as anti-solvent. Phase equilibrium measurements were conducted on the polymer+DMSO+CO_2 system. These measurements allowed the identification of operating conditions for SAS. Polycrystalline spherulites were obtained in batch experiments. Continuous experiments yielded thin microfibers, a morphology suggestive of chain-induced chain reorientation during nucleation.

Para-linked aromatic polyamides (aramids) are thermally stable polymers that can be used to produce high-modulus and heat-resistant fibers. Because of the rigidity of the polymer backbone, they have unusual solution properties, including the formation of a lyotropic liquid crystalline phase in concentrated solutions [17]. This liquid crystalline behavior is key to processing these materials into high-modulus, high-tensile strength fibers. The high viscosity of liquid crystalline aramid solutions in many organic solvents restricts their ease of processability. Thus, the successful SAS processing of several aramids is a promising development; it suggests that this process is a viable route to the formation of high-performance fibers.

IV. MATHEMATICAL MODEL OF RESS

A mathematical model of nucleation and growth during partial expansion in steady, adiabatic, one-dimensional flow of a supercritical solution in a capillary or a nozzle allows the calculation of particle size distributions along the expansion device [12]. The calculations suggest that partial expansions can be an effective route to the production of small and monodisperse particles. Comparison of model calculations with experimental results suggest that inter-particle coagulation plays a major role in free-jet expansions such as are commonly used in laboratory RESS units.

Undoubtedly, the one-dimensional model of nucleation and growth during RESS contains important simplifications. Obvious refinements include taking into account radial gradients, and modelling coagulation during free-jet expansion, and including particle shape as a variable. Co-precipitation during RESS, including the possibility of exploiting non-overlapping retrograde regions [18,19] is another interesting problem, the kinetic aspects of which have not been studied. The applicability of classical nucleation theory to RESS [12, 20] must also be critically examined.

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