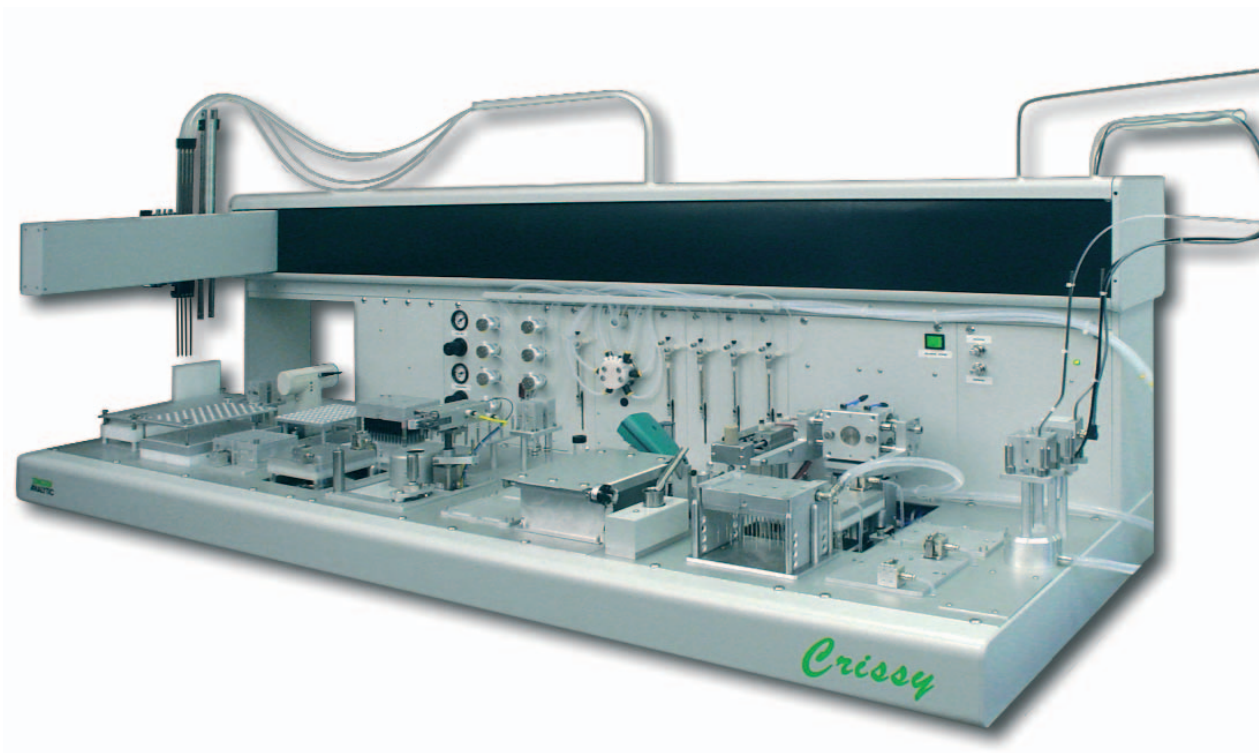


# CRISSY

Automation Platform for Salt Pre-Screening and Polymorph Screening Studies



Polymorphism has become a serious concern in today's pharmaceutical research as it affects a number of issues in pharmaceutical systems varying from processing characteristics & shelf life, to bioavailability. To reduce "surprises" and secure potential product patents, polymorph screening is considered at a very early stage in the drug discovery process. At this stage, since a large number of candidates with very small sample volumes have to be tested, only an automated system could cope with the requirements. Zinsser Analytic developed CRISSY®, an automatic workbench for salt pre-screening and polymorph screening studies.

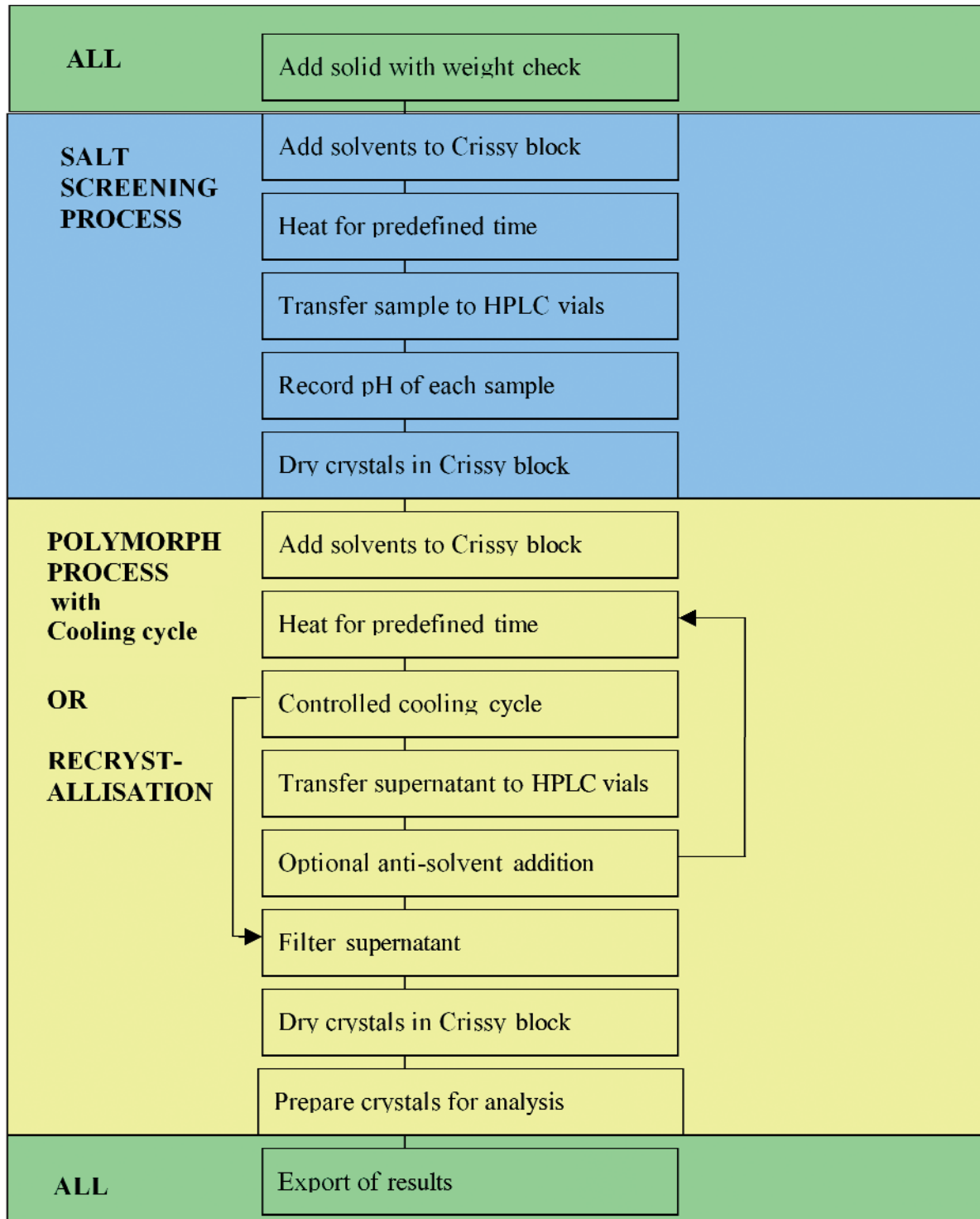
- Experimental planning
- Precise gravimetrically controlled distribution of API
- Liquid handling of solvent arrays
- Controlled heating and cooling cycles
- pH measurement and adjustment
- Special blocks for direct analysis without any additional sampling steps
- Customised import and export functions

## The Workflow

CRISSY automates the entire workflow of the crystallisation process:

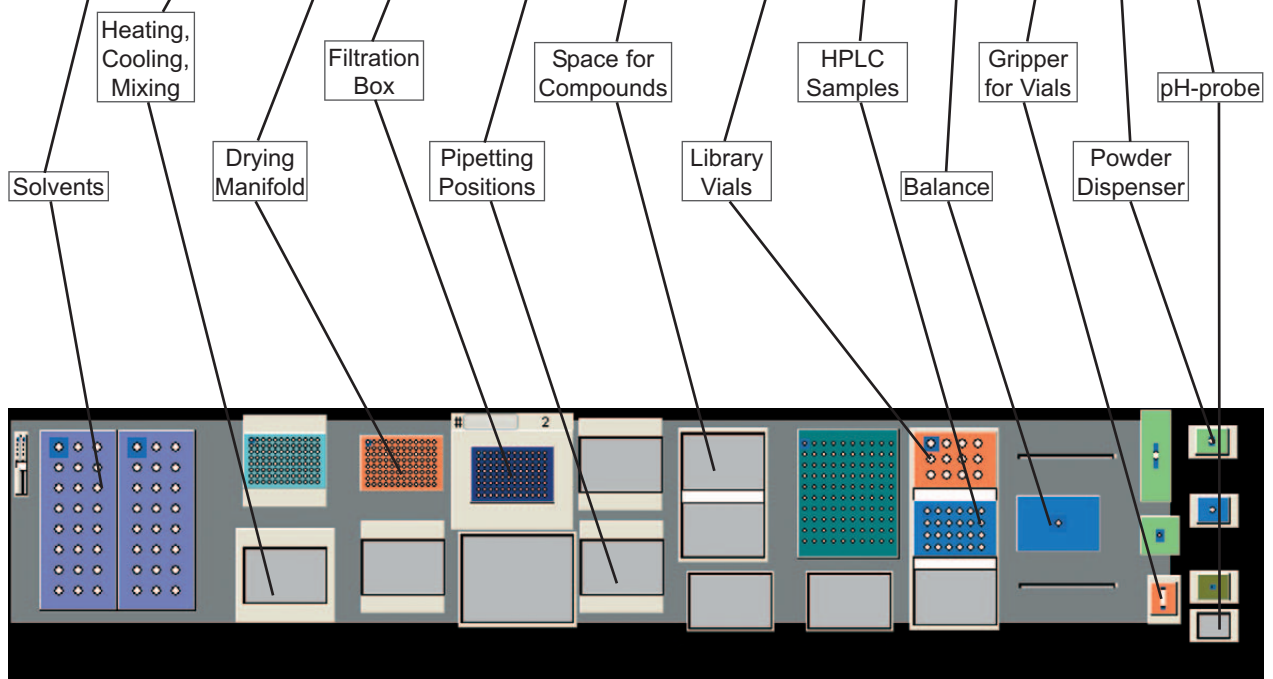
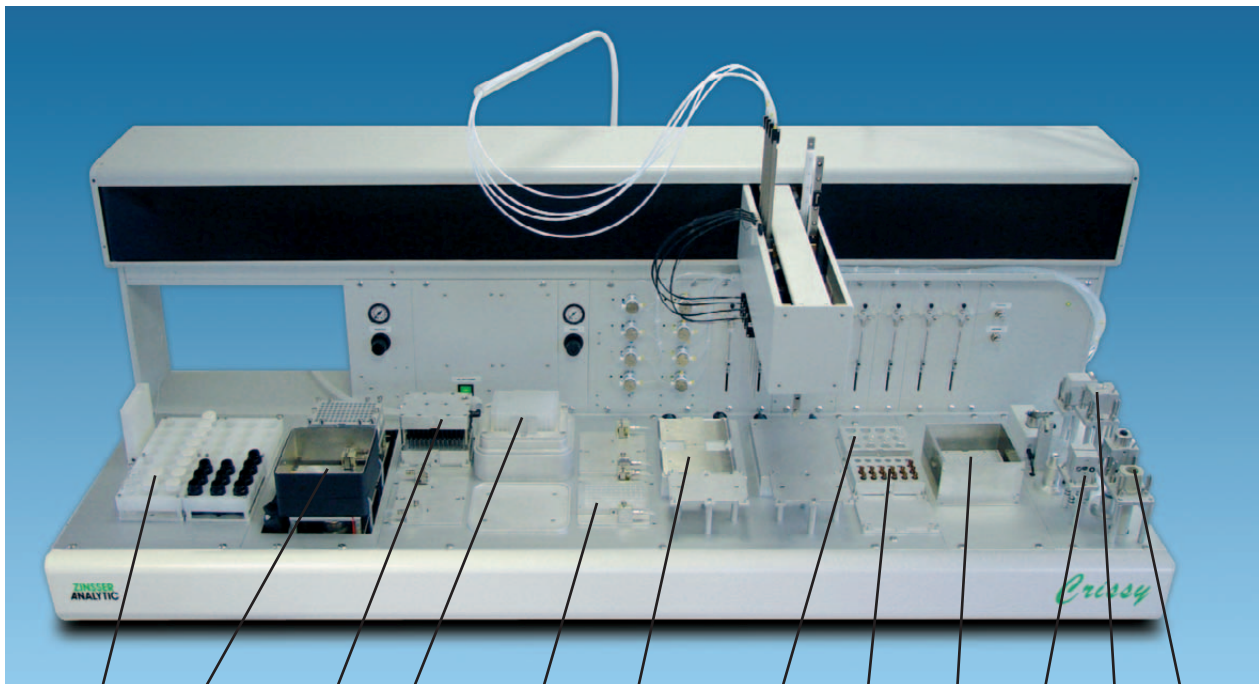
### EXPERIMENTAL DESIGN AND SETUP

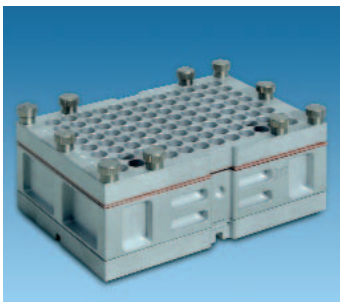
Determine solid concentration, solvent composition array, cooling cycle, type of crystallisation: Slow solvent evaporation, fast solvent evaporation, anti-solvent addition, slurry screening, cooling, melt crystallisation etc.



## The System

The system is based on an x, y, z-platform with 4 independent liquid handling probes with variable spacing and an integrated robotic arm for the transportation of reactor blocks, individual vials and pick-up tools.

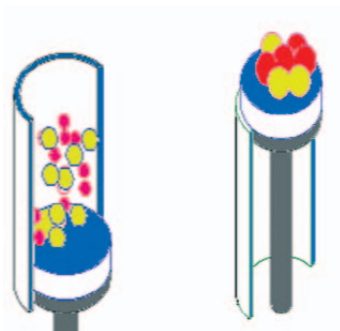




## The Crissy Block

The heart of the polymorph screening platform is the CRISSY block. The reactor consists of an aluminium carrier for excellent heat transfer with PTFE-inserts (reusable and cleanable in an ultrasonic bath) and adjustable bases with a borosilicate glass disc on top.

The reactors can be sealed with the seals and sandwich plates of the "DESY-RE®"-reactor system. The ELAS®-mat or SILTEF®-mat (PTFE coated) with cross-slitted sealing rings are highly recommended as the first seal on top of the reaction cavities.



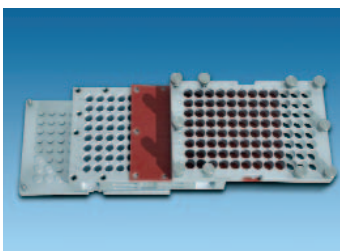
An aluminium top plate secures the cross slitted seals which are held down by thumbscrews for easy opening and closing. If necessary, further sealing layers can be added, also an inert gas shield can be added.

For long term incubation – where the pierced sealing mats may cause evaporation of the solvents in the reactors – a solid seal can replace the septum seals.

CRISSY® reactors are also available that are suitable for automatic sealing, an automatic lidding station can be provided as an option, to remove the manual step required, to remove a solid seal before pipetting can begin again.

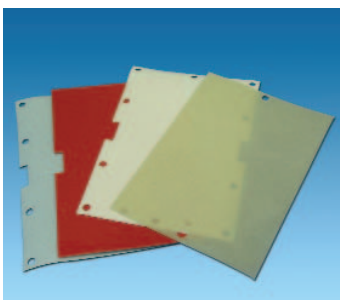
At the end of the process a simple hand operated external ejection tool is available to move the reactor bases into the "up"-position so that the glass discs move to the surface of the reactor block. The reactor block just needs to be positioned on top of a guide plate in the press. With a few strokes of the lever the bases move smoothly up into the detection position.

An automatic solution to lift all wells simultaneously is available as an option.



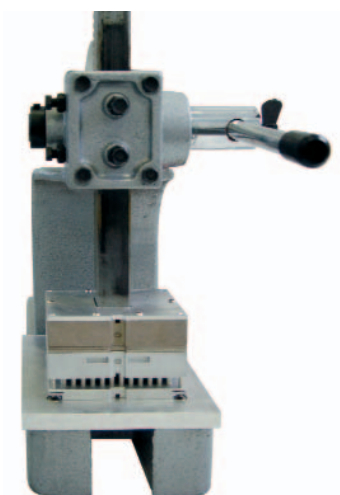
The glass disc of the reactor base is ideal for XRPD-detection. The CRISSY®-reactor can be directly presented to the XRPD system without any additional sampling steps.

Cross contamination caused by electrostatic force from moving the powders, is minimised as the detector block itself is grounded and the individual reactor cavities are isolated from each other in the "up"-position.



The CRISSY blocks are available in different sizes:

Catalogue No.	Description
40038650	<b>CRISSY Reactor block, 96 pos (7mm) for 540µl / cavity</b>
40038680	<b>CRISSY Reactor block, 96 pos (5mm) for 270µl / cavity</b>
40038630	<b>CRISSY Reactor block, 96 pos (3.5mm) for 120µl / cavity</b>
40038640	<b>CRISSY Reactor block, 96 pos (2.5mm) for 65µl / cavity</b>
40038670	<b>CRISSY Reactor block, 48 pos (11mm) for 1.4ml / cavity</b>
40038660	<b>CRISSY Reactor block, 24 pos (16mm) for 2.8ml / cavity</b>



For Raman detection special blocks are available on request.

The reaction volume can be modified in each block by inserting different spacing plates into the press underneath the Crissy block to change the height of the bottom.

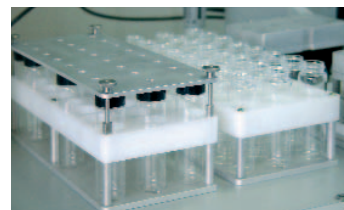
### Filling the reactors with the dry candidates

CRISSY® comes with a set of PickFix® tips with a calibrated volume for contamination free distribution. Optional Varix® powder pipettes for 5-795 µl, masses can be supplied. In combination with the integrated balance the WeighWizard software allows automatic precision target weighing of powders with both tools starting from approximately 1mg. To minimise contamination the powder-dispensing tool is cleaned after each distribution by an integrated vacuum cleaning station. A REDI-shaker with exchangeable powder reservoirs or storage bottles shakes the material before each distribution, to level the surface, to ensure consistent sampling.



### Addition of Solvents & Library Reagents

The system is a 4-channel liquid handling device with full liquid handling capabilities plus additional filtration functions. It is supplied with four patented 2 or 3-channel filtration probes for liquid deliveries and filtration from the top. The CRISSY® is also supplied with a rack of 24 bottles for a range of solvents covering the elutropic range and for acids and bases if required. For bulk liquid addition the six-way valve allows the addition of six different liquids that can be stored in bulk containers below or next to the instrument.



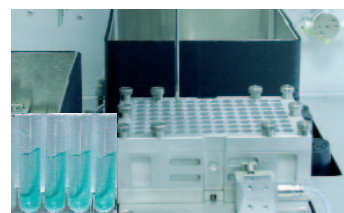
To avoid contamination CRISSY® is equipped with a special "active wash station", which provides intensive cleaning of the tip inside and outside as well as vacuum drying of the probe from the outside after each wash step.



A sonication wash station is available as an option, which eliminates blockages, for example, crystals inside the probe, by combining washing with high-energy sonication.

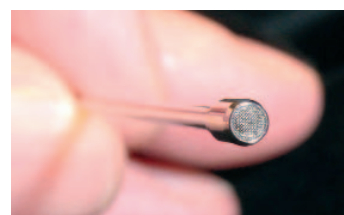
### Crystallisation under mixing, heating or cooling

For incubation and mixing the CRISSY®-reactor is transferred to one of the DESYRE®-Mix high-speed vortexers for heating (up to +150°C or optional 250°C) or cooling (down to -40°C) with mixing speeds of up to 1,800 rpm. The vortexers have a specially selected amplitude to ensure efficient vortexing in small cavities. During vortexing the reactor is securely clamped to the top plate of the vortexers. For long reaction times it also may be advisable to take the reactor blocks off the platform and let them incubate on external DESYRE®-Mix hotplate vortexers to save valuable space on the automatic workbench.



### Liquid / solid separation by filtration

CRISSY is equipped with four patented 2 or 3-channel filtration probes with a stainless steel mesh on the centre channel (mesh size to be specified from 2, 10, 60 or 120µ mesh) for liquid deliveries and filtration from the top. There is a choice to use vacuum from an external vacuum pump, if the liquid can go to waste or to use the syringes for controlled filtration and separation of the supernatant. The 2nd channel can supply inert gas for sensitive or reactive studies as well as liquids to dispense two liquids simultaneously. The probe will penetrate the top cross-slitted septum, which reseals extremely well, when the probe is retracted. The centre channels and the 2nd channels of all 4 probes are each individually connected to a syringe pump. The optional 3rd channel of the probes is reserved for providing an inert gas during aspiration or filtration.



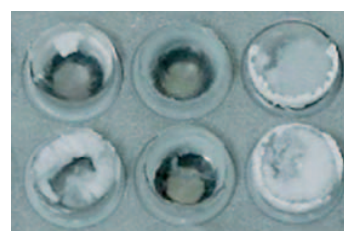
### Drying of solvents

To enhance the drying process of the solid residue, a controlled dose of nitrogen can be applied with a drying manifold to the unlidded CRISSY®-reactor (or even through the ELAS®-seal), which is picked up by the handler and automatically transported to the reactor. The reactor can still stay on a vortexer for moderate heating while nitrogen is applied.



### Ready for Detection

Now the crystals are ready for detection. For RAMAN analysis the CRISSY block can be placed directly onto the x, y, z table holder or a Raman probe can be picked up by the gripper and placed into the individual cavities. For XRPD analysis the crystals are lifted to the top of the block. For reflection systems the block is placed directly onto the plate holder. For transmission systems, the crystals are first transferred onto a transparent carrier and then placed into the XRPD system.





## Options

### 2D Barcode Reader

High resolution CCD barcode reading including 2D barcode reading of plates and tubes, allows you to track and store information relating to your samples.

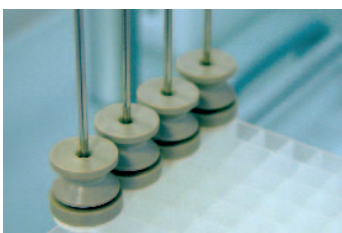


### HPLC & LC/MS sampling

Samples can be taken at any given time. There are several ways of preparing the samples. With the filtration probes the samples can be filtered from the top and transferred directly into the auto sampler vials.

Alternatively, the samples can be purified on an integrated filtration station, processing the samples with controlled positive pressure through a filtration plate before they are transferred into HPLC vials. The filtration is described under the heading 'Filtration' below.

Additionally, the samples can be transferred into pre-crimped HPLC vials with a very thin bevelled HPLC probe to pierce through the septa of the vials. Open top vials can be automatically capped with either screw caps or aluminium caps. The samples can be stored on cooling plates to avoid evaporation and degradation.



### Filtration

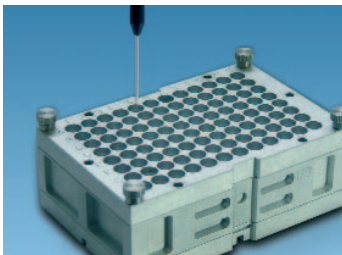
In addition to using Zinsser Analytic's patented filtration probes, samples can also be filtered using filter plates on an integrated vacuum manifold. The instrument transfers the samples to the filtration plate and the filtration can be achieved using vacuum or controlled positive pressure.

The process is totally automated as the system can place the elution plate into the manifold and remove them for sampling.



### Drying of solvents – digitally controlled vacuum pump

As an option the drying can be executed on an evaporation station with a vacuum manifold. The sophisticated vacuum pump allows software control and monitoring which guarantees reproducible results.



### pH-monitoring (pH-adjustment if necessary)

An integrated pH probe can measure the pH value of the samples. The data is stored in a database and can be exported if required.

The pH can also be adjusted, if necessary, with the addition of acid or base to reach a pre-defined value. The gripper transports the probe and places it in the sample for monitoring.

If acid or base is required this is pumped into the vessel through a channel on the probe. The probe is thoroughly washed between samples.



### Camera tool

A pick up camera tool can be used to document the status of the samples on-line. The camera can take pictures, either of each cavity individually or also of the entire block. The pictures are stored in a database so that you can keep them for documentation of your experiments.

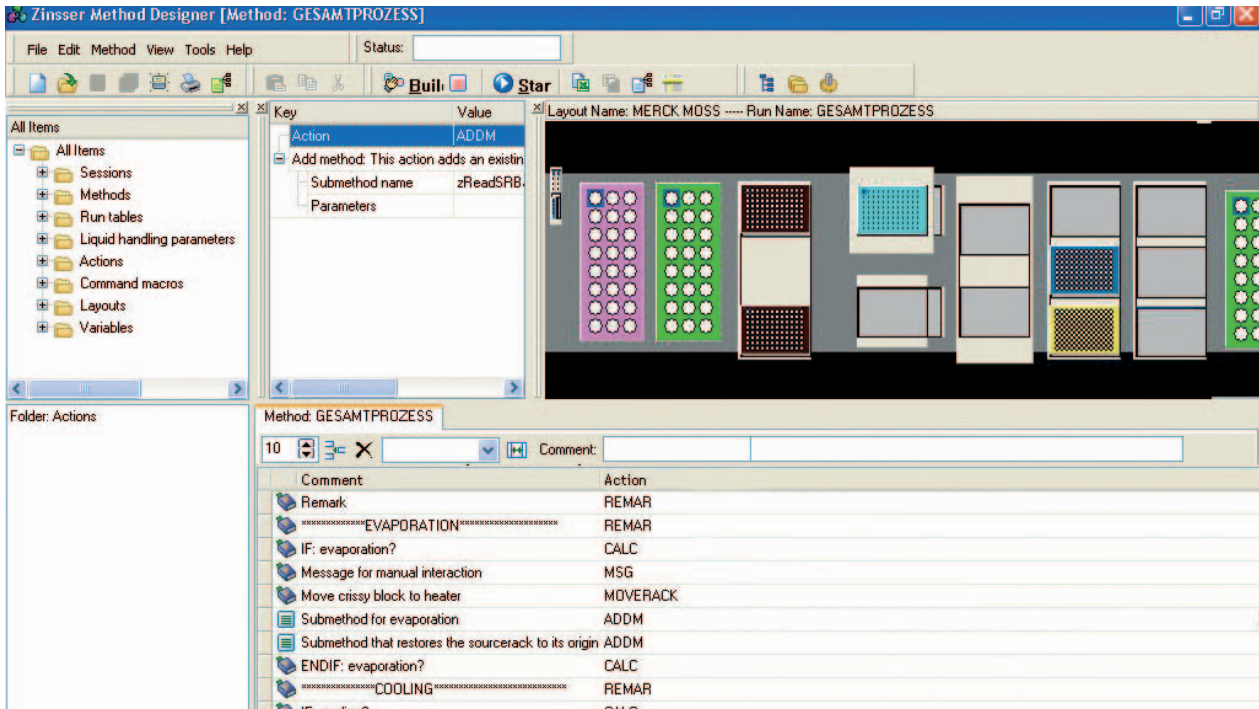
Special blocks are available which allow back lighting from a light box that the block sits on to ensure a clear picture.



### Customised options

At Zinsser Analytic we like to supply systems tailor made to both your process and your preferred working practices. If there is anything you require on your system, which is not mentioned here, we will be happy to accommodate your needs.

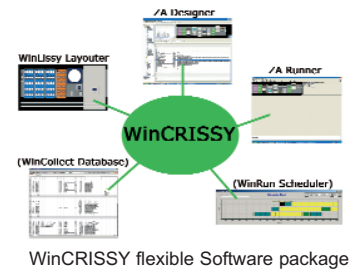
# Intelligent Software



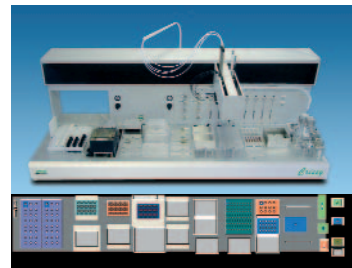
The software is able to control all the different operations, collect all the data and produce customised result files.

The software is composed of several parts; the 'Layouter' is for teaching the system where the various parts are on the workbench. The 'Designer' is for writing the methods and the 'Runner' is for running the methods.

The 'Designer' can be used while the system is running to make changes to the existing method or to write new methods. The 'Scheduler' is an optional part of the software that can be used for running different processes simultaneously in the most efficient manner.



In the 'Layouter' the component parts that make up the instrument are represented in a picture in the software. They can be colour coded to group various items together. When the method is running the dispensing into racks is displayed by changing colours to instantly check the progress of the method. The racks required in the layout can be dragged into place from a list in the software and new racks created very easily.



The solvent array mapping can be executed straight from an Excel sheet and the software is able to filter and sort the relevant information directly into a method. Simply changing the Excel sheet changes the method.

Alternatively, the mapping can be set up as a 'sequence' in the 'Designer' where the names of solvents can be dragged from the source containers into the sequence editor in the required destination format.

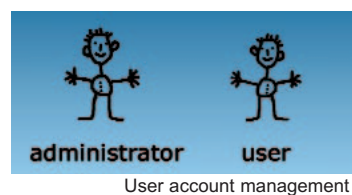


In the 'Designer' a list of sub-methods are available for controlling all the modules on the system. These can be dragged and dropped into a method as required. By changing the user input regarding the number of samples or types of racks and plates then these can be generic for all of the methods required.

Questions can be posed to the user, for example, asking if anti-solvent addition is required and the method is altered depending on the response.

By defining the start and end conditions over a chosen time scale a controlled cooling cycle can be performed.

Different user accounts can be setup, from the unlimited access for the administrator to the user who can only select and execute methods.



## System Configuration of **CRISSY®**

### Platform

X,Y,Z - Platform 2000 x 710 with  
4 independent liquid handling drives with variable spacing (8-38mm tip to tip)  
with robotic gripper arm for transportation of vials or plates

### Liquid Handling, Weighing and Mixing Moduls

- 1 Integrated 4-digit balance
- 4 Precision syringe pumps
- 4 patented single channel 10 micro filtration probes  
level detection at each probe
- 1 6-way valve with integrated manifold to switch between 6 external media
- 1 Active Wash & Dry-station with vacuum drying for 4 probes
- 1 Hotplate Vortexer DESYRE-Mix (300 to 1.800 rpm, up to 150°C)
- 1 Cooling Vortexer DESYRE-Mix (300 to 1.800 rpm for external chiller)
- 1 Manifold for nitrogen drying with park station

### Precision Powder Dispensing **REDI PickFix**

- 1 Park station for powder dispenser PickFix
- 1 Powder shaker for powder containers
- 1 Pick-up tool for powder reservoir with park station

### Carriers and Racks on the Platform

- 1 Rack for 24 solvents (volume to be determined by customer)
- 1 Rack for 96 chromatography vials or
- 1 Pipetting Position and park station for "CRISSY block"
- 1 Cooling plate carrier for HPLC racks (MTP-footprint)

### Accessories

- 5 CRISSY reactor blocks (choice of 96, 48 and 24 well blocks) with one set of spacer plates
- 1 Loading plate for CRISSY block
- 1 set of spacer plates (distance frames); set of 3 (10, 11, 12mm)
- 1 Power press for opening of reactors

Including PC with flat screen monitor and control software WINDOWS operating system  
Complete with WinCRISSY Software Package

### Options

- 1 2-dimensional barcode reader (for vials and plates)
- 1 Pick-up sampling tool for HPLC samples with precision syringe pump
- 1 Vacuum filtration station for pulsating vacuum and positive pressure
- 1 Intergrated Vortex-Evaporation station with digital controlled vacuum pump
- 1 pH-measuring module with pick-up pH-probe
- 1 Pick-up camera for visualisation of reaction stages