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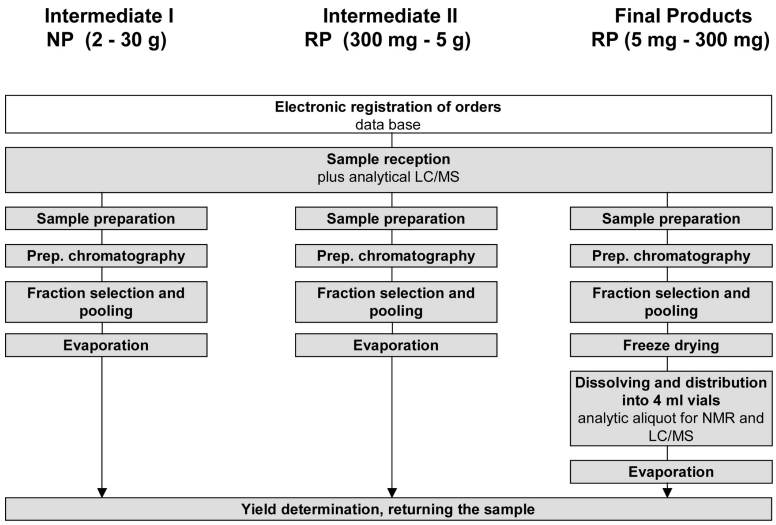

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High-Throughput Purification of Single Compounds and Libraries

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The need for increasing productivity in medicinal chemistry and associated improvements in automated synthesis technologies for compound library production during the past few years have resulted in a major challenge for compound purification technology and its organization. To meet this challenge, we have recently set up three full-service chromatography units with the aid of in-house engineers, different HPLC suppliers, and several companies specializing in custom laboratory automation technologies. Our goal was to combine high-throughput purification with the high attention to detail which would be afforded by a dedicated purification service. The resulting final purification laboratory can purify up to 1000 compounds/week in amounts ranging from 5 to 300 mg, whereas the two service intermediate purification units take 100 samples per week from 0.3 to 100 g. The technologies consist of normal-phase and reversed-phase chromatography, robotic fraction pooling and reformatting, a bottling system, an automated external solvent supply and removal system, and a customized, high-capacity freeze-dryer. All work processes are linked by an electronic sample registration and tracking system.

Introduction

Purification of crude products is usually the most time-consuming part of organic compound preparation.[1] An internal survey in the Aventis medicinal chemistry department in Frankfurt in 2000 showed that a standard lab was occupied more than 50% of the time with workup procedures and chromatography. It was clear that we had to improve the purification abilities of the chemistry department to achieve increased productivity. There appeared to be three different strategies to accomplish this goal, each having its own advantages and disadvantages: (1) equipping standard laboratories with purification technology; the staff have direct access and are responsible for their equipment; (2) purification technology being located in centralized open-access labs; the technology is supervised and maintained by trained staff, but every chemist is operating the purification technology himself; and (3) a service purification unit in which specially trained and dedicated operators purify the samples for their colleagues.[2]

We came to the conclusion that the first two possibilities are only appropriate for easy-to-use equipment, which needs little training and maintenance. Examples for such purification technologies are normal-phase flash chromatography and preparative RP-HPLC with UV detection. Open-access operation of more advanced and more complex systems for purification, such as preparative HPLC/MS techniques, is questionable. Many occasional users often avoid complex systems in an open access mode because with every use, it takes time and energy to familiarize oneself and get the system running. We felt that for these reasons, open-access systems should be limited to a set of user-friendly standard features. Of course, the advantage of open-access systems is the possibility for a spontaneous, time-flexible use of the equipment without the need for planning individual work processes. On the other hand, dedicated service units better utilize high-value equipment, especially if run in a 24-h mode. The equipment is better maintained, and the specialists will acquire skills so that they can continuously develop and improve the equipment, the processes, and the surrounding infrastructure.

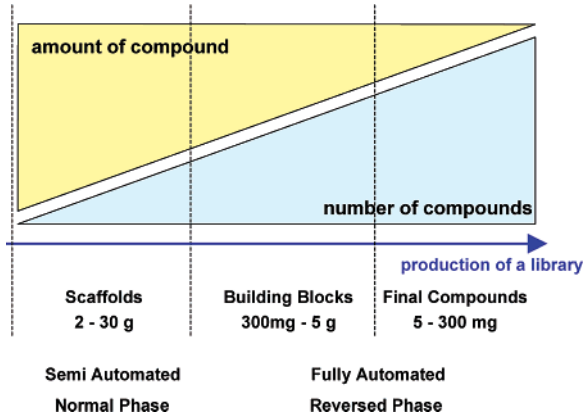

Figure 1. Compound amounts and numbers needed in the process of library production.

For this reason, we have organized purification in Frankfurt in specialized units that work in conjunction with a library chemistry group and two automated synthesis laboratories.[3] In the early phase of compound preparation by multistep chemical synthesis procedures, particularly in the case of library synthesis, intermediates (building blocks and scaffolds) have to be purified; that means a smaller number of samples, but in high quantities. On the other hand, final products usually arise in small amounts of material but

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Table 1. Overview of the Purification Technology

	intermediate purification I	intermediate purification II	final purification
expected samples, year	800	4000	40 000
amt/sample (av)	1−100 g, (20 g)	0.2−20 g, (2 g)	5−300 mg, (50 mg)
possible amt/injection	1−7.5 g	0.2−1 g	5−100 mg
separation technology	normal phase HPLC 2 Labomatic HPLC	reversed phase HPLC/MS 2 Waters HPLC/MS	reversed phase HPLC/MS 4 Waters HPLC-MS
typical column size, mm	57 × 300	50 × 250	30 × 100
stationary phase	irreg. silica gel, 40−63 μm	RP-C18, 10 μm (X-Terra, Polaris)	RP-C18, 10 μm (X-Terra, Polaris)
flow, mL/min	400	150	120
time/injection, min	25	25	5
solvent supply by lab infrastructure	petroleum ether, EtOAc, CH_2Cl_2, MeOH	CH_3CN/water (0.1% TFA)	CH_3CN/water (0.1% TFA)
waste collection	individual waste for every injection, central waste sewage	individual waste for every injection, central waste sewage	individual waste for single compounds, central waste sewage
fraction handling	manually pooling	pooling robot	reformatting and pooling robot
solvent evaporation	rotating evaporators	parallel evaporators	freeze-drying
registration and sample tracking	paper registration form	electronic sample management	electronic sample management
final product analysis	HPLC/MS report	HPLC/MS report	HPLC/MS report + NMR
special features		automated sample preparation	automated bottling of products in bar-coded vials

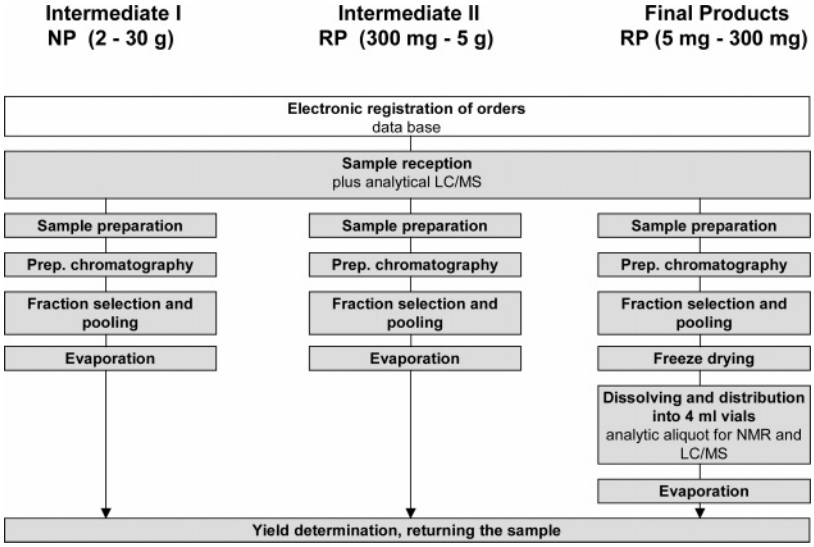


Figure 2. Different workflows in the three purification units.

around 2 orders of magnitude more samples. We decided to combine the purification needs for high-throughput library production with single compound purification for the entire chemistry department. This resulted in a dedicated full-service purification facility for high-quality purification of final products and synthesis intermediates ranging from 5 mg to 100 g.

There are many different methods to separate substance mixtures. Most important are crystallization, rectification, absorption, extraction, and chromatography. All of these purification methods are widely used and have been continuously refined over the last 150 years, but lately, chromatography has emerged as the most generally applicable method for druglike molecules. The development of HPLC technology and the introduction of reversed-phase silica gels has broadened the scope of purification. Finally, combination with mass spectrometry has opened the field for high-throughput purification because fractions can be immediately identified.[4] We installed our first preparative mass-triggered Waters Fraction Lynx HPLC system in 1998. At that time, the system lacked "user-friendliness" and robustness. Nonetheless, it soon became clear that this would be the future of preparative high-throughput chromatography and a main component of our planned new purification service.[5]

The Purification Units. On the basis of the expected number and quantity of samples, we decided to build three purification units, differentiated by the amount of sample they handle and, therefore, the technology in use (Table 1). While Intermediate Purification I uses normal-phase HPLC technology as a separation method, Intermediate Purification II and Final Purification are based on reversed-phase HPLC with coupled mass detection. The three units also differ in the degree of automation. Apart from the HPLC systems, no further automation is required in Intermediate I, because the normal phase chromatography needs an individual method selection for every sample, and the expected

throughput is ~800 compounds per annum. Intermediate II and Final Purification are fully automated, and up to 4000 or 40 000 compounds per annum, respectively, can be purified in an unattended 24-h mode.

Intermediate I (Normal Phase) Unit. The service team of two technicians requires the sample, a filled registration form, an analytic HPLC/MS spectrum and a TLC. The samples, in the range of 1−100 g, usually originate directly from chemical synthesis and are most conveniently submitted in round-bottom flasks. The paper registration form simply contains information about the molecular weights and formulas of all wanted main and side products. The HPLC/MS spectrum is usually measured by the "customer" under standardized conditions on one of the many analytic open access Agilent 1100 HPLC/MS instruments in the chemistry department. The TLC gives the operators in the lab a first hint for the selection of the right separation parameters. In most cases, the crude product is dissolved in pure dichloromethane (50 mL per 10 g crude product) with the help of an ultrasonic bath. If the product is very polar, a small portion of methanol is added; in the case of very lipophilic substances, some *n*-heptane is added. Nondissolved material is filtered off over disposable filter cartridges or is removed by centrifugation, and the remaining solids are dissolved in DMF and are analyzed by LC/MS to determine whether they contain any of the desired products, in which case the solid material is returned to the customer. If the filtrate or centrifugate contains the desired compounds, it is separated on one of the two preparative Labomatic HPLC systems.

The HPLC systems are located in a large fumehood, which is equipped with a fire extinguishing system and detectors in case of solvent leakage. The preparative Labomatic HPLC systems consist of an auto sample injector with a 100-mL injection loop, a HD-300 pump for flow rates up to 600 mL/min, a low-pressure gradient mixing device, a two-wavelength UVIS-205 UV detector, and a custom-made fraction collector for 115 fractions (250- or 500-mL screw cap bottles). The fraction collector is equipped with a second arm with a pipetting device which can automatically transfer an aliquot from each fraction into a microtiter plate for subsequent analysis by HPLC/MS.

The laboratory infrastructure includes a solvent delivery system for four different solvents, such as petroleum ether, dichloromethane, ethyl acetate, and methanol. Up to 90 L (three 30-L drums connected in series) of each solvent is stored in a safety cabinet. Stainless steel plumbing transfers the solvents to the HPLC systems, and sensors monitor the solvent levels for an automatic repeat order. As an additional precaution, each HPLC is connected to a waste-collecting device so that the waste from six injections can be collected separately in 10-L drums. After the operator is sure that all product fractions have been correctly collected, the waste containers can be automatically emptied into an organic waste-collecting sewage system. The sewage system empties into 1000-L containers outside the building, and the solvents are burned in an incineration plant. A measuring and control system, which also includes safety features to alert the fire department in case of leakages and fire, manages the waste system. This was developed and engineered in-house.

The Labomatic system, the solvent supply, and the waste containers are controlled by a customized version of the PrepCon HPLC software from SCPA, Stuhr-Brinkum, Germany.

We consider that normal-phase chromatography is most suitable for the separation of larger amounts of material. Our standard stationary phase is ordinary flash chromatography grade irregular silica gel from Merck (Si60, 43−63 μm) prepacked in 57 × 300 mm plastic (FEPD) columns from Götec. Smaller particle size or spherical silica gel does not seem to have any beneficial effects on separation quality. In comparison to reversed-phase silica gel, roughly five times higher loading can be achieved, and it is only a fraction of the cost to replace the stationary phase. In practice, we reuse the columns for 100−200 injections and wash between samples with pure methanol.

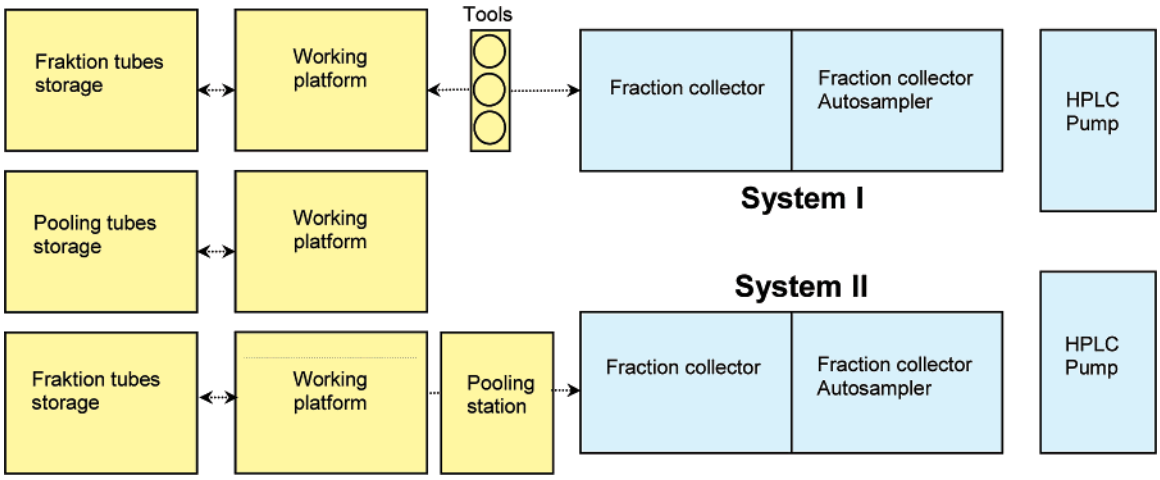
In most cases, separations are carried out by fairly flat two-component solvent gradients or by the use of pure solvents. Gradients of three and four solvents are possible; in practice, we usually use mixtures of petroleum ether/ethyl acetate, dichloromethane/ethyl acetate, and dichloromethane/methanol. These cover a wide range of compound polarity, and the addition of additives such as water, acetic acid, or triethylamine can almost always be avoided.

Once a suitable separation method has been found, the system performs a fully automated reinjection for the whole sample. The fractions are collected by either a UV trigger or a timed collection. The fractions can be analyzed by HPLC/MS, but often simply manual TLC analysis is sufficient. The separated product fractions are combined, and a sample for a final HPLC/MS analysis is taken before the solvent is subjected to rotary evaporation. The customers receive the purified products in round-bottom flasks again, together with the analysis report, usually within 24 h after the initial delivery.

Intermediate II (Reversed Phase). Samples in the range 0.2−20 g are registered in the in-house-developed sample registration and tracking database, Plab. Plab is accessible to all members of the chemistry department. The users enter all necessary information, guided by an electronic wizard. Chemical structures of the compounds, sample quantity, and additional sample properties are mandatory information. At the end of the registration process, the Plab user is asked to print a barcode label for the sample container, in most cases a round-bottom flask, and to take this to the submission cupboard of Intermediate II. Using Plab, the customer can check the processing status. For these quantities, the customer makes the initial choice between Intermediate I on normal phase or Intermediate II on reversed phase, but this can be overidden with customer agreement by the operators of the two units to achieve the most appropriate techniques and equipment usage.

Intermediate II is equipped with an automated sample preparation and analysis system co-developed with Accelab, Kusterdingen, Germany, a company specializing in custom laboratory automation. Samples are registered on the system by barcode scanning, and all required information is passed from Plab. Samples in round-bottom flasks are put on defined positions on a 48-position shaker accessed by a portal robot with pipetting device. Depending on sample amounts, a cer-

Scheme 1. Schematic Overview of the Two HPLC/MS Systems and the Adjacent Fraction Robotics in the Intermediate Unit II



tain quantity of DMF is added, and samples are shaken for a predetermined time with a program of different velocities. The different velocities are necessary to ensure an optimal wetting inside the different flasks with different solvent levels. A pipetting robot transfers the dissolved samples into filters in a filter rack. The filtration is performed under positive pressure, and the filtrate is collected in disposable plastic tubes in bar-coded racks. The robot takes an aliquot from every filtered sample to a microtiter plate located in an autosampler of an analytic Waters LC-MS system, which is an integrated part of the sample preparation system, and analysis automatically starts. The racks with the samples are manually transferred to the preparative HPLC/MS systems.

The two HPLC/MS systems, together with a fraction rack stacker and a robotic system for fraction handling and pooling, are located in a large fumehood equipped with detectors in case of of solvent leakage. Each HPLC consists of a Waters 2525 high-pressure gradient pump for flow rates up to 150 mL/min, a Waters 2996 photodiode array UV detector, and a Waters ZQ mass detector with an ESI source. A 2767 Waters autosampler with a 10-mL injection loop is combined with a fraction collector for 108 100-mL fraction tubes. An additional Waters 2757 fraction collector takes another fraction rack with 180 tubes. The fraction collector racks are stocked from a stacking hotel that can store three pairs of fraction racks. If needed, the fraction collectors can be provided automatically with fresh fraction tubes to prolong the operation time. The hotel stacker also keeps up to six racks with 25 tubes, 500 mL each. These larger tubes are used to combine fractions with the same product. A pouring device carries out the combination of the fractions in a pooling tube. A portal robot handles the tubes with grippers.

The prepared samples are registered into the system by scanning the barcode of the rack and put into the autosampler. From a Plab-produced sample table, the operator manually adds a suitable gradient and method for fraction triggering. For difficult separations, optimized gradients can be simulated on the basis of the analytical data with the simulation software DRYLAB.

Our standard stationary phase for preparative reversed phase chromatography is 10 μm, C18 material. We use X-Terra from Waters for nonpolar substances and Polaris from Varian for more polar compounds, which we pack ourselves in 50 × 250-mm columns with axial compressible packing devices from Merck, Darmstadt, Germany. A column switch valve switches the two columns. The main columns are protected with Waters cartridge guard columns. These two materials in combination with axial compressible packing devices result in long lifetimes. More than 3000 injections are possible without deterioration of separation. Prepacked 50 × 250-mm columns were not comparable. The standard flow is 150 mL/min and run time per injection is ~30 min.

Depending on detection method, 1−10 fractions are collected per injection. Selecting fractions containing the desired product in sufficient purity was one of the most tedious and time-consuming operations in the process. Because there is no practical software tool commercially available, we have developed the software tool “Fracfinder” in-house, which presents just the necessary information, such as UV and total/extracted ion chromatograms in a convenient way. Colored bars within the chromatograms indicate the fractions, and fraction tubes are selected just by clicking directly on the bar. The mass spectrum of the selected tube is displayed, and the signal with the searched mass is colored red. The selected fractions (max 80 mL volume) are directly assigned for a later combination by the pooling robot into a larger 500-mL tube (Figure 3). Fracfinder also allows pooling of fractions coming from multiple injections of the same sample into one tube.

The fractions selected by Fracfinder are transferred automatically to the pooling robot. The selected fractions are combined into the bar-coded 500-mL pooling tubes; subsequently, the robot takes an aliquot for LC/MS analysis and empties the unselected fractions directly into the organic waste system.

The pooling tubes are put manually into special adapted parallel evaporators from Büchi, Switzerland, and the solvent is removed at 40 °C. The whole evaporation process takes a couple of hours because the pressure must be gently lowered automatically to prevent spilling. After the sample is dried, yield is determined, and the customer is automatically requested from the Plab database via e-mail to pick up the sample and the analysis.

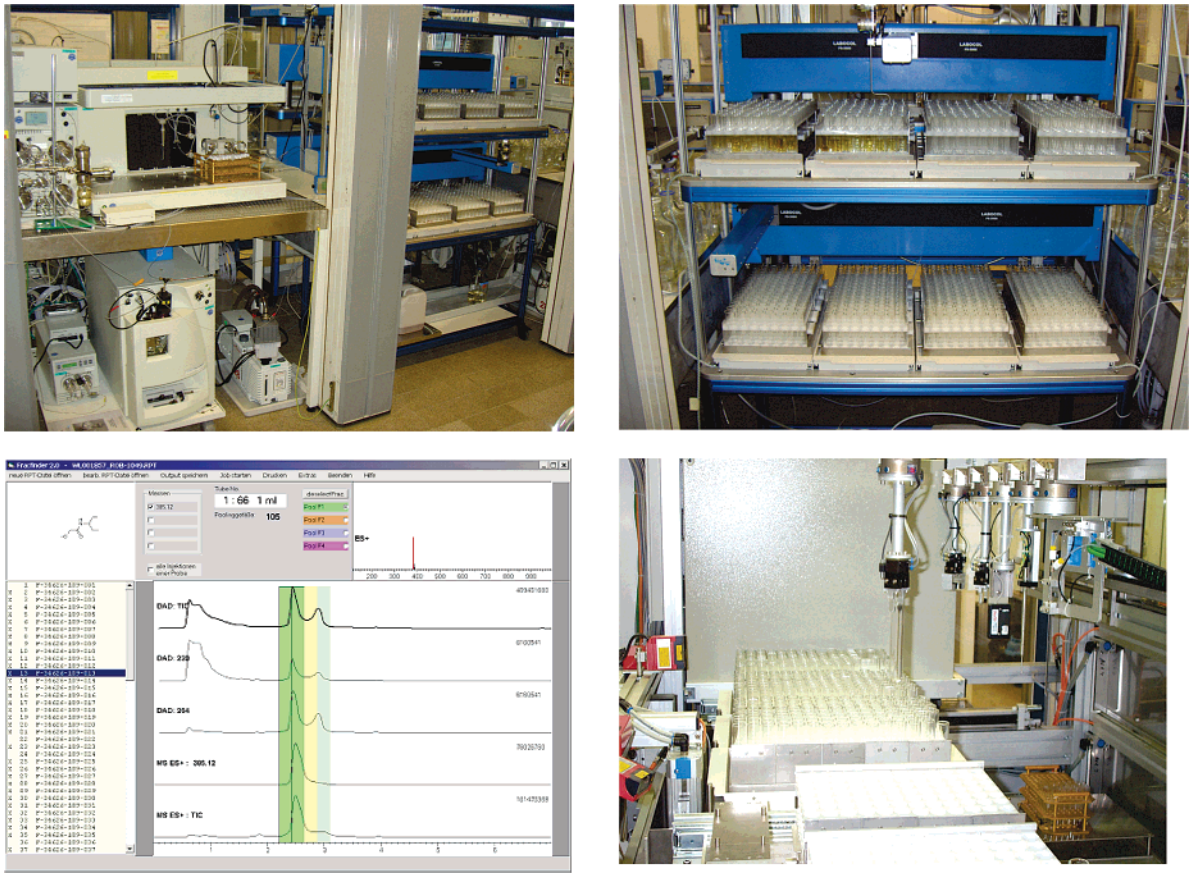


Figure 3. Views on features in unit III (reversed-phase chromatography) HPLC setup, customized fraction collectors, Fracfinder software, and fraction handling robot.

A major disadvantage of the parallel evaporators is the long evaporation time. Coupled with an increasing concentration of TFA in the sample, this means that acid-labile compounds are not suitable for this method. In this case, the samples are manually transferred to a round-bottom flask, which is handed over to the customers. The customers remove the acetonitrile with a rotary evaporator, and afterward, the remaining water is frozen and removed by standard lyophilization. At the moment, we are investigating trapping techniques to overcome the harsh and time-consuming processes of evaporating and freeze-drying.

Final Purification and Intermediate Purification II have a combined consumption of ~1000 L of acetonitrile and 1000 L of water (containing 0.1% TFA) per week. This amount of solvent can only be handled with proper infrastructure. Acetonitrile is delivered through a solvent supply system to all HPLC systems with a constant prepressure of 4 PSI. The 1000-L stainless steel containers are housed in a custom-made storage unit outside the building (Figure 4). Two acetonitrile containers are automatically switched from an empty container to a full container by the supply system. Apart from ordering and connecting the acetonitrile containers, no further work is required. HPLC-grade water containing 0.1% TFA is provided fully automatically by an almost maintenance-free system. The HPLC grade water is produced by a water purification system from Membrapure, Bodenheim, Germany. TFA is added to 30-L batches of water, and then the solution is pumped to a 200-L water container located in the upper floor, which guarantees a constant prepressure of 4 PSI. All HPLC systems are connected to this container. An in-house-developed control system manages the whole solvent supply and alerts the fire department in case of leakages and fire.

Similar to Intermediate I, the two HPLC/MS systems of Intermediate II are connected to a waste-collection device (Figure 4) so that waste from 48 injections can be collected separately in 5-L containers. After the operator is sure that all product fractions have been collected, the waste containers are automatically emptied into the organic waste collecting system.

Final Purification (Reversed Phase). Final Purification utilizes separation techniques similar to those of Intermediate II; however, the techniques, methods and processes are tuned to cope with a far higher number of samples. Furthermore, this unit also transfers the samples into the company bar-coded storage bottles.

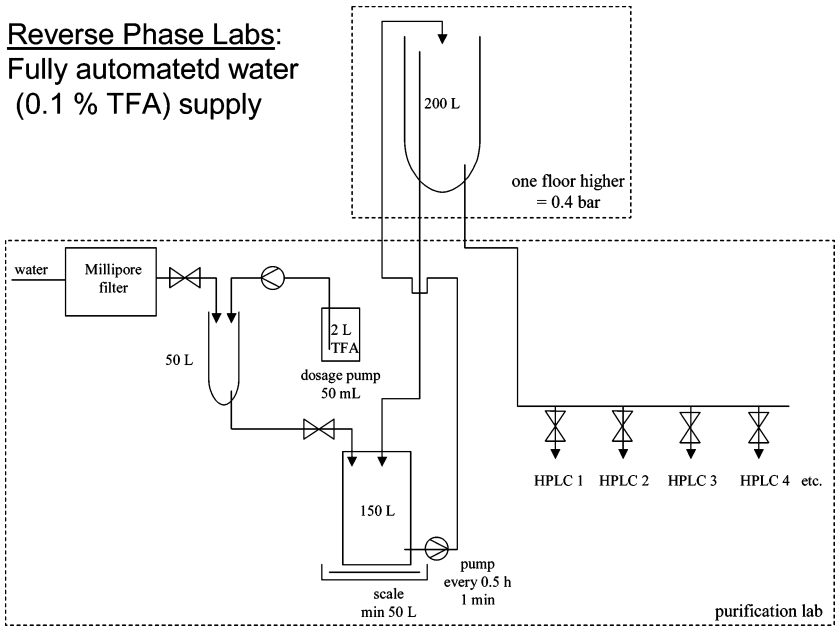
Most samples for Final Purification come from the automated synthesis group, but also a number of single compounds from the entire department are purified. Samples between 5 and 300 mg are dissolved, usually in 1−2 mL of DMF and filtered by the customers. The bar-coded samples are again registered in the database Plab and handed over, together with an HPLC/MS analysis, to the operators directly in 96-format auto-sampler racks. A sample table is produced by Plab and manually extended by the operator with one out of four generic gradients and a method for fraction triggering.

Four identical preparative HPLC/MS systems combined with high-capacity customized fraction collectors are located

Figure 4. Waste recovery system in unit II, external acetonitrile supply, and waste containers (2 × 1000 L each) and the high capacity freeze-dryer of unit III.

in a large fumehood equipped with detectors in case of solvent leakage. Each HPLC consists of a Waters 2525 high-pressure gradient pump for flow rates up to 150 mL/ min, a Waters 2996 photodiode array UV detector, and a Waters ZQ mass detector with an ESI source. The 2767 Waters autosampler with a 5-mL injection loop is combined with a fraction collector for one fraction rack with 120 40-mL fraction tubes. An additional Labomatic fraction collector takes another four racks with 120 tubes each, which adds up to a total of 600 fraction tubes per system. The standard flow is 120 mL/min, and the overall runtime per injection is only 5 min so that up to 200 samples can be purified on one system in 24 h. The achievement of this short cycle time without any loss in terms of the separation quality and process robustness was only possible with the development of a number of hardware and software solutions. For example, the Labomatic fraction collectors had to be equipped with stronger drives to achieve very short stepping

Scheme 2. Fully Automated Water Supply and TFA Dosage



times, and the new hardware had to be implemented into Waters Mass Lynx Software. The HPLC systems from Final Purification use the same waste system and are connected to the same acetonitrile and water (0.1% TFA) supply as Intermediate II.

The standard stationary phase in Final Purification is again 10 μm, X-Terra and Polaris C18-material. Prepacked columns of 30 $\times$ 100 mm and Waters cartridge guard columns are used. More than 4000 injections can be achieved per column.

As described before, product-containing fractions are selected by the operators with the in-house-developed software tool Fracfinder. The fraction tube racks are manually transferred to a second fumehood, which houses two identical robotic systems for fraction handling and many pipetting jobs. Usually, the product-containing tubes are combined into one or more tubes in a second pooling rack by a pipetting tool. In most cases, just one tube is required per sample. Each robot system, again engineered and built together with Accelab, has four drawers, and in each drawer can be stored a set of racks with 360 fraction tubes and two pooling racks together with 192 pooling tubes. For processing, a lifting device moves each drawer into the working position so that the drawers can be automatically processed one after the other. The drawers can be stocked with other racks and glassware. The hardware and software are very flexible and not limited to certain processes. Pooling from a set of 360 fraction tubes takes 2−4 h, and the system operates unattended 24 h a day.

The pooling rack fits directly into the high-capacity customized freeze-dryer from Hof Sonderanlagenbau, Lohra, Germany. Two chambers can be manually loaded with seven 96-tube pooling racks each. Automatic freeze-drying takes 48 h. Initially, the chambers are cooled to −58 °C so that the fractions with water/acetonitrile solutions freeze to solids. The two condensers defrost automatically in turn, and the solvents are pumped into the waste system described before. Except for regularly vacuum pump oil-changing, the system works maintenance-free year-round.

After the solvent has been removed by the freeze-dryer, the pooling racks are returned to the robotic system. The lyophilisates are redissolved in 4 mL of organic solvent and transferred to 4-mL standard bar-coded compound collection bottles. A small aliquot is taken to a second set of bottles for NMR and LC/MS analysis in the analytical department. The organic solvents are removed in a vacuum-drying cabinet, and the weight is determined automatically. The bottles with the final compounds are registered in the company database and sent directly to the compound collection department. The customers are informed automatically by e-mail. The compound collection department takes over all subsequent weighing, dissolution, distribution, and delivery tasks and serves all biological assays. The whole procedure for a set of compounds in the final purification lab takes a maximum of 7 days.

Conclusion

The purification capabilities of medicinal chemistry in Frankfurt have been centralized in specialist units. Our goal was to increase the productivity of medicinal chemistry and to build up high-throughput library purification. After three years of operation, it is clear that these goals have been met. Today, the three purification units are a critical part of chemistry and library production. The output of single compounds is currently increasing by 20% every year, and 30 000 samples from automated synthesis were purified in 2004. A centralized purification unit is only appropriate if a number of prerequisites are fulfilled: the department and the number of users has to exceed a certain size; the size of the unit has to have a critical mass; redundancy for staff and facilities is needed to provide a reliable service (the minimum is two separate systems with two FTEs for one particular task to maintain the service in case of breakdowns); and high quality standards have to be achieved in order to get acceptance by the costumers. We feel that only in this organizational setup is the use of automation truly beneficial.

Laboratory automation is sometimes viewed negatively within discovery chemistry research. Perhaps the reason for this is that in attempting to increase productivity, automation has often been introduced to a "traditional" laboratory without a corresponding introduction of new organizations and working methods. Often, the effort required for implementation and proper use of automation is underestimated, and staff do not have the right specialist skills. The level of automation has to match the skillset and time available of the users. Thus, in a traditional laboratory, automation should not be excessively complex and, indeed, should only be introduced where it is absolutely necessary. However, proper application of complex automation delivers high productivity, and we would not have been able to achieve our current output without it.

This article depicts the setup of our purification facilities at one moment in time. There are many new innovations that we would like to add to the system. For example, we are investigating a pre-LC/MS analysis that automatically exchanges data with the preparative systems for optimized separation conditions. To meet the ever increasing demands of chemists, it is essential that the system be flexible and seen not as a completed work, but as a constantly evolving facility.

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