1. PROJECT FINAL REPORT

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[1] The home page of the website should contain the generic European flag and the FP7 logo which are available in electronic format at the Europa website (logo of the European flag: http://europa.eu/abc/symbols/emblem/index_en.htm ; logo of the 7th FP: http://ec.europa.eu/research/fp7/index_en.cfm?pg=logos). The area of activity of the project should also be mentioned.

Contents

1 Executive summary

Continuous Annular Electrochromatography (CAEC) constitutes high-performance process equipment, adaptable to special requirements of new production lines, allowing for small-scale production of high-value products and in chemical, biochemical and pharmaceutical industries.

Capillary electro-chromatography (CEC) is a rapidly evolving hybrid technique between HPLC and capillary electrophoresis. It is possible to obtain unique separation selectivity using CEC compared to both HPLC and capillary electrophoresis. The beneficial flow profile of electro-osmotic flow reduces axial dispersion and separation efficiencies of several hundred thousand plates per meter can be obtained. Since back pressure limitations are negligible, it is possible to improve the separation efficiency by using packings with small particle sizes of 1-3 µm.

CAEC is a very powerful tool for the separation of complex mixtures with chemically similar compounds since it combines the high separation efficiency of capillary electrophoresis with the applicability of high performance liquid chromatography to a wide range of both neutral and charged components. The proposed integration of these two innovative technologies increases the productivity of electro-chromatography by several magnitudes whilst maintaining substantially increased separation efficiency. As a fully continuous technology, CAEC is optimally suited to transform production processes from batch to continuous operation.

One of the CAEC's main objectives was the establishment of novel design and manufacturing procedures for highly sophisticated mechanical equipment, and as a consequence the development and production of new functionalised materials tailored to process requirements, including the design of the stationary and the functionalization of materials for reversed phase chromatography, allowing the operation of the intensified unit under a broad range of conditions. As a part of the objectives in the process control area, the implementation of on-line sensors for continuous monitoring of product specifications was introduced. Also, the design and integration of adaptive control strategies for automatic real time adjustment of operating parameters was done. The development of predictive process models for a knowledge-based design of production processes was also planned, and the assembly, optimisation and validation of a fully equipped CAEC plant for the use in the pharmaceutical production was performed at last. The validation step was shifted to the academic and research partners but still an industrial test system was used.

CAEC can extend the range of application towards a small-scale production of extremely high-value-added products such as pharmaceuticals for clinical trials early on in the development stages and represents a continuous purification technology for highly complex mixtures that satisfies the need for a real-time product analysis and control, required to establish Quality-by-Design in pharmaceutical and chemical production. As a fully continuous technology, CAEC is optimally suited to transform production processes from batch to continuous operation.

Due to the better separation and purification efficiency of CAEC, as compared to conventional technologies and the number of purification steps, the consumption of auxiliary chemicals can be reduced to increase the sustainability of the production process. CAEC also allows the production of pharmaceuticals with a high biological activity at low dosage, as it allows the separation between very similar chemical compounds, such as position isomers. Easy scale-up from drug characterisation to drug production for clinical trials can be facilitated, since capillary electrochromatography is an established analytical technology and its continuous operation allows a direct transfer of the separation principle to a larger scale. A breakthrough in capacity allows the

use of CAEC in the small-scale production of personalised medicine and pharmaceuticals for rare diseases. Predictive methods for model based process design can give an extra push to the use of CAEC technology as a reliable and highly efficient purification technology.

By considering the benefits for the development of a new pharmaceutical product, tremendous reductions in time and costs can be foreseen at different stages of the development process.

Continuous Annular Electro-Chromatography

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2 Summary description of the project context and main objectives

The ongoing shift of the European chemical and pharmaceutical industry from resource intensive large scale production towards dedicated high value-added products enforces the need for flexible production systems that can easily be adapted to the special requirements of new product lines. CAEC belongs to such new generation of high-performance process equipment that allows for the small-scale production of extremely high-value added products in chemical, biochemical and pharmaceutical industries.

Capillary electro-chromatography (CEC) is a very powerful tool for the separation of complex mixtures with chemically similar compounds since it combines the high separation efficiency of capillary electrophoresis with the applicability of high performance liquid chromatography (HPLC) to a wide range of both neutral and charged components. So far, this technology has been applied exclusively for analytical purposes since the small column dimensions limit the productivity to a few millilitres per day. Moreover, continuous annular chromatography, as the only continuous chromatographic technique that fulfils the high demands raised by modern biotechnological production, has been transferred from research laboratories to fully developed industrial process scale and is consequently the main aim of this project. The proposed integration of these two innovative technologies will increase the productivity of electro-chromatography by several magnitudes whilst maintaining an efficiency of more than 20,000 theoretical separation stages per meter. This breakthrough in productivity will provide potential for tremendous process intensification in chemical, biochemical and pharmaceutical industry. The resulting continuous annular electro-chromatography (CAEC) technology will thus extend the range of application towards a small-scale production of extremely high-value-added products like pharmaceuticals for clinical trials early on in the development stages. As a fully continuous technology, CAEC is optimally suited to transform production processes from batch to continuous operation.

The project addressed the process intensification in the production of chemicals because “it targeted a new generation of extremely flexible, high–performance process equipment”, “whose local operating conditions adapt automatically and in real-time to changes in feed composition, operating conditions, product specifications, etc.“ In the longer term a “substantial drop in capital expenditure for new plant and/or for retrofit of high–performance intensified devices into existing infrastructure can be expected”.

The CAEC prototype unit marks the beginning of a new generation of extremely flexible high-performance process equipment requiring specialised engineering skills and high-precision manufacturing techniques. This holds in particular for the highly demanding development of the hardware which has to combine moving parts, local dimensions in the micrometer range and the application of high electric voltage. The conceptual design of the prototype involving all project partners included apparatus dimensions, inlet and outlet geometry, heat release and heat exchangers, flow rate in an empty and a packed gap, and dimensioning of feed nozzle drive. Reference mixtures and test systems including artificial test system for benchmarking experiments and industrial test systems were done for real case applications. CFD simulations of the fluid flow in different scales were used to establish a novel approach to equipment design. New functionalised and modifiable stationary phases were designed to allow for tailoring the unit to the product specifications and thus guaranteeing an optimum use of the equipment.

Advanced research was performed to gain information about transport phenomena in the pore system and molecular interactions between the feed compounds and the stationary phase. This information was used to establish a computer-aided design of functionalised materials and was

transferred to a detailed model allowing for a predictive simulation of the process performance of CAEC units. Suitable miniaturised sensors were developed and integrated in the CAEC unit to facilitate an on-line control of the product quality and thus facilitating the shift from Quality-by-Testing to Quality-by-Design in pharmaceutical industry. This went along with a process control concept enabling an automatic real-time adaptation of local operating conditions to external influences like feed compositions. The integration of the CAEC prototype and all peripheral equipment into a fully equipped but compact and movable plant makes the new technology optimal for flexible, small or even single batch-oriented production.

The optimisation of the CAEC technology for industrial production required functional tests with reference systems and an accurate validation with complex mixtures from pharmaceutical industry, which was carried out during a demonstration phase at the end of the project duration. The experimental results from industrial validation were used to verify the accuracy of the process model, and the validated process model was implemented into a generic process design methodology to allow for a reliable assessment of potentials for process intensification in the downstream processing of pharmaceutical products. This ensured a fast implementation of the project results and thus facilitating the design of dedicated small continuous processes at reduced costs. All necessary provisions to enable GMP equipment manufacturing was made in parallel and thus providing the opportunity for an FDA approval and commercialisation of the CAEC technology.

The main drawback of the traditional separation concepts is the application of a radial electrical field that does not allow for the use of small bed dimension and thus significantly reduces the performance of the device. These limitations are overcome by following a novel concept for annular chromatography where the feed and sampling lines are rotating above respectively beneath an immobile annular bed (see Figure 1). The bed has a monolithic stationary phase and the field is imposed in an axial direction in contrast to earlier concepts described in the literature. This innovative design enables the transfer of electro-chromatography to continuous operation at a simultaneous consideration of safety aspects and implementation of on-line sensors.

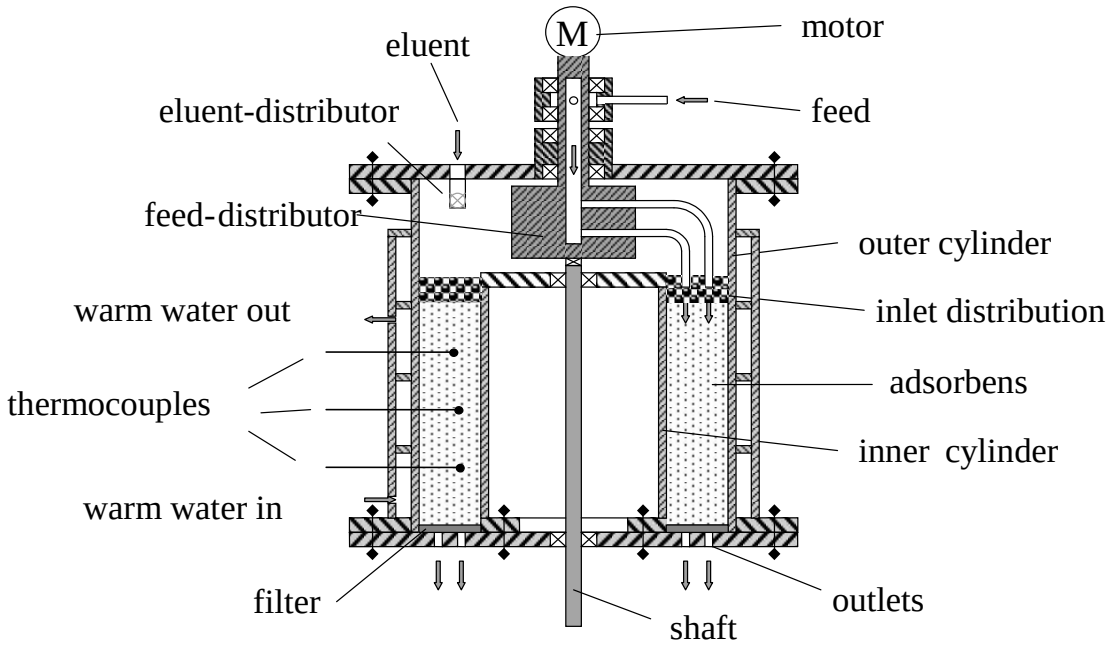


Figure 1: Innovative design concept for continuous annular chromatography

The electrodes are isolated from the separation media via separate electrode channels which are formed from permeable membranes. Heat accumulation within the sorption bed is controlled using

buffer streams flowing through the electrode chambers and acting as coolants. The intensity of the cooling is also be increased by a reduced thickness of the annular bed and the integration of micro-structured heat exchangers.

Extensive buffer consumption is a challenge for the design of new chromatographic production processes. CAEC provides an excellent opportunity to minimise the buffer requirement and thus to enhance the sustainability of new applications. The outflow of target product and side components is limited to a certain sector of the annulus and thus allows recycling the non-contaminated buffer solution in a closed loop system. In addition contaminated buffer solutions with different quality is reprocessed with limited effort due to separation of certain classes of contaminants by the CAEC unit itself.

The development of an industrially validated CAEC plant, the main project objective, was divided into the following sub-goals which are elements for knowledge-based production systems and holistic engineering concepts.

- The establishment of novel design and manufacturing procedures for highly sophisticated mechanical equipment
- The development and production of new functionalised materials which are tailored to process requirements and thus allow for the operation of the intensified unit under a broad range of conditions
- The implementation of on-line sensors for a continuous examination of product specifications
- The design and integration of adaptive control strategies for an automatic real-time adjustment of operation variables
- The development of predictive process models for a knowledge-based design of production processes
- The assembly and optimisation of a fully equipped CAEC plant for the future use in pharmaceutical production

To accomplish the expected breakthrough in the production of high-value-added products, the CAEC plant must fulfil the following two performance criteria:

1. Productivity scale-up by a factor of at least 10,000
2. Separation efficiency of up to 25,000 stages per meter.

3 Description of the main S&T results/foreground

The establishment of a totally new production technology for the chemical and pharmaceutical industry within the timeframe of CAEC required a careful scheduling and stepwise procedure. The following approach was followed:

- A design of stationary phases, i.e. development of the appropriate chemical pathways for synthesis of silica based monoliths, functionalization of materials for reversed phase chromatography with amino, thiol and cyano groups, and testing of one step and two step approaches for material synthesis was made.
- Establishing a working range of the planar cell, as well as determining the influence of different eluents and the possibility to increase the fluid throughput by an optimization of the gap width were part of the main results achieved. The successful separations tests with an analytical capillary electro chromatography and the performed pre examination experiments from the batch analytical separation methods could be transferred to the monolithic gap and mounting of a UV-VIS spectrometer at the outlet geometry of the planar test cell. The latter did show a separation of the artificial test system, PAH and the phenols in the planar gap, which is important for the proof of the concept and the comparison between chromatograms from the planar device and the CEC and serves as a basis for scale-up from batch to continuous operation.
- Advanced process modelling, i.e. the development of consistent sets of model equations based on one dimensional and two dimensional differential mass balances were carried out and combined with an ideal model of electro osmotic flow in porous media, and implementation and testing of steady state and dynamic process models.
- The validation of the 1D simulation gave good agreements between measured and simulated chromatograms based on automated parameter estimation. Nevertheless, the predictive accuracy of this model is yet not satisfying due to a not modelled drift of the peaks from measurement to measurement for constant process inputs.
- The design of the industrial plant, i.e. the specification components, interfaces and basic and detailed engineering of the CAEC unit were accomplished. Based on the user specifications, the technical specifications of the equipment were made and the proper equipment was selected and purchased in order to build a 3D model of the plant. Furthermore, a control system was developed, along with the proceeding programming of the software and building of a rack containing the required hardware.
- The plant was assembled and commissioned. A risk analysis was made. Functional tests were made and the plant was approved by a notified body. A user manual was written and a comprehensive documentation was compiled. As a result a fully functional and save CAEC plant with CE marking and EC declaration of conformity is ready for operation.
- The industrial validation was planned as the last phase in the project. Instead of the validation of in the industrial infrastructure as it was initially planned, the validation shifted to the academic and research partners but still an industrial test system was used. The rather young Capillary Electrochromatography proved its skills for highly difficult separations of charged and uncharged molecules, yielding up to and over 100,000 separation steps per meter. This analytical method for nanograms was upscaled for the continuous separation of small production quantities, currently in the g/h range purified material. As such, it adds itself as an elaborated and advantageous purification method to known but limited methods.

3.1 Conceptual Design

The starting point of the project was the **conceptual design** of the new CAEC unit, which included the definition of dimensions and test systems for the last two years of the project. The involvement of all project partners not only ensured that all aspects for the design of the new technology are considered, but also allowed to establish well defined criteria for the workflow on other aspects like the design of stationary phases, process modeling, instrumentation and process control. Software standards for the modelling and simulation environment were also set.

3.2 Detailed Engineering

The **detailed engineering and manufacturing** of the first CAEC prototype was the most challenging task of the project, which was broken down into three different steps to reduce the required resources and minimise the risk. Instead of starting with an annular geometry, the first equipment design is developed with planar test cells, which represent a fraction of the annular gap of the final device. The dimensions of the planar test cell were identical to a segment of the annular bed, as can be seen in Figure 2. This approach significantly helped to reduce the effort for the production of test cells, allowing “for product and buffer supply, a selective liquid removal, and a concept for an efficient heat management”. Both the design and the filling frame were designed flexible to enable the manufacturing and testing of different monolith layer thicknesses as well as the use of cheap and well accessible glass window plates at least for the basic testing.

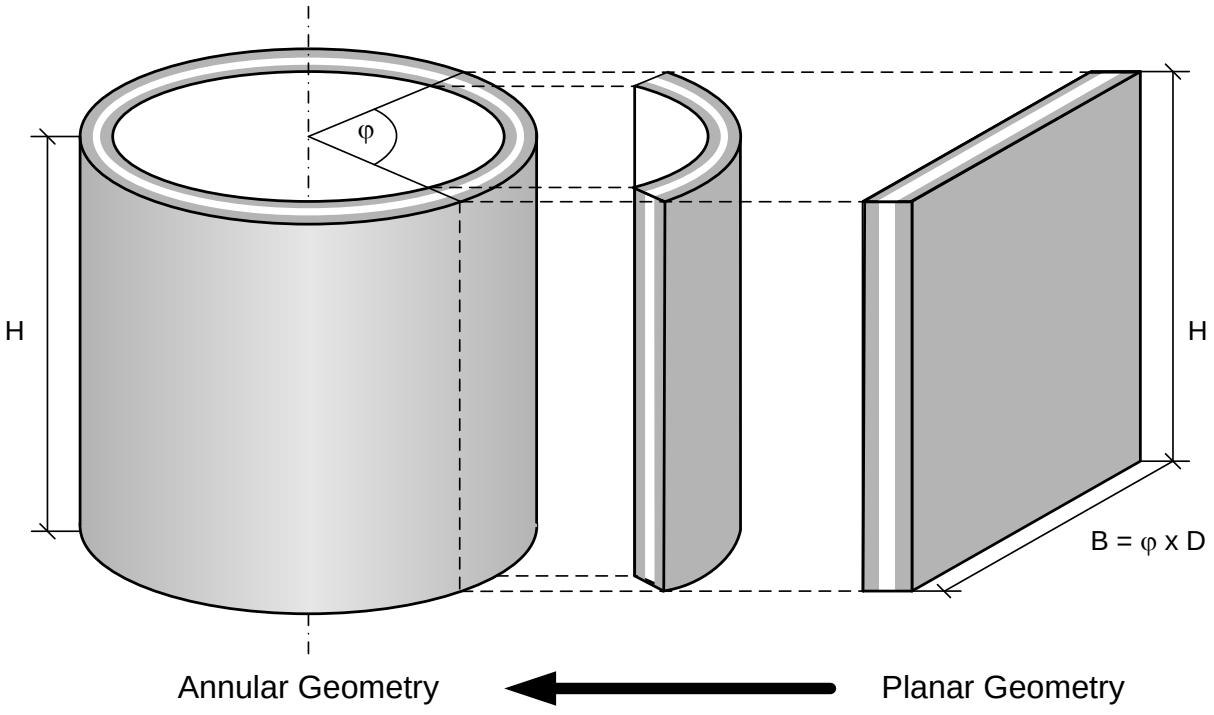


Figure 2: Transformation from planar to annular geometry

Glass was chosen as the cylinder construction material to ensure anchoring of stationary monolithic phase, to have sufficient electrical insulation and to reach highest precision in realisation. Although alternative materials such as silicon carbide, boron nitride, PEEK, have been taken into account for the improvement of heat removal, cost issues and the uncertainty about the interaction with the stationary phase render these materials prohibitive. The **filling frame** which allows for equipment testing as well as for the development of stationary phase and its assembly is shown in Figure 3.

Optimal performance in an empty frame could be shown impressively by the equi-distribution in a movie of IMM when feeding with simple water blue solution.

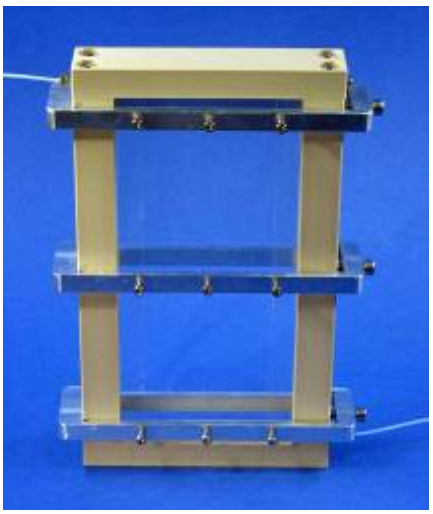


Figure 3: Planar filling frame (Source IMM)

IMM designed, manufactured, and TUK tested an elaborate **2D planar geometry** which is depicted in Figure 4. Both the design and the filling frame were designed flexible to enable the manufacturing and testing of different monolith layer thicknesses as well as the use of cheap and well accessible glass window plates at least for the basic testing. A heat exchanger from Al was later replaced by a PEEK heat exchanger to avoid problems when working at high field strengths.

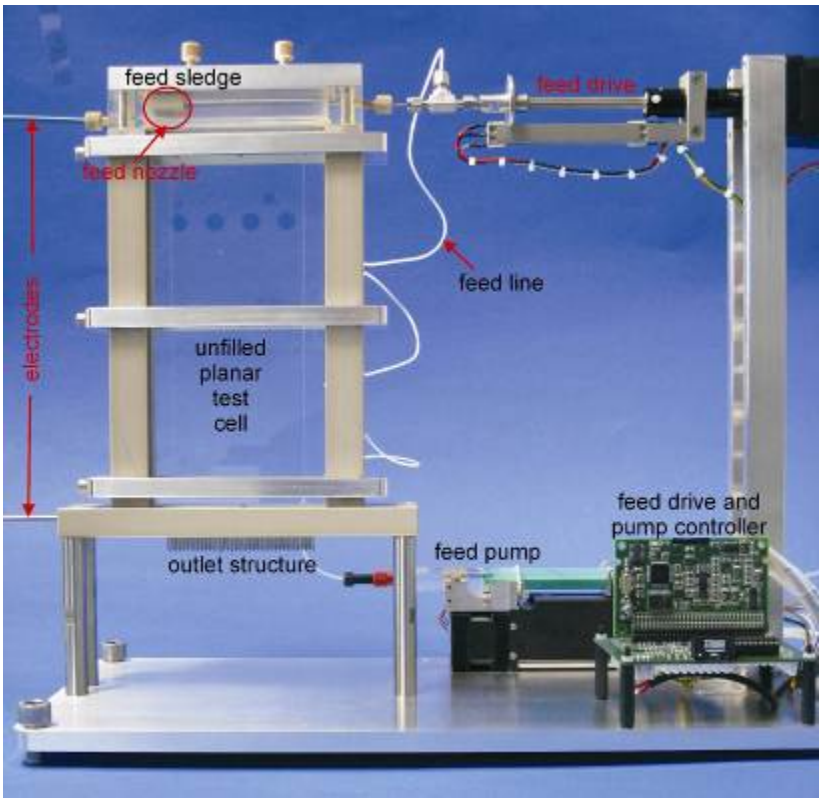


Figure 4: left: Complete planar geometry including feed drive and pump as well as control electronics; right: planar heat exchanger plate from aluminium (Source IMM)

As a new feature to be included in the planar geometry, IMM included a movable and **exchangeable feed nozzle** in its set-up to allow for controlled application of test substances for separation experiments. Furthermore, this controlled supply line is equipped with an IMM developed syringe pump to test varying feed flow rates.

The first CAEC prototype V1 was available after the 2nd year but showed some major problems or drawbacks which need to be overcome to reach the project objectives. Therefore, the Consortium decided to develop an improved second generation of the CAEC prototype V2. This new version allows for continuous and sharp separation of industrial test systems. Both versions can be operated in parallel thus allowing for gaining the fundamental knowledge on electrochromatography (like the influence of the electroosmotic flow) in V1 which can be transferred into the operation of the V2 prototype at industrial conditions.

3.3 Design of Stationary Phases

The design of the stationary phases deals with the **development, functionalisation and characterisation of customised stationary phases**. This offers the possibility to tailor the performance to individual separation tasks and to extend the application area of the CAEC technology. TUG took responsibility on this due to his expertise in the controlled preparation of functionalised materials.

Three different approaches to prepare thin modifiable stationary phases (sol-gel process, micro-particle fusion, organic polymeric monoliths) were explored by TUG. To reduce the effort, stationary phase modification will first be done with the planar test cells, before transferring the procedure to the annular geometry. An annular stationary phase which can be used for the reference test systems as well as for the industrial systems was available after 2 years. The structural characterisation of the stationary phase were performed by TUG whereas suitable methods to evaluate their performance and thus to determine the relevant model parameter for predictive process simulations were be developed by UNIKL and TUDO. These procedures were standardised to establish a fast and reliable performance for the scale-up from analytical towards industrial application. Advanced modelling approaches for mass transport in the porous monolithic structure and molecular interaction between the feed components and the stationary phase were performed at TUG to provide additional information on the stationary phase behaviour and set up a computer-aided design for new CAEC applications.

Preparation

Chemistry Development

Since the CAEC prototype combines the principles of continuous annular chromatography and capillary electro-chromatography (CEC), the development of the stationary phase bases on the concepts and materials used for CEC technology. For CEC applications, three major categories of column design are known including (i) packed, (ii) open-tubular and (iii) monolithic capillaries, which can be classified as either inorganic or organic polymer-based. Considering the advantages of inorganic monolithic materials, the stationary phase for the CAEC prototype was made of **silica-based sol-gel monoliths**.

Silica-based sol-gel monoliths can be prepared either using a one-step or a two-step approach, The one-step method uses silanes ($Si(OR')_4$) and organosilanes ($RSi(OR')_3$) together with amphiphilic surfactants in a single step. The silanes form the silica backbone while the organosilanes yield the

desired organic moiety. The surfactants are needed for the formation of a three dimensional pore structure. Another possibility is to prepare functionalized silica-based monoliths in a two-step approach, which involves the preparation of a silica based material via a sol-gel process and drying at elevated temperatures (>100°C) in the first step followed by the functionalization step where the silica is brought into contact with an organic solvent containing organosilanes.

For the CAEC prototype it was decided to start with a **one-step approach** based on procedures reported by Ding et al.[2] and Yan et al.[3] because of the following benefits:

- The sol-gel technology can be carried out at room temperature, thus shrinking of the material could be avoided.
- The preparation and functionalization of the stationary phase can be done in one step.
- The stationary phase is bound covalently to the surface of the outer cover if it includes SiOx groups. Therefore, the designated material of the outer cover is glass.
- By varying the used precursors, different kinds of stationary phases can be prepared applying this approach.

For the test systems (i.e., the test systems anthracene and napthalene as well as the industrial test systems rapamycin, ascomycin and dihydrotacrolimus) it was decided to concentrate on materials for **reversed phase (RP) chromatography**. In addition, we also functionalized the stationary phase with **amino**, **thiol and cyano groups** and we prepared **normal phase (NP)** materials. The involved chemicals and their functions are summarized in Table 2. The stationary phases were successfully implemented in the following entities:

- Microscope slides (2.5 x 10 cm with 100 µm gap)
- Glass capillaries (300 µm x 10 cm)
- Glass columns (0.5 x 10 cm)
- CE Standard capillaries (100 µm x 25 cm)
- Electrophoresis plates (10 x 10 cm, 100 µm gap)
- Planar plates (10 x 20 cm, 100 – 300 µm gap)

All entities were pretreated with HCl and NaOH before the monolithic material was filled into the filling frames. The microscope slides were filled utilizing capillary forces, all the other devices were filled manually with a syringe. For the filling of the analytical capillaries the arrangement shown in Figure 5 was developed.

[2] Ding, G.; Da, Z.; Yuan, R.; Bao, J. J. *Electrophoresis* **2006**, *27*, 3363-3372

[3] Yan, L.J.; Zhang, Q.H.; Feng, Y.Q.; Zhang, W.B.; Li, T.; Zhang, L.H.; Zhang, Y.K. *J. Chromatogr. A* **2006**, *1121*, 92-98

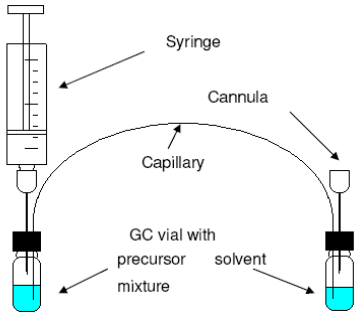


Figure 5: Arrangement to implement the silica-based monolithic material in the analytical CEC capillaries

According to the investigations by TUK, the procedure for the preparation of the stationary phase was done in a **two-step approach** for more chemical and mechanical stability, including the preparation of a normal phase in the first step (chemicals used see Table 1) and the functionalization of the monolith in the second step to give a RP material. This approach helped to increase the homogeneity of the filling as well as the chemical and mechanical stability. For the functionalization of the NP monolith several approaches were tested, the method using a solution of trichlorooctylsilane in toluene (25 V%) gave the best results. CEC capillaries filled with this material were sent to TUK and generated a reproducible separation of anthracene/ naphthalene.

Characterization and Testing

In order to confirm the successful functionalization of the monolithic material the stationary phases were analyzed with FTIR and RAMAN spectroscopy. Analyses of the specific surface area, the pore volume and the pore diameter were carried out applying the BET method. The heat capacity of the materials was analyzed using differential scanning calorimetry. Furthermore, simple separation tests with two dyes were carried out in order to illustrate the separation ability of the monolithic material (Figure 6). Additionally, the materials were analyzed with scanning electron microscopy.

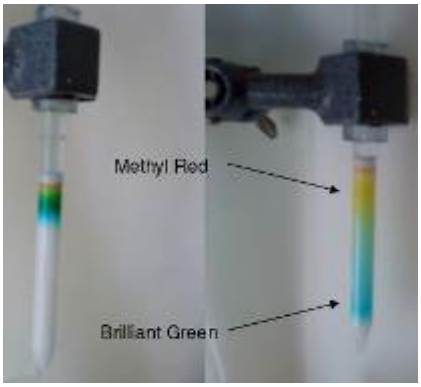


Figure 6: Separation of a dye mixture in a glass column filled with silica-based monolithic material

Planar Geometry

The following method was developed for the filling of the planar geometry with monolithic material: The stationary phases were filled between two glass plates (10x20cm) which were assembled in the filling frame sent to TUG by IMM. The appropriate gap between the plates was provided using Teflon tape. After the glass plates are implemented in the filling frame, they have to be pre-treated in order to clean and activate the inner surface of the glass plates. To prepare the silica-based monolith (NP) the compounds specified in Table 1 are well mixed in a Teflon beaker in

water and ethanol using a shaker and ultrasound. Then the mixture is filled bottom up in the pretreated device using a syringe.

Table 1: Compounds and amounts for the preparation of a silica-based monolithic stationary phase (normal phase) (Amounts given for the filling of planar geometry with 10cm x 20cm x 300µm)

Compound	Abbreviation	Equiv.	Amount	Function
tetraethoxysilane	TEOS	1	2.0 ml	silica backbone
diethylamine	DEA	0.5	0.3 ml	catalyst
cetyltrimethylammonium-bromide	CTAB	0.04	0.06 g	porogen
dimethylformamide	DMF	1.3	0.40 ml	drying control chemical agent
Water	H_2O	7.4	0.80 ml	solvent
Ethanol	EtOH	6	2.4 ml	solvent

To allow a **homogeneous polymerization** the filling tubes have to be sealed with silicone caps and the filled plates have to be kept at room temperature for 3 days until the whole surface is white and opaque. Then the stationary phase has to be washed with ethanol or electrolyte to remove the porogen. Finally, the material is dried with nitrogen at room temperature. After the successful preparation of the NP monolith it can be functionalized with trichlorooctylsilane to give a RP material. A picture of the planar test cell filled with monolith is shown in Figure 7.

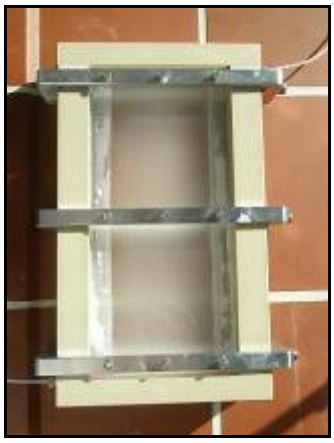


Figure 7: Planar test cell filled with monolith

Stationary phase modification

In addition to the RP and NP stationary phases, monolithic materials functionalized with **amino, thiol and cyano groups** were also prepared and sent to TUK for further testing. Analysis of these materials using FTIR and RAMAN spectroscopy as well as elemental analysis carried out by TUG confirmed the successful functionalization with the appropriate functional groups. The involved chemicals and their functions are summarized in Table 2.

Table 2: Involved chemicals and their function for the preparation of functionalized and non-functionalized sol-gel silica-based monolith

Compound	Abbreviation	Function
Tetraethoxysilane	TEOS	silica backbone
triethoxy(octyl)silane	C8-TEOS	reversed phase (RP)
3-aminopropyltriethoxysilane	APTES	catalyst, amino groups
3-cyanopropyltriethoxysilane	CPTES	cyano functionalization
3-mercaptopropyltrimethoxysilane	MPTMS	thiol functionalization
Octyltrichlorosilane	OTCS	RP, 2-step functionalization

Annular geometry

To fulfil the specifications of the project, a silica-based monolithic stationary phase functionalised with C8-groups was selected. In the last period of the project, TUG was assigned to prepare the monolith in the annular geometry. After employing a standardised filling procedure, the preparation of the annular monolith was moved to UNIKL, since the transport of the filled cylinders led to cracks in the monolith. TUG was further in the position of giving advice and helping out when needed.

The standardised filling procedure involves the following steps:

- Activation of the glass surface: flushing with HCl 1M for 30 min, washing with water, flushing with NaOH 1M for 30 min, washing with water and MeOH, drying
- The precursor mixture (namely TEOS 1 mol equivalent (equiv.), C_8-TEOS 0.4 mol equiv., HCl 0.5 M, 0.01 mol equiv., H_2O 1.25 mol equiv., MeOH 22.2 mol equiv. and Polygosil particles 15 wt%) is stirred at 60°C for 1 h. After cooling to room temperature, diethylamine (0.25 mol equiv.) is added
- The solution is quickly filled into two 60 ml syringes. These are put into a syringe pump and the cylinders are filled from bottom to top
- The monolith is left for polymerization for 48 h at room temperature
- After that the monolith can be transferred into the adapted filling frame and washed with MeOH (see below)

The structure and performance were characterised (TUG, UNIKL). In the last period of the project the focus was laid on the material in the annular geometry. After filling the monolithic material into the device, several characterisation tests were performed in Graz, before the preparation of the monolith was transferred to Kaiserslautern.

The stationary phase was implemented in CEC-capillaries, in the planar prototype (with 0.3 mm and 1 mm gap) and in the annular prototype (with 0.3 mm and 1 mm gap width). Pictures of the filled molds are shown in Figure 8.

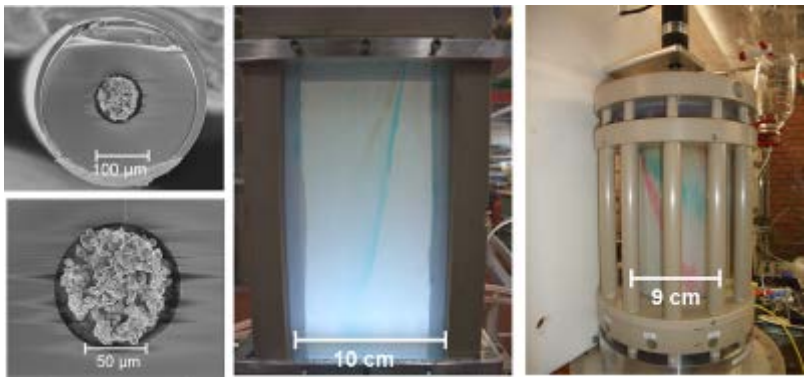


Figure 8: Pictures of a CEC capillary (left), the planar test system (middle) and the annular prototype (right) filled with stationary phase

Distribution of the discharged liquid

Figure 9: Distribution of discharged liquid

An adapted filling frame for the annular geometry manufactured by the IMM was sent to TUG. This frame allows the observation of the eluent pumped through at the bottom outlet (see Figure 9). In order to investigate the distribution of the discharged liquid 15 ml of MeOH were pumped through the monolith manually. The discharged liquid was collected in eight vessels; each vessel included the liquid of 10 outlet needles. After the whole eluent was pumped through, the amount of discharged liquid was determined via the mass of collected MeOH. The distribution was analysed three times, the results of the determined weights (weight 1= experiment 1, weight 2 = experiment 2, weight 3 = experiment 3) are shown in Table 3.

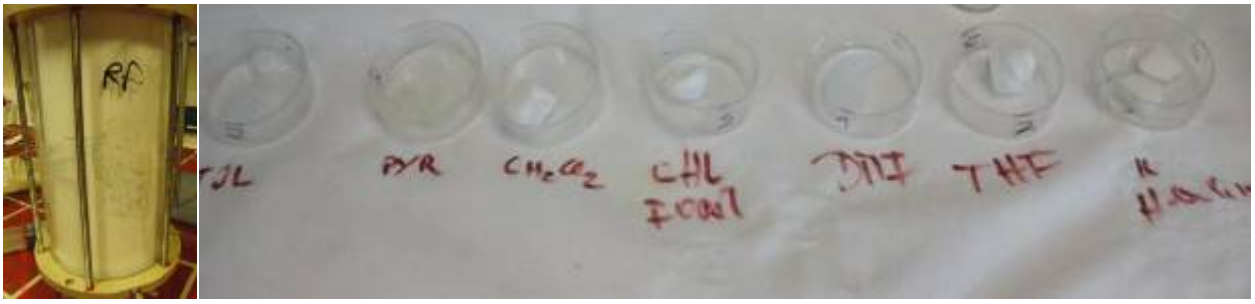
Table 3: Results of distribution measurements

Number of vessel	Weight [g] 1	Weight [g] 2	Weight [g] 3
1	2.771	1.181	1.650
2	1.187	1.290	1.400
3	1.993	1.763	1.868
4	1.101	0.485	1.358
5	1.355	1.551	0.874
6	1.420	2.808	1.465
7	1.067	1.699	2.931
8	1.064	0.999	2.255
	$\bar{x}$=1.465, σ^2=0.36	$\bar{x}$=1.472, σ^2=0.46	$\bar{x}$=1.725, σ^2=0.40

The results in Table 3 indicate that the distribution of the amounts is relatively broad. However, none of the outlet positions seem to be preferred, thus the distribution can be seen as rather uniform. Further results concerning the liquid distribution are presented by UNIKL.

Influence of different eluents

In the course of the experiments we discovered that the monolithic material cannot be operated with all eluents used in conventional chromatography. Therefore, the influence of several common solvents on the stationary phase was analysed. For that purpose monolithic material was put into sealed vials, the appropriate solvent was put onto the material for 72h and the influence of the solvent was determined visually and the consistency was tested with a spatula. The obtained results are summarised in Figure 10, Figure 11 and in Table 4.



(a) (b)

Figure 10: (a) Influence of water on RP phase. (b) Influence of different eluents on the stationary phase – wet state (used solvents: TOL = toluene, PYR = pyridine, CH_2Cl_2 = dichloromehane, CHL FORM =chloroform, DMF = dimethylformamide, THF = tetrahydrofurane, n-hexane)

Figure 11: Influence of different eluents on the stationary phase – dry state (solvents used: TOL = toluene, PYR = pyridine, CH_2Cl_2 = dichloromehane, CHL FORM =chloroform, DMF = dimethylformamide, THF = tetrahydrofurane, n-hexane, ISO PROP = iso-propanol, cyclohexane, ethyl acetate, Et_2O = diethyl ether, acetone)

Considering Figure 10 and Figure , one could assume that the different solvents do not have any influence at all, because in the dry state there seems to be no difference. However, one should keep on mind that in the annular geometry swelling and shrinking has a huge impact on the performance of the stationary phase. In Table 4 a summary of the influence of the different solvents is given.

Table 4: Influence of different eluents on the monolithic structure

Eluent	Influence on the monolith
MeOH, EtOH	None, ok to use
n-Hexane	None, ok to use
Cyclohexane	None, ok to use
Diethyl ether	None, ok to use
Tetrahydrofuran	None, ok to use
Acetone	None, ok to use
Ethyl acetate	None, ok to use
Isopropanol	None, ok to use
Acetonitrile	None, ok to use
Water	Structure breaks, only temporary use
Chloroform	Structure breaks, only temporary use
Dichloromethane	Reaction, avoid use
Toluene	Monolith swells, avoid use
Dimethylformamide	Monolith swells, avoid use
Pyridine	Monolith swells, avoid use

Separation in the annular geometry

The separation efficiency was tested with the same systems as in the planar test cell and in the capillaries. The first experiment was the separation of thiourea, naphthalene and anthracene. Although several problems occurred because of peak tailing, a sharp separation of 3 single peaks could be achieved.

A method for the prediction of chromatographic retention times based on molecular properties of the analytes and the mobile phase composition was presented. Different systems, containing the analytes daunorubicin and doxorubicin, were particularly investigated. Table 5 and Table 6 show the resulting free energies of solvation for the two investigated analytes in different solvents. The log P values were calculated according to equation (1)

$$P_{o/w} = \exp\left(\frac{\Delta_{hyd}G - \Delta_{oct}G}{RT}\right) \quad (1)$$

Where $P_{o/w}$ denotes the octanol water partition coefficient that is frequently used to describe the hydrophilic and hydrophobic properties of solute molecules, $\Delta_{hyd}G$ is the solvation free energy in water and $\Delta_{oct}G$ is the solvation free energy in octanol. R and T denote the gas constant and thermodynamic temperature, respectively.

Table 5: Free energy of solvation of daunorubicin in different solvents

Solvent	$\Delta_{solv}G$ [kJ/mol]			log P
Water (charged molecule)	-324.72	+/-	1.82	-35.8
Water (uncharged molecule)	-100.87	+/-	0.43	3.1
Methanol	-139.68	+/-	1.43	-3.6
Octanol	-118.86	+/-	0.51	

Table 6: Free energy of solvation of doxorubicin in different solvents

Solvent	$\Delta_{solv}G$ [kJ/mol]			log P
Water (charged molecule)	-326.28	+/-	2.00	-35.4
Water (uncharged molecule)	-116.55	+/-	0.62	1.1
Methanol	-153.57	+/-	1.46	-5.3
Octanol	-123.05	+/-	0.51	

The results indicate that when the analytes are charged the electrostatic interactions with the environment are dominant. Since the electrostatic interactions are very similar for both analytes (one protonated amino group each) the difference in the log Po/w values is very low and a prediction of the separation is not valid. For the uncharged species the hydrophobic interaction dominates and the difference in the log Po/w values is significant. Therefore, the retention behaviour can be predicted using the hydrophobic interactions. The results show that daunorubicin has a higher affinity towards the stationary phase and elutes slower than doxorubicin with a difference in log P of 2. A hypothetical distribution between octanol and methanol shows significantly lower values for the log P for both analytes. This means that a higher methanol content leads to a faster elution of both substances. The difference in log P for this system is slightly lower with a value of 1.7 indicating a lower separation factor. Experimental results performed by UNIKL show a separation factor of 1.12 for a system with water/methanol composition of 1:4 and a separation factor of 1.04 for a system with water/methanol composition of 1:6 validating the simulation results.

Because of the insufficient stability of the silica-based monoliths for reversed phase (RP) chromatography, the concept for the functionalized stationary phase preparation had to be altered, leading to a delay of 3 months. As a corrective measure, the preparation method was changed and other materials were evaluated. The new approaches helped to increase the homogeneity as well as the chemical and mechanical stability of the fillings in the CE capillaries and in the planar test cells.

Annular Cell

Based on simulation of TUE and experimental results of TUK, IMM had to develop, design, engineer and build the annular prototype as next task after having established the planar test device and further having done optimization to ease its use.

As a system pressure of 10 bar was supposed to be a necessary new feature for the annulus, IMM developed, realized and tested *prior* to the annulus design itself a model system of a multichannel-

back-pressure-valve. This was built as a compressed-air driven valve allowing for opening and closing within less than ~100 µs by a rather simple external feed valve (for the compressed-air). Thus, this valve not only allows to open and close in parallel 90 channels at once but also to control the throughput *via* the length of the opening time. IMM attempts to apply for a patent whilst literature evaluation etc. is yet undone.

In Figure 12, the final annular demonstrator is depicted. The most important parts for the determination of hydrodynamics are the electrodes, the eluent reservoir, the outlet valve and the fractioning table with their bottles. This possibility to work under overpressure was implemented to minimize the formation of gas bubbles, to stabilise the electroosmotic flow and to create a permanent well distributed eluent outflow into the fractioning bottles. The same high voltage power supply like the planar experiments was used for the generation of the electrical field.

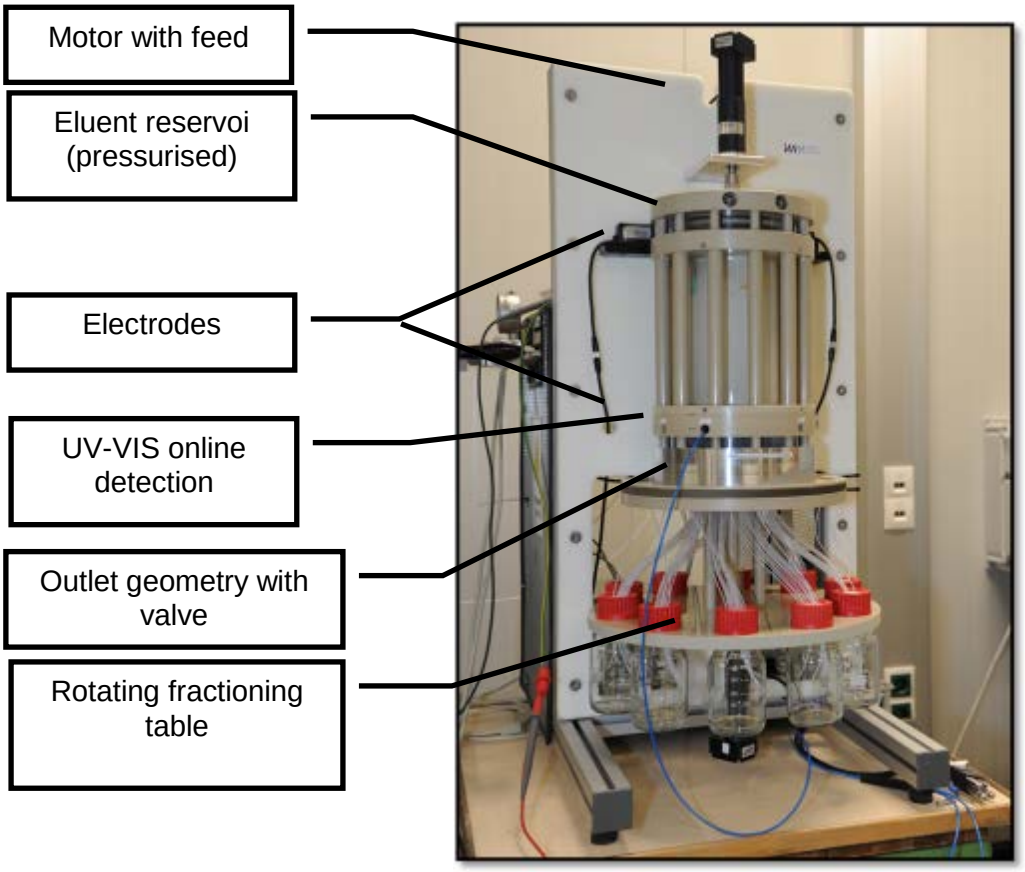


Figure 12: Final annular demonstrator

The detection of the eluent flow was followed by contactless measurement methods. Due to the annular design a usage of the image analysis system (developed by UNIKL for the planar test cell) was not necessary. Therefore, the volumetric flow was determined by a gravimetric measurement of the outflowing eluent under different voltages and cooling media temperatures. This measurement was performed under full process conditions using the annular demonstrator. The fluid flow was collected inside one or more bottles. After that, the increases in weight were noted. The generated Joule heating was detected by a contact-free MIR image analysis method. For these measurements, a thermal camera system from FLIR (T250, FLIR Systems GmbH, Frankfurt am Main, Germany) was utilized to record the time-dependent surface temperatures. The thermal imaging allowed an estimation of the generated Joule heating over the outer surface area and the detection of the

resulted temperature profiles. Due to an internal calibration of the camera system it was possible to minimize the identified measurement errors, such as environmental influences and the emissivity of the target.

Design of microstructured heat exchanger (TU/e)

A 3D numerical analysis concerning the heat transfer of water single-phase laminar flow in a square microchannel and different arrays of micro-pin-fins was carried out using the COMSOL Multiphysics in this work. Compared to the Nusselt number of 2.978 in a square microchannel, the micro-pin-fins have much better convection heat transfer. Several advanced materials with low electric conductivity and at the same time with high heat conductivity were put forward to be used in the CAEC system. As essential design point, it is proposed to constitute the micro heat exchanger from two different parts of the CAEC system, namely a microstructrured fin-pins plate and a so-called conductive plate. This decouples the manufacture and design of these two parts allowing the fin-pins part to be made by inexpensive and readily micromachinable materials and the heat conducting, separation plate to rely on more expensive specialty materials, yet with no need for complex microstructure manufacture. The conduction/convection coupling effect was significantly improved by micro-pin-fins when using SiC as the conductive plate.

Table 7: Local Nusselt number and pressure drop of the different microstructures

Micro-pin-fin Array	D_e ($\times 10^{-3}$ m)	Re	L ($\times 10^{-3}$ m)	α (kW/(m^2 · K))	Local Nu	$\triangle P$ (bar/m)
1	0.2	98.4	12	16.259	4.756	0.533
2	0.2	98.4	12	13.782	4.031	0.160
3	0.2	98.4	12	8.733	2.554	0.202
4	0.5	246	70	7.391	5.405	0.076
Square channel	0.5	246	70	4.073	2.978	0.021

The eluent droplet size defines the number of sampling compartments in a continuously operated annular electro-chromatograph and therefore influences separation efficiency. In this work, an assembly of two capillaries, a feeding capillary on the top and a receiving capillary placed under it, has been investigated to control droplet size. The receiving capillary prevents the liquid droplet formation beyond a critical size, which reduces the volume of sampling compartment as compared with the case of the electrolyte flow driven solely by gravity. With a receiving capillary, the electrolyte droplet size was reduced from 1.5 to 0.46 mm. Further decrease of droplet size was not possible due to a so called droplet jump upwards effect which has been observed on a hydrophilic glass surface with water. A typical electrolyte used in CAEC has high methanol content. In attempt to improve methanol-repellent properties of the glass surface, two approaches have been implemented: (i) self-assembled chemisorbed monolayers of an alkylsiloxane and (ii) fabrication of a nano-pin film. The methanol repellent surface of the feeding capillary suppressed the droplet jump upwards effect. The surface remained methanol-repellent in different solutions with lower polarity than that of water.

Hydrodynamics in the annular demonstrator

Volumetric distribution of the sample fractionation

Most important for a continuous annular system are constant process conditions. One important parameter is the volumetric distribution between the ten fractioning bottles. To get a constant and uniform distribution at the outlet it must be set the annular system under an overpressure (approx. 0.3 bar). The necessary pressure drop for a permanent well distributed eluent outflow is generated with a pulsed outlet valve. All experiments were performed under similar experimental conditions (see Table 8).

Table 8: Experimental conditions

Condition	**Value**
Voltage	10 kV
Eluent	Cit/MeOH 1:29
Pressure	0.3 bar
Rotation fractioning table	0.3 °/s
Cooling temperature	0 °C

The results show a mean deviation between all ten bottles after an experimental time of 30 minutes in a range from 3.5 to 6 % over six different experiments (Figure 13). The total deviation of 4.9 % is given by a averaging the depicted six results.

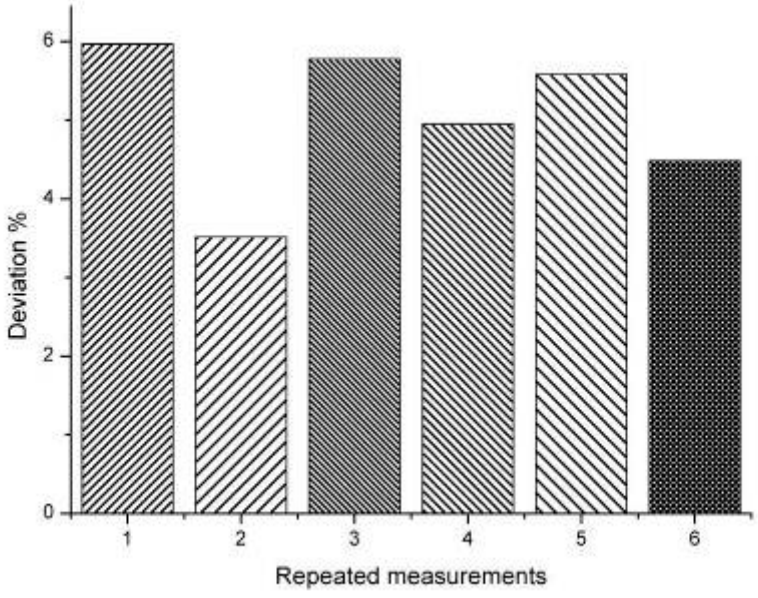


Figure 13: Mean volumetric deviation between ten fractioning bottles; voltage 10 kV; eluent: citrate/methanol 1:29; six repeated experiments

Flow behaviour in contrast to electrolyte properties

In this experiment were changed the eluent properties to check their usability and to determine the total flow rate from the annular device. The effects and the resulting flow rates from these different eluent concentrations are depicted in Figure 14 and every measured point represents the volumetric value from an experimental time of 15 minutes. The results show a constant increase from the volumetric flow by a rising voltage from all examined eluent variations. Some differences from the linearity can be explained by a generation of Joule heating. In addition, one was able to observe a decrease from the flow rates by a rising solvent concentration. A similar relation was found in the planar experiments and also in investigations with the analytical CEC device. Such results are very important to estimate the productivity of the system.

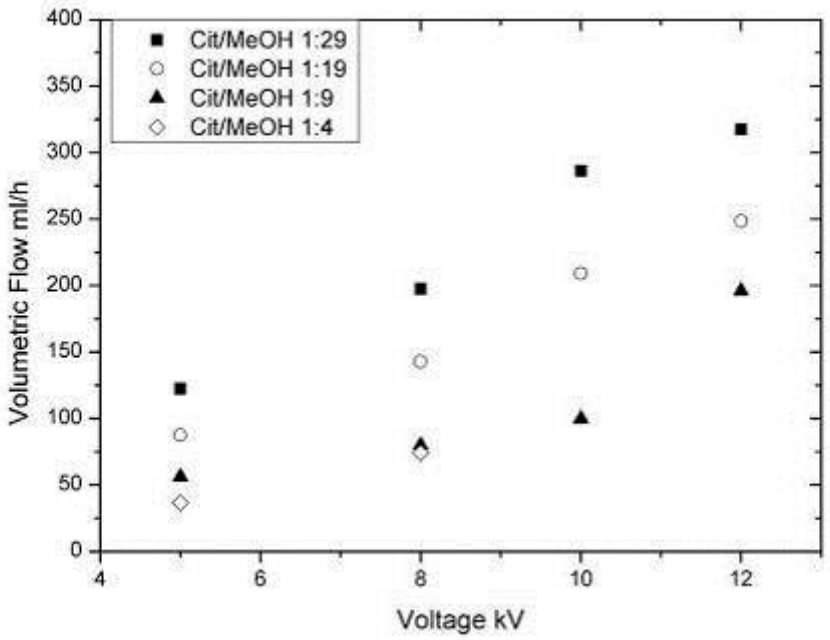


Figure14: Volumetric flow vs. voltage, monolithic stationary C8 reversed phase, gap width: 1 mm; cooling temperature 0°C

Cooling efficiency of the annular demonstrator

These results show a different formation of temperatures caused by the generation of Joule heating caused by different ionic strengths. These experiments demonstrate the successful working of the cooling environment and the resulting well-balanced temperature differences. The results confirmed the good operation of the cooling system and give an outlook to the limits and open capacities. One limitation in the view of cooling was the high conductivity of eluent Cit/MeOH 1:4 (100 µS/cm). The curve in Figure 15 shows an exponential increase of heat generation and therefore the experiments at 10 kV are very close to the limits of apparatus performance. A counter action to this is clearly given by the possibility of a reduction of the cooling temperature. A reduced temperature can allow also an increase of the voltage when using higher eluent conductivities.

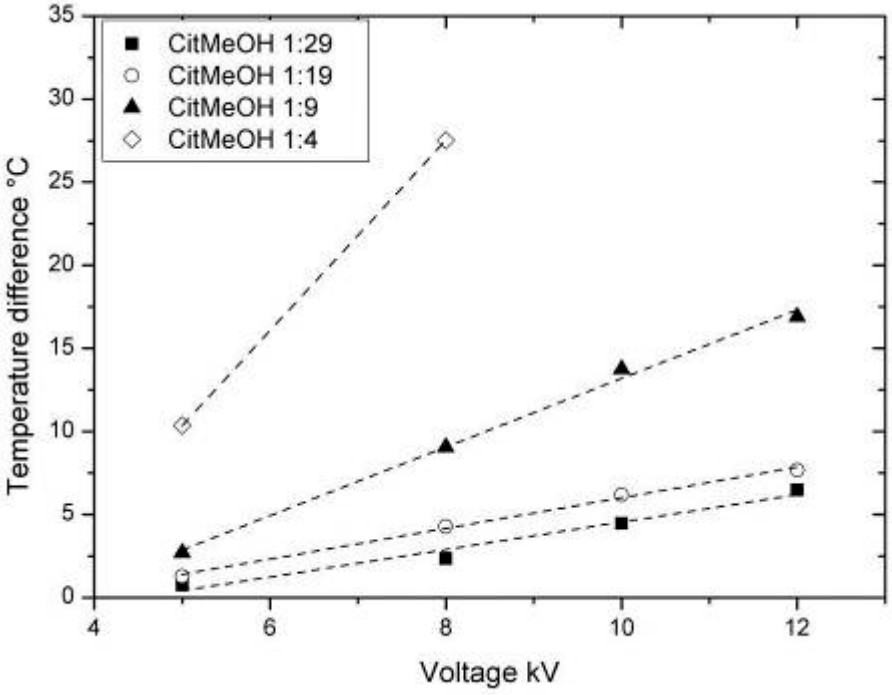


Figure 15: Temperature differences vs. voltage, monolithic stationary C8 reversed phase, gap width: 1 mm; cooling temperature 0°C

3.4 Equipment Testing and Optimisation

Equipment testing and optimisation was used to prove its functionality in terms of hydraulic behaviour, separation performance, process control, and operation stability. To accomplish the preliminary testing of the CAEC equipment in the most efficient manner, the choice of reference test mixtures followed a logical sequence. The hydraulic behaviour of the unit and the functionality of the inlet and outlet devices in the rotating equipment will be tested with buffer solutions that are similar to buffers which are used in industrial production.

A well-defined artificial test mixture was used for characterising the separation efficiency of the unit. To provide a sound basis for the industrial validation, it was ensured that the target molecules can be separated with a stationary phase whose functionalisation follows the same principle as the phases which was used for the separation of the industrial test mixtures from GAL and NOV. By this means the prototype was prepared for testing with test systems delivered by the industrial partners and the potential of the new technology in industrial production was already revealed within the technical development phase.

The final optimization of the CAEC included the support by IMM during the startup and the preparation for test certification, which comprised the integration of the control system and some primary function tests. The main issues of these tests were tightness, pressure stability, and high voltage performance of the complete equipped device. As a result, the device got the certificate and then was delivered to UNIKL afterwards. A CAD-model for simulations of the electric field was created. While the CAEC prototype allows contacting the electrodes at up to five points each, the aim was getting a correlation between numbers of contacting points and equal distribution of the electric field over the annulus. Redesigning and reworking of components as a result of findings – when running the system under operating conditions - it was found out that several parts of the prototype should be replaced or added; i.e. some redesigning and reworking had to be performed.

Most crucial and challenging hereby was the redesign and manufacture of a new optical detection unit. The already redesigned optical cell showed poor performance, i.e. the output signal was too weak for detection of the diluted products. After changing joining and sealing technologies from laser welding to screwing and refabricating a new optical cell proof of function could be demonstrated. To guarantee proper and equal distribution of the eluent over the annulus, a tube made of silicone with 90 laser-structured tiny holes was inserted into the groove above the eluent reservoir leading to an equal feeding of the "eluent-lake" avoiding turbulences. Another improvement was closing the swimmer, which indicates the level of eluent, with a cover to avoid flushing and sinking of the swimmer stemming from an overflow of eluent or strong movements, e.g. during transport. Furthermore, a new port containing the cooling connector was manufactured to enlarge the distance between cooling feed and HV-supply, mainly done to apply an additional insulation to the cooling feed. To increase electro-chemical resistance of both electrodes (above and below the annulus) an electro polishing procedure to reduce surface roughness was applied. Last but not least, IMM took care of the maintenance of the device (e.g. turning valve) and provided spare parts such as e.g. gaskets and filters.

Summary:

- A constant good volumetric distribution in the sample fractioning flasks could be achieved
- A similar hydrodynamic behaviour like the preliminary planar experiments was found
- A successful heat removal was achieved and system limits are recorded
- A successful operating online detection cell was implemented
- Fractionation and purification of thiourea, naphthalene and anthracene is possible
- Strong peak overlappings with other solutes generated by diffusion processes in the stationary phase have been observed
- Constrained purification of PAH due to peak overlapping was found.

3.5 Process Modelling & Simulation

Validation of the separation model for reference systems

The separation of Thiourea, Naphtalene and Antracene was measured in the annular device and corresponding model parameters were obtained by the automated parameter estimation based on the 1D model from one experimental run. These parameters were transferred to the 2D model and different operating parameters were used to predict the behavior of the real system in other experimental runs. Figure 16 shows the results for Naphtalene. The prediction for the three set point changes shows that the 2D model predicts the peak position well for set point changes in the rotational speed and feed flow rate, but the area and shape prediction is not always good. The reason for the different areas might be that they also depend on the background electrolyte. If the eluent changes its composition over time, the areas can be different in different experiments. The mismatch in the shape can be compensated by a re-estimation of adsorption and mass transfer parameters (Figure 16, bottom right). As a conclusion a frequent re-estimation would improve the prediction used in the model based set point optimization such that larger set point changes per iteration can be accepted resulting in less overall iterations to find the optimum.

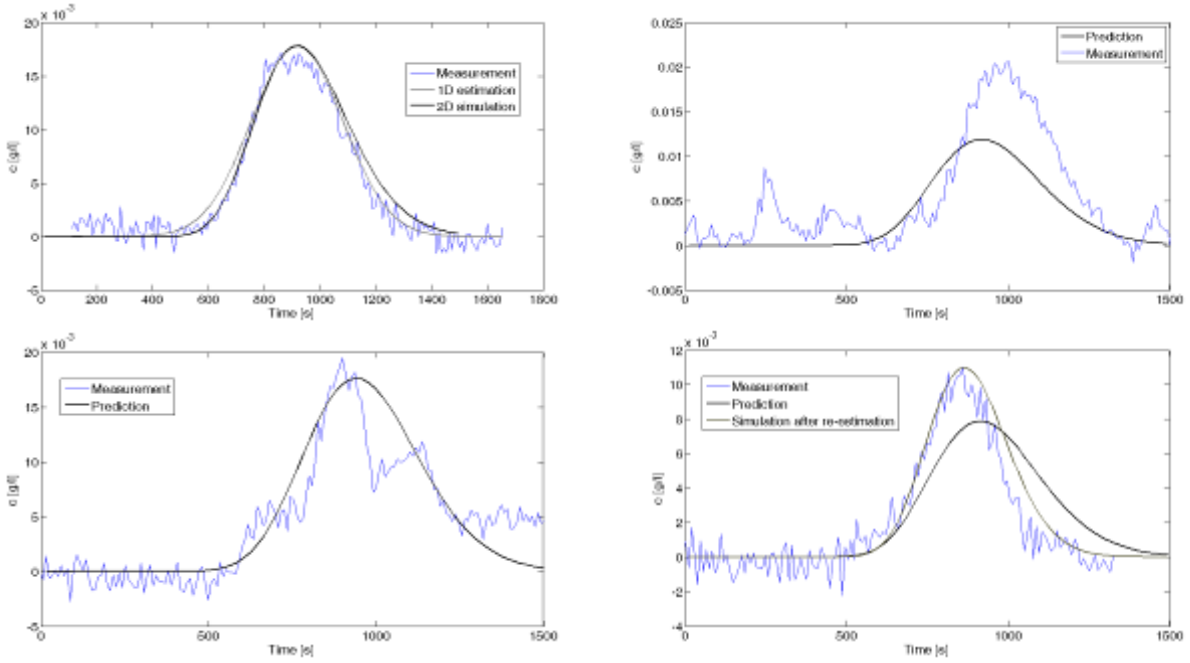


Figure 16: Chromatograms of Naphtalene at different set points (10 kV). Top left: 0.3 °/s, 0.03 ml/min. Top right: 0.3 °/s, 0.02 ml/min. Bottom left: 0.02 °/s, 0.02 ml/min. Bottom right: 0.02 °/s, 0.01 ml/min.

Description of the flow behaviour

In CEC, a known relationship between voltage and resulting EOF can be assumed, because the composition of the eluent outside the column and thus the ionic composition inside the column can assumed to be constant for a constant electrical field. In a CAEC system the ratio between the volume of the reservoir and the chromatographic system is much lower, resulting in a dynamical change of the eluent composition in the reservoir and consequently in the electrical double layer at the stationary phase. This explains the peak drifts observed (see report for the second period, WP3) but it was not considered during the modelling in the early phase of the project. In the third period, dynamic experiments to determine the change of the eluent composition in the reservoir of the planar test device were made by UNIKL. Figure 17 shows the change in the current over time for different set point changes of the voltage and for two different electrolytes in the planar test system.

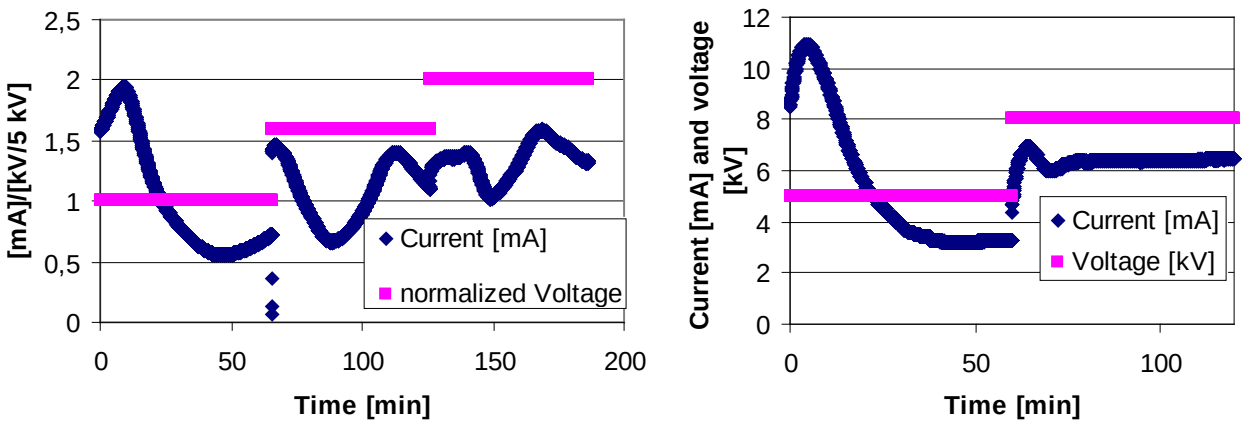


Figure 17: Current during set point changes of the voltage for citrate/methanol 1/29 (left) and 1/4 (right) in the planar device

The experimental set up did not allow determining the corresponding volume flow during these experiments. Such measurements are even more complicated to realize in the annular prototype, but they are necessary to give a correlation between EOF and the changing electro physical parameters of the system. We propose two different strategies for further research:

Set up of a low level control loop to keep the electrolyte composition constant. As feedback information the pH, ionic strength, conductivity and current measured in the reservoir or in the collecting vessels could be used. Adequate small scale multi-parameter sensors to be installed in the collecting vessels are commercially available.

Formulation and training of a neuronal network resulting in a dynamical black box model for the correlation between electrolyte composition and resulting EOF. The training of such a neuronal network can be performed online if one of the collecting vessels can be equipped with a high precision level measurement device (beside the above mentioned pH, ionic strength and conductivity monitoring).

For investigating the influence of non-homogeneities by outlet effects or by a non-homogeneous stationary phase/EOF, the time depending concentration of methyl red fed to the annular prototype was measured in three rotating collecting vessels by UNIKL. Strong fluctuations were observed in the vessel collecting methyl red (a standard deviation of 41% between all samples for experiment 1, a std. of 26% for experiment 2) showing that either a non-homogeneous outlet collecting device or a non-homogeneous stationary phase/EOF is present. If the outlet concentrations at fixed points between different rotations are compared, smaller deviations were observed (12% for experiment 1, 22% for experiment 2). As a result, spatially distributed chromatographic parameters must be considered in the 2D model, which is possible with the numerical method used. Not enough information could be obtained to derive exact values for the standard deviation in the model parameters like the EOF or porosity which would lead to the standard deviation in the concentration as observed in the experiment because the online sensor was not available.

Procedure for parameter estimation

The 1D and 2D modelling of the CAEC process has been reported in D3.2. One vertical strip of the annular device can be modelled as a batch chromatography by considering the analogous relationship between the 1D and 2D separation processes. The 1D parametric model is adapted by fitting the simulated model output to the measured chromatograms.

Selection of identifiable parameters

The high number of unknown parameters in the process model increases the difficulty of parameter estimation in the model calibration. A selection of the most sensitive parameter set due to be identified was performed. Two well-developed methods for selecting identifiable parameters were applied: parameter sensitivity analysis and criteria calculated from Fisher information matrix. The former accesses how changes in model parameters contribute to model output variability and the latter reveal the parameter interdependence. However, the selection result is only valid within a small neighbourhood of the assumed parameter values for the calculation depends on the point in the parameter space. To overcome this limitation the parameter space was sampled according to the Latin hypercube sampling scheme and the selection methods were applied on all sampling points. According to the results, Henry parameter and film mass-transfer resistance are identifiable.

3.6 Plant Design

As a result of the HAZOP study the following measures were taken to prevent possible malfunctions:

- Alarm in case of exceeding the maximal level or temperature
- Limiting the eluent pump to the maximal allowed pressure
- Automatic switch off at pressure loss
- Connecting the vent tube to the waste bottle to avoid overflow

A control system for the CAEC plant was developed, realized with a PLC with I/O modules, auxiliary components and a PC. Figure 18 shows the user interface containing the panels for controlling the individual devices.

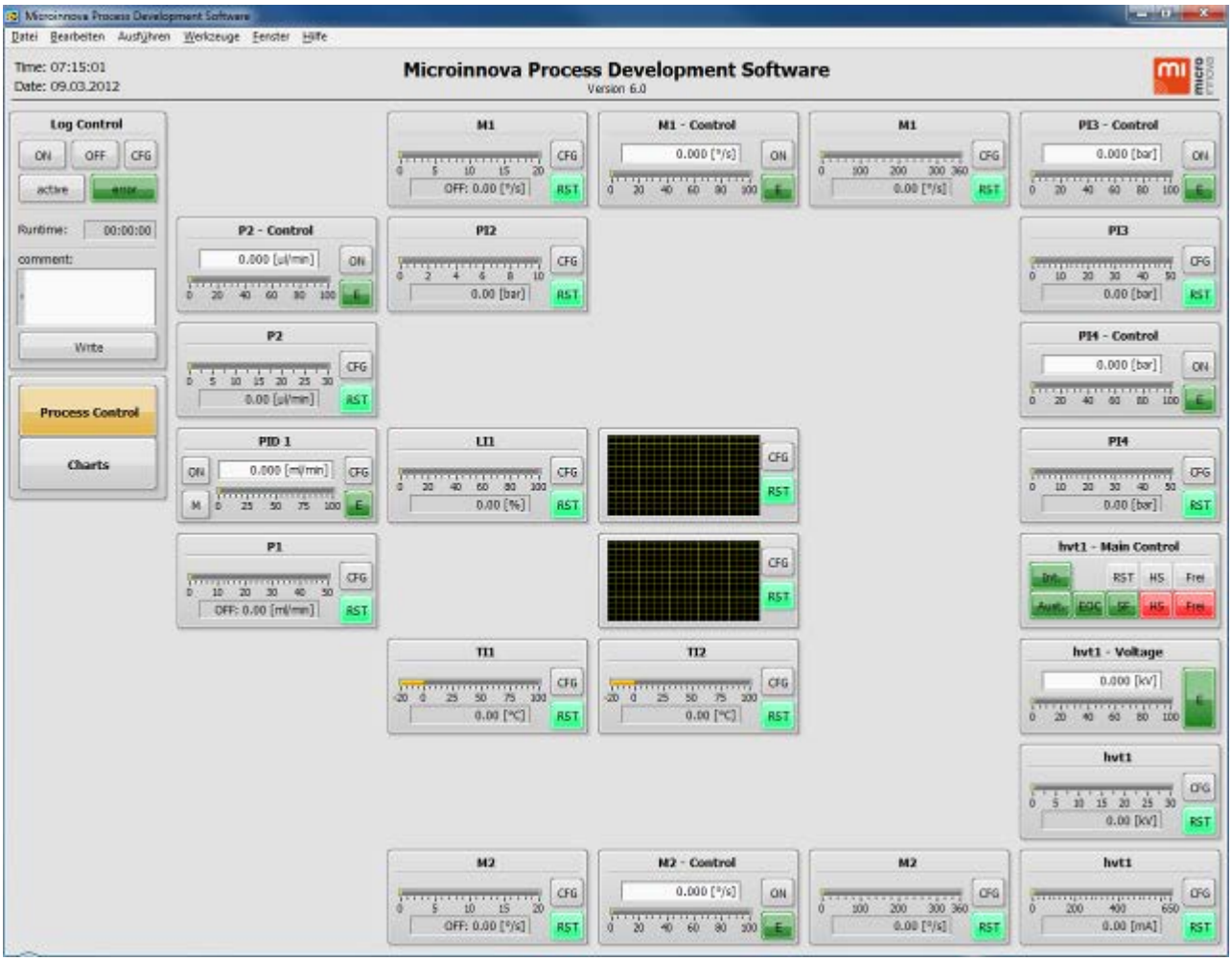


Figure 18: Process control tab

The functions of the automation system are the following:

- Control of the plant
- Continuous readout of all sensors
- Visualisation

- Trending of the data
- Data logging

Additionally an extension to the software was implemented in form of a feedback loop to log periodic data that are transferred to the optimizer. The controller values created by the optimizer are read out and applied. All necessary functional tests were performed.

A skid was constructed on which the CAEC prototype V2 was mounted. Also installed on this skid are the pumps, measuring instruments, valves, tubing, cabling and junction boxes. Figure 19 shows the assembly of the plant.

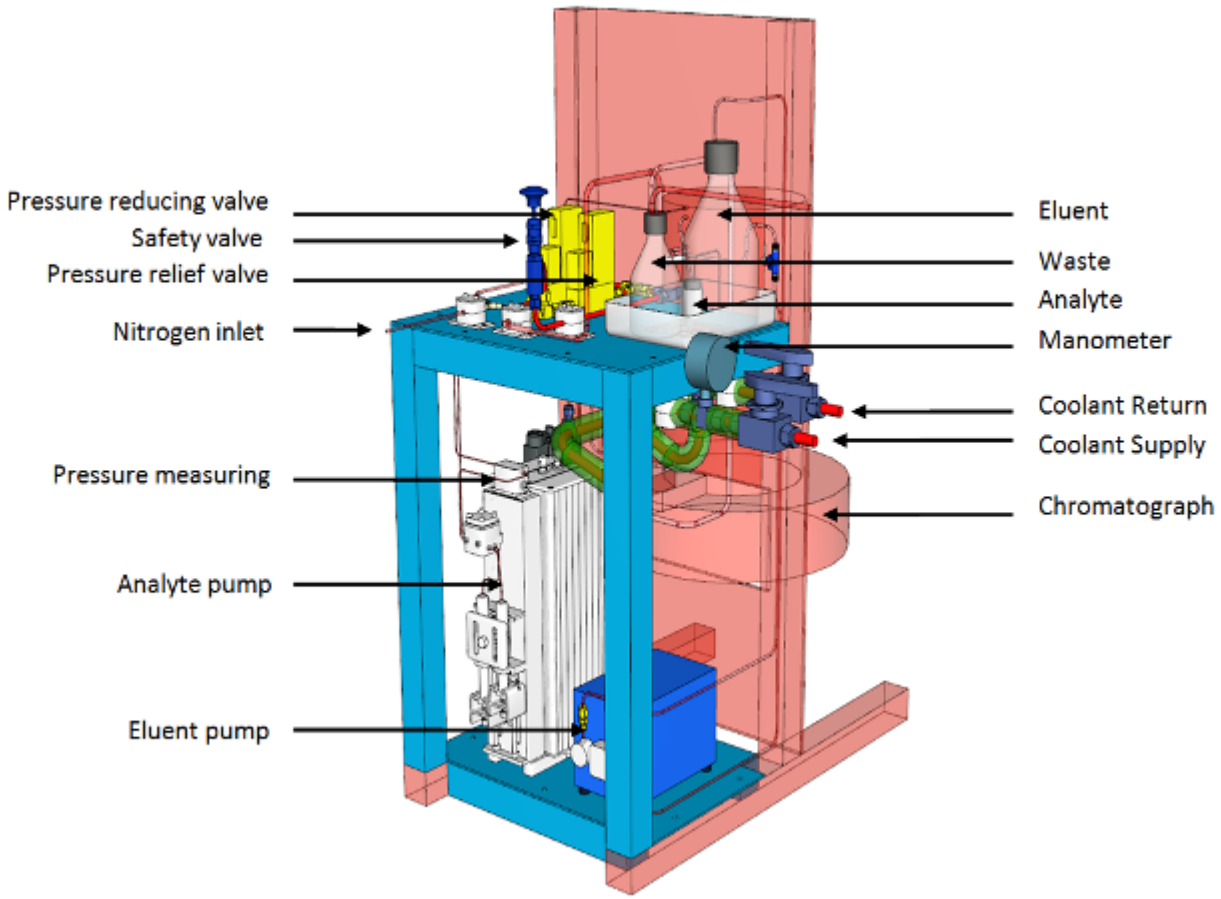


Figure 19: Assembly of the CAEC plant

The CAEC plant was connected with the peripheral equipment:

- High voltage power supply
- Cooling thermostat
- Nitrogen supply
- Spectrometer and light source
- Control rack

In Figure 20, the set-up of the overall plant can be seen, from left to right the thermostat, the rack, the CAEC plant and the HV power supply.

Figure 20: Set-up of the overall plant

A special solution was elaborated to connect the annulus to the power supply that ensures both, functionality and safety. Figure 21 shows the result.

Figure21: High voltage connection

The following tests were carried out successfully and documented:

- Pressure test
- Test high voltage
- Safety inspection according to EN 60204, performed by TÜV Austria

The certification and documentation for the plant was attained. An EC declaration of conformity has been issued that confirms the compliance with the following EU directives:

- 2006/42/EC Machinery Directive
- 97/23/EC Pressure Equipment Directive
- 2006/95/EC Low Voltage Directive
- 2004/108/EC Electromagnetic Compatibility

The CE marking has been affixed on the nameplate.

A comprehensive plant documentation has been compiled including test protocols, P&ID, layout, complete supplier documentation of all equipment and the user manual of the CAEC plant.

The CAEC user manual is written according to the requirements of the Machine Directive 98/37/EC. It contains the following main parts:

- EC Declaration of conformity
- Description
- Safety issues
- Assembly instructions
- Start-up
- Operating instructions

cGMP compliance with the GMP regulations is required when using the CAEC plant for pharmaceutical production. The plan of necessary changes includes the following items:

- Hygienic design of the equipment
- Capability for CIP
- Control system according to GAMP 5 and CFR 21 Part 11
- Material certificates 3.1 according to EN 10204
- FDA certifications of conformity
- A suitable procedure for CIP was worked out in Deliverable 5.6.

3.6.1 Industrial Validation

Equipment

Final optimization of the CAEC device from IMM's side mainly included the following items (in chronological order):

Support during starting up and preparation for test certification at MIC

In mid-January 2012 (month 42), IMM supported MIC with the final starting up, i.e. integration of the control system from MIC with the CAEC annular device. Additionally, some primary function tests were performed to be ready for test certification done by TÜV. Main issues of these tests were tightness, pressure stability, and high voltage performance of the complete equipped device. As a result, the device got the certificate and then was delivered to UNIKL.

Creating a CAD model for simulations to UNIKL

The idea was having a 3D model, which allows making some simulations concerning electrical field over the annulus as well as getting a theoretical hint of heat transfer in the system. While the prototype allows contacting the electrodes at up to five points each, the aim was getting a correlation between numbers of contacting points and equal distribution of the electric field over the annulus. The picture in Figure 22 illustrates the model, all spaces which are filled with liquids (eluent and HX-fluid) as well as electrodes and their contacts were integrated.

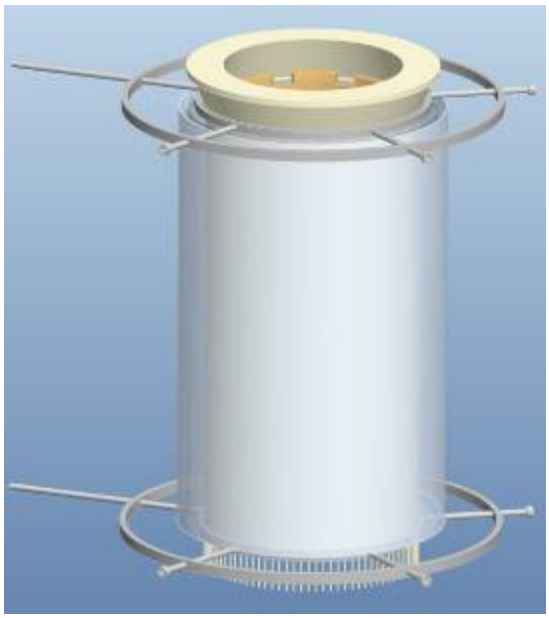


Figure 22: CAD model created for simulation of electric field distribution and heat transfer over the annulus (Source IMM)

Redesigning and reworking of components

Running the system under operating conditions it was found out that several parts of the CAEC prototype should be replaced or added; i.e. some redesigning and reworking had to be performed. Most crucial and challenging hereby was the redesign and manufacture of a new optical detection unit. The already redesigned optical cell (described in the 2nd periodic report) unfortunately showed poor performance, i.e. the output signal was too weak for detection of the diluted products. In the first moment this was rather surprising, as the channels of the cell were designed analogous to the metallic test cell, where proof of principle was already shown. After changing joining and sealing technologies from laser welding to screwing and refabricating a new optical cell, proof of function could be demonstrated in the presence of Prof. Bart (Figure 21).

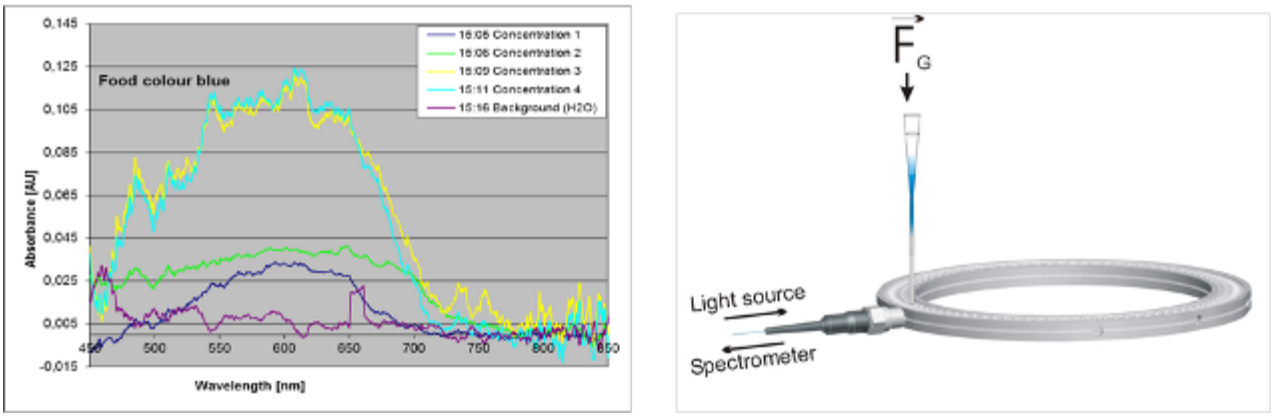


Figure 21: The absorbance curves (left); the drawing of the final ring system in the measurement geometry (right). The closed ring system was assembled, connected via an Eppendorf-pipet tip, and therewith filled with water and a drop of blue food colour in the middle of the water column. The flow through the detection cell is driven by gravitation (Source IMM)

In Figure 22, the final version of the annular on-line sensor system (V3) is shown.

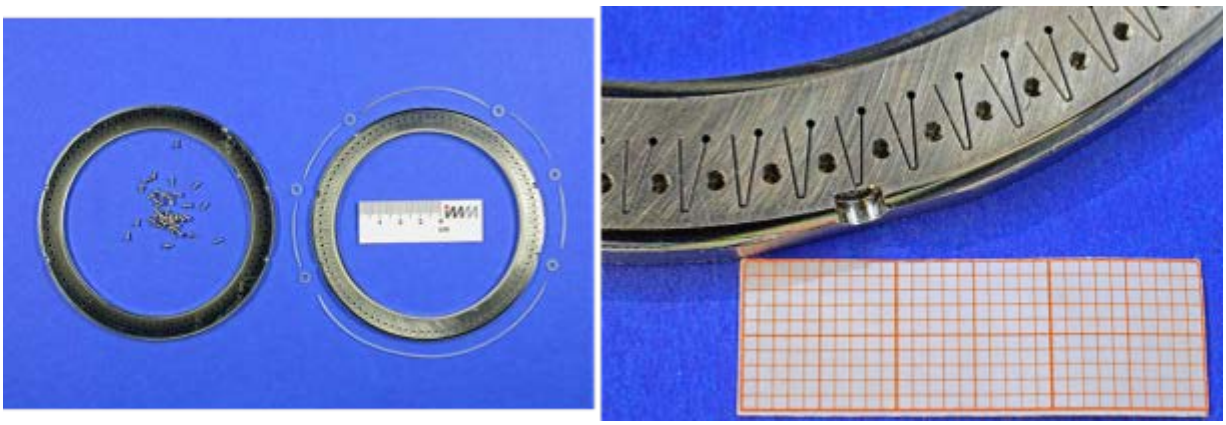


Figure 22: V3 of annular on-line sensor system (Source IMM)

More details and the history of development of the optical sensor system are described in D 4.6.

With the following components, further improvements were realized

To guarantee proper and equal distribution of the eluent over the annulus, a tube made of silicone with 90 laser-structured tiny holes was inserted into the groove above the eluent reservoir leading to an equal feeding of the “eluent-lake” avoiding turbulences. Another improvement was closing the swimmer, which indicates the level of eluent, with a cover to avoid flushing and sinking of the swimmer stemming from an overflow of eluent or strong movements, e.g. during transport. A detailed sketch is given in Figure 23.

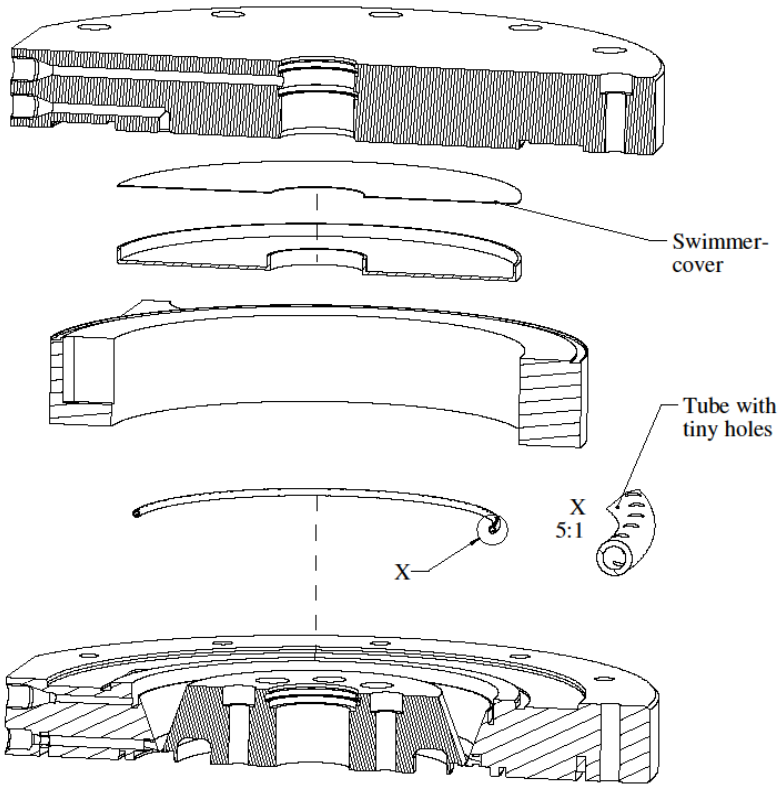


Figure 23: Improvements in the upper housing part of the CAEC V2 (Source IMM)

Furthermore, a new port containing the cooling connector was manufactured to enlarge the distance between cooling feed and HV-supply, mainly done to apply an additional insulation to the cooling feed. To increase electro-chemical resistance of both electrodes (above and below the annulus) an electro polishing procedure to reduce surface roughness was applied. Last but not least, IMM took care of the maintenance of the device (e.g. turning valve) and provided spare parts such as e.g. gaskets and filters.

4 Description of the potential impact, the main dissemination activities and the exploitation of results

4.1 Strategic Impact

The proposed CAEC technology provides an extremely powerful tool to promote the shift of the European chemical and pharmaceutical industry from resource intensive large-scale production towards dedicated high value-added products since it meets the demand for flexible production systems that can easily be adapted to the special requirements of new product lines. CAEC belongs to a **new generation of high-performance process technology** that considerably improves the small-scale production in chemical, biochemical and pharmaceutical industries in several ways.

- CAEC represents a **continuous purification technology for highly complex mixtures** that satisfies the need for a real time product analysis and control required to establish Quality-by-Design in pharmaceutical and chemical production.
- Due to the **outstanding separation and purification efficiency** of CAEC compared to conventional technologies, the number of purification steps and thus the consumption of auxiliary chemicals can be reduced to **increase the sustainability** of the production process. This also allows to distinguish between very similar chemical compounds like position isomers and thus to produce pharmaceuticals with a high biological activity at low dosage.
- **Easy scale-up** from drug characterisation towards its production for clinical trials can be facilitated since capillary electrochromatography is an established analytical technology and its continuous operation allows a direct transfer of the separation principle to a larger scale. This will significantly **reduce the time-to-market**, which is essential for the commercial success of new pharmaceuticals.
- The expected **breakthrough in capacity** will allow the use of CAEC in the small-scale production of personalised medicine and pharmaceuticals for rare diseases. This leads to a considerable reduction in the production costs and may help to improve the overall medical care.
- **Predictive methods for model based process design** will give an extra push to the use of CAEC technology as a reliable and highly efficient purification technology.

By considering all these benefits for the development of a new pharmaceutical product, tremendous reductions in time and costs can be foreseen at different stages of the development process. The impact can be demonstrated in the best way by looking at novel pharmaceutical products of different production scales.

Even though drugs, which are developed for common diseases and should therefore be produced at large scale, cannot be purified by CAEC technology, the direct scale-up from drug characterisation to small-scale production for clinical trials allows for a significantly earlier introduction to the market. The **financial turnover** for a company can reach **up to several billion euros** per year for a blockbuster like the asthma medication ADVAIR from GlaxoSmithKline (4.6 Bio €)[4] or Rituxan®, a monoclonal antibody for the treatment of cancer from Genentech Inc. (3.0 Bio €)[5].

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4 GlaxoSmithKline Annual Report 2006

5 Roche Geschäftsbericht 2006

Looking at a rare disease like Chronic Myeloid Leukaemia (CML), which annually affects only 1 to 2 people per 100,000, the use of CAEC technology can promote success stories like the development of Glivec® at Novartis. This new medicine brought about a 89% overall survival rate in 5 years with <5% of deaths for patients who had only a few treatment options before, which only effected a delay by a few years before in the progression of the disease. Since the production of such drugs proceeds only at small scale, the major part of the purification process can be accomplished by CAEC which significantly **reduces the costs for process development by up to 90% and product manufacturing by up to 50%** and thus bringing new products to the profit zone.

The participation of universities performing **high-level research on different fields enforces the impact on the scientific community** by gaining an improved understanding of the complex processes which occur at different scales in the CAEC unit. The close collaboration will establish a new way of equipment design that combines rigorous modelling of the flow behaviour on a microscale (TUE) with sophisticated design (UNIKL) and innovative production techniques (IMM). Successful molecular modelling of the stationary phase behaviour (TUG) provides an all new approach for the design of interactive materials that allows for a tailored computational design of material properties. The establishment and implementation of an industrially validated process model into an existing simulation environment for chemical and pharmaceutical processes significantly enhances the acceptance of the CAEC technology by providing the opportunity to determine the advantage for new applications via predictive simulations (TUDO). The use of self-adaptive process control strategies with real-time assessment of product quality (TUDO) is also entirely in line with the latest EMEA and FDA initiatives to **establish a Quality-by-Design approach for pharmaceutical production**. This know-how will provide the basis for new technical developments and accelerate the **transition to a knowledge-intensive European industry.**

European Dimension

An ageing society and the resulting demand for new pharmaceutical products is a fundamental problem for the whole European continent. The high health care standard in most European nations can only be retained if pharmaceutical research is continued on a high level and the resulting drugs can be produced at affordable costs. Therefore, the provision of new production technologies that allow for a fast transfer of new results into small-scale production for clinical trials or even final drug manufacturing is of cross-national interest and should be established by collaborative European research.

Multi-disciplinary expertise in universities, research centres and enterprises from different EU Member States is required to solve the complex technical problems within the proposed time scale. The consortium formed for the project constitutes an excellent example of complementarity and clearly shows how a greater degree of cohesion can be reached inside the European Union. This type of collaboration is useful for both scientific and industrial partners since it promotes the penetration of the scientific accomplishments into the business and inspires the advancement of new inter-disciplinary knowledge in the science.

4.2 Plan for the use and dissemination of foreground

The potential impacts outlined above can only be achieved if the project is visible for the scientific community as well as for the chemical and pharmaceutical industry. Therefore, special attention has been paid to establish a reliable plan for use, dissemination and exploitation of the knowledge generated by the CAEC project. The main objectives of this plan are

- to **create a high visibility** for all relevant groups of people like representatives of the chemical and pharmaceutical industry, scientist working in the corresponding fields, as well as regulative authorities as EMEA or FDA,
- to **protect the generated knowledge** in an efficient way to guarantee that the project results are exploited by consortium members or other European institutions,
- to **procure acceptance for the new CAEC technology** by potential users in research for new medicine and pharmaceutical production,
- to **promote knowledge-based manufacturing techniques** in pharmaceutical industry to achieve a paradigm shift from Quality-by-Testing (QbT) towards Quality-by-Design (QdB),
- to **exploit the results** inside and outside of the consortium and
- to enable a **rapid commercialisation** within 1 to 2 years after the end of the project.

The necessary measures to achieve these goals can be divided into the two different categories explained below.

4.3 Dissemination

All academic partners have a **vital interest to publish their results** in the open literature, present them at scientific conferences, and use them for teaching and training material for students and industrial audiences. By contrast, industrial partners often tend to keep results confidential to secure a competitive advantage. The conception of the CAEC project avoided such dilemma without violating the specific interests of the individual partners. The two partners from pharmaceutical industry (GAL and NOV) gained a significant advantage by having the chance to get familiar with the new technology at an early stage of development and to incorporate their individual requirements while partners involved in the manufacturing of the equipment (IMM and MIC) had a joint interest to bring CAEC to the market. This led to a **"win-win" situation** in which the industrial partners were willing to publish the results in order to inform their professionals about the innovative technology.

In order not to prevent the protection of intellectual properties, an easy procedure was foreseen in the consortium agreement that allows all partners to review publications outside the consortium by keeping a realistic timeline for the authors. **Publications in peer-reviewed journals with high impact factors** in the respective areas like automation were done to create an awareness of the research and its potential to a broad audience. In addition, a number of **well recognised scientific conferences** were selected for scientific presentations that match the scope. These took place within the duration of the project:

- AIChE Annual Meeting (2009,2010, 2011)
- European BioPerspectives (2009, 2011)
- ProcessNet-Jahrestagung (2010)
- ECCE 8th European Congress of Chemical Engineering (2011)
- CHISA 20th International Congress of Chemical and Process Engineering (2010)
- ITP 17th International Symposium on Liquid Phase Separations and Capillary Electroseparation Techniques (2010)
- ISPPP (2008, 2009, 2010, 2011) Int. Symp. on the Separation of Proteins, Peptides & Polynucleotides

- SPICA (2008, 2010) Int. Symp. on Preparative and Ind. Chromatography and Allied Techniques

The marketing of the new technology was promoted by presenting the prototype and the outcome of the industrial validation during trade fairs. **ACHEMA 2012**, the worldwide biggest Exhibition-Congress on Chemical Engineering, Environmental Protection and Biotechnology, took place during the last months of the project. The annular prototype was also shown on the **IMPRET 2012** (International Conference on Microreaction Technology), complemented with a poster. The details on the **ACHEMA 2012** and IMPRET 2012 presentations of the project are explained on chapter 6.

The public area of the **CAEC website** provides another powerful tool for the dissemination of up-to-date information on the project to the public. The general information on the current status of the project was regularly be updated and presentations as well as public deliverables were accessible to everyone. It also contained a calendar to announce all public events, where information on the project was given (conferences, trade fairs, etc.). To create an awareness of the website, a reference was indicated in each presentation and publication. On the side of the scientific work, besides the already published papers, new publications are planned for the near future in order to keep the dissemination going after the project is finished.

Protection of Intellectual Property Rights (IPR)

Even though a high visibility of the project is a prerequisite to achieve the expected impact, precautions must be taken to prevent the hindrance of IPR protection. This was ensured by the **Exploitation Panel (EP)**, which was responsible for the protection of project results by patents or other measures like (Trademarks, Servicemarks or Copyrights). Since the proper protection of the new CAEC prototype is of major importance, the EP consisted of representatives from four partners playing a major role in the design and manufacturing of the CAEC plant and in the use of the new technology for pharmaceutical production. Here, Prof. Bart from UNIKL, Dr. Löb from IMM, Dr. Kirschneck from MIC, and Ms. Piia Hara from GAL were particularly involved.

In case of joint inventions, suitable **IPR regulations** which guarantee royalties for all partners involved were applied, as **drafted in the Consortium Agreement**. In order to avoid IPR conflicts during project execution, the Consortium Agreement also includes **description of the background** of each partner. This information is currently collected by the legal manager Ms. Trimpe. It is important to emphasise that **unlimited access to inventions** is given to all project partners. This removes all obstacles against knowledge protection and generates a **joint interest**.

4.4 Exploitation

The main issue for the exploitation of the project results is a rapid commercialisation of the CAEC technology which was foreseen within 1 to 2 year after the end of the project. To realise this extremely ambitious timeline, the following measures were taken during the duration of the project.

- A **direct involvement of end users** considered potential User Requirement Specifications (URS) right from the beginning and guarantees the practicability in pharmaceutical production.
- The requirement for **cGMP compliance** were considered and detailed plan containing all necessary changes to the prototype plant were worked out to facilitate a fast approval from regulatory authorities.
- The CAEC prototype was not only be developed towards functionality but also extensively tested under industrial conditions during a one year demonstration phase. This allowed for

an **industrial validation** of the technology within the duration of the project and significantly enhanced the perspective for commercialisation.

- A **marketing strategy** was already worked out by MIC and IMM during the demonstration phase (not funded by the EC) to pave the way for sales and distribution.
- The Academic Partners exploited the modelling tools and simulation software by offering them to providers for **commercial process simulation software** (e.g. ASPENTECH, PSE) or through **spin-offs** founded after the end of the project.

The establishment of continuous production processes like the CAEC technology with an on-line control of the product quality will result in tremendous improvements which will first be exploited by project partners from pharmaceutical industry (NOV, GAL) and later by pharmaceutical companies from outside the consortium.

Since the project results are not restricted to the invention of the new technology and the resulting improvements in pharmaceutical production, but include several side aspects that also have a potential for exploitation, a preliminary exploitation plan was established in order to identify and promote such developments. For example, Malte Behrens from the TU Dortmund modified and applied a relatively new a numeric procedure, which was not compared to the usual procedures until now. Such a comparison is mostly of interest for a future publication, since the method was not relevant for the project itself.

The plan was regularly be updated in the EP, offering an assessment of the potential for new project results. The plan contains were structured into categories, which represent the different current status of the exploitation plan is shown below.

5 Contact Details

5.1 Project Coordination

Continuous Annular Electro-Chromatography

www.caec-eu.de

Coordinator: Andrzej Górak

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Project manager and communicator: Dorota Pawlucka

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5.2 Project Consortium

Partner	Partner leader	Email address
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Galileaus Oy, (GAL) Kaarina, Finland	Dr. Piia Hara	piia.hara@galilaeus.com

6 Use and dissemination of foreground

Regarding the dissemination of the results and in order to ensure a clear visibility of the project and to search an exchange with relevant scientific and industrial groups, the CAEC technology was to be exhibited during trade fairs. This has been done by MIC and IMM during the ACHEMA 2012 taking place in Frankfurt Main, Germany from June 18th-22nd. At the IMM booth, the first version of the annular prototype was displayed, the MIC booth showed version 2.0. Figure 24 shows two photographs of the exhibition of the CAEC prototype which was accompanied by a 1-page leaflet with further information and found a lot of interest.

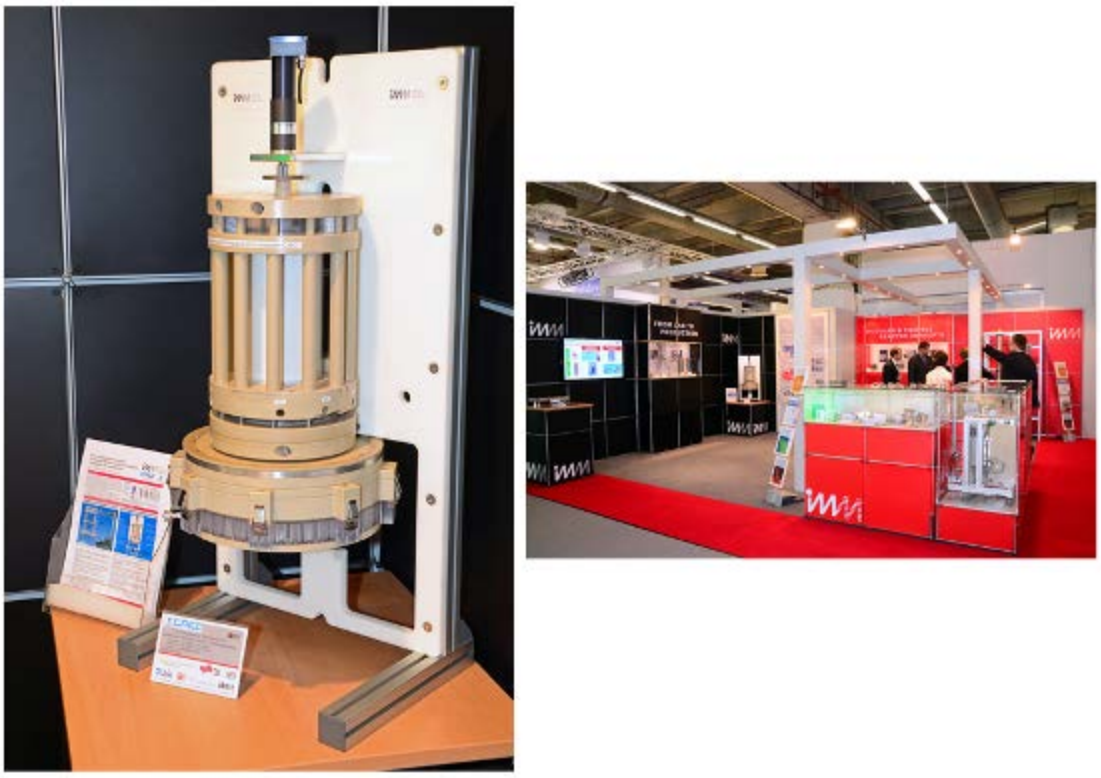

Figure 24: CAEC prototype as displayed by IMM at ACHEMA 2012 in Frankfurt Main, Germany

Additionally, the annular prototype was shown at the IMRET 2012 (International Conference on Microreaction Technology) which took place from February 20th-22nd 2012 in Lyon, France. Here, also a poster entitled “Novel Preparative-continuous Purification method: Continuous Annular Gap ElectroChromatography” was presented. Figure 25Figure25 shows the exhibition booth with the CAEC prototype.

Figure25: CAEC prototype as displayed by IMM at IMRET 2012 in Lyon, France

Lastly, the CAEC prototype was exhibited at the ECCE ProcessNet 2011 Conference taking place from September 25th-29th 2011 in Berlin Germany. Figure 26 shows the exhibition booth prominently displaying the CAEC prototype.

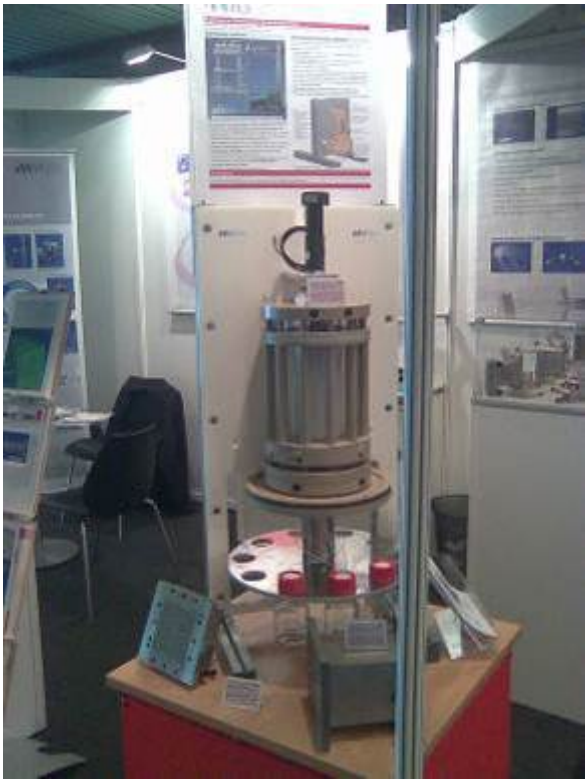

Figure 26: CAEC prototype as displayed by IMM at ECCE ProcessNet 2011 in Berlin, Germany

Dissemination statistics

The CAEC consortium has been active in the dissemination of project results and the networking with scientific and industrial partners.

The following presentations and publication activities were accomplished in the course of the project: 17 oral presentations, 16 posters, 9 conference proceedings, 8 journal papers, 11 student theses and 1 technical contribution. The exploitation plan can be seen on Table 9, and a list of the publications is displayed inTable A1.

To comply with the exploitation of CAEC results, special attention was paid to the protection of knowledge and to the identification of possible exploitable results. Main actions were to strictly observe the release procedure for all publications and the confidentiality rules within the consortium. Every year the exploitation plan was updated under control of the Exploitation Panel. No exploitable results have been identified to be patented at the end of the project, nevertheless, the Consortium agreed to keep the confidentiality for a period of at least one year after the end of the project. The Website and the member login will be maintained. The exploitation is submitted in Table 9.

Table 9: Exploitation plan

Exploitable knowledge (description)	**Exploitable product or measure**	**Sectors of application**	**Timeline for commercial use**	**Protection**	**Owner**
Simulation methods for CAEC plants in the production of biopharmaceuticals	Simulation software for downstream processing of biological products	Pharmaceutical industry, fine & speciality chemicals	2012	NO	TUDo
Simulation methods for the transport and affinity in the chromatographic packing	Simulation tool and for material design	Pharmaceutical industry, fine & speciality chemicals	2012	NO	TUG
Method for the synthesis of annular monolithic stationary phases	Annular monolithic stationary phases	Pharmaceutical industry, fine & speciality chemicals	2012	NO	TUG
Method for the modification of annular monolithic stationary phases	Functionalised stationary phases	Pharmaceutical industry, fine & speciality chemicals	2012	NO	TUG
Testing of stationary phase and model development	Parameter identification and simulation tool	Pharmaceutical industry, fine & speciality chemicals	2012	NO	TUG

Development of CAEC equipment	Construction details and design concept	Pharmaceutical industry, fine & speciality chemicals	2012	NO	UNIKL, IMM, TUE
Coupling CAEC units to micro-structured reactors	R&D services for up-graded micro process technology with continuous separation	Pharmaceutical industry, fine & speciality chemicals	2012	NO	UNIKL, IMM, TUE
Gain in expertise and profile in micro separation technology	R&D services for up-graded micro process technology with continuous separation	Pharmaceutical industry, fine & speciality chemicals	2012	NO	UNIKL, IMM, TUE
Assembly of CAEC plant	cGMP compliant manufacturing concept, equipment list	Pharmaceutical industry, fine & speciality chemicals	2012	NO	MIC
Development of CAEC PLC and user interface	Control concept and software concept	Pharmaceutical industry, fine & speciality chemicals	2012	NO	MIC, TUDo
Knowledge on handling and performance of CAEC	New downstream process with CAEC technology	Pharmaceutical industry, fine & speciality chemicals	2015	NO	NOV, GAL
	Use of CAEC in clinical trials	Pharmaceutical industry	2015	NO	NOV
	Offering improved service for contract manufacturing	Pharmaceutical industry	2020	NO	GAL

6.1 Section A (public)

This section provides an overview of the reviewed publications that resulted from the CAEC project. The list is sorted by relevance in that journal papers are provided first, followed by books and book chapters and finally by peer-reviewed conference contributions. Within these categories, the papers are sorted alphabetically by partner ID.

This section includes two Tables:

- Table A1: List of all scientific (peer reviewed) publications relating to the foreground of the project.
- Table A2: List of all dissemination activities (publications, conferences, workshops, web sites/applications, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters).

Several publications that resulted from the CEAC project are freely available, unless distribution is prohibited by the publisher. If available, the column “Permanent Identifiers” provides the name of the file that contains the publication in the CEAC publications repository (permanently available for download here or under www.caec-eu.de and/or a permanent link to the publication on the internet.

Table A1: List of scientific (peer reviewed) publication, starting with the most important ones

No.	Title	Authors	Title of the periodical or the series	Number, date or frequency	Publisher	Place	Date of public-cation	Relevant pages	Permanent identifiers (if available)	Open access is/will be provided to this public-cation
1	Iterative Fahrweisenoptimierung der annularen Elektro-Chromatographie	Behrens, M.; Engell, S.	Automatisierungstechnik	59	Oldenbourg Verlag	Munich	2011	382-392	10.1524/auto.2011.0931	NO
2	Iterative Set-point Optimization of Continuous Annular Electro-chromatography	Behrens, M.; Engell, S.	Proc. IFAC, 18th IFAC World Congress 2011	18	IFAC	Milan	2011	3665-3671	10.3182/20110828-6-IT-1002.03008	NO
3	Dynamische Simulation und Optimierung annularer Elektro-Chromatographie	Behrens, M.; Engell, S.	Proc. ASIM 2009, 20. Symposium Simulationstechnik, Cottbus, Germany, September 2009	2009	Shaker	Cottbus	2009	131-138	ISBN: 978-3-8322-8509-8	NO
4	Dynamische Simulation und Optimierung annularer Elektro-Chromatographie	Behrens, M.; Engell, S.	Proc. ProcessNet, Jahrestreffen der FA Fluidverfahrenstechnik und Hochdruckverfahrenstechnik 2010	2010	./.	./.	2010	Paper ID 2322	./.	NO
5	Parameter Estimation	Behrens, M.;	Proc. IEEE International	2012	IEEE	Athens	2012	236-241	10.11	NO

	and Iterative Set-point optimization of Continuous Annular Electrochromatography	Yu, Y.; Engell, S.:	Conference on Industrial Technology						09/ICIT.2012.6209944	
6	Simulation and optimizing control of continuous annular electro-chromatography (CAEC)	Behrens, M.; Yu, Y.; Engell, S.	Proc. SPICA, 13th International Symposium on Preparative and Industrial Chromatography and Allied Techniques	2010	SPICA		2010	ID 2098		NO
7	Funktionalisierte mesoporöse Monolithen für kontinuierliche Ringspalt-Elektrochromatographie	Braunbruck, M.-G.; Feenstra, P.; Gruber-Wölfler, H.; Laskowski, R.; Bart, H.-J.; Khinast, J.	CIT	4/8/2012	Gesellschaft Deutscher Chemiker	Weinheim	2012	1400	10.1002/cite.201250520	http://onlinelibrary.wiley.com/doi/10.1002/cite.201250520/pdf
8	Reversed Phase Monolithic Stationary Phases for Defined Separation Tasks in Continuous Annular Electro-chromatography		Tagungsband 8. Minisymposium der Verfahrenstechnik	./.	Johannes Kepler Universität Linz, Institut für Verfahrens-technik	Linz	2012	92-93	ISBN 978-3-200-02647-6	./.
9	Implementation of Monolithic Materials in Planar Test Cells for Continuous Electro-chromatography	Braunbruck, M.-G.; Feenstra, P.; Gruber-Wölfler, H.;	Tagungsband 6. Minisymposium der Verfahrenstechnik	./.	Universität für Bodenkultur, IFA-Tulln, Institut für Umwelt-	Tulln	2010	115-117	./.	./.

		Khinast, J.			biotechnologie					
10	Monolithic Silica-based Stationary Phase for Continuous Annular Electro-chromatography	Braunbruck, M.-G.; Feenstra, P.; Gruber-Woelfler, H.; Khinast, J. G.	Tagungsband zum Minisymposium der Verfahrenstechnik, Technische Universität Wien, Austria	./.	Technische Universität Wien	Vienna	2009	./.	ISBN 978-3-95027 31-0-6	./.
11	Novel Approaches for the Preparation of a Stationary Phase for Continuous Annular Electro-chromatography (CAEC)	Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Laskowski, R.; Bart, H.-J.; Khinast, J.	International Congress of Chemical and Process Engineering, Summaries 5, Systems and Technology	./.	Czech Society of Chemical Engineering	Prague	2010	1896-1897	ISBN 978-80-02-02250-3	./.
12	Tailored Stationary Phases for Continuous Electro-chromatographic Separation of APIs	Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Laskowski, R.; Bart, H.-J.; Khinast, J.	Central European Symposium on Pharmaceutical Technology	./.	./.	./.	2010	703	./.	http://dx.doi.org/10.3797/scipharm.cespt.8.PPAT14
13	Aufreinigung mit hoher Wertschöpfung: Kontinuierliche anulare Elektrochromatografie	Laskowski, R.; Bart, H.-J.	CITplus	12/2010	GIT VERLAG	Darmstadt	2010	30-31	ISSN: 1436-2597	09.12.2010
14	Kontinuierliche annulare	Laskowski, R.; Bart, H.-J.	www.analytik-news.de; http://www.analytik-news.de/Fachartikel/2009/65.html	08/2009	Dr. Beyer Internet-	Ober-Ramstadt	2009	./.	./.	31.08.2009

	Elektrochromatographie				Beratung					
15	Separation, Hydrodynamics and Heating Effects in Continuous Annular Electro-Chromatography (CAEC)	Laskowski, R.; Bart, H.-J; Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G; Khinast, J.	Procedia Engineering	2012	Elsevier		2012	1755-1772	10.1016/j.proeng.2012.07.555	./.
16	Trenneffizienz, Hydrodynamik und Joule'sche Erwärmung in der annularen Elektrochromatographie	Laskowski, R.; Bart, H.-J; Hofmann, C.; Gruber-Wölfler, H.; Braunbruck, M.-G; Khinast, J.	Chemie Ingenieur Technik; Special Issue: ProcessNet-Jahrestagung 2012 und 30. Jahrestagung der Biotechnologen	08/2012	WILEY-VCH Verlag	Weinheim	2012	1372	10.1002/cite.201250411	./.
17	Durchströmung von stationären Phasen in einem elektrischen Feld unter Anwendung der planaren Elektrochromatographie	Laskowski, R.; Bart, H.-J; Hofmann, C.; Menges, G.; Feenstra, P.; Gruber-Wölfler, H.	Chemie Ingenieur Technik; Special Issue: ProcessNet-Jahrestagung 2010 und 28. Jahrestagung der Biotechnologen	09/2010	WILEY-VCH Verlag	Weinheim	2010	1372	10.1002/cite.201050737	./.
18	3-D Analysis of Heat Transfer Intensification by Re-entrance Flow	Wang, Q.; Hessel, V.; Rebrov, E.;	Chemical Engineering & Technology	34(3)	WILEY-VCH Verlag	Weinheim	2011	379-390	10.1002/ceat.2010	NO

	Pin-fins Microstructures with Highly Thermal Conductive Plate	Werner, B.							00376	
19	Droplet Size Control with Methanol-repellent Surface in a Sampling Device for Continuous Annular Electrochromatography	Wang, Q.; Rebrov, E.; Hessel, V.	Journal of Separation Science	35(3)	WILEY-VCH Verlag	Weinheim	2012	445-451	10.1002/jssc.201100622	NO
20	Monolithic Materials for Analytic and Preparative Continuous Electro-chromatography	Braunbruck, M.-G.; Feenstra, P.; Gruber-Wölfler, H.; Khinast, J.	Tagungsband 7. Minisymposium der Verfahrenstechnik	1. Aufl.	Verlag der Technischen Universität Graz	Graz	2011	78-80	./.	./.

By the way: A permanent identifier should be a persistent link to the published version (full text if open access or abstract if article is pay per view) or to the final manuscript accepted for publication (link to article in repository). Open Access is defined as free of charge access for anyone via Internet. Please answer "yes" if the open access to the publication is already established and also if the embargo period for open access is not yet over but you intend to establish open access afterwards.

Student Theses:

Akin, B.:

Investigation of Electrophoretic Behaviours and Separation in Capillary Electrochromatography (CEC) Dependence of Different Stationary Phases, Bachelor Thesis, University of Kaiserslautern, Germany, 2011.

Blum, E.:

Untersuchung von Ionenmigration schwacher Elektrolyte im Hochspannungsfeld zur Bestimmung von Leitfähigkeitsgradienten in der planaren Elektrochromatogarphie, Studienarbeit, University of Kaiserslautern, Germany, 2012.

Braunbruck, M.-G.:

Development of a Stationary Phase for Continuous Annular Electro-chromatography, Master Thesis, Institute for Process and Particle Engineering, Graz University of Technology, Austria, 2009.

Conrad, P.:

Entwicklung eines 3-dimensionalen CFD Modells zur Abschätzung elektrokinetischer Eigenschaften eines annularen Elektrochromatographen in OpenFoam, Studienarbeit, University of Kaiserslautern, Germany, 2012.

Dernbecher, A.:

Simulation von Hydrodynamik und Wärmeentwicklung in der präparativen Elektrochromatographie unter Verwendung unterschiedlicher Eluenten, Studienarbeit, University of Kaiserslautern, Germany, 2012.

Feenstra, P.:

Tailoring and Characterisation of Silica-based Monoliths for the Use in Continuous Annular Electro-chromatography, Master Thesis, Graz University of Technology, Austria, 2009.

Gauer, T.:

Kontinuierliche annulare Elektrochromatographie: Energetische und photometrische Betrachtung zur experimentellen Ermittlung der Prozessparameter, Studienarbeit, University of Kaiserslautern, Germany, 2010.

Merz, M.:

Entwicklung eines Modelles zur Simulation von elektrokinetischen Effekten mit gekoppelter Wärmegleichung, Studienarbeit, University of Kaiserslautern, Germany, 2011.

Schüring, Y.:

Modellierung und Simulation von Trennprozessen mittels kontinuierlicher Elekrochromatographie, Studienarbeit, Technische Universität Dortmund, Germany, 2009.

Teufel, K.:

Implementierung von stationären Phasen für die kontinuierliche Elektro-Chromatographie, Bachelor Thesis, Institute for Process and Particle Engineering, Graz University of Technology, Austria, 2010.

Yazdani, A.:

Anwendung einer Wärmebildkamera zur Temperaturmessung und Untersuchung der Jouleschen Wärme am Beispiel eines planaren Elektrochromatographen, Studienarbeit, University of Kaiserslautern, Germany, 2010.

Table A2: List of all dissemination activities (publications, conferences, workshops, web sites/applications, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters).

No.	Type of activities	Main Leader	Title	Date	Place	Type of audience	Size of audience	Countries addressed
1	Presentation	Bart, H.-J.; Werner, B.:	Ringspalt-Elektrochromatographie als kontinuierliche Aufreinigungsmethode	February 14, 2011	Infotag Mikrotrenntechnik, Frankfurt a.M., Germany	Scientific community, industry	40-50	Germany
2	Presentation	Behrens, M.; Engell, S.	Dynamische Simulation und Optimierung annularer Elektro-Chromatographie	March 3-5, 2010	ProcessNet, Jahrestreffen der FA Fluidverfahrenstechnik und Hochdruckverfahrenstechnik 2010, Magdeburg, Germany	Scientific community	250	Germany
3	Presentation	Braunbruck, M.-G.; Gruber-Woelfler, H.; Feenstra, P.W.; Laskowski, R.; Bart, H.J.; Khinast, J.G.	Continuous Annular Electro-Chromatography – a Future Concept for a Continuous Purification Process of APIs	October 16-21, 2011	AIChE Annual Meeting, Minneapolis, MN, USA	Scientific community	30	Worldwide/ International
4	Presentation	Braunbruck, M.-G.; Gruber-Woelfler, H.; Feenstra, P.W.; Laskowski, R.; Bart, H.J.; Khinast, J.G.	Continuous Electro-chromatographic Separations Using Silica-based Monolithic Stationary Phases	September 25-29, 2011	8th European Congress of Chemical Engineering (ECCE), Berlin, Germany	Scientific community	50	Germany, Austria
5	Presentation	Gruber-Woelfler, H.; Braunbruck,	Development of a Stationary Phase for	November 8-13,	AIChE Annual Meeting,	Scientific	50	Worldwide/

		M.-G.; Feenstra, P.; Khinast, J.G.	Continuous Annular Electro-Chromatography (CAEC)	2009	Nashville, TN, USA	Community		International
6	Presentation	Gruber-Woelfler, H.; Feenstra, P.; Braunbruck, M.-G.; Laskowski, R.; Bart, H.J.; Khinast, J.G.	Novel Approaches for the Preparation of a Stationary Phase for Continuous Annular Electro-chromatography (CAEC)	August 28 – September 2, 2010	CHISA 2010, Prague, Czech Republic	Scientific community	30	Worldwide/ International
7	Presentation	Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Laskowski, R.; Bart, H.-J.; Khinast, J.	Preparation of Monolithic Materials for Continuous Annular Electro-chromatographic Separations of Active Pharmaceutical Ingredients	November 7, 2010	AIChE Annual Meeting 2010, Salt Lake City, UT, USA	Scientific community	30	Worldwide/ International
8	Presentation	Laskowski, R.; Bart, H.-J.	Kontinuierliche annulare Chromatographie, Doktorandenseminar Präparative Chromatographie	March 21-23, 2010	Doktorandenseminar Präparative Chromatographie, Muggendorf, Germany	Scientific community	40	Germany
9	Presentation	Laskowski, R.; Bart, H.-J.	Mikroverfahrenstechnik – Kontinuierliche annulare Elektrochromatographie	January 08-10, 2011	Doktorandenseminar Separation Science, Hohenroda, Germany	Scientific community	30	Germany

10	Presentation	Laskowski, R.; Bart, H.-J.; Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Khinast, J.; Hofmann, C.; Menges, G.; Werner, B.; Löb, P.	Hydrodynamics and Separation in Continuous Annular Electro-chromatography	June 18-22, 2012	ACHEMA 2012, Frankfurt a.M., Germany	Scientific community	150	Worldwide/ International
11	Presentation	Laskowski, R.; Bart, H.-J.; Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Khinast, J.; Hofmann, C.; Menges, G.; Werner, B.; Löb, P.	Separation, Hydrodynamics and Heating Effects in Continuous Annular Chromatography (CAEC)	August 25-29, 2012	20th International Congress of Chemical and Process Engineering (CHISA 2012), Prague, Czech Republic	Scientific community	100	Worldwide/ International
12	Presentation	Laskowski, R.; Bart, H.-J.; Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Khinast, J.; Hofmann, C.; Menges, G.; Werner, B.; Löb, P.	Trenneffizienz, Hydrodynamik und Joulesche Erwärmung in der annularen Elektrochromatographie	September 10-13, 2012	ProcessNet-Jahrestagung 2012, Karlsruhe, Germany	Scientific community	100	Germany, Austria

13	Presentation	Laskowski, R.; Bart, H.-J.; Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Khinast, J.; Hofmann, C.; Menges, G.; Werner, B.; Löb, P.; Hessel, V.	Durchströmung von stationären Phasen in einem elektrischen Feld unter Anwendung der planaren Elektrochromatographie	September 21-23, 2010	ProcessNet-Jahrestagung 2010, Aachen, Germany	Scientific community	100	Germany, Austria
14	Presentation	Laskowski, R.; Bart, H.-J.; Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Khinast, J.; Hofmann, C.; Menges, G.; Werner, B.; Löb, P.; Hessel, V.	Flow in a Planar Electro-chromatograph	August 29 – September 1, 2010	17th International Symposium on Liquid Phase Separations and Capillary Electroseparation Techniques, Baltimore, USA	Scientific community	150	Worldwide/ International
15	Presentation	Laskowski, R.; Bart,H.-J.; Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Khinast, J.; Hofmann, C.; Menges, G.; Werner, B.; Löb, P.; Hessel, V.	Hydrodynamics and Heating Effects in a Planar Electro-chromatograph	September 25-29, 2011	8th European Congress of Chemical Engineering (ECCE), Berlin, Germany	Scientific community	100	Worldwide/ International

16	Presentation	Puthirasigamany, M.; Schüring, Y.; Hoffmann, A.; Górak, A.; Molga, E.; Lewak, M.	Model-based Investigation of Capillary Electro-chromatography at Continuous Operation Mode	September 6-10, 2010	KichP10, Gdansk, Poland	Scientific community	30	International
17	Presentation	Wang, Q.; Hessel, V.; Rebrov, E.	Structure Design for Methanol Repellent Surface of Capillary Outlet to Improve the Separation Efficiency in CAEC	March 27-31, 2011	ACS National Meeting, Anaheim, CA, USA	Scientific community	30	Worldwide/ International
18	Poster	Behrens, M.; Yu, Y.; Engell, S.	Simulation and Optimizing Control of Continuous Annular Electro-chromatography (CAEC)	September 13-15, 2010	13th International Symposium on Preparative and Industrial Chromatography and Allied Techniques, SPICA 2010, Stockholm, Sweden	Scientific community	1000	Worldwide/ International
19	Poster	Braunbruck, M.-G.; Feenstra, P.; Gruber-Wölfler, H.; Laskowski, R.; Bart, H.-J.; Khinast, J.	Reversed Phase Macroporous Monoliths for Continuous Annular Electro-chromatographie	September 10-13, 2012	ProcessNet-Jahrestagung 2012, Karlsruhe, Germany	Scientific community	100	Worldwide/ International
20	Poster	Braunbruck, M.-G.; Feenstra, P.; Gruber-Wölfler, H.; Laskowski, R.; Bart, H.-J.; Werner, B.;	Functionalized Monolithic Stationary Phases for Continuous Electro-chromatography	August 25-29, 2012	20th International Congress of Chemical and Process Engineering (CHISA 2012), Prague, Czech Republic	Scientific community	100	Worldwide/ International

		Hofmann, C.; Khinast, J.						
21	Poster	Braunbruck, M.-G.; Banko, C..; Feenstra, P.; Gruber-Wölfler, H.; Khinast, J.	Monolithic Materials for Analytic and Preparative Continuous Electro-chromatography	June 30, 2011	7. Minisymposium der Verfahrenstechnik, Graz, Austria	Scientific community	60	Austria
22	Poster	Braunbruck, M.-G.; Feenstra, P.; Gruber-Woelfler, H.; Khinast, J.	Monolithic Silica-based Stationary Phase for Continuous Annular Electro-chromatography	June 24-25, 2009	5. Minisymposium der Verfahrenstechnik, Vienna, Austria	Scientific community	60	Austria
23	Poster	Braunbruck, M.-G.; Gruber-Wölfler, H.; Feenstra, P.; Laskowski, R.; Bart, H.-J.; Khinast, J.	Continuous Annular Electro-chromatography – a Preparative Multidimensional Separation System for APIs	June 13, 2011	3rd PharmSciFair – Pharmaceutical Sciences for the Future of Medicines, Prague, Czech Republic	Scientific community	50	Worldwide/ International
24	Poster	Braunbruck, M.-G.; Feenstra, P.; Gruber-Wölfler, H.; Khinast, J.	Implementation of Monolithic Materials in Planar Test Cells for Continuous Electro-chromatography	June 24, 2010	6. Minisymposium der Verfahrenstechnik, Tulln	Scientific community	60	Austria
25	Poster	Gruber-Woelfler, H.; Braunbruck, M.-G.; Banko, C.; Feenstra, P.W.; Mohr, S.; Schmid, M.;	Particle-loaded silica monoliths as Stationary Phases for Electro-chromatography: From Analytical to Preparative Separation	September 29-30, 2011	5th International Congress for Pharmaceutical Engineering, Graz, Austria	Scientific community	50	Worldwide/ International

		Laskowski, R.; Bart, H.-J.; Khinast, J.G.	of APIs					
26	Poster	Gruber-Wölfler, H.; Braunbruck, M.-G.; Feenstra, P.; Laskowski, R.; Bart, H.-J.; Khinast, J.	Design, Characterization and Molecular Modelling of Stationary Phases for Continuous Annular Electro-chromatography (CAEC)	June 5, 2011	9th International Symposium on the Characterisation of Porous Solids (9th COPS), Dresden, Germany	Scientific community	50	Worldwide/ International
27	Poster	Gruber-Woelfler, H.; Feenstra, P.; Braunbruck, M.; Khinast, J.	Functionalized Stationary Phases for Continuous Annular Electro-chromatography	September 17-18, 2009	International Graz Congress for Pharmaceutical Engineering, Graz, Austria	Scientific community	50	Worldwide/ International
28	Poster	Gruber-Woelfler, H.; Feenstra, P.; Braunbruck, M.; Khinast, J.	Silica-based Chromatographic Stationary Phase for Continuous Annular Electro-chromatography	August 25-28, 2009	13. Österreichische Chemietage, Vienna, Austria	Scientific community	50	Austria, Slovenia
29	Poster	Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Laskowski, R; Bart, H.-J.; Khinast, J.	Tailored Stationary Phases for Continuous Electro-chromatographic Separation of APIs	September 16, 2010	Central European Symposium on Pharmaceutical Technology, Graz, Austria	Scientific community	50	Worldwide/ International
30	Poster	Laskowski, R.; Bart,H.-J.;	Electro-osmotic Flow and Generated Joule	September 13-15,	13th Symposium on Preparative and Industrial	Scientific	100	Worldwide/

		Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Khinast, J.; Hofmann, C.; Menges, G.; Werner, B.; Löb, P.; Hessel, V.	Heating in a Planar Electro-chromatograph	2010	Chromatography and Allied Techniques, Stockholm, Sweden	community		International
31	Poster	Laskowski, R.; Bart,H.-J.; Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Khinast, J.; Hofmann, C.; Menges, G.; Werner, B.; Löb, P.; Hessel, V.	Evaluation of a Continuous Separation Process with a Planar Electro-chromatograph	September 25-29, 2011	8th European Congress of Chemical Engineering (ECCE), Berlin, Germany	Scientific community	100	Worldwide/ International
32	Poster	Laskowski, R.; Bart,H.-J.; Gruber-Wölfler, H.; Feenstra, P.; Braunbruck, M.-G.; Khinast, J.; Hofmann, C.; Menges, G.; Werner, B.; Löb, P.; Hessel, V.	Flow in a Planar Electro-chromatograph	August 29 – September 1, 2010	International Symposium on Liquid Phase Separations and Capillary Electroseparation Techniques, Baltimore, USA	Scientific community, industry	100	Worldwide/ International
33	Poster	Wang, Q.; Hessel, V.;	3-D Analysis of Heat Transfer Intensification by Pin-fins with a	October 25-27,	Netherlands Process Technology Symposium (NPS-10), Veldhoven, The	Scientific community,	50	Netherlands

		Rebrov, E.	Highly Thermal Conductive Plate	2010	Netherlands	industry		
34	Exhibition	Institut für Mikrotechnik Mainz GmbH (IMM)	CAEC Device Version 1 as Exhibit at IMM Booth	September 25-29, 2011	8th European Congress of Chemical Engineering (ECCE), Berlin, Germany	Scientific community, industry	Participants of conference; several hundred visitors	Europe
35	Exhibition	Institut für Mikrotechnik Mainz GmbH (IMM)	CAEC Device Version 1 as Exhibit at IMM Booth	February 20-22, 2012	International Conference on Microreaction Technology (IMRET 2012), Lyon, France	Scientific community, industry	Several hundred visitors	Europe
36	Exhibition	Institut für Mikrotechnik Mainz GmbH (IMM)	CAEC Device Version 1 as Exhibit at IMM Booth	June 18-22, 2012	ACHEMA 2012, Frankfurt a.M., Germany	Scientific community, industry	Several hundred visitors	Europe
37	Exhibition	Kirschneck, D.; Linhart, W.:	MIC Booth	June 18-22, 2012	ACHEMA 2012, Frankfurt a.M., Germany	Scientific community, industry	Several hundred visitors	Europe
38	Flyer	Woels, C.; Linhart, W.	CAEC Preparative Continuous Annular Electro-chromatography	2012	Handout on Business Trips, Conferences, Fairs and Exhibitions	Scientific community, industry	40	Europe
39	Press Release	Woels, C.;	Invitation to Press Conference at ACHEMA 2012	June 18-22, 2012	ACHEMA 2012, Frankfurt a.M., Germany	Scientific community, industry	40	Europe

By the way: A drop down list allows choosing the dissemination activity: publications, conferences, workshops, web, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters, Other.

A drop down list allows choosing the type of public: Scientific Community (higher education, Research), Industry, Civil Society, Policy makers, Medias ('multiple choices' is possible.

6.2 Section B (confidential or public: confidential information to be marked clearly)

There were no applications for patents, trademarks, or registered designs.

Table B2: Overview of exploitable foreground

Type of exploitable foreground	Exploitable foreground (description)	Confidential (yes/no)	Foreseen embargo date	Exploitable product(s) or measure(s)	Sector(s) of application	Timetable for commercial use or any other use	Patents or other IPR exploitation (licenses)	Owner & other beneficiaries involved
General advancement of knowledge	Simulation methods for CAEC plants in the production of biopharmaceuticals	NO	./.	Simulation software for downstream processing of biological products	Pharmaceutical industry, fine & speciality chemicals	2012	no	TUDO
General advancement of knowledge	Simulation methods for the transport and affinity in the chromatographic packing	NO	2012	Simulation tool and for material design	Pharmaceutical industry, fine & speciality chemicals	2012	no	TUG
Exploitation of R&D results via standards	Method for the synthesis of annular monolithic stationary phases	YES	2015	Annular monolithic stationary phases	Pharmaceutical industry, fine & speciality chemicals	2012	NO	TUG
Exploitation of R&D results via	Method for the modification of annular monolithic	YES	2015	Functionalised stationary	Pharmaceutical industry, fine & speciality	2012	no	TUG

standards	stationary phases			phases	chemicals			
General advancement of knowledge	Testing of stationary phase and model development	NO	./.	Parameter identification and simulation tool	Pharmaceutical industry, fine & speciality chemicals	2012	no	UNIKL, TUDO
General advancement of knowledge	CAEC equipment	NO	./.	Principal design idea, simulation within equipment engineering	Pharmaceutical industry, fine & speciality chemicals	2012	No	UNIKL, TUE
Exploitation of R&D results via standards	CAEC device (core of the device including sensor implementation and multiple valve system but without packing and process control)	YES	./.	Detailed construction and establishment of full fabrication chain for the CAEC device as developed in the project	Pharmaceutical industry, fine & specialty chemicals	2012	NO	IMM
Exploitation of R&D results via standards	Optical integrated sensor	YES	./.	Special inline UV-sensors as described in Deliverable 4.6	Pharmaceutical industry, fine & specialty chemicals	2012	NO	IMM
General advancement of	Special design and fabrication	YES	./.	Increase in design and fabrication	Apparatus engineering	2012	NO	IMM

knowledge	knowledge			knowledge concerning complex apparatuses with moving parts and electrical field (HV)				
General advancement of knowledge	Gain in expertise and profile in micro separation technology	NO	No “active marketing” foreseen	R&D services in micro separation in collaboration with industry	Pharmaceutical industry, fine & speciality chemicals	2012	on demand	TUE, IMM, UNIKL
General advancement of knowledge	Assembly of CAEC plant	NO		cGMP compliant manufacturing concept, equipment list	Pharmaceutical industry, fine & speciality chemicals	2012	NO	MIC
General advancement of knowledge	Development of CAEC PLC und user interface	NO	./.	Control Concept and Control Software	Pharmaceutical industry, fine & speciality chemicals	2012	NO	MIC, TUDO
General advancement of knowledge	Knowledge on handling and performance of CAEC	YES	2015	New down-stream processes with CAEC technology	Pharmaceutical industry, fine & speciality chemicals	2015	NO	NOV, GAL
General advancement of	Knowledge on handling and performance of	NO		Use of CAEC in clinical	Pharmaceutical industry	2015	No	NOV

knowledge	CAEC			trials				
General advancement of knowledge	Knowledge on handling and performance of CAEC	YES	2018	Offering improved service for contract manufacturing	Pharmaceutical industry	2020	No	GAL

In the table, for each row, please provide a text to explain the exploitable foreground, in particular:

- Its purpose
- How the foreground might be exploited, when and by whom
- IPR exploitable measures taken or intended
- Further research necessary, if any
- Potential/expected impact (quantify where possible)

By the way: A drop down list allows choosing the type of foreground: General advancement of knowledge, Commercial exploitation of R&D results, Exploitation of R&D results via standards, exploitation of results through EU policies, exploitation of results through (social) innovation.

A drop down list allows choosing the type sector (NACE nomenclature): http://ec.europa.eu/competition/mergers/cases/index/nace_all.html

7 Report on societal implications

Replies to the following questions will assist the Commission to obtain statistics and indicators on societal and socio-economic issues addressed by projects. The questions are arranged in a number of key themes. As well as producing certain statistics, the replies will also help identify those projects that have shown a real engagement with wider societal issues, and thereby identify interesting approaches to these issues and best practices. The replies for individual projects will not be made public.

7.1 Ethics

Did your project undergo an Ethics Review (and/or Screening)?

No

If Yes: Have you described the progress of compliance with the relevant Ethics Review/Screening Requirements in the frame of the periodic/final reports?

No

7.1.1 Research on humans

Did the project involve children? No

Did the project involve patients? No

Did the project involve persons not able to give consent? No

Did the project involve adult healthy volunteers? No

Did the project involve Human genetic material? No

Did the project involve Human biological samples? No

Did the project involve Human data collection? No

7.1.2 Research on human embryo/foetus

Did the project involve Human Embryos? No

Did the project involve Human Foetal Tissue / Cells? No

Did the project involve Human Embryonic Stem Cells (hESCs)? No

Did the project on human Embryonic Stem Cells involve cells in culture? No

Did the project on human Embryonic Stem Cells involve the derivation of cells from Embryos?

No

7.1.3 Privacy

Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)? No

Did the project involve tracking the location or observation of people? No

7.1.4 Research on animals

Did the project involve research on animals? No

Were those animals transgenic small laboratory animals? No

Were those animals transgenic farm animals? No

Were those animals cloned farm animals? No

Were those animals non-human primates? No

7.1.5 Research involving developing countries

Did the project involve the use of local resources (genetic, animal, plant etc)? No

Was the project of benefit to local community (capacity building, access to healthcare, education etc)? No

7.1.6 Dual use

Research having direct military use - No

Research having the potential for terrorist abuse - No

7.2 Workforce statistics

Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of position	Number of women	Number of men
Scientific coordinator	TUDO: 0 UNIKL: 0 TUG: 0 IMM: 0 MIC: 0 NOV: 0 TUE: 0 GAL: 0	TUDO: 1 UNIKL: 0 TUG: 0 IMM: 0 MIC: 0 NOV: 0 TUE: 0 GAL: 0
Work package leaders	TUDO: 2 UNIKL: 0 TUG: 1 IMM: 0 MIC: 0 NOV: 0 TUE: 0 GAL: 0	TUDO: 1 UNIKL: 1 TUG: 1 IMM: 2 MIC: 2 NOV: 0 TUE: 0 GAL: 0

Experienced researchers (i.e. PhD holders)	TUDO: 0 UNIKL: 0 TUG: 0 IMM: 2 MIC: 0 NOV: 0 TUE: 1 GAL: 1	TUDO: 1 UNIKL: 0 TUG: 0 IMM: 1 MIC: 1 NOV: 1 TUE: 1 GAL: 0
PhD students	TUDO: 1 UNIKL: 1 TUG: 1 IMM: 0 MIC: 0 NOV: 0 TUE: 0 GAL: 0	TUDO: 8 UNIKL: 2 TUG: 1 IMM: 0 MIC: 0 NOV: 0 TUE: 0 GAL: 0
Other	TUDO: 6 UNIKL: 6 TUG: 1 IMM: 2 MIC: 0 NOV: 0 TUE: 0 GAL: 2	TUDO: 4 UNIKL: 11 TUG: 1 IMM: 11 MIC: 1 NOV: 0 TUE: 0 GAL: 1

How many additional researchers (in companies and universities) were recruited specifically for this project?

TUDO: 3
UNIKL: 4
TUG: 2
IMM: 0
MIC: 0
NOV: 0
TUE: 2
GAL: 0

Of which, indicate the number of men:

TUDO: 2
UNIKL: 1
TUG: 1
IMM: 0
MIC: 0
NOV: 0
TUE: 1
GAL: 0

7.3 Gender aspects

Did you carry out specific Gender Equality Actions under the project?

TUDO: Yes
UNIKL: Yes
TUG: Yes
IMM: No
MIC: No
NOV: No
TUE: No
GAL: No

Which of the following actions did you carry out and how effective were they?

Design and implement an equal opportunity policy

TUDO: Very effective
UNIKL: Very effective
TUG: Very effective
IMM: Very effective
MIC: Not applicable
NOV: Not applicable
TUE: Not applicable
GAL: Not applicable

Set targets to achieve a gender balance in the workforce

TUDO: Effective
UNIKL: Very effective
TUG: Very effective
IMM: Not applicable
MIC: Not applicable
NOV: Not applicable
TUE: Effective
GAL: Not applicable

Organise conferences and workshops on gender

TUDO: Not applicable
UNIKL: Very effective
TUG: Not applicable
IMM: Not applicable
MIC: Not applicable
NOV: Not applicable
TUE: Not applicable
GAL: Not applicable

Actions to improve work-life balance

TUDO: Very effective
UNIKL: Effective

TUG: Effective
IMM: Not applicable
MIC: Not applicable
NOV: Not applicable
TUE: Not applicable
GAL: Not applicable

Was there a gender dimension associated with the research content - i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed? No

7.4 Synergies with science education

Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?

TUDO: No
UNIKL: No
TUG: Yes
IMM: No
MIC: No
NOV: No
TUE: No
GAL: No

9. Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)? No

7.5 Interdisciplinarity

Which disciplines (see list below) are involved in your project?

Main discipline: other engineering sciences

Associated discipline: mathematics and computer sciences

Associated discipline: chemical sciences

FIELDS OF SCIENCE AND TECHNOLOGY

1. NATURAL SCIENCES

1.1 Mathematics and computer sciences [mathematics and other allied fields: computer sciences and other allied subjects (software development only; hardware development should be classified in the engineering fields)]

1.2 Physical sciences (astronomy and space sciences, physics and other allied subjects)

1.3 Chemical sciences (chemistry, other allied subjects)

1.4 Earth and related environmental sciences (geology, geophysics, mineralogy, physical geography and other geosciences, meteorology and other atmospheric sciences including climatic research, oceanography, vulcanology, palaeoecology, other allied sciences)

1.5 Biological sciences (biology, botany, bacteriology, microbiology, zoology, entomology, genetics, biochemistry, biophysics, other allied sciences, excluding clinical and veterinary sciences)

2 ENGINEERING AND TECHNOLOGY

2.1 Civil engineering (architecture engineering, building science and engineering, construction engineering, municipal and structural engineering and other allied subjects)

2.2 Electrical engineering, electronics [electrical engineering, electronics, communication engineering and systems, computer engineering (hardware only) and other allied subjects]

2.3. Other engineering sciences (such as chemical, aeronautical and space, mechanical, metallurgical and materials engineering, and their specialised subdivisions; forest products; applied sciences such as geodesy, industrial chemistry, etc.; the science and technology of food production; specialized technologies of interdisciplinary fields, e.g. systems analysis, metallurgy, mining, textile technology and other applied subjects)

3. MEDICAL SCIENCES

3.1 Basic medicine (anatomy, cytology, physiology, genetics, pharmacy, pharmacology, toxicology,

immunology and immunohaematology, clinical chemistry, clinical microbiology, pathology)

3.2 Clinical medicine (anaesthesiology, paediatrics, obstetrics and gynaecology, internal medicine, surgery, dentistry, neurology, psychiatry, radiology, therapeutics, otorhinolaryngology, ophthalmology)

3.3 Health sciences (public health services, social medicine, hygiene, nursing, epidemiology)

4. AGRICULTURAL SCIENCES

4.1 Agriculture, forestry, fisheries and allied sciences (agronomy, animal husbandry, fisheries, forestry, horticulture, other allied subjects)

4.2 Veterinary medicine

5. SOCIAL SCIENCES

5.1 Psychology

5.2 Economics

5.3 Educational sciences (education and training and other allied subjects)

5.4 Other social sciences [anthropology (social and cultural) and ethnology, demography, geography (human, economic and social), town and country planning, management, law, linguistics, political sciences, sociology, organisation and methods, miscellaneous social sciences and interdisciplinary, methodological and historical S1T activities relating to subjects in this group. Physical anthropology, physical geography and psychophysiology should normally be classified with the natural sciences].

6. HUMANITIES

6.1 History (history, prehistory and history, together with auxiliary historical disciplines such as

archaeology, numismatics, palaeography, genealogy, etc.)

6.2 Languages and literature (ancient and modern)

6.3 Other humanities [philosophy (including the history of science and technology) arts, history of art, art criticism, painting, sculpture, musicology, dramatic art excluding artistic "research" of any

kind, religion, theology, other fields and subjects pertaining to the humanities, methodological, historical and other S1T activities relating to the subjects in this group]

7.6 Engaging with civil society and policy makers

Did your project engage with societal actors beyond the research community? (if 'No', go to “Use and Dissemination”) No

If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?

In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)? No

Did you engage with government / public bodies or policy makers (including international organisations)? No

Will the project generate outputs (expertise or scientific advice) which could be used by policy makers? No

If Yes, in which fields?

If Yes, at which level?

7.7 Use and dissemination

How many Articles were published/accepted for publication in peer-reviewed journals?

Total: 20

To how many of these is open access provided?

4

How many of these are published in open access journals?

4

How many of these are published in open repositories?

4

To how many of these is open access not provided?

16

Please check all applicable reasons for not providing open access:

- publisher's licensing agreement would not permit publishing in a repository
- no suitable repository available
- no suitable open access journal available
- no funds available to publish in an open access journal
- lack of time and resources
- lack of information on open access
- If other - please specify (e.g. classification for security project):

How many new patent applications ('priority filings') have been made? 0

("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).

Indicate how many of the following Intellectual Property Rights were applied for (give number).

Trademark: 0
Registered design: 0
Other: 0

How many spin-off companies were created / are planned as a direct result of the project? 0

Indicate the approximate number of additional jobs in these companies:

0

Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project:

- In small and medium-sized enterprises
- In large companies

For your project partnership please estimate the employment effect resulting directly from your participation in Full Time Equivalent (FTE = one person working fulltime for a year) jobs:

- Difficult to estimate / not possible to quantify

7.8 Media and Communication to the general public

As part of the project, were any of the beneficiaries professionals in communication or media relations? No

As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public? No

Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?

- Media briefing
- Brochures /posters / flyers
- Coverage in specialist press
- Website for the general public / internet

In which languages are the information products for the general public produced?

- Language of the coordinator
- English