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Process Design Method for Manufacturing of Natural Compounds and Related Molecules

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Abstract: Natural active compounds from plants have an increasing economic meaning in all areas of life sciences like e.g., food additives, cosmetics, pharmaceuticals and crop protection. The main task in manufacturing larger amounts of these plant based products besides raw material supply, product stabilization, and quality assurance, is an efficient process development method and economic production technology. State of the art approach is used in standard extraction methods. Initially their quantities are determined in isolation of laboratory scale testing and then transferred into large-scale production by keeping all operation parameters constant in order to keep product quality constant. Nowadays the problem is that in most cases besides any missing process optimization with regard to necessary economical objectives, equipment is used with no modern process control, automation or process integration design applied. This study is a first proposal for a systematical process development and design methodology.

It should address the need for efficient process evaluation of many compounds at an early stage and process optimization for manufacturing. Due to sustainability and economy the maximal yield contained of any target compounds in plants should be extracted, but this increases as well the side component amount and type extracted and thereby decreases product purity. Therefore, any approach to optimization, should be integrated with a process development and evaluation of additional purification steps. This article describes the experimental setup as well as modeling

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approaches, combined with experimental model parameter determination, to generate the basis for any total process optimization by simulation. As an example the extraction of target compounds from wood is chosen.

Keywords: Natural compounds, solid-phase extraction, purification, process development and design

INTRODUCTION

The selective desorption of natural active compounds from plants has an increasing economic meaning. Plant extracts are used in large amounts in pharmaceutical products, including food additives and cosmetic products. Alone, the market for extracts from herbs (e.g., balm, green, tea and blueberry) to food supplement amounts up to 6.7 billion Euro in Europe and up to 17.5 billion Euro worldwide. The worldwide commercial volume of medicinal plant raw material amounts to 1 billion US $ according to FAO, the market value in USA amounted to 440 million US $ in 1997 and the annual growth rates for medical food and drugs based on plants are given with 6–8% (1).

Table 1 shows the market and the market growth for plant extracts in USA. The growth rates lay even with more than 15%. Like in other industrial areas, this growing market for natural products is associated with economical and environmental requirements, namely low production costs, high purity, and high regulatory constraints. Nevertheless, the technical realization of desorption into process steps and process equipment is often characterized by few ways and approaches, which are primarily based on empiric experiences (1).

Table 1. Market and Market growth for plant extracts in USA (1)

					Growth rate (%)	
Item	1993	1998	2003	2008	98/93	03/98
Plant-based chemicals	168	243	336	451	7.7	6.7
Mean price per Kilogram [10^6 US$/Kg]	7.05	7.78	8.74	9.96	2.0	2.3
Demand for plant-based chemicals [10^6 US$]	1185	1890	2935	4495	9.8	9.2
Ethereal oils [10^6 US$]	465	625	820	1054	6.1	5.6
Plant extracts [10^6 US$]	268	560	1120	1990	15.9	14.9
Rubber, Gels, Polymers [10^6 US$]	274	392	500	660	7.4	5.0
Others	178	313	495	791	11.9	9.6

Therefore, this study particularly lays emphasis on an elaborate methodical approach, which can enable the systematic study of selective desorption of active compounds from solid plants as well as the efficient match of their solid-phase extraction step with further product purification operations like liquid extraction, chromatography, ion-exchange, crystallization etc. Such a methodical approach should facilitate the search for process operating conditions, enabling achievement of maximal extract yield under consideration of all relevant solid extraction desorption parameters.

DESORPTION PROCESS OF SOLID-PHASE EXTRACTION

Many parameters are playing an important role in desorption processes for isolation of natural compounds from plants by solid-phase extraction. These parameters are systematically summarized in Fig. 1. Prior to desorption, the disintegration procedure releasing the substances to be extracted is of determining meaning, in addition to raw material properties and preparation. During the desorption step by solid-phase extraction, different methods ranging from pressing over distillation and solvent extraction up to high-pressure extraction can be applied according to raw material properties. Further parameters such as the operating mode, temperature, or used solvents are involved during desorption.

In addition to the target components, the extract solution obtained after plants desorption contains side components, which are removed in a purification or downstream process. Unit operations like liquid-to-liquid extraction, chromatography, ion-exchange, membrane technology, and distillation, are considered in the purification process. The optimal process in terms of highest overall product yield and purity depends on the suitable choice of one or a combination of these unit operations.

Besides experimental studies, validated models enable the sensitivity analysis of operating parameters and therefore minimize laboratory efforts and facilitate process scale-up. Parameters affecting solid-phase extraction of natural compounds from plants are presented in detail in the following sections.

Raw Material

Raw materials for the production of natural active substances are sheets, blossoms, branches, bark, Rhizome, roots, seeds, fruits, and algae etc. Because they are very manifold in their consistency, raw materials substantially determine the operating method and the equipment design of the solid-phase extraction process. Since some handling problems occur during grinding, transport, and disintegration, some plants such as wood and hart fruit are rarely used as raw materials. Leaves are mostly extracted and the portion of bark or seed extract is very low.

The concentration of the target substance in raw material usually lies in the range of 0,03 to 3% and is subject to variation according to year or cultivation

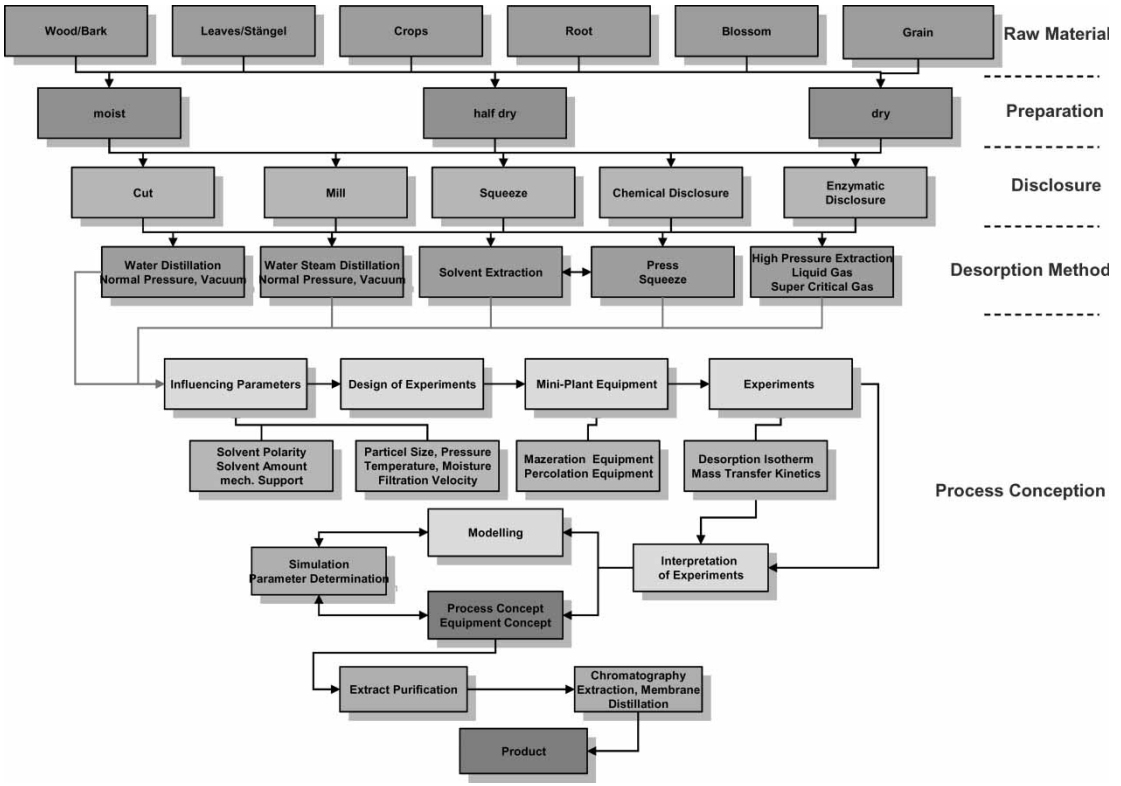


Figure 1. Schematic approach by desorption process investigation.

region. The distribution as well as the localization of the desired substances in raw material is important. The target compounds can be located on the external surface of the solid core, on the internal surface of solid pores, evenly distributed within the solid or within the plant cells (2). Diffusion processes can therefore take place inside the pores of the solid matrix or through cell walls, if these have been preserved after material disintegration.

Preparation and Disintegration

By plant desorption using water soluble organic solvents, plant water is removed to prevent alteration of desorption solvent properties due to plant water take-up. Plant drying prior to desorption also reduces swelling.

To reduce mass transport resistances and provide optimal mass transfer, the target compounds in raw material are released in a disintegration step prior to desorption. Raw material grinding is the most used disintegration method. It provides a large surface for mass transfer and small capillary paths to achieve high mass transfer rates.

The localization of desired natural compounds in solid system plays a significant role for the choice of the disintegration method. In the case of intracellular localization, the raw materials are not only grinded but also pre-pressed. The material compression and shear stress by pressing causes an additional substance mobilization. Such combination of grinding and pressing is often used in vegetable oil production. During the plant desorption step, vegetable oil is extracted from cell assembly by means of a solvent, mostly technical n-hexane. To guarantee an unhindered solvent penetration into the seed and minimize diffusion paths, the seed cell walls must be broken. The seeds are therefore first mechanically grinded and then pressed on roller chairs to fine flakes. If necessary, the seeds are warmed up in order to cause additional cell wall destruction by coagulation of the contained egg white and by steam formation (3).

Mechanical grinding in mill machines usually suffices by non intracellular localization of substances to be extracted. Special raw materials like fruits and fruit bowl are often cut to prevent side component desorption and avoid decrease of selectivity. In addition to grinding, chemicals or enzymes are often also used for disintegration. The objective of using these media is the conversion of the substances to be extracted in a form which allows reduction of desorption time and effort.

Desorption Method

Depending on the raw material constitution and requested qualities for the substances to be extracted, different desorption methods are applied, namely pressing, extraction, and distillation.

Pressing

Pressing is often used as a preliminary process step in order to reduce extraction time and effort. In case of vegetable oil production, for example, pre-pressing is recommended in any extraction facility in order to win the main oil amount on mechanical ways, and not directly by utilization of extraction solvents.

Moreover, pressing is used in special applications. Thus, citrus oils, for example, are won exclusively by pressing. For this purpose, citrus bowls are given in a large drum which is lined with many small sharp vertices. The bowls are slit by these vertices and the oil is pressed out top-down with a piston. The so-called cold-pressed oils of orange, lemon, bergamot, tangerine, grapefruit, and lime are obtained in this manner (4). Press and filter are often integrated into desorption facilities in order to press out extract solution from desorption residues more efficiently.

Distillation often serves for production, cleaning, and concentration of natural substances. This extraction method is also called steam distillation since water vapor is used as desorption agent. One makes a distinction between direct and indirect steam distillation. Based on ethereal oils extraction, these two procedures are described in the following sections.

Direct Steam Distillation

By direct steam distillation, the most used method in ethereal oils production, the distillation tank is loaded with plant material and water vapor is fed on the distillation tank bottom through a distributor ring. Volatile components present in raw material build a steam mixture with water vapor. This steam mixture is then separated in water and oil by condensation.

As a variation of direct steam distillation, a procedure called "hydro-diffusion" should be mentioned. The main difference between conventional direct steam distillation and hydro-diffusion consists in the fact that water vapor is not introduced on the distillation tank bottom but on the distillation bubble top. The steam mixture condensation occurs directly at the distillation tank bottom where a condenser is integrated. Compared with conventional direct steam distillation, this technique shows lower water vapor consumption, shorter distillation times and better oil yield (4).

Indirect Steam Distillation

During indirect steam distillation, also called water distillation or boiling, plant material and water are filled together in a distillation vessel and water is brought to boil. As by direct steam distillation, water vapor and the volatile compound contained in plant material build a steam mixture. Water is led back in the distillation vessel after steam mixture condensation and separation.

Indirect steam distillation finds only sporadic application, since this procedure needs longer distillation time and more energy by small oil yield in comparison to direct steam distillation. An example of indirect steam distillation is the iris root oil production (4).

Steam distillation can also be realized under vacuum conditions, especially used for extracting sensitive compounds. The water boiling point decreases under vacuum conditions, so that desorption can take place at low temperatures.

Solvent Extraction

Distillation is based on energy supply, volatility, displacement, and segregation. Exactly contradictory to distillation, another desorption method relies on mixture processes of substances to be extracted with liquid organic solvents. This desorption method is called solvent extraction. Since the used organic solvents usually exhibit low boiling points, a similar but technical non-costly desorption temperature lowering effect can be accomplish as by vacuum steam distillation.

High Pressure Extraction

In high pressure extraction processes, compressed gases in near- or supercritical state are used as extracting agents. The advantage of this desorption method in comparison to solvent extraction is the possibility of a solvent-free extract and raffinate production. Supercritical fluids possess liquid-similar densities and thus good extraction capacities. In addition, they exhibit gas typical low viscosities and relatively high diffusion coefficients so that they can fast diffuse into and out the substrate. Because of this combination of gas and liquid properties, extractions are realizable in short times.

Carbon dioxide is the most used fluid in high pressure extraction processes. Since it is a non polar solvent and thus not a priori suitable for each extraction system, small quantities of modifier (e.g., methanol, ethanol and similar polar solvents) are added to adjust the polarity.

Operational Modes used for Desorption in Solid-Phase Extraction

Depending on plant material properties, different operational modes are carried out for product desorption. For permeable materials, desorption solvent is percolated through a fixed bed of plant particles (“percolation”). Percolation can lead up to the nearly complete desorption of the raw material. By simple percolation, the raw material is extracted by continuously fed fresh solvent. This operation mode is accompanied with high solvent consumption, long extraction times, and high diluted extract solutions. By the so called re-percolation, the desorption solvent is recycled. Re-percolation is

therefore economically advantageous, since the used solvent quantities are lower than those for simple percolation.

Impermeable materials or materials that disintegrate during desorption are dispersed into desorption solvent and the extract solution is separated at desorption end. The extraction process is completed, when equilibrium is reached and compounds partitions coefficients between solvent and residue are constant. Depending on the design of the desorption equipment, the solvent can be purged continuously or discontinuous. This "maceration" can also be applied on permeable materials.

Another operation mode is counter-current extraction where fresh raw material is brought in contact with the loaded solvent, while the fresh solvent meets the already pre-extracted solid. This results in most efficient mass transfer and thereby high yields.

Operating Parameters for Desorption by Solid-Phase Extraction

The operating parameters of desorption can be divided into parameters influencing the extraction time and parameters affecting both, the quantitative yield and the qualitative composition of the extract solution.

Parameters, which influence extraction time, are:

Swelling of Raw Material

By intracellular localization of target compounds, an expansion of cell capillaries by swelling enhances cell walls permeability and thus accelerates diffusion. For high slime containing raw materials, swelling can however prevent extraction.

Extraction Temperature

Target compounds usually dissolve better and faster at high extraction temperatures. Increasing the temperature therefore generally also increases the extraction rate. In some cases, e.g., in vegetable oil production, product yield is improved. The increased oil yield counterbalances the cost factor, which is needed for solvent heating (5). However, the stability of natural compounds does not always permit to operate at high temperatures. This has to be clarified before.

Volume Flow

The volume flow rate of desorption solvent plays an important role in percolation, since it determines the contact time between solvents and material to be extracted. High volume flow rates reduce residence time in raw material fixed bed column. At constant extraction time the extraction yield can be increased

due to a large solvent quantity used, if the plants constituents are easy extractable without mass transfer hindrance.

Agitation, Stirring

By mechanical agitation of raw material during maceration, the mass transfer film between liquid and solid phase becomes thinner. The diffusion rate thus increases and the same product yields are realized in substantial shorter times.

Parameters, which affect extraction yield and selectivity, are:

Degree of Grinding

Extraction of target compounds from finely grinded solid particles takes place faster than from rough particles. A high grinding degree thus causes faster equilibrium setting in maceration and shorter extraction times for both maceration and percolation.

By compounds with intracellular localization such as oils in seeds, the particle size has a special influence on extraction time and yield. The smaller the particles are, the higher is the oil quantity at identical extraction times. This results from the biological structure of the seeds. Large destruction of oil cells occurs by fine grinding and the compounds need only to be washed out. By coarse-grained seeds only compounds present at the particle surface can be easily extracted. The main oil mass is in inaccessible inclusions. Besides, the diffusion paths are comparatively long, so that an additional mass transfer resistance occurs. A too high grinding degree can however lead to increase pressure drops and blockages by percolation.

Solvent pH-Value

The pH-value of the used solvents affects the extraction selectivity. It has influence on the quantitative yield of the compounds to be extracted, but also on the nature and quantity of side components.

Degree of Lipophily

The degree of lipophily often has substantial influences on the selectivity, when using organic solvents or solvent mixtures. Lipophily designates the capacity of a substance to dissolve in non polar solvents. Any change of lipophily can change both the quantitative yield and the qualitative extract composition (6).

Additives

Additives are used to shift the distribution coefficient of the compounds to be extracted towards the extract phase, for example (6):

- Addition of low alcohols (e.g. ethanol) reduces solvent polarity for extraction with water.
- Addition of acids or bases (e.g. acetic acid or sodium hydroxide) leads to salt formation and avoid compounds dissociation.
- Addition of interface active agents (e.g. tenside) increases cell membrane permeability.

Process Design

The overview in Fig. 1 is the conceptual strategy, suggesting how all relevant parameters and their influence can be included in desorption process development. Starting from the raw material, there are three decision levels playing an important role. The following questions have to be clarified in these levels:

- Which preparation of the raw material has to be realized?
- How should the raw material constituents be disintegrated?
- Which desorption method has to be used?

The answers to these questions depend on the properties of the material system. Close co-operation between natural substance chemists and process engineers will be essential to improve centuries ago established operations.

After the questions above are successfully answered, the following methodical procedure is recommended to be chosen for process development:

- List of all relevant parameters and variation levels.
- Generation of a statistic experimental design plan for the experimental investigation in order to minimize experiments and prepare the experiment equipments.
- Realization of experiments and evaluation of results. Integration of the experimental evaluation into modeling and simulation to determine model parameters.
- Proposal of an equipment concept with information gained from experimental evaluation and model predictions.
- Purification of the extract solution obtained after desorption by means of other separation operations up to the desired specification.

EXPERIMENTAL SETUP

The proposed generic method for target compounds desorption was applied to a test system of interest. The objectives of the investigations were the quantitative analysis of desorption parameters, the identification of optimal operating conditions, and the generation of experimental data for model parameter estimation. Conclusions derived from this test system should be generalized by further studies.

Material

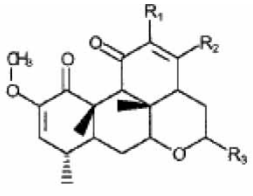
Wood of the neotropical specie *quassia amara* was used as test system for experimental investigations and was a donation of Triofio-M GmbH (Lahnau, Germany). The objective of the experiments was the selective desorption of two quassinoid compounds: quassin and neoquassin. Quassinoids are terpernoid compounds. Chemically, these molecules are seco-triterpene-δ-lactones (Fig. 2). They have important pharmaceutical and insecticidal properties and their intensely bitter nature make them ideal as bittering agent for beverage and foodstuffs.

Wood samples were prepared by milling and sieving the supplied dried coarse chips to obtain fractions of different mean particle sizes. These fractions were stored under room temperature. Desorption solvent was a 20% (w/w) water/ethanol solution. A chromatogram of an extract solution obtained after desorption is exemplary shown in Fig. 3. Besides the target components, side components are also desorbed. The desorbed solution was therefore regarded as a three components mixture of quassin (TC1), neoquassin (TC2) and side components combined under SC. All chemicals were obtained from Merck (Darmstadt, Germany) in analytical grad.

Experiments

Maceration and percolations experiments for different operating parameters were carried out and the target compound yield and selectivity were determine to evaluate the desorption process. The realized experiments can be summarized as follows:

- Quantitative evaluation of the operating parameters (particle size, solvent polarity and solvent pH-value)



		R_1	R_2	R_3
I.	Quassin	OCH_3	CH_3	=O
II.	Neoquassin	OCH_3	CH_3	HOH

Figure 2. Structure of quassinoids extracted.

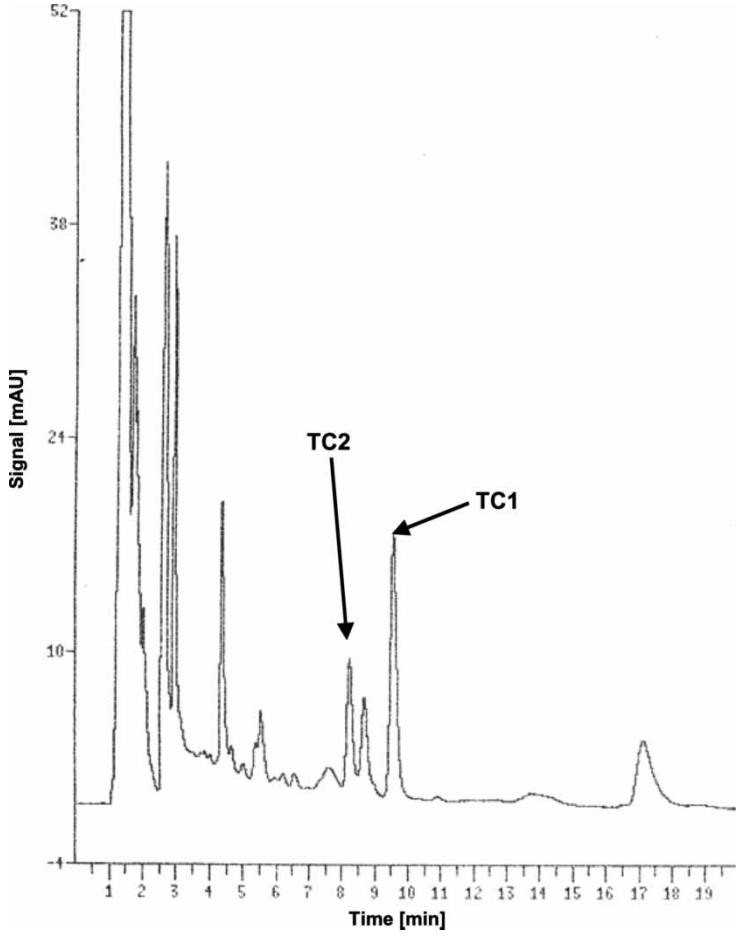


Figure 3. Chromatogram of an extract solution on a Eurospher-100 C18 column. UV detection at 254 nm. Solvent A: acetonitrile, solvent B: acetonitrile/water (40/60). Flow rate, 0.9 ml/min. Isocratic elution with 5% A and 95% B. Temperature, 27°C. TC1 = Quassin, TC2 = Neoquassin (α and β isomers).

- Comparison of maceration and percolation
- Purification of the extraction solution by chromatographic separation and liquid-liquid extraction.

Experimental Apparatus

For maceration experiments, grinded wood chips were loaded together with desorption solvent in a stirred tank with temperature control jacket. A reflux cooling was set on the stirred tank top to prevent solvent losses by evaporation.

Percolation experiments were performed on two different equipments. In the first equipment, 50 g of wood chips were packed as fixed bed into a glass column with temperature control jacket. A vessel with temperature control jacket containing the desorption solvent and provided with a valve was connected at the column inlet. Percolation was carried out by opening the solvent vessel valve and samples were collected at different times at tube outlet and analyzed.

In the second percolation equipment, 15 g of wood chips were packed into a stainless steel column with an inlet liquid distributor and an outlet liquid collector. The desorption solvent was pumped by a KronLab HD 2-200 solvent delivery system. Extract solution samples were taken at different times at the column outlet and analyzed.

Analytical Method

Extract solutions obtained after wood chips desorption were analyzed by HPLC. The analysis was performed on a Varian ProStar HPLC system equipped with a Varian ProStar 240 solvent delivery system, a Varian Photodiode Array Detector Model 330 and a Varian ProStar Autosampler Model 410. The column used was a 25 cm × 4 mm i.d. reversed-phase Eurospher-100 C18, 5 μm particle size. Two solvents (A: Acetonitrile and B: Acetonitrile/water (70/30)) were applied. The analyses were carried out by isocratic elution with 5% A and 95% B at a flow rate of 1 mL/min and by injection volumes of 10 μL. The column was maintained at 27°C and peak detection was done at 254 nm. Quassia powder containing a defined mixture of quassin and neoquassin was provided by Trifolio-M GmbH (Lahnau, Germany) and used as standard for analysis calibration and validation.

Yield and Selectivity Determinations

The evaluation of the experimental data was done using the following definitions for yield and selectivity:

- Component yield

$$A_c = \frac{\text{mass of component c extracted}}{\text{mass of component c in dry wood}} \tag{1}$$

- Total yield

$$A_{Total} = \frac{\text{mass of all components extracted}}{\text{mass of all components in dry wood}} \tag{2}$$

- Target component 1 selectivity

$$S_{TC1} = \frac{\text{mass of TC1 extracted}}{\text{mass of all components extracted}} \tag{3}$$

- Target component 1 and 2 selectivity

$$S_{TC1,TC2} = \frac{\text{mass of TC1 and TC2 extracted}}{\text{mass of all components extracted}} \quad (4)$$

The initial amount of extractable substance in the tested wood samples results from the highest component yield obtained after evaluation of all operating parameters. The following initial contents were obtained: 0,744 mg/g wood for TC1, 1.03 mg/g wood for TC2 and 21 mg/g wood for SC. Reference is mass of dry wood to a standard procedure checked due to reproducibility.

PROCESS MODELING

Modeling Approach

There are different modeling approaches used to describe desorption mechanism. A classification of these modeling approaches according to number and kind of considered mass transfer processes leads to the following possible groups (7):

- Models with extraction as a first order reaction (8, 9, 10)
- Models without concentration gradient in the solid phase (11, 12)
- Models with concentration gradient in the solid phase (13, 14, 15)
- Models considering adsorption/desorption equilibriums as well as chemical reactions in the solid phase (16, 17, 18).

While theses models differ in the description of solid phase behavior, the liquid phase description remains identical for all models. The approach used in this work is a model with concentration gradient in the solid phase. As shown in Fig. 4, this modeling approach is general, comprehensive, and illustrative, since intraparticle diffusion and external mass transfer are separately treated. The extraction driving force is the difference between mean solute molecule concentration in the solid phase and solute molecule concentration in the liquid phase. The concentration profile in the solid phase particles is approximated with a 2nd order parable.

Solid Phase Mass Balance

Mass transfer processes are assumed as isotherm and energy balances are therefore not considered. Diffusion processes within the solid particle are expressed through the 2nd Fick law with an effective diffusion coefficient D_e. For spherical particles, the following differential equation for the

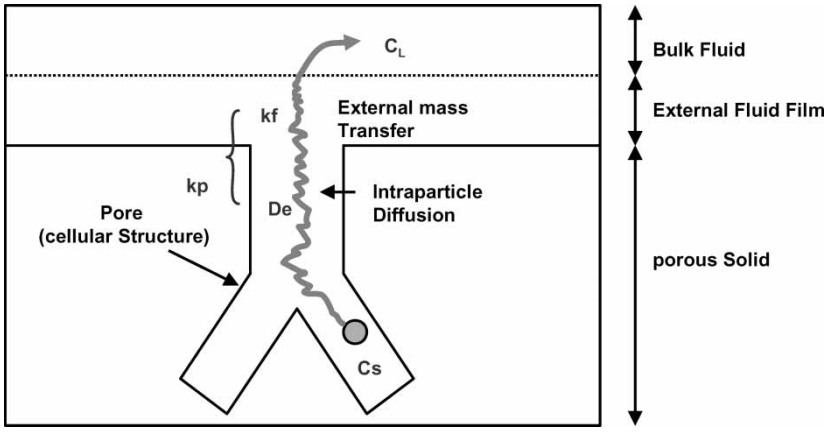


Figure 4. Schematic diagram of extraction mechanism (16).

time-depending solute molecule concentration within the particle is obtained:

$$\frac{\partial C_s(z,r,t)}{\partial t} = D_e \cdot \frac{1}{r^2} \cdot \frac{\partial}{\partial r}\left(r^2 \cdot \frac{\partial C_s(z,r,t)}{\partial r}\right) \tag{5}$$

The initial and boundary conditions are given as follows:

$$\left(\bar{C}_s(z,t)\right)_{t=0} = \bar{C}_{s,0} \tag{6}$$

$$\left(\frac{\partial C_s(z,r,t)}{\partial r}\right)_{r=0} = 0 \tag{7}$$

$$D_e \cdot \left(\frac{\partial C_s(z,r,t)}{\partial r}\right)_{r=R} = k_f \cdot [C_L(z,t) - C_s(z,R,t)] \tag{8}$$

K_f is the external mass transfer coefficient and $C_L\,(z,\,t)$ is concentration of the solute compound in the liquid phase. With the assumption of a parabolic concentration profile within the particle,

$$C_s(z,r,t) = b_1(z,t) + b_2(z,t) \cdot r^2 \tag{9}$$

a particle volume averaged concentration $\bar{C}_s\,(z,\,t)$ is determined, in order to replace the radius-dependent concentration within the particle. Thus the parameters $b_1\,(z,\,t)$ and $b_2\,(z,\,t)$ are not explicit needed. The solid phase mass balance can then be transferred into a simple form:

$$\frac{\partial \bar{C}_s(z,t)}{\partial t} = k_P \cdot a_P \cdot [C_L(z,t) - \bar{C}_s(z,t)] \tag{10}$$

The mass transport within the particle by pore diffusion and the mass transfer into the liquid phase by film diffusion are combined in an overall mass transfer coefficient:

$$k_P = \frac{5 \cdot k_f}{5 + B_i} \tag{11}$$

with

$$B_i = \frac{k_f \cdot R}{D_e} \tag{12}$$

The effective intra-particle diffusion and the external mass transfer coefficients are related by dimensionless Biot number B_i to compare the effect of internal and external mass transfer resistance involved in the desorption process. The larger the Biot number, the smaller the influence of the external mass transfer or the more largely the influence of the mass transport within the particle. When $B_i \gg 5$, the resistance of the intra-particle diffusion would dominate over the external mass transfer resistance (17).

The external mass transfer coefficient k_f is calculated with the correlation of Wakao and Funazkri 1978 (2). They give the following relationship of characteristic numbers for gases and liquids:

$$Sh = 2 + 1,1 \cdot Sc^{0,33} \cdot \mathrm{Re}^{0,6} \tag{13}$$

The Reynolds number Re is defined as formulated in equation (14).

$$\mathrm{Re} = \frac{u_z \cdot d_p \cdot \rho}{\varepsilon \cdot \eta} \tag{14}$$

ρ is the density of the desorption solvent and η its viscosity. The Sherwood number Sh and the Schmidt number Sc are calculated according to:

$$Sh = \frac{k_f \cdot d_p}{D_{12}} \tag{15}$$

$$Sc = \frac{\eta}{\rho \cdot D_{12}} \tag{16}$$

The molecular diffusion coefficient D_{12} was determined by the Wilke and Chang equation (19):

$$D_e = \frac{D_{12} \cdot \varepsilon_P}{2 - \varepsilon_P} \tag{17}$$

ε_P is the internal raw material porosity. The overall mass transfer coefficient k_P was determined by fitting simulated curves to experimentally obtained desorption curves.

Liquid Phase Mass Balance

To describe the concentration change of a solute molecule with time in the liquid phase, the following equation can be derived by performing a mass balance over a differential volume of the column:

$$\frac{\partial C_L(z,t)}{\partial t} = D_{ax} \cdot \frac{\partial^2 C_L(z,t)}{\partial z^2} - \frac{u_z}{\varepsilon} \cdot \frac{\partial C_L(z,t)}{\partial z} - \frac{1-\varepsilon}{\varepsilon} \cdot k_p \cdot a_P \cdot \left[C_L(z,t) - \bar{C}_s(z,t)\right] \tag{18}$$

The axial dispersion coefficient D_{ax} was determined from the Péclet number. The Péclet number describes the ratio between convection and dispersion in flowed packing as given in (19).

$$P\acute{e} = \frac{d_p \cdot u_z}{\varepsilon \cdot D_{ax}} \tag{19}$$

An empirical approximation of the Péclet number supplies equation (20) (20).

$$P\acute{e} = \frac{0{,}2}{\varepsilon} + \frac{0{,}011}{\varepsilon} \cdot (\varepsilon \cdot \mathrm{Re})^{0{,}48} \tag{20}$$

The initial and boundary conditions are:

$$(C_L(z,t))_{t=0} = 0 \tag{21}$$

$$\frac{u_z}{\varepsilon} \cdot (C_L(z,t))_{z=0} = D_{ax} \cdot \left(\frac{\partial C_L(z,t)}{\partial z}\right)_{z=0} \tag{22}$$

$$\left(\frac{\partial C_L(z,t)}{\partial z}\right)_{z=L} = 0 \tag{23}$$

RESULTS AND DISCUSSION

Effect of Particle Size

Wood chips with three different particle sizes (2.75, 1.5, and 0.25 mm) were extracted with desorption solvent at 70°C under maceration conditions. The mass ratio of wood chips to solvent was 1:10. Regarding the total yield, a clear dependence of achievable yield on wood chips particle size is observed. The total desorption yield increases when wood particle size decreases (Table 2). A particle size variation from 2.75 to 0.25 mm increases the total yield by 33%.

As shown in Fig. 5, the increase of the total yield is more pronounced on TC2 and SC. The TC1 yield remains approximately constant. Side components

Table 2. Effect of particle size on yield and selectivity

	Particle size		
	2.75 mm	1.5 mm	0.25 mm
A_{Total}[%]	74.4	78.6	99.1
S_{TC1}[%]	3.4	3.1	2.4
$S_{TC1,TC2}$[%]	8.6	8.3	7.0

are increasingly extracted when using small particles and desorption is therefore more unspecific. Thus, the SC yield rises by approx. 36% in the given example.

Effect of Solvent Polarity

15 g of wood chips (particle size 1.125 mm) were packed in a column with a diameter of 2.5 cm up to a bed height of 12.5 cm and extracted at 70°C. Two solvent polarities were examined: a first solution with 80% (w/w) water and a second solution with 25% (w/w) water. As Fig. 6 shows, a nearly identical total yield is obtained for both solvents. The compositions of the extract solutions obtained are however different. Contrary to TC1 and TC2, side components are better extracted by low solvent polarity (solution with 25% (w/w)

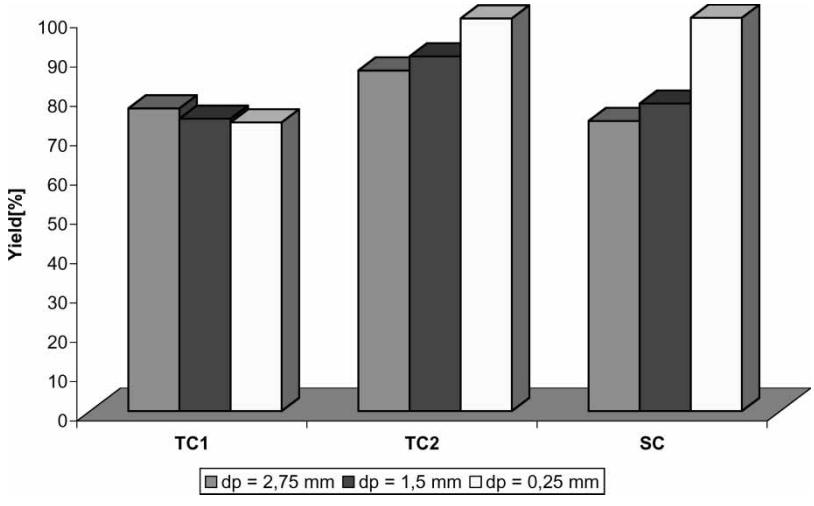


Figure 5. Yield obtained by desorption of wood chips with different particle sizes. Desorption with water/ethanol (80/20) at 70°C for 2 h under maceration. Ratio of solvent mass to wood mass: 10/1. TC1 = Quassin, TC1 = Neoquassin and SC = Side components.

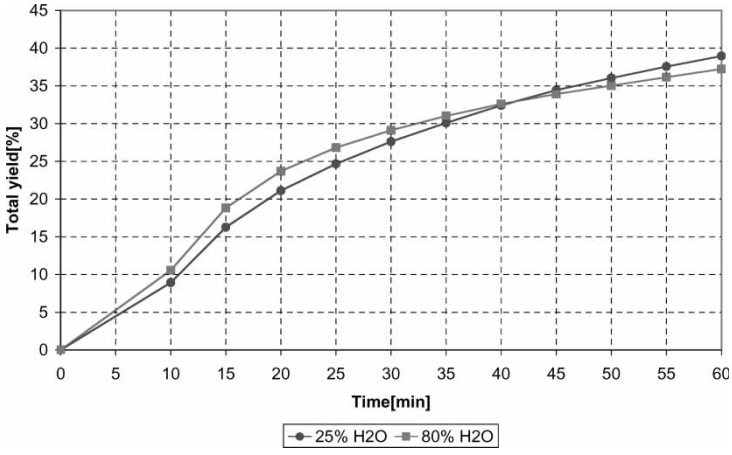


Figure 6. Effect of solvent polarity on total yield. Desorption of 15 g wood chips (1.125 mm particle size) packed as fixed bed (column length: 12.5 cm, column diameter: 2.5 cm) at 70°C. Flow rate: 5 mL/min.

water). With the more polar solution, a higher TC1 yield can be reached as shown in Fig. 7 and also a higher selectivity can be obtained, see Table 3.

A similar behavior can also be observed for TC2. If one combines TC1 and TC2, the extraction with the solvent containing 80% (w/w) water gives a selectivity of 4.7%. This corresponds to a selectivity increase of 97% in comparison to the solvent with 25% (w/w) water. In conclusion, a reduction

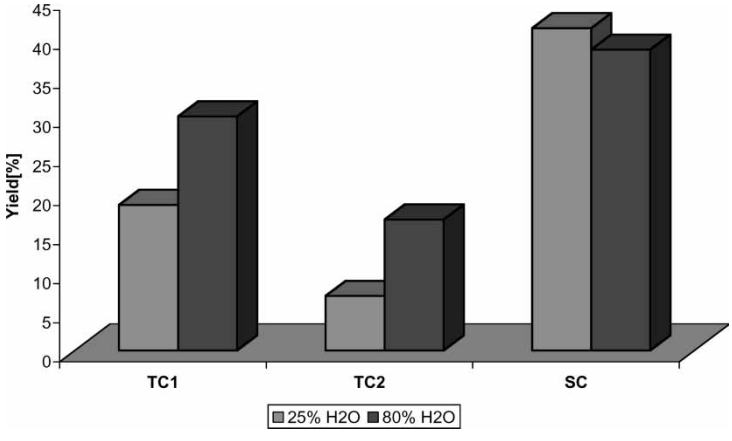


Figure 7. Effect of solvent polarity on component yield. Desorption of 15 g wood chips (1.125 mm particle size) packed as fixed bed (column length: 12.5 cm, column diameter: 2.5 cm) at 70°C. Flow rate: 5 mL/min. TC1 = Quassin, TC2 = Neoquassin and SC = Side components.

Table 3. Effect of solvent polarity on yield and selectivity

	25% H_2O	80% H_2O
A_{Total} [%]	39	37.2
S_{TC1} [%]	1.6	2.6
$S_{TC1,TC2}$ [%]	2.4	4.7

of the solvent polarity leads to lower TC1 and TC2 yields, but higher SC yield, which means a decrease of the selectivity (Table 3).

Effect of Solvent pH-Value

Solvents with pH-values of 9 and 4 were made by adding sodium hydroxide and acetic acid respectively in an initial desorption solvent with 80% (w/w) water. 15 g wood chips (particle size 1.5 mm; fixed bed length 12.5 cm, fixed bed diameter 2.5 cm) were then treated with the prepared solvents at a temperature of 70°C and with a solvent volume flow rate of 5 mL/min. As Fig. 8 shows, higher total yields are achieved when using acid and alkaline media.

By desorption with a solvent of pH-value 9, the TC1 yield increases by 75%, the TC2 yield increases by 79% and the side components yield

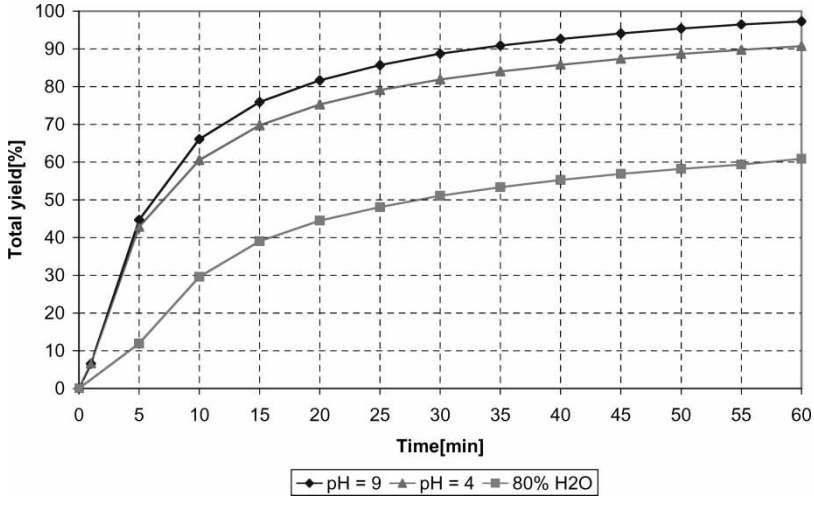


Figure 8. Total yield dependence from solvent pH-value. Desorption of 15 g wood chips (1.5 mm particle size) packed as fixed bed (column length: 12.5 cm, column diameter: 2.5 cm) at 70°C. Flow rate: 5 mL/min. Solvent with pH value of 9 and 4 prepared by respectively adding sodium hydroxide and acetic acid to water/ethanol (80/20) initial solution.

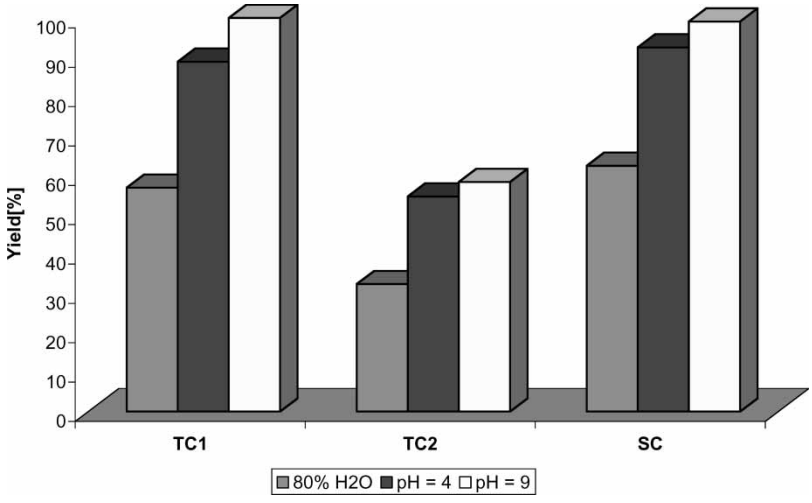


Figure 9. Component yield by different solvent pH-value. Desorption of 15 g wood chips (1.5 mm particle size) packed as fixed bed (column length: 12.5 cm, column diameter: 2.5 cm) at 70°C. Flow rate: 5 mL/min. Solvent with pH value of 9 and 4 prepared by respectively adding sodium hydroxide and acetic acid to water/ethanol (80/20) initial solution. TC1 = Quassin, TC2 = Neoquassin and SC = Side components.

increases by 58% (Fig. 9). TC1 and TC2 tend probably to dissociate more than side components. The addition of sodium chloride and acetic acid avoid dissociation and thus improve their yield. The TC1 selectivity increases by 10% (Table 4).

Comparison of Maceration and Percolation

Percolation experiments were carried out in a fixed bed with a diameter of 2.5 cm and a height of 36.5 cm corresponding to a volume of 179 ml. The bed was filled with 50 g wood chips (particle size 0.25 mm) and extracted for one hour. The ratio of solvent mass used to wood mass was approx. 12. To compare the obtained results, maceration experiments were performed with the same extraction time and mass ratio of solvent to wood.

Table 4. Effect of solvent pH-value on yield and selectivity

	pH = 9	pH = 4	80% H_2O
A_{Total} [%]	97.3	90.7	60.9
S_{TC1} [%]	3.4	3.2	3.1

For the study raw material, no serious differences can be observed between maceration and percolation results for the realized laboratory experiments. For the chosen conditions, equitable TC1 yields are obtained for both operational modes. Slightly higher TC2 and total yields are observed when extracting under maceration conditions (Table 5).

In contrast to classical solid extractions, where higher solute initial concentrations in raw material are often present (e.g., oil extraction from oil seeds); TC1 and TC2 yields are relatively low. Desorption is strongly controlled by diffusion in particle pores. By maceration with a solvent mass to wood mass ratio of 10:1, the extraction is probably less limited by equilibrium, due to the low initial solute concentrations in raw material. The good solvent and wood chips mixing in stirred tank in fact provides an improved mass transport within the particles.

Purification of Extract Solution

Since we intend to make a priori suggestions for desorption downstream process, a purification of the extracted solution was carried out by chromatographic separation and liquid-liquid extraction. Although the investigations were not detailed, they should allow assessing the potential of these unit operations for the purification of the extract solution. The chosen purification strategy for the extract solution is schematically represented in Fig. 10. Before chromatographic separation, the extract solution obtained after desorption was first concentrated. A sample of the concentrated extract solution was then separated analytically in a HPLC column. The obtained fractions were then analyzed. Before chromatographic analysis, side components in the concentrated extract solution constituted 92% (w/w) of the extracted mass. The fractions obtained after chromatographic separation are nearly pure solutions containing only TC1 and TC2. The fraction containing TC1 has a purity of 93%. Chromatography can thus crucially contribute to the extract solution purification. Chromatography is scaled up from the analytical method to preparative and technical scale by increasing the particle diameter of the adsorbens to 15 μm and maximizing the feed amount

Table 5. Comparison between maceration and percolation

	Percolation	Maceration
A_{TC1} [%]	77.2	73.4
A_{TC2} [%]	72.7	99.9
A_{SC} [%]	97.2	100
A_{Total} [%]	95.5	99.1
S_{TC1} [%]	2.6	2.4
$S_{TC1,TC2}$ [%]	6.1	7.0

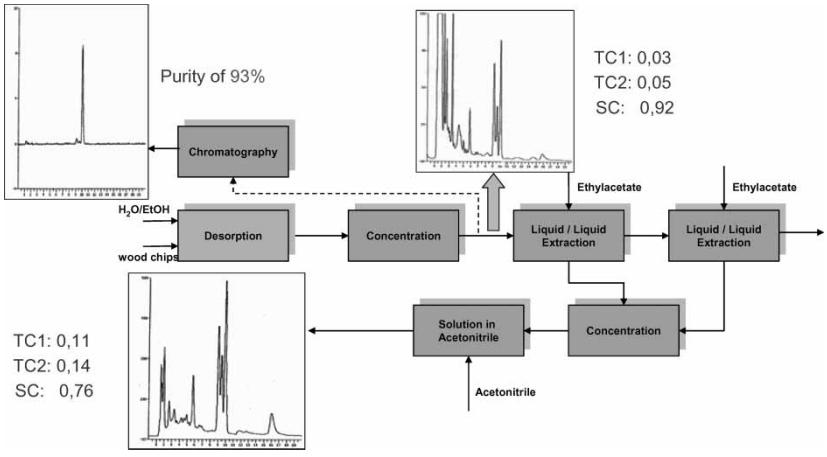


Figure 10. Schematic representation of extract solution purification.

injected and the flow rate. The scale-up approach is described in detail in (21). Typical productivities and separation costs given in literature for reversed phase separation (21) could be gained. Further work will be implied to try to transfer the method to normal phase in order to reduce separation costs further on.

For liquid-liquid extraction experiments, the concentrated extract solution was twice successively extracted with ethyl acetate in the cross current operational mode. In the first stage an ethyl acetate (w)/extract solution (w) ratio of 3:1 was used. The aqueous phase obtained after this stage was then re-extracted with ethyl acetate by a ratio of 1:1. The organic phases of both stages were mixed and concentrated. Since the ethyl acetate presence in the solution to be analyzed damages the HPLC packing material, the obtained extract was dissolved in acetonitrile and analyzed. The side components concentration amounts 76% (w/w) after liquid-liquid extraction. Compared with concentrations before extraction, the TC1 and TC2 concentration in the extract obtained after liquid-liquid extraction are increased by 213%. So, coupling of desorption, extraction, and chromatography in this order of separation sequence is the efficient combination for the production of TC1 and TC2.

Simulation

Two typical forms of desorption curves were observed at the fixed bed outlet during simulation (Fig. 11): Desorption curves with washing phase and desorption curves without washing phase. In the first form, similar to any drying process, a washing phase is observed, resulting in stationary

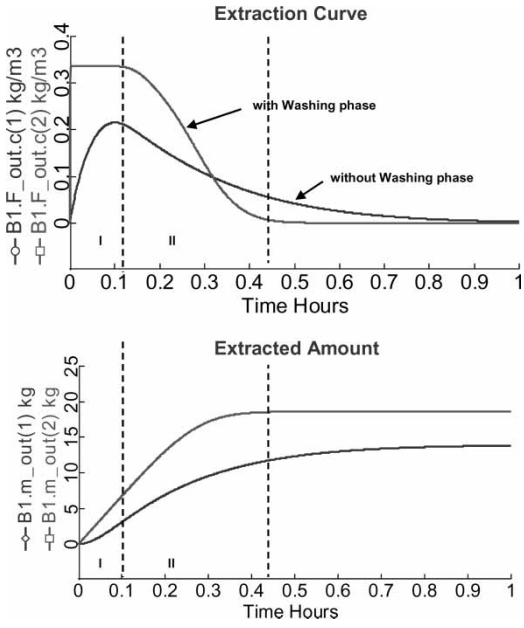


Figure 11. Simulation of different types of extraction curves.

solvent loading (1st step). The solvent loading subsequently decreases and tends against zero (2nd step). This curve type represents the case, by which a high initial solute concentration in raw material is available and quite easily accessible. During the 1st step (washing phase), the mass transfer is controlled only by the mass transfer at the solid/liquid interface. The solute concentration in the liquid phase depends on external mass transport and solvent mass flow rate. In the 2nd step (diffusion phase), solutes present on the particle surface are ready extracted. Desorption solvent must now cover longer diffusion paths within the particles and this leads to an increasing transport resistance.

In the case of desorption without any washing phase, a constantly falling solute concentration is registered immediately from extraction start. The extraction takes place at any time within the particles and at the particle surfaces. The mass transport resistance becomes higher in the course of extraction.

Parameters Estimation and Model Validation

For model parameters determination in laboratory scale, experimental curves of TC1 and TC2 yield obtained after desorption of 50 g wood chips (particle size of 1.125 mm) at 70°C were fitted to simulation curves. The result is graphically shown in Fig. 12. Desorption was carried out at volume flow

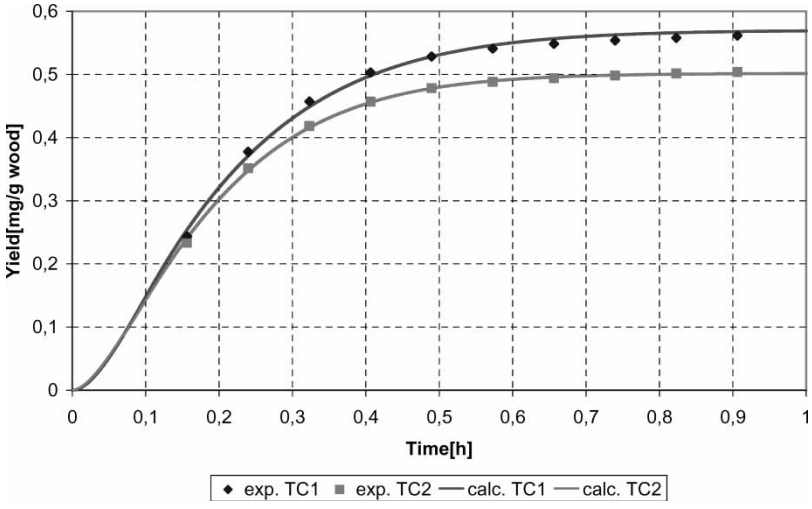


Figure 12. Fitting simulated quassin and neoquassin yield curves to experimental data. Desorption of 50 g wood chips (1.125 mm particle size) packed as fixed bed (column length: 36.5 cm, column diameter: 2.5 cm) at 70°C. Flow rate: 11.64 mL/min.

rate of 11.64 mL/min in a fixed bed of 36.5 cm length and 2.5 cm diameter. The fitted model parameter is the overall mass transfer coefficient (k_P). All the other model parameters result from equations (11), (12), and (13). All important data are summarized in Table 6.

The values of the estimated intraparticle effective diffusion coefficients lay within the range of data published in literature (7). The target components 1 and 2 do have the same kinetic behavior, since their external mass transfer coefficients (k_f) and their intra particle effective diffusion coefficients (D_e) are rather identical. The Biot numbers are larger than 5, indicating that target compounds desorption is controlled by intraparticle diffusion as postulated by comparison of maceration and percolations results.

The parameters determined above were used to predict a percolation under different operation conditions. 15 g of wood chips (particle size of 1.125 cm) are extracted in a column with 12.5 cm length and 2.5 cm diameter at the volume flow rate of 5 mL/min. The simulation results are represented in the Fig. 13. A good agreement between experiments and

Table 6. Model parameters estimation

	k_P $[10^{-3}\ 1/h]$	k_f $[10^{-2}\ m/h]$	D_e $[10^{-7}\ m^2/h]$	B_i $[-]$
TC1	2.18	1.29	3.84	19
TC2	2.26	1.31	3.92	19

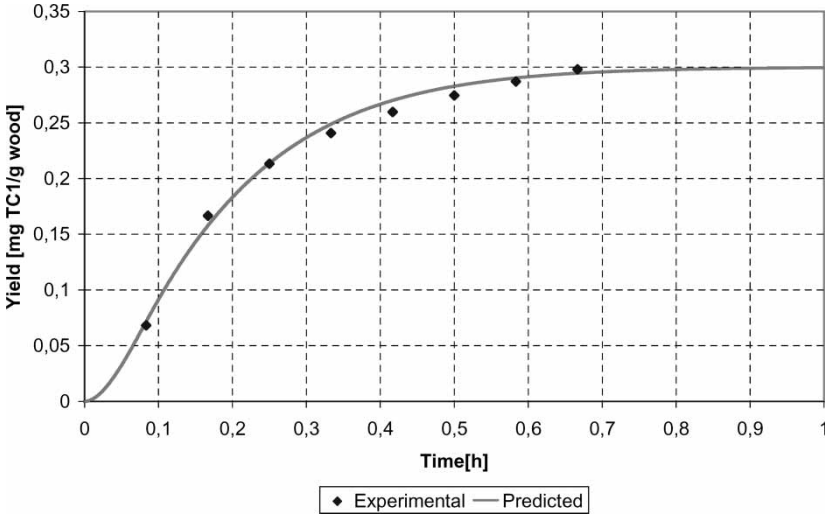


Figure 13. Comparison of experimental and simulated quassin yield. Desorption of 15 g wood chips (1.125 mm particle size) packed as fixed bed (column length: 12.5 cm, column diameter: 2.5 cm) at 70°C. Flow rate: 5 mL/min.

simulation can be observed indicating that the model parameters are nearly constant in the volume flow rate range investigated.

SUMMARY AND CONCLUSIONS

Due to the results of this study it can be concluded that the proposed systematic process development and design approach could be successfully applied the extraction of natural compounds from plant sources.

Process modeling combined with experimental model parameter determination in laboratory scale with help of standardized laboratory mini-plant equipment for each needed unit operation proved to be applicable to the complex natural molecules. The operation conditions of each unit which contributes to product purification—solid phase extraction, extraction and chromatography—can thus be varied by simulation studies and an optimal process sequence can be proposed. Further studies with different examples will be done, to generalize and extend the design methodology.

NOTATION

ε	Fixed bed porosity [−]
ε_P	Particle porosity [−]

ρ	Extraction solvent density [kg/m^3]
η	Extraction solvent dynamic viscosity [Pas]
a_P	Specific surface area [m^2/m^3]
A_{Total}	Total yield [%]
A_C	Component C yield [%]
B_i	Biot number [−]
C_L	Solute concentration in the liquid phase [kg/m^3]
C_s	Solute concentration in the solid phase [kg/m^3]
$\bar{C}_s$	Mean solute concentration in the solid phase [kg/m^3]
d_p	Particle diameter [m]
D_{12}	Molecular diffusion coefficient [m^2/h]
D_{ax}	Axial dispersion coefficient [m^2/h]
D_e	Effective intra-particle diffusion coefficient [m^2/h]
k_f	External mass transfer coefficient [m/s]
k_p	Overall mass transfer coefficient [1/h]
L	Fixed bed length [m]
$Pé$	Péclet-number [−]
r	Radial position in spherical particle [m]
R	Radius of spherical particle [m]
Re	Reynolds number [−]
Sc	Sherwood number [−]
Sh	Schmidt number [−]
S_{TC1}	Selectivity referring to TC1 [%]
$S_{TC1,TC2}$	Selectivity referring to TC1 and TC2 [%]
u_z	Superficial velocity [m/h]

Abbreviations

SC	Side components
TC1	Target component 1, Quassin
TC2	Target component 2, Neoquassin

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