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Process design for integration of extraction, purification and formulation with alternative solvent concepts



Maximilian Sixt, Iraj Koudous, Jochen Strube*

Institute for Separation and Process Technology, Clausthal University of Technology, 38678 Clausthal-Zellerfeld, Germany

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ABSTRACT

Methods of Green Chemistry are in the meantime established in process design for extraction of natural products [1]. Moreover, natural products do have the inherent societal benefit of being a priori bio-degradable and therefore do not cause any additional wastewater and recycling problems in hospitals, cities and municipalities or environmental enrichment [2].

Nevertheless, those inherent benefits could be easily compromised if they are not combined with the design and operation of fully integrated processes in manufacturing. One isolated action of Green Chemistry is not sufficient to gain the entrepreneurial balance of economy and ecology with competitive manufacturing, new marketable products, and sustainability. While any process modification could be implemented in substituting simply one existing step, a fully integrated new process needs to be set up to exceed the existing benchmark or best practice and to be transferred into manufacturing.

Finding alternative solvents and enhancing mass transfer in extraction need to be integrated. This integration into a complete process from extraction over purification to formulation, considering recycling at all steps, is a complex task which could not be fulfilled on a purely experimental basis. The efforts would be too high and costly. Therefore, the paper reviews the existing status shortly and exemplifies based on a case study, choosing 10-deacetylbaccatin III as a typical example, a theoretical approach in thermodynamics and process modeling, and how they can contribute to an alternative process design. Still, these steps in conceptual process design and basic engineering seem to be the major challenge in industrial acceptance of alternative ideas.

The authors have described the transfer into innovative manufacturing concepts already elsewhere [1–3].

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1. Introduction

The need for natural, plant-based products in food, cosmetic and pharmaceutical industry is still increasing [1,2,4]. In 2011, the annual turnover with phytopharmaceuticals alone was about \$100 billion, corresponding to

a market share of 25% of the worldwide pharmaceutical market [5]. To meet these needs in the future as well, optimization of extraction and purification techniques for the important substances is needed. One special focus is on new products, where a methodical approach in process development is of major importance, especially because the process design is even nowadays widely experience-based [6,7]. Last but not least, the development costs and the time to market depend on the moment in process development, where optimization

* Corresponding author.

E-mail address: strube@itv.tu-clausthal.de (J. Strube).

possibilities to take course are spotted and realized [8]. Heuristics and systematic approaches for the extraction of plant-based substances have been described in the literature and more are still under development [4,6–15].

The aim of this work is to show the model-based design for the extraction of a typical example system like 10-deacetylbaecatin III (10-DAB) from European Yew (*Taxus baccata* L.), based on a methodical and molecular structure-orientated procedure. 10-DAB is used as an educt for anti-cancer drugs. With the quantum-chemical model COSMO-RS [16] relevant physico-chemical data of the important substances, like the solubility of 10-DAB in various solvents or their mixtures, are determined. The gained values are experimentally validated. Thereby optimization can take place early in the process development, so experimental efforts and the corresponding costs are reduced. Here the application of thermodynamically consistent methods, e.g., COSMO-RS for the determination of physico-chemical properties of single components in complex mixtures like phytoextracts, is investigated and optimizations are shown.

The solid-liquid extraction of 10-DAB from yew needles will be optimized with a rigorous model in the frame of Green Extraction. This is followed by a suitable process selection for the extraction and purification of 10-DAB. With this process, guidelines of the Green Chemistry like the reduction of the energy demand, the efficient use of renewable resources and the appliance of alternative additives will be implemented. On the basis of a feasibility study, the new design process is assessed. An already patented process serves as a benchmark.

2. Green extraction of natural products

Generally, Green Chemistry is associated with the design and realization of processes that are performed without the use or the appearance of hazardous substances. Chemat et al. [17] broadened and substantiated this general definition of Green Chemistry for the extraction of plant-based substances as follows: “Green Extraction is based on the discovery and design of extraction processes which will reduce energy consumption, allows the use of alternative solvents and renewable natural products, and ensures a safe and high quality extract/product” [17]. Moreover, three categories were developed, to realize green extraction either in lab- or in production-scale [17].

1. Improving and optimization of existing processes.
2. Using non-dedicated equipment.
3. Innovation in processes and procedures but also in discovering alternative solvents.

The following is an overview of recent topics of the state-of-the-art in Green Extraction. This includes alternative and green solvents plus innovative, mass-transport enhancing extraction methods. In the very focus of this work are the first and the second of the three categories,

proposed by Chemat et al.: “Improving and optimization of existing processes” and “Using non-dedicated equipment”.

2.1. Alternative solvents

Recent regulations put the operators of processes with conventional organic solvents increasingly under pressure. Many of these solvents are highly flammable, volatile and often toxic. Moreover, they are jointly responsible for environmental pollution and the greenhouse effect. In the final product there must be proven that potential solvent traces pose no risk to health [17]. This is linked to high effort and costs so there is even more focus on alternative solvents in recent research and industrial application.

An already widespread green solvent is ethanol. Among other advantages, this solvent can be produced by fermentation and is cost effective, easily available and biodegradable. Moreover, it is a commonly used agent in the chemical industry, so corresponding processes are already established.

Terpenes, like α -pinene or δ -limonene, are available from natural sources as well. These substances have been successfully used for the extraction of fats and oils [18].

Another promising approach is the pressurized hot water extraction which is also called sub-critical water extraction. The polarity of water can be changed over a wide range, only by changing its temperature and pressure. This is due to the water's easily changeable dielectric constant ϵ . Under normal conditions, the dielectric constant of water has a value of 80 and water has its commonly known, polar properties. If both temperature and pressure are increased to 250 °C and 40 bar, the dielectric constant changes to a value of 27. Under those conditions, the polarity of water is comparable to that of ethanol [19].

Another green solvent which is already in use for the extraction of coffee and hop, is supercritical CO₂. This process is performed with pressures up to 3000 bar and moderate temperatures of about 35 °C. After the extraction process, a simple pressure drop causes the CO₂ to change its state to the gas phase again. By that, it can easily be separated which is the most important advantage of the procedure. High investment costs and problems in performing a continuous process design are potential drawbacks [17,20,21].

As far as green solvents are concerned, ionic liquids (ILs) and deep eutectic solvents (DESSs) are of increasing interest in recent publications [1,22–24]. Ionic liquids and DESSs are mixtures of solids where the mixture's melting point is far below the melting point of each individual substance. Commonly, DESSs are mixtures of hydrogen-bond-acceptors and -donors. The low melting point is considered to be caused by the formation of hydrogen-bonds between these acceptors and the corresponding donors [22]. ILs and DESSs have a very low vapor pressure, therefore they are considered to be green solvents, because they cannot evaporate and thus are not able to escape from the process [1]. It can be assumed that there is an ideal IL or DES for every process due to the limitless combination possibilities of available salts. As far as the design of separation processes is concerned, the non-volatility of ILs and DESSs is the major drawback. The solvent can no longer be separated by

simple distillation. At the present state that is considered to be the most challenging part. This is underlined by the fact that there are only concepts of integrating ILs and DESs into downstream processing but no scale-up to an industrial plant was done, yet [1].

Besides the above mentioned green solvents, further alternatives are described, e.g., 2-methyl-tetrahydrofuran as a possibility to replace the widely used tetrahydrofuran (THF). 2-methyl-tetrahydrofuran is available through natural sources and has superior physico-chemical properties, thus processes can be performed more efficiently and cost saving, only to list some of the advantages [25,26]. Table 1 provides an overview of alternative solvents. Herein the *n*-hexane which is used for extraction of fat and oils, is listed as a benchmark. It has been successfully replaced by an agro-solvent [18].

2.2. Mass transport-enhancing methods

In the focus of Green Extraction, mass transport-enhancing methods, like microwave-assisted, or ultrasound-assisted extraction ones, provide the necessary potential to accomplish processes faster, more gentle and with less solvent amounts than comparable conventional processes. An overview of these methods is outlined below. Although there is a wide variety of mass transport-enhancing methods, only the two examples above are outlined because of recent publications of the institute [27].

2.2.1. Microwave-assisted extraction (MAE)

Because of high investment costs, microwave-assisted extraction is mainly used for extraction of valuable substances such as active pharmaceutical ingredients, components for functional foods and bioactive compounds. By the application of microwaves, intracellular water of the plant material vaporizes. This is associated with an expansion, thus leading the cells to burst and release their ingredients. The main advantages are a reduced solvent consumption compared to conventional

extraction processes, a shorter extraction time, high yield and selectivity. Moreover this process can easily be automated and fulfills the guidelines of GLP; thus it is suitable for the pharmaceutical industry [1].

2.2.2. Ultrasound-assisted extraction (UAE)

The ultrasound-assisted extraction was developed in the 50s of the last century and has been established as a standardized process, suitable for all plant materials. The basis of this process is the cavitation. Driven by ultrasound, gas bubbles are formed in the water. They grow to a certain size and then finally burst. This leads to local pressure peaks of some thousands of bars which cause high shear stress to the cell walls disrupting them and releasing their ingredients. The ultrasound-assisted extraction has to be carried out under efficient cooling to protect heat-sensitive substances, because the main part of the applied energy is transferred into heat. Besides the needed low temperature level of the extraction process, a high yield and a short process time are the main advantages of the procedure, compared to conventional extraction techniques. Due to the cavitation, the cells of the plant material are highly disrupted. These small particulates tend to cause problems in solid-liquid separation [1,27].

All of the techniques mentioned above serve to achieve the principles of Green Chemistry. With MAE and UAE, the amount of organic solvents can be reduced dramatically, so waste and energy for solvent recycling are reduced as well. By extraction with pressurized hot water (PHWE) or supercritical CO₂ organic solvents can be avoided in the whole process thus being “green” by definition. For a more detailed summary of benefits of Green Extraction, the authors highly recommend the following literature [28].

2.3. Improving and optimization of existing processes

Besides a complete change and redesign of existing processes towards alternative solvents and mass transport-enhancing methods like ultrasound-assisted or microwave-

Table 1
Alternative solvents according to [17].

Solvent	Extraction technique (Application)	Solvent power			Health & safety	Cost	Environmental impact
		Polar	Weakly polar	Non-polar			
Solvent-free	Microwave hydrodiffusion and gravity (antioxidants, essential oils)	+++	+		+++	+	+++
Water	Pulse electric field (antioxidants, pigments)	+++	+		+++	+	+++
	Steam distillation (essential oils)	++	+		+	++	+
	Microwave-assisted distillation (essential oils)	+++	+++	+	+	+	++
CO ₂	Extraction by sub-critical water (aromas)	+	++		+	+	+
	Supercritical fluid extraction (decaffeination of tea and coffee)	–	+	+++	+	+	+
Ionic liquids	Ammonium salts (artemisinin)	–	+	+++	–	–	++
Agrosolvents	Ethanol (pigments and antioxidants)	+	+			++	+
	Glycerol (polyphenols)	+	+		–	+	+
	Terpenes such as 6-limonene (fats and oils)	–	–	++	–	+	+
Benchmark: petrochemical solvents	<i>n</i> -Hexane (fats and oils)	–	+	+++	–	++	–

assisted extraction, optimization of existing processes can be a possibility to increase their efficiency, as well. By that, aims of a Green Chemistry approach, like reducing the amount of plant material, additives and energy consumed, can also be achieved.

In the literature, criteria and approaches for process design are described and still under development [6,11]. Besides for process design, these methods are suitable for process optimization, as well. A combination of rigorous modeling and a model parameter determination by design of experiments (DOE) shows the highest potential for cost efficient and fast optimization [4,6,9,10]. An overview of modeling and model parameter determination is given in Fig. 1.

Nowadays even the development of new processes for phytoextraction is mostly experience-based [6,7]. Thus thermodynamic aspects and a molecular structure based approach have to be taken into account for the new development and optimization of processes. A promising method is the property model COSMO-RS which will be described in detail in Section 4.2. If neither physico-chemical data are available for the interesting substances of the feed in commonly used databanks like Reaxys [29] or the Dortmund Datenbank [30] nor can they be calculated by property models, feed characterization provides the possibility to design single unit operations based on thermodynamic aspects and furthermore gain data for modeling [6,11,31]. This is done by measuring characteristic parameters of corresponding unit operations. As already shown elsewhere [31], feed characterization can be performed reproducibly with small sample amounts. Fig. 2 provides an overview of the various methods of this procedure.

For example, vapor–liquid equilibria can be determined by distillation. The distribution coefficient of a substance in two immiscible phases is measured on lab scale by shake

flask experiments. The polarity of the corresponding substances is measured by chromatography, while crystallization provides solubility values [11]. For this approach, not all unit operations must be taken into account for process development or optimization. If the target component is a solid, the estimation of a vapor–liquid equilibrium is useless [11].

In this work, a new process selection and optimization of an already patented process as a benchmark is done. This takes place on the basis of feed characterization and the property model COSMO-RS to fulfill aims of the Green Chemistry such as the reduction of energy and solvent consumption.

2.4. Alternative solvent selection in solid–liquid extraction

The choice of a suitable solvent for extraction is of major importance for the entire process. Therefore, some aspects of solvent selection are listed below [6].

- **Solubility:** A high solubility of the target component is the most important criterion for the solvent selection. The higher the solubility, the lower is the necessary solvent amount.
- **Selectivity:** The distribution of side components with regard to the target component is called selectivity. A high selectivity towards the target component is able to reduce the necessary purification effort, due to a reduced amount of side components.
- **Recycling capability:** Recycling capability is of high financial interest because the solvents are often one of the most cost-intensive parts of extraction processes. Especially if the solvent is recycled by distillation, a low heat of evaporation is desirable to keep the costs for solvent recycling small.

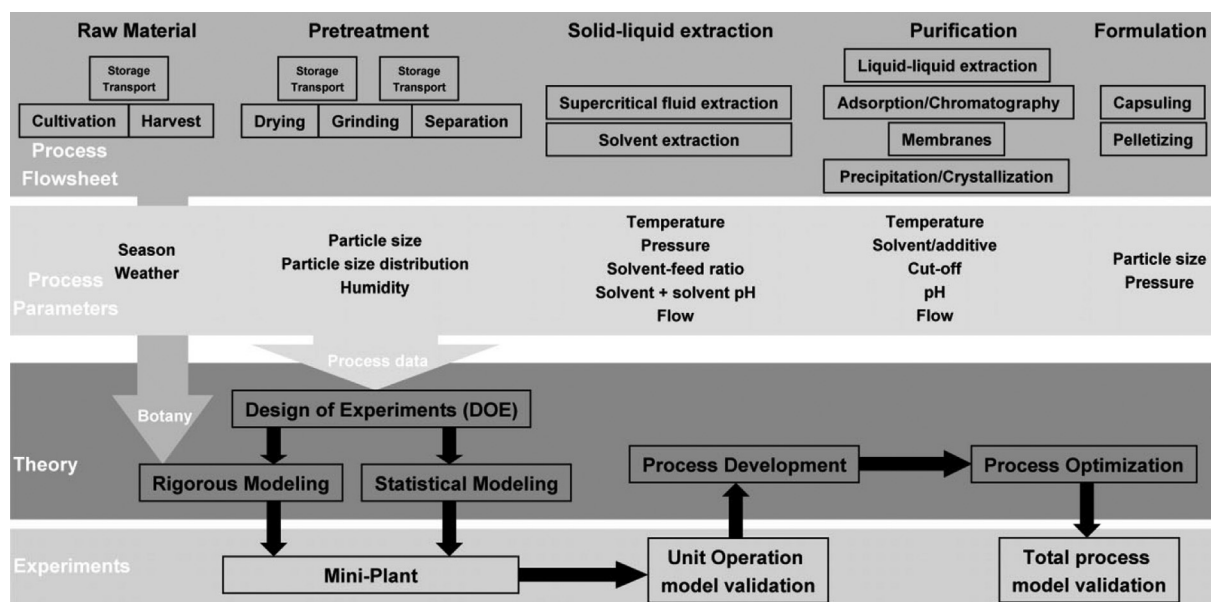


Fig. 1. Chemical engineering process design approach according to [6,8].

- **Toxicity:** Especially in the food industry, the toxicity of the solvents is of major importance. As a consequence, even solvents which are not the best choice according to the terms listed above, are chosen. Often water, ethanol and acetone are used.

Furthermore, aspects like corrosiveness, density and surface tension as well as the price and the accessibility are factors that should be taken into account in solvent selection.

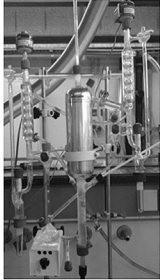
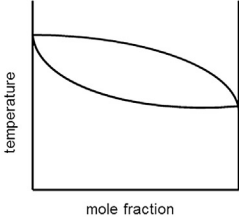

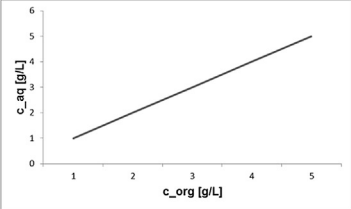

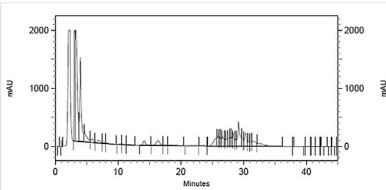
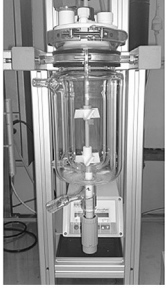
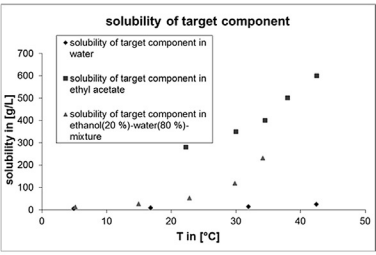
Unit Operation	Equipment	Measuring parameters	
<p style="text-align: center;">Distillation</p>			<p style="text-align: center;">Boiling curve</p>
<p style="text-align: center;">Liquid-Liquid Extraction</p>			<p style="text-align: center;">Partition Coefficient</p>
<p style="text-align: center;">Reversed/normal phase chromatography</p>			<p style="text-align: center;">Hydrophobicity</p>
<p style="text-align: center;">Crystallization</p>			<p style="text-align: center;">Solubility</p>

Fig. 2. Feed characterization according to [11].

Besides experimental methods, there are some models for solvent selection. A rather simple one is the so-called Hildebrand solubility parameter, as shown in Eq. (1) [8].

$$\delta = \sqrt{\frac{\Delta H_v - R \cdot T}{V_m}} \quad (1)$$

To calculate the Hildebrand solubility parameter, only properties of pure substances, like the molar heat of evaporation ΔH_v and the molar volume V_m , are needed. Furthermore, the universal gas constant R and the absolute temperature T are taken into account. Because the Hildebrand solubility parameter cannot reproduce mixture effects, it is not suitable for predicting solubility values of plant-based substances in phytoextracts. Moreover, this model is not applicable for complex molecules. Therefore, the more precise solubility model of COSMO-RS, which will be described in Section 4.2, is used in this work.

2.5. Purification strategy in green extraction

The basic approach in process selection and design is shown in Fig. 3. If the relevant target and side components of the feed are known and there are physico-chemical data available in databanks like Reaxys or the Dortmund Datenbank, a molecular structure based design of respective unit operations is possible. This also applies if physico-chemical data are not available but can be calculated with methods like COSMO-RS, PC-SAFT, UNIFAC or NRTL. If both methods are not applicable, the properties of pure substances have to be determined experimentally e.g., the solubility. For this to happen, pure reference substances can either be ordered or have to be extracted and purified on miniplant scale. An alternative approach is the feed

characterization described in Section 2.3. Thus relevant parameters for potential unit operations like the distribution coefficient can be determined and used for process design, modeling and simulation studies [11].

3. Materials and methods

3.1. European Yew (*T. baccata* L.)

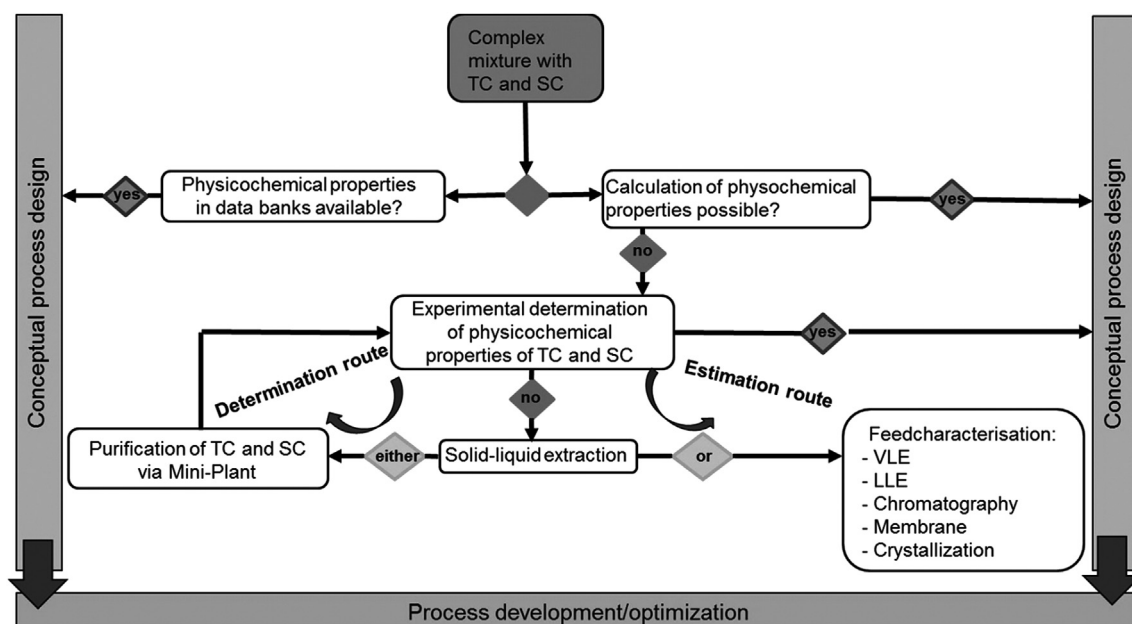
The European Yew (*T. baccata* L.) is an evergreen plant which grows as a tree or bush depending on its growing conditions. Every part of the plant, apart from the red seed covering, contains toxic alkaloids, also called taxanes. Especially toxic are the needles with a taxane content of about 0.6–2% by weight. One of these taxanes is 10-deacetylbaccatine III (10-DAB) which is an educt for the anti-cancer drug Paclitaxel. This medicinal drug is used mainly against breast, lung and ovarian cancer [32,33].

3.2. Storage and pretreatment of the raw material

The yew needles are air dried and have a residual moisture of about 8% by weight. They are stored in a cooling chamber at 8 °C. For maximization of the raw material's mass transfer area during solid-liquid extraction, the needles are ground in a knife mill Retsch Grindomix GM 2000 for 4 s at 4000 rpm. The particulates are later on classified with sieves to determine the mean particle diameter needed for proper modeling.

3.2.1. Solid-liquid extraction

The solid-liquid extraction is carried out on a lab scale either as percolation or as stirred maceration. In the



percolation the solid–liquid separation takes place with a frit that holds back the particulates during extraction. After the maceration process has taken place, the particulates are separated in a nutche-type filter under slight over pressure. All of these procedures are carried out in standardized apparatus which have already been described elsewhere [8,15].

3.3. Analytics

The analysis of 10-DAB in the extract is carried out with HPLC. Besides that, toluene distillation is used for the determination of solid sample's water content, while Karl-Fischer titration serves the same function for liquid samples. A dry balance is used for analysis of the raw material's moisture. Table 2 summarizes the used analytical methods. They are standardized procedures that are described in other institute's publications [4,10,15].

3.3.1. Target component

The 10-DAB in the liquid extract is analyzed with an Elite La Chrom® HPLC using a diode array detector DAD-L 2455 from Hitachi and a PharmPrep P100 RP phase analytical column from Merck. The samples are filtered

Table 2

Overview of analytical methods according to [4]

	In raw material	In solvent/extract
TC (10-DAB)	Multi-staged maceration	HPLC
Water	Toluene-distillation	Karl Fischer titration
Dried mass raw material	Drying balance	–
Solvent mass	Calculation	Calculation

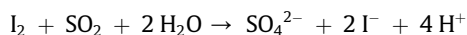
through a 0.2 µm syringe filter and fed undiluted into the HPLC (see Fig. 4). The calibration is carried out by using an external standard. Therefore, the needed pure 10-DAB was ordered from Sigma-Aldrich.

The calibration curve of 10-DAB in ethanol has been determined in the fore-field for concentrations up to 1.5 g/L, thus being far above concentrations reachable during extraction. The regression coefficient is 0.999. The concentration of 10-DAB in the extract is calculated with Eq. (2).

$$\text{Concentration TC [g L}^{-1}] = \frac{\text{Area TC [min L}^{-1}]}{\text{Gradient calibration [min L g}^{-1}]} \quad (2)$$

3.3.1.1. Water determination in the extract

The water content of the extract is measured with Karl-Fischer titration. This method is based on the reaction between iodine and sulfur oxide to sulfate and iodide ions which can only take place in the presence of water as shown in the chemical equation below [34].



The procedure is carried out with a titrator TitroLine KF from Schott Instruments. It is counted to the volumetric Karl-Fischer titrators because the iodine solution is added with a piston burette to the reaction vessel. The measurement range has a span from 100 ppm up to 100% by weight water content. The standard deviation of the measurements is about 1% only [35].

3.3.2. Water determination in the plant material

Toluene distillation is carried out for determination of the plant material's water content. The principle is azeotropic distillation of the water containing raw material with an immiscible solvent like toluene. This takes place in a Dean–Stark apparatus as described in the European

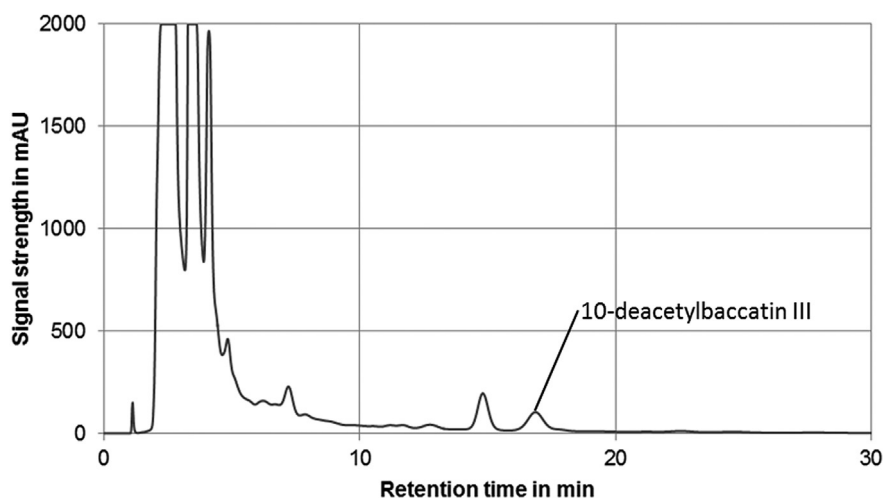


Fig. 4. HPLC chromatogram of the yew extract.

pharmacopoeia [36]. The separated amount of water is measured volumetrically with a scale attached to the Dean–Stark apparatus.

3.3.3. Dry balance

To measure the plant material's moisture, a MA 150 dry balance from Sartorius is used. The sample is given on a small metal bowl and heated up to 105 °C with an integrated heating device. The measuring process is stopped automatically, when the reduction of the sample's mass falls below 1 mg/min. The unprocessed yew needles have a moisture content of about 8% by weight. After extraction, the moisture content reaches levels from 60 to 80% by weight.

4. State-of-the-art

4.1. Modeling of solid–liquid extraction

The solid–liquid extraction is described by several sub-models. These models and the corresponding model parameter determination have already been described in detail [4,9,10,15,37]. Thus, only a brief overview of the model is given.

On the one hand, the distributed plug flow (DPF) model serves for modeling the macroscopic mass transport in the percolation column. On the other hand, a pore diffusion model describes the mass transport in the plant material's pores. The dependency of the raw material's residual load of target components and the corresponding extract's concentration is considered as well, with the use of equilibrium curves.

The target component's mass balance in the fluid phase is shown in Eq. (3). It contains accumulation, axial dispersion, convective mass transport and mass transport from the plant material's pores into the fluid.

$$\frac{\partial c_L(z, t)}{\partial t} = D_{ax} \cdot \frac{\partial^2 c_L(z, t)}{\partial z^2} - \frac{u_z}{\epsilon} \cdot \frac{\partial c_L(z, t)}{\partial z} - \frac{1 - \epsilon}{\epsilon} \cdot k_f \cdot a_p \cdot [c_L(z, t) - c_p(r, z, t)] \quad (3)$$

Under the assumption of spherical particulates, the following equation can be derived as a mass balance for the target component in the porous solid.

$$\frac{\partial q(z, r, t)}{\partial t} = D_{eff}(r) \cdot \left(\frac{\partial^2 c_p(z, r)}{\partial r^2} + \frac{2}{r} \cdot \frac{\partial c_p(z, r)}{\partial r} \right) + \frac{\partial D_{eff}(r)}{\partial r} \cdot \frac{\partial c_p(z, r)}{\partial r} \quad (4)$$

There is an adsorption/desorption equilibrium in the pores which is described by equilibrium curves. Herein, q is the plant material's residual load linking the equilibrium curve with the pore diffusion model. One well-known approach is the exponential Freundlich equilibrium. Thereby, the linear Henry equilibrium is extended with an exponent n . Both n and K_F can be derived through measurements.

$$q = K_F \cdot c^n \quad (5)$$

4.2. Calculation of physico-chemical properties with COSMO-RS

COSMO-RS (Conductor-like Screening Model for Real Solvents) is a quantum-chemical model for the determination of thermodynamic properties of pure substances and mixtures. In contrast to group contribution models (GCM) e.g., UNIFAC, no additional experimental data are needed [38].

While GCMs are extrapolating the considered molecule's properties with groups, COSMO-RS derives physico-chemical properties from the molecule's structure directly. Therefore, a spatial model of the molecule's surface is generated with quantum-chemical methods. This happens with the “Conductor-like Screening Model” [39] introduced by Klamt in 1993. The quantum-chemical part of the model (COSMO) delivers a molecular surface embedded in a virtual conductor. Besides others, this molecular surface is characterized through its surface charge density σ and σ' . Based on that, a fluid consisting of narrowly packed single molecules is simulated by COSMO-RS.

The basis of every COSMO-RS calculation is the quantum-chemical model of the molecule's surface. From this model, the charge density distribution $p^X(\sigma)$ of the pure substance is derived from the charge density σ and σ' . For the calculation of thermodynamic properties, the probability distribution of the mixture $p_S(\sigma)$ is calculated. This is derived from the sum of the σ -profiles of the pure substances X_i rated with their corresponding mole fraction x_i as shown in Eq. (6).

$$p_S(\sigma) = \sum_i x_i \cdot p^{X_i}(\sigma) \quad (6)$$

In reality, there is no conductor between the individual molecules; thus electrostatic forces induced from the different charge distributions take place which are considered by Eq. (7). Herein, the effective contact area of neighboring surface elements is a_{eff} and a' is a model parameter.

$$E_{misfit}(\sigma, \sigma') = a_{eff} \frac{a'}{2} (\sigma + \sigma')^2 \quad (7)$$

The interaction energy of hydrogen bridge bonds is considered with COSMO-RS, as well. In Eq. (8), c_{HB} and σ_{HB} are model parameters. With σ_{donor} and $\sigma_{acceptor}$ the surface charge distribution of the hydrogen bridge donor and the acceptor is taken into account. The acceptor has highly positive values, whereas the donors are highly negative.

$$E_{HB} = a_{eff} c_{HB} \min(0; \min(0; \sigma_{donor} + \sigma_{HB}) \cdot \max(0; \sigma_{acceptor} - \sigma_{HB})) \quad (8)$$

With the values of the individual kinds of interactions, the σ -profile is transformed into the chemical potential of a surface segment $\mu_S(\sigma)$ according to Eq. (9).

$$\mu_S(\sigma) = - \frac{RT}{a_{eff}} \ln \left[\int p_S(\sigma') \exp \left\{ \frac{a_{eff}}{RT} (\mu_S(\sigma') - E_{misfit}(\sigma, \sigma') - E_{HB}(\sigma, \sigma')) \right\} d\sigma' \right] \quad (9)$$

Based on $\mu_S(\sigma)$, the chemical potential of each component X in the system S is calculated with Eq. (10) where $\mu_{C,S}^X$ is a model parameter.

$$\mu_S^X = \mu_{C,S}^X + \int p^X(\sigma) \mu_S(\sigma) d\sigma \quad (10)$$

With the aid of the chemical potential, all relevant thermodynamic properties can be calculated, e.g., the solubility, shown in Eq. (11). The solubility S_S^X of a single component X in the solvent S is dependent on the difference of the component's chemical potential in the corresponding solvent and as a pure substance, according to Eq. (12).

$$\log S_S^X = \log \left(\frac{MW^X \cdot \rho_S}{MW_S} \right) + \frac{\ln(10)}{k_B T} \left[-\Delta_S^X + \min(0, \Delta G_{fus}^X) \right] \quad (11)$$

$$\Delta_S^X = \mu_S^X - \mu_X^X \quad (12)$$

The chemical potentials are calculated with COSMO-RS. Moreover physical properties like the molar weight of the solved component MW^X , the solvent's molar weight MW_S and the solvent's density ρ_S are needed. If the component is a solid, melting has to be taken into account with the enthalpy of fusion ΔG_{fus}^X . Furthermore, the Boltzmann constant k_B and the absolute temperature T are needed [38].

The applicability of COSMO-RS for the prediction of physical properties of single components in the extract of fennel (*Foeniculum vulgare* L. MILL.) has been shown by Koudous et al. [11]. Thereby, the octanol–water distribution coefficient K_{OW} of substances like α -pinene, camphene, myrcene and α -phellandrene and estragole was estimated either with COSMO-RS, UNIFAC and modified-UNIFAC. In all cases, the most precise values were gained with COSMO-RS [11]. Lapkin et al. [40] described the solvent selection with the help of COSMO-RS for the extraction of artemisinin from the annual mugwort (*Artemisia annua* L.). Durand et al. [41] did an extensive division of 153 different organic solvents into ten classes. By validating their results with the solubility of nitrocellulose the classes were confirmed, and the classification done by Chastrette could be extended. Besides that, there is a host of further publications dealing with COSMO-RS in detail [42–44].

After the presented literature review, a new study based on 10-deacetylbaccatin III as a typical example system of industrial importance will be regarded in the following chapters. By that, the general structure of process development for plant based substances of both conventional and Green Extraction will be shown in detail.

5. Alternative solvent selection in solid–liquid extraction

There is a big variety of solvents available for the extraction of plant-based substances. The bandwidth varies from supercritical media, non-polar alkanes and cyclic molecules up to medium and highly polar substances like water, alcohols or esters. Moreover, there are the green

solvents outlined above. Often an optimized yield and purity of the target component cannot be achieved with one single solvent alone but with a mixture. In this case, an experimental screening is extremely time and money consuming. For that reason, a quantum-chemical approach with COSMO-RS is shown and rated with respect to complex mixtures like phytoextracts. This takes place with some representative solvents and their mixtures. All of the calculated values are validated experimentally. Above all, ethanol and acetone have to be taken into account due to their low price and high availability. Moreover, both solvents can easily be recycled by distillation because 10-DAB is a solid under normal conditions. Further potential solvents are methanol, diethyl ether and water as well as mixtures of ethanol and water and respectively acetone and water. The solubility values of 10-DAB from the experiment and the calculation are plotted against each other in Fig. 5.

Because COSMO-RS calculates the saturation concentration of 10-DAB in the corresponding solvent, these values are significantly higher compared to the experimental ones. Thus they are plotted in logarithmic scale.

In Fig. 5, the calculated values are plotted on the ordinate in logarithmic scale. The experimentally gained data are plotted linear on the x-axis. As shown in the diagram, the experimentally determined absolute values deviate highly from the calculated ones. Especially for water, there is a high difference between the calculated and experimentally found values. Pure 10-DAB is almost non-soluble in water which is predicted correctly by COSMO-RS (about 0.00003% by weight) [45]. Nevertheless, concentrations up to 0.025% by weight can be achieved during extraction which is even above the solubility values of ethanol and acetone. Probably this is due to natural solubilizers like diterpene glycosides which are described in the literature [46].

Contrary to COSMO-RS, the best experimentally determined solubility is achieved with a mixture of 80 vol.-% of

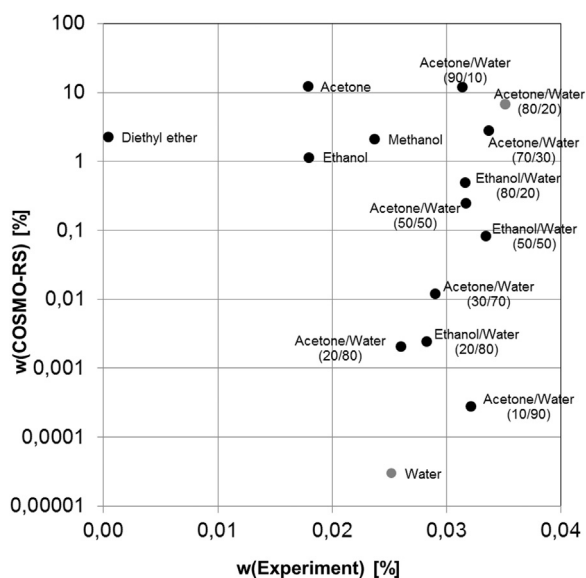


Fig. 5. Solubility calculation with COSMO-RS and experimental screening.

acetone and 20 vol.-% of water. For that reason, this mixture is used for the following process design.

There is a way to predict solubility values even of complex molecules with the quantum-chemical approach COSMO-RS. For an exact prediction of physical properties in complex mixtures like phytoextracts, side components e.g., natural solubilizers have to be taken into account, as well. In the example shown above, only 10-DAB and the corresponding solvent were considered. The outcome is an inaccurate prediction. This is clearly visible for the 10-DAB's solubility in pure ethanol and acetone. The calculated values deviate in the range of one order of magnitude, whereas the experimental data of both are almost the same. Moreover, 10-DAB can be extracted with water which cannot be predicted with COSMO-RS yet, underlining the significant influence of natural solubilizers.

6. Purification strategy for yew

Based on experiments on lab-scale and calculations with the COSMO-RS unit, operations for the purification of 10-DAB are selected and basically designed. The planning depth is at the level of a feasibility study and well before the basic-engineering. The aim is to find an optimized process design at the very beginning of the process development with low experimental effort, carried out with a structured and property data-based approach. With respect to physical properties, economic and ecological aspects, the process selection shown in Fig. 6 was chosen.

First of all, the extraction is carried out with percolation and subsequently the extract is filtered. As a solvent, a mixture of acetone and water is used being the best solvent for the extraction of 10-DAB from yew according to the experimental screening.

Afterwards, acetone is separated and recycled by distillation. During that step chlorophyll which is non-soluble in water, precipitates and is removed by filtration. The remaining extract is further purified by a series of

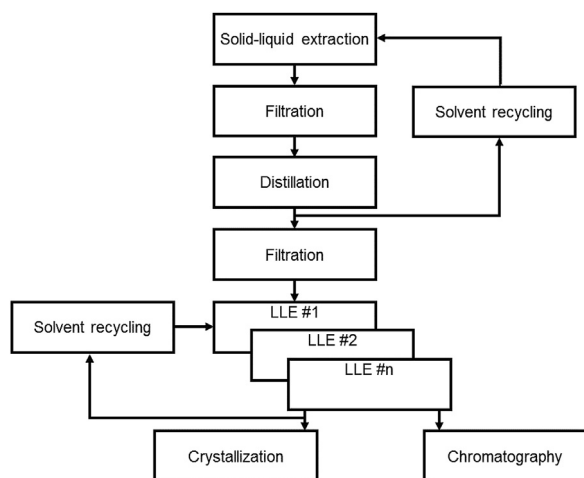


Fig. 6. Basic process design.

liquid-liquid extraction steps and further on 10-DAB is crystallized. In the following, the single unit operations are shown in detail. As an alternative to crystallization, a SMB process is basically designed, as well.

6.1. Percolation and filtration

The percolation is carried out in the standardized apparatus with the integrated frit for solid-liquid separation, as mentioned above [8]. The parameters of the extraction process have been obtained in an optimization study done with the model shown in Section 4.1.

6.2. Distillation and separation of chlorophyll

About 80 vol.-% of the extract is removed in a rotary evaporator. Thus the acetone used can be regained almost completely. During that step chlorophyll which is non-soluble in water, precipitates and is separated by filtration.

6.3. Liquid-liquid extraction

The further purification of 10-DAB from the aqueous extract takes place with a series of liquid-liquid extraction steps, aiming at the highest possible purity and yield. For solvent selection, a screening in COSMO-RS is done and experimentally validated. Thus, an optimized solvent for liquid-liquid extraction should be found in the very beginning of the process design. The calculated and experimentally found mass fractions of 10-DAB in the corresponding solvents are plotted in Fig. 7.

As already pointed out in Section 5, COSMO-RS calculates saturation concentrations; thus, they are in general higher than the experimental values because of the low content of 10-DAB in the yew needles. Moreover, the

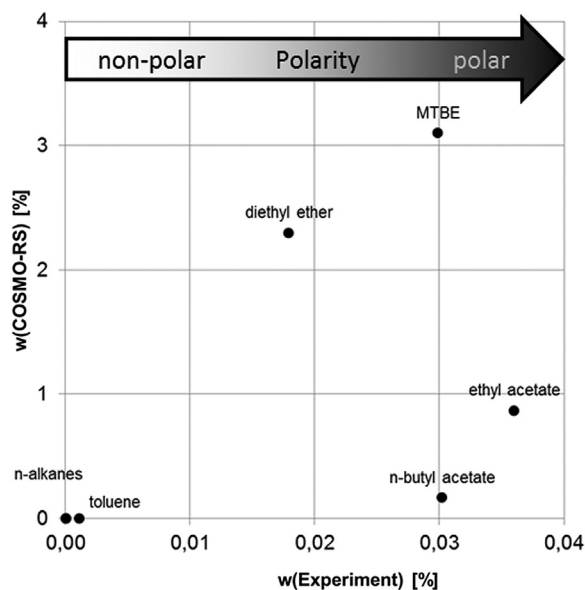


Fig. 7. Solvent screening for LLE.

natural solubilizers have a major influence on the whole system which is not taken into account in the current screening yet. According to the simulation, methyl-*tert*-butyl ether is the best solvent, whereas in the experiment ethyl acetate shows the best results. The calculated and experimentally determined values match best for the *n*-alkanes and toluene.

At the present state, there is no way to determine the best solvent with COSMO-RS alone. Due to its correct prediction of the solubility values as a function of the molecule's polarity, COSMO-RS is able to reduce the effort of an experimental screening because a pre-selection is possible. The *n*-alkanes and the toluene show the lowest solubility. The measured solubility then increases with an increasing polarity which is predicted correctly by COSMO-RS.

In the first liquid–liquid extraction step, toluene is used although ethyl acetate shows the best solubility values. By this procedure, it is possible to selectively extract an unknown side component with high yield by only losing about 5% by weight of 10-DAB, according to the analysis of

the experimental screening. This is shown in the chromatograms in Fig. 8. After the extraction has taken place, the side component is dissolved in toluene and has a purity of about 80%.

A one step extraction with ethyl acetate follows, which is the best solvent for 10-DAB according to the experimental screening. The target component is extracted with a yield of about 95%, as shown in Fig. 9.

During the extraction with ethyl acetate, some polar side components are extracted as well, so the organic phase has to be washed. The selection of a potential washing solution is based on the polarity of the fractions involved. According to their low retention time on the RP phase and the high solubility in water, their polarity must be high. For further increasing the polarity and thus shifting the distribution equilibrium to the side of the aqueous washing solution, the components have to be protonated or deprotonated. For that reason, screenings with two different acid solutions, pure water and two different basic solutions were carried out. An aqueous solution of sodium carbonate shows the best results in both purity and yield of 10-DAB in the organic phase. In a

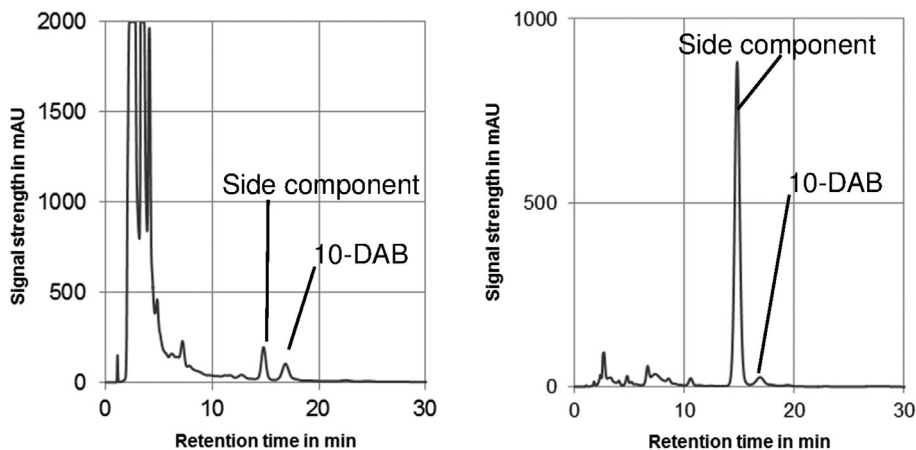


Fig. 8. Selective purification of one side component. Left: raw extract, and right: toluene phase.

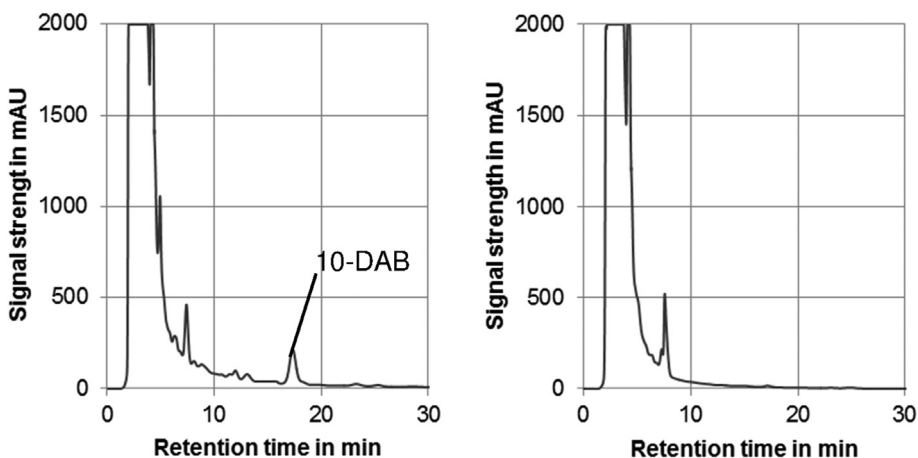


Fig. 9. Extraction of 10-DAB with ethyl acetate. Left: pre-processed extract before extraction with ethyl acetate, and right: pre-processed extract after extraction with ethyl acetate.

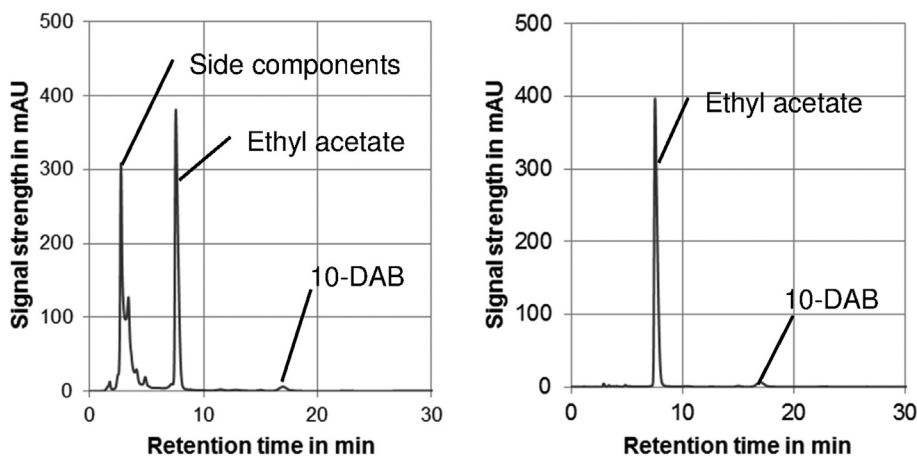


Fig. 10. Washing of the extract with sodium carbonate solution. Left: raw extract (ethyl acetate phase). Right: extract after washing with sodium carbonate solution.

two-step cross-flow process, practically all side components can be separated with only about 5% by weight loss of 10-DAB in that way (see Fig. 10).

6.4. Crystallization

One possible way for final purification and formulation of 10-DAB is crystallization. Thus, corresponding experiments and calculations are carried out for the determination of the most relevant design and operation parameters. Among others, a suitable solvent for crystallization has a steep solubility curve. Thus, a high yield in cooling crystallization can be obtained with passing through a small temperature range only. Moreover, the concentration occurring should not be too high to avoid losses. With the help of COSMO-RS, solubility curves of potential solvents like acetone, ethanol, ethyl acetate and acetonitrile are calculated. Although there are

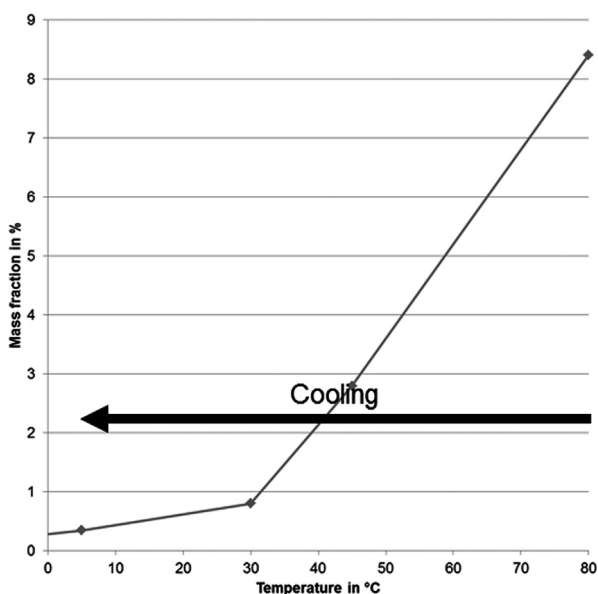


Fig. 11. Solubility curve of 10-DAB in acetonitrile.

some limitations of COSMO-RS concerning complex mixtures as shown in Section 5, the extract is highly purified in this state of the procedure and thus COSMO-RS is applicable for a molecular structure-based design of the crystallization process.

According to COSMO-RS, acetonitrile has the best properties for crystallization. In this case, the solubility of pure 10-DAB at 80 °C is about 8.4% by weight and only 0.34% by weight at 5 °C. The solubility curve is plotted in Fig. 11. In a one step process, a theoretical yield of about 96% can be estimated. The feasibility of the cooling crystallization of 10-DAB from acetonitrile was shown on lab-scale.

Formulation for the chosen example of 10-DAB is defined by the need for a dry and long-term stable and therefore crystalline intermediate product for further redissolution before final synthesis. While not related to the scope of this study, the final product on the market has to be sterile and is applied as an injection from vials, which calls for complete solubility and stability in the final sterile liquid for injection.

6.5. Chromatography

As an alternative to liquid–liquid extraction and crystallization, chromatography is considered, being described as a suitable process for the purification of 10-DAB from the yew extract on an industrial scale [6].

Initially, the Henry coefficients of the corresponding fractions are determined by analytical HPLC to apply the triangular method. The chromatogram is shown in Fig. 12.

Due to the low content of 10-DAB in the extract, linear adsorption isotherms are assumed so the corresponding Henry coefficients can directly be derived through Eq. (13) to be 37.6 for fraction A and 44.0 for fraction B (10-DAB). The porosity of the column packing ϵ is appr. 0.8.

$$K^k = \frac{\epsilon}{1 - \epsilon} \left(\frac{t_R^k}{t_0} - 1 \right) \quad (13)$$

With the Henry coefficients, the triangular method is applied for estimating an operation point of a potential

SMB process as shown in Fig. 13. For the detailed mathematical description see Refs. [47–50]. The closed polyline is the area of complete separation in the case of linear adsorption isotherms. At higher loadings, other forms of isotherms like Langmuir must be considered. In Fig. 13 this is schematically shown as dashed lines. In this case, the operating point shifts to a lower feed throughput.

6.6. Cost accounting

With a cost accounting, the production costs of Paclitaxel from the benchmark process [51,52] are compared to the costs of the newly designed process. Due to the low level of detail of the first process proposal, a typical error of about $\pm 50\%$ occurs (cost estimation class V). The annual production of both processes is set to 250 kg.

6.7. Investment costs

All relevant processes and design parameters derive from a scale-up of the performed experiments in the process design studies and the patented instructions, directly from lab-scale to production. With these parameters, the costs of the corresponding apparatus are determined with the help of established table values such as [53]. Inflation is taken into account with the CEPCI and piping, instrumentation and other periphery with the Lang factor. In Fig. 14 the relative investment costs of the newly designed process are plotted against the values from the benchmark process.

The previously estimated overall amount of 10-DAB in the yew needles of 0.18% by weight is the basis for the newly designed process. Due to the mass related yield of the semi-synthesis of only 9%, 2800 kg/a of 10-DAB need to be extracted from the yew needles to produce 250 kg/a of Paclitaxel. With these data and an assumed loss in extraction and the following purification steps of 35% in total, 2,400 t of yew needles have to be extracted with about

30,000 m³ of solvent. This is performed batch-wise in one single percolation equipment.

In the benchmark process, an extraction yield of only 0.3% of the possible overall amount is achieved. Therefore, about 500,000 t/a of yew needles have to be extracted with 1.2 m³ of solvent to gain 2,800 kg of 10-DAB. In the benchmark process, these amounts can be handled in 40 Sliding-Cell-Extractors from Lurgi [8], for example.

- The main difference between the two processes is the number and the size of the used extraction equipment. In the newly developed process, the costs for solid–liquid extraction are only 1% of the benchmark process's costs.
- In downstream processing, the investment costs for both processes are comparable. This is because in the newly developed process only the acetone is recycled, whereas the 20 vol.-% of water are further processed. In the benchmark process, nearly the total amount of methanol is recycled, thus only a concentrate remains. So the volume flow rates are comparable in both processes

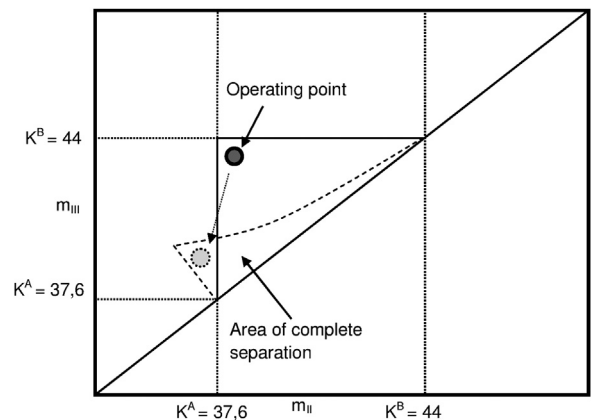


Fig. 13. Triangular method for basic design of a SMB process.

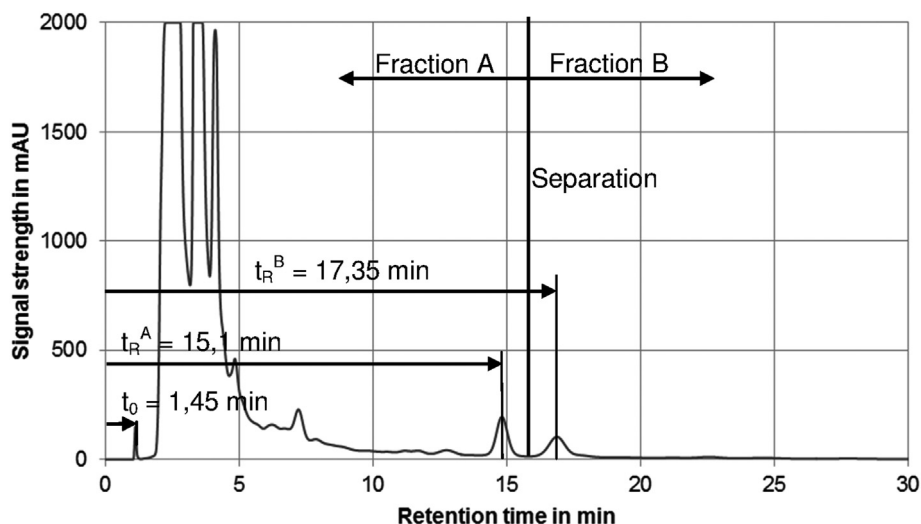


Fig. 12. Chromatogram for determination of the Henry coefficients.

although the amount of extract is significantly higher in the benchmark process. Due to the comparable volume flow rates, the necessary apparatuses have nearly the same dimensions in both processes, resulting in almost the same investment costs. In the newly designed process, investment costs for downstream are 1.5 times the investment costs of the benchmark process.

- The following semi-synthesis of 10-DAB to Paclitaxel is the same in both processes and was not in the focus of the process optimization.

With the molecular structure based approach in extraction and purification of yew, about 90% of the investment costs can be saved.

6.8. Operating costs

The annual operating costs of each plant are comprised of several items: amortization, maintenance, solvents and additives, yew needles, energy and labor costs.

Due to the significant reduction of yew needles in the newly designed process, almost 99.5% of the corresponding resource and costs can be saved. All other costs of the newly designed process are also below the costs of the benchmark process. For example, the amount of solvent used in the benchmark process is 40 times higher and thus consumes much more energy in distillation compared to the alternative process design. There are also 9 times higher costs for amortization and higher costs for maintenance, labor and additives, only because the total size of the benchmark plant is much higher than that of the newly designed one. The overall savings of the newly designed process are about 97% compared to those of the benchmark process. Thereby, the main part can be reduced to the significantly lower consumption of yew needles (see Fig. 15).

6.9. Evaluation and comparison of the two process designs

With the newly developed process, 97% of the production costs can be saved compared to the benchmark process. It was shown that even with conventional methods, a green process can be realized due to the efficient use of

renewable resources and consequent solvent recycling, by which even the extraction with toluene is no contradiction because toluene is kept into the system. Moreover, the energy consumption can be reduced dramatically.

7. Conclusion

In this work, an overview of recent topics of Green Extraction such as alternative solvents has been presented. To underline the potential of Green Extraction, a methodical approach for extraction and purification of plant based substances from a typical system like 10-DAB from European Yew was shown and further improved. One special focus was using the property model COSMO-RS for prediction of physico-chemical data of single substances in complex mixtures. With a reproducible solvent screening in COSMO-RS, the experimental effort and costs can be considerably reduced in the future. At the present state, the specific choice of one single solvent only relying on COSMO-RS is limited, because of natural solubilizers. These are under investigation in ongoing studies at our institute and will be a research topic in future. In addition to solid-liquid extraction modeling, COSMO-RS was used for solvent selection in liquid-liquid extraction. The experimental screening showed an increasing solubility of 10-DAB in the chosen organic solvents, improving further with increasing polarity. COSMO-RS is able to predict this trend correctly. Based on physical properties and experiments, a process design for the extraction of 10-DAB from the yew extract was developed. The production costs were compared to those of a benchmark process. Savings up to 97% are possible.

As a conclusion, the correct choice of alternative solvents in a total process is most challenging in purification steps as the operating window in purification is narrowed by predefined formulation needs as well as high yield extraction demands. Therefore, any degree of freedom is welcome, but has to be gained by economic benefits, which have to be sophisticatedly earned by total process integration, i.e., avoiding a number of steps, increasing yield of each step and avoiding solvent changes. But, in any appropriate optimized process, a solvent change may be economic and ecological, besides the additional energy

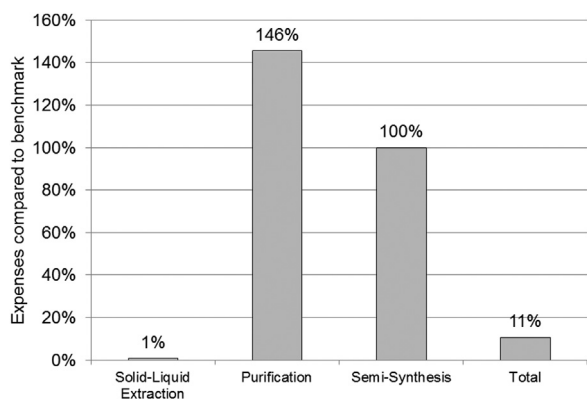


Fig. 14. Investment costs of the new process design compared to the benchmark process.

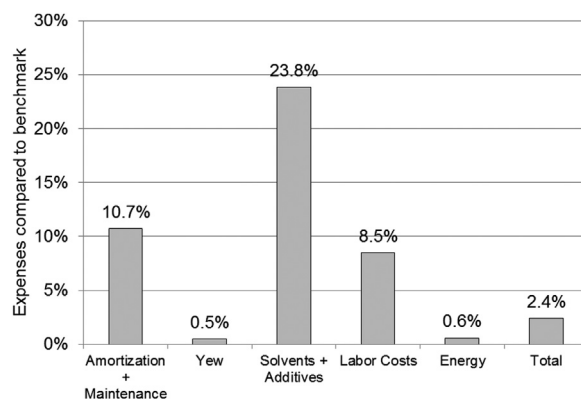


Fig. 15. Operating costs of the new process design compared to the benchmark process.

demand. This depends on the magnitude of economic and ecological benefits gained by total process optimization in all manufacturing steps.

Symbols

a_{eff}	effective contact area, 1/m
C_{HB}	parameter
C_L	concentration in the fluid phase, kg/m ³
C_p	concentration in the pore, kg/m ³
D_{12}	binary diffusion coefficient, m ² /s
D_{ax}	axial dispersion coefficient, m ² /s
D_{eff}	effective diffusion coefficient, m ² /s
E_{HB}	energy of hydrogen bridge bonds, J
E_{misfit}	energy of electrostatic interaction, J
K^A	Henry coefficient of component A
K^B	Henry coefficient of component B
K^K	Henry coefficient of component K
k_B	Boltzmann constant, J/K
k_f	mass transfer coefficient of the fluid film, m/s
K_H	Henry coefficient
m_{III}	flow rate in zone 3
m_{IV}	flow rate in zone 3
MW_S	molecular weight of the solvent S, kg/mol
MW^X	molecular weight of the component X, kg/mol
n	Exponent of the Freundlich isotherm
p_S	probability density distribution of the mixture
p^X	probability density distribution of the component X
q	loading, kg/m ³
R	universal gas constant, J/molK
r	distance in the radial direction, m
S_S^X	solubility of the component X in the solvent S
T	temperature, K
t	time, s
t_R^K	retention time of component K, s
t_0	downtime, s
u_z	superficial velocity, m/s
V_m	molar volume, m ³ /mol
w	mass fraction
x	distance, m
x_i	mass fraction of component i
z	distance in the DPF model, m
ΔG_{fus}^X	enthalpy of fusion of component X, J/mol
ΔH_v	molar heat of evaporation, J/mol

Greek letters

α'	parameter, Jm ⁵ /C ²
δ	hildebrand solubility parameter, (J/m ³) ^{0.5}
Δ_S^X	Difference of the chemical potentials of component X and solvent S, J/mol
ϵ	Porosity
ϵ_p	Porosity of the particulates
$\mu_{C:S}^X$	parameter, J/mol

μ_S^X	chemical potential of component X in solvent S, J/mol
μ_X^X	chemical potential of pure component X, J/mol
ρ_S	density of the solvent, kg/m ³
σ	surface charge density, C/m ²
σ_{acceptor}	surface charge density of the hydrogen bridge acceptor, C/m ²
σ_{donator}	surface charge density of the hydrogen bridge donator, C/m ²
σ_{HB}	parameter, C/m ²

Abbreviations

10-DAB	10-deacetylbaccatin III
CEPCI	chemical engineering plant cost index
COSMO-RS	conductor like screening model for real solvents
DPF	distributed plug flow
GCM	group contribution model
HPLC	high performance liquid chromatography
LLE	liquid–liquid extraction
MAE	microwave-assisted extraction
NRTL	non-random two liquid
PC-SAFT	perturbed-chain statistical associating fluid theory
SLE	solid–liquid extraction
UAE	ultrasound-assisted extraction
UNIFAC	universal quasichemical functional group activity coefficients

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