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

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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].

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

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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-deacetylbaccatin 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 CO_2. 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 CO_2 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 (DESs) are of increasing interest in recent publications [1,22–24]. Ionic liquids and DESs are mixtures of solids where the mixture's melting point is far below the melting point of each individual substance. Commonly, DESs 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 DESs 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 DESs is the major drawback. The solvent can no longer be separated by