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ENVIRONMENTALLY FRIENDLY PRODUCTION OF HERBAL MEDICINES

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Резюме. Трав'яні лікарські засоби у більшості випадків все ще виготовляються за допомогою традиційного обладнання та процесів. Інноваційні методи розробки хіміко-технологічних процесів, такі як моделювання та інтенсифікація процесу за допомогою зелених технологій, можуть сприяти економічному та екологічному майбутньому лікарських ботанічних рослин. Наведено приклад інтеграції сучасних технологічних методів, таких як екстракція гарячою водою під тиском на основі води та вбудованих вимірювальних пристроїв для аналітичних технологічних підходів до традиційних процесів екстракції. Концепція регулювання базується на вимогах щодо якості за проектом для автономної роботи рецептів на основі добавок за допомогою цифрових двійників у розширеному контролі процесу. Це може включати тестування продукції у режимі реального часу для автоматичного вирішення проблем перевірки.

Resume. Herbal remedies are in most cases still manufactured with traditional equipment installations and processes. Innovative chemical process engineering methods such as modeling and process intensification with green technology could contribute to the economic and ecologic future of medicinal botanicals. The integration of modern unit operations such as water-based pressurized hot water extraction and inline measurement devices for process analytical technology approaches in traditional extraction processes is exemplified. The regulatory concept is based on the quality-by-design demand for autonomous feed-based recipe operation with the aid of digital twins within advanced process control. This may include real-time release testing to the automatic cleaning of validation issues.

Keywords: herbal remedies manufacturing, green technology, quality by design, process analytical technology, autonomous operation.

Introduction. Medicinal plants and their importance in medicinal therapy are characterized among the lay public as medicinal tea and preparations derived from it, mostly as dragee, tablet, or juice. In fact, the spectrum of their use is much wider. While medicinal teas use the entire dried part of a medicinal plant, extractions can be used to focus on the relevant groups of constituents. Subsequently, there is the possibility of

purification to obtain a pure substance, which is combined with the option for a final partial synthesis to arrive at the desired molecular structure.

The classic plant preparation is made either directly from the plant or with an extract produced from the plant. In both cases, mixtures of substances form the active ingredient. Phytopharmaceuticals, which follow the allopathic doctrine in pharmacology, represent the largest share of medicinal products. If one's own studies on efficacy and safety have been carried out in the respective preparation, it can be approved in the European Union as "well-established use" (WEU). On the other hand, if a reference to the (pre)clinical results in one of the monographs of the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) is chosen, registration will follow [1]. In other regions, medicinal plants and the preparations derived from them may be legally categorized differently. For example, there are examples where a preparation is declared as a prescription drug in China, a pharmacy or over-the-counter drug in Europe, and a foodstuff in the USA.

In Germany, for example, important indications for phytopharmaceuticals are the treatment of colds with an increase in the body's immunological defenses and gastrointestinal/bile complaints. Mild forms of depression or anxiety can be treated with St. John's wort (*Hypericum perforatum*) and lavender (*Lavandula angustifolia*). Important niche indications of phytopharmaceuticals include preparations in gynecology for menopausal symptoms or the therapy of premenstrual syndrome, hemorrhoid remedies, urological drugs, and prostate and vein therapeutics [2].

A different therapeutic theory underlies homeopathic products, which, from a regulatory point of view, also belong to medicinal products. Medicinal plants or extracts obtained from them, such as mother tinctures, are also used for them. Food supplements, which have gained importance over the past two decades and are considered to be an interesting future option for health products based on herbs, fall into the legal area of foodstuffs. Herbal products have a niche character, which from a regulatory point of view fall into the group of medical products since their healing effect is not based on a pharmacological but a physical mechanism.

The production of medicinal plants for the extraction of pure substances or as starting materials for phytopharmaceuticals is subject to strict regulations. For example, the use of herbicides and pesticides is prohibited, with very few exceptions. Mechanical weed removal is therefore used instead of herbicides. With the good agricultural and collection practice (GACP), which is a set of rules of the European Union, there are comprehensive and binding rules for cultivation, permanent cultivation, and wild collection [3].

The cultivation of medicinal plants takes place as a special crop, which differs from the usual agriculture not just because of the GACP requirements. An essential feature is the significantly low land requirement, which results from the required quantities for plant-based active ingredients or extracts and can be easily understood [4]. The extraction of medicinal plants is a sustainable production, which conserves resources through the careful use of renewable raw materials. In the entire process chain, from the plant to the drug, a consideration of CO_2-based energy expenditures should be made.

Aim. Comprehensive study of the characteristics of green herbal medicine production, its advantages over traditional methods. Prospects for the introduction of modern technologies for the green production of herbal medicines.

Methods. A literature search was conducted in Google Scholar, PubMed, Scopus and Web of Science databases using keywords.

Results. When processing medicinal plants into drugs, the specifications of the European Pharmacopoeia must be taken into account [5]. Two categories exist for the definition of extracts: a pharmaceutical-technological consideration and a pharmacological classification. While the first category is binding for all extractions of plants, the second concerns only phytopharmaceuticals that contain extracts as active ingredients. Depending on the recognized state of scientific knowledge, the pharmacological classification differentiates between standardized extracts of medicinal plants for which the group of ingredients responsible for the effect has been defined, quantified extracts with specifications of relevant ingredient groups, and other extracts for which neither of the characteristics of the other two types of extracts is present.

The work on future process technologies for the extraction of plant parts is characterized by the principle of rationality rather than empiricism. New extraction processes can be developed into efficient and robust productions using the techniques of quality by design (QbD) and process analytical technologies (PAT) in a goal-oriented manner [6].

The Use of Hot Water Extraction for the Preparation of Extracts of Phytopharmaceuticals Using the Example of Bearberry (Arctostapylos uva-ursi). Drugs containing extracts from the leaves of bearberry are prescribed for the treatment of mild urinary tract infections and are a proven alternative to the use of antibiotics for this indication [7]. Hydroquinones are responsible for their efficacy, and arbutin has been established as the reference substance from the group of ingredients. The extracts belong to the class of “standardized extracts” according to the pharmacological classification of the European Pharmacopoeia. Based on the study situation, national WEU approvals could therefore be granted for some preparations in Europe.

Water-based processes totally exemplify the green extraction [8] approach perfectly. Additionally, they are kosher and halal-friendly, directly generally recognized as safe (GRAS), and therefore, represent ideal manufacturing technologies to meet market demands. A process sequence of PHWE and nanofiltration (NF) for concentration, followed by purification based on chlorophyll precipitation, liquid–liquid extraction for pre-purification and/or chromatography with final formulation by crystallization or direct lyophilization seems to be the most direct and logical manufacturing technology approach for the future, efficiently generating reliable product quality under all marked regulation demands. This could be systematically achieved by the quality-by-design (QbD) approach, which is demanded by regulatory authorities such as the FDA and EMA [9]. A central part of such innovative approval documentation is manufacturing operation robustness gained by the implementation of process analytical technologies [6, 10].

In conclusion, a suitable approach may be to switch to, or at least to put more emphasis on standardized extracts, complete with efficacy studies and a new approval

process supported by QbD-based process design, which enables process operation at its economical optimum.

This is beneficial, if not essential, for maintaining or regaining competitiveness in existing markets. Firstly, the batch variability of typical natural feedstock can be accounted for in the process design. Beyond that, it creates the technical basis for addressing increasing societal needs in the product development of innovative, plant-based antibiotics, and/or green and sustainable, resource-efficient manufacturing concepts with additional consumer benefits. The key role of plants in the medicinal and pharmaceutical fields for thousands of years is undisputed; however, it has had its difficulties. Nevertheless, even today, innovative molecules with therapeutic potential are quite often based on plants, which, in principle, have been known for decades or even centuries. Being able to break down complex natural mixtures into individual molecules or groups of molecules by advanced analytical tools allows for the characterization and testing for specific pharmaceutical/medicinal applications. Some of the best examples of successful applications in cancer and malaria treatments are taxol and artemisinin. Maybe the variety of plants and their broad scope of beneficial applications in healthcare might be exploited to find solutions to one of the biggest therapies needed by mankind.

Optimization of Hawthorn (Craetaegus monogyna). Extracts from the leaves and flowers of hawthorn belong to the pharmacological class of "other extracts" according to the specifications of the European Pharmacopoeia with hyperoside as the lead substance. Traditionally, hawthorn preparations are used for the treatment of mild cardiac complaints [11, 12].

Traditionally used herbal medicines are deep in the consciousness of patients for the treatment of only minor diseases by self-medication. However, manufacturers of herbal medicinal products suffer from major problems such as increasing market pressure, e.g., from the food supplement sector, increasing regulations, and costs of production. Moreover, due to more stringent regulation and approval processes, innovation is hardly observed, and the methods used in process development are outdated. Therefore, this study aims to provide an approach based on modern process engineering concepts and including predictive process modeling and simulation for the extraction of traditional herbal medicines as complex extracts. The commonly used solvent-based percolation is critically assessed and compared to the so-called pressurized hot water extraction as a new possible alternative to replace organic solvents. In the study, a systematic process design for the extraction of hawthorn (*Crataegus monogyna*) is shown. While for traditional percolation the solvent is optimized to a mixture of ethanol and water (70/30 v/v), the PHWE is run at a temperature of 90°C. The extracts of various harvest batches are compared to a commercially available product based on a chromatographic fingerprint. For the first time, natural batch variability was successfully incorporated into the physicochemical process modeling concept. An economic feasibility study reveals that the PHWE is the best choice not only from a technical point of view but also from an economic aspect.

The study showed a systematic and model-based comparison of two different manufacturing methods for a traditionally used herbal extract. Both a percolation using a mixture of ethanol and water (70/30 v/v) as solvent as well as extraction with water at 90°C show high productivity and yields. A high yield of the main flavonoid hyperoside as well as the desired range of the drug extraction ratio (DER) is reached. The chromatographic fingerprints revealed that all extracts were comparable to a commercially available product. The combination of experimental model parameter determination and rigorous process model is an efficient method of predictive process simulation, not only for the extraction of substances that are afterward purified to pharma-grade but also for the processing of traditionally used complex extracts. For the first time, natural batch variability was successfully incorporated into the physicochemical process modeling concept. These generated data sets are required by regulatory authorities demanding quality-by-design (QbD) and process analytical technology (PAT) approaches as modern tools with data-driven decisions documented for filing due to technological change, entering of markets of other countries, as well as changes in regional regulations and authority inquiry. An economic feasibility study showed that the PHWE can overcome the financial drawbacks of solvent storage and renewal efficiently, thereby justifying the higher investment costs for the necessary high-pressure equipment.

The consequent application of the process engineering toolbox of physical property calculations for solvent choice, miniaturized laboratory experiments for model parameter determination of all units, and efficient model validation with regards to accuracy and precision, as well as any process optimization based on cost modeling, allows for the gain in green processing benefits, the significant reduction in solvent consumption by up to a factor of 10, water-based processing technology, yield improvement to spare agricultural resources of about 90%, and COGs reduction of about 50% is realistic. Any change from batch to continuous operation results in significant operational and investment cost reductions by factors of about 5-10.

Conclusions. Innovative manufacturing technologies such as water-based processing based on pressurized hot water extraction followed by concentration with membrane technologies such as nanofiltration and ultrafiltration have general potential to gain the targets of climate neutrality and cost of goods savings to compete in worldwide markets successfully. Major reductions such as by a factor of five are feasible by using modern process design.

Drug quality assurance and improvement will be gained by applying the quality by design approach proposed and demanded by regulatory authorities. Such the transfer from classical batch-wise to continuous operation for a significant reduction of main resources needed is demonstrated.

Even feed-based recipe operations with simple proportional-integral-derivative-based process control and measurement devices such as pH, conductivity, and turbidity allow robust modern autonomous operation performances based on digital twins and process analytical technology. Such digitalization including machine learning and

artificial intelligence, are capable of enabling traditional natural product extraction to compete with existing and future competition in markets.

The potential of fresh plant manufacturing is exemplified and the potential to gain new entities by efficacy studies for main therapies needed like anti-viral supporters, adjuvants and diabetes and heart insufficiency. Natural remedies, which are traditionally of great benefit, are thus enabled to continue to provide significant support to global health in the future within the context of recent increases in regulatory requirements for drug safety and improvements in manufacturing technology.

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