CHEMICAL ENGINEERING TRANSACTIONS, Volume 12, 2007
Edited by Jiri Klemeš

Process Intensivation With Integrated Separation Principles

H.-J. Bart, P. Dimitrova, A. Kostova, M. Schmidt
University of Kaiserslautern
Institute of Chemical Engineering
P.O. Box 3049, 67653 Kaiserslautern, Germany
www.uni-kl.de/LS-Bart/

Sustainable production of nutraceuticals and pharmaceuticals from plant materials is highly demanding in respect to product purification. After a short review on extraction principles the focus is on chromatography, as is with impregnated resins, micellar and microemulsion chromatography. In contrast to conventional operation the implementation of a second selector principle lead to process intensivation as discussed on examples.

1. Introduction

The extractive treatment of plant material in order to get elixirs, scents and flavours is first documented in 3500 B.C. in Mesopotamia (Blass et al., 1997) and can also be found with Assyrian and Egyptian sources (Homyard, 1957; Joachim, 1993). Even nowadays there is an enormous resource for the modern pharmaceuticals, cosmetics and food industry, which is also confirmed in a position paper of Dechema with the title "Phytoextrakte" (see http://dechema.de/Extraktion). The global market for extracts from plant material as food additives (e.g. green tea, balm, blueberry, etc.) is of about 17.5 billion euro. There is a dramatic increasing trend with a higher demand of nutraceuticals and novel food. A similar tendency is with pharmaceutics. Here the global market of the plant feed materials is at about 1 billion US$ with an annual growth of 6-8 %. The global marked of pharmaceutics from plants was in 2002 about 31 billion US$. Triterpenes have highest annual growth and they share about 40 % market volume. Several of these lead structures are of pharmaceutical interest for anti-HIV, cancer and diabetes treatment. A development of new pharmaceutics is partly hindered due to purity and availability of the drugs. Oleanolic acid and its structural isomers can be found at higher concentrations in sage, hibiscus and cloves. Recovery and purification is even more difficult compared to stereoisomers, as usually more than two components have to be separated.

2. Extraction

Prior extraction the dried material has to be crushed and optionally be swollen for better extractability in an appropriate solvent. This pre-treatment increases the quantity of extracted substances in a significant way. This influence is time depending and changes in pH-value also effect the extraction as shown in Fig. 1 for the yield of oleanolic and ursolic acid extracted from sage. A specific pulping (e.g. only in respect to destroy the cell membrane, etc.) is to be aspired. For instance, sugar recovery from sugar beet is from chips, since finer grinding would destroy the cell membrane and release proteins, which spoil the molasses recovery.

The products may either be temperature, pressure or light sensitive, which leads to maceration, digeration and depending on their shape to percolation and slurry extraction. The choice of the solvent is decisive to extract a key component.

The solvent phase may be an aqueous or a surfactant solution, a bulk organic chemical or organic mixture respectively a critical/subcritical fluid. Water is a classical extractant (e.g. tea, coffee) and admixture of enzymes may modify the solute or influence its availability. A change in pH value or ionic strength may alter the dissociation of charged solutes and thus can influence solubility and extractability.

Organic solvent systems generally offer high selectivities and capacities. However, there are legal restrictions with food applications to consider (THV, 2006). A new class of extractants are ionic liquids, which are organic salts being liquid at room temperature. They are usually very polar and viscous, mostly hygroscopic and have virtually no vapour pressure, the latter relates to the name "green solvents" (Wasserscheid, 2000). However, markedly differences of an ethanol extract compared to an ionic liquid (Ecoeng 212) can be found, which could serve as a basis for selective enrichment (Schmidt, 2007)

Surfactant solutions are already used in analytics, e.g. to extract cholesterol with Triton X114 (neutral surfactant), when applying cloud point extraction (Tamura et al., 2002). More industrial impact is with aqueous-2-phases extraction.
Here admixture of two polymers or one polymer and a salt give a phase split, allowing complex molecules (proteins, enzymes, etc.) to be extracted without denaturation, which would occur in an organic solvent (Platis, 2006; Großmann, 1997).

Liquified CO_2 is a common solvent for decaffeinating of coffee and tea and extraction of hops (Lack, 2001). The extraction of spices, natural colorants and antioxidants is limited due to the solubility limit of polar solutes in CO_2-admixture of modifies can improve this as given in Fig. 2 with triterpene extraction with ethanol as modifier. Other substances also show a positive effect on the extractability of triterpenoic acids. The influence of menthol and camphor, two monoterpenes, can potency the yield of extracted triterpenoids (see Fig. 3).

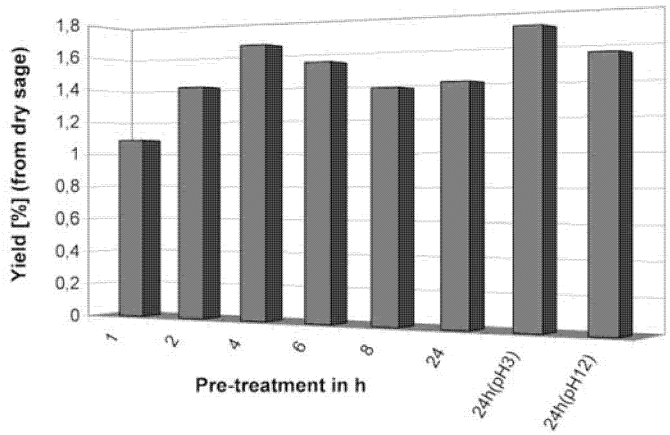

Fig. 1: Influence of pre-treatment

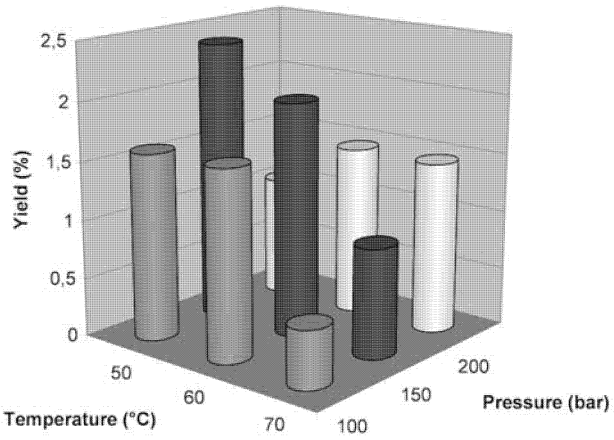

Fig. 2: Extraction yield of triterpenoic acids, with 2.5 % modifier (ethanol)

3. Chromatography

After extractive enrichment there is usually a high performance separation necessary in order to get ultra pure products. In the pharma field this is often done with chromatography, where to separate isomers is still a challenge. Here the separation principle is the affinity of a solute dissolved in an eluent to the stationary phase. The chemical principle may be due physical adsorption, ion exchange, size exclusion, affinity interaction, etc. In order to enhance selectivity a second selector principle can be applied in the eluent phase, when using surfactant containing systems (Garcia, 2005). Either in micelles or in a microemulsion a further selector is immobilized, which helps to separate isomeric mixtures (Bart, 2005).

The separation of isomers is up to now really a challenge since separation factors even with chiral stationary phases are usually in the range of 1.2 to 1.7 (Subramanian, 2001).

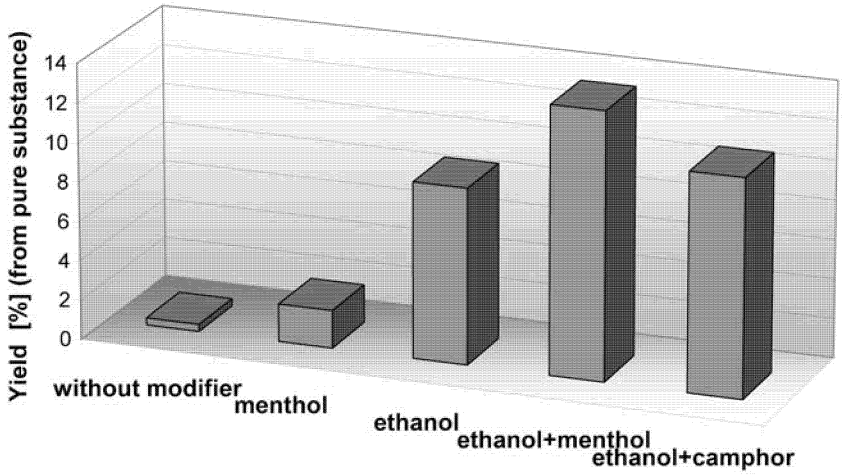

Fig. 3: Extraction yield of triterpenoic acids with several modifier

In that respect it is also advantageous to impregnate a non-chiral stationary phase with a specific chiral selector, as described elsewhere (Warshawsky, 1981). It is essential that the chiral selector operates according to the host-guest principle (see Fig. 4) (Easson, 1933), as demonstrated by Kostova (2007) when separating racemic amino acid mixtures (see Fig. 5) using N-hexadecyl-L-hydroxyprolin as selector.

In respect to process intensification it is one aspect to make the stationary phase more selective with impregnation. A further improvement is when dissolving and immobilizing a second carrier in the eluent phase. This can be accomplished in micelles and microemulsions, where both on a macroscopic scale appear as a single pseudo-homogeneous phase, which is advantageous for pumping, flow control etc. The basic microstructure is formed by surfactants (see Fig. 6), whereas the co-surfactant (usual an alcohol) in microemulsions allows incorporation of an oil phase, which enhances capacity.

In micelles a selector 'S' can be embedded in the hydrophobic core of the micelle and in the microemulsion dissolved in the organic diluent. The recycling and regeneration of the micelles can be done with the help of ultrafiltration units. The flow sheet is depicted in Fig. 7. In a rotating annular chromatography the feed is introduced at a fixed position at the top of the annular bed, while the eluent is distributed everywhere else around the upper circumference (Fox, 1969). Each solute in the feed is forced to flow down through the packed bed and exit from it at the angle determined by the flow rate of the liquid, the rotating speed and its affinity with the packed media.

At the bottom the separated products can be collected at certain stationary exit angles. The eluent contains the surfactant phase which can be recovered in micellar systems by ultrafiltration (Bielska, 2005) and the selector be regenerated by pH-shift etc.

Using microemulsions instead of ultrafiltration a temperature change gives a phase split, where from the organic phase the selector can be regenerated accordingly (Bart, 2005). After proper readjustment the surfactant solutions can be reused.

Microemulsions have already been used as alternative mobile phases in chromatography. An example is the microemulsion elektrokinetic chromatography (MEKC) which is applied for enantiomeric separations, whereby the selectivity is achieved with chiral surfactants (Altira, 2003; Hue, 2006). But this process can be applied only in labscale for analytical purposes, as otherwise heating and electrolysis would occur because of the electrical field. An alternative is to use the microemulsion as mobile phase in HPLC (Marsch, 2005) as well as in rotating annular chromatography.

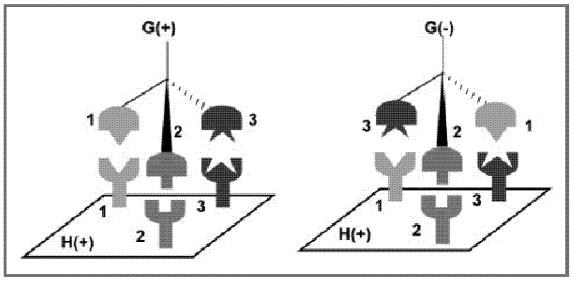

Fig. 4: Host-guest complexation principle

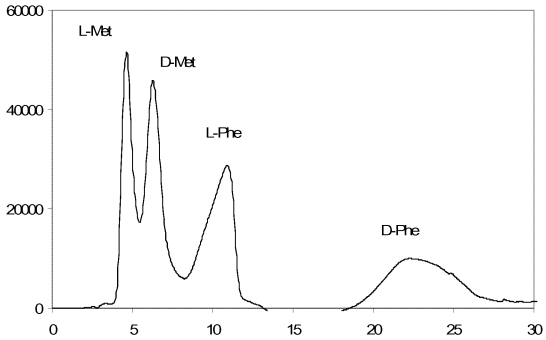

Fig. 5: Enantiomer separation from a mixture of DL-Phe and DL-Met, $C_{DL\text{-}Phe}$= 2.8 mM/L, $C_{DL\text{-}Met}$= 2.7 mM/L, $\dot{V}$ =2 mL/min, V_{inj}=25 µL.

The big variety of system components like surfactants, co-surfactants, solvents as well as their composition enable the preparation of a tailored microemulsion. Most of the works concerning microemulsions are focused mainly on the separation of pharmaceutics or drugs, whereas the separations regarding the duration, selectivity, efficiency or easy sample preparation are always better compared to conventional chromatographic separations. The separation can be improved with optimized system parameters or by using a shorter column (Berthod, 1992; Pascoe, 2002; Pedersen-Biergaard, 2000). The increasing numbers of articles for the application of microemulsions as a mobile phase in the MEKC for chiral separations show the increasing interest of microemulsions as chiral carrier phases (Merzman, 2005).

Conclusions

Chemical reactions and surfactant solutions give rise to intensify and enhance mass transfer processes. The use of microemulsion or micellar solutions as eluents in annular chromatography allows a continuous multi-component separation. A second selector in the microemulsion phase additionally improves the overall separation factor. However, this integration of two selector activities leads to some limitations, as is here for instance the composition of the eluent phase. Both selectors (on the stationary phase resp. in the emulsion droplet) must have their best performance in the same pH, ionic strength or temperature area, since e.g. a pH adjustment inside the annular bed is not possible.

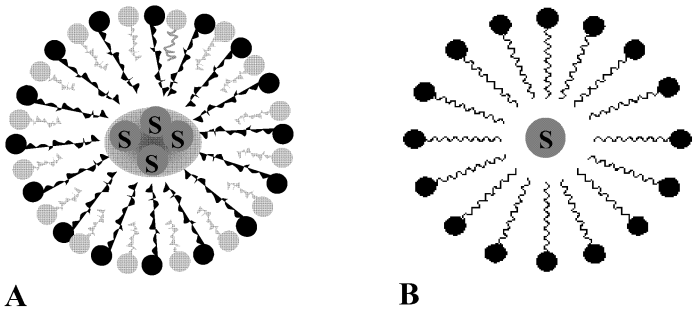

Fig. 6: Microemulsion (A) and micellar (B) structure

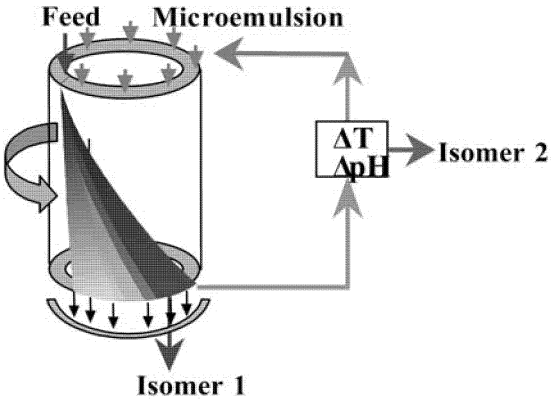

Fig. 7: Flow sheet of annular chromatography

Acknowledgement

The authors wish to thank the Max-Buchner-Stiftung and Stiftung Rheinland-Pfalz for their support.

4. References

Altira, K. D., Mahuzier, P., Clark, J. B., 2003, Electrophoresis 24, 315-324
Bart, H.-J., 2005, Chem. Ing. Techn. 77, 1773.
Berthod, A., de Carvalho, M., 1992, Anal. Chem. 64, 2267-2272.
Bielska, M., Garcia Diez, L., Materna, K., Bart, H.-J., Szymanowski, J., 2005, Desalination 172, 19.
Blaß, E., Liebl, T., Häberl, M., 1997, Chem. Ing. Techn. 69, 431.
Easson, L.H., Stedman, E., 1933, Biochem. J. 27, 157.
Fox, J.B., 1969, J. Chromatogr. 43, 55.
Garcia Diez, L., Bart, H.-J., Szymanowski, J., 2004, Chem. Eng. Techn. 27, 38.
Großmann, C., Tintinger, R., Zhu, J., Maurer, G., 1997, Fluid Phase Equil. 137, 209.
Homyard, E.J., 1957, Alchemy, Pelican Books, A348.
Huie, C. W., 2006, Electrophoresis 27, 60-75.
Joachim, M., 1993, Papyros Ebers: Das älteste Buch über Heilkunde, de Gruyter, Berlin.
Kostova, A., 2007, PhD thesis TU Kaiserslautern, Kaiserslautern, Germany.
Lack, E., Simandi, B., 2001, in High Pressure Technology: Fundamentals and Applications (Eds. A. Bertucco, G. Vetter) Elsevier, Amsterdam.
Marsch, A., Clark, B.J., Altria, K. D., 2005, J. Sep. Sci. 28, 2023-2032.
Merzman, M. D. and Foley, J. P., 2005, Electrophoresis 26, 4153-4163.
Pascoe, R. and Foley, J. P., 2002, Analyst 127, 710-714.
Pedersen-Biergaard, S., Naess, O., Moestue S., Rasmussen, K. E., 2000, J. Chromatogr. A 876, 201-211
Platis, D., Labron, N.E., 2006, J. Chromatogr. A 1128, 114.
Schmidt, M., Bart, H.-J., 2007, Paper at PROCESSNET 'Extraktion' 22./23.3.07, Asselheim.
Subramanian, G. (Ed.), 2001, Chiral Separations, Wiley-VCH, Weinheim, Germany.
Technische Hilfsstoff-Verordnung (THV), 2006, Bundesministerium für Justiz.
Warshawsky, A., 1981, Solvent Extr. Ion Exch. 37, 229.
Wasserscheid, P., Klein, W., 2000, Angew. Chemie 112, 3296.