Institute of Chemical Engineering[1], Bulgarian Academy of Sciences, Sofia, Bulgaria; Laboratoire de Genie Chimique[2], UMR 5503-INP-UPS-CNRS, Toulouse, France

Extraction of valerenic acids from valerian (*Valeriana officinalis* L.) rhizomes

L. Boyadzhiev[1], D. Kancheva[1], C. Gourdon[2], D. Metcheva[1]

Received October 14, 2003, accepted March 24, 2004

Prof. L. Boyadzhiev, Institute of Chemical Engineering, Bulgarian Academy of Sciences, BG-1113 Sofia, Bulgaria
lboyadz@bas.bg

Pharmazie 59: 727–728 (2004)

Extraction of valerenic acids (valerenic, acetoxyvalerenic and hydroxyvalerenic) from dry ground rhizomes of valerian (*Valeriana officinalis* L.) was studied. The effect of ethanol concentration in the solvent, extraction temperature and drug particle size on extraction kinetics were investigated and the optimum values of these process parameters were determined for the case of intensively stirred two-phase dispersion. It was found that increased processing temperature favors extraction kinetics, but provokes moderate degradation of valerenic acids.

The therapeutic effect of the extracts of valerian rhizomes is generally assigned to the combined action of the sesquiterpenic acids (valerenic acid (VA), acetoxyvalerenic acid (AVA) and hydroxyvalerenic acid (HVA)) and the valerian essential oil, contained in plant rhizomes (Houghton 1994; Bos et al. 1996; Bos 1997)

Standardized extracts are usually obtained by extracting dry *Valeriana officinalis* L. rhizomes with ethanol-water mixtures. The vast literature on this topic lacks, however, data on the kinetics of the extraction process itself, namely the effect of major process parameters as ethanol concentration, extraction temperature and of the solid particles.

The aim of the present study was to elucidate the influence of these parameters and to estimate the effect of increased temperature on valerenic acids degradation.

The experiments were performed with dried valerian rhizomes, cultivated in the Kazanlak valley. The herb used contained 7% water, 10.5% ash and 0.21% total valerenic acids. Extraction was carried out with ethanol-water mixtures, containing 40, 50 70, 80 and 96% (v/v) pharmacopoeian purity ethanol (Neochim). Liquid extracts were dried at 50 °C under vacuum and the residue was analyzed for the three sesquiterpenic acids. The latter were determined by HPLC analysis, using a C18 column packed with NUCLEOSIL 100-5 and an UV detector at a wavelength of 225 nm (Gobbato et al. 1996). Extract samples were dissolved in methanol (HPLC grade, Fluka). The mobile phase was a 1 : 1 mixture of acetonitrile (HPLC grade, Merck) and a 0.1% aqueous solution of phosphoric acid (p.a., OSS Samokov). The elution rate was 0.33 ml/min. Biphenyl (Merck) was used as an internal standard. Valerenic acid (HPLC grade, Extrasyntese) was used as an external standard in order to confirm the reported coefficients (Gobbato et al. 1996) for HPLC area ratios between the internal standard and the corresponding valerenic acids.

The studies on the extraction kinetics were performed in a thermostated 150 ml glass extraction cell equipped with a reflux cooler and a magnetic stirrer. In each run 1g of ground and fractionated rhizomes was extracted with 100 ml of the corresponding water-ethanol mixture. Samples of 1 or 2 ml were dried, weighed and analyzed.

Fig. 1 shows the effect of the solvent composition, on the quantity (total mass) and the quality (valerenic acids content) of the obtained extracts. For this purpose samples of fraction 0.177–0.250 mm were stirred for 6 h at 25 °C with 40, 50, 70, 80 or 96% (v/v) ethanolic solutions. As can be seen, the total concentration of the valerenic acids in the obtained dry extracts increases with the increase of ethanol content, while the total extract mass decreases. Therefore, concentrated ethanolic solutions produce lower amounts of dry extract, which is, however enriched in valerenic acids.

The temperature has two opposite effects: On the one hand, higher temperatures intensify the extraction process owing to the increased solubility and the increased diffusion coefficients of all extractable ingredients. On the other hand, higher temperatures favor the degradation of other components, mainly the valepotriates (Bos 1997; Thies 1969).

In the present study an attention was paid to the second effect – the stability of valerenic acids at elevated temperatures. To this purpose, ethanol-water liquid extracts (70 : 30), obtained according to the above procedure and containing initially 176.9 mg/l valerenic acids (81.3 mg/l VA, 89.1 mg/l AVA and 6.5 mg/l HVA, respectively) were thermostated at 70 °C for 22 h. After this treatment the total concentration of the acids was reduced to 156.3 mg/l, i.e., representing a decrease of 11–12%. For the individual acids these final concentrations were: VA – 71.9 mg/l, AVA – 78.0 and for HVA 7.4 mg/l. From these results one can conclude that VA and AVA are moderately thermo-sensitive ingredients. The slight increase in HVA amount could be attributed to the transformation of acetoxyvalerenic acid into hydroxyvalerenic acid at elevated temperatures (Bos 1997).

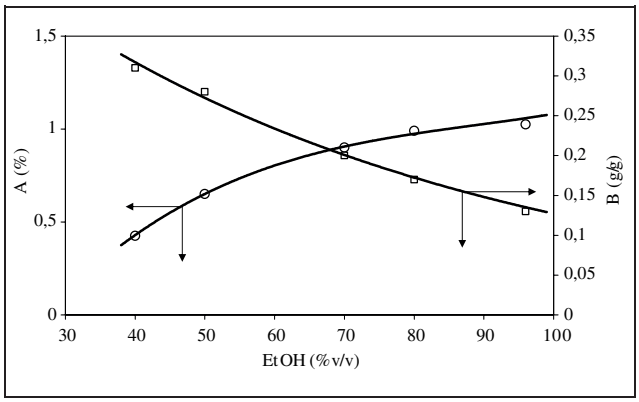

Fig. 1: Effect of ethanol concentration on total content of the valerenic acids in the dried extract (A) and the quantity of extracted mass (B) ○ – Total content of valerenic acids in the dried extract in% (wt). □ – Ratio of the mass of dried extract to the initial mass of the herb (g/g). Particle size – 0.177–0.250 mm, temperature – 25 °C, extraction duration – 6 hours

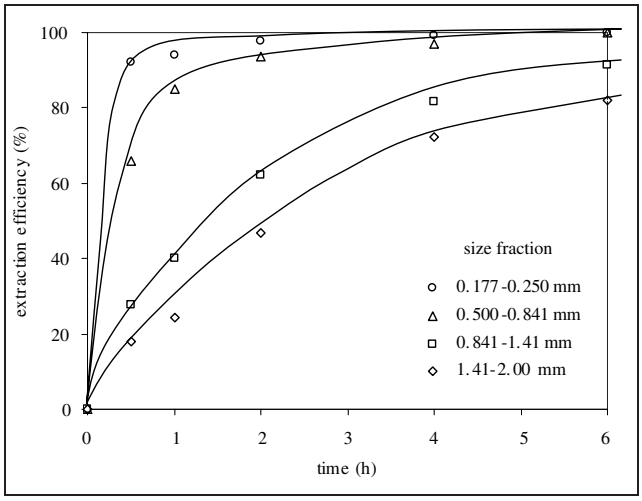

Fig. 2: Effect of the size of herb particles on the amount of extracted matter. Extraction temperature –70 °C, ethanol concentration in the solvent –70% (v/v)

The rate of the extraction process strongly depends on the size of the solid particles. The intensively stirred extraction cell used in the present study suggests that intraparticular diffusion of the solutes is the only rate controlling factor. In the experiments four fractions of ground dry rhizomes of valerian – 0.18–0.25 mm, 0.50–0.84 mm, 0.84–1.41 mm and 1.41–2.00 mm were subjected to the described extraction procedure. In all cases 10 g of each fraction were extracted with 70% (v/v) ethanol at a temperature of 70 °C. The total residue after extract drying was a measure for the extraction kinetics. The results are shown in Fig. 2. In the case of finely ground particles ($d_p < 0.25$ mm), extractable matters are rapidly and almost completely (above 90%) recovered during the first hour of the treatment (taking as 100% efficiency the weight of the extracted mass, obtained after 6 h). In the case of largest (1–2 mm) particles used extraction efficiency was 80–85% after 6 h treatment. It should be kept in mind that the obtained results refer to an intensely stirred dispersion, i.e., in complete absence of diffusion resistance in the continuous liquid phase.

On the basis of the obtained results some useful conclusions about the recovery of valerenic acids, the content of which is the specifying and standardizing characteristic of valerian products (Annon 2002), can be drawn. Ethanol-water mixtures containing 50–96% ethanol extract all three valerenic acids, the higher ethanol concentrations yield a lower amount of dry extract, being enriched in the mentioned acids. Extraction, extract concentration or drying at elevated temperatures up to 70 °C does not lead to a significant degradation of the valerenic acids. The extraction rate of the active components is favored by reducing the size of the solid particles, thus shortening the process duration. However, very fine solid fractions would hamper liquid circulation and extract filtration. A reasonable compromise in this respect should be found.

References

Annon (2002) European Pharmacopoeia 4rd ed. Eropean Dept. for the Quality of Medicines. Council of Europe Strasbourg, p. 2109

Bos R, Woerdenbag HJ et al. (1996) Analytical aspects of phytoterapeutic valerian preparations. Phytochem Anal 7: 143–151.

Bos R (1997) Analytical and phytochemical studies on valerian based preparations. Dr. nat. sci. Thesis Univ. Gronningen.

Gobbato S, Lolla E (1996) A new HPLC method for the analysis of valerenic acids in Valeriana officinalis extracts. Fitoterapia 57: 159.

Houghton PJ (1994) Valerian. Pharm J 253: 95–96.

Thies PW (1969) Zum chromogenen Verhalten der Valepotriate. Arzneim Forsch 19: 319.

Research Institute for Industrial Pharmacy[1] and Department of Pharmaceutics[2], North-West University, Potchefstroom Campus[2], Potchefstroom, South Africa, and Department of Basic Pharmaceutical Sciences[3], School of Pharmacy, University of Louisiana at Monroe, Monroe LA, USA

Compatibility of sennoside A and B with pharmaceutical excipients

Q. Verloop[1], A. F. Marais[2], M. M. de Villiers[3], W. Liebenberg[1]

Received March 03, 2004, accepted April 12, 2004

Dr. Wilna Liebenberg, Research Institute for Industrial Pharmacy, North-West University, Potchefstroom Campus, Potchefstroom 2520, South Africa
iifwl@puk.ac.za

Pharmazie 59: 728–730 (2004)

This study reports the incompatibility of sennoside A and B with the following commonly used pharmaceutical excipients: stearic acid, sodium carbonate, glucose, lactose, propyl paraben, sodium carbonate, stearic acid, citric acid, PEG, and sorbitol. Drug-excipient compatibility was tested using thermal (DSC) and analytical (HPLC) methods of analysis. Compatibility evaluation showed that dry powder mixtures could be used to formulate sennoside A and B products. However, when mixed with water – propyl paraben, sodium carbonate, stearic acid, citric acid, PEG, and sugar derivatives such as lactose, glucose and sorbitol – should not be used in sennoside containing products.

In order to relieve the symptoms of constipation, laxatives are used to achieve comfortable defecation. Until recently, the laxative most frequently used was the stimulant laxative phenolphthalein. However, phenolphthalein has proven to be a concern, starting in the USA where the National Cancer Institute of America nominated phenolphthalein for study because of its widespread use and lack of adequate testing for carcinogenety (Dunnick and Hailey 1996; Dunnick et al. 1997; FDA 1997; Tice et al. 1998). These studies confirmed the potential carcinogenicity of phenolphthalein prompting the Food and Drug Administration in the USA on 29 January 1999 to issue a final rule on the use of phenolphthalein as an OTC laxative proposing a ban of all phenolphthalein products (Collins et al. 2000). Many other countries quickly followed suit. This ban meant that many laxative products had to be reformulated and it seems the laxatives of choice to replace phenolphthalein are the sennosides. Sennosides fall within the same category of stimulant laxatives as phenolphthalein. This renewed interest in the sennosides prompted this study, which aimed to determine the compatibility of sennoside A and B with commonly used pharmaceutical excipients. Sennosides are anthraquinones and the two stereoisomers sennoside A and sennoside B form the principal constituents of various Senna extracts. Senna extracts come from the leaves and fruits of various species of *Cassia*. In this study thermal (DSC) and analytical (HPLC) methods