

**CONCENTRATION OF LISINOPRIL PURIFIED BY LIQUID  
CHROMATOGRAPHY - A COMPARISON BETWEEN REVERSE OSMOSIS  
AND EVAPORATION<sup>#</sup>**

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**Abstract**

Angiotensin-converting enzyme (ACE) inhibitor lisinopril is an active pharmaceutical ingredient produced through a stepwise chemical synthesis. After the synthesis lisinopril is purified by a low pressure liquid chromatography. A polar, water-based mobile phase is used as an eluent. Purified lisinopril is precipitated from the concentrated chromatography main fractions which are presently concentrated to a specified lisinopril concentration in a simple, single stage vacuum evaporator. Evaporation of large volumes of water is not economical and as an alternative solution a reverse osmosis can be used. A suitability of the reverse osmosis for concentrating the main fractions from the lisinopril chromatography was tested under various process conditions on the pilot plant unit of our own design. The results of the experiments are shown and discussed. A required full-scale production capacity and the results of the experiments formed a base for a calculation of a membrane area for a full-scale unit and for an estimate of energy and investments for the reverse osmosis and the evaporator. A simplified calculation showed that the use of reverse osmosis is economically justified.

**Introduction**

Angiotensin-converting enzyme (ACE) inhibitors, such as enalapril and lisinopril are effectively used for the control of hypertension and congestive heart failure.<sup>1-3</sup> Lisinopril dihydrate, chemically *N*-[*N*-[(1*S*)-1-carboxy-3-phenylpropyl]-*L*-lysyl]-*L*-proline dihydrate, is produced synthetically by means of a stepwise chemical synthesis. After the synthesis, lisinopril is purified by a low pressure liquid chromatography. A polar, water-based mobile phase is used as an eluent. Purified lisinopril is precipitated from the concentrated chromatography main fractions which are presently concentrated to the specified lisinopril concentration by evaporation of water in a vacuum evaporator.

Evaporation of large volumes of water is not economical and as an alternative solution a reverse osmosis can be used.

Reverse osmosis is a pressure-driven membrane process whereby the natural phenomenon of osmosis is reversed by the application of pressure to a concentrated solution in contact with a semi-permeable membrane.<sup>4</sup> If the applied pressure exceeds the solution's natural osmotic pressure, the solvent will flow through the membrane. Ions and molecules dissolved in the solution are rejected. The rate of solvent transport across the membrane depends on the membrane properties, the solution temperature, the osmotic pressure of the solution and the applied pressure. The phenomenon of reverse osmosis has been known for more than a century, but there has been no commercial interest in the industrial use of membranes due to their low permeability. The breakthrough in the industrial use of reverse osmosis membranes was the development of asymmetric, thin-skin cellulose acetate membranes by Loeb and Sourirajan in 1960. Nowadays, reverse osmosis membranes are of a broad commercial interest and used in many industrial applications in various industry branches, such as chemical process industry, biotechnology, pharmaceutical industry, food processing, textile, semiconductor, metals and metal finishing industry, pulp and paper industry, etc. Applications are varied and include potable and high purity water production, process and effluent water reuse, recovery of chemicals and metals from process streams, water/organic and organic mixtures separation, dairy, juice and beverages processing, light beer and wine production and fermentation products recovery and purification.<sup>4</sup>

Traditional technologies are substituted for by reverse osmosis due to lower investment, operating and maintenance costs and other advantages such as low operating temperatures, simple automation and straightforward scale-up. Unfortunately, reverse osmosis membranes have limited temperature and pH operating ranges and limited resistance to some chemicals such as chlorine and certain organic solvents, and therefore it can not be used in every application. Reverse osmosis can also not be used, when solubilities of solutes in the feed solution are very low and they precipitate readily. Other drawbacks, such as concentration polarization and fouling phenomena, which lower the process efficiency, arise from the nature of the process itself and are common to all

membrane processes. Both phenomena can be substantially reduced with the use of the cross-flow technique, with the proper construction of the membrane elements and with the proper pretreatment of the feed. Concentration polarization and fouling are of a complex and transient nature and they are very difficult to predict, especially fouling. Design of a full-scale reverse osmosis unit has therefore to be based on pilot-plant tests results. The influence of transmembrane pressure, temperature, permeate recovery, volumetric concentration factor and feed pre-treatment methods on flux, fouling rate and membrane rejection properties have to be carefully evaluated during pilot plant testing, and as a result, the membrane area, operating pressure and temperature ranges, cleaning intervals and feed pretreatment methods of a full-scale unit are determined. Finally, based on the results of pilot-plant tests, investment and operating costs are estimated.

The suitability of the reverse osmosis for concentrating the main fractions from the lisinopril liquid chromatography was tested under various operating conditions on the pilot plant unit of our own design. The results of the pilot scale experiments and the required full-scale production capacity formed a base for the calculation of a membrane area for a full-scale plant and for an estimate of investment and operating costs of the reverse osmosis unit and the evaporator.

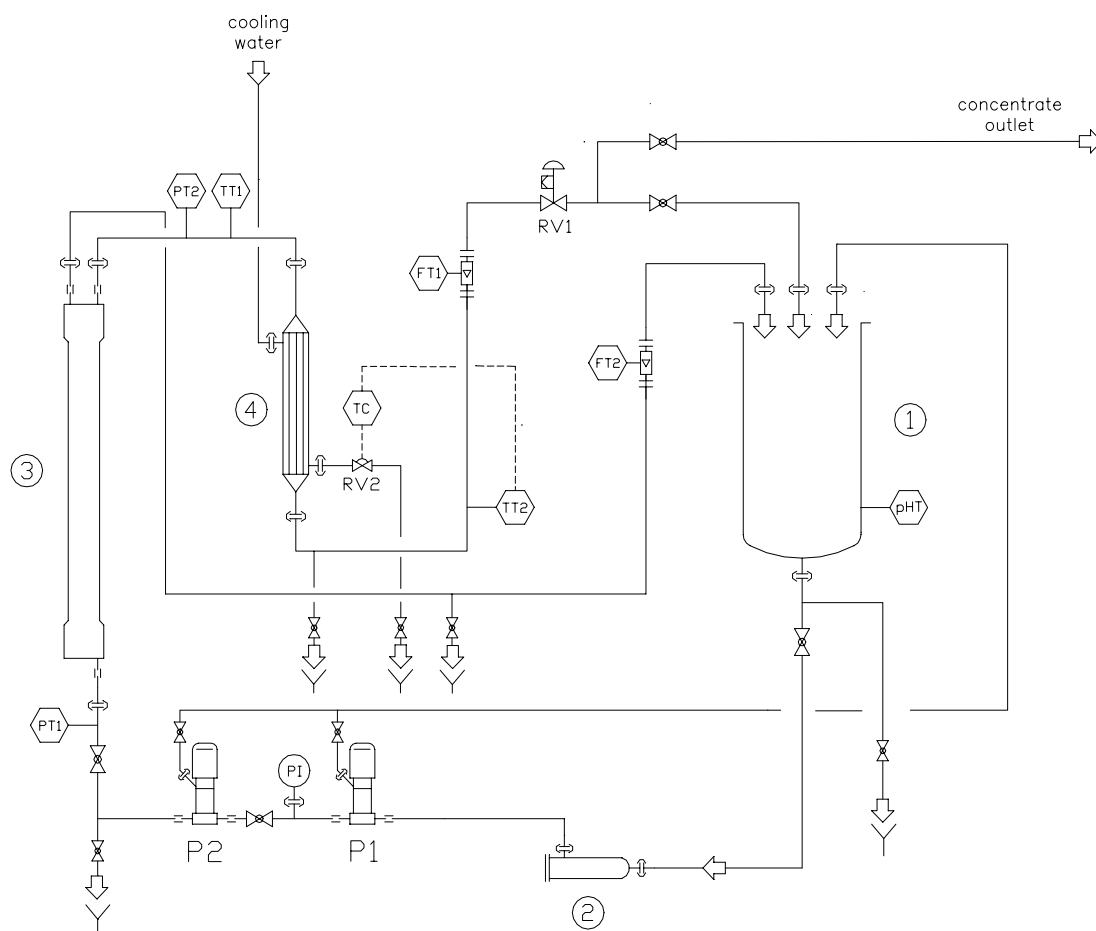
### **Description of the reverse osmosis pilot plant unit**

The reverse osmosis pilot plant unit has been designed for a pilot-scale testing of various applications and for a pilot-scale production. The unit can be operated either in a batch or in a continuous, single-pass mode of operation. In the batch operation mode the permeate is removed from the system and the concentrate is recycled back to a feed tank. At the end of the batch process the concentrate is drained from the feed tank. Batch systems are usually designed to operate with a constant feed pressure and declining permeate flow while the feed becomes more concentrated. In the continuous, single-pass mode of operation both the concentrate and the permeate are removed from the system. The flow of the permeate and a permeate recovery are usually kept constant in continuous mode, while the variations in feed concentration, temperature and fouling effects are compensated for by adjusting the feed pressure.

The pilot plant unit was constructed from two feed tanks, two high pressure pumps, a pressure vessel for a spiral-wound membrane element, a heat exchanger, measuring sensors, regulating valves, an electro-cabinet with programmable logic controller, tubing and manual valves. A simplified flow-chart of the pilot plant unit is shown in Figure 1.

The feed is pumped from one of the stainless-steel feed tanks through a prefilter (2) to the membrane element by two high-pressure centrifugal pumps, P1 and P2 (CRN-2, Grundfos, Denmark). The flow-rate of the feed is regulated manually by ball valves V3, V4, V5 and V6. The 4" spiral-wound-membrane element is placed in the pressure vessel (3) made of a composite material (Phoenix Vessels Ltd., United Kingdom). The operating limits of the pressure vessel are 70 bars and 45°C. The vessel is mounted in a vertical position with a drain valve at its bottom. With such a construction a complete drainage of the concentrate is possible. The concentrate can flow from the membrane element through the tube and shell heat exchanger (4) back to one of the feed tanks or through the concentrate outlet. The concentrate pressure/concentrate flow is regulated by a pneumatic regulating valve RV 1 (Samson, Germany). The retentate flow-rate is measured by a flow-meter FT 1 (Rotameter<sup>®</sup>, Rota, Germany) and the flow-rate of the permeate by a flow-meter FT 2 (Rotameter<sup>®</sup>, Rota, Germany). The concentrate inlet and outlet pressures are measured with piezoelectric sensors PT1 and PT2 (measuring range 0-60 bar, Wikatronic, Wika, Austria). The temperature of the concentrate is regulated by a self-operated temperature regulator. Temperature sensor TT2 is coupled to a thermostat TC and to a regulating valve RV 2 (Samson, Germany) which controls the outflow of the cooling water from the tube and shell heat exchanger (4). The temperature of the concentrate is measured by the Pt-100 sensor TT1 (Jumo, Austria). Both feed tanks are equipped with the standard pH weld-in sockets (Ingold, Mettler Toledo, Switzerland) in which the standard pH electrode housings (Mettler Toledo, Switzerland) can be mounted. The pH is measured with a pH meter pHT (Endress+Hauser, Germany) and pH electrode (Mettler Toledo, Switzerland).

The pilot plant unit operation is controlled by an industrial programmable logic controller (Sysmac C200HS series, Omron, Japan). The PLC is connected through a



**Figure 1.** Simplified flow-chart of a reverse osmosis pilot plant unit. Legend: (1) feed tanks, (2) prefilter, P1-first stage high pressure feed pump, P2-second stage high pressure feed pump, PI-pressure indicator, (3) pressure vessel with the 4" spiral-wound membrane element, PT1-pressure sensor at the inlet of the feed to the pressure vessel/membrane element, PT2-pressure sensor at the outlet of the concentrate from pressure vessel/membrane element, FT1-concentrate flow-meter, FT2-permeate flow-meter, TT1-Pt100 temperature sensor, RV1-electropneumatic regulating valve for the concentrate outlet pressure/concentrate flow-rate control, (4) tube and shell heat exchanger, TT2-temperature sensor, TC-temperature regulator, RV2-cooling water outflow regulating valve, pHT-pH meter.

RS232C port with a touch sensitive LCD graphical display (Omron, Japan). For the communication with a personal computer an interface has to be used (CIF-01, Omron, Japan). The programmable logic controller has eight analog inputs (4-20 mA), two analog outputs (4-20 mA), sixteen digital inputs and sixteen digital outputs. Analog signals from two pressure transmitters (PT1, PT2), temperature transmitter (TT1), concentrate flow transmitter (FT1), permeate flow transmitter (FT2) and pH meter (pHT) are transferred to the PLC and shown on the display. The PLC is programmed to support four different control modes/feed back control loops: constant feed pressure, constant

permeate flow-rate, constant concentrate flow-rate and constant volumetric concentration factor. A simplified flow-chart of the pilot plant unit and measured values as well as the menu and the mode of operation keys are shown on the display. The pumps are switched on/off by pressing the touch sensitive pump symbols on the flow-chart. Similarly, menus and modes of operation are chosen by pressing touch sensitive keys. The set points, low- and high-alarm limits, regulators constants and other parameters can be set in menus. A beeping sound and blinking light are turned on to signalize that the alarm limit, either low or high, has been reached, while the alarm description is shown in the alarm history log.

### Experimental

**Experimental methods:** Pilot scale tests of the concentrating of the lisinopril chromatography main fractions with the reverse osmosis were done both in a batch and in a continuous operation mode under various operating conditions. A 4" Filmtec® BW30-4040 spiral-wound reverse osmosis membrane element with 7.6 m<sup>2</sup> of the active surface area was used (The Dow Chemical Company, U.S.A). A rated product water flow rate of the membrane element is approximately 350 L/h or 45 L/hm<sup>2</sup> and the minimum salt rejection is 98 %. The permeate flow-rate and salt rejection are based on the standard test conditions: 2000 ppm NaCl, 16 bars, 25°C, pH 8, permeate recovery 15% (The Dow Chemical Company, U.S.A). The maximum permissible operating pressure is 41 bars and the maximum operating temperature 45°C. The operating pH range is 2-11.<sup>14,15</sup>

Effects of the concentration of the lisinopril in a feed solution on the performance of the process were evaluated with batch experiments, where the concentrate was recycled back to the feed tank and the permeate was drained. The experiments were done within the lisinopril concentration range from 1 g/L to 100 g/L. The fouling rate was studied in a continuous, single pass operation mode at a constant feed solution concentration. To keep the feed concentration constant, both the concentrate and permeate were recycled back to the feed tank. The experiments, both in the batch and in the continuous operation mode, were run at a permeate flux 20-35 L/hm<sup>2</sup>, temperature

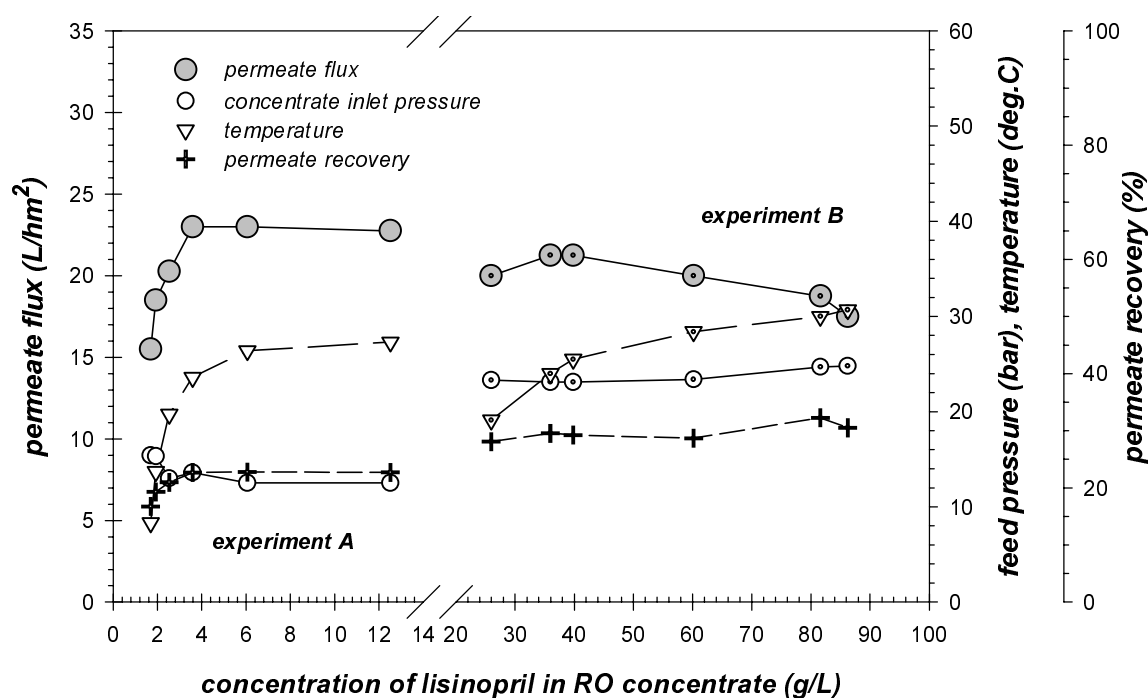
20-30 °C and permeate recovery 15-25%, to simulate the full-scale industrial process, which is normally operated with the constant flux, as close as possible.

Membrane rejection properties were evaluated with a monitoring of lisinopril concentrations in the concentrate and in the permeate. Samples of the concentrate and the permeate were taken at certain intervals during the test runs and analyzed with the described analytical method.

**Analytical method:** The concentration of lisinopril in samples was determined with a high performance liquid chromatography. An HP 1100 HPLC system (Hewlett Packard, USA) with a degasser, gradient pump, autosampler, column thermostat and UV detector was used. The chromatographic system was connected to a personal computer and controlled with a ChemStation software (Agilent Technologies, USA). An HPLC column with the dimensions of 250 x 4.6 mm was packed with 5µm Hypersil ODS stationary phase (ThermoHypersil Ltd., UK). A gradient was used for chromatographic separation (0 min, 5% B; 7 min, 15% B; 16 min, 35% B; 16.5 min, 100% B, 18 min 100% B, 19 min 5% B; 25 min, 5% B). The mobile phase A was made with 95% of the phosphate buffer solution and with 5% of acetonitrile (isocratic grade, Merck, Germany) and the mobile phase B with 50% of the phosphate buffer solution and 50% of acetonitrile. The buffer solution was prepared by dissolving 6.24 g of sodium dihydrogen phosphate dihydrate (p.a., Merck, Germany) in 1000 mL of MilliQ water and with adjusting of pH of solution to 4.0 with a solution of 85% phosphoric acid (p.a., Merck, Germany). The flow rate of the mobile phase was 2.5 mL/min and the temperature of the column 60°C. Lisinopril was detected at 210 nm. The retention time was 3.3 minutes.

### Results and discussion

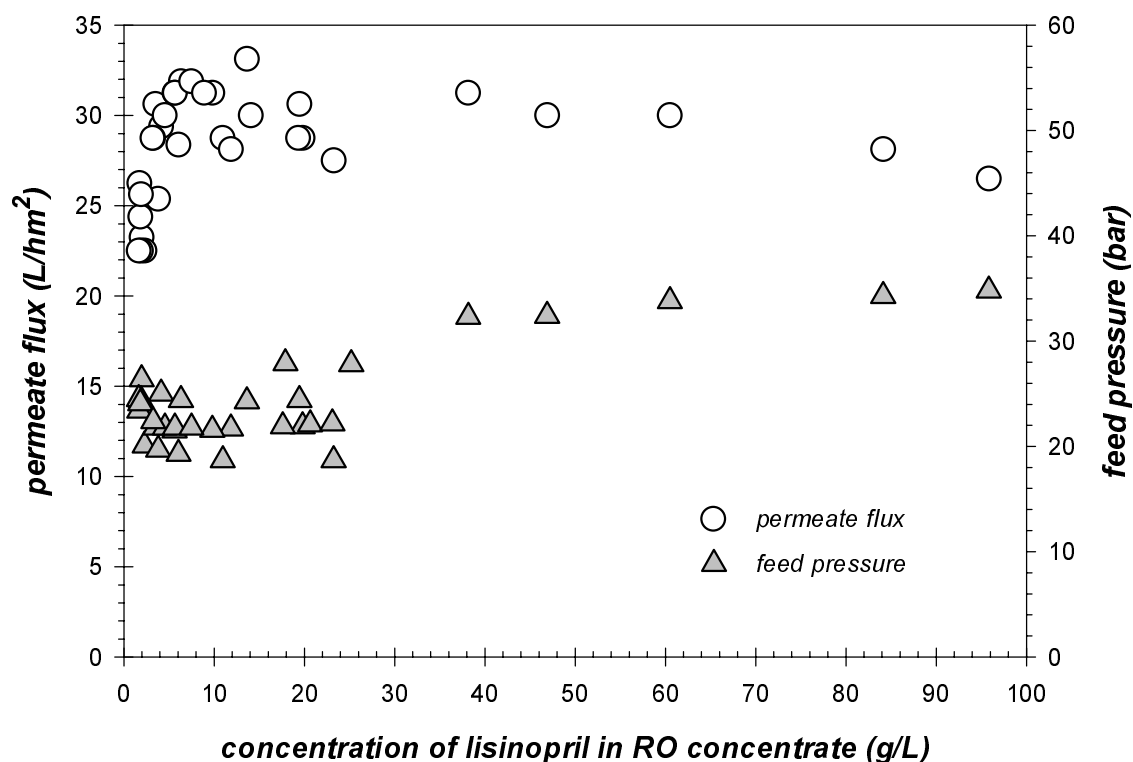
Some results of an extensive pilot plant testing programme are summarized to illustrate the most important aspects which have to be considered for the RO process design, such as effects of various operating variables (concentration of lisinopril in the feed solution, pH, temperature, permeate recovery and feed pressure) on the process performance and membrane rejection properties.



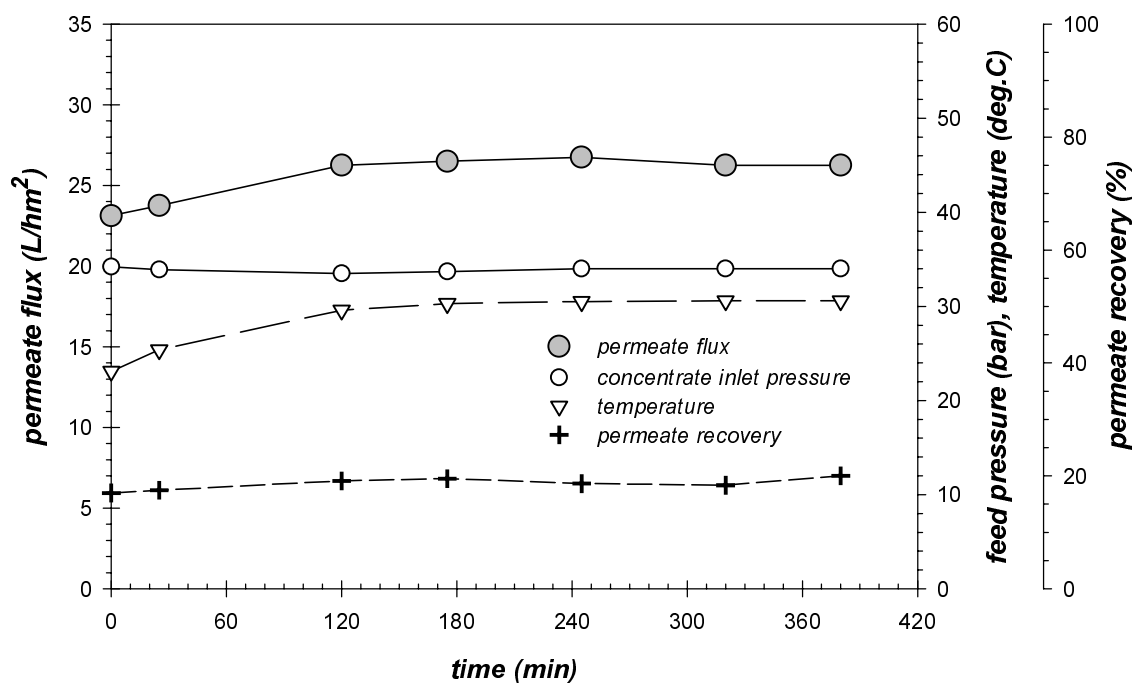
**Figure 2.** The influence of the lisinopril concentration, the temperature and the permeate recovery on the permeate flux and the feed pressure during batch concentration of lisinopril — results of two experiments (Filmtec® BW30-4040 4" spiral-wound RO membrane, pH 10.5).

The results of two experiments where the influence of the concentration, the temperature and the permeate recovery on the permeate flux and the feed pressure was studied are shown in Figure 2. In the experiment A lisinopril solution was concentrated in a batch mode from 1.7 to 12.5 g/L. The permeate flux raised from initial 15 L/hm<sup>2</sup> to 23 L/hm<sup>2</sup>, despite of higher lisinopril concentrations and decrease of the feed pressure from 15.4 bars to 12.5 bars. The reason for such behaviour was the change in temperature, which increased due to friction losses from the initial 8.3 °C to 27.3 °C at the end. The reverse osmosis phenomenon exhibits a strong dependence on the temperature. If the temperature increases and all other parameters are kept constant, the permeate flux will increase almost linearly.<sup>9,10,13</sup> In the experiment B the solution concentration was between 25.7 g/L and 86.2 g/L, the temperature rose from 19.1 °C to 30.7 °C, the feed pressure from 23.3 to 24.8 bars and the permeate flux dropped from 21.3 L/hm<sup>2</sup> to 17.5 L/hm<sup>2</sup>. The flux decreased due to the concentration change during the operation. To keep the permeate flux constant the feed pressure should have been raised. The summarized data of a few batch concentration experiments are shown in the





**Figure 3.** The influence of the lisinopril concentration on the permeate flux and the feed pressure during batch concentration of lisinopril — summarized results of five experiments. The permeate flux was kept approximately  $25\text{--}30\text{ L/hm}^2$  during the experiments. (Filmtec® BW30-4040 4" spiral-wound RO membrane, permeate recovery 15-23%,  $20\text{--}30\text{ }^\circ\text{C}$ , pH 10.5.)



**Figure 4.** Study of a fouling phenomenon during the continuous, single-pass operation mode at a constant feed solution concentration. (Filmtec® BW30-4040 4" spiral-wound RO membrane, lisinopril concentration  $95.8\text{ g/L}$ , permeate recovery 17-20%,  $20\text{--}30\text{ }^\circ\text{C}$ , pH 10.5.)

Figure 3. The permeate recovery was 16-20% and the temperatures 20-30 °C. The average permeate flux was 25-30 L/hm<sup>2</sup> and the feed pressure 20-25 bars at a concentration lower than 20 g/L and about 35 bars at a higher concentration.

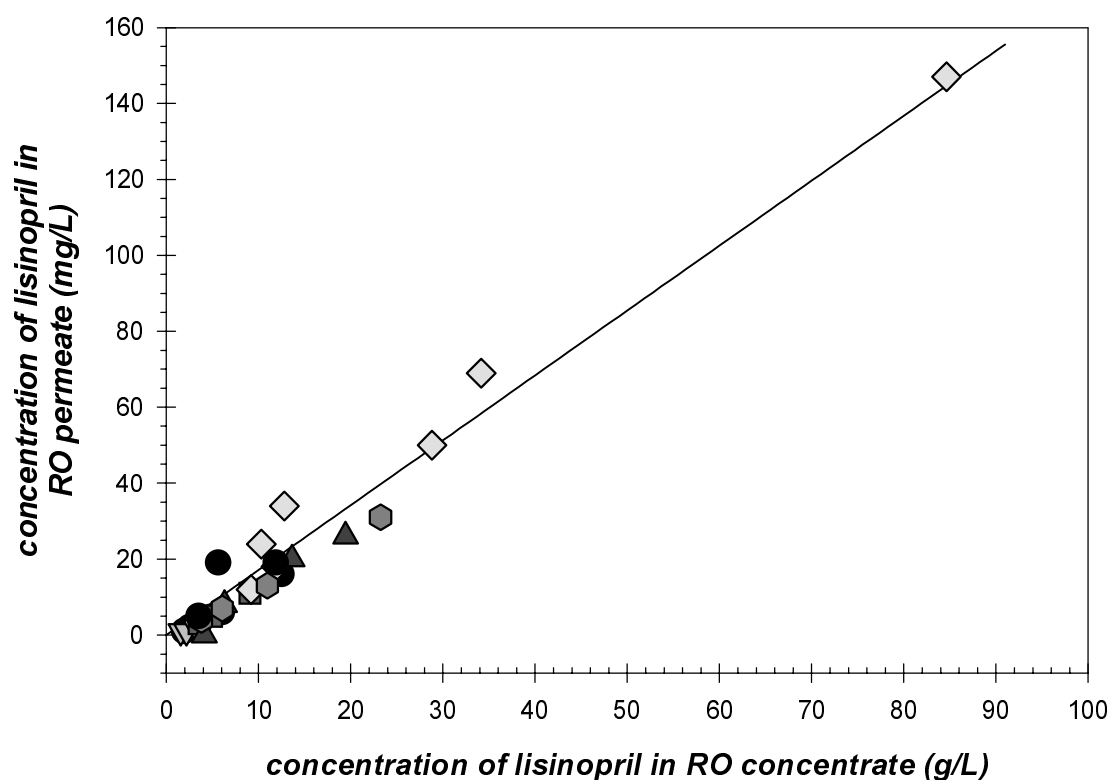
A fouling phenomenon was studied in the continuous, single-pass operation mode at a constant feed solution concentration. The results are shown in Figure 4. The concentration of lisinopril was 95.8 g/L, the permeate recovery 17-20% and the temperature 20-30 °C. The permeate flux and the feed pressure were nearly constant for more than 6 hours. The flux was 23-26 L/hm<sup>2</sup> and the feed pressure approximately 34 bars. Fouling was negligible because of the good quality of the feed solution not containing any problematic solutes which could reversibly or even irreversibly foul the membrane.

The pilot plant testing showed that with a moderate feed pressure the permeate flux 25-30 L/hm<sup>2</sup> can be kept over the whole concentration range. The permeate flux of the lisinopril solution is, compared to the permeate flux of a salt solution reported in the membrane specification<sup>14,15</sup>, relatively high. The reason for the high flux is the low osmotic pressure of the lisinopril solution, which is, calculated for the concentration 100 g/L 5.8 bars.

Membrane rejection properties, which are also one of the important aspects when considering the RO process design, were evaluated together with the study of the permeate flux behaviour. The concentration of lisinopril in the concentrate and in the permeate were monitored during test runs. The results are shown in the Figure 5. Negligible concentrations of the lisinopril in the permeate throughout the whole concentration range indicate a very high, almost complete rejection of the molecule. The rejection of any solute can be described mathematically, with the rejection coefficient, which is defined as<sup>11,12</sup>

$$R = 1 - \frac{C_p}{C_c} \quad (1)$$

where  $C_p$  is the concentration of the solute in the permeate and  $C_c$  is the concentration

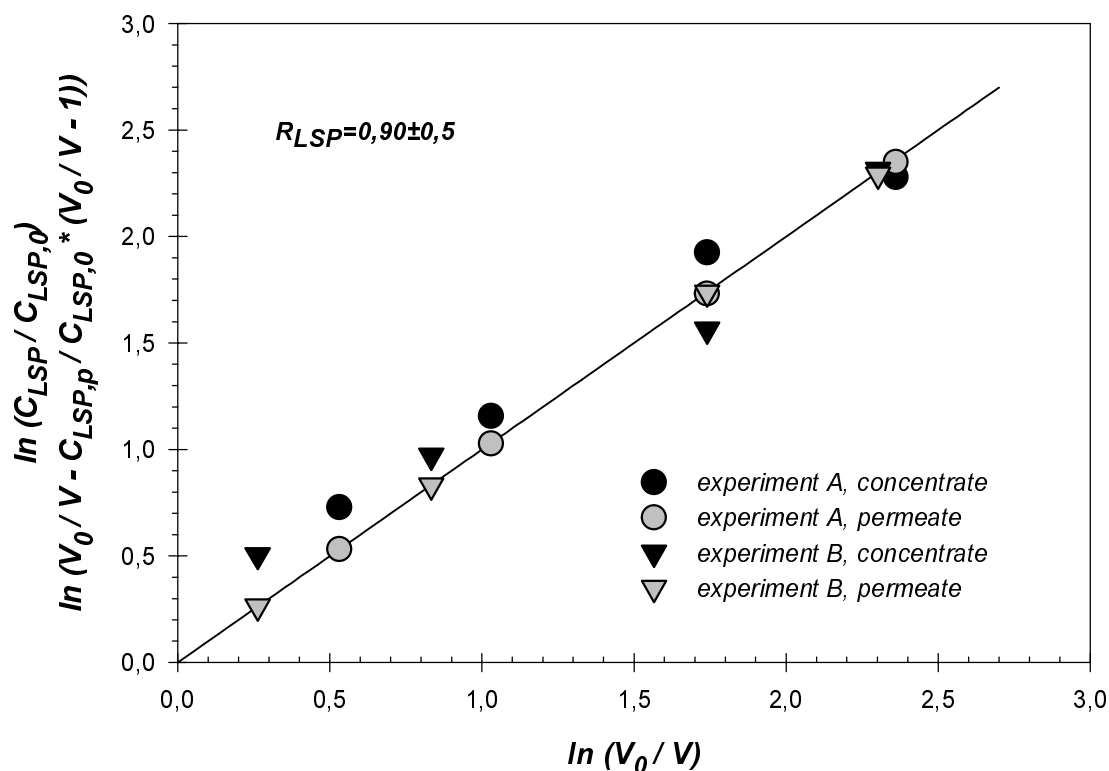


**Figure 5.** The concentration of the lisinopril in the permeate as a function of the concentration of the lisinopril in the concentrate — summarized results of seven experiments. (Filmtec® BW30-4040 4" spiral-wound RO membrane, permeate flux 15-30 L/hm<sup>2</sup>, permeate recovery 15-20%, 20-30 °C, pH 10.5.)

of the solute in the concentrate. When the solute is not present in the permeate then the rejection coefficient is 1 and the membrane rejects the solute entirely. When the concentrations of the solute in the permeate and in the concentrate are equal, then the rejection coefficient is 0 and the membrane does not reject the solute. The lisinopril rejection coefficient can be calculated from the batch concentration experiment data with the use of the following equations<sup>11-13</sup>

$$\ln \frac{C_c}{C_{0,c}} = R \cdot \ln VCF \quad (2)$$

$$\ln \left[ VCF - \frac{C_p}{C_{0,c}} \cdot (VCF - 1) \right] = R \cdot \ln VCF \quad (3)$$



**Figure 6.** The plot of the natural logarithms of the concentration ratios against the natural logarithms of the volumetric concentration factors (VCF) for the lisinopril (LSP) — summarized results of two experiments. The black coloured symbols represent the values calculated from the concentrations of lisinopril in the concentrate and the grey coloured symbols the values calculated from the concentrations of lisinopril in the permeate. (Filmtec® BW30-4040 4" spiral-wound RO membrane, permeate flux 15-30 L/hm<sup>2</sup>, permeate recovery 15-20%, 20-30 °C, pH 10.5.)

where  $C_c$  is the lisinopril concentration in the concentrate in time  $t$ ,  $C_{0,c}$  is the initial lisinopril concentration in the concentrate and  $C_p$  is the lisinopril concentration in the permeate in time  $t$ . The volumetric concentration factor  $VCF$  is defined as

$$VCF = \frac{V_0}{V} \quad (4)$$

where  $V$  is the concentrate volume in time  $t$  and  $V_0$  is the initial concentrate volume. The detailed derivation of the equations can be found in the literature.<sup>13</sup> If the natural logarithms of the concentration ratios are plotted against the natural logarithms of the volumetric concentration factors, a straight line with the slope equal to the rejection

coefficient is obtained. The plot for lisinopril is shown in Figure 6. The slope of the line was calculated with a linear regression. The almost complete rejection of the lisinopril was expected, because of its relatively high molecular weight (423.5 g/mol).

A simple example illustrates the calculations of the membrane area for the full-scale RO unit and the estimation of energy requirements and their comparison with the energy requirements of a single-stage vacuum evaporator. The calculations are based on the results of the experiments. **Example:** 3 m<sup>3</sup> of the lisinopril solution has to reach the concentration of 90 g/L from the initial concentration of 3 g/L within 4 hours. The permeate flux is 25 L/hm<sup>2</sup>, the feed pressure 30 bars and the permeate recovery 15%.

The volumetric concentration factor (*VCF*) is calculated from the ratio of the final concentration of the lisinopril (*C*) to the initial (*C*<sub>0</sub>) concentration

$$VCF = \frac{C}{C_0} = \frac{90 \text{ g/L}}{3 \text{ g/L}} = 30 \quad (5)$$

the volumes of the concentrate (*V*) and the permeate (*V*<sub>*p*</sub>) are calculated as follows

$$V = \frac{V_0}{VCF} = \frac{3000 \text{ L}}{30} = 100 \text{ L} \quad (6)$$

$$V_p = V_0 - V = 3000 \text{ L} - 100 \text{ L} = 2900 \text{ L} \quad (7)$$

the required membrane area (*A*) is calculated from the permeate volume, proces time (*t*) and permeate flux (*j*<sub>*p*</sub>)

$$A = \frac{V_p}{t \cdot j_p} = \frac{2900 \text{ L}}{4 \text{ h} \cdot 25 \text{ L/hm}^2} = 29 \text{ m}^2 \quad (8)$$

finally the feed flow (*Q*<sub>*feed*</sub>), the power of the feed pump (*P*<sub>*FP*</sub>) end the theoretical

energy consumption for concentrating the solution with the RO ( $E_{RO}$ ) are calculated from the required permeate flow ( $Q_p$ ), the permeate recovery ( $PR$ ) and the feed pressure ( $\Delta p_{feed}$ )

$$Q_{feed} = \frac{Q_p \cdot 100\%}{PR} = \frac{725L/h \cdot 100\%}{15\%} = 4840L/h \quad (9)$$

$$P_{FP} = Q_{feed} \cdot \Delta p_{feed} = 4840L/h \cdot 30bars = 4.03kW \quad (10)$$

$$E_{RO} = P_{FP} \cdot t = 4,03kW \cdot 4h = 16.2kWh \quad (11)$$

Evaporation of an equal amount of water at 30 °C in the single-stage vacuum evaporator ( $p=42,4$  mbars,  $\Delta H_{evap.}=2431$  kJ/kg water) requires ( $E_{EV}$ )

$$E_{EV} = m \cdot \Delta H_{evap.} = 2900kg \cdot 2431kJ/kg = 19.6MWh \quad (12)$$

or 2.7 tons of a superheated steam (2 bars, 120 °C), condensed and cooled to 30 °C ( $\Sigma\Delta H=2581$  kJ/kg steam). Simplified calculations not include hydraulic and electric efficiencies of pumps, any hydraulic and thermal losses and energy requirements of a vacuum system, RO heat exchanger and evaporator condensers.

Electricity costs for industrial customers equals \$0.05/kWh and steam \$15/ton (\$0.021/kWh). The costs for concentration of one batch ( $3m^3$ ) of the lisinopril solution with the reverse osmosis are \$0.81. The costs for the evaporation are higher, \$40.5, despite the more expensive electricity.

Investment costs of a full-scale RO unit are \$50.000 to \$100.000 and of a single-stage vacuum evaporator \$150.000 to \$200.000.

### Conclusions

Evaporation of large volumes of water for concentrating the main fractions from the lisinopril chromatography is not economical. For this reason a comparative study of energy and investment costs for the reverse osmosis and evaporation was done. The pilot plant testing showed that with a moderate feed pressure the permeate flux 25-30 L/hm<sup>2</sup> can be kept over the whole concentration range. Fouling was negligible because of the good quality of the feed solution not containing any problematic solutes which could reversibly or even irreversibly foul the membrane. Rejection of lisinopril by the membrane is practically complete. A required full-scale production capacity and the results of the experiments formed a base for a calculation of a membrane area for a full-scale unit and for an estimation of energy requirements and energy costs for the reverse osmosis and the single-stage vacuum evaporator. The calculation showed that the use of reverse osmosis is more economical than evaporation.

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The authors wish to sincerely thank Mr. Janez Nosan from ABN d.o.o, Celje, Slovenia, who unselfishly shared his vast knowledge of membrane processes with us. Mr. Nosan has also constructed the described RO pilot plant unit.

### List of symbols used

$A$	membrane area (m <sup>2</sup> )	$j_p$	permeate flux (L/hm <sup>2</sup> )
$C$	concentration (mg/L, g/L)	$m$	quantity of water for evaporation (kg)
$C_c$	concentration of solute $i$ in concentrate (mg/L, g/L)	$LSP$	lisinopril
$C_{0,c}$	initial concentration of solute $i$ in concentrate (mg/L, g/L)	$p$	pressure (mbar, bar)
$C_p$	concentration of solute $i$ in permeate (mg/L, g/L)	$\Delta p_{feed}$	feed pump pressure (bar)
$E_{EV}$	energy consumption of evaporation (kWh)	$P_{FP}$	feed pump power (kW)
$E_{RO}$	energy consumption of RO (kWh)	$PR$	permeate recovery
$\Delta E_{evap.}$	enthalpy of evaporation (kJ/kg)	$R$	rejection coefficient of solute $i$
		$Q_{feed}$	feed flow (L/h, m <sup>3</sup> /h)
		$Q_p$	permeate flow (L/h, m <sup>3</sup> /h)
		$t$	time (s, h)
		$V$	volume of concentrate (L, m <sup>3</sup> )

$V_0$	initial volume of concentrate (L, m <sup>3</sup> )	$VCF$	volumetric concentration factor
$V_p$	volume of permeate (L, m <sup>3</sup> )		

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### Povzetek

Lizinopril je aktivna farmacevtska učinkovina iz skupine ACE inhibitorjev. Proizvajamo ga sintetsko z večstopenjsko sintezo. Po končani sintezi ga očistimo z nizekotlačno tekočinsko kromatografijo pri kateri uporabljamo polarno mobilno fazo na vodni osnovi. Lizinopril po končani kromatografiji izoliramo iz glavnih frakcij z oborjanjem. Glavne frakcije koncentriramo v enostavnem enostopenjskem vakuumskem uparjalniku. Ker uparjanje velikih količin vode ni ekonomično lahko za koncentriranje uporabimo reverzno osmozo. Uporabnost reverzne osmoze za koncentriranje glavnih frakcij smo pri različnih obratovalnih pogojih preverili s poskusi v pilotnem merilu. Rezultati pilotnih poskusov ter željena kapaciteta industrijske naprave so bili osnova za izračun potrebne površine membran ter za oceno stroškov energije in investicije za reverzno osmozo in uparjalnik. Poenostavljen izračun je pokazal, da je uporaba reverzne osmoze ekonomsko upravičena.