SUMMARY

An ordinary approach to conduct the chemical synthesis of Active Pharmaceutical Ingredients (API) would be to partially or completely extract, or exchange, solvents by method of multiple-effect vacuum evaporation, or concentration of intermediates and end-products. Due to the accessibility of the equipment (conducting chemical reactions, crystallization, extraction, etc.), the most frequently used method is the single-stage vacuum evaporation, using evaporators equipped with a vacuum vessel with a condenser and tank. However, when carrying out a technological procedure using water as a solvent, such as in the case of concentrating the main fractions of Lisinopril collected by using column chromatography, it might be more rational to perform membrane separation instead of vacuum evaporation, for example reverse osmosis. This method would also be particularly more reasonable to use when dealing with evaporation of greater quantities of water, however, reverse osmosis may also be used for evaporating mixtures of organic solvents and water, which is described and presented in this dissertation/master's thesis.

The purpose of this dissertation is to illustrate the development of applying reverse osmosis to the procedure of concentrating the aqueous solution of Lisinopril following purification by column chromatography.

The results obtained from the pilot experiments are presented in the initial section of this dissertation. Based on these results and information concerning the production capacity, we were able to devise a plan for a reverse osmosis plant unit. We have also included in the dissertation a comparison of the projected and actual purchase costs of the equipment, as well as a comparison between the equipment expenses for vacuum distillation and for reverse osmosis.

The actual operating parameters of the plant unit are presented in the definitive section of this paper, along with a comparison between the requirements and the actual parameters, and the pilot and industrial data. The pilot experiments have shown that reverse osmosis is suitable for use in concentrating the aqueous phases of Lisinopril. The permeate flux may be maintained between 25 and 30 L/hm^2 by regulating the feed pressure up to 35 bar. Membrane fouling has been kept to a minimum, due to Lisinopril's high solubility and the purity of its main fractions. The retention of Lisinopril in the concentrate stream was higher than 99%. The initial concentration of Lisinopril in the aqueous solution was approximately 2 g/L, whereas the final was between 90 and 100 g/L. Thus, we have reduced the volume from approximately 4000 L to about 100 L of final concentrate. Throughout the concentration procedure, the medial permeate flow was roughly 1500 L/h, and the medial permeate flux 25 L/hm^2. The total membrane surface was 60 $m^{2,}$ which has proven sufficient for the projected industrial-scale production capacity of Lisinopril, as well as for an eventual possibility of amplifying the early stages of the synthesis.

The estimated purchase costs of equipment were based on prices of similar equipment acquired beforehand by several manufacturers, which ranged between US$70,000 and US$80,000. We can see this would lead to major purchasing savings considering the procurement price for a new vacuum evaporator is between US$150,000 and US$200,000. The final price for the reverse osmosis equipment was circa 40% higher than the projected, equalling US$115,000, but even so, the latter equipment was still cheaper than the cost of a new vacuum evaporator.

We have also included a comparative estimate of energy consumption and membrane-replacement costs, as well as investment costs. Energy consumption for carrying out a concentration procedure of one batch of Lisinopril, 100 kg, is estimated at US$1,9 (0.23 cents/kg of Lisinopril), while costs incurred by using the classic method of vacuum evaporation are estimated at approximately US$55.5 (6.8 USD/kg of Lisinopril). Taking into account this contrast between the energy consumption expenses, coupled with the yearly production of Lisinopril, we can observe the significant energy economisation that may be achieved.

Based on precedent experience, costs of yearly membrane replacement are estimated between US$600 and 1000, depending on the frequency of the procedure. The expected life expectancy of membranes – bearing in mind regular maintenance and cleaning operations – is 2 to 3 years.

In the course of this study, we have also conducted a reflux of the permeate in the technological procedure, with which we have confirmed the reported membrane permeability data points for Acetonitrile and Ammonia for reverse osmosis. By reusing the permeate, we have built up positive pressure on the environment as well as reduced the costs of end-product production.

Utilising technological validation, we were able to confirm the suitability and efficiency of the equipment. The unit proved to work without having major technological difficulties nor undergoing unforeseen maintenance works.

Based on the demonstrated results of using reverse osmosis, instead of vacuum evaporation, in the process of manufacturing and concentrating Lisinopril, the work was carried out in an expertly manner. Reverse osmosis has proved to be an adequate technological solution and an appropriate alternative to the method of vacuum evaporation.