

# MULTI-STAGE LIQUID/LIQUID EXTRACTION WITH A ZAIPUT APPARATUS

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## ABSTRACT

Poorly separable liquid/liquid mixtures often pose a major challenge in pharmaceutical extraction. In particular, compounds containing a low difference of density are difficult to separate using mixer-settler setups. The Zaiput device can prove an advantage over present liquid/liquid extractors. The research work involves characterizing the Zaiput apparatus for liquid/liquid extraction of pharmaceutical compounds with the model solvent system toluene-water. The extraction efficiency was investigated for a solvent mixture containing toluene-acetone-water residence times. To evaluate the separation success, the outlet's concentrations are measured via IR spectroscopy.

*Keywords: multi-stage liquid/liquid extraction, countercurrent liquid/liquid extraction, continuous extraction, membrane separation*

## INTRODUCTION

Liquid/liquid extraction (LLE) represents an important processing step in the pharmaceutical industry and becomes more popular among the separation techniques. Compared to distillative separation, LLE provides reduced energy consumption and additionally, there is the opportunity to process thermosensitive compounds due to the low operating temperature. In practice, multi-stage processing is often carried out to achieve efficient separation and increase the recovery of a product. This approach is required when a small partition coefficient impedes the separation.

The Zaiput (Figure 1) represents a new device in which multi-stage countercurrent liquid-liquid extraction (MCCE) can be realized continuously even on a laboratory scale. Improved extraction rates result from higher mass transfer coefficients at the micro and milli scales. The high mass transfer rates in the slug flow led to equilibrium at each stage prior to the separation unit.

However, the separation of the phases is challenging since the surface forces dominate over the traditionally used gravity force. Membrane separation is based on the utilization of surface forces and suitable for realizing phase separation. This type of separation is used in the zaiput.

Advantages of the Zaiput compared to conventional LLE apparatus include: continuous operation,

separation of liquids with the same density or emulsions, the plug-and-play functionality, as well as the easy and direct possibility to scale-up due to a modular design.

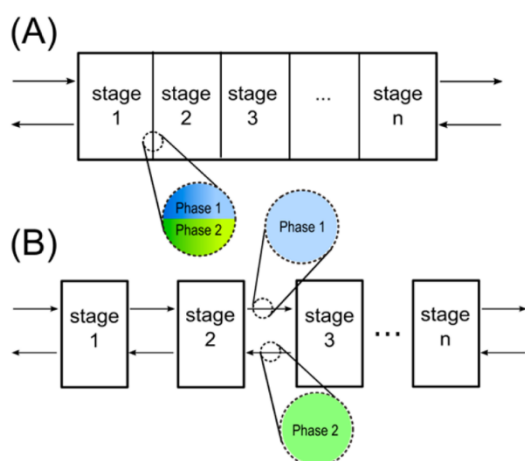


**Figure 1:** Zaiput multi-stage extraction platform [Weeranoppanant, 2020]

MCCE can be divided into two types based on the arrangement of the contacting units: differential and discrete arrangement (Figure 2). Differential contacting includes multiple stages operating continuously in a single device with no separator between the stages. On the contrary, discrete MCCE requires phase separation prior to pumping to subsequent stages. As in the Zaiput extraction and separation operate independently, this setup is scalable to a large number of stages.

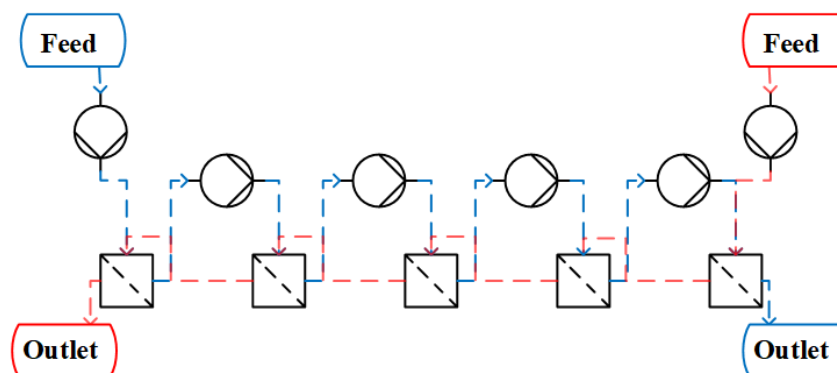
LLE in industrial applications is usually arranged by countercurrent flow design (CC-LLE), which offers the

lowest consumption of extractant. With this approach, the aqueous raffinate is supplied from one stage to an earlier stage as feed, while the organic phase is conveyed in the reverse flow direction. Therefore, the overall system can achieve high recovery even if the recovery of the product in each stage is low. In multi-stage extraction, selectivity and process yield are accordingly decoupled, since yield depends on the number of extraction stages used.



**Figure 2:** Two categories of MCCE's contacting unit arrangement: (A) differential and (B) discrete [Weeranoppanant, 2017].

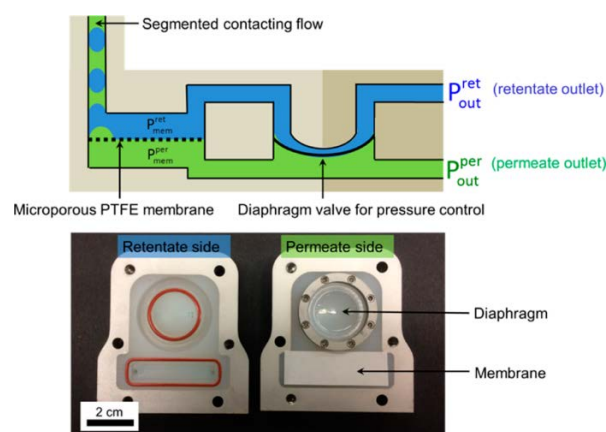
Figure 3 displays the experimental set-up. Multi-channel peristaltic pumps convey the liquids from one stage to the next. Mass transfer is realized by droplet formation in capillaries by segmented flow mixing. In order to achieve equilibrium after each stage, a phase separation via membrane follows subsequently. A membrane acts as a barrier for the two immiscible phases. Preferably, the membrane is wetted by one of the phases whereas the other remains non-wetting. Moreover, each separator incorporates a self-tuning pressure regulating



**Figure 3:** Flow diagram of countercurrent extraction process; aqueous phase in blue; organic phase in red

element which allows fluctuations caused by inaccurate pumping still allow robust operation (Figure 4). In case of a hydrophobic membrane, the organic (wetting phase; green) flows through the membrane, while the aqueous (non-wetting phase; blue) retains it.

Equilibrium stage is obtained when the mass transfer in the mixing tube is sufficiently long and the separator operates effectively.



**Figure 4:** Schematic and photographic illustration of the membrane-based separator with self-tuning element (heavy curved line) providing a constant pressure difference across the membrane (vertical lines). The aqueous and organic liquids are shown in green and blue [Adamo, 2013; Weeranoppanant, 2017].

## CHARACTERIZATION OF THE DEVICE

In this study, the applicability of the Zaiput device for the liquid/liquid extraction of pharmaceutically relevant compounds is investigated. In the first step, a model compound system (toluene-water) without a transition component is considered and investigated with regard to the separation performance of the membrane.

For this purpose, the residence time was varied over the volumetric flow rates of the organic and aqueous feed streams at a constant number of stages  $N=2$ . The experimental matrix is shown in the Table 1.

**Table 1:** Variation of the volumetric flow rates of the experiments.

$Q_{org}$ , mL/min	$Q_{aq}$ , mL/min
1	2
2	1
2	2
3	1
2.5	1

In the preliminary tests without transition component, no influence could be detected when varying the volume flow. In all experiments, perfect separation occurred so that retentate and permeate can already be obtained pure after the first residence time.

### EXTRACTION EFFICIENCY

The obtained findings are applied to a classical ternary system to test the extraction efficiency. Water as the extraction solvent was used to extract acetone from toluene feed solvent. A high percentage of acetone was added to evaluate the system's ability to manage variations in flow rates across different stages. In addition, acetone significantly reduces the interfacial tension making it a challenging case study.

Analogous to the experiments without transition component, different residence times were set (Table 1). The organic phase constituted a mixture of toluene and acetone in a ratio of 1:1. In all experiments, a sample was taken after 1, 3 and 5 residence times. The duration of the sampling is set in each case equal to the duration of one residence time. Characteristic parameters for the extraction process, such as the minimum residence time, the depletion of the transition component as a function of the throughput, and the stage efficiency are determined.

The separation performance drops significantly during experiments with acetone. The permeate sample contain more than 20% acetone, whereas it should actually

consist only of toluene. However, there is a trend toward worse separation performance in the experiments with a volumetric flow rate of 2.5 mL/min and above.

### MEMBRANE SELECTION

The influence of the membrane is particularly noticeable, as the best results were obtained after the membrane was replaced. During the experiment, a deterioration of the separation performance is already evident, so that the amount of acetone in the organic phase increases over the course of the experiment. Since the duplicate determination of the tests was always carried out exactly one after the other, a similar course should have been shown if the membrane had not deteriorated. However, this conclusion does not occur, leading to the assumption that the membrane loses its filtering effect in the presence of toluene. Furthermore, the poor separation performance indicates that the membrane is not suitable for toluene. The influence of the mixing ratio of acetone and toluene is to be checked further, since different results can be expected with a lower proportion of acetone.

### ANALYTICS

Furthermore, analytics are developed to evaluate the extraction success by determining the percent extraction and efficiency. The outlet concentration of each component was analyzed by IR spectroscopy. For calibration, signals with the highest intensity are used which are  $1222.95\text{ cm}^{-1}$  for acetone,  $733.54\text{ cm}^{-1}$  for toluene and  $3551.12\text{ cm}^{-1}$  for water.

The three substances exhibit a miscibility gap, resulting in the formation of a two-phase system at certain mixing ratios which prevents the homogeneity of the sample. Thus, it is impossible to describe exactly the mixing ratio of the sample by means of a partial quantity of the sample. By adding a diluent, a homogeneous system is obtained but the detection capability decreases due to the dilution. The system also proves to be significantly more complex in terms of analysis.

A further challenge constitutes the high volatility of acetone (306 hPa at  $25^{\circ}\text{C}$ ), which leads to falsified sample compositions. To counteract volatilization, the samples must be measured immediately or stored refrigerated.

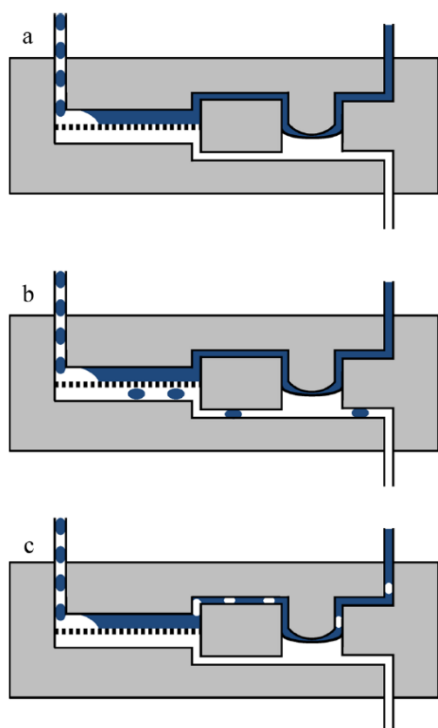
Additionally, water has a high absorption coefficient compared to acetone and toluene. This leads to a

homogeneous broadening at certain intensities, since the linearity of the Lambert Beer law is limited by the Einstein coefficients and therefore, not all molecules can be energized. The high rate constant of autoproteolysis of water also proves troublesome. As a result, the natural linewidth is greatly widened and consequently, other signals are overlapped.

## DISCUSSION

Operating limits can be caused by pressure difference either too large or too small (Figure 5). If the pressure difference across the membrane is large, the retained phase may break through. Possible reason for a high pressure difference can generate a low surface tension, which would require a replacement of the membrane. The flow rate also affects the internal pressure, so that a lower flow rate has to be set. Changing the solvent ratio could also led to better results.

If the pressure is unsuitably, the permeate phase is partially retained by the membrane and exits with the retentate phase. A possible solution could be to lower the flow rate of the permeating phase or changing the solvent ratio.



**Figure 5:** Schematic representation of the different modes of membrane-based separation: (a) under normal conditions; (b) breakthrough of the retained phase; (c) retention of the permeate phase [Adamo, 2013].

In the initial trials, only two-stage extractions were performed. For future work, higher numbers of stages will be investigated. Moreover, the statements obtained need to be reviewed by multiple determinations and transferred to other systems.

## ACKNOWLEDGMENT

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## NOMENCLATURE

N total number of stages in the setup

Q volumetric flow rate, mL/min

## SUBSCRIPT

aq aqueous

org organic

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