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# Sustainability benefits of a continuous phase transfer catalyzed process for a model pharmaceutical intermediate

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## ABSTRACT

We have developed processes for the phase transfer catalyzed O-alkylation of 3-phenyl-1-propanol. Firstly a batch solid-liquid (S-L) implementation was tested with toluene solvent. By running the organic phase neat and with 6 mol equivalents of 50 w/w% NaOH (aq.) at ambient temperature, the conversion for a batch liquid-liquid (L-L) process was found to be as good as for the S-L process with a shorter reaction duration. A continuous counter-current L-L process was also developed. The sustainability performance of the batch S-L, batch L-L and continuous L-L processes was compared at a design output of 100 te/a. The synergy of phase transfer catalysis and continuous processing demonstrated a number of green and sustainability benefits, i.e. higher energy efficiency, lower VOC emission, better volume efficiency, smaller processing inventory, smaller equipment footprint, lower product loss through waste and lower operating cost.

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## 1. Introduction

Phase transfer catalysis (PTC) has long been used by chemists to facilitate reactions between two immiscible phases via a phase transfer agent, e.g. quaternary ammonium salts, that transfers a reactive species from one phase to the other (Starks et al., 1994). The environmental benefits of phase transfer catalysts include the following possibilities (Makosza, 2000; Ooi and Maruoka, 2007; Starks et al., 1994):

- to replace environmentally damaging dipolar aprotic solvents such as DMF, DMSO, THF;
- to replace stronger and/or highly toxic bases such as NaH and organic bases;
- to increase reaction conversion, selectivity and/or yield and hence reduce waste generation.

Since time immemorial, batch processing has dominated pharmaceutical and fine chemical manufacturing. Compared to continuous

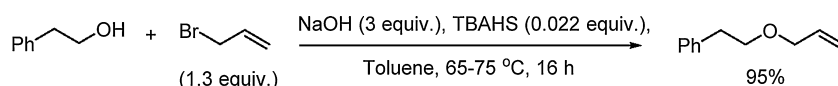
processing, batch operation in general is less robust, less mass and energy efficient, resulting in higher costs and more solvent waste. Continuous manufacturing potentially offers other attractive benefits like greater reliability and safety, and better sustainability (Fletcher, 2010; Mascia et al., 2013).

There have been a number of studies focused on continuous (counter-current as well as co-current) PTC reactions but they mostly emphasized on the performance of an individual continuous reactor-settler unit. For instance, Hayashi et al. (1991) proposed a continuous counter-current laboratory scale tower reactor for continuous operation of a liquid-solid-liquid triphasic catalysis. Weng et al. (1997) designed a five-section, vertical, continuous-flow, stirred laboratory reactor with 163 cm<sup>3</sup> total volume at about 1 mL/min continuous flow rate. Hsiao et al. (2005) similarly evaluated the feasibility of using a continuous-flow stirred vessel reactor (CFSVR) (250 mL effective volume, 0.5 cm<sup>3</sup> min<sup>-1</sup> for each phase) for a triphasic etherification catalyzed reaction. A microchannel with two inlets and two outlets was also used to carry out two-phase catalytic phase transfer reaction (Aljbour et al., 2009).

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**Fig. 1 – Referenced reaction: O-alkylation of 2-phenyl-1-ethanol.**

A third-liquid phase transfer catalysis (TLPTC) was developed in a continuous two-phase-flow reactor at an eluent flow rate of  $1.0 \text{ cm}^3 \text{ min}^{-1}$  (Yang and Huang, 2011). The third-liquid phase was designed to reside in the middle of the reactor with the aqueous and organic phases flowing through it counter-currently. Two membranes were installed in the reactor to prevent the entrainment of the catalyst into the outlet streams. Zani and Colombo (2012) deployed segmented flow produced by a T-junction inlet (10-mL volume PTFE-tubing reactor, flow rate up to 2 mL/min for each solution) with 1-mm internal diameter for liquid-liquid biphasic O-alkylation of substituted phenols with alkyl halides. Studies on the mixing effects in the O- and S-alkylation of selected phenol and thiophenol substrates with TBAB were performed in lab scale continuous flow reactor like coil reactor, packed bed reactor (filled with stainless steel beads) and glass chip microreactor (Reichart et al., 2013). However, none of the above publications evaluated or reported sustainability comparisons between the batch and continuous processes as a whole.

The objective of this work is to evaluate the sustainability benefits of operating a phase transfer catalyzed process in a continuous flow system as compared to a traditional batch process. In this paper we extend the scope and compare the sustainability performance of a batch and continuous phase transfer catalyzed system for the whole process (from raw materials to product purification) at a hypothetical design scale of 100 te/a. The benefits that could potentially be attained are minimization or replacement of solvent, higher reactivity and selectivity of the active species, higher yields and cleaner reaction, minimization of wastes, reduced cycle time, lower energy consumption and greater safety.

In order to provide a basis for comparison at a whole process level we have developed both the batch and continuous processes to a comparable level. Of course, it would only be possible to make a fully realistic comparison of the continuous and batch systems by carrying the design through to operation at industrial scale. The following paper reports sufficient analysis to identify the major performance differences that would be expected between batch and continuous processes, focusing on materials and energy efficiency, major equipment costs and waste generation issues as the main discriminators. In doing this we do not artificially try to enforce inappropriate operating conditions on either batch or continuous designs, but rather design each separately, adapting the process to fit. By this means we seek to make a more robust and fair comparison.

## 2. Experimental work

### 2.1. Model chemistry system

The Williamson ether synthesis is one of the basic organic reactions which have been greatly simplified by phase transfer catalysis, and that has become the method of choice in many such processes today. Literature reports the batch, phase transfer catalyzed O-alkylation reaction of 2-phenyl-1-ethanol (Fig. 1) at kg scale (Giles et al., 2004). The batch process conditions were temperature at 65–75 °C, use of TBAHS (n-Bu<sub>4</sub>NHSO<sub>4</sub>, 0.022 mol eq.) as catalyst, 3 mol eq. of NaOH microparticles and a lot of solvent (toluene) at a long reaction time (minimum 16 h) to produce 95 mol% [2-(2-propenyloxy)ethyl]benzene product (by GC). The product was an intermediate used for the synthesis of Sibenadet Hydrochloride, the active ingredient of a former phase III candidate drug Viozan.

With reference to this system, we identified heteroatom O-alkylation of 3-phenyl-1-propanol (Fig. 2) as the model reaction for this study.

Three process schemes based on this reaction were evaluated for sustainability comparisons:

- (1) Solid-liquid (S-L) system in batch mode – a traditional manufacturing process using NaOH solids in the reaction
- (2) Liquid-liquid (L-L) system in batch mode – an improved batch method using NaOH aqueous in the reaction, which could facilitate flow processing
- (3) Liquid-liquid system in continuous mode.

The final product was specified to have at least 95 w/w% of (3-(allyloxy)propyl)benzene with at most 0.1 w/w% of residual TBAB. As the isolation of 3-phenyl-1-propanol (SM) from the product, (3-(allyloxy)propyl)benzene (P) would be difficult due to their similar boiling temperatures (SM: 235 °C; P: 255 °C) compared to that of allyl bromide (AB: 71 °C), SM was selected as the limiting reagent and its complete conversion was sought. Similar to the referenced reaction, 0.028 mol eq. of TBAB was used in all our case studies.

### 2.2. Experimental procedures

Experiments in small scale (40–120 mL) were carried out to evaluate the reaction at different conditions. Using these data and the BRITEST methodology (Sharratt et al., 2003), we identified the critical parameters required to enhance the reaction performance, the knowledge gaps and also the feasible regime of operation. Experiments on the 40 mL scale were conducted in the Multi-max<sup>TM</sup> reactor while the 120 mL experiments were conducted in a 250 mL 3-neck-round bottomed flask equipped with a condenser and magnetic stirrer bar stirred at the maximum achievable agitation speed.

For S-L system conducted at 120 mL scale, NaOH pellets were added to the flask followed by toluene (64 mL) and the reaction mixture was heated to 45 °C using an oil bath with a thermostat controller. The homogenous mixture of AB, TBAB and SM was then added via a syringe and the reaction mixture was heated to 55 °C. At the end of the reaction, water (36 mL) was added to dissolve the precipitates before pouring the mixture into a 250 mL separation funnel. The NaOH layer was separated. Three water washes were carried out to extract TBAB from the product. The amount of water required for each wash was 3.2, 1.6 and 2.4 mL respectively. Formation of the middle layer was observed during the first water wash and was removed for analysis.

For L-L system conducted at 120 mL scale, 50 w/w% aqueous NaOH solution was added to the flask followed by a homogenous mixture of AB, TBAB and SM via syringe addition at room temperature. At the end of the reaction, water (11 mL) was added to dissolve the precipitates before pouring the mixture into a 250 mL separation funnel. The NaOH layer was separated. Three water washes were carried out to extract TBAB from the product. The amount of water required for each wash was 3.2, 1.6 and 1.2 mL respectively. Formation of the middle layer was observed during the first water wash

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