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Rapid process development using oscillatory baffled mesoreactors – A state-of-the-art review

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Abstract: The mesoscale oscillatory baffled reactor (meso-OBR) is a novel technology for reaction engineering and screening applications. The meso-OBR exhibits high degrees of plug flow at low and moderate net flow rates (0.3–8 mL/min). For example, central and integral baffle configurations give good plug flow at net flows of $Re_n = 4.3$ –34 for $\psi = 4$ –8 and $\psi = 5$ –10 respectively using $St = 0.4$ –0.8. Recently, the batch equivalency of plug flow has been exploited to screen multiple equivalent batch reactions in a single experiment, minimising waste generation and reducing process development time. In addition, good multiphase mixing has been demonstrated using a variety of baffle configurations, presenting a wide range of potential applications for the technology. In this review, the characteristics of the mesoreactor that are beneficial for rapid process screening are explained. The results of all public domain reports of the use of mesoscale OBRs for screening are reported and the outlook for the technology is discussed. Throughout, the technology is compared and contrasted with the findings for “conventional scale” (>15 mm diameter) OBRs. A variety of case studies are used for illustrative purposes.

Keywords: Mesoscale, plug flow, rapid screening, temperature, reactor, flow chemistry

Contents:

1 Introduction	2
2 Oscillatory baffled mesoreactors	2
2.1 Oscillatory flow mixing	2
2.2 Mesoscale oscillatory baffled reactors	3
2.3 Governing dimensionless groups	4
2.4 Characteristics for screening	5
2.4.1 Plug flow	5
2.4.2 Enhanced mass transfer	7
2.4.3 Multi-phase mixing	8
2.5 Current uncertainties in the literature	9
2.5.1 Heat transfer	9
2.5.2 Power density	10
2.5.3 Scale-up	11
2.6 Comparison with other flow chemistry platforms	12
3 Rapid screening using mesoreactors	12
3.1 Summary of oscillation conditions for flow chemistry	14
3.2 Temperature screening	15
3.2.1 Heat pipes/thermosyphons	15
3.2.2 Rapid temperature management and isothermalisation	15
3.3 Next steps for meso-OBR screening	16
3.4 Limitations of the meso-OBR screening platform	17
4 Conclusions	17
Nomenclature	18
Acknowledgements	19
References	19

1 Introduction

Process development often involves identification of optimum operating conditions or determination of chemical kinetic data through chemometrics using small scale screening experiments [1]. The objectives are to improve chemical yields and selectivities whilst reducing process variability (or increasing robustness). Often, standard experimental design techniques are employed to reduce the development time and costs of screening.

Process/product development is increasingly competitive, making it increasingly desirable to minimise the time from product inception to market [2, 3]. One of the major bottlenecks is the process screening stage. This is exemplified in the pharmaceutical industry, where very high numbers of candidate chemicals must be characterised [2] and the more promising synthesis routes optimised.

Common screening platforms include the conventional bench-scale batch reactor (typical 50–500 mm diameter [4]) and more efficient microwell plate array. Plate arrays consisting of numerous small-scale (mL– μ L) sample wells have been used in processes from biology, biochemistry, chemistry and pharmacology [5]. They facilitate high throughput screening by enabling many (e.g. 96, 384, 1536) reactions to be performed sequentially in parallel to generate a full response surface. When combined with process automation in the form of robotics, basic screening sequences can be conducted quickly without an operator [2, 6]. The use of process automation and multi-parallel batch reactors facilitates a shift in development bottleneck from the small-scale screening stage to the scale-up stage [2].

Efficient mixing is essential for screening in order to distinguish between mass transfer and kinetic effects [7]. However, small scale batch mixing (order of 10–100 mL) is not optimal due to low mixing Reynolds numbers and dominant tangential flows in the absence of baffles [7]. Additionally, due to the different surface area to volume ratios between scales, mass and heat transfer inconsistencies are often observed, unless addressed with robust control models and re-optimisation [8, 9]. Thus, continuous screening (flow chemistry) is desirable to reduce the challenges of scale-up [8, 10], potentially removing the development bottleneck altogether. Additionally, continuous flow screening at bench-scale can be more efficient due to reductions in size, better mixing and superior controllability, leading to reduced development times and costs.

A technology that may realise these benefits is the mesoscale oscillatory baffled reactor (meso-OB or mesoreactor), which has recently been presented as a novel platform for reaction engineering and screening applications [11]. This review presents an overview of continuous process screening using meso-OBs, including the outlook and potential future work.

2 Oscillatory baffled mesoreactors

2.1 Oscillatory flow mixing

The earliest examples of oscillatory flow devices for enhanced process operation are the pulsed packed/plate column (PPC) and reciprocating plate column (RPC) [12, 13]. Adopted by the nuclear industry in the 1940s and 1950s [14], these designs involve plate columns where either the plates or the process fluid are oscillated to enhance inter-phase dispersion and droplet breakage between two immiscible liquids [12, 15]. In 1973, Bellhouse *et al* [16] utilised oscillatory flows inside furrowed channels to enhance blood oxygenation across a membrane. Sobey (1980) [17] and Stephanoff *et al* (1980) [18] found that vortex formation behind each groove and subsequent ejection into the main flow provided increased exposure of the bulk fluid to the surface. Concurrently, Knott and Mackley (1980) [19] observed oscillatory flows at the periphery of sharp-edged tubes and found that flow separation and stable periodic vortex ring formations were produced. Brunold *et al* (1989) [20] later examined periodic fluid motion

in a closed duct and concluded that in the presence of regularly spaced baffles, a reversing flow could readily achieve efficient mixing inside each baffle cavity. Dickens *et al* (1989) [21] reported residence time distributions for a baffled tube subjected to both oscillatory and bulk flow components and observed plug flow behaviour at laminar net flow conditions.

The mechanism of eddy mixing has been described by numerous authors. Fundamentally, the aim is to achieve flow separation around a sharp edge within a fully reversing flow [20, 22]. During flow acceleration, flow separation occurs at the baffle edge and a vortex forms downstream of the baffle (Figure 1a) [20]. This vortex then grows to fill most of the cross-section of the baffle cavity [23]. After flow reversal, fluid is drawn into the new downstream side of the baffle forming fluid channels between the eddy and the geometry boundary, detaching the eddy and leaving a free vortex (Figure 1b) [19]. The free vortices are then swept into the bulk fluid in the inter-baffle zone and unravel and interact with the vortices from the previous oscillation cycle (Figure 1c–d). The flow patterns are rapidly restored after each oscillation cycle generating highly efficient and uniform mixing in the inter-baffle zones. These flows can also be used to purge surfaces [15, 20].

Figure 1 – Sketch of eddy formation in oscillatory flow in a baffled tube (drawn from [19, 20])

2.2 Mesoscale oscillatory baffled reactors

In their basic form, conventional scale (>15 mm diameter) oscillatory baffled reactors (OBRs) consist of a tube fitted with equally spaced baffles presented transversely to an oscillatory flow (Figure 1). Several baffle geometries have been reported, with the choice dependent on either minimising frictional losses or maximising mixing, but the most common type is the orifice plate baffle [24, 25]. The baffles disrupt the laminar boundary layer at the tube walls, while the action of fluid oscillation gives rise to improved mixing [20]. The visualisation studies of Brunold *et al* [20] showed that the mixing mechanism downstream of the baffle is independent of the upstream flow. Oscillatory flow mixing is therefore independent of the number of baffles in the tube.

A fairly recent development is the “mesoscale” (or millimetre scale) OBR, first presented by Harvey *et al* (2003) as a novel technology for reaction engineering or screening applications [11]. **The motivation in reducing scale in the context of process screening is to minimise waste and feedstock costs, and to develop a process screening platform.** The meso-OBR has a characteristic diameter of 4.4–5 mm. The device can operate at very low net flow rates (mL/hr), **whereas the conventional scale cannot (whilst maintaining plug flow),** and is relatively inexpensive to construct. The meso-OBR also has a variety of different baffle configurations including: integral, central axial, helical and wire wool designs (Figure 2). **The purpose of these geometries is to further increase the flexibility of the screening platform due to their “plug and play” nature. Each baffle design has a different application.** The “integral baffle” design is particularly advantageous for shear-sensitive applications such as bio-processes [26, 27]

because of the smooth constriction. They have also been used for gas-liquid [28] and solids suspension applications [11]. The helical baffles with central insert and wire wool designs are beneficial for enhanced inter-phase dispersion between immiscible liquids [29, 30]. The central axial design has been used for homogeneous liquid reactions due to the higher shear compared with the integral design [4], while the helical baffles can provide a high degree of plug flow over a wide range of oscillation conditions [31].

Figure 2 – Mesoscale baffle configurations; (a) integral baffles, (b) central axial baffles, (c) round-edged helical baffles, (d) sharp-edged helical baffles, (e) sharp-edged helical baffles with a central insert, (f) wire wool baffles

2.3 Governing dimensionless groups

The fluid mechanics in the OBR and meso-OBR are governed by both geometric (baffle spacing ratio, n_b , and open baffle flow area, S) and dynamic (net flow Reynolds number, Re_n , oscillatory Reynolds number, Re_o , and Strouhal number, St) parameters, as shown in **Table 1** below.

Table 1 – Governing dimensionless groups

Dimensionless Group	Symbol	Equation	Description
Baffle Spacing Ratio	n_b	l_b/D	Influences eddy expansion
Open Baffle Flow Area	S	$(d_o/D)^2$	Controls eddy width
Net Flow Reynolds Number	Re_n	$\rho u D / \mu$	Describes the net flow
Oscillatory Reynolds Number	Re_o	$2\pi f x_o \rho D / \mu$	Describes the oscillation intensity
Velocity Ratio	ψ	Re_o / Re_n	Ratio of oscillatory & net flow velocities
Strouhal Number	St	$D / 4\pi x_o$	Describes eddy propagation

In these groups, l_b is the baffle spacing, D is the inner diameter of the meso-OBR, d_o is the baffle constriction diameter, ρ is the fluid density, u is the superficial fluid velocity, μ is the fluid viscosity, f is the oscillation frequency and x_o is the oscillation amplitude (centre-to-peak). Figure 3 visualises these parameters.

Figure 3 – Diagram of geometric parameters and net flow superimposed with oscillatory motion

Geometric parameters influence both the shape and size of the vortices generated within each inter-baffle region [32]. Specifically, the open baffle flow area, S , controls the width of the eddies generated and the baffle spacing, l_b , must be optimised to ensure full expansion of the eddies within each baffle cavity [32, 33]. The baffle spacing ratio, n_b , typically ranges from 1–2 [15], but optima have been identified as 1.5 [20] and 1.8 [34] in pulsed-liquid conventional scale OBRs. This difference is probably due to the methodology; the former optimum was obtained via visual analysis of flow patterns, while the latter was determined by analysing the mass transfer

coefficient between air and water. The baffle spacing of 1.5 is most commonly used in the literature. The optimum spacing has also been reported as 2 for oscillated baffle configurations at conventional scale [32]. This is larger than the pulsed liquid configurations because a larger oscillation amplitude was needed to compensate for the smaller applied momentum to the fluid. For the helically baffled meso-OBR, plug flow can be achieved providing the helical pitch (l_b) is chosen in the range: $x_o/l_b = 0.2-0.6$ [35]. Both high and low flow constriction baffles have been used, but typical open flow areas, S , range from 0.2–0.4. A free flow area of 0.25 is common as it provides an orifice diameter half that of the tube [36, 37]. Optima of 0.2–0.22 and 0.32–0.4 have been reported for the pulsed liquid configuration [32] and oscillated baffle configuration [33] respectively at conventional scale. Gough *et al* (1997) found that larger orifice diameters lead to flow channelling, while smaller orifices produce stagnant regions [33]. Thinner baffles are preferred for efficient mixing, as thicker baffles cause vortex distortion from prolonged surface adhesion. Ni *et al* [32] identified the optimum thickness to be 1–3 mm for conventional scale OBRs. The gap size between the baffles and tube wall has also been analysed at conventional scale in a batch OBR [38]. It was found that larger gaps lower the axial dispersion coefficient, presumably due to the formation of a second vortex ring.

The oscillatory Reynolds number, Re_o , describes the mixing intensity. It is similar to the net flow Reynolds number, Re_n , but the superficial velocity (u) is replaced by the maximum oscillation velocity ($2\pi f x_o$). Flow separation, the point of asymmetric vortex formation, occurs when $Re_o > 50$ for standard OBRs, and $Re_o > 10$ for meso-OBRs [23]. For reference, the point at which transition to turbulent flow occurs in a smooth-walled tube reactor is $Re_n \approx 2100$ [37]. The mixing intensity can range from ‘soft’, characterised by 2D axi-symmetrical flows where plug flow is attainable, to very intense where the flow becomes non-axisymmetric and 3D, and approaches complete mixed flow conditions. The points at which flow symmetry breaks for the standard OBR and meso-OBR containing smooth constrictions are $Re_o > 250$ [39] and $Re_o > 100$ [23], respectively. To ensure efficient mixing (full flow reversal) the velocity ratio, ψ , defined by the ratio of oscillatory to net flow velocities, must be at least greater than 1 [37].

The Strouhal number, St , describes eddy propagation in the OBR. Classically, the Strouhal number is defined as $St = fL/u$, where L is a characteristic length and f is the frequency of eddy shedding. By replacing the characteristic length with the channel half-width as Sobey (1980) [17] and Stephanoff *et al* (1980) [18] did, and replacing the eddy shedding frequency and fluid velocity with the oscillation frequency and maximum oscillatory velocity, the St number shown in Table 1 is obtained. High St numbers ($St > 0.2$) indicate there is insufficient eddy generation to effectively mix the baffle cavity, whilst low St numbers ($St < 0.13$) indicate intense eddy generation causing vortex propagation into adjacent baffle cavities [31]. In both cases, the quality of plug flow decreases. Ni and Gough (1997) [40] also suggested a modified St number (Eq. 1), by taking into account that two eddies are produced during each oscillation cycle and that the characteristic length should be the orifice diameter. However, Equation 1 has not been widely adopted.

$$St = \frac{d_o}{\pi x_o} \quad 1$$

2.4 Characteristics for screening

2.4.1 Plug flow

Oscillatory flow inside a baffled tube leads to a vortex formation and dissipation cycle on each flow reversal, which generates intense mixing inside each baffle cavity [15]. Upon addition of a net flow, the OBR can be thought of as a number of tanks-in-series [21]. Therefore, several studies have quantified the plug flow performance of the OBR and meso-OBR using the tanks-in-series model to describe the residence time distribution, RTD (Eq. 2). This model uses a single parameter, N (number of tanks), to compare the model to the experimental response. When

$N \geq 10$, reasonable plug flow is achieved, while decreasing N leads to the approach of complete stirred tank behaviour [31]. Mixing efficiency is defined in Equation 3, below, which compares the number of theoretical tanks-in-series with the actual number of baffle cavities used in the experiment [37].

$$E(\theta) = \frac{N(N\theta)^{N-1}}{(N-1)!} e^{-N\theta} \quad 2$$

$$\eta = \frac{N}{M} \quad 3$$

In these equations, E is the exit age distribution of a tracer, θ is the dimensionless time (defined as time divided by mean residence time), η is the mixing efficiency, N is the number of theoretical tanks-in-series and M is the number of experimental OBR baffle cavities.

In their detailed investigation of residence time distribution in a conventional OBR (24 mm i.d., 2.8 m length) using the tanks-in-series model and standard tracer pulse experiments, Stonestreet and Van der Veeke (1999) [37] found that the number of tanks (N) could be characterised using just the oscillatory Reynolds number, Re_o . At net flows corresponding to $Re_n = 95$ –252, the authors also observed interdependence between the oscillatory and net flow components which they characterised using the velocity ratio, ψ . For a particular Re_n , ψ could be specified to give optimal plug flow where the mixing efficiency (Eq. 3) was maximised or approached 1. The maximum in N occurred in the range $2 < \psi < 4$, and acceptable plug flow in the range of $2 < \psi < 12$. **It is clear that the OBR is suited to longer residence time applications (laminar net flow regime) where independent control of the mixing can be realised using Re_o .**

Phan and Harvey (2010) [41] similarly evaluated the plug flow quality in a 5 mm i.d. meso-OBR containing integral, central axial and smooth-edged helical baffle configurations for net flows corresponding to $Re_n = 4.3$ –34.0. With appropriate oscillation conditions, Gaussian RTDs were obtained. Interdependence between the net and oscillatory flow components was also studied by plotting N against the velocity ratio, ψ . For the central and integral baffles, optimal ψ were identified in the range of 4–8 and 5–10 respectively, compared with 2–4 reported for conventional OBRs [37]. At the mesoscale, diffusion is more significant, contributing to the plug flow. This renders scale-up from mesoscale more challenging (Section 2.5.3).

Phan and Harvey [41] found that the central and integral baffle designs provided good plug flow at lower oscillation intensity, but the helical configuration could provide a high degree of plug flow over a wider range of oscillation conditions. This was later attributed by Phan and Harvey (2012) [31] to the addition of a swirl flow component to eddy formation behind the helical baffles, redistributing the axial flow in the tangential direction at higher oscillatory velocities. This swirl flow regime was also observed by Solano *et al* [42], who simulated fluid oscillation in a helically baffled domain and observed an off-centre axial velocity profile in the radial direction. For net flows corresponding to $Re_n = 2.55$ –7.2, good plug flow ($N > 20$) has been reported for a 350 mm length helically baffled meso-OBR at $Re_o = 50$ –800 using $St = 0.13$, and $Re_o = 50$ –300 using $St = 0.2$ [31]. **This extended window for plug flow in the helically baffled design is advantageous when considering other characteristics such as heat transfer (Section 2.5.1) and gas-liquid contacting (Section 2.4.3.1), where more intense mixing is desirable.**

The central and integral baffles have also been characterised at low flow rates to establish the lower limit of operation: $Re_n < 3$ and $Re_n < 5$ respectively. Phan *et al* [43] found that at mesoscale for $St = 0.13$ –0.20, the central baffle configuration achieved narrow, Gaussian RTD profiles ($N > 20$) over a wide range of oscillation conditions ($Re_o = 50$ –700) for net flows corresponding to $Re_n = 1.27$ and $Re_n = 2.55$. **The authors [43] concluded that diffusion plays a more significant role in the mixing mechanism at lower net flows. This occurs as the time scale for diffusion approaches the residence time. However,** the RTD of the integral baffle design was

insensitive to the oscillation intensity, evidenced by the meso-OBR behaving as ~ 7 stirred tanks-in-series for most St and Re_o conditions tested. This difference in performance may be due to the greater thickness of the integral baffle (3 mm compared to 1.5 mm). In conventional scale OBRs, Ni *et al* [32] demonstrated that thinner baffles (order of 1 mm) favour more intense mixing while thicker baffles lead to eddy deformation. For continuous screening, being able to achieve plug flow (batch equivalency) at lower flow rates is beneficial because it minimises waste generation and increases the range of available residence times.

2.4.2 Enhanced mass transfer

High mass transfer rates are desirable for many gas-liquid systems, notably in aerobic biological processes. To increase the mass transfer rate, either the concentration driving force for mass transfer or the volumetric mass transfer coefficient ($k_L a$) can be increased. For biological systems, the former often involves sparging with pure oxygen, leading to increased handling costs and safety concerns [44]. For general gas-liquid configurations, the latter has been demonstrated by several authors using batch OBRs.

Hewgill *et al* [45] compared the mass transfer performance of an air-water system in both a conventional scale batch OBR and STR as a function of power density. The authors determined the $k_L a$ values by measuring the dissolved oxygen content, and correlated them using the quasi-steady state power density model using Equation 4. Hewgill *et al* [45] found the OBR could deliver up to 6-fold increases in $k_L a$ compared with STRs on a power density basis. Ni and Gao (1996) [46] similarly observed much higher $k_L a$ values for a particular power density, representing increased efficiency for a particular mass transfer duty.

Enhanced mass transfer has also been demonstrated in an air-yeast culture [47, 48]. Here, a batch OBR (50 mm i.d., 0.75 L) produced $k_L a$ values 75% larger, on average, than a stirred tank fermenter (120 mm i.d., 2 L) using the same aeration rate (0.5 vvm) at the same power density. In a later study, Oliveira and Ni (2001) [49] found that the $k_L a$ enhancements arose due to increased gas hold-up and reduced bubble size at higher oscillation velocities, with the gas hold-up having the greatest effect.

$$k_L a = b \left(\frac{P}{V} \right)^n (U_g)^m \quad 4$$

In Equation 4, b , n and m are empirical constants, P is the power consumption, V is the system volume and U_g is the superficial gas velocity.

Similar mass transfer enhancements have been obtained in a 4.4 mm i.d. mesoscale OBR containing smooth periodic constrictions (SPC) [26, 27]. The SPC is similar to the integral baffle design, but it has a larger baffle spacing ($l_b/D = 3$ rather than $l_b/D = 1.5$) and constriction length (6 mm as opposed to 3 mm). In one study, γ -decalactone was produced via the aerobic biotransformation of a yeast (*Yarrowia lipolytica*) [26]. An air sparging rate of 0.064 vvm produced γ -decalactone concentrations of comparable magnitude to conventional lab-scale stirred tank bioreactors, which typically use aeration rates of the order of 1 vvm [26]. The linear increase in γ -decalactone production rate with increased Re_o indicated that the intense mixing of the meso-OBR enables good control of the liquid droplet size, providing increased interfacial area for mass transfer [26]. In a second study, a mesoscale bioreactor (4.5 mL volume) was compared with a standard 5 L stirred tank bioreactor (4.7 L working volume) for ethanol fermentation from glucose using yeast (*Saccharomyces cerevisiae*) [27]. Under aerobic growth of the yeast, the meso-bioreactor exhibited an 83% increase in biomass formation per volume using an aeration rate of 0.064 vvm, compared to the STR at an aeration rate of 1.1 vvm. Under anaerobic conditions, the authors found the mesoscale bioreactor could achieve similar biomass growth rate to a 2 L STR.

The enhanced mass transfer characteristics (increased $k_L a$) of the mesoreactor were later attributed by Reis *et al* [28, 50] to **separate** increases in both the **mass transfer coefficient (k_L) and gas-liquid interfacial area (a)** and increased gas hold-up. Vortex formation produces radial flows which redistribute the gas bubble motion leading to increased residence time, while the shear generated in the flow promotes bubble breakage and increased interfacial area. **The increased turbulence also provides continual liquid renewal at the gas-liquid boundary, which effectively decreases the interfacial boundary resistance. I.e. the gas-phase is exposed to a greater amount of liquid with the same surface area, which increases k_L [50].** Reis *et al* [50] also associated increased k_L with a high power density according to quasi-steady theory, although the applicability of this model still remains unproven for meso-OBRs (Section 2.5.2).

These studies show that the same enhancements in mass transfer observed in conventional scale OBRs are also apparent at the mesoscale. Thus, the mesoscale-OBR also presents the possibility for screening biological processes with minimal waste while preserving controllability.

2.4.3 Multi-phase mixing

2.4.3.1 Gas-liquid

Reis *et al* (2007) [50] presented the meso-OBR containing SPCs as a gas-liquid contactor for an air-water system and found that two different bubble sizes were produced. The formation of micro-bubbles (~ 0.2 mm diameter) was observed to increase with increasing oscillation amplitudes and frequencies, while the formation of larger bubbles (1.5–3.5 mm diameter) was suppressed using oscillation conditions of $f \geq 10$ Hz and $x_o \geq 2$ mm. Consequently, the interfacial area, a , between phases increased with increasing mixing intensity. Reis *et al* [50] also found that fluid oscillations could increase the gas hold-up in the meso-OBR, which is in agreement with previous studies [11, 23]. In these latter studies, it was also found that the meso-OBR has an ‘auto-cleaning’ feature, whereby gas bubbles are not retained if the tube is positioned at an angle greater than 45° from the horizontal. This angle is a function of the SPC constriction angle.

2.4.3.2 Liquid-liquid

The production of biodiesel via the transesterification of fatty acid methyl esters (FAME) with methanol is initially biphasic due to the immiscibility of the triglyceride and alcohol, thus mixing plays a significant role in the kinetics of the reaction [51]. Phan *et al* (2011) [29] investigated this reaction as a case study for enhanced liquid-liquid mixing in a meso-tube containing a variety of baffle configurations. The most significant enhancement in mixing was observed when using sharp-edged helical baffles with a central insert (Figure 2e). **The sharp-edge of the baffles reduced the oscillation intensity required for the onset of oscillatory flow mixing due to increased shear. The central insert disrupted the core flow of the reactor, lessening the amount of liquid bypassing the baffles leading to improved homogeneity [29].** This enhanced bi-phase mixing was later used to reduce the residence time of biodiesel production to ~ 5 min, compared with 1 hr for standard commercial processes [30]. Additionally, this enhanced mixing was exploited for the rapid screening of the same biodiesel synthesis using a meso-OBR (discussed in Section 3) [29].

The meso-OBR has also recently been used to identify new conditions for biodiesel production by Eze *et al* (2014) [52]. Base-catalysed transesterification is conventionally performed at low water concentrations (<0.3 wt%) and free fatty acid (FFA) (<0.5 wt%) conditions, and low alkali catalyst concentrations, to prevent the competing saponification reaction from dominating [52]. Eze *et al* [52] showed that high conversions (>95 %) could be achieved within 2 min before the saponification reaction became dominant. Here, a methanol:oil molar ratio of 12:1 allowed moisture of up to 1 wt% and FFA of up to 1 %, and a KOH catalyst concentration of 1.5 wt% to be used. Thus, using the high degree of control of residence time in the meso-OBR, the reaction can be rapidly quenched at the point of maximum biodiesel production.

2.4.3.3 Solids suspension

It has been found that meso-OBRs configured as 4.4 mm i.d. tubes containing smooth constrictions can uniformly suspend polymer resin particles (40–180 μL) in vertical and near-horizontal configurations [11, 23]. It was observed that higher oscillation frequencies and lower oscillation amplitudes are beneficial, with 12.1 Hz and 4 mm ($Re_o \approx 1490$) oscillations reported as optimal for vertical suspensions and 12.1 Hz and 3 mm ($Re_o \approx 1120$) for tube angles of 45° and 10° from the horizontal [11, 23].

Eze *et al* (2013) [53] later exploited the solids suspension capability of the meso-OBR to suspend catalyst particles and demonstrated heterogeneous catalysis (sulphonic acid functionalised nano-porous silica) of hexanoic acid esterification with methanol. Similar catalyst behaviour was reported for the continuously operated meso-OBR and conventional batch STR, with the added benefit of continuous water removal in the OBR reducing the effects of water poisoning [53]. The authors noted that catalyst poisoning could be quickly/easily detected in this apparatus. Eze *et al* [53] achieved catalyst suspension at an oscillation amplitude of 8 mm and frequency of 4.5 Hz ($Re_o \approx 2400$), which was different to the studies of Harvey *et al* [11] and Reis *et al* [23]. This was due to the significant geometric difference of the reactors employed in each study. The SPCs used by Reis *et al* [23] consisted of 6 mm thick constrictions, with $l_b/D = 3$ and $S = 13\%$. In contrast, the integral baffles used by Eze *et al* [53] had a thickness of 3 mm with $l_b/D = 1.5$ and $S = 25\%$. Additionally, the sedimentation velocities were probably different, as the densities and sizes of the solid particles were different.

Continuous micro-reactors can minimise waste generation and can have very high mass and heat transfer rates due to their compact designs [54]. However, one of the challenges of micro-reactors is multiphase processing. Typically, gas-liquid and liquid-liquid reactions are conducted under slug flow regimes, while solid catalysts are integrated with the channel walls in packed-bed configurations [55], as the suspension of solid particulates in the flow is difficult to accomplish at this scale. Thus a further advantage of the meso-OBR is the ability to use catalysts “off-the-shelf”, presenting a large relative saving in development time.

The solids suspension characteristics of meso-OBRs have also been exploited in the cooling crystallisation of L-glutamic acid by Abernethy *et al* (2013) [56] using a series of jacketed meso-OBRs containing integral baffles. It was demonstrated that more intense mixing produces smaller crystals than in a conventional STR. Furthermore, in the OBR there was no physical damage to the crystals, whereas this was often substantial in the STR. Also in this study, a previously unreported tetrahedral crystal structure was discovered. It was later shown to be the early stage of the α -polymorph. This opens up the possibility of using the meso-OBR as a novel platform for crystallisation research [56].

2.5 Current uncertainties in the literature

2.5.1 Heat transfer

Several important results concerning heat transfer enhancements in conventional OBRs were presented by Mackley *et al* [57, 58, 59] using shell-and-tube heat exchanger configurations. For net flows in the laminar regime in a 12 mm i.d. and 1 m long stainless steel tube, a 5-fold increase in tube-side Nusselt number was observed when baffles were incorporated into the tube-side, and up to 30-fold enhancements in Nu_t when oscillations were also applied [58]. Stephens and Mackley [59] observed similar Nu_t enhancements when pulsing the column contents in a batch OBR.

A phenomenological model based on the Dittus-Boelter correlation for turbulent flow has been developed for $100 < Re_n < 1200$ and $0 < Re_o < 800$, as shown in Equation 5 [55]. It can be seen that the effect of the oscillation is greatest in the laminar flow regime ($Re_n < 1000$).

Mackley *et al* [57] asserted that the heat transfer enhancement was mainly due to substantial

flow modification, i.e. the creation of primary vortices in the flow. As in Sobey [17] and Stephanoff *et al* [18], the increased radial flow generated by the vortices is observed to result in increased exposure of the bulk fluid to the heat transfer surface.

$$Nu_t = 0.0035 Re_n^{1.3} Pr^{\frac{1}{3}} + 0.3 \left[\frac{Re_o^{2.2}}{(Re_n + 800)^{1.25}} \right] \quad 5$$

In Equation 5, Nu_t is the tube-side Nusselt number ($= h_t D/k$) and Pr is the Prandtl number ($= C_p \mu/k$). Additionally, h_t is the tube-side heat transfer coefficient, k is the liquid thermal conductivity and C_p is the liquid heat capacity.

Although the heat transfer characteristics of conventional OBRs have been established, there is little work in this area reported for the mesoscale OBR. Solano *et al* (2012) [42] reported numerical heat transfer results for a helically baffled domain using the standard Navier-Stokes and energy conservation equations with an imposed uniform heat flux of 1500 W/m^2 . Advective heat transfer was found to generate temperature difference fluctuations between the wall and fluid which produced Nu variations over the oscillation cycle. The maximum value of Nu occurred during the formation of the vortex behind the baffle. Solano *et al* [42] also obtained a 4-fold increase in the time-mean Nu when increasing the oscillatory Reynolds number from 10 to 320. This is a similar finding to conventional scale OBRs, as reported by Mackley *et al* [58]. However, a major limitation of this study was that there were no corresponding experimental results to support the numerical simulations. Generally, the heat transfer characteristics of all mesoscale OBR designs (integral, central and helical baffles) remain undefined.

2.5.2 Power density

The dissipation of power in an oscillatory flow affects scale-up performance as well as heat transfer, mass transfer and mixing characteristics. To quantify the power consumption in OBRs, the power density is typically defined. The power density is the power consumption time-averaged over an oscillation cycle divided by the system volume. Two models have been reported in the literature [60]. The first is the quasi-steady state model, which assumes the instantaneous pressure drop in the oscillation cycle is the same as the pressure drop that would be produced in a steady flow with the same velocity [60]. Based on a standard pressure drop correlation for flow through an orifice, Equation 6 was derived [60]. The second is the eddy acoustic model, suggested by Baird and Stonestreet [60] and given by Equation 7. Here, a single parameter, l (mixing length), is used to fit the model to experiment results.

$$\varepsilon_v = \frac{P}{V} = \frac{2N\rho}{3\pi Z C_D^2} \left(\frac{1 - S^2}{S^2} \right) (\omega x_o)^3 \quad 6$$

$$\varepsilon_v = \frac{P}{V} = 1.5 \frac{\rho \omega^3 x_o^2 l}{l_b S} \quad 7$$

In these equations, ε_v is the power density, Z is the system length, C_D is the orifice discharge coefficient, ω is the angular frequency ($= 2\pi f$) and l is the mixing length.

The pressure drop across a conventional lab-scale OBR (12 mm i.d., 1 m length) containing 55 orifice baffles ($l_b/D = 1.5$, $S = 0.34$) was experimentally measured to determine the power density, which was compared with both the quasi-steady state and eddy acoustic models [60]. The quasi-steady state model under-predicted the pressure drop, and subsequently, the power density for low oscillation amplitudes ($x_o < 6 \text{ mm}$) [60]. This was due to the assumption of steady flow through an orifice, where the pressure drop is derived from a mechanical energy balance between the flow prior to the orifice and the subsequent *vena contracta*. In practice, the vortices generated behind each baffle and their subsequent interactions create much more complex flow structures. Instead, the authors [60] found that the eddy acoustic model could

accurately describe the power density for the amplitude range tested ($x_o = 1\text{--}6.4\text{ mm}$) with a mixing length of 7 mm . Baird and Stonestreet [60] also found that during flow reversal, the experimental pressure drop increased slightly suggesting energy recovery; this effect was more significant at lower oscillation frequencies where the flow was less chaotic. The same findings were also reported by Mackley and Stonestreet [58].

Baird and Stonestreet [60] **observed** that the quasi steady model was **more suitable** for high amplitudes/low frequencies ($x_o = 5\text{--}30\text{ mm}/f = 0.5\text{--}2\text{ Hz}$), while the eddy acoustic model was **more promising** for low amplitudes/high frequencies ($x_o = 1\text{--}3\text{ mm}/f = 5\text{--}14\text{ Hz}$) **in their OBR containing mineral oil. However, wider acceptance of these models is still hindered by the limited number of studies. In addition, no results assessing the applicability of these models have been reported for the meso-OBR.**

2.5.3 Scale-up

The scale-up of continuous conventional OBRs was reported by Smith and Mackley (2006) [61]. They performed tracer pulse experiments in three geometrically similar (l_b/D and S) and dynamically similar (Re_n , Re_o and St) orifice baffled tubes. Axial dispersion was found to be independent of the tube diameter (24 mm , 54 mm and 150 mm) for the conditions studied. Similar dispersion characteristics were found in a 150 mm diameter multi-perforated baffled tube, with the added advantage of the removal of stagnant regions at lower oscillation intensities [61]. **There have also been several scale-up studies conducted with batch OBRs, but these are not discussed here [34, 62, 63].**

One potential application of rapid screening could see lab-scale data used to optimise larger scale reactors, necessitating a linear scale-up capability [26, 27]. An ongoing study has shown that the plug flow in continuous helically baffled meso-OBRs can be scaled from tubes of 5 mm i.d. to 10 mm and 25 mm i.d. by maintaining the values of Re_o and St , whilst scaling Re_n with diameter. I.e. ensuring that $Re_{n,2}/Re_{n,1} \sim D_2/D_1$ [64]. Several authors have also qualitatively inferred the potential scalability of the mesoscale OBR. Reis *et al* (2005) [23] conducted particle image velocimetry (PIV) experiments in a 350 mm long, 4.4 mm i.d. meso-OBR containing SPCs along with a companion numerical simulation of the flow patterns. The eddy mixing mechanism observed at larger scales was also apparent in the meso-OBR. More recently, Phan and Harvey (2010) [41] observed that integral and central baffle configurations exhibited similar plug flow behaviour to conventional OBRs and reasoned that scale-up of the mesoreactor to industrial scales is feasible. However, the mesoreactor required more intense mixing to generate plug flow, so it is clear that scale-up cannot be achieved on a power density basis.

There are several fundamental differences between conventional and mesoscale OBRs. For instance, the points of flow separation and loss of vortex axisymmetry occur at different Re_o 's (Section 2.3). Additionally, diffusion plays a significant role in the generation of plug flow at mesoscale. Consequently, new scaling rules are needed. Based on the significance of diffusion, the **Schmidt number (Sc)** and Péclet number (Pe) should be included. **These numbers concern the ratios of momentum diffusion to mass diffusion and advective transport to diffusion transport respectively.**

$$Sc = \frac{\mu}{\rho D_f} \quad 8$$

$$Pe = \frac{uL}{D_f} \quad 9$$

Here, D_f is the diffusion coefficient, u is the superficial liquid velocity and L is a characteristic length.

Overall, little direct quantification of the linear scale-up performance of the meso-OBR has been reported. However, scalability does not necessarily matter: the principal application currently envisaged for this technology is as a flow chemistry platform for kinetics/process screening. Processes do not need to be scaled up from the laboratory in the same technology in which their optimal conditions or reaction kinetics were determined.

2.6 Comparison with other flow chemistry platforms

Other flow chemistry platforms include conventional plug flow reactors (PFRs), modified PFRs (containing inserts) and microreactors. Typically, a PFR is a tubular reactor where plug flow is generated via a flat velocity profile due to fluid turbulence. Unlike the OBR where the mixing is controlled using the fluid oscillation, the mixing in a PFR is controlled by the fluid velocity. This makes scale-down difficult as there is a minimum necessary throughput in order to achieve plug flow. Adding pipe inserts (e.g. baffles or meshes) lowers the Re_n number required for the onset of turbulence and consequently reduces the flow rate required. However, the mixing is still dependent on the fluid velocity. As a consequence, such reactors are seldom used for flow screening, and would be very difficult to envisage for long residence time processes.

Microreactors consist of small channels (<1 mm). They exhibit very high heat and mass transfer properties. At this scale mixing occurs via diffusion and is therefore not dependent on the net velocity. However, the main disadvantages of this technology are high cost per unit volume [65] and difficulty handling multiphase mixtures, particularly involving solids [66].

The niche application of the meso-OBR is thus to allow screening of processes at laboratory scale at long residence times (if required) and with multiple phases, if required. In principle it represents a more ubiquitous screening platform.

3 Rapid screening using mesoreactors

Plug flow is characterised by negligible axial mixing and strong radial mixing. Thus a small volume of fluid under plug flow operation can be considered equivalent to a batch vessel. The meso-OBR, as any plug flow reactor, can be thought of as accommodating many batch reactions successively. If each fluid plug is given a unique set of operating conditions, a reaction can be rapidly screened.

Reis *et al* (2006) [26, 27], in their proof-of-concept studies, presented the meso-OBR as a novel scaled-down bioreactor, which was intended for use as a parallel high throughput screening device for the optimisation of bioprocesses. They initially studied the production of γ -decalactone from yeast in a two immiscible liquid phase biotransformation. A 50 % reduction in time to maximum product concentration was obtained in a 4.4 mm i.d. mesoreactor containing SPCs [26] compared to an equivalent reaction in a standard 2 L STR [67]. A comparison of the power densities was not given. For the aerobic fermentation of ethanol from yeast, the same mesoscale bioreactor demonstrated an 83 % increase in biomass formation compared to a 5 L STR with 93 % less air sparging due to improved mass transfer [27].

The transesterification reaction for biodiesel production was used by Zheng *et al* (2007) [68] for the comparison of a standard laboratory stirred vessel and batch/continuous operated mesoscale OBR. Similar conversions were reported in each vessel indicating that the continuous mesoreactor had minimal axial dispersion and therefore good quality plug flow. By taking advantage of the mixing independence from the bulk flow, the authors noted that the mesoreactor can also be sampled at different points along the tube enabling the residence time to be logically and rapidly screened in a single experiment.

For the determination of reaction kinetics parameters, a continuous meso-OBR has been used to determine the same rate constants as an equivalent batch laboratory vessel, but with higher reproducibility, for an imination reaction observed using *in situ* FT-IR spectroscopy [69]. Furthermore, this design also demonstrated a capability for reducing reagent usage by up to 75 % and reduced process development time by up to 50 % when compared with an equivalent batch laboratory vessel for the same kinetics screening task [69].

Dynamic screening (or dynamic design of experiments) is a relatively new concept where the purpose is to rapidly screen process operating conditions in real time in order to rapidly determine kinetic data or establish optimality [4]. Phan *et al* (2011) [29] first demonstrated the concept in a base-catalysed biodiesel production process in a continuous meso-OBR using sharp-edged helical baffles with a central insert. Methanol and rapeseed oil were the reactants and the yield of the product, methyl ester, was determined by offline GC. Multi-steady state screening was initially established by maintaining a constant molar ratio for several minutes, then rapidly stepping up the methanol excess. Clear step changes between steady-states were observed in the yield of methyl ester sampled for each molar ratio employed. Dynamic screening was then performed in which the molar ratio of feed reactants was changed after every sample collection. Here the sampling rate limited the process, as the analysis was via offline GC. However, in principle the molar ratio can be changed much more rapidly, if a rapid response online measurement is used. The yield obtained matched the steady-state screening results indicating that rapid screening of process operating conditions is possible.

Plug flow is desirable for rapid screening, as other RTDs will necessarily lead to longer response times. The RTD of the commonly used continuous stirred tank reactor (CSTR) for instance is an exponential decay, meaning the induction time between steady-states is significantly higher than in plug flow. In screening this means more waste and longer processing times. Oscillation conditions to maximise the plug flow and thus minimise the transition time between steady states have been identified using the same transesterification reaction as above in three different meso baffle configurations [30]. For integral and sharp-edge helical baffles with a central rod, $Re_o > 107$ was found to minimise the induction time, while for wire-wool baffle inserts, $Re_o > 36$ was optimal.

Similar screening experiments to Phan *et al* [29] were conducted by Mohd Rasdi *et al* [4, 69], but using on-line analysis. In these studies, an *in situ* FT-IR spectrometer was used to monitor the progress of an imination reaction between benzaldehyde and n-butylamine reagents. When the residence time was increased periodically (every 200 s), clear step changes in benzaldehyde concentration were observed between different steady-state operating regions (residence times of 10–600 s) [69]. Mohd Rasdi *et al* [4] then demonstrated dynamic screening of the reaction kinetics of the same imination reaction by changing the residence time every 20 seconds in the continuous meso-OBR. The outlet concentration of benzaldehyde obtained for the dynamic screening agreed very well with that obtained in the multi-steady state experiments. Moreover, the rate constants obtained from the dynamic screening experiments matched the rate constants obtained from a similar stirred batch vessel (100 mL volume), but with higher reproducibility: standard deviations of 0.006 s^{-1} and 0.02 s^{-1} , respectively [4]. This reaction has also been used to demonstrate bivariate screening, whereby the molar ratio of reactants and residence time were varied simultaneously and continuously in a single experiment and the effect on outlet benzaldehyde concentration monitored [70].

Rapid screening in the OBR has also been reported for 3-phase systems, i.e. liquid-liquid-solid, where the solid was a catalyst, suspended uniformly. The first example of screening a three phase reaction in a meso-OBR was the heterogeneously catalysed esterification of hexanoic acid with methanol. Eze *et al* (2013a) [53] performed the reaction in a 5 mm i.d., 340 mm long meso-OBR containing integral baffles. Increasing the residence time from 30 min to 60 min resulted in increased hexanoic acid conversion (from 15 % to 20 %). Eze *et al* (2013b) [71] then

investigated dynamic screening in two dimensions for the same solid acid-catalysed reaction. The reaction was monitored by offline GC. Multi-steady state screening was initially demonstrated for ramped residence times and methanol:acid molar ratios. Increasing residence time and molar ratio led to increased hexanoic acid conversion. Clear step changes were also observed between each steady-state operating region. Operating conditions for maximum conversion were established quickly in the meso-OBR by varying the methanol:acid molar ratio and residence time in a single experiment. This was equivalent to performing 20 separate batch experiments, although the process time and volume reductions were not reported.

3.1 Summary of oscillation conditions for flow chemistry

Table 2 summarises the oscillation conditions identified in the literature which have been used to either generate plug flow or optimise the mixing between two phases. For the plug flow data, the St number defines the oscillation amplitude while ψ/Re_o defines the oscillation frequency for the Re_n number displayed.

Table 2 – Summary of meso-OBR design parameters for flow chemistry reported in the literature

Baffle Type	Plug Flow	Liquid-Gas Mixing	Liquid-Liquid Mixing	Liquid-Solid Mixing
Central $n_b = 1.5$ $S = 0.36$	Re_n 1.27–4.3 L [43]	4.3–34 L [41]	3–57 L [4]	$Re_o > 107$ [30]
	St 0.13–0.2	0.4–0.8	0.4	
	ψ	4–8		
	Re_o 20–650		62	
Integral $n_b = 1.5$ $S = 0.25$	Re_n	4.3–34 L [41]	6–49 L-L-S [53, 71]	Vertical Tube: $f = 4.5$ Hz & $x_o = 8$ mm L-L-S [53]
	St	0.4–0.8	0.05	
	ψ	5–10		
	Re_o		2400 ($f = 4.5$, $x_o = 8$)	
SPC $n_b = 3$ $S = 0.13$	Re_n 1.9 L-L [68]		10–58 L [72]	Vertical Tube: $f \geq 12.1$ Hz & $x_o \geq 4$ mm [11] Angle = 10°–45°: $f \geq 12.1$ Hz & $x_o \geq 3$ mm [11]
	St 0.2		0.4–0.8	
	ψ		>10	
	Re_o 134 ($f = 10$, $x_o = 2$)			
Helical (No Insert) $n_b = 1.5$ $S = 0.26$	Re_n 2.55–7.2 L [31]			
	St 0.13			
	ψ			
	Re_o 50–800			
Helical (Insert) $n_b = 1.5$ $S = 0.26$	Re_n 0.3–0.8 L-L [29]			$Re_o > 107$ [30]
	St 0.1			
	ψ			
	Re_o 92–316			
Wire Wool				$Re_o > 36$ [30]

Study: L Homogeneous Liquid, L-L Liquid-Liquid, L-L-S Liquid-Liquid-Solid

3.2 Temperature screening

3.2.1 Heat pipes/thermosyphons

Thermosyphons and heat pipes are two-phase heat transfer devices that rely on the latent heat of evaporation and condensation of a working fluid to generate very high effective thermal conductivities with only a small temperature change across the unit [73]. The thermosyphon consists of an evacuated, sealed tube which is partially filled with a working fluid. Upon heating, the working fluid evaporates and the vapour generated moves upwards to the colder side of the tube where it condenses, releasing the latent heat of condensation, before flowing in a condensate film back towards the heated end [74].

Figure 4 – (a) Thermosyphon & (b) heat pipe (Reproduced from [74])

The main limitation of the thermosyphon is that the tube must be orientated such that the heat load is applied at the lowest point in the system to ensure the condensate is returned to the heated end by gravity [74]. This can be overcome using capillary forces generated by a saturated wick structure to transport the working fluid condensate against gravity (heat pipe). Figure 4 explains the operation of each device, with the heat pipe wick acting directly against gravity.

3.2.2 Rapid temperature management and isothermalisation

The ability to passively isothermalise reactors is appealing for screening applications. To obtain representative results, uniformity in axial temperature is necessary. Additionally, rapid heat transfer is desirable to minimise the transition time between steady states to reduce waste. There are very few reports of this being achieved using heat pipes in the context of reaction engineering:

(i) The oxidation of naphthalene to phthalic anhydride was chosen by Parent *et al* (1983) [75] for the comparison of an annular heat pipe and conventional cooling jacket for the thermal control of a tube wall catalytic reactor. The reaction was highly exothermic, required a high operating temperature (673 K), and was thermally sensitive to hot spots (with the product decaying at higher temperatures). Through numerical simulation, Parent *et al* [75] demonstrated that the heat pipe's improved heat transfer characteristics produced more uniform axial temperature and heat load distribution profiles than a standard jacket. The authors also found that the improved heat transfer could accommodate higher reaction rates, allowing a reactor length of 1.35 m to be used, opposed to 2.25 m with the conventional jacket.

This was because the “ignition” of product phthalic anhydride to by-product maleic anhydride was also attenuated. However, these simulations were not verified with experimental results.

(ii) Löwe *et al* (2009) [76] used a heat pipe system designed for electronics cooling to control the temperature of an ionic liquid synthesis reaction in a micro-reactor etched onto a flat polymer plate. With no heat management, a total reactant flow rate of 1.713 mL/min caused thermal runaway, where the reaction temperature exceeded the boiling point of one of the reactants. Using the heat pipe system, good thermal control was reported with a total flow rate up to 9.7 mL/min with no fan assistance, and 20 mL/min with fan-assisted forced convection cooling, demonstrating that safe operation of highly exothermic reactions under continuous conditions is possible. Since then, Löwe *et al* (2010) [54] have commented that the very fast thermal response times and passive heat transfer of the heat pipe can suppress thermal runaways, as any heat transfer fluctuations can be removed at a maximum velocity corresponding to sonic conditions, or a Mach number of 1 for the working fluid. Ehm and Löwe (2011) [77] also used the same heat pipe micro-reactor for ionic liquid synthesis. By rapidly increasing/decreasing the operating temperature in discrete steps, the authors demonstrated that the maximum temperature spike from the reaction could be shifted within the reactor.

(iii) Wong *et al* (2014) [78] used a heat pipe for the thermal control of CO removal from a CO/H₂ stream using preferential oxidation in a packed catalytic bed. The authors used a 6 mm diameter, 120 mm long copper-water heat pipe surrounded by a 25.75 mm i.d. copper tube containing the catalyst pellets. The apparatus was placed in a thermostat bath set at 100 °C to control the reaction temperature while thermocouples embedded in the catalyst material measured the axial temperature profile. The spike temperature at the inlet was lowered at all feed flow rates and O₂/CO ratios, whilst increasing the downstream temperature, thereby demonstrating a degree of isothermalisation.

It is envisaged that a heat pipe could be integrated with a mesoscale OBR for temperature screening as shown in Figure 5. The heat pipe would provide longitudinal isothermalisation, whilst heat input and cooling would control the temperature.

Figure 5 – Proposed annular heat pipe meso-OBR hybrid

3.3 Next steps for meso-OBR screening

Present meso-OBR screening studies include gas-liquid [26, 27], liquid-liquid [43, 68], solid-liquid-liquid [71] and homogeneous liquid processes [4], highlighting the broad range of potential applications. Phan *et al* [29] and Eze *et al* [71] have demonstrated that there is no hysteresis in the reaction screening, as operating conditions have been increased and decreased within a single experiment to give the same output response. Mohd Rasdi *et al* [4] have additionally demonstrated on-line screening, which is more flexible and dynamic than the off-line methods of Phan *et al* [29] and Eze *et al* [71] because it enables instant feedback from the screening process. Another benefit of dynamic screening is that each data point obtained from the mesoreactor is equivalent to that from an equivalent batch experiment [4]. Thus, by

collecting several data points at each operating condition, the repeatability can be affirmed in a single experiment run, providing greater degrees of freedom for subsequent analysis.

Bivariate screening has recently been demonstrated for imination and esterification, where two process operating variables (molar ratio and residence time) were changed in a single experiment and the output monitored [70, 71]. Dynamic screening is not limited to two dimensions. By utilising higher dimensional screening spaces, a wider range of operating variables can be adjusted quickly in order to perform rapid design of experiments, **presenting an alternative to current parallel high throughput screening platforms**. An example of dynamic screening is visualised in Figure 6. The aim here would be to vary three process variables until a local/global maximum in desired output is observed. **As well as molar ratio and residence time, other operating variables of interest could include: concentration (controlled via solvent flow rate), pH (controlled via acid/base concentration) or solvent type (performed using a manifold and several pumps). The main technical challenge here is handling the coupled nature of these variables.**

An additional important operating condition to be considered is temperature. The operating temperature can be used to identify important kinetic information such as activation energy, and usually has a significant impact on the rate of reaction. However, rapid temperature screening is difficult. The axial temperature profile of the reactor must be held constant due to the continuous nature of the flow. One method of achieving this isothermal behaviour is the heat pipe, identified by Reay & Harvey (2012) [73] for isothermalisation (temperature flattening) applications because of the passive heat transfer effect and small internal temperature differences.

Figure 6 – Envisaged rapid sequential optimisation in a 3-dimensional screening space

3.4 Limitations of the meso-OBR screening platform

The main constraint in operating the mesoOBR as a screening platform is the loss of plug flow. Multivariate continuous screening requires a high degree of plug flow in order to distinguish the effects of each operating variable. For some polymerisation reactions for example, where the viscosity increases as the reaction progresses [79], the mixing efficiency is likely to change resulting in a loss of batch equivalency, as well as poorer mixing and heat transfer.

4 Conclusions

In this review, the concept of rapid process screening using mesoscale oscillatory baffled reactors has been discussed. The features of the mesoreactor which are beneficial for screening

have been highlighted, and the uncertainties that remain in the literature identified. Potential future work has also been described.

The meso-OBR has been shown to deliver high intensity mixing, and produce high degrees of plug flow at low net flow rates and over a wide range of oscillation conditions. Different baffle configurations also allow good multiphase contact and high mass transfer rates, providing a broad range of potential applications. The meso-OBR has been used to screen gas-liquid bio-processes and rapidly screen homogeneous liquid reactions, liquid-liquid reactions and solid-liquid-liquid reactions. Additionally, rapid bivariate screening has been demonstrated where two operating variables were varied in a single experiment to find the optimum operating condition with minimal waste.

The next step for rapid screening in the mesoreactor is to **further demonstrate rapid multivariate screening, with multiple phases present. This should serve to illustrate the wide range of applications of this new screening platform.** An important variable to consider is temperature. A potential technology for achieving the rapid screening of temperature is the heat pipe **meso-OBR. Similar heat pipe reactors have been** utilised in the literature for isothermalisation and rapid thermal control.

Nomenclature

a	Gas-liquid interfacial surface area, m^2
b	Empirical constant in $k_L a$-power density relationship
d_o	Orifice diameter, m
C_p	Heat transfer coefficient, $J/kg K$
D	OBR diameter, m
D_f	Diffusion coefficient, m^2/s
E	Exit age distribution (RTD)
f	Oscillation frequency, Hz
k	Thermal conductivity, $W/m K$
k_L	Mass transfer coefficient, m/s
$k_L a$	Volumetric mass transfer coefficient, m^3/s
l	Mixing length, m
l_b	Baffle spacing/helical baffle pitch, m
L	Characteristic length, m
m	Empirical constant in $k_L a$-power density relationship
M	Number of experimental baffles
n	Empirical constant in $k_L a$-power density relationship
n_b	Baffle spacing to diameter ratio
N	Number of theoretical baffles
Nu_t	Nusselt number
P	Power, W
Pe	Péclet number
Pr	Prandtl number
Q	Volumetric flow rate, m^3/s
Re_n	Net flow Reynolds number
Re_o	Oscillatory Reynolds number
S	Baffle free flow area ratio
Sc	Schmidt number
St	Strouhal number
u	Mean superficial flow velocity, m/s
U_g	Superficial gas velocity, m/s
V	System volume, m^3

x_o	Oscillation amplitude, m
Z	OBR tube length, m

Greek letters:

ε_v	Power density, W/m^3
η	Mixing efficiency
θ	Dimensionless time
μ	Viscosity, $Pa\ s$
ρ	Density, kg/m^3
ψ	Velocity ratio
ω	Angular frequency of oscillation ($= 2\pi f$), Hz

Abbreviations:

CSTR	Continuous Stirred Tank Reactor
FFA	Free Fatty Acid
FT-IR	Fourier Transform Infrared
OBR	Oscillatory Baffled Reactor
PFR	Plug Flow Reactor
PPC	Pulsed Packed Column
RPC	Reciprocating Plate Column
RTD	Residence Time Distribution
SPC	Smooth Periodic Constriction
STR	Stirred Tank Reactor

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