CHAPTER 7

Radical Polymerisation under Flow Conditions

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7.1 Polymer Synthesis

Currently, the majority of commercially produced polymers are chain growth polymers also often called 'addition polymers'. Historically, Staudinger was the first to propose the concept of chain growth polymerisation and to define the resulting architecture of the polymer molecules produced through these mechanisms.[1] Chain polymers are generally synthesised *via* either free radical, cationic or anionic polymerisation,[2] however, several other common variations are also available such as controlled radical polymerisation;[3] condensation polymerisation;[4] plasma polymerisation[5] and photo-polymerisation.[6] From an industrial perspective uncontrolled free radical polymerisation is often a preferred approach. A major virtue of uncontrolled free radical polymerisation is that it can typically be carried out under relatively undemanding conditions. The reactions also exhibit a good tolerance to trace impurities, such as stabilizers, air and water; which are often present in commodity monomers and bulk solvents.[7,8] It is also considered operationally the simplest type of polymerisation process to run (considering reactor design and specifications) especially when the characteristics of the polymer product are relatively broad in terms of parameters such as molecular weight, tacticity, dispersity ($Đ$), degree of branching and cross

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linking. Therefore, to appreciate how new technological solutions might impact upon the development or production of polymers it is worth considering the current general industrial production methods utilized in uncontrolled free radical polymerisation.

7.1.1 Free Radical Polymerisation

Within an industrial setting, free radical polymerisation is usually carried out by one of four methods; bulk, solution, suspension or emulsion polymerisation. For bulk polymerisation, the initiator is typically directly solubilized in the monomer which gives a high monomer concentration. The resultant polymer's dispersity will tend to increase due to the increase in viscosity and results in poor heat and mass transfer in the sample. The polymerisation of certain rapidly reacting monomers, for example acrylic acids or esters, (undiluted or in concentrated solution) is accompanied by a marked deviation from first-order kinetics with an increase in reaction rate and molecular weight termed auto acceleration, or gel effect, as originally summarised by Trommsdorf, Schulz and Norrish.[9,10] Due to the highly exothermic nature of the reaction more initiator becomes activated and, therefore, more chains initiate propagation. To overcome this problem, the reaction can be terminated at low conversion, or run in a restricted approach by adding chain transfer agents (also termed modifiers or regulators). These are species which have at least one weak bond (*i.e.* the S–S bond in *e.g.* dodecyl mercaptan), and, therefore, chain transfer reactions occur limiting the natural runaway nature of the reaction. In addition to controlling the auto acceleration, these agents help regulate the molecular weight of the polymer and/or act as polymer end groups.[11,12]

7.1.2 Solution Polymerisation

In solution polymerisation, a solvent is used which reduces the viscosity and prevents the reaction from achieving auto acceleration. The reduction in the monomer concentration also gives rise to a proportionate decrease in the rate and degree of polymerisation. An issue with this approach can be chain transfer to the solvent; this results in a decrease in the degree of polymerisation and a reduction in the final molecular weight. Solution polymerisation is mostly applied to the preparation of polymers in which the polymer is ultimately used as a solution, ideally the same solution as it is prepared in (*i.e.* as is the case of varnishes and adhesives).

7.1.3 Suspension Polymerisation

This type of polymerisation is often used on an industrial scale when the polymer easily separates from the reaction mixture. However, one of the major restrictions of suspension polymerisation is the solubility of the initiator in the monomer; the polymer must form a biphasic mixture with the

bulk media. For this, water is often used as the inert bulk medium and surfactants are often required as dispersion stabilisers. The polymerisation process then takes place in the generated micelles (through induced high shear) with the polymers normally being collected as particulates or beads. In an industrial setting this is the primary process for preparing polymeric materials that end up in paints, coatings and latexes.

7.1.4 Emulsion Polymerisation

This polymerisation technique is the most widely used commercial process for free radical diene and vinyl monomer polymerisations. In these reaction systems, water is often used as the solvent in combination with a water soluble initiator, an immiscible monomer and often a surfactant which is used to stabilise the formation of droplets in the solution. Emulsion polymerisation is preferred for the synthesis of polyacrylates over bulk polymerisations because of the high exothermicity, the increase in viscosity during solution polymerisation and the likelihood of soft particles aggregating together during the suspension polymerisation.

In general, many of the polymerisation processes are rapid, and employ toxic/hazardous monomers and initiators that are also, by their very nature, highly unstable. Combined with the overall observation that polymer transformations are highly exothermic this makes them very good theoretical candidates for continuous manufacture using flow processing. However, as can be noted from the different polymerisation processes described above involving multiple phases and different mixing requirements a single reactor design is unlikely to be viable for all processes.

7.2 Viscosity and Mixing in Flow

In most polymerisation reactions, it is expected that viscosity will increase with increasing monomer conversion, although it should be noted this is not always a linear phenomenon and the onset of step changes can occur quite suddenly. It is also important to remember that excessive gelation or very high viscosity solutions can be associated with high pressures in a flow reactor or even result in reactor blockage. To ensure effective chemical reaction and heat transfer in a flow process it is important to understand the dimensions and characteristics of the reactor. For many flow processes the Reynolds number (Re) is important as it indicates the mixing and diffusion with respect to viscosity and flow rate: this is a non-dimensional parameter defined by the ratio of dynamic pressure and shearing stress (eqn (7.1)). In this equation $V =$ velocity ($\mathrm{m\,s^{-1}}$), $L =$ length (m), $\rho =$ density ($\mathrm{kg\,m^{-3}}$), $\mu =$ dynamic viscosity ($\mathrm{N\,s\,m^{-2}}$) and $\nu =$ kinematic viscosity ($\mathrm{m^2\,s^{-1}}$).

$$\mathrm{Re} = \frac{V \cdot L \cdot \rho}{\mu} = \frac{\text{inertial forces}}{\text{viscous forces}} \tag{7.1}$$

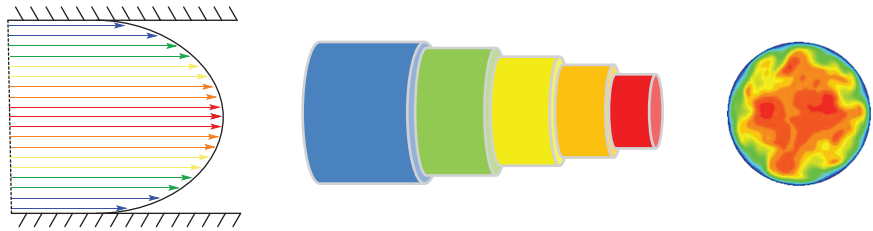

Figure 7.1 Laminar flow velocity profiles: Left: Fluid flow in a pipe indicating the laminae with blue representing slow moving material, green to orange increasing velocity and red indicating the fastest moving planes of fluid. Middle: Concentric cylinders of relative fluid movement; blue indicates slow moving, red faster moving fluid. Right: The aggregate fluid flow in a cross section of pipe; blue indicates slow moving, red faster moving fluid.

A low Reynolds number (<2300) indicates a laminar flow regime involving characteristics of a constant and smooth fluid motion in a lateral field with little mixing occurring except *via* interlayer diffusion. Essentially the fluid particles are moving in straight parallel lines (in the principle direction of the flow path) with low velocity and viscous forces are dominant. Wall interactions (friction) slow the motion of the exterior fluid relative to the interior laminae creating a forward moving parabolic velocity flow profile (Figure 7.1).

At medium Reynolds numbers ($2300 > Re < 4000$) there is a transitional flow. The fluid particles have a medium velocity but only modest mixing is induced. However, at high Reynolds numbers (>4000) turbulent flow is achieved, with very efficient mixing. The characteristics of the flow are then an irregular and chaotic fluid motion with molecules possessing high velocities albeit the principle motion is still in the direction of the flow path. Turbulent flow is predominant when solution viscosity is low and flow rates are high to increase throughput. However, as noted previously as polymerisation leads to an increase in viscosity we would expect to transition to a more turbulent flow regime. This is beneficial as it should lead to better mixing as required in the more viscous reaction media. It is also possible to facilitate the turbulent mixing effects by adding in-line mixing elements, either as architecture components of the reactor channels or as static mixing elements which can be added to the flow path as required.

7.3 Polymers in Flow

Over the past 20 years various polymerisation techniques have been translated from batch and evaluated in flow resulting in a comprehensive body of scientific literature. However, only a few review papers summarising the area have been produced.[13–21] For those requiring additional or more in-depth discourse we highly recommend these reviews which summarise many of the polymerisation processes from different perspectives and with greater focus on the kinetics and analysis of the polymer characterisation numerical data.

It should be stressed that not all polymerisation techniques or polymer preparations are suited for running in flow. Polymerisation reactions that result in very viscous solutions (gel) or generate extensive solids should, in most cases, be avoided, as this will cause major challenges to running in flow.[22] However, polymers which form precipitate or suspended particles can be successfully performed when special processing equipment is used.[23] Indeed, several reactor designs have been utilised including reactors that incorporate a secondary dilution stream,[22] systems with added ultrasonic mini agitation cell devices to create mini emulsions[24] and also two phase plug flow systems.[25] Consequently, reactor design and configuration are critically important factors, contributing to the success of the polymerisation and/or particle synthesis.

A wide variety of flow set-ups have already been reported in the literature for conducting polymerisation reactions, each possessing its own beneficial characteristics. Often specific fluidic flow regimes within the reactor are used to categorise the reactors, however, it should be acknowledged that reactors can have multiple zones with different flow regimes through the incorporation of additional residence time modules, static mixers and fluid connectors (*i.e.* T- or Y-connectors). Therefore, a variety of flow patterns can be defined, such as laminar flow, tunnel or pipe flow,[26] turbulent flow[27] and Stokes flow.[28] In straight smooth tubes laminar and near laminar flow regimes and their corresponding residence time distributions are well investigated.[29] A problem which can arise in a flow reactor is the lack of efficient mixing in the polymer synthesis (see Section 7.2 on viscosity and mixing in flow). A polymerisation reaction often involves an increase in viscosity. Polymers can therefore stick to the walls of the reactor distorting their progression and affecting the polymer distribution. Therefore, static mixers and agitators are highly favoured when a polymerisation reaction is being performed. To further avoid any issues of wall fouling, flow pulsing in straight smooth tubes can be applied,[30] which helps to also narrow the residence time distribution.[22] To improve the reaction further and prevent the reactor from chocking, coiled tubing reactors can be used, which result in an increase in turbulent flow. The counter-rotating vortices generated increase mixing in a perpendicular direction to the main flow. The use of this type of reactor creates superimposed secondary flow patterns (Dean vortices) leading to enhancing mass and heat transfer over the cross-section of the tubular reactor (Figure 7.2).[22]

For emulsion polymerisation it is particularly important that shear rates are distributed evenly and large heat exchange areas are of additional value to ensure homogeneous viscosity when the different phases do not efficiently mix. This ensures droplet break-up is consistent which ultimately determines the resultant particle size. To take advantage of secondary flow patterns Tanaka *et al.* were one of the first groups to propose the use of a torus reactor as a suitable device for semi flow/batch suspension polymerisation.[31] The working principle of a torus reactor (Figure 7.3) is that the dispersion of the flow through the reactor is created by an incorporated mechanical stirrer.

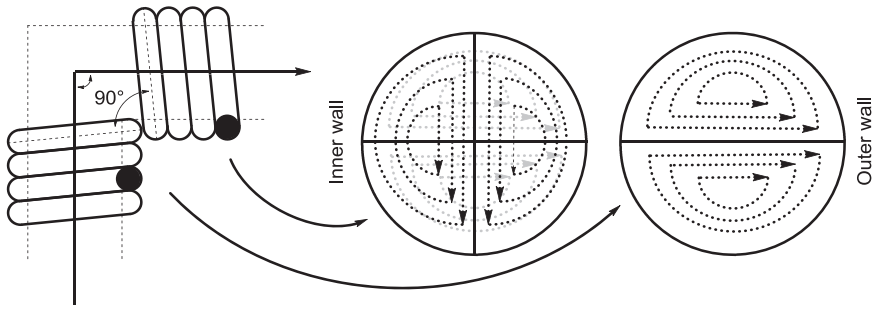

Figure 7.2 Dean vortices produced in a tightly coiled tube reactor.

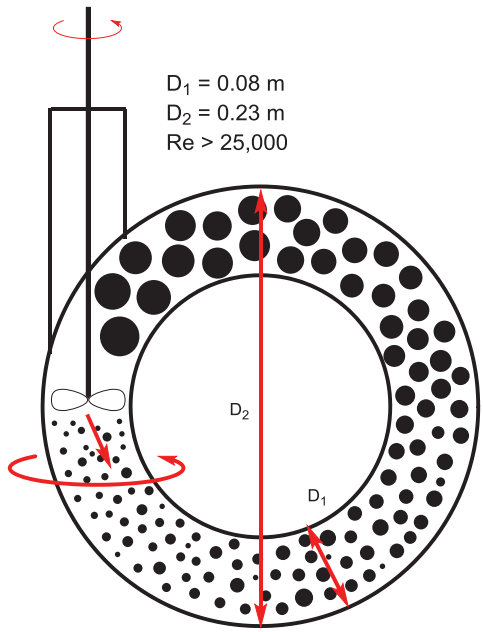

Figure 7.3 Torus reactor for the semi flow/batch emulsion polymerisation, dots representing the emulsion.

The stirrer not only moves the dispersion through the reactor, but also superimposes a secondary flow. The high symmetry and the forced circulation induced should, therefore, result in a uniform particle size distribution as droplets will be continuously broken up. The reactor is characterised by a high Reynolds number (Re) inherent to the improved small dimensional mixing zone but coupled with a potentially batch-like residence time and reactor volume. Of particular note is the higher surface area of this reactor, which allows for greater heat transfer compared to an equivalent volume batch reactor. This reactor type was used by Tanaka *et al.* to perform suspension polymerisation of styrene and the results were compared to the same batch polymerisation.[32] Table 7.1 summarizes the difference between the torus

Table 7.1 Comparison of dispersity between torus and stirred tank reactors. Dispersity was defined as the ratio between the standard deviation and the mean diameter (σ/d_p). Therefore, the smaller the dispersity, the higher the degree of uniformity of the droplet produced. Where N_r was the stirrer speed (rotations per second), ϕ was the styrene monomer volume fraction and C_T is the concentration of the stabilizer (wt%).

Torus reactor				Stirred tank reactor			
N_r	ϕ	C_T	σ/d_p	N_r	ϕ	C_T	σ/d_p
20	0.5	0.3	0.19	4.2	0.5	0.3	0.55
25	0.5	0.3	0.18	5.0	0.5	0.3	0.60
30	0.5	0.3	0.20	6.0	0.5	0.3	0.62
40	0.5	0.3	0.21	7.5	0.5	0.3	0.65
50	0.5	0.3	0.24	8.2	0.5	0.3	0.66

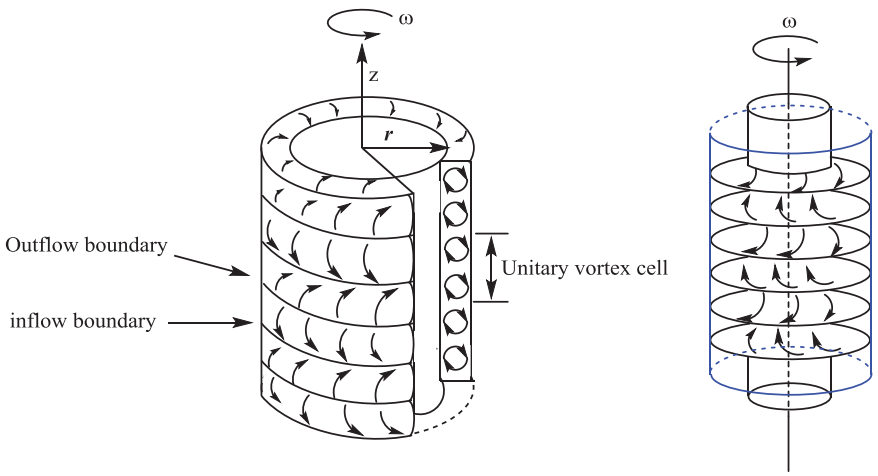

Figure 7.4 Couette–Taylor vortex reactor.

reactor and a normal stirred tank reactor. Dispersity was used as a measure of the degree of uniformity of the droplet diameters. The particle size distribution (σ/d_p) in the torus reactor was more consistent when compared to the stirred tank reactor (Table 7.1). This can be explained by the rotatory stirrer which induces gravitational forces and thus a more even density gradient. As a result, the dispersed phase is more homogeneously distributed and, therefore, this provides a better option for suspension polymerisation.[32]

Alternatively, to perform flow emulsion polymerisation, a Couette–Taylor vortex reactor was selected by Kataoka *et al.*[33] This reactor consists of a rotating inner cylinder and fixed outer cylinder with an inlet positioned at the bottom and an outlet at the top.[34–36] The rotation speed of the inner cylinder influences the mixing of the material (Figure 7.4). A threshold needs to be overcome before the reactor will have the desired effect (flow). This threshold is given by the dimensionless Taylor number (Ta) and can be calculated by eqn (7.2), this parameter for rotating flow replaces that of the Reynolds

number. For low Taylor numbers above the critical Taylor number, the residence time distribution (RTD) becomes narrow due to effective radial mixing. Using this system, the standard deviations of the particle size distribution were in the range 15.2–13.7 nm which compared well to the comparative batch reactor where the deviation was greater at 26.4 nm.

$$\mathrm{Ta} = \left(\frac{\omega \cdot b \cdot R_\mathrm{i}}{\nu}\right)\left(\frac{b}{R_\mathrm{i}}\right)^{1/2} \tag{7.2}$$

R_i = inner cylinder radius (cm), b = radial clearance between concentric cylinders, ν = kinematic viscosity ($\mathrm{cm^2\,s^{-1}}$) and ω = angular velocity of inner cylinder ($\mathrm{s^{-1}}$).

Imamura *et al.*[37] also conducted the continuous emulsion polymerization of styrene in a Couette–Taylor flow reactor. The intention of this investigation was to evaluate the reactor to generate latex particles of a narrow size distribution under continuous operation whilst maintaining a consistent output quality. When operated near the defined critical Taylor number (eqn (7.2)) plug flow conditions were achieved allowing the unit to act like a combination of 60 continuously stirred tank reactors operating in series (CSTR). In addition, since no physical stirrer was used, the reactor avoided issues associated with coagulation of the latex particles that are very sensitive to mechanical shear which can cause blockage due to the deposition of flocculated particles. Ultimately the flow reactor produced particles with an average diameter of 85 nm and a dispersity of 1.31 compared to an optimised batch reactor which admittedly gave a slightly narrower average diameter 81 nm and dispersity of 1.08. This latter result could be a consequence of imperfect mixing due to the lower Reynolds number producing some laminar flow characteristics in the system. However, as an initial investigation this was considered highly encouraging with the reactor showing no signs of fouling or blockage and demonstrating consistency over prolonged steady state operation. This was considered to make the Couette–Taylor reactor highly suited as a pre-reactor (a seeder unit) for feeding a subsequent emulsion polymerization reactor. As a proof of principle, a further polymerisation was performed using the system to seed a continuous emulsion polymerisation of an aqueous mixture of styrene ($36\ \mathrm{g\,L^{-1}}$). The resulting emulsion was then measured using an electron microscope to determine the dispersity which was improved at 1.05.

Nomura *et al.* also employed a Couette–Taylor vortex reactor to compare against a pulse flow system and a continuous stirred tank reactor in the emulsion polymerisation of styrene.[38] A systematic study investigating the effects of initiator concentration, emulsifier feed, the Taylor number (rotation speed of inner cylinder) and the reactor mean that residence time on the steady-state monomer conversion and particle number were screened. Overall, using a pulse flow reactor a high monomer conversion was obtained. The continuously stirred tank reactor resulted in significantly fewer polymeric particles and a lower monomer conversion (approximately 60%

for pulse flow reactor and 40% for continuously stirred tank reactors). Interestingly, the emulsion polymerisations performed in the Couette–Taylor reactor showed that all values between the range of the pulse flow reactor and the continuously stirred tank reactors could be replicated. This is achievable because the overall flow pattern in a Couette–Taylor flow reactor can be changed from a perfectly mixed flow to a flow pattern close to plug flow/batch by altering the rotational speed of the inner cylinder, decreasing the rotational speed results in a decrease in the Taylor number (Ta; eqn (7.2), ω value). Therefore, as a process tool for investigating the extent and critical limits of a polymerisation process the unit is highly valuable.

A Couette–Taylor flow reactor has also been used to study the continuous emulsion polymerisation of vinyl acetate, a partially water-soluble monomer.[39] In this process sodium lauryl sulfate was used as the emulsifier and potassium persulfate as the initiator. The results obtained were at variance with the previous experiments described above using styrene. In this case the monomer conversions obtained with the Couette–Taylor flow reactor essentially mirrored those performed in a continuous stirred tank reactor. This equated to approximately 20% conversion within 30 min. However, a pulse flow reactor was also evaluated for the same process and in this case the conversion was found to be much higher in the range of 91% for a residence time of 32 min. Although it would appear the plug flow reactor is far superior, a potential problem was the diffusion of material in the axial direction a phenomenon which has been described in several papers.[27,28,40–43] Although it was not clear why there was a significant variation in the reactivity of vinyl acetate compared to styrene it may be explained by the more homogeneous nature of the reacting solution or the stability of the obtained radical. Propagating styrene radicals would be stabilised by the adjacent phenyl ring, whereas vinyl acetate, by contrast, does not possess such a strong stabilising group and, therefore, termination is more likely. For vinyl acetate polymerisation in flow this theoretically means less control can be exerted over the molecular weight, this was however not evaluated as part of the study.

It has also been reported that the group of Nishikawa[44] tested the polymerization of methyl methacrylate using a Couette–Taylor flow type reactor and similarly Moritzetal *et al.*[45] carried out the continuous emulsion polymerization of *n*-butyl methacrylate, however, full details of the experiments conducted are difficult to fully appreciate from the published sources.

7.3.1 Controlled Radical Polymerisation

Modern polymerisation techniques give greater control over polymers than they used to meaning it is now readily possible to tune polymers and design advanced structures having specific physical and chemical properties. Controlled radical polymerisation (CRP) is one of these key advances and was first disclosed over 30 years ago.[46] Since its inception it has been extensively used to prepare a variety of polymers in both academic and

industrial settings. The value of CRP is that it enables the synthesis of macromolecules with complex architectures and well-defined microstructures.[47] These same macromolecules could alternatively be synthesised *via* ionic living polymerisation techniques but with much less precision.[48] CRP competes with both the high standard of ionic polymerisation (ionic polymerisation is relatively insensitive to temperature and could be performed at low temperatures, therefore, it will form more regular polymers) and the versatility of free radical polymerisation with regards to (chemical) impurities, process parameters (exothermic reactions), choice of monomer and operational conditions. It not only enables control over polymeric architecture, which includes molecular weight, dispersity, functionality and composition, it also minimises the occurrence of premature termination resulting in a very narrow dispersity.

Despite the numerous benefits there are relatively few examples of CRP being used at large industrial scale when compared to free radical polymerisation. The main reasons are that the polymerisation rate is significantly slower (the lifetime of growing chains is more than one hour) than compared to free radical polymerisation (the lifetime of growing chains is about one second), there is a need for the addition of an extra mediating or chain-transfer agent and the associated cost of these agents.[49,50] This mediating or chain-transfer agent is often required in stoichiometric amounts relative to the number of chains being formed. These additives are often toxic and/or harmful and so need removal before formulating the final product. This necessitates the purification of the material from the polymer; a potentially very costly process on an industrial scale.[51] Consequently a great deal of work has been invested into evaluating mediators to improve the cost/performance ratio of the added chain-transfer agents, one of the most valuable being copper mediated CRP.

Copper mediated CRP can be subdivided into three main categories; nitroxide mediated polymerisation (NMP),[52,53] reversible addition fragmentation transfer (RAFT) polymerisation[54] and atom transfer radical polymerisation (ATRP).[55–58] Of these three techniques, ATPR has attracted most of the attention, resulting in substantial progress regarding increasing the polymerisation rate and decreasing the concentration of chain-transfer agent.

7.3.1.1 ATRP Reactions

The general ATRP polymerisation sequence starts with the initiation of an alkyl halide or dormant polymer, in Figure 7.5 this is indicated with P_n–X. This species is often activated by a Cu(I) complex to form an active polymer chain and a Cu(II) complex which is now a deactivator. The active polymer chain then undergoes propagation, deactivation or termination. The dominant reaction process is deactivation promoted by the Cu(II) complex which upon reaction reforms the activator [Cu(I)] and a dormant chain. The kinetics of this step are highly dependent on the redox potential of the copper complex, as well as the stability of the radical formed. If the ratio between

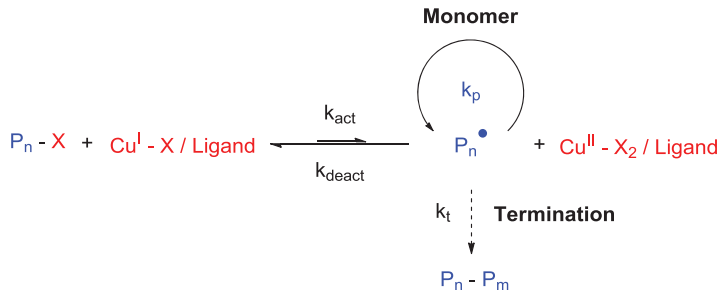

Figure 7.5 ATRP mechanism.

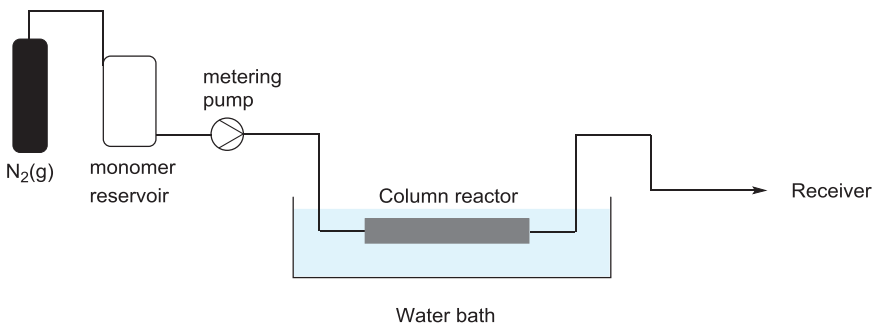

Figure 7.6 Cu mediated ATRP packed bed reactor.

k_{act} and k_{deact} is small, control over the propagation step will be lost and a runaway reaction occurs.

The large body of work investigating ATRP has led to the development of several sub-categories such as activator regenerated by electron transfer (ARGET) ATRP,[59] initiators for continuous activator regeneration (ICAR) ATRP,[60] supplemental activator and reducing agent (SARA) ATRP,[61] single electron transfer living radical polymerisation (SET-LRP)[62] and photo-induced ATRP.[63] All of these variants of ATRP have reasonably fast polymerisation rates and, therefore, can be conducted with reduced levels of copper. A specific discussion regarding the mechanisms of SET-LRP and SARA-ATRP is beyond the scope of this chapter but for those interested details can be found in the following citations.[62,64,65]

7.3.1.2 ATRP Reactions Performed in Flow

The first reported ATRP process performed in flow was conducted on methyl methacrylate (MMA) by Shen *et al.* in 2000.[66] The flow system was constructed from off the shelf, commercially available parts, using a simple metering pump delivery and a glass fitted column packed with the active CuBr–hexamethyltriethylenetetramine (HMTETA) complex (Figure 7.6). It was shown that when using low flow rates (equating to long residence times)

high conversions could be obtained. The highest monomer conversion (87%) was obtained using a flow rate of 1.2 mL h^{-1} equating to a residence time of 300 min.[67] It was demonstrated that the conversion rapidly dropped to 23% at a higher flow rate of 9.6 mL h^{-1} (40 min residence time). Furthermore, the longer residence time also resulted in higher molecular weights (11 kg mol^{-1} for 300 min *versus* 5 kg mol^{-1} for 40 min). The flow system gave a narrower molecular weight range of 3400–11 000 g mol^{-1} against a 23%–87% conversion. For comparison, the range equivalent range in batch was 2800–15 200 g mol^{-1} at conversions between 21% and 87%. Unfortunately, this flow reactor set-up was not competitive with traditional batch chemistry in terms of dispersity of the polymer molecular weights.[68] The dispersity in flow was around 1.80 (conversion 87%) compared with 1.15 (conversion 70%) in batch.

A tubular reactor system has also been used to polymerise methyl methacrylate using ATRP by Haddleton *et al.*[69] High conversions and similar molecular weights were obtained to those previously achieved by Shen.[66,68] For this flow reaction CuBr–*N*-octyl-2-pyridylmethanimine (CuBr–NOPMI) was used as the catalyst and *tert*-butyl-2-bromoisobutyrate (*t*BiB) as the initiator. The dispersity achieved using this set-up was considerably better, namely 1.06 at 90 °C, with a conversion of 60.7%, a residence time of 150 min and molecular weight of 11 000 g mol^{-1}. The authors claimed good control over number average molecular weight, dispersity and conversion. As expected at higher flow rates, lower conversions were achieved (Table 7.2). Changing the ratio between monomer and initiator was also shown to influence the molecular weight with an increase in the ratio resulting in a corresponding rise in molecular weight (Table 7.2).

The reactor set-up was also modified to perform block co-polymerisation reactions. A second inlet was added after the first (10 mL) reactor and connected to a second reactor (10 mL) *via* a T-piece (Figure 7.7). A solution of methyl methacrylate dissolved in toluene was pumped through the first reactor (10 mL), at a flow rate of 3.0 mL h^{-1}, a block polymer of poly(methyl methacrylate) was obtained after 180 min (conversion = 70%, $M_n = 12\,600$ g mol^{-1}, $Đ = 1.12$). Addition of a second flow, containing *n*-butyl methacrylate (*n*BMA) also dissolved in toluene, with a flow rate of 1.8 mL h^{-1} and a residence time of two hours resulted in an 17% conversion of *n*BMA. The polymerisation was

Table 7.2 Influence of flow rate and ratio on the polymerisation of methyl methacrylate.

Flow rate (mL h^{-1})	Ratio [MMA]/[*t*BiB]	Conversion (%)	M_n (g mol^{-1})	$Đ$
5	50	81.9	6370	1.13
20	50	33.7	5000	1.12
2.5	100	89.9	13 200	1.07
5	100	60.7	11 000	1.06
20	100	16.0	6240	1.06
2.5	200	61.4	18 200	1.09
5.0	200	36.5	12 700	1.09

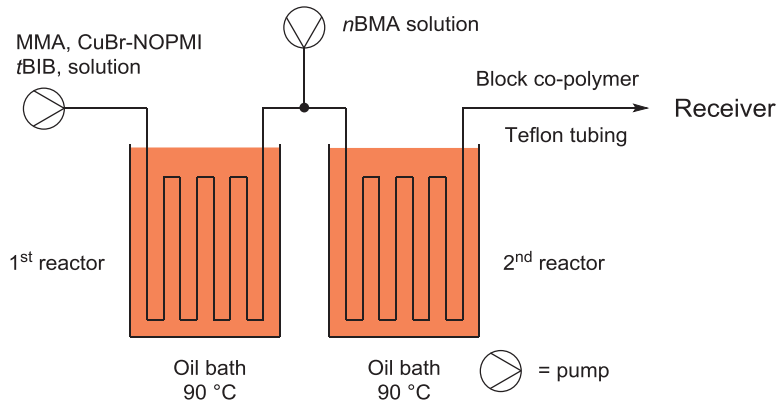

Figure 7.7 Block co-polymerisation of MMA and *n*BMA using a tubular reactor system.

not completely selective as a gradient co-polymer of MMA (5%) and *n*BMA was formed. The value of M_n also increased to 16.3 kg mol^{-1} with a corresponding dispersity of 1.2.

Further co-polymerisations with longer residence times for the second stage polymerisation were performed to improve the conversions and increase the molecular weight. This was realised by shortening the first reactor and decreasing the flow rate; from 10 mL reactor volume with flow rates of 3 mL h^{-1} to 5 mL reactor volume and a flow rate of 1.5 mL h^{-1}. The flow for the second reactor was 1.8 mL h^{-1}. Under these conditions the conversion of *n*BMA increased slightly (17 → 21%) and the molecular weight rose from 16 300 g mol^{-1} to 23 200 g mol^{-1} with a dispersity of around 1.10 for all experiments. In analogy, benzyl methacrylate was also successfully used to form a range of co-polymers in combination with MMA (M_n = 15 300–29 100 g mol^{-1} and $Đ$ = 1.22–1.49).

However, *n*-butyl acrylate (*n*BA) was not successfully co-polymerised with MMA. The reasons for this might be due to insufficient reaction time (80 min), using similar reaction conditions a conversion of 50% was reached[70] albeit after ten hours. Another reason might be the failure of the activation of the propagation reaction involved in the polymerisation. According to the literature the relative rate constants for propagation are ordered: methacrylates > styrene ≫ alkyl acrylates.[71] The equilibrium constants for the activation of methacrylate polymerisation are much smaller than those of *n*-butyl acrylates.[72] A possible solution, which was presented in the paper, was the introduction of CuCl in the second step of the polymerisation to enable an halogen exchange.[73]

Serra *et al.* have published on the polymerisation of the monomer 2-(dimethylamino)ethyl methacrylate (DMAEMA) using ATRP.[74] Their publication highlighted an improved reactor design where, instead of a capillary spiral coiled tube, a coil flow inverter reactor was used (Figure 7.8).[75,76]

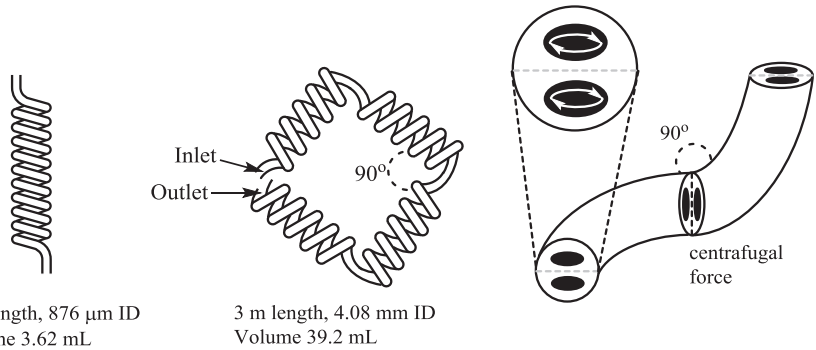

Figure 7.8 Left: Spiral coil reactor. Middle: Coil flow inverter (CFI) reactors. Right: Induced Dean mixing zone through right angle rotation.

The coil flow inverter reactor used comprised four 90° angles in the coiled tube which, due to rotation of the Dean mixing zones, induces better mixing. The new flow coil set-up gave marginally improved monomer conversion (74% ± 1% *versus* 71% ± 1%) and was also associated with a marginal increase in molecular weight (22 874 *versus* 21 142 g mol^{-1}) and a decrease in dispersity (1.43 *versus* 1.53) using identical operating parameters. Importantly though, it was shown that independent of the reactor length and tube diameter (therefore the volume of the reactor) the coil flow inverter reactor gave improved results over the classical spiral design coiled tube reactor, this gives significant benefits when scaling the reactor. As shown the processing volume could be easily increased but dispersity was increased slightly ($Đ = 1.43$ *versus* 1.59) moving from a small diameter tubular reactor (876 μm ID) to a larger coil flow inverter reactor (4083 μm ID).

Co-polymerisation of DMAEMA and benzyl methacrylate (BzMA) has been conducted in flow as reported by Parida *et al.* using ATRP conditions.[77] The reactor set-up comprised two pumps, a micromixer and a coiled tube reactor (Figures 7.9 and 7.10). The study showed the importance of effective mixing by evaluating various mixing devices such as a simple T-junction, an interdigital multi-lamination and an impact jet micromixer.

Statistical co-polymers of DMAEMA and BzMA were synthesised in batch and in flow, containing 20% and 40% BzMA composition (by molecular weight). As an initial assessment the difference in conversion between batch and flow was determined and was established as +31% and +35% for BzMA and DMAEMA respectively, in favour of the flow approach. The type of in-line flow mixer did not unduly influence the total conversion. Interestingly, changing the composition of BzMA did have an influence on the total conversion using batch chemistry but not when evaluated using flow conditions. As observed during the reaction, after one hour the viscosity noticeably increased along with the dispersity (Table 7.3). This rise in viscosity affects the ongoing polymerisation, as it leads to slower mass diffusion and hence poor polymer growth and increasing termination. Hence, flow processing

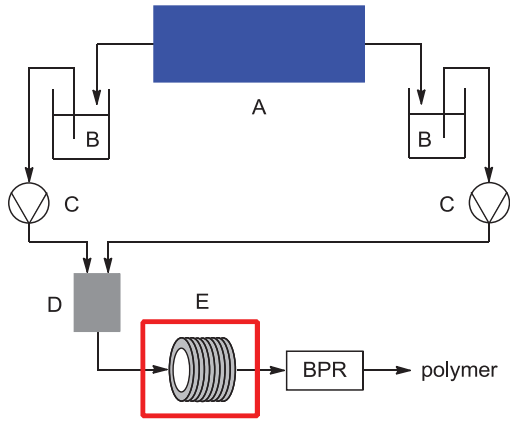

Figure 7.9 Reactor set-up for co-polymerisation of DMAEMA and BzMA. (A) Nitrogen generator, (B) reservoirs, (C) HPLC pump, (D) micromixer, (E) microreactor inside oven (60 °C).

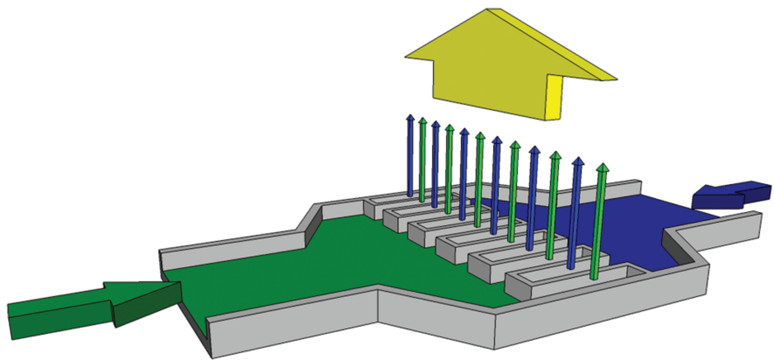

Figure 7.10 Operating principal of the interdigital micromixer. Channel dimensions 45×200 μm, approximately 8 μL internal volume.

Table 7.3 Influence of flow rate and ratio on the co-polymerisation of BzMA and DMAEMA.

Reactor	Sample	DMAEMA[a] (%)	BzMA[a] (%)	Theoretical M_n	M_n (g mol^{-1})	$Đ$
Batch	20% BzMA	44.75	41	14 315	11 095	1.62
Batch	40% BzMA	45.2	48	15 208	13 457	1.55
Flow[b]	20% BzMA	55.55	61.8	18 523	17 210	1.50
Flow[b]	40% BzMA	59.5	64.9	19 705	18 847	1.54

[a]Conversion DMAEMA and BzMA as determined by ^{1}H NMR.
[b]Flow reactor, multi-lamination mixer.

proved particularly valuable by providing improved mixing using a multi-lamination mixer. Utilising this device allowed improved control over the molecular weight and reduced dispersity was achieved (Table 7.3).

Several processes for SET-LRP have been performed in flow using a simple flow reactor set-up, as described by Hutchinson *et al.*[78–80] and Haddleton *et al.*[81] SET-LRP is a robust and versatile method used to polymerise vinyl monomers at ambient temperatures.[62] To perform this polymerisation in flow a Cu(0) derived catalyst was used. The polymerisation sequence starts with the activation of the initiator or dormant polymer chain by Cu(0)/CuX_2 species (Figure 7.11). The solvent of choice is usually a polar solvent which is important.[82,83] Solvents such as H_2O, alcohols, dipolar aprotic solvents, ethylene and propylene carbonate, and ionic liquids help to very rapidly disproportionate the CuX into Cu(0) and CuX_2 species in the presence of a *N*-containing donor ligand. Therefore, *N*-containing donor ligands that destabilise Cu(I) species are used. Induction of the catalytic cycle is proposed to occur *via* the heterolytic dissociation of the C–X bond promoted by the Cu(0) mediated *via* an outer sphere electron transfer. Following this, CuX is generated but rapidly disproportionates to yield inactive CuX_2 and regenerating an active Cu(0) atom.

SET-LRP has a few inherent limitations, such as strong exotherms and long induction periods. However, if the reactor design is chosen carefully these limitations can be mitigated against. Hutchinson *et al.*[78–80] designed a flow reactor with the active reactor coil being constructed from copper tubing which was used to perform the controlled copper mediated radical polymerization of methyl acrylate at ambient temperature. A rapid polymerization was achieved obtaining 67% conversion in a residence time of 16 min. It was also noted that unlike in batch the auxiliary ligand concentration could be significantly reduced without incurring any detrimental effect on the polymerization rate. This indicates the bulk copper surface acts as a redox sink for the polymerisation. The process was also noted to be highly exothermic with temperatures of up to 32 °C being detected at the mixing inlet but quickly returning to ambient before the outlet (the reactor surface area to volume ratio was 24.2 $cm^2\,mL^{-1}$).

In a follow-up paper the same group looked to increase the methyl acrylate monomer conversion by increasing the reactor length.[79] A new reactor design

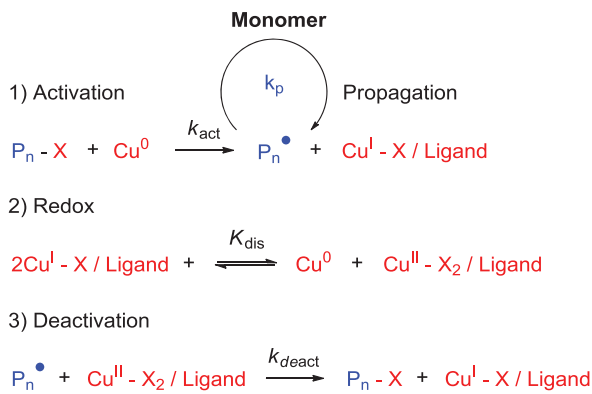

Figure 7.11 General mechanism for SET-LRP process.

was assembled comprising a short segment of copper tubing to initiate polymerization by acting as a source of soluble copper whilst the majority of the bulk reaction took place in a secondary extended segment of inert stainless steel tubing (Figure 7.12). To control the redox chemistry in the absence of the copper surface the additive ascorbic acid was mixed into the flow as a reducing agent to regenerate the activate copper enabling the SET-LRP to continue. At steady state operation a conversion of 78% for a residence time of 62 min was attained producing a polymer ($M_n = 4780$ g mol^{-1} and $Đ = 1.34 \pm 0.02$) with a final residual copper concentration of 10 ppm.

Haddleton *et al.*[81] adopted a different approach building a copper reactor comprised of PTFE tubing with a Cu(0) wire threaded insert. The results obtained were remarkable from such a simple set-up. It was noted that the flow rate greatly affected the molecular weight with longer residence time (thus longer contact time) leading to much higher molecular weight. Increasing the flow rate from 0.05 mL min^{-1} to 0.3 mL min^{-1} and, therefore, decreasing the residence time (80–13 min) decreased the molecular weight from 4200 g mol^{-1} to 3200 g mol^{-1}. A high 90% conversion was achieved at the low flow rate with a reasonable 69% conversion at the high flow rate. The dispersity was also reported as being very low (1.14–1.20) for all flow reactions performed. Overall, the obtained results were comparable with equivalent batch procedures,[84] however, in the flow process operational safety was increased as runaway reactions were prevented. Of further note was that an at-line automated GPC sampling method was also appended to the reactor to enable more efficient analysis of the reactions (Figure 7.13). To facilitate this, the copper tubular reactor was directly connected to a low-pressure mixing chamber (LPMC), enabling dilution of the reaction mixture with THF. The diluted mixture was then injected to a high-pressure mixing chamber (HPMC) where further dilution with a make-up feed was used to reach the necessary concentration for analysis by gel permeation chromatography (GPC). This set-up enabling an automated sample to be run approximately every 30 min.

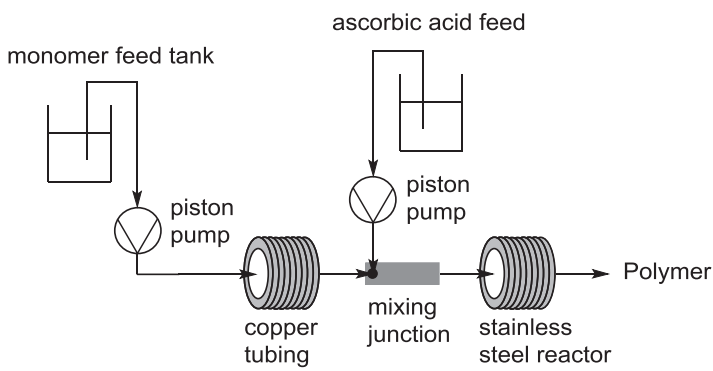

Figure 7.12 Dual residence time flow reactor for polymerisation.

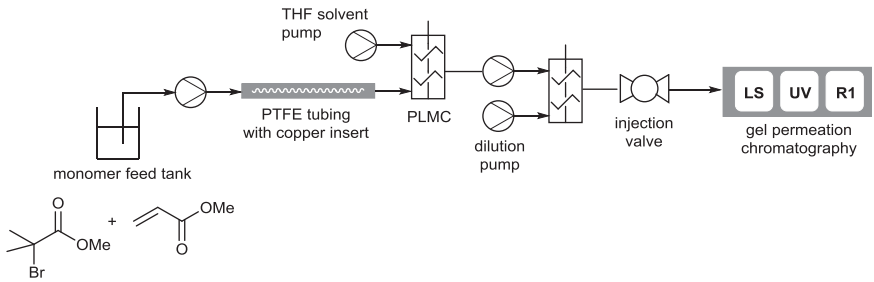

Figure 7.13 Integrated reactor with at-line molecular weight monitoring.

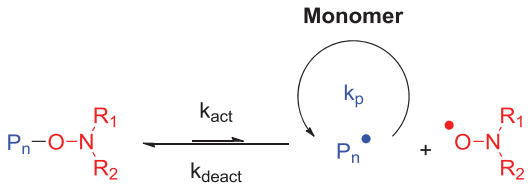

Figure 7.14 Nitroxide mediated polymerisation mechanism.

7.3.2 Nitroxide Mediated Polymerisations

Nitroxide mediated polymerisations (NMP) are controlled by the formation of a capped propagating chain. The chain extends through addition of a monomer to a reversibly generated radical (Figure 7.14). The nitroxide thus acts as a control agent mediating the reaction through the inert alkoxyamine as the predominant species. Homolytic cleavage is most often induced through thermolysis and is, therefore, highly suited to flow processing.

7.3.2.1 Nitroxide Mediated Polymerisations in Flow

Nitroxide mediated polymerisations have also been performed in flow although not at the same scales as the related ATRP's.[85–87] Cunningham *et al.* described the preparation of a latex polystyrene homo-polymer *via* nitroxide mediated polymerisation. This research was published over two papers. In the first publication[85] the initial step, the polymerisation of styrene in the presence of TEMPO, was performed in a batch reactor while the mini-emulsion styrene polymerisation was performed in a continuous tubular reactor. In a subsequent paper[86] the entire polymerisation process was conducted as a fully integrated flow sequence.

The initial flow mini-emulsion polymerisation of polystyrene was performed at 135 °C in a 167 m length of stainless steel tube (3.2 mm OD and 2.05 mm ID) (Figure 7.15).[85] This gave a mean particle size of 170 nm (standard deviation of 59 nm) which compared well to batch which delivered a particle of 164 nm (SD 61 nm). The major difference observed between the flow set-up and batch processing mode was a lower average molecular weight and reduced conversion in batch compared to flow. This is most

likely explained by the longer reaction times in batch caused by the extra time required to warm up and cool down the reactor. Additionally, due to different temperature regimes, the associated rates of the polymerisation will differ. In contrast, the flow reactor is essentially preheated and thermally balanced with a fixed temperature regime for the entire polymerisation.

In the extended synthesis, the initial bulk polymerization of styrene in the presence of TEMPO was also conducted in flow and was then further processed *via* mini-emulsion polymerisation also in a second continuous flow tube reactor to synthesise a latex polystyrene homo-polymer.[86] In practice the same reactor set-up (Figure 7.15) was used for each polymer processing step with the material being collected in batch between the stages.

For the second stage, the latex was formed by dispersing the 'living' polymer chains and styrene monomer into an aqueous phase. Using styrene as monomer, an average M_n of 15 500 g mol^{-1} with relatively narrow dispersity of 1.19 was obtained as analysed by GPC. This stands up well against an anticipated theoretical value of 17 211 g mol^{-1}. As these experiments demonstrated that the polymer chains were still 'alive', it enabled their extended use in the formation of di-block co-polymers.

Subsequently, the synthesis of a di-block co-polymer with *n*-butyl acrylate was performed. A broader distribution compared to the mono-polymer was obtained (1.25 *versus* 1.19). In addition, the number-average molar mass for the di-block co-polymer was only 20 500 g mol^{-1}, indicating that only moderate conversion of *n*-butyl acrylate was achieved. To increase the reactivity, ascorbic acid was dosed into the reaction as an additive. As a result, it was found that higher conversion could be achieved but at the expense of the concentration of living polymer chains which had a corresponding negative influence on the dispersity (1.34 mono-polymerisation, 1.92 di-block copolymerisation). The achieved M_n for homo-polymerisation was 24 300 g mol^{-1} where the theoretical M_n was 19 124 g mol^{-1} and for co-polymerisation the achieved M_n was 37 200 g mol^{-1} where the theoretical M_n was 28 366 g mol^{-1}. Finally, the di-block co-polymer was further processed to form a tri-block copolymer using styrene. This second chain extension was also performed in the continuous tubular reactor resulting in a tri-block co-polymer with a number-average molar mass of 57 876 g mol^{-1} and dispersity of 2.30. This simple designed

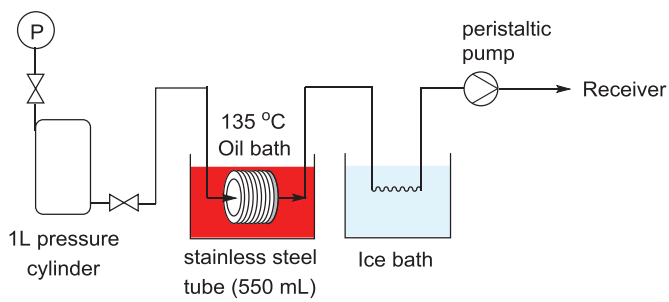

Figure 7.15 Stainless steel tubular reactor for flow mini-emulsion polymerisation.

system shows the ability of flow reactors to perform multiple reactions in-line, resulting in a more continuous output of advanced polymer architectures.

Similarly, Serra *et al.*[87] employed a nitroxide-mediated radical polymerization (NMRP) of styrene and *n*-butyl acrylate in a microtube reactor (900 μm ID). This was compared to a conventional lab scale batch reactor to assess the high surface to volume ratio aspects with the aim of gaining better control over the highly exothermic polymerisation processes. For styrene, which has a lower exothermicity, the researchers found a generally linear correlation in molecular weights (M_n) with increasing conversion, this also mapped well to their theoretical predictions. Furthermore, the dispersities obtained from the flow processes were essentially identical to those obtained in batch and were below 1.5 thus being indicative of a high degree of control over the polymerization. Interestingly, *n*-butyl acrylate conversion was found to be significantly lower in the micro reactor than batch which was ascribed primarily to better heat transfer. In batch the heat released by the *n*-butyl acrylate polymerization reaction is much higher than that of styrene and readily leads to thermal runaway. This is further compounded by inefficient mixing, meaning less homogenization of the reactive medium, and poor heat removal capacity generating reactive hot spots. This superior heat transfer in the micro reactor negates these thermal self-propagating aspects which is observed as a lower comparative conversion at batch equitable time points but displaying a more linear conversion/time plot. It is also reflected in the lower dispersity index at higher comparative conversions.

7.3.3 RAFT Polymerisation

Reversible addition–fragmentation chain transfer (RAFT) is another controlled radical polymerisation method. With this polymerisation technique, additional control over molecular weight, molecular weight distribution, composition and architecture can be gained. This method is also suitable for a wide range of monomers. The most common functional polymerisation head is the trithiocarbonate group, although benzyl benzodithioate, 1-(methoxycarbonyl)ethyl benzodithioate and several others can also be employed.[88]

7.3.3.1 RAFT Polymerisation in Flow

RAFT polymerisation in flow was first reported by Seeberger *et al.* in 2010,[89] 12 years after its discovery at the Commonwealth Scientific and Industrial Research Organisation in 1998 (CSIRO, Australia).[54] It was shown that, in flow, a general decrease in reaction time could be achieved compared to the traditional batch process. As an aside, an investigation into the use of microwave irradiation of reactions showed reaction times similar to the flow polymerisations indicating the enhancements came from more efficient heating. The flow set-up used to polymerise *N*-isopropylacrylamide was a very simple construction prepared from two syringe pumps, a T-piece, PTFE tubing and an oil bath for heating. With this set-up, Seeberger *et al.* managed

to obtain good dispersity ($Đ = 1.11$) and molecular weights of 20 kg mol^{-1}. Rapid reaction screening was not possible as it took time to heat/cool the oil bath and the size of the syringes placed a limitation on scale.

Hornung *et al.*, only months later, showed an interesting RAFT polymerisation using a commercial flow system (Vapourtec R2/R4).[90] Their paper describes the polymerisation of various monomers, initiators, solvents and RAFT additives (Figure 7.16). Several flow set-ups were tested before a suitable system was identified. It was highlighted that oxygen exclusion was very important to perform successful RAFT polymerisations. Initially the RAFT

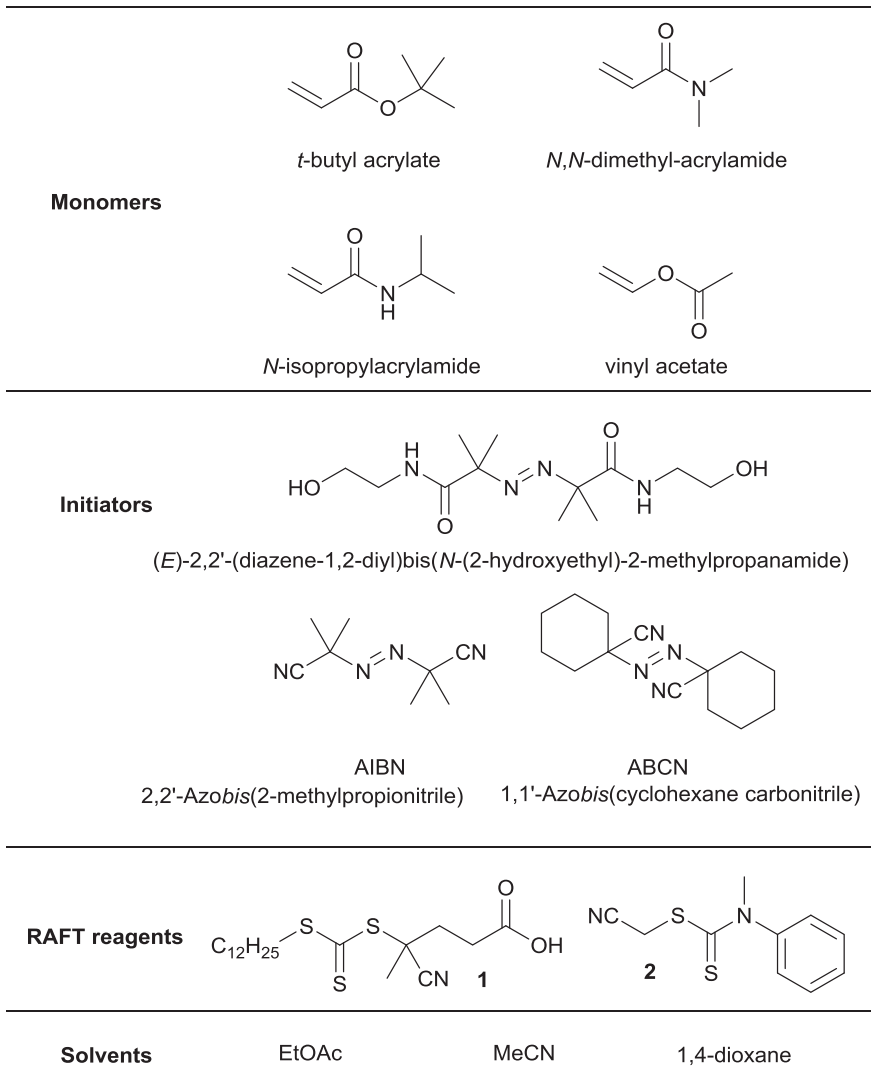

Figure 7.16 Monomers, initiators, solvents and RAFT additives.

polymerisation was performed in a perfluoroalkoxy alkane (PFA) polymer reactor but failed to give good results. However, using a stainless steel reactor for the polymerisation gave much better result and thus it became clear that PFA polymer reactors were not suitable for oxygen sensitive processes.

The flow reactions were performed following a segmented flow procedure using a 2 mL reactant injection loop (Figure 7.17). It was shown that increased control over the polymerisation could be gained using RAFT when *N*-isopropylacrylamide was used as a monomer but, as expected, a major decrease in the number average molecular weight was also observed (Table 7.4), as the propagation rate is much lower for RAFT than compared to direct free radical polymerisation.

Overall, only small differences were observed in the percentage conversion of the monomer, average molecular weight or dispersity between the batch and segmented flow procedure for the different techniques. Free radical polymerisation in batch or in a stainless steel reactor both gave full conversion and similar number average molecular weight and dispersity. The difference between batch and segmented flow polymerisation is more noticeable when the RAFT technique was used, with shorter polymer chains being synthesised compared to batch. Initially due to the high levels of diffusion in the segmented flow the conversion and dispersity achieved was not as good as in batch. This was especially the case for reaction times of less than 2 h. For reaction times of 2 h, the difference in dispersity between batch and flow was approximately 0.08 higher. However, when a continuous flow polymerisation was performed and steady state was reached, conversion and dispersity were better at reaction times of 1.5 h (Table 7.5).

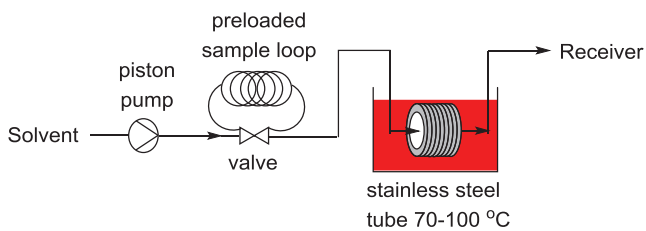

Figure 7.17 Segmented flow where the monomer, initiator, and RAFT agent are preloaded into a sample loop and injected into a constant solvent stream as a separated plug.

Table 7.4 Polymerisation of *N*-isopropylacrylamide at 90 °C using free radical polymerisation and RAFT in a batch reactor, PFA and stainless steel flow coil.

Parameters	Batch		PFA coil[a]		Stainless steel coil	
Polym. Tech.	Free rad.	RAFT	Free rad.	RAFT	Free rad.	RAFT
Conv. (%)	100	89	77	0	100	85
M_n (g mol^{-1})	316 000	19 500	233 000	na	327 000	20 500
Dispersity	1.78	1.14	1.88	na	1.77	1.17

[a]na = not available.

Table 7.5 Polymerisation of DMA (*N*,*N*-dimethyl-acrylamide) in batch, segmented flow and continuous flow.

Output	Batch	Segmented flow[a]	Continuous flow[b]
Conversion (%)	97	90	95
Dispersity	1.10–1.15	1.16	1.09–1.16

[a]Polymerisation performed in a stainless steel coil reactor.
[b]Reactions were performed at 80 °C, [DMA] = 1.8 mol L^{-1}, [AIBN] = 5.4 mmol L^{-1}, RAFT additive **1** (Figure 7.16) = 9 mmol L^{-1} in MeCN.

A main advantage of the simple flow set-up described (Figure 7.17), was the opportunity to perform rapid screening of various reaction conditions, especially as continuous operation was possible. However, when using a segmented flow screening approach, it has to be acknowledged that diffusion can be a major issue and steady state operation will never be reached. This is important as the concentrations of reactants are not the same in the entire plug (affected by size/volume/reactor length and mixing elements) especially if the plug is miscible with the bulk system solvent. As a result, further optimisation is often required to refine the conditions when moving to a continuous flow scenario. Such investigations were undertaken by Hornung *et al.* evaluating both potential scale-up and modification of RAFT polymers in flow.[91–93]

Further to these studies a looped flow process was devised that also allowed the preparation of RAFT multi-block copolymers (Figure 7.18).[94] Arcylamide monomers were selected for the investigation due to their high propagation rate coefficients resulting in short polymerisation times, high aqueous solubility and the lack of competing side reactions such as chain transfer. The system was first primed by filling with solvent and then a solution containing the monomer was injected. The system was then equilibrated allowing the solution to become homogenised by circulation at high flow rate through the system. The polymerisation occurs as the reactor reaches its set temperature and the product can be systematically sampled or the bulk media collected at the output valve. As each block reaches completion a second monomer can be added. Using the system depicted, a series of different polymerizations were performed at 70 °C allowing the polymerization time for each block to be reduced to 2 h. A triblock copolymer with a degree of polymerization (DP) of 20 for each block ($pNAM_{20}$-*b*-$pDMAm_{20}$-*b*-$pDEAm_{20}$) and two hexamer block polymers (ABCABC; DP 10 each) were prepared (*e.g.* $pNAM_{10}$-*b*-$pDMAm_{10}$-*b*-$pDEAm_{10}$-*b*-$pNAM_{10}$-*b*-$pDMAm_{10}$-*b*-$pDEAm_{10}$) with near full monomer conversion being achieved for each block (>98%). As an example, the synthesis of the hexa block took around 12 h of active processing time, spread over two days, by producing three blocks per day (solutions of intermediates were left at RT in the reactor when not being processed).

Another report was published[95] describing a two-stage process involving sequential RAFT polymerisation of selected monomers (Figure 7.19) followed by aminolysis by polymer-supported or solution phase amines. A UV spectrometer was placed in-line and allowed for direct analysis of the aminolysis reaction. Following aminolysis, conjugate addition to form thioether

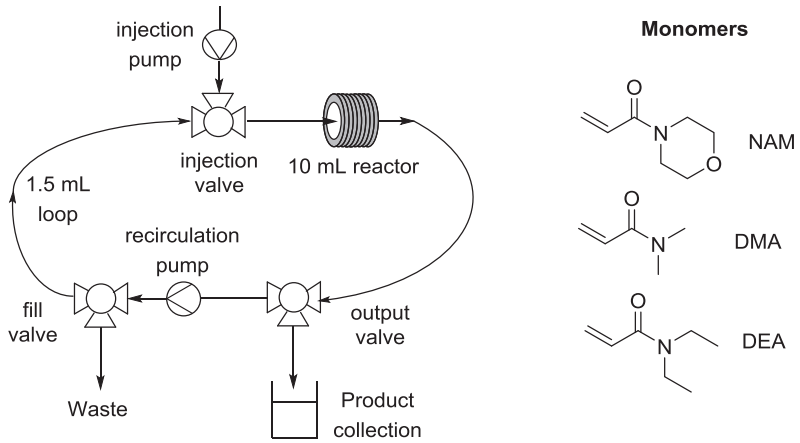

Figure 7.18 Stainless steel loop reactor design.

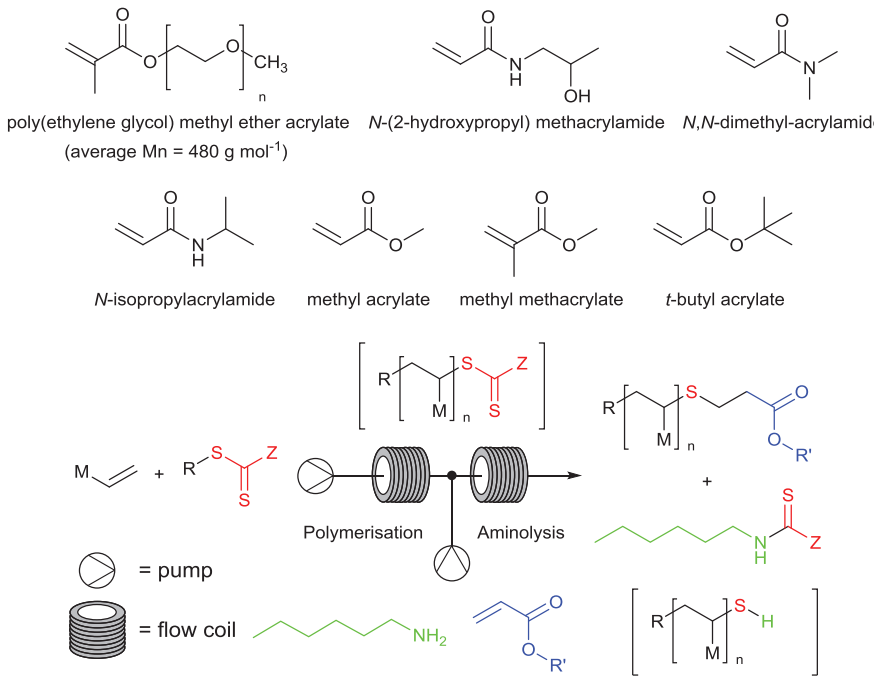

Figure 7.19 Multi-step RAFT polymerisation and aminolysis.

terminated polymers was conducted which did not have any influence on the dispersity.

End group manipulation post-polymerisation is an important research area. A series of investigations[96,97] led by Hornung *et al.* focused on the radical-induced end-group removal of RAFT polymers, an issue is that the

residual thiocarbonylthio groups can be associated with negative physical characteristics such as colour and smell. Thermolysis is a simple approach used for desulfurisation of RAFT polymers. This has also been described by Hornung *et al.* starting from different RAFT polymers prepared in flow from acrylamides, acrylates, methacrylates and styrenes.[97] The polymer backbone needs to be stable at high temperatures as the thermolysis was carried out between 220–250 °C. To perform thermolysis in flow a continuous set-up was designed (Figure 7.20).

A comparison between a batch and a flow process for the preparation of poly(methylacrylate) (pMA) was conducted. The polymer produced was then used for the thermolysis (Table 7.6). The dispersity did not increase significantly and good control was achieved over the two steps. The synthesis of RAFT end group polymers in flow allows for a process to synthesise colourless and non-odorous polymers. Furthermore, the authors deemed the flow process to be more easily scalable and giving higher reproducible compared to batch.

A continuous RAFT polymerisation was conducted as a scale-up process by Micic *et al.*[93] In their publication they describe the differences between large-scale batch processing and scale-up *via* flow. Acrylic acid and 2-acrylamido-2-methylpropane-1-sulfonic acid (AMPS) were used as monomers in an aqueous solution RAFT polymerisation. Conversion in the flow RAFT polymerisation was >90% at a temperature of 80 °C and a reaction time of 40 min. In comparison, the batch process showed non-stable temperature profiles. This was particularly noticeable at larger scales with exotherms reaching 98 °C for a 500 mL scale and 17.7 wt% of the monomer. The same issue was noticed performing the polymerisation in a microwave. Although the volume was limited to 20 mL instead of 500 mL the temperature overshot to 94 °C. This overheating caused higher proportions of radicals, resulting in a loss of

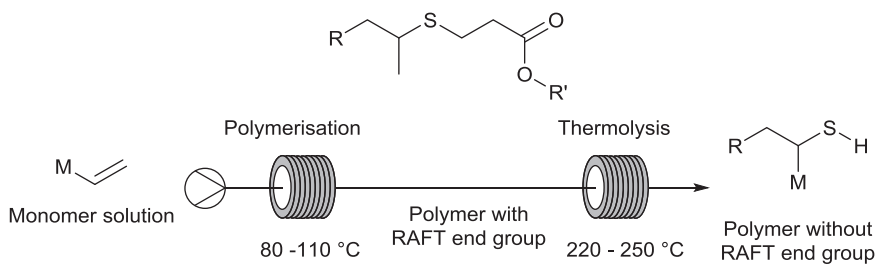

Figure 7.20 Polymerisation and thermolysis in flow.

Table 7.6 Polymerisation and thermolysis of pMA.

Type	Conversion[a] (%)	M_n (g mol^{-1}) (B)[b]	M_n (g mol^{-1}) (A)[b]	$Đ$ (B)[c]	$Đ$ (A)[c]
Batch	97/54	9900	9100	1.33	1.33
Flow	96/87	8300	7400	1.24	1.25

[a]Conversion of monomer/thermolysis.
[b]Number average molecular weight before (B) and after (A) thermolysis.
[c]Dispersity before and after thermolysis.

Table 7.7 Conversion, M_n and dispersity of poly(acrylic acid) in batch and flow, polymerised at 80 °C, 500 mL scale and 17.7 wt% acrylic acid.

	Conversion (%)	M_n (g mol^{-1})	$Đ$
Batch	97.4	21 600	1.45
Flow	94.7	23 200	1.53

control over the polymerisation process. The exotherm was not encountered in flow, the temperature profile was extremely stable and held at 80 °C. Conversion, number average molecular weight and dispersity for batch and flow polymerisation of acrylic acid were obtained (Table 7.7). This enable up to 90 g of material to be produced in a short run as a continuous flow process.

However, a disadvantage of the flow set-up was the requirement for an increase in reaction time. Based on the throughput of the reactor described, it would take about five times longer to process the total volume equating to a single batch. Although it could be argued that this 'lost' time could be recouped during the purification of the polymer produced as, in flow, better quality material was obtained.

Junkers *et al.* developed a flow microreactor protocol for the synthesis of acrylate multi-block (up to five blocks) co-polymers using RAFT polymerisations.[98,99] Poly(*n*-butyl acrylate) (P*n*BuA) was synthesised in flow using different RAFT reagents. By tuning the reaction parameters various molecular weights could be produced. The key parameters controlling the molecular weight were the reaction time and ratio of monomer to RAFT reagent. The dispersity of the P*n*BuA polymers was retained within the expected limits (1.10–1.13) for this type of polymerisation. The functionalised material was subsequently used in co-polymerisations with different acrylates (ethyl hexyl acrylate, *tert*-butyl acrylate and *n*-butyl acrylate) in a microreactor. Ultimately a co-polymer with five different acrylate blocks was synthesised with a number average molar mass of 32 000 g mol^{-1} and a dispersity of 1.46. Unfortunately, a final yield of only 100 mg of polymer was achieved and there was a need for intermittent work-up between each chain extension, which renders this method less amenable to scale-up. However, directly comparing flow and batch co-polymerisations indicated better results for the flow process. For example, the co-polymer P*n*BuA-*b*-P*t*BuA-*b*-PEHA had a number average molar mass of 10 700 g mol^{-1} in flow and 9300 g mol^{-1} in batch with dispersity of 1.28 and 1.93 respectively. This provides a highly convincing case as to the strength of flow chemistry for precision polymer synthesis.

In an interesting extension to some of their early work, Junkers *et al.*[100] showed that previously synthesised RAFT polymers, which had end group modifications involving terminal alkynes, could be directly used in copper catalysed click coupling chemistry with azides under flow conditions. Short polymer sequences with azide and alkyne termini were prepared in flow and united to make new polymer conjugates.

The application of system pressure to a flow reactor easily allows access to temperatures above the standard boiling points of a solvent, a concept which

has successfully been utilized for RAFT polymerisation in a binary aqueous ethanol solvent mixture.[101] The flow polymerization of poly(ethylene glycol) methyl ether methacrylate (PEGMEMA) was conducted with a conversion of 52% at 100 °C under a system pressure of 73 bar (Figure 7.21). A simple pressurised 8 mL reactor loop, which was housed in an oven, enabled the reaction in a 40 min residence time to deliver a polymer of narrow molar mass dispersity ($Đ < 1.25$) and high weight M_n 28.6 kDa.

The generation of self-assembled nanoparticles *via* a RAFT promoted polymerisation in a tubular reactor was studied by Zhu and co-workers.[102] In a two-stage reactor, first a hydrophilic soluble poly-PEGMA was synthesized *via* solution RAFT polymerization before it was chain extended with methyl methacrylate (MMA) which induces self-assembly nanoparticle formation in a water/ethanol solvent mixture (Figure 7.22). Using an interchangeable second stage reactor (reactor lengths of 3–24 m, 1.75 mm ID) the residence time was varied allowing different compositions of the diblock copolymers to be assembled. A wide range of resultant nanoparticles were produced in physical sizes of 78.4–172.5 nm as measured by dynamic light scattering equating to a comparable M_n of 29 000–122 200 g mol^{-1}.

Controlled radical polymerization (CRP) techniques have significantly advanced polymer synthesis by exerting greater governance over molecular weight, structure, and dispersity ($Đ$). With a desire to further such control, several groups have looked to the use of photo switchable and photo redox mediated polymerisation processes.

Melker *et al.*[103] combined the small reactor dimensions of a capillary flow system with the spatial and temporal control imparted by light stimulation for the polymerisation of methyl methacrylate. They found the polymerisations in the presence of a redox mediator, *fac*-Ir(ppy)$_3$, to be very sensitive allowing the chain growth to be turned 'on' or 'off' on demand allowing for control over the molecular weight and dispersity ($Đ$) of the resultant polymer (Figure 7.23).

The flow reactor was simple and constructed from thin walled polymer tubing (550 cm, 0.02 inch ID –Halar, PFA, FEP or Tefzel) wrapped around a glass inner tube (air cooled) ensuring full light penetration to the flowing reaction media (Beer–Lambert's law). At flow rates of 1–20 μL min^{-1} a broad range of residence times spanning 25–500 min could be evaluated. Oxygen diffusion through the permeable polymer tubing was noted as a problem leading to inhibition of the polymerisations especially over longer residence times. This varied with the different polymer tube formulations evaluated, with Halar® being determined the least permeable and, therefore, best suited for use in flow. Using the optimised Halar® constructed reactor monomer conversions >80% for a 450 min residence times could be achieved. In all cases narrow molecular weight distributions (1.15–1.24) were obtained.

Gardiner *et al.*[104] utilized a commercially available Vapourtec UV-150 tubular photo flow reactor for the UV-initiated continuous synthesis of RAFT polymers. A 150 W medium pressure mercury lamp was used as the light source which could be fitted with interchangeable UV filters.

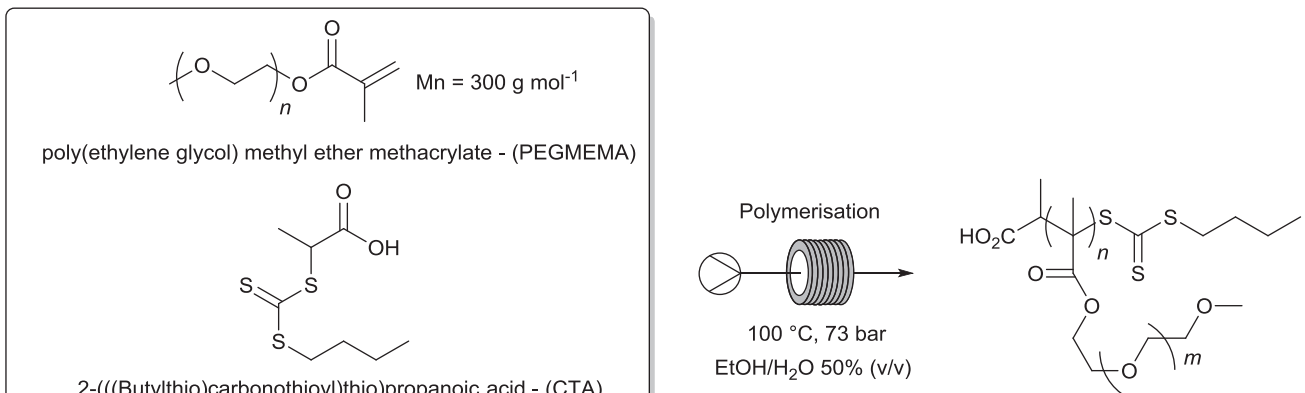

Figure 7.21 RAFT polymersiation within a pressurised flow reactor.

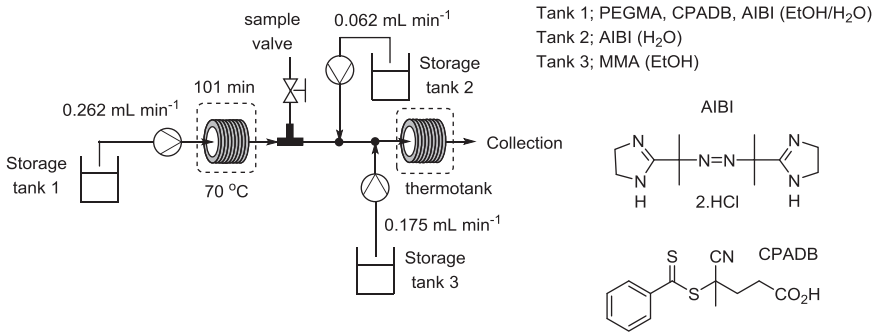

Figure 7.22 RAFT polymerisation in a continuous tubular reactor using 4-cyano-4-(thiobenzoylthio)pentanoic acid (CPADB) as the chain transfer agent, and 2,2′-azo*bis*-[2-(2-imidazolin-2-yl) propane]dihydrochloride (AIBI) as the initiator.

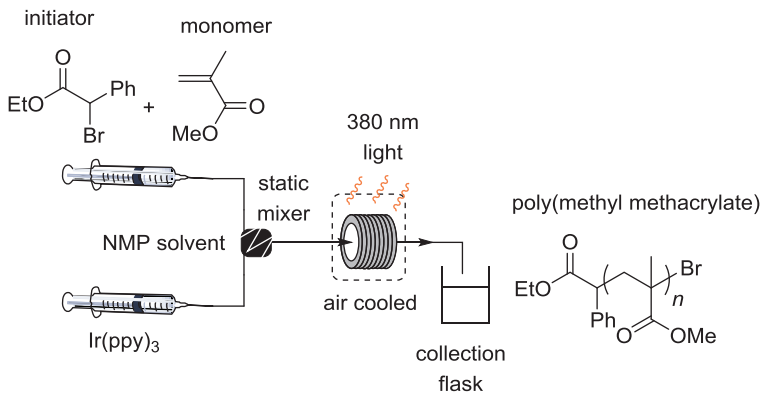

Figure 7.23 Controlled light-mediated radical polymerisation.

A long-pass filter with transmission above 310 nm was found to be optimal when employing a photo initiator, Irgacure 369, which is commonly applied in industry for UV-curing of pigmented coatings and varnishes (Figure 7.24). In an example polymerisation of DMA a residence time of 30 min led to a high monomer conversion of 99%. This was accompanied by good control over the molecular weight of 17.5 kg mol^{-1}, and dispersity 1.5.

The results indicate that photo-initiated RAFT polymerisation under continuous flow conditions has great potential for wider adoption across polymer research and industrial manufacture.

During initial studies[105] Chen *et al.* found that, although light intensity increased the reaction rate of trithiocarbonate mediated photo-CRP processes, it had a negative effect on dispersity when performed in batch. This requirement to use low light intensity and, therefore, long reaction times, rendered the batch processing inconvenient. In an effort to improve the practicality of their photo-CRP they reasoned that the use of a continuous-flow reactor may prove advantageous. They settled upon a simple syringe driven

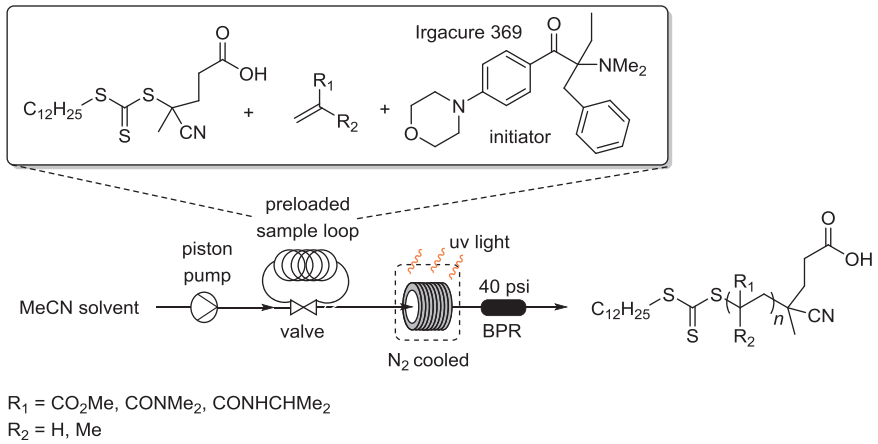

Figure 7.24 The selection of acrylic monomers, methyl acrylate (MA), methyl methacrylate (MMA), *N*,*N*-dimethyl acrylamide (DMA) and *N*-isopropyl acrylamide (NIPAM) used in the UV-initiated continuous flow synthesis of RAFT polymers.

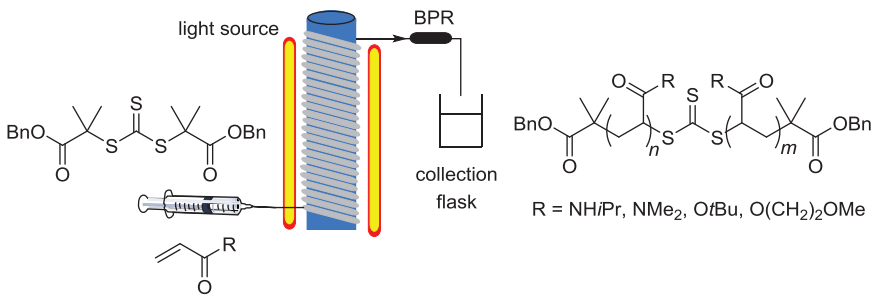

Figure 7.25 Photo-CRP reaction performed in flow.

system and a reactor prepared from fluoropolymer tubing and a compact fluorescent lamp (peak emission at 352 nm) to synthesise a series of homopolymers and block-copolymers with low dispersities in the range 1.1–1.4 (Figure 7.25).[106] They showed that significant enhancements in scalability and reaction rates could be attained compared to the analogous batch reactions. As an exemplification the polymerisation of DMA was run for 400 min which allowed the collection 2.95 g (84% isolated yield, from 36 mmol of monomer) with a satisfactory molecular weight distribution $M_w/M_n = 1.11$. In addition, the same set-up was used to prepare a triblock PDMA-*b*-PEGMEA-*b*-PDMA of molecular weight 34 900 g mol^{-1} and possessing a narrow dispersity of 1.17.

7.3.4 Free Radical Polymerisation

Continuous free radical polymerisation of acrylic acid was performed by Qui *et al.*[107] As part of this work, a study of the kinetics of free radical

polymerisation of acrylic acid in a micro reactor device, using potassium persulfate as initiator, was performed. The designed reactor allowed different reaction times as a switch-on valve (5-way tap) was introduced to alter the reactor length. Quick screening was possible allowing rapid access to kinetic parameters. The kinetic orders of acrylic acid and potassium persulfate were determined as 1.5 and 0.5 respectively, which were in line with the literature values.[108,109] The measured activation energy was 67.4 kJ mol^{-1} which was in line with the previous literature.[109] Different polymers with variable molecular weights were synthesised, in the range 103 326–176 052 g mol^{-1}. The dispersity was slightly broader compared to controlled radical polymerisation, but still good for a free radical process. Poly(acrylic acid) with the smallest molecular weight (103 326 g mol^{-1}) had a dispersity of 2.42 and poly(acrylic acid) with the highest molecular weight (176 052 g mol^{-1}) had a dispersity of 2.03. This design is particularly suitable for screening multiple parameters. The residence time could be increased easily by adding further residence loops without changing the flow rate. Other free radical polymerisations in flow were performed by Yoshida *et al.* involving the polymerisation of butyl acrylate, benzyl methacrylate, methyl methacrylate, vinyl benzoate and styrene using AIBN as initiator for the reaction.[110] Similar molecular weights were obtained. The dispersity in flow for butyl acrylate was much lower compared to batch (3.14 *versus* 9.61), which was explained by the efficient removal of heat. Benzyl methacrylate (dispersity in flow 1.98 *versus* dispersity in batch 2.71) and methyl methacrylate (dispersity in flow 1.83 *versus* dispersity in batch 2.21) showed a smaller improvement for the dispersity. Vinyl benzoate (dispersity in flow 1.16 *versus* dispersity in batch 2.16) and styrene (dispersity in flow 1.76 *versus* dispersity in batch 1.76) gave similar dispersity for batch and flow. These reactions indicate flow chemistry could be used for a variety of free radical polymerisations.

Broken *et al.*[111] also studied the free radical polymerisation of acrylic acid in a commercially available FlowSyn general purpose flow reactor (Figure 7.26). Through the use of a design of experiment (DoE) approach the aqueous polymerisation with different stoichiometries of initiator, 2,2′-azobis(2-methylpropionamide) dihydrochloride (AMPA), and concentrations of monomer (0.4–1 mM) were assessed. Various trends in conversion, M_n

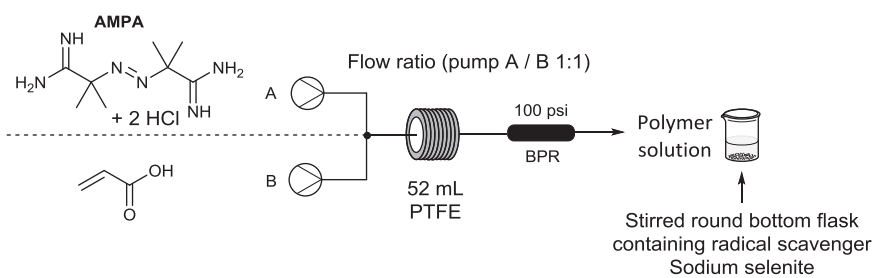

Figure 7.26 Free radical polymerisation of acrylic acid in a flow reactor.

and dispersity were correlated with changes in the reagent ratios, temperature and residence time. The target of the study was to ultimately devise a model which allowed future prediction of conditions for the synthesis of new polymers with tailored physical properties (M_n and dispersity). In practice, a good correlation with molecular weight was achieved but dispersities varied more widely being higher than desired.

In an attempt to prepare more environmentally benign polymers, Sainz *et al.*[112] investigated a series of acrylic monomers derived from naturally abundant terpenes. These were polymerised under free radical conditions to create novel renewable polymer coatings with the challenge of providing matched or improved properties and performance to existing oil-based polymers without adding significant production costs. For the monomer construction a two-step assembly was perused starting from either a hydroboration/oxidation (alkene derived terpenes) or lithium aluminium hydride carbonyl reduction (ketone derived terpenes), followed by esterification of the resulting alcohol with (meth)acryloyl chloride or the use of the acid with propyl phosphonic anhydride (T3P®) (Figure 7.27).

The terpene-based acrylate and methacrylate monomers could all, apart from one, be polymerised *via* simple free-radical techniques to yield a range of polymers with different properties. Interestingly, the carvone-derived acrylate monomer showed a very low reactivity (AIBN initiator at 65 °C) and when the temperature was raised to 110 °C, monomer conversion increased, but quickly resulted in the formation of an insoluble cross-linked gel. In contrast, the related carvone methacrylate monomer reacted smoothly at 65 °C in the presence of AIBN without any sign of cross linking. In general, the molecular weights of the polymers could also be controlled by the addition of standard chain transfer agent *e.g.* dodecanemercaptan. For example, the α-pinene derivatives produced polymers with controllable molecular weights in the range 4800–23 600 $g\,mol^{-1}$. The most successful polymers were taken forward and used in powder coating applications.

7.4 Overall Summary and Future Outlook

Over the last 30 years flow chemistry has been slowly adopted across all areas of chemistry, impacting research strategy and manufacturing campaigns. Interestingly the discipline of polymer chemistry has been relatively reluctant to embrace this technology. However, it is, as a technique, starting to find its way into more polymer laboratories. The principle advantages of flow chemistry as discussed in this chapter are summarised in Table 7.8.

In many ways it is completely understandable that flow chemistry has not been fully adapted by the polymer chemistry community as introducing flow chemistry can be a costly endeavour. Another problem is scalability, the investment in equipment to achieve scale-up (*i.e.* often the construction of a new plant) is currently higher compared to using existing batch facilities. This is especially true if a new process developed in a laboratory is being scaled up to industrial scale for the first time.

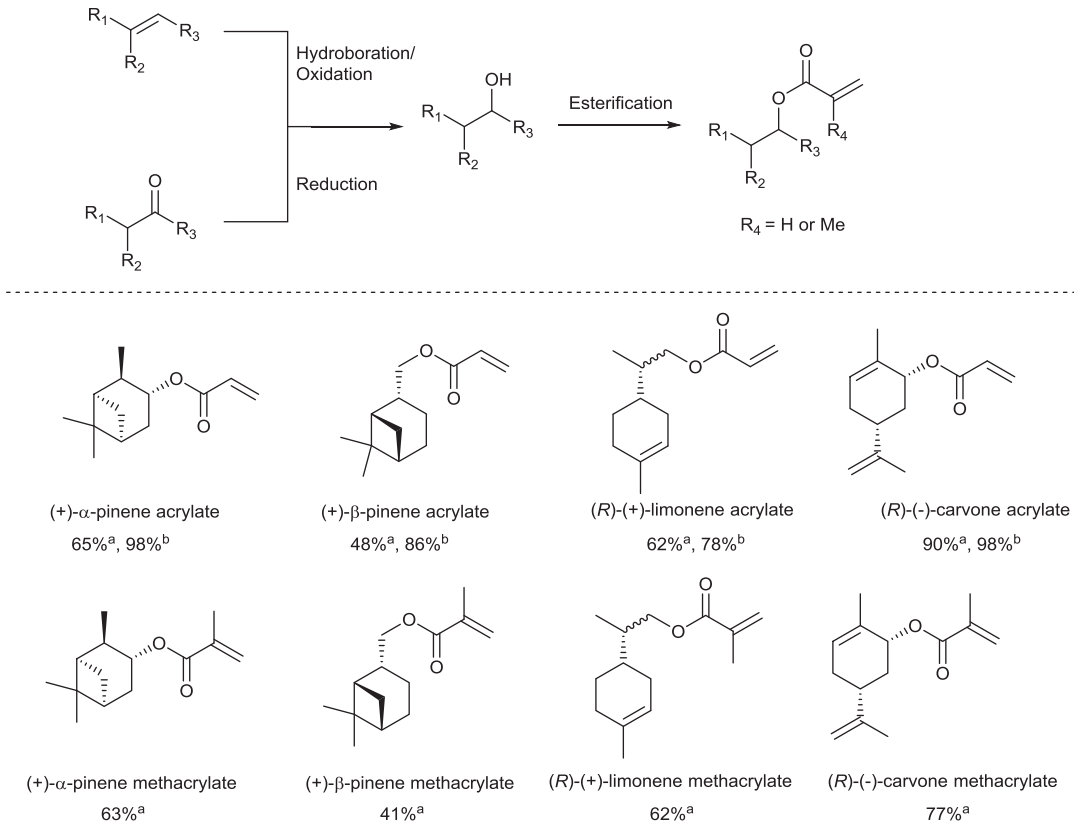

Figure 7.27 Various (meth)acrylate monomers derived from terpenes. (a) Esterification performed using (meth)acryloyl chloride. (b) Esterification performed using T3P®.

Table 7.8 Properties batch *versus* flow.

	Batch	Flow
General applicable procedures	+	+
Automated pre- and post-conditioning	+	+
In-line pre- and post-conditioning	−	+
Atom-efficiency	±	+
Efficient temperature regulation	−	+
Simple optimisation	−	+
Reproducibility	±	+
Increased safety	−	+

Indeed, increasing the scale of a reaction in flow requires systems which can process larger volumes of fluid or mitigation of the output by changing the total collection time, which is not always favourable, especially in an industry setting. For certain processes, scale-up can be easily achieved by directly increasing the diameter of the reactor tubing or increasing the length of the reactor which, in combination with higher flow rates, results in equitable residence times but greater throughput.[113–120] However, this often changes critical reactor characteristics such as mixing[121,122] or heat transfer that influence the quality (or properties) of the polymers produced. Alternatively, multiple smaller systems can be combined to work in parallel (numbering-up principle). It is likely, however, that this will substantially increase the equipment costs. To operate systems in parallel fed by one inlet is technically very challenging. This is due to the fact that it is hard to evenly divide the flow stream, and small pressure changes can lead to large variations in flow and residence time distributions.

Therefore, to perform polymerisation in flow as shown in this overview, many different devices have been used and careful consideration of the benefits and limitations of the reactor need to be considered. The majority of reactor designs presented in this review are based upon laboratory scale units and so are based on simple, low cost, plastic or stainless steel tubing. Such plastic, glass or stainless steel devices are relatively easy to construct and, therefore, simple to replace should blockage or rupture become an issue. Taking these designs for the laboratory to the pilot plant and beyond is an engineering challenge and a significant capital investment for any organisation. Consequently, there must be a clear business case, often for low-cost bulk products like polymers this is a hard case to make. However, it should be noted that other aspects such as increased safety and also changes in production practices such as just in time manufacturing (reduced stock inventories) fit well with the concepts of continuous flow production. In addition, the ability to perform in-line and on-line analysis is a strong advantage of flow polymerisations. Direct real-time process analytical technologies are extensively adopted as best practice in most chemical industries. This is, therefore, a key driving force for industry, as products can be studied in detail and changes to composition or output made in real time, thus ensuring quality control over the product during the manufacturing stage, not post-production.

Currently, flow synthesis of polymers is at an early stage but it is anticipated that this industry will also follow other chemical producing sectors such as pharmaceutical and agrochemical production to adopt more continuous manufacturing practices. It is advantageous that due to the early adoption in other sectors many of the potential problems regarding technical challenges of up-scaling and regulation will have been previously investigated and overcome, meaning a streamlined incorporation can happen. Although batch processing will never be entirely superseded by flow approaches it should be seen that in another 10 years at least 50% of polymer synthesis performed at scale will be under flow conditions.

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