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High-throughput experimentation applied to atom transfer radical polymerization: Automated optimization of the copper catalysts removal from polymers

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Abstract: Combinatorial chemistry and high-throughput experimentation have drawn great attention in recent years because of their significant advantages in increasing the research productivity. One of the emerging fields is their application in polymer science. Herein we describe the high-throughput optimization of purification conditions for polymers prepared via atom transfer radical polymerization using an automated synthesizer. The effects of the column materials, column lengths and eluent volumes on the purification efficiency as well as the molecular weights of the obtained purified polymers were systematically investigated for the first time. The optimum purification conditions for the removal of copper catalysts are provided. As a result an online high-throughput purification workflow using SPE cartridges is now available for the utilization in automated parallel synthesizers for ATRP screening experiment.

Introduction

Recent years have witnessed a fast development of combinatorial chemistry and high-throughput experimentation (HTE) in many areas of the discovery of new compounds including pharmaceuticals, inorganic materials, catalysts and polymers due to their significant advantages in increasing the research productivity [1]. In particular, our group has been interested in the application of these approaches in the field of polymer science and some of our research progresses in this field have been recently reviewed [2-4].

Nowadays controlled radical polymerizations (CRPs) have attracted great attention due to their versatility for providing simple and robust routes to the synthesis of polymers with controlled molecular weights and architectures under relatively mild reaction conditions [5-8]. One of the most popular CRP systems is atom transfer radical polymerization (ATRP) because of the easy availability of many kinds of catalysts, initiators, and monomers [5, 6]. However, many parameters in ATRP such as the structures and concentrations of the utilized monomers, catalysts (metals/ligands) and initiators, solvents, reactant ratios, and reaction temperatures can significantly influence the controllability of polymerizations, which makes the optimization of reaction conditions very time-consuming, in particular when a new reaction system is investigated. Therefore, practical techniques such as HTE by using an automated parallel synthesizer, which would allow a fast and efficient optimization of the reaction conditions, are highly suitable for this research direction [9-12].

An important prerequisite for the success of HTE in a specific experiment is that every step in the entire experimental process chain should be performed in a high-throughput way so that the complete workflow is not hampered by bottlenecks at certain points. This principle should be taken into consideration when a HTE workflow applied to ATRP is designed. One of the main issues in ATRP is the removal of catalysts from the obtained polymers prior to their characterization [13], e.g., the determination of the molecular weights and polydispersity indices of the polymers by size exclusion chromatograph (SEC). Therefore, the development of a fast and efficient online purification method for the obtained polymers is highly important for the successful HTE of ATRP. In this paper, we describe the high-throughput optimization of the purification conditions for polymers prepared via ATRP by using an automated parallel synthesizer. The factors influencing the purification efficiency, such as the column materials, column lengths and eluent volumes, have been systematically investigated for the first time and the optimum purification conditions for the removal of copper catalysts are presented.

Results and discussion

ATRP is a controlled radical polymerization process with transition-metal complexes as catalysts. It is a very versatile technique for preparing polymers with predefined structures [5, 6]. However, one disadvantage of ATRP is that a high concentration of a catalyst is usually required and thus has to be removed from the obtained polymers prior to their characterization and application [13]. The removal of catalysts from the obtained polymers was typically conducted by a manual chromatographic process. So far, many different column materials have been utilized for this purpose, such as silica gel and various aluminium oxides. To the best of our knowledge, however, the effects of the column materials on the purification efficiency for the polymers prepared via ATRP have never been studied under the same conditions and the optimum purification conditions are thus not available. The purification of the polymers prepared via ATRP was performed in a parallel and automated way, to end up with an efficient high-throughput purification method for ATRP systems.

A computer-controlled Chemspeed ASW 2000 automated parallel synthesizer together with a solid phase extraction unit (SPE) was utilized for this purpose (Fig. 1). Hand-made aluminium oxide (active neutral, active basic and deactivated standard ones) or silica gel SPE cartridges (length = 5.6 cm, diameter = 0.6 cm) including porous polyethylene frits and ASPEC caps (Chemspeed Technologies AG) were used to purify the polymers (Fig. 1b, c). Small amounts of cotton were placed on top of the aluminium oxides or silica gel in order to distribute the polymer solutions homogeneously on the columns. The polymer solutions were then automatically transferred to the columns and tetrahydrofuran (THF) was used as the eluent to wash down the polymers. The copper catalysts should stay on the columns to some extent depending on the efficiency of the columns and the purified polymers. The eluent was then collected in an automated way in vials under the SPE columns. The column materials, column lengths and eluent volumes were varied in order to optimize the purification conditions and totally 64 different purification conditions were investigated.

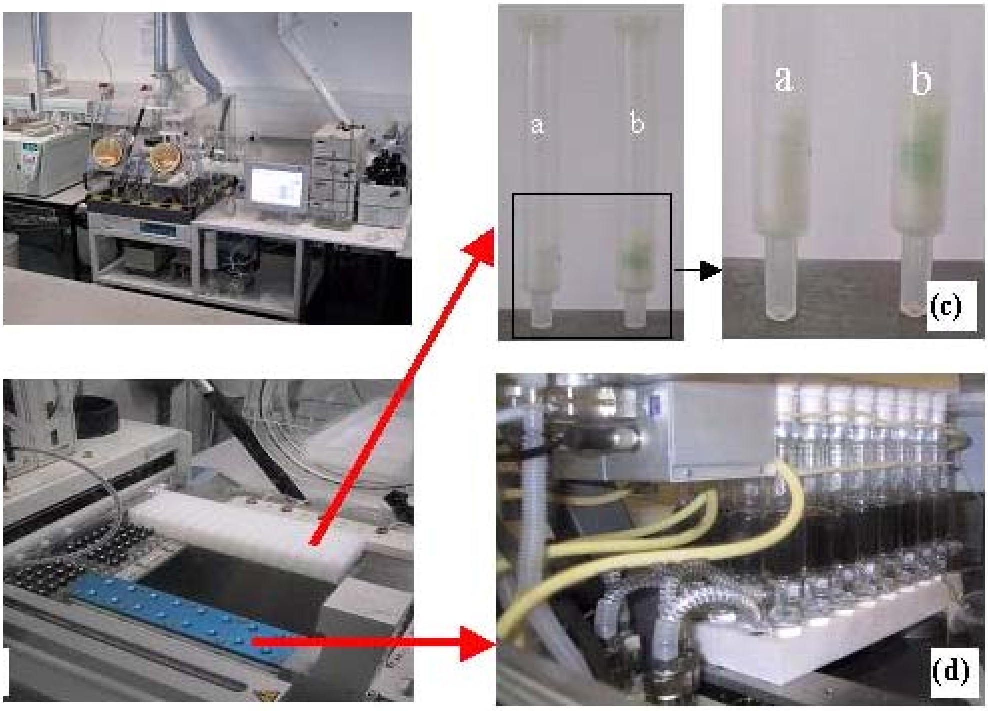
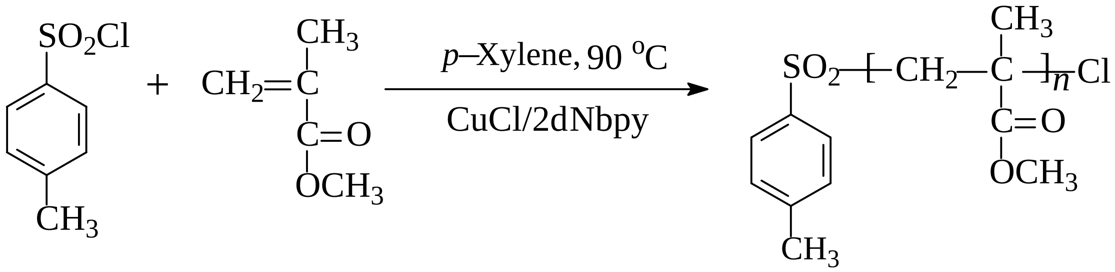


Fig. 1. Visualization of the experimental set-up: (a) automated synthesizer (middle) in combination with an online SEC (right) and gas chromatograph (GC) (left), (b) detailed view of the automated synthesizer, (c) filtration columns in SPE unit and (d) reactors.



Scheme 1. Schematic representation of the ATRP of MMA with $[MMA]_0/[TsCl]_0/[CuCl]_0/[dNbpy]_0$ = 150/1/1/2 and MMA/*p*-xylene = ½ v/v.

The ATRP of methyl methacrylate (MMA) with *p*-toluenesulfonyl chloride (TsCl) as the initiator and CuCl/4,4'-dinonyl 2,2'-bipyridine (dNbpy) as the catalyst was chosen as the model reaction for the present study (Scheme 1) [12]. The polymerization was carried out in *p*-xylene at 90 °C in a conventional set-up in the laboratory with a volume ratio of *p*-xylene to MMA of 2 and a molar ratio of MMA to TsCl to CuCl to dNbpy of 150/1/1/2. A homogeneous dark brown solution was obtained when the reaction mixture was heated to 90 °C. The reaction was quenched by quickly cooling down to room temperature at a reaction time of 10 h. The monomer conversion was determined to be 71% by GC and the obtained polymer had a number average molecular weight ($M_{n,SEC}$) of 12000 dalton and polydispersity index (PDI) of 1.15 as determined by SEC. The isolated dark brown solution was bubbled with air in order to oxidize Cu(I) to Cu(II) with the expectation to determine the copper contents in the obtained polymers with UV-Vis spectroscopy by using a calibration curve of Cu(II)/2dNbpy. A homogeneous dark green solution was obtained after 1.5 h of air bubbling. The solution was then transferred into a bottle, which was subsequently placed in the stock solution holder of the automated synthesizer and vortexed for 20 min prior to the purification of the polymer. Certain amount (350 µL) of the above prepared reaction mixture was robotically loaded onto the SPE columns, which were pre-washed with THF. Different volumes (1, 2, 3, and 4 mL, respectively) of THF were then transferred to the columns to wash down the polymers with the aid of an air push.

The $M_{n,SEC}$ and PDIs of the purified polymers were directly measured by an online SEC. Fig. 2 shows that the $M_{n,SEC}$ and PDI values of the purified polymers were quite similar in all cases, indicating that the purification conditions with different column materials, column lengths and eluent volumes had little influence on the properties of the purified polymers.

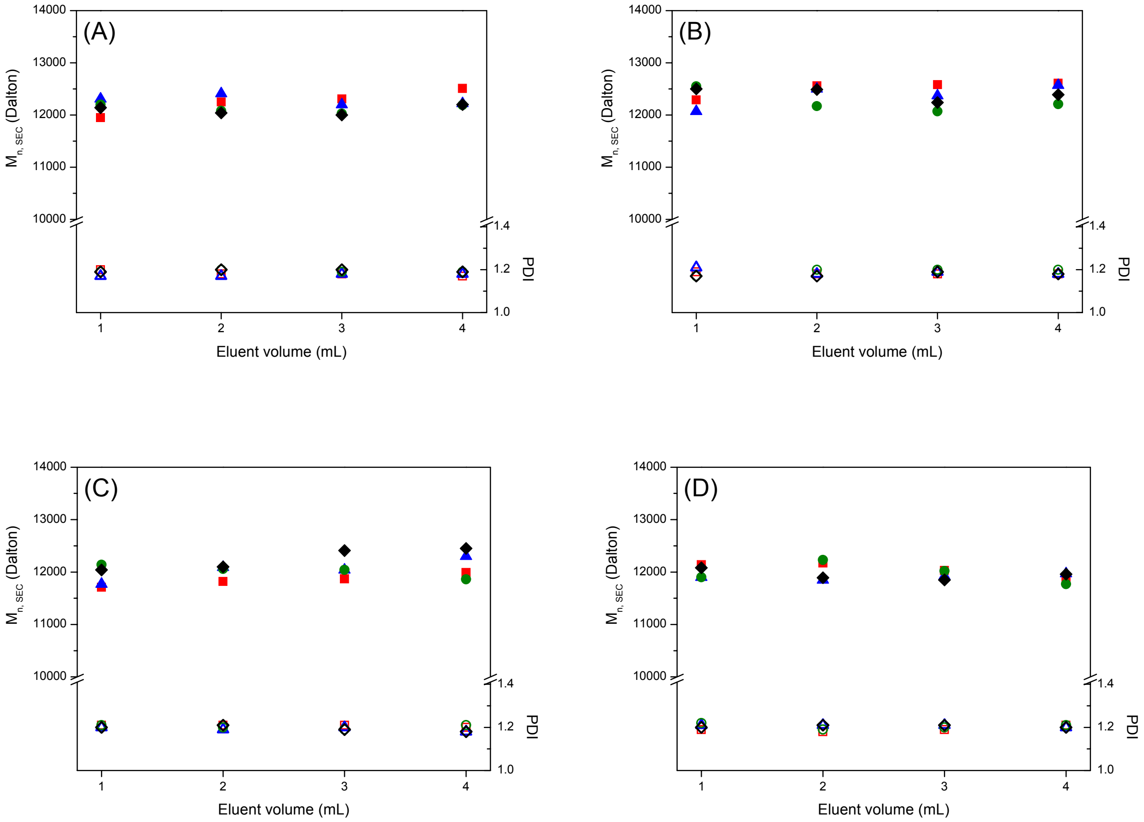


Fig. 2. Effects of the eluent volumes (1, 2, 3 and 4 mL), column materials [(a) standard aluminium oxide, (b) activated neutral aluminium oxide, (c) activated basic aluminium oxide, and (d) silica gel], and column lengths [0.25 cm (red), 0.50 cm (blue), 1.0 cm (green), and 1.50 cm (black)] on the $M_{n,SEC}$ (solid symbols) and PDI values (empty symbols) of the purified polymers.

The solvents (THF + *p*-xylene) of the collected polymer solutions under different purification conditions were then evaporated under air flow at ambient temperature until solid polymers were obtained. The obtained samples were further dried in a vacuum oven at 40 °C for 48 h. Fig. 3 shows the weights of the obtained polymers under different purification conditions. It can be seen that about 80 mg of polymers were obtained when more than 2 mL of eluent were used (the theoretical value is 80 mg). And even with the lowest eluent volume utilized in the study (i.e. 1 mL) most of the polymers loaded onto the SPE columns with different column materials and column lengths could be recovered.

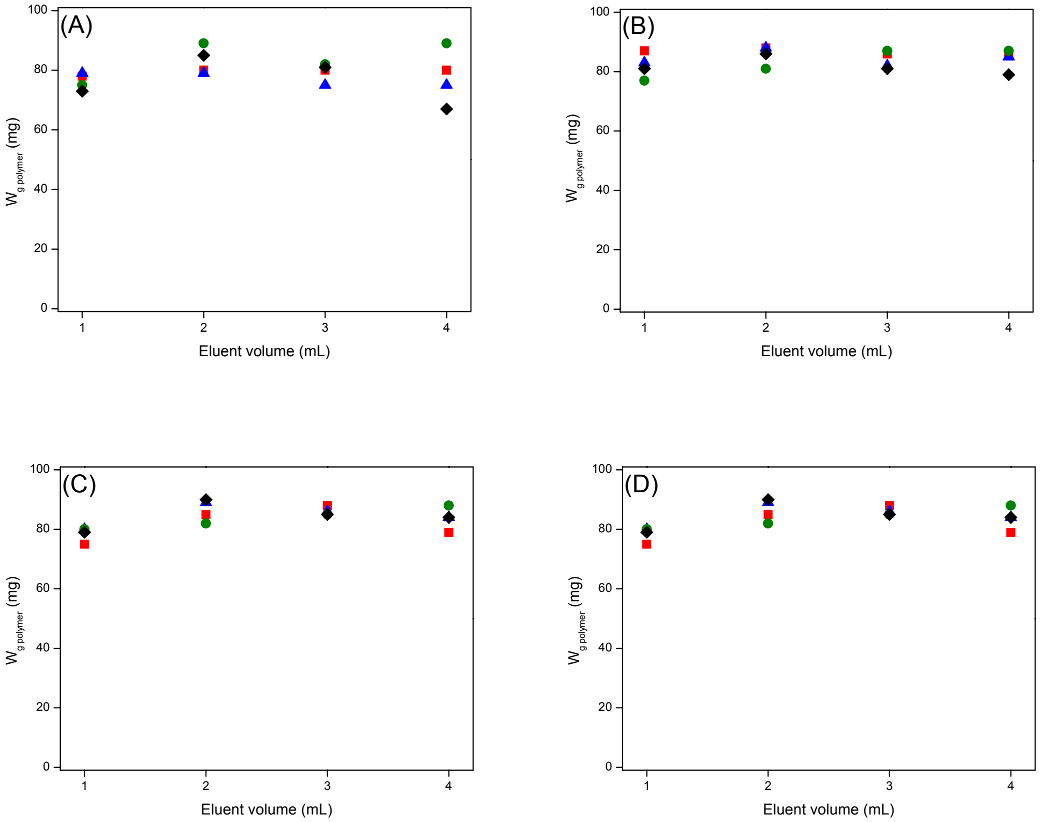


Fig. 3. Effects of the column materials [(a) standard aluminium oxide, (b) activated neutral aluminium oxide, (c) activated basic aluminium oxide, and (d) silica gel], column lengths [0.25 cm (red), 0.50 cm (blue), 1.0 cm (green), and 1.50 cm (black)] and eluent volumes (1, 2, 3 and 4 mL, respectively) on the obtained weights of the purified polymers.

We firstly attempted to quantitatively determine the copper contents in the obtained polymers with UV-Vis spectroscopy. Fig. 4 shows the UV-Vis spectra of CuCl/2dNbpy, the oxidized CuCl/2dNbpy (after bubbling with air), the unpurified polymer sample (after bubbling with air), and a purified polymer sample in acetonitrile, respectively.

The solution of CuCl/2dNbpy in acetonitrile revealed a typical signal around 430 nm, while the signal shifted to about 720 nm after bubbling air through the solution for 30 min, indicating the occurrence of oxidation of the complex from Cu(I) to Cu(II) [14]. Surprisingly, the unpurified polymer revealed one relatively strong signal around 430 nm and one very weak signal around 700 nm while the purified polymer only showed one signal around 430 nm. Moreover, the signals around 430 nm in the unpurified and purified polymers were multiple peaks instead of a single peak as that from the solution of CuCl/2dNbpy, probably indicating that different complex species were present in the solutions of CuCl/2dNbpy and polymer. This makes it difficult to quantitatively measure the copper contents in the polymer containing solution utilizing UV-Vis spectroscopy.

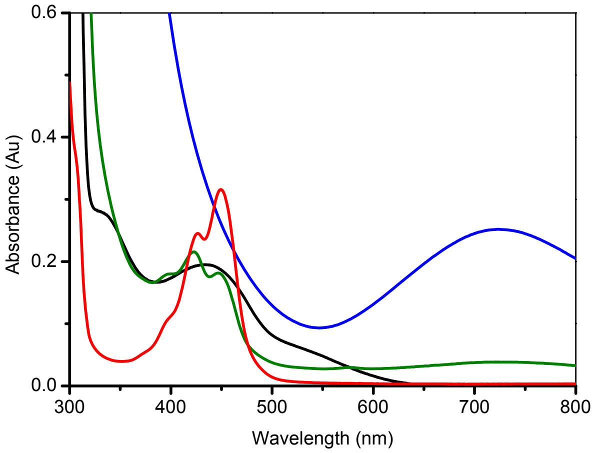


Fig. 4. UV-Vis spectra of CuCl/2dNbpy (black line), the oxidized CuCl/2dNbpy (after bubbling air, blue line), the unpurified polymer sample (after air bubbling, green line), and a purified polymer sample (red line) in acetronitrile, respectively.

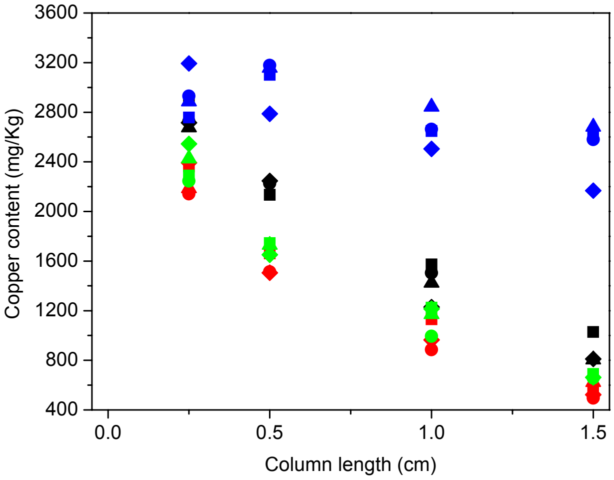


Fig. 5. Effects of the column materials [silica gel (blue), standard aluminium oxide (black), activated basic aluminium oxide (green), and activated neutral aluminium oxide (red)], column lengths, and eluent volumes [1 mL (diamond), 2 mL (square), 3 mL (uptriangle), and 4 mL (circle)] on the purification efficiency.

Atomic absorption spectrometer (AAS) was then applied to determine the copper contents in the polymers. The experimental results (Fig. 5) revealed that the column materials and column lengths had a significant influence on the purification efficiency while the eluent volumes did not influence much the copper contents in the purified polymers. The aluminium oxide columns displayed much better performance than the silica gel column probably due to their stronger affinity towards the copper catalysts. Furthermore, the activated neutral and basic aluminium oxide columns provided more or less the same optimum purification results. As expected, the longer columns exhibited better purification effects for the same column materials. Therefore, the optimum purification conditions for the removal of copper catalysts obtained in this study (under the restrictions of the available sizes of SPC cartridges and the vials to collect the eluent fitting into the synthesizer) is the utilization of a 1.5 cm long activated neutral or basic aluminium oxide column with 2 mL of THF as the eluent. The copper contents in the purified polymers using the optimum purification conditions are 520 and 660 mg/Kg with the activated neutral and basic aluminium oxide columns, respectively, which are significantly lower than that in the unpurified polymer (6700 mg/Kg).

Experimental part

Materials

MMA (Aldrich, 99%) was washed twice with an aqueous solution of sodium hydroxide (5%) and twice with distilled water, dried with anhydrous magnesium sulfate overnight, and then distilled over calcium hydride under vacuum. The distillate was stored at –25 °C before use. CuCl (Aldrich, 98%) was purified according to a literature procedure [13] and was stored in an argon atmosphere before use. dNbpy (Aldrich, 97%), *p*-xylene (Aldrich, 99+%, anhydrous), TsCl (Acros, 99+%), THF, aluminium oxide (Merck, activated neutral, activated basic, and standard, for column chromatography), silica gel (Merk, 0.040-0.063 mm for column chromatography), and all the other chemicals were used as received.

Instruments and measurements

The automated purification was carried out in a computer-controlled Chemspeed ASW 2000 automated parallel synthesizer (Fig. 1), where a Gilson liquid handling system was used to transfer liquid samples. The automated synthesizer was connected to an online SEC (Shimadzu SEC equipped with a LC-10AD VP pump and a RID-6A differential refractometer), with which the $M_{n,SEC}$ and PDI values of the polymers were measured at ambient temperature. THF was used as eluent at a flow rate of 1.0 mL/min. A linear column (PLgel 5 μm Mixed-D, Polymer Laboratories, 30 cm) was used and the calibration curve was prepared with poly(methyl methacrylate) (PMMA) standards. The SEC measurement of one sample required 15 min. Monomer conversion was determined from the concentration of the residual monomer using an Interscience Trace GC with an autosampler, equipped with an Rtx-5 (Crossbond 5% diphenyl-95% dimethyl polysiloxane) capillary column (30 m x 0.25 mm ID x 0.25 μm df) with *p*-xylene as an internal reference. The UV-Vis spectra were recorded on a Perkin-Elmer Lambda 45 UV-Vis spectrometer. The copper contents in the obtained polymers were determined with an atomic absorption spectrometer (flame AAS, Analytik Jena AAS vario® 6) for ultratrace analysis of real-world samples with complex matrix. A calibration of 5 different concentrations of a standard provided by a special supplier was done ($R^2 > 0.99$). The polymer samples were firstly dried at 40 °C for 48 hours and further at 70 °C for 48 hours and then dissolved in certain amounts of THF for AAS analyses.

ATRP of MMA

The ATRP of MMA was carried out in a conventional set-up as follows: CuCl (0.0926 g, 0.94 mmol) and dNbpy (0.7637 g, 1.87 mmol) were added to a solution of MMA (14.0418 g, 140.25 mmol) and anhydrous *p*-xylene (22.5160 g) in a three-neck round-bottom flask (100 mL). After the reaction mixture was bubbled with argon for 45 min, the flask was immersed into a thermostated oil bath at 90 ^{o}C and stirred for 10 min. The initiator TsCl (0.1783 g, 0.94 mmol) in *p*-xylene (3.4640 g) was added slowly (in 2.5 min) into the system to start the reaction. The polymerization was performed under stirring for 10 h and then stopped by quickly cooling down to room temperature. The reaction mixture was then bubbled with air for 1.5 h and then subsequently used for the automated purification investigation.

Conclusions

The high-throughput optimization of purification conditions for polymers prepared via ATRP has been efficiently carried out by using an automated parallel synthesizer. The factors influencing the purification efficiency such as the column materials, column lengths and eluent volumes were systematically investigated under the same conditions for the first time. The results revealed that the obtained weights, $M_{\mathrm{n,SEC}}$ and PDI values of the purified polymers were hardly influenced by the purification conditions and the utilized eluent volumes did not significantly affect the copper contents in the purified polymers. However, both the column materials and column lengths revealed a significant influence on the purification efficiency. The aluminium oxide columns displayed much better performance than the silica gel column. Furthermore, the activated neutral and basic aluminium oxide columns provided more or less the same optimum purification results. Besides, the longer columns exhibited better purification effects for the same column materials. Therefore, the optimum purification conditions for the removal of copper catalysts obtained in this study are as follows: the use of the activated neutral or basic aluminium oxide as the column material + a column length of 1.5 cm + 2 mL of THF as the eluent. As a result a high-throughput purification procedure for the automated parallel synthesizers has been established, which can purify in the present case (Chemspeed ASW2000) up to 80 polymer samples without user interruption for further characterization steps (e.g. SEC, GC, etc.) in a ATRP screening experiment (and 160 purification steps in case of the Chemspeed Accelerator).

Acknowledgements

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References:

[1] Nicolaou, K. C.; Hanko, R.; Hartwig, W.; "*Handbook of Combinatorial Chemistry*"; Weinheim: Wiley-VCH, **2002**.

[2] Zhang, H.; Hoogenboom, R.; Meier, M. A. R.; Schubert, U. S.; *Meas. Sci. Technol.* **2005**, *16*, 203.

[3] *A*: Hoogenboom, R.; Meier, M.A.R.; Schubert, U.S.; *Macromol. Rapid Commun.* **2003**, *24*, 15. *B*: Meier, M.A.R.; Hoogenboom, R.; Schubert, U.S.; *Macromol. Rapid Commun.* **2004**, *25*, 21.

[4] Meier, M.A.R.; Schubert, U.S.; *J. Mater. Chem.* **2004**, *14*, 3289.

[5] Matyjaszewski, K.; Xia, J.; *Chem. Rev.* **2001**, *101*, 2921.

[6] Kamigaito, M.; Ando, T.; Sawamoto, M.; *Chem. Rev.* **2001**, *101*, 3689.

[7] Hawker, C. J.; Bosman, A. W.; Harth, E.; *Chem. Rev.* **2001**, *101*, 3661.

[8] Sebastein, P.; Pittaya, T.; *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 5347.

[9] Nielsen, R. B.; Safir, A. L.; Petro, M.; Lee, T. S.; Huefner, P.; *Polym. Mater. Sci. Eng.* **1999**, *80*, 92.

[10] Zhang, H.; Fijten, M. W. M.; Hoogenboom, R.; Reinierkens, R.; Schubert, U. S.; *Macromol. Rapid Commun.* **2003**, *24*, 81.

[11] Zhang, H.; Fijten, M. W. M.; Hoogenboom, R.; Schubert, U. S.; "*Advances in Controlled/Living Radical Polymerization*"; *ACS Symp. Ser. 854;* American Chemical Society: Washington DC **2003**, 193.

[12] Zhang, H.; Marin, V.; Fijten, M. W. M.; Schubert. U. S.; *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 1876.

[13] Shen, Y.; Tang, H.; Ding, S.; *Prog. Polym. Sci.* **2004**, *29*, 1053.

[14] Qiu, J.; Pintauer, T.; Gaynor, S. G.; Matyjaszewski, K.; Charleux, B.; Varion, J. P.; *Macromolecules*, **2000**, *33*, 7310.