

RESEARCH ARTICLE

Automated screening of precipitation polymerizations and evaluation using image recognition for divinylbenzene and methacrylic acid

Timo Schuett^{1,2}  | Patrick Endres^{1,2} | Julian Kimmig^{1,2}  | Robert Lorenz^{1,2} |
Yannik Köster^{1,2}  | Steffi Stumpf^{1,2} | Stefan Zechel^{1,2} | Ulrich S. Schubert^{1,2,3} 

¹Laboratory of Organic and Macromolecular Chemistry (IOMC), Friedrich Schiller University Jena, Jena, Germany

²Jena Center for Soft Matter (JCSM), Friedrich Schiller University Jena, Jena, Germany

³Helmholtz Institute for Polymers in Energy Applications Jena (HIPOLE Jena), Jena, Germany

Correspondence

Ulrich S. Schubert, Laboratory of Organic and Macromolecular Chemistry (IOMC), Friedrich Schiller University Jena, Humboldtstr. 10, Jena 07743, Germany.
Email: ulrich.schubert@uni-jena.de

Funding information

Thüringer Aufbaubank, Grant/Award Number: 2021 FGI0005; Deutsche Forschungsgemeinschaft

Abstract

By applying automated high-throughput experimentation, 63 precipitation polymerizations of divinylbenzene and methacrylic acid were performed with a total of 1638 samples analyzed by gas chromatography (GC), nuclear magnetic resonance (NMR) spectroscopy, and scanning electron microscopy (SEM). The conversion of each reaction was investigated revealing the best substrate concentrations within the current setup. The GC evaluation was performed automatically via a new custom-made Python script significantly reducing the time to evaluate the results. Furthermore, the particle growth was monitored by utilizing an innovative image recognition tool to identify particles and their respective sizes using SEM images. Furthermore, a statistical particle size distribution analysis was performed, which is hardly achievable in reasonable time by classical evaluation methods. Using this new procedure, the highest conversion (70%) as well as the largest particles (3700 nm) have been obtained utilizing a high initial monomer (5 vol%) and initiator (5 mol%) concentration. Accordingly, the smallest particles (245 nm) yielded from the lowest starting concentration (1 vol% monomer and 1 mol% initiator).

KEYWORDS

emulsion polymerization, microscopy, nanostructured polymers

1 | INTRODUCTION

Different heterogeneous polymerization techniques can be applied to obtain solid polymeric structures such as particles in a size range from nano- to micrometer.^{1,2} Among others, emulsion-,^{3,4} suspension-,⁵ precipitation-,^{6,7} and supramolecular polymerizations⁸ were already

utilized. In particular, precipitation polymerization (PP) is often considered as easy to use⁹ and capable of producing uniform particles in the nanometer range.¹⁰ One reason for this is that no further substances, like emulsifiers, are required in addition to the monomer and initiator, so that the polymerization products are easy to purify.¹⁰ Therefore, polymers obtained from PP are applied in a

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Author(s). *Journal of Applied Polymer Science* published by Wiley Periodicals LLC.

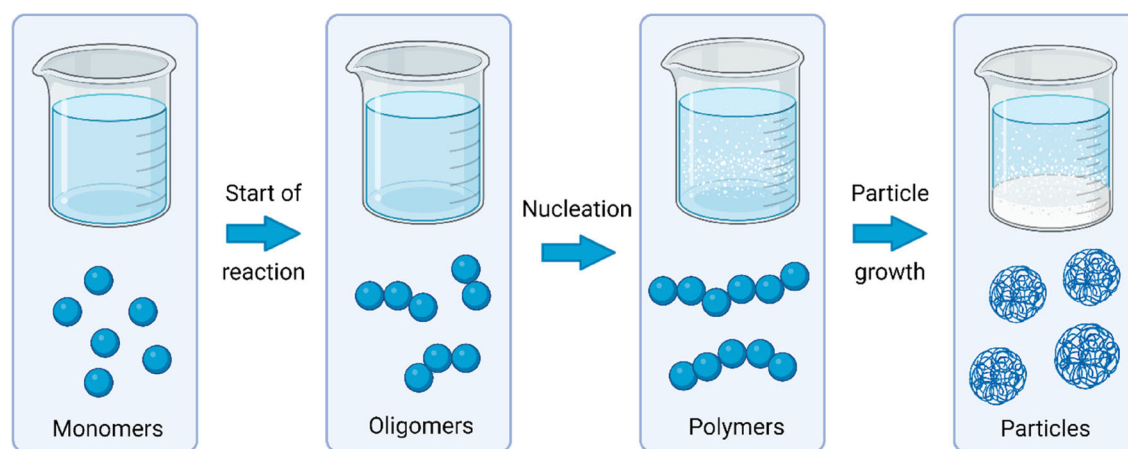


FIGURE 1 Schematic overview of the precipitation polymerization process. The figure was created with [Biorender.com](#). [Color figure can be viewed at [wileyonlinelibrary.com](#)]

variety of different applications, such as catalysis,^{11,12} solid phase extraction,^{13,14} drug delivery,^{15,16} or molecular imprinting.¹⁷ Although different types of PP, like distillation,¹⁸ reflux,¹⁵ or solvothermal PP,¹⁹ are known, the general process is always similar. The monomer and the initiator are dissolved in a suitable solvent and the reaction is started, either by thermal- or photoinitiation. The mechanism can be split into three parts. Firstly, the reaction starts with the formation of oligomers. Secondly, after a certain reaction progress, the oligomer chains reach a critical size and precipitate from the solution. Finally, after this so-called nucleation, the polymer particles stay active and the particles grow further.²⁰ A schematic overview of the PP mechanism is shown in Figure 1.²¹ Parameters influencing this process are mainly the type of monomer and solvent that effects the solubility of the oligomeric chains in the reaction mixture.²² Furthermore, time, heat, and dilution of the reaction influence the kinetics of particle growth.²³ In general, these reactions are performed under high dilution to prevent the particles to agglomerate. Often a functional monomer, such as methacrylic acid (MAA),²⁴ is combined with a multifunctional crosslinker like divinylbenzene (DVB).²⁵ After the monomers for polymerization have been selected, screening of the influence of the above mentioned reaction parameters is required to obtain particles with the desired properties. However, such screenings are rarely performed in literature for these methods due to the lack of high-throughput experimentation (HTE). Moreover, as manual screening experiments are often too time-consuming, particularly in the case of filtrating each sample after the PP, only automated HTE bears the possibility of effective screening.²⁶ However, a few publications used in situ infrared

(IR)²⁷ and UV-Vis spectroscopy²⁸ for screenings of precipitation reactions to avoid filtration.

Robot-based polymer synthesis has already been utilized extensively to study homogeneous polymerization processes such as reversible addition fragmentation chain transfer (RAFT) polymerizations²⁹ or atom transfer radical polymerization (ATRP).³⁰ Nevertheless, most of the studies in the field of HTE investigation of polymerizations focused on solution based processes and no studies on PPs have been performed so far, since the handling of two different phases in one reaction is particularly difficult in automated synthesis robots.

For this purpose, in the current study, a setup in an automated synthesizer was developed to systematically screen the influence of different parameters. As a representative polymeric system, MAA and DVB in a ratio of 1 to 4 in acetonitrile with azobisisobutyronitrile (AIBN) as initiator was utilized, since it is a common system applied in PP.^{31,32} For the high-throughput screening, temperature, total reaction time as well as the monomer ratio were set constant and the influence of the total monomer loading, and the initiator concentration were investigated. From each reaction, 20 samples were taken for gas chromatography (GC) and three each for nuclear magnetic resonance (NMR) spectroscopy and scanning electron microscopy (SEM) analysis. GC and NMR spectroscopy revealed the conversion throughout the reaction, whereas the SEM analysis showed the particle growth depending on the reaction time and substrate concentration.

However, a major challenge of HTE is the data analysis.³³ In particle size analysis, dynamic light scattering (DLS) is a common tool,^{34,35} which is also applicable for HTE.³⁶ However, as the particles become larger, they

descend to the bottom of the vessel faster, which makes analysis via DLS challenging in dependence of the reactive system. Consequently, our characterization is based on SEM. However, the data analysis of SEM images is very time-consuming, as the images as well as every particle within the image had to be evaluated by hand up to now. To enhance the efficiency, an image recognition tool was developed to automatically detect and analyze the size of each particle in each SEM image.

2 | EXPERIMENTAL SECTION

2.1 | Materials and methods

All chemicals were used as received from Sigma Aldrich (Merck KGaA, Darmstadt, Germany) (AIBN, DVB, MAA, dodecane) and VWR (Darmstadt, Germany) (acetonitrile (CH_3CN) and chloroform), if not otherwise stated. Liquid monomers, DVB and MAA, were destabilized over a short AlOx column (neutral AlOx , obtained from Molecula [Munich, Germany]).

GC was performed on a Shimadzu GC-2010 equipped with a flame ionization detector (FID), AOC-20s autosampler and AOC-20i injector. As carrier gas helium was used and a Carl Roth, RotiTM Cap-5 MS column (30 m length, 0.25 mm ID, 0.25 μm film thickness) was utilized for compound separation. The temperature program of the GC was set as follows: 5 min at 35 $^\circ\text{C}$, heating with 15 K min^{-1} , 10 min at 280 $^\circ\text{C}$, FID temperature 320 $^\circ\text{C}$.

Data evaluation was performed using a customized Python script. The script can be found in the Supporting Information. For the outlier test, a fit with a function of the form $a x^2 + b x + c$ was performed. The residuals obtained from the fit and the measured values were tested for outliers using a boxplot. A 1.5-fold interquartile range was set as the limit. The detected outliers were removed.

SEM imaging was performed with a Sigma VP Field Emission Scanning Electron Microscope (Carl-Zeiss AG, Germany) using the InLens detector with an accelerating voltage of 4 kV. The samples were coated with a thin layer of platinum via sputter coating (CCU-010 HV, Safe-matic, Zizers, Switzerland) before the measurement.

NMR spectra of the synthesized polymers were acquired by using a Bruker AC 300 (300 MHz) spectrometer at 298 K. The deuterium signal of the utilized solvent was used as internal reference.

Automated liquid transfers were performed using an automated parallel synthesizer Chemspeed SWING XL (Basel, Swiss) equipped with an overhead robot arm that could pick up several tools such as a 4-needle head (4-NH) for automated liquid handling. The 4-NH is

equipped with septum piercing needles. Reactions were performed in a Chemspeed iSynth, capable of 24 parallel reactions with a reaction volume of 20 mL each. All reactors are stirrable, and a nitrogen atmosphere can be applied. Furthermore, heating can be applied via an external Huber Cryostat Tango (heating range: -40 to 190°C) and reflux was enabled through the iSynth with a peripheral Huber Polystat CC3. The synthesis robot was programmed utilizing the AutoSuite software (Version 2.2) by Chemspeed (AutoSuite Editor, AutoSuite Executor, and AutoSuite Driver Manager).

2.2 | Automated precipitation polymerization

Reaction solutions were prepared by mixing acetonitrile (CH_3CN), dodecane as well as stock solutions of DVB, MAA, and AIBN in 100 mL vials using the 4-NH of the synthesis robot. MAA and DVB were mixed in a ratio of 1 to 4. All amounts are listed in Table 1. Afterwards, the prepared solutions were homogenized and degassed by flushing with nitrogen for 5 min. Subsequently, a sample was taken, and the reaction mixtures were transferred into the preheated reactors, heated and stirred for 24 h at 60 $^\circ\text{C}$. During the reaction, 19 samples (0.5 mL each) were taken after 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11.5, 13, 14.5, 16, 17.5, 19, 20.5, 22 and 24 h. The automated sampling process was performed according to a prior study.³⁷ After the reaction was finished, the samples were filtered manually, 1 mL chloroform was added, and the samples were measured by GC. Furthermore, 0.5 mL of each reaction were taken after 8, 16, and 24 h for SEM analysis and after 0, 11.5, and 24 h for NMR analysis.

2.3 | Analysis of GC data

For the evaluation of the chromatograms a customized Python script was utilized in order to minimize the effort for data analysis. Therefore, the name of the samples given during analysis is crucial for a successful data evaluation. The name must contain all required information. In this study, this information is the reaction mixture as well as the time, when the sample was taken. For the analysis, the chromatograms were converted to ASCII files with the Shimadzu Labsolution software. The collected ASCII files were imported into a data-frame using the Pandas Python package. The retention times were determined via the Labsolution software and set as integration boundaries in the Python program. Integration was performed following Simpson's rule by the respective function of the SciPy package. The signals of MAA and

TABLE 1 Summary of the utilized amounts and volumes for the precipitation polymerizations of methacrylic acid (MAA) and divinylbenzene (DVB).

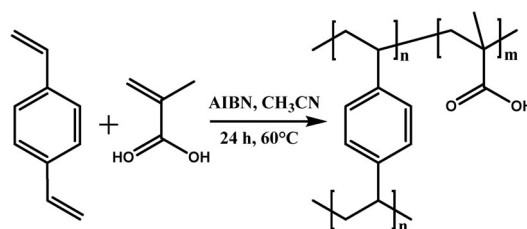
Exp.	Monomer (Vol%)	Initiator (Mol%)	m_{MAA} (g)	m_{DVB} (g)	m_{AIBN} (g)	V_{Dodecane} (mL)	$V_{\text{CH}_3\text{CN}}$ (mL)
E5:5a-b	1	1	25.7	155.2	2.5	0.20	18.2
E5:4a-b		2	25.7	155.2	4.9	0.20	18.1
E5:3a-f		3	25.7	155.2	7.3	0.20	18.0
E5:2a-b		4	25.7	155.2	9.8	0.20	17.8
E5:1a-b		5	25.7	155.2	12.2	0.20	17.7
E4:5a-c	2	1	51.3	310.5	4.9	0.20	17.1
E4:4a		2	51.3	310.5	9.8	0.20	16.9
E4:3a		3	51.3	310.5	14.7	0.20	16.6
E4:2a-c		4	51.3	310.5	19.6	0.20	16.4
E4:1a-d		5	51.3	310.5	24.5	0.20	16.1
E3:5a	3	1	76.96	465.7	7.3	0.20	16.0
E3:4a-g		2	76.96	465.7	14.7	0.20	15.7
E3:3a		3	76.96	465.7	22.0	0.20	15.3
E3:2a-b		4	76.96	465.7	29.4	0.20	14.9
E3:1a-b		5	76.96	465.7	36.7	0.20	14.5
E2:5a-d	4	1	102.6	621.0	9.8	0.20	14.9
E2:4a-b		2	102.6	621.0	19.6	0.20	14.4
E2:3a-b		3	102.6	621.0	29.4	0.20	13.9
E2:2a-b		4	102.6	621.0	39.2	0.20	13.5
E2:1a-c		5	102.6	621.0	49.0	0.20	13.0
E1:5a	5	1	128.3	776.2	12.2	0.20	13.8
E1:4a		2	128.3	776.2	24.5	0.20	13.2
E1:3a-c		3	128.3	776.2	36.7	0.20	12.6
E1:2a		4	128.3	776.2	49.0	0.20	12.0
E1:1a-b		5	128.3	776.2	61.2	0.20	11.4

DVB were normalized via division by the standard dodecane and the relative change over time was calculated. As three measurements were performed per sample the average of the percentage change was utilized. To determine possible outliers, a fitting was performed with the curve_fit function of the SciPy module based on a quadratic function. Afterwards the residuals and R^2 were calculated. As criteria for the definition of outliers, the 1.5-fold inter-quantile range of the first and third quantile of the residuals within one reaction data set were utilized. Measurements, which are detected as outliers, were removed from the dataset subsequently.

3 | RESULTS AND DISCUSSION

For an efficient screening, a suitable concentration range (1%–5%) was chosen for both monomers (DVB and

		Conc. initiator [mol%]				
		5	4	3	2	1
Conc. Monomer [vol%]	5	E5:5a-b	E5:4a-b	E5:3a-f	E5:2a-b	E5:1a-b
	4	E4:5a-c	E4:4a	E4:3a	E4:2a-c	E4:1a-d
	3	E3:5a	E3:4a-g	E3:3a	E3:2a-b	E3:1a-b
	2	E2:5a-d	E2:4a-b	E2:3a-b	E2:2a-b	E2:1a-d
	1	E1:5a	E1:4a	E1:3a-c	E1:2a	E1:1a-b

**SCHEME 1** Overview of all performed experiments (top) as well as the schematic representation of the respective reaction scheme (bottom).

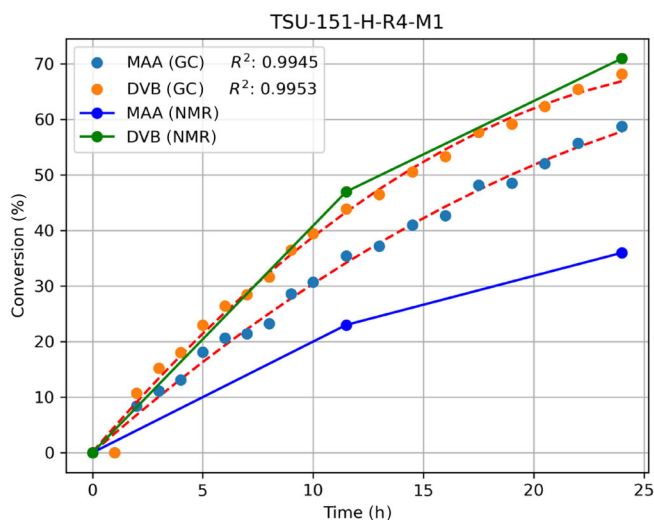


FIGURE 2 Kinetic diagram of the monomer conversion (MAA or and DVB), obtained via NMR and GC depending on the reaction time of **E5:5b** after outlier removal. DVB, divinylbenzene; GC, gas chromatography; NMR, nuclear magnetic resonance; MAA, methacrylic acid. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

MAA) to enable GC und SEM analysis. Steps of 1% were set to result in a reasonable number of experiments to recognize the trends. An overview of all experiments as well as the respective reaction scheme are shown in Scheme 1.

3.1 | Investigation by GC

3.1.1 | Analysis

To minimize consumption of chemicals and chemical waste, a high conversion is beneficial. During each reaction, 20 samples ($t = 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11.5, 13, 14.5, 16, 17.5, 19, 20.5, 22, 24$ h) have been collected for filtration and subsequent GC analysis. For analysis, dodecane was utilized as internal standard. As the aim of this study was to analyze a broad range of starting concentrations, the gas chromatographic setup was optimized for the highest concentration of 5 mol%. Under these conditions, it was not possible to monitor the reactions with starting concentrations of 1 mol%, as this starting concentration led to very high standard deviations during the reaction. An exemplary kinetic plot of **E5:5b**, including all GC samples, is shown in Figure 2 and all kinetic plots can be found in the Supporting Information. The plots were calculated from the GC data by comparing the respective monomer (DVB or MAA) to the internal standard (dodecane) concentration. Afterwards outliers were removed by performing an outlier test by

boxplots, as described in the Supporting Information, for each reaction.

For the evaluation of the chromatograms a customized Python script was utilized in order to minimize the effort for data analysis. For this purpose, the name of the samples given during analysis is crucial for a successful data evaluation. The name must contain all required information. In this study, this information is the reaction mixture as well as the time, when the sample was taken. For a detailed description of the Python script see Section 2.

3.1.2 | Conversion

The final conversions are summarized in Table 2 and Table 3. The highest conversions were achieved when a highly concentrated reaction solution was utilized, for instance, 5 mol% monomer and 4 vol% initiator (**E5:4a-b**) yielded more than 71% DVB conversion and about 62% MAA conversion in the GC analysis after 24 h reaction time. Thus, dropping either the initiator and/or the monomer concentration decreases the conversion of both DVB and MAA.

Outliers could have occurred due to anomalies within the sampling process, such as a temporarily blocked needle or nontight sampling vials, due to an irregularly pierced septum. The same anomalies as well as nontight reactors could have caused minor deviations in the concentration of each sample of a reaction, influencing the final values and plots. To overcome this issue, up to seven iterations (a–g) of each reaction were performed resulting in the averaged final conversion values mentioned in Table 2.

Regarding the kinetic plots, the reaction velocity is mostly linear within the first 10 h and decreases slightly afterwards. However, the monomer conversion did not reach 100% after 24 h. Nevertheless, the data suggests that monomer conversion can be further increased with a prolonged reaction time of more than 24 h. Furthermore, in every case, the conversion of DVB was about 10% higher compared with the conversion of MAA after 24 h, which is caused by a higher radical polymerization activity of DVB, as described in literature.³⁸ Furthermore, hydrogen bonds from the carboxylic acid groups of different polymer chains can facilitate an early precipitation and agglomeration of the particles, which consequently restricts the mobility of the unreacted monomers, resulting in a lower conversion.³¹ Finally, as DVB has two active double bonds, the probability of a reaction is higher compared with a reaction of MAA with one active double bond.

TABLE 2 Averaged DVB and MAA conversions after 11.5 and 24 h reaction time measured after filtration via GC and NMR spectroscopy given in %. [Color table can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/app.55986)]

Nr.	c(M)	c(I)	Conversion (GC) after 11.5 h (%)		Conversion (GC) after 24 h (%)		Conversion (NMR) after 11.5 h (%)		Conversion (NMR) after 24 h (%)	
			DVB	MAA	DVB	MAA	DVB	MAA	DVB	MAA
E5:5a-b	5	5	52	49	66	58	47	23	71	36
E5:4a-b		4	48	41	71	62	38	18	65	33
E5:3a-f		3	39	29	53	43	41	21	65	33
E5:2a-b		2	37	25	60	47	44	21	68	32
E5:1a-b		1	31	23	54	44	27	13	49	24
E4:5a-c	4	5	39	24	65	50	42	20	66	32
E4:4a		4	51	35	72	61	^b	^b	^b	^b
E4:3a		3	46	30	71	57	45	23	70	33
E4:2a-c		2	32	20	55	41	23	10	47	23
E4:1a-d		1	26	17	44	33	22	11	41	21
E3:5a	3	5	46	30	68	50	49	25	70	35
E3:4a-g		4	35	26	58	45	35	18	59	30
E3:3a		3	32	23	56	46	31	15	55	29
E3:2a-b		2	31	22	51	41	27	14	47	24
E3:1a-b		1	23	18	42	35	18	9	36	18
E2:5a-d	2	5	35	25	58	43	38	21	65	31
E2:4a-b		4	29	14	51	32	23	12	44	21
E2:3a-b		3	28	20	44	32	24	13	45	23
E2:2a-b		2	27	22	45	36	18	10	39	20
E2:1a-d		1	15	10	33	29	29	14	43	19
E1:5a	1	5	27	7	47	22	24	8	44	19
E1:4a		4	25	12	44		20	14	^b	^b
E1:3a-c		3	20	20	32	28	11	11	25	17
E1:2a		2	^a	^a	30	28	24	13	41	20
E1:1a-b		1	10	6	21	13	9	4	17	8

Note: Dark green: >60%, light green: 51–60%, yellow: 41–50%, orange: 31–40%, red: <31%.

Abbreviations: DVB, divinylbenzene; GC, gas chromatography; NMR, nuclear magnetic resonance; MAA, methacrylic acid.

^aMonomer concentration too low.

^bError during sampling process.

3.2 | Conversion obtained via NMR spectroscopy

3.2.1 | Analysis

To verify the results obtained via GC, three samples of each reaction (0, 11.5, and 24 h) were collected, filtered, and measured via NMR spectroscopy. The values were obtained by comparison of the dodecane signal at 0.88 ppm, with the double bond signals of both monomers at 5.2 and 5.7 ppm for the total monomer conversion (see Tables S1 and S2) and the CH signal at 6.7 ppm for the DVB concentration. An exemplarily NMR

spectrum analysis is demonstrated in the Supporting Information.

3.2.2 | Conversion

The monomer conversions after 11.5 and 24 h are summarized in Table 2. Both methods for conversion analysis, obtained via NMR spectroscopy and via GC, are mostly comparable to each other regarding the DVB monomer (Figure 2). In comparison, most DVB values differ less than 3% from each other, with singular outliers with up to 11%. As the overall concentration of

TABLE 3 Particle sizes of each experiment (E5:5—E1:1) after 8, 16, and 24 h, number, and averaged number of the particles on the respective image. [Color table can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/app.55986)]

Exp.	Particle size (nm)			Particles on image		
	8 h	16 h	24 h	8 h	16 h	24 h
E5:5a	3732	- ^a	- ^a	144	- ^a	- ^a
E5:4a	2377	- ^a	- ^a	332	- ^a	- ^a
E5:3b	2231	- ^a	- ^a	178	- ^a	- ^a
E5:2b	1578	- ^a	- ^a	172	- ^a	- ^a
E5:1b	879	1148	1409	1013	1188	391
E4:5a	957	1190	1359	539	34	352
E4:4a	1058	- ^a	2199	8	- ^a	10
E4:3a	930	1136	1236	617	888	417
E4:2c	2182	2844	- ^a	210	10	- ^a
E4:1a	718	851	929	283	547	930
E3:5	- ^a	- ^a	- ^a	- ^a	- ^a	- ^a
E3:4b	771	906	976	381	1065	1205
E3:3a	865	1093	1154	276	136	20
E3:2b	642	845	905	22	665	1595
E3:1a	409	506	547	364	1245	770
E2:5d	716	840	912	377	640	643
E2:4a	862	1085	1200	331	193	233
E2:3a	454	568	621	245	595	1501
E2:2b	506	608	692	268	943	328
E2:1a	764	929	1020	270	209	512
E1:5a	506	660	731	34	318	828
E1:4a	332	405	455	274	288	688
E1:3a	339	434	489	107	367	312
E1:2a	235	254	279	29	165	702
E1:1b	229	231	245	55	140	308

Note: Dark green: >2000 nm, light green: 1501–2000 nm, yellow: 1001–1500 nm, orange: 501–1000 nm, red: <500 nm.

^aNo value due to error during sampling process (such as a syringe blocked with particles) or no particles detectable (for e.g., due to agglomeration).

MAA is significantly lower in the reaction solution (ratio of 1:4), the values calculated via NMR spectroscopy and GC differ more. Here, the values reveal a difference of up to 29%. The NMR is more suitable for higher concentrations, whereas the GC is more versatile in terms of concentration range changes and enabled the analysis of the samples with the higher diluted MAA monomer.

3.3 | Particle investigation

Enabling an application of particles in drug delivery, catalysis, or other fields, the particle size needs to be

reproducibly. Therefore, a screening of the respective values has been performed regarding the PP of MAA and DVB. SEM was chosen to study the particle size. There are several reaction parameters, which are affecting the reaction and which could potentially be screened. In our case, the concentration (ratio) had a high influence on the product conversion. Depending on the application, the particle size is crucial and regulation of the monomer concentration is the most accurate and efficient possibility to adjust it.

3.3.1 | Sampling

To analyze the particle growth, three samples were taken from each reaction solution after 8, 16, and 24 h for SEM investigation. A 5 μ L of each sample were dispensed on a mica surface dried under standard conditions, coated with a thin layer of platinum and investigated via SEM.

3.3.2 | Evaluation

However, up to now, particle size analysis is mostly performed via DLS and proven optically via SEM without further analysis.^{39–41} However, this data analysis technique is very time-consuming and not applicable for analysis of a high number of particles in an image. Furthermore, as not all particle sizes in the image are calculated, the particle size as well as their size distribution can be inaccurate. Finally, as the borders of the particles are not totally clear in certain cases, the particle sizes are different based on the investigating researcher.

First approaches of image recognition tools for SEM applications have already been published, to decrease the amount of work and to enhance the quality of the resulting data.^{41–44} However, these approaches focus on categorizing SEM images⁴³ or suffer from low amount of training data in case of machine learning approaches.⁴² Our approach focusses on particle recognition only and is based on a workflow of classical image recognition procedures without the incorporation of machine learning techniques. We opted for this approach due to the lack of fitting training data, which would consist of a large number of fully labeled images, while many datasets contain only partially selected particles; and in particular for our use case, the development of machine learning models, while certainly possible, is simply not required. Furthermore, the usage of classical methods enables a much faster processing, easier tunability of the different parameters, like the thresholding values, and the usage of multiple preselectable masks, which would not work

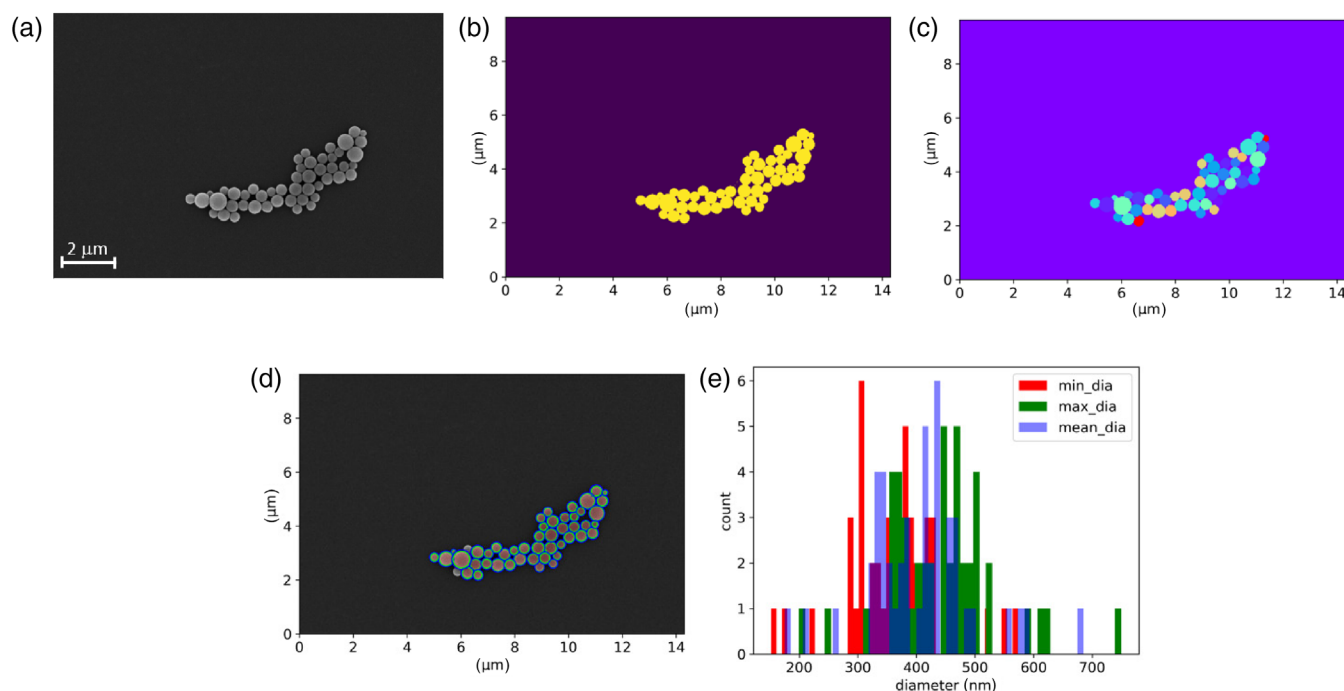


FIGURE 3 Example of particle detection on **E2:1d**. (a) Original scanning electron microscopy image, (b) generated mask for particle detection, (c) generated segmentation map of the image, (d) marked valid detections with inscribed and circumscribed circle, and (e) calculated particle size distribution. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/app.55985)]

in a fixed pretrained model. Additionally, the use of a classical script runs on any computer or laptop without the need for hardware acceleration by graphics processing units (GPUs), for example, making it more usable in everyday workflows. Furthermore, the compactness of the code allows for deployment as a backend script on local servers, enabling access to it from everywhere. Accordingly, to calculate the particle size based on the SEM images, a custom-made processing script was developed.

For the image analysis, a combination of multiple classical image-analysis methods was utilized to generate methods as robust as possible on the whole dataset. The raw image analysis results in some wrongly detected regions and particles, but the spherical nature of the particles enables the removal of nearly all wrongly detected particles, such as merged particles or background fragments, which usually are not spherical. Due to the exclusion of regions with a higher probability of wrong identification, also not all particles of each image are selected, but random evaluation still shows that the vast majority of particles were identified correctly. A complete overview of the underlying procedure is provided in the Supporting Information. A systematic overview of the particle recognition process is shown in Figure 3.

3.3.3 | Particle sizes and growth

The respective values obtained by the analysis are summarized in Table 3.

As the area of investigation in each image of the SEM is within a microscale, only random spots can be investigated and not the whole sample. A major challenge in the automated particle recognition was the agglomeration, as the border between the particles can be ambiguous. To overcome this issue and to improve the quality of the results, areas with as much separated particles as possible were chosen for data collection. The dependency of the particle size from the initiator and monomer concentration is visualized in Figure 4.

Similar to the conversion results, the largest particles were obtained with higher concentrated reaction solutions (**E5:5** to **E3:2** >700 nm). By decreasing the reactant concentration, the particles are formed slower resulting in a lower particle size. The particle growth depending on the reaction time is visualized in Figure 5. The particles grew throughout the whole reaction time of 24 h. However, the strongest growth was detected within the first 8 h (for e.g., **E4:5a**: 8 h: 957 nm; 16 h: 1190 nm; 24 h: 1359 nm). This result is not surprising, as a small particle requires less material to grow by a certain size compared with a large particle. Based on these results it

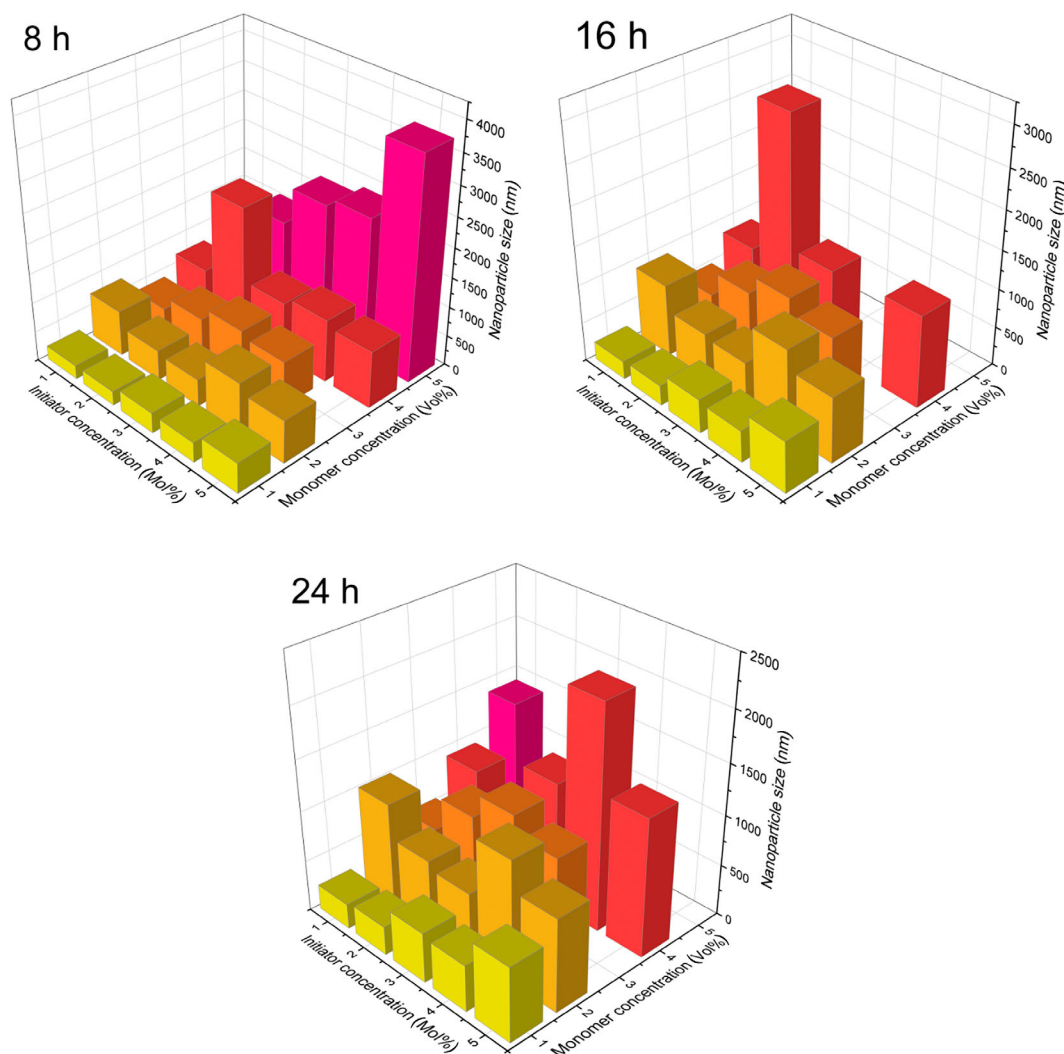


FIGURE 4 Visualization of the dependency of the particle size from the monomer and initiator concentration after 8 h (left), 16 h (right), and 24 h (bottom). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/app.55986)]]

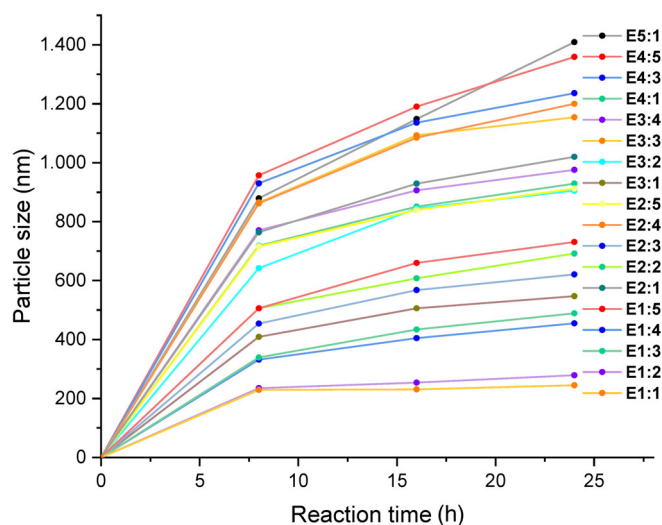


FIGURE 5 Visualization of the particle growth depending on the reaction time summarized for each reaction type (for e.g., **E5:1a-b** equals average conversion of **E5:1**). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/app.55986)]]

is possible to choose a desired particle size as well as reaction time and mix the reaction accordingly to result in the respective particles.

4 | CONCLUSION

In conclusion, 25 different PPs of DVB and MAA were performed automatically in several iterations using a synthesis robot. In total, 63 reactions with 26 samples each were analyzed via GC, NMR spectroscopy, and SEM to provide a deeper insight into the conversion of the reaction depending on the reaction time and the particle growth behavior. The characterization via GC revealed an increasing conversion throughout the whole reaction time of 24 h. The highest conversion of 70% was achieved with the highest monomer (5 vol%) and initiator concentration (5 mol %). NMR measurements proved these results regarding

the DVB values and revealed the comparability of these two techniques. However, as the MAA concentration in the reaction solution was significantly lower, NMR spectroscopy was not as suitable as GC regarding this monomer. Furthermore, the particle growth was monitored via SEM. To increase the efficiency of the data analysis, a new tool was developed for automated particle recognition. By combining multiple image analysis techniques, this tool was able to identify the borders of the particles and to calculate the total number and their size in each image.

The particles have the greatest increase in diameter within the first 8 h of the reaction. The largest particles (3700 nm) yielded from the most concentrated reaction solutions. Consequently, by starting with highly diluted reaction solutions, the smallest particles (230 nm) could be obtained.

In conclusion, this investigation gave new insights into the PP of DVB and MAA by applying HTE for this polymerization type for the first time. Furthermore, a powerful tool for particle recognition was introduced and its applicability was proven by identifying 30,000 particles and its respective sizes within this study, increasing the efficiency of future SEM data analysis.

AUTHOR CONTRIBUTIONS

Timo Schuett: Conceptualization (equal); data curation (lead); writing – original draft (lead). **Patrick Endres:** Data curation (equal); investigation (equal); writing – original draft (equal). **Julian Kimmig:** Investigation (equal); writing – original draft (equal). **Robert Lorenz:** Investigation (equal); writing – original draft (equal). **Yannik Köster:** Investigation (equal); writing – original draft (equal). **Steffi Stumpf:** Investigation (equal). **Stefan Zechel:** Conceptualization (equal); writing – review and editing (equal). **Ulrich S. Schubert:** Conceptualization (equal); supervision (lead); writing – review and editing (lead).

ACKNOWLEDGMENTS

The authors thank the Thüringer Aufbaubank (TAB) (2021 FGI0005). The TOC figure was created with [BioRender.com](https://www.biorender.com) (SFB1278). The SEM facilities of the Jena Center for Soft Matter (JCSM) were established with a grant from the German Research Council (DFG). Open Access funding enabled and organized by Projekt DEAL.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Timo Schuett <https://orcid.org/0000-0003-3680-3617>

Julian Kimmig <https://orcid.org/0000-0002-4478-3874>

Yannik Köster <https://orcid.org/0000-0002-9125-3067>

Ulrich S. Schubert <https://orcid.org/0000-0003-4978-4670>

REFERENCES

- [1] J. Wang, P. A. G. Cormack, D. C. Sherrington, E. Khoshdel, *Pure Appl. Chem.* **2007**, 79, 1505.
- [2] C. Chen, Y. Wang, S. Ding, C. Hong, Z. Wang, *Microchem. J.* **2019**, 147, 191.
- [3] P. A. Lovell, F. J. Schork, *Biomacromolecules* **2020**, 21, 4396.
- [4] M. Esfandyari-Manesh, M. Javanbakht, R. Dinarvand, F. Atiyabi, *J. Mater. Sci. Mater. Med.* **2012**, 23, 963.
- [5] A. Motaharian, M. R. M. Hosseini, K. Naseri, *Sens. Actuators, B* **2019**, 288, 356.
- [6] A. Beltran, R. M. Marcé, P. A. G. Cormack, F. Borrull, *J. Chromatogr. A* **2009**, 1216, 2248.
- [7] K. Yoshimatsu, K. Reimhult, A. Krozer, K. Mosbach, K. Sode, L. Ye, *Anal. Chim. Acta* **2007**, 584, 112.
- [8] P. K. Hashim, J. Bergueiro, E. W. Meijer, T. Aida, *Prog. Polym. Sci.* **2020**, 105, 101250.
- [9] Z. Chen, L. Ye, *J. Mol. Recognit.* **2012**, 25, 370.
- [10] Y. Shi, H. Lv, X. Lu, Y. Huang, Y. Zhang, W. Xue, *J. Mater. Chem.* **2012**, 22, 3889.
- [11] A. Ahmad, P. G. Roy, S. Zhou, A. Irfan, F. Kanwal, R. Begum, Z. H. Farooqi, *Int. J. Biol. Macromol.* **2023**, 240, 124401.
- [12] M. S. Bashir, *Chem. Eng. Res. Des.* **2021**, 175, 102.
- [13] W. Zhang, N. Tan, X. Jia, G. Wang, W. Long, X. Li, S. Liao, D. Hou, *Mater. Sci. Eng. C* **2015**, 53, 166.
- [14] J. Otero-Romani, A. Moreda-Piñeiro, P. Bermejo-Barrera, A. Martin-Esteban, *Anal. Chim. Acta* **2008**, 630, 1.
- [15] M. Fan, F. Wang, C. Wang, *Macromol. Biosci.* **2018**, 18, 1800077.
- [16] H. Wen, J. Guo, B. Chang, W. Yang, *Eur. J. Pharm. Biopharm.* **2013**, 84, 91.
- [17] Y. Long, J. Y. N. Philip, K. Schillén, F. Liu, L. Ye, *J. Mol. Recognit.* **2011**, 24, 619.
- [18] G. He, J. Zhao, S. Hu, L. Li, Z. Li, Y. Li, Z. Li, H. Wu, X. Yang, Z. Jiang, A. C. S. Appl, *Mater. Interfaces* **2014**, 6, 15291.
- [19] Y. Wang, L. Bao, J. Sun, Y. Ding, J. Shi, Z. Duan, Z. Chen, *J. Chromatogr. A* **2022**, 1680, 463428.
- [20] S. Pardeshi, S. K. Singh, *RSC Adv.* **2016**, 6, 23525.
- [21] J. S. Downey, R. S. Frank, W.-H. Li, H. D. H. Stöver, *Macromolecules* **1999**, 32, 2838.
- [22] M. Zhao, H. Zhang, F. Ma, Y. Zhang, X. Guo, H. Zhang, *J. Polym. Sci. Part A: Polym. Chem.* **2013**, 51, 1983.
- [23] H. Zhang, *Eur. Polym. J.* **2013**, 49, 579.
- [24] H. Sambe, K. Hoshina, R. Moaddel, I. W. Wainer, J. Haginaka, *J. Chromatogr. A* **2006**, 1134, 88.
- [25] N. Jatkowska, L. Olszewska, M. Marć, *Microchem. J.* **2023**, 194, 109251.
- [26] T. Schuett, M. Wejner, J. Kimmig, S. Zechel, T. Wilke, U. S. Schubert, *Polymers* **2022**, 14, 361.
- [27] P. Fandrich, L. Wiehemeier, M. Dirksen, O. Wrede, T. Kottke, T. Hellweg, *Colloid Polym. Sci.* **2021**, 299, 221.
- [28] I. Dimitrov, R. Faust, *Macromolecules* **2004**, 37, 9753.
- [29] T. Schuett, J. Kimmig, S. Zechel, U. S. Schubert, *Polymers* **2022**, 14, 292.
- [30] H. Zhang, H. Richard, M. W. M. Fijten, U. Schubert, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2002**, 43, 17.

- [31] M. Piccaglia Neto, J. A. Castanharo, M. G. D. Oliveira, M. A. D. S. Costa, *Mater. Res.* **2019**, 22, e20170909.
- [32] H. T. Nguyen, N. T. Vuong Bui, W. G. Kanhounon, K. L. Vu Huynh, T.-V.-A. Nguyen, H. M. Nguyen, M. H. Do, M. Badawi, U. D. Thach, *RSC Adv.* **2021**, 11, 34281.
- [33] L. M. Mayr, D. Bojanic, *Curr. Opin. Pharmacol.* **2009**, 9, 580.
- [34] T. Bätz, I. Anufriev, C.-H. Pai, T. Schuett, I. Nischang, S. Zechel, M. D. Hager, Y.-T. Chan, U. S. Schubert, *ACS Appl. Polym. Mater. Polym. Mater.* **2023**, 5, 1354.
- [35] S. Parkinson, S. T. Knox, R. A. Bourne, N. J. Warren, *Polym. Chem.* **2020**, 11, 3465.
- [36] J. Kimmig, T. Schuett, A. Vollrath, S. Zechel, U. S. Schubert, *Adv. Sci.* **2021**, 8, 2102429.
- [37] M. Ringleb, T. Schuett, S. Zechel, U. S. Schubert, *Digital Discovery* **2023**, 2, 1883.
- [38] J. Huang, S. Wan, M. Guo, H. Yan, *J. Mater. Chem.* **2006**, 16, 4535.
- [39] T. Xiong, H. W. Kua, K. W. Shah, G. F. Hussein, B. Zhang, *J. Energy Storage* **2024**, 80, 110195.
- [40] J. Li, J. Sun, F. Meng, Y. Chen, H. Liu, Y. Gao, *J. Food Eng.* **2023**, 369, 111932.
- [41] F. Behrendt, Z. Cseresnyés, R. Gerst, M. Gottschaldt, M. T. Figge, U. S. Schubert, *J. Biomed. Mater. Res. A* **2023**, 111, 1734.
- [42] A. Y. Kharin, *Ultramicroscopy* **2020**, 219, 113125.
- [43] M. H. Modarres, R. Aversa, S. Cozzini, R. Ciancio, A. Leto, G. P. Brandino, *Sci. Rep.* **2017**, 7, 13282.
- [44] R. Mohsenzadeh, B. H. Soudmand, A. H. Najafi, M. Fattahi, D. P. Uyen, *Compos. Sci. Technol.* **2024**, 245, 110360.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: T. Schuett, P. Endres, J. Kimmig, R. Lorenz, Y. Köster, S. Stumpf, S. Zechel, U. S. Schubert, *J. Appl. Polym. Sci.* **2024**, 141(38), e55985. <https://doi.org/10.1002/app.55985>