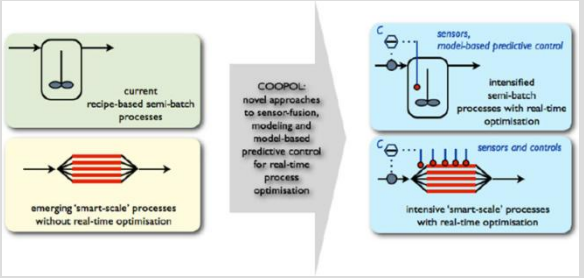
Flow Chemistry Activation, Flow Polyreactions and Flow-Made Polymer Particles

Frankfurt, Dechema,
COOPOL Symposium
14. January 2015



Volker Hessel

v.hessel@tue.nl

Eindhoven University of Technology
Department of Chemical Engineering and Chemistry

Micro Flow Chemistry and Process Technology

DEFINITION & CONTENTS

Flow Chemistry = chemistry in micro-, milli- and meso-scaled flow devices; not naturally microfabricated: capillaries, tubes, packed-beds, monoliths, …

1 – 1000 t/a; 10 ml/h – 1000 l/h; 10 μm – 5 mm ID, 5 cm – 1 m OD

- **Activation in micro-flow = chemical intensification = flow chemistry**

>> as opposed to transport intensification

- **Activation of polyreactions by transfer and chemical activation in micro-flow**

>> free radical, living radical, (living) cationic, living anionic, dendrimers, emulsion pol.

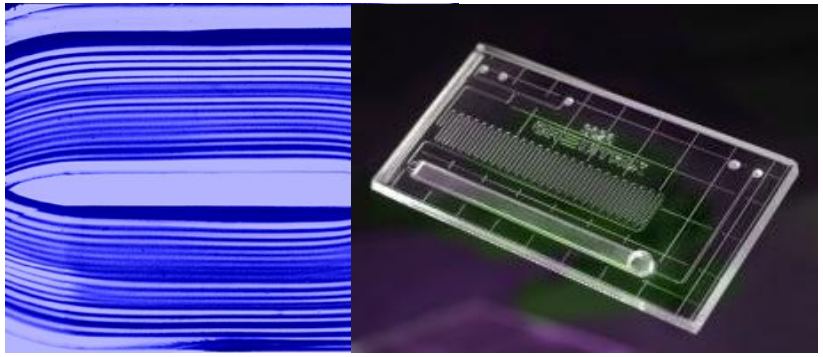
- **Opportunities for polyreactions in micro-flow**

- **Opportunities for making polymeric micro- and nano-particles in micro-flow**

Technische Universiteit Eindhoven University of Technology

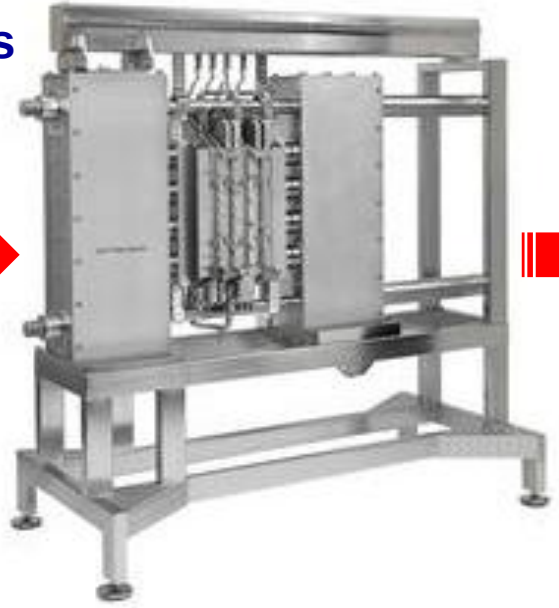
MICRO/MILLI FLOW REACTORS AND FLOW CHEMISTRY

Lab microchip



Milli-flow production lines

Milli-flow pilot setups



Flow-chemistry lab station

Milli-flow production reactors

RELEVANT REVIEWS

" Polymerisationen in mikrostrukturierten Reaktoren: ein Überblick“
V. Hessel, C. Serra, H. Löwe, G. Hadziioannou *Chemie, Ingenieur, Technik* **77**, 11 (2005) 39-59.

"Micro-flow technology in polymer synthesis"
C. Tonhauser, A. Natalello, H. Löwe, H. Frey, *Macromolecules* **45** (2012) 9551-9570.

“Micromixer-assisted polymerization processes: a review”
F. Bally, C. Serra, V. Hessel, G. Hadziioannou, *Chem. Eng. Sci.* 6**6** (2011)1449-1462.

“Homogeneous polymerization: benefits brought by microprocess technologies to the synthesis and production of polymers”
F. Bally, C. Serra, V. Hessel, G. Hadziioannou, *Macromol. Reaction Eng.* **4**, 9-10 (2010) 543-561.

“Coupling microreaction technologies, polymer chemistry, and processing to produce polymeric micro and nanoparticles with controlled size, morphology, and composition”
C. Serra, B. Cortese, I. Ullah Khan, N. Anton, M.H.J.M. de Croon, V. Hessel, T, Ono, Th. Vandamme, *Macromol. Reaction Eng*. **7**, 9 (2013) 414-439.

“Controlled polymerization in flow microreactor systems”
Aiichiro Nagaki and Jun-ichi Yoshida, *Adv Polym Sci* **259** (2013) 1–50.

POTENTIAL OF MICRO FLOW PROCESSING FOR POLYMERIZATIONS

- **Large surface-to-area** (even in laminar regime)
- **Small characteristic length**
- **Large interfaces**
- **Small internal volumes**

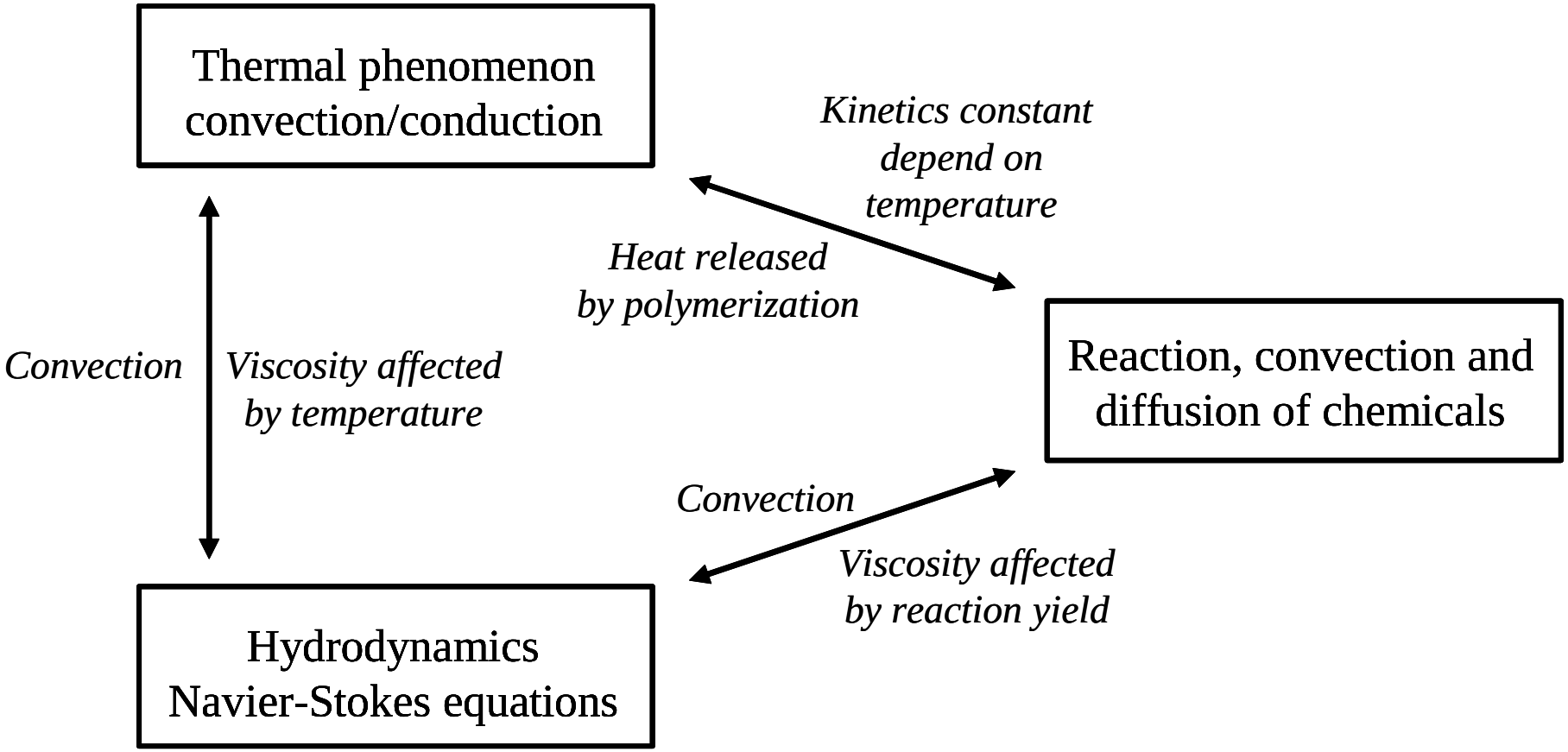
- **Good mixing: uniform species concentration profiles**
- **Good heat release: diminishing of hot spots**
- **Large interfacial mass transfer**
- **Fast parameter changes**
- **Low sample consumption**
- **Uniform, periodic flow**
- **Safety**

Transfer intensification

- **Conversion, X**
- **Reaction time, t**
- **M_n**
- **PDI**
- **Trommsdorff effect**
- **Continuous block copolymer synthesis**
- **Particle size, shape, morphology**
- **High quantum yield**
- **…**

V. Hessel, C. Serra, H. Löwe, G. Hadziioannou, *Chem. Ing. Tech.* **77**, 11 (2005) 39-59.

FLOW POLYMERIZATIONS HAVE TIME-DEPENDENT TRANSFER INTENSIFICATION



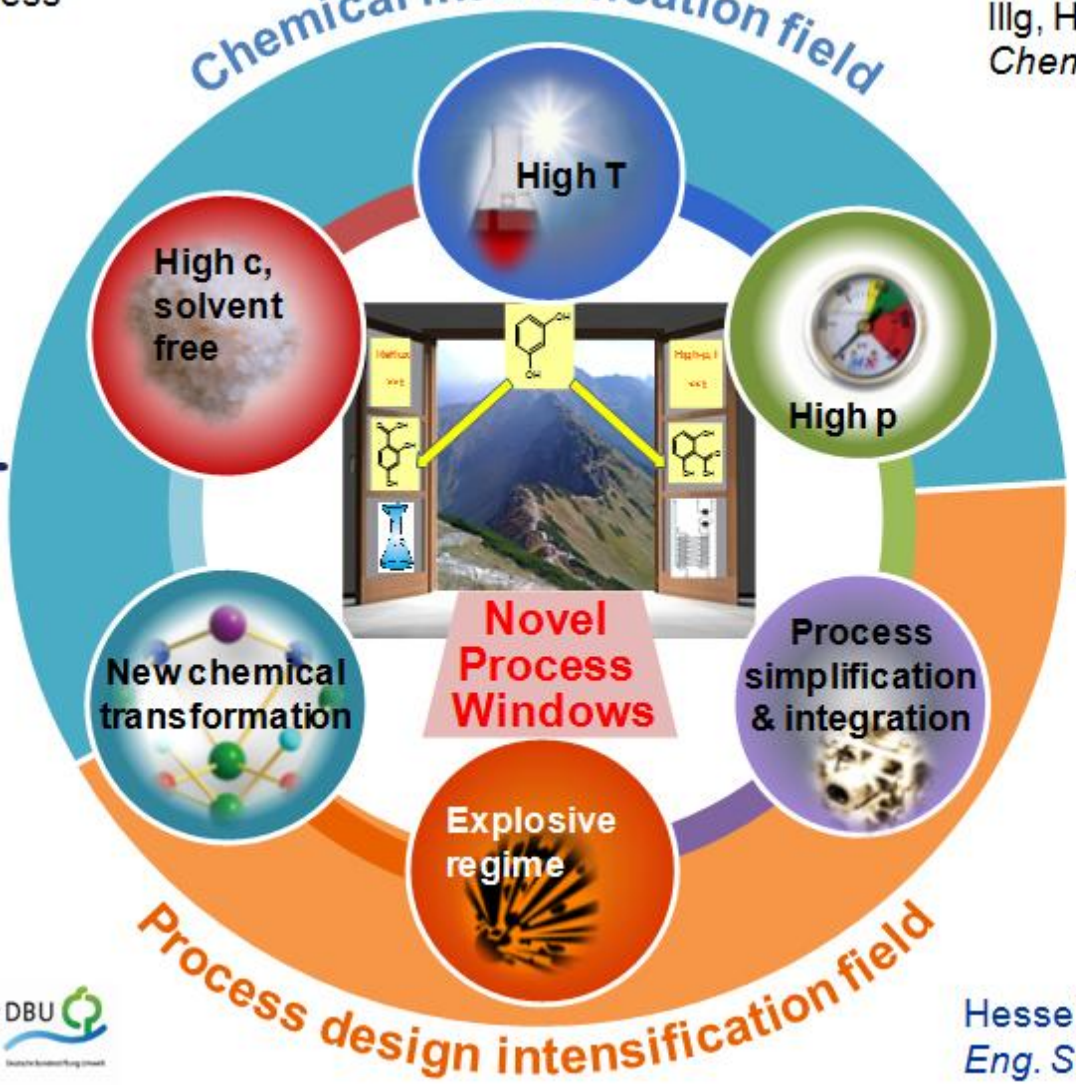
C. Serra, N. Sary, G. Schlatter, G. Hadziioannou, V. Hessel *Lab Chip* **5**, 9 (2005) 966-973.

NOVEL PROCESS WINDOWS
2nd and 3rd INTENSIFICATION FIELDS

Technische Universiteit Eindhoven University of Technology

erc Novel Process Windows

Top-25 cited paper on NPW
Illg, Hessel, Löb, *Bioorg. Medic. Chem.* 18, 11 (2010) 3627-4154



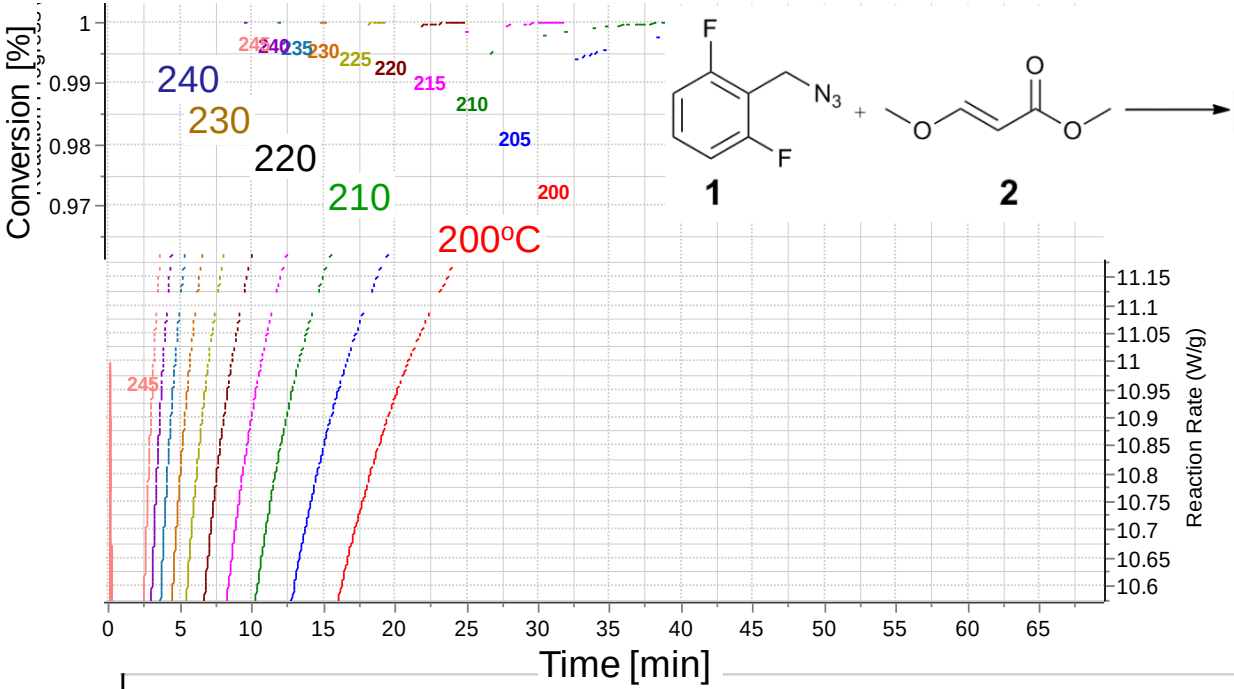
Activate
Confine
Orient
Boost

Simplify
Integrate
Synergize
Minimize

NPW Research Cluster DBU
Forschungscluster „Novel Process Windows"

Hessel, Cortese, de Croon *Chem. Eng. Sci.* 66, 7 (2011) 1426-1448.

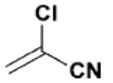
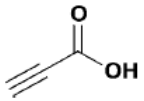
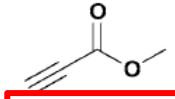
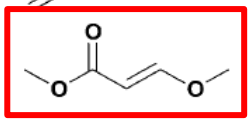
GOOD MOLECULES MAY BE (TOO) SLOW …
… YET THIS IS NOT NATURAL LAW = INTRINSIC



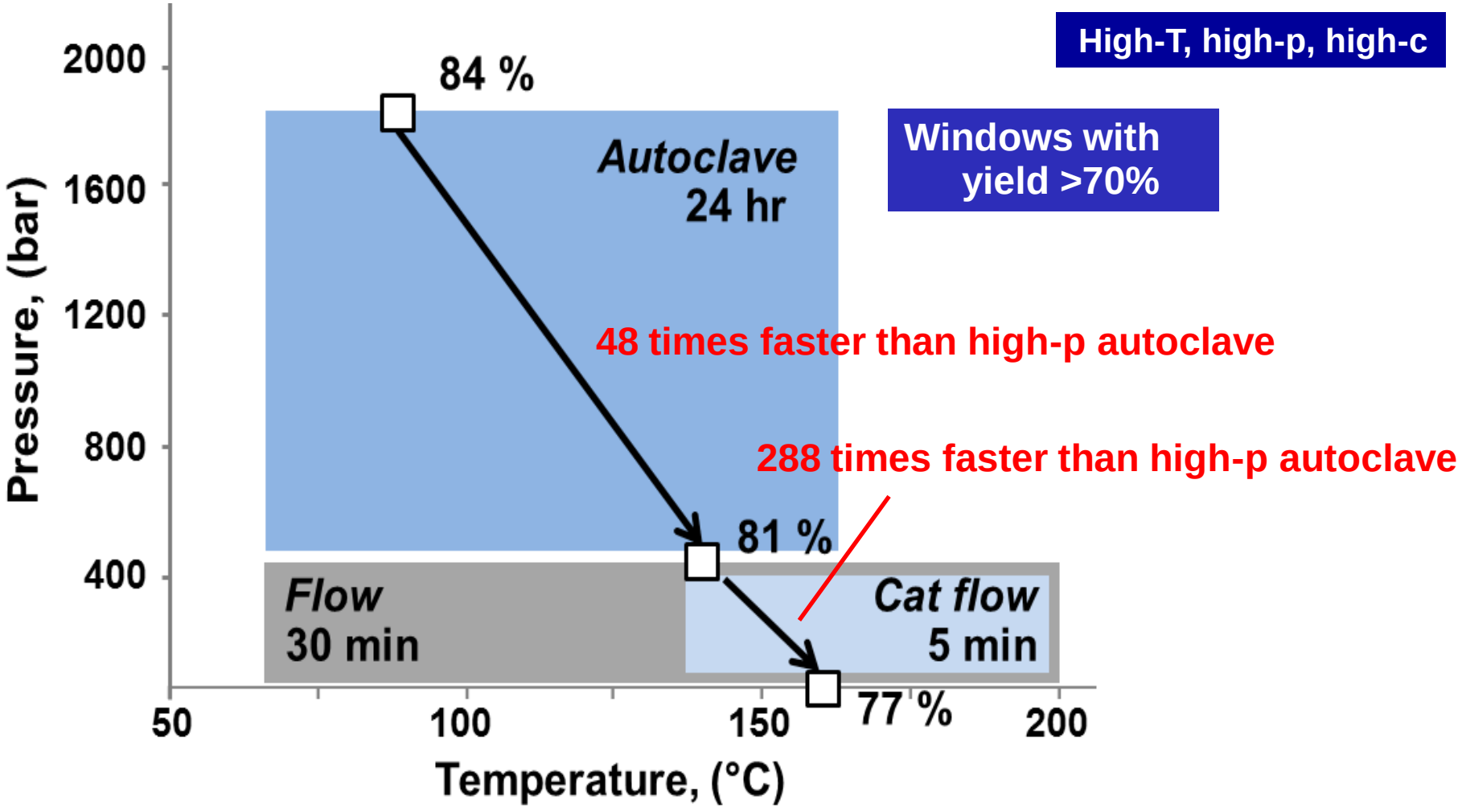
High-T

OMNICHEM

L. Borukhova, T. Noel, B. Metten, E. de Vos, V. Hessel *ChemSusChem* **6**, 12 (2013) 2220–2225

Entry	Dipolarophile	–R	Toxicity (NFPA[a])	Cost[b] [$ mol^{-1}]	*t* [h]	Yield [%]	*T* [°C]	Equiv-alents	Solvent/Additives
1[7a]		–CN	4	12	24	72	80	1.5	neat
2[7b]		–COOH	3	13	2	80	25	1	water–*t*BuOH/ascorbic acid/$CuSO_4$
3[7c]		–COOMe	2	45	5	48	65	1	water
4[9]		–COOMe	0	2	28	85	135	1.2	neat

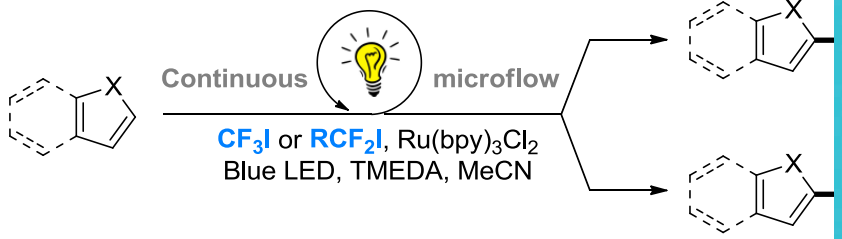
LARGER WINDOWS COMPRISE BETTER POINTS OF OPERATION

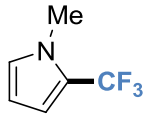


S. Borukhova, V. Hessel, T. Noel, Q. Wang et al. *ChemSusChem* (2014) accepted

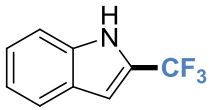
TU/e Technische Universiteit Eindhoven University of Technology

PHOT
DC



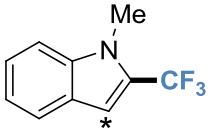


2a, 95%[b]
t_R = 8 min

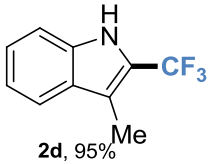


2b, 80%
t_R = 8 min

2g,
t_R =

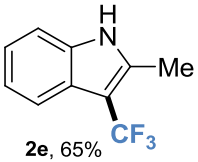


2c, 91% (3:1)
t_R = 8 min

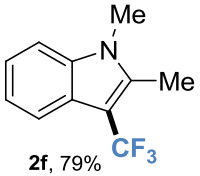


2d, 95%
t_R = 8 min

2i
t_R =



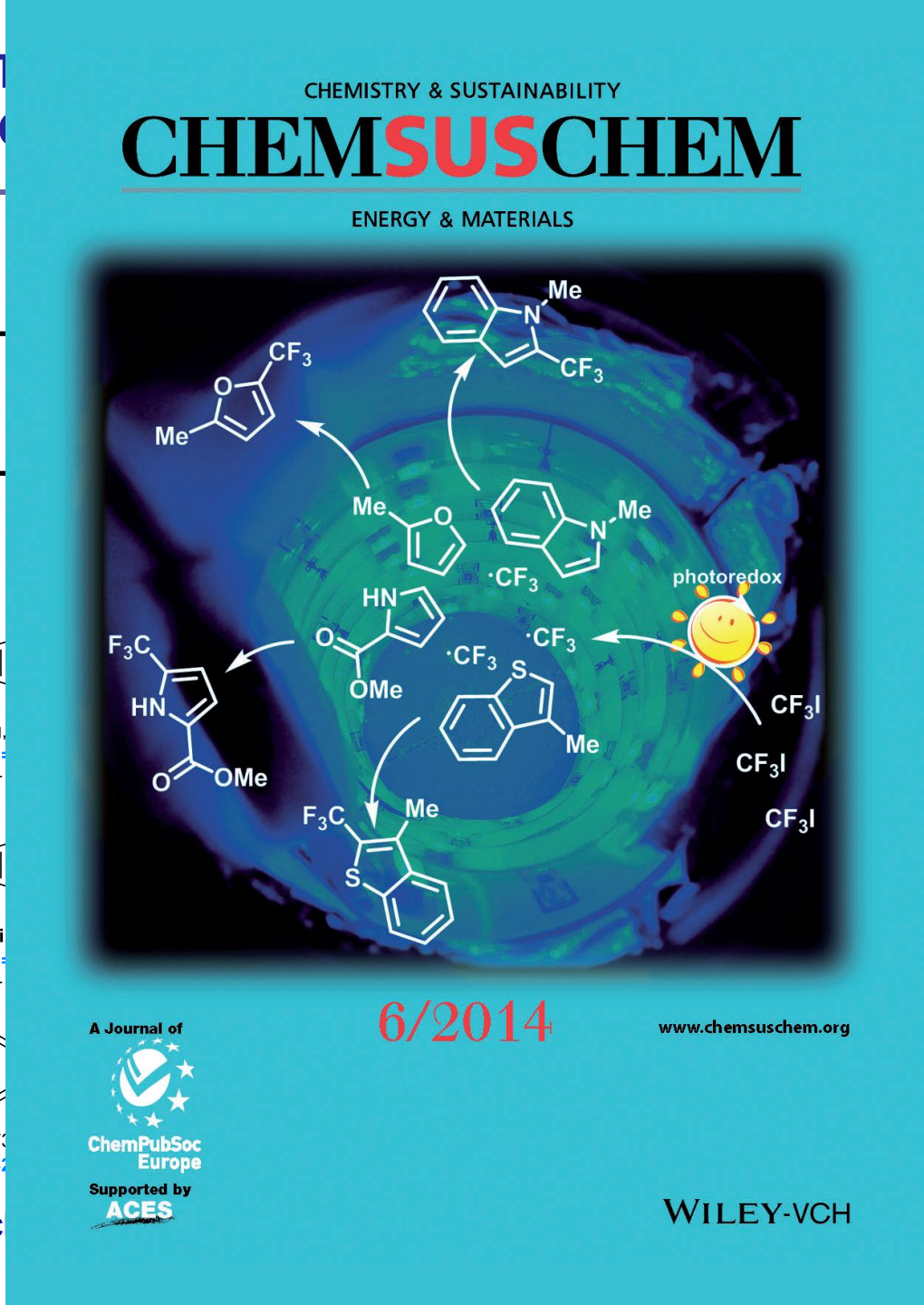
2e, 65%
t_R = 8 min



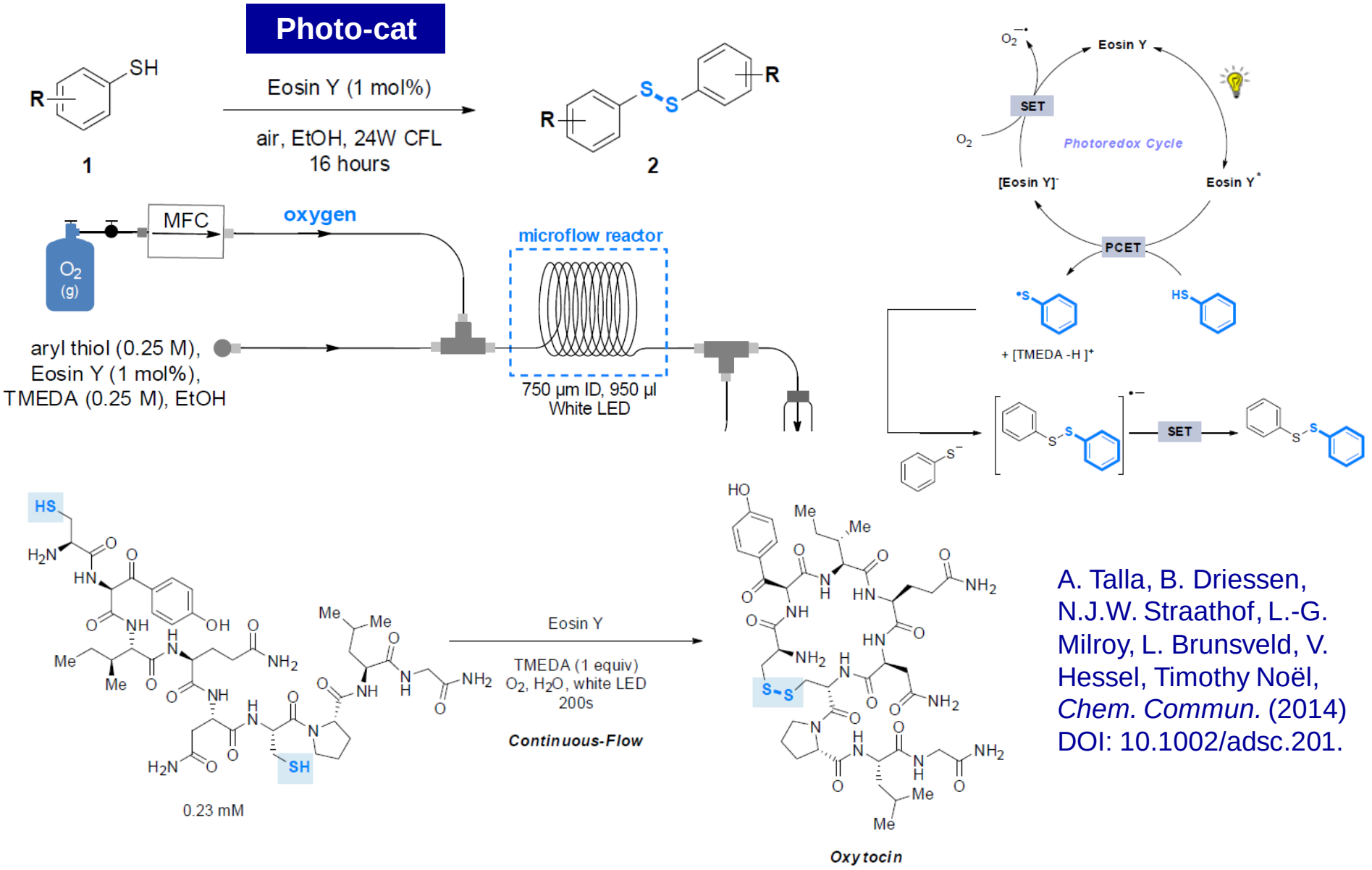
2f, 79%
t_R = 8 min

2k, 73
t_R = 32

N.J.W. Straathof, H.P.L. Gemoets, X. Wang, J.C. Sc
1612-1617.



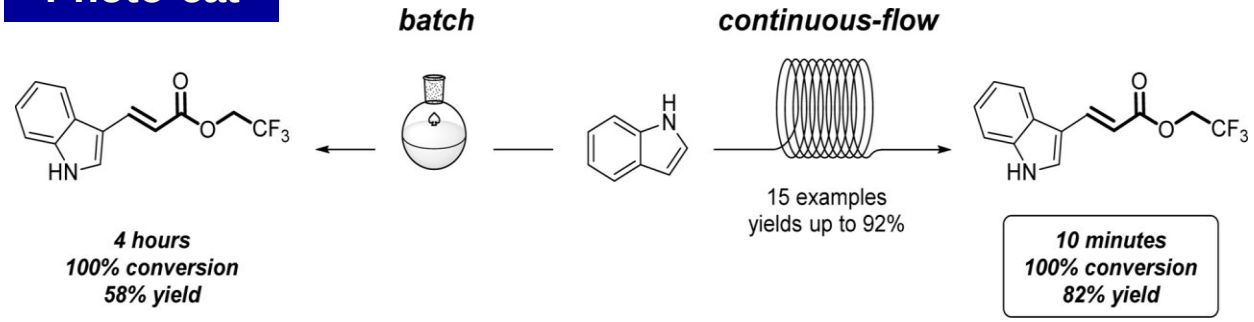
METAL-FREE PHOTOCATALYTIC AEROBIC OXIDATION TO THIOLS



A. Talla, B. Driessen, N.J.W. Straathof, L.-G. Milroy, L. Brunsveld, V. Hessel, Timothy Noël, *Chem. Commun.* (2014) DOI: 10.1002/adsc.201.

DREAM REACTION
- AEROBIC C-H ACTIVATION

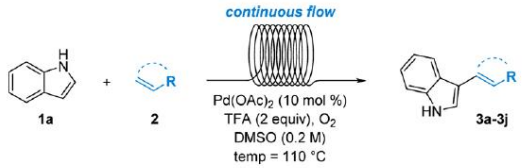
Photo-cat



H.P.L. Gemoets, V. Hessel, T. Noël *Org. Lett.* **16**, 21 (2014) 5800-5803.

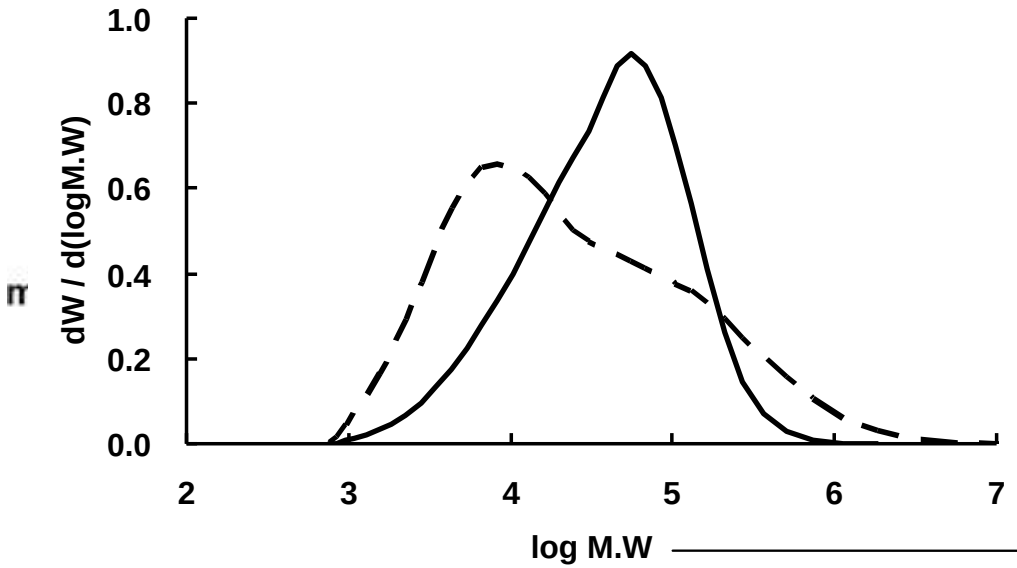
Microreactor

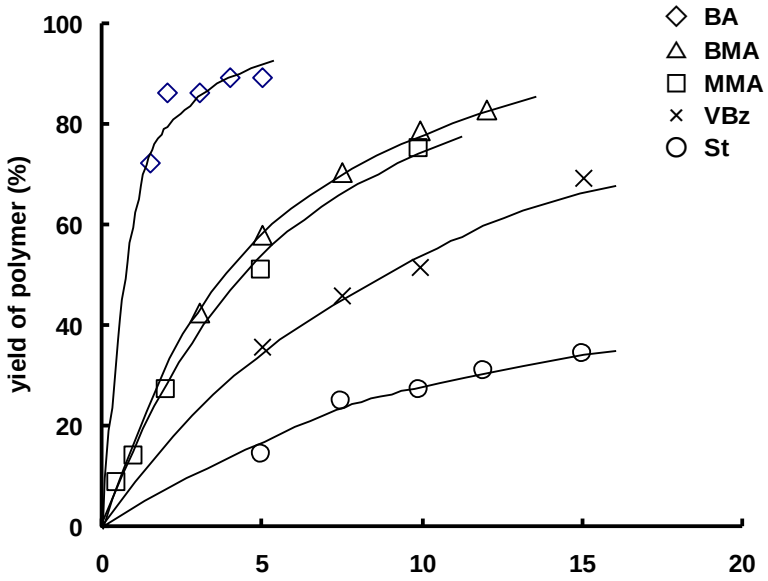
- **Avoids safety concerns: due to use of oxygen with flammable solvents, especially on larger scale**
- **Speeds up reaction: by eliminating transfer hindrances and using harsh conditions**
- **Prevents catalyst deactivation: promoting desired direct oxidation of Pd(0) by oxygen rather than palladium bulk agglomeration**



entry	olefin	product	t_r (min)	yield (%)[b]
1	2a	3a	10	82;58[c]
2	2b	3b	20	75
3	2c	3c	15	72
4	2d	3d	10	92
5	2e	3e	10	83
6[d]	2f	3f	10	67
7	2g	3g	20	70
8	2h	3h	15	49
9	2i	3i	20	27
10	2j	3j	20	43[e]

FREE-RADICAL POLYMERIZATION – IMPACT OF HEAT RELEASE



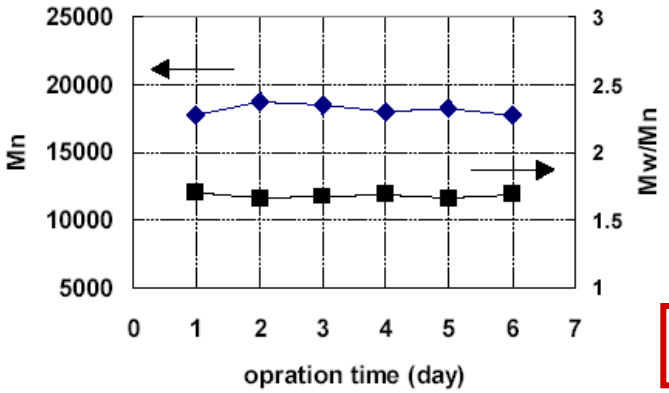


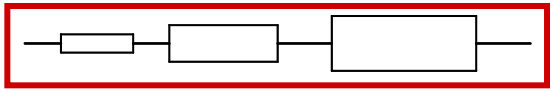
Significant improvement in molecular weight distribution control

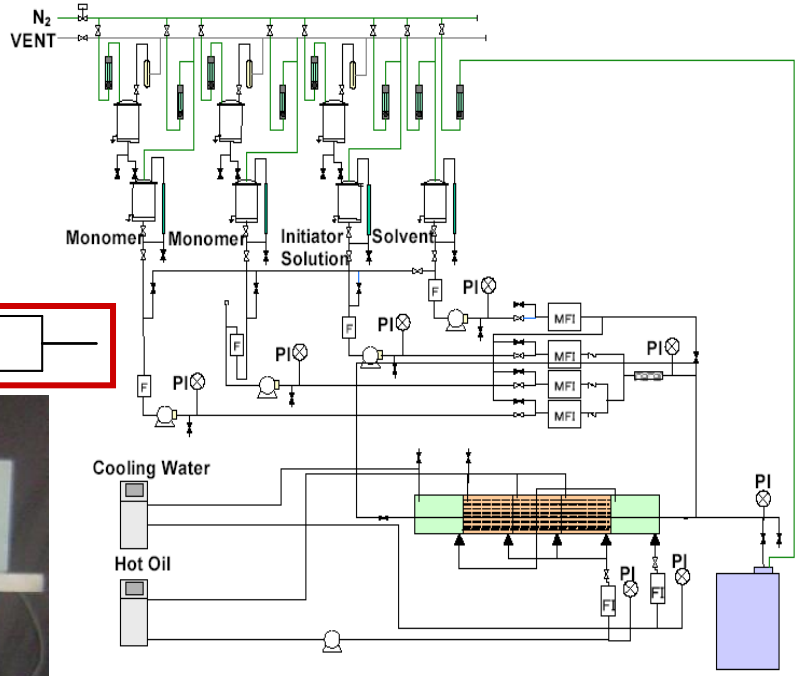
T. Iwasaki, J. Yoshida *Macromolecules* **38**, 4 (2005) 1159-1163.

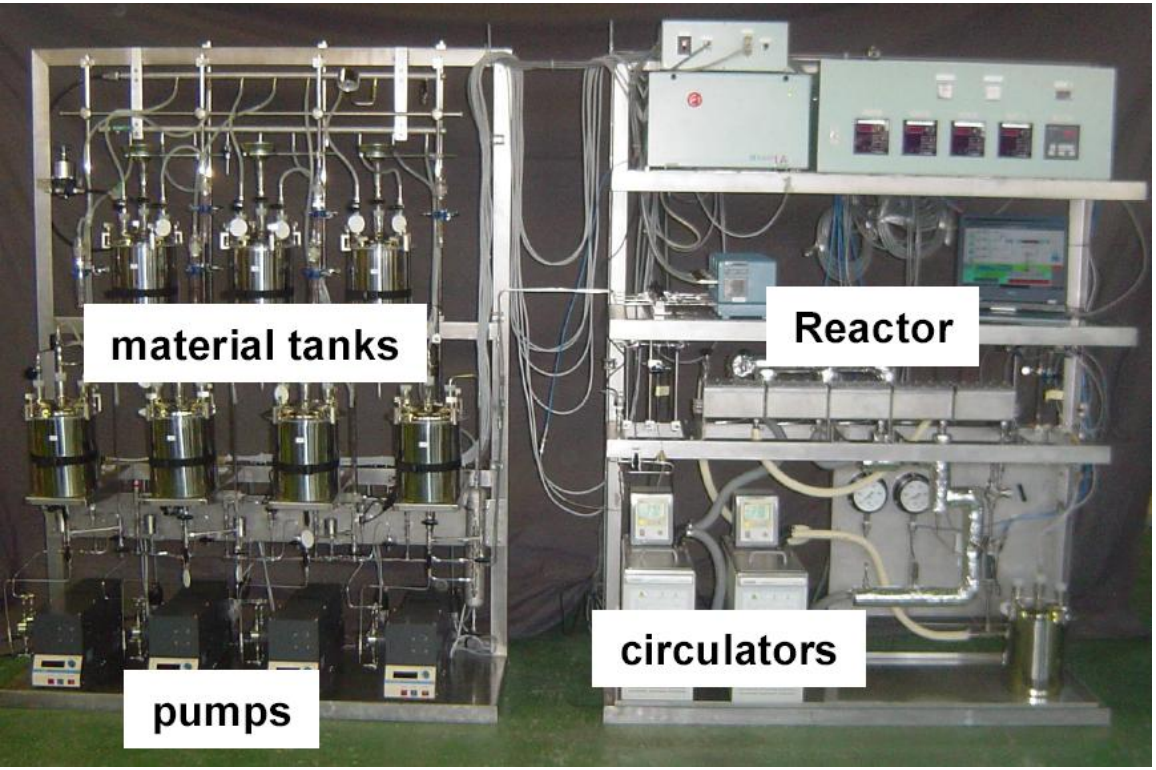
Reactor	Monomer	Yield (%)	M_n (x10^3)	PDI (M_w/M_n)
Micro-reactor	Butyl Acrylate	89.3	19.2	3.35
	Styrene	34.2	5.3	1.74
Macro-batch reactor	Butyl Acrylate	88.0	9.3	10.3
	Styrene	29.4	5.5	1.72

PILOT PLANT FOR RADICAL POLYMERIZATION









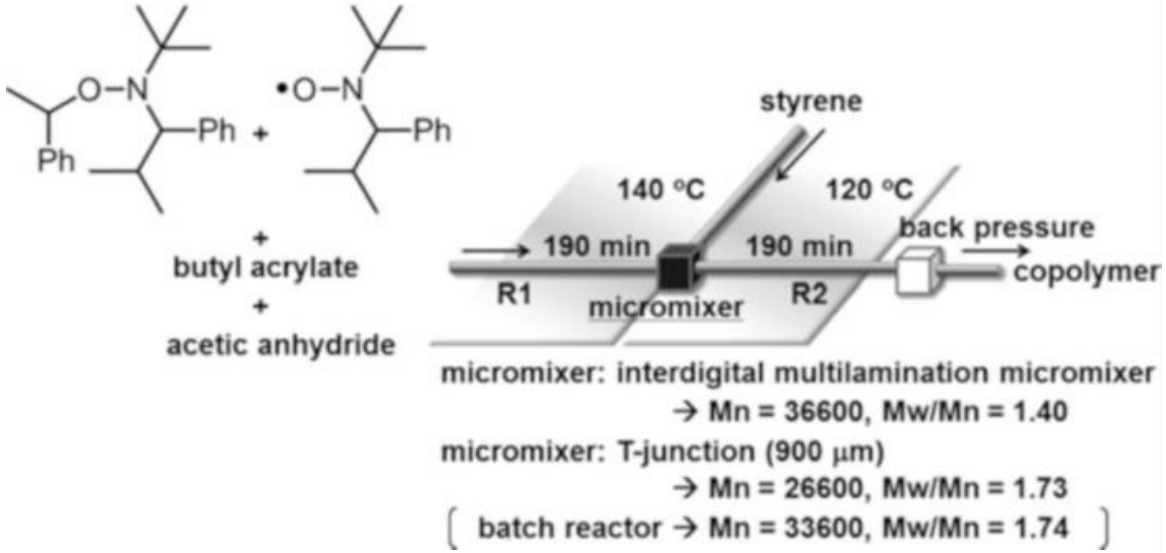
Plant running at industrial site: Idemitsu Kosan Co. Ltd.

T. Iwasaki, N. Kawano, J.-i. Yoshida, *Org. Proc. Res. Dev.* **10** (2006) 1126–1131.

10 t/a 3.5m × 0.9m

MIXING AS GOAL - NMP LIVING-RADICAL POLYMERIZATION

PDI advantages over batch can be realised (only) with best micro-equipment



C. Rosenfeld,C. Serra, C. Brochon et al. (2008) *Chem Eng J* **135S** (2008) S242-S246.

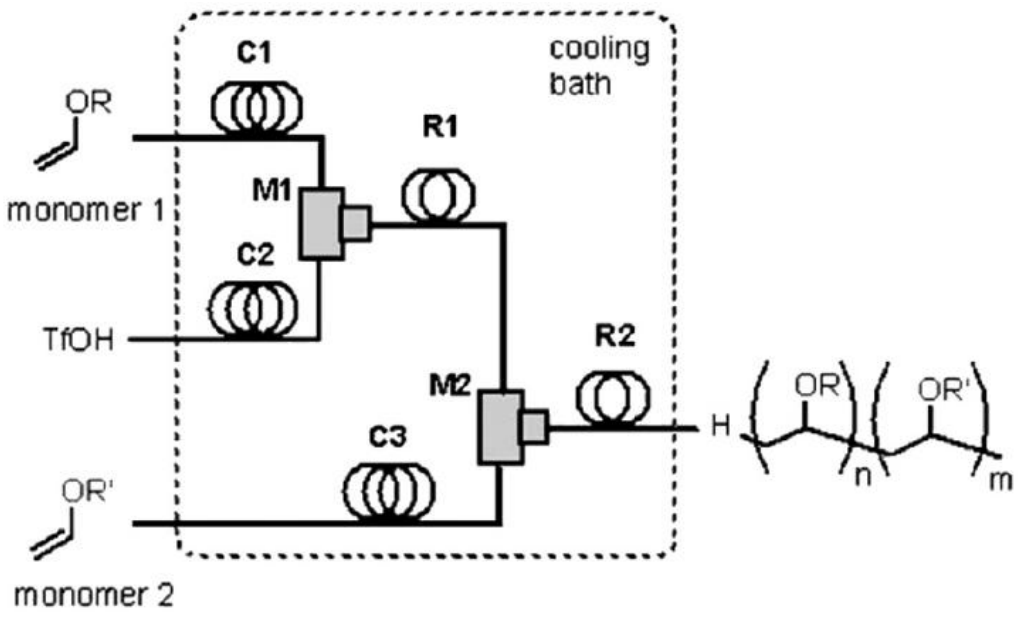
Form factor F has linear relationship to blockcopolymer properties

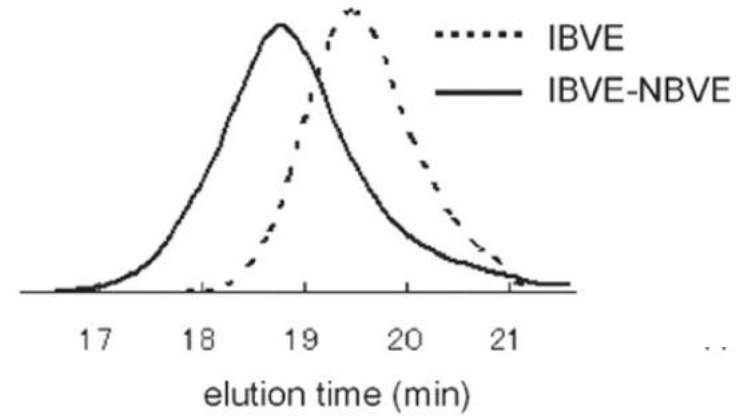
	HPIMM		LH2
Micromixer	ML45	ML20	ML50
Number of channels per inlet, N	16	15	10
Channel width, W_C (μm)	45	20	50
microstructure thickness (μm)	250	100	300
Slit or aperture width, W_L (μm)	60	60	50
Form factor, F (mm^{-1})	0.59	0.83	1.0

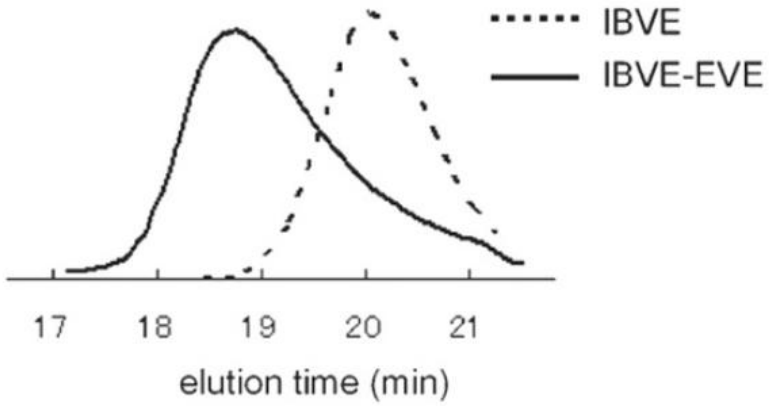
C. Rosenfeld, C. Serra, C. Brochon C et al. *Lab Chip* **8** (2008) 1682-1687.

PROCESS INTEGRATION AS GOAL - COPOLYMERIZATION

Block copolymers from IBVE, n-butylvinylether (NBVE) + ethylvinylether (EVE)



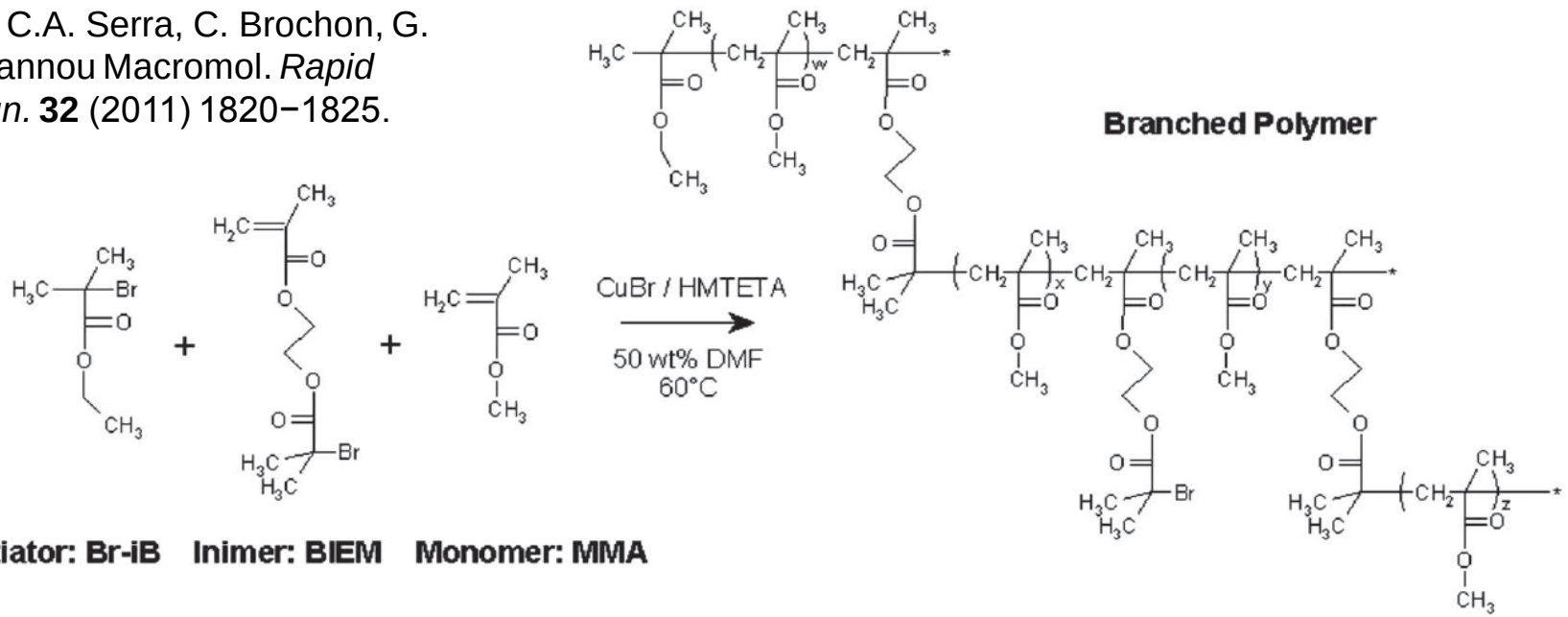


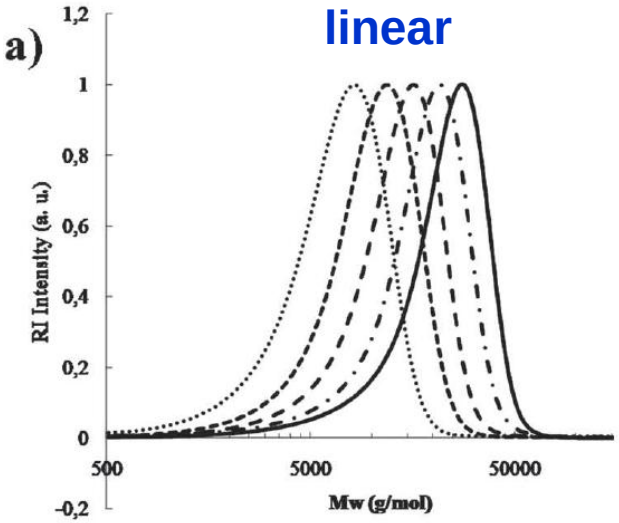


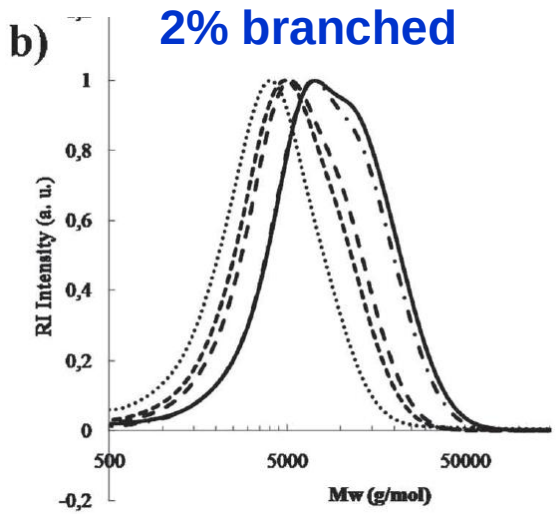
T. Iwasaki, A. Nagaki, J.I. Yoshida, *Chem. Comm.* **12** (2007)1263-1265.

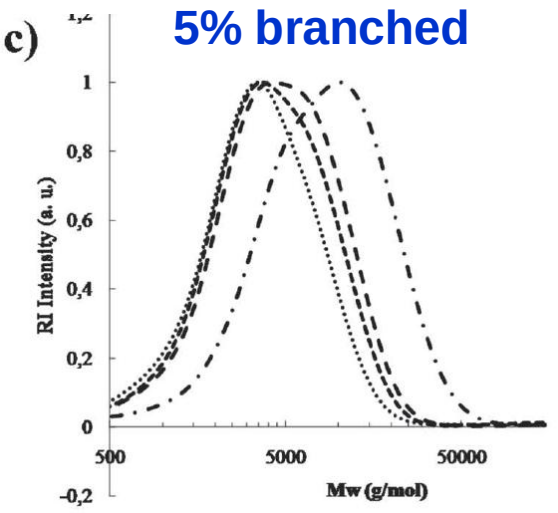
ADVANCED CONTROL OF MACROMOLECULAR ARCHITECTURE

F. Bally, C.A. Serra, C. Brochon, G. Hadziioannou Macromol. *Rapid Commun.* **32** (2011) 1820−1825.

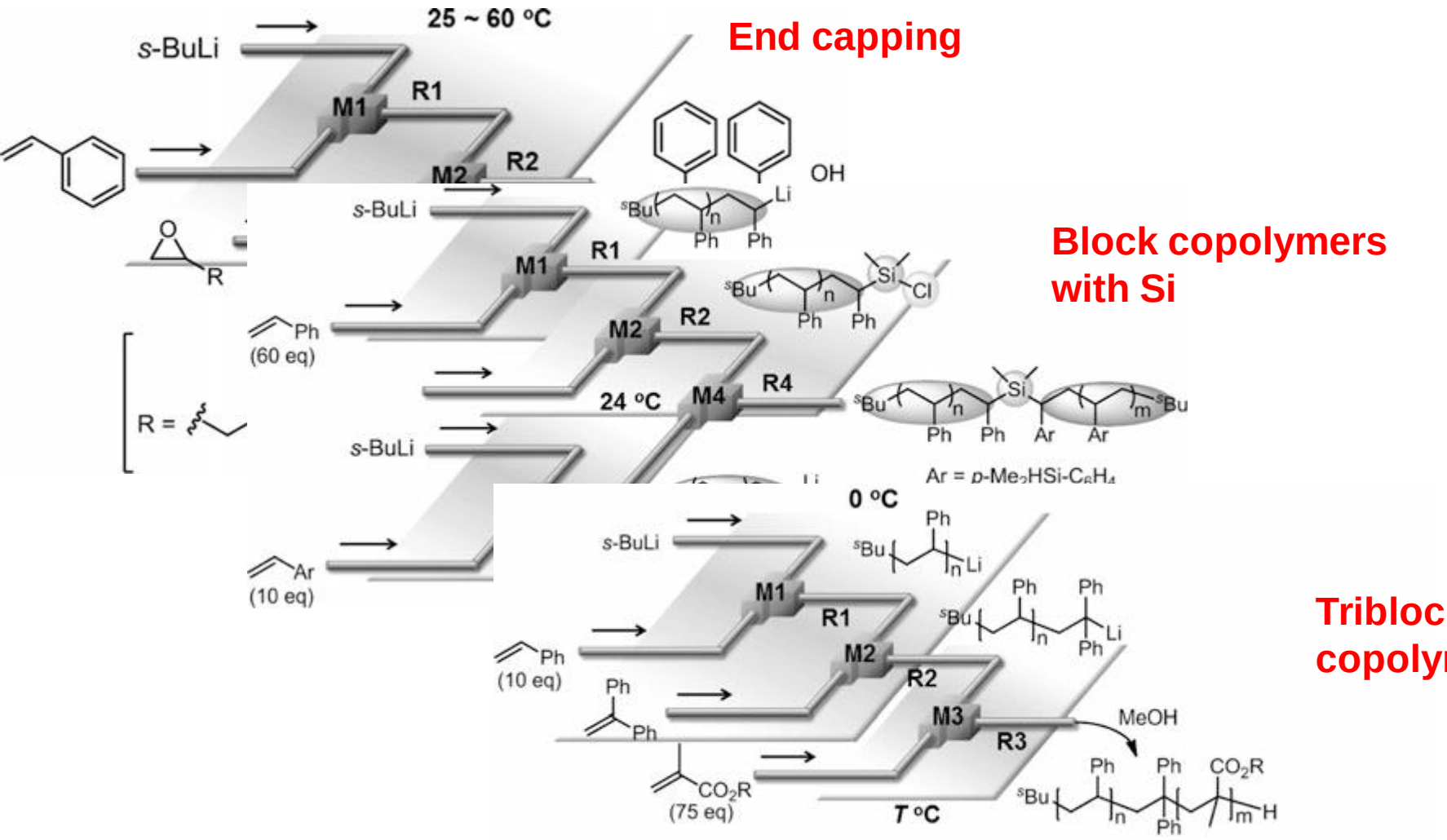






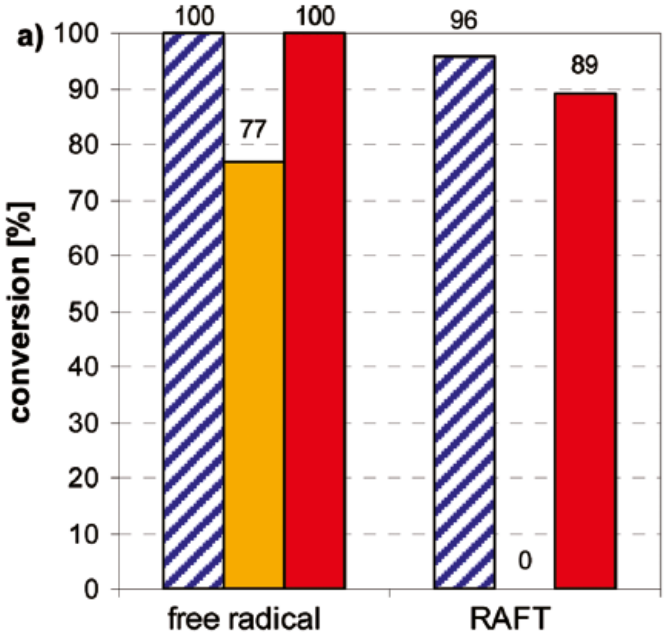


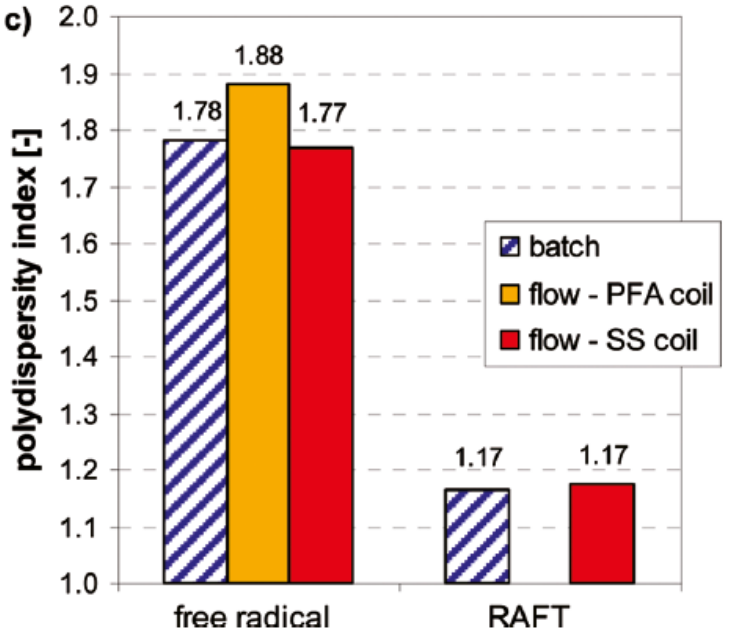
FLOW CASCADING - ADDING POLYMERS, END CAPS, ….

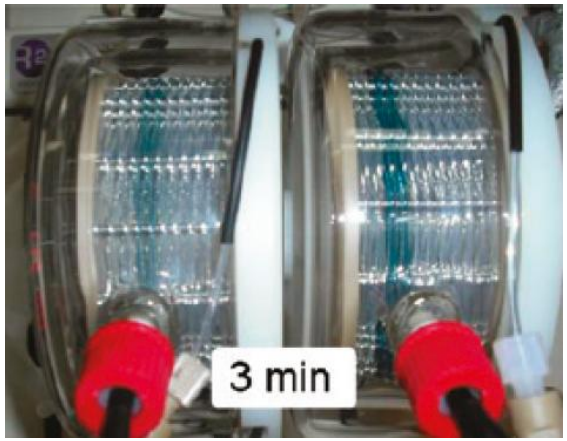


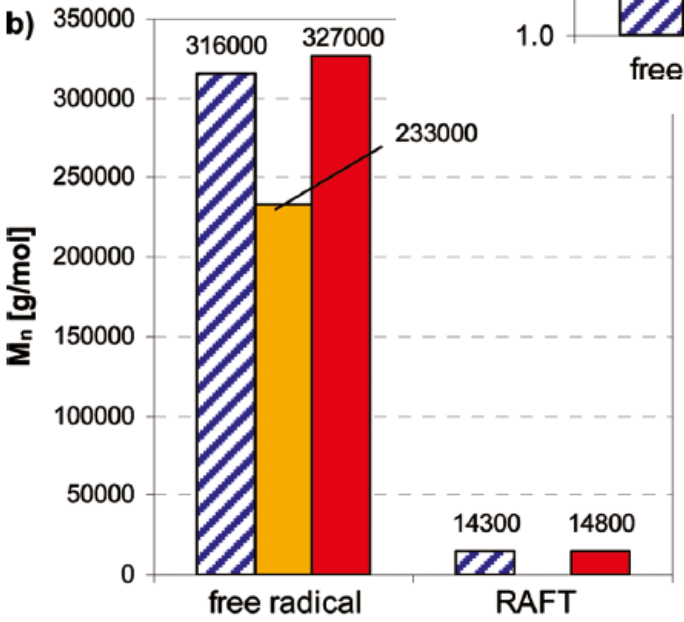
R = Me (T = -28 °C): Mn = 9000, Mw/Mn = 1.30
R = Bu (T = 0 °C): Mn = 12200, Mw/Mn = 1.55
R = ^{t}Bu (T = 24 °C): Mn = 9200, Mw/Mn = 1.19

CONTROLLED RAFT POLYMERIZATION
IMPACT OF FLOW REACTOR MATERIAL



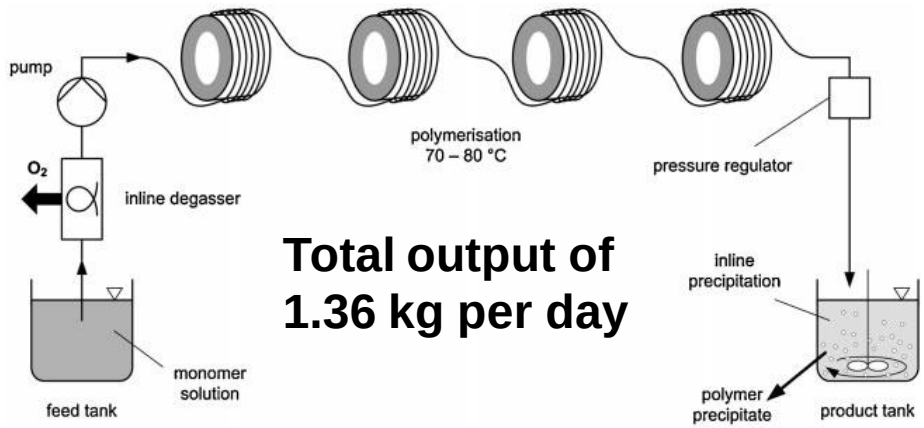






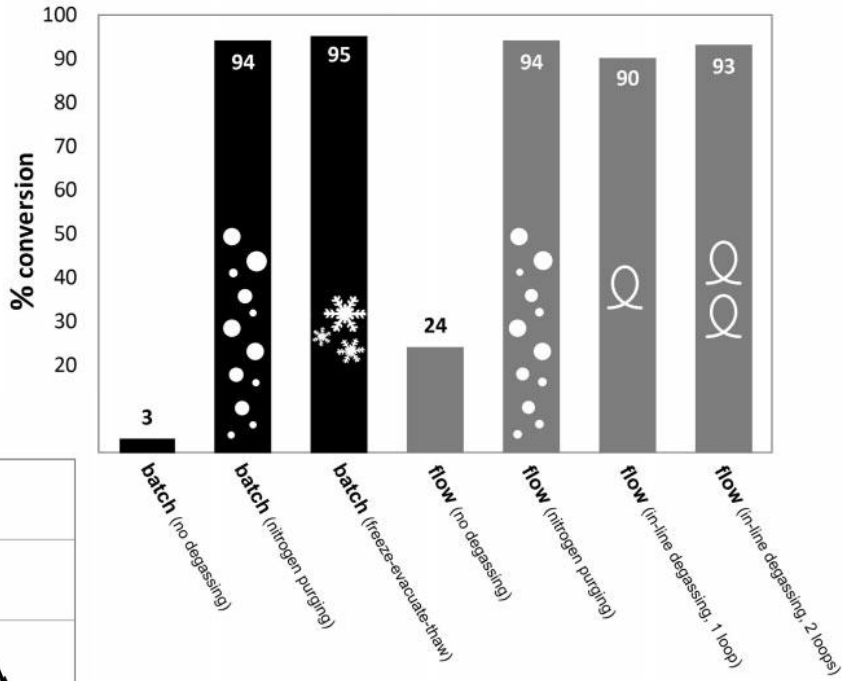
C.H. Hornung, C. Guerrero-Sanchez, M. Brasholz, S. Saubern, J. Chiefari, G. Moad, E. Rizzardo, S.H. Thang *Org. Process Res. Dev.* **15** (2011) 593–601.

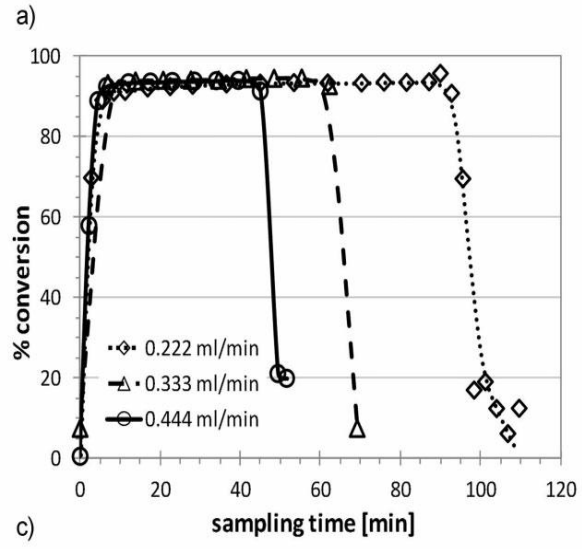
CONTROLLED RAFT POLYMERIZATION
IMPACT OF OXYGEN AND AXIAL DISPERSION

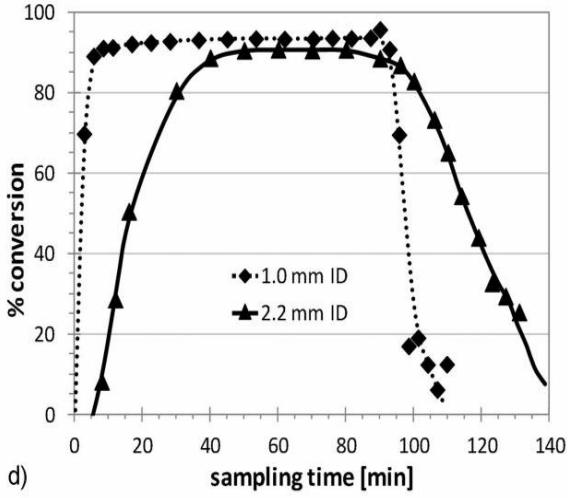


Total output of 1.36 kg per day

Oxygen exclusion





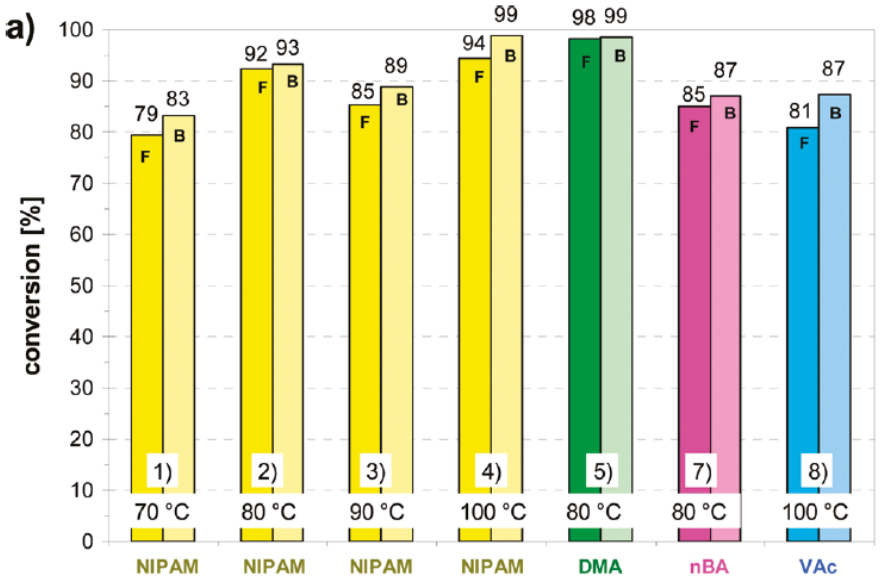


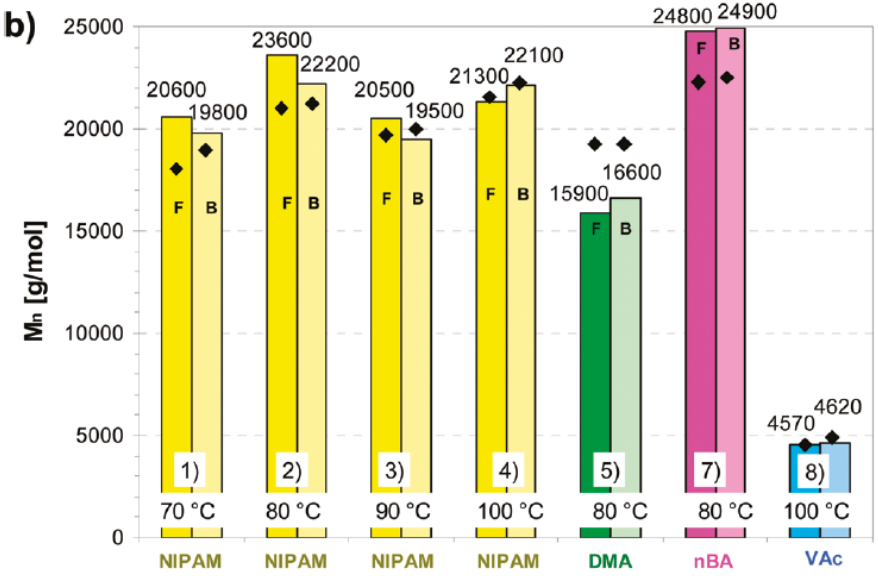
Sample broadening

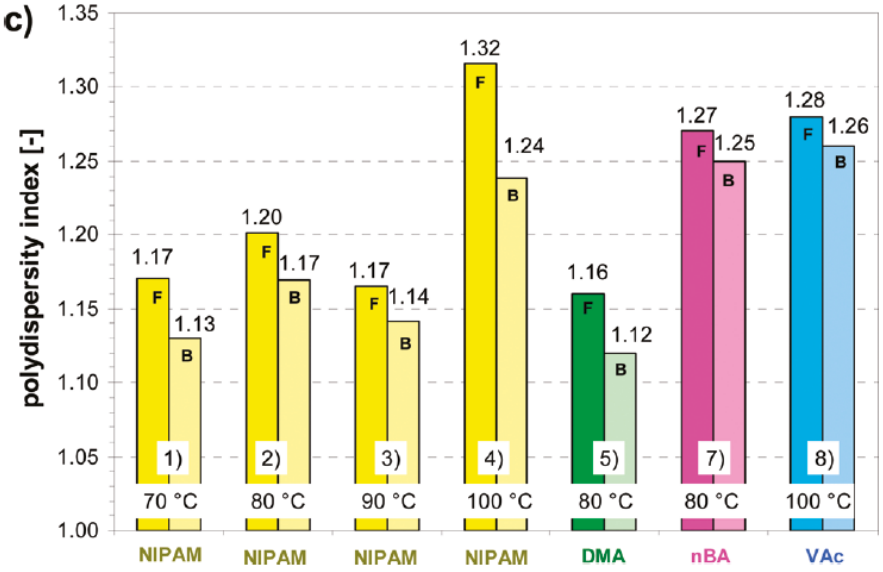
C.H. Hornung, X. Nguyen, G. Dumsday, S. Sau-bern *Macromol. React. Eng.* **6** (2012) 458-466.

Technische Universiteit Eindhoven University of Technology

CONTROLLED RAFT POLYMERIZATION



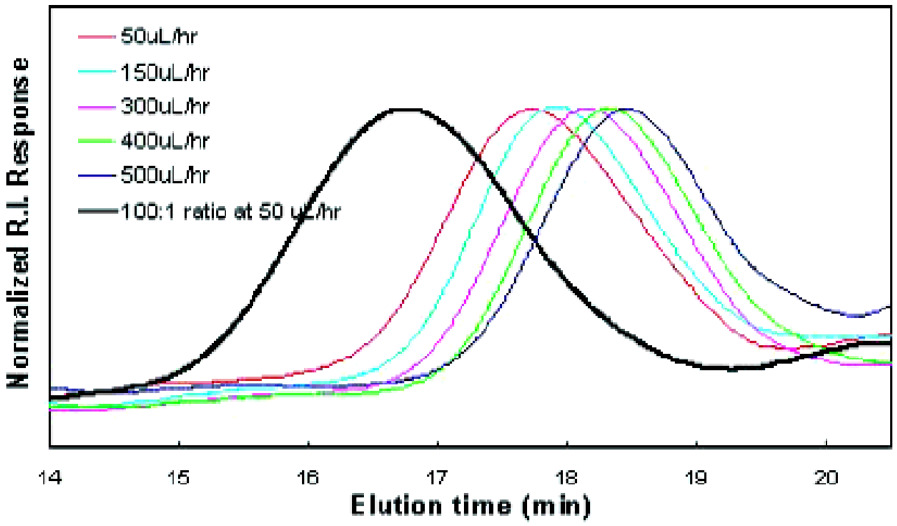


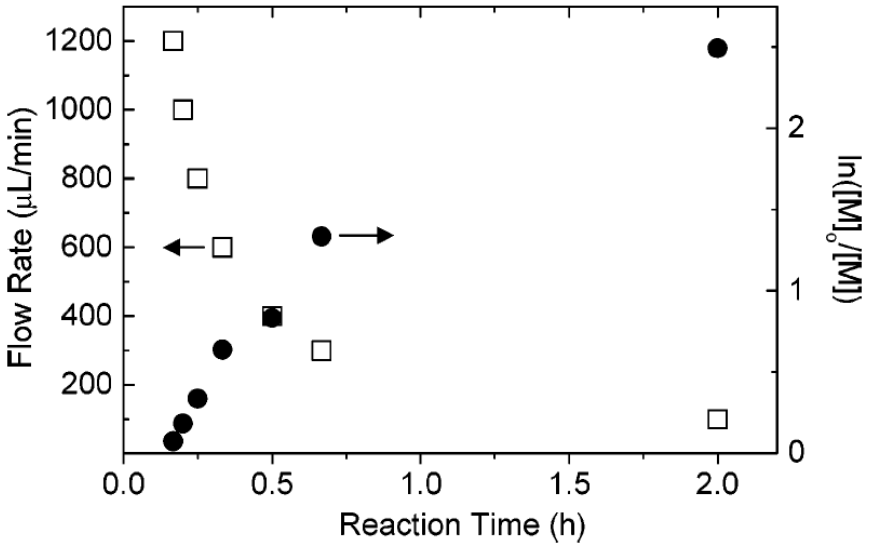


C.H. Hornung, C. Guerrero-Sanchez, M. Brasholz, S. Saubern, J. Chiefari, G. Moad, E. Rizzardo, S.H. Thang *Org. Process Res. Dev.* **15** (2011) 593–601.

ATRP HOMOPOLYMERIZATION AS TEST FOR USE OF MICROREACTORS AS KINETIC TOOLS

T. Wu, Y. Mei, J. T. Cabral, C. Xu, K. L. Beers *J. Am. Chem. Soc.* **126**, 32 (2004) 9880-9881.





Atom transfer radical polymerization (ATRP) of 2-hydroxypropyl methacrylate (HPMA) was used to compare the kinetics and controllability in this reactor relative to batch reactions.

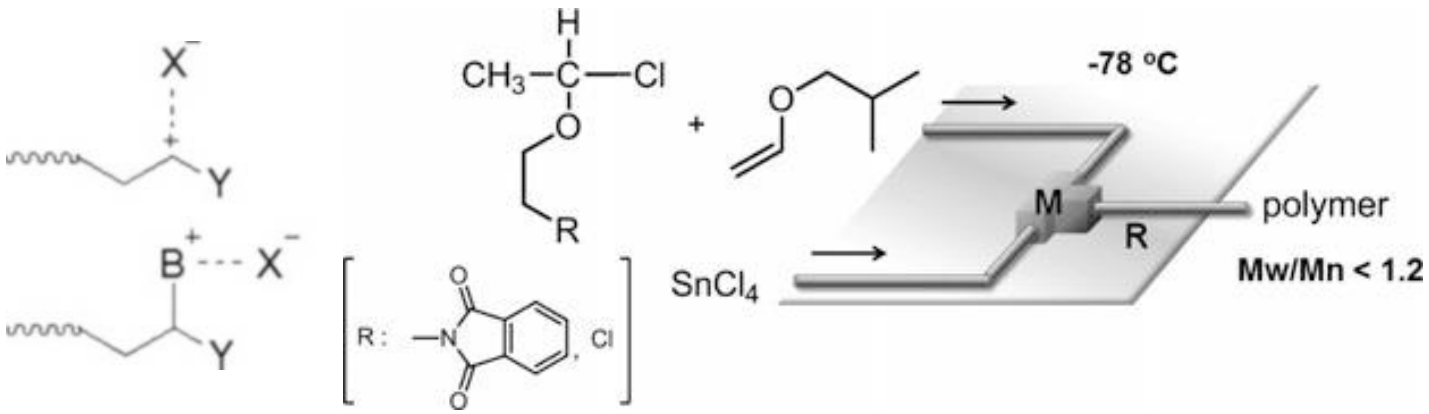
Rate of polymerization fairly constant and compares to batch data from

M. Save, J.V.M. Weaver, S.P. Armes, P. McKenna *Macromolecules* **35** (2002) 1152-1159.

Potential for library build-up for high-throughput screening

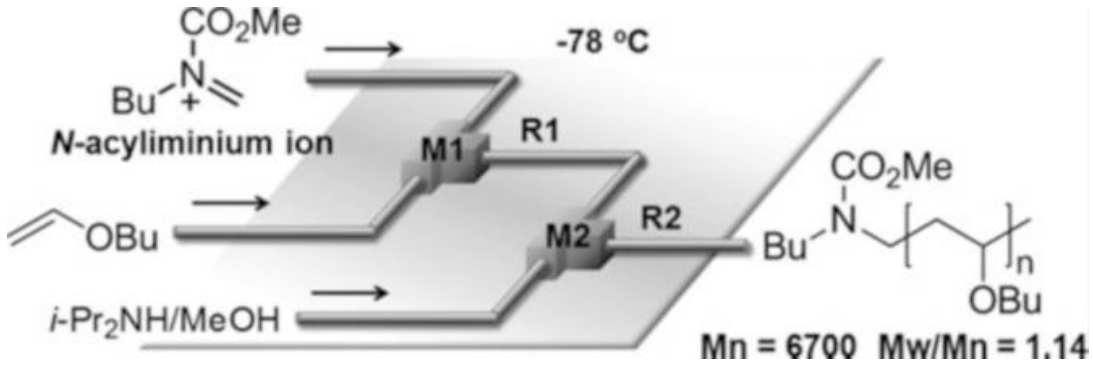
CATIONIC POLYMERIZATION - WITH MASKED AND HIGHLY ACTIVE CATION

Masked cation = slow reaction rate = good PDI throughout



N. Inagaki, T. Ando, M. Sawamoto et al. *Polym Repr Jpn* **53** (2004) 2416-2417.

Highly active cation pool = very fast reaction rate
= avoid mixing masking = good PDI for good microfluidics + chemistry

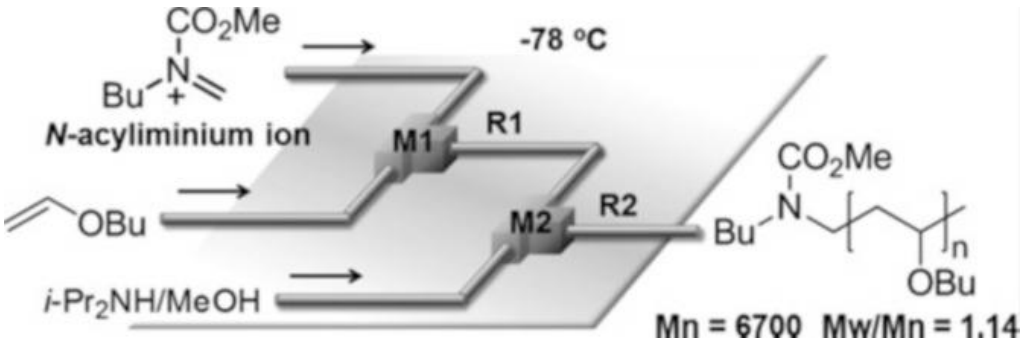


A. Nagaki, K. Kawamura, S. Suga et al. *J Am Chem Soc* **126** (2004) 14702-14703.

CATIONIC POLYMERIZATION - WITH MASKED AND HIGHLY ACTIVE CATION

Table 1 Cationic polymerization of NBVE initiated by *N*-acyliminium ion using a flow microreactor system

Run	Monomer (equiv.)	Flow rate (mL/min)	Temperature (°C)	M_n	M_w/M_n
1	10	5.0	−78	1,500	1.40
2	25	5.0	−78	2,900	1.26
3	35	5.0	−78	4,400	1.17
4	50	5.0	−78	6,700	1.14
5	50	3.0	−78	5,600	1.35
6	50	1.0	−78	6,200	2.84
7	50	5.0	−48	8,200	1.30
8	50	5.0	−27	5,500	1.34
9	50	5.0	0	6,500	1.61



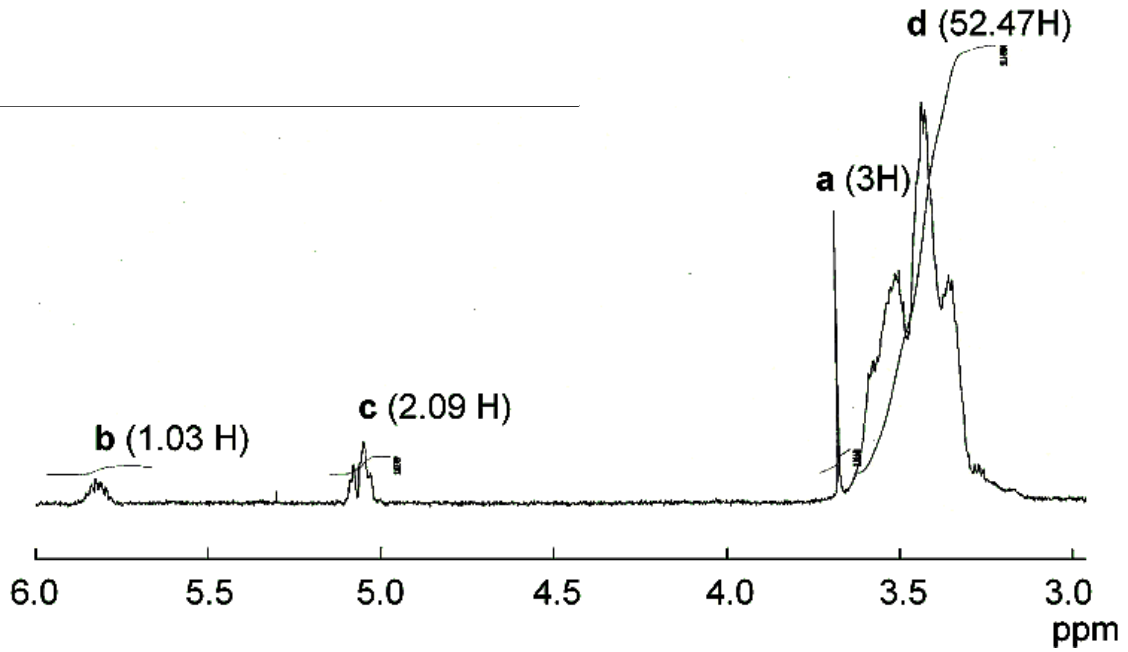
Nagaki, K. Kawamura, S. Suga et al.
J Am Chem Soc **126** (2004) 14702-14703.

BENCHMARKING CATION-POOL LIVING POLYMERIZATION

Reactor	Monomer	Flow rate (ml/min)	M_n (x10^3)	PDI (M_w/M_n)
Micro-reactor	n-Butyl vinyl ether	5.0	6.7	1.14
	n-Butyl vinyl ether	1.0	6.2	2.84
Macro-batch reactor	n-Butyl vinyl ether	---	5.7	2.56

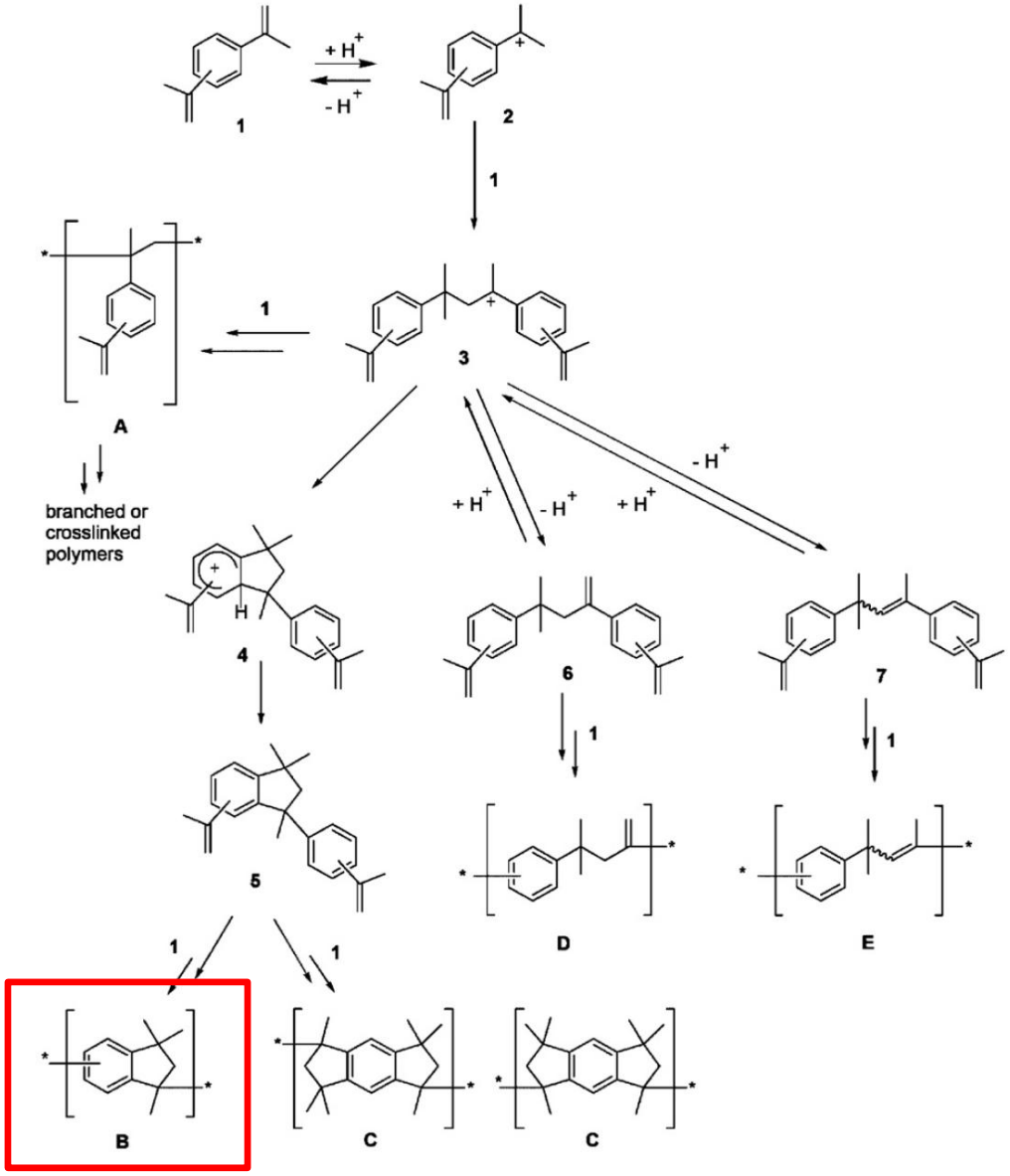
Significant improvement in molecular weight distribution control

Proof of living polymerization by trapping experiment



A. Nagaki, K. Kawamura, S. Suga, T. Ando, M. Sawamoto, Yoshida, J. *J .Am. Chem. Soc.* **126**, 45 (2004) 14702-14703.

SELECTIVITY AS GOAL - INDANE CYCLIZATION



Cationic polymerization of diisopropenylbenzenes

initiated by a Brønsted acid (trifluoro-methane-sulfonic acid) instead of conventional slower acids (such as sulfuric acid) in micro flow

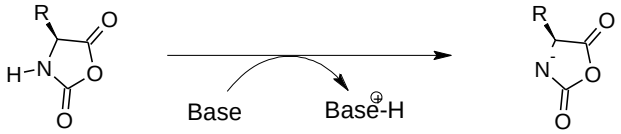
Indane (B) content improves thermal properties

95% indane (B) – conventionally: 80%

T. Iwasaki, A. Nagaki, J.I. Yoshida, *Chem. Comm.* **12** (2007)1263–1265.
T. Iwasaki, J.I. Yoshida, Macromol. *Rapid Comm.* **28** (11 (2007) 1219–1224.

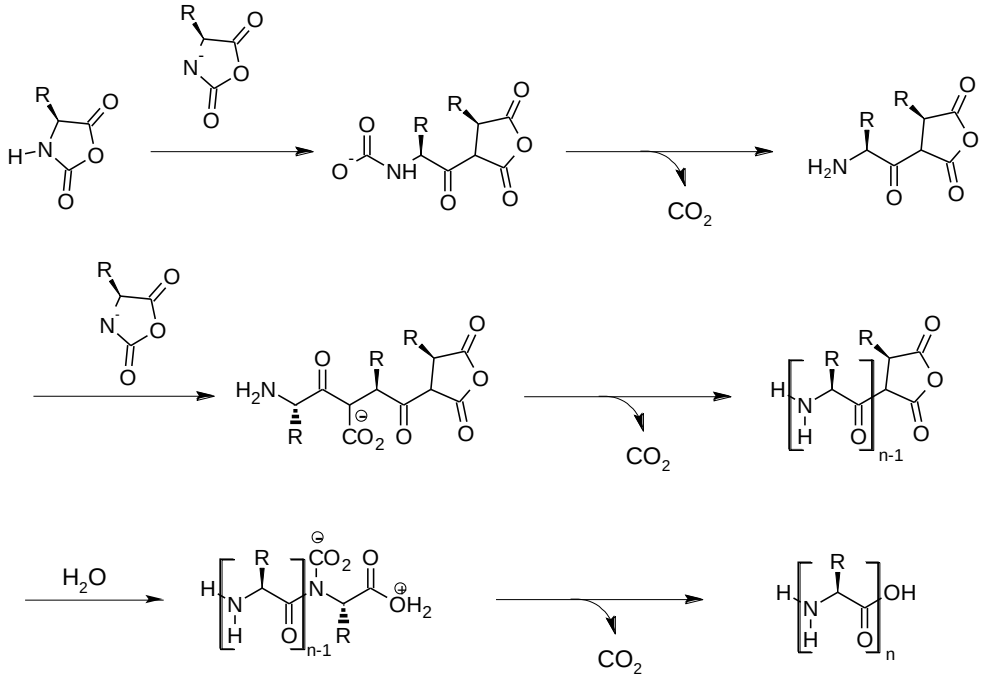
ANIONIC RING-OPENING POLYMERIZATION

Initiation



Amino acid NCA **Active monomer**

Chain growth

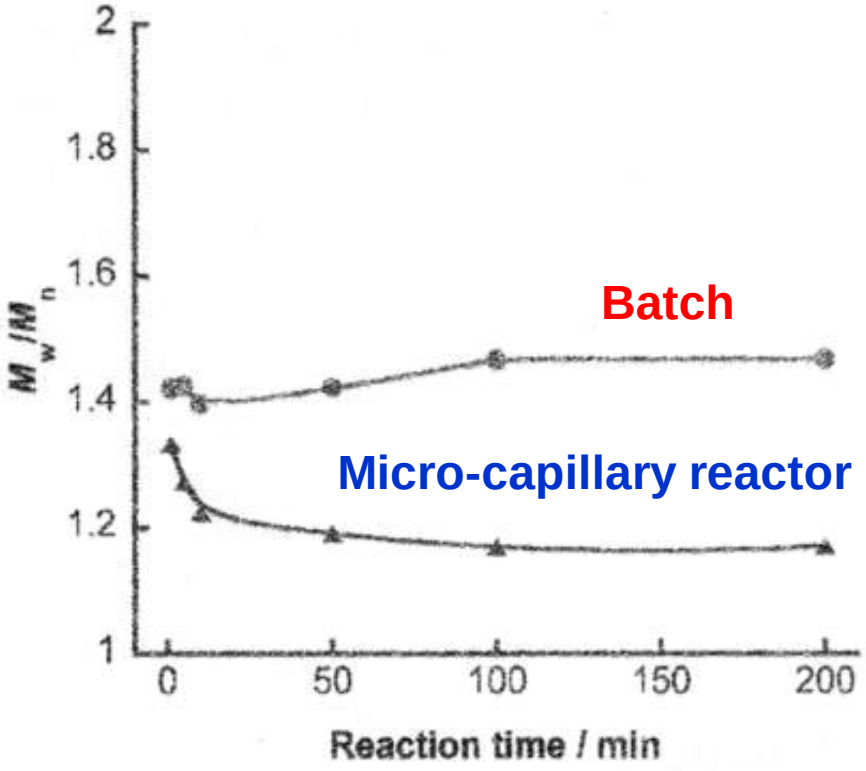


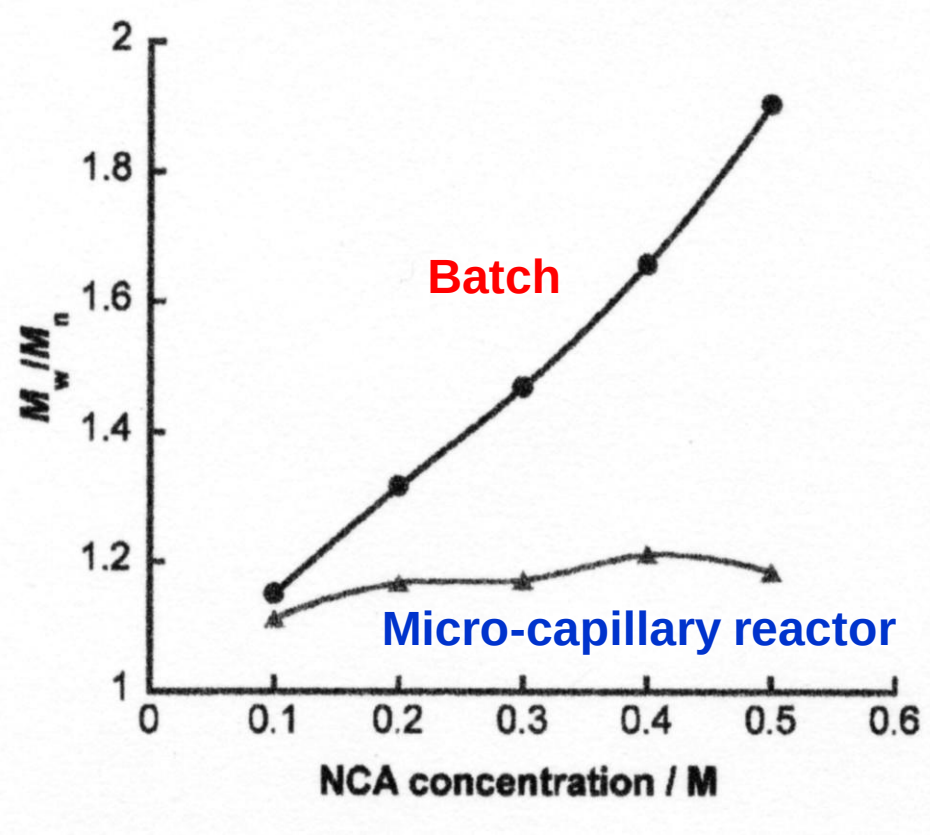
Poly (aminosäure)

Micro-capillary reactor (250 µm)

T. Honda, M. Miyazaki, H. Nakamura, H. Maeda *Lab Chip* **8** (2005) 812-818.

POLYDISPERSITY INDEX FOR THE NCA ANIONIC POLYMERIZATION



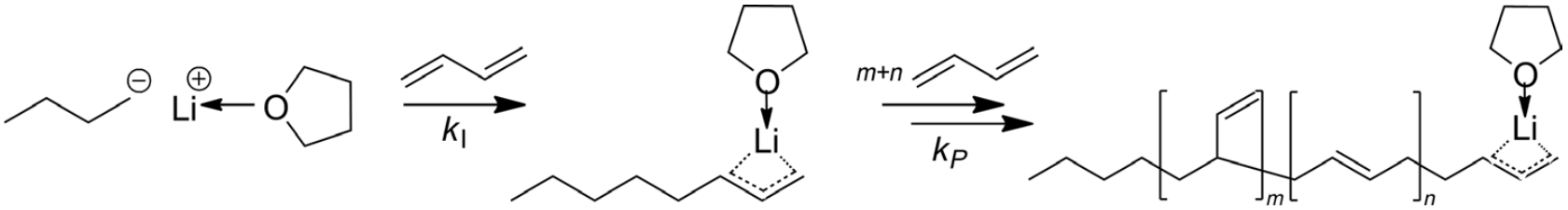


Reduction of polydispersity index by using micro-capillary reactor

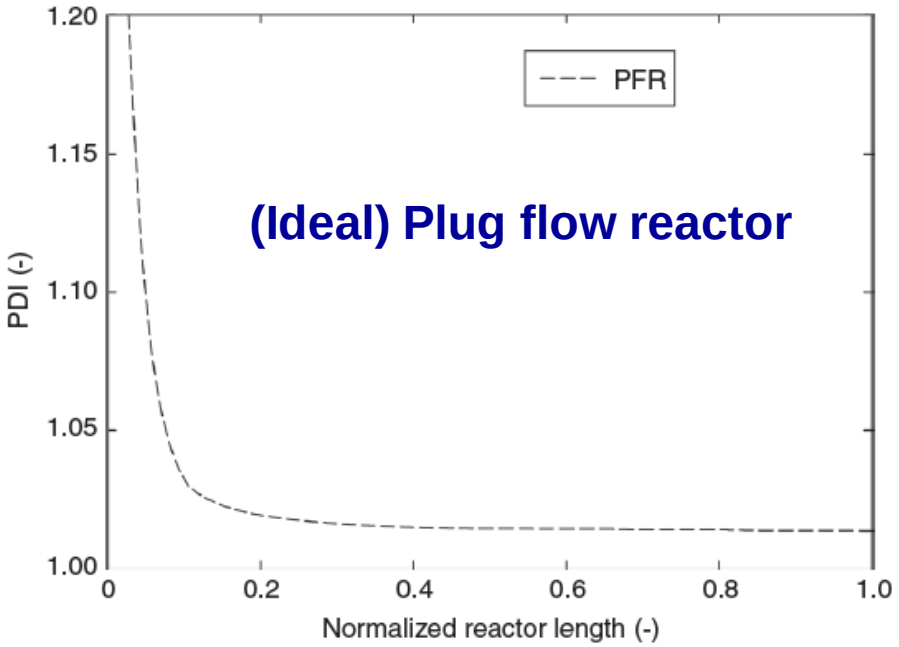
Even at high monomer concentrations only weak increase in polydispersity index for micro-capillary reactor

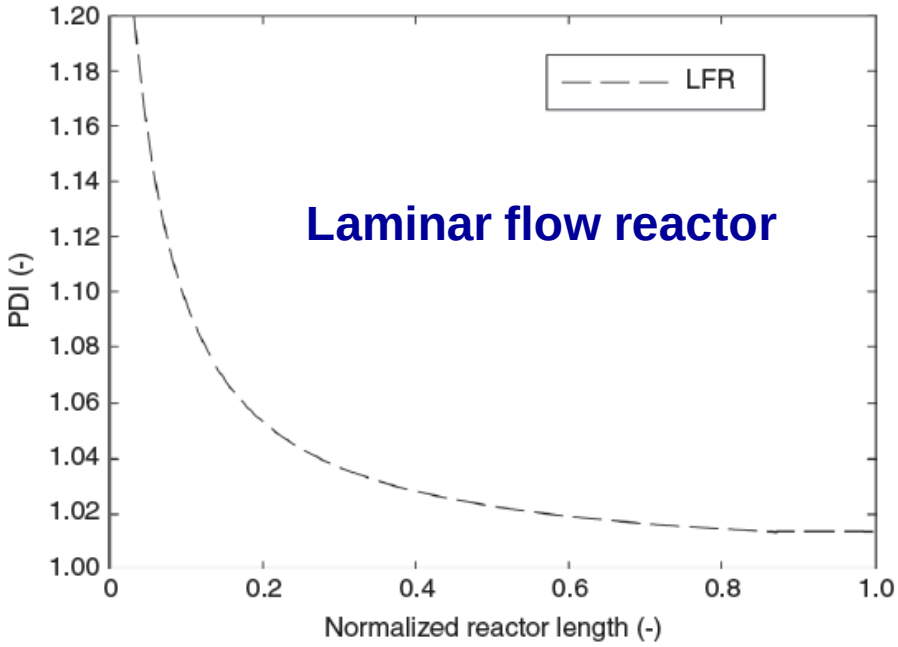
T. Honda, M. Miyazaki, H. Nakamura, H. Maeda *Lab Chip* **8** (2005) 812-818.

ANIONIC POLYMERIZATION - POLYDISPERSION INDEX AND FLOW



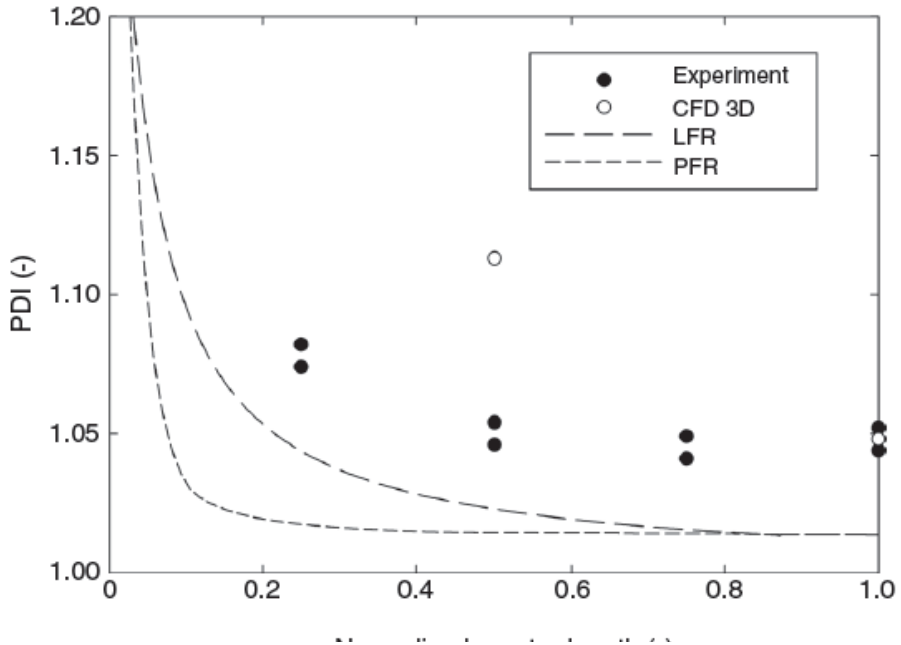
Polydispersion index is sum of fluiddynamic and statistical effects





S. Schulze, B. Cortese, Hessel, J. Lang, E. Klemm et al. *Green Process. Synth.* **2**, 5 (2013) 381-395.

SIMULATION STUDY OD SEGREGATED BEHAVIOUR IN ANIONIC POLYMERIZATION



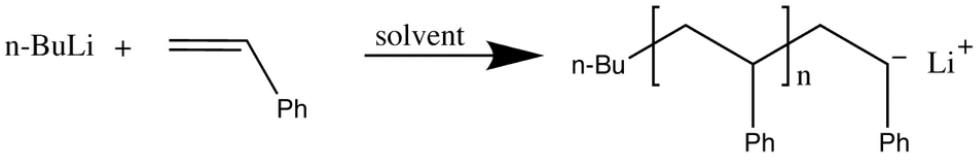
Model - Experiment

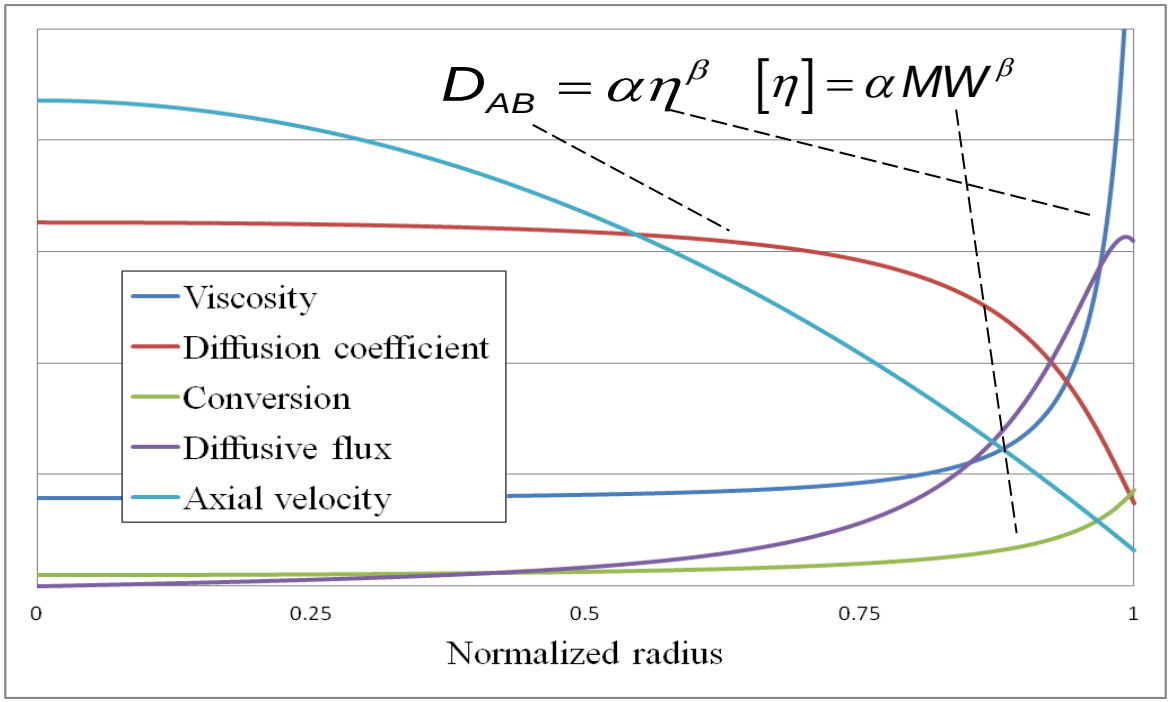
Benchmarking in flow

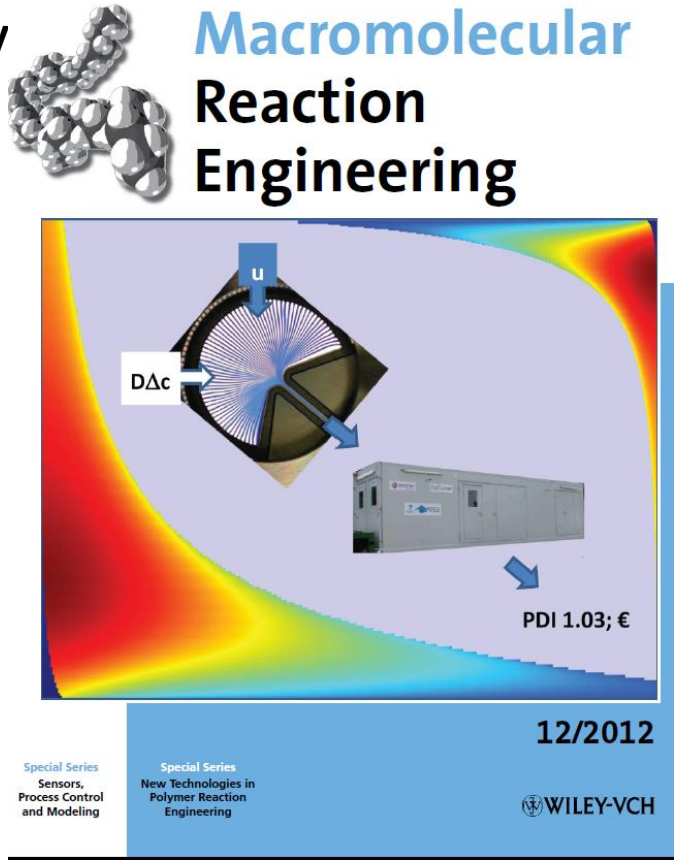
Ref.	Setup/mixer	Monomer	Solvent	$V_{M/I}$ (ml min^{-1})	T_R (°C)	M_w (g mol^{-1})	Lowest PDI
[30, 31]	SIMM	Styrene	THF	–	25	11300	1.09
[30, 31]	SIMM+Cap.	Styrene	CHx	–	25	8000	1.08
[32]	Caterpillar	Styrene	CHx	1.99/0.026	25	6000	1.07
[33]	T-junc.+Cap.	Styrene	THF	6.0/2.0	-28	3600	1.07
[33]	T-junc.+Cap.	Styrene	THF	6.0/2.0	0	3200	1.08
[34]	T-junc.+Cap.	Styrene	CHx	0.017/0.017	35	5300	1.09
[34]	T-junc.+Cap.	Isoprene	CHx	0.008/0.008	30	8300	1.10
This Work	T-junc.+Cap.	Butadiene	CHx/THF	1.33/0.33	45	9500	1.04

S. Schulze, B. Cortese, Hessel, J. Lang, E. Klemm et al. *Green Process. Synth.* **2**, 5 (2013) 381-395.

ANIONIC POLYMERIZATION – 'ANTI-TRANSPORT INTENSIFICATION'

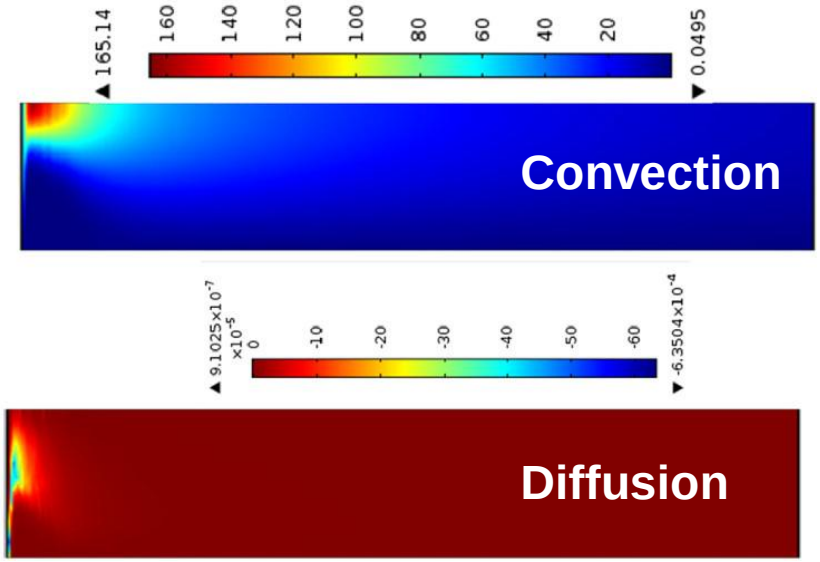




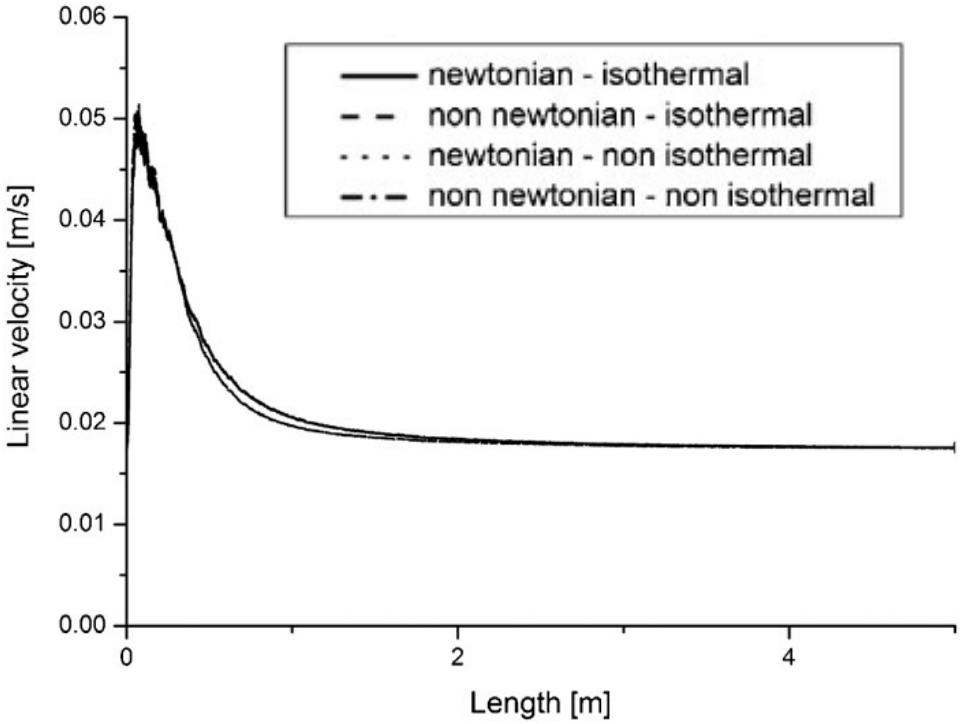


B. Cortese, S. Schulz, E. Klemm, V. Hessel et al. *Macrom. React. Eng.* **6**,*12* (2012) 507–515;
S. Schulze, B. Cortese, V. Hessel, J. Lang, E. Klemm et al. *Green Process. Synth.* **2**, 5 (2013) 381-395.

SIMULATION STUDY OD SEGREGATED BEHAVIOUR IN ANIONIC POLYMERIZATION

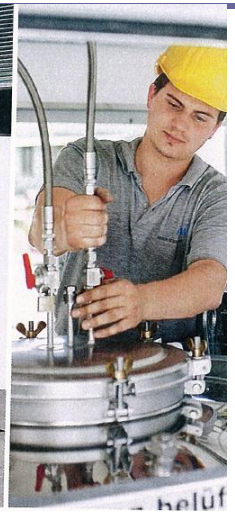


Are complex models (non-Newtonian; non-isothermal) needed?



B. Cortese, S. Schulze, M. de Croon, V. Hessel, E. Klemm *Macromol. Symp.* **333** (2013) 55-61.

TOWARDS INDUSTRIAL PRODUCTION



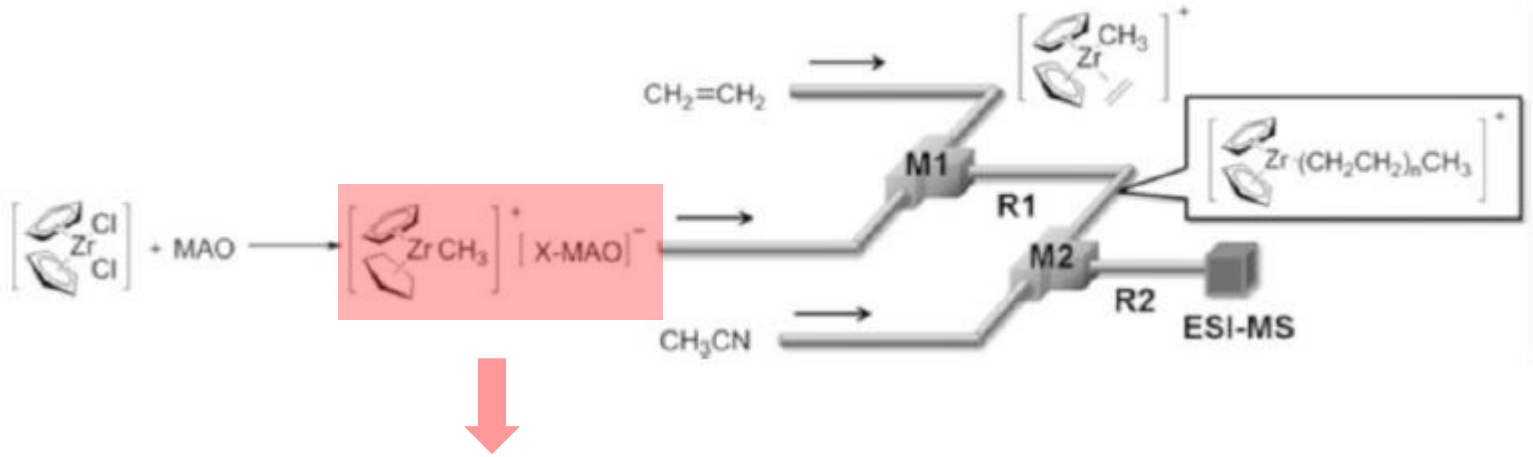
EVONIK INDUSTRIES

Universität Stuttgart

TU/e Technische Universiteit Eindhoven University of Technology

MECHANISTIC UNDERSTANDING AS GOAL - ZIEGLER-NATTA POLYMERIZATION

Microreactor system coupled directly to the electrospray ionization (ESI) source of a quadrupole time-of-flight (Q-TOF) mass spectrometer



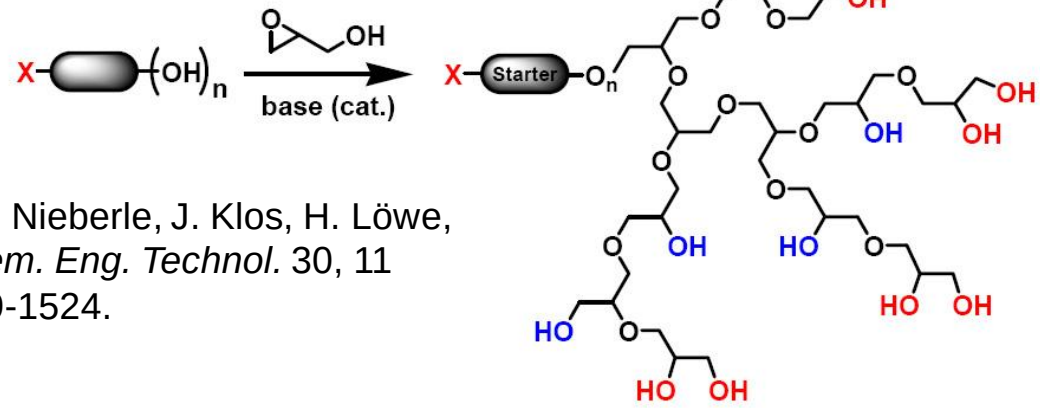
Transient cationic species detected

L.S. Santos, J.O. Metzger *Angew Chem Int Ed* **45** (2006) 977-981.

HYPERBRANCHED POLYGLYCEROLS BY RING-OPENING MULTIBRANCHING POLYMERIZATION

Slow addition of glycidol monomer

A. Sunder, R. Hanselmann, H. Frey, R. Mülhaupt, *Macromolecules* 32 (1999) 4240.



D. Wilms, J. Nieberle, J. Klos, H. Löwe, H. Frey *Chem. Eng. Technol.* 30, 11 (2007) 1519-1524.

Possible formation of „hot spots“ due to inadequate mixing and heat transfer

Macro Batch:

- **Time Consuming (24 hours)**
- **Complex assembly**
- **Molecular weights: 500 – 10,000g/mol**
- **Polydispersities 1.5**

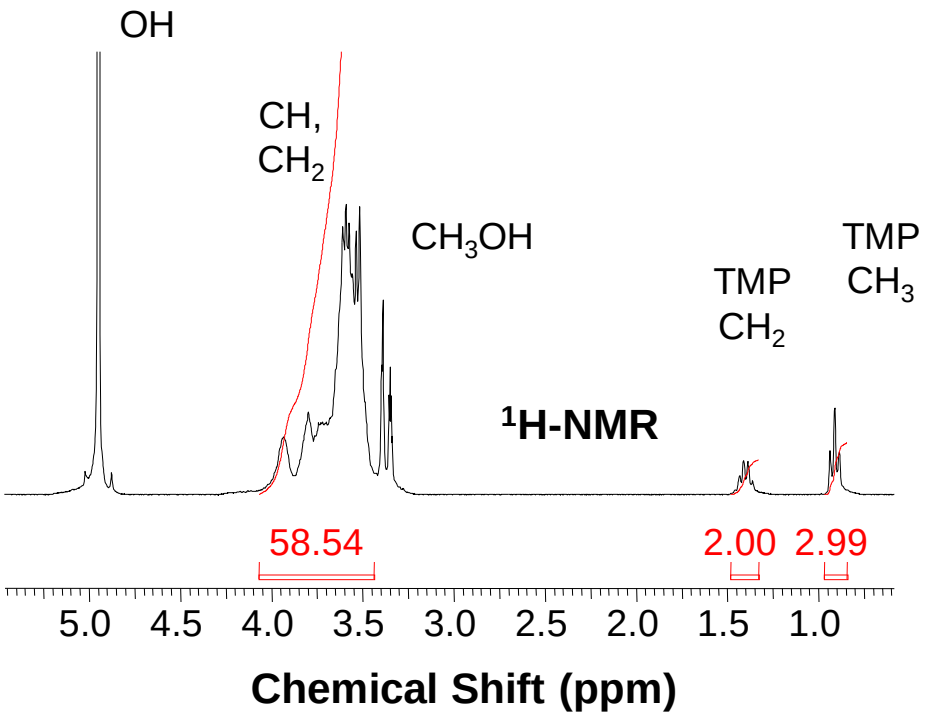
Microreactor:

- **Short Reaction Times (10-30 min)**
- **Easy to scale up**
- **Molecular weights: 500 – 700 g/mol**
- **Polydispersities 1.4 – 1.7**

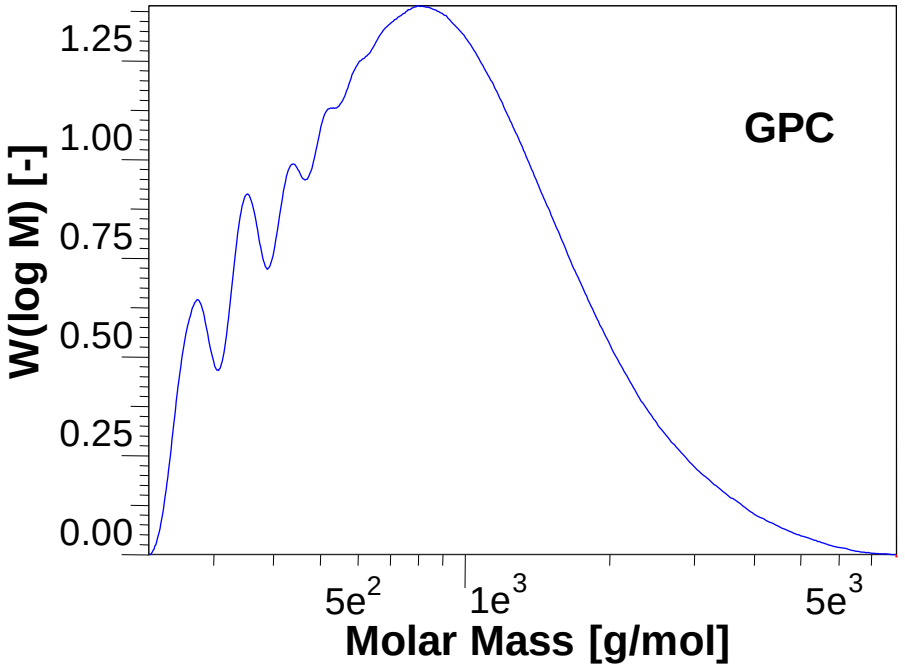
CHARACTERIZATION OF THE CONTINUOUSLY PRODUCED HYPERBRANCHED POLYGLYCEROLS

Residence time: 5 - 15 min *(reaction time conventional synthesis: Several hours - days)*

Flow Rate Initiator [mmol/min]	Flow Rate Monomer [mmol/min]	Ratio Initiator : Monomer	M_w (NMR)	M_n (GPC) PS Standards	M_n (GPC) PEG Standards	M_w / M_n
3.44	17	1 : 4.95	910	690	620	1.5

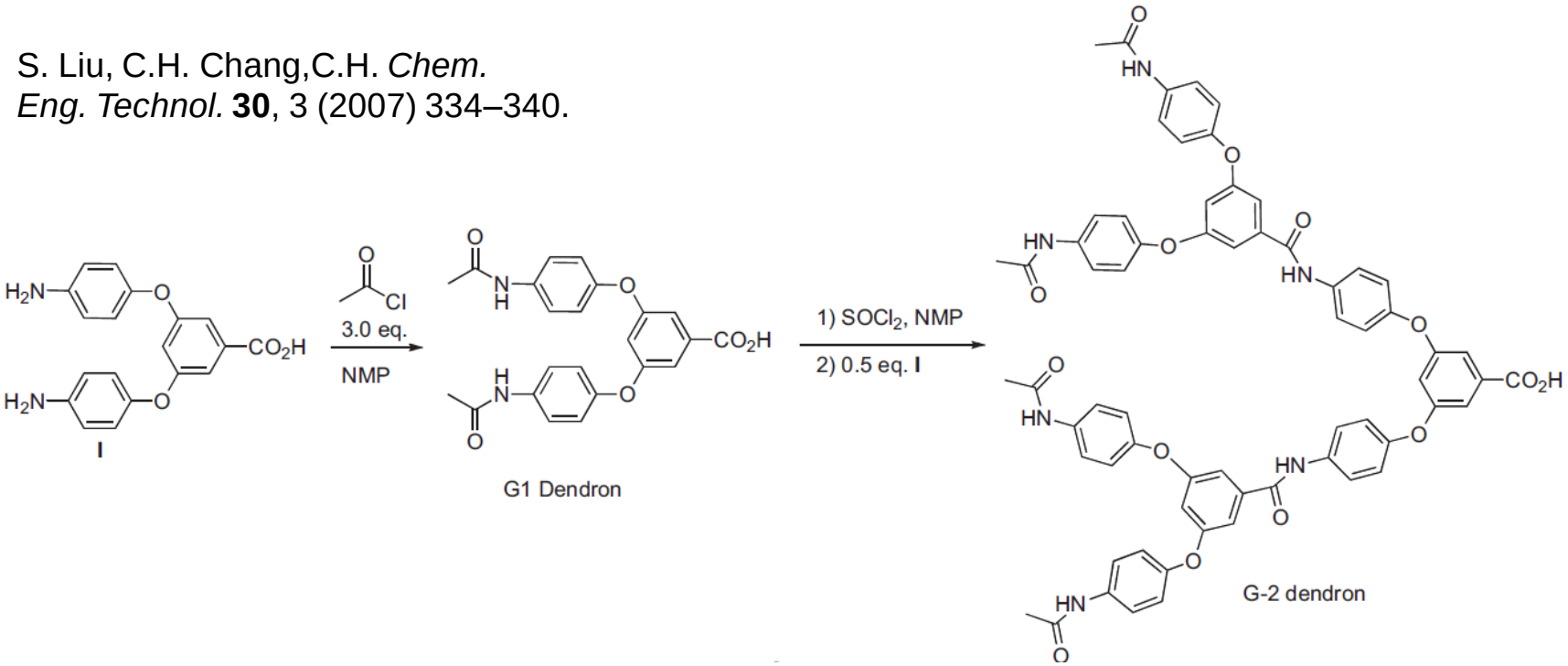


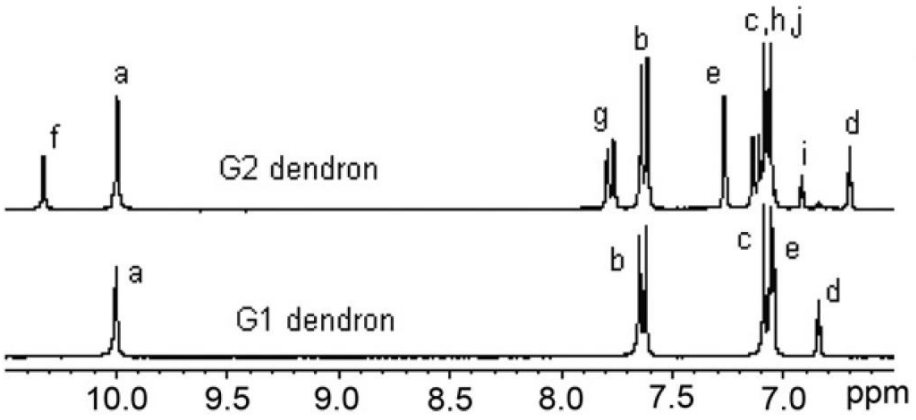
D. Wilms, J. Nieberle, J. Klos, H. Löwe, H. Frey
Chem. Eng. Technol. 30, 11 (2007) 1519-1524.

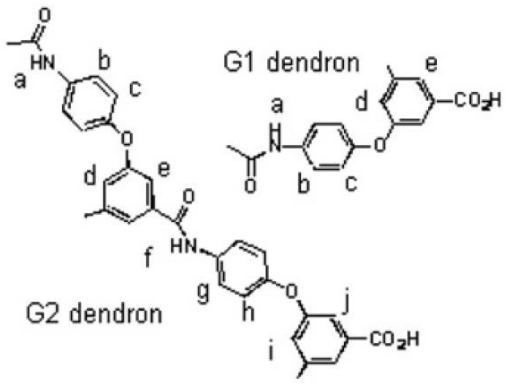


SELECTIVITY AS GOAL - DENDRIMERS

S. Liu, C.H. Chang,C.H. *Chem. Eng. Technol.* **30**, 3 (2007) 334–340.

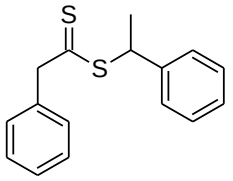




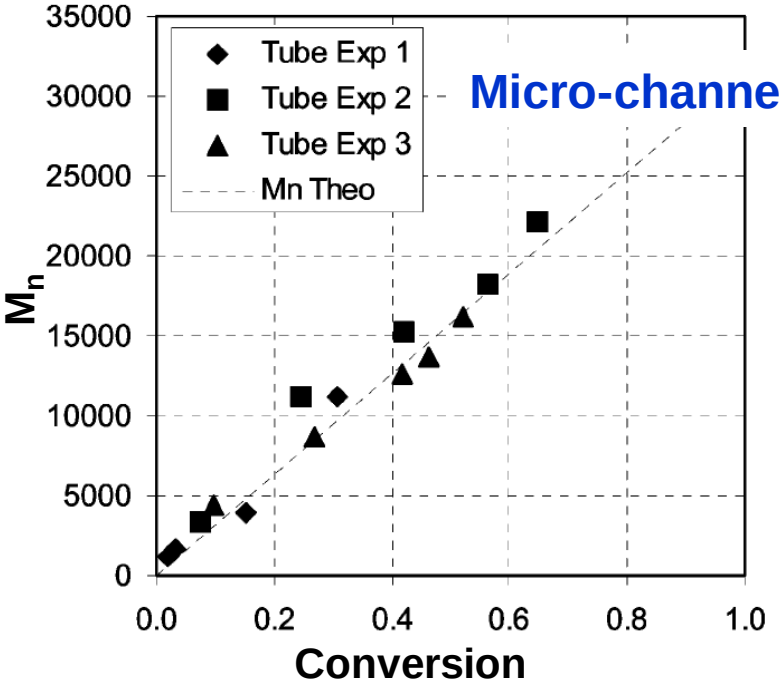


MINIEMULSION POLYMERIZATION - REVERSIBLE ADDITION-FRAGMENTATION CHAIN-TRANSFER (RAFT)

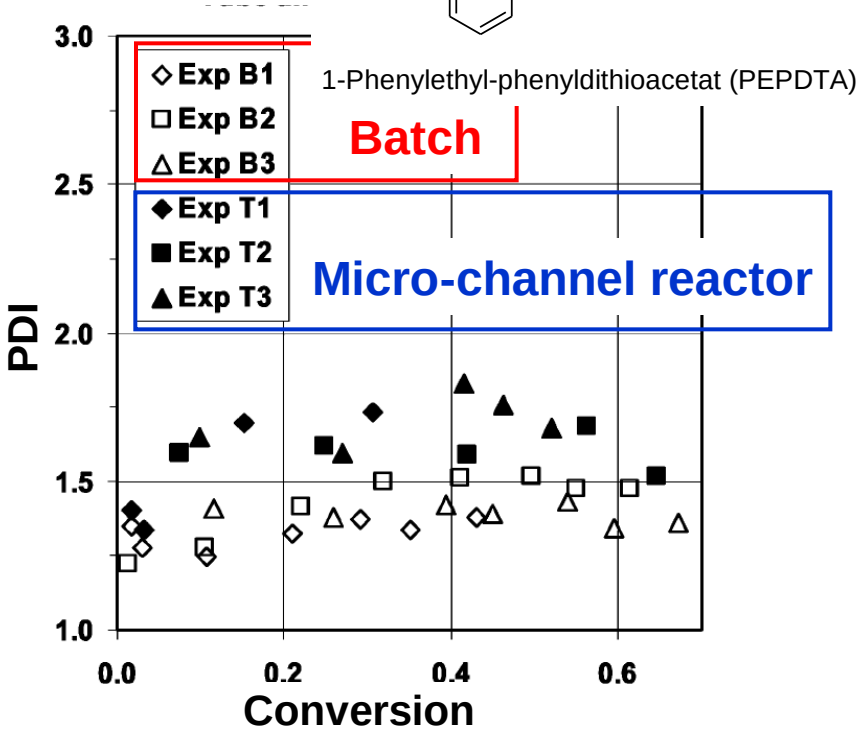
Styrene homopolymerisation: Triton X-405 / SDS + Costabiliser hexadecan + potassium persulfate + RAFT agent PEPDTA



1-Phenylethyl-phenyldithioacetat (PEPDTA)



Proof of living nature



Higher PDI for the microtube reactor: back-mixing and axial dispersion

- **Excellent stability of emulsions: no latex separation and coalescence**

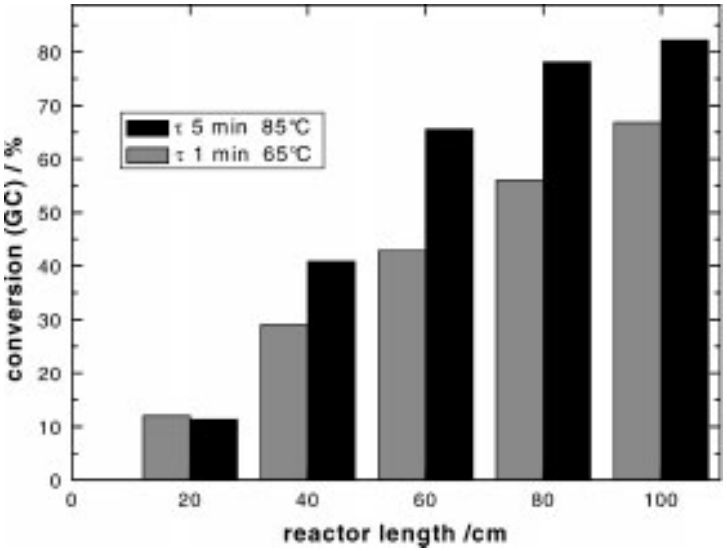
J. P. Russum, C. W. Jones, F. J. Schork *Macromol. Rapid Commun.* **25** (2004) 1064-1068.

Technische Universiteit Eindhoven University of Technology

CONTINUOUS EMULSION POLYMERIZATION OF STYRENE

Taylor flow

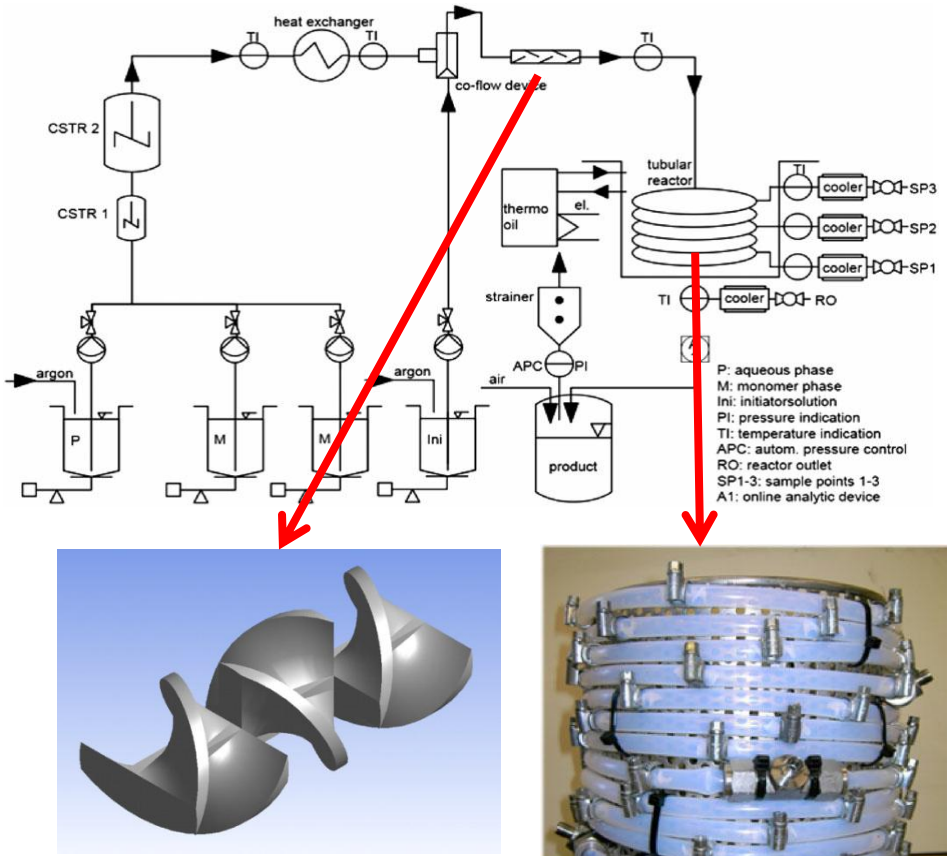
Increase in space-time yield by 200



Dimension	Laboratory scale	Industrial scale
Volume [l]	0.673	100.2
Length [mm]	1107	5867
Gap length [mm]	5.2	27.56
Length/Gap length	213	213

D. Ruttgers, I. Negoita, W. Pauer, H.-U. Moritz *Macromol. Symp.* **259** (2007) 26-31.

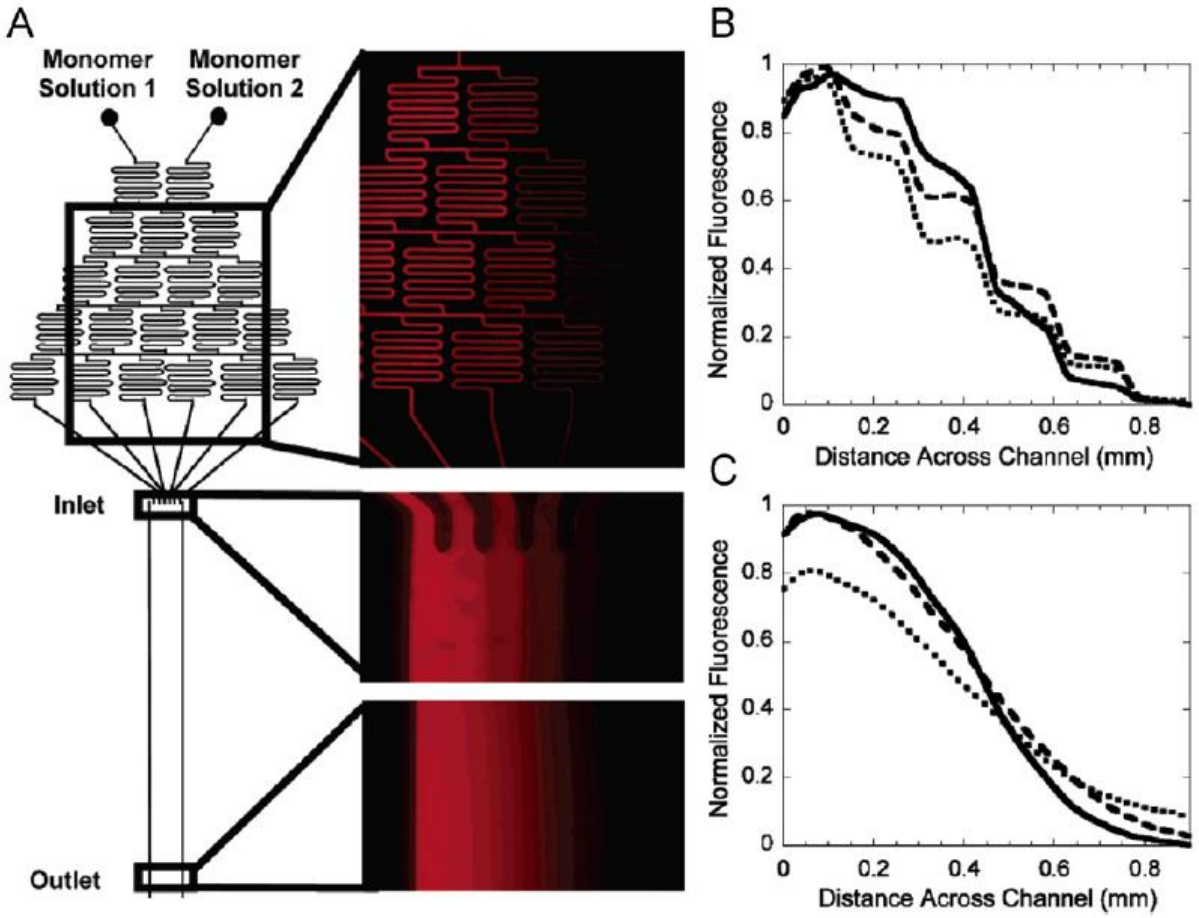
Dean vortices in smart-scale reactors



F.G. Lueth, W. Pauer, H.-U. Moritz *Macromol. Symp.* **333** (2013) 69-79.

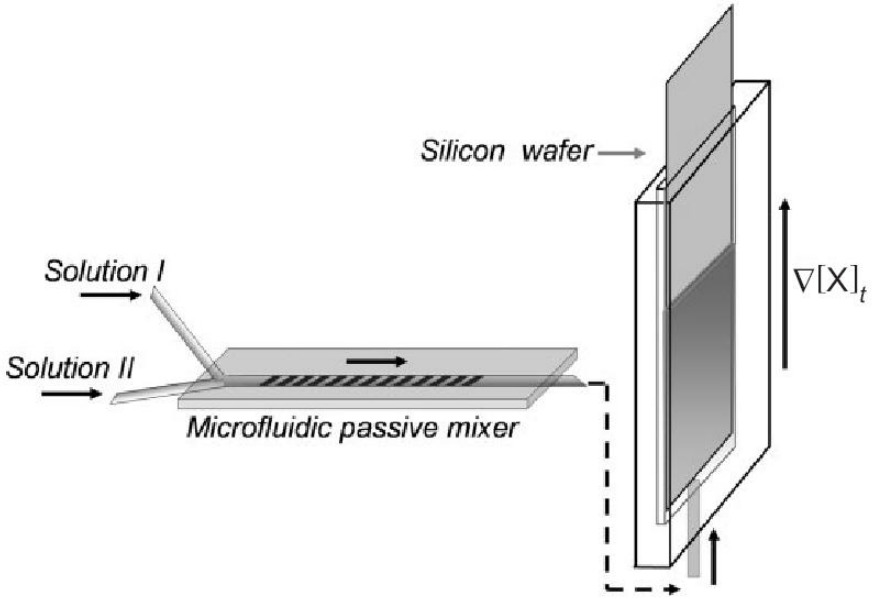
LIBRARIES AS GOAL - HYDROGELS WITH GRADIENT OF TETHERED HUVEC

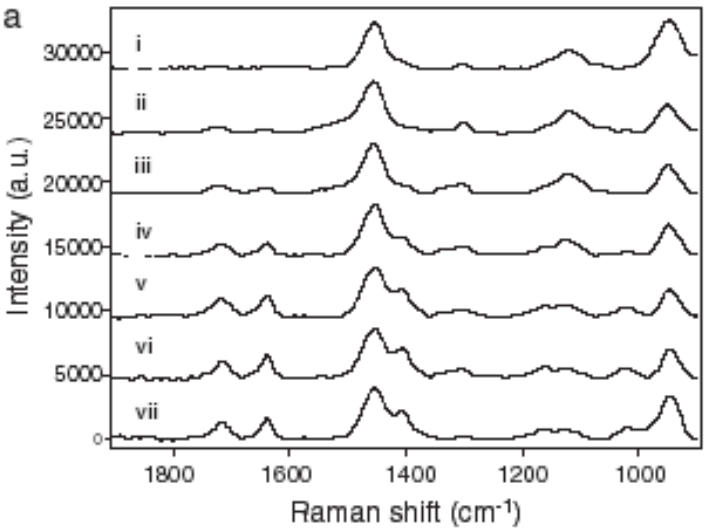
Mixing poly(ethyleneglycol)-4000 diacrylate with acryloyl-poly(ethylene-glycol) linked with adhesive ligands (RGDS) for endothelial cells (HUVEC)

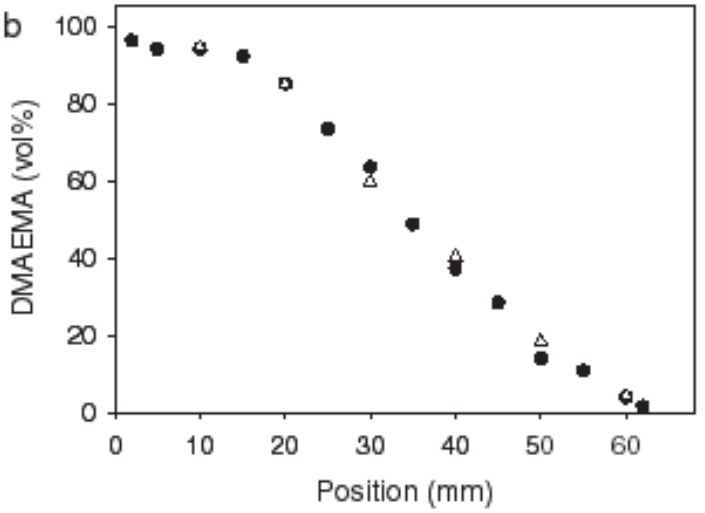


J.A. Burdick, A. Khademhosseini, R. Langer *Langmuir* **20**,13 (2004) 5153-5156.

STATISTICAL COPOLYMER-BRUSH COMPOSITION GRADIENT BY SURFACE-INITIATED ATOM TRANSFER RADICAL POLYMERIZATION (ATRP)







Water / isopropyl alcohol solutions with isobutyric acid *n*-butyl ester (IABE) and 2-N,N-dimethylamino ethyl methacrylate (DMAEMA) as monomers.

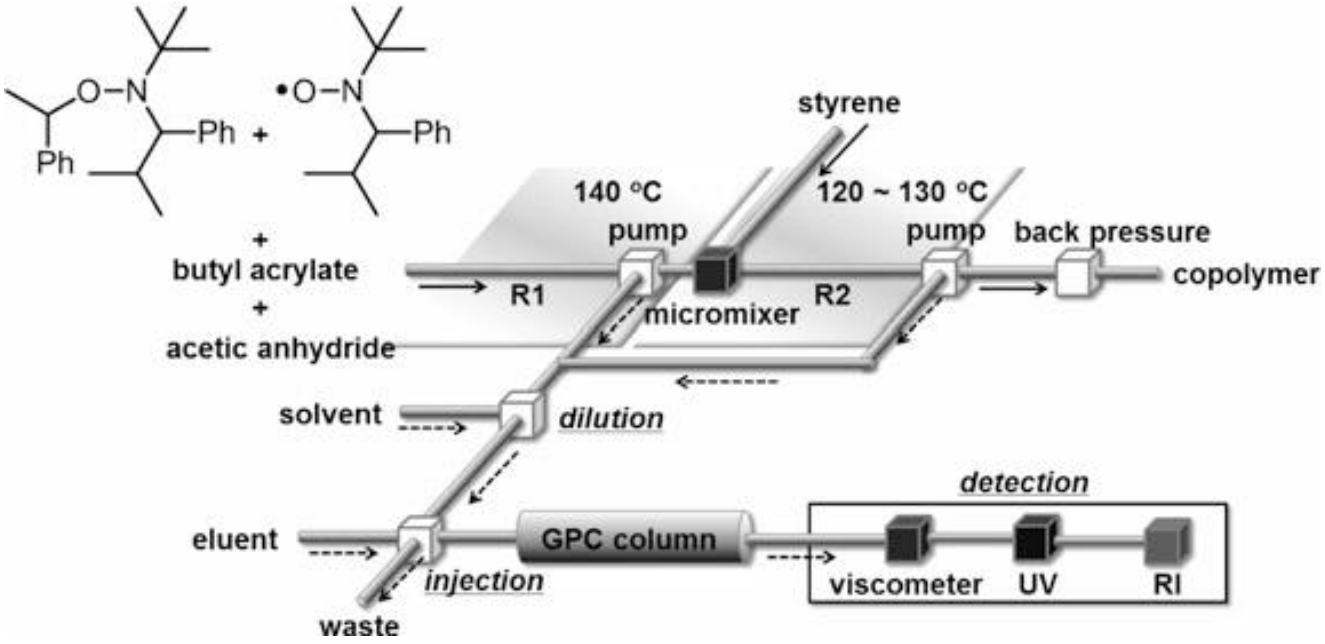
C. Xu, S. E. Barnes, T. Wu, D. A. Fischer, D. M. DeLongchamp, J. D. Batteas, K. L. Beers *Adv. Mater.* **18** (2006) 1427–1430.

Kinetic investigation:

T. Wu, Y. Mei, J. T. Cabral, C. Xu, K. L. Beers *J. Am. Chem. Soc.* **126**, 32 (2004) 9880-9881.

RAFT POLYMERIZATION AND ONLINE GPC

Automatic samplings, dilutions, and injections every 12 min



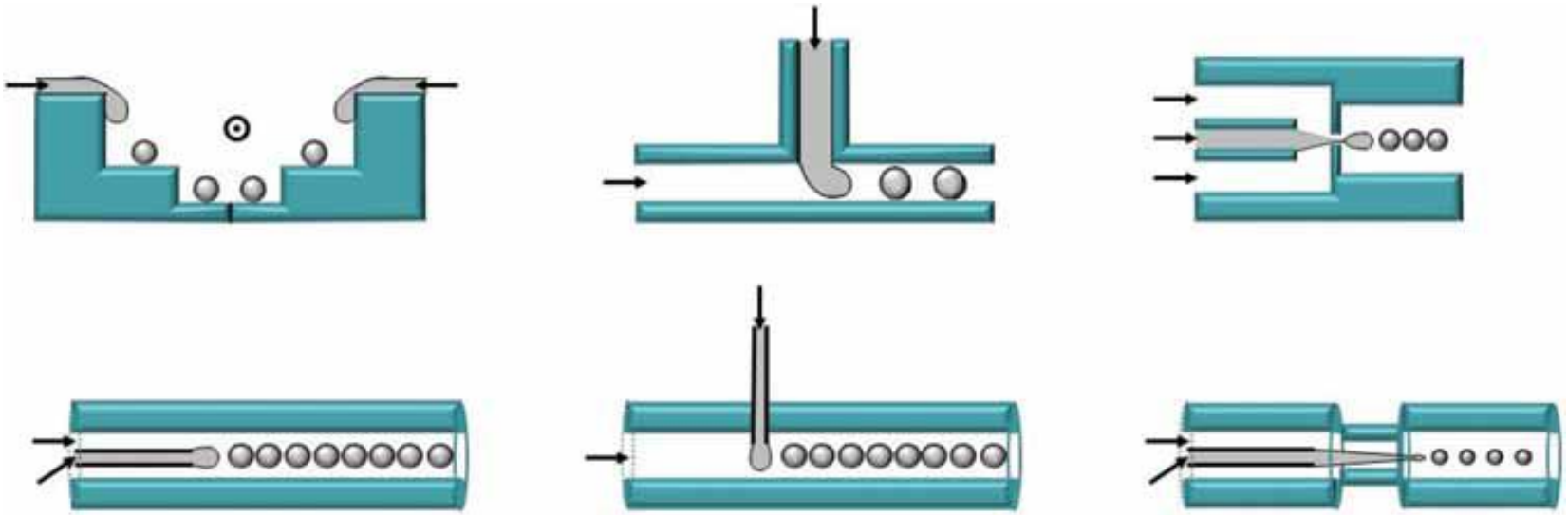
C. Rosenfeld, C. Serra, S. O'Donohue et al. *Macromol React Eng* **1** (2007) 547-552.

Bifurcation analysis and grade transition dynamic optimization for NMP of styrene in a tubular reactor

A.G. Zitlalpopoca-Soriano, E. Vivaldo-Lima, A. Flores-Tlacuahuac *Macromol React Eng* **4** (2010) 599-612.

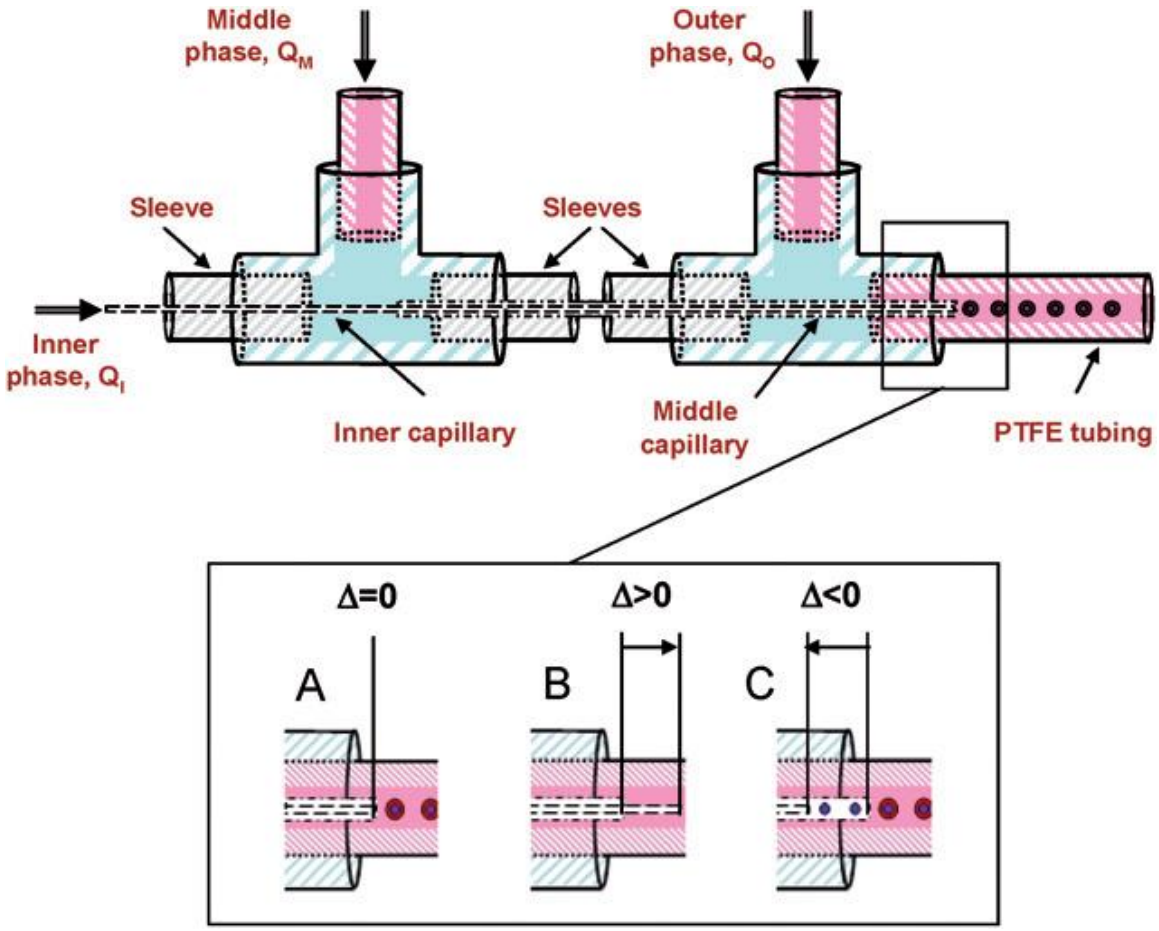
MICROFLUIDIC MEANS OF GENERATING UNIFORM DROPLETS

Terrace cutting and T-type or coaxial flow in jet or stripping mode



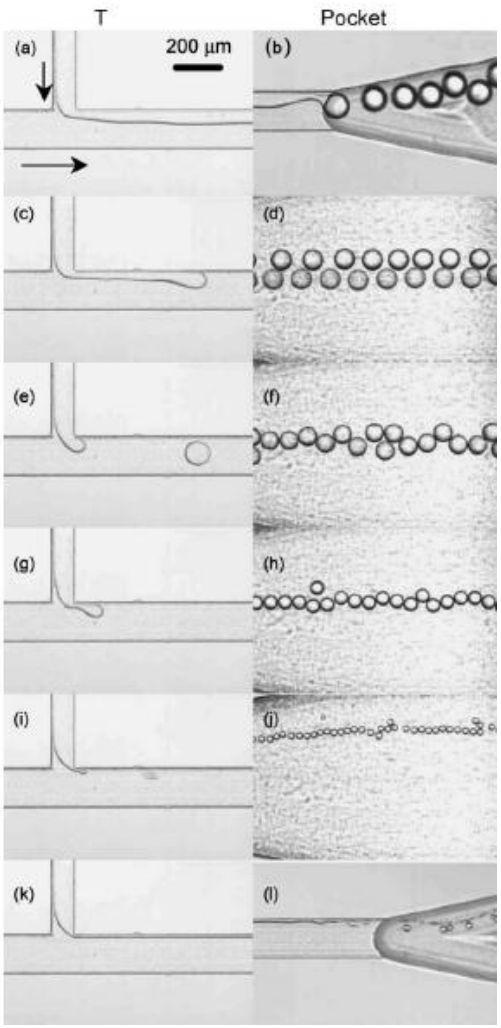
I.U. Khan, C.A. Serra, N. Anton, T. Vandamme *J Control Release* **172**, 3 (2013) 1065-74.

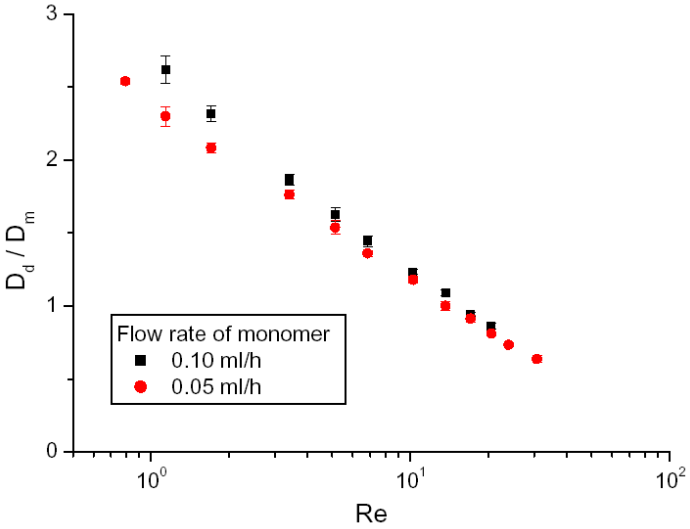
DIFFERENT CO-FLOW INJECTION SCHEMES

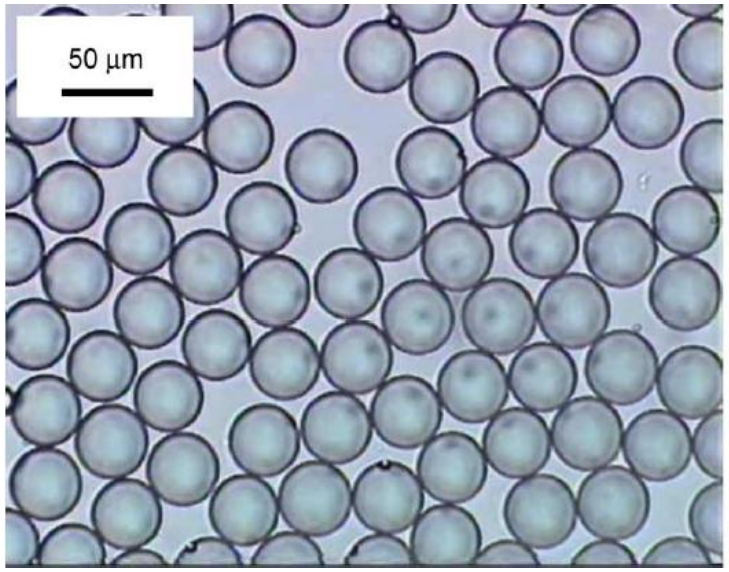


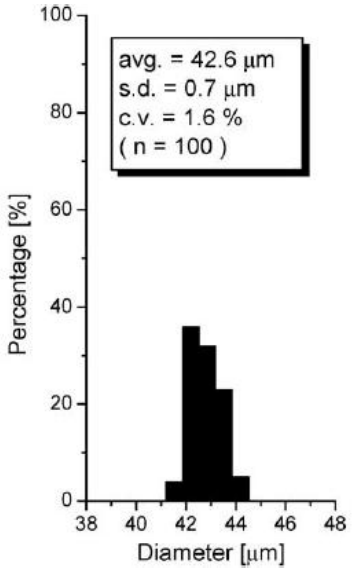
FUNCTIONAL POLYMER BEADS: MONODISPERSE ACRYLIC MICROSPHERES

T. Nisisako, T. Torii, T. Higuchi *Chem. Eng. J.* **101**, 1-3 (2004) 23–29.







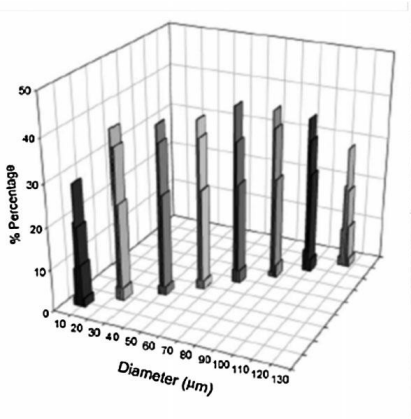


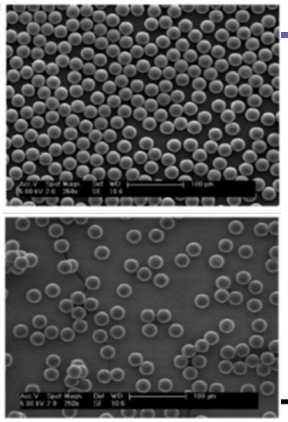
1,6-Hexanediol diacrylate: disperse organic liquid phase.

Polyvinyl alcohol (PVA) aqueous solution (2.0 wt.%): continuous phase liquid.

Initiator of photo-induced polymerization: DAROCUR® 1173, Ciba Specialty Chemicals K.K., Japan)

MONODISPERSE POLYMER PARTICLES

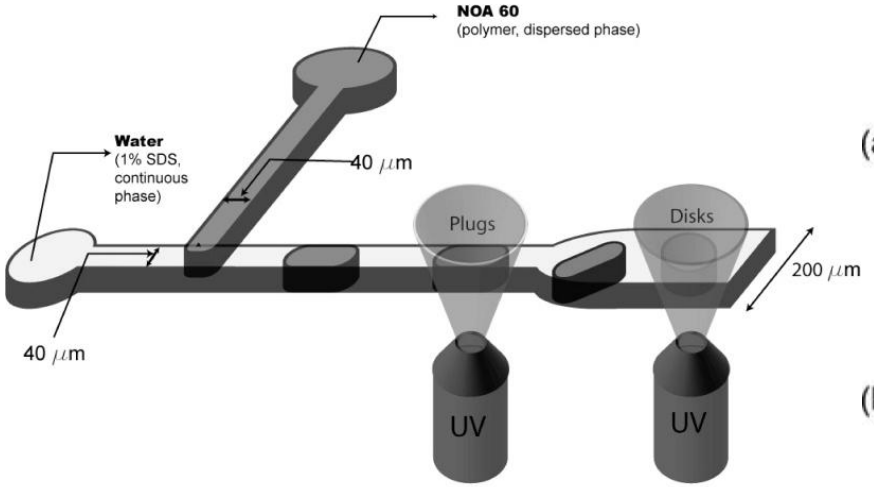


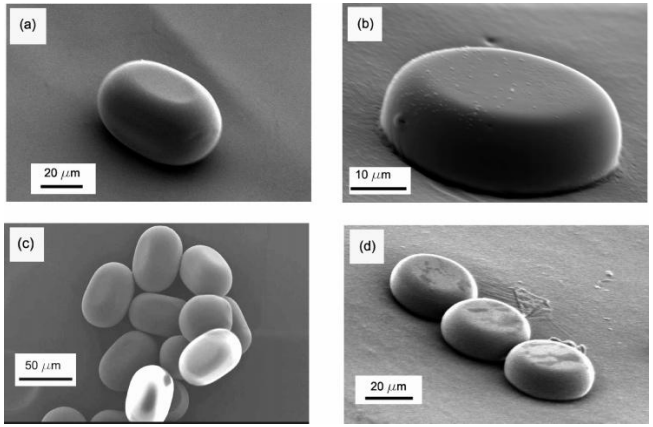


Reference	Year	Polymer	Diameter [μm]	CV
Dendukuri et al.[1]	2005	Not specified	40	–
Seo et al.[3]	2005	TPGDA	<100	0.02
Lewis et al.[8]	2005	TPGDA	120	0.02
Chen et al.[9]	2009	Complex	60	–
Hwang et al.[10]	2008	PEGDA	30	0.013
Okubo et al.[2]	2012	PS	20	–
Okubo et al.[2]		PMMA	120	–
Liu et al.[4]	2011	PBA	100	–
Nie et al.[11]	2005	TPGDA	50	0.025
Choi et al.[12]	2008	PNIPAM	70	1.1
Zourob et al.[13]	2006	Polymethyl acrylates	10	1.8
Nisisako et al.[14]	2004	PVA	50	1

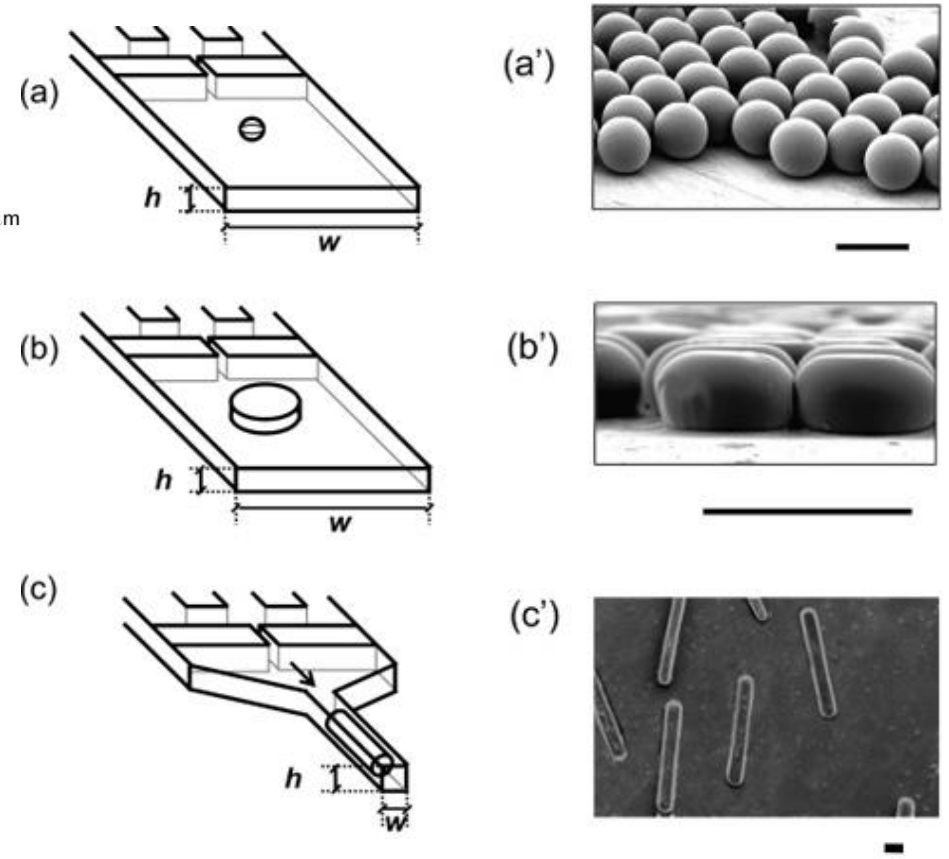
M. Zourob, S. Mohr, A.G. Mayes, A. Macaskill, N. Perez-Moral, P.R. Fielden, N.J. Goddard *Lab Chip* **6** (2006,) 296.

SHAPE PRECISION & FLEXIBILITY





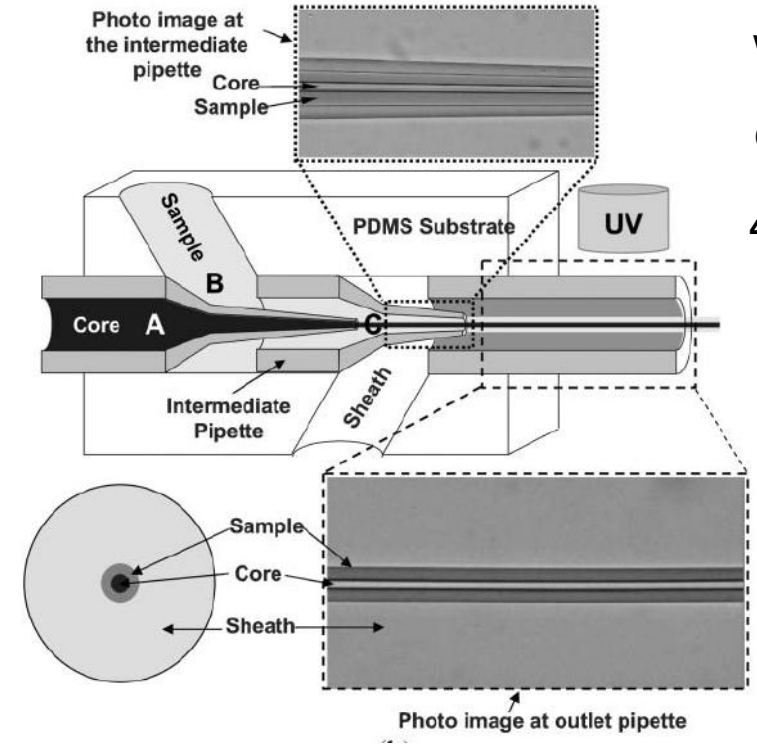
M. Zourob, S. Mohr, A.G. Mayes, A. Macaskill, N. Pérez-Moral, P.R. Fielden, N.J. Goddard *Lab Chip* **6** (2006) 296-301.



M. Seo, Z. Nie, S. Xu, P.C. Lewis, E. Kumacheva, E. *Langmuir* **21** (2005) 4773-4775.

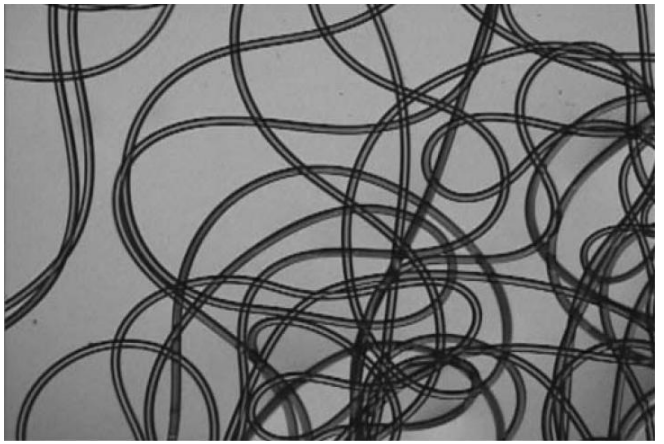
S. Xu, Z. Nie, M. Seo, P. Lewis, E. Kumacheva, H. A. Stone, P. Garstecki, B. Douglas, G.M. Whitesides, *Angew. Chem. Int. Ed.* **44**, 5 (2005) 724-728.

FIBERS AND TUBES

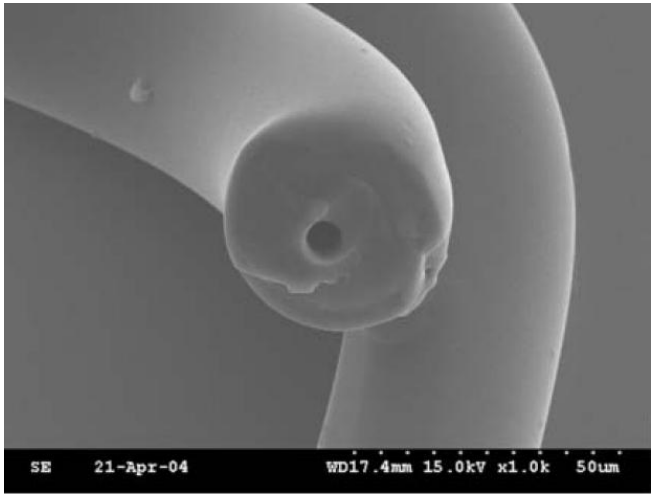


W. Jeong, J. Kim, S. Kim, S. Lee, G. Mensing, D. J. Beebe, *Lab Chip* **4** (2004) 576-580.

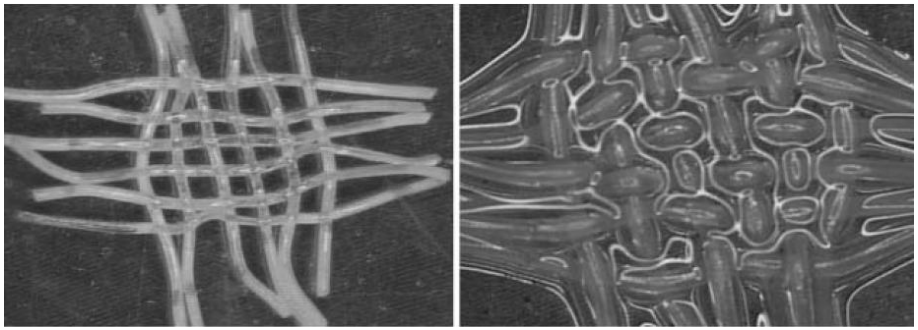
Microfibers



Microtubes

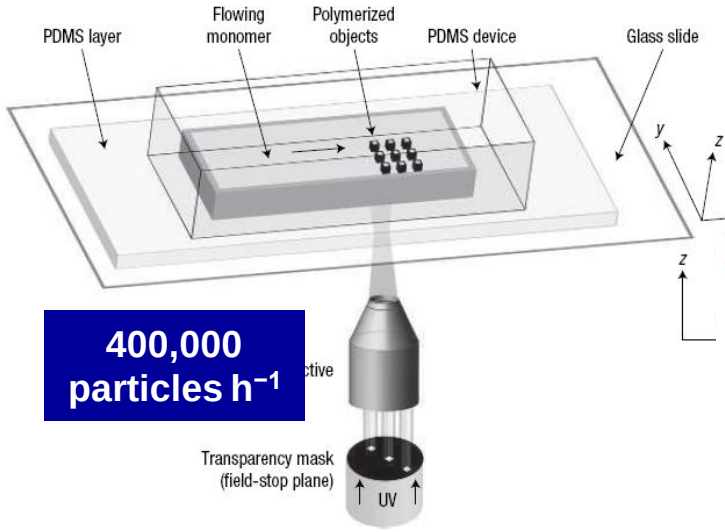


Responsive woven fabric fibers



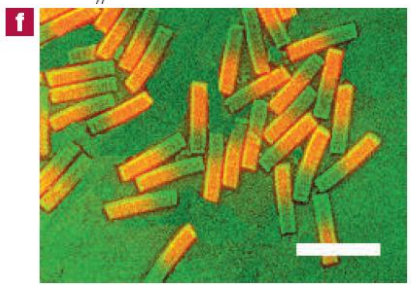
Also shown: biosensing fibers

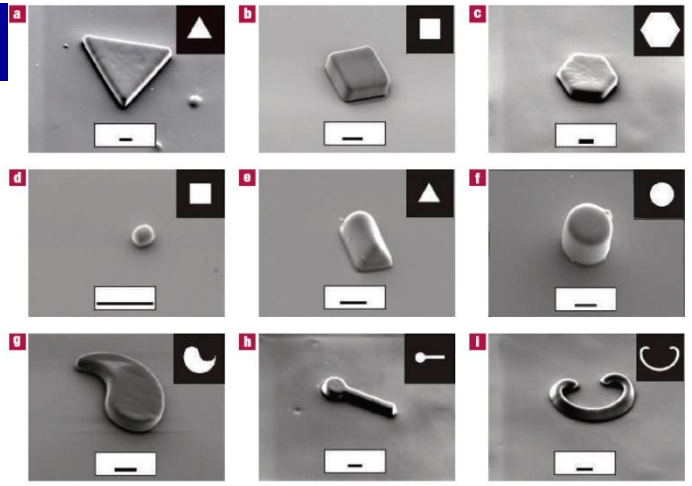
FLOW PROJECTION PHOTOLITHOGRAPHY



400,000 particles h^{-1}

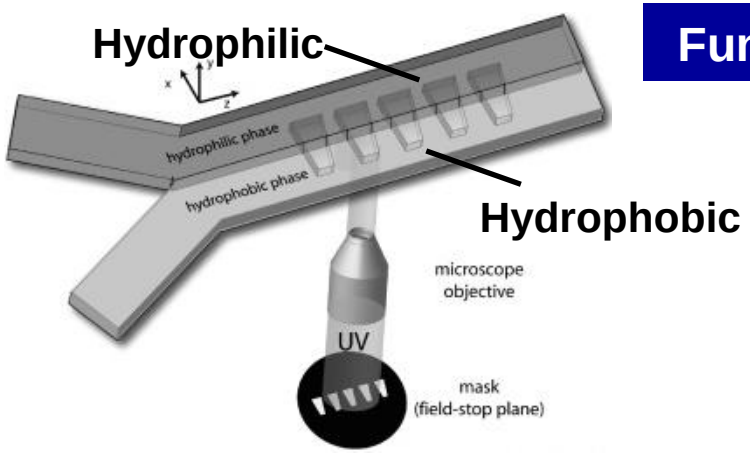
Shape patterning

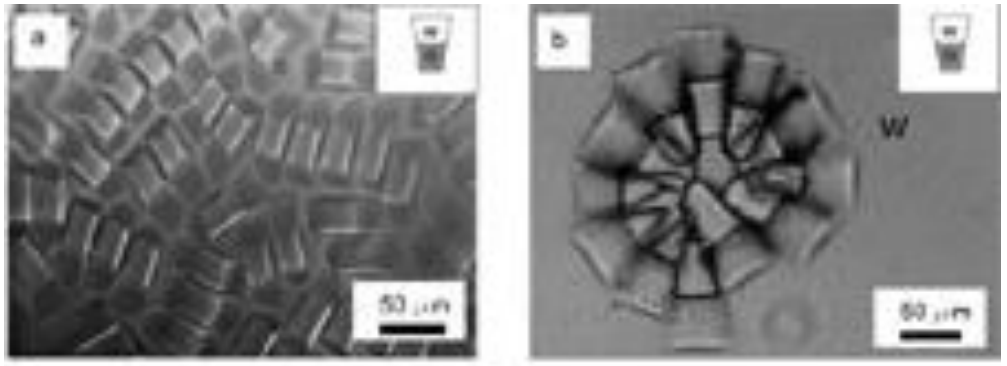




D. Dendukuri, D.C. Pregibon, J. Collins, T.A. Hatton, P.S. Doyle *Nat. Mater.* **5** (2006) 365-369.

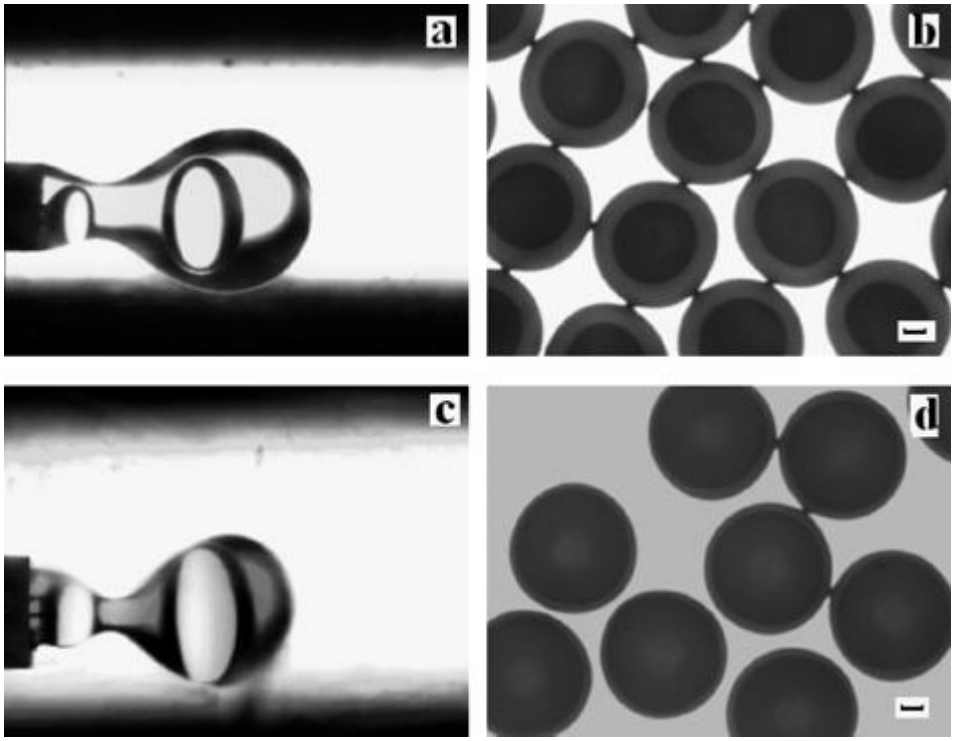
Functional compartments





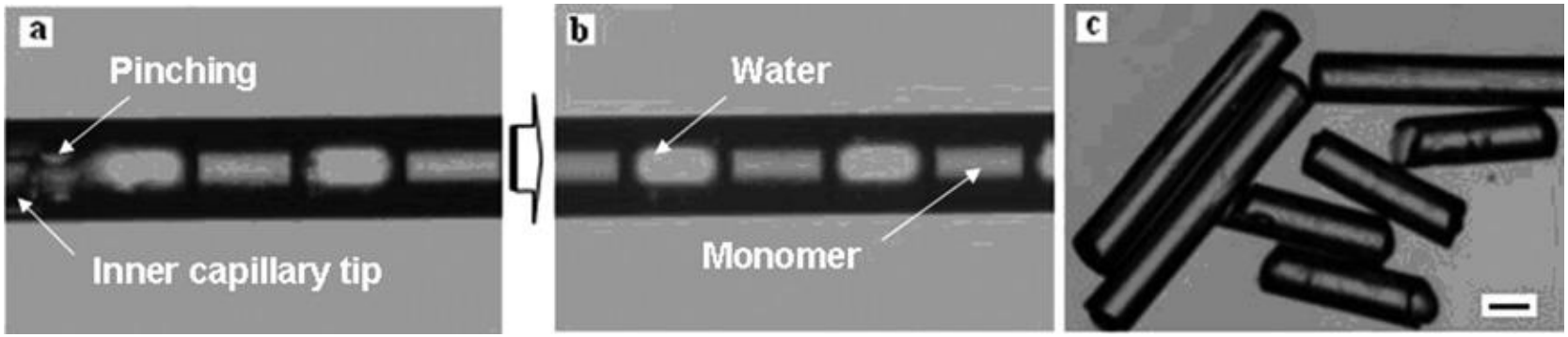
D. Dendukuri, T.A. Hatton, P.S. Doyle *Langmuir* **23** (2007) 4669-4674.

POLYMER CORE-POLYMER SHELL PARTICLES



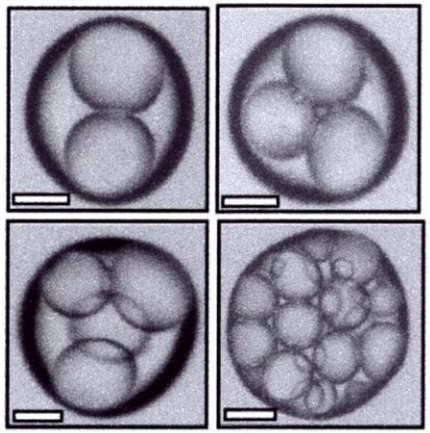
Poly(acrylamide) core-poly(tri(propylene glycol) diacrylate) shell particles

Z. Chang, C.A. Serra, M. Bouquey, L. Prat, G. Hadziioannou *Lab Chip* **9** (2009) 3007–3011

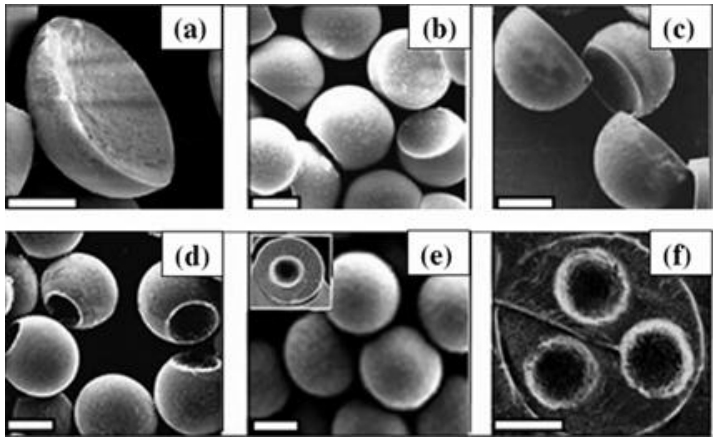


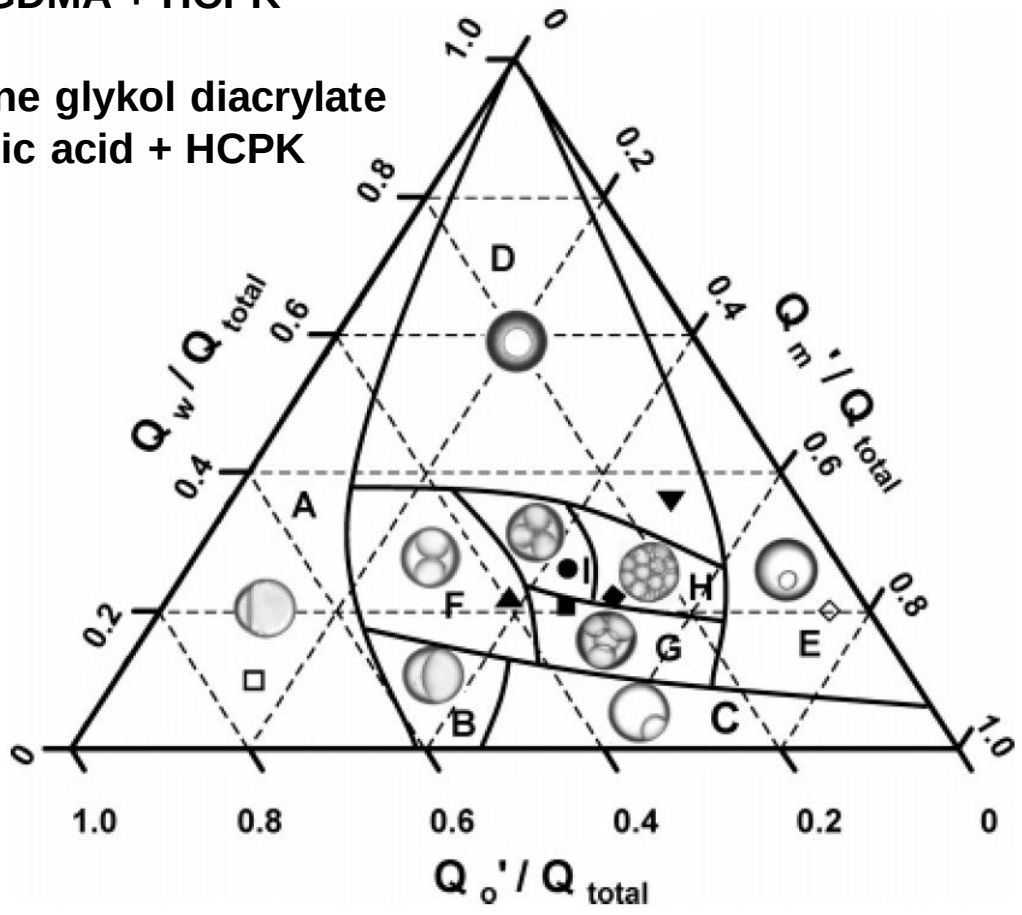
FLOW FOCUSSING OF THREE PHASES – CORE-SHELL PARTICLES

Silicon oil phase with sorbitan monooleate (SPAN 80) + monomer streams TPG-DA or EGDMA + HCPK



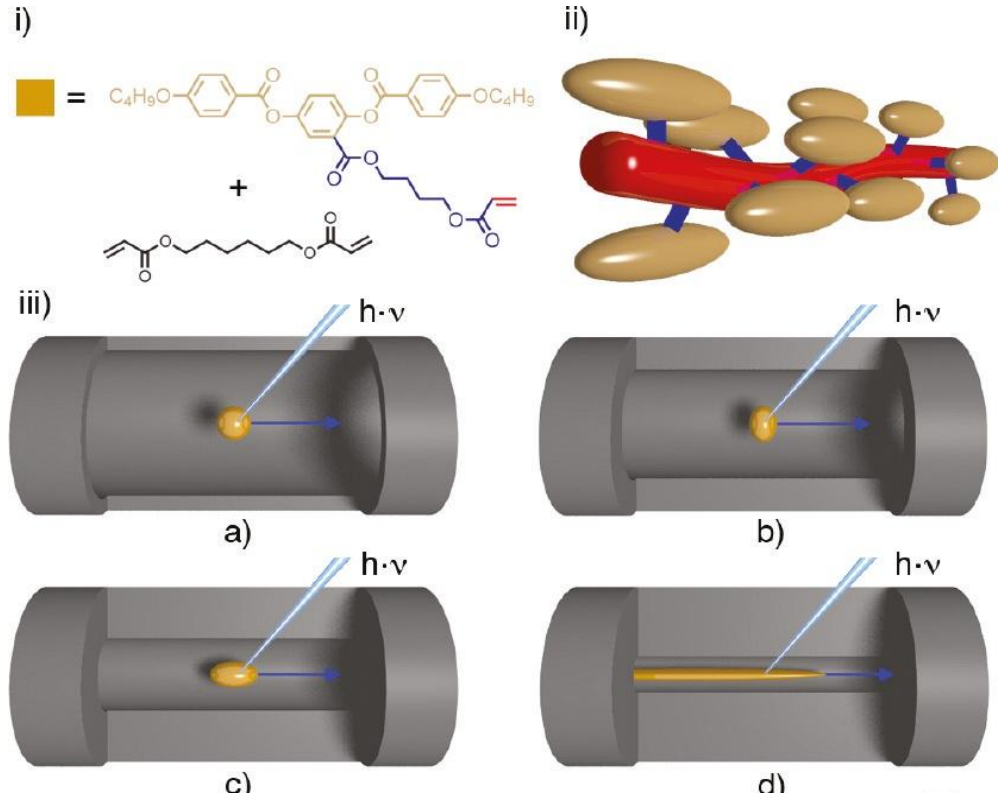
Tripropylene glykol diacrylate + acrylic acid + HCPK





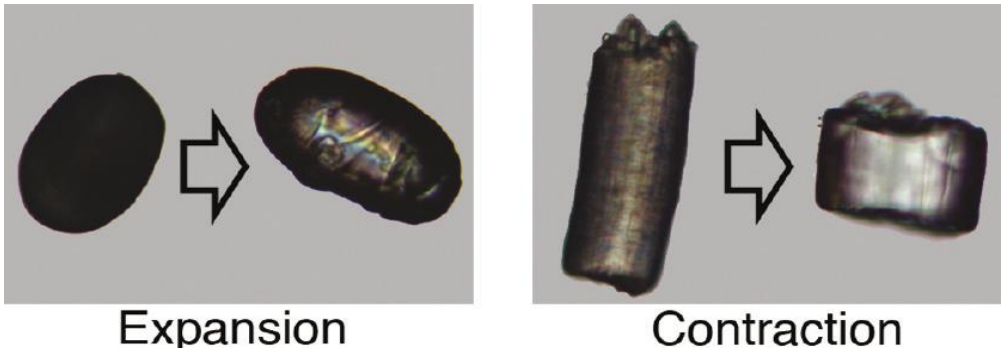
Z. Nie, S. Xu, M. Seo, P. C. Lewis, E. Kumacheva, *J. Am. Chem. Soc.* **127**, 22 (2005) 8058-8063.

HIGHLY SHAPE-ANISOTROPIC PARTICLES



Highly shape-anisotropic particles from liquid crystalline elastomers with defined director field configurations

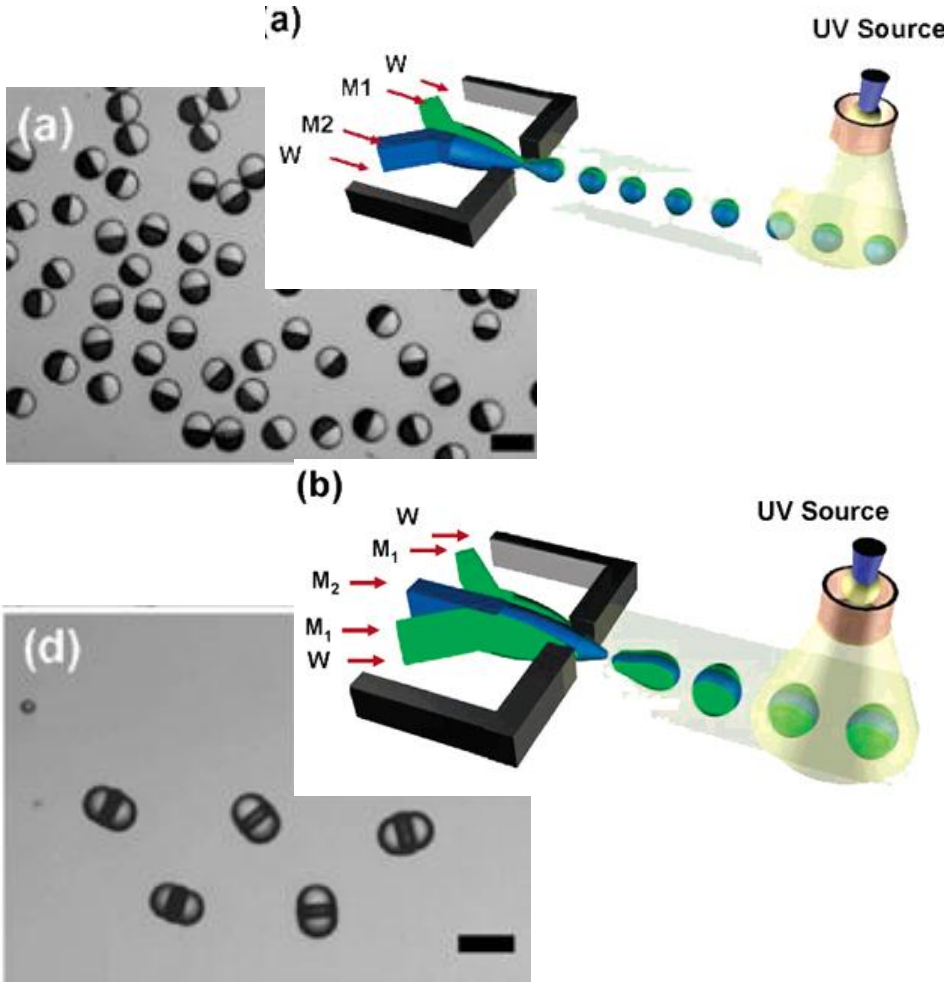
C. Ohm, N. Kapernaum, D. Nonnenmacher, F. Giesselmann, C. Serra, R. Zentel *J. Am. Chem. Soc.* **133** (2011) 5305–5311.



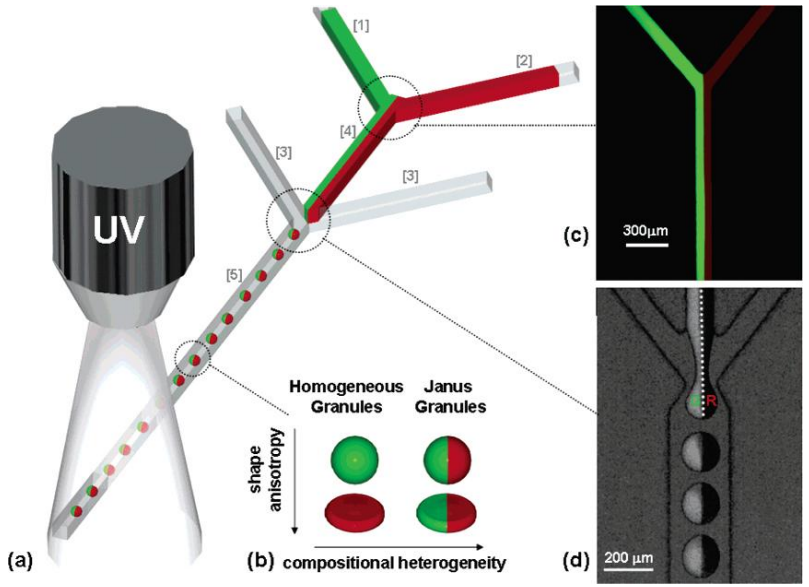
Movement during phase transition from nematic to isotropic phase

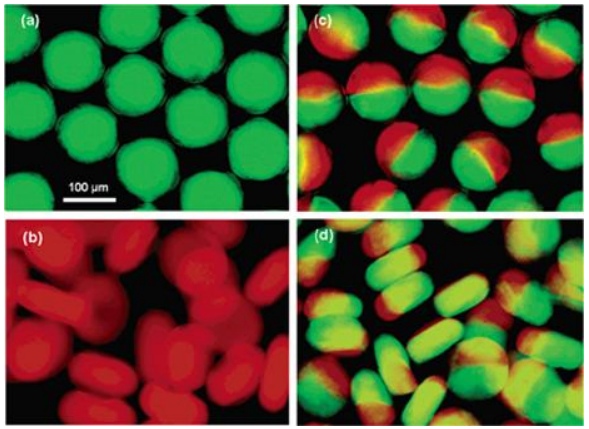
> Application as actuators

JANUS- AND TERNARY POLYMER PARTICLES



Colloid-filled hydrogel granules

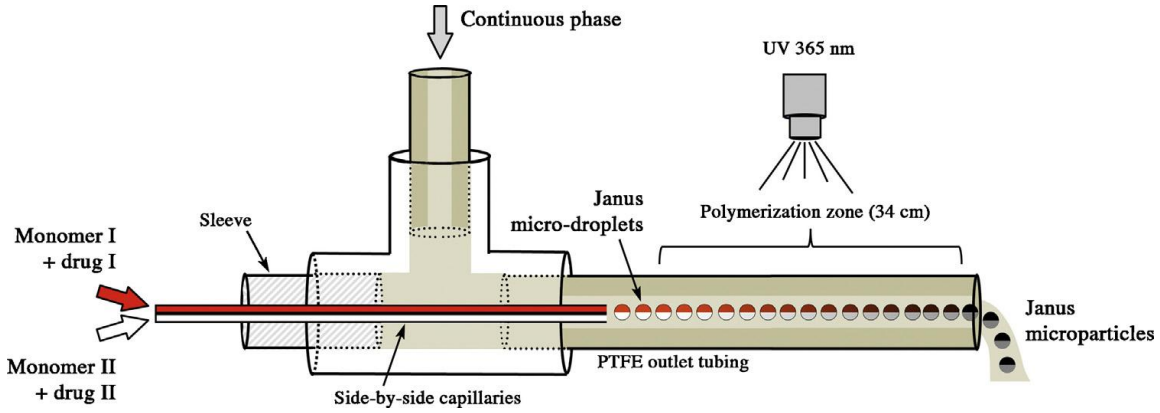


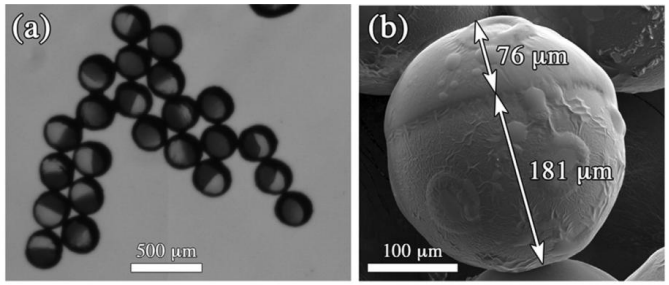


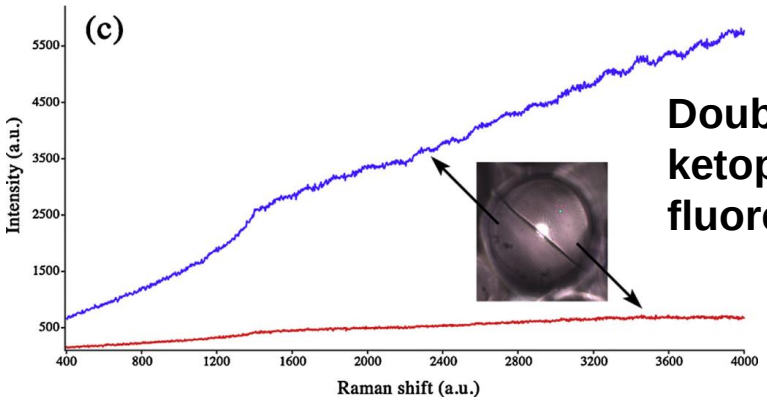
Nie, Z.; Li, W.; Seo, M.; Xu, S.; Kumacheva, E. *J. Am. Chem. Soc.* **128** (2006) 9408 -9412.

Shepherd, R. F.; Conrad, J. C.; Rhodes, S. K.; Link, D. R.; Marquez M.; Weitz, D. A.; Lewis, J. A. *Langmuir* **22** (2006) 8618-8622.

JANUS-SHAPED PARTICLES

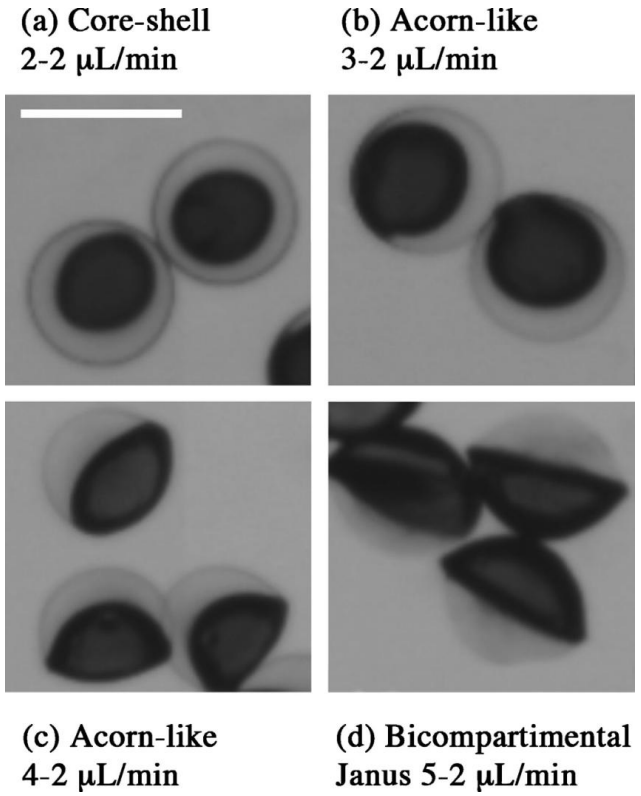






Double encapsulation ketoprofen (red); sodium fluorescein (blue)

Variation of the Janus pattern and outer shape to control drug release

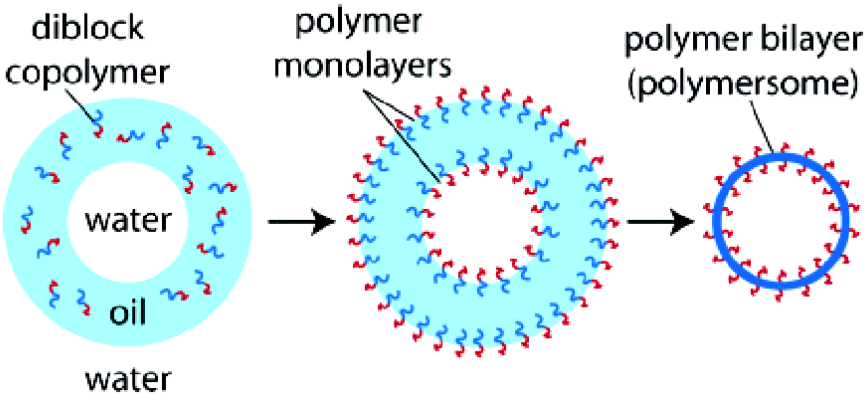


I. U. Khan, C.A. Serra, N. Anton, X. Li, R. Akasov, N. Messaddeq I. Kraus, Th.F. Vandamme *Int. J. Pharmaceutics* **473** (2014) 239-249.

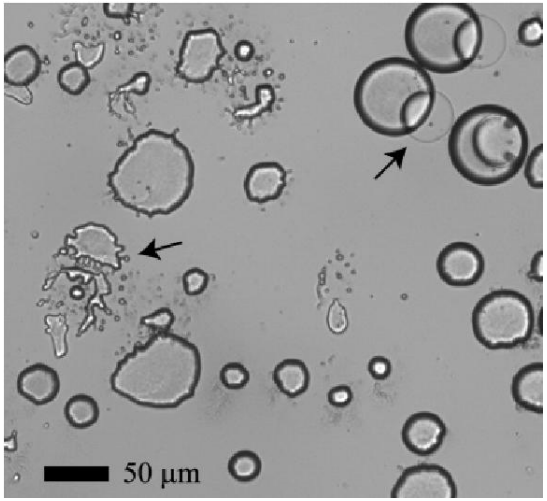
Technische Universiteit Eindhoven University of Technology

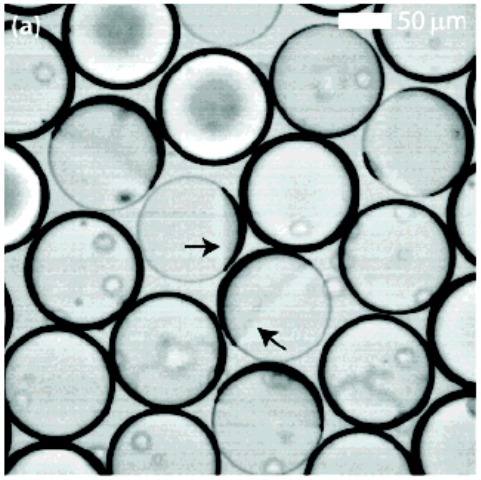
POLYMERSOMES FROM BLOCK-COPOLYMER STABILISED DOUBLE EMULSIONS

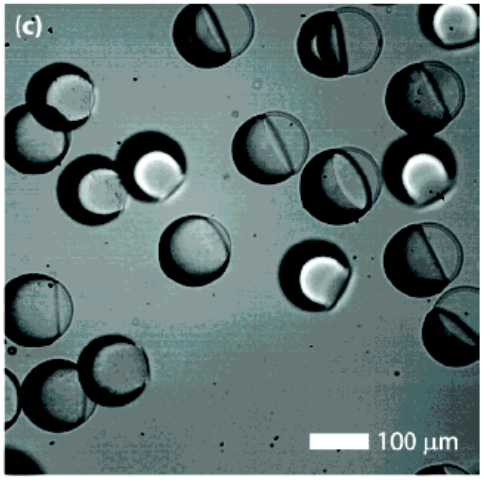
R. C. Hayward, A. S. Utada, N. Dan, D. A. Weitz *Langmuir* **22**, 10 (2006) 4457-4461.

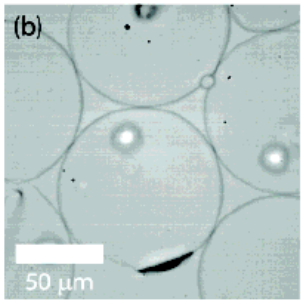


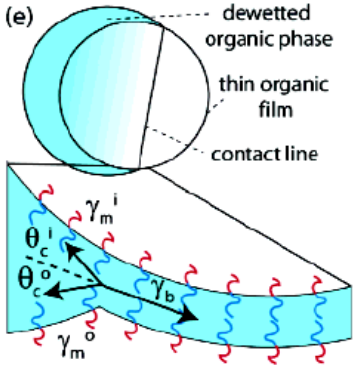
Polystyrene-*block*-poly(ethylene oxide) diblock copolymers

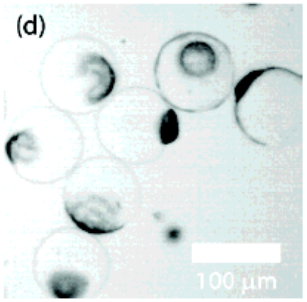






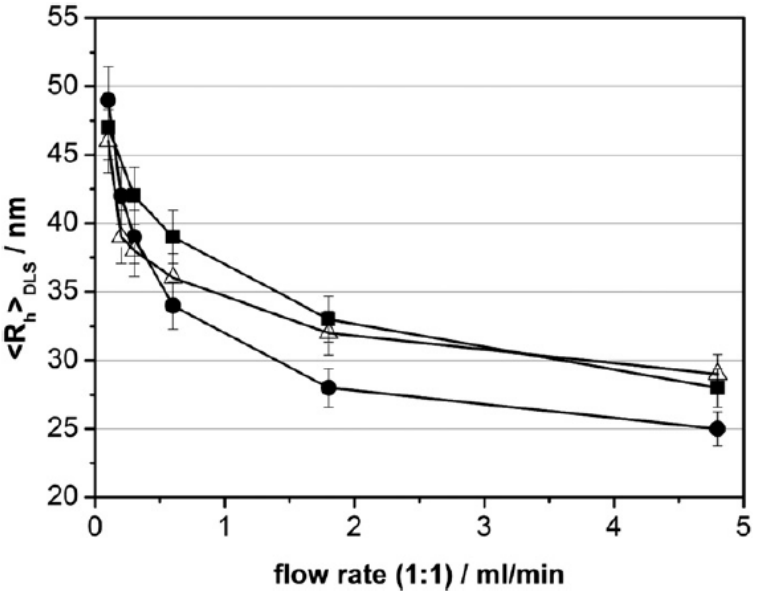






Polymeric vesicles, or polymersomes, are of interest for the encapsulation and delivery of active ingredients.

NARROWLY DISTRIBUTED COPOLYMER VESICLES OF DIFFERENT SHAPE (POLYSOMES)



R. Thiermann, W. Müller, A. Montesinos-Castellanos, D. Metzke, P. Löb, V. Hessel, M. Maskos, *Polymer* **53**, 11 (2011) 2205-2210.

Amphiphilic poly(butadiene)-b-poly(ethylene oxide) (PB130-b-PEO66) block copolymer

Key: controlled mixing process of polymer/THF and water by micromixers for defined self-assembly

DLS: sizes and size distribution

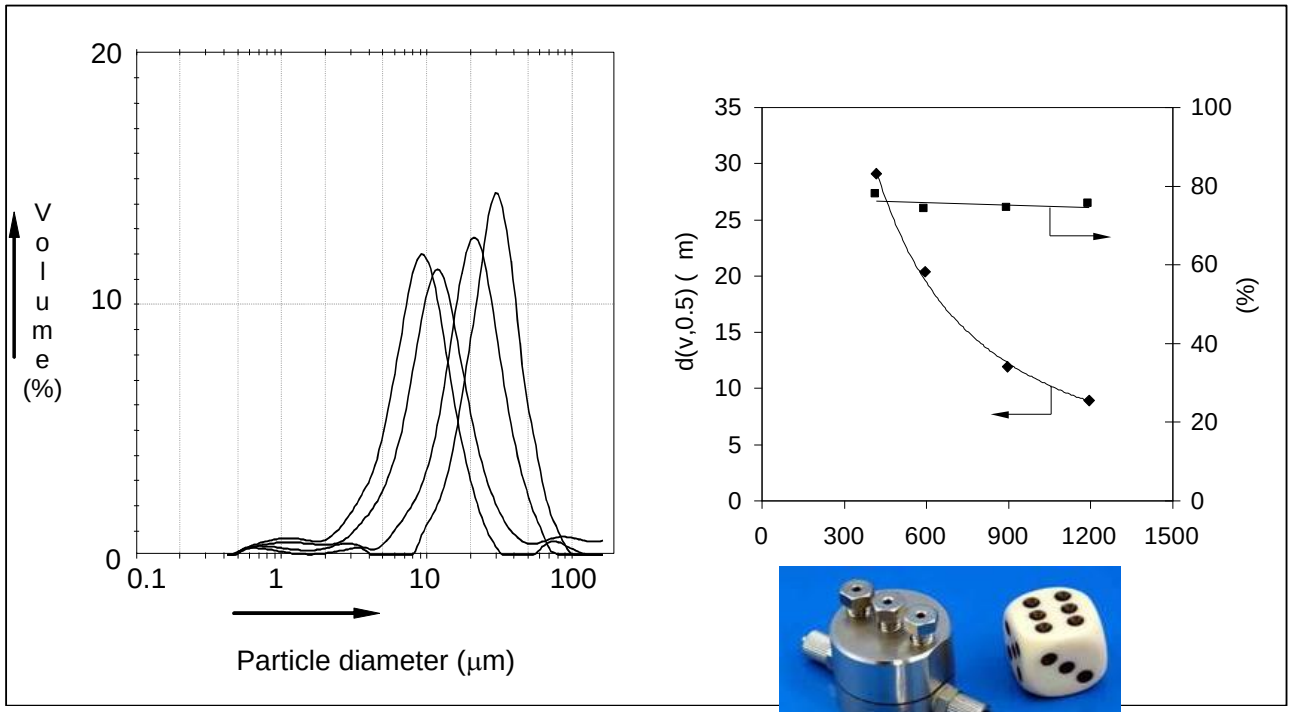
TEM: spherical, cylindrical, worm-like and disk micelles, vesicles

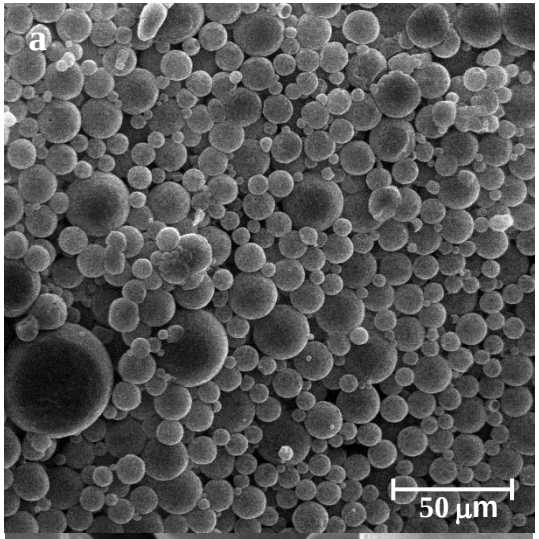
Mixing parameters and characterization results for CPMM samples 1B.

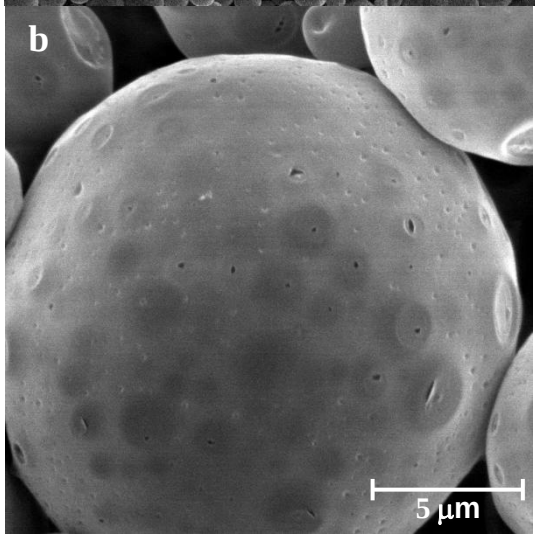
Sample	Mixing parameters			Characterization after THF evaporation			
	Flow rate (ml/min)		Volume ratio	C_P (g/l)	DLS $\langle R_h \rangle$ (nm)	μ2 (90°)	TEM Morphology
	H_2O	P/THF	H_2O:P/THF				
CPB1	10.00	0.24	42:1	1.0	35	0.13	s, c, v
CPB2	2.10	0.05	42:1	1.0	41	0.13	s, v
CPB3	10.00	0.16	63:1	0.7	51	0.13	s, v
CPB4	10.00	0.12	84:1	0.5	56	0.19	s, v
CPB5	10.00	0.10	105:1	0.4	65	0.17	s, v
CPB6	6.30	0.05	126:1	0.4	71	0.18	s, w, d, v
CPB7	7.35	0.05	147:1	0.3	92	0.16	s, w, v

P = PB_{130}-PEO_{66}-B polymer; $C_{P/THF}$ = 42 g/l; C_P = final polymer concentration in water; s = spheres, v = vesicles, c = cylinders, w = worms, d = discs; underlined = dominating morphology; DLS: $\langle R_h \rangle = \langle 1/R_h \rangle_z^{-1}$.

MICROENCAPSULATION BY PRECIPITATION OF DROPLETS FROM IN MICROMIXER





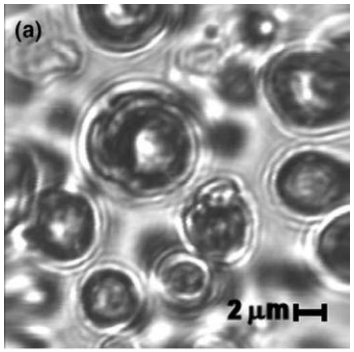


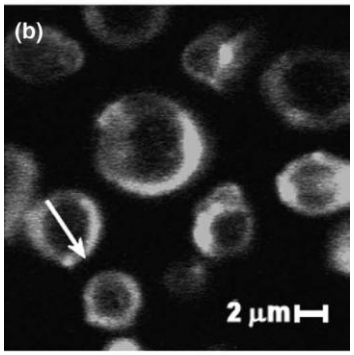
Solution-extraction process

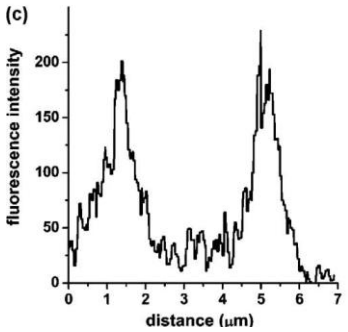
- **Extraction: aq. polyvinylalcohol + polysorbate 20-solution**
- **Micro-capsules: poly-lactide-co-glycolide (resomer, RG502H, RG503, RG503H + RG752)**
- **Model protein: bovin serum albumin (BSA, fraction V),**

S. Freitas, A. Walz, H. P. Merkle, B. Gander, *J. Microencapsulation* **20**, 1 (2003) 67-85.

ANTIGEN DELIVERY TO DENDRITIC CELLS

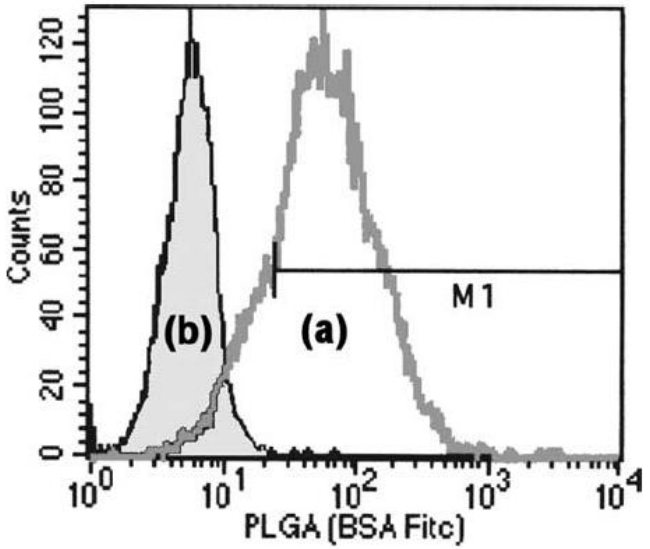




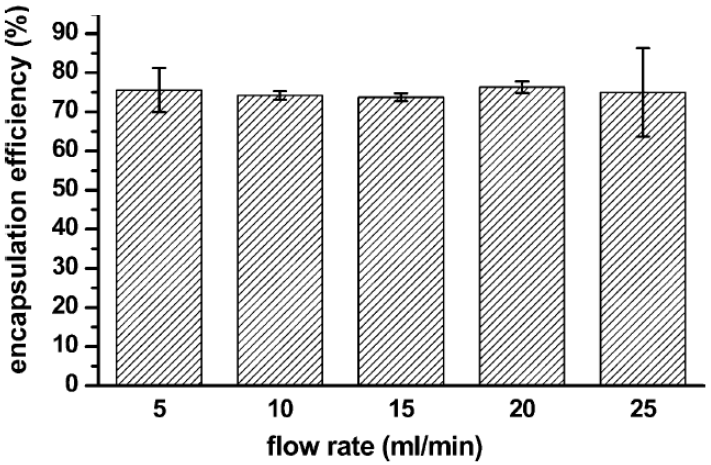


Poly(lactide-co-glycolide) (PLGA) microparticles with bovine serum albumin bearing fluorescein isothiocyanate (FITC–BSA)

Demonstration: deliver a model antigen to human dendritic cells



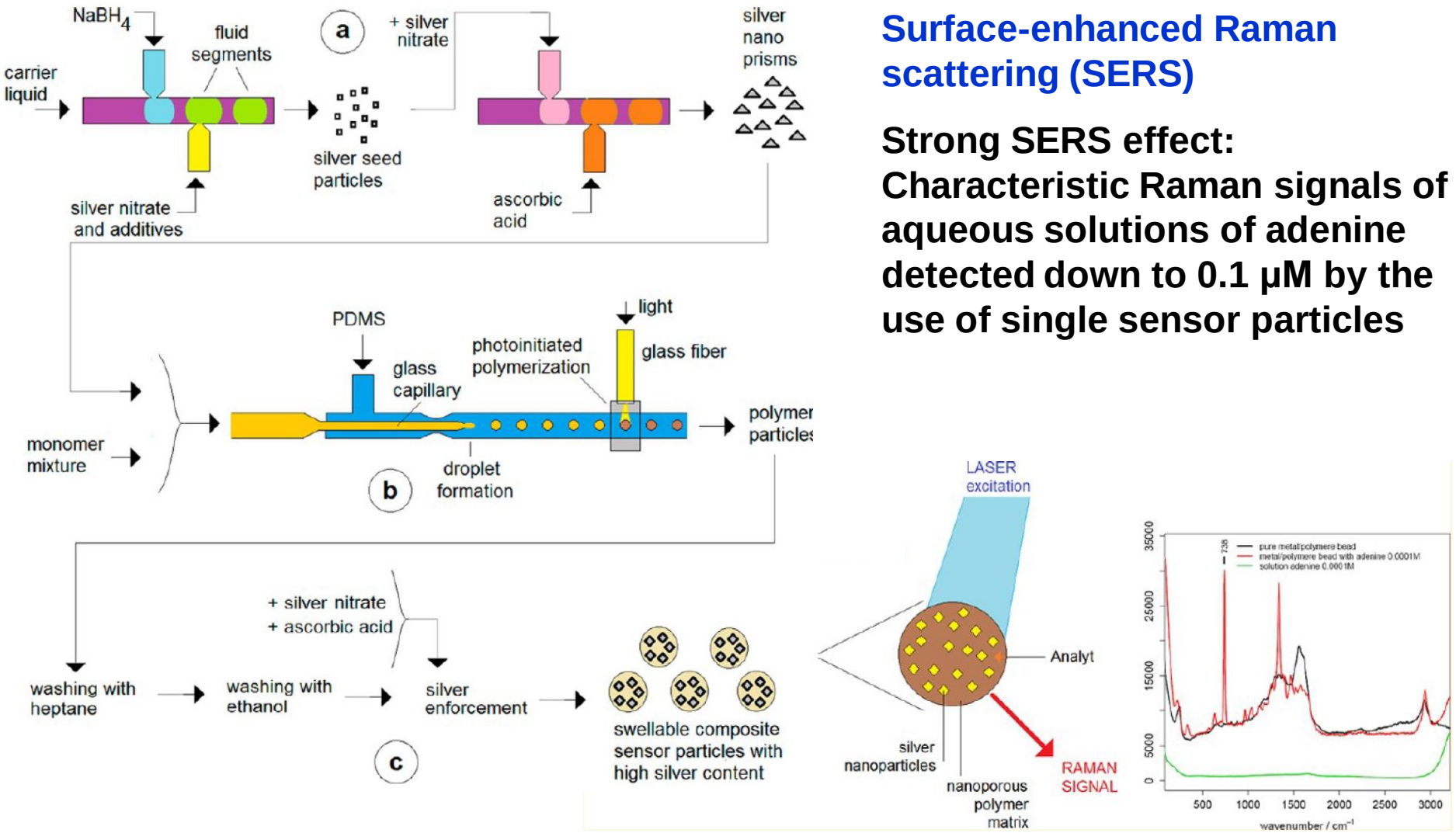
Sensitivity to flow and particle size variation



Fluorescence: distribution of the antigen

C. Wischke, D. Lorenzen, J. Zimmermann, H.-H. Borchert *Eur. J. Pharm. Biopharm.* **62** (2006) 247–253

SILVER-ENCAPSULATED POLYMER PARTICLES FOR SENSING



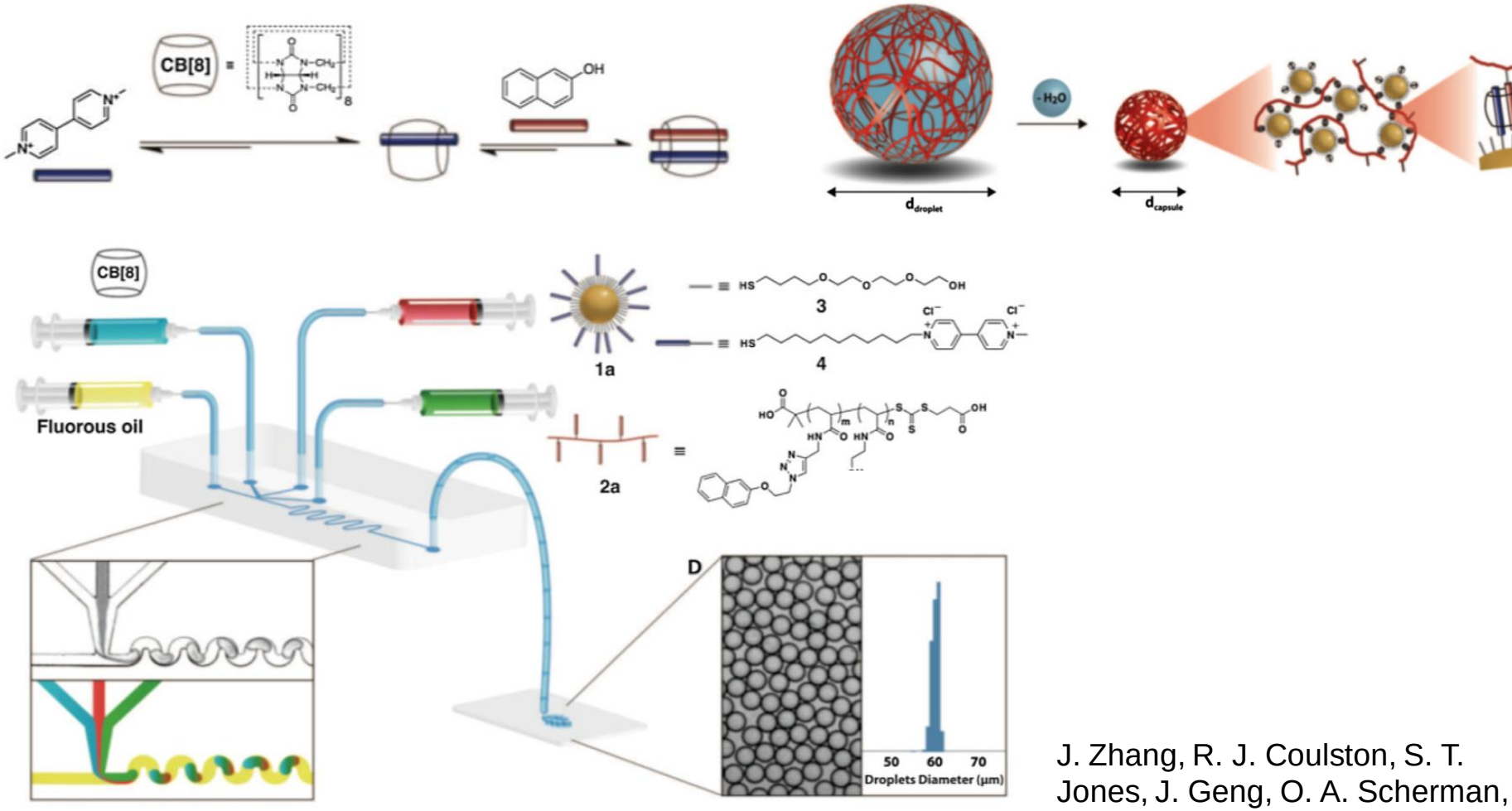
Surface-enhanced Raman scattering (SERS)

Strong SERS effect: Characteristic Raman signals of aqueous solutions of adenine detected down to 0.1 µM by the use of single sensor particles

J.M. Köhler, A. März, J. Popp, A. Knauer, I. Kraus, J. Faerber, C. Serra *Anal. Chem.* **85** (2013) 313−318.

COMPLEX FLOW INJECTION SCHEMES = HIGHLY FUNCTIONAL PARTICLES

Two-step, three-component formation of the cucurbit[8]uril (CB[8]) ternary complex in water with methyl viologen (MV2þ) (blue) and naphthol (Np)

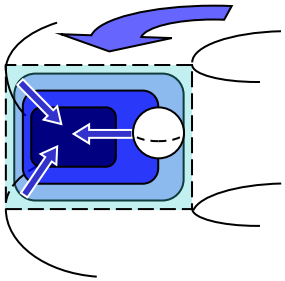


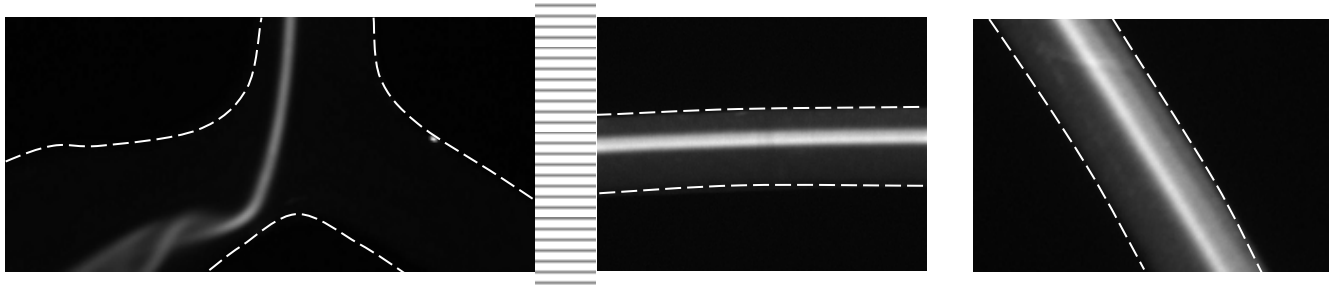
J. Zhang, R. J. Coulston, S. T. Jones, J. Geng, O. A. Scherman, C. Abell, *Science* **335** (2012) 690.

LIFT-FORCE PARTICLE CLASSIFIER

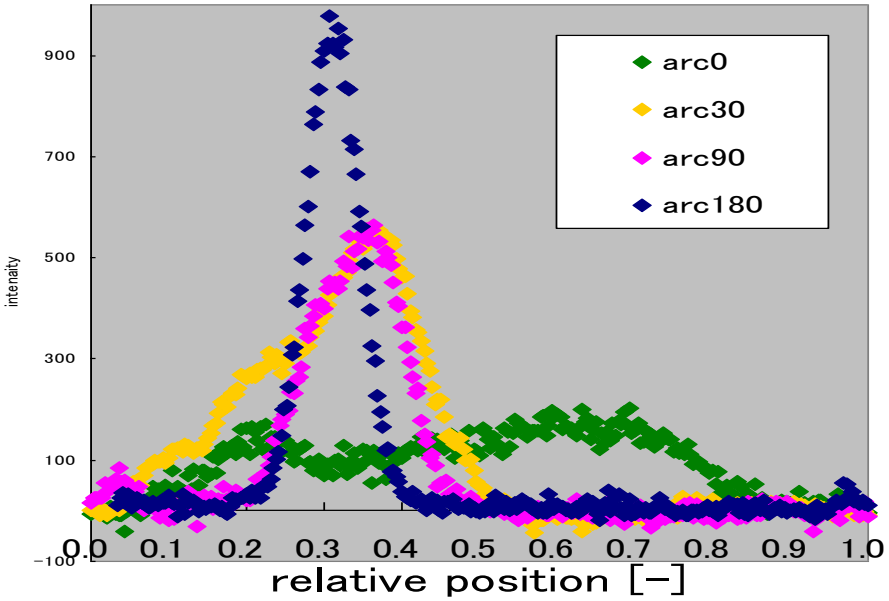
Prof. Okawara, Nobuo Oozeki, Tokyo Institute of Technology

Fig. 20 µm at De=60





Lift force

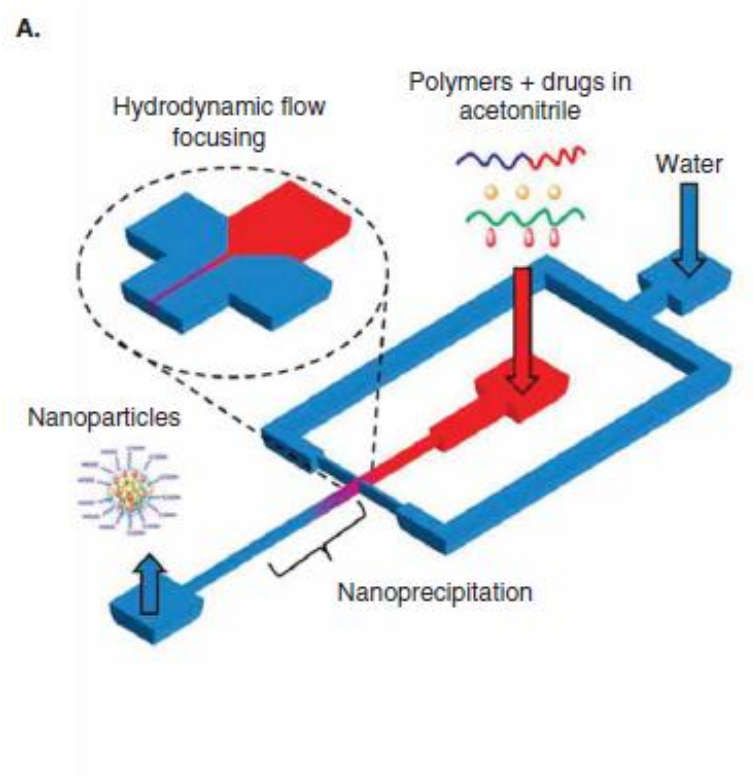


- **20 µm particle**

S. Okawara, N. Oozeki, K. Ogawa, P. Löb, V. Hessel *AIChE J.* **55**, 1 (2009) 24-34.

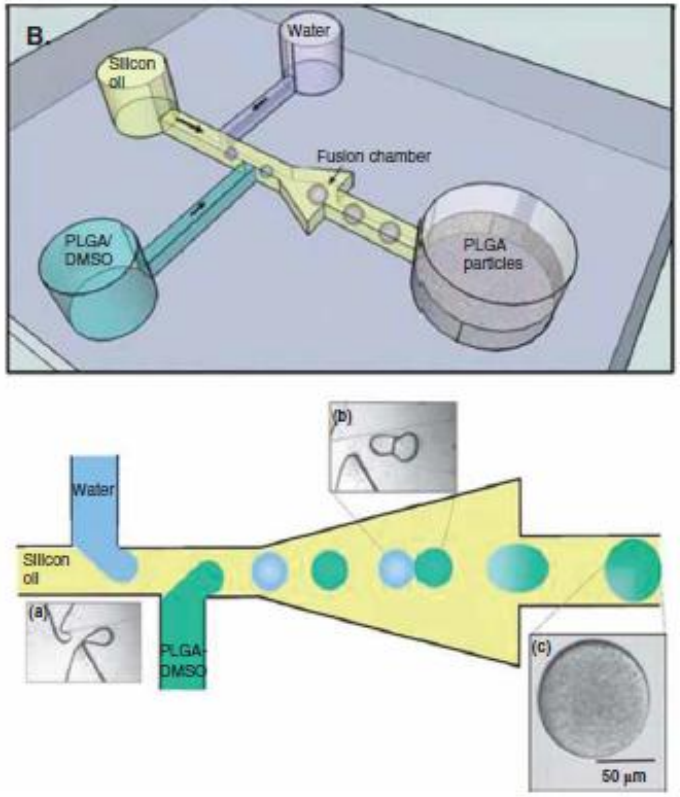
2D MICROFLUIDICS FOR POLYMER NANOPARTICLES (35 – 180 nm)

Nanoprecipitation by hydrodynamic focusing



N. Kolishetti, S. Dhar, P.M. Valencia et al. *Proc Natl Acad Sci USA* **107**, 42 (2010) 17939-17944.

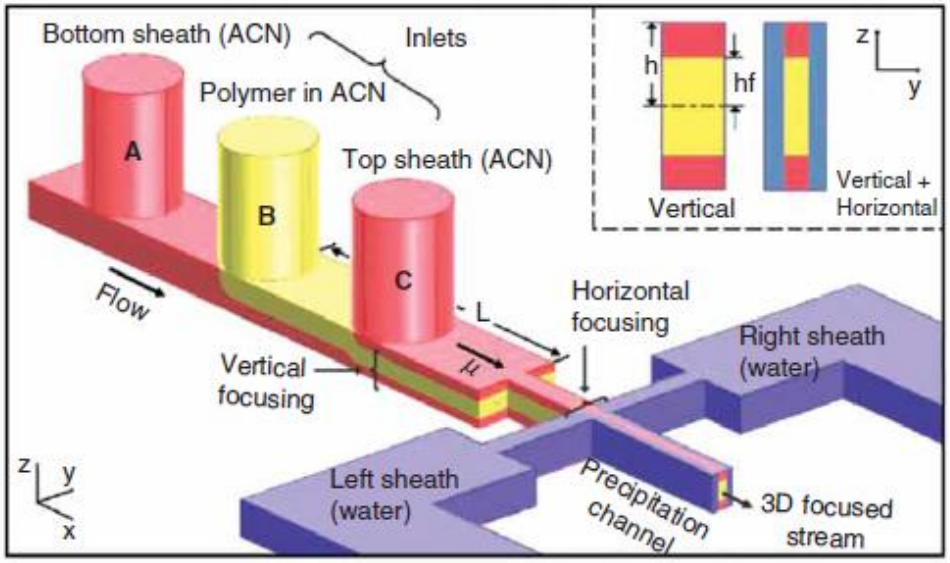
Reverse emulsion method

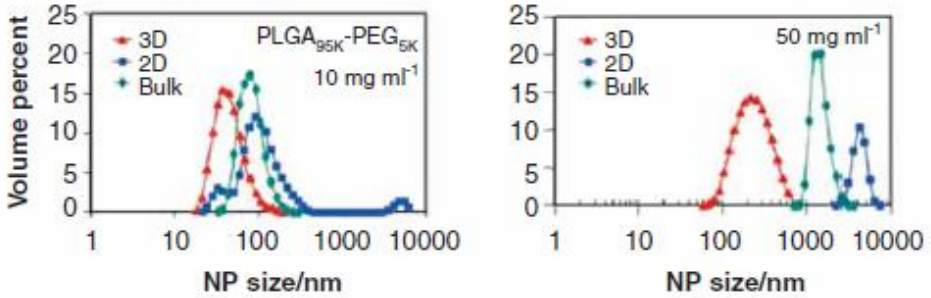


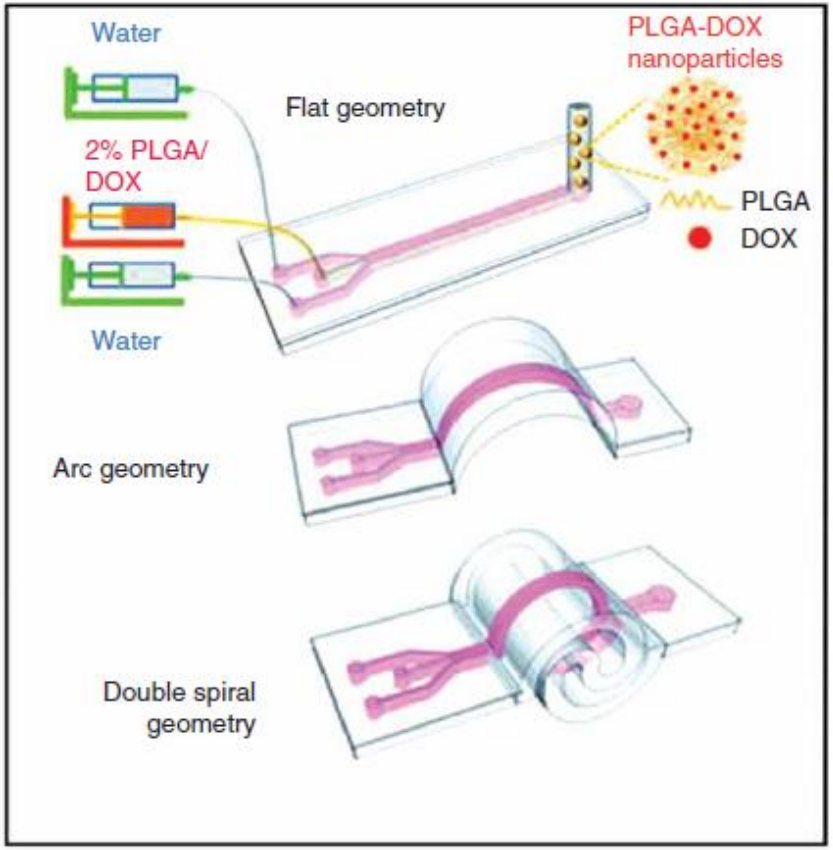
L.H. Hung, S.Y. The, J. Jester, A.P. Lee *Lab Chip* **10** (2010) 1820-1825.

Drugs encapsulated: platinum prodrug, docetavel, doxorubicine, sorafenib

3D MICROFLUIDICS FOR POLYMER NANOPARTICLES (13 – 150 nm)





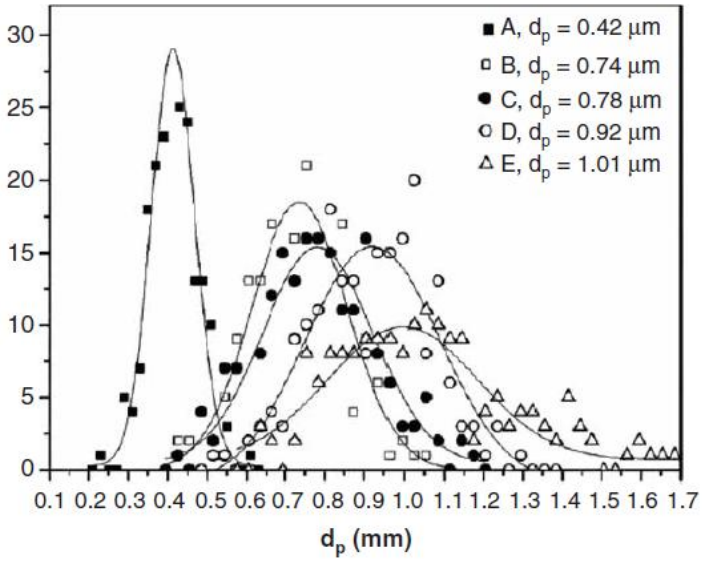


M. Rhee, P.M. Valencia, M.I. Rodriguez et al. *Adv Mater* **23**,12 (2011) H79-83.
J. Sun, Y. Xianyu, M. Li et al. *Nanoscale* **5** (2013) 5262-5265.

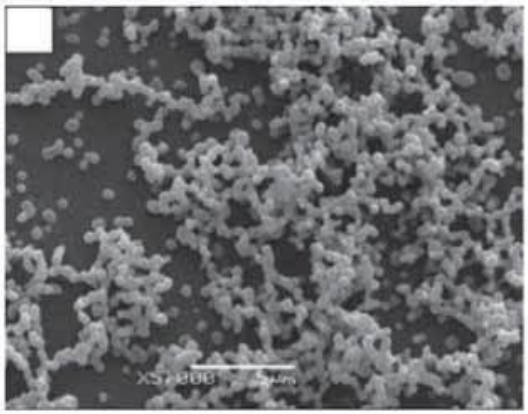
Technische Universiteit Eindhoven University of Technology

MOTIVATION FOR POLYMER ARMOPHOUS NANOPARTICLES

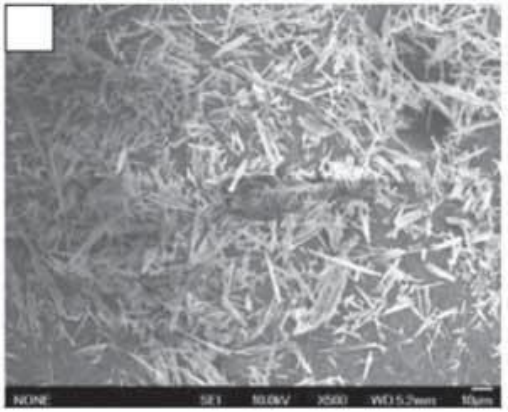
Cefuroxime axetil, CFA



CFA nanoparticles *Flow*

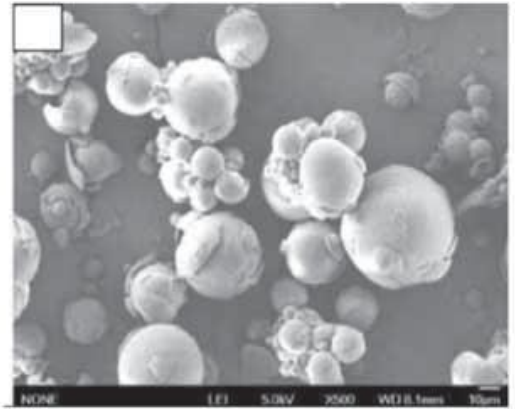


Raw CFA



Commercial CFA

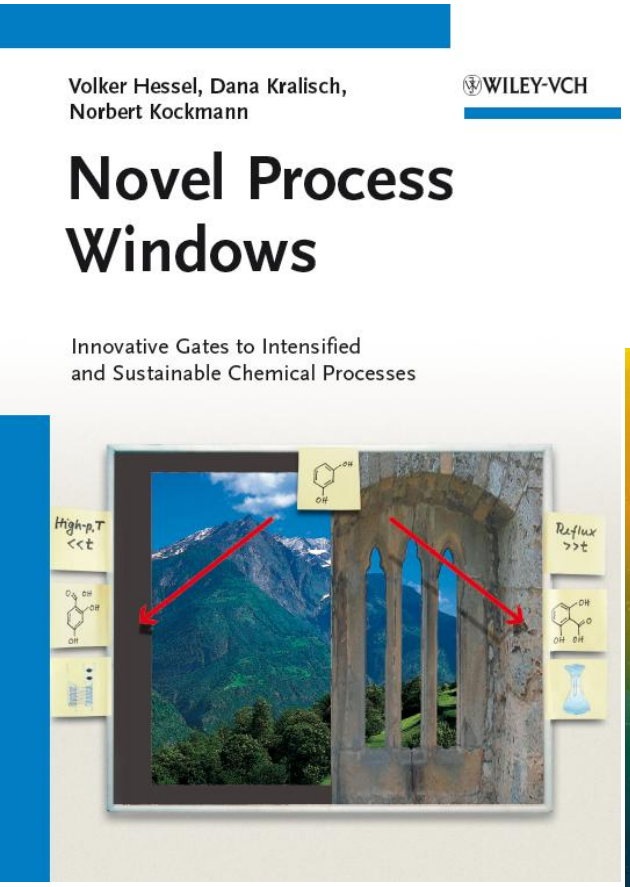
Spray drying

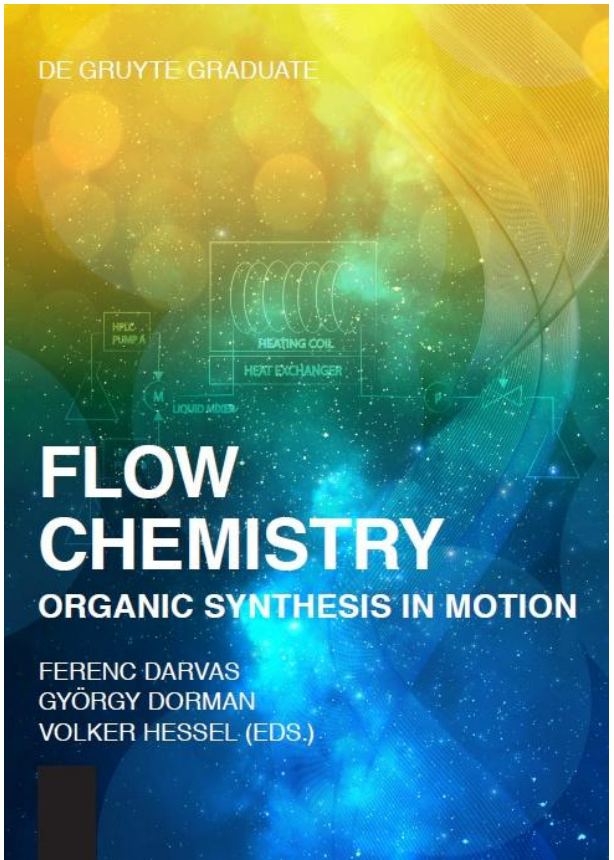


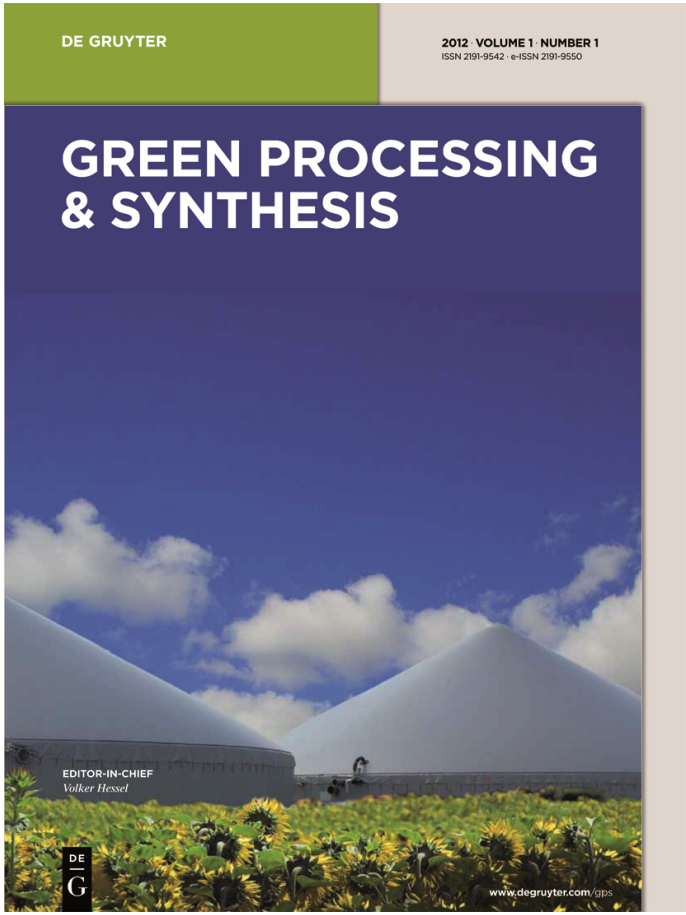
J.X. Wang, Q.X. Zhanga, Y. Zhou et al. *Chem Eng J* **162** (2010) 844-51.

Technische Universiteit Eindhoven University of Technology

NEW BOOKS & JOURNAL
related to contents presented





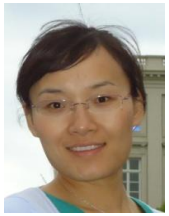


SFP Group: Micro Flow Chemistry and Process Technology (31 members)

Dr. T. Noel,
Assistant prof.

S. Sundaram
PhD

J. Tibhe,
PhD



Dr. Q. Wang
Assistant prof.

I. Dencic
PhD

A. Anastasopolou
PhD

G. Kolb
Part-time prof.

I. Vural,
PhD

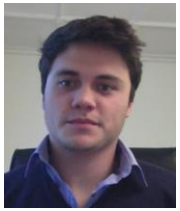
B. Patil
PhD

N. Straathof
PhD

S. Stouten,
PhD

L. Borukhova
PhD

E. Shahbazali
PhD



H. Gemoets
PhD

J. Smit
Editorial Assistant

M. Shang
PhD

B. Spasova
PhD at IMM/TUD

A. Hemert
Secretariat

QUESTIONS??

Art Galley of Western Australia