3D-PEG-based resins tailored for chemical biology and cell studies: MPM-encoded beasds

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Abstract (300 word limit)

Tailoring resins is a prerequisite for performing assays on solid support. PEG-based resins, SPOCC, POEPOP, PEGA, ChemMatrix and other have shown particularly favorable properties in this regard because the unmodified resins show no interaction with biomolecules or cells and they have no absorption or emission of light. PEGA resins are particularly promising in this regard, since the swell 15-20 fold even in salt containing buffers used in bioassays and their polymer matrix is penetrated with proteins up to at least 70 kD. They swell evenly well in non-polar solvents used in synthesis of small molecule ligands. These resins have been equipped with cell binding ligands to form cell monolayers used in combinatorial one-bead-two-compound screening of GPCR's interacting with ligand libraries on the support. Here we present a novel sustainable large scale microchannel synthesis of highly regular PEGA beads for use in screening and precise binding assays. The continuous flow-synthesis equipment was composed from standard laboratory items and allowed the "green" production of precisely monosized beads with controlled size in 90% yield for all use even for a larger solid-phase synthesis laboratory. The synthesis is performed by inverse radical suspension polymerization in a limited amount of recirculating silicon oil and creates no waste. Furthermore, the beads could be MPM-encoded with a matrix of fluorescent tentagel microparticles anchored during the radical polymerization in the polymer matrix for rapid assessment of structure-activity in combinatorial libraries. The monosized beads also allowed well-based or microchannel determination of protein binding constants in a robust, easy-to-use, inexpensive binding assay using a standard fluorescence microscope. The properties of the resins can be tailored by additives in the radical polymerization to match any requirement of the screening processes.

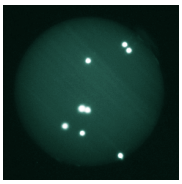


Figure 1. Macrobead encoded with fluorescent microparticles immobilized in the polymer matrix.

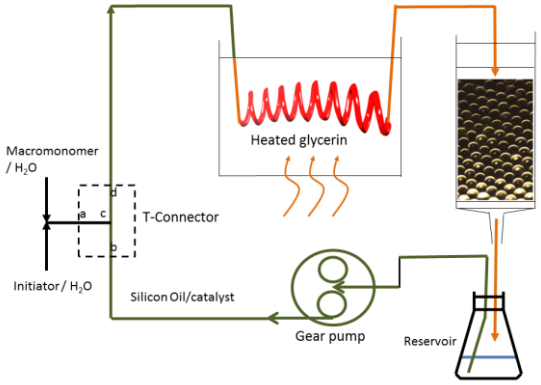


Figure 2. The continuous polymerization of droplets formed in a microchannel provides uniform beads as those presented in the image.

Recent Publications (minimum 5)

1. Auzanneau, F.-I.; Meldal, M.; Bock, K., Synthesis, characterization and biocompatibility of PEGA resins. J. Peptide Sci 1995, 1, 31-44.
2. Grøtli, M.; Rademan, J.; Groth, T.; Lubell, W.; Miranda, L. P.; Meldal, M., Surfactant mediated cationic and anionic suspension polymerization of PEG-based resins in silicon oil; beaded SPOCC 1500 and POEPOP 1500. J. Comb. Chem 2001, 3, 28-33.
3. Miranda, L. P.; Lubell, W. D.; Halkes, K. M.; Gotfredsen, C. H.; Meldal, M., SPOCC 194, A new high functional group density PEG-based resin for solid phase organic synthesis. J. Comb. Chem 2002, 523-529.
4. Meldal, M.; Wu, B.; Diness, F.; Michael, R.; Hagel, G., Metabolically stable cellular adhesion to inert surfaces. ChemBioChem 2011, 12, 2463-2470.
5. Hu, H.; Nikitin, S. V.; Berthelsen, A. B.; Diness, F.; Schoffelen, S.; Meldal, M., Sustainable Flow Synthesis of Encoded Beads for Combinatorial Chemistry and Chemical Biology. ACS Combinatorial Science 2018, 2156-8952.



Morten Meldal graduated in carbohydrate synthesis, structure and immunology, and developed peptide synthesis technology. He headed the SPOCC Center for Combinatorial Chemistry at Carlsberg Laboratory 1997-2008 where he found an interest in PEG based resins. As professor at Department of Chemistry, University of Copenhagen and Director of Nano Science Center since 2011, he was appointed Director of the multidisciplinary Center of Evolutionary Chemical Biology in 2013. He coauthored ~ 350 publications and coinventor on 30 patents. CECB is engineering polymers with properties facilitating combinatorial chemistry and selection assays. We use bead-based assays to study molecular recognition and binding, synthetic and natural enzymes and cell signaling by combinatorial solid phase and cells-on-bead technology. The technology involve novel chemistry, polymer design, MS, protein chemistry and cell biology. Targets includes interleukins, caspases XIAP, MCR's, and disordered proteins. The controlled tailoring of biocompatible PEG-resins with MPM- encoding provides information of structure-activity of combinatorial ligands.

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