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Sequence-controlled Polymers *via* Controlled Radical Polymerization

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Synthetic polymer chemists have always sought to approach the precision over monomer sequence exemplified by natural biopolymers (*e.g.* DNA and proteins). The ability to translate this molecular precision to sequence-controlled synthetic analogues would allow polymer chemists to not only mimic but also potentially enhance the properties of biomacromolecules paving the way for many applications in a wide range of fields including materials science and nanomedicine. Solid-phase peptide synthesis enabled the preparation of sequence-defined oligomers although this approach can be time-consuming, costly (due to many protection/deprotection steps), challenging to scale up and limited to the synthesis of low molecular weight materials.[1]

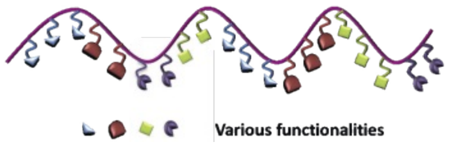

Fig. 1. Sequence-controlled multiblocks.

On the contrary, the synthesis of sequence-controlled multiblocks (Fig. 1) through controlled radical polymerization strategies is more scalable (already demonstrated up to 100 grams) and can lead to the production of higher molecular weight materials (up to 150,000 g/mol).[2] In addition, no specialized equipment is needed as in most cases use of a glass vial can be adequate and deoxygenation methods include simple bubbling with nitrogen/argon. Importantly, the preparation of these complex materials can be conducted in a one-pot process thus saving time, hassle and materials. Last but not least, the number of functionalities (and hence the number of various physiochemical properties) that can be incorporated along the polymer backbone can only be limited by our imagination.

The first report of one-pot sequence-controlled multiblocks *via* controlled radical polymerization was by Whittaker and co-workers in 2011 using copper-mediated reversible deactivation radical polymerization (Cu-RDRP).[3] In this very first paper, only the synthesis of very low molecular weight multiblocks were attempted (degree of polymerization ~2 per block). Anastasaki *et al.* (within the Haddleton group) then expanded the scope to include high molecular weights multiblocks although the total number of blocks was limited to three and gradual cessation of the polymerization was observed.[4] In addition, Anastasaki *et al.* introduced the first example of multiblocks using light as external stimuli which is, arguably, the most versatile Cu-RDRP approach for the preparation of such complex materials.[5] The Haddleton group has also developed multiblock synthesis in aqueous media exploiting the rapid disproportionation of CuBr/ligand. Given the known limitations of Cu-RDRP in water, significant side reactions (*e.g.* hydrolysis of the bromine end group) were found.[6] Moreover, Perrier and co-workers introduced an optimized reversible addition-fragmentation chain transfer (RAFT) approach enabling the synthesis of icosablock (20) copolymers.[7]

Despite this progress, all the aforementioned methodologies rely on the use of catalysts containing transition metals (*e.g.* copper) or sulfur and as such multiple purification steps are essential to isolate the final materials. Other limitations include high dispersities, non-quantitative conversions, extended reaction times and undesirable side reactions. Perhaps the most important drawback of these methods is the incompatibility with low k_p monomers such as methacrylates. To address this, Haddleton, Anastasaki, Davis and co-workers developed a rapid, quantitative and metal-free emulsion polymerization method that allows for the preparation of the challenging methacrylic multiblocks thus paving the way for a new class of sequence-controlled materials.[8]

In summary, synthesis-wise, many important breakthroughs have been achieved towards the preparation of sequence-controlled multiblocks although important limitations are still hindering the tremendous applications of these materials. For example, the synthesis of sequence-controlled polymers consisting of different monomer classes remains a big challenge and adequate characterization of such materials is currently not available. Overcoming such challenges would pave the way for a range of applications in various fields including single chain folding, drug delivery, polymeric phase separation and other applications whereby sequence control is required.

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