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Orthogonal ligation to spherical polymeric microparticles: Modular approaches for surface tailoring

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ABSTRACT

Modular ligation strategies for the functionalization of polymeric microspheres provide new perspectives for their applications in material science. In the current trend article we highlight variable synthetic procedures for generating functional microspheres *via* orthogonal modular conjugation chemistries. An overview of the different surface chemistries available is provided, followed by surface-sensitive characterization techniques relevant for the microparticles. Finally, we explore future trends in modular orthogonal modification approaches on microparticles and provide an outlook on the perspectives that the field of surface-modification of polymeric microparticles holds.

Contents

Abbreviations: AIBN, azo-bis-isobutyronitrile; ATR, attenuated total reflectance; ATRP, atom transfer radical polymerization; Con A, Concanavalin A; CRP, controlled radical polymerization; CuAAC, copper-catalyzed azide alkyne cycloaddition; DIPEA, diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMSO, dimethylsulfoxide; DVB, divinyl benzene; GPC, gel permeation chromatography; GMA, glycidyl methacrylate; HDA, hetero Diels–Alder; HEMA, hydroxyethylmethacrylate; HPLC, high performance liquid chromatography; HIPE, high internal phase emulsion; LCST, lower critical solution temperature; μ-HPLC, Microcolumn High Performance Liquid Chromatography; O/W, oil in water emulsion polymerization; pCL, poly(ε-caprolactone); pDVB, polydivinylbenzene; PEG, poly(ethylene glycol); PLGA, poly(lactide-co-glycolide); pNIPAM, poly(*N*-isopropylacrylamide); PMMA, poly(methyl methacrylate); ptBA, poly(tert-butyl acrylate); RAFT, reversible addition-fragmentation chain transfer; ROP, ring opening polymerization; SEM, scanning electron microscopy; SPE, solid phase extraction; SPOS, solid phase organic synthesis; SPPS, solid phase peptide synthesis; TBAF, tetra-butylammonium fluoride; THF, tetrahydrofuran; W/O, water in oil emulsion polymerization.

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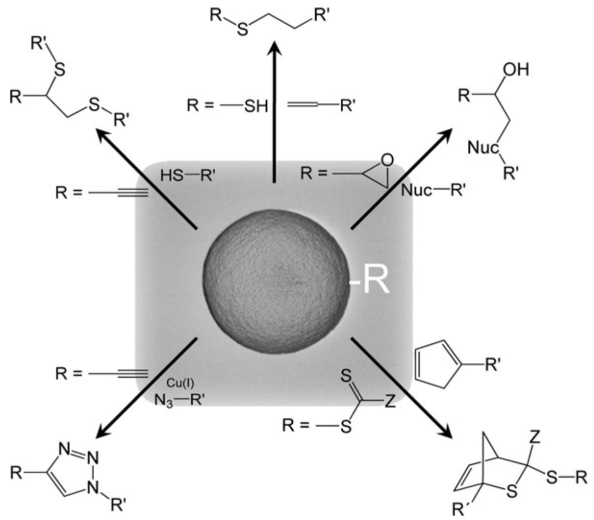
1. Introduction

Cross-linked polymeric microparticles play an important role in applications ranging from diagnostic kits and drug delivery applications [1], stationary phases for chromatographic columns (high performance liquid chromatography (HPLC) [2], gel permeation chromatography (GPC)) [3], solid supported catalysis [4], ion exchange [5], enzyme immobilization [6], solid phase extraction (SPE) [7], scavenging [8], solid phase organic synthesis (SPOS) [9], and solid phase peptide synthesis (SPPS) [10]. These particles range in diameter between one and approximately 400 μm – reliant on the synthesis procedure – and may be prepared with variable topologies ranging from smooth and hollow to highly porous as well as degradable and non-degradable variants, depending on the envisaged application. Of particular importance for the performance of polymeric microparticles is their surface functionalization with synthetic polymer strands – leading to core–shell entities. In the current article, we wish to highlight the current trends in modular orthogonal modification approaches to polymeric microspheres and provide an outlook on the perspectives that the field holds. Although – as the name implies – we will focus our trend article on polymeric (cross-linked) spherical geometries, alternative configurations will be briefly addressed.

Since the emergence of the *click* chemistry concept in the early years of the last decade, a range of modular conjugation methodologies *via* so-called 'grafting-to' approaches to variable surfaces have been developed [11]. Although the achievable grafting densities *via* such 'grafting-to' approaches tend to be lower than 'grafting-from' approaches, precision engineering of the surface properties is made more controllable due to the fact that the tethered macromolecules can be thoroughly characterized prior to conjugation. For certain applications – mostly where functional microspheres have to be generated in large amounts – it is also desirable to have a production process for the functionalization of microparticles which involves no polymerization step, but rather a single – preferentially fast and ambient temperature – reaction onto the solid microspheres with subsequent simple purification (e.g. filtration). Such high production-load applications mostly include chromatographic packing materials which require several grams for a single column. Depending on the application, not every modular orthogonal ligation chemistry is suitable for the microsphere modification, such as the grafting of certain molecules which does not allow exceeding certain temperature limits (i.e. when tethering temperature sensitive biomarkers such as proteins) or the presence of transition metal catalysts which can potentially interfere with particles that are to be employed in biological systems. In addition, the resistance of the generated covalent linkage to elevated temperatures and harsher chemical regimes (e.g. acids and bases) has to be considered in the context of each specific application (Scheme 1).



Scheme 1. Strategies for orthogonal 'grafting-to' ligation with microspheres.

Herein we will provide an overview of the modular ligation strategies that have been employed during the last six years and to which types of microspheres they have been applied. A special emphasis will lie on the inherent surface chemistries available due to the synthetic process employed for generating microspheres (e.g. vinyl functionalities and alcohols or acids which are contained in the monomers or cross-linking agents). Furthermore – and equal in importance to the synthetic tasks – an emphasis will be placed on how the modular functionalized microspheres are quantitatively characterized, which can be a challenging exercise due to the often porous structures of these materials.

2. Types of microparticles

Without any doubt considerable progress in the synthesis of (functional) polymeric microparticles with different shapes has been made in recent years. Particle shape plays a key role when it comes to the control over