Nano Today (2014) 9, 457—477

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/nanotoday

REVIEW

Surface ligands in synthesis, modification, assembly and biomedical applications of nanoparticles

Daishun Ling[a,b], Michael J. Hackett[a,b], Taeghwan Hyeon[a,b,*]

[a] *Center for Nanoparticle Research, Institute for Basic Science (IBS), Seoul 151-742, Republic of Korea*
[b] *School of Chemical and Biological Engineering and Institute of Chemical Processes, Seoul National University, Seoul 151-742, Republic of Korea*

Received 5 March 2014; received in revised form 29 May 2014; accepted 16 June 2014
Available online 15 July 2014

KEYWORDS
Ligand;
Nanoparticle;
Assembly;
Surface modification;
Nanomedicine

Summary Nanotechnology has received extraordinary attention recently due to its burgeoning role in biomedical science. The materials composing the nanoparticles produce fascinating and diverse functionalities as a result of their exceptionally small size. In fact, even seemingly insignificant changes in particle size can have profound effects on these properties. Thus size control, both during synthesis and in particle suspensions, is a *sine qua non* for functionality. This can be accomplished by masking the particle surface with a multitude of different ligands. Not only can surface ligands constrain the growth of nucleation, they can also direct the shape of crystallization. However no single ligand can do everything. Fortunately ligands are essentially fungible and can be exchanged at various times to confer the desired properties to the particle. This can include protecting the particle from harsh aqueous conditions, such as pH extremes, maximizing optical properties for diagnostics or shielding the particle from potentially hostile conditions found in the body. Because these moieties interact ubiquitously with various biological materials, particularly proteins, there needs to be a rationalized design of surface ligands. The design of the ligand can have crucial effects on biodistribution as well as evasion of biological defenses. Ligands can even be designed to provide new functionality in response to various environmental stimuli to improve their therapeutic or diagnostic capabilities. Considering the importance of ligands then on this emerging field, this review will thoroughly consider the ligand design for the various steps of nanodevelopment, from synthesis and assembly through biomedical translation.

* Corresponding author at: Center for Nanoparticle Research, Institute for Basic Science (IBS), Seoul 151-742, Republic of Korea/School of Chemical and Biological Engineering and Institute of Chemical Processes, Seoul National University, Seoul 151-742, Republic of Korea. Tel.: +82 2 880 7150; fax: +82 2 886 8457.
E-mail address: thyeon@snu.ac.kr (T. Hyeon).

http://dx.doi.org/10.1016/j.nantod.2014.06.005
1748-0132/

Introduction

Nanomaterials naturally occupy the niche between molecular species and bulk solids [1]. Their surface chemistry and physics are described using a mix of languages originally developed for coordination compounds (*e.g.* ligands [2]), bulk solids (*e.g.* capping agent or self-assembled monolayer [3]) and biomaterials (*e.g.* coating layer [4]). Surface ligands play a very important role in nanomaterial research [5,6]. For example, they can control the size and shape of nanoparticles during synthesis [7,8], act as a template for assembly [9—11], protect the nanoparticles from oxidation [12], prevent leaching into the surrounding solution [13] or even bolster properties such as the photoluminescent yield of semiconductor nanocrystals [14] or relaxivity of magnetic nanoparticles [15]. Because of this control, the nanoparticles can be endowed with many different functionalities for various biomedical applications.

For nanobiomaterials, ligands affect their toxicity [16,17], cell permeability [18,19] and even *in vivo* fate [20,21]. Often nanoparticles are cleared too rapidly by the reticuloendothelial system (RES) which limits their utility [22]. Thus biocompatible ligands are used to create a buffer between the nanoparticle and the biological ambiance. However ligands are usually expected to do too much. During circulation, the ligands should prevent interactions of nanoparticles with proteins and help avoid cellular uptake. However in the target site, the ligands are usually involved in binding specific proteins and inducing cellular uptake. The contradictory expectations are a significant reason why translation is particularly difficult and *in vivo* success so rare. To better understand these complex processes and interactions, this review will briefly summarize the chemistry, physics and biophysicochemical interactions of surface ligands for nanoparticles. It will discuss the different requirements applied to ligands during different stages of nanomaterial design from synthesis and assembly through biomedical translation. It will briefly cover the chemical strategies of ligands used to control size, shape and phase of nanoparticles during synthesis and assembly process, and discuss the design of ligands for biocompatible nanomaterials and their biomedical applications. Drawing connections to these mature fields can be very useful since many important similarities were somewhat overlooked by the nanocommunity. Overall the focus of this review will be on the unique aspects of nanoparticle ligands, particularly their roles in synthesis, modification, assembly and biomedical applications of nanoparticles.

Ligands for nanoparticles synthesis

Generally, there are two different strategies for the synthesis of nanoparticles: top-down and bottom-up [23,24]. The top-down method involves the mechanical fragmentation of bulk materials into nano-sized debris. However, the resulting fragments usually have a broad size distribution. The bottom-up approach begins with molecular precursors, such as organometallic compounds or salts, which are decomposed by either thermal/optical excitation or a reducing agent to generate individual metal atoms with an organic residue. Consequently, the metals nucleate forming nanoparticles with a controllable, narrow size distribution. A typical bottom-up synthetic system for colloidal nanoparticles consists of three components: precursors, organic ligands (usually in the form of surfactants) and solvents, all three of which play important roles for controlling the size and shape of the nanoparticles. This review will specifically focus on the ligands' (surfactant) effect on the growth of the nanoparticles. A prerequisite to controlling the growth for this approach is compartmentalization of the precursors which is usually achieved using ligands in solution that form micelle-like structures [12]. These serve as templates that limit the nucleation and growth of the inorganic phase. As a result, the binding strength of the ligand to particle strongly affects the growth behavior of the metal cluster. In general, stronger chelates to the metal crystal planes will result in smaller particles [8]. Peng et al. reported that the concentration of ligands in a non-coordinating solvent could be responsible for tuning the reactivity of metal precursors to achieve the desired balance between nucleation and growth allowing the formation of high quality nanocrystals [25,26]. The critical size of the resulting nanocrystals is also dependent on the concentration of ligand monomers; usually lower concentrations lead to larger critical sizes [7,27].

Selective adhesion

Despite the equilibrium and anisotropic nature of different inorganic crystal facets (the high-energy facets grow more quickly than low energy facets in a kinetic regime), different shaped nanoparticles can be generated under thermodynamic control [7]. Ligands are used to kinetically control the shape of nanoparticles *via* selective adhesion. If only a single binding ligand is used, such as in the case of trioctylphosphine oxide (TOPO) for CdSe nanoparticle synthesis, there is a constant dissociation occurring along the particle surface which induces an isotropic growth [28,29]. However in a faceted crystal, the dissociation rates may be different for the various facets. Consequently, using a ligand that selectively binds to a particular crystal facet will lower the energy and reduce the growth rate of that facet compared to the others [30]. Furthermore, if more than one ligand is used, multiple binding affinities of the ligand mixture lead to different binding affinities along different crystal planes [28]. Therefore, the growth in specific dimensions can be modulated resulting in anisotopic growth [7,28]. This process is schematically presented in Fig. 1, where organic surfactants preferentially adhere to one facet of the nanocrystal forcing the crystal to grow anisotropically into a disk or a rod.

Amphiphilic polymeric ligands

However, because of the many different binding affinities between various ligands and inorganic particles, there is no widely accepted rule for estimating the adhesion energy of a small organic ligand on a nanoparticle's surface. As a result, most ligand based procedures for nanoparticle synthesis require stringent experimental conditions and are difficult to generalize. Linear amphiphilic polymeric ligands have been used as a general templates to synthesize different nanocrystals [31,32], but this ''polymeric micelle-like'' approach often fails to produce well-defined inorganic