Egon Matijević *Editor*

Fine Particles in Medicine and Pharmacy

Springer

Fine Particles in Medicine and Pharmacy

Egon Matijević
Editor

Fine Particles in Medicine and Pharmacy

Springer

Editor
Egon Matijević
Center for Advanced Materials Processing
Clarkson University
Potsdam, New York 13699-5184,
USA
ematijevic@clarkson.edu

ISBN 978-1-4614-0378-4 e-ISBN 978-1-4614-0379-1
DOI 10.1007/978-1-4614-0379-1
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011937020

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

There are several areas in medicine and pharmacy in which finely dispersed matter plays a significant role. Drugs in solid state can be produced as particles of diverse shapes and structures, in modal sizes ranging from a few nanometers to a few micrometers. Such medication is commonly combined with inactive diluents, while the pills themselves are often coated with layers which protect them from the effects of the environment, such as humidity. Both these chemically inert components in the delivery systems (diluents and shells) may also control the release of the active component.

Thus, there are many physical aspects of the medication which can affect its functionality. The first deals simply with the size of the active substance to be delivered. For example, in recent years much emphasis has been placed on the use of nanosize active materials. A recent issue of ACS NANO published several articles on the subject, including "Impact of Nanotechnology on Drug Delivery", by O.C. Farukhzad and R. Langer (3, 2009, 16–20), and "Virtual Issue on Nanomaterials for Drug Delivery" by P.T. Hammond (5, 2011, 681–684).

Another significant aspect of the drug in the pill form is the morphology of active molecules, which affects many properties of a medication, including its stability, solubility, and release. Most of the medically active compounds tend to form polymorphs, i.e., the same molecules being differently packed in the solid state, which determines their functionality. This aspect of drugs was dealt with in great detail by A.M. Rouhi in *Chemical and Engineering News* (American Chemical Society), February 24, 2003 issue, under the title "The Right Stuff: From research and development to the clinic, getting drug crystals right is full of pitfalls." It is, therefore, of great importance to produce drug delivery systems (e.g. pills) that contain the active compound in the stable state, and assure its controlled delivery.

Fine particles of different size and other properties (optical, magnetic, adhesive, etc.) play an essential role in the diagnostics, such as barium sulfate slurries in the X-ray of intestines, or well defined magnetic particles used as a biosensor, or nanodispersed gold used in bioimaging, to mention a few. Such specific uses of fine particles are described in several chapters. A short description of the contents of individual chapters is given below.

In the first chapter Vladimir Privman addresses the advancement of modeling approaches aimed at explaining morphological and geometrical features of fine particles. Specifically, discussed are certain aspects of particle shape selection and size uniformity, emerging as results of kinetics involving diffusional transport of matter in solution synthesis of nanocrystals and colloids. Processes ranging from nucleation to growth by aggregation, and mechanisms of uniform shape development are reviewed, with selected results outlined in some detail.

In the second chapter, Egon Matijević demonstrates that uniform drug dispersions can be prepared by precipitation in solutions. Indeed, in some cases, the same substance is obtained as particles of different, but uniform shapes, by altering the experimental conditions, or by varying additives. Furthermore, it is possible to coat so prepared drugs with an inorganic layer of alumina or silica, thus altering the surface reactivity and charge of the resulting particles. Such layers protect the cores and may promote specific reactions within the body.

The chapter by Silvana Andreescu, Maryna Onatska, Joseph Erlichman, Ana Estevez, and J.C. Leiter focuses on the interactions of the most widely used nanoparticles of metal oxides with cells and tissues in relation to the physico-chemical properties, biocompatibility, and cytotoxic reflexes in model biological systems, and selected biomedical applications. New and emerging uses of these particles as neuroprotective and therapeutic agents in the treatment of medical diseases related to reactive oxygen species, such as spinal cord repair, stroke, and degenerative retinal disorders are discussed. Furthermore, issues related to biocompatibility and toxicity of these nanoparticles for *in vivo* biomedical applications are dealt with in some detail.

Dan Goia and Tapan Sau contribute a comprehensive review of uniform colloidal gold, as applied in medicine and biology. Specifically, they describe how functionalized gold particles are used in bioimaging (optical, immunostaining, computed tomography, magnetic resonance, phagokinetic tracking), biosensing (optical and electrochemical), drug delivery, and therapeutic applications. Also described are additives for the preparation of highly dispersed active nanogold, including the complex (core–shell) and hierarchical structures, involving both inorganic and organic phases.

In their chapter Evgeny Katz and Marcos Pita deal with magnetic particles (microspheres, nanospheres, and ferrofluids), which are extensively used as labeling units and immobilization platforms in various biosensing schemes, mainly for immunosensing and DNA analysis, as well as in environmental monitoring. Biomolecule-functionalized magnetic particles generally exist in a ‘core–shell’ configuration through organic linkers, often organized as a polymeric ‘shell’ around the core. The state-of-the-art in the preparation, characterization, and application of biomolecule-functionalized magnetic particles and other related micro/nano-objects allows for efficient performance of various *in vitro* and *in vivo* biosensors, many of which are directed to biomedical applications.

The focus of the chapter by Devon Shipp and Broden Rutherglen is on the degradable polymer particles in drug delivery applications, based on their architectural design. Specifically, the authors consider polyanhydrides, which have the un-

usual property of undergoing surface erosion, and to predictable therapeutic agent release rates of approximate zero-order kinetics.

Artem Melman, in his contribution, describes an innovative method for the preparation of uniform nanoproteins, which involves their growth on monodispersed protein templates. This process is extensively involved in biomineralization in a multitude of living organisms, providing structures of exceptional complexity and uniformity. Current availability of pure recombinant cage shaped proteins and viruses offer limitless possibilities for their modification, and for targeted delivery on nanoparticles.

The chapter by Philip K. Hopke and Zuocheng Wang deals with the delivery and the effectiveness of medicine dosages deposited in the respiratory tract. Their study was originally driven by the concern regarding the effects of radioactive particles in this application. Empirical studies in animals and physical models of human airways have provided data which allows the prediction of regional deposition roles.

The chapter by Maria Hepel and Magdalena Stobiecka describes new bioanalytical sensing platforms, based on functionalized nanoparticles, for the detection of biomarkers of oxidative stress. These biomarkers and biomolecules indicate the diminished capacity of a biological system to counteract an invasion (or overproduction) of reactive oxygen species and other radicals. The oxidative stress has been implicated in a number of diseases, including diabetes, cancer, Alzheimer's, autism, and others. The detection methods for the oxidative stress biomarkers, such as glutathione, homocysteine, and cysteine, presented in this chapter, are based on their interactions with monolayer-protected gold nanoparticles. Such functionalized particles have also been shown to amplify the analytical signal in molecularly-templated conductive polymer sensors for the detection of biomolecules, and novel designs of molecularly-imprinted poly(orthophenylenediamine) sensor films.

In his chapter Sergiy Minko discusses the synthesis and applications of multifunctional hierarchically organized, multilevel structured, active hybrid colloidal particles, uniform in size and shape. Such particles are capable of programmed and controlled responses to changes in the environment or to external signals. Furthermore, various core–shell structures were synthesized in two steps consisting of metals, oxides, or polymers of different sizes and shapes, and functionalized with stimuli-responsive polymers. Specifically, deposition, precipitation on colloidal templates, grafting to the surface of particles, and self-assembly of amphiphilic block-copolymers, were extensively used for the synthesis of the core–shell colloids. A properly engineered combination of sensitivity to external stimuli with resulting changes in the particles' properties is critically important for drug delivery capsules, capsules for diagnostics and, particles-biosensors. The development of these stimuli-responsive colloids is driven by several important applications: including, biosensors that respond to changes in the chemical and biological environment, stimuli-responsive capsules that can release the cargo upon external stimuli for delivery of drugs and contrasting agents, and biocomposite materials that can adapt to living tissue.

In the final chapter, Richard Partch, Adrienne Stamper, Evon Ford, Abeer Al Bawab and Fadwa Odeh, deal with the incidence of overdoses of chemicals into

the body, causing either serious injury to organs or even death. The latter is more common than what is generally believed to be the case. Among such chemicals are prescription therapeutics, illicit derivatives, biotoxins, and those found in beverages and food, leached from packaging. In this chapter it is demonstrated that both oil–water microemulsions and functionalized carrier nanoparticles are capable of removing overdosed concentrations of several of the problem chemicals from liquids including blood, both *in vitro* and *in vivo*.

Egon Matijević

Contents

Contributors

Prof. Silvana Andreescu Department of Chemistry & Biomolecular Science, Clarkson University, 8 Clarkson Avenue, SC, Box 5810, Potsdam, NY 13699, USA
e-mail: eandrees@clarkson.edu

Abeer Al Bawab Faculty of Science, and Director of Nanotechnology Center, University of Jordan, Amman, Jordan

Joseph S. Erlichman Department of Biology, St. Lawrence University, Canton, NY 13617, USA

Ana Estevez Department of Biology, St. Lawrence University, Canton, NY 13617, USA

Prof. Dan V. Goia Center for Advanced Materials Processing, Department of Chemistry & Biomolecular Science, Clarkson University, 8 Clarkson Avenue, CAMP, Box 5814, Potsdam, NY 13699, USA
e-mail: goiadanv@clarkson.edu

Prof. Maria Hepel Department of Chemistry, State University of New York, Potsdam, NY 13676, USA
e-mail: hepelmr@potsdam.edu

Prof. Philip Hopke Department of Chemical & Biomolecular Engineering, Clarkson University, 8 Clarkson Avenue, CAMP Annex, Box 5708, Potsdam, NY 13699, USA
e-mail: phopke@clarkson.edu

Center for Air Resources Engineering and Science, Clarkson University, Box 5708, Potsdam, NY 13699, USA

Prof. Evgeny Katz Department of Chemistry & Biomolecular Science, Clarkson University, Potsdam, NY, USA
e-mail: ekatz@clarkson.edu

J. C. Leiter Department of Physiology, Dartmouth Medical School, Lebanon, NH 03756, USA

Prof. Egon Matijević Department of Chemistry & Biomolecular Science, Clarkson University, 8 Clarkson Avenue, CAMP, Box 5814, Potsdam, NY 13699, USA
e-mail: matiegon@clarkson.edu

Prof. Artem Melman Department of Chemistry & Biomolecular Science, Clarkson University, 8 Clarkson Avenue, SC, Box 5810, Potsdam, NY 13699, USA
e-mail: amelman@clarkson.edu

Prof. Sergiy Minko Department of Chemistry and Biomolecular Science, Clarkson University, 8 Clarkson Avenue, SC, Box 5810, Potsdam, NY 13699, USA
e-mail: sminko@clarkson.edu

Fadwa Odeh Chemistry Department, University of Jordan, Amman, Jordan

Maryna Ornatska Department of Chemistry and Biomolecular Science, Clarkson University, 8 Clarkson Avenue, SC, Box 5810, Potsdam, NY 13699, USA

Prof. Richard Partch Chemistry Department and Center for Advanced Materials Processing, Clarkson University, Potsdam 13699-5814, NY, USA
e-mail: partch@clarkson.edu

Evon Ford Chemistry Department and Center for Advanced Materials Processing, Clarkson University, 503 Queensgate Rd, Baltimore, MD 21229, USA

Baltimore, MD, USA

Marcos Pita Instituto de Catálisis y Petroleoquímica, CSIC. C/Marie Curie 2, 28049 Madrid, Spain
e-mail: marcospita@icp.csic.es

Prof. Vladimir Privman Department of Physics, Center for Advanced Materials Processing, Clarkson University, 8 Clarkson Avenue, CAMP, Box 5721, Potsdam, NY 13699, USA
e-mail: privman@clarkson.edu

Tapan K. Sau International Institute of Information Technology, Gachibowli, Hyderabad 500032, India

Prof. Devon Shipp Department of Chemistry & Biomolecular Science, Clarkson University, 8 Clarkson Avenue, Box 5810, Potsdam, NY 13699, USA
e-mail: dshipp@clarkson.edu

Mannkind Corp., North Avenue Paine, Valencia, CA 91355, USA

Adrienne Stamper Chemistry Department and Center for Advanced Materials Processing, Clarkson University, Mannkind Corporation, 1 Casper St., Danbury, CT 06810, USA

Magdalena Stobiecka Department of Chemistry, State University of New York, Potsdam, NY 13676, USA

Zuocheng Wang Department of Chemical & Biomolecular Engineering, Clarkson University, 8 Clarkson Avenue, CAMP Annex, Box 5708, Potsdam, NY 13699, USA

Center for Air Resources Engineering and Science, Clarkson University, Box 5708, Potsdam, NY 13699, USA

Chapter 1
Models of Size and Shape Control in Synthesis of Uniform Colloids and Nanocrystals

Vladimir Privman

Abstract We review approaches to explain mechanisms of control of uniformity (narrow distribution) of sizes and shapes in solution synthesis of nanosize crystals and colloid particles. We address aspects of modeling of geometrical features and morphology selection, emerging as results of kinetic processes involving diffusional transport of matter, ranging from nucleation to growth by aggregation and to mechanisms of formation of well-defined shapes.

Keywords Aggregation • Cluster • Colloid • Crystal • Deposition • Detachment • Diffusion•Growth•Morphology•Nanocrystal•Nanoparticle•Nanosize•Nucleation• Symmetry

1.1 Introduction

Many applications of synthetic microscopic particles require them to be uniform. Kinetic mechanisms of formation of particles of narrow size and shape distributions in solutions, differ for various types of the particles: Here we refer to colloids as suspensions of few-micron down to sub-micron size particles, whereas nanoparticles and nanostructures are objects of smaller sizes, typically under 0.01 μm (10 nm). More generally, synthesis of well-defined products has to aim at uniformity of composition, internal structure/morphology, and surface properties.

Theoretical modeling approaches have to identify key mechanisms of particle size and shape selection. Indeed, frequently the actual modeling approach is limited by the computational difficulties because numerous multi-scale kinetic processes are involved: nucleation, growth, aggregation, and surface interactions of atoms/molecules/ions (including their chemical reactions with each other and with the solution species), of nanosize building blocks, and of the forming particles. Therefore, a realistic modeling approach typically singles out a subset of those kinetic processes that can explain size and/or shape uniformity for situations of experimental relevance. Here we review aspects of several approaches and results [1–17], includ-

V. Privman (✉)
Department of Physics, Center for Advanced Materials Processing, Clarkson University, 8 Clarkson Avenue, CAMP, Box 5721, Potsdam, NY 13699, USA
e-mail: privman@clarkson.edu

E. Matijević (ed.), *Fine Particles in Medicine and Pharmacy,*
DOI 10.1007/978-1-4614-0379-1_1,

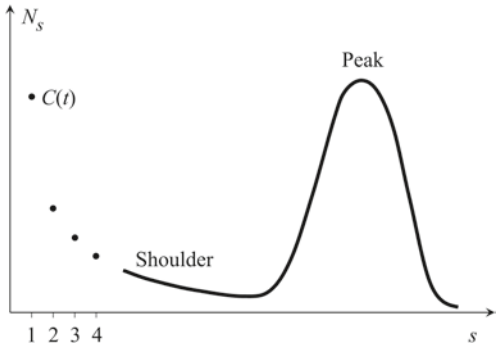

Fig. 1.1 A desirable particle size distribution at large time, t, peaked at the large cluster sizes. The peak forms and evolves due to the consumption of singlets, supplied/nucleated/maintained at the concentration $C(t)$, by a kinetic process which keeps the relative width of the peak small. The depiction for $s = 1, 2, 3, 4$ emphasizes that the particle sizes, s, are actually discrete, even though for larger s, the distribution can be treated as continuous, with $\infty > s \geq 0$

ing studies of burst-nucleation of crystalline nanoparticles in solution, the accompanying process of diffusional aggregation of these nanoparticles to form uniform polycrystalline colloids, and shape selection in nonequilibrium growth.

In applications, colloids dispersions are typically regarded as "monodispersed" for particle size distributions of relative spread up to 6–12%. At the nanoscale, we expect that most nanotechnology device applications will necessitate even stricter control: "uniform" size and shape requiring particles/structures to be "atomically identical." Thus, methodologies for uniform particle synthesis, which have a long history in colloid chemistry [1, 18, 19], have drawn renewed interest, but also faced new challenges with the advent of nanotechnology.

Here we consider those systems and synthesis processes which involve both the particles and "building blocks" from which they are formed, suspended typically in an aqueous solution of controlled chemical conditions. The transport of matter in the system, at all scales, is assumed to be diffusional. The "building blocks," termed monomers or singlets, in nanoparticle/nanostructure synthesis are solute species: atoms, ions, molecules. For colloids, the singlets are in many cases the nanosize, typically nanocrystalline precursor "primary" particles. The supply of the latter is controlled by their own burst nucleation. In both cases the monomers can also be introduced externally as a means to control the process kinetics.

Particle (cluster) size, s, distribution with a peak at large sizes, is schematically drawn in Fig. 1.1. Most processes that make the peak mean-s value grow also broaden it, for example, cluster-cluster aggregation or cluster ripening due to exchange of monomers. Therefore, they cannot yield a relatively narrow peak. This occurs because larger particles have bigger surface area for capturing small clusters/monomers, as well as on average less surface curvature, resulting in slightly better binding and thus less detachment of monomers. As a result, the larger-particle side of

the peak "runs away" from the smaller particle side (see Fig. 1.1) resulting in peak broadening as the clusters grow.

Approaches to obtain a narrow size (and shape) distribution include blocking the growth of the "right side" of the peak (see Fig. 1.1) by synthesizing the particles inside nanoporous structures or objects such as micelles or inverse micelles, e.g., [20, 21]. This technique has a disadvantage that additional chemicals then remain part of the formed particles. Another approach has been by seeding, i.e., growth on top of separately/earlier prepared/synthesized smaller uniform size and shape template particles, e.g., [22].

In Sect. 1.2, we consider [9–11] the process of burst nucleation: rapid growth of particles forming in a supersaturated solution of constituent atoms, molecules or ions. This process exemplifies a size selection mechanism whereby the left side of the peak (Fig. 1.1) is eroded fast enough as compared to the peak broadening due to its growth by consumption of monomers. As a result, narrow size distribution is obtained. In practice, additional coarsening processes broaden the distribution after the initial nucleation burst, typically limiting this mechanism to nanosize crystal growth stage.

In Sect. 1.3, we describe a two-stage colloid growth mechanism [1, 6, 10, 11] yielding particle size distributions narrow on a relative scale. This involves a large supply of primary-particle (precursor nanocrystal) monomers/singlets, of concentration $C(t)$, see Fig. 1.1. Availability of these monomers allows the peak to grow to large sizes in a process fast enough that the central peak is not significantly broadened. At the same time, a proper control of $C(t)$ is needed in order to avoid buildup of a significant "shoulder" always present for such growth processes at small cluster sizes (see Fig. 1.1). The monomer building blocks for such a process yielding uniform polycrystalline colloids, are actually the burst-nucleated nanocrystalline precursors (primary particles). For nanoparticle growth, there have also been studies of stepwise processes [23, 24], with batches of atomic-size monomers added for further growth of the earlier formed nanoparticles.

Let $N_s(t)$ denote the density of particles containing s singlets, at time t. Except for the small s values, see Fig. 1.1, the distribution can be treated as a function of continuous size variable. However, according to the preceding discussion the singlet concentration,

$$C(t) \equiv N_1(t), \tag{1.1}$$

has to be separately controlled in some situations. They can be supplied as one or more batches at specific times, or generated by another process at the rate $\rho(t)$ (per unit volume). They are depleted as a result of processes involving the emergence of small clusters (the "shoulder" in Fig. 1.1), and also consumed by the growing large clusters in the main peak.

For nanoparticles, a mechanism of the early formation of the peak is by burst nucleation: nuclei of sizes larger than the critical, form from smaller "embryos" by growing over the nucleation barrier. For colloid synthesis, the initial peak formation can be facilitated by cluster-cluster aggregation of at the early growth stages. In Sect. 1.4, we generally discuss some of the issues important for improving models

of uniform colloid growth, in the framework of elaboration of the two-stage model of Sect. 1.3. Specifically, we address the role of cluster-cluster aggregation. Seeding is another approach to initiating the peaked size distribution both for colloid and nanoparticle growth.

Section 1.5 addresses the problem of particle shape distribution and its control aimed at attaining uniformity. More generally, particle structure ranging from internal microscopic morphology and defects, to surface properties and to overall shapes, in both nanoparticle and colloid synthesis, are as important in applications as is particle size. Several mechanisms for particle shape control in fast, nonequilibrium growth are possible, and likely some or most apply on the case by case basis, depending on the details of the system and its kinetics. For uniform-shape growth, we have advanced a model [14], outlined in Sect. 1.5, suggesting that fast growth without development of large internal defect structures can lead to shape selection with non-spherical particle "faces" similar to those obtained in equilibrium crystal structures, but of different aspect ratios. The latter ideas have also been successfully applied [17] to explain shapes of certain growing nanostructures on surfaces, of interest in catalysis. Emergence of a relatively uniform distribution of surface structures evolving from nanoclusters to nanopyramids and then to nanopillars, was modeled [17] (not reviewed here). Finally, Sect. 1.6 offers concluding comments.

1.2 Growth of Nanoparticles by Burst Nucleation

Burst nucleation [9–11, 25, 26] is a model for growth dominated by large supply of monomers in solution. The formed embryos are assumed to be small enough that they can practically instantaneously thermally equilibrate. Therefore, the model can at best be used for growth of nanosize particles, consisting of n monomers. Indeed, a cutoff is assumed as one of the model's approximations, such that particles with $n > n_c$, where n_c is the critical cluster size (to be defined shortly), irreversibly capture diffusing solutes (monomers): atoms, ions or molecules. Whereas the dynamics in the shoulder, for $n < n_c$, see Fig. 1.2, is such that the subcritical ($n < n_c$) embryos, are instantaneously thermalized.

Burst nucleation in a supersaturated solution is driven by externally supplied or, more commonly, chemical-reaction produced supply of monomers, of concentration, $c(t)$, well over the equilibrium value c_0. In nucleation theory approaches, thermal fluctuations are assumed to cause formation of the embryos. Their surface free energy results in a free-energy barrier peaked at n_c. The actual dynamics of few-atom embryos involves complicated transitions between various sizes, shapes, and internal restructuring, and is not well understood. However, these processes are so fast that the $n < n_c$ embryo sizes are assumed approximately thermally distributed according to the Gibbs free energy of an n-monomer cluster,

$$\Delta G(n, c) = -(n-1)kT \ln(c/c_0) + 4\pi a^2 (n^{2/3} - 1)\sigma. \tag{1.2}$$

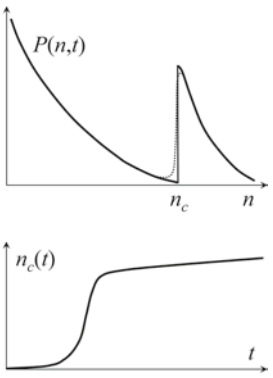

Fig. 1.2 The large-time nanoparticle size distribution in the burst nucleation model is sketched in the top panel. The actual distribution, depicted by the *dotted line*, if steep but continuous near n_c. The time dependence of the critical cluster size, n_c, is shown in the bottom panel. A short induction period is followed by the "burst," and then linear growth but with a negligibly small slope

Here k is the Boltzmann constant, T is the temperature, and σ is the effective surface tension. The effective solute radius, a, is defined in such a way that the radius of an n-solute embryo is $an^{1/3}$. It can be estimated by requiring that $4\pi a^3/3$ equals the unit-cell volume per singlet (including the surrounding void volume) in the bulk material. This free-energy attains maximum (the nucleation barrier) at n_c,

$$n_c(c) = \left[\frac{8\pi a^2\sigma}{3kT\ln(c/c_0)}\right]^3. \tag{1.3}$$

The first term in Eq. (1.2) is due to the bulk of the n-monomer cluster and is negative (since $c > c_o$), favoring growth of clusters. The logarithmic dependence on the monomer concentration derives from the entropy of mixing of noninteracting solutes. The second term represents the surface free-energy, proportional to the area, $\sim n^{2/3}$, and positive, thus suppressing growth of clusters. This term dominates for $n < n_c$, and results in the nucleation barrier. Thus, clusters with $n < n_c$ are assumed instantaneously thermally distributed. However, the kinetics of larger clusters, $n > n_c$, is assumed to correspond to fast, irreversible capture of monomers. These assumptions are typical for homogeneous nucleation. The unique aspect of burst-nucleation in solution is that the bulk free energy term in Eq. (1.2), is dependent on the monomer concentration and therefore varies with time. As a result, the critical cluster size, $n_c((c(t))$, as well as the height of the nucleation barrier, are time-dependent.

A standard assumption in the nucleation theory has been that, for approximate estimates and understanding of the growth of the cluster sizes, the distribution of their shapes can be ignored. A representative particle is assumed spherical in the calculation of its surface area and the monomer transport rate to it. There are many possible effect of the actual particle shape distribution and surface structure at various faces (for crystals) on the transport of the surrounding solute/suspension matter and on other properties and parameters. For example, effective surface tension of spherical particles depends on their radius via surface curvature. All these geometry- and structure-dependent modifications are usually ignored not just because of the computational difficulties of treating multi-parameter distributions but primar-