

**Industrial Applications of Nanoparticles**

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ARTICLE

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Research efforts in the past two decades have resulted in thousands of potential application areas for nanoparticles – Which materials have become industrially relevant? Where are sustainable applications of nanoparticles replacing traditional processing and materials? This tutorial review starts with a brief analysis on what makes nanoparticles attractive to chemical product design. The article highlights established industrial applications of nanoparticles and then moves to rapidly emerging applications in the chemical industry and discusses future research directions. Contributions from large companies, academia and high-tech start-ups are used to elucidate where academic nanoparticle research has revolutionized industry practice. A nanomaterial-focused analysis discusses new trends, such as particles with an identity, and the influence of modern instrument advances in the development of novel industrial products.

1. Introduction: What makes nanoparticles different from solids or chemicals?

Successful products in the chemical industry provide a specific benefit: Pharmaceuticals interact with organisms, construction polymers sustain mechanical stress and paints provide surface protection. Simple things we know from our everyday life, but, why is the chemical industry so competitive in moving into new markets? Why is there a respectable flow of new technology, patents, companies and jobs in the chemical industry? The following article explores the role of nanoparticles in industrial applications. We specifically show how scientific work has led to novel products, or replaces established chemical solutions through a nano-particulate formulation. This analysis is valuable when designing nano-related research studies and results in a number of currently emerging fields of research.

Why nanoparticles? At first sight, the use of heterogeneous materials (i.e. blends of a particle and a continuous phase such as a polymer) appears unattractive. If one might stick with a chemically well known “simple” but homogeneous product, later strategy appears more elegant and attractive in terms of costs, environmental impact and ease of design. When we look at current chemical industry products, however, we already realize how many components and additives are used, i.e. we rarely use chemically pure materials in a final product. The following section therefore first analyses the purpose of presently used ingredients. In parallel, this permits investigating where and why a given ingredient may be successively replaced by a nanoparticle-enabled material. By analogy, this type of analysis is of obvious interest to the academic community: It provides farther reaching ideas, through which nanoparticle research can make an industrial impact.

1.1. Particle-specific properties: Movement, hardness, magnetization, rheology and colour

Chemical products can be a result of a defined chemical property (i.e. a pharmaceutical that blocks a specific enzyme), or a set of properties (strength, colour, UV-protection, taste...).

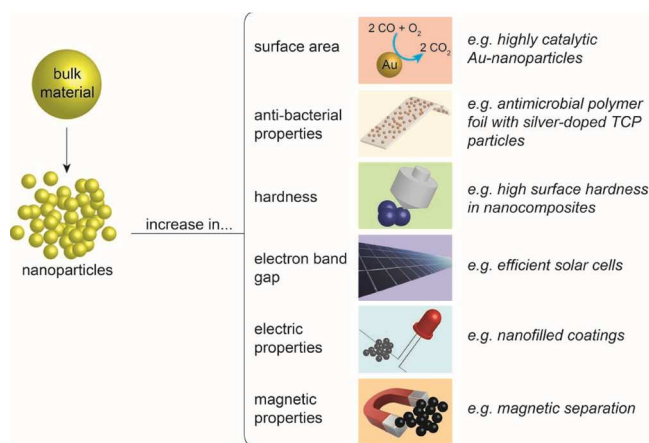


Fig. 1: Bulk materials cannot be implemented in most fluid products unless made very small. Diminution affords an enormous change in surface area – a key economical aspect of nanoparticle synthesis and provides a huge interface between the constituents. For catalytic, antimicrobial and many electronic properties, these interface properties add significant value to the final product.

The properties of an enzyme inhibitor are clearly related to a specific arrangement of atoms. Hence, traditional chemical companies rely on chemists with skills required to get constituents in place. Most

industrially important material properties in the consumer goods sector, however, can be realized through different means (e.g. inorganic or organic stabilizers). This opens tremendous opportunities for the incorporation of nanoparticles, particularly where non-traditional material properties are needed, such as catalytic, biological or electrochemical activity.

Valuable chemical industry products are a result of designing a set of properties within a material. Today, industrial development therefore considers nanoparticles as an extended toolbox containing traditionally difficult to realize properties. An example shall illustrate this: Classical petrochemical polymers such as polystyrene or poly(butadiene) have become most sophisticated products available at low price and high purity. Their production is global, and characterized by a fierce competition in costs. In most consumer applications, however, additional properties are required, and additives for colour, thermal and light stability or improved strength significantly improve the value of the polymer. From an economic point of view, a company may often make more revenue from modifications and property adaptations, than from the pure base polymer itself. As a result of this, the Western chemical industry has often moved to higher integrated products (multiple components). As a consequence this is by far the largest area, where academic nanoparticle research has made a true impact.

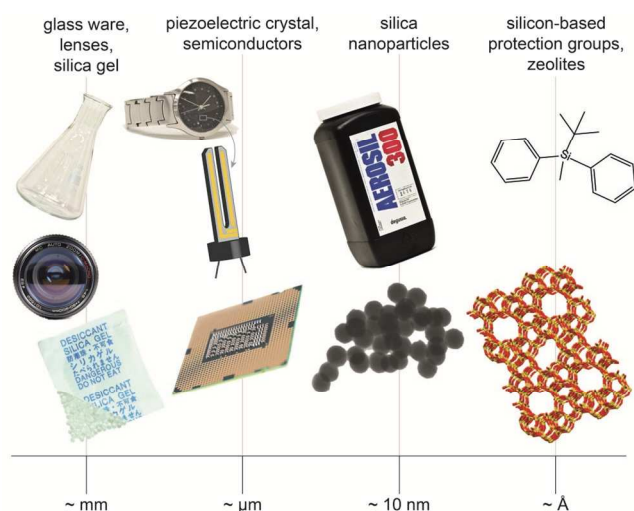


Fig. 2: From atomic/molecular Si to bulk Si-based materials: Size-dependent forms of Si and SiO₂ visualize the diverse application areas of one and the same chemical element. Size is clearly a property defining use of Si-based materials. Chemists may best design at the nm-level, material scientists at the intermediate 10–100 nm range, and mechanical/process engineers at the bulk scale.

Key examples of inorganic solid properties are given in Figure 1. Silicon best serves as an example where chemical (molecular) properties at the sub-nm to few nm level are used in chemistry and crystallographically well-defined materials (see Figure 2). Particulate properties define additives, and bulk properties make up for what we use in glass, quartz and desiccants. Well-known material attributes such as hardness, for example, are typical property of ceramics or metals, but rarely associated with polymers. Hardness, however, can be added to a product through the use of small, hard particles, i.e. we can think of the “additive” as an ingredient conveying hardness. Similarly, UV-radiation absorption,

magnetization, colour, or reflectivity can be added to an otherwise sensitive polymer base in the form of nanoparticles.

Most of the nanoparticulate additives have become very established: For example nanoparticulate carbon was developed early in the 20th century as so called carbon black, and makes up several 10% of a typical car tire. Obviously, the term “nano” was only coined much later. Similarly, a number of most established chemical products would be called “nano” if introduced today. All of these products have been around for decades and are generally recognized as safe.

1.2. Chemically functionalized nanoparticles as equivalents to complex molecules

Chemists design molecular products using thousands of well-established building blocks or subunits. An example shall be discussed in Figure 3: A dye (a betanin) shall have linker properties for attachment and processability (e.g. solubility in water). A chemist will easily identify suitable modifications to the dye’s functional core part (the conjugated system), to alter the molecules solubility and material affinity.

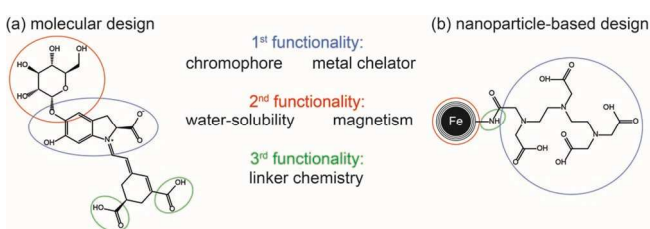


Fig. 3: Molecules combine properties of sub-units (left). The structure of a functional nanoparticle follows a similar design concept: (a) The functional dye betanin with a carboxylate attachment unit, and water-solubility conveying sorbitol (top) and (b) a magnetic metal chelator (“magnetic EDTA”) with acid protection (carbon layer), force anchor (magnetic metal core) and complexing surface ligands.

When incorporating the solid properties of a nanoparticle in a product (e.g. magnetization), an analogous procedure can be used, and the particle’s surface is chemically modified (Fig. 3b). The similarity between a traditional industrial chemist’s job and a nanoparticle modification is striking – and suggests emergence of much more complicated nanoparticles in the coming years. For chemists, carbon surfaces may eventually be looked at as “large” ligands, with a need for surface specific reactions and complex 2D nomenclature. It is obvious, that our present, highly elaborate reaction concepts from homogeneous phase chemistry (organic solvents; traditional organic chemistry) will change when being used on surfaces and liquid/solid interfaces.

1.3. Small particles allow sustainable application of solids on large areas

Solid materials, particularly inorganic materials, display a fascinating plethora of behaviour, most of which meet societal needs at some point (and can become an industrial product). Solar cells, for example, provide a recent example, where a whole research field and associated industry attempt to spread a solid material property (light induced charge separation and collection) over large area in an economic way. Where do we find existing analogies within established products? Paints, particularly water-based effect pigments, are successful developments where complex optical

behaviour has become a commodity product (e.g. water based car paints).

1.4. Manufacturing of nanoparticles: Direct processes are often more sustainable

Nanoparticles rarely form spontaneously and their large surface area usually demands for sophisticated manufacturing routes. Two key pathways can be distinguished (Figure 4): A raw material may be cut up into “molecular” entities through a (chemical) dissolution process and yield a usually distinct molecular intermediate form of the material. That intermediate is then reacted in a kinetically controlled way, or using interface stabilizing reagents (e.g. high affinity surfactants)¹. The probably best known examples are the preparation of quantum dots using a capping agent, and the preparation of silver nanoparticles from silver nitrate (obtained from dissolving bulk silver with nitric acid). Alternatively, one may directly apply mechanical energy to split a bulk material into smaller and smaller particles, eventually ending up with nanoparticles. This non-chemical process requires complex milling equipment and is much less established in the academic world. Industrially, however, paint and ink mills have been around for several decades, and many traditional printing industry products would be called “nano” today. In both routes, most particles are chemically modified before use.

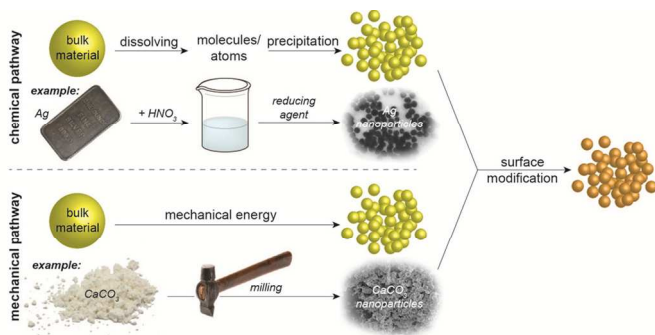


Fig. 4: Two classical pathways yield nanoparticles: Chemical concepts and energy can be used to split a bulk piece of a starting material (e.g. metallic silver) into molecular/ionic subunits (Ag nitrate), that is then converted into a nanoparticulate material. Cutting a raw material into very small pieces by mechanical energy (bottom) appears cumbersome at first sight, but often provides an energy efficient and more sustainable access to nanoparticles.

Chemists will intuitively favor the use of chemical intermediates. Here, a highly reactive chemical is typically used to split up the raw material solids into single ions (dissolution of Ag by HNO₃). It comes to a surprise, however, that many mechanical or physical methods for nanoparticle synthesis are less energy demanding than these chemically well accessible routes. This is a direct result of surface energy of typical nanoparticles that lies in the area of 0.2 – 4 J per m². For a typical nanoparticle sample (e.g. silver with 100 m²/g specific surface area), the surface energy of the product per mol silver is 108 g/mol x 100 m²/g x 1.25 J/m² = 13.5 kJ/mol. If we compare this (small) energy with typical reaction enthalpies (e.g. dissolution of silver in nitric acid, reduction; usually a few hundred kJ/mol), it is obvious that most of the chemically invested energy is lost (Figure 5).

Nanoparticle samples are never of equal size, hence, reporting on the size distribution is a key quality aspect of a material. Here, the chemical synthesis route is often advantageous as partially reversible formation reactions allow preparation of technically attractive

products such as monodisperse silica (so called Stöber process). In contrast, any mechanical or condensation-type nanoparticle synthesis always results in much broader particle size distributions (see Figure 6). Chemists will immediately be reminded of the narrow molecular weights from living polymerization if compared to conventional polymerizations.

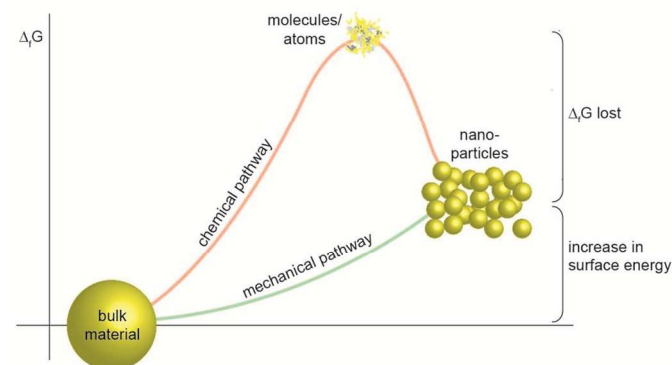


Fig. 5: Energy profile (Gibbs free energy) along chemical or mechanical nanoparticle preparation. The chemical pathway suffers from an *a priori* unnecessary diminution step (high intermediate ΔG) since the atomic/ionic or molecular intermediates are then again combined to intermediate (i.e. nm) size particles. For the majority of the constituents, their local state in a nanomaterial resembles the one in the bulk.

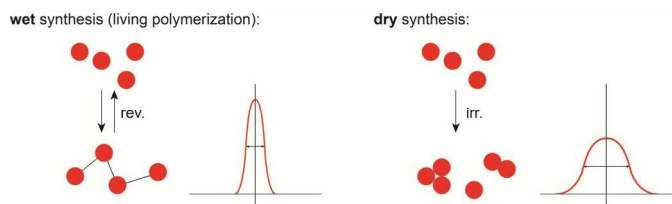


Fig. 6: Nanoparticle synthesis in liquids often involves partially reversible steps, and exchange of constituents between different particles may even permit monodisperse particle size distribution. In parts, this is similar to living polymerization, where all polymer chains are of similar length. In dry synthesis methods, however, particles and constituents usually combine in an irreversible process. The broad product size distribution is a result of particle-particle collision statistics and kinetics.

2. Established industrial applications

Nanoparticle application may best be viewed along material classes: Metals², oxides³ and polymers⁴ have been reviewed earlier, and usually reflect a tight dependence on available preparation methods, i.e. easy accessible materials rapidly caught industrial interest:

2.1. Particles as chemically inert additives

Small, chemically inert particles have been prominently used in pigments, polymer fillers and surface finishing next to bulk applications such as ceramics. None of them were traditionally called “nano”, and most scientist are little aware of the rather broad, established use of small particles. Historically most interesting is the use of various carbon soot pigments in cave and pottery paintings and carefully reduced iron oxide colloids as red and yellow pigments.

Carbon, titania and silica polymer fillers. The availability of industrially manufactured polymers in the early 20th century resulted in a rapid development of additives and fillers. Improvement in strength, abrasion resistance (tyres) and rheology triggered mass production of nanoparticulate carbon (“carbon black”, Figure 7) and chemically functionalized nano-carbon particles⁵. Titania (TiO_2) as a non-toxic, abundant material with one of the highest whitening properties (high refractive index $n = 2.2$) was initially manufactured over a wet route using sulphuric acid as a solvent. More recently, the so called chloride process has been established. Here, gaseous TiCl_4 is first manufactured from illmenite ore, carbon and chlorine. Aerosol flame synthesis then converts the TiCl_4 to submicron size TiO_2 aerosols as the key ingredient to white paint. Today over 6.5 Mio tons of pigmentary titania are globally manufactured per year. Since silica is amenable to a similar process (preparation of SiCl_4 and conversion to SiO_2 aerosols), so called fumed silica soon became an industrial base chemical.⁶

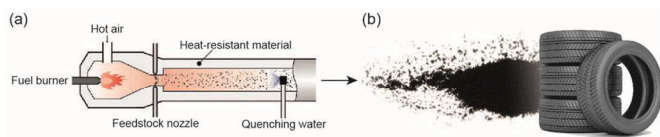


Fig. 7: (a) Large-scale carbon black production by flame spray pyrolysis (FSP) (reproduced with permission from Ashai Carbon JP). Hydrocarbons are partially combusted and decomposed into soot particles using large burners. (b) The major industrial application of carbon black is in rubber reinforcement and as a black pigment in car tires.

2D particles as polymer fillers. Apart from the modification of the mechanical, electrical, surface or optical properties, polymer fillers are also broadly used for altering the permeability of polymer films. This is usually achieved by dispersing plate-like fillers in a polymer matrix; ideally the platelets are aligned with the plane of the polymer film. The crystalline and thus impermeable 2D particles allow reducing the permeability of a film by orders of magnitude compared to the polymer alone.⁷ Often applied flakes include nanoclays, graphite, mica or vermiculite.

Effect pigments, dyes and UV protection. More recent advances in aerosol synthesis permitted the low cost manufacturing of nanoparticulate titania and zinc oxide.

In pigments, the high-refractive index titania permits strong optical effects and high colour depth. After recognizing the oestrogen-like activity of numerous organic sunscreen additives, inorganic UV absorbing pigments based on titania and zinc oxide were introduced at large scale to the cosmetics industry, in polymers, consumer goods and surface treatments. There, nanoparticles were advantageous since below about 50 nm, visible light scattering becomes negligible, and corresponding UV protection can be realized with a visually (human eye) nearly transparent additive (Figure 8).

Processing aids. Amorphous silica (E551) is used as rheology additive in powders (enhanced flow), anti-caking agent in food products, as additive in animal feed or as support for heterogeneous catalysts. This fumed silica products are made by flame synthesis, a result of an unusual discovery, namely the possibility to combust volatile silicon compounds at large scale whilst handling the demanding corrosive high temperature gas stream (Cl_2 and HCl at 500 – 1000 °C).⁸ This industrial development opened applications of silica at a size window between chemical effects (Si as part of a

molecule) and bulk property (glass window, see Figure 2). Today that size window has become the playground of nanotechnology.

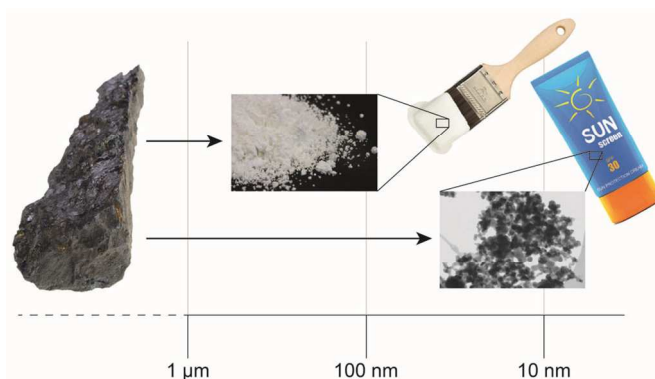


Fig. 8: Classical submicron sized TiO_2 pigments ($\sim 0.2 \mu\text{m}$) as e.g. used in paints and as opacifiers in various applications are prepared from illmenite (a titania ore) using chemical processes (dry or wet). Further reducing the particle size to nano-sized particles ($< 50 \text{nm}$) recently allowed increasing light absorbance in the UV region whilst reducing (undesired) skin whitening in high-quality sunscreen.

Functional surfaces. Large application area dependent industries (e.g. housing, vehicle shells, solar cells) profit in particular from advances in nanoparticle research for a most simple reason: Nanometer-thick active ingredients are often applied as coatings, and thus become very cost attractive. Coating an area of 1m^2 with particles of 50 nm as a monolayer requires only 20-200 mg material. Since large surface area properties are usually traded at a “function per area” basis, the benefit from a small amount of nanomaterial is enormous. A prominent example of a successful application is window glass with self-cleaning property⁹ (Figure 9) or improved anti-scratch properties for consumer exposed surfaces. On flexible substrates (polymer films, paper), roll to roll coating at high line speed is particularly amenable for low cost manufacturing of products with high surface value. This industry profits from abundant experience over decades in the paper printing industry.

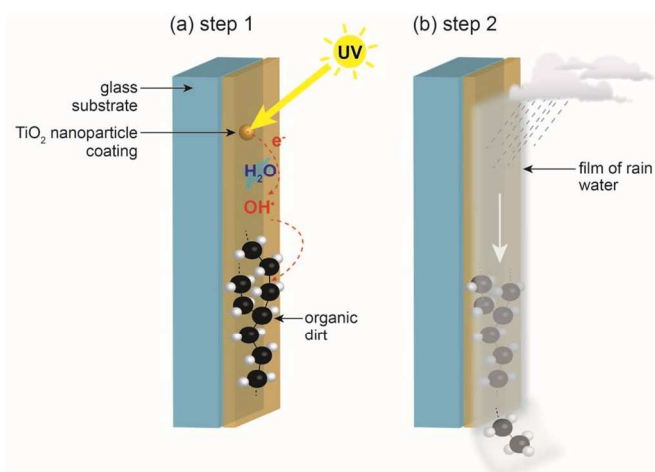


Fig. 9: Self-cleaning window or car glass (e.g. Pilkington ActivTM) functions in two steps: (a) a photo-catalytic coating containing TiO_2 nanoparticles reacts with UV light and breaks down organic matter (dirt). (b) The organic residues are then easily washed from the hydrophilic surface by rain water.

2.2. Chemically active particles: Catalysts, biomaterials and antimicrobial additives

Active surfaces on solids display chemical reactivity that is industrially applied as heterogeneous catalysis. Bioactivity, i.e. the benign interaction with living tissue/cells, is a key condition for biomedical implants and devices. In the case of activity against small organisms, e.g. antimicrobial activity, the inhibition or killing of microorganisms is part of the product definition. In all areas, the surface effect is directly related to particle size for obvious geometric reasons, and smaller particles have become advantageous for their better mass or volume related performance (effect per volume or per mass of material). The academically most advanced active surfaces are part of catalysis, which became a field of research on its own in the mid-20th century. Again, at that time, the term “nano” was not regularly used.

Heterogeneous Catalysis. The surface activity of gold is undoubtedly the most prominent and outstanding example for a “nano” effect with industrial relevance.¹⁰ Technically used catalysts, however, were already using Ni, Pd and Pt nanoparticles for over half a century and the beneficial use of small (nm sized) metal particles dates back to the Doebereimer’s lighter (ignition of hydrogen on Pt sponge in the 19th century). There are a number of excellent reviews on nanoparticles in catalysis¹¹ therefore this large and most fascinating area shall not be treated farther within this article.

Biomaterials. The discovery of the nanoparticulate form of minerals in bone and teeth has initiated research on nanostructured biomaterials almost three decades ago. The use of “nano” surface, morphology and architecture continues to fascinate biologists. Orthopedic surgery has been the first to profit from nanoparticulate biomaterials.¹² Here, mainly inert or biologically tolerated materials were used for improving healing, implant adhesion and tissue response. Chemically active biomaterials such as bioglass strongly profit from smaller particle size since the improved surface to volume ratio increases the materials activity.¹³ Particle size enables mobility – a key aspect in transporting or delivering a material to a site of application. As a consequence, this enabled the huge field of nanoparticle-based drug delivery and therapy.¹⁴

Antimicrobial additives. The traditional use of certain heavy metals (silver, copper) against microorganisms has been known for several millennia. The possibility, however, to prepare metals in the form of very small particles, and reliably spread them over large consumer surfaces, has provided an astonishing revival in interest around these “old” antimicrobial agents (see Figure 10). Here, the benefit from making a well-known bulk material very small is immediately visible.

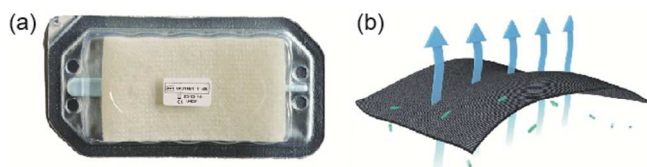


Fig. 10: (a) Antimicrobial polymer foil with silver/additive nanoparticles (Perlazid®, Perlen Packaging, Switzerland) and (b) antimicrobial textile with silver nanoparticles (active>silver™ technology, Schöller Textil AG, Switzerland) which inhibit the reproduction of odor-causing bacteria and improves the moisture management. (Reproduced with permission by Perlen Packaging and Schöller).

3. Insights from the chemical industry: Cosmetic UV protection and colour filters for LCDs

3.1. Replacing traditional pigments

Colour in consumer goods is omnipresent. Traditionally, providing colour has been in the hands of inorganic (pigment) chemists or organic synthetic chemists linking structure (e.g. substitution in an indanthrene moiety) to colour information. A new way to look at colour was initiated by the development of quantum dots, small semiconductor particles with size controlled electronic levels and therefore also colour.¹⁵ The size dependent optical properties of such particles are a true “nano” effect and can be understood in terms of classical quantum mechanics.

3.2. UV protection for cosmetic products

Background. When light hits a particle, it can be reflected, scattered or absorbed. For sub-micrometer particles, the reflection is often very small. Scattering and absorption are therefore the major attenuation mechanism for nano-sized particles and the predominance is related to the particle size and the chemical composition.

Inorganic sub-micrometer UV filters. Besides the widely used oil- or water soluble organic UV filters, nano-sized inorganic materials like titanium dioxide (TiO₂) and zinc oxide (ZnO) have been used as physical sunscreen actives since many years and are still indispensable components in sun care products. The popularity of such inorganic UV filters results from their effectiveness and safety. For sunscreen application, cosmetic grade TiO₂ and ZnO with a primary particle size of less than 100 nm are used to minimize the unwanted skin whitening effect and to provide high UV protection efficacy and pleasant skin aesthetics.¹⁶

A new class: Organic sub-micrometer UV filters. In search for a new UV absorber exhibiting a good solubility in cosmetic solvents, researchers at BASF got increasingly frustrated, because the large molecules they were looking at showed mostly very low solubility. One day they came up with a creative idea. Making a virtue of necessity, UV absorbing molecules with weakest solubility were identified in order to create organic UV absorbers in sub-micrometer pigment form as already known from inorganic filters. This led to a new class of UV filters.¹⁷

Methylene bis-benzotriazolyl tetramethylbutylphenol (MBBT) was the first representative of this new class of UV absorbers. The structure of MBBT is depicted in Figure 11a. The commercial form is produced by a milling process as a 50% aqueous dispersion of colourless organic microfine particles with a size < 200 nm (d_{0,5}). These small particles are stabilized in their size by a surfactant.¹⁸

Figure 11c shows the UV spectra of MBBT dispersions at different particle sizes. The highest extinction is achieved at a particle size of d(0,5) = 160 nm, which corresponds to the end point of the milling process. It has been shown through fractionation by centrifugation that for this UV absorber the optimal particle size would be at d(0,5) = 80 nm. With particles smaller than 80 nm the extinction decreases again. Obviously at this point the absorption has reached a saturation level, but further micronization causes less scattering, resulting in lower extinction.¹⁹

With tris-biphenyl triazine (TBT) a second UV filter based on organic, sub-micrometer, UV absorbing particles has been developed

by BASF and recently registered for cosmetic use in the EU.²⁰ The chemical structure of this filter, which exhibits exceptionally strong photo-protection in the range of 290-340 nm, is depicted in Figure 11b.

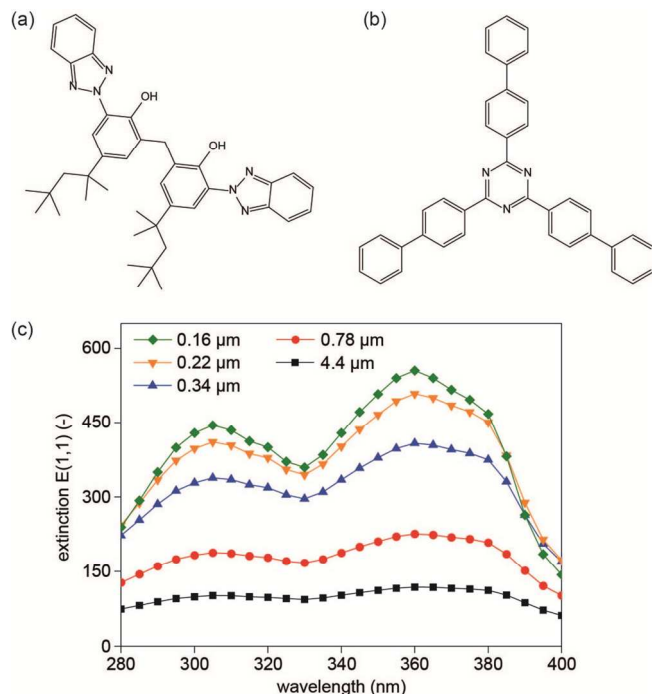


Fig. 11: A new class of organic UV filters. Chemical structures of (a) methylene bis-benzotriazolyl tetramethyl-butylphenol (MBBT) and (b) tris-biphenyl triazine (TBT). (c) The UV extinction of MBBT particle dispersions is strongly influenced by the particle size. $E(1,1)$ is the extinction of 1% (w/v) active at 1 cm optical path length.

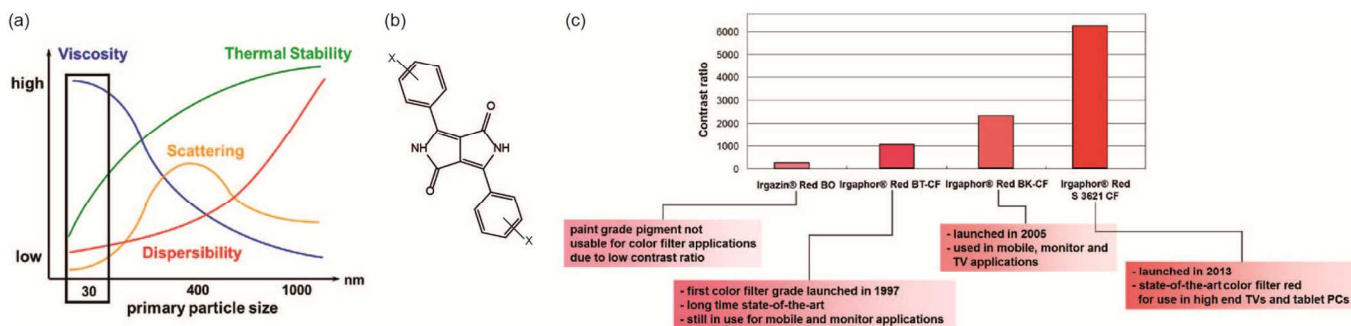


Fig. 12: (a) The crystal size is one of the key properties of pigments for LCD screens as small particle sizes enables less scattering. (b) Chemical structure of Irgaphor® Red BT-CF, a pigment designed for LCDs. (c) The evolution of BASF colour filters show an impressive increase in contrast ratio.

4. Product safety and sustainability

Market introduction of chemicals, pharmaceuticals and food components became regulated in the Western world in the early 20th century. Since then, government controlled regulatory authorities have been providing protocols for publicly available procedures deciding on the permission to apply a material in the public. For chemicals, the corresponding legal framework has grown nearly exponentially, now providing significant hurdles to innovative

3.3. Novel organic colour filters for LCD-technology

Liquid-crystal display (LCD) technology, developed in the 1990s, is today the dominant display technology and widely used in mobile phone displays, desktop and tablet computers, notebooks and high-definition television screen. Apart from the liquid crystal layer, the most important components of a LCD screen are the red, green and blue (RGB) colour filters based on organic high-performance pigments. These pigments have played a key role in improving the image quality of LCD screens over the years. Screen performance parameters such as colour purity, brightness and contrast ratio are primarily dependent on the properties of the pigments used (see Figure 12a). The key properties for colour filter pigments are a small crystal size for a high transmission and contrast ratio of the colour filter and a tailor-made surface treatment to ensure good dispersibility and high thermal stability of the pigment in the formulation and during processing.

Former Ciba now BASF launched the first colour filter grade pigment in 1997 named Irgaphor® Red BT-CF based on Diketopyrrolopyrrole (DPP) (Figure 12b) discovered in the early 1980s. Due to its high transparency it became the state of the art colour filter pigment for notebook and desktop monitors, and later for the rapidly growing TV applications. Recently, high-definition television (HDTV) based on LCDs have been developed, which created a demand for further improved colour filter pigments with higher contrast ratio. BASF's answer to this market request is the newly developed launched Irgaphor® Red S 3621 CF in 2013. The new product also is based on a novel pigment chemistry combined with a special manufacturing process using tailor made crystal growth inhibitors. This allows a better control of the pigment morphology with crystal sizes of less than 40 nm, resulting in a considerably lower scattering of light.²¹ The new product is equipped with a new proprietary surface modification technology. The final result is a new LCD colour filter pigment system with outstanding properties.

chemical design. For nanoparticles, the executive government in Switzerland was amongst the first to globally issue binding recommendations for industrial product development (a) and evaluation criteria (b). Within the last decade, the then emerging field of nano(eco)toxicology has evolved into an established field of research. Here, non-classical parameters play a key role in chemical toxicology: Nanoparticle dispersion stability, dissolution, surface activity and complex bio-distribution pattern complicate the already demanding toxicology investigations of (traditionally) molecular compounds available as well defined solutions.²² Carbon nanotubes

are the most prominent example of a product development stopped as a result of raising toxicity concerns.

4.1. Product evaluation: Role of physicochemical properties, solubility and composition

Risks are evaluated as the product of the (internalized) exposure and the hazard potential. If no exposure occurs throughout the lifecycle, there is no risk, regardless of the toxicity. Prominent examples of industrial products considered as safe based on reliable exposure limitation are found in electronics. Here, some very toxic compounds are used inside tightly sealed containers – semiconductor chips. Another contemporary example would be battery components, as shown in Figure 13 top left.

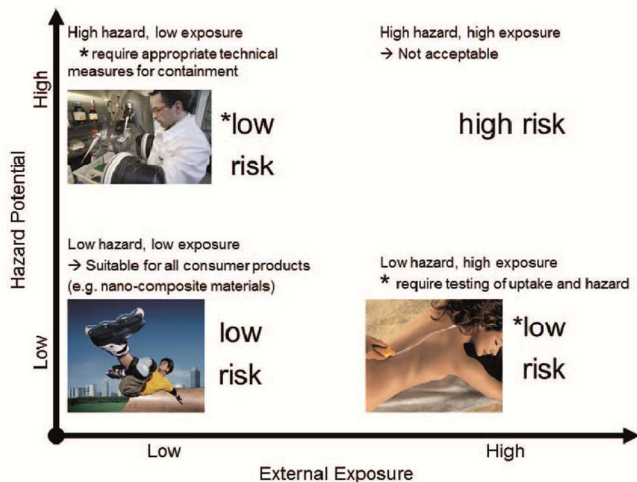


Fig. 13: The risk assessment paradigm states Risk = Hazard x Exposure. The examples given are energy-storage materials (handled in the glove box, upper left), nanocomposite plastics materials (lower left) and cosmetics with UV absorbing nanoparticles (bottom right). Risk is low only under the conditions indicated.²³

Risk management can alternatively mitigate adverse effects by controlling the composition of a material. If exposure is part of an application of a material (e.g. a food additive, a sunscreen cosmetic or a consumer good surface) and can per se not be avoided, then the use of biologically safe or well tolerated constituents is a prerequisite in design (Figure 13 bottom right). The ideal product is inherently safe by a combination of low hazard of the nanomaterial and low probability of release during the intended use, e.g. nanocomposite plastics with embedded silicates (Figure 13 bottom left). On the academic research level, a first rough estimate on a maximum exposure dose is often useful as a first gate to estimate later success.

Since for academic projects, but also for exploratory industrial projects, the final product is not available for testing its hazard potential, the recent proposals for grouping strategies are highly useful as orientation. Based on the simple parameters of shape, composition and solubility (as a simple, and often tabulated proxy to more complex persistence measurements), even a very innovative material can be assigned to one of four groups, which are derived from the key mechanisms of biological damage.^{24, 25}

- Low solubility, fiber-shape: need to test inhalation effects and bio-persistence in depth. Occupational exposure limits have been established on the $\mu\text{g}/\text{m}^3$ level.²⁶
- Low solubility, low toxicity by the chemical composition (LSLT): primarily generic dust toxicology by the

particulate shape, with generic occupational exposure limits on the mg/m^3 level.²⁷

- Low solubility, toxic components: e.g. heavy metals, need a case-by-case assessment.
- Soluble nanomaterials: are assessed by their composition, without regard of their size.

Scenarios of safe use can be derived from the constantly growing research results. These increasingly not only consider the pristine nanomaterial from industrial production, but also its formulation into products, the characteristics and rates of release from products, and the biophysical identity of the nanomaterial after interaction with physiological fluids. Considering the entire lifecycle, the composition remains the most important parameter, followed by shape and solubility, and finally the surface functionality and size as modulating effects.²⁷

4.2. Regulatory compliance

Nanomaterials are considered as chemicals, and as such are regulated under REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) in Europe, and under the TSCA (Toxic Substances Control Act) in the U.S.A. Nanospecific guidance for regulatory testing, e.g. REACH R7.1, typically requires a much enhanced physical-chemical characterization of structure, persistence, surface chemistry and surface reactivity, but requires only minor adaptation of established toxicological OECD (Organisation for Economic Co-operation and Development) protocols. To minimize animal testing despite the large diversity of nanomaterials that are often commercialized in variations of size or coating, grouping concepts as sketched above are a matter of priority for regulators and industry, but are as yet not commonly established. The scope of regulation is globally very different. The Environmental Protection Agency (US-EPA) has a strong focus on truly novel materials: the class of carbon nanotubes alone contributes 60 of the 160 nanomaterials that were evaluated by the EPA. In contrast, the precautionary principle in Europe has motivated a very inclusive definition that results in the re-evaluation of the possible nanostructure-related properties not only of novel but also of 10,000s of conventional particulate materials such as manufactured pigments or fillers, mined clays and many more.²⁸ The initially risk-neutral definition is applied for market screening in legally binding product inventories in Denmark, Belgium and France. These inventories and also sector-specific regulation often use – besides the size range of 1 to 100nm – additional properties such as insolubility or the probability of release to focus on the most relevant materials that may require risk assessment by nanospecific methods. Compliance to the European Cosmetics Directive requires cosmetics products to label all materials that are contained in nanoparticulate form since 2012, so that e.g. UV filters are listed with the addition of “(nano)” on the sunscreen package. Consumers can thus make an informed choice based on their personal perception and balancing of risks and benefits.

4.3. Learn from (huge) past errors?

When looking back at the largest chemistry-related problems in food chains (DDT, halogenated biphenyls, dioxins), the atmosphere (fluorochlorohydrocarbons) or the ocean (plastic), the common denominator is persistence. Large scale use of persistent technical products has resulted in the most costly liability cases ever (Figure 14, e.g. asbestos ban) and still affects the health of hundreds of thousands of people. The IUPAC defines persistence as the length of time that a substance remains in a particular environment before it is

physically removed or chemically or biologically transformed.²⁹ As such, persistence is not only a specific criterion of nanomaterials but also concerns molecular and macroscopic chemicals. The most central element in a proactive design for (novel) nanoparticle containing products, therefore, is the possibility to degrade the nanoparticle.²²

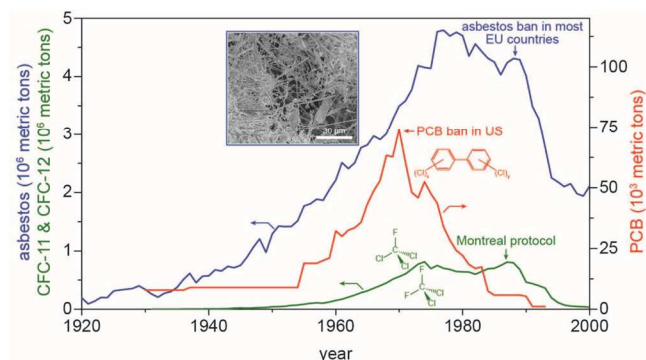


Fig. 14: Persistent substances from the chemical industry led to major health and environmental problems in the 20th century. The global production volumes for asbestos, polychlorinated biphenyls (PCB) and chlorofluorocarbons (e.g. CFC-11 or CFC-12) show a similar trend: during decades, the production steadily increased until the substance's danger was finally identified. In most cases, international or national bans provoked sudden collapse of the market.

5. Emerging industrial applications

5.1. Interaction with light: Energy, materials and diagnostics

Electromagnetic radiation shows most complex interaction behaviour with particles resulting in scattering, angle dependent reflection and various non-linear optic effects. These size-dependent effects are typical for a given size range (visible light is strongly scattered in the 20-500 nm range) and a property of materials with discontinuities (such as a particle surface). For nanoparticle research, these fundamental effects are a huge source for new and improved properties.

Inorganic solar cell constituents. Solar cells are exposed to intense radiation – this creates a strong demand for extremely bleach resistant materials, and puts severe limitations on the use of organic materials, particularly when designing organic photovoltaics. As a result, the design of increasingly or even predominantly inorganic solar cells is a major research area, and functional layers are subsequently replaced using nanoparticle based inks. A recent example are so called hole injection layers, today accessible using transition metal oxide nanoparticles.³⁰ An established application of titania nanoparticles is the Grätzel cell, which allowed to significantly decrease the cost of photochemical electricity generation.³¹ The heart of the cell is an optically transparent film of TiO₂ nanoparticles (~15 nm in diameter), which are coated by a monolayer of a charge-transfer dye to sensitize the film for light harvesting.

Colouration, radiation protection and filters. The phase out of many traditional heavy metal based pigments creates a huge demand for advanced (novel) pigments, consisting of ingredients considered more safe (i.e. different elements from presently used heavy metals). Traditional UV radiation protection in consumer goods has been a topic for organic chemistry.

Here, design of extremely stable compounds has yielded high performance UV protection additives for polymers and surfaces. Unfortunately such high molecular stability implies often a high resistance to environmental degradation, and therefore accumulation in food chain is a possible risk, increasing the chance for unexpected effects (see section 4.3. above). As a result of these environmental and human health concerns, substitution products have a chance to enter these traditional application areas.

Imaging and molecular diagnostics. Since gold nanoparticles combine mobility, strong colouration and the possibility for attachment of biomolecules, these noble metal particles are being used in diagnostic tools, e.g. pregnancy tests that can be read optically (see Figure 15). This is a fascinating example for how nanoparticles permit an unusual combination of properties: Flow of Au nanoparticles through the channel; reaction with a substrate (detection) and immobilisation at a given site resulting in a strong colour (signal generation).

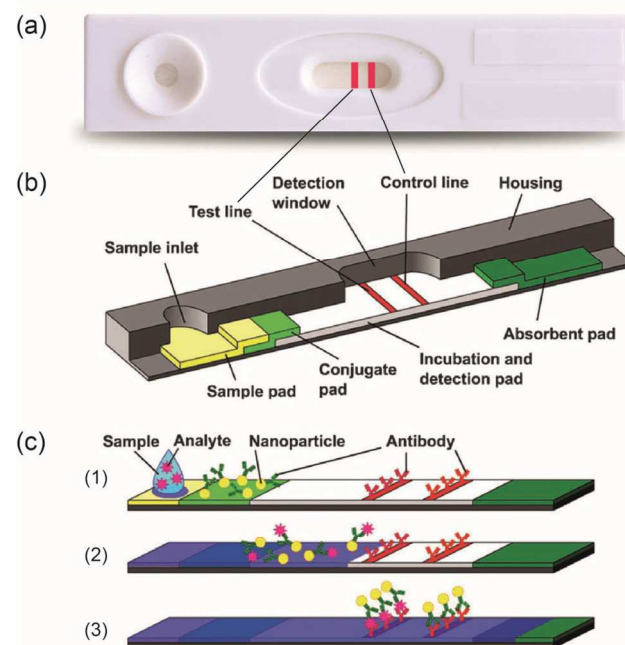


Fig. 15: Apart from catalysis, gold nanoparticles find various applications in electronics, therapeutics, sensors and diagnosis. (a) A well-known example is the application in lateral flow immunoassays, as e.g. in home pregnancy tests. (b) Schematic overview and (c) functionality of a pregnancy test (reproduced from Ref. ³² with permission from The Royal Society of Chemistry). The analyte flows on a nitrocellulose pad (1) and binds to antibody-conjugated gold nanoparticles. (2) Particles with antigens bind to a second, immobilized antibody (test line = positive readout), while particles without antigens bind to a third antibody (control line).

5.2. Magnetic chemistry and processing

Chemistry nowadays permits cost-efficient technical manufacturing of useful compounds in processes of several dozen steps. A key environmental and cost driver, however, remains separation and isolation of desired constituents, catalysts, reagents or intermediates. Dozens of elegant unit operations (distillation, chromatography,

crystallisation etc.) are standard repertoire in industrial chemistry. A new unit operation today emerges around chemically stable metal nanomagnets. Magnetic chemicals combine ease of separation and chemical functionality.³³

Magnetic catalyst supports. Nanoparticle surfaces as supports for heterogeneous catalysts permit the materials to be dispersed in a reaction medium and rapidly removed when isolating a product. Pioneering work on magnetic catalysts is reviewed by Basset and coworkers.³⁴ Carbon coated metal nanomagnets solved key problems around core stability (leaching) and improved reliability of the linker since all carbon backbones became accessible.³⁵

Chemistry at low concentrations. Ore refining, active ingredient isolation, impurity removal and pharmaceutical manufacturing are confronted with low concentrations of important constituents in large liquid volumes. At present, low concentrations of desired metals are a key economic limitation in traditional and emerging attempts for urban mining. Similarly, low contaminants in water are left untreated due to economic constraints. Most recently, dilute nanomagnet dispersions were used to handle exceptionally low contaminant concentrations based on the diffusion of reactants to the nanomagnet and efficient nanomagnet capture (Figure 16).³⁶

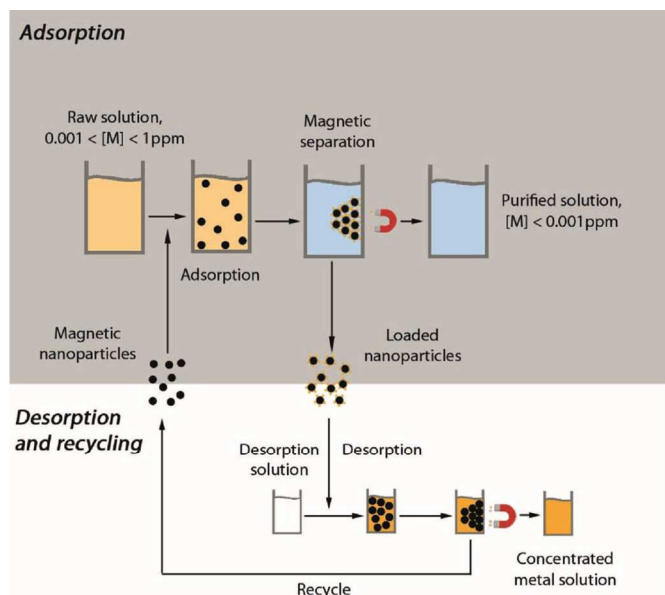


Fig. 16: Diagram for the recovery of noble metal by the use of magnetic nanoparticles. The noble metal is bound to nanomagnets which can easily be separated. The noble metal is subsequently desorbed and the nanomagnets are re-used. Reproduced with permission of The Royal Society of Chemistry.

Superparamagnetic iron oxide nanoparticles (SPIONs). SPIONs comprise iron oxide particles of about 5–20 nm, most often prepared by precipitation.³⁷ SPIONs are primarily interesting due to their superparamagnetism, which means the particles do not show magnetic interaction without an external magnetic field. As such they receive great interest in biomedical applications, e.g. drug delivery, magnetic resonance imaging, cell labelling and many more.

5.3. Large scale use of nanoporous materials

Soluble nanoparticles may serve as templates for nanopores that are otherwise difficult to manufacture, especially at large scale. Particularly sustainable particles are based on limestone, and permit nanopore introduction at low environmental burden.

Membranes and filters. Traditional manufacturing of water filtration membranes is based on so called phase inversion. Here, a non-solvent is used to precipitate a polymer in the form of a pre-shaped, partially dissolved film. This elegant process suffers from huge solvent consumption and a difficult process control. Splitting up film formation and nanopore generation recently afforded an easy to control process first leading to a composite film that is subsequently converted into the final porous membrane (Figure 17).^{38, 39}

Multiphase systems: batteries, flow through reactors and fuel cells. Separation of two compartments is a key design element in numerous technical products. Small pores are usually important for selective exchange or transport of some components. With the rapidly emerging availability of soluble nanoparticles (e.g. salts), and the robustness of nanoparticle templating (a physical method), it is expected that most consumer polymers can become available in a nanoporous form.

6. Key directions in future academic research

6.1. Material availability driven research

Rapid access to nanomaterials permits thousands of research laboratories to explore applications. Material availability has increased from a few dozen materials commercially sold at the turn of the millennium to millions of customized compositions today. The rate of application development hence has shifted from material limited (a decade ago) to applying materials (today). This has changed academic research from a recipe discovery modus to a more mature, systematic engineering of compositions and applications.

Multielement compositions. Early components from solar or fuel cells, batteries and other technical objects have been manufactured from simple compositions (e.g. pure or mixed oxides; single or two-component electrolytes etc). The past decade has witnessed a shift to more elaborate compositions and academic research now involves 4, sometimes 5 element constituents. We now observe a development well known from metallurgy, where high performance alloys shifted from two metals to half a dozen constituents in the second half of the 20th century. With this the bottle neck shifts from material preparation to material testing, however, we can expect the rate of developments to rapidly accelerate.

Inhomogeneous materials with phase boundaries. Pioneering nanoparticle products had only one phase boundary (particle surface) – with the emergence of two-phase particles, such as Janus particles, core/shell material and others suddenly material interphase have become a design component. This is of particular interest where boundaries have special (new) properties, such as in solar cells (charge separation), catalysis (e.g. spill-over), electrocatalysis (flow of electrons in a conductor; reagents in pores; non-conducting catalyst supports). Designing interfaces as a bulk commodity enables unprecedented properties, as single constituents traditionally did not permit discovery of such effects. Spintronics, even though not a nanoparticle field, is a typical example of such an effect.

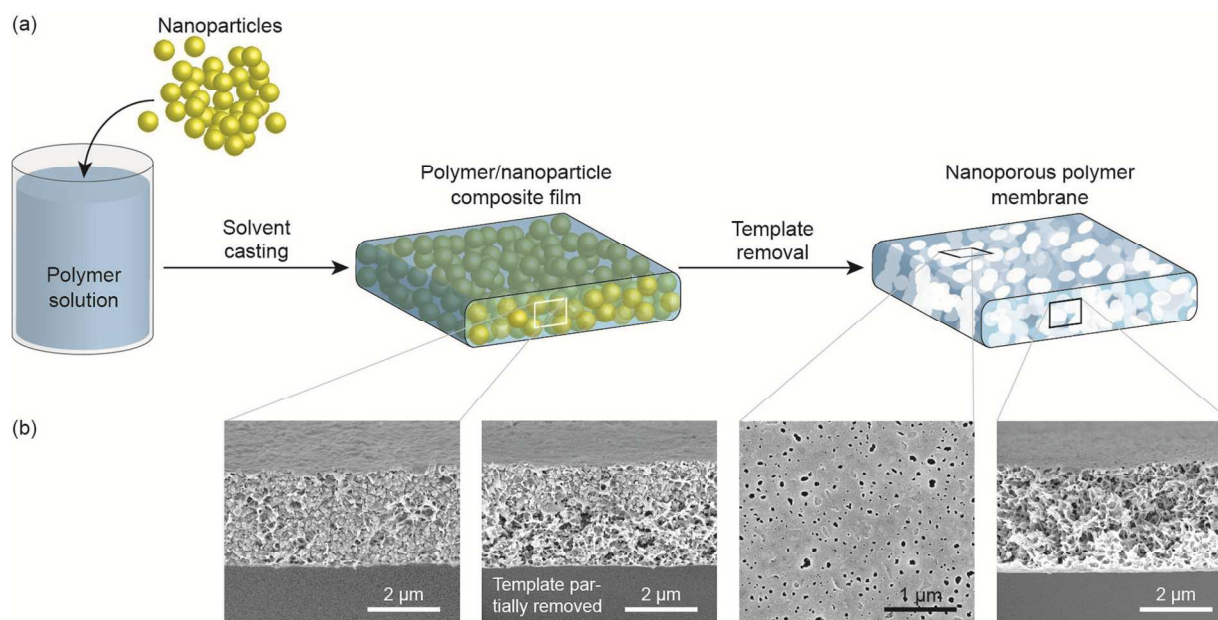


Fig. 17: (a) Membrane preparation process: a polymer/ nanoparticle dispersion is solvent casted in order to build a composite film. A polymer membrane is obtained by dissolving the pore templates (e.g. carbonate nanoparticles) by an acid treatment. (b) Scanning electron microscopy pictures before and after the template removal visualize this process.

Materials with an identity. Lately, nanoparticles of silica encapsulated DNA have been proposed for consumer goods tagging, e.g. for anti-counterfeiting.⁴⁰ Such particles are of astonishing chemical stability (silica layer), can be opened selectively with buffered oxide etch (an established technology from computer chip manufacturing) and detected using polymerase chain reaction in conventional instruments. Most recently, particles with an identity have even permitted labelling of living organisms, and thus provide a valuable tool to ecological research when elucidating food web architecture or evaluating species habitat for conservation or sustainable use (e.g. sustainable fishing).⁴¹

6.2. Instrumentation and analytical capabilities permit novel research fields

Structure elucidation and chemical analysis at the level of atoms changes experimental design. The rapid development of instrumentation for analysis at the nanometer scale therefore pushes established research areas into novel territory:

Physico-chemical analysis. Traditional material science has seen bulk materials during analysis as an object with averaged (mean) properties. Modern instrumentation often permits routine analysis of inhomogeneous properties and many traditional materials turn out to be less uniform than previously assumed. With more spatial resolution, the role of local structure, composition and function becomes accessible to routine research. It is difficult to image, what will emerge from the possibility to atomically precise design of nanoparticles. Similar to organic chemistry, atomically precisely defined nanoparticles will create millions of new chemical compounds, a need for new terminology²² and opens up way to unprecedented studies on activity, e.g. in heterogeneous catalysis.

Single particle analysis. Nanoparticle samples have traditionally been analysed as bulk, and compositions reported as mean values – most recent instrumentation now permits chemical analysis at the single particle level.⁴² Particularly nano(ecotoxicology) profits from this rapidly emerging single particle analysis, as this allows increasingly reliable source tracking.

6.3. Nanoparticles in novel application area: The dominant role of costs and material availability

Nanotechnology has been cherished in the first decade of the millennium and enthusiastic market estimates forecasted around 1000 billion US-\$ revenue for 2010.⁴³ Well, that has not happened, and more recent analysis estimates the real market to be around 6.5 billion US-\$ by 2015.⁴⁴ Where does that discrepancy come from? When reading through some of the highest cited papers from the emerging nanotech research field, one expects almost magical benefits from this then called technology revolution. A key aspect why this has never happened in the expected huge range may be related to the erroneous assumption of “nano” products as a high demand market. When we leave universities, however, and look at buying decisions of customers, most people’s strong needs are traditional human needs. As such, new materials and science/technology are competing with established players in these markets. This puts a cost constraint around new technology.

Nanomaterials as building blocks. Present material science, in particular polymer industry, metallurgy and ceramics uses bulk raw materials and blending as key design directions for new products. Using very small building blocks, i.e. nanoparticles, permits going between traditional design directions (metals; ceramics; polymers) and thus access to unusual properties (e.g. soft and strongly magnetic)⁴⁵. The above cost constraints, however, should be part of scientific discussions, too, as most scientific success studies later fail

when trying to realize the benefits of a scientific breakthrough. Fortunately, today millions of compounds are in principle accessible at industrial production volumes – this is good news to academic work as it improves university's claim of economic relevance when pursuing nanoparticle-based investigations.

Large volume applications. Non-traditional nanoparticle properties often become visible only when used at non-academic scale, i.e. when using large samples or large areas of applications. When fumed silica or carbon black entered the commodity market at the mid-20th century, many present applications of these fascinating nanomaterials had not been identified. A similar phenomenon can be witnessed right now when laboratories start to work with kg quantities of novel materials. Colour effects, haptic feel (touch), flow and many thermal properties need large samples. Here, the ongoing rapid expansion in nanomaterial availability for academic research is expected to yield a next generation of applications.

7. Conclusions

Engineered nanoparticles have been around for at least a century under different names. The incredible boost in interest since 2000, however, has pushed small particles into the focus of application related research in materials, chemistry and biology. Originally over-euphoric market estimates for the nanoparticle industry have not been proven true yet, if we look at more recent market analysis of nanoparticle production volume and sales. Several academic initiatives and industrial market intelligence reports provide global production volumes for nanomaterials.⁴⁶⁻⁴⁹ However, these reports define their scope quite differently so that the volumes reported necessarily scatter, and remain indicative for possible applications only. Technological revolutions, as often witnessed in the past, take time. Our analysis shows how the initial academic excitement around nanoparticle application has become a more disciplined and systematic research field. Nanoparticles, considered a “new” word in the early 2000, has become a classical technical term, part of standard teaching in universities and well integrated in everyday language. Nanoparticle research has found its position as a recognized discipline, hence, we expect the field to continue thriving, with even more fuel as nanoparticles are now globally available to laboratories similar to our more traditional chemical reagents.

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Notes and references

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