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REVIEW

Use and potential of nanotechnology in cosmetic dermatology

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Abstract: Biotechnology and nanotechnology are the key technologies of the twenty-first century, having enormous potential for innovation and growth. The academic and industrial goals for these technologies are the development of nanoscale biomolecular substances and analytical instruments for investigating cell biology at the cellular and molecular levels. Developments in nanotechnology will provide opportunities for cosmetic dermatology to develop new biocompatible and biodegradable therapeutics, delivery systems and more active compounds. Cosmetics have the primary function of keeping up a good appearance, changing the appearance, or correcting body odors, while maintaining the skin and its surroundings in good conditions. Thus cosmetic dermatology, recognizing the new realities of skin care products, has to emphasize the functional aspects of cosmetics through an understanding of their efficacy and safety in promoting good health. Nanoscience may help the scientific community to find more innovative and efficacious cosmetics. Understanding the physical model of the cell as a machine is essential to understand how all the cell components work together to accomplish a task. The efficacy and safety of new nanomaterials has to be deeply studied by ex vivo tests and innovative laboratory techniques. New delivery systems and natural nanocompounds, such as chitin nanofibrils for wound healing, are being used in cosmetic dermatology with good results, as are nanostructured TiO_2 and ZnO sunscreens. The challenge is open.

Keywords: nanotechnology, nanobiotechnology, delivery systems, chitin nanofibrils, TiO_2, ZnO

The significance of nanotechnology and nanobiotechnology

Nanotechnology is a relatively young discipline. Today nanotechnology is not only essential for marketing-oriented chemical companies, but also a tool for developing science-based solutions for innovative therapeutics and cosmetics, enhancing well-being and addressing anti-aging issues.[1] Nanotechnology is defined as the study of matter on an atomic or molecular scale. Generally, nanotechnology deals with structures the exact size and shape of which must be measured on a nanometric scale.[2–4] A nanometer (nm) is one billionth of a meter (ie, 10^{-9}) and typical atoms are about one third of a nanometer. In comparison the medial thickness of a human hair is about 10000 nm and an influenza virus has a diameter of 100 nm (see Figure 1). Nanobiotechnology, the interface between nanotechnology and biotechnology, is the branch of nanotechnology that deals with its biological and biochemical applications or uses.

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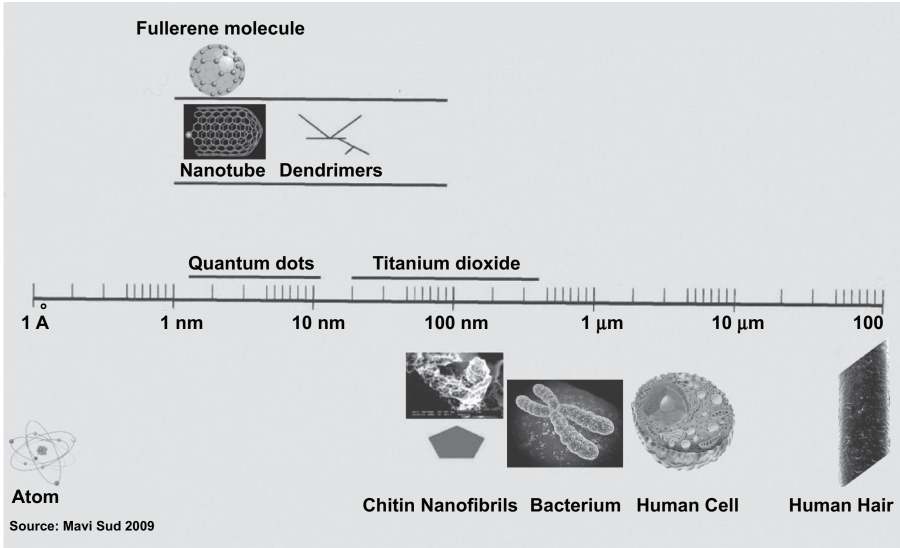


Figure 1 The nanometer dimension.

Nanotechnology is thus the set of methods and techniques for processing matter on atomic and molecular scales to create products with both special and improved chemico–physico features compared to conventional products.[5] Therefore, the goal of nanobiotechnology is the development of nanoscale biomolecular components and analytical instruments for the investigation of cell biology at both the cellular and molecular levels.

The expectations

The potential uses and benefits together with the expectations of nanosciences are enormous. Accordingly, the European Commission (EU) supports the new nanotechnologies through its seventh framework program (Figure 2). Thus, the use of nanomaterials in cosmetic dermatology is the subject of intense debate in the EU, and efforts to establish fundamental rules for their use and risk assessment are ongoing throughout universities, government laboratories and industry. Investment of public funds in basic nanotechnology research has increased, which has, in turn, heightened the interest of private industry in developing patented products.[6] The nanoscale production of a raw material may not only reduce costs, but also enhance its properties. In the biomedical and cosmetic fields nanotechnology has enormous potential, and nanobiotechnological methods are already being used in both medicine and the pharmaceutical industry.

For all these reasons, the International Organization for Standardization (ISO)[7] is developing uniform standards for nanotechnology and supporting innovation, research and development, including appropriate risk assessment research, in this innovative field.

However, to obtain nanoscale materials a combination of physical micro-nanoelectronic, chemical and biological technologies are necessary. Currently, the three main areas of development include the following:[8]

nanomaterials: building specialized structures whose dimensions are controlled on a nanoscale;

nanobiotechnology: the manipulation of living systems using nanoscale engineering;

nanoelectronics: the development of microelectronics for devices such as radio frequency identification.

Nanomaterials in cosmetic dermatology

Nanomaterials and nanobiotechnology have the potential to radically change the way cosmetics and drugs deliver their benefits. Specifically, nanoparticles are being developed to encapsulate a wide range of ingredients benefical to the skin.

To obtain nanoparticles, two principles approaches are used:

a) the bottom-up method in which nanoparticles are assembled from the molecular dimension
b) the top-down approach that reduces larger particles by the use of chemico–physico methods. In cosmetics the top-down approach is more commonly used to produce different kind of structures. Examples of such structures include nanosomes, cubosomes, niosomes, and liposomes.

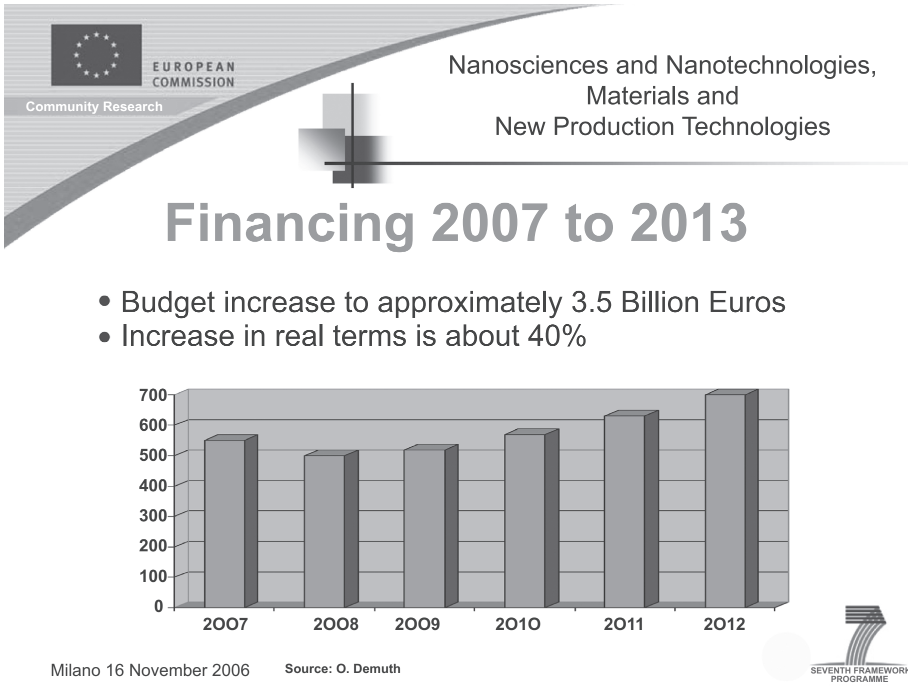
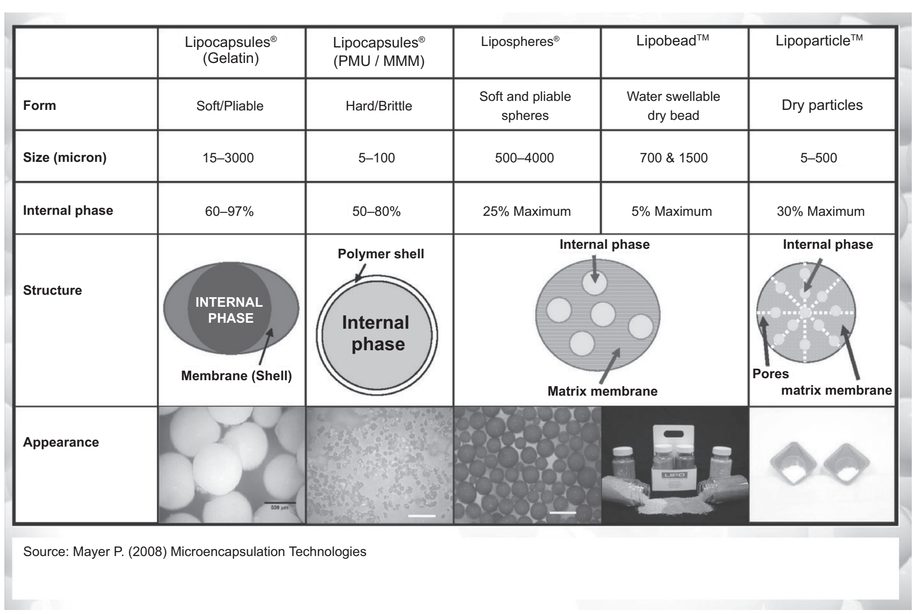


Figure 2 Provisional increase of nanotechnology.

These labile particles with diameters from 50 to 5000 nm are used to produce micro- or nanoemulsions capable of carrying and protecting active compounds from oxidation, and also improve their penetration through the skin layers[9] (Figure 3).

One of the major factors that determines the ability of substances to penetrate the skin is the size of the molecule. According with Johann Wiechers, the role of a delivery system is to ensure that the right concentration of the right chemical is reaching the right site in the body for the correct period of time.[10] However, the efficiency of an active compound depends largely on its bioavailability – it is vital that it reaches the site of action and be released for a prolonged period of time.

To this end, recent extensive research has developed different nanotechnology oriented, controlled delivery



	Lipocapsules® (Gelatin)	Lipocapsules® (PMU / MMM)	Lipospheres®	Lipobead™	Lipoparticle™
Form	Soft/Pliable	Hard/Brittle	Soft and pliable spheres	Water swellable dry bead	Dry particles
Size (micron)	15–3000	5–100	500–4000	700 & 1500	5–500
Internal phase	60–97%	50–80%	25% Maximum	5% Maximum	30% Maximum
Structure	INTERNAL PHASE; Membrane (Shell)	Polymer shell; Internal phase	Internal phase; Matrix membrane		Internal phase; Pores; matrix membrane
Appearance					

Source: Mayer P. (2008) Microencapsulation Technologies

Figure 3 Types of delivery systems. Reproduced courtesy of Pat Meyer, Lipo Chemicals.

systems, from the simplest to the most sophisticated[10] (Figure 4).

Thus nanovesicles, as a skin delivery system, and solid lipid nanoparticles (SLN) or nanostructured lipid carriers (NLC), have been developed for cosmetic and pharmaceutical applications.[11]

Vesicles are hollow colloidal particles, consisting of amphiphilic molecules. Because of their amphiphilic properties, these molecules can, in the presence of water, form unilamellar or multilamellar vesicles. Both water-soluble and water-insoluble compounds can be entrapped in such vesicles and a wide variety of lipids and surfactants can be used to prepare them.

These vesicles might act: (a) as carriers to deliver entrapped molecules into or across the skin; (b) as penetration enhancers to modify the intercellular lipid lamellae; (c) as a depot for sustained release of active compounds; (d) as a site-limiting membrane barrier for a controlled transepidermal or transdermal delivery system.

In contrast to a vesicles-based delivery system, SLN and NLC have the great advantage of high stability. Moreover, these lipid carriers create a nanolayer lipid film on top of the skin, thereby avoiding water evaporation and thus increasing skin hydration.

Furthermore, the small size of all the nanostructured compounds ensures a closer contact with the stratum corneum, thus increasing the amount of incorporated active ingredients reaching the site of action. Wetting, spreading and penetration also may be enhanced as a result of the low surface tension of the whole system and the low interfacial tension of the oil/water (O/W) nanodroplets.

However, all the nanoparticles obtained from different emulsions have to be considered labile forms, because of the total disintegration of their components after application to the skin surface. Moreover, their mean dimension in cosmetic emulsions is about 100 nm.

Another group of nanoparticles widely used in cosmetic dermatology and totally insoluble both in water and oil includes the inorganic physical UV filters titanium dioxide (TiO_2) and zinc oxide (ZnO), considered sunscreen in the US and Japan, and in Germany only among the EU countries. These two substances are used in particles of 60 to 200 nm to obtain a transparent emulsion, thus increasing cosmetic compliance (Figure 5). Of note is that the miniaturization of these minerals increases not only their transparency, but also their filtering capacity,[12] because of their higher reflective index.

Therefore, these minerals may be considered as broad-spectrum UV blockers when used in micronized form, becoming invisible after application to the skin[13] (Figure 6). Additionally, the surface of these nanofilters may be coated with a neutral material such as silica, polysiloxane compounds, glass, or aluminium oxide, to improve their dispersion state, photostability and efficacy, eliminating direct contact with the skin (Figure 7) and increasing their margin of safety.[14] As TiO_2 is not only a UVA filter, but also an extremely efficient UVB filter, it shows by far the highest versatility of any sunscreen product.[15]

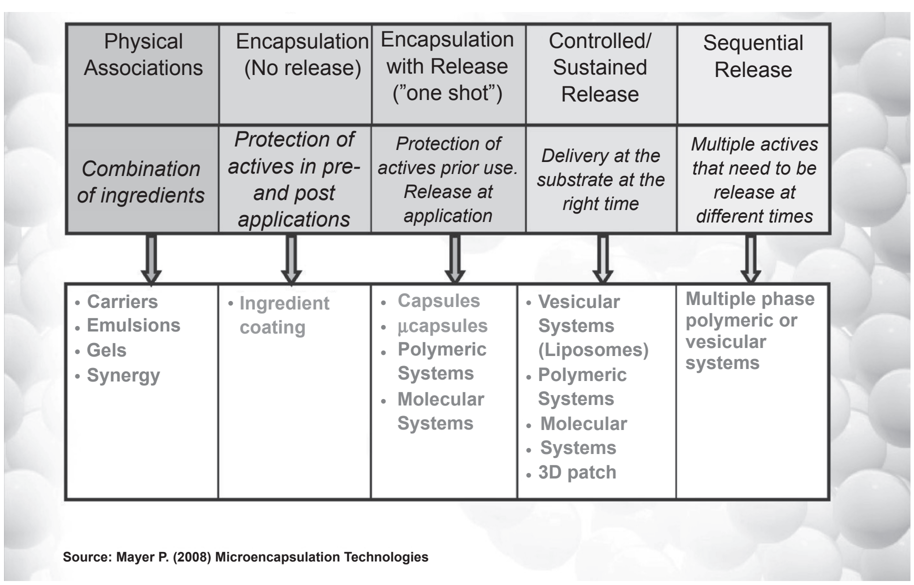


Figure 4 Delivery systems: from the simplest to the most complicated. Reproduced courtesy of Pat Meyer, Lipo Chemicals.

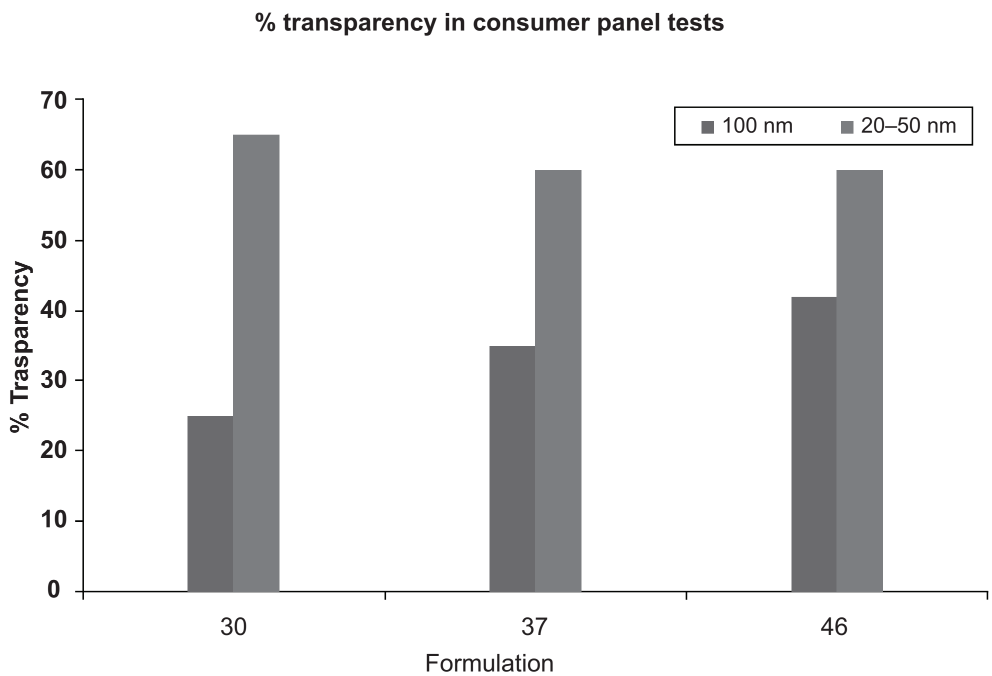


Figure 5 The level of transparency in consumer panel tests depending on the dimension of ZnO/T_iO_2 particles. Courtesy Antaria Limited.

Another important group of insoluble nanoparticles used in cosmetics are microcapsules. These are small particles containing an active agent or core material surrounded by a coating layer or shell. Their diameter may vary from 1 to 1000 μm; capsules smaller than 1 μm are called nanocapsules and capsules larger than 1000 μm are called macrocapsules.[16–18] Microcapsules may help to solve problems in cosmetic dermatology such as incompatibility of different ingredients, and protection of substances liable to oxidation or affected by atmospheric moisture.

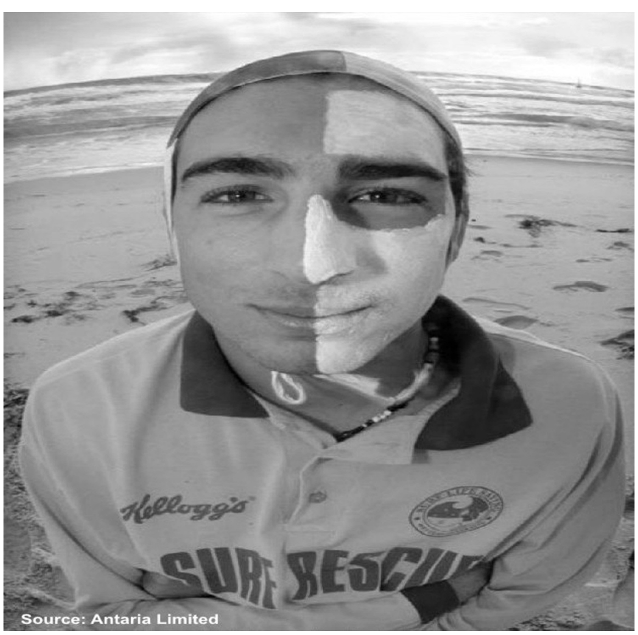


Figure 6 A face covered with standard ZnO (on the right, ie, subject's left side) or nano-size ZnO (on the left, ie, subject's right side). Reproduced courtesy of Geoff Trotter, Antaria Limited.

The general outcome of EU discussions on the safety of nanomaterials in cosmetic dermatology indicates that some risks are inevitable, although conventional toxicological methodologies are not adequate to assess their safety. At present, these risks remain hypothetical because these discussion statements are not supported by documented research results.[19–23] Recently the EU Parliament has passed a resolution on the regulatory aspect of nanomaterials,[24] considering them necessary for EU citizens, if made and distributed in a responsible manner.

The EU Parliament has stressed the need for legislation that includes a more comprehensive science-based definition of nanomaterials, together with a clear assignment of liability to producers and employers arising from the use of nanomaterials, through all routes of exposure (such as inhalation and the skin).

Recent studies on the safety of nanomaterials for human health have led, for example, to false-positive or false-negative results and conclusions because of shortcomings in applied protocols (Table 1).[25–36] Thus the Commission on Nanoscience has provided a "Code of Conduct for all individuals and civil society organizations involved or interested in nanosciences and nanotechnologies (N&N) research".[37]

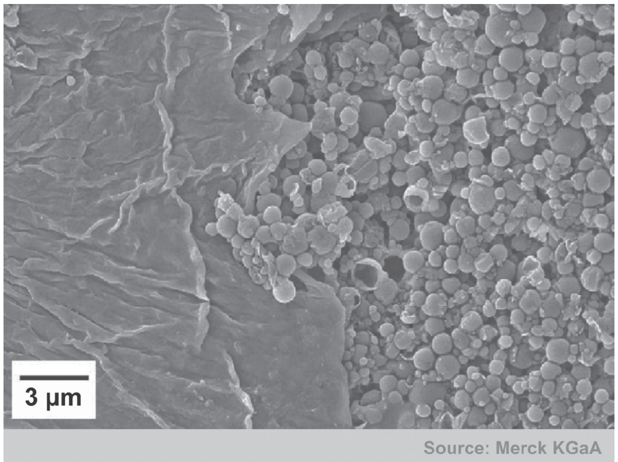


Figure 7 Sunscreen covered by glass at level of horny layer. Courtesy Merck KGaA.

This Code of Conduct aims to promote integrated, safe and responsible nanoscience and nanotechnology research in Europe for the benefit of society as a whole. Moreover the code must be considered complementary to existing regulations. Thus far nanobiotechnology seems to pose no special risks for medicine and pharmacology.[38,39]

However, nanotechnology is a very broad term, and most fears about human health arise as a result of the specific properties of nanomaterials and nanoparticles, whether natural or man-made. In fact, natural nanoparticles do occur in the environment, for example in waste matter, some of which are are not materials engineered by scientists.[39,40]

One type of natural nanoparticle, chitin nanofibrils, are currently used by our research group as an active compound

Table 1 A review of the results of TiO_2 and ZnO percutaneous absorption studies

Test material	Particle size	Skin model/technique	Results	Reference
TiO_2 and ZnO (no information on coating)	TiO_2: 50 to 100 nm ZnO: 20 to 200 nm	Human skin, in vitro	Penetration limited to upper layers of stratum corneum	27
TiO_2 Al_2O_3/stearic acid coated	150 nm to 170 nm	Human subjects (biopsy)	Particles on and in the upper layers of stratum corneum. About 1% of particles in the ostium of the follicle. No penetration into living skin	28
Various TiO_2 anatase and rutile, coated and uncoated materials	14 nm to 200 nm	Pig and human skin in vitro, human subjects (skin stripping or biopsy)	No penetration beyond the stratum corneum in any study	29
TiO_2 (SiO_2 Al_2O_3 + SiO_2 coated)	10 nm to 100 nm	Human skin, in vitro	Penetration of particles into the upper layers of stratum corneum. No penetration into living skin	30
TiO_2 (SiO_2 – $Al_2O_3Al_2O_3$/ SiO_2 coated)	10 nm to 100 nm	Human subjects (biopsy)	Particles on or in the outmost surface of the stratum corneum. No penetration into living skin	31
TiO_2 (no coating)	20 nm	Human skin, in vitro	Penetration in restricted to the topmost 3–5 corneocyte layers in the stratum corneum disjunctum. No penetration into living skin	32
TiO_2 in various formulations (no information on coating)	Needles: 45 to 150 nm $\times$ 17 to 35	Pig skin, in vitro	Particles on/in the stratum corneum; minimal penetration into stratum granulosum. No penetration into living skin	33
ZnO	15 nm to 30 nm	Human skin, in vitro	Less than 0.03% of applied Zn recovered in the receptor solution, no particles detected in epidermis or dermis	34
TiO_2 (SiO_2 or dimethicon coated) and ZnO (uncoated)	TiO_2: 30 to 60 nm ZnO: $<$160 nm	Pig skin, in vitro	No penetration beyond stratum corneum. Receptor solution recoveries of 0.8%–1.4% of applied dose	35
TiO_2 in a sunscreen formulation, silicone coated	20 nm	Human skin in vitro and human subjects, skin stripping, TEM, backscattering spectometry	Penetration limited to upper layers of stratum corneum. No penetration in skin furrows or follicular opening may be mistaken for penetration in the epidermal compartment	36

in cosmetic dermatology. Research results obtained to date suggest this particle poses no risks to consumers but offers numerous benefits.[41,42]

Chitin nanofibril

A chitin nanofibril is a nanocrystal of a natural polysaccharide obtained from the crustacean exoskeleton after elimination of the carbonate and protein portions. Having a backbone like hyaluronic acid, chitin nanofibrils are easily metabolized by the body's endogenous enzymes and thus is used in cosmetic dermatology and biotextiles. The crystal is so named because its average size is 240 × 7 × 5 nm (nano), and because it is shaped like a thin needle (fibril). Moreover, because it occurs naturally and is considered a safe raw material, it is safe to use. As it is easily metabolized by enzymes, it is both bio- and eco-compatible. As the nanofibril has an average size one-quarter that of a bacterium, 1 g of the product covers a surface area of 400 m^2.[43,44] Many studies have shown that chitin nanofibrils can activate the proliferation of keratinocytes as well as fibroblasts, regulating not only collagen synthesis but also cytokine secretion and macrophage activity.[45,46]

Our group has obtained interesting results showing how chitin nanofibrils can ameliorate not only the appearance of photoaged skin[47–51] but also promote wound healing by reducing hypertrophic scar formation[52,53] (Figure 8). *In vitro* studies have shown how chitin nanofibrils can increase the reproduction of fibroblasts with a subsequent increase in collagen synthesis and in adenosine triphosphate production. In an *in vivo* double-blind study, skin hydration and superficial skin lipids were improved, with a simultaneous reduction in lipid peroxides and transepidermal water loss.[49–51] By using different types of emulsions, chitin nanofibrils have an interesting wound healing activity.[52,53] Healthy biotextiles have also been produced.[54]

Research efforts in cosmetic dermatology are currently aimed at developing new environmentally friendly nanosized chemicals and new nanoparticulate systems for the skin. Therefore, during recent years several delivery systems have been developed (visible beads, microcapsules, nanocapsules and liposomes, or lipid nanoparticles, SLN) for the cosmetic and dermatological industry, and successively introduced into many marketed products. Many different active components can be encapsulated in these delivery systems, such as vitamins fragrances, botanical extracts, and drugs, which have a wide range of cosmetic or dermatological properties.

Some of these delivery systems, such as SLN, are innovative drug carrier systems first designed for intravenous administration and more recently investigated for peroral and transdermal applications in cosmetic dermatology. Thus, chemically labile agents should be protected from degradation and the release profile modulated. The much higher surface-to-mass ratio of nanomaterials should increase the efficacy of many active compounds.

In conclusion it is necessary to understand better the potential of these new technologies, so that the potential negative effects of their chemistry on human health and the environment may be minimized or avoided.

Nanoscience and nanoengineering could significantly improve our understanding of nanoscale processes at the molecular level that occur in the environment. Consequently it should be possible to develop new green technologies that minimize the production of undesirable byproducts released into the environment, into waste sites and streams for example.[55] Nevertheless, to speed up the development of both nanotechnology and nanobiotechnology, multidisciplinary teams of highly trained people with backgrounds in biology, medicine, applied and computational mathematics, physics, chemistry, and electrical, chemical and mechanical engineering will be needed. Despite the current international

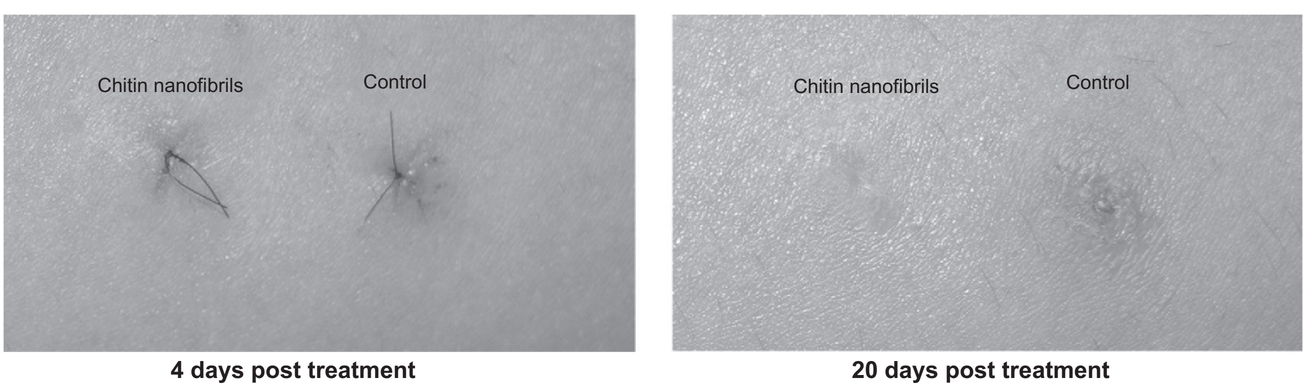


Figure 8 Wound healing activity of chitin nanofibrils.

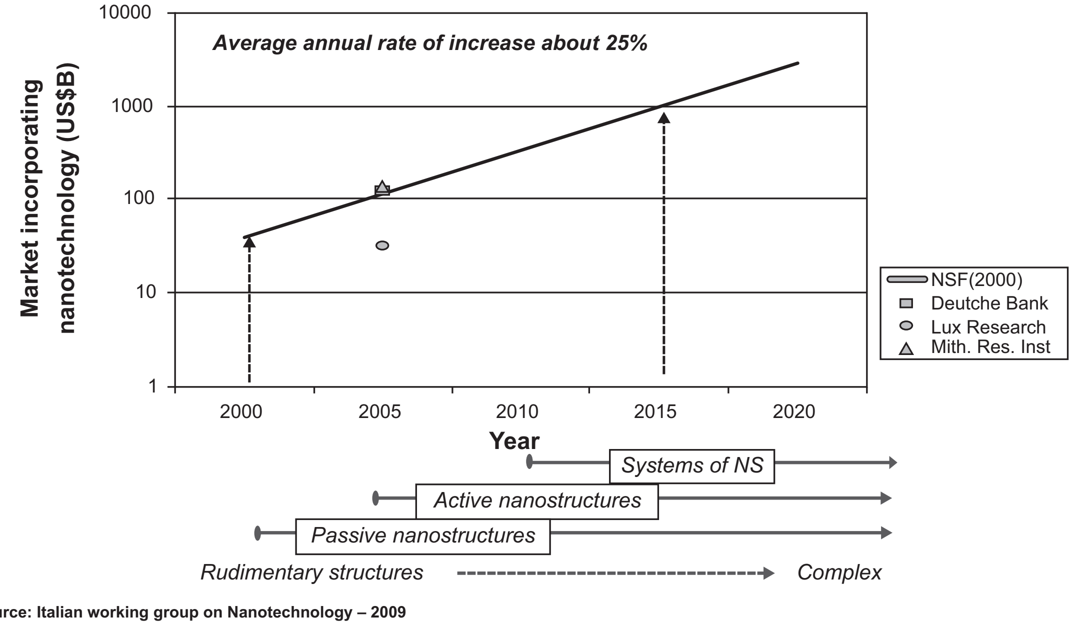


Figure 9 Estimated economic impact of nanotechnologies.

financial crisis, nanotechnology and innovative cosmetic dermatology, may have the potential to help reinvigorate a nation's economy (Figure 9). However, apart from helping to overcome some new challenges in molecular imaging techniques, quantitative analytical tools, physical models of the cell as a machine, better in vivo tests and better drug/cosmetic delivery systems, nanotechnology could play an important role in the sustainability of not only cosmetic dermatology but also of agriculture, water filtering, energy materials, and a clean environment.

In conclusion, the most complex and highly functional nanoscale systems have been invented by nature. We have to find ways of how to best use them for ameliorating our well-being and the environment. Thus, nano-products should be designed and sold in a way that fully respects the health of consumers and the environment. Both nanotechnology and biotechnology have the potential to revolutionize both our industries and way of life. They represent the key technologies of the twenty-first century, offering excellent opportunities for both research and business.

Disclosure

The author declares no conflicts of interest.

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