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COMMENTARY

Application of Nanotechnology in Cosmetics

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INTRODUCTION

The National Nanotechnology Initiative (NNI), established in 2001 to coordinate Federal nanotechnology research and development, defines nanotechnology as i) research and technology development at the atomic, molecular, or macromolecular levels in the length scale of approximately the 1- to 100-nanometer range; ii) creating and using structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size; and iii) the ability to control or manipulate on the atomic scale (1). Generally speaking, nanotechnology can be defined as the application of scientific and engineering principles to make and utilize very small things. Nanotechnology is moving into the centre of world-wide public attention because of its broad range of applications which could dramatically impact both the scientific community and the commercial marketplace. Nanotechnology applications have been applied across biomedical, optical, electronic, mechanical, and chemical fields as well as in consumer goods such as foods and cosmetics. Nanotechnology is merging with information technology, biology and social sciences and is expected to reinvigorate discoveries and innovations in many areas of the economy. Nanomedicine is dominated by nanoparticulate drug delivery systems because of their ability to cross biological barriers, accumulate at tumor sites and/or increase the solubility of drugs. Approved nanotechnology-based products include nanoscale liposomal doxorubicin (Doxil®/Myocet ™, Ortho Biotech, Bridgewater, NJ, USA/Zeneus Pharma, Oxford, UK) for breast cancer and kaposi sacoma, lipid micelles of estradiol (Estrasorb ®, Novavax, Malvern, PA, USA) for menopausal therapy, and nanocrystalline sirolimus (Rapamune, Elan Drug Delivery, Wyeth Pharmaceuticals, Collegeville, PA, USA) for immunosuppression.

NANOMATERIALS, HUMAN AND ENVIRONMENTAL RISK ASSESSMENT

There is considerable concern regarding the safety of manufactured nanomaterials (nanoparticles, nanotubes, nanowires, fullerene derivatives, and other nanoscale materials), as nanoscale materials may have characteristics (e.g. chemical, physical, electrical, and biological) different from their large-scale counterparts and may behave differently than conventional materials, even when the basic material is the same. The United States, Europe, and Japan, among other nations, have developed and supported programs to assess hazards posed by nanomaterials in realistic exposure conditions in order to promote and expand the use of nanotechnology for commercial use. The primary focus of these programs is to develop reliable and informative risk and safety evaluations for these materials to ensure their safety for human health and the environment.

As a consequence of their novel characteristics, risk assessments developed for ordinary nanomaterials may be of limited use in determining the health and environmental risks of nanotechnology products. Nanometer-scale particles can get to places in the environment and the human

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body that are inaccessible to larger particles, and unusual or unexpected exposures can occur. Since nanoparticles have a larger surface-area-to-mass ratio than materials of the same composition and biological/chemical reactions typically take place at the nanomaterial's surface, it has been hypothesized that nanoparticles will be more reactive than the bulk material (1,2). It is well documented that nanoparticles/nanomaterials undergo dynamic interactions with components of their environment with which they are in contact (1–3). As a consequence of this interaction, physical/chemical characteristics, such as dissolution, agglomeration, disagglomeration, coalescence and the adsorption of substances onto their surfaces, may change over time. These changes must be considered in conducting a risk assessment related to both human health and the environment, as changes in these physio-chemical properties affect the behavior of the nanomaterial. While new exposure routes and increased reactivity can be useful attributes for nanomaterials, they also carry the potential for health and environmental risk. A recent report which assessed the toxicity of inhaled nanotubes (4) demonstrated that mice who were exposed to inhaled multi-walled carbon nanotubes developed fibrosis after 2 weeks of exposure. The nanotubes were found accumulating in immune cells in the region just below the pleura. Since the initiation of the NNI in 2001, over $12 billion has been invested in research addressing the safety of nanotechnology products for use in humans and the environment and in research on ethical, legal, and other related uses of nanotechnology (1). The FDA has issued a report to consider developing guidance for the science and regulation of products containing nanoscale materials (5).

CHARACTERIZATION OF NANOMATERIALS

Nanomaterial characterization is accomplished using a variety of different techniques drawn from interdisciplinary areas. A summary of investigative methods for nanoparticle characterization is listed in Table I. Briefly, common techniques/tools utilized to evaluate a particle's morphological properties include transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM) and dynamic light scattering (DLS). X-ray photoelectron spectroscopy (XPS), X-ray diffraction (XRD), and Fourier transform infrared spectroscopy (FTIR) are used to analyze the particle's surface characteristics. The separation and quantification of nanoparticles with different particle sizes could be processed using High Performance Liquid Chromatography (HPLC) with Size Exclusion Chromatography. An understanding of nanomaterial interaction with the environment in combination with an understanding of the route of exposure will provide useful information on nanoparticle biological fate and toxicity. For example, the penetration of nanoparticles through the skin, their biodistribution, rate of excretion and toxicity are determined by the nanoparticle's characteristics (e.g., shape, size, surface charge, surface composition, coating, type of materials, and other components in the nanoparticle's formulations). For nanomaterials used in

Table I Investigation Methods for Nanoparticles Characterization

Method or Equipment	Measurement Consideration
Laser Light Scattering System/Particle Size Analyzer	Measurement of particle size and size distribution of nanoparticles in liquid solutions or suspensions
Zeta Potential Analyzer	Measurement of surface charge of nanoparticles in aqueous solutions or suspensions
Scanning Electron Microscope (SEM)	Examination of the consistency of nanoparticle's surface and the shape of nanoparticles
Transmission Electron Microscope (TEM)	Determination of surface property and shape morphology of nanoparticles
Atomic Force Microscope (AFM)	Measurement of the shape and surface morphology (including friction and softness) of nanoparticles with high lateral and vertical resolutions
Laser Scanning Confocal Microscope (LSCM)	Non-invasive measurement of nanoparticle's morphology in 3D, investigating the migration of nanoparticles into bio-barrier
Surface Area Analyzers and Pore Size Analyzer	Determination of single and multipoint surface-area analysis, multigas capability and full adsorption capability for nanoparticles
X-Ray Photoelectron Spectroscope (XPS, ESCA)	Providing important chemical composition (both elemental and chemical state) information on nanoparticle's surface
Fourier Transform Infrared Spectroscope (FTIR)	Assisted analytical tool for chemical composition of nanoparticle's surface
Differential Scanning Calorimetry (DSC)	Providing thermal analysis (and component interactions) of nanoparticles and related materials during fabrication process
High Performance Liquid Chromatography (HPLC)	Detection, separation and quantification of nanoparticles/ nanomaterials with different particle size

sunscreens, an assessment of phototoxicology is necessary to determine if nanoparticles/nanomaterials have the capacity to generate free radicals in the presence of sunlight and if the addition of antioxidants in the formulation could eliminate any free-radical damage.

NANOMATERIALS AND COSMETICS (DERMAL ABSORPTION)

Nanoparticles used in drug delivery systems are of interest to the cosmetic industry. Examples include nano-encapsulation vesicular delivery systems, including nanoemulsions and nanocrystals, liposomes and niosomes, micelles, polymeric nanocapsules, solid lipid nanoparticles and nanostructured lipid carriers, carbon nanotubes and fullerenes, and dendrimers. Nanoparticles are also used as ultraviole (UV) filters, such as insoluble mineral based nanoparticles titanium dioxide (TiO_2), zinc oxide (ZnO). They are produced in a variety of compositions, shapes, structures, sizes, and reactivity. The primary advantages of using nanoparticle formulations in cosmetic products are to i) improve the stability of various cosmetic ingredients like unsaturated fatty acids, vitamins, or antioxidants encapsulated within the nanoparticles; ii) enhance penetration of certain ingredients, such as vitamins and other antioxidants; iii) increase the efficacy and tolerance of UV filters on the skin surface; and iv) make the product more aesthetically pleasing (e.g., in mineral sunscreens, making the particles of the active mineral smaller allows them to be applied without leaving a noticeable white cast) (6).

Potential routes of exposure to nanomaterials contained in cosmetic products include dermal, inhalation, oral or ocular. A number of modern cosmetic-related products contain nano-sized components, such as moisturizers, hair-care products and make-up. For instance, liposome-based anti-aging topical formulations (creams, lotions, gels and hydrogels) have been formulated into the cosmetic market since 1986 by L'Oreal in the form of niosomes and by Christian Dior in the form of liposomes (Capture™). Liposomes are used in cosmetic applications or for transdermal delivery with the expectation that their use will result in an increase in the concentration of active agents (e.g. vitamins A, E, and CoQ10) in the epidermis with no toxicity (acute and chronic) (7). Fullerenes display potent scavenging capacities against radical oxygen species (ROS), and, as such, they have been considered for use in the preparation of skin rejuvenation cosmetic formulations (8); however, there is still some controversy regarding their safety. Nanocrystals could be formulated for dermal use (9). Dendrimers, which are unimolecular, monodisperse, micellar nanostructures with a well-defined, regularly branched symmetrical structure and a high density of functional end groups at their periphery, have been considered for use in both pharmaceutics and cosmetics (10). Solid lipid nanoparticles and nanostructured lipid carriers are well-tolerated carrier systems for dermal application of cosmetic products. They provide controlled release profiles for many cosmetic agents, e.g. coenzyme Q10, ascorbyl palmitate, tocopherol (vitamin E) and retinol (vitamin A), over a prolonged period of time, exhibiting low toxicity and low cytotoxicity (11). Lipid nanoparticles have also been investigated to improve the treatment of skin diseases such as atopic eczema, psoriasis, acne, skin mycosis and inflammations (12). Recently, nanoparticles of zinc oxide (ZnO) and titanium dioxide (TiO_2) have become popular because they retain the UV filtration and absorption properties while eliminating the white chalky appearance of traditional sunscreens. Meanwhile, a number of modifications to the standard ZnO or TiO_2 UV protection system have been reported to increase the sun protection factor (SPF) (13).

Concerns have been raised regarding the potential dangers which may occur as a consequence of nanoparticle contact with human skin (14,15). This has initiated an integrated approach including advanced physico-chemical characterization of different types of nanoparticles. Many of the investigative techniques utilized for the characterization of nanoparticles in drug delivery systems are being applied to the application and development of nanotech products in cosmetics. These techniques include understanding and controlling the synthesis, applications and stability of nanoparticles and understanding the mechanisms by which nanoparticles penetrate intact skin. Some physico-chemical characteristics which may be important in understanding how far a nanoparticle may penetrate the skin include particle morphology and size, size distribution, surface chemistry, surface coating, surface charge, specific surface area, pore density, porosity, water solubility, agglomeration or aggregation, crystalline phase, crystallite size, photocatalytic activity, balance of hydrophobicity and hydrophilicity, redox potential, and the potential for free radical formation.

There is a paucity of information regarding the mechanisms of uptake of nanoprticles by mammalian cells. Nanoparticle's effects on mammalian cells has been evaluated both *in vitro* and *in vivo*. Various nanomaterials have been evaluated for their toxicity (e.g. phototoxicity, genotoxicity, photo-genotoxicity, etc.), carcinogenicity and capacity to penetrate into or through the skin. For these purposes, *in vitro* cell culture and tissue equivalent models based on the use of well-characterized cells and cell line play a vital role (16). For the evaluation of the penetration of nanomaterials contained in cosmetic ingredients into the skin, various *in vivo* or *in vitro* studies are typically conducted using a number of suitable animal models, including rat, pig, guinea pig, monkey and excised skin (e.g. guinea pig and human). Continued research is required to understand/evaluate the behavior of nanomaterials, including whether the

nanoparticles remain on the surface of the skin and/or in the outer dead layer (stratum corneum) of skin, or if they are absorbed into the bloodstream and affect living skin cells. Additionally, other considerations relating to the distribution of substances into the different skin compartments are the affinity of the test substance for various skin compartments, the proportion of the substance absorbed, the proportion of the substance that penetrated the skin and the quantity of the substance applied. An understanding of how a nanomaterial's physio-chemical property might affect its ability to penetrate into the skin would permit the engineering of the nanomaterial to prevent it from either affecting skin cells or possibly passing into the dermis and gaining access to the bloodstream.

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