Journal of Nanomedicine & Biotherapeutic Discovery

Arif et al., J Nanomedine Biotherapeutic Discov 2015, 5:3
DOI: 10.4172/2155-983X.1000134

Review Article Open Access

Therapeutic and Diagnostic Applications of Nanotechnology in Dermatology and Cosmetics

Tasleem Arif*, Nuzhatun Nisa, Syed Suhail Amin, Sheikh Shoib, Raheel Mushtaq and Muzafar Rashid Shawl

Department of Dermatology, STDs and Leprosy, Jawaharlal Nehru Medical College (JNMC), Aligarh Muslim University (AMU), Aligarh, India

Abstract

Nanoscience is the branch of science pertaining to the study of minute particles on an atomic or molecular scale, whose size is measured in nanometers. A nanometer represents one billionth of a meter (i.e., 10^{-9} m). Nanotechnology is an emerging branch of engineering that involves the use of particles on a nanoscale (1-100 nm). Thus, the application of nanotechnology in the field of dermatology is the Nanodermatology. Nanodermatology represents one of the most emerging fields for which an increasing interest is rising among scientists as well as pharmaceutical companies. Nanotechnology has revolutionized the treatment of several skin diseases. It is effective in targeted delivery of active medicaments and cosmetic ingredients. The skin forms the first point of contact for a diverse number of nanomaterials. Nanomedicine in dermatology has opened a new era in the diagnosis and treatment of various skin disorders. Possible applications of nanotechnology in dermatology and cosmetics include sunscreens, moisturizers, anti-aging formulations, phototherapy, anti-sepsis, vaccines, skin cancers, hair and nail care, etc. In this review after an introduction of nanotechnology, authors have described various types of nanoparticles followed by various possible indications of nanotechnology in dermatology and cosmetics. An account on safety of nanoparticles has also been added to the review.

Keywords: Cosmetics; Dermatology; Engineering; Nanodermatology; Nanotechnology

Introduction

Nanoscience is the branch of science pertaining to the study of minute particles on an atomic or molecular scale, whose size is measured in nanometers which is one billionth of a meter (i.e., 10^{-9} m) [1]. Nanotechnology is an emerging branch of engineering which involves the use of particles on a nanoscale [2]. The application of this novel technology has revolutionized the treatment and diagnostic modalities of several skin diseases. An increasing need is seen among scientists and pharmaceutical companies for nanodermatology which is dictated by the exponential number of registered patients with regard to dermatology, particularly cosmetology.

The word "Nano" in nanotechnology has been derived from a Greek word "Nanos" which means "dwarf" [3]. The use of nanotechnology dates back to 4000 years when prehistoric Egyptians, Romans and Greek researchers were applying the concept of nanotechnology in hair dye preparations [3]. Richard Feynman introduced the concept of manipulating atoms and molecules resulting in very minute components which are not visible to the naked eye [4]. However, it was Professor Norio Taniguchi who described the term nanotechnology. According to him,"Nanotechnology is a process of separating, consolidating and deforming materials atom by atom or molecule by molecule" [5]. Nanotechnology is mainly concerned about how materials react or work at atomic, subatomic or molecular level (i.e., nano scale.). Nanotechnology involves the manipulation of matter in the size range of 1- 100 nanometers approximately while the typical atoms are about one third of a nanometer [6,7]. Thus, Particles with such a size range are nanoparticles. These nanoparticles exhibit novel physicochemical properties in comparison to the same material without nanoscale features which makes it an interesting field of research and technology. It is surprising to know that nanotechnology can introduce a new use of an already existing material [3].

In dermatology and cosmeceuticals, the use of nanotechnology has been increasing since its inception. The possible uses of nanotechnology in this field of science are diverse. Some of the important indications include sunscreens, moisturizers, anti-aging formulations, phototherapy, anti-sepsis, vaccines, skin cancers, hair and nail care, antimicrobials, skin fillers, corticosteroids, visualization of tumors and sentinel lymph nodes, etc [8].

Nanoparticles in Dermal and Cosmetic Preparations

Nanoparticles are extremely small substances with size ranging from 1 nm to 100 nm and behave and react as a total unit. They can be divided into various types according to their size, surface, shape and physicochemical Properties [9]. The various types of nanoparticles mainly used in dermatology and cosmetics have been described as under (Table 1).

Liposomes

Mezei and Gulasekharam have reported the efficacy of liposomes as a topical drug delivery system [10]. The size of a Liposome usually varies from 20 nm to a few hundred micrometers. These are basically spherical vesicles in which a part of the solvent is sequestered in a phospholipid bilayer. Their ability to protect the encapsulated drug from external environment makes them suitable for delivery of both hydrophobic as well as hydrophilic compounds. One key component of a liposome is Phosphatidylcholine which has been used in various skin care formulations (creams, moisturizer, etc.) and hair care products (conditioner, shampoo) due to its softening and conditioning

***Corresponding author:** Tasleem Arif, Senior Resident, Postgraduate Department of Dermatology STDs and Leprosy, Jawaharlal Nehru Medical College (JNMC), Aligarh Muslim University (AMU), Aligarh, India, Tel: +919557480345/ +919906637164; E-mail: dr_tasleem_arif@yahoo.com

Received March 15, 2015; **Accepted** May 26, 2015; **Published** June 02, 2015

Citation: Arif T, Nisa N, Amin SS, Shoib S, Mushtaq R, et al. (2015) Therapeutic and Diagnostic Applications of Nanotechnology in Dermatology and Cosmetics. J Nanomedine Biotherapeutic Discov 5: 134. doi:10.4172/2155-983X.1000134

Liposomes	Cubosomes
Solid lipid nanoparticles (SLNs)	Fullerene
Nanostructured lipid carrier (NLC)	Niosome
Nanocapsule	Virosomes
Dendrimers	Nanosilver and Nanogold
Lipid drug conjugate (LDC) nanoparticles	Microsponges
Nanocrystals	

Table 1: Various types of nanoparticles used in Nanotechnology.

properties. Various other agents including vitamins (Vit. A, E, and K) and certain antioxidants like Carotenoids, lycopene, etc have been introduced in liposomes. These increase the physical and chemical stability of liposomes when dispersed in water [12]. Due to their biocompatible, biodegradable and nontoxic nature, liposomes find uses in a variety of cosmeceuticals as they encapsulate active moiety easily [11]. When associated to medication; liposomes ensure a high penetration into hair follicles [13].

Solid lipid nanoparticles (SLN)

SLNs are colloidal carriers with size varying from 50 nm to 1000 nm. In these particles, Lipids (physiological lipids) are dispersed in an aqueous solution of surfactant or water [14]. SLNs possess various favourable properties viz., a) Presence of physiological and biodegradable lipids with low toxicity b) Occlusive properties which increase skin moisture level, c) Having a small size which ensures increased penetration of active ingredients, and d) Possessing characteristics of physical sunscreens of their own. These properties have made them popular in cosmetics [15,16]. SLNs have also been employed as topical vehicles for perfumes. When perfumes or fragrances are incorporated in SLNs, their release is delayed giving a prolonged effect of the perfume [17].

Nanostructured lipid carrier (NLC)

NLC particles are manufactured by using blends of solid lipids with oils (liquid lipids).The solid lipid component is usually kept in a ratio of 70:30 while for oils, the preferred ratio is 99.9: 0.1. The overall melting point of such formulations decrease in comparison to the pure solid lipid which can be explained because of the increased oil content. It is to be noted that the total solid content of NLC can be increased up to 95% [18,19]. The properties of NSLs which make them superior to SLNs include the increased loading capacity of active ingredients and avoidance of its expulsion during storage. Different types of NLCs are prepared depending upon the composition of the lipid blend and the process of producing them. They can carry drug or active ingredient in various ways viz., drug or active agent is carried in between the lipid layers or sandwiched between the fatty acid chains or in imperfections of the lipid matrix [20-22].

Nanocapsule

It consists of a vesicular system where each vesicle comprises of a covering polymeric membrane homing an inner liquid core. In this liquid core are floating active ingredients or drug. The size of nanocapsule varies between 10 nm to 1000 nm [23]. L'Oreal, a French company, was the first to launch a nanocapsule-basesd formulation in 1995 to improve the impact of their Cosmetic products [24].

Dendrimers

Dendrimers have a semipolymeric tree-like structure and are organic in nature. They provide a good source of nanoparticles as their branch terminals contain a number of nanoparticles. They are very small and the size ranges between 2 to 10 nm [25]. A carbosiloxane based dendrimer in cosmetic formulation claimed that it can provide better resistance to sebum and water [26]. Dendrimers are being studied as delivery systems for chemotherapeutics [27].

Lipid drug conjugate (LDC) nanoparticles

LDC nanoparticles were designed to increase the drug loading capacity since SLNs drawback was their low loading capacity of hydrophilic drugs. Not only this, LDCs have other advantages like improved carriage of both lipophilic as well as hydrophobic drugs, better stability of pharmaceuticals, easy sterilization, easy validation and getting regulatory authorization, biocompatibility and enhanced targeted drug release [28-30].

Nanocrystals

These are crystalline aggregates which are formed by several hundreds to thousands of atoms. These combine to form a crystalline cluster of atoms with a size of 10nm to 400nm. These are specially designed for the delivery of poorly soluble ingredients or actives [31]. Juvena was the first company to introduce nanocrystals in the cosmetics by launching its product Juvedical in the market in 2000 which contained rutin [32]. Subsequently, it was demonstrated that nanocrystal based formulation of rutin molecules possess 500 times higher bioactivity as compared to the water-soluble rutin glucoside [33].

Cubosomes

These are discrete, nanostructured particles of bicontinuous cubic liquid crystalline phase which are packed in a cube-like fashion, hence the name cubosome [34]. They are being tried to be used as oil-in-water emulsion stabilizers and absorbents for pollutants in Cosmeceuticals [35,36].

Fullerene

The term fullerene is used to describe a molecule of carbon in which the individual carbon atoms are joined together to form a hollow sphere, ellipsoid, tube, etc. When fullerene attains a spherical shape, it's called as buckyball resembling to a football (soccer). Carbon fullerene possesses antioxidative properties as well as potent scavenging capacities against oxygen free radicals. These properties have enabled their use in the preparation of skin rejuvenation cosmeceuticals [37].

Niosome

A niosome is a nanostructure containing a central aqueous cavity which is surrounded by layers of nonionic surfactant in lamellar phase. The size of a nanosome ranges between 100 nm to 2 μm [38]. They can be considered as nonionic surfactant vesicles [39]. Niosomes possess enhanced penetration, better chemical stability and an efficient entrapment quality. Besides, their cost of production is comparatively lower than that of liposomes [38]. These are being studied for providing vesicular carriers for a diverse number of topical drugs and cosmetics.

Virosomes

These consist of viral hybrid liposomes and proteins which are used in vaccines against certain viruses like hepatitis B virus (HBV) and human papilloma virus (HPV) [40,41].

Nanosilver and nanogold

Nanoparticles of gold and silver have been investigated for their

strong antibacterial and antifungal properties. Due to these properties, they are widely used in cosmeceutical products in the preparation of deodorants, face packs, antiaging creams, etc. Silver nanoparticle ointments have been claimed to have antibacterial properties which make them good skin disinfectants [42].

Microsponges

These represent novel carriers for dermatological and cosmeceutical formulations. Microsponges consist of microporous beads (average size 10-25 microns) designed for the controlled release of topical actives. They are loaded with active agents having properties like adequate stability in contact with polymerization catalyst, inertness with monomer, and slight water solubility. In Microsponge delivery system (MDS), active drug is released in a timely manner and also in response to certain stimuli like temperature, rubbing, pH, moisture etc. onto the skin [43]. Microsponge delivery system is mainly used for drugs like benzyl peroxide, retinol, fluocinolone acetonide, etc [44]. A microsponge possesses a good number of qualities which makes it a novel carrier for a variety of drugs. Some of these properties include extended release formulations with reduced irritation and improved patient compliance; stablility over pH range of 1to11 and thermal stability up to 130°C [45].

Skin Penetration of Topical Formulations

Human skin is mainly composed of three layers namely, the epidermis which is the outermost layer of skin; the dermis which contains tough connective tissue, sweat glands and hair follicles; and the hypodermis which is made up of fat and connective tissue. The skin poses a barrier for the drug penetration due to the structural integrity of the epidermis. A drug must first be absorbed through the skin, cross the stratum corneum (horny layer) and subsequent layers of the epidermis and dermis to reach the blood flow and has its systemic action. However, the aim of cosmetic products is not to have a systemic action, but most of these formulations should have enough penetration to cross layers of epidermis [5,24]. There are three possible pathways for a solute to pass through the horny layer of intact skin [46-48].

a) Transcellular permeation: In this route, the solutes pass directly through the horny cells and the intercellular lipid matrix.

b) Trans-appendageal permeation: In this pathway, the solutes pass via hair follicles and sudoriparous hair ducts.

c) Intercellular permeation: Here, the solutes diffuse tortuously around the cells of stratum corneum and constantly remaining in the lipid matrix.

For molecules with size larger than 200-350 Daltons, permeation through intact skin is very difficult. The maximum size for permeation through intact skin is considered to be 400 Daltons [49]. Most of the small water soluble molecules (non-electrolytic) diffuse up to one thousand times faster into the systemic circulation when the horny layer is absent. So, in order to enhance the absorption of topical medicament this barrier has to be reduced or bypassed. This brings us to the concept of delivery through the follicular route and its importance in medical science [50]. The human skin can be considered as a mechanical nano-porous barrier which is intercepted by a large number of small microscopic channels or pathways. Studies have revealed that these hydrophilic "pores or channels" have an average size of 0.4 nm to 36 nm. Since the majority of molecules cross the skin through these intercellular "microchannels"; many techniques have been designed to improve this route for better permeation to enhance the therapeutic effect. Nanoparticles are one of the participants in this strategy [46,50].

Recent investigations have revealed that the size of a microparticle is proportional to the level of penetration through cutaneous appendages [51]. It has been studied that no microparticle whose size is more than 10 μm penetrates through hair follicle orifices or via horny layer. Particles whose size is between 9 and 10 μm concentrate around the follicle opening without any penetration. Those particles with a diameter of 7 μm are frequently seen in deeper regions of the follicular canal, but rarely can these penetrate the horny layer of skin. Microparticles of 5 μm do not penetrate through the intact horny layer but display high concentrations in the follicular duct [51]. Rolland et al. studied the site-specific drug delivery to pilosebaceous structures using polymeric microspheres and showed that particles smaller than 3μm, reach the interior of the hair follicle and also detected in surface layers of the horny layer, but never in viable epidermis [52].

Applications of Nanotechnology in Dermatology and Cosmetics

The applications of Nanotechnology in dermatology and cosmetics are varied. The various possible indications (Table 2) of nanotechnology in dermatological science have been described as follows:

Sunscreens

Many sunscreen active ingredients are composed of metal oxides which include insoluble zinc oxide (ZnO) and titanium dioxide (TiO_2) held as microparticles [53]. These physical sunscreens block both UVA and UVB radiations. However, there are some disadvantages with these formulations like, requiring a greasy vehicle for dissolution, leaving chalky white residues on skin, and their texture appears to be thick and dense. These de-merits limit their use [54]. When these are broken down to the nano-scale particles, their texture changes making them appear invisible and hence cosmetically more acceptable. Nanoparticles of compounds like titanium dioxide (TiO_2) and zinc oxide (ZnO) have capability to reflect, adsorb or disperse UV- radiation. Studies have shown that although nanoparticles can permeate up to the upper regions of human hair follicle or reach superficial layers of Horny layer, they are not able to pass through the intact skin and reach the viable epidermal layers [55-57]. Nanoparticles such as liposomes or SLNs have been incorporated in various sunscreen formulations to act as penetration enhancers. In addition, their stability and tolerance for the active ingredient improves [58-61].

Moisturizers

These are the cornerstones in the management of various skin disorders viz., atopic dermatitis, psoriasis, ichthyosis, etc. One of the important drawbacks of the conventional emollients is their inability to sufficiently deliver components such as ceramides to the active site. On

Sunscreens	Targeting inflammatory skin disorders
Moisturizers	Hair Applications
Phototherapy	Transdermal delivery of drugs
Antiseptics	Nail Cosmetics
Cosmetics and innovations in cosmetics	Lip Cosmetics
Vaccines	Diagnostic applications
Anti-Aging Formulations	Treatment of cancer
Targeting of sebaceous glands	

Table 2: Various potential indications of nanotechnology in dermatology and cosmetics.

the contrary, nanoemulsions (oil/water) are novel colloidal drug carrier systems which can adequately replace the ceramides of a diseased skin especially in atopic dermatitis. In nanoemulsions, the size of the emulsified particle decreases which adds multiple favorable properties to the formulation including invisibility of applied preparation, sensory texture enhancement, and a non-greasy feel. As we know, ceramides are important in forming the water impermeable barrier of skin, which implies that they must be extremely insoluble compounds [62]. Nanoemulsions contain a lipophilic interior which makes them a good delivery system for transporting hydrophobic substances in aqueous environments [63,64]. This technique is being applied in gamma-amino-butyric acid (GABA), which is an inhibitory neurotransmitter with muscle relaxing properties, as anti-aging formulation for wrinkle reduction. Other possible uses of nanoemulsions may be in delivering and stabilizing enzymes such as transgluataminases. Not only this, there is possible scope for treating genetic diseases such as ichthyosis by replacing the defective component such as filaggrin which will restore the defective barrier function of Atopics [65-67]. Since their therapeutic effects are prolonged, nanoemulsions, SLNs and liposomes are widely employed for making moisturizers [24].

Phototherapy

Targeting melanosomes with short pulses of Lasers has been used in dermatology for treating hyperpigmentation disorders of skin like melasma. Immune conjugates of gold nanoparticles and iron oxide microparticles are being studied as light absorbers for specific cell targeting. When a laser pulse is generated, these particles absorb light and liberate this absorbed energy in the form of heat radiation which causes a high temperature in the tissue leading to microscopic tissue rupture and cell damage [68]. Another field of application is Photothermal Therapy (PTT). It involves use of agitated gold nanoparticles to inhibit tumor cell growth. It has been studied in rats with squamous cell carcinoma. Its advantage lies in that it causes less surrounding tissue damage [69]. Melanocyte stimulating hormone (MSH) analogues conjugated with gold nanospheres have been studied for their potential selective photothermal ablation in murine melanoma. Hence, employing such novel techniques in humans can be promising for the treatment of skin tumors [70].

The use of nanoparticles is also emerging in photodynamic therapy. The mechanism behind this mode of phototherapy is based on the principle of optical activation of a photosensitiser leading to the generation of local tissue oxygen free radicals which cause local tissue damage like tumor cells [71]. Nanoparticles can be employed as passive carriers for photosensitisers or used as active participants in photodynamic therapy. A good Therapeutic effect is attained by passive carriers causing a prolonged release of photosensitiser. They can specifically concentrate in target cells (e.g., tumor cells) saving the surrounding healthy tissues from the undesired effects of generalized exposure [72]. Apart from this, the selective accumulation of nanoparticles in the tissue which is under study, also improves efficacy of the drug. Keeping the dose same for nanoparticles and conventional formulation; a higher concentration of photosenstiser of the nanoformulation is found in target cells [73].

Antiseptics

Nanoparticles have been introduced in the field of antiseptics. Various substances have been employed as antiseptics in nano-formulations like Chlorhexidine gluconate, naked TiO_2, silver, etc. [5].

Chlorhexidine gluconate employed as nano-formulation exhibits both immediate as well as sustained antibacterial effects. The former is due to fast absorption from the capsular wall while the latter is due to prolonged liberation of the antibacterial from the nucleus of the particle [74,75].

Nanosilver is an antibacterial nano-formulation of silver. It has been employed as antiseptic for wound and burn dressings. Apart from this, Nanosilver has been also used as water disinfectant and room spray. The antiseptic mechanism is presumed to be its toxicity on the mitochondria of microbial cells [76].

Uncoated TiO_2 nanoparticle is another antiseptic. The photocatalytic property of TiO_2 makes it a good antibacterial agent. In the presence of UV radiation, uncoated TiO_2 particles cause damage to the prokaryotic cell membrane by causing peroxidation of the polyunsaturated phospholipid component of their cell membranes [77].

Cosmetics and innovations in cosmetics

Nanoparticles have been introduced in many cosmetic formulations in order to improve their quality and cosmetic elegance. Nanoparticle use is being introduced in shampoos and conditioners, perfumes, deodorants, lipsticks, eye shadows and after-shave products [17].

An innovation in the field of cosmetics is the chitin nanofibril. These chitin nanofibrils are made up of natural polysaccharide obtained from the shells of crustaceans. Chitin is safe for use as it is biocompatible and can be easily metabolized by endogenous enzymes of our body [78,79]. Studies have shown many promising properties of these nanoparticles which include keratinocyte and fibroblast proliferation; regulation of collagen synthesis; cytokine and macrophage secretion [80,81]. Apart from these, chitin nanofibrils have been shown to promote wound healing [82,83].

Vaccines

Nanotechnology can be helpful in prevention of infectious diseases by topical delivery of vaccines. The skin immune system is mainly comprised of a network of immune cells viz., Langerhan's cells and dendritic cells. Langerhan's cells process the antigen and express it on their surface along with major histocompatibility complex (MHC). These cells leave the epidermis and enter the dermal lymphatics and then migrate to the paracortical areas of the draining lymph nodes where they present the antigen–MHC complex on their surface to the TCR on T cells and elicit a specific immune response to a particular antigen. The clones of T-cell which are thus produced home the skin sites which bear the antigen under survey [84]. Topical vaccination is a novel method to activate effector-T-cells which can lead to an efficient immune response [85,86]. Delivery of topical vaccines via hair follicular route is very advantageous and practical. Firstly, hair follicles contain a good number of immunecompetent cells in its infundibular part and also around the duct of the sebaceous gland. Secondly, it offers a practical pathway for vaccine penetration. Thirdly, it has the potential to act as an intracutaneous reservoir for topically applied medicaments [87]. A study was performed by Jung et al. [88] to assess the strategy of topical vaccination using nanosized liposomes. They concluded that follicular penetration of the liposomes was the major route while the interfollicular penetration via horny layer is a minor one. Thus, Nanodermatology by employing topical vaccines can be a future strategy against preventable skin and systemic infectious and neoplastic diseases.

Anti-Aging formulations

Anti-aging products form one of the armamentarium of

nanotechnology in the field of cosmetics. Retinoids form the cornerstone of these nano-based anti-aging prepararions. Retinoids are the derivatives of Vitamin A and are used in the treatment of many dermatological diseases like photoaging, acne, psoriasis, etc. These modulate the growth and differentiation of keratinocytes by acting at the nuclear level via retinoic acid receptor (RAR) and retinoid X receptor (RXR) [2].

Anti-aging formulations containing nanosomes of Pro-Retinol A have been launched in the market. The manufacturer claims that this preparation reduces the appearance of wrinkles and causes tautening of the skin instantly [89]. The possible therapeutic mechanism of retinol in these formulations is supposed to be due to the epidermal hyperplasia and enhanced collagen synthesis [90]. Retinol has been seen to inhibit matrix metalloproteinases which cause collagen breakdown. Apart from this, it also interferes with melanogenesis thus causing lightening of lentigines and improving appearance of actinically damaged skin [91].

Targeting of sebaceous glands

The sebaceous gland involvement is seen in a number of dermatological diseases including acne. Sebaceous gland with its duct opening into the pilar canal forms one of the important structures of pilosebaceous apparatus. Various topically applied nanoparticles like biodegradable poly-lactic acid (PLA) and poly (lactic-co-glycolic) acid [PLGA] SLN's and liposome loaded actives can be employed to target hair follicle related diseases like acne via the follicular route [52,63,92]. Schaefer et al. studied delivery of adapalene particles by polymerizing them with PLA and PLGA via intrafollicular route and showed better success in treating acne and other pilosebaceous related disorders [52].

Castro et al. studied all-trans-retinoic (ATRA) loaded in SLN's and showed that this formulation is significantly less irritant than commercial retinoid preparation [93,94]. Bernard et al. [95] demonstrated SLNs can be employed for follicular delivery of various antiandrogens. They showed that antiandrogenic RU-58841 loaded in liposomes displayed much deeper penetration into the hair follicles [96].

Recently benzoyl peroxide (BP) has been the subject of research for microsphere technology in the management of acne. Microsphere formulation of BP containing 5.5% BP cream and a microsphere facewash containing 7% BP have been launched in the market. The use of microsphere technology has showed better skin tolerability, improved cosmetic elegance and higher patient satisfaction [9,97].

Targeting inflammatory skin disorders

Topical steroids form one of the main treatment options for a variety of inflammatory skin conditions like eczema, psoriasis, atopic dermatitis, etc. But continous use of topical steroids is associated with a basket of side effects like skin atrophy, telangiectasia, striae, etc. Corticosteroids have also been employed as nanoparticles. Liposomal formulations employing topical steroids minimize some of their side effects like cutaneous atrophy [98]. SLN encapsulating podophylotoxin has been introduced in the treatment of genital warts [99]. Liposomal cyclosporine and tacrolimus have shown promising results [100,101]. Methotrexate (Liposomal methotrexate hydrogel), Psoralens (lipid nanoparticles), Dithranol (liposomal formulation), Clotrimazole, and other antifungal drugs have shown encouraging results. Besides providing better patient tolerability, nanoparticles have proved to be more safe and with excellent therapeutic results [102-104].

Hair applications

Hair forms a special innovative research field for nanotechnology. The scope of nanotechnology in hair is vast and is not limited to androgenetic alopecia, alopecia areata, hair gene therapy and hair cosmetics. Nanoparticle formulations are better than aqueous and alcohol based formulations in the treatment of hair disorders like alopecia areata and androgenic alopecia. It has been shown that encapsulated hair growth medicaments have 2.0 to 2.5 time's longer permanence in hair follicular regions in comparison to aqueous solutions [9]. Minoxidil is a good candidate for Encapsulation. Studies of minoxidil encapsulated in 40-130 nm polyethylene glycol nanoparticles have shown improved permanence in the hair follicle region [105]. Jain et al. carried out a study on minoxidil encapsulated in neutral liposomes and demonstrated that this formulation had better penetration of minoxidil in pilosebaceous units compared to conventional formulations of the same drug [106]. Another drug in this armamentarium against androgenetic alopecia is finasteride. When carried in liposomes, finasteride can be delivered more effectively. It will also limit systemic side effects and has been proposed to be an alternative to the oral finasteride [107].

Alopecia areata has also been a target of nanodermatology. Nanoformulations can be effective in treating this autoimmune disease of the hair follicles. Various immunosupressants/immunomodulators can be incorporated into nanoparticles to bypass their systemic side effects [9]. Promising treatment option for alopecia areata is the liposomal cyclosporine [108].

Hair cosmetics are an attractive field for nanotechnology for its huge cosmeceutical market. Nanotechnology is being employed in hair care products to maintain shine, silky appearance, and health of hair shafts. Ordinary hair straightening products destroy the cuticle of hair causing weathering of hair shafts. However, nanoparticle based hair cosmetics do not damage it [109]. Cationic sericin nanoparticles have been studied for hair cosmetics and have shown that sericin nanoparticles adhere to the hair shaft and treat the damaged cuticles [110].

Transdermal delivery of drugs

Nanoparticles are the potential candidates for transdermal delivery of drugs. Some analgesics like diclofenac, opiates, etc. are commercially available as patches for transdermal delivery of the drug. The drug in the transdermal preparation penetrates the skin and reaches systemic circulation to show the therapeutic effect. However there are certain limitations in this type of transdermal formulation. Stratum corneum (being highly lipophilic) retains the highly lipophilic drugs, while obstructing the permeation of hydrophilic molecules. To bypass this limitation, hair follicular route can be employed as a shunt for the topically applied drugs to reach the systemic circulation. Encapsulating substances in nanoparticles can enhance their transdermal delivery via the follicular route. SLN and NLC nanoparticles have been developed for transdermal delivery of drugs [3,111]. Rastogi et al recently investigated the electroporation of polymeric nanoparticles of insulin as an alternative technique for transdermal delivery of insulin. This will limit the side effects of subcutaneous drug administration like localized drug reaction, pain at the injection site, lipoatrophy and granuloma formation [111].

Nail cosmetics

Nanobased cosmeceuticals are being developed for nail care. Nail paints based on nanoparticles improve the toughness and resistance of the nails [112]. Nanoparticle based nail polish and lacquers have many advantages like drying to a very hard state; resisting chipping, cracking and scratching. A better elasticity of such formulations provide crack-less application [113]. A novel strategy will be the incorporation of

nanoparticles (silver and metal oxide) with antifungal activity in nail polish to treat onychomycosis. It can serve both cosmetic and therapeutic purposes.

Lip cosmetics

Lip cosmetics has also been the focus of nanotechnology. Nanoparticle based lipstick and lip gloss can be developed which can keep the lips soft and supple by preventing transepidermal loss of water. A Korean Research Institute has developed a patent which they claim to prepare various colored pigments employing silver and gold nanoparticles by mixing them in various ratios. The color of this formulation can be maintained for a relatively longer period of time [114]. Silica nanoparticles have been introduced in the making of lipsticks. By this, there occurs homogenous distribution of pigment in the formulation. When such a cosmetic is applied on the lips, the migration of pigment into the fine lines of lips is prevented giving a better cosmetic outlook [115].

Diagnostic applications

Nanoparticles are now being employed in various diagnostic modalities because of certain advantages including higher sensitivity of permissible detection methods which enable them to perform analysis on smaller tissue samples. Higher specificity is achieved by conjugating them with monoclonal antibodies. Due to the alteration in the surface of the particle preventing their aggregation and enhancing their uptake by the cells [10]. Nanoparticle based diagnostic applications are presumed to be highly sensitive and specific; will require minimum quantity of tissue sample and will give results in a very short period of time [5]. The various possible nanoparticles employed in nanodiagnosis are Optical fabric, Gold nanoparticles, Quantum dots, nanoparticles with magnetic properties, etc [116,117].

Clothes made up of fabrics containing optical fibers can be the promising option for nanodiagnosis. They can be employed for measuring dimensions of skin lesions, mapping of nevus, tracking psoriasis or atopic dermatitis on body surface areas. They can be also used for monitoring of various inflammatory skin diseases. Since 'calor' (temperature) forms one of the components of inflammation; detecting changes in the temperature of the skin can be used for monitoring of diseases like atopic dermatitis, psoriasis, mycosis fungoides, etc [118].

Gold nanoparticles have been studied for nanodiagnosis. A large number of techniques are available which can help in tracing of gold nanoparticles like fluorescence, optical absorption, electrical conductivity, atomic and magnetic force. Hence, Gold nanoparticles form excellent label for sensors [117].

Quantum dots are highly fluorescent nanoparticles. They are composed of solid semiconductor particles which can absorb light of varying wavelength but re-emit it in a single wavelength which depends upon the size of the particle [119]. They contain an envelope having anionic oligomeric phosphine residue. The fluorescence emitted by them is strong and stable for many hours [120]. They have been studied for identifying sentinel nodes employing infrared fluorescence [121]. Mapping of sentinel lymph-node is one of the cornerstones in the management of various tumors including melanoma. During surgical procedures, the dye is obscured and it becomes difficult to localize due to the bleeding. This means that tracers designed for sentinel-node-mapping must be standardized for contrast, charge, surface and diameter. Particles with size less than 10 nm can overshoot the draining lymph node. On the other hand, using larger molecules (50 to 100 nm) too have limitations. Either they do not enter lymphatics or travel very slowly so that 24 hours or more may be required for the uptake of the tracer. As a result of these limitations, sentinel node is missed and possibly nodal basins are labeled. These limitations can be bypassed by the use of quantum dots. The quantum dots are easily visualized in near-infrared wavelength and enable excellent realtime visualization of course of the dye during mapping of sentinel-node. Apart from this, they also allow nonradioactive detection [2].

Treatment of cancer

This is a fertile field for nanotechnology as ten million cases of cancer are expected every year globally. In most of the cases, treatment of cancer is mainly palliative in nature [122]. Besides this, Chemotherapy as a modality of treatment for cancers has several drawbacks which include need for high doses, development of resistance by tumor cells and serious side effects of the chemotherapeutic drugs [7,123,124]. Nanotechnology aims at increasing drug concentration in tumor cells at lower effective doses while mitigating side effects [125]. Encapsulated nanoparticles comprising these drugs can have better attributes like preferential uptake by tumor cells, improved circulation time, and reducing side effects. Liposomes form an important carrier in the treatment of melanoma. Various actives can be delivered through liposomes like chemotherapeutic drugs, radioactive particles, siRNA, asODNs. and DNA [126].

Gold nanoparticles offer a promising treatment option for melanoma. Gold nanoshells have been investigated in animals for the treatment of melanoma. Anti-tumor antibodies can be coupled with Gold nanospheres. As a result, antibody bound to gold nanoparticle gets attached to the surface of tumor cells; laser light is absorbed by gold particles and in turn causes selective photothermolysis of the tumor under study [66]. Dendrimers have also been employed in the delivery of chemotherapeutic drugs for the treatment of neoplastic diseases [27].

Safety of Nanoparticles

Though the nanoparticles find a large number of both therapeutic and diagnostic indications, their safety has been the topic of debate. There are uncertainties, limitations and probable risk in their use. Since the use and production of nanoparticles is becoming widespread, there also grows an increasing number of workers and consumers who are getting exposed to these nanoparticles. The possible routes by which humans can get exposure to these particles include inhalation, ingestion, and dermal routes [127]. For airborne nanoparticles, Inhalation seems to be the most common route of exposure [128]. Consumers may get exposure via respiratory route to the aerosolized cosmeceuticals like perfumes while workers get exposure during production of these nanoparticles. In the respiratory tract the interaction between the type of nanoparticle and the respiratory epithelium will decide the outcome. Nanoparticles can be transported after passing through the olfactory epithelium during inhalation and enter the brain via the nasal nerves [129]. Another route of transmission is the Ingestion. This can occur from the cosmetics like lip color, lip gloss etc, or due to the unintentional hand to mouth transfer of these nanoparticles. Most of these ingested particles are rapidly cleared from the body while a minute fraction may be retained by the body which can migrate to different organs [130].

A lot of controversy exists on the safety of nanoparticles. A large number of manufacturers have designed sunscreens containing nanosized particles of Zinc, titanium and iron. Before prescribing these to our patients, it is mandatory for us to be well versed with the properties of TiO_2 and ZnO nanoparticles in relation to the size of the particle, their phototoxicity and their ability to permeate skin. Studies

on skin penetration by TiO_2 and ZnO nanoparticles have shown that they are safe when applied to the healthy normal skin. However, their behavior on a skin whose integrity has been lost poses some theoretical threat to the consumers [55,56,131-139]. Phototoxicity of titanium dioxide nanoparticles has been studied. Exposure to UV radiation causes these particles to generate oxygen free radicals like hydrogen peroxide [140,141]. These highly reactive oxygen species can damage DNA and can induce mutations in the chromosomes. There are also probable adverse effects on the cellular proteins and lipids which can lead to irreversible damage to the cells [142-144].

It is interesting to know how a conventional molecule is considered to be safe and when the same molecule is used in the nano-size, safety issues arise. The explanation to this query will follow in the subsequent lines. From the basic principles of physics, we know that smaller particles occupy less volume, but they possess a higher surface area per unit mass. As the size of particle shrinks, the relative number of atoms exposed on its surface increases [8]. Thus, decreasing the size of the particle, the availability of groups situated on its surface for biologic interaction increases exponentially. This mere alteration in the size of the particle can generate new classes of allergens, irritants, haptens and cross-reactants. Besides this, there is also a calculated risk of unanticipated particle-particle interactions. So from this we can infer that the toxic potential of nanoparticle is inversely proportional to its size [127,145,146].

Takeda L et al. [147] investigated the effects of Nanoparticles transferred from pregnant mice to their offspring. They administered nano-sized TiO_2 particles subcutaneously to pregnant mice. These got transferred to the offspring and led to the brain damage and reduced sperm production in the male offspring. Cobalt-chromium nanoparticles (29.5 nm in diameter) have the potential to cross through the normal skin barrier and damage human fibroblasts [148]. Similarly, nanoformulations of silver are being used in dermatology for their antimicrobial action. But it should be born in mind that the concentration of silver which is lethal for bacteria has been seen to be lethal for fibroblasts and keratinocytes as well raising the issue of safety with this preparation [149]. However there is no evidence that these nanoparticles penetrate normal intact skin of adults. Another possible hazard of wide spread use of nanoparticles in cosmetics is Foreign body granuloma or Melkersson–Rosenthal like granulomatous cheilitis which can be attributed to the reaction to exogenous materials [150].

Conclusion

The use of nanoparticles is a relatively new concept. Nanotechnology has been explored in the last few years. Its use is in diverse fields which include engineering, chemistry, oncology, dermatology, infectious diseases, preventive medicine, etc. In dermatology and cosmetics, it provides therapeutic, diagnostic as well as preventive applications. Nanotechnology is one of the key technologies of the twenty-first century with excellent opportunities for both the scientists and Pharma industry. However, there are still some unexplored possible grey areas regarding the safety of these nanoparticles which makes an appeal for more meticulous studies on their safety profile.

Conflict of Interest

The authors declare that they have no competing interests.

References

1. Bhushan B (2007) Springer handbook of nanotecnology. (2nd edn). Heidelberg, Germany: Springer-Verlag.
2. Saraceno R, Chiricozzi A, Gabellini M, Chimenti S (2013) Emerging applications of nanomedicine in dermatology. Skin Res Technol 19: e13-19.
3. Bangale MS, Mitkare SS, Gattani SG, Sakarkar DM (2012) Recent nanotechnological aspects in cosmetics and dermatological Preparations. Int J Pharm Pharm Sci 4: 88-97.
4. Drexler KE (2001) Machine-phase nanotechnology. Sci Am 285: 74.
5. Antonio JR, Antônio CR, Cardeal IL, Ballavenuto JM, Oliveira JR4 (2014) Nanotechnology in dermatology. An Bras Dermatol 89: 126-136.
6. Stylios GK, Giannoudis PV, Wan T (2005) Applications of nanotechnologies in medical practice. Injury 36 Suppl 4: S6-6S13.
7. Sahoo SK, Parveen S, Panda JJ (2007) The present and future of nanotechnology in human health care. Nanomedicine 3: 20-31.
8. Nasir A (2010) Nanodermatology: a glimpse of caution just beyond the horizon - part II. Skin Therapy Lett 15: 4-7.
9. Papakostas D, Rancan F, Sterry W, Blume-Peytavi U, Vogt A (2011) Nanoparticles in dermatology. Arch Dermatol Res 303: 533-550.
10. Mezei M, Gulasekharam V (1980) Liposomes--a selective drug delivery system for the topical route of administration. Lotion dosage form. Life Sci 26: 1473-1477.
11. Kaur IP, Agrawal R (2007) Nanotechnology: a new paradigm in cosmeceuticals. Recent Pat Drug Deliv Formul 1: 171-182.
12. M'uller-Goymann (2004) Physicochemical characterization of colloidal drug delivery systems such as reverse micelles, vesicles, liquid crystals and nanoparticles for topical administration. European Journal of Pharmaceutics and Biopharmaceutics 58: 343–356.
13. Jung S, Otberg N, Thiede G, Richter H, Sterry W, et al. (2006) Innovative liposomes as a transfollicular drug delivery system: penetration into porcine hair follicles. J Invest Dermatol 126: 1728-1732.
14. Ekambaram P, Sathali AAH, Priyanka K (2012) Solid lipid nanoparticles: a review. Scientific Reviews & Chemical Communications.
15. Pardeike J, Hommoss A, Müller RH (2009) Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm 366: 170-184.
16. Wissing SA, Mader K, Muller RH (2000) Solid lipid nanopartices (SLN) as a novel carrier system offering prolonged release of the perfume Allure (Chanel). In: Proceedings of the International Symposium on Controlled Release of Bioactive Materials, Paris.
17. Souto EB, Müller RH (2008) Cosmetic features and applications of lipid nanoparticles (SLN, NLC). Int J Cosmet Sci 30: 157-165.
18. Puri D, Bhandari A, Sharma P, Choudhary D (2010) Lipid Nanoparticles (Sln, Nlc): A Novel Approach For Cosmetic And Dermal Pharmaceutical. Journal of Global Pharma Technology 2: 1-15.
19. Mehnert W, Mäder K (2001) Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev 47: 165-196.
20. Müller RH, Souto EB, Radtke M (2005) Nanostructured Lipid Carriers: A Novel Generation of Solid Lipid Drug Carriers. Pharmaceutical Technology Europe 17: 45-50.
21. Müller RH, Souto EB, Radtke M (2000) PCT application PCT/EP00/04111.
22. Patidar A, Thakur DS, Kumar P, Verma J (2010) A Review on Novel Lipid Based Nanocarriers. International Journal of Pharmacy and Pharmaceutical Sciences 2.
23. Kothamasu P, Kanumur H, Ravur N, Maddu C, Parasuramrajam R, et al. (2012) Nanocapsules: the weapons for novel drug delivery systems. Bioimpacts 2: 71-81.
24. Lohani A, Verma A, Joshi H, Yadav N, Karki N3 (2014) Nanotechnology-based cosmeceuticals. ISRN Dermatol 2014: 843687.
25. Dendrimers & Dendrons: Facets of Pharmaceutical Nanotechnology. Drug-Dev Newsletter.
26. Furukawa H, Limura T (2012) Copolymer having carbosiloxane dendrimer structure, and composition and cosmetic containing the same. U.S. Patent 20120263662A.
27. Wei C, Wei W, Morris M, Kondo E, Gorbounov M, et al. (2007) Nanomedicine

and drug delivery. Med Clin North Am 91: 863-870.

28. Schwarz C, Mehnert W, Lucks JS, Muller RH (1999) Solid lipidnanoparticles (SLN) for controlled drug delivery: I. Production, characterization and sterilization. J Control Release 30: 83-96.

29. Muiller RH, Mehnert W, Lucks JS, Schwarz C, Miihlen A, et al. (1995) Solid lipid nanoparticles (SLN)—an alternative colloidal carrier system for controlled drugdelivery. Eur J Pharm Biopharm 41: 62-69.

30. The Royal Society and the Royal Academy of Engineering (July 2004). Nanoscience and Nanotechnologies. The Royal Society and the Royal Academy of Engineering Report.

31. Keck CM, Müller RH (2006) Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm 62: 3-16.

32. Sakamoto J, Annapragada A, Decuzzi P, Ferrari M (2007) Antibiological barrier nanovector technology for cancer applications. Expert Opin Drug Deliv 4: 359-369.

33. Petersen R (2010) Nanocrystals for use in topical cosmetic formulations and method of production thereof. US Patent US 20100047297A1.

34. Hyde S, Andersson A, Larsson K (1997) The Language of Shape, Elsevier, New York, USA.

35. Ribier A, Biatry B (2000) Cosmetic or dermatologic oil/water dispersion stabilized with cubic gel particles and method of preparation. European Patent 0711540B1.

36. Albrecht H and Schreiber J (May 2002) Hair care products with disperse liquid crystals exhibiting the cubic phases. W.O. Patent 2002041850A1.

37. Lens M (2009) Use of fullerenes in cosmetics. Recent Pat Biotechnol 3: 118-123.

38. Bei D, Meng J, Youan BB (2010) Engineering nanomedicines for improved melanoma therapy: progress and promises. Nanomedicine (Lond) 5: 1385-1399.

39. Anisha S, Kumar S P, Kumar G V, and Garima G (2010) Approaches used for penetration enhancement in transdermal drug delivery system. International Journal of Pharmaceutical Sciences, vol.no. , pp. 708–716.

40. de Vries JJ, Bungener L, Ter Veer W, van Alphen L, van der Ley P, Wilschut J, et al. (2009) Incorporation of LpxL, a detoxified lipopolysaccharide adjuvant, in influenza H5N1 virosomes increases vaccine immunogenicity. Vaccine. 27:947-955.

41. Ludwig C, Wagner R (2007) Virus-like particles-universal molecular toolboxes. Curr Opin Biotechnol 18: 537-545.

42. Lin Y and Yan L (March 2004) Broad spectrum anti-bactericidal ointment nano. CN Patent. CN 1480045 A.

43. Panwar AS, Yadav CS, Yadav P, Darwhekar GN, Jaina DK, Panwar MS, Agrawal A (July 2011). Microsponge A Novel Carrier for Cosmetics, Journal of Global Pharma Technology 3(7):15-24.

44. Patel G, Patel JK (2008) Use of a Microsponge in Drug Delivery Systems. Pharmaceutical processing, 158.

45. Parveen S, Misra R, Sahoo SK (2012) Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. Nanomedicine 8: 147-166.

46. Lourenco VA (2006) Desenvolvimento e avaliacao de microparticulas de quitosana para a veiculacao de dimetilaminoetanol (DMAE) na pele [dissertacao]. Ribeirao Preto (SP): Universidade de Sao Paulo :117p.

47. Gupchup GV, Zatz J (1997) Target delivery to pilosebaceous structures. Cosmet Toiler 112:79-88.

48. Abraham MH, Chadha HS and Mitchell RC (1955) The factors that influence skin permeation os solutes. J Pharm Pharmacol 47:8-16.

49. Cevc G, Blume G, Schatzlein A, Gebauer D, Paul A (1996) The skin: a pathway for systemic treatment with patches and lipid based carriers. Adv Drug Deliv Rev 18:349-78.

50. Barry BW (2001) Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 14: 101-114.

51. Toll R, Jacobi U, Richter H, Lademann J, Schaefer H, et al. (2004) Penetration profile of microspheres in follicular targeting of terminal hair follicles. J Invest Dermatol 123: 168-176.

52. Rolland A, Wagner N, Chatelus A, Shroot B, Schaefer H (1993) Site-specific drug delivery to pilosebaceous structures using polymeric microspheres. Pharm Res 10: 1738-1744.

53. Schilling K, Bradford B, Castelli D, Dufour E, Nash JF, et al. (2010) Human safety review of “nano” titanium dioxide and zinc oxide. Photochem Photobiol Sci 9: 495-509.

54. Zhang LW, Yu WW, Colvin VL, Monteiro-Riviere NA (2008) Biological interactions of quantum dot nanoparticles in skin and in human epidermal keratinocytes. Toxicol Appl Pharmacol 228: 200-211.

55. Cross SE, Innes B, Roberts MS, Tsuzuki T, Robertson TA, et al. (2007) Human skin penetration of sunscreen nanoparticles: in-vitro assessment of a novel micronized zinc oxide formulation. Skin Pharmacol Physiol 20: 148-154.

56. Lademann J, Weigmann H, Rickmeyer C, Barthelmes H, Schaefer H, et al. (1999) Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. Skin Pharmacol Appl Skin Physiol 12: 247-256.

57. Newman MD, Stotland M, Ellis JI (2009) The safety of nanosized particles in titanium dioxide- and zinc oxide-based sunscreens. J Am Acad Dermatol 61: 685-692.

58. Durand L, Habran N, Henschel V, Amighi K (2010) Encapsulation of ethylhexyl methoxycinnamate, a light-sensitive UV filter, in lipid nanoparticles. J Microencapsul 27: 714-725.

59. Xia Q, Saupe A, Müller RH, Souto EB (2007) Nanostructured lipid carriers as novel carrier for sunscreen formulations. Int J Cosmet Sci 29: 473-482.

60. Alvarez-Román R, Barré G, Guy RH, Fessi H (2001) Biodegradable polymer nanocapsules containing a sunscreen agent: preparation and photo protection. Eur J Pharm Biopharm 52: 191-195.

61. Padamwar MN, Pokharkar VB (2006) Development of vitamin loaded topical liposomal formulation using factorial design approach: drug deposition and stability. Int J Pharm 320: 37-44.

62. Gaetani Q, Guey C, Arbey E, Castiel I (2003). Ceramides and their use in pharmaceutical and/or cosmetic formulations. EP 1329447.

63. Jenning V, Gysler A, Schäfer-Korting M, Gohla SH (2000) Vitamin A loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. Eur J Pharm Biopharm 49: 211-218.

64. Yilmaz E, Borchert HH (2006) Effect of lipid-containing, positively charged nanoemulsions on skin hydration, elasticity and erythema--an in vivo study. Int J Pharm 307: 232-238.

65. Nasir A (2010) Nanotechnology and dermatology: part I--potential of nanotechnology. Clin Dermatol 28: 458-466.

66. Ding L, Stilwell J, Zhang T, Elboudwarej O, Jiang H, et al. (2005) Molecular characterization of the cytotoxic mechanism of multiwall carbon nanotubes and nano-onions on human skin fibroblast. Nano Lett 5: 2448-2464.

67. Sayes CM, Wahi R, Kurian PA, Liu Y, West JL, Ausman KD, Warheit DB, Colvin VL. (2006) Correlating nanoscale titania structure with toxicity: a cytotoxicity and inflammatory response study with human dermal fibroblasts and human lung epithelial cells. Toxicol Sci 92: 174–185.

68. Pitsillides CM, Joe EK, Wei X, Anderson RR, Lin CP (2003) Selective cell targeting with light-absorbing microparticles and nanoparticles. Biophys J 84: 4023-4032.

69. Dickerson EB, Dreaden EC, Huang X, El-Sayed IH, Chu H, et al. (2008) Gold nanorod assisted near-infrared plasmonic photothermal therapy (PPTT) of squamous cell carcinoma in mice. Cancer Lett 269: 57-66.

70. Lu W, Xiong C, Zhang G, Huang Q, Zhang R, et al. (2009) Targeted photothermal ablation of murine melanomas with melanocyte-stimulating hormone analog-conjugated hollow gold nanospheres. Clin Cancer Res 15: 876-886.

71. Henderson BW, Dougherty TJ (1992) How does photodynamic therapy work? Photochem Photobiol 55: 145-157.

72. Chatterjee DK, Fong LS, Zhang Y (2008) Nanoparticles in photodynamic therapy: an emerging paradigm. Adv Drug Deliv Rev 60: 1627-1637.

73. Rancan F, Helmreich M, Mölich A, Ermilov EA, Jux N, et al. (2007) Synthesis and in vitro testing of a pyropheophorbide-a-fullerene hexakis adduct immunoconjugate for photodynamic therapy. Bioconjug Chem 18: 1078-1086.

74. Lboutounne H, Chaulet JF, Ploton C, Falson F, Pirot F (2002) Sustained ex vivo skin antiseptic activity of chlorhexidine in poly(epsilon-caprolactone) nanocapsule encapsulated form and as a digluconate. J Control Release 82: 319-334.

75. Lboutounne H, Faivre V, Falson F, Pirot F (2004) Characterization of transport of chlorhexidine-loaded nanocapsules through hairless and wistar rat skin. Skin Pharmacol Physiol 17: 176-182.

76. Chen X, Schluesener HJ (2008) Nanosilver: a nanoproduct in medical application. Toxicol Lett 176: 1-12.

77. Tsuang YH, Sun JS, Huang YC, Lu CH, Chang WH, et al. (2008) Studies of photo killing of bacteria using titanium dioxide nanoparticles. Artif Organs 32: 167-174.

78. Muzzarelli RAA (1993) Chitin and its derivates: new trends off applied research. Carbohydr Polym 3:53-75.

79. Percot A, Viton C, Domard A (2003) Optimization of chitin extraction from shrimp shells. Biomacromolecules 4: 12-18.

80. Muzzarelli RA, Mattioli-Belmonte M, Pugnaloni A, Biagini G (1999) Biochemistry, histology and clinical uses of chitins and chitosan's in wound healing. EXS 87: 251-264.

81. Muzzarelli RAA, Muzzarelli C. Chitin nanofibrils (2005) In: Dutta PK, editor. Chitin and Chitosan: Research Opportunities and Challenges. Contai: SSM International Publication 129-146.

82. Mattioli-Belmonte M, Zizzi Z, Lucarini G, Giantomassi F, Biagini g, Tucci G, et al. (2007) Chitin nanofibrils linked to chitosan glycolate as spray, gel and gauze preparations for wound repair. J Bioact Compat Polym 22:525-538.

83. Mezzana P (2008) Clinical efficacy of a new chitin nanofibrils-based gel in wound healing. Acta Chir Plast 50: 81-84.

84. Archer CB. Functions of the skin. In: Burns T, Breathnach S, Cox N (2010) Griffiths C. Eds. Rook's Textbook of Dermatology. Wiley-Blackwell, U.K, 8th edition 1: 4.1-4.11.

85. Clements CJ, Larsen G, Jodar L (2004) Technologies that make administration of vaccines safer. Vaccine 22: 2054-2058.

86. Huang CM (2007) Topical vaccination: the skin as a unique portal to adaptive immune responses. Semin Immunopathol 29: 71-80.

87. Lademann J, Otberg N, Richter H, Jacobi U, Schaefer H, et al. (2003) [Follicular penetration. An important pathway for topically applied substances]. Hautarzt 54: 321-323.

88. Jung S, Patzelt A, Otberg N, Thiede G, Sterry W, et al. (2009) Strategy of topical vaccination with nanoparticles. J Biomed Opt 14: 021001.

89. L'Oreal Paris, http://www.lorealparisusa.com/en/Products/ SkinCare/ Moisturizers/RevitaLift-Anti-Wrinkle-Firming-Day- Cream-SPF-18.aspx.

90. Draelos Z D, "Retinoids in cosmetics (2005) Cosmetic Dermatology 18:3–5.

91. Choi CM, Berson DS (2006) Cosmeceuticals. Semin Cutan Med Surg 25: 163-168.

92. Patel VB, Misra A, Marfatia YS (2000) Topical liposomal gel of tretinoin for the treatment of acne: research and clinical implications. Pharm Dev Technol 5: 455-464.

93. Castro GA, Coelho AL, Oliveira CA, Mahecha GA, Oréfice RL, et al. (2009) Formation of ion pairing as an alternative to improve encapsulation and stability and to reduce skin irritation of retinoic acid loaded in solid lipid nanoparticles. Int J Pharm 381: 77-83.

94. Castro GA, Oliveira CA, Mahecha GA, Ferreira LA (2011) Comedolytic effect and reduced skin irritation of a new formulation of all-trans retinoic acid-loaded solid lipid nanoparticles for topical treatment of acne. Arch Dermatol Res 303: 513-520.

95. Bernard E, Dubois JL, Wepierre J (1997) Importance of sebaceous glands in cutaneous penetration of an antiandrogen: target effect of liposomes. J Pharm Sci 86: 573-578.

96. Münster U, Nakamura C, Haberland A, Jores K, Mehnert W, et al. (2005) RU 58841-myristate--prodrug development for topical treatment of acne and androgenetic alopecia. Pharmazie 60: 8-12.

97. Bikowski J, Del Rosso JQ (2008) Benzoyl peroxide microsphere cream as monotherapy and combination treatment of acne. J Drugs Dermatol 7: 590-595.

98. Santos Maia C, Mehnert W, Schaller M, Korting HC, Gysler A, et al. (2002) Drug targeting by solid lipid nanoparticles for dermal use. J Drug Target 10:489-495.

99. Chen H, Chang X, Du D, Liu W, Liu J, et al. (2006) Podophyllotoxin-loaded solid lipid nanoparticles for epidermal targeting. J Control Release 110:296-306.

100. Erdogan M, Wright JR Jr, McAlister VC (2002) Liposomal tacrolimus lotion as a novel topical agent for treatment of immune-mediated skin disorders: experimental studies in a murine model. Br J Dermatol 146:964-967.

101. Egbaria K, Ramachandran C, Weiner N (1991) Topical application of liposomally entrapped cyclosporin evaluated by in vitro diffusion studies with human skin. Skin Pharmacol 4:21-28.

102. Ali MF, Salah M, Rafea M, Saleh N (2008) Liposomal methotrexate hydrogel for treatment of localized psoriasis: preparation, characterization and laser targeting. Med Sci Monit 14: I66-174.

103. Fang JY, Fang CL, Liu CH, Su YH (2008) Lipid nanoparticles as vehicles for topical psoralen delivery: solid lipid nanoparticles (SLN) versus nanostructured lipid carriers (NLC). Eur J Pharm Biopharm 70:633-640.

104. Saraswat A, Agarwal R, Katare OP, Kaur I, Kumar B (2007) A randomized, double-blind, vehicle-controlled study of a novel liposomal dithranol formulation in psoriasis. J Dermatolog Treat 18:40-45.

105. Shim J, Seok Kang H, Park WS, Han SH, Kim J, et al. (2004) Transdermal delivery of mixnoxidil with block copolymer nanoparticles. J Control Release 97:477-484.

106. Jain B, Singh B, Katare OP, Vyas SP (2010) Development and characterization of minoxidil-loaded liposomal system for delivery to pilosebaceous units. J Liposome Res 20:105-114.

107. Kumar R, Singh B, Bakshi G, Katare OP (2007) Development of liposomal systems of finasteride for topical applications: design, characterization, and in vitro evaluation. Pharm Dev Technol 12:591-601.

108. Vogt A, Combadiere B, Hadam S, Stieler KM, Lademann J, Schaefer H (2006) 40 nm, but not 750 or ,500 nm, nanoparticles enter epidermal CD1a+ cells after transcutaneous application on human skin. J Invest Dermatol 126:1316-1322.

109. Ereno D,"WellgroundedBeauty,"http://revistapesquisa.fapesp.br/en/2008/04/01/wellgrounded-beauty/.

110. Carmen M D, Pereda V, Polezel A et al. (June 2012) Sericin cationic nanoparticles for application in products for hair and dyed hair. U.S. Patent 20120164196A1.

111. Rastogi R, Anand S, Koul V (2010) Electroporation of polymeric nanoparticles: an alternative technique for transdermal delivery of insulin. Drug Dev Ind Pharm 36: 1303-1311.

112. Amato S W, Farer A, Hoyte W M, Pavlovsky M et al. (August 2007) Coatings for mammalian nails that include nanosized particles, U.S. Patent 2007/002207.

113. NanoLabs, http://nanolabs.us/press-releases/green-chemistryand- new-thinking-at-playas-nano-labs-ctle-receives-provisional-patent-for-unique-nanotech-nail-polish/.

114. Ha T H, Jeong J Y, Jung B T Y H, and Kim J K (April 2008) Cosmetic pigment composition containing gold or silver nano-particles. European Patent 1909745A.

115. Viladot P J L, Delgado G R, and Fernandez B A (January 2013) Lipid nanoparticle capsules.European Patent 2549977A.

116. Hia J, Nasir A (2011) Photonanodermatology: the interface of photobiology, dermatology and nanotechnology. Photodermatol Photoimmunol Photomed 27:2-9.

117. Zuo L, Wei W, Morris M, Wei J, Gorbounov M, et al. (2007) New technology and clinical applications of nanomedicine. Med Clin North Am 91:845-862.

118. Eden JG, Park S-J, Ostrom NP, Chen K-F (2005) Recent advances in microcavity plasma devices and arrays: a versatile photonic platform J Phys D Appl Phys 38:1644-1648.

119. Shiohara A, Hoshino A, Hanaki K, Suzuki K, Yamamoto K (2004) On the cyto-toxicity caused by quantum dots. Microbiol Immunol 48:669-675.

120. LovriÄ‡ J, Bazzi HS, Cuie Y, Fortin GR, Winnik FM, et al. (2005) Differences in subcellular distribution and toxicity of green and red emitting CdTe quantum dots. J Mol Med (Berl) 83:377-385.

121. Kim S, Lim YT, Soltesz EG, De Grand AM, Lee J, et al. (2004) Near-infrared fluorescent type II quantum dots for sentinel lymph node mapping. Nat Biotechnol 22:93-97.

122. Ahmed N, Fessi H, Elaissari A (2012) Theranostic applications of nanoparticles in cancer. Drug Discov Today 17:928-934.

123. Persidis A (1999) Cancer multidrug resistance. Nat Biotechnol 17:94-95.

124. Parveen S, Sahoo SK (2006) Nanomedicine: clinical applications of polyethylene glycol conjugated proteins and drugs. Clin Pharmacokinet 45:965-988.

125. Wang MD, Shin DM, Simons JW, Nie S (2007) Nanotechnology for targeted cancer therapy. Expert Rev Anticancer Ther 7:833-837.

126. Tran MA, Watts RJ, Robertson GP (2009) Use of liposomes as drug delivery vehicles for treatment of melanoma. Pigment Cell Melanoma Res 22:388-399.

127. Oberdörster G, Oberdörster E, Oberdörster J (2005) Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 113:823-839.

128. Yah CS, Simate G, Iyuke SE (2012) Nanoparticles toxicity and their routes of exposures. Pakistan Journal of Pharmaceutical Sciences 25:477–549.

129. Paul JAB, Roel PFS (2006) Toxicological characterization of engineered nanoparticles. In: Nanoparticle Technology for Drug Delivery. Gupta RB and Kompella UB (Eds), Taylor & Francis, New York, USA.

130. Raj S, Jose S, Sumod US, Sabitha M (2012) Nanotechnology in cosmetics: Opportunities and challenges. J Pharm Bioallied Sci 4: 186-193.

131. Tan MH, Commens CA, Burnett L, Snitch PJ (1996) A pilot study on the percutaneous absorption of microfine titanium dioxide from sunscreens. Australas J Dermatol 37: 185-187.

132. Dussert AS, Gooris E, Hemmerle J (1997) Characterization of the mineral content of a physical sunscreen emulsion and its distribution onto human stratum corneum. Int J Cosmet Sci 19:119-129.

133. Schulz J, Hohenberg H, Pflücker F, Gärtner E, Will T, et al. (2002) Distribution of sunscreens on skin. Adv Drug Deliv Rev 54 Suppl 1:157-163.

134. Gontier E, Ynsa M-D, Biro T, Hunyadij J, Kiss B, Gaspar K, et al. (2008) Is there penetration of titania nanoparticles in sunscreens through skin? A comparative electron and ion microscopy study. Nanotoxicology 2: 218-231.

135. Mavon A, Miquel C, Lejeune O, Payre B, Moretto P (2007) In vitro percutaneous absorption and in vivo stratum corneum distribution of an organic and a mineral sunscreen. Skin Pharmacol Physiol 20:10-20.

136. Pinheiro T, Pallon J, Alves LC, Verissimo A, Filipe P, Silva JN (2007). The influence of corneocytes structure on the interpretation of permeation profiles of nanoparticles across skin. Nucl Instrum Methods Phys Res B 260:119-23.

137. Zvyagin AV, Zhao X, Gierden A, Sanchez W, Ross JA, et al. (2008) Imaging of zinc oxide nanoparticle penetration in human skin in vitro and in vivo. J Biomed Opt 13: 064031.

138. Sadrieh N, Wokovich AM, Gopee NV, Zheng J, Haines D, et al. (2010) Lack of significant dermal penetration of titanium dioxide from sunscreen formulations containing nano- and submicron-size TiO2 particles. Toxicol Sci 115: 156-166.

139. Filipe P, Silva JN, Silva R, Cirne de Castro JL, Marques Gomes M, et al. (2009) Stratum corneum is an effective barrier to TiO2 and ZnO nanoparticle percutaneous absorption. Skin Pharmacol Physiol 22:266-275.

140. Johnston HJ, Hutchison GR, Christensen FM, Peters S, Hankin S, et al. (2009) Identification of the mechanisms that drive the toxicity of TiO(2)particulates: the contribution of physicochemical characteristics. Part Fibre Toxicol 6:33.

141. Hirakawa K, Mori M, Yoshida M, Oikawa S, Kawanishi S (2004) Photo-irradiated titanium dioxide catalyzes site specific DNA damage via generation of hydrogen peroxide. Free Radic Res 38:439-447.

142. Wamer WG, Yin JJ, Wei RR (1997) Oxidative damage to nucleic acids photosensitized by titanium dioxide. Free Radic Biol Med 23:851-858.

143. Nakagawa Y, Wakuri S, Sakamoto K, Tanaka N (1997) The photogenotoxicity of titanium dioxide particles. Mutat Res 394:125-132.

144. Hidaka H, Kobayashi H, Koike T, Sato T, Serpone N (2006) DNA damage photoinduced by cosmetic pigments and sunscreen agents under solar exposure and artificial UV illumination. J Oleo Sci 55:249-61.

145. Nel A, Xia T, Mädler L, Li N (2006) Toxic potential of materials at the nanolevel. Science 311:622-627.

146. Oberdo¨ rster G, Maynard A, Donaldson K et al. (2005) ILSI Research Foundation/Risk Science Institute Nanomaterial Toxicity Screening Working Group. Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. Part Fibre Toxicol. 2:8.

147. K. Takeda, K.-I. Suzuki, A. Ishihara et al. (2009) Nanoparticles transferred from pregnant mice to their offspring can damage the genital and cranial nerve systems. Journal of Health Science 55:95–110.

148. De Jong WH, Borm PJ (2008) Drug delivery and nanoparticles:applications and hazards. Int J Nanomedicine 3:133-149.

149. Poon VK, Burd A (2004) In vitro cytotoxity of silver: implication for clinical wound care. Burns 30:140-147.

150. Lansdown AB, Taylor A (1997) Zinc and titanium oxides: promising UV-absorbers but what influence do they have on the intact skin? Int J Cosmet Sci 19: 167-172.