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Review Article

RECENT NANOTECHNOLOGICAL ASPECTS IN COSMETICS AND DERMATOLOGICAL PREPARATIONS

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ABSTRACT

Nanotechnology represents one of the most capable technologies of the 21st century. Recently Nanotechnology is emerging in the field of cosmetics and dermal preparations as it offers a revolutionize treatment of several skin diseases. It is proved effective in attaining Safe and targeted delivery of active medicaments as well cosmetic ingredients. Use of carrier system in nanotechnology has added advantage of improved skin penetration, depot effect with sustained release drug action. This review article discusses advantages, disadvantages, method of preparation and pharmaceutical applications of various unconventional nanoparticles like Solid Lipid Nanoparticles, Nanostructured Lipid Carrier, and Lipid Drug Carrier and also some novel drug carrier systems like Microsponge Drug Delivery system, Vitamin and Gold loaded Nanofibre facial mask etc. Apart from this it also covers toxicological concern about nanoparticles.

Keywords: Nanotechnology, Cosmetic and dermal preparation, Skin penetration.

INTRODUCTION

Nanotechnology is a big boon for cosmetic and dermal product manufacturers in near future as it is the fastest developing area of research involved in developing science-based solutions for innovative therapeutics and cosmetics, thus improving wellbeing[1-3]. Over 4000 years ago, prehistoric Egyptians, Greeks and Romans researchers were making use of nanotechnology in hair dye preparations. But recently the concept of nanotechnology came enforce from 1959 in different fields like science, biology, physics, chemistry, and engineering, nearly 40 years ago it has been entered in the field of cosmetics, dermal preparations and other health products with moisturising creams prepared by using liposomes[4, 5]. The prefix "Nano" from nanotechnology is a Greek word "Nanos" means "little old man or dwarf".

Nanotechnology is nothing but the fundamental understanding about how materials react or works at nano scale (i.e. at atomic, molecular or subatomic level) in the creation and utilization of structures, devices and systems that have novel properties and functions. Nanotechnology deals with manipulation of structures of matter in the size range of 1-100 nanometers (10^{-9} of meter) approximately[6-13]. Particles of these size ranges are called as nanoparticles which are having one or more external dimensions or an internal structure, on the nanoscale, and could exhibit novel characteristics compared to the same material without nanoscale features. Nanoparticles are considered to be separated into two groups: i) labile nanoparticles which get disintegrated into its molecular components upon application to skin (e.g. liposomes, microemulsions, nanoemulsions), and ii) insoluble particles (e.g. Titanium dioxide (TiO_2), fullerenes and quantum dots[14].

Currently nanotechnology has been utilised in the development of elaborated nanoparticles of even size, shape, and composition for their rising utilization in tires, sports commodities, catalysts, electronic components, window sprays, paints, varnishes, coatings, foods, and in cosmetic and dermal preparations for its wide variety of applications like improved safeguard against UV-radiation, deeper skin access, longer-lasting effects, controlled drug release action with respect to skin, skin appendages, hair follicle particular cell population, trancutaneous vaccination, transdermal gene therapy and also for better colour and quality finished product. Nanotechnology can promote newer use of already existing materials[15-20]. However, the toxicological and environmental safety of micro and nanoparticles has to be evaluated using specific toxicological studies prior to a wider implementation of the new technology[19, 21].

DERMAL ABSORPTION AND APPLICATIONS OF NANOPARTICLES

Though skin is considered as less permeable and also associated with low risk, the absorption of nanoparticles is primarily carried out through it[22, 23]. But literature survey shows that skin is the fundamental route of entry for nanoparticles both in occupational and unintentional contact and it should be considered as risk evaluation [4, 24-27]. Depending on physicochemical properties of the compound, different pathways of penetration across the skin have been recognized that are intercellular, trans-cellular, and transappendageal like through hair follicles and sweat glands[4, 24]. Number of factors that influence the dermal absorption of nanoparticles can be divided into three groups as location and skin conditions at the application site, physicochemical properties of the penetrating molecule, and physicochemical properties of the vehicle dispersing the penetrating molecule[4, 28]. Apart from these factors like lipophilic-hydrophilic gradient, pH gradient and isoelectric point have their vital role which influences dermal absorption of nanoparticles[4, 29-31]. The presence of molecules such as solvents, surfactants, enhancers, and others may alter or damage stratum corneum by different processes thus causing a potential increase in the absorption of all or selected ingredients of the applied formulation[4, 28, 32, 33].

In cosmetic and dermatological preparations, nanoparticles play an important role in various ways like;

Photoprotection

Since UV- radiation and sun exposure have been linked with the increased rate of epithelial skin cancer and melanoma, sunscreens play a critical role in prevention of skin cancer. Sunscreens are considered to be a vital part of cosmetic anti-aging products. At present three photoprotecting methods exist that are antioxidants, repair mechanisms stimulators and physical photon blockers[19, 34]. Organic chemical compounds like titanium dioxide (TiO_2) and zinc oxide (ZnO) at nanoscale are capable to adsorb, disperse, or reflect UV- radiation. There are enough evidences that although nanoparticles can penetrate into the upper regions of human hair follicle or the superficial layers of the stratum corneum, they cannot penetrate the barrier of intact skin and reach the viable epidermis[35-37]. Quantum dot nanoparticles are similar in size to that of particles in sunscreen formulations (30 nm), it simulate the behaviour of TiO_2 nanoparticles after cutaneous application on UV-exposed skin [38]. Depending on their size and surface chemistry, a penetration into the viable epidermis and dermis has been shown raising safety concerns. Other nanoparticulate structures such as liposomes or SLN have been used in sunscreen formulations as penetration enhancers which also improve stability and tolerance for the active moiety[39-42]. Daylong Actina is a novel liposome based sunscreen developed for the requirements of transplanted and immune compromised patients.

Barrier creams

The barrier function of the stratum corneum could prove inadequate in protecting the skin from certain irritants such as chemotherapeutics, allergens or some pathological condition such as

dermatitis. A boost of this function may be required. Earlier studies had already proved that particulate barrier creams are more capable in protecting the skin from water loss and thus minimizing the potential risk of irritant hand eczema than moisturizers with high lipid content [19, 43], for e.g. nanoparticles possessing antioxidative properties have been proposed as components of anti-aging cosmetic products, fullerene (C_{60}) for its anti-wrinkle efficacy[44]. Nanoparticles are also used in galenical formulations which are already in market like Eczemel cream (DERMAVIDUALS USA), Regenerations crème Intensiv. The list of commercially available products is continuously expanding, indicating the significance of nanoparticles for the cosmetic industry.

Antiseptic properties

Antisepsis is one more important application of nanoparticles. The most commercialised nanomaterial with antibacterial properties till now is nanosilver, used not only for the coating of wound and burn dressings but also as a water disinfectant and room spray. Other examples are Chlorhexidin-loaded nanoparticles (Nanochlorex) [45, 46], uncoated TiO2 possess antibacterial properties due to their photocatalytic action.

Laser ablation and phototherapy

Short laser pulses already have been used in ophthalmology and dermatology to target melanosomes and thus treat hyper-pigmentation disorders of the skin or retinal disorders. Examples of nanoparticles used are iron oxide, gold. Photodynamic therapy (PDT) by using gold nanoparticles have been seen as a promising treatment strategy of skin cancer and various skin diseases, but its use has been limited due to the costs and patient compliance (pain) [19, 47].

Treatment of hair diseases

Particulate drug delivery systems rather than aqueous alcohol solutions are gaining importance in the treatment of hair disorders like alopecia androgenetica and alopecia areata. They do so by increasing drug penetration into the hair follicle openings and can act as a depot for a sustained drug release within the hair follicle. Examples of nanoparticles used to treat hair disease are poly(lactic-co-glycolic) acid, poly (e-caprolactone)-blockpolyethylene glycol, neutral liposomes, solid lipid nanoparticles. Due to lack of other therapeutic options, gene therapy of hair and the novel particle-based drug delivery systems for a promising active follicular targeting of disease-related cell populations in the hair follicle are gaining importance[19, 48-50].

Sebaceous gland targeting

The sebaceous gland is a key component of the pilosebaceous unit. The sebaceous duct opens into the hair follicle canal, i.e., targeting strategies for hair follicle related disease like acne, rosacea get benefit from the follicular penetration of topically applied particles like poly(lactic-co-glycolic) acid, biodegradable poly-lactic acid, solid lipid nanoparticles and liposomes loaded with active drug moiety [51-53]. A major advantage of such delivery systems is the better tolerability of irritating retinoid improving patient compliance as well as the avoidance of systemic absorption and side effects. The extensive research in recent years has led to the commercialization of certain particle-based anti-acne products of benzoyl peroxide (BP, such as a BP microsphere cream 5.5% (NeoBenz Micro(R), SkinMedica, Inc.) and a BP microsphere wash 7% (NeoBenz Micro Wash Plus Pack(R), SkinMedica, Inc.). Clinical studies showed high levels of skin tolerability, esthetic attributes and patient satisfaction after treatment with BP-loaded microsphere creams[19, 54].

Topical dermatotherapy

As nanoparticulate drug delivery system had been developed firstly place for controlled drug release, it could be easily postulated that their use would prove beneficial for local treatment of inflammatory skin diseases as well. Glucocorticoids are key drugs in dermatology, but with side effects like skin atrophy which limits their chronic use. It has recently been shown that a targeting of the epidermis, where the inflammatory process takes place, instead of the dermis, can be achieved by using liposomal formulations, thus minimizing skin atrophy[19,55]. Several other studies indicate that various drugs such as podophyllotoxin, cyclosporine A, tacrolimus methotrexate, psoralen, dithranol, clotrimazole and other antifungal drugs could be integrated in nanoparticles to achieve a better tolerability, an increased safety and an optimal therapeutic effect[55-62].

Gene therapy

As previously mentioned, the hair follicle and more specifically the bulge region and the hair matrix accommodate a substantial population of stem cells. Since nanoparticles can penetrate selectively into the hair follicle canal, nanoparticulate formulations could be used for gene delivery, creating new potential in the emerging field of gene therapy[19].

Targeting of antigen-presenting cells

In recent years a great number of vaccines and vaccine carriers with potent humoral immunologic response have been developed for the prevention of infectious diseases. Since the use of living or attenuated viruses (e.g., measles and rubella vaccine) for such purposes is not without threat, new approaches are being required. The dense network of antigen presenting cells, the dermal cells and the Langerhans cells, which are particularly easy to get to in the lower infundibulum of the hair follicle, could be a more suitable target for vaccination purposes than the limited population of muscle drug delivery system[63]. Current research is focused on the use of nanoparticles as vaccine carriers due to their additional adjuvant function. Besides enhancing the immunologic response, they are able to transform it as well. Due to their particulate nature, they are acknowledged by the cells of the immune system and promote the uptake of the antigen along with an activation of the immune system[64]. Currently, only a handful of transdermal vaccines is commercially available, but diverse nanomaterials such as liposomes, Immune stimulating complexes, non-degradable particles (e.g., latex, silica, gold, polystyrene) and biodegradable particles like Poly-lactic acid and Poly(lactic-co-glycolic) acid are being tested, promising new challenging results in the emerging field of particle-based transcutaneous vaccination[19, 65, 66].

Transdermal drug delivery

Several opiates are already commercially available as a patch. The therapeutic effect follows upon transdermal penetration and systemic absorption of the drug. Unfortunately, the strong lipophilic stratum corneum hinders the permeation of hydrophilic molecules and retains high lipophilic drugs, thus limiting the transdermal delivery of strong lipophilic or hydrophilic molecules. Hair follicles could play an important role as a shunt for the systemic absorption of topically applied drugs. Recently nanoparticles have been used as a drug carrier for transdermal drug delivery system. It has been found that encapsulation of substances in nanoparticles enhances their transdermal penetration and permeation as a result of the follicular targeting. The nanoparticles used for transdermal drug delivery are calcium carbonate, solid lipid nanoparticle, nanostructured lipid carrier. More recently, polymeric nanoparticles and electroporation were successfully used for the transdermal delivery of insulin. To overcome drawbacks of subcutaneous drug administration like patient discomfort, localised drug reaction e.g., lipoatrophy and granuloma formation etc, transdermal drug delivery could modernize treatment strategies for Diabetes and chronic pain by offering much more patient compliance[67].

Nanodiagnostics

Number of nanoparticles has currently been tested in new diagnostic applications due to certain advantages such as the higher sensitivity of related detection methods, which allow performing analysis on small amounts of tissue samples. For e.g. Gold nanoparticles, Quantum dots, nanoparticles with magnetic properties, super paramagnetic nanoparticles etc[68-70].

DERMAL TOXICITY OF NANOPARTICLES

Dermal exposure of smaller size (less than 10 nm) of nanoparticles is more ruinous as it penetrates easily and shows long-lasting erythema, oedema and eschar formation, Hyperkeratosis and papillomatosis in irregular epidermis and fibrosis, hyperemia,

erythema, intracellular edema and hyelinisation of collagen in dermis than larger ones (more than 30nm) which do not enter in the skin through transappendegeal route also. Following are the probable pathways of cellular uptake of nanoparticles - phagocytosis, macropinocytosis, clathrinmediated endocytosis, nonclathrin, non-caveolaemediated endocytosis, caveolae-mediated endocytosis or diffusion[4, 71-74].

Types of nanoparticles mostly used in cosmetics and dermal preparations are solid lipid nanoparticles, nanostructured lipid carriers, lipid drug conjugates. These are discussed below.

SOLID LIPID NANOPARTICLES (SLN)

At the beginning of the 1990's as an unconventional carrier system like solid lipid nanoparticle (SLN) was developed over the existing conventional carriers, such as emulsions, liposomes and polymeric nanoparticles as a colloidal barrier for controlled drug delivery[9, 21, 75-77]. These particles are prepared from extremely purified triglycerides, complex glycerides mixtures or even waxes by replacing the liquid lipid (oil) of an o/w emulsion by 0.1% (w/w) to 30% (w/w) of solid lipid or a blend of solid lipid (i.e. lipids that are solid at room temperature and also at body temperature) and stabilized by surfactant(s) with a preferred concentration of 0.5% (w/w) to 5% (w/w). The mean particle size of SLN is in submicron range, ranging from 40 to 1000 nm[75, 78]. SLN have been developed and investigated by different analytical techniques like Photon Correlation Spectroscopy (PCS), Atomic Force Microscopy (AFM), Scanning Electron Microscopy (SEM), for parenteral, pulmonary and dermal application routes[79-82].

Table 1: Drugs administered as Solid Lipid Nanoparticles[83-88]

Categories	Drugs	Categories	Drugs
Steroids	Prednicarbate Ethinyl estradiol Cyproterone acetate	Antitubercular	Rifampicin Isoniazide Pyrizinamide
Anti cancer	Isotretinoin Methotrexate	Anti inflammatory	Triptolide
Vitamins	Vitamin-A		

There are different methods used for preparation of SLNs like:

Hot homogenization technique

In the hot homogenization method the drug is dissolved or dispersed in melted solid lipid for SLN or in a mixture of liquid lipid (oil) and melted solid lipid for nanostructured lipid carrier. This lipid melt containing drug is then mixed by high speed stirring in a solution of the hot surfactant at same temperature (5–10^{0}C above the melting point of the solid lipid or lipid blend). This pre-emulsion is then passed through a high pressure homogenizer adjusted to the same temperature, generally applying three cycles at 500 bar or two cycles at 800 bars. This technique can be used for lipophilic and insoluble drugs as well as for the heat sensitive drugs because the exposure time to high temperature is comparatively short. The technique is not suitable for inclusion of hydrophilic drugs into solid lipid nanoparticle because of larger portion of drugs is in water during homogenization which leads to low entrapment capacity [91-93].

Cold homogenization technique

In the cold homogenization method, the lipid microparticles are obtained by melting and subsequent cooling of drug containing lipid melt followed by crushing, grounding and diffusing in cold surfactant to obtain a cold pre-suspension of micronized lipid particles. This suspension is then forced to pass through a high pressure homogenizer at room temperature applying typically 5–10 cycles at 1500 bar[82, 91]. This method is the first choice for hydrophilic drugs with good as well as low solubility (surfactants are added to improve solubility). This technique avoids and shortens melting process of lipid and hence it is appropriate for thermosensitive and thermolabile drugs.

Microemulsification- solidification technique

SLNs can also be prepared by microemulsification of inner molten lipids phase (oil) which is preloaded with drug (at 65-70^{o}C), followed by dispersion in cold aqueous phase with mechanical stirring (at 2-3^{o}C). The dispersion is washed two times with distilled water by ultrafiltration. After washing, the suspension is freeze dried. The diameter of the disperse phase droplet should be always below 100nm. There is no need of energy for this preparation [94-99].

Multiple microemulsion- solidification

Multiple emulsions can also be employed as a controlled drug delivery system. Warm w/o/w multiple microemulsions can be prepared in two step process. SLNs can be obtained under mechanical stirring by dispersing the warm micromultiple emulsion in cold aqueous medium in a predetermined ratio followed by washing by ultrafiltration system with dispersion medium. Multiple emulsions have intrinsic instabilities because of coalescence of the aqueous droplets within the oil phase, coalescence of oil droplets, and breaking of the oil layer on the surface of the internal droplets[100-102].

Ultrasonication or High speed homogenization

SLNs can also be prepared by sonication or high speed stirring. This is very general and simple technique and can be beneficial over other methods like hot and cold homogenization but with drawback of distribution of larger particle size ranging between micrometer range leading to physical instability such as particle growth upon storage and also metal contamination due to ultrasonication[103, 104].

SLNs preparation using supercritical fluid

This is new technique for preparation of SLN giving the benefit of processing without solvent. Rapid growth of supercritical carbon dioxide (99.99%) solutions which is considered to be a good solvent is used in the formation of solid lipid nanoparticle. This method is known as RESS method[105, 106, 107].

SLNs prepared by solvent emulsification/evaporation

In this method, lipid precipitation in aqueous phase upon evaporation of water immiscible organic solvent is carried out by dispersion of nanoparticles in o/w emulsions[108, 109].

Double emulsion method

It is a novel method of preparation of solid lipid nanoparticles loaded hydrophilic drug moiety and is based on solvent emulsification evaporation by drug encapsulation in the outer water phase of w/o/w double emulsion along with a stabilizer to avoid partitioning of the drug to outer water phase during solvent evaporation[110].

Spray drying method

It is less costly method than lyophilisation. In this method particle aggregation occurs due to elevated temperature, shear forces and partial melting of particle. The most excellent outcome is obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v)[82, 111].

In comparison with other particulate carriers, SLN has many advantages like good tolerability, stability, high drug pay load, great adjustability in controlling the release profile of drug, bypasses liver and spleen infiltration, outstanding reproducibility by use of cost effective high pressure homogenization method of preparation, possible incorporation of hydrophilic and lipophilic drugs, topical treatment of skin disease is possible, biodegradability[21, 82, 112-122]. Solid lipid nanoparticles are also associated with few drawbacks as of poor drug loading capacity, unpredicted drug expulsion during storage after polymorphic transition, high water content of dispersion, low capacity to load hydrophilic drug due to partitioning effect[21, 82, 123-126].

Solid lipid nanoparticles have a wide variety of pharmaceutical applications like in topical glucocorticoid preparations (primary therapy for atopic dermatitis and contact dermatitis) for separation

of desired anti-inflammatory effects and undesired antiproliferative effects[127], in antiandrogenic preparations like cyproterone acetate (used to decrease sebum secretion rate and acne lesions) or cyproterone acetate with ethinyl estradiol (to avoid teratogenic effects of cyproterone acetate like feminization of the male foetus and loss of libido, gynecomastia, vasomotor flushing and loss of bone mineral density in male patients) they are used to avoid systemic side effects[128, 129], for topical application for various drug like anticancer, isotretinoin, vitamin-A (for getting better penetration with sustained release, flurbiprofen (provides a potential benefit in delivering the drug straight to the place of action, which will give higher tissue concentrations)[130-132], In conventional Chinese medicines e.g. Triptolid (having inflammatory, immunosuppressive, infertility and anticancer activity) for getting better bioavailability, decrease in required dose and also dose-dependent side effects such as irritation and stinging[133], in antitubercular chemotherapy by using drugs like rifampicin, isonizide, pyrazinamide to decrease the dosing frequency and get better patient compliance[134], in cosmeceuticals it acts as an as an active carrier agent for both molecular sunscreens and UV- blockers, it also act in a way to achieve better targeting of vitamin A[82, 135], in Gene Vector formulation (because it carries materials like DNA, plasmid DNA and other nucleic acids)[136], in the preparations used to treat breast cancer and Lymph Node Metastases e.g. Mitoxantrone, SLN are used to minimise the level of toxicity and to improve the therapeutic safety level and thereby bioavailability of drug molecule[137], doxorubicin to increase efficiency and decreases breast cancer cells, In tumour targeting preparations it is used to prolong release of drugs like methotrexate, camptothecin, tamoxifen[138, 139]. In certain novel distinctive drug-delivery system like stealth nanoparticles like dipalmitoyl phosphatidylethanolamine-PEG 2000 and stearic acid-PEG 2000 to get away rapid clearance by the immune system[140, 141] apart from these applications, solid Lipid nanoparticles also play role in agriculture field by acting as a suitable carrier of ecologically harmless pesticides[82, 142].

NANOSTRUCTURED LIPID CARRIER (NLC)

The second generation of the lipid nanoparticle technology is called as Nanostructured Lipid carrier (NLC), these particles are prepared by using blends of solid lipids preferably in a ratio of 70:30 with liquid lipids (oils) in a ratio up to 99.9:0.1; in these mixtures a decrease in melting point as compared to the pure solid lipid is observed, because of oil content. The total solid content of NLC could be increased up to 95%.[75, 143]. The fundamental idea behind developing NLCs is to boost the pay-load for active ingredients and to avoid expulsion of it during storage (with exceptional case of highly purified monoacid glycerides), which are considered mainly as a drawbacks of SLNs. Depending on the way of production and the composition of the lipid blend, different types of NLC are obtained with active (drug or cosmetic agent) sandwiched between the fatty acid chains or in between the lipid layers or in imperfections of the lipid matrix e.g. amorphous drug clusters[21, 144, 145].

LIPID DRUG CONJUGATES (LDC) NANOPARTICLES

A major problem associated with solid lipid nanoparticles is the low loading capacity of hydrophilic drugs during production process due to partitioning effects as only extremely potent hydrophilic drugs with low dose may be properly included in the solid lipid matrix. To overcome from this drawback, LDC nanoparticles with increased drug loading up to 33% have been developed. Apart from this LDC have other advantages like improved stability of pharmaceuticals, Feasibility of carrying lipophilic as well as hydrophilic drugs, easy to scale up and sterilize, easy to validate and get regulatory authorization, biodegradability and biocompatibility, avoidance of organic solvents, and also in obtaining control and targeted drug release. The LDC can be prepared either by salt formation with a fatty acid or by covalent linkage with ester or ethers followed by subsequent processing with aqueous surfactant e.g. Tweens using high pressure homogenization (HPH) [8, 146, 147].

Table 2: Currently available cosmetics (with Lipid nanoparticles) in market[75, 82, 148-150]

Products name	Name of producers or distributors	Date of market launching
Cutanova Cream Nano Repair Q10	Dr. Rimpler	10/2005
Intensive Serum NanoRepair Q10	Dr. Rimpler	10/2005
Cutanova Cream NanoVital Q10	Dr. Rimpler	06/2006
SURMER Crème Legère Nano-Protection	Isabelle Lancray	11/2006
SURMER Crème Riche Nano-Restructurante	Isabelle Lancray	
SURMER Elixir du Beauté Nano-Vitalisant	Isabelle Lancray	
SURMER Masque Crème Nano-Hydratant	Isabelle Lancray	
NanoLipid Restore CLR	Chemisches Laboratorium	04/2006
Nanolipid Q10 CLR	Dr. Kurt Richter, (CLR)	07/2006
Nanolipid Basic CLR	Dr. Kurt Richter, (CLR)	07/2006
NanoLipid Repair CLR	Dr. Kurt Richter, (CLR)	02/2007
IOPE SuperVital	Amore Pacific	09/2006
Cream,Serum	Amore Pacific	
Eye cream	Amore Pacific	
Extra moist softener	Amore Pacific	
Extra moist emulsion	Amore Pacific	
NLC Deep Effect Eye Serum	Beate Johnen	12/2006
NLC Deep Effect Repair Cream	Beate Johnen	
NLC Deep Effect Reconstruction Cream	Beate Johnen	
Regenerations cream Intesive	Scholl	06/2006
Swiss Cellular White Illuminating Eye Essence	La prairie	01/2007
Swiss Cellular White Intensive Ampoules	La prairie	
SURMER Crème Contour Des Yeux Nano-Remodelante	Isabelle Lancray	03/2008
Olivenöl Augenpflegebalsam	Dr. Theiss	02/2008
Olivinol Augenpflegebalsam	Dr. Theiss	

NOVEL CARRIERS FOR COSMETICS AND DERMATOLOGICAL PREPARATIONS

Microsponge

It is a distinctive technology which utilizes microporous beads (10-25 microns in diameter) for the controlled release of topical agents. These microporous beads are loaded with active agent having properties like inertness with monomer, adequate stability in contact with polymerization catalyst and process, immiscibility or slight solubility in water. Microsponge delivery system (MDS) release of active drug is carried out in a timely manner and also in response to other stimuli like rubbing, temperature, pH, moisture etc, onto the skin. MDS is being used in cosmetics, over-the counter (OTC) skin care, sunscreens and prescription products[151].

Microsponges are formulated by several methods like by using Emulsion Solvent Diffusion (ESD) method with oil-in-water (o/w) emulsion systems as well as by suspension polymerization in a liquid–liquid system[152]. Commonly used drugs for microsponge delivery system are flubriprofen, benzylperoxide, fluocinolone acetonide, retinol etc[153]. A microsponge formulation provides extended release with reduced irritation and improved patient compliance. These are stable over pH range of 1to11 and also at the temperature up to 130°C and also having improved thermal, physical and chemical stability; these are having enhanced material processing and flexibility to develop novel product forms[9]. This novel system is having self sterilizing capacity as particles are very small (0.25µm) size where bacteria cannot penetrate. This system overcomes the disadvantages of SLNs that are having higher pay-load (50 to 60%) and still free flowing nature and also cost effective[154].

Factors affecting mechanism of drug release from Microsponge includes physical and chemical properties of entrapped drug and microsponge system, particle size, pore features, resiliency and monomer composite which can be considered as programmable parameters of well designed microsponges which will respond to external stimuli like pressure, temperature and solubility of actives by releasing predetermined amount of actives. The release of actives from solubility microsponges (loaded with water soluble ingredients) like antiperspirants and antiseptics will be carried out in presence of water and also can be activated by diffusion between the microsponges and the outside system[151, 155, 156].

Assessment of Microsponges can be carried out by doing tests like particle size determination, morphology and surface topology of microsponges, determination of loading efficiency and production yield, determination of true density, polymer / monomer composition, compatibility studies, dissolution tests etc [151, 157-162].

In cosmetic and dermal preparation Microsponges are having wide variety of applications like in sunscreens for long lasting product efficiency and with improved safeguard for better protection from sunburns and sun related injuries even at high concentration and with decreased irritancy and sensitization, in antipruritics for long-lasting and enhanced activity, In rubefacients for prolonged activity with decreased irritancy Greasiness and odour, In antifungals for continuous release of active drug moiety, In antidandruff preparations like zinc pyrithione, selenium sulphide it is used to decrease obnoxious odour and also to minimise irritation and increase level of safety and effectiveness for long duration, In skin depigmenting agents e.g. hydroquinone for enhanced stabilization against oxidation with better efficacy and aesthetic appeal, In anti-acne preparations e.g. Benzoyl peroxide to maintained efficiency with reduced skin irritation and sensitization, in anti-inflammatory preparations e.g. hydrocortisone for longer duration of activity with decreased skin allergic response and dermatoses, Microsponge drug delivery system can also be used in Line Eliminator Dual Retinol Facia treatment-In this immediate and time released action of vitamin A is obtained by fading the appearance of fine lines, wrinkles and skin discolorations coupled with aging[163].

Following are the some marketed products of Microsponge drug delivery system with advantages[164]

- Aramis fragrances- High Performance Antiperspirant Spray for 24 Hours release of fragrance.
- Carac Cream – It is prescribed as a single dose/day for the treatment of actinic keratosis (AK).
- EpiQuin Micro- This is a prescription moisturizing fading cream that decreases effects of conditions like melasma, post inflammatory hyper pigmentation or solar lentigines and also helps in Age spots, Sun spots, and Facial discoloration.
- Retin- for topical treatment of acne vulgaris.
- Retinol cream, Retinol 15 Night cream-A night time treatment cream, continued use of Retinol 15 will help to reduce fine lines and wrinkles, and prominent improvement in the skin discolorations occur due to aging, and enhanced skin smoothness.
- Sports creams RS and XS - Topical analgesic-anti-inflammatory and counterirritant used for managing musculoskeletal conditions.
- Micro Peel Plus/Acne Peel- These microcrystals target the correct areas on the skin that need improvement.
- Oil Control Lotion- Day cream used to give matte finish and eliminates shine for hours after application. It soothes inflammation and leaves tighten skin and thus promote healing of acne-Prone oily skin conditions.
- Lactrex™ 12% Moisturizing Cream- helps to moisturize dry, flaky, cracked skin.

Vitamin and gold loaded nanofibre facial mask for topical delivery

Conventional beauty face masks existing in the market are cotton masks that are pre-moistened with skin nutrients. The aqueous phase of the pre-moistened mask can raise the degradation rate of the unstable ingredients such as ascorbic acid. To overcome this problem a novel polymeric face mask have been developed that can accommodate several skin nutrients such as ascorbic acid, retinoic acid, gold, and collagen.

Many marketing tactics include the inclusion of antioxidants and other skin nutrients into cosmetic products. The strength and function of the skin depends upon an important factor i.e. Collagen which also play an important role in skin rejuvenation and wrinkle reversal effect. The quantity of collagen in the skin decreases along with age; therefore, it is extensively used as a moisturizer in cosmetic creams and products. Generally Vitamin C (L-ascorbic acid) has been used in cosmetic and dermatological preparations for its photoprotective action, ability to destroy free radicals and oxidizing agents. It can also encourage collagen synthesis and suppress the pigmentation of the skin. Vitamin C is chemically unstable, and can be oxidized very easily; therefore, more stable derivatives (with ability to convert into active compound i.e. ascorbic acid after ingestion) like ascorbyl palmitate, ascorbyl tetraisopalmitate, and magnesium ascorbyl phosphate formulated as a emulsion are extensively used in pharmaceutical industry[165-167]. Retinoic acid can be used in treatment of acne and also promotes the repair of skin damaged by ultraviolet and can decrease wrinkles caused by photoaging[168-175]. Gold nanoparticles have been studied as potential vaccine carriers and in transdermal delivery. Nowadays Gold facial masks are being used in beauty clinics and saloons. It works by improving the blood circulation, skin elasticity, and thereby revitalizes the skin and also reduces the formation of wrinkles. Skin permeation studies demonstrate that spherical gold nanoparticles are not inherently toxic to human skin cell[176-179]. Electrospinning is an extremely simple and successful method for fabricating polymeric nanoscale fibers with high surface area to volume ratio and porosity[180, 181].

Currently there are few social issues about the impact of nanoparticles used extensively in sunscreens like Titanium dioxide, Zinc oxide, on environment, health and safety. Recent sunscreens contain insoluble nanoparticles (colourless) of titanium dioxide (TiO_2) or zinc oxide (ZnO), which reflect/disperse ultraviolet more effectively than bigger particles. The nano-sized particles are used in sunscreens as a substitute to existing chemical UV absorbers, such as p-aminobenzoic acid and benzophenones, which can cause sensitivity reactions individuals. Sunscreen lotions are generally marketed as cosmetic products in the majority of countries including the European Union. In the United States, because of oversight of the US Food and Drug Administration (FDA) sunscreens are considered as over-the-counter (OTC). All studies incorporated in the EU Scientific Committee on Cosmetics and Non-Food Products SCCNFP opinion as well as in print investigations concluded that micro or nanosized TiO2 particles stay on the outer surface or stratum corneum of the skin and do not penetrate through the living skin. Nano-sized formulations may enhance or diminish skin penetration at a limited rate. In general, the current fact indicates that nano-materials such as nano-sized vesicles or TiO_2 and ZnO are relatively nontoxic, One paper claiming that invitro toxicity studies on

nanoparticulate forms of TiO2 that show oxidative cell damage and genotoxicity should be interpreted 'with caution'; The same paper is uniquely unambiguous in its claim that nanoparticulate forms of ZiO_2 and ZnO used in sunscreens pose harmless with respect to human skin or health. The National Institute for Occupational Safety and Health (NIOSH) has published a report in 2005 with conclusion that little concentrations of inhaled TiO2 were an unlikely cause of cancer in humans. Although other nanoparticles like carbon nanotubes, fullerene derivatives and quantum dots may have properties that require safety assessment on case to case basis prior to human use[182, 183].

Recently manufacturers are incorporating nanosized carbon particles, including fullerenes (e.g., C_{60} and C_{70}), into consumer products such as cosmetics for their recommended "anti-aging" or radical scavenging properties[184, 185]. In spite of this commercial use, research has revealed that fullerenes can cause undesirable biological effects[186], and unfortunately remains with respect to the environmental and human health effects[187]. Fullerenes in cosmetics will enhance human exposure through product utilization, and like other chemicals found in personal care products, can potentially be released into the environment after being rinsed "down the drain"[188]. A satisfactory assessment of the environmental and human health impacts of nanoparticles (e.g., C60) in consumer products would be valuable information for decision- making, and could therefore help prevent public distrust[189] and the slow financial growth of nanotechnology[190]. Such evaluations must use validated analytical techniques like high-performance liquid chromatography (HPLC) for fullerene detection in complex matrices like cosmetics. Detection methods are essential to quantify fullerenes in commercial applications to make available potential exposure levels for future risk assessments of fullerene technologies.

CONCLUSION

Nanotechnology is considered to be a new industrial revolution and also proved to be beneficial in many dermatological and cosmetic preparations. Over the last dozen of years, the field of nanoparticle drug delivery to the skin has progressed to a well categorise tools like SLN, lipid nanoparticle, lipid drug conjugates etc for more safe and targeted delivery of active drug moiety as well cosmetic ingredients. Nanoparticles are also having capacity to increase or decrease the flux, customize the drug depot location and size, and even to selectively permeabilize the stratum corneum. Understanding the interactions of nanoparticles with the common structures of skin i.e. furrow, hair follicles, eccrine ducts, etc., are extremely important to the enhancement of percutaneous drug delivery. It is also essential to assess nanomaterial skin absorption potential and its toxicity particularly for the formulations meant to apply on diseased skin. Nonetheless, current research is focused on biodegradable nanomaterials, which are thought to constrain toxicological and environmental concerns and increase safety. It is also important to understand from current facts suggests that nano-materials such as nano-sized vesicles or TiO_2, ZnO and fullerene used presently in cosmetic preparations or sunscreens are harmless to human skin or health. Other nanoparticles may have properties that warrant a safety evaluation on a case-by-case basis before human use or exposure.

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