



Latest Technology Advances in Cosmeceuticals

Nageen Arora, Shilpi Agarwal, R.S.R. Murthy*

I. S. F. College of Pharmacy, Ferozepur G.T Road, Ghalkhalan, Moga, Punjab, India

ABSTRACT

World consumers are looking for personal care products that supply multiple benefits with minimal efforts. They also expect the latest technology advances to be incorporated into innovative formulations. The trend toward therapeutic cosmetics will lead to a better understanding of modern ingredients and their assessment techniques. To obtain skin care formulations with real consumer-perceivable benefits and to optimize sensory attributes, formulators are resorting to technology that until recently was exclusively used in cosmetic products. Various formulations come under special delivery systems like Vesicular, Particulate systems, emulsions type Particulate type and other delivery systems along with their applications are shown in this article, as it results in an economic uplift of cosmetic industry in various parts of the world. Little evidence is seen that nanoparticles in cosmetics and sunscreen might be a problem at this time and its need is further explored for a better understanding of these novel technologies. Thus, novel cosmeceutical delivery systems reviewed here possess enormous potential as next-generation smarter carrier systems.

Keywords: Skin care formulations, novel cosmetic drug delivery systems, Vesicular Systems, Particulate systems, Latest cosmetic technologies.

INTRODUCTION

Today, consumers worldwide are looking for personal care products that supply multiple benefits with minimal efforts. Not only women but there is increasing number of males are using cosmetics usually to enhance their own facial are products that are created for application on the body for the purpose of cleansing, beautifying or altering appearance and enhancing attractive features. Cosmetics are substances used to enhance the appearance or odour of the human body. ^[1] Cosmetic pharmaceuticals, or cosmeceuticals, are cosmetic products that contain biologically active ingredients and claim to have medicinal or drug-like benefits. Like cosmetics, cosmeceuticals are topically applied, but they contain ingredients that influence the biological function of the skin. ^[2] Raymond Reed, founding member of the US Society of Cosmetic Chemists, coined the term in 1961. ^[3]

Tracing the origin of cosmetics, the first recorded use of cosmetics is attributed to Egyptians, circa 4000 BC. ^[4] Later on, development of cosmetics with health claims is rapidly and also expects the latest technology advances to be incorporated into innovative formulations. Faced with these trends, formulators strive to develop highly differentiated

multifunctional products that focus on treatment as well as aesthetics that contains active ingredients.

This innovative reference highlights the uses of delivery systems in cosmetics, analysing new approaches for obtaining sophisticated cosmetic products and examining the most common methods for enhancing the skin's penetration properties. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. In cosmetics, the main concern is to reach cutaneous cell while limiting the passage into the blood circulation.

The objectives of topical therapy can therefore be classified into two major areas ^[5]:

1. To modulate or assist the barrier function of skin.
2. To administer an active ingredient to one or more skin layers or compartments while minimizing systemic involvement.

Depending on the composition, a vehicle is used to exert mainly five types of effects on the skin cleansing, decoration, care, hydration and protection. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as nanoparticles, microspheres, liposomes, etc. which modulate the release and absorption characteristics of the drug.

Almost all the major cosmetic manufacturers use novel delivery systems in their products. The worldwide cosmetics and perfume industry currently generates an estimated annual turnover of US\$170 billion (according to Eurostat-May 2007). L'Oréal has a number of nanotechnology-related

***Corresponding author: Prof. (Dr.) Rayasa Ramachandra Murthy**, Head, Pharmaceutics & Director, ISF College of Pharmacy, Firozpur Road, Moga-142001, Punjab, India; **Tel.:** +91-1636-239934, +91-9898368187; **E-mail:** m_rsr@rediffmail.com

products in the market and ranks 6th in US, which devotes about \$600 million of its annual \$17 billion revenues to research in the number of nanotech related patents.^[6] These products cross female and male markets, and male grooming is one of the fastest growing markets. In 2004, the U.S. market for cosmeceuticals products was valued at \$12.4 billion and is expected to grow to over \$16 billion by 2010.^[7] The European Commission estimated in 2006, that 5 % of cosmetic products contained nanoparticles. Cosmetics cross international borders. The European Union imports nearly \$8 billion worth of cosmetics each year and exports \$32 billion. Consequently, the ICCR (International Cooperation on Cosmetic Regulation) composed of public authorities from the USA, Canada, Japan and Europe continue to support increasing cooperation within the industry.^[8] The application of novel delivery systems in cosmetic products has been the subject of continuous discussion in the media, scientific circles and among policy makers for the past few years. There are a number of classes of novel delivery technologies used, or proposed for use, in cosmetic applications. Further, the products launched by various cosmetic giants will be discussed at length.

Advances in Cosmetic Formulation Technology

There are number of innovative cosmetic delivery systems used in cosmetic products. A cosmetic delivery system is a composition or a process that can enhance perceptual or measured performance of cosmetic product. A recent article in *Happi* presented a selection of new delivery systems.^[9] A pointed discussion of a select group of delivery systems (Table 1) of current interest shall be presented in this article.

Table 1: Novel cosmetic Delivery systems

I.	Vesicular Delivery systems
	Liposomes
	Niosomes
	Silicone vesicles and Matrices
	Multi-walled Delivery systems
II.	Particulate Systems
	Microparticulates
	Porous polymeric systems
	Nanoparticulates
III.	Emulsion Delivery Systems
	Microemulsions
	Liquid crystals
	Multiple emulsions
	Nanoemulsions
	Pickering emulsions
IV.	Other Delivery systems
	Cyclodextrin complexes
	Carbosomes
	Dendrimers and hyperbranched polymers
	Nano Crystals
V.	Delivery Devices
	Iontophoresis
	Cosmetic patches

VESICULAR DELIVERY SYSTEM

Liposomes

Liposomes are vesicular structures with an aqueous core surrounded by a hydrophobic lipid bilayer membrane composed of a phospholipid and cholesterol as shown in Fig. 1. Phospholipids are GRAS (generally recognised as safe) ingredients, therefore minimising the potential for adverse effects. Solutes, such as drugs, in the core cannot pass through the hydrophobic bilayer however hydrophobic molecules can be absorbed into the bilayer, enabling the liposome to carry both hydrophilic and hydrophobic molecules by Murthy *et al.*^[10] The lipid bilayer of liposomes

promotes release of its contents, making them useful for drug delivery and cosmetic delivery applications. Liposomes can vary in size, from 15 nm up to several μm and can have either a single layer (unilamellar) or multilayer (multilamellar) structure. There are several hundreds of products which utilise liposomal delivery capabilities have been introduced into the market, however only some contain liposomes in the nanoscale. The first liposomal cosmetic product to appear on the market was the anti-ageing cream 'Capture' launched by Dior in 1986.

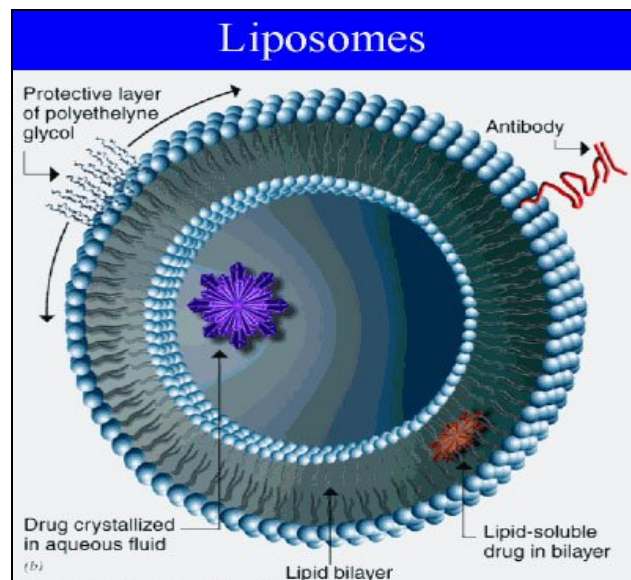


Fig. 1: Structure of Liposome

One of the reasons for the widespread use of liposomes in the cosmetic industry is their ease of preparation and the ability to improve the absorption of active ingredients by skin. Liposomes are generally utilised in aqueous systems. Recently, water-sensitive 20 to 30 micron-size microspheres of polymer structure have been developed for the delivery of fragrances, botanicals, and vitamins from anhydrous formulations, such as lipsticks, deodorants, antiperspirants and body sprays. Liposomes are unstable due to their susceptibility to oxidation and the breakdown of liposomal structure; it is overcome by optimising the storage conditions and adding chelators and anti-oxidants.^[11] Several active ingredients, biomolecules (e.g. vitamins A and E) and antioxidants (e.g. CoQ10, lycopene and carotenoids) have been incorporated into liposomal membranes to increase their delivery.^[12] Efforts to improve the encapsulation capability of liposomes by adding emulsifiers have been proposed. Phosphatidylcholine, one of the main ingredients of liposomes, has been widely used in skin care products and shampoos due to its softening and conditioning properties. Liposomes have proved to be a convenient way to deliver Phosphatidylcholine.

Some of the specialized liposomal preparations are as follows:

Transferosomes

A new type of liposomes called transferosomes, which are more elastic than liposomes and have improved efficiency, have been developed.^[13] Transferosomes with sizes in the range of 200-300 nm can penetrate the skin with improved efficiency than liposomes.^[14] These self-assembled lipid droplets with elastic bilayers are capable of spontaneous

penetration of the stratum corneum through intracellular or transcellular routes and have potential applications in cosmetics and drug delivery.^[15]

Table 2: Formulations of various Liposome delivery systems and their applications

Type of delivery system	Active ingredient	Formulation	Applications	Reference
Liposome	CoQ10, Avocado, Rosehip, Carrot Oils and with Vitamins A, B, C and E, <i>Aloe barbadensis</i>	Anti-Wrinkle Cream	Assist in Skin	[22]
Liposome	(Organic Aloe) Juice, <i>Cocos nucifera</i>	Deep moisturizing cream	Prevent premature	[23]
Liposome	Tyrocine, <i>Aloe vera</i> , α linoleic acid	Sunscreen cream	Sun-protection formulations with UV absorbers.	[24]
Liposome	Minoxidil sulphate, propylene glycol	Nanominox-MS, for hair loss treatment	Improve the flux of contents through the skin	[25]
Phytosome	<i>Ginkgo biloba</i> Dimeric Flavonoids	Beauty cream	Improves the absorption of the compounds exerting the biological activity, but also increases the duration of the activity	[26]
Nanosome (Nanosomin Serum)	Vitamins	anti-aging treatment serum	Enhanced performance designed to upgrade skin to a healthy and youthful looking state	[27]
Fullersomes	—	Skin cream	To refresh dark circles under the eyes	[8]
Ultrasome	coQ10	stopping wrinkles	To prevent the damage to collagen and elastin production enabling the skin to recover from past UV damage	[28]
Photosomes		Age Retaliator Serum A.M.		[29]
Photosome	DNA repair enzymes	Moisture SPF 15	Multi-purpose photoprotectant	[30]
Tranferosome	<i>Curcuma longa</i>	Anti-wrinkle cream	Anti-aging, anti-Wrinkle, anti-irritant, antimicrobial and anti-inflammatory activities	[31]

Marinosomes (Bordeaux, France) are liposomes based on a natural marine lipid extract containing high ratio of polyunsaturated fatty acids like, eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3). They are not present in normal skin epidermis. However, they are metabolized by skin epidermal enzymes into anti-inflammatory and anti-proliferative metabolites that are associated with a variety of benefits with respect to inflammatory skin disorders.^[16] In one study, Marinosomes were prepared and characterized in conditions that mimic

topical application in terms of pH and temperature. Further, preliminary freeze-fracture TEM observations concerning. The first toxicology file indicated a good skin and eye tolerance towards Marinosomes. All these results allowed considering Marinosomes as potential candidates for cosmeceutical in view of the prevention and treatment of skin diseases.^[17]

Ultrasomes are specialized liposomes encapsulating an endonuclease enzyme extracted from *Micrococcus luteus*. Endonuclease recognizes UV damage and is reported to accelerate its repair four-fold. Ultrasomes also protect the immune system by repairing UV-DNA damage and reducing the expression of TNF- α , IL-1, IL-6 and IL-8.^[18]

Photosomes

Photosomes are incorporated in sun-care product to protect the sun-exposed skin by releasing a photo-reactivating enzyme extracted from a marine plant, *Anacystinidulans*. Photosomes on light activation reverse the cell DNA damage, reducing immune suppression and cancer induction.^[19-20]

Ethosomes

Ethosomes are non invasive delivery carriers composed mainly of phospholipids, with 20-50% ethanol and water, which enable drugs to reach the deep skin layers.^[21] These are soft, malleable vesicles tailored for enhanced delivery of active agents.

AOCS liposome

Asymmetric oxygen carrier system (AOCS) liposomes are designed to carry oxygen into the skin. These vesicles are composed of perfluorocarbon core surrounded by a monolayer of phospholipids, followed by a bilayer system. Perfluorocarbons are excellent carriers of oxygen and so this system is used to transport molecular oxygen into the skin.^[19-20]

Yeast-based liposomes: Yeast cell derivatives repair, soothe and oxygenate the skin by the incorporation of vitamin-C into the cell.^[19] In its liposomal form, it stimulates dermal fibroblasts and provides a feeling of well-being.^[20]

Niosomes

Niosomes are non-ionic surfactant based vesicles that have a similar structure to that of phospholipid vesicles like liposomes. They can be used to encapsulate aqueous solutes and act as drug and cosmetic carriers. The hydrophobic parts are shielded from the aqueous solvent while the hydrophilic head groups are in contact with it. The advantages of using niosomes in cosmetic and skin care applications include their ability to increase the stability of entrapped drugs, improved bioavailability of poorly absorbed ingredients and enhanced skin penetration. However, niosomes do not contain GRAS components and are known to be more irritating than liposomes. Van Hal *et. al*^[32] reported that niosome encapsulated estradiol can be delivered through the stratum corneum, which is known to be a highly impermeable protective barrier. Niosomes made from a novel surfactant (Bola surfactant), have been found highly effective for percutaneous drug delivery applications.^[33]

The *in-vitro* release rate of azelaic acid was more rapid from ethosomal systems than from liposomal systems.

Niosomes have been used for the delivery of anti-inflammatory agents and anti-infective agents. They have also been used to enhance transdermal drug delivery. Niosomes were developed and patented by L'Oreal (www.loreal.com) in the 1970s and 80s.^[34-35] The first product 'Niosome' was introduced in 1987 by Lancome.^[36]

Proniosomes are non-ionic based surfactant vesicles, which may be hydrated immediately before use to yield aqueous noisome dispersions.^[37] Proniosomes are nowadays used to enhance drug delivery in addition to conventional niosomes. They are converted into niosomes respectively upon simple hydration or by the hydration of skin itself after application. Proniosomes exist in two forms, i.e. semisolid liquid crystal gel and dry granular powder, depending on their method of preparation. Out of these two forms, the proniosome gel is mainly used for topical/transdermal applications. Preparation of proniosome gel was adopted by the method given by Perrett S, *et al.* for pro liposome preparation which was then modified and used for preparation of proniosomal gel.^[38]

Silicone vesicles and matrices

Silicones in physical association with various active ingredients can function as delivery vesicles for the actives. Cross-linked silicones such as elastomers and adhesives are a relatively new class of cosmetic raw materials that have utility in delivery systems for active ingredients. Silicone elastomers and elastomer blends can be used to entrap a variety of actives. Various studies have been conducted to evaluate the ability of silicone-based technologies to meet these objectives, while providing a range of desirable features and benefits. A range of silicone polymers technologies were reported that can act as delivery vehicles for active ingredients for skin and hair.^[39] Physical associations of these polymers with active ingredients, improved conditioning, shine, manageability, reduced flyway and number of other benefits.^[39] Several silicone-based technologies illustrate the synergistic properties of silicones with a variety of personal care actives.^[5] These technologies offer a wide scope to bring about a range of innovative personal care applications.

Induction of silicone polyether into nanomicro- to submicron-sized vesicular structures provides excellent stability in aqueous medium.^[40-41] These are called 'assembly-required' vesicles. Actives that can be delivered by silicone-based vesicles are:

1. Conditioning agents such as vitamin A, vitamin E acetate and lanolin oil, humectants such as lanolin alcohol, cetearyl octanoate and sodium stearyl lactylate, colorants.
2. Emollients such as mineral oil, jojoba oil and polydimethylsiloxane.
3. Common silicone fluids such as dimethicone are well known to cosmetic formulators. The permeability of silicones makes them suitable for controlled release applications and for this reason they are used widely in transdermal delivery systems.

Most of the active ingredients that can be loaded into an elastomer matrix are listed below

Water Soluble actives

- Vitamins such as vitamin C and vitamin H (biotin)
- Conditioning agents such as gelatin and hydrolyzed collagen
- Deodorant actives such as triclosan
- Antiperspirant salts such as aluminium chlorohydrate and aluminium/zirconium tetrachlorohydrate glycine
- Preservatives such as salicylic acid, DMDM hydantoin and cetrimonium bromide
- Humectants such as glycerin, sorbitol and propylene glycol
- Enzymes such as papain, trypsin and chymotrypsin

- Drugs such as aspirin and nicotine
- Hydroxy carboxylic acids such as hydroxyacetic acid (glycolic acid)

Water-insoluble actives

- Vitamins such as vitamin A and vitamin E acetate
- Preservatives such as sodium pyrrithione
- Esters such as stearamide DIBA stearate and ethylene glycol monostearate
- Emollients such as mineral oil, jojoba oil, dimethicone, lanolin alcohol, cetearyl octanoate, and sodium stearyl lactylate

Multi-walled delivery systems

The multi-walled delivery system is based on a combination of structured vesicle-forming materials and high shear processing. It provides exceptional long-term stability to cosmetic skin treatment products. Multi-walled delivery system is analogous to the structure of membrane lipid found in the intracellular matrix and made up of non-phospholipid amphiphilic molecules (oleic acid, derivatives of polyglycerols, amino acid residues). Stability of these types is predicted by zero-order kinetics. When they are produced, Multi-walled delivery system vesicles form five to seven bilayer walls. Multi-walled delivery system gives stability to liposomes but by combining hydration and delivery, Multi-walled delivery system also nourishes and protects the skin, bringing the formulator closer to optimizing product performance.^[42]

Table 3: Formulations of vesicular delivery system and their application

Type of delivery system	Active ingredient	Formulation	Applications	Reference
Silica nanoshells	'UV Pearls TM	Sunscreen cream	Improved photostability and reduces the filter uptake by the skin.	[46]
Silicone vesicle	stearyl dimethicone	Sunscreen cream	Sun protecting factor (SPF)	[47]
Silicone elastomer	Cyclopentasiloxane	Skin Moisturizer	Improve compatibility with active ingredients Stimulates cell growth and	[47]
Silicone vesicles	Retinyl Palmitate	—	increases enzyme activity and normalized cell division	[47]
Niosomes	methotrexate	methotrexate gel	In the treatment of localized psoriasis NSAIDS, enhance the anti-inflammatory action	[48]
Proniosomal gel	Flurbiprofen	Gel	Enhance the skin permeation of female hormone estradiol across the skin	[49]
Proniosomal gel	Estradiol	Gel	Blend to modulate the release rate of fragrance has been reported	[50]
silicone elastomer	Fragrance	—		[51]

Multi-wall delivery systems have various applications in cosmeceuticals as listed below

- Derivatives of essential fatty acids (EFAs) and ceramides multi-walled delivery system^[43] form flexible membranes that smoothen stratum corneum

- Encapsulated peptide fraction showed no degradation over a period of 70 days and was also found to enhance the percutaneous absorption of peptide in human skin^[44]
- Multi-walled delivery system forms effective delivery of sunscreens
- Multi-walled delivery system is stable over a period of time and ready for incorporation into any desired number of formulations
- Small amino acid peptide chains have been encapsulated using multi-walled delivery system approach and formulated into a cream. Encapsulated peptide fraction showed no degradation over a period of 70 days and was also found to enhance the percutaneous absorption of peptide in human skin^[45]

Cosmetic formulations with vascular delivery systems along with their applications are listed in Table 3.

PARTICULATE SYSTEMS

Microparticulate systems

Microparticles are solid polymeric particles falling in the range of 0.1–1000µm and include microcapsules and microspheres. Microcapsule is defined as a spherical particle with the size varying in between 50nm to 2 mm containing a core substance. Microspheres are in strict sense, spherically empty particles.^[52] In general, microparticles are used in cosmetics to avoid incompatibility of substance, reduce odour of actives and for protection of substances prone to oxidation or action by atmospheric moisture.

Listed below are some of the applications of microcapsules in controlled delivery

1. Microcapsules containing sun filters such as octylmethoxycinnamate, octyl salicylate.
2. Depilatory pastes containing microencapsulated enzyme for protection against surface active agents. E.g. Sodium Lauryl Sulphate (SLS), Skin tanning agent containing Dihydroxyacetone (DHA) and glycerine in separate compartments within a microcapsule.
3. Microcapsule with encapsulated oils like, mineral oil, vegetable oil, isopropyl myristate and isopropyl palmitate contained in cleansing creams.
4. Skin depigmentation products containing microencapsulated anti-oxidants such as tocopherols, which will prevent lipid peroxidation in the skin.
5. Nylon microspheres are being used in cosmetic make-up and skin care products because of the feel and skin adhesion they impart, because of their particle size and narrow particle size distribution.^[53] Chemical inertia of nylon microspheres allows them to hold hydrophilic and lipophilic ingredients including vitamins, sun filters, moisturizers, fragrances and many other actives such as retinylpalmitate, d-panthenol, ascorbic acid, tocopheryl acetate and dimethicone. Nylon microspheres containing 40–50% water can function as a delivery system when incorporated in a moisturizing lipstick. It can also avoid exudation observed in lipsticks. Microspheres loaded with vitamin E showed enhanced concentration of vitamin E in the epidermis because of continued contact with skin and microspheres, slow release of vitamin from the particles and protection of

vitamin E from chemical interactions before absorption.

6. Egg albumin microspheres of size 222µm, containing vitamin A ($15.7 \pm 0.8\%$) were used to prepare O/W creams. The *in-vitro* and *in-vivo* drug release of a microencapsulated vitamin A cream was studied and compared with a non-microencapsulated vitamin A cream.^[54]
7. Botanical microspheres such as 'Elespher' of natural origin are composed of algae extract, which forms spheres containing a system of internal canals. Release of actives occurs by diffusion from sphere or by breaking when applied to the skin. They can be even coloured to achieve a pleasing visual effect.^[55]
8. Unispheres are an alternative to liposomes in preparations like shampoos containing high concentration of surfactants. These are small, coloured cellulose beads that hydrate and swell in aqueous media and disappear when rubbed into the skin leaving behind no shell.

Porous polymeric systems

In the last fifteen years, new polymeric systems have been developed to provide predictable rates of skin absorption for topical active agents. Such systems have been employed for both pharmaceutical and cosmetic products. These products are typically presented to the consumer in conventional forms, like creams, gels, or lotions.^[56] Porous polymeric systems utilize microentrapment technology wherein the particles have an open, porous structure compared with the continuous shell structure associated with microencapsulation, which results in sustaining the activity of the active ingredients over longer periods of time. They contain relatively high concentration of active ingredient and release the entrapped active ingredient in a controlled time release pattern or a pre-programmed manner over through the use of several different triggers such as rubbing or pressing the system after it has been applied to the skin, elevating the skin surface temperature, introducing solvents such as water, alcohol, perspiration for the entrapped material.

Sorption-based polymer systems provide optimal medication over a moderate period of time and hence overcome the problems like rashes or other energetic responses, prevent irritation. Significant reduction in undesirable properties such as, oiliness, greasiness, tackiness, stickiness or undesirable odour and feel of ingredients was also seen.

Microsponges

A Microsponge Delivery System (MDS) is "Patented, highly cross-linked, porous, polymeric microspheres polymeric systems consisting of porous microspheres that can entrap wide range of actives and then release them onto the skin over a time and in response to trigger".^[57] Each microsphere consisting of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface. The porous sphere polymers vary in diameter from 5 to 300µm. A 25µm sphere can have up to 3000 mm of pore length providing a total pore volume of about 1 ml/g. When applied to the skin, the MDS releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc). Depending upon their particle size, these porous systems can be divided into microporousmicrobeads (particle below 50µm) and microporous-macrobeads (particle range of 100-200µm). Microsponge particles are made by free radical

suspension polymerization technique. This approach involves the synthesis of a dispersed phase made up of a monomer, cross-linkers, an initiator, water immiscible active ingredient/s and surfactants to promote suspension. These systems have a myriad of applications. Microsponge Delivery System Technology is being used currently in cosmetics, over the counter (OTC) skin care, sunscreens and prescription products. By delivering the active ingredient gradually to the skin, MDS-benzoyl peroxide formulations, for example, have excellent efficacy with minimal irritation. Anti-inflammatory activity of hydrocortisone could be sustained with reduction in skin allergy responses and dermatoses.

In anti-dandruff products, the unpleasant odour of zinc pyrithione and selenium sulphide was reduced. Irritation was lowered, whereas safety and efficacy were found to be extended. All day treatment and symptomatic relief of fungal problem have been achieved through such systems. Reduced allergenicity was observed when insensitizing ingredients are entrapped in microsponge systems, as in the case of cinnamic aldehyde.^[58]

Another polymeric sorption system prominent in cosmetic delivery is 'Polytrap'. These are highly cross-linked methacrylate copolymer powders, which are capable of sorbing up to four times their weight of lipophilic and hydrophilic liquids while maintaining flowable powder form. The systems can sorb liquid dispersions, emulsions and solids that can stay long enough to be sorbed by and in the form of polymer aggregate.^[9]

Table 4: Shown below consist of formulations comes under Microsponge delivery system along with their Applications:

Formulation type	Active agents	Applications	References
Microsponge	Sunscreens	Improved protection against sunburns and sun related injuries, reduced irritancy and sensitization.	[59]
Microsponge	Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.	[59]
Microsponge	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.	[59]
Microsponge	Anti-fungals	Sustained release of actives.	[59]
Microsponge	Anti-dandruffs e.g. zinc pyrithione, selenium sulphide	Reduced unpleasant odour with lowered irritation with extended safety and efficacy.	[59]
Microsponge	Antipruritics	Extended and improved activity.	[59]
Microsponge	Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.	[59]
Microsponge	Hydroquinone and retinol. EpiQuin Micro	Minimize skin irritation.	[60]
Microsponge	Sportscream RS and XS	Topical analgesic-anti-inflammatory and counterirritant activity prevent changes in colour and odour in the final products	[61]
Microcapsules	Retinol Anti-wrinkle		[62]

Some other examples Microsponge Delivery Systems along with name of Manufactures are listed below:

Table 5: Microsponge Delivery Systems along with name of Manufactures

Product name	Advantages	Manufacturer
Retin-A-Micro	0.1% and 0.04% tretinoin for topical treatment of acne vulgaris.	Ortho-McNeil Pharmaceutical, Inc.
Carac Cream, 0.5%	Carac Cream contains 0.5% fluorouracil, for the treatment of actinic keratoses (AK), reduced dosage frequency.	Dermik Laboratories, Inc. Berwyn, PA 19312 USA
Line Eliminator Dual Retinol Facial Treatment	Lightweight cream with a retinol (pure Vitamin A) in MDS, delivers both immediate and time released wrinkle-fighting action.	Avon
Retinol cream	Retinol, to protect the potency of the vitamin A, reducing the possibility of irritation. Helps maintain healthy skin, hair and mucous membranes.	Biomedic
Retinol 15Nightcream	Pure retinol, Vitamin A, cause diminishment of fine lines and wrinkles, a noticeable improvement in the skin discolorations due to aging, and enhanced skin smoothness.	Sothys

Chronospheres: Chronospheres are polyurethane/acrylate polymer (PAP)-based powders. PAP powders with pre-loaded actives represent a finished topical product with controlled/sustained release capabilities.

Nanoparticulate Systems

Nanoparticulate systems include nanospheres and nanocapsules and can be defined as submicron colloidal systems having a mean particle diameter of 0.003-1µm. Such nanosized particles which have a shell and an interior space that can be used to load drugs are called nanocapsules.^[63] Nanocapsules differ from nanospheres in that the former is a reservoir type of system, whereas the latter is a matrix system. The active ingredient in nanocapsules and nanospheres can be incorporated in different patterns; dissolved in the nanosphere matrix, adsorbed at the nanosphere surface, dissolved in the liquid-phase nanocapsules, adsorbed at the nanocapsules surface. Different types of nanocapsules are required depending on the nature of the material (hydrophobic or hydrophilic) to be incorporated. These polymer capsules could be incorporated into perfumes to release the contents on exposure to sunlight or hot weather. They are stable in aqueous solution, non-toxic and biodegradable.

As of 2010, cosmetics companies are increasing their use of nanospheres in skin care products, especially those designed to address the visible signs of aging. Nanosphere technology poses both promise and potential dangers in the field of cosmetics and skin care.^[64] Cosmetics companies that market skin care products containing nanospheres claim that their products are more effective because they penetrate the outer layer of skin to deliver their beneficial effects to affected skin areas more efficiently and precisely than products that do not contain nanospheres, according to the Beauty Brains website. Nanospheres could provide more effective delivery of salicylic acid and benzoyl peroxide, both common ingredients in acne treatments, Gupta claims, and 2012.

Solid lipid nanoparticles

Another important system is solid lipid nanoparticles (SLNs). SLN is typically spherical shown in Fig. 2, with an average diameter between 10 to 1000 nanometers. SLN has many cosmetic and dermatological features, such as enhanced skin

hydration, protection against degradation, active penetration enhancement, and controlled-release properties.^[65] These represent a particulate dispersion of solid spherical particles consisting of hydrophobic core of triglycerides or fatty acid derivatives surrounded by a layer of phospholipids. Nanostructured lipid carriers (NLC) are mixtures of solid and fluid lipids, in which the fluid lipid phase is embedded into the solid lipid matrix.^[65] The advantage of SLNs over polymeric Nanoparticulate systems is the absence of harmful additives required for polymerization and biodegradability of physiological lipids. When compared with liposomes, they have better stability against coalescence because of the solid nature and reduced mobility of incorporated active molecules, preventing the active leakage from the carrier.

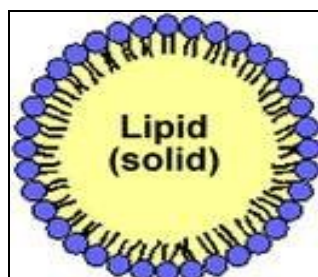


Fig. 2: Structure of Solid Lipid nanoparticles (SLN)

SLNs possess some features, which make them promising carriers for cosmetic applications:

1. The protection of labile compounds against chemical degradation (e.g. for retinol and tocopherols).
2. Depending on the produced SLNs type, controlled release of the active ingredients is possible. SLNs with a drug-enriched shell show burst release characteristics whereas SLNs with a drug-enriched core lead to sustained release.
3. SLNs act as occlusive, they can be used to increase the water content of the skin.
4. SLNs show a UV-blocking potential. They act as physical sunscreens on their own and can be combined with molecular sunscreens to achieve improved photo-protection.

Nanostructured Lipid Carriers

In order to overcome issues associated with SLNs, a second generation of lipid particles have been developed by mixing solid lipids with liquid lipids. These are known as nanostructured lipid carriers (NLCs). Compared to SLNs, NLCs have a distorted structure which makes the matrix structure imperfect and creates spaces to accommodate active compounds as shown in Fig. 3.

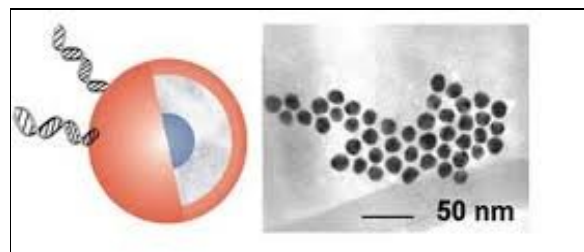


Fig. 3: Nanostructure Lipid Carrier (NLC)

The high loading capacity and long term stability offered by the NLCs make them superior to SLNs in many cosmetic

applications. However, Müller *et al.*^[66] suggest that SLNs are better for applications such as UV protection where a high level of crystallinity is required for the carrier. Similar to SLNs, NLCs are also capable of preventing the active compounds from chemical degradation. They also possess a high occlusion factor and high level of skin adherence properties. When the particles adhere to the skin a thin film layer is created which prevents dehydration, as the size of the particles decreases the occlusion factor increases.^[67] Due to this, NLCs offer the possibility of controlling occlusion without altering the properties e.g. increasing the occlusion of day creams without the glossiness of night creams. It has also been found that the release profile of the active compounds can be manipulated by changing the matrix structure of nanoparticle. Lipid nanoparticles have been found to increase the penetration capabilities of active compounds compared to microparticles.^[68] The lubricating effect and mechanical barrier of lipid nanoparticles are also desired in skin care applications for reducing irritation and allergic reactions. Lipid nanoparticles can make products appear white, rather than yellowish, which is more desirable for consumers.^[69]

Table 6: Various e.g. Particulate delivery system along with their applications

Type of delivery system	Properties	Applications	Reference
Nanocapsule	polyvinyl alcohol (PVA) with fatty acids (FAs) have been used to create polymeric nanoparticles, cause the absorption of benzophenone-3 (BZP) The in vitro release of OMC-nanocapsules is governed by	a widely used UV filter	[70]
Nanocapsule	hydrophobicity and crystallinity of the polymer and by the high lipophilicity of the drug	octylmethoxycinnamate (OMC)-nanocapsules provided partial protection against UV-induced erythema	[71]
Nanospheres containing β -carotene	functional ingredient is retained in a solid structure, presence of charges and moieties on the nanospheres surfaces nature of the UV-B screening agent	to promote adhesion Density improves the deposition onto the target site and prevents them from being washed off during the rinse process.	[72]
SLN	The amount of molecular sunscreen could be decreased by 50% while maintaining the protection level comparable with a conventional emulsion.	Increase in skin hydration by 31% after 4 weeks. Incorporation of molecular sunscreens in SLNs leads to synergistic UV-blocking effects	[72]
SLN	The MN-SLN dispersion which showed good stability for a period of 1 month was selected	Used for the treatment of fungal infection	[73]
Nanostructured lipid carriers	Excellent moisturizer for all types of skin		[74]
SLN	3, 4, 5-trimethoxybenzoylchitin	factor Enhanced UV blocking have anti-inflammatory, immunosuppressive, anti-fertility and anti-neoplastic activities	[75]
SLN	Contain tripolide, SLN dispersions could serve as efficient promoters for the TP penetrating into skin		[76]

The first products containing lipid nanoparticles appeared on the market in 2005 (Nanorepair cream and lotion, Dr. Rimpler GmbH, Germany), offering increased skin penetration. There are many other cosmetic products containing NLCs are currently available worldwide.

Various e.g. Particulate delivery systems along with their applications are shown in Table 6.

EMULSION DELIVERY SYSTEM

Microemulsions

Microemulsions are stable, liquid dispersions of water and oil that are made homogenous, transparent (or translucent), dispersions of oil and water stabilized by an interfacial film of surfactant molecules and having diameter of the droplets in the range of 100 – 1000 Å (10 – 100 nm) shown in Fig. 4. Microemulsion formation usually involves a combination of three to four components – water, oil, surfactant/s and co-surfactants. The surfactants chosen are generally those in the non-ionic group because of their good cutaneous tolerance and balanced lipophilic and hydrophilic property. The most important role of co-surfactant in the formation of microemulsions is to increase interfacial fluidity and to modify the Hydrophilic-Lipophilic Balance (HLB) of surfactant to optimal value. Thus, their combination is more effective than a single surfactant.

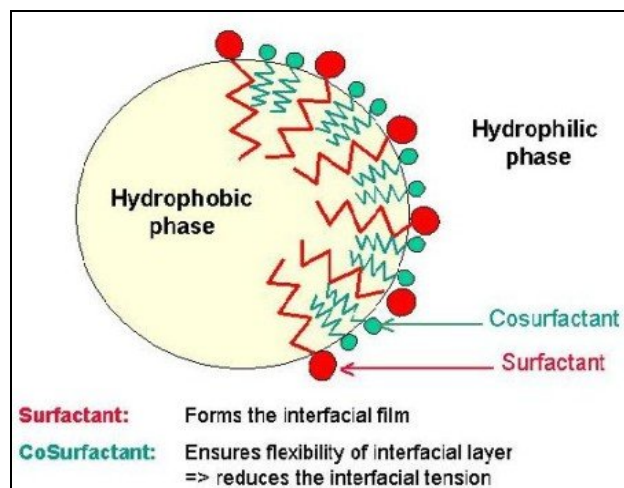


Fig. 4: Microemulsion delivery system

In microemulsions, the active is solubilized rather than suspended as in the vesicles and is available for immediate absorption, generally more rapidly and effectively. Their optical transparency and low viscosity ensure that they are of good appearance, easy to handle and pack. They act as supersolvents of drug. They can solubilize hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents. This is due to existence of micro-domains of different polarity within the same single-phase solution.

The dispersed phase, lipophilic or hydrophilic (oil-in-water, O/W, or water-in-oil, W/O microemulsions) can behave as a potential reservoir of lipophilic or hydrophilic drugs, respectively. The drug partitions between dispersed and continuous phase, and when the system comes into contact with a semi-permeable membrane, the drug can be transported through the barrier. Drug release with pseudo-zero-order kinetics can be obtained, depending on the volume of the dispersed phase, the partition of the drug and the

transport rate of the drug. The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects. [77]

Uses of Microemulsion in cosmetics

Microemulsions are preferred to be used in moisturizing formulation because they provide occlusivity and fulfill criteria for aesthetic appearance, ease of removal from container, ease of application and adherence to treated area without tackiness. Various drugs are to be incorporated in microemulsion are given below:

- Carotenoids formulated in a microemulsion are employed for treatment in skin cancers
- Cosmetic microemulsion containing di-decanoyl glycerol is used to increase melanin content of melanocytes thereby increasing pigmentation of skin
- Moisturizing effect and penetration of vitamin E is enhanced when employed in a microemulsion
- The efficiency of tri-decyl salicylic acid was increased when incorporated in microemulsion as an anti-ageing composition
- Benzotriazoles, bisoresocinyltriazine and S-triazine have been incorporated in microemulsion for photo-protective efficacy

Liquid crystals

Liquid crystals (LCs) are a state of matter that has properties between those of a conventional liquid and those of a solid crystal. [78] For instance, an LC may flow like a liquid, but its molecules may be oriented in a crystal-like way. Crystalline phase is thermodynamically stable and represents a state of incomplete melting. Liquid crystals are mainly of two classes-thermotropic liquid crystals (smectic and nematic type) and lyotropic liquid crystals. [79] Liquid crystals exhibit birefringence and dichroism and hence enhance the cosmetic appeal because of the coloured appearance of the preparations into which they are incorporated. Lipophilic materials such as vitamins, incorporated into liquid crystalline matrix, are protected from both thermal and photo-degradation. Emulsions containing liquid crystals have been observed to have a rate of active release much slower than those without this stabilizing component. This effect is because of multilayer structure of liquid crystalline material around droplet, which effectively reduces the interfacial transport of the dissolved actives from within the droplet.

Multiple emulsions

Multiple emulsions are emulsions in which globules of the dispersed phase encapsulate smaller droplets, which in most of the cases are identical with continuous phase. The two major types of multiple emulsions are W/O/W in which internal and external aqueous phases are separated by an oil layer and O/W/O in which water separates the two oil phases. In cosmetics, the most widely used type is W/O/W. Although multiple emulsions especially W/O/W systems have potential applications in controlled release systems for delivery of the active ingredient, their use has been limited by lack of stability. Primary emulsifiers are decaglyceroldecaoleate, mixed triglyceroltrioleate and sorbitantrioleate. Secondary emulsifiers include polysorbates and poloxamers for W/O/W emulsion. [80]

Stability of the multiple systems can be improved by forming a polymeric gel in either the internal or external aqueous phase. Two principle hypotheses were proposed for

the mechanism of transport of solute from multiple systems. In the first hypothesis, the active substance is released in the internal phase by virtue of the rupture of multiple oily globules. This rupture takes place either by shearing (induced by rubbing the preparation on the skin) or by swelling of internal phase. In the second hypothesis, the encapsulated active substance diffuses through the oily membrane. In cosmetics, multiple emulsions are useful when one wishes to prepare sustained release aerosol fragrances, prolonged skin moisturizers and protection of sensitive biologicals, personal care formulations for perfumes, skin lipids, vitamins and free radical scavengers.^[81-83]

Polyaphrons

Polyaphrons are oil-in-water or water-in-oil dispersions of colloidal dimensions that have foam like properties and related to, yet significantly different from conventional emulsions. Individual droplets in a Polyaphron Dispersion are called 'aphrons' the internal phase being stabilized by encapsulation in a thin aqueous soapy film. Polyaphrons exhibit foam-like character in which the oil-encapsulated cells aggregate to form stable polyhedral structures. The rheology of the continuous phase can be tailored by a variety of gelling agents to match the required characteristics of feel, drag and finish.^[84] In another example, a five-phase novel emulsion consists of water, perfluorinated oil and liquid crystal dispersed in a continuous silicone phase along with coarsely dispersed aqueous gel phase. Lipophilic actives can be incorporated into the liquid crystalline phase; hydrophilic actives can be dissolved in either of the two aqueous phases. Such systems can be used to incorporate two incompatible hydrophilic actives in different aqueous phases.

Topical applications may comprise the delivery of drugs, such as NSAIDs or anti-acne compositions, in a cream or gel preparation, or the delivery of drugs such as nicotine, estradiol, nitroglycerin, testosterone, scopolamine, etc., via transdermal drug delivery devices or in a cream or gel preparation.

Nanoemulsions

Nanoemulsions consist of very fine oil-in-water dispersions, having droplet diameter smaller than 100 nm. Compared with microemulsions, they are in a metastable state and are very fragile systems by nature. The nanoemulsions are easily valued in skin care because of their good sensorial properties (rapid penetration, merging textures) and their biophysical properties (especially, hydrating power). In general, the o/w nanoemulsified emulsion should be formulated with compatible vehicles and additives. The components of internal and external phases of nanosized emulsion should be chosen to confer enhanced solubility and stability to the incorporated lipophilic drug. They lead to a large variety of products from water-like fluids to ringed gels. Lotions, transparent milks, crystal-clear gels with different rheological behaviors, visual aspects, richness and skin feel are allowed with nanoemulsions. A significant improvement in dry hair aspect (after several shampoos) is obtained with a prolonged effect after a cationic nanoemulsion use. Hair becomes more fluid and shiny, less brittle and non-greasy.^[85]

Pickering emulsions

Pickering emulsions have been a laboratory curiosity since their discovery almost a century ago. Recent technological advances in this field have resulted in the introduction of amphipathic nanoparticles that enable the production of surfactant-free, particle-stabilized emulsion. It has been

revealed that 'the emulsifier-free' O/W Pickering emulsion shown in Fig. 5, can be formed in which the stabilizing particles are zinc oxide or titanium dioxide that have been coated with aluminium stearate or dimethicone and aluminium hydroxide or silicon dioxide.^[86]

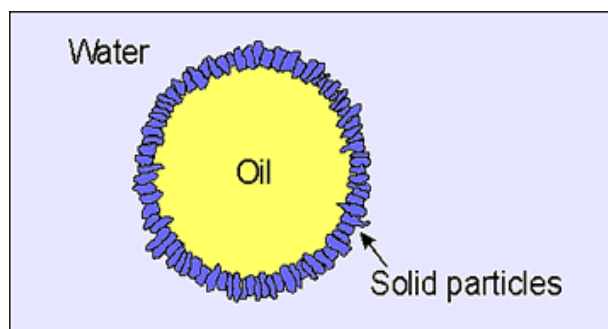


Fig. 5: Structure of Pickering emulsion

Table 7: Examples of some therapeutic and cosmetic agents used in Emulsion delivery Systems.

Formulation type	Active ingredient	Application	Reference
Liquid crystal	Pseudo-ceramide	Anti-wrinkle	[89]
Liquid crystal	Benzophenone-4 octylmethoxycinnamate	Sunscreen agent	[90]
Liquid crystal	Vitamin A	Antioxidant	[91]
Liquid crystal	Cosmetic composition	Skin cleansing agent	[92]
Microemulsion	Ascorbylpalmitate	prevents UV-A-induced lipid peroxidation	[93]
Microemulsion	silicone quaternary polymer	for hair conditioning as well as protection from heat, improved colour retention, nail lacquers reportedly adhere well to the nails, are characterized by good gloss, exhibit good water resistance	[94]
Nanoemulsion	oxyalkylene glycols and selected oils,		[95]
Nanoemulsion	protein-adherent polymers with hydroxyl-substituted aromatic groups	to increase the adhesiveness and durability of nail polish compositions	[96]
Nanoemulsion	Nitrocellulose	Nail enamel, kept the nails in good condition.	[86]
Pickering emulsion	Retinol	high storage of retinol inside the stratum corneum was favoured, Anti-ageing cream, increased the moisture of the skin, improves the synthesis of collagens resulting in the increase in suppleness of the skin	[97]
Multiple emulsion	Vitamin C, Wheat proteins		[98]
Polyaphrons	Caffeine	anti-cellulite creams	[99]
Proniosome gel	Flurbiprofen	NSAID, enhance penetration	[100]

The ultra-fine amphiphilic particles are defined as having particle sizes <200 nm. The specifications of the patents disclosed that these formulated emulsions are characterized by excellent skin tolerability and exhibit higher effectiveness in sunscreen formulations. The inventors also reveal that these particle-stabilized emulsions are remarkably stable in the presence of electrolytes and this makes it possible to design systems containing both astringents and antimicrobial. These stable compositions can also contain non-

amphiphilic pigments such as hydrophobically modified titanium dioxide.^[87] Polymeric moisturizers can also be included.^[88]

OTHER DELIVERY SYSTEMS

Cyclodextrin complexes

Cyclodextrins (CDs) shown in Fig. 6, are cyclic oligosaccharides containing a minimum of six d-(+)-glucopyranose units attached by α (1 $\rightarrow$ 4) glucosidic bonds. The three natural CDs are α , β and γ which differ in their ring size and solubility. Most of the molecules fit into the internal CD cavity forming a complex and the resulting structure is called CD clathrates or inclusion complexes. α -CD typically forms inclusion complexes with both aliphatic hydrocarbons and gases. β -CD forms complexes with small aromatic molecules.^[101] γ -CD can accept more bulky compounds like vitamin D.

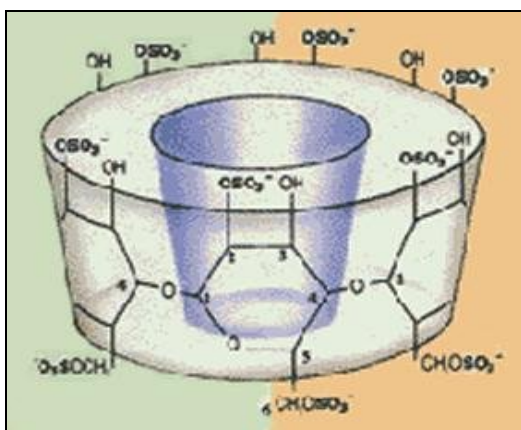


Fig. 6: Cyclodextrin Complexes

Complexation with CDs can bring about stabilization of the active ingredient against oxidative, photolytic and thermal degradation. It can keep the molecules in a more rigid form, inhibit occurrences of reactive confirmation (e.g. vitamin E and vitamin C phosphate included in hydroxylated cyclodextrin showed improved light stability compared with un-complexed form of the compound), isolates the molecules from environment and diminishes the incompatibilities (decreasing skin penetration of guest molecules by CD encapsulation thereby reducing undesirable side effects). Drawback of particle containing emulsion is dull or dry impression on the skin, which can be overcome by the addition of cyclodextrin preferably β - and α -cyclodextrin.^[102-103]

Cubosomes

Cubosomes are discrete, sub-micron, nanostructured particles of bi-continuous cubic liquid crystalline phase. Bicontinuous cubic liquid crystalline phase is an optically clear, very viscous material that has a unique structure at the nanometer scale.^[104] It is formed by the self-assembly of liquid crystalline particles of certain surfactants when mixed with water and a microstructure at a certain ratio. They have high heat stability and are capable of carrying hydrophilic and hydrophobic molecules.^[105] Combined with the low cost of the raw materials and the potential for controlled release through functionalization, they are an attractive choice for cosmetic applications as well as for drug delivery. However, at present they have also been modified using proteins.^[106] A number of companies including L'Oreal, Nivia^[107-108] and

Procter and Gamble are investigating cubosomes for cosmetic applications. The methods of formation must be efficient and cost-effective for scale up before this type of technology can be applied. The presence of large amounts of water during cubosome formation makes it difficult to load water soluble actives.

Dendrimers and hyperbranched polymers

Dendrimers and hyperbranched polymers have also been considered for use in the cosmetic industry. Dendrimers are unimolecular, monodisperse, micellar nanostructures, around 20 nm in size, with a well-defined, regularly branched symmetrical structure and a high density of functional end groups at their periphery. Hyperbranched polymers are effectively disorganised, unsymmetrical dendrimers that are prepared in a single synthetic polymerisation step, making them much more cost-effective than dendrimers. A recent review on this topic concluded that it will only ever be possible to designate a dendrimers as "safe" when related to a specific application. The so far limited clinical experience with dendrimers makes it impossible to designate any particular chemistry intrinsically "safe" or "toxic".

Large numbers of external groups are suitable for multi-functionalisation, which is a requirement for its use as a cosmetic agent carrier. L'Oreal has a patent for a formulation containing hyperbranched polymers or dendrimers which form a thin film when deposited on a substrate.^[109] This formulation could be used for a wide variety of cosmetics e.g. mascara or nail polish. A problem of current polymers is that films are formed too soon after deposition. The new formulations will form highly adherent, water washable films only upon oxidation, usually by exposure to air. It is also possible to incorporate cosmetic agents into the medium to help form films for different applications. They have also developed a formulation comprising of a tanning agent and dendrimers for artificial skin tanning.^[110] Unilever have a patent for hydroxyl-functionalised dendrimers from polyester units to create formulations for use in sprays, gels or lotions.^[111] Several patents have been filed for the application of dendrimers in hair care, skin care and nail care products.^[112]

Nanocrystals

Nanocrystals have been used in the pharmaceutical industry for the delivery of poorly soluble actives (Elan; see Therapeutics subsector report). They are aggregates comprising several hundred to tens of thousands of atoms that combine into a "cluster". Typical sizes of these aggregates are between 10-400nm. The crystals must be stabilised to prevent larger aggregates from forming.

A further characteristic is that drug nanocrystals are composed of 100% drug; there is no carrier material as in polymeric nanoparticles. Dispersion of drug nanocrystals in liquid media leads to so called "nanosuspensions" (in contrast to "microsuspensions" or "macrosuspensions"). In general the dispersed particles need to be stabilized, such as by surfactants or polymeric stabilizers. Dispersion media can be water, aqueous solutions or non-aqueous media (eg, liquid polyethylene glycol [PEG], oils).

Fullerenes

Fullerenes are molecules composed entirely of carbon that resemble a hollow sphere. Rouse, *et al.*, showed that once fullerenes come into contact with the skin, they migrate through the skin intercellularly, as opposed to moving through cells. Therefore, a fullerene could be used to "trap" active compounds and then release them into the epidermis