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Review Article

Biodegradable polymers as encapsulation materials for cosmetics and personal care markets

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Synopsis

The topical and transdermal delivery of active cosmetic ingredients requires safe and non-toxic means of reaching the target sites without causing any irritation. Preservation of the active ingredients is also essential during formulation, storage and application of the final product. As many biologically active substances are not stable and sensitive to temperature, pH, light and oxidation, they require encapsulation to protect against unwanted degradation and also to target specific and controlled release of the active substance. The use of biodegradable polymers as encapsulation materials offers several advantages over other carrier materials. Encapsulation of active ingredients using biodegradable polymeric carriers can facilitate increased efficacy and bioavailability and they are also removed from the body via normal metabolic pathways. This article reviews current research on biodegradable polymers as carrier or encapsulation materials for cosmetic and personal care applications. Some of the challenges and limitations are also discussed. Examples of biodegradable polymers reviewed include polysaccharides, poly α-esters, polyalkylcyanoacrylates and polyamidoamine dendrimers.

Résumé

L'administration topique et transdermique de principes actifs cosmétiques exige des moyens sûrs et non toxiques pour atteindre les sites cibles sans causer d' irritation. La préservation des ingrédients actifs est également essentielle au cours de la formulation, du stockage et de l'application du produit final. Étant donné que beaucoup de substances biologiquement actives ne sont pas stables et sensibles à la température, le pH, la lumière et l'oxydation, elles ont besoin d'encapsulation pour les protéger contre la dégradation indésirable et également de cibler la libération spécifique et contrôlée de la substance active. L'utilisation de polymères biodégradables comme matériaux d'encapsulationoffre plusieurs avantages par rapport aux autres matériaux porteurs. L'encapsulation des ingrédients actifs à l'aide des supports polymères biodégradables peut faciliter l'augmentation de l'efficacité et de la biodisponibilité; ceux-cisont également éliminés de l'organisme par l'intermédiaire des voies métaboliques normales. Cet article passe en revue les recherches actuelles sur les polymères biodégradables comme matériaux de support ou d'encapsulation pour les cosmétiques et les applications de soins personnels. Les défis et les limites sont également discutés. Des exemples de polymères biodégradables passés en revue comprennent des polysaccharides, des poly-α-esters, des polyalkylcyanoacrylates et les polyamidoaminedendrimères.

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Introduction

A variety of synthetic and natural biodegradable polymers are finding increasing applications in cosmetics and personal care markets as well as pharmaceutical and biomedical fields. Polymeric carriers have been employed for a wide variety of therapeutic substances including active pharmaceutical ingredients [1]. Encapsulation of active ingredients using biodegradable polymeric carriers can facilitate increased drug efficacy and bioavailability. They can also be chemically functionalized to give enhanced properties over conventional carrier materials.

The main advantages of using biodegradable polymers in cosmetics applications over non-biodegradable polymers is that they are generally non-reactive when in contact with the human body and can be broken down or metabolized and removed from the body via normal metabolic pathways. In contrast, non-biodegradable polymers could potentially accumulate in various body tissues and cause irritation. The usual mechanism for degradation of biodegradable polymers is by hydrolysis or enzymatic cleavage of labile heteroatom bonds, which results in scission of the polymer chains [2]. To be used in biomedical applications the biodegradable polymer must also be biocompatible. The chemical nature of the degradation products, rather than the product itself, is often what influences biocompatibility. For example, polyesters based on polylactide (PLA), polyglycolide (PGA) and their copolymers have been extensively employed as biomaterials with degradation yielding the corresponding hydroxyl acids that are safe for *in vivo* use. Biodegradable polymers derived from natural polymers, particularly, modified polysaccharides such as starch and chitosan are also widely used.

Many personal care products (for skin, hair or body care) contain biologically active substances such as vitamins and as such require encapsulation for increased stability of the active materials. As many biologically active substances are not stable and sensitive to temperature, pH, light and oxidation, they require encapsulation to protect against unwanted degradation and also to target specific release of

the active substance. This article aims to provide an overview of the use of biodegradable polymers as encapsulation materials for cosmetics and personal care applications. Recent developments in this field are addressed and some of the challenges are identified.

Topical and transdermal delivery

In general the topical application of cosmetic formulations requires the successful delivery of active ingredients through the skin's lipid barrier to reach the targeted lower layers. Transdermal drug delivery has been well documented with studies dating back to 1924 proposing that the main resistance to transdermal transport was in a layer of cells joining the stratum corneum to the epidermis [3]. In 1944, Winsor and Burch [4] found that skin could become freely permeable to water after the removal of the stratum corneum. Similarly in 1957, Monash [5] observed that high concentrations of topical anaesthetics did not provide any action on skin until the stratum corneum was stripped away with tape. In addition Malkinson in 1958 found that only 1–2% radiolabelled hydrocortisone permeated skin but when the skin was stripped with tape up to 90% was absorbed [6]. These studies demonstrated that the stratum corneum itself limited transport. In what is regarded as a landmark paper, Kligman in 1964 [7] outlined that the stratum corneum was not a dead, passive structure as was previously thought. Kligman described the structure of the stratum corneum as being made up of cellular structures that he termed 'corneocytes'. The work of Blank and Scheuplein [8, 9] later demonstrated the highly impermeable nature of the stratum corneum and the structure was likened to 'plastic wrap'. Permeability through this layer, in particular for hydrophilic molecules, has remained as one of the major challenges in effective transdermal delivery. Today, the stratum corneum is considered to be very much a 'living' tissue involved in a number of metabolic processes. Elias has given a good account of these in a recent publication [10]. The currently accepted structure of the skin is described in the following section.

Skin structure

Human skin is comprised of several distinct layers as represented in Fig. 1. The epidermis is the outermost layer and acts as a protective sheath against environmental influences. It consists of several layers starting with the stratum corneum to the basal cell layer and is continually being regenerated. The dermis lies beneath the epidermis and contains collagen and glycosaminoglycans. This layer is where collagen and elastin are synthesized and it contains the blood vessels, nerves, sweat glands, hair follicles and sebaceous glands. The hypodermis or sub-cutaneous layer contains the adipose tissue (subcutaneous fat) and provides a thermal barrier.

The stratum corneum is the upper 10–20-μm layer that is a lipid-rich matrix composed primarily of ceramides, cholesterol and fatty acids that are assembled into a multi-lamellar bilayer structure. Elias proposed a 'brick and mortar' model [12] which is often used to describe the structure of the stratum corneum where the 'bricks' represent the protein rich cells (corneocytes) embedded into the intercellular lipid domains or 'mortar' as shown in Fig. 2 [13]. Corneodesmosomes act to link neighbouring corneocytes together and provide structural integrity to the stratum corneum. It should also be noted that there are wide variations in permeability observed at different body sites (e.g. face vs. legs vs. palms) which together with factors such as age and external environment can all influence the skins barrier function [13].

The lipophilic stratum corneum contains around 13% water. In contrast, the viable epidermis becomes significantly more hydrophilic containing about 50% water. The water content in the dermis is even higher at 70% [14]. Highly lipophilic actives do not transfer well across the highly lipophilic stratum corneum into the more aqueous epidermis, and it is important to understand these properties to design carriers to achieve the desired delivery of cosmetic active substance.

Skin penetration pathways

A number of pathways are possible for the transportation of molecules through the skin. The intercellular route occurs at the interface between cells through the lipid bilayers following a tortuous permeation pathway. In contrast, transcellular pathways can occur directly through the cells. These pathways are depicted in Fig. 3 [15]. Transportation via the hair follicles or sweat ducts is also possible. Permeation enhancers can also alter the pathway. Some common enhancers are discussed in the next section.

It is generally reported that transport of molecules through the epidermis is restricted to molecules of low molecular mass (<500 Da) and moderate lipophilicity (partition coefficients, log $K_{o/w}$

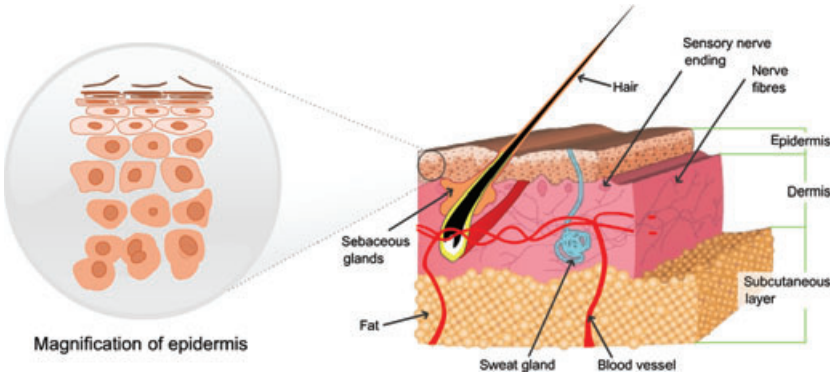

Figure 1 Schematic representation of a cross-section of human skin [11].

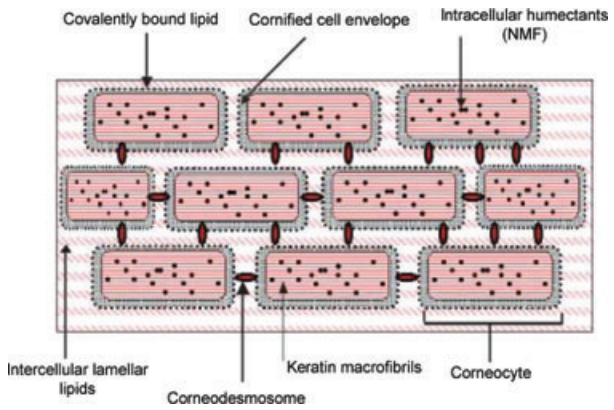

Figure 2 Schematic representation of the bricks and mortar model of the stratum corneum [13].

values between 1 and 3), having enough solubility in the lipid domain of the stratum corneum while still having sufficient hydrophilic nature to allow partitioning into the epidermis [14]. Some examples of drugs successfully administered via transdermal patches range in size from nicotine (162 Da) to oxybutinin (359 Da) [3].

There are also numerous articles describing the use of mathematical models to predict skin permeability [16–19]. Generally, these are based on quantitative structure-permeability relationships (QSPR), diffusion mechanisms or combinations of both.

Permeation enhancers

The disruption of the structural organization of the intercellular lipid domain of the stratum corneum can enhance skin permeation [14]. This may be achieved via chemical enhancers or physical techniques. In summary, the use of physical techniques includes *Iontophoresis* (the use of an electric current to enable penetration of charged species), *Electroporation* (application of a voltage pulse), *Sonophoresis* (the use of ultrasound energy) and *Microneedling* (needle arrays that pierce the upper epidermis). These techniques are outlined in more detail in a number of recent articles [3, 20, 21].

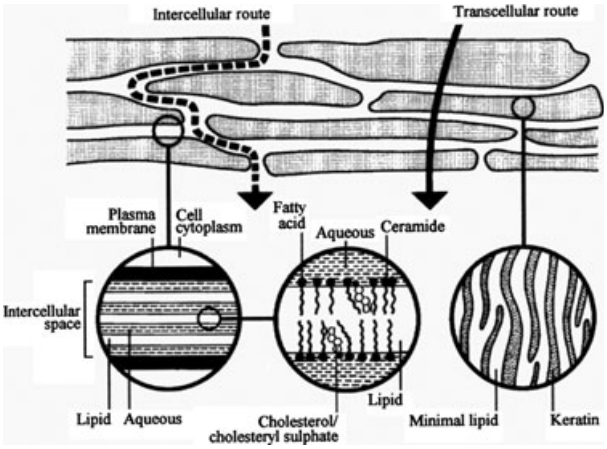

Figure 3 Schematic representation of intercellular and transcellular permeation pathways through the stratum corneum [15].

Generally, biodegradable polymers fall into the category of chemical permeation enhancers, however, they have also been reported as materials used in microneedle arrays [22]. Interestingly, the paper reports on the use of biodegradable microneedles made from poly-lactide-co-glycolide (PLGA) which are left on the skin and can release encapsulated drugs by slow release. The study also reported that the microneedles made from PLGA were of sufficient mechanical strength that they did not break when inserted into the skin.

Specific examples of the use of biodegradable polymers as encapsulation materials for the delivery and controlled release of cosmetic active ingredients are presented in the following sections.

Polysaccharides

Chitosan

Chitosan is a natural polymer that contains a high percentage of glucosamine within its structure as shown in Fig. 4. Chitosan is derived from chitin via a deacetylation reaction.

Chitosan has been widely reported for use in topical and transdermal delivery systems largely due to its non-toxicity and susceptibility to degradation. It has been reported that chitosan has the ability to enhance permeation across the skin by altering the structure of keratin. It also increases the water content of the stratum corneum and cell membrane fluidity. Further, due to its positive charge under slightly acidic conditions, it can depolarize the negatively charged cell membrane and in doing so, it decreases the membrane potential and drives the active component or drug through the skin [23].

The mechanism by which chitosan and its derivatives can be used as a transdermal permeation enhancer has been studied recently by He *et al.*[24]. The study involved infrared examination of the secondary structure changes of keratin in stratum corneum of mice as well as the examination of water content. HaCaT cells were employed as cell models. A shift of one of the amide absorption peaks to lower wavelength after treatment with chitosan indicated a change in keratin structure. Further peak deconvolution also indicated the β-turning structure of keratin was converted to β-sheeting and random coiling or α-helix. The authors suggest that these secondary structural changes to keratin lead to a more loose structure with greater degree of freedom for carbon movement that can lead to enhanced transdermal permeation of drugs.

In addition to the structural changes to keratin described previously, the use of chitosan and its derivatives has also been demonstrated to increase water content of the stratum corneum [24]. Once again, the use of infrared absorption gave information on water content by examination of the ratio of amide I (1700–1600 cm^{-1}) and amide II bands (1600–1500 cm^{-1}). Amide I shows the absorbance of water and proteins in skin, whereas amide II shows only protein absorbance. The derivative N-trimethyl chitosan had the greatest

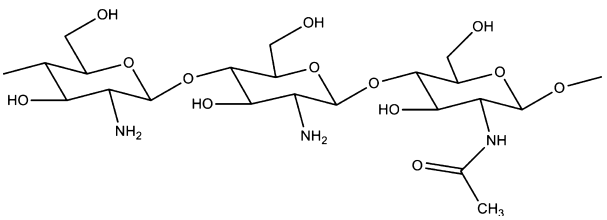

Figure 4 Structure of chitosan.

effect of increased water content. The study also demonstrated that the increased amount of water was able to be retained in the stratum corneum for significant lengths of time.

Encapsulation of active ingredients using chitosan is also possible. Controlled release has been demonstrated by increasing the viscosity of the polymer matrix [25]. A skin permeability study confirmed that encapsulation of retinoic acid with chitosan delivered the retinoic acid at much slower and controlled rates as compared to free retinoic acid (shown in Fig. 5) [25]. This ability to control delivery of retinoic acid is important in reducing skin irritation.

The same author has also reported on crosslinking and coacervation methods to trap actives within the chitosan matrix. This encapsulation technology under the tradename Chitosphere™ has been developed by Ivrea Laboratories, Inc. [26]. Water insoluble active ingredients like retinoic acid are able to be delivered topically in the form of encapsulated microparticles less than 100 μm in size. This is achieved by using the active agent, a high-viscosity chitosan biopolymer and a suitable dispersing agent (e.g. soybean oil) in the presence of anionic polymers (e.g. poly(acrylic acid)) at pH values greater than 6. A wide range of actives can be delivered using this technology without the use of surfactants or emulsifiers, making it particularly appealing for topical delivery systems.

In the field of gene therapy, chitosan has been reported to enhance drug delivery of nucleic acids such as DNA [23]. Recently, a topical cream for the treatment of asthma has been reported [27]. The research involved transdermal application of chitosan encapsulated siNRPA (a small interfering peptide receptor). Results showed successful delivery to the lungs upon topical application in mice with significantly decreased lung inflammation.

In addition to topical skin delivery, chitosan-based systems have also been reported in oral and transmucosal delivery applications [28–30]. Chitosan appears to boost immune responses by enhancing the uptake of antigen across nasal mucosa and as a result, it is a good candidate for effective mucosal vaccine delivery systems [28].

Hyaluronic acid

Hyaluronic acid is an anionic polysaccharide that consists of N-acetyl-glucosamine and glucuronic acid (Fig. 6). It is naturally found throughout the body in extracellular tissue, cartilage and synovial fluid.

Skin application of hyaluronic acid containing cosmetics has been reported to achieve antiwrinkle effects via its ability to effectively moisturize and enhance elasticity of the skin [31, 32]. Hyaluronic acid is a very effective topical humectant, attracting water from the air to plump the skin. It is also commonly used as an injectable dermal filler under the name Restylane®.

In addition to its moisturizing properties, the biodegradability of hyaluronic acid also makes it very attractive for wound healing applications [33–35]. Laserskin® (developed by Fidia Advanced Biopolymers, Italy) is a membrane made from benzyl esterified hyaluronic acid. It is used as a delivery system to transfer keratinocyte cells from tissue culture to skin wounds, in particular burns, with high rates of healing [33].

The stability of hyaluronic acid-based nanoemulsions as transdermal carriers was recently reported [36]. Electrostatic, steric and hydrophobic effects were found to play a key role in the stability of the emulsions. Encapsulation experiments with vitamin E also demonstrated that the emulsions were capable of successfully carrying lipophilic additives. In further studies the same group investigated skin penetration and carried out histological experiments using vitamin E-hyaluronic acid nanoemulsions [37]. It was reported that the formulation had desirable stratum corneum permeability, efficient partitioning capacity and was able to be diffused deeper into the dermis compared with the control group containing ethanol solution. The small size of the emulsion droplets (50–200 nm) was also noted as significant as this enabled greater surface-to-volume ratio which has greater contact points between the emulsion and the skin. In addition, the authors claim that the flexibility of the

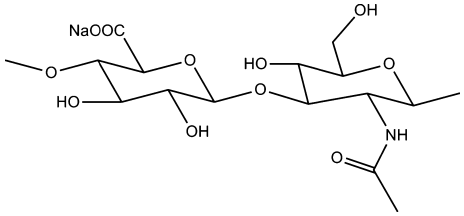

Figure 6 Structure of hyaluronic acid (sodium hyaluronate).

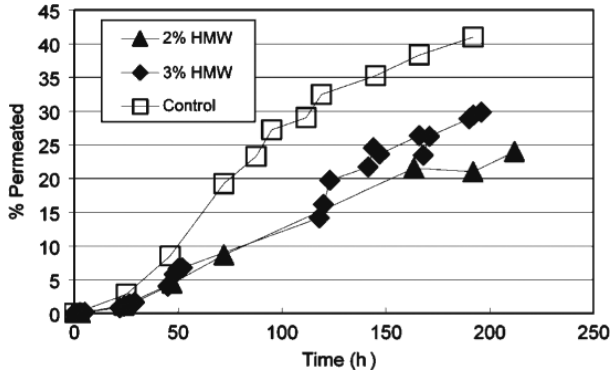

Figure 5 all-trans-retinoic acid (ATRA) permeation through a skin model using Franz diffusion cells for free retinoic acid (□) or a chitosan-entrapped retinoic acid (▲ and ◆) as a function of the concentration of high molecular weight chitosan (HMW) [25].

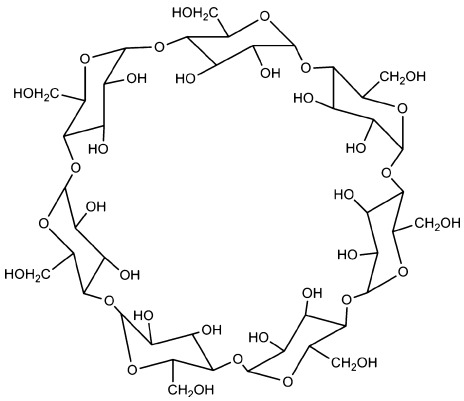

Figure 7 Typical structure of a cyclodextrin.

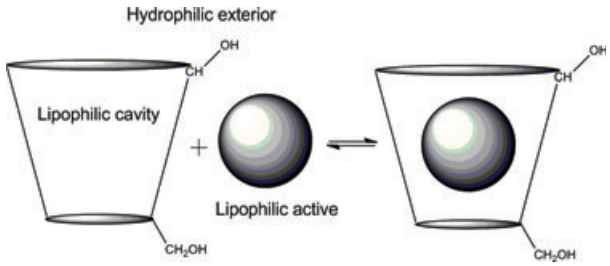

Figure 8 Schematic representation of a cyclodextrin inclusion complex.

droplets was important in the skin penetration as they were capable of adapting their shape when passing through the stratum corneum.

Although the exact mechanism of action of topically applied hyaluronic acid has not been fully explored, Brown *et al.* [38] have described some key factors in a recent review article. It is known that the degree of hydration of the stratum corneum influences skin permeability and with the excellent hydrating properties of hyaluronic acid, this can lead to enhanced topical delivery of actives across the skin. The authors suggest that this increased hydration of surface layers not only enhances drug absorption across the stratum corneum, but also facilitates the retention of the drug within the more hydrated epidermal layers (possibly by exposure of potential drug binding sites) which can decrease the drug diffusion into lower skin layers, limiting systemic absorption.

Table 1 Examples of marketed cosmetic cyclodextrin formulations. Adapted from [42]

Trade Name	Active substance	Application	Company
Lipo CD-SA	Salicylic acid	Delivery system for salicylic acid (keratolytic)	Lipo Chemicals, Inc. (US)
Lipo CD-E	Tocopherol	Antiageing	Lipo Chemicals, Inc. (US)
Lipo CD-OMC	Ethylhexyl methoxycinnamate	Sunscreen	Lipo Chemicals, Inc. (US)
Biolin Sebo Care Impure Skin Cream	–	Acne prone skin	Ganassini (Italy)
Cellutex	L-Carnitine	Anticellulite cream	Regina Neu Cosmetic (Germany)
Mirakelle	Vitamin A	Antiageing	Vor Laboratories, Inc (Sweden)
Novo Flex	Vitamins A and E	Antiageing	Revlon (South America)
Self-Action Super tan	Dihydroxyacetone	Self-tanning	Estèe Lauder (US)
Klorane Extra Gentle Dry Shampoo	–	Dry shampoo	Klorane, Pierre Fabre Dermo Cosmetique (France)

Cyclodextrins

Cyclodextrins are cyclic oligosaccharides consisting of glucopyranose units bound with 1, 4 bonds having hydrophobic inner cavities and hydrophilic outer surfaces (Fig. 7). An important characteristic of cyclodextrins is their ability to form inclusion complexes with hydrophobic (lipophilic) molecules bound within the inner cavity, making them ideal compounds for cosmetics delivery systems (Fig. 8).

Cyclodextrins and chemically modified cyclodextrins have been utilized for a wide range of applications in cosmetics and personal care markets including controlled release of fragrances, stabilization of drugs, encapsulation of vitamins, reduction of the dermal penetration of preservatives and masking of odours [39, 40].

Cyclodextrins have also been reported to enhance effectiveness of sunscreen formulations [41]. The study reported both an *in vitro* model, using ethanol-propylene glycol solution, as well as a more realistic model using an oil-in water emulsion. It was demonstrated that the photostability of sunscreen agents can be improved by encapsulation. Photodecomposition products were analysed by chromatography and mass spectrometry where it was revealed that the cyclodextrin inclusion complex decreased the degradation of UV absorber significantly. In addition it was suggested that any potential for skin irritation is also decreased by encapsulation.

Some examples of marketed cosmetic formulations using cyclodextrins are listed in Table 1 [42].

The mechanism by which cyclodextrins can influence transdermal drug delivery has been reported recently by Kear *et al.* [43]. The study looked at hydroxypropyl-β-cyclodextrin (HPCD). Because of its large molecular size it does not penetrate into the skin. The authors found that pre-treatment of skin with up to 20wt% HPCD did not alter transdermal flux and skin accumulation of the model corticosteroids which suggested the stratum corneum barrier properties remained intact. In addition, differential scanning calorimetry (DSC) examination showed that the lipid structure had no signs of lipid disorganization or altered fluidity. An increase in structural disorder of the epidermis has been correlated with a decrease in lipid melting temperature. The study did show a decrease in melt temperature did occur and this was attributed to disruption of the protein structure due to hydrogen bonding interactions between the hydroxyl groups of the cyclodextrin and hydrogen donating keratins in the stratum corneum. Overall the authors concluded that the penetration enhancement properties of cyclodextrins are most likely due to increased in aqueous solubility of the drugs and hence the thermodynamic driving force for permeation across the skin.

Alginates

Alginates are linear polysaccharides derived from brown algae that are comprised of varying proportions of 1,4-linked β-D-mannuronic acid (M) and α-L-glucuronic acid (G) as shown in Fig. 9. The composition can vary from homopolymeric blocks of consecutive G-blocks, consecutive M-blocks or alternating MG-blocks.

Widely used as thickening agents in cosmetic formulations, alginates are also reported for drug delivery applications as they can form gels with divalent metal ions such as calcium. The fact that relatively mild conditions can be used to incorporate drugs within alginates makes them excellent candidates for delivery of proteins that can minimize any denaturation [44].

A transdermal nicotine patch containing alginate has been reported where the release rate can be controlled by polymer concentration, drug concentration, membrane thickness and degree of cross-linking [45]. Similarly, the anti-inflammatory drug meloxi-

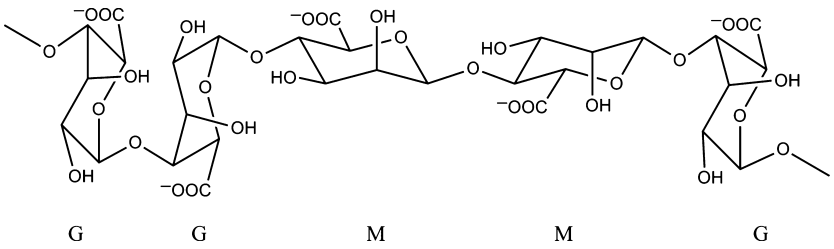

Figure 9 Structure of alginate.

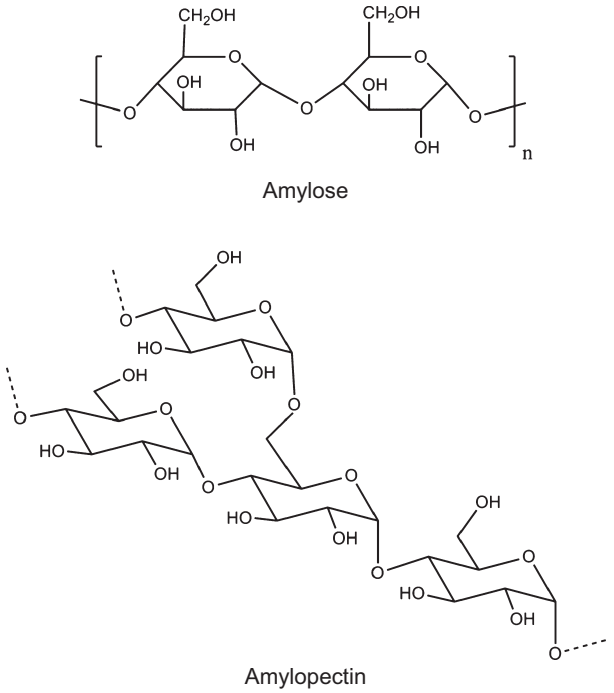

Figure 10 Structures of amylose and amylopectin.

cam has been encapsulated for controlled release through a chitosan-alginate transdermal film [46].

Alginates are also commonly reported for wound dressings where they can maintain a moist microenvironment and minimize bacteria at the wound site. Incorporation of silver or zinc can further enhance antimicrobial activity [44].

L'Oreal have described the production of spherical alginate capsules for cosmetics [47]. These capsules can contain water-soluble or dispersible active agents as well as liposoluble additives and can include biological compounds, coloured pigments, sunscreens and perfume.

Starch

Starch and modified starch have been used in cosmetics as absorbents, thickeners and film forming agents. Most starches consist of a mixture of two polysaccharide types: amylose and amylopectin (Fig. 10). The ratio of amylase to amylopectin varies depending on the type of starch. Film forming properties are dependent on this ratio with high amylose content (50–75%) having higher gelling tendencies and creating stronger films [48].

The Grain Processing Corporation (Iowa, US) markets a range of starch additives for use in a wide variety of personal care products [49]. One example is Zeina® B860 hydroxypropyl starch. The film forming properties of this starch allow for encapsulation of active ingredients in the form of oil droplets. A water-soluble protective film can be formed via spray drying methods.

Thixogel™ is a thixotropic oil-encapsulating emulsion system that comprises natural starches [50, 51]. The formulations form semi-solids upon standing but become pourable gels and lotions after moderate mechanical agitation. Thixogel emulsions are described as being particularly useful for delivery of hydrophobic botanical plant extracts and volatile compounds such as essential oils, flavours, perfumes as well as vitamins [50].

Encapsulation of the essential oil *Melissa Officinalis* (Lemon Balm) using modified starch has been reported recently [52]. The main active compounds contain phenolic acids that have antioxidant, antifungal and antiviral properties. To use the lemon balm extract as a nutraceutical, encapsulation is required to protect the phenolic acids against oxidation and evaporation. The study revealed that lemon balm could be effectively encapsulated in modified starch (as well as a cyclodextrin complex) using emulsification and spray drying techniques.

The film forming properties of starch-chitosan blends have been reported in the formation of a transdermal patch [48]. The patch has been used to deliver tamarind fruit extract for applications such as skin lightening. Various properties were assessed using a range of different starch types (corn, tapioca and potato). Films made using corn starch were found to give higher porosity.

Other reports of encapsulation using starch include the encapsulation of soy-based ferulic acid derivatives that have UV absorbing and antioxidant properties [53]. These are attractive as natural replacements for petroleum-based sunscreen active ingredients. Starch-encapsulation was even found to enhance the ultraviolet absorbance of the feruloylated lipids with encapsulated compounds only requiring half of the coverage to block the same amount or more UV radiation as the un-encapsulated additive.

Poly α-esters (PGA, PLA, PLGA, PCL)

This class of polymer includes polyglycolide (PGA), poly(L-lactide) (PLA), poly(lactide-co-glycolide) (PLGA) and poly(ε-caprolactone) (PCL) (structures shown in Fig. 11). These polymers are able to undergo degradation via hydrolytic cleavage of the ester linkages that make up the polymer backbone. For PGA, PLA and PLGA, the degradation by-products, lactic acid and glycolic acid, are water-

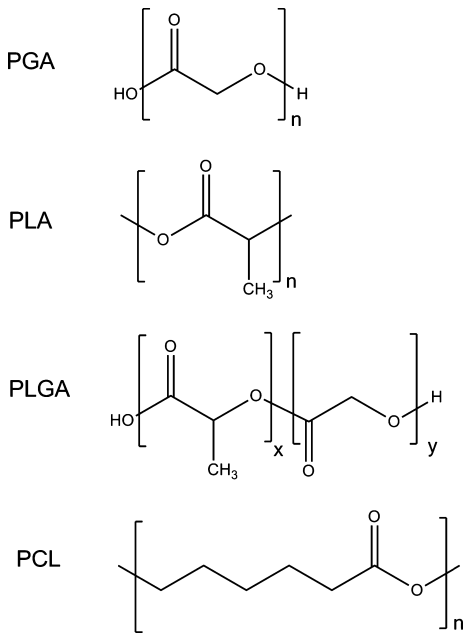

Figure 11 Structures of poly α-esters.

soluble and non-toxic products of normal metabolism [28] with the rate of degradation dependent on the chain length (molecular weight) and the lactide/glycolide ratio [31]. PCL has a much slower degradation rate and gives less acidic degradation products [54, 55]. The acid dissociation constants (pKa) of lactic acid (3.9) and glycolic acid (3.8) are lower than that for 6-hydroxy-caproic acid (4.8) (the product from hydrolysis of PCL) so the use of PCL may be advantageous if acidic environments could interfere with the encapsulated material during release. The slower degradation rate of PCL may also be tailored for a faster release through copolymerization or blending with other polymers [54–56].

In the area of drug delivery, the use of poly α-ester polymers to encapsulate proteins, vaccines and anticancer drugs have been widely reported [57], [1], [58]. The possibility of needle-free vaccines has also been discussed through the production of topically applied particles [59]. Similarly, oral delivery of hormones and insulin may be improved through encapsulation, offering advantages of decreased dosage frequency [1]. Various methods have been used to synthesize such materials including emulsification, solvent evaporation and interfacial deposition [1].

In cosmetic applications, the use of PLA has been recently reported to encapsulate retinyl retinoate as an anti-wrinkle treatment [60]. Skin penetration studies revealed the PLA retinyl retinoate microspheres (Fig. 12) were able to penetrate into deeper layers of skin (~eight-fold higher) compared with formulations without PLA. A faster rate of wrinkle improvement was also reported with no adverse effects.

PLGA encapsulated urea has been described for use in topical delivery creams [61]. Urea is used as a moisturizing agent and a common problem for urea containing cosmetics is its lack of stability in water containing products. PLGA microcapsules of 1–5 μm were used to stabilize the urea and provide an effective means of controlled release.

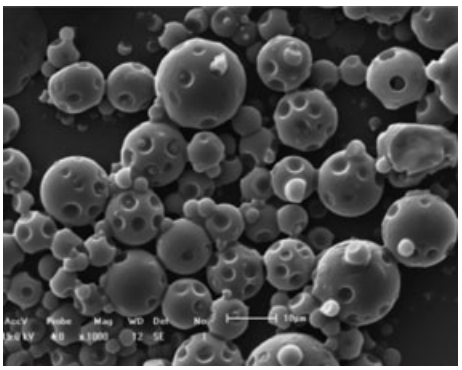

Figure 12 Scanning electron microscope (SEM) image of PLA retinyl retinoate microspheres, mean diameter 12.87μm [60].

The encapsulation of ascorbic acid using PLGA and the subsequent degradation behaviour over 8 weeks has been described in a recent study [62]. Ascorbic acid is a water-soluble vitamin with a variety of biological and dermatological functions and it is very unstable to air, light, heat and moisture. The study involved the synthesis of a range of encapsulated nanospheres where the particle size varied with different PLGA/ascorbic acid ratios. As the amount of ascorbic acid was increased from 15% up to 50% the particles went from small spherical shape to larger, more irregular shapes. This is important as the authors report that the size and shape of the encapsulated particles plays a key role in the adhesion and interaction with the body's cells. Degradation was studied in a physiological solution and assessed by a number of techniques including scanning electron microscopy (SEM) as shown in Fig. 13. Here it can be seen that the particles agglomerate and then create a porous film before complete degradation. It was also noted that for all samples less than 10% of ascorbic acid was released within the first 24 days, allowing for a successful and controlled rate of release.

The encapsulation of the highly lipophilic sunscreen, octyl methoxycinnamate (OMC), using PCL carrier systems has been recently reported [63]. The study used tape stripping experiments and imaging with the lipophilic dye Nile red to investigate the enhanced topical delivery of the encapsulated sunscreen. Results showed that encapsulation using PCL gave a 3.4-fold increase in the level of OMC in the stratum corneum and after some time the dye was detected at greater depths (up to 60 μm) within the skin.

Polyalkylcyanoacrylates (PACA)

Polyalkylcyanoacrylates (Fig. 14) are another class of biodegradable polymer that are reported mainly for use as surgical glues and skin adhesives [23]. One example is the product Dermabond™, 2-octylcyanoacrylate, used as a topical skin adhesive to close wounds [64]. Shorter chain alkyl derivatives are described as being tissue toxic and causing inflammatory reactions and as such they are limited to non-medicinal uses.

Cyanoacrylate, when placed in contact with body moisture, polymerizes in an exothermic reaction. A strong, flexible and waterproof bond forms that can stay in place for 7–14 days, eventually sloughing off with the epidermis [64].

For more general cosmetics applications, L'Oreal have described the use of polyalkylcyanoacrylates in encapsulating oils for treat-

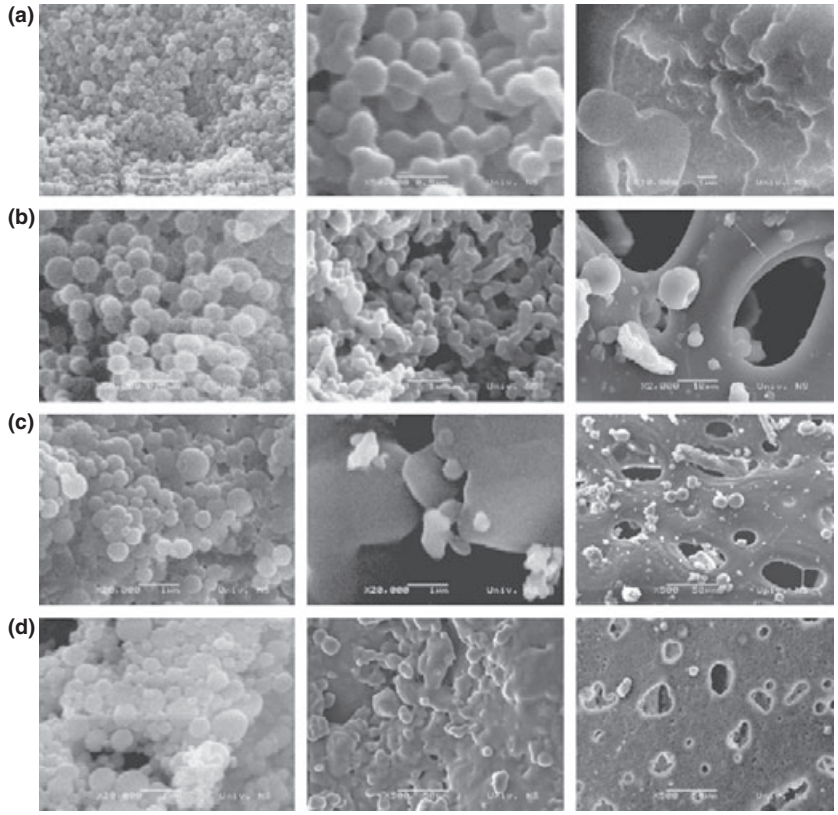

Figure 13 SEM images of (a) PLGA nanospheres and (b) PLGA/ascorbic acid 85/15%, (c) PLGA/ascorbic acid 70/30% and (d) PLGA/ascorbic acid 50/50% particles after 2, 24 and 39 days of degradation [62].

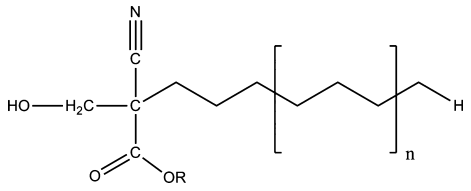

Figure 14 Structure of PACA (R = alkyl group)

ment of the upper layers of the epidermis [65]. Examples of the active oils described include α-tocopherol and trigylcerides rich in linoleic acids.

Polyamidoamine (PAMAM) dendrimers

Dendrimers are polymeric molecules composed of branched monomers emanating radially from a central core. Polyamidoamine (PAMAM) dendrimers, as shown in Fig. 15, are the most commonly reported for bioapplications [66]. The number of branch points moving from the core to the periphery is known as the generation number (G1, G2, G3, G4, etc.) and this number can be altered to enhance the drug loading capacity [67]. The interior of the dendrimer contains void spaces that are well suited for encapsulation of guest molecules. In addition, the outer surface contains a number of potentially reactive sites that can be tailored to alter the dendrimers' solubility, making this class of polymers more efficient carriers compared to other conventional complexing agents.

An important characteristic that distinguishes dendrimers from more conventional polymers is their intrinsic viscosity [68]. With traditional linear polymers, larger molecular weights increase the viscosity. Dendrimers, however, will reach a maximum viscosity which then decreases with increasing molecular weight. This feature can be of significant benefit to cosmetic formulators, where highly viscous formulations may be avoided.

A patent by L'Oreal [69] has described the use of terminal hydroxyl functionalized polyester dendrimers in combination with film forming polymers for use in cosmetics intended for skin application as well as to keratinous fibres, nails or mucous membranes. The patent describes how the disadvantages associated with using high molecular weight polymers can be avoided through the use of dendrimers. Low-viscosity formulations using dendrimers were found to have superior performance including good sensory properties.

In other patents by L'Oreal, the use of PAMAM dendrimers in deodorant compositions has been described and claimed as deodorant active agents, with odour absorbing properties [70]. The dendrimers were able to be formulated in water-based compositions and were non-irritating and non-toxic. The use of dendrimers in self-tanning compositions has also been described by L'Oreal [71]. In this application, dendrimer containing composi-

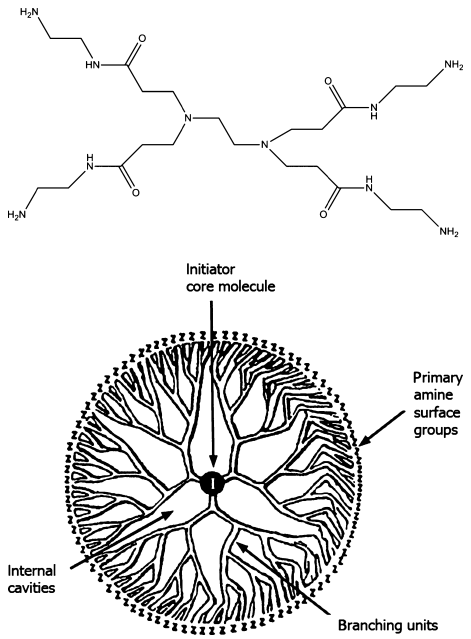

Figure 15 Structure of PAMAM monomer unit and spherical dendrimer [66].

tions were shown to have enhanced intensity and good fastness over time, in particular good resistance to washing. In addition the colouration was obtained in faster times compared to using no dendrimer.

Revlon have reported the use of PAMAM dendrimers in cosmetics and personal care applications for the encapsulation of salicylic acid in anti-acne compositions [72]. In addition to the salicylic acid being sequestered in the core, the free acid groups on salicylic acid are also able to ionically bond to the amino groups on the surface of the PAMAM dendrimer. The resulting complex stabilizes the salicylic acid, until such time that it is applied to the skin where it dissociates from the PAMAM carrier. Various compositions are described including creams, shampoos and conditioners, toners as well as make-up. One advantage of using PAMAM complexed salicylic acid in make-up is that the reaction with iron oxide pigments can be avoided [72].

The use of PAMAM dendrimers was also recently reported for assisting the transdermal diffusion of riboflavin [73]. The low water solubility of riboflavin is a limiting factor for high skin load of this vitamin and this was overcome through the use of water-soluble PAMAM carriers. Similarly, the water solubility of quinolone antimicrobial drugs was reported to increase by using PAMAM dendrimers in topical applications [74]. The antimicrobial activity of the encapsulated/complexed quinolones was found to be similar to that for the pure drugs.

The Australian-based company, Starpharma [75], has commercialized several products based on dendrimer technology. Although these are mainly in pharmaceutical applications, wider opportunities in cosmetics are being developed to provide encapsulation, solubilization and controlled release.

The mechanism of dendrimer systems for skin delivery is still not well understood; however, several theories have been proposed in a recent review [76]. These include i) the ability of dendrimers to increase the thermodynamic activity by increasing the concentration and solubility of the drug, ii) the use of penetration enhancers with dendrimers to fluidize the lipid bilayers and iii) follicular penetration.

Limitations of existing technology

One of the challenges (e.g. with alginates) is matching the physical properties of the biodegradable gel to the need in a specific application. Like many other hydrogels, alginates have very limited mechanical stiffness. This may be altered by varying the molecular weights and altering the degree of cross-linking or by using variants on the chemical structures. However, covalent cross-linking may sometimes be detrimental to the active material being encapsulated and thorough removal of unreacted species is necessary [44]. Microcapsules employed in cosmetics may need to be easily crushed on the skin (e.g. under the action of slight massage) without leaving any residue. They also need to have sufficient rigidity so that their structure is not modified during storage or manufacture into the cosmetic composition [47].

Another challenge involves the encapsulation of proteins. Preservation of the protein structure during encapsulation as well as during its controlled release from the system is essential and this has been the topic of some recent reviews [77, 78]. Proteins can become inactive or denatured by a number of chemical and physical (conformational) factors. The presence of water or water-oil interfaces during the preparation of encapsulated proteins can often be problematic and can cause protein unfolding or aggregation. This can be overcome through the addition of additives (e.g. polyols) or by using alternative non-aqueous manufacturing techniques (e.g. solid-in-oil-in-oil) [78].

In addition to the need for improved manufacturing of protein encapsulation there is also a need to maintain the protein stability during its release from the biodegradable polymer shell. The major challenge here is for poly α-esters where the polymers degrade into acidic products. The drop in pH can inactivate proteins. This can be overcome by co-encapsulation of a basic salt such as $Mg(OH)_2$ [78]. Another approach to overcome the pH decrease is to create porosity within the microsphere that allows acidic biodegradation products to diffuse out and for buffer components to permeate within [78]. As mentioned previously the use of alternative polymers such as PCL may also be considered as it is less acidic.

Both fungal and bacterial degradation can be a problem in cosmetic formulations using biodegradable polymers. For example, in the starch containing Thixogel^{TM} systems, it is necessary to add preservatives to extend the shelf life. Natural preservatives like Tea Tree oil and CITRICIDAL (oil from grapefruit seeds) have proven to be effective and low levels of benzalkonium chloride may also be added, serving a dual purpose of antimicrobial agent and emulsifier [50].

Future directions

In today's cosmetic and personal care markets, there is a growing trend towards more complex and sophisticated products with consumers expecting improved product performance and formulators desiring a greater competitive advantage. The use of biodegradable polymers as encapsulation materials offers many opportunities for improved stability and delivery of active substances.

It is foreseeable that this technology will continue to expand to keep up with demands for multifunctional products that comprise more than one active substance. In addition, the gap between cosmetics and pharmaceuticals is closing with the increasing use and availability of so-called 'cosmeceuticals'. These products contain many natural substances like vitamins, oils, and therapeutic extracts that would greatly benefit from the use of this technology. This growing consumer demand for products containing natural ingredients can be expected to result in more widespread use and design of new tailor-made biodegradable polymers for the encapsulation of active ingredients.

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