

Encyclopedia of Polymer Applications

Edited by
Munmaya Mishra, PhD



CRC Press

Taylor & Francis Group

Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

Momentive EX1028
U.S. Patent No. 12,337,057

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

© 2019 by Taylor & Francis Group, LLC
CRC Press is an imprint of Taylor & Francis Group, an Informa business

No claim to original U.S. Government works

Printed on acid-free paper

International Standard Book Number-13: 978-1-4987-2993-2

This book contains information obtained from authentic and highly regarded sources. Reasonable efforts have been made to publish reliable data and information, but the author and publisher cannot assume responsibility for the validity of all materials or the consequences of their use. The authors and publishers have attempted to trace the copyright holders of all material reproduced in this publication and apologize to copyright holders if permission to publish in this form has not been obtained. If any copyright material has not been acknowledged please write and let us know so we may rectify in any future reprint.

Except as permitted under U.S. Copyright Law, no part of this book may be reprinted, reproduced, transmitted, or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission from the publishers.

For permission to photocopy or use material electronically from this work, please access www.copyright.com (<http://www.copyright.com/>) or contact the Copyright Clearance Center, Inc. (CCC), 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of users. For organizations that have been granted a photocopy license by the CCC, a separate system of payment has been arranged.

Trademark Notice: Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation without intent to infringe.

Visit the Taylor & Francis Web site at
<http://www.taylorandfrancis.com>

and the CRC Press Web site at
<http://www.crcpress.com>

Cosmetics: Polymers in Delivery of Actives

Azila Abdul-Aziz, Rosnani Hasham, and Mariani Abdul Hamid

Department of Bioprocess and Polymer Engineering, University of Technology, Malaysia, Skudai, Malaysia

Abstract

Due to the versatility of polymers, multiple uses of polymers have been found in the cosmetic and personal care industry and one important use of polymers is as the vehicle or in the vehicle for transdermal delivery. Polymer based transdermal systems for cosmetic applications can be broadly classified as transdermal patches and polymeric penetration enhancers. Polymers are suitable to be used as transdermal delivery systems because they provide consistency and stability, drug release, drug targeting, enhanced bioavailability and consumer acceptability. Technologies relevant to the preparation of polymer based delivery systems include spray drying, spray coating, extrusion techniques, sponge technology, gel technology, coacervation, in-situ polymerization and self-assembly. Modifications of the polymers through surface modifications, hydrophilic-hydrophobic grafting and conjugation with biodegradable links improve their encapsulation capability and polymer-skin interaction. To investigate the efficiency of a polymer based transdermal carrier in delivering cosmetic actives, analyses such as morphology and drug distribution; entrapment efficiency and drug loading capacity; drug-excipient compatibility studies; stability studies; skin penetration study, in vitro biological activity evaluation and safety testing are conducted. Applications of polymer based delivery systems in cosmetic products include cosmetic patches, polymeric porous systems, polyurethane based delivery systems and activated delivery systems.

Keywords: Cosmetic actives; Encapsulation; Penetration enhancement; Polymer; Skin; Transdermal delivery.

INTRODUCTION TO POLYMER-BASED DELIVERY SYSTEMS IN COSMETICS

The global beauty market is a market segment that provides a wide range of products to the consumers. The scope of cosmetics and personal care products includes formulations that target healthy skin, hair, nails, and teeth. These seemingly diverse sectors are actually complementary and are able to satisfy consumers' expectations with regard to beauty.

A wide range of ingredients need to be used to formulate the cosmetic and personal care products. One important class of material is polymers. Polymers, whether natural or synthetic, are used in cosmetic and personal care formulations as emollients, conditioners, humectants, film formers, emulsifiers, thickeners, modifiers, protective barriers, or delivery systems. The bulk of the market share for polymers in the beauty industry is as surfactants;^[1] however, the demand for other innovative uses of polymers is on the rise.

Skin care products, particularly for antiaging, dark spot reduction, and sensitive skin, dominate the cosmetic and personal care industry.^[1] Innovations in this area include delivery systems for effective penetration of active

compounds into the skin. Thus, knowledge of the anatomy of the skin and the routes of transdermal penetration is crucial for the design of effective transdermal delivery systems.

Anatomy of the Skin

The skin is the largest organ of the human body. It accounts for approximately 10%–15% of the body's mass.^[2,3] The skin acts as a barrier between the body and the environment, protecting the body from UV radiation, foreign substances, and water loss. In addition, the skin is also involved in thermal regulation of the body.

The skin is composed of three layers: epidermis, dermis, and subcutaneous tissue (Fig. 1). The epidermis consists mostly of keratinocytes, the dermis consists primarily of collagen, and subcutaneous tissue is made up of lipocytes. The thickness of these layers depends on body parts.^[4] The epidermis is thickest in the palm and soles of the feet and thinnest in the eyelid. The dermis is thickest on the human back.

In the epidermis, apart from the keratinocytes, other cell populations include melanocytes, Langerhans cells,

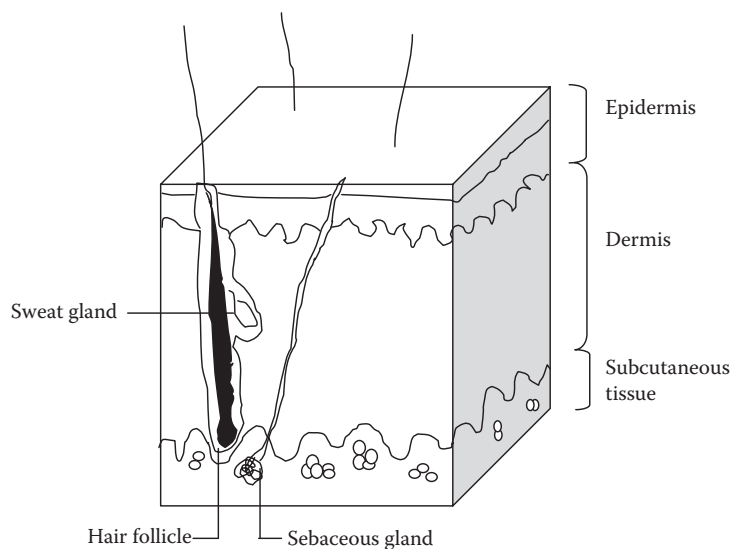


Fig. 1 A schematic diagram showing the different layers of the skin

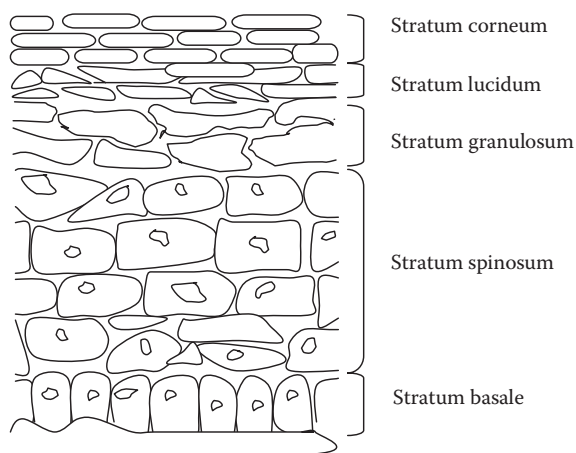


Fig. 2 The five layers of the epidermis: stratum corneum, stratum lucidum (only in thick epidermis), stratum granulosum, stratum spinosum, and stratum basale

and Merkel cells.^[5] The epidermis is divided into five layers that include stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (Fig. 2).^[5] However, stratum lucidum is normally only well seen in thick epidermis. The epidermis is a continually renewing layer where living cells (keratinocytes) at the basal layer will slowly migrate to the upper layers.^[6] Epidermal renewal process takes approximately 28 days where migration to the stratum corneum takes about 14 days and another 14 days are required to transit through the cornified layer. The large, flat, polyhedral corneocytes (horny cells) lost their nuclei during the differentiation process and are considered to be dead cells.

The stratum corneum is a very thin layer of the epidermis. It is only 10–15 cells deep with a thickness of only about 0.1–0.2 mm.^[7] It is the primary barrier that protects the body from water loss and invasion by foreign

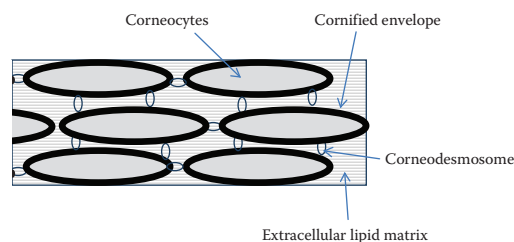


Fig. 3 A schematic representation of the stratum corneum

substances, and is thus the principal barrier for transdermal penetration of any active material. The architecture of this layer has been modelled as a brick and mortar structure (Fig. 3), where corneocytes (bricks) are embedded in a matrix of extracellular lipid (mortar).^[6] The flat polyhedral-shaped corneocytes are keratinocytes which have lost their nuclei during terminal differentiation. They are filled with keratin fibers and degraded products of proteins, lipids, and nuclei. Endogenous natural moisturizing factor is generated from the degradation of histidine-rich proteins.^[8] For corneocytes, the lipid bilayer plasma membranes are replaced by a cornified envelope of cross-linked proteins. The cornified envelope is rigid and has the ability to resist mechanical barrier stress.^[9] The outer leaflet of the cornified envelope is covered by a monolayer of corneocyte lipid envelope (CLE).^[10] The extracellular domain of the stratum corneum is filled with lipid-enriched lamellar membranes. This extracellular lipid is mostly composed of ceramide, cholesterol, and free fatty acids.^[11] This unique structure of the stratum corneum provides the groundwork for the effective barrier property of the skin.

The dermis provides the skin with its elasticity and tensile strength. The dermis is an integrated system of fibrous, filamentous, and amorphous connective tissue that contains blood vessels, nerve endings, epidermally derived appendages, fibroblasts, macrophages, and mast cells, and can be

divided into a deep reticular layer and a superficial papillary layer. Fibroblasts synthesize reticulum fibers, elastic fibers, and collagen. Collagen is the skin's stress-resistant material that accounts for 70% of the skin's dry weight.^[4] Elastic fibers are composed of protein and elastin, and they maintain skin's elasticity. The capillaries in the dermis provide sink conditions for most molecules that are able to penetrate the skin barrier.

Subcutaneous tissue supports the dermis and epidermis. It is formed by a network of fat lobules (lipocytes) and connective tissue septa made up of large blood vessels and collagen.^[4] The subcutaneous tissue serves as a fat storage area and provides the body with buoyancy.

Skin Permeation

The stratum corneum, with its unique composition and structure, provides the skin with a very effective barrier property. However, molecules (usually less than 500 Da in size) can still penetrate the epidermis through three possible pathways: transcellular route, intercellular route, and through the appendages (Fig. 4). Most substances penetrate the skin through a combination of pathways based on the properties of the substances.^[12]

Transcellular route involves the penetration of the molecules through the corneocytes and lipid matrix as a straight path to the dermis. Molecules penetrating the stratum corneum using the intercellular route will travel through the lipid matrix surrounding the corneocytes. This route is widely considered as an important route and a major barrier to the permeation of molecules. Both polar and nonpolar molecules can traverse this route, but the amount and rate of diffusion depend upon the property of the permeant.^[13] Nonpolar molecules pass through the lipid matrix of the stratum corneum, whereas polar molecules “jump” through the polar heads within the lipid matrix. Appendageal route is the transport through hair follicles and sweat glands. This route is considered to be important for ions and large polar molecules.^[14]

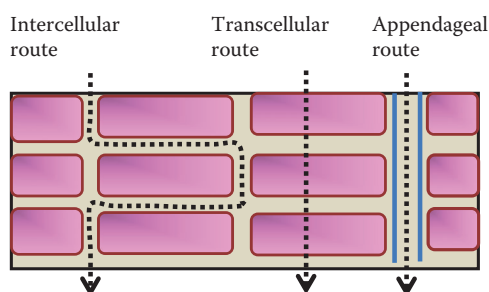


Fig. 4 The three possible pathways for skin penetration: transcellular route involves the penetration of molecules as a straight path to the dermis. Intercellular route involves the penetration of molecules through the lipid matrix surrounding the corneocytes. Appendageal route is the transport of molecules through hair follicles and sweat glands

Transdermal permeation is based on passive diffusion which involves a series of processes. It starts with diffusion through the stratum corneum. Then, the molecules partition into the more viable epidermis and diffuse through the deeper layers of the skin or uptake of the molecules by the blood vessels. The transport characteristics of the molecules at each step depend on their physicochemical properties. That is why the information regarding the solubility, diffusivity, and partition coefficient ($\log P$) of the permeants among others is important to predict the transdermal transport properties of permeants.

Polymer-Based Delivery Systems for Cosmetic Actives Delivery

There is a close relationship between pharmaceutical delivery systems and cosmetic delivery systems. Most of the delivery systems developed for the pharmaceutical industry are eventually adopted by the cosmetic and personal care industry. Of particular importance to the cosmetic and personal care industry is the transdermal delivery system.

In delivery systems, the term vehicle refers to the carrier where the active principle is embedded into. Due to the versatility of polymers, a broad spectrum of polymers can be used as vehicles or in vehicles for transdermal delivery. In this entry, the classes of polymer-based transdermal delivery systems, properties of polymers suitable for cosmetic delivery systems, technologies relevant to polymer-based delivery systems, analytical testing involved in the development of polymer-based delivery systems, and the application of polymer-based delivery systems in cosmetic products will be discussed.

CLASSIFICATION OF POLYMER-BASED TRANSDERMAL DELIVERY SYSTEMS

Polymer-based transdermal delivery systems can be broadly categorized into two types: transdermal patches and polymeric penetration enhancers. Transdermal patches can be further classified into reservoir (membrane-controlled) systems and matrix (monolithic) systems (Fig. 5).

Transdermal Patches

Reservoir Systems

This system is a combination of a reservoir containing the active ingredient and a rate-controlling membrane. The active ingredient is in a solution, suspension, or gel and is separated from the adhesive layer by a rate-controlling permeable membrane. The advantage of this system is that it has zero-order kinetics. On the other hand, the disadvantages of this system are the need for a large patch to achieve its delivery goal, high initial delivery rates due to the saturation of all membranes with the active ingredient

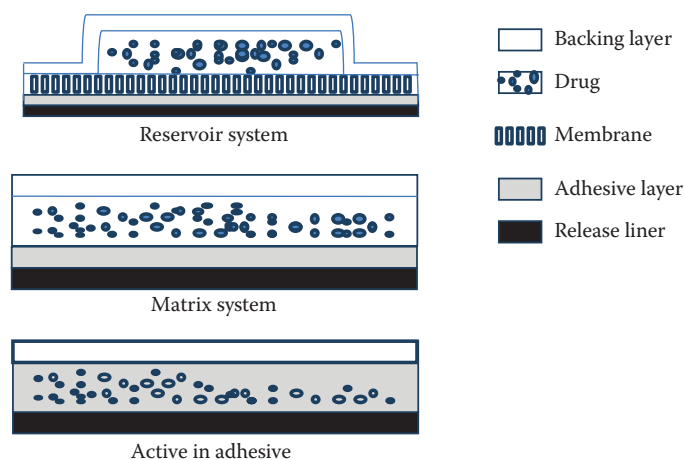


Fig. 5 Reservoir systems and matrix systems dominate the transdermal delivery system market. The matrix system can exist in several forms including active in matrix, active in adhesive, and multilayer matrix system

during storage, and potential leakage from its sealed liquid reservoir. There have been reports of uncontrolled drug release from the reservoir resulting in the possibility of overdosing due to rupture of the backing membrane.^[15,16]

Matrix Systems

The matrix system can exist in several forms including active in matrix, active in adhesive, and multilayer matrix system. For this system, the active ingredient is dispersed homogeneously in the polymer matrix. For the simple matrix system, a single polymer matrix layer sits on top of the adhesive layer. For the active in adhesive system, the active ingredient is directly dispersed in the adhesive polymer. The adhesive layer is pressure sensitive, i.e., the material can adhere to the skin with no more than applied finger pressure, exerts strong force, and can be removable without leaving a residue.^[17] For the multilayer matrix system, different layers of polymer matrix contain corresponding concentrations of the actives, resulting in a sequential concentration gradient. In principle, the delivery of the matrix systems can be tailored to follow zero-order kinetics; however, the rate of active ingredient release can result in first-order kinetics with wear time.^[18] Constant rate of delivery can only be achieved if the amount of active ingredient at the end of wear time is at least 80% or if the active ingredient is in suspension.

Polymers in Transdermal Patches

In transdermal patches, polymers are used as matrix formers, rate-controlling membranes, adhesive layers, backing layers, and release liners. Among others, polymers used as matrix formers include cross-linked poly(ethylene glycol),^[19] acrylic acid matrices,^[20] ethyl cellulose/polyvinylpyrrolidone,^[21] and hydroxypropyl methylcellulose.^[22] Polymers such as poly(ethylene-vinyl acetate)^[23] and polyurethane^[24]

have been used as rate-controlling membranes. Acrylic-, polyisobutylene-, and silicone-based adhesives are usually used as pressure-sensitive adhesives.^[25,26]

Polymeric Penetration Enhancers

Polymeric penetration enhancers can be divided into polymeric absorption enhancer and polymeric transdermal carriers. Polymeric penetration enhancers have been purported to be nonirritant to skin and to show no acute toxicity.^[27]

Chemical penetration enhancers can increase skin permeation by interfering with stratum corneum lipid bilayers,^[28] and this process has been linked to protein denaturation and lipid extraction in the stratum corneum.^[29] Polymeric absorption enhancers, on the other hand, is a class of substance that can trigger the reversible opening of the tight junctions of mucosal epithelia and thus allowing paracellular transport of molecules.^[30] Tight junctions are intercellular contacts that seal the space between individual epithelial sheet. Polyacrylates, chitosan, thiolated polymers of polyacrylates, and thiolated polymers of chitosan have been used as polymeric absorption enhancers.^[31] Polyacrylates bind with calcium ions to trigger the reversible opening of the tight junction.^[32] For chitosan, direct interaction of the cationic polymer molecule with the negatively charged cell membrane sugar residues has been said to trigger the transient effect on the tight junction's permeability.^[33] In the past few years, tight junctions have also been found in the skin,^[34] and this opened up the possibility of using these polymers for percutaneous penetration enhancement.

Polymeric materials offer a unique opportunity as a delivery platform. Polymeric carriers of controlled size and structure offer increased functionality and can be utilized to enhance transdermal delivery. Among others, polysaccharides, polyesters, amphiphilic polymers, and

poly(amidoamine) (PAMAM) dendrimers have been used as the encapsulation material for cosmetic and personal care active ingredients.

Polysaccharides

Chitosan is a cationic polysaccharide made up of polymers of glucosamine and *N*-acetyl-glucosamine. Controlled release can be achieved by increasing the viscosity of the polymer matrix.^[35] Chitosan transdermal drug delivery system has demonstrated sustained release profile of actives while reducing skin irritation.^[30]

Cyclodextrins are cyclic oligosaccharides consisting of glycopyranose units bound with 1,4 bonds having hydrophobic inner cavities and hydrophilic outer surfaces. Cyclodextrins do not penetrate the skin because of their fairly large molecular size. The penetration enhancement property of cyclodextrin is most likely due to the increase in the solubility of the active ingredient that acts as the thermodynamic driving force for transdermal permeation.^[36]

Polyesters

This class of polymers include polylactic acid, polyglycolic acid, poly(lactic-co-glycolic acid), and poly(ϵ -caprolactone) (PCL). Encapsulations of cosmetic actives in polyesters have been reported.^[37–39] Sustained active ingredient release can be obtained through hydrolysis of ester linkages.^[40] Degradation by-products have minimal skin irritation effects.^[41]

Amphiphilic Polymers

Amphiphilic polymers of tunable hydrophile–lipophile balance (HLB) can be utilized as effective transdermal delivery systems. Encapsulation of active materials can be achieved within the self-assembled supramolecular nanostructures. One very interesting feature of the amphiphilic polymer is they can be designed with the optimum HLB for drug encapsulation and skin interaction. Some of the amphiphilic polymers used as transdermal delivery carriers include methoxy-terminated poly(ethylene glycol)-poly(ϵ -caprolactone) micelles,^[42] tri-block copolymer containing a central poly(propylene glycol) flanked by two polyethylene glycols (PEGs),^[43] and star block copolymer with bromide surface functionalities dendritic cores and oligo(ethylene glycol) methacrylate and lauryl methacrylate conjugated onto the branching units of the dendritic cores.^[44]

PAMAM Dendrimers

PAMAM dendrimers have treelike branched structures that can be altered to enhance drug loading capacity.^[45] The interior of the dendrimer contains void spaces that can be utilized for the encapsulation of active ingredients, and the outer surface can be tailored to alter the dendrimer's

solubility. PAMAM dendrimer–skin interactions depend on the dendrimer's size and surface groups.^[46] Skin penetration of low-generation dendrimers is better than larger generation dendrimers. The mechanism of skin delivery of dendrimers is proposed to include the ability of dendrimers to increase the concentration and solubility of drug, the use of penetration enhancers with dendrimers to fluidize lipid bilayers, and follicular penetration.^[47]

POLYMER PROPERTIES SUITABLE FOR COSMETIC DELIVERY SYSTEMS

Polymers are used in the cosmetic delivery system as they provide consistency and stability, drug release, drug targeting, enhanced bioavailability, and patient acceptability.

Polymer Types

Polymers can be classified based on whether they are natural, synthetic, or semisynthetic. Natural polymers are found in plants and animals such as proteins, cellulose, and rubber. They exist in abundance, and they are biodegradable. However, natural polymers are very difficult to reproduce and purify. Synthetic polymers are man-made polymers such as plastic (polythene) and fibers (nylon). These polymers can be biodegradable and nonbiodegradable. Synthetic polymers have high immunogenicity, which prevent their long-term usage.^[48] Therefore, in developing cosmetic delivery systems, the selection of polymers materials is very important. Several criteria should be considered such as safety, efficacy, stability, biological inactivity, and sufficient pharmacokinetics.

Physicochemical Properties

Polymer Solubilization Capacity

The important factors in polymer solubilization capacity of drugs are hydrophobicity and HLB factors. The significance of HLB in surfactant micelle system has been reported in a few literatures.^[49,50] HLB value of amphiphilic block copolymers is driven by hydrophobic interaction^[51] in the formation of micelle (drug vehicle). In the stratum corneum, the lamella structure is composed of fatty acids, cholesterol, and ceramide. The layered morphology is strongly affected by pH and firm in the presence of water.^[52] This layered lamella structure can be effectively disturbed by chemical enhancers with appropriate HLB.

Polymer Size and Morphology

Non-covalent interactions also known as hydrogen bonding or van der Waals interaction can form a self-assembled structure of block copolymers. The morphology of block copolymer aggregates relies on the chemical nature of the

repeating unit and the block length.^[51] A diverse of morphologies such as rods, spheres, lamella, vesicles, and tubules have been reported to have potential possibility for drug delivery.^[53] This architecture of drug vehicle can be achieved by adjusting the solution conditions.

Amphiphilic block polymers are dissolved in a solvent suited to both blocks and added with a poor solvent for one block (e.g., “A”). The A-block association will be derived by increasing the interfacial tension and concentration of the poor solvent. Thus, the shape of the aggregate is transformed from spheres to rods and vesicles. However, the effect of morphology on drug release behavior is still not clear. Polymeric vehicles with amphiphilic domain are applicable for drug delivery due to its ability to encapsulate both hydrophilic and hydrophobic drugs as compared to other morphologies.^[54]

Another important factor is the size of vehicle. Polymeric microparticles with diameters of 3–10 μm selectively permeate through hair follicles or sweat ducts, whereas particles greater than 10 μm will reside on the skin surface.^[55] Intercellular uptake of particles can be increased by reducing the size of the vehicles.^[56,57] The penetration efficiency of 100 nm nanoparticles was reported to be 15–250-fold higher than microparticles.^[58] Ultrafine (30 nm) nanoparticles are best suited for penetration via the intercellular route.

Polymer Structure

The study of a single copolymer molecular structure is known as the polymer topology. Polymer topology is an important factor that might affect the polymer's suitability in drug delivery.^[59] Homopolymers and AB-type diblock, ABA- or BAB-type triblock, and multi-block copolymers^[60] are the simplest structures of linear polymers reported. The most significant aspect of drug conjugation is by an efficient cleavage mechanism that lies in the center of the polymer. Other important factors in the polymer design include non-immunogenicity, non-toxicity, sterilization, and biodegradability.^[61]

Graft copolymer is another type of polymer which provides considerable functionalities onto polymer backbone by chemical modification of its structure. The graft copolymers can easily undergo intermolecular entanglement among the longer main chains or intramolecular association to form spherical micelles called comb-shaped or brush-shaped copolymers. The longer main chain acts as a backbone, and shorter side chains act as graft segments.^[62]

As an example of graft copolymers, amphiphilic dextran was prepared by coupling PCL monocarboxylic acid and the hydroxyl groups onto dextran.^[63] The comblike copolymers (dextran–PCL) were used to prepare nanoparticles containing bovine serum albumin for which the surface was enriched with lectin. The surface-bounded lectin preserved its hemagglutinating activity for possible application as a targeted drug delivery system.^[63]

Star polymers are the simplest class of branched polymers with a three-dimensional hyperbranched structure. The use of star polymers as drug carriers seems rather limited although it has superior structure stability compared to linear or graft copolymers. One study reported that star-shaped polymers exhibit a lower solution viscosity and smaller hydrodynamic radius as compared to linear polymers with the same molecular weight and composition.^[64]

Dendrimers are repetitively branched polymer molecules. Dendrimers have a high density of functional groups, low viscosity, and well-defined shapes and sizes (monodispersity). A void space and high-density functional groups of dendrimers make it well suited as carrier molecules in drug delivery. Micelles prepared with larger dendrimer as drug-loading core showed higher encapsulation capability.^[65,66]

Biological Properties

General biological properties of drug describe the beneficial or adverse effects of the drugs on the human beings. The crucial properties of drugs are that they should not directly irritate the skin (topical delivery) or degrade in the gastrointestinal tract (oral delivery). To form an effective and suitable drug, a compound must possess the appropriate ADME (absorption, distribution, metabolism, and excretion) properties on top of being active against a target compound.^[67] The drug development tolerance must be below the near zero-order release profile of topical delivery. The drug also should not stimulate an immune reaction in the skin or cause adverse effects to nontarget tissue.

Properties of Polymeric Penetration Enhancers

Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for topical delivery. Penetration enhancers (also called accelerants or sorption promoters) are described as substances that have the ability to penetrate through the skin by reversibly decreasing the skin barrier resistance^[68] and can interact with skin constituents to promote the drug flux.

Skin (percutaneous, dermal) absorption is the transportation of drug molecule from the outer surface of skin into the stratum corneum under the influence of a concentration gradient.^[69] The human skin behaves as a passive barrier to the penetrant molecule and may contact with many agents intentionally and unintentionally.

The stratum corneum is the rate-limiting step in percutaneous absorption which provides high resistance to drug penetration.^[69] The resistance of the stratum corneum for drug diffusion has to be reduced to allow drug molecules to cross the skin surface and maintain the therapeutic levels in blood. The skin's barrier penetration can be modified by interacting with the formulation that is applied or with the skin itself.

Ideally, these compounds should be pharmacologically inert, nontoxic, nonirritating, nonallergenic, and

compatible with the drug and excipients, colorless, tasteless, odorless, inexpensive, and have good solvent properties. The enhancer should not lead to the loss of body fluids and other endogenous materials so that the skin can immediately regain its barrier properties on its removal.

TECHNOLOGIES RELEVANT TO POLYMER-BASED DELIVERY SYSTEMS

Encapsulation is needed for many biologically active substances that are sensitive to temperature, pH, light, and oxidation. Encapsulation is also needed to target specific areas of the body and for controlled release of the active substances. The techniques available for encapsulation of active materials and other technologies relevant to the development of polymer-based delivery systems are discussed next.

Spray Drying

The most common technique is spray drying of the active payload when blended with natural gums. These gums may include gelatine, acacia, maltodextrin, agar, chitosan, and food-approved synthetic polymers. Such active/polymer blends are typically sprayed in atomization towers to remove required solvents and, therefore, produce actives dispersed in a polymer matrix. In the pharmaceutical sector, supercritical carbon dioxide finds increasing use as a solvent of choice. This preference results from its ability to offer extremely mild encapsulation conditions suitable for dealing with fragile bioactive molecules such as enzymes and peptides.

Spray drying provides the most rudimentary level of functionality often used for the purpose of providing easier handling of liquid actives or fragrances. Payload capacity in this type of process is limited and seldom approaches a 1:1 ratio of payload to encapsulating polymer. In the personal care sector, this technology finds its main use in fragrance encapsulation.^[70]

Spray Coating

Spray coating technology operates on a principle similar to spray drying. However, the payload is insoluble; hence, the gum forms a coating on the surface of the encapsulated payload particle. This method is often employed to encapsulate pigments in order to prevent their agglomeration in a formulation.^[71]

Extrusion Techniques

Apart from spray drying and spray coating, a number of extrusion-based technologies are also employed to encapsulate actives. The most common of these are the hot-melt processes. Many variations on these themes exist. The

key principle of this approach always remains the same: the payload of actives and the encapsulating polymers are extruded through a system of concentric tubes and the payload occupies the central tube. Consequently, extrusion techniques result in a capsule architecture in which the polymer membrane surrounds a payload of the active.

As for the polymers used in extrusion technologies, these are typically natural or semisynthetic materials such as starch, cellulose, and alginates. However, simple polyacrylates and polyacrylamide are also useful in this regard. On the whole, payloads employed in this type of process cannot be too fragile. Further, they should be soluble in organic solvents and also be able to withstand oxidative processing conditions.^[72]

Actives encapsulated in membranes obtained by extrusion technologies, referred to as *spheres*, have a higher level of functionality than those obtained by the spray drying process. Such spheres exhibit a higher degree of stability in many cosmetic formulations, hence providing some of the formulation stability benefits listed previously.

The Sponge Technology

The polymeric sponge is often made of cross-linked polymethacrylate. Such synthetic, super-absorbing sponges are able to absorb a large payload of actives. Uptake of actives is dependent upon polarity of the payload and its chemical similarity to the polymer. Typically, the capacity of sponges for hydrophobic payloads is higher than their capacity for hydrophilic ones. A key property of the sponge technology is its ability to provide controlled release mechanism. This mechanism results from a combination of diffusion and shearing conditions applied during product application. If diffusion of the active out of the matrix is too rapid, active transport may be reduced to more useful rates. Such lower rates can be achieved by means of a surface coating covering the sponge particle. An example of such a coating is a phospholipid bilayer. Control of the diffusion rate is especially important due to the hydrophobic environment presented by the skin's surface.^[73]

Gel Technologies

Some classes of super-absorbing polymers produce gels when swollen with an organic payload. These gels find uses in skin treatment and as delivery vehicles. A new type of gel technology results in sol-gel conversion at body temperature.^[74] This property may be of interest for applications including oral care, invisible skin patches, and shaving creams.

Coacervation

The coacervation process is initiated by dispersing or emulsifying the payload of active in a gelatine solution (2%–10% gelatine) containing a polyanion such as gum

arabic. When the pH is adjusted to about 4, and the solution is cooled to about 10°C, the positively charged gelatine and the negatively charged polyanion react to form a “complex coacervate” membrane on the surface of the payload. This membrane is further strengthened by cross-linking it with an aldehyde. Such complex coacervates based on cationically modified hydroxy ethyl cellulose have been used to entrap silicone oil in foams.^[70]

Variations on the polymers described above have been employed. For example, gum arabic may be replaced by a number of synthetic and natural polyanions. However, it is more difficult to find a material that would replace gelatine without some loss of product quality. Overall, gelatine remains the best material for the majority of coacervation processes.^[70]

Membranes obtained by coacervation are known to break under the applied shear of the application process (i.e., rubbing on the skin), and it is this breakdown that releases the payload. This process is a valuable release mechanism, although it is limited in its scope since it does not offer the possibility of providing sustained release characteristics. The key benefit of the coacervation technique is that it provides good protection from surfactants, which is useful in the presence of sensitive payloads. In addition, the coacervation technique leads to large, visible capsules that are attractive to consumers. Such capsules must have sufficient strength to resist breakdown during their incorporation into a formulated product prior to their use. The strength of the outer wall can be adjusted to increase its resistance to breakdown by applied shear during processing.^[71]

Urea-Formaldehyde Membrane Formed by In Situ Polymerization

The urea-formaldehyde (polyoxymethylene urea) encapsulation system was commercially developed by G.W. Matsen of the 3M Company in the 1960s.^[75] This system was developed as an alternate method for the encapsulation of water-insoluble liquids and solids. *In situ* polymerization is a process in which the capsule shell is formed by the polymerization of monomers added to the encapsulation reactor. In this process, polymerization occurs exclusively in the continuous phase and at the interface formed by the dispersed core material and the continuous phase. Polymerization of reactants located in the continuous phase produces a low molecular weight prepolymer. As this prepolymer grows in size, it deposits onto the surface of the dispersed core material. Continued polymerization, with cross-linking, continues to generate a solid capsule shell.^[75]

Amphiphilic Block Copolymer Self-Assembly

This process is based upon the principle that amphiphilic block polymers, in water, form micellar nanostructures whose core is hydrophobic. Once formed, these micelles may be swollen with a hydrophobic payload and the hydrophilic

exterior may then be cross-linked to form a “shell.” This technology appears very promising, especially for applications requiring release triggers such as pH triggers, ionic strength triggers, or change in polarity triggers.^[70]

TESTING: ANALYTICAL TESTING

Particle Morphology and Drug Distribution

Determination of Particle Size and Polydispersity Index

Dynamic light scattering or also known as photon correlation spectroscopy is used to determine particle size and polydispersity index (PDI). The size of particle is calculated based on spherical particles. Hence, the size of particles with different shape might be incorrectly evaluated.^[76] This technique gives information regarding the mean size and PDI of samples. However, it is very sensitive towards particle aggregates; even a large few particles will increase the mean size significantly.

Evaluation of Particle Morphology

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are commonly used analyses to determine the shape and morphology of particle in cosmetic delivery system. SEM and TEM are also used to provide supplemental data on particle sizes, because imaging of a large number of particles to make approximate observations on mean size is time-consuming.^[76] Other than SEM and TEM, atomic force microscopy (AFM) is another technique which can be used to determine the morphology of particles. Generally, AFM measures the force between the probing tip and the sample surface which allows analysis of the sample directly without pretreatment. The AFM technique is efficient to provide three-dimensional surface profiles with nanometer- to angstrom-scale resolution.^[77] This explains why AFM can be used to determine the size of particles, which could not be measured with laser diffraction method.^[78]

Entrapment Efficiency and Drug Loading Capacity

Entrapment efficiency is a very important property of cosmetic delivery systems. It is a basic calculation of the amount of drug entrapped within the carrier after the encapsulation process. Interaction between cosmetic actives and polymers can change the entrapment efficiency because the solubilization capacity of vehicle may be different towards the properties of actives.^[79] The drug loading capacity indicates the percent weight of encapsulated cosmetic actives to the weight of nanoparticles. The capacity of drug loading can be affected by various parameters that include emulsifier type, weight ratio of polymer to drug, and organic

to aqueous phase ratio. Numerous methods can be used to measure the entrapment efficiency and drug loading capacity of the cosmetic delivery system such as size-exclusion gel chromatography and ultracentrifugation method.

Drug-Excipient Compatibility Studies

Drug-excipient compatibility studies are conducted using Fourier transform infrared spectroscopy analysis. The compatibility of drugs, polymers, and formulation is analyzed separately and then correlated for their incompatibility.

Stability Study of Cosmetic Delivery System

When suspending particles in a medium, the resulting suspension will be unstable. This is probably due to the coagulation, flocculation, or phase separation processes that occur over time if the attractive forces are larger than repulsive ones. According to Derjaguin–Landau–Verwey–Overbeek theory, the stability of suspension depends mainly on the balance between attractive van der Waals forces and repulsive coulombic forces. Therefore, the stability of particle suspensions does not only depend on the surface properties of the particles but also on the medium properties such as ionic strength and pH value. Additionally, the physical stability of suspension in a defined medium can be manipulated through two different actions such as steric stabilization, which can be achieved via adsorbing polymers to the surface of the particles, and charge modification by means of changing the actual chemistry of the particles.^[80] The most important stability indicating the parameter for nanoparticles is the zeta potential or also known as the electrokinetic potential, which is the potential drop between the electric double layer of the particle and the bulk of the liquid phase.

Determination of Zeta Potential

Zeta potential can be defined as the electric potential of a particle in a suspension which acts as the main parameter in order to investigate the long-term stability of the nanoparticles. Zeta potential indicates the electrokinetic potential of the particle. The stability of the suspension is greater when the electrostatic repulsion between the particles is higher.^[81] Zeta potential values of above 30 mV (positive or negative values) lead to a more stable suspension due to the repulsion between the particles that prevent their aggregation.

Storage Stability

Storage stability can be performed according to ICH guidelines at different temperatures and relative humidity. Stability of samples can be monitored at temperatures and relative humidity of 25°C–30°C (60% relative humidity) and 45°C–50°C (75% relative humidity) over a period of

60 days. The samples can be withdrawn at predetermined time intervals and analyzed with regard to their physical appearance and drug content.

Skin Penetration Study

In Vitro Diffusion Study

The objective of *in vitro* diffusion study is to predict the permeation characteristic of the drug *in vivo*. Commonly, Franz diffusion cell is used to investigate the release profile of the drug from the film forming system. The cell consists of two compartments which are the donor and receiver compartments. Reconstructed human skin or animal skin is a commonly used membrane which is placed in between the donor and receiver compartments. Predetermined quantity of a drug in a diffusion medium is placed in the donor compartment. The receptor compartment contains only the diffusion medium. Samples are collected at suitable time intervals and analyzed using suitable methods.^[82]

In Vitro Biological Activity Evaluation

Generally, *in vitro* studies are more cost-effective and less labor-intensive compared to *in vivo* studies. In addition, the *in vitro* models do not require ethical requirements needed for animal or human studies. Extrapolating *in vitro* observations to *in vivo* effects in an intact organism is essentially a difficult challenge. Hence, the *in vitro* models often raised some questions on their applicability and validity.

Safety Testing

Legislation regarding the use of nanomaterials in cosmetic products has been included in European Cosmetic Regulation 1223/2009, in 2009, and the legislation has been in effect since July 11, 2013. This regulation defines nanomaterials as insoluble or bio-persistent and intentionally manufactured materials with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.^[83] If the European Commission has concerns, full safety assessment should be done to the cosmetic product that contains the nanomaterial ingredient. The required testing includes toxicological profiles such as skin and eye irritation, as well as skin sensitization (Annex I, 6). In addition, in the list of ingredients of the cosmetic product, the word “nano” in brackets must follow the name of the substance.

APPLICATIONS OF POLYMER-BASED DELIVERY SYSTEMS IN COSMETIC PRODUCTS

Transdermal Patches

Nicotine patches were the first successful transdermal system that raised the market value of transdermal drug delivery

system (TDDS) in medicine to newer heights. Estradiol, fentanyl, testosterone, lidocaine, and some other drug combinations are the TDDSs available in the present pharma market. Methotrexate, repaglinide, diclofenac, and aceclofenac are the few drugs for which TDDSs have been reported. Combination of drugs such as theophylline–salbutamol sulfate and ketoprofen fumarate–salbutamol sulfate TDDS was also formulated and evaluated *in vitro*.^[84]

Cosmetic patches evolve from the transdermal patches of the pharmaceutical industry. Most of the cosmetic patches are based on the principle of the matrix patch. The cosmetic patch categories include pore cleansers, black-head removers, masks, short-term treatment patches, and overnight treatment patches in the following cosmetic categories: anti-blemish, pore cleansers, eye contour, antiaging, and skin firming.^[85]

Polymeric Porous Delivery Systems

Polytrap® Technology

Polytrap® polymers are prepared from lauryl methacrylate and ethylene glycol dimethacrylate monomers using peroxide as catalyst. The lauryl methacrylate makes the internal surface area of the finished polymer very lipophilic. The combination of low surface energy and high surface area makes the oil absorption potential of these particles exceptional. Due to its extraordinary lipophilic properties, it is widely used in cosmetics as an oil absorber. Beyond the oil absorption property and use, however, the technology has also been used to entrap lipophilic active ingredients and deliver them to the skin. In one commercial approach, special large Polytrap® particles that physically disintegrate with the typical shear forces of application have been created for use in scrubs.^[86]

Microsponge®

Microsponge® polymers are obtained from the polymerization of styrene and divinylbenzene or methyl methacrylate and ethylene glycol dimethylacrylate. Some cosmetic ingredients such as alpha-hydroxy acids and retinol are accompanied by similar side effects commonly associated with pharmaceutical ingredients such as tretinoin (e.g., peeling, drying, erythema, etc.). In view of this, entrapping such ingredient in Microsponge® polymers becomes a viable alternative.^[87]

Microsponge® technology has also been utilized to formulate products that contain two or more mutually incompatible actives (e.g., hydroquinone and retinol), thereby allowing the formulator greater flexibility. Also, aqueous gels can be made containing lipophilic materials without the use of any emulsifying agents. This is because the entrapped materials are inside the Microsponge® particles, and these are easily wetted and suspended in the aqueous phase. On the other hand, very lipophilic formulations can

be prepared with hydrophilic materials being added in the entrapped form, again without surfactants or emulsifying agents since the Microsponge® particles are easily “wetted” and suspended in the lipid phase due to the amphiphilic nature of the polymer. A similar rationale can be used to prepare formulations with actives that have limited solubility in the desired vehicle. Using this principle, several commercial formulations have been prepared in soft-gelatin capsules where the anhydrous vehicle is silicone based. Retinol, vitamin K, vitamin C, and combinations of these agents are just some of the entities that have successfully been incorporated into formulations filled in soft-gelatin capsules using Microsponge® entrapments.^[86]

Polyurethane Delivery Systems

Cleansing

One of the best functional uses for hydrophilic polyurethane products is skin cleansing. This is because hydrophilic polyurethane polymers can accept a variety of aqueous detergent systems ranging from simple solutions to multiple combinations of surfactants in an emulsified state. Nonionic, anionic, cationic, and amphoteric types of surfactants can be incorporated into these reactive polymers with relative ease. Even ingredient combinations that may be unstable prior to foaming can be formulated due to the stabilizing effect of the resultant foam.^[88]

One example of the hydrophilic polyurethane technology in skin cleansing is the removal of facial makeup from the skin. The product utilizes an aqueous phase consisting of a water-based lotion combined with emollients and pigment dispersants. The aqueous phase is reacted with hydrophilic polyurethane prepolymer and molded in a tubular configuration. The cured product is then die-cut into ready-to-use round, thin, spongy disks. The finished product is a soft, moist, reticulated foam that dispenses an effective moisturizing cleanser that efficiently dissolves and removes all types of facial and eye makeup including waterproof mascara.^[88]

Makeup Application

Hydrophilic polyurethane foam systems have also been used to encapsulate color cosmetics. However, pigmented formulations such as foundation makeup must be water based in order to react with the hydrophilic polyurethane prepolymers. Moreover, the key to the uniform release of the pigment color is the selection of an appropriate prepolymer, or a combination of prepolymers, to allow a smooth transfer of the makeup from the foam to the skin.^[88]

Dermabrasion

Hydrophilic polyurethane systems have also been used as the vehicle for the entrapment of various cosmetically

acceptable abrasive materials such as aluminum oxide crystals, feldspar, ground fruit pits, mini-fibers, and polyethylene granules. These can be processed into a finished foam product that will exhibit a special “soft abrasive” action. An additional benefit of this system is that the abrasives can be chemically locked into the foam matrix structure, thereby eliminating the usual residual grit that conventional abrasive creams leave on the skin or in the washbasin. If a formula does contain levels of abrasive particles in excess of 50%, the foam is not recommended for this purpose since it tends to dry out.^[89]

The inclusion of other hydrophilic or hydrophobic polymers in the formulation can modify the functional characteristics of the hydrophilic polyurethane prepolymers. Durability, stiffness, flexibility, rubbery-ness, surface feel, encapsulation of solids, retention or release of ingredients from within the foam matrix, etc., are just some of the properties that can be designed into finished products by including selected combinations of various polymers. Polymer solutions, emulsions, or solids, such as acrylics, polyvinyl pyrrolidones, polyvinylidene dichlorides, and acrylic latex copolymers, can be added to the aqueous phase along with other ingredients prior to being combined with a hydrophilic polyurethane prepolymer.^[88]

Activated Delivery Systems

Activated delivery systems are delivery systems that employ stimuli-responsive polymers. These delivery systems release their payloads due to changes in pressure, temperature, pH, osmotic pressure, or enzymatic digestion.^[90]

Drug in adhesive transdermal patches utilized pressure-sensitive polymer adhesives. Microspheres and microcapsules in cosmetic product formulations can release their payloads as a response to pumping action prior to skin application or finger pressure during skin application.

Thermo-responsive polymers are polymers that undergo sol(liquid)/gel at specified temperature. This activated delivery system is usually employed in the food industry. However, a newer study has suggested the possibility of employing thermo-responsive hydrogels for wound dressing purposes. For this purpose, thermo-responsive hydrogels containing poly(*N*-isopropylacrylamide)(PNIPAAm) reinforced with cellulose nanocrystals (CNCs) were synthesized via free-radical polymerization in the absence of any additional cross-linker.^[91] The volume-phase transition temperature for the PNIPAAm–CNC hydrogel was 36°C–39°C, which is close to the normal body temperature. The hydrogels showed a burst drug release followed by slow and sustained release at 37°C.

pH-responsive delivery systems are usually utilized in oral pharmaceutical formulations to make use of the harsh pH environment of the gastrointestinal system. However, the possibility of using pH-sensitive polymers for cosmetic applications has also been explored.^[92] pH-responsive copolymer of methacrylic acid (MAA) and poly(ethylene glycol)

methacrylate (P(MAA-*co*-EGMA)) was studied as the carrier for arbutin, adenosine, and niacinamide. At pH 4, almost none of the cosmetic ingredients permeated through the skin, whereas at pH 6, relatively high skin permeability was observed. This shows the potential of using this pH-sensitive polymer hydrogel in cosmetic formulations as cosmetic formulations are usually formulated at pH 5–7.

REFERENCES

1. Ow, C.; Chee, P.L.; Loh, X.J. A global analysis of the personal market. In *Personal Care Products and Cosmetics*, RSC polymer chemistry series no. 20; Loh, X.J.; Ed.; The Royal Society of Chemistry, Cambridge, UK, 2016, 1–7.
2. Washington, C.; Washington, N. Drug delivery to the skin. In *Physiological Pharmaceutics, Biological Barriers to Drug Absorption*, 1st Ed.; Wilson, C.G.; Washington, N.; Eds.; Ellis Horwood: Chichester, UK, 1989, 109–120.
3. Kolarsick, P.A.J.; Kolarsick, M.A.; Goodwin, C. Anatomy and physiology of the skin. In *Site Specific Cancer Series: Skin Cancer*; Muehlbauer, P.; McGowan, C.; Eds.; Oncology Nursing Society: Pittsburgh, PA, 2009, 1–11.
4. James, W.D.; Berger, T.G.; Elston, D.M. *Andrew's Diseases of the Skin: Clinical Dermatology*; Elsevier Saunders: Philadelphia, PA, 2006.
5. Murphy, G.F. Histology of the skin. In *Lever's Histopathology of the Skin*, 8th Ed.; Elder, R.; Elenitsas, R.; Jaworsky, C.; Johnson Jr., B.; Eds.; Lippincott Williams & Wilkins: Philadelphia, PA, 1997, 5–45.
6. Chu, D.H. Overview of biology, development, and structure of skin. In *Fitzpatrick's Dermatology in General Medicine*, 7th Ed.; Wolff, K.; Goldsmith, L.A.; Katz, S.I.; Gilchrist, B.A.; Paller, A.S.; Leffell, D.J.; Eds.; McGraw Hill: New York, 2008, 57–73.
7. Elias, P.M. Epidermal lipids, membrane and keratinization. *Int. J. Dermatol.* **1981**, *20*, 1–19.
8. Scott, I.R.; Harding, C.R.; Barrett, J.G. Histidine-rich protein of the keratohyalin granules. Source of the free amino acids, urocanic acid and pyrrolidone carboxylic acid in the stratum corneum. *Biochim. Biophys. Acta* **1982**, *719* (1), 110–117.
9. Rice, R.H.; Green, H. The cornified envelope of terminally differentiated human epidermal keratinocytes consists of cross-linked protein. *Cell* **1977**, *11* (2), 417–422.
10. Wertz, P.W.; Downing, D.T. Covalently bound omega-hydroxyacylsphingosine in the stratum corneum. *Biochim. Biophys. Acta* **1987**, *917*, 108–111.
11. Uchida, Y.; Park, K. Stratum corneum. In *Immunology of the Skin. Basic and Clinical Sciences in Skin Immune Responses*; Kabashima, K.; Ed.; Springer: Tokyo, Japan, 2016, 15–30.
12. Roberts, M.S. Targeted drug delivery to the skin and deeper tissues; The role of physiology, solute structure and disease. *Clin. Exp. Pharmacol. Physiol.* **1997**, *24*, 874–879.
13. Scheuplin, R.J. Permeability of the skin. *Physiol. Rev.* **1971**, *51*, 702–747.
14. Misra, A.N. Transdermal drug delivery. In *Controlled and Novel Drug Delivery*; Nain, J.K.; Ed.; CBS Publisher and Distributor: New Delhi, India, 1997, 100–129.

15. Govil, S.K. Transdermal drug delivery devices. In *Drug Delivery Devices: Fundamentals and Applications*; Tyle, P.; Ed.; Marcel Dekker: New York, 1988, 385–419.
16. Peterson, T.A.; Wick, S.M.; Ko, C. Design, development, manufacturing and testing of transdermal drug delivery systems. In *Transdermal and Topical Drug Delivery Systems*; Ghosh, T.K.; Pfister, W.R.; Yum, S.I.; Eds.; Interphar Press: Buffalo Grove, IL, 1997, 249–297.
17. Pocius, A.V. Adhesives. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Howe-Grants, M.; Ed.; Wiley-Interscience: New York, 1991, 445–466.
18. Levin, C.; Maibach, H.I. Transdermal drug delivery systems: An overview. In *Marzulli and Maibach's Dermatotoxicology*, 7th Ed.; Zhai, H.; Wilhelm, K.P.; Maibach, H.I.; Eds.; CRC Press: Boca Raton, FL, 2008, 101–106.
19. Bromberg, L. Cross-linked poly(ethylene glycol) networks as reservoirs for protein delivery. *J. Appl. Poly. Sci.* **1996**, *59*, 459–466.
20. Costa, P.; Ferreira, D.C.; Morgado, R.; Sousa Lobo, J.M. Design and evaluation of a lorazepam transdermal delivery system. *Drug Dev. Ind. Pharm.* **1997**, *23* (10), 939–944.
21. Ramarao, P.; Diwan, P.V. Formulation and in vitro evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal administration. *Drug Dev. Ind. Pharm.* **1998**, *24* (4), 327–336.
22. Guyot, M.; Fawaz, F. Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol. *Int. J. Pharm.* **2000**, *204*, 171–182.
23. Gale, R.; Spitze, L.A. Permeability of camphor in ethylene-vinyl acetate copolymers. In *Proceedings: Eighth International Symposium on Controlled Release of Bioactive Materials*; Controlled Release Society: Minneapolis, MN, 1981, 183.
24. Baker, R.W.; Tuttle, M.E.; Lonsdale, H.K.; Ayres, J.W. Development of an estriol-releasing intrauterine device. *J. Pharm. Sci.* **1979**, *68* (1), 20–26.
25. Barnhart, S.; Carrig, T. Critical role of PSAs. In *Transdermal Drug Delivery: Adhesives and Sealants Industry*; BNP Media: Troy, MI, 1998, 1–6.
26. Tan, H.S.; Pfister, W.R. Pressure-sensitive adhesives for transdermal drug delivery systems. *Pharm. Sci. Technol. Today* **1999**, *2* (2), 60–69.
27. Aoyagi, T.; Yamamura, M.; Suzuki, N.; Matsui, K.; Nagase, Y. Preparation of alkyl-substituted pyrrolidone derivatives and their evaluation as transdermal penetration enhancers. *Drug Des. Discov.* **1991**, *8* (1), 37–46.
28. Ahad, A.; Aqil, M.; Kohli, K.; Chaudhary, H.; Sultana, Y.; Mujeeb, M.; Talegoankar, S. Chemical penetration enhancers: A patent review. *Expert Opin. Ther. Pat.* **2009**, *19*, 969–988.
29. Karande, P.; Jain, A.; Ergun, K.; Kispersky, V.; Mitragotri, S. Design principles of chemical penetration enhancers for transdermal drug delivery. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 4688–4693.
30. Junginger, H.E.; Verhoef, J.C. Macromolecules as safe penetration enhancers for hydrophilic drugs – a fiction? *Pharma. Sci. Technol. Today* **1998**, *1*, 370–376.
31. Junginger, H.E. Polymeric permeation enhancers. In *Oral Delivery of Macromolecular Drugs*; Bernkop-Schnurch, A.; Ed.; Springer Science and Business Media: New York, 2009, 103–122.
32. Leuben, H.L.; de Leeuw, B.J.; Perard, D.; Lehr, C.M.; de Boer, A.G.; Verhoef, J.C.; Junginger, H.E. Mucoadhesive polymers in peroral drug delivery. I. Influence of mucoadhesive excipients on the proteolytic activity of intestinal enzymes. *Eur. J. Pharm. Sci.* **1996**, *4*, 117–128.
33. Borchard, G.; Lueben, H.L.; de Boer, A.G.; Verhoef, J.C.; Lehr, C.M.; Junginger, H.E. The potential of mucoadhesive polymers in enhancing peptide drug absorption. III. Effects of chitosan glutamate and carbomer on the epithelial tight junction in vitro. *J. Control. Release* **1996**, *39*, 131–138.
34. Malminen, M.; Koivukangas, V.; Peltonen, J.; Karvonen, S.L.; Oikarinen, A.; Peltonen, S. Immunohistological distribution of the tight junction components ZO-1 and occluding in generating human epidermis. *Br. J. Dermatol.* **2003**, *149*, 255–260.
35. Cattaneo, M.V. Topical delivery systems based on polysaccharide microspheres. In *Delivery System Handbook for Personal Care and Cosmetic Products*; Rosen, M.R.; Ed.; William Andrew Publishing: New York, 2005, 273–282.
36. Kear, C.L.; Yang, J.; Godwin, D.A.; Felton, L.A. Investigations into the mechanism by which cyclodextrins influence transdermal drug delivery. *Drug Deliv. Ind. Pharm.* **2008**, *34*, 692–697.
37. Kim, H.; Kim, M.; Quan, Y.; Moon, T.; Mun, J.; Cho, H.; Park, N.; Moon, W.; Lee, K.; Kim, H.; Lee, J.; Ryoo, H.; Jung, H. Novel antiwrinkle effect of cosmeceutical product with new retinylretinoate microsphere using biodegradable polymer. *Skin Res. Tech.* **2012**, *18*, 70–76.
38. Haddadi, A.; Aboofazeli, R.; Erfan, M.; Farboud, E.S. Topical delivery of urea encapsulated in biodegradable PLGA microparticles: O/W and W/O creams. *J. Microencapsul.* **2008**, *25*, 379–386.
39. Stevanovic, M.; Savic, J.; Jordovic, B.; Uskokovic, D. Fabrication, in vitro degradation and the release behaviours of poly(dl-lactide-co-glycolide) nanospheres containing ascorbic acid. *Colloids Surf.* **2007**, *59*, 215–223.
40. Lau, W.M.; Ng, K.W.; Sakenyte, K.; Heard, C.M. Distribution of esterase activity in porcine ear skin, and the effects of freezing and heat separation. *Int. J. Pharm.* **2012**, *433*, 10–15.
41. Wang, S.; Wu, M.; Li, D.; Jiao, M.; Wang, L.; Zhang, H.; Liu, H.; Wang, D.; Han, B. Preparation, characterization and related in vivo release, safety and toxicity studies of long acting lanreotide microspheres. *Biol. Pharm. Bull.* **2012**, *35*, 1898–1906.
42. Xue, B.; Wang, Y.; Tang, X.; Xie, P.; Wang, Y.; Luo, F.; Wu, C.; Qian, Z.J. Biodegradable self-assembled MPEG-PCL micelles for hydrophobic oridonin delivery in vitro. *Biomed Nanotechnol.* **2012**, *8*, 80–89.
43. Tong, Y.C.; Yu, T.Y.; Chang, S.F.; Liaw, J.H. Nanopolymeric Micelle Effect on the Transdermal Permeability, the Bioavailability and Gene Expression of Plasmid. *Mol. Pharm.* **2012**, *8*, 80–89.
44. Poree, D.E.; Giles, M.D.; Lawson, L.B.; He, J.; Grayson, S.M. Synthesis of amphiphilic star block copolymers and their evaluation as transdermal carriers. *Biomacromolecules* **2011**, *12*, 898–906.
45. Parveen, S.; Misra R.; Sahoo, S.K. Nanoparticles: A boon to drug delivery, therapeutics, diagnostics and imaging. *Nanomed. Nanotechnol. Biol. Med.* **2012**, *8*, 147–166.

46. Venuganti, V.; Sahdev, P.; Hildreth, M.; Guan, X.; Perumal, O. Structure-skin permeability relationship of dendrimers. *Pharm. Res.* **2011**, *28*, 2246–2260.
47. Sun, M.J.; Fan, A.P.; Wang, Z.; Zhao, Y.J. Dendrimer-mediated drug delivery to the skin. *Soft Matter*. **2012**, *8*, 4301–4305.
48. Agrawal, P. Significance of polymers in drug delivery system. *J. Pharmacovigil.* **2015**, *3*, 2329–6887.
49. Wu, W.; Olesen, K.R.; Shay, G.D.; Dockery, J.R. Effect of temperature on surfactant co-thickening in model hase polymer solutions. *Polym. Mater. Sci. Eng.* **2001**, *85*, 213–214.
50. Thevenin, M.A.; Grossiord, J.L.; Poelman, M.C. Sucrose esters/cosurfactant microemulsion systems for transdermal delivery: Assessment of bicontinuous structures. *Int. J. Pharm.* **1996**, *137*, 177–186.
51. Signori, F.; Chiellini, F.; Solaro, R. New self-assembling biocompatible–biodegradable amphiphilic block copolymers. *Polymer* **2005**, *46*, 9642–9652.
52. Friberg, S.E. Micelles, microemulsions, liquid crystals, and the structure of stratum corneum lipids. *J. Cosmet. Sci.* **1990**, *41*, 155–171.
53. Discher, D.E.; Eisenberg, A. Polymer vesicles. *Science* **2002**, *297*, 967–973.
54. Harrington, K.J.; Lewanski, C.R.; Stewart, J.S. Liposomes as vehicles for targeted therapy of cancer. Part 2: Clinical development. *Clin. Oncol. (R. Coll. Radiol.)* **2000**, *12*, 16–24.
55. Lauer, A.C. Percutaneous drug delivery to the hair follicle. *J. Pharm. Sci.* **1999**, *9*, 427–449.
56. Panyam, J.; Labhasetwar, V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. *Adv. Drug Deliv. Rev.* **2003**, *55*, 329–347.
57. Bencini, M.; Ranucci E.; Ferruti P.; Trotta F.; Donalisio M.; Cornaglia M.; Lembo D.; Cavalli, R. Preparation and in vitro evaluation of the antiviral activity of the Acyclovir complex of a beta-cyclodextrin/poly(amidoamine) copolymer. *J. Control. Release* **2008**, *126*, 17–25.
58. Desai, M.P.; Labhasetwar, V.; Amidon, G.L.; Levy, R.J. Gastrointestinal uptake of biodegradable microparticles: Effect of particle size. *Pharm. Res.* **1996**, *13*, 1838–1845.
59. Gaucher, G.; Dufresne, M.H.; Sant, V.P.; Kang, N.; Maysinger, D.; Leroux, J.C. Block copolymer micelles: Preparation, characterization and application in drug delivery. *J. Control Release* **2005**, *109*, 169–188.
60. Qiu, L.Y.; Bae, Y.H. Polymer architecture and drug delivery. *Pharm. Res.* **2006**, *23*, 1–30.
61. Elvira, C.; Gallardo, A.; San, R.J.; Cifuentes, A. Covalent polymer–drug conjugates. *Molecules* **2005**, *10*, 114–125.
62. Wang, C.; Li, G.; Guo, R. Multiple morphologies from amphiphilic graft copolymers based on chitooligosaccharides as backbones and polycaprolactones as branches. *Chem. Commun.* **2005**, 3591–3593.
63. Gref, R.; Rodrigues, J.; Couvreur, P. Polysaccharides grafted with polyesters: Novel amphiphilic copolymers for biomedical applications. *Macromolecules* **2002**, *35*, 9861–9867.
64. Cho, H.K.; Cho, J.H.; Jeong, S.H.; Cho, D.C.; Yeum, J.H.; Cheong, I.W. Polymeric vehicles for topical delivery and related analytical methods. *Arch. Pharm. Res.* **2014**, *37* (4), 423–434.
65. Tolia, G.T.; Choi, H.H. The role of dendrimers in topical drug delivery. *Pharm. Tech.* **2008**, *32*, 88–98.
66. Liu, M.; Kono, K.; Frechet, J.M.J. Water-soluble dendritic unimolecular micelles: Their potential as drug delivery agents. *J. Control. Release* **2000**, *65*, 121–131.
67. Jagan, A.; Mohan, R.; Manas, R.B.; Gajendra, L.M.; Parthasarathy, T. Computational approach for designing and development of potent inhibitor for Hepatitis - B virus X- associated protein through molecular docking studies. *J. Chem.* **2012**, *4* (1), 265–271.
68. Williams, A.C.; Barry, B.W. Penetration enhancers. *Adv. Drug Deliv. Rev.* **2004**, *56* (5), 603–618.
69. Brisson, P. Percutaneous absorption. *Can. Med. Assoc. J.* **1974**, *110* (10), 1182–1185.
70. Lidert, Z. Microencapsulation: An overview of the technology landscape. In *Delivery System Handbook for Personal Care and Cosmetic Products*; Rosen, M.R.; Ed.; William Andrew Publishing: New York, **2005**, 181–190.
71. Liechty, W.B.; Kryscio, D.R.; Slaughter, B.V.; Peppas, N.A. Polymers for drug delivery systems. *Annu. Rev. Chem. Biomol. Eng.* **2010**, *1*, 149–173. doi:10.1146/annurev-chembioeng-073009-100847.
72. Peppas, N.A. Drug delivery using smart polymers: Recent advances. In *Smart Polymers: Applications in Biotechnology and Biomedicine*, 2nd Ed.; Galaev, I.M.; Mattiasson, B.; Eds. CRC Press: Boca Raton, FL, 2008, 311–358.
73. Agrawal, P. Significance of polymers in drug delivery system. *J. Pharmacovigil.* **2014**, *3*, e127. doi:10.4172/2329-6887.1000e127.
74. Tamada, J.A.; Langer, R. Erosion kinetics of hydrolytically degradable polymers. *Proc. Natl. Acad. Sci. USA* **1993**, *90* (2), 552–56.
75. Bae, Y.; Kataoka, K. Intelligent polymeric micelles from functional poly(ethylene glycol)-poly(amino acid) block copolymers. *Adv. Drug Deliv. Rev.* **2009**, *61*, 768.
76. Gaumet, M.; Vargas, A.; Gurny, R.; Delie, F. Nanoparticles for drug delivery: The need for precision in reporting particle size parameters. *Eur. J. Pharm. Biopharm.* **2008**, *69* (1), 1–9.
77. Das, S.; Chaudhury, A. Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. *AAPS Pharm. Sci. Tech.* **2011**, *12* (1), 62–76.
78. Ravi Kumar, M.N.V.; Bakowsky, U.; Lehr, C.M. Preparation and characterization of cationic PLGA nanospheres as DNA carriers. *Biomaterials* **2004**, *25* (10), 1771–1777.
79. Yeo, Y.; Park, K. Control of encapsulation efficiency and initial burst in polymeric microparticle systems. *Arch. Pharm. Res.* **2004**, *27*, 1–12.
80. Christophersena, P.C.; Fanø, M.; Saaby, L.; Yanga, M.; Nielsena, H.M.; Mu, H. Characterization of particulate drug delivery systems for oral delivery of peptide and protein drugs. *Curr. Pharm. Des.* **2015**, *21*, 1–18.
81. Dandagi, P.M.; Dessai, G.A.; Gadad, A.P.; Desai, V.B. Formulation and evaluation of nanostructured lipid carrier (NLC) of lornoxicam. *Int. J. Pharm. Sci.* **2014**, *6* (2), 73–77.
82. Vij, N.N.; Saudagar, R.B. Formulation, development and evaluation of film forming gel for prolonged dermal delivery of terbinafine hydrochloride. *Int. J. Pharm. Sci. Res.* **2014**, *5* (9), 537–554.
83. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on Cosmetic Products. *Off. J. EU* **2009**, *L342*, 59.

84. Cherukuri, S.; Batchu, U.R.; Mandava, K.; Cherukuri, V.; Ganapuram, K.R. Formulation and evaluation of transdermal drug delivery of topiramate. *Int. J. Pharm. Investig.* **2017**, *7* (1), 10–17.
85. Fotinos, S.A. Cosmetic patches. In *Handbook of Cosmetic Science and Technology*; Paye, M.; Barel, A.O.; Maibach, H.I.; Eds.; CRC Press: Boca Raton, FL; 2005, 211–221.
86. Saxena, S.; Nacht, R. Polymeric porous delivery systems: Polytrap and microsp sponge in delivery system. In *Handbook for Personal Care and Cosmetic Products*; Rosen, M.R.; Ed.; William Andrew Pub.: Norwich, NY, 2005, 333–351.
87. Kaity, S.; Maiti, S.; Ghosh, A.K.; Pal, D.; Ghosh, A.; Banerjee, S. Microsponge: A novel strategy for drug delivery system. *J. Adv. Pharm. Technol. Res.* **2010**, *1* (13), 283–290.
88. Smith, J.A.; Murphy, B.J. Soft cell approach to personal care hydrophilic active-filled polyurethane delivery system. In *Delivery System Handbook for Personal Care and Cosmetic Products*; Rosen, M.R.; Ed.; William Andrew Publishing: New York, 2005, 513–532.
89. Patravale, V.B.; Mandawgade, S.D. Novel cosmetic delivery systems: An application update. *Int. J. Cosmet. Sci.* **2008**, *30*, 19–33.
90. Cabane, E.; Zhang, X.; Langowska, K.; Palivan, C.G.; Meier, W. Stimuli-responsive polymers and their applications in nanomedicine. *Biointerphases* **2012**, *7*, 9.
91. Zubik, K.; Singhsa, P.; Wang, Y.; Manuspiya, H.; Narain, R. Thermo-responsive Poly(N-Isopropylacrylamide)-cellulose nanocrystals hybrid hydrogels for wound dressing. *Polymer* **2017**, *9* (119), 1–17.
92. Lee, E.; Kim, B. Smart delivery system for cosmetic ingredients using pH-sensitive polymer hydrogel particles. *Korean J. Chem. Eng.* **2011**, *28* (6), 1347–1350.